NOVARTIS

Clinical Development

PDR001 and LAG525

Oncology Clinical Protocol CPDR001XUS01 / NCT03365791

Modular phase 2 study to link combination immune-therapy to patients with advanced solid and hematologic malignancies
Module 9: PDR001 plus LAG525 for patients with advanced solid and hematologic malignancies

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List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
CBR	Clinical Benefit Rate
[redacted]	[redacted]
CMO&PS	Chief Medical Office and Patient Safety
CPB	Checkpoint blockade
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CRS	Cytokine Release Syndrome
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
eSAE	Electronic Serious Adverse Event
FAS	Full Analysis Set
FIH	First In Human
FU	Follow Up
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
IO	Immuno-oncology
i.v.	intravenous(ly)
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IG	Immunogenicity
IRB	Institutional Review Board
LAG-3	Lymphocyte activation gene-3
mAb(s)	monoclonal Antibody(ies)
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MTD	Maximum Tolerated Dose
ORR	Overall Response Rate
OS	Overall survival
PD	Pharmacodynamics
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PFS	Progression free survival
PHI	Protected Health Information
Q3W	Every 3 weeks dosing schedule
RAP	Report and Analysis Plan
RECIST	Response Evaluation Criteria In Solid Tumors
REB	Research Ethics Board

[redacted]

RP2D	Recommended phase two dose
SAE	Serious Adverse Event
SCLC	Small Cell Lung Cancer
SOP	Standard Operating Procedure
TCR	T Cell Receptor
TIL(s)	Tumor Infiltrating Lymphocyte(s)
TTP	Time To Progression
TTR	Time To Response

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q21 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Screen failures	Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failures
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. The cohorts are not expanded, new cohorts will be enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time-points
Withdrawal of consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

[redacted]

Amendment 1

Amendment Rationale

The primary purpose of this amendment is to address health authority requests:

- Inclusion of a Criterion that patients have locally advanced or metastatic disease
- For patients who have previously received anti PD-1, PD-L1, CTLA-4, or LAG-3 agent, modification of the exclusion criteria to include the following additional restrictions:
  - Patients with a history of any grade immune-related ocular adverse event.
  - Patients with a history of Grade ≥ 3 immune-related adverse event.
  - Patients with evidence of active noninfectious pneumonitis or history of interstitial lung disease.
  - Patients with risk of reactivation of hepatitis B or C
  - Patients who are on endocrine replacement therapy should be stable on the dose.
- Addition of a simple schematic of the protocol design which outlines the two-staged futility and expansion stage and succinctly captures the number of patients in each cohort.
- Modification of Table 7-1 to clearly indicate that the cycle length is 3 weeks.
- Inclusion of safety data obtained from trial CLAG525X2101C for the combination of LAG525 and PDR001, in Section 1.2.3.2.
- Modification of the protocol to define and use the terms "expansion cohort" and "expanded tumor group" consistently.
- [redacted]

The secondary purpose of this amendment is to incorporate the following changes:

- [redacted]
- Remove the cytokine sample collection, storage and sample analysis
- Update safety data per release of most recent investigator brochures
- Correct minor inconsistencies and typographical errors throughout the document
- To align with recently published guidelines on the clinical management of suspected immune-related toxicities, the dose modification section of the protocol and corresponding table were updated.
- After the recent occurrence of a case of Stevens Johnson Syndrome in a study with PDR001, the dose modification guidelines for protocols using PDR001 were updated to mandate permanent discontinuation of study treatment for patients who experience SJS or Lyell syndrome/toxic epidermal necrolysis (TEN). This change has already been implemented as part of an urgent safety measure released on June 15, 2018. This protocol amendment is now formalizing these changes in the table 6-1.
- Inclusion of the liquid formulation of PDR001, in addition to the powder for solution formulation, in the drug description.

[redacted]

Study Status

At the time of this amendment, the trial has enrolled 70 patients at 24 centers across the United States. Initial enrollment into 6 of the 7 tumor cohorts is completed, pending futility analysis to determine if the cohorts will re-open to enrollment.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

The Protocol Summary has been updated to incorporate the changes implemented throughout the document.

Section 1.2.1.2. updated to include most recent data per PDR001 Investigator Brochure Editions 7 and 7.1.

Section 1.2.2.2. updated to include the most recent single agent safety data from LAG525 Investigator Brochure Edition 4.

Section 1.2.3.2 updated to include safety data for the combination of PDR001 and LAG525 per the LAG525 Investigator Brochure Edition 4.

[redacted]

Section 4 updated to change the name of table 4-1 from Tumor Groups to Tumor Cohorts. Similar language change implemented throughout this section, and to sections 4.3, 4.4, and 5.1.

Section 4.3 updated to include a simple schematic of the study design.

Section 5.3 updated to:

- [redacted]
- Include a criteria that patients have locally advanced or metastatic disease
- Clarified the language in inclusion criteria #4

Section 5.4 updated as follows:

- Criteria #6: Correct and inconsistency by indicating it is applicable to the IO exposed sub-group.
- Criteria #13: Expand the list of prior IO therapies that patients may receive
  - Criteria #13(b): Revised the exclusion criteria for the expansion phase IO sub-group to restrict:
    - Patients with a history of any grade immune-related ocular adverse event.
    - Patients with a history of Grade ≥ 3 immune-related adverse event.
    - Patients with evidence of active noninfectious pneumonitis or history of interstitial lung disease.
    - Patients with risk of reactivation of hepatitis B or C.
    - Patients who are on endocrine replacement therapy should be stable on the dose.

[redacted]

Sections 6.1 and 6.6 updated to include descriptions of [redacted] formulation [redacted].

Section 6.3.2. updated to align with the recently published guidelines on the clinical management of suspected immune-related toxicities. Table 6-1 reflects these changes.

Section 7 updated to implement changes to Table 7-1 as follows:

- A notation indicating cycle length is 21 days/3 weeks added to top of the table
- [redacted]
- Cytokines for Safety removed from the table
- Study Drug Administration LAG525- added notation "(Q3W)"
- Study Drug Administration PDR001- added notation "(Q3W)"
- Measurement of superficial B symptoms- added assessment to Cycle 3, Day1, to correct typographical error in original protocol, where the x was missing.
- [redacted]

Section 7.1.2: corrected the length of the screening period in paragraph 4 to reflect the correct duration of 21 days.

Section 7.2.1.1: corrected inconsistency in paragraph 3 to indicate that the window for radiological assessments is +/- 7 days.

Section 7.2.1.1.5: corrected inconsistency. Section incorrectly indicated that tumor assessments would continue after EOT, during the safety follow-up period. That language has been removed.

Table 7-3: removed the cytokine related assessments from the table

Section 7.2.2.5.6.: removed the cytokine section from the protocol

[redacted]

[redacted]

Changes to the remainder of the document include grammatical corrects/clarifications of minor inconsistencies.

IRBs/IECs

[redacted]

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised informed consent that takes into account the changes described in this protocol amendment.

Protocol summary:

Title	Modular phase 2 study to link combination immune-therapy to patients with advanced solid and hematologic malignancies
Brief title	Module 9: PDR001 plus LAG525 for patients with advanced solid and hematologic malignancies
Sponsor and Clinical Phase	Novartis 2
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this signal seeking study is to determine whether treatment with PDR001 and LAG525 demonstrates sufficient efficacy in advanced malignancies to warrant further study.
Primary Objective(s)	Assess CBR at 24 weeks of PDR001+LAG525 in multiple solid malignancies and lymphoma.
Secondary Objectives	Assess ORR, TTR, DoR, TTP, PFS rate at 1 and 2 years Safety incidence and severity of adverse events (AEs) and serious adverse events (SAEs) including changes in laboratory parameters, vital signs and ECGs Tolerability: Dose interruptions, reductions and dose intensity.
Study design	This is a phase II, open-label, parallel-cohort study to determine the efficacy and safety of treatment with the combination of PDR001+LAG525 across multiple tumor types that are relapsed and/or refractory to available standard of care therapies. Patients will receive study treatment for a maximum of 2 years, or until disease progression, unacceptable toxicity, death or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, start of a new anti-neoplastic therapy or at the discretion of the investigator or patient). All patients who discontinue from study treatment due to disease progression must have their progression clearly documented. All disease assessments will be performed locally by the investigator.
Population	This study will be conducted in patients with select solid tumors or lymphoma as outlined in Table 4-1. Tumor types may be excluded or added during the course of the study in the case of early futility or success based upon an interim analysis or at the discretion of Novartis.
Selected Inclusion criteria	Patients eligible for inclusion in this study have to meet all of the following criteria: 1. Written informed consent must be obtained prior to any screening procedures. 2. Patient is ≥ 18 years of age on the day of consenting to the study 3. Patient must have had at least one prior line of therapy for their disease and must not be beyond 4th progression/relapse of disease (5 maximum prior lines). 4. Patient has a pathology confirmed diagnosis of a solid tumor or lymphoma listed in Table 4-1 and measurable disease as per appropriate guidelines: • **All Solid Tumors: by RECIST 1.1 (Appendix 1)** ○ For advanced well-differentiated neuroendocrine tumors, the following also apply: ▪ Pathologically confirmed, well-differentiated (Grade 1 or Grade 2), advanced (unresectable or metastatic), neuroendocrine tumor ▪ No history of and no active symptoms related to carcinoid syndrome ▪ Patient has not had hepatic intra-arterial embolization within the last 6 months or cryoablation or radiofrequency ablation of hepatic metastases within 2 months of first dose

[redacted]

	• **Diffuse Large B-cell Lymphoma:** by the Revised Response Criteria for Malignant Lymphoma (Cheson et al 2007) (Appendix 2) o Relapsed/refractory disease as defined by relevant standardized response criteria (see Section 4) o Patients with prior autologous transplant are eligible o Patient has at least one measurable nodal lesion (≥2 cm). In case where the patient has no measurable nodal lesions ≥ 2 cm in the long axis at screening, then the patient must have at least one measurable extra-nodal lesion 5. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 6. Patients must have locally advanced or metastatic disease
Selected Exclusion criteria	Patients eligible for this study must not meet **any** of the following criteria: 1. Presence of symptomatic CNS metastases, or CNS metastases that require local CNS-directed therapy (such as radiotherapy or surgery), or increasing doses of corticosteroids within the prior 2 weeks. Patients with treated brain metastases should be neurologically stable (for 4 weeks post-treatment and prior to study enrollment) and off steroids for at least 2 weeks before administration of any study drug. 2. History of severe hypersensitivity reactions to other mAbs. 3. Patient with out of range laboratory values: a) Creatinine clearance (calculated using Cockcroft-Gault formula, or measured) < 40 mL/min b) Total bilirubin > 1.5 x ULN, except for patients with Gilbert's syndrome who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN c) Alanine aminotransferase (ALT) > 3 x ULN, except for patients that have tumor involvement of the liver, who are excluded if ALT > 5 x ULN d) Aspartate aminotransferase (AST) > 3 x ULN, except for patients that have tumor involvement of the liver, who are excluded if AST > 5 x ULN e) Absolute neutrophil count (ANC) < 1.0 x 10^9/L f) Platelet count < 75 x 10^9/L g) Hemoglobin < 9 g/dL 4. Impaired cardiac function or clinically significant cardiac disease, including any of the following: a) Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (NYHA Grade ≥ 2), uncontrolled hypertension or clinically significant arrhythmia b) QTcF > 470 msec on screening/baseline ECG or congenital long QT syndrome c) Acute myocardial infarction or unstable angina pectoris < 3 months prior to study entry 5. Active, known or suspected autoimmune disease or a documented history of autoimmune disease within three years prior to screening with exception of: a. Patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to an autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. 6. If otherwise eligible for the expansion phase IO sub-group, Patients previously exposed to anti-PD-1/PD-L1 treatment who are adequately treated for skin rash or with replacement therapy for endocrinopathies should not be excluded

[redacted]

	7. Active infection requiring systemic antibiotic therapy. Patients requiring systemic antibiotics for infection must have completed therapy before screening is initiated. 8. Known history of HIV infection. Testing for HIV status is not necessary unless clinically indicated 9. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Testing for HBV or HCV status is not necessary unless clinically indicated or the patient has a history of HBV or HCV infection. 10. Patient with second primary malignancy within < 3 years of first dose of study treatment. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma in situ of any type. 11. Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns, compliance with clinical study procedures or interpretation of study results. 12. Systemic anti-cancer therapy within 2 weeks of the first dose of study treatment. For cytotoxic agents that have major delayed toxicity, e.g. mitomycin C and nitrosoureas, 4 weeks is indicated as washout period. 13. Prior immunotherapy treatment with PD-1, PD-L1, CTLA-4, or LAG-3 antibodies, CAR-T therapy, gene therapies, and/or Provenge therapy a. This exclusion does not apply to patients enrolled in the immunotherapy pre-exposed subgroup (n=6 per tumor type) in those cohorts that undergo expansion to 30 patients. b. For patients in the immunotherapy pre-exposed subgroups: i. Prior IO therapy with PD-1, PD-L1, or LAG-3 antibodies, within 4 weeks of first dose of study treatment ii. CTLA-4 antagonist or vaccine as anticancer therapy within 6 weeks of first dose of study treatment iii. Patients who discontinued prior anti-PD-1, PD-L1 or anti LAG-3 therapy due to therapy related toxicity iv. Patients with a history of any grade immune-related ocular adverse event. v. Patients with a history of Grade ≥ 3 immune-related adverse event. vi. Patients with evidence of active noninfectious pneumonitis or history of interstitial lung disease. vii. Patients with risk of reactivation of hepatitis B or C. viii. Patients who are on endocrine replacement therapy should be stable on the dose. 14. Systemic chronic steroid therapy or any immunosuppressive therapy (>10mg/day prednisone or equivalent). Topical, inhaled, nasal and ophthalmic steroids are allowed. 15. Use of any live vaccines against infectious diseases within 4 weeks of initiation of study treatment. 16. Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) or erythroid stimulating agents ≤ 2 weeks prior to start of study drug. If erythroid stimulating agents were initiated more than 2 weeks prior to the first dose of study treatment and the patient is on a stable dose, they can be maintained.

	17. Presence of CTCAE ≥ grade 2 toxicity (except peripheral neuropathy and ototoxicity, which are excluded if ≥ CTCAE grade 3) due to prior cancer therapy. 18. Allogeneic stem cell transplant recipients 19. Major surgery within 2 weeks of the first dose of study treatment (mediastinoscopy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery). 20. Participation in an interventional, investigational study within 2 weeks prior to the first dose of study treatment. 21. Pregnant or lactating women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. 22. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 150 days after the last dose of PDR001 and LAG525. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential. Highly effective contraception methods include: a) Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. b) Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment. c) Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject. d) Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. e) In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. 23. Sexually active males unless they use a condom during intercourse while taking the drug and for 150 days after stopping study treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via seminal fluid.
Investigational and reference therapy	LAG525 and PDR001
Efficacy assessments	The primary efficacy endpoint is clinical benefit rate as defined in Section 10.4. The secondary efficacy endpoint is overall response rate of PR or greater as defined in Section 10.5. Other secondary endpoints are time from the date of first dose to the date of first documented disease progression or relapse or death due

[redacted]

	to any cause, time from the date of first dose to the date of death due to any cause, time from the first documented response to the date first documented disease progression or relapse or death due to any cause, and other safety measurements as defined in Section 10. The local investigator's assessment will be used for the analysis and for treatment decision making.
Safety assessments	Adverse events. Physical examination Performance status evaluation Cardiac monitoring (ECGs, and assessment of LVEF) Laboratory evaluations (hematology, biochemistries, pregnancy tests)
Data analysis	The Full Analysis Set (FAS) will include all patients who have received at least one dose of study drug.
Key words	PDR001 LAG525 Immune checkpoint blockade Solid tumor malignancy lymphoma Small cell lung cancer (SCLC) Gastric/esophageal adenocarcinoma Castration resistant prostate adenocarcinoma (CRPC) Soft tissue sarcoma Ovarian adenocarcinoma Advanced well-differentiated neuroendocrine tumors (NETs) Diffuse large B cell lymphoma (DLBCL)

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Immune checkpoint blockade in cancer

Expression patterns of co-inhibitory and co-stimulatory receptors on tumor-specific T cells vary by both the maturation stage of the T cell as well as the location of the T cell (peripheral circulation v. intra-tumoral) (Baitsch 2012, Woo 2012). These patterns of expression together with early studies of the effects of signaling suggest that the network of co-receptors may deliver differential signals (Baitsch 2012). Tumor antigen-specific T cells isolated from the tumor-draining lymph nodes of melanoma patients have an activation profile, whereas T cells derived from the tumor bed display an exhausted phenotype with strong expression of multiple checkpoints, impaired cytokine secretion and activity (Matsuzaki 2010).

PD-1 (Programmed Death-1, CD-279) is a critical co-inhibitory receptor that is upregulated on T cells upon activation (Freeman 2008). It is also expressed by B cells, NK cells, dendritic cells, and activated monocytes. The ligands for PD-1, Programmed Death-Ligand 1 (PD-L1) and Programmed Death-Ligand 2 (PD-L2), are expressed by macrophages and monocytes, and can be induced on numerous cell types (T cells, endothelial cells, and tumor cells) during inflammation (Keir 2008). Engagement of PD-1 by its ligands transduces a signal that inhibits T-cell proliferation, cytokine production, and cytolytic function (Riley 2009). During tumorigenesis, cancer cells from a wide range of tumor types exploit immune checkpoint pathways, such as PD-1, to avoid detection by the adaptive immune system (Murphy 2011). Blockade of the PD-1 pathway has been shown to lead to both accumulation and increased activity of antitumor effector T cells and a reduced numbers of regulatory T cells (Tregs) at the tumor site (Wang 2009, Mangsbo 2010, Mkrtichyan 2011, Rosenblatt 2011).

LAG-3 (Lymphocyte Activation Gene-3, CD223) is a cell-surface molecule expressed on activated CD4+ and CD8+ T effector cells, multiple populations of regulatory T cells, NK cells, B cells and plasmacytoid dendritic cells (Huard 1994, Triebel 1990, Kisielow 2005). LAG-3 binds its ligand MHC Class II, and this interaction negatively regulates T cell signaling (Workman 2011). Blockade of LAG-3 has been shown to increase T cell proliferation and cytokine secretion, most notably IFN-γ (Huard 1997, Workman 2003). LAG-3 expression is also correlated with increased suppressive function in both FoxP3-positive natural regulatory T cells and induced FoxP3-negative regulatory cells (Huang 2004, Camisaschi 2010, Scurr 2014).

Checkpoint inhibitors have been successfully introduced to clinical practice with the approval of the antagonists to the CTLA-4 checkpoint (ipilimumab, BMS) and PD-1 (e.g nivolumab [BMS] and pembrolizumab [Merck]). Although the checkpoint inhibitors generally result in similar enhanced anti-tumor T cell activation, their effects are mediated by distinct pathways and they demonstrate enhanced activity in combination. The combination of ipilimumab and nivolumab is more active than either single agent in advanced melanoma (Wolchok 2013). LAG-3 is a distinct co-inhibitory receptor that may cooperate with PD-1 to dampen immune responses. In preclinical studies, the combined inhibition of PD-1 and LAG-3 checkpoints synergistically enhances antitumor responses over inhibition of either checkpoint alone (Drake

[redacted]

2014, Woo 2012). Taken together, these data suggest that combined inhibition of LAG-3 and PD-1 in the clinic may have significant anti-tumor activity in several tumors.

1.1.2 Disease Background and overview

Although there is clinical evidence for activity of checkpoint blockade (CPB) monotherapy in several tumor types including melanoma, NSCLC, and Hodgkins lymphoma, multiple tumor types have significantly less response to CPB monotherapy. Despite the finding of somewhat predictive biomarkers of response to CPB, including mutational burden, PD-L1 expression, and presence of tumor infiltrating lymphocytes (TILs), there is to date, no biomarker or set of biomarkers that universally predicts response to CPB therapy. However, it is generally accepted that in order for CPB therapy to be effective in a tumor, the tumor must first have established immunogenicity and second, be actively engaged in immunosuppressive mechanisms, either through direct expression of immunosuppressive ligands on the tumor or indirectly through manipulation of cellular and molecular components of the tumor microenvironment (Pardoll 2012).

Therefore, we hypothesize that those tumors in which CPB monotherapy has shown low to moderate clinical activity (<30% overall response rate) must be immunogenic, but are so to a lesser degree or exhibit more effective immune blockade mechanisms than those tumors in which CPB monotherapy has high activity. Furthermore, the lower immunogenic response of such tumors may necessitate combination CPB or CPB -immune accelerator combinations to overcome immunosuppressive mechanisms and achieve responses similar to those seen with CPB monotherapy in highly immunogenic tumors.

The tumor types being evaluated in this study include advanced solid tumors and lymphoma that are relapsed and/or refractory to available standard of care therapies. The study will evaluate the efficacy and safety of combination CPB therapy with PDR001+LAG525 in patients with select advanced solid tumors and lymphoma that have suboptimal response rates (ORR<30%) to CPB monotherapy. Other tumors in which clinical data are not presently available with CPB therapy, but have pre-clinical evidence supporting use of CPB therapy or clinical data showing efficacy of other immune modulating therapies (e.g. cytokine therapy, IMIDs, adoptive cellular therapy) will also be studied in this trial. For the list of tumors included in the study, refer to Table 4-1. Tumor types may be excluded during the course of the study in the case of early futility or success, based upon an interim analysis or at the discretion of Novartis. Tumor types may be added at the discretion of Novartis based on emerging pre-clinical or clinical data.

1.1.2.1 Small Cell Lung Cancer

Small cell lung cancer (SCLC) accounts for 15% of all lung cancers. The standard of therapy for patients with extensive stage SCLC consists of combination chemotherapy with a platinum doublet, typically cis/carboplatin plus etoposide. Despite response rates of 60-70% with combination chemotherapy, median overall survival is only 9-11 months. Recurrent SCLC with extensive stage disease has an even poorer prognosis with standard chemotherapy regimens, with a median PFS of only 1.5 months, underlining the high-unmet need for new therapies in this disease.

[redacted]

Clinical studies of CPB therapy in SCLC show moderate activity of both monotherapy and combination approaches. In a recently reported study (Antonia 2015) of the PD-1 inhibitor nivolumab in 128 patients with recurrent SCLC, ORR was 18% with nivolumab monotherapy and 17% with nivolumab/ipilimumab combination therapy. The disease control rate was 38% with monotherapy and 54% with combination therapy. The median OS was 4.4 months with monotherapy (95% CI [2.9, 9.4]) and 8.2 months with combination therapy (95% CI [3.7, not reached]). Another study of the PD-1 inhibitor, pembrolizumab (Ott 2015), in a similar population pre-selected for PD-L1 expression, the overall response rate (ORR) to pembrolizumab was 35% (95% CI [15%, 59%]), and the responses appeared durable with a median duration of response of 29.1 weeks (range: 0.1-29.1 weeks). Expression of both PD-L1 and LAG-3 has been observed in SCLC cell lines and/or primary tumor samples, although its predictive utility as a marker of response to CPB therapy is still unclear. In light of the moderate, but encouraging, response rates seen in studies with anti-PD-1 monotherapy, this study will explore combination CPB therapy with dual blockade of PD-1 and LAG-3 in patients with recurrent SCLC who have exhausted available SOC chemotherapies.

1.1.2.2 Gastro-esophageal adenocarcinoma

Gastric cancer is the second leading cause of cancer related death globally and is the fifth most common malignancy overall (Ferlay 2013). Esophageal carcinoma is the sixth most common malignancy and accounts for an additional 400,000 deaths annually (Ferlay 2013). The majority of gastric and esophageal cancer patients present with advanced disease, and have limited therapeutic options in the setting of relapsed disease. First-line treatment for advanced stage gastro-esophageal cancer (GEC) is platinum/5-FU-based chemotherapy with or without an anthracycline, in patients with good performance status. Such combination chemotherapy approaches result in median PFS and OS of 6 months and 9 months, respectively (Ruafi 2015). Although targeted therapies directed at HER2 or VEGF2 have shown responses in chemotherapy-refractory patients, overall survival for patients with metastatic disease still only approaches 1 year, highlighting the need for novel therapies.

Translational and molecular profiling studies of gastric and esophageal cancers strongly suggest these tumors to be good candidates for immune therapies including checkpoint blockade therapy. Expression of the immune checkpoint PD-L1 has been observed in a substantial proportion of gastric adenocarcinoma resection specimens, ranging from 40% to 63% across various studies (Wu et al 2006, Hou et al 2014, Muro et al 2015). Increased PD-L1 expression in gastric and esophageal tumors correlates with poorer disease features, including nodal metastases, advanced stage, and worse PFS and OS. Further molecular characterization of gastric adenocarcinoma by the Cancer Genome Atlas Research Network has revealed four tumor subtypes that could categorize these tumors by levels of immunogenicity: Epstein Barr virus positive tumors, microsatellite unstable tumors, genomically stable tumors, and tumors with chromosomal instability (TCGA 2014). EBV positive and MSI high tumors had higher rates of inhibitory checkpoint expression and tumor infiltrating lymphocytes, suggesting high likelihood of response to checkpoint blockade therapy.

Checkpoint blockade therapy has been evaluated in patients with advanced GEC, although patient numbers have been small. The largest trial in gastric cancer to date was the KEYNOTE-12 study, a phase 1 study of the PD-1 inhibitor pembrolizumab. A total of 39 PD-L1 positive

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(>1% by IHC) gastric cancer patients were enrolled in this trial and received pembrolizumab 10mg/kg every 2 weeks until disease progression. An updated analysis of this trial showed an ORR of 22% with a median response duration of 24 weeks in a heavily pretreated population. The moderate ORR seen with single agent PD-1 blockade, combined with evidence of several other checkpoints being expressed within the tumor microenvironment, provide strong rationale to evaluate combination checkpoint blockade therapy in patients with advanced GEC.

1.1.2.3 Castrate resistant prostate adenocarcinoma

Prostate cancer accounts for 14% of all male cancers, making it the second most common cancer diagnosed in men (Gerristen 2012). Since it is a cancer strongly associated with aging, routine clinical screening with physical exams and PSA captures a large proportion of patients at early stages of the disease. In such patients, surgical resection or radiation therapy results in up to 80% of patients being free of metastatic disease for up to 15 years. With careful surveillance, recurrent or newly diagnosed late stage disease can be initially managed effectively with surgery/radiation combined with androgen deprivation. Eventually, most patients become refractory to androgen deprivation, and develop castrate resistant prostate cancer (CRPC). Patients with metastatic CRPC have a grim prognosis and limited treatment options. Current standards of therapy for such patients include docetaxel based systemic chemotherapy (for symptomatic patients), newer generation hormonal therapy, bisphosphonates, and radioisotope therapy (Gerristen 2012). Once patients have failed chemotherapy regimens and novel hormonal therapies, therapeutic options are very limited with median overall survival being less than a year.

Various principles of immune therapy have been successfully tested clinically in prostate cancer, including the FDA-approved tumor vaccination therapy, Sipuleucel-T. Studies of prostate cancer samples have shown tumor infiltration by several immune cell subtypes, including natural killer cells and T cells, suggesting roles for both the innate and adaptive branches of the immune system in anti- tumor response. Sipuleucel-T, an autologous dendritic cell vaccine generated by *ex vivo* culture of patient leukocytes with a GM-CSF-linked vaccine target (prostatic acid phosphatase), improved median overall survival by 4 months (HR 0.78, p=003) in a placebo controlled phase 3 study in patients with metastatic CRPC (Kantoff et al 2010). As with other immunotherapies, responses were often delayed and there was minimal difference in progression free survival between the two arms. Other vaccine approaches, including a poxvirus based vaccine (PROSTVAC-VF), are currently being explored in CRPC. CPB therapy has also been investigated in CRPC with encouraging early results. In a 14 patient pilot study of the CTLA-4 inhibitor ipilimumab, 8 patients had PSA declines <50%, and 2 patients >50% PSA decline lasting 135 and 60 days, respectively (Fong L et al 2008). In a phase 2 study of the same drug given as monotherapy, 14% of chemotherapy naïve patients had >50% decline in PSA (Small et al 2006). Therefore, combination strategies with CPB in CRPC are highly desirable to improve upon these single agent response rates.

1.1.2.4 Soft tissue Sarcoma

Soft tissue sarcomas comprise a heterogeneous group of rare mesenchymal tumors that can arise from multiple different tissues, including soft tissue and bone (Wilky et al 2014). Approximately 13,000 new cases of sarcoma are diagnosed annually in the US (Brennan et al

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2012). Standard of care for newly diagnosed patients entails multimodality therapy involving surgery, radiation, and perioperative chemotherapy for several subtypes, including rhabdomyosarcoma, osteosarcoma, and Ewing's sarcoma (D'Angelo et al 2014). Despite such aggressive therapy, 25-50% of patients develop recurrent or metastatic disease (Weitz et al 2003). There are no curative therapies for metastatic, refractory disease in adults, unlike pediatric sarcomas, where multimodality therapies have dramatically improved outcomes (Wilky et al 2014). Overall survival for metastatic, refractory sarcomas in adults remains less than a year, highlighting a dire need for novel therapies.

Multiple historical observations support an important role for immune mediated anti-tumor effects in sarcomas, including patients whose tumors respond after infections (Curiel 2012), to the finding that sarcomas more commonly develop in immunosuppressed patients (Gatti et al 1971). In a study of over 8000 allograft transplant recipients, 7.4% of 8724 malignancies that occurred were sarcomas, an incidence three times that seen in the general population (Penn et al 1995). Tumor mediated immune editing has been observed in murine models of sarcoma (Swann et al 2008). Several case reports of spontaneous tumor regression in sarcoma patients with various histologies, including Ewing's sarcoma and GIST, have demonstrated lymphocytic infiltration of the tumor (Berghuis et al 2011, Brinkrolf et al 2009, Rusakiewicz et al 2013). Additionally, many sarcomas express several highly immunogenic epitopes including cancer testis antigens (NY-ESO1, LAGE-1, MAGE) and gangliosides, proteins that are typically expressed at much higher levels in tumor compared to normal tissue (D'angelo et al 2014). With respect to CPB therapy, a small phase 2 study of the anti-CTLA-4 antibody, ipilimumab did not demonstrate clinically meaningful activity in synovial sarcoma (Maki RG et al 2013). Although single agent CPB has failed to demonstrate clinical activity in selected sarcoma subtypes, other immune therapies including dendritic cell based vaccines (Mackall et al 2008), and cancer testis antigen directed adoptive T cell therapy (Rosenberg et al 2011) have demonstrated clinical activity in phase 2 studies. Therefore, exploring combination CPB therapy across a wide variety of sarcoma histologies may successfully identify responsive subtypes.

1.1.2.5 Ovarian cancer

Ovarian cancer accounts for the fifth leading cause of cancer death in women, and the leading cause of death among gynecologic cancers (Liu et al 2010). Approximately 22,000 new cases of ovarian cancer are diagnosed annually in the US and accounts for up to 15,000 deaths a year (Liu et al 2010). Two thirds of patients with ovarian cancer are diagnosed at stages 3 and 4, accounting for the relatively low 5-year survival rate of 39% and 17% for stage 3 and 4 tumors, respectively (NCCN Guidelines 2015.2). Standard therapy for newly diagnosed patients involves maximal cytoreductive surgery, combined with intraperitoneal chemotherapy, followed by platinum-based adjuvant systemic chemotherapy (NCCN Guidelines Version 2.2015). Patients with recurrent disease are divided into those with platinum resistant and sensitive disease, and are often treated with multiple courses of systemic chemotherapy. Platinum sensitive patients may have responses to retreatment with cisplatin/carboplatin as single agents or in combination with taxanes. For those who are platinum resistant, current options include single agent therapy with other drugs such as liposomal doxorubicin, etoposide, and gemcitabine. Prognosis for patients with recurrent disease, particularly those with platinum resistant disease, is poor with a median PFS of 3 months.

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Similar to other immunogenic tumors, the presence of tumor infiltrating lymphocytes (TILs) has been shown to impact prognosis in ovarian cancer. In an immunohistochemical study of 186 specimens from stage 3 and 4 ovarian cancer patients, CD3+ TILs were present in 55% of tumors and absent in 38% of tumors (Zhang et al 2003). The numbers of CD4+ and CD8+ tumors closely correlated in those tumors with TILs. Patients whose tumors contained TILs had a 5-year overall survival of 38% compared to 4.5% in those without TILs (Chang et al 2003). Other studies have corroborated the finding that presence of intraepithelial TILs in ovarian cancer correlated strongly with improved PFS and OS (Tomsova et al 2008). In ovarian tumors with high TILs, a higher CD8:CD4 and CD8:Treg ratio correlated with better disease outcomes, indicating the important suppressive role of regulatory T cells in the tumor microenvironment (Sato et al 2005).

There is evidence that immune checkpoints specifically downregulate the anti-tumor activity of TILs in ovarian cancer. In a recent small study of the PD-1 inhibitor nivolumab, patients with refractory ovarian cancer had an ORR of 15%. In a study of tumor and peripheral blood samples of patients with NY-ESO-1 expressing ovarian cancer, tumor derived NY-ESO-1 specific CD8+ T cells demonstrated impaired effector function and enriched co-expression of LAG-3 and PD-1 (Matsuzaki et al 2010). PD-1 and LAG-3 expression was upregulated by cytokines found in tumor-derived ascites, including IL10 and IL6 (Matsuzaki et al 2010). Consequently, dual blockade of PD-1 and LAG-3 during T cell priming augmented proliferation and IFN-gamma production by these CD8+ TILs, providing strong rationale for dual CPB therapy in ovarian cancer (Matsuzaki et al 2010).

1.1.2.6 Advanced Neuroendocrine tumors

Neuroendocrine tumors (NET) are neoplasms with characteristic neuroendocrine differentiation markers that can arise in multiple anatomic locations, and are uniquely characterized by functionally active tumor cells that secrete various bioactive peptides (Kunz 2015). Although NETs have a low annual incidence of 2-5 per 100,000 patients, given the overall indolent nature of these tumors, their prevalence exceeds that of pancreatic and gastric cancers combined (Kunz 2015). Median overall survival for metastatic NETs originating in the pancreas and small bowel with currently available therapies are 24 and 56 months, respectively (Yao et al 2008). Thus, there remains a high-unmet need for new therapies.

NETs are highly heterogeneous tumors with highly variable location, function and grade. Therefore, in addition to TNM staging, tumor location and grade are important factors in therapeutic decision-making (Dong et al 2012). Low-grade NETs (<2 mitoses/10 hpf) are typically well differentiated, have an indolent course, and produce secretory granules that often express chromogranin A and synaptophysin. In general, low grade NETs are functionally active and secrete bioactive peptides such as serotonin, histamine, prostaglandins, substance P, and others (Dong et al 2012).

High grade NETs (>10 mitoses/hpf) are usually non-functional and poorly differentiated, often behaving like small cell lung cancer, and treated similarly with combination chemotherapy with platinum/etoposide doublet therapy (Dong et al 2012). Advanced, well differentiated (Grade 1 or Grade 2) NETs will be considered for enrollment. Small Cell Lung Cancer NETs will be included in the SCLC group.

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The treatment of advanced well-differentiated NETs generally involves a multidisciplinary approach which includes systemic therapy with somatostatin analogues (SSA) such as octreotide to alleviate symptoms from peptide release, and may entail surgical resection and liver directed therapies to additionally control symptoms and tumor growth (Kunz 2015). Other systemic therapies that have been evaluated in differentiated NETs include biologic therapies including interferon alfa and drugs targeting VEGF and mTOR (Kunz P 2015). Two separate phase 3 studies of everolimus (mTOR inhibitor) and sunitinib (multikinase inhibitor) in combination with octreotide demonstrated improved PFS in both, but failed to show significant differences in ORR and OS, likely owing to crossover designs in both studies (Yao et al 2011, Raymond et al 2011). Although both drugs are approved for the treatment of advanced pancreatic NETs, median PFS remains less than a year for advanced NETs.

The role of immune modulation in the progression of NETs is suggested by the efficacy of immune activating therapies such as interferon-alfa in these tumors. Interferons are thought to exert antitumor effects through several mechanisms, including stimulation of T cells, induction of cell cycle arrest, and inhibition of angiogenesis (Detjen et al 2000). A recent study by Pyonteck *et al* revealed an important immunosuppressive role for tumor associated macrophages (TAM) in pancreatic NETs. When tumor specimens from patients with pancreatic NETs were immunohistochemically stained for the macrophage marker, CD68, a significant correlation was seen between increased macrophage levels and tumor stage, grade, and metastases to the liver (Pyonteck et al 2012). In subsequent mouse models of pancreatic NETs in animals deficient in the TAM promoting protein CSF1, tumor burden was significantly reduced compared to wild type mouse (Pyonteck et al 2012). Similar emerging evidence for the role of immune suppression within the tumor microenvironment in NETs argues for further exploration of combination immunotherapeutic approaches in these tumors.

1.1.2.7 Diffuse Large B-cell lymphoma

Diffuse large B cell lymphomas (DLBCL) are the most common lymphoid malignancies in adults accounting for 30% of NHLs diagnosed annually (NCCN Guidelines v2.2015). DLBCL comprises a large and heterogenous group of lymphomas comprising several subtypes including primary mediastinal large B cell lymphoma (PMBL), transformed indolent lymphomas including CLL and follicular lymphomas, gastric MALT, intravascular large B cell lymphoma, EBV-positive DLBCL, and chronic inflammation associated DLBCL, all of which are managed similarly (NCCN Guidelines v2.2015). Immunohistochemical and genomic profiling of DLBCL has revealed additional heterogeneity in the genetic and molecular profiles of DLBCL. Expression of surface markers such as CD10, BCL6, and IRF4/MUM1 correlates with gene expression profiling that categorizes DLBCL into 2 subtypes: germinal center B-cell (GCB) and non-GCB subtype, with the GCB subtype carrying better prognosis. While more refined molecular and genomic subtypes have revealed additional prognostic factors, such as Myc and Bcl2 rearrangements ("double hit" lymphomas), treatment paradigms have not yet evolved to a genomic/molecular profile based selection of therapy.

Therapy for newly diagnosed DLBCL is based on stage and risk prognostication using the International Prognostic Index (IPI) which takes into account several disease factors including age, performance status, stage, LDH, and extranodal involvement (NHL LPF Project 1993). Patients with Stage 1-2 disease typically get multimodality therapy involving radiation and

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combination chemo-immunotherapy with anti-CD20 directed therapy. Those patients with advanced stage (stage 3-4) get induction chemo-immunotherapy (R-CHOP 21), or alternate regimens tailored to patient age, performance status, and sites of extranodal disease (NCCN Guidelines v2.2015). For the 30-40% of patients who have disease relapse, re-induction combination chemotherapy followed by autologous transplantation demonstrated a 5 year EFS rate of 46% compared to patients who did not undergo transplant (5 year EFS=12%) in an international randomized phase 3 study (Philip et al 1995), and is generally the standard approach for fit patients with relapsed disease. For patients unable to undergo autologous SCT, less intensive chemotherapy regimens such as bendamustine combined with rituximab (BR) has demonstated clinical benefit in small studies, with ORR of 45% and median PFS of 3.6 months (Vacrica et al 2014). Patients with relapsed/refractory disease after second line therapy including autologous transplant, have very poor outcomes with median survival ranging from 3-6 months (Raut et al 2014).

There is accumulating evidence of active immune regulation in the tumor microenvironment of NHL, including cellular elements such as Tregs, myeloid derived suppressor cells, as well as proteins including IL10 and TGF-beta. Upregulation of inhibitory immune checkpoints such as CTLA-4 and PD-1 have been observed in various subsets of NHL in clinical trials of drugs blocking these pathways (Zhou et al 2010, Ansell et al 2009). To date small clinical trials of anti-CTLA-4 and anti-PD-1 blockade has shown preliminary signals of efficacy to single agent CPB therapy with response rates of less than 20% in heavily pre-treated patients, suggesting the potential efficacy of combination approaches. A recent trial in which the anti-PD-1 agent pidilizumab was given to patients immediately post-autologous transplant met its primary endpoint of exceeding the 16 month PFS threshold, with a continued response rate of approximately 50% in those patients with residual measurable disease after transplant (Armand et al 2013). While it is difficult to estimate the individual attributions of ASCT and pidilizumab to efficacy in this single arm phase 2 study, the observed efficacy signal with single agent CPB therapy argues strongly for the therapeutic potential of such therapy in relapsed/refractory DLBCL.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of PDR001

PDR001 is a high-affinity, ligand-blocking, humanized anti-programmed death-1 (PD-1) IgG4 antibody, (stabilized hinge, S228P), that blocks the binding of Programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2) to PD-1. PDR001 recognizes PD-1 in cynomolgus monkeys and shows functional activity *in vitro/ex vivo*. For further details, please refer to [PDR001 Investigator's Brochure].

1.2.1.1 Non-clinical experience

PDR001 binds specifically and with high affinity to human PD-1. In Biacore assays, the K_D of PDR001 on human PD-1 is 0.083 nM. In *ex vivo* lymphocyte stimulation assays using human blood, PDR001 enhances IL-2 production by approximately 2-fold in response to super antigen stimulation with Staphylococcal enterotoxin B (SEB). PDR001 does not cross-react with rodent

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PD-1, and cannot be evaluated in murine tumor models. It does cross-react with cynomolgus monkey PD-1, and is functionally active, making cynomolgus monkey a relevant species for toxicology studies. A GLP tissue cross reactivity study using frozen human and cynomolgus monkey tissues was also done in support of the safety of PDR001. There was no unexpected binding observed.

The non-clinical toxicology of PDR001 was evaluated in a five week GLP toxicology study in cynomolgus monkeys with safety pharmacology endpoints and an eight week recovery. Repeat administration of PDR001 to monkeys was well tolerated at all doses tested in the GLP toxicology study. No test article-related in-life, mortality, organ weight changes, or macroscopic findings were noted. There were no PDR001-related effects seen in any of the safety pharmacology endpoints assessed (cardiovascular, neurobehavioral, and respiratory). Macrophage infiltrates into the splenic white pulp were observed in animals given 100 mg/kg/week and mononuclear cell infiltrates, often associated with fibrosis, around the injection site blood vessel (saphenous vein) in a few animals given ≥25 mg/kg/week. These PDR001-related microscopic changes were fully reversible after an eight week recovery.

The following changes were noted in main phase and recovery treated animals as well as control recovery animals. Mostly low grade changes were noted in several tissues in the form of mononuclear infiltrates in the vascular and perivascular space. In general, in most organs, vascular/perivascular changes were limited to one or a few blood vessels in each organ and sometimes involved a segment of a blood vessel with occasional vessel wall degeneration. No evidence of parenchymal damage was associated with the vascular/perivascular changes in any of the organs examined and the changes were not associated with any frank tissue injury. While these effects were not exclusive to treated animals, because of their nature and close association with the expected pharmacology of PD1 blockade, a potential PDR001 related effect cannot be excluded and possibly explained by mild enhanced pharmacology of PDR001. There were no test article related effects seen in the cardiovascular (CV) assessments. All other microscopic findings were considered spontaneous or otherwise unrelated to PDR001 administration.

Dose-dependent exposure to PDR001 in each dose group was confirmed. A pharmacodynamic *ex vivo* superantigen stimulated whole blood assay measuring IL-2 release was performed. Blood from untreated control animals showed augmentation of IL-2 release when PDR001 was added ex vivo, whereas blood from treated animals at all doses did not show augmented IL-2 release, indicating target engagement and inability to further dis-inhibit the SEB induced response with the further addition of PDR001. The HNSTD dose in this study was 100 mg/kg.

1.2.1.2 Clinical experience

The CPDR001X2101 study started enrollment on 27 April 2015 and is ongoing. As of November13, 2017, a total of 303 patients had been treated in the study. In the phase I part of the study, 58 patients had been treated at doses of 1 mg/kg Q2W (16 patients) for up to 78 weeks, 3 mg/kg Q2W (15 patients) for up to 60 weeks, 10 mg/kg Q2W (11 patients) for up to 34 weeks, 3 mg/kg Q4W (6 patients) for up to 33 weeks and 5 mg/kg Q4W (10 patients) for up to 57 weeks. In the phase II part of the study, 245 patients had been treated in five groups: NSCLC 400 mg Q4W (59 patients), NSCLC 300 mg Q3W (59 patients), melanoma 400 mg Q4W (61 patients), TNBC 400 mg Q4W (40 patients) and anaplastic thyroid cancer 400 mg

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Q4W (26 patients). In the Phase II part of the study, the median duration of exposure to study treatment was 8.0 weeks (range 1.0 - 35.1).

The PK analysis of the dose escalation data using a population approach and the expected wide therapeutic index of PD-1 inhibitors support the use of flat dosing for PDR001 of 400 mg Q4W or 300 mg Q3W. The expected PDR001 Ctrough concentrations using either dosing regimen exceed the EC50 for PD-1 blockade by approximately 75-fold in an ex vivo assay in PBMCs. Based on the available PK and safety data, the RP2D of PDR001 has been declared as 400 mg i.v. Q4W or 300 mg i.v. Q3W for combination treatment regimens for which this may be more convenient. For further details, please consult the most recent edition of the [PDR001 Investigator's Brochure].

PDR001 is currently being studied alone or in combination with other agents in ongoing phase I/Ib/II clinical trials. As of January 19, 2018, 1,239 patients across 23 Novartis-sponsored studies have been treated with PDR001. The preliminary toxicity profile appears to be similar to that of marketed inhibitors of PD-1 including the type, severity and frequency of occurrence of immune-mediated adverse events. As observed with other PD-1 inhibitors, immune-mediated toxicities observed with PDR001 are reversible in many cases. In some cases, they may require treatment with corticosteroids. Certain toxicities are expected to be lifelong and may require replacement therapy with hormones, for example in the case of hypothyroidism. Based on the preliminary data, PDR001 is well tolerated with a safety profile similar to those of other marketed anti-PD-1 antibodies. For further details, please consult the most recent edition of the [PDR001 Investigator's Brochure].

1.2.2 Overview of LAG525

LAG525 is a high-affinity, ligand-blocking, humanized anti-LAG-3 IgG4 antibody (stabilized hinge, S228P) which blocks the binding of the known LAG-3 ligand MHC class II to LAG-3. LAG525 is cross-reactive in cynomologus monkeys and shows functional activity.

1.2.2.1 Non-clinical experience of LAG525

LAG525 binds specifically and with high affinity to human LAG-3. In Biacore assays, the K_D of LAG525 on human LAG-3 is 0.109 nM and in cell binding assays, LAG525 binds CHO-hLAG-3 expressing cells with an affinity of 1.9 nM. LAG525 does not cross-react with rat or mouse LAG-3, and therefore cannot be evaluated in murine tumor models. It does cross-react with cynomolgus monkey LAG-3 (affinity of 2.3 nM on cynomolgus LAG-3-expressing cells), making cynomolgus monkey a relevant species and the only species for toxicology studies. A GLP tissue cross reactivity study was conducted with both human and cynomolgus monkey tissue specifically to assess the potential for off target binding. There was no binding observed even for tissues known to express LAG-3. This was likely due to reagent sensitivity issues and possibly the lower expression of the target.

Safety was evaluated in a five week repeat dose GLP toxicology study as well as in a limited panel in a single dose PK study, both in cynomolgus monkeys. In the single dose study, clinical observations, clinical chemistry, and hematology endpoints were evaluated as part of an in-life assessment of safety. There were no findings related to LAG525 administration in this single dose study.

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In the five week GLP toxicology study, repeat administration of LAG525 to monkeys (3/sex/main and 2/sex/recovery groups) at doses of 6, 25, and 100 mg/kg was well tolerated at all doses tested. After the fifth dose, the eight week recovery period began for control and high dose animals assigned to recovery. Animals assigned to the main phase were sacrificed seven days after the last dose was administered. Minimal increases in fibrinogen at 100 mg/kg and globulin (relative change from pretest only) in males at 25 and 100 mg/kg were noted. Association with LAG525 administration is unclear but cannot be excluded. A female animal in the 6 mg/kg group displayed a hypersensitivity reaction soon after the third dose, consisting of vomiting and clinical signs of a swollen muzzle and flushed face. The animal was subsequently treated with diphenhydramine and the symptoms resolved shortly after treatment. This animal was then pre-treated with diphenhydramine prior to the last two doses and no further intervention was required. It was confirmed that this animal was positive for the presence of anti-drug antibodies. A statistically significant increase in proliferating CD4+ T cells was observed in animals given 100 mg/kg/week compared to control animals, a pharmacodynamic effect observed in vitro with LAG-3 blockade (Huard 1997; Workman 2003). There were no other test article related effects. The highest non-severely toxic dose (HNSTD) and the 'no observed adverse effect level' (NOAEL) was 100 mg/kg. LAG525 has a favorable safety profile in monkeys that supports the proposed human starting dose of 1 mg/kg.

1.2.2.2 Clinical experience

The first in human (FIH) study for LAG525 began in June 2015. The Phase I part of the study is ongoing for both single agent and combination. The safety information is summarized below. As of the data cut-off date of October 18, 2017, a total of 320 patients were treated on the first-in-human clinical study of LAG525, 134 as a single agent and 186 in combination with PDR001.

In the single-agent part of the study 134 patients were treated with LAG525 at doses ranging from 1 to 15 mg/kg on Q2W and Q4W schedules. Preliminary PK parameters demonstrated approximately dose-proportional increases in exposure observed from 1 to 15 mg/kg with low to moderate interpatient variability. The observed median half-life for LAG525 ranged from 7.4 to 15.4 days.

Dose Limiting Toxicities (DLTs): Four DLTs have been reported and include: Gr 3 localized intra-abdominal fluid collection (1mg/kg Q2W); Gr 3 lipase increase (5mg/kg Q2W); Gr 3 vomiting (5mg/kg Q2W) and Gr 4 acute kidney injury (10mg/kg Q4W).

Adverse events (AEs): all grades, regardless of relationship to study drug, were reported in 132 patients (98.5%) overall, with the most frequently reported (>20%) AEs being constipation (33 patients, 24.6 %), fatigue (35 patients, 26.1%), nausea (35 patients, 26.1%), abdominal pain (31 patients, 23.1%), decreased appetite (32 patients, 23.9%), and anemia (31 patients, 23.1%). The safety profile appeared similar across different dose groups.

Grade 3/ Grade 4 AEs: Of the 134 patients treated, 75 (56%) experienced Grade 3 or Grade 4 AEs regardless of relationship to study drug. The most frequently reported AEs occurring in 5% or more of patients included anemia (14 patients, 10.4%) and dyspnea (7 patients, 5.2%),

AEs suspected to be related to study treatment: Of the 134 patients treated, 76 (56.7%) experienced AEs (all grades) suspected to be related to study treatment. The most frequently reported events, occurring in >3% of patients, included fatigue (12 patients,9.0%), nausea (11

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patients, 8.2%), pyrexia (6 patients, 4.5%), increased alanine aminotransferase, (4 patients, 3.7%), decreased appetite (7 patients, 5.2%), arthralgia (5 patients, 3.7%), pruritus 7 patients, 5.2%), hypothyroidism (5patients, 3.7%), vomiting (7 patients, 5.2%), myalgia (6patients, 4.5%), diarrhea (5 patients 3.7%), rash (4 patients, 3%), lipase increased (4 patients, 3%), lethargy (4 patients, 3%), dry mouth (4 patients, 3%). Of the 76 patients who experienced AEs suspected related to study treatment the following Gr 3 or 4 AEs were reported in 10 patients, (7.5%): intra-abdominal fluid collection (1 patient), increased lipase (2 patients), anemia (1 patient), abdominal pain (1 patient), melena (1 patient), increased AST (2 patients), and fatigue (1 patient). One patient experienced multiple Gr 3 or 4 AEs suspected related to study treatment which included increased lipase and increased amylase. Another patient experienced multiple AEs including wound infection, nausea, and vomiting. Another patient experienced multiple AEs including acute kidney injury, tumor lysis syndrome, vomiting, decreased urine output, increased blood creatinine, hyperuricemia, hypotension, multiple organ dysfunction syndrome and metabolic acidosis.

Serious adverse events (SAEs): of all grades, and regardless of relationship to study drug, were reported in 53 patients (39.6%). The majority of SAEs (49 out of 53 patients who experienced SAEs) were Grade 3 or 4 in severity. Of the 53 patients who experienced SAEs, 19 events among 7 patients were suspected related to study treatment and included localized intraabdominal fluid collection (DTL) (1 patient, 1 mg/kg Q2W),abdominal pain and melena (1 patient, 3 mg/kg Q2W), infection and vomiting (DLT) (1 patient, 5 mg/kg Q2W), increased lipase, (DLT), diarrhea (1 patient, 5 mg/kg Q2W), diarrhea (1 patient, 5 mg/kg Q2W), and nausea, vomiting, anorexia, fatigue, and failure to thrive (1 patient, 240 mg Q2W). One patient experienced multiple SAEs suspected related to the study treatment which included acute kidney injury, tumor lysis syndrome, vomiting (worsening), multiple organ failure, and metabolic acidosis. This patient was treated with LAG525 at a dose of 10mg/kg Q4W and presented with acute kidney injury 26 days after the first and only dose of LAG525. The patient rapidly deteriorated in hospital and died 3 days after admission. An autopsy showed widespread metastatic disease consistent with the underlying diagnosis of cancer. The events, (acute kidney injury, vomiting, metabolic acidosis and tumor lysis syndrome) were considered possibly related to LAG525.

1.2.3 Overview of the combination of LAG525 and PDR001

1.2.3.1 Nonclinical experience with the combination of LAG525 and PDR001

Woo (Woo 2012) described a series of experiments with dual LAG-3/PD-1 knockout (KO) mice evaluating both tumor efficacy and the KO phenotype in these animals. Compared to wild-type (WT), the dual KO mice developed an early onset (4 weeks of age) of a lethal autoimmune condition that resulted in approximately 80% of the mice moribund by approximately 10 weeks. The major histopathologic manifestations included diffuse fibrosing lymphohistiocytic endocarditis, myocarditis, and pancreatitis. In contrast, LAG-3 and PD-1 single KO mice lacked any disease manifestations or histopathology over this period of observation. These results show that the PD-1 and LAG-3 pathways synergistically regulate immune self-reactivity. These results demonstrate a theoretical risk of the simultaneous disinhibition of both the LAG-3 and PD-1 receptor pathways. However, intermittent blocking of both receptors in patients where the pathways have been biologically and physiologically intact since birth seems unlikely to

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produce such a severe clinical picture. In addition, in the setting of a clinical trial with intense safety monitoring and clear guidance on drug interruption and withdrawal, the management of immune adverse events should be possible. Any theoretical risk is also balanced by the well-documented efficacy of these agents, both alone and in combination, in a host of tumor models and for PD-1 inhibition in the clinical setting.

1.2.3.2 Clinical experience with the combination of LAG525 and PDR001

LAG525 combined with PDR001 is being tested in an ongoing, multicenter, open-label study CLAG525X2101C with a phase I dose escalation part followed by a phase II dose expansion part. Dosing began in June 2015.

As of a data cut-off date of October 18, 2017, a total of 320 patients were treated on the first-in-human clinical study of LAG525 as a single agent and in combination with PDR001. The Phase I part of the study is ongoing for both single agent and combination. In the single-agent part of the study 134 patients were treated with LAG525 at doses ranging from 1 to 15 mg/kg on Q2W and Q4W schedules. Preliminary PK parameters demonstrated approximately dose-proportional increases in exposure observed from 1 to 15 mg/kg with low to moderate interpatient variability. The observed median half-life for LAG525 ranged from 7.4 to 15.4 days. In the combination part of the study, 186 patients were treated with LAG525 in combination with PDR001. PDR001 or LAG525 in combination with showed comparable PK to the single-agent data at the same dose levels from the ongoing PDR001 studies. The observed median half-life for PDR001 ranged from 7.2 to 23.8 days, which was similar to the results from the ongoing CPDR001X2101 study.

Adverse Events: Of the 186 patients treated, with the combination of PDR001-LAG525, AEs, all grades, regardless of relationship to study treatment, were reported in 171 patients, (91.9 %). The most frequently reported, occurring in more than 15 % of patients include; fatigue (51 patients, 27.4 %), nausea, (51 patients, 27.4 %), diarrhea (39 patients, 21%), decreased appetite (37 patients, 19.9%), vomiting (36 patients, 19.4%), constipation (35 patients, 18.8%), and cough (30 patients, 16.1%).

Dose-Limiting Toxicities (DLTs): Four patients experienced DLTs which included: Gr3 hyperglycemia (80 mg LAG525 Q2W and 400 mg PDR001 Q4W), Gr4 autoimmune hepatitis and Gr3 fatigue (1000 mg LAG525 Q4W and 400 mg PDR001 Q4W), Gr3 brain tumor edema (600 mg LAG525 Q3W and 300 mg PDR001 Q3W), Gr3 pneumonitis (400 mg LAG525 and 400 mg PDR001 Q4W).

Grade 3/ Grade 4 AEs: 79 patients, (42.5%), experienced Grade 3 or Grade 4 AEs regardless of relationship to study treatment. The most common Grade 3/grade 4 AEs, regardless of relationship to study treatment, occurring in more than 20% of patients, include: anaemia (11 patients, 5.9%), asthenia (5 patients, 2.7%), fatigue (4 patients, 2.2%), and dyspnea (4 patients, 2.2%).

AEs suspected to be related to study treatment: 110 patients,(59.1%), experienced AEs (all grades) suspected to be related to study treatment. The most common AEs, suspected to be related to study treatment, occurring in more than 5% of patients include: fatigue (26 patients, 14 %), diarrhea (19 patients, 10.2%), nausea (17 patients, 9.1 %), rash (16 patients, 8.6%), and

[redacted]

rash maculo-papular (11 patients, 5.9%). The safety profile appeared similar across the different dose groups.

Serious adverse events (SAEs): SAEs, all grades, regardless of relationship to study treatment, were reported in n=65 (34.9%). The majority of these patients (53 out of 65) experienced SAEs that were Grade 3 or 4 in severity. Among the 65 patients who experienced SAEs, 17 events in 12 patients were suspected related to study treatment. The most common SAEs, regardless of relationship to study treatment, experienced by more than 2% patients, include: pyrexia (6 patients, 3.2%), dyspnea (4 patients, 2.2%), fatigue (4 patients, 2.2%), and nausea (4 patients, 2.2%).

2 Rationale

2.1 Study rationale and purpose

Although there is clinical activity of checkpoint blockade (CPB) monotherapy in several tumor types including melanoma, NSCLC, and Hodgkin lymphoma, multiple tumor types have significantly less response to CPB monotherapy. Despite the finding of somewhat predictive biomarkers of response to CPB, including mutational burden, PD-L1 expression, and presence of tumor infiltrating lymphocytes (TILs), there is to date, no biomarker or set of biomarkers that universally predicts response to CPB therapy. However, it is generally accepted that in order for CPB therapy to be effective in a tumor, the tumor must first have established immunogenicity and second, be actively engaged in immunosuppressive mechanisms, either through direct expression of immunosuppressive ligands on the tumor or indirectly through manipulation of cellular and molecular components of the tumor microenvironment (Pardoll 2012).

Therefore, we hypothesize that those tumors in which CPB monotherapy has shown low to moderate clinical activity must be immunogenic, but to a lesser degree than those in which CPB monotherapy has high activity. Furthermore, the lower baseline immunogenicity of such tumors may necessitate combination CPB or CPB -immune accelerator combinations to overcome immunosuppressive mechanisms and achieve responses similar to those seen with CPB monotherapy in highly immunogenic tumors. Accordingly, we propose to conduct a phase II open-label study evaluating the efficacy and safety of combination CPB therapy with PDR001+LAG525 in patients with select advanced solid tumors and lymphoma that have suboptimal response rates (less than 30% ORR) to CPB monotherapy. Other tumors in which clinical data are not presently available with CPB therapy, but have pre-clinical evidence supporting use of CPB therapy or clinical data showing efficacy of other immune modulating therapies (e.g. cytokine therapy, IMIDs, adoptive cellular therapy) will also be studied in this trial. Tumor types may be excluded during the course of the study in the case of early futility or success based upon an interim analysis or at the discretion of Novartis. Tumor types may be added at the discretion of Novartis based on emerging pre-clinical or clinical data.

2.2 Rationale for the study design

There is currently a lack of validated patient preselection markers for combination immunotherapy. Given robust early clinical and/or preclinical evidence supporting the potential

[redacted]

efficacy of combination CPB in several tumor types, a clinical trial employing a broad signal finding strategy across multiple tumor types is warranted. This is a phase II, open-label, study to determine the efficacy and safety of treatment with the combination of PDR001+LAG525 in patients with a diagnosis of select solid tumors or lymphoma, that are hypothesized to respond to combination CPB therapy based on existing clinical and/or preclinical data.

There are patterns of disease response unique to CPB therapy including delayed responses and apparent disease progression prior to response (pseudoprogression). In melanoma patients treated with CTLA-4 blockade, the median time to response in patients who achieved an ultimate complete response was 30 months (Prieto PA et al 2012). In a study of the anti-PD-1 mAb pembrolizumab, 10% of patients had apparent disease progression before achieving clinical benefit in the form of either stable disease or partial response (Hodi SF et al 2014). Consequently, there are limitations to using time-dependent overall response rate as the primary endpoint in a study evaluating combination CPB therapy, since immune-mediated anti-tumor effects may manifest clinically as long standing stable disease or delayed responses. Therefore, the primary endpoint for this study will be the clinical benefit rate (CBR) at 24 weeks of treatment, with a secondary endpoint of overall response.

2.3 Rationale for dose and regimen selection

PDR001+LAG525 combination is being tested in an ongoing, multicenter, open-label study CLAG525X2101C with a phase I dose escalation part followed by a phase II dose expansion part. The recommended phase II dose is PDR001 300 mg Q3W with LAG525 400 mg Q3W

2.4 Rationale for choice of combination drugs

In vivo studies have demonstrated a synergistic effect in antitumor activity of the dual blockade of the LAG-3 and PD-1 co-inhibitory receptors when compared to the inhibition of either checkpoint alone. CD4+ and CD8+ TIL from Sa1N fibrosarcoma, MC38 colon carcinoma and B16 melanoma have previously been shown to co-express PD-1 and LAG-3; Woo and colleagues demonstrated some single agent activity of anti-LAG-3 treatment in both Sa1N fibrosarcoma and MC38 colon carcinoma. Importantly, combined LAG-3 and PD-1 blockade led to rapid and complete regression of established tumors in 70% of Sa1N fibrosarcoma and 80% of MC38 colon carcinoma within 50 days of the initiation of therapy. Using the maximum likelihood model, this demonstrated synergy of co-blockade over single agent activity. Both TILs and lymphocytes from draining lymph nodes harvested from treated mice had increased numbers of CD8+IFN-gamma+ TIL, further supporting the anti-tumor role of co-blockade (Woo 2012).

The growth of syngeneic tumors was also studied in LAG-3 and PD-1 double deficient mice (*Lag3*$^{-/-}$*Pdcd1*$^{-/-}$). While combination blockade (using murine antibody reagents) did not show efficacy in B16 melanoma, both *Pdcd1*$^{-/-}$ and doubly deficient mice showed inhibited tumor growth. Depletion of CD4+ and CD8+ T cells led to restoration of normal tumor growth, demonstrating the dependency of the phenotype on T cell alteration. MC38 colon carcinoma implanted in doubly deficient mice showed 80% reduction (compared to 40% in *Pdcd1*$^{-/-}$ mice), confirming the synergistic action of PD-1 and LAG-3 seen in the co-blockade experiments (Woo 2012).

Taken together, these preclinical data demonstrate that co-blockade of the PD-1 and LAG-3 pathways leads to anti-tumor activity superior to blockade of either inhibitory protein alone. (Woo 2012).

2.5 Rationale for choice of comparators drugs

Not applicable

2.6 Risks and benefits

Appropriate eligibility criteria, as well as specific dose delays and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6. The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, and stopping rules.

Infusion of drugs such as PDR001 and /or LAG525 can be associated with reactions especially during the first exposure. Infusion reactions usually consist of symptoms such as fever, chills, nausea, vomiting, headache, dizziness, dyspnea, hypotension, rash, and asthenia.

PDR001: The most frequent side effects caused by single-agent PDR001 include: diarrhea, nausea, vomiting, constipation, gastritis, hypothyroidism, hyperthyroidism, itchiness, skin reactions (such as rash, dryness, redness, hives), low red blood cell count, dry mouth, inflammation in the mouth, canker sores, loss of appetite, decreased blood sodium, increased blood sugar, pain in joints, muscles, nerves & skin, swelling in the face or limbs, pneumonia, abnormal liver function tests, increased lipase, decreased lymphocytes, weight loss, fever, chills, malaise, weakness, fatigue, abdominal discomfort and pain, shortness of breath during exercise or at rest, cough, vertigo/dizziness, and headache.

Less frequent side effects caused by single agent PDR001 include the following severe immune reactions: colitis requiring hospitalization; pneumonitis & pneumonia, hepatitis with abnormal liver test results; and polymyositis with muscle weakness,

LAG525: The most frequent side effects caused by single-agent LAG525 include: fatigue, nausea, vomiting, fever, abnormal liver function tests, loss of appetite, joint and muscle pain, itchiness, skin reactions such as rash, dryness, redness & hives, hypothyroidism, increased amylase, increased lipase, hyperkalemia, hyperuricemia, constipation, dry mouth, lack of energy, abdominal pain, diarrhea, and weight loss.

One case of acute kidney injury possibly related to LAG525 occurred in the setting of widespread metastatic disease, tumor lysis syndrome, and multiple organ failure leading to death. Kidney function is evaluated in all patients regularly throughout this study.

Combination of PDR001 and LAG525: While the incidence of immune related adverse events with single agents has been well characterized, there may be a higher incidence of immune related adverse events with combination immune therapies including the combination of PDR001 and LAG525. These adverse events may be serious and include, but are not limited to, allergic reactions, inflammation of the heart, pneumonitis, colitis, diabetes, hepatitis, and other autoimmune disorders, increased phosphate, distortion of taste, flatulence, flushing, and headache.

[redacted]

The combination of PDR001 and LAG525 is hypothesized to improve upon responses to single-agent anti-PD-1/PD-L1 therapies. The ongoing study, LAG525X2102C, A Phase I/II, open-label, multicenter study of the safety and efficacy of LAG525 single agent and in combination with PDR001 administered to patients with advanced malignancies, provides encouraging data on the tolerability and response rate of this combination treatment, lending support to this hypothesis.

Therefore, the potential benefit of combination therapy with PDR001 and LAG525 is thought to outweigh the risk in those patients with advanced malignancies and minimal therapeutic options who are still eligible by standard criteria for participation in clinical trials.

For additional information on risk-benefit assessment, please refer to [PDR001 Investigators Brochure] and [LAG525 Investigators Brochure].

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary	Assess CBR at 24 weeks of PDR001+LAG525 by tumor type in multiple solid and lymphoma	Refer to Section 10.4 The primary objective is to assess clinical benefit rate after 24 weeks of treatment with PDR001+LAG525 based on local investigator assessment. For patients with solid tumors the assessment criteria will be RECIST 1.1 and will include responses of CR or PR or SD. For lymphoma, assessment criteria will be the Revised Response Criteria for Malignant Lymphoma, (Cheson et al 2007).
Secondary	Assess ORR by RECIST 1.1 in solid tumors and by the Revised Response Criteria for Malignant Lymphoma (Cheson et al 2007) in lymphoma TTR, DoR, TTP, PFS/ rate at 1 and 2 years Safety incidence and severity of adverse events (AEs) and serious adverse events (SAEs) including changes in laboratory parameters, vital signs and ECGs Tolerability: Dose interruptions, reductions and dose intensity.	Refer to Section 10.5. To assess Overall Response (OR) of Partial Response (PR) or Complete Response (CR) based on local investigator assessment. Time to response (TTR) is defined as the time from the date of first dose to the date of first documented response of CR or PR. The duration of response (DOR) applies only to patients whose best response was PR or CR. The duration of response is defined as the time from the first documented response to the date first documented disease progression or relapse or death due to any cause. The duration of response will be summarized descriptively for each tumor cohort. Time to progression (TTP) is defined as the time from the date of first dose to the date of first documented disease progression or relapse. Progression free survival (PFS) is defined as the time from the date of first dose to the date of first documented disease progression or relapse or death due to any cause.

[redacted]

4 Study design

4.1 Description of study design

This is a phase II, open-label study to determine the efficacy and safety of treatment with the combination of PDR001+LAG525 across multiple tumor types that are relapsed and/or refractory to available standard of care therapies (Table 4-1).

Table 4-1 Tumor Cohorts

Group	Malignancy
1	Small cell lung cancer
2	Gastric/esophageal adenocarcinoma
3	Castration resistant prostate adenocarcinoma (CRPC)
4	Soft tissue sarcoma
5	Ovarian adenocarcinoma
6	Advanced well-differentiated neuroendocrine tumors*
7	Diffuse large B cell lymphoma (DLBCL)*

*Please refer to Section 5 for disease specific inclusion/exclusion

Tumor cohorts may be excluded during the course of the study in the case of early futility or success based upon interim analyses or at the discretion of Novartis. Additional tumor cohorts may be added at the discretion of Novartis based on emerging pre-clinical or clinical data.

Patients will receive study treatment for a maximum of 2 years, or until disease progression (assessed by investigator per RECIST 1.1 or the Revised Response Criteria for Malignant Lymphoma criteria (Cheson et al 2007)), unacceptable toxicity, death or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, start of a new anti-neoplastic therapy or at the discretion of the investigator or patient). All patients who discontinue from study treatment due to disease progression must have their progression clearly documented. All disease assessments will be performed locally by the investigator.

Radiological disease assessments will be performed every 6 weeks (±7days), starting 12 weeks after first dose of study drug and continuing through week 24. The frequency of radiological disease assessments will be reduced to every 12 weeks after patients have completed 24 weeks on treatment and will continue until confirmed disease progression. Additional response assessments may be performed at the discretion of the investigator.

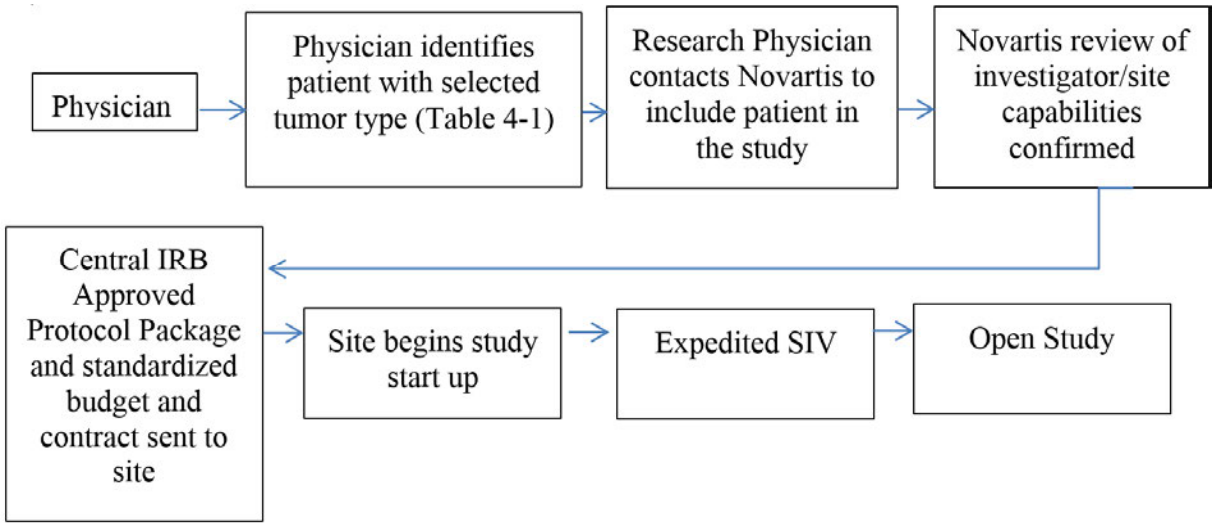
4.2 Enrollment model

This study is intended for patients who have a pathologically confirmed diagnosis of any tumor listed in Table 4-1, and have relapsed and/or refractory disease. Once the patient has been identified, treating physicians who are qualified investigators may contact Novartis or designee to consider enrollment in the appropriate tumor cohort. Informed consent must be signed before any screening activities take place. If all eligibility criteria are met (see Section 5), the patient will initiate therapy with the combination of PDR001 and LAG525. The patient may not receive any additional anti-cancer therapy during treatment with PDR001 and LAG525.

A schematic representation of the study start-up design is shown in Figure 4-1.

[redacted]

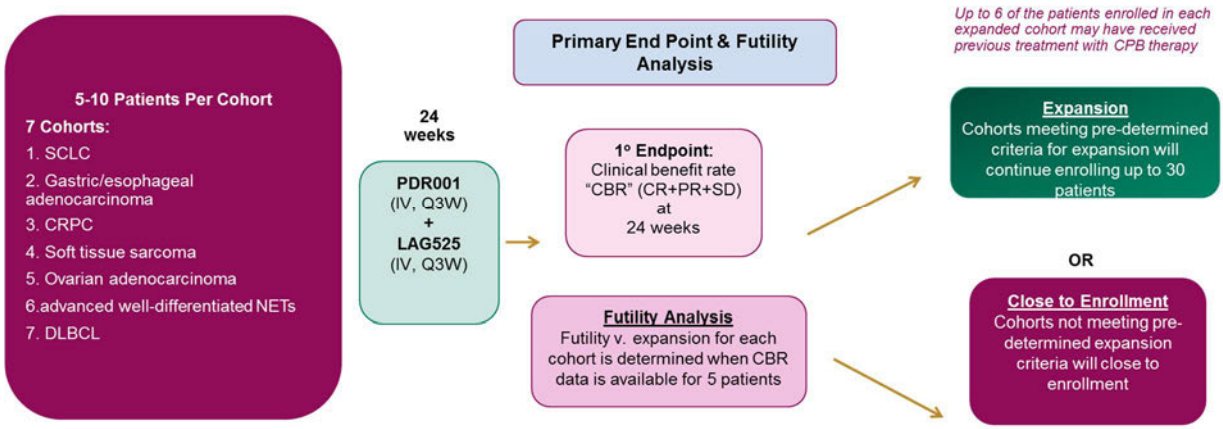
Figure 4-1 Study Start-up Design



4.3 Tumor cohort enrollment schema

Accrual to each tumor cohort will consist of a futility and expansion stage based on the observed 24 week CBR rates. The 24 week CBR rate will be continually assessed for futility and early success by comparing posterior quantities for the rate to pre-specified futility and expansion criteria for each cohort (see Section 10). Analysis for both futility and expansion will borrow information across cohorts with a hierarchical model (see Section 10). The hierarchical model allows dynamic borrowing of information between cohorts such that more borrowing occurs when the cohorts are consistent and less borrowing occurs when the cohorts differ. In this way, the model is a compromise between the two alternate extremes of either a completely pooled analysis or a separate analysis in each cohort. We additionally incorporate a clustering mechanism that allows borrowing within clusters but treats clusters separately. This minimizes borrowing across cohorts that are quite different in terms of CBR.

Figure 4-2 Study Design



[redacted]

Depending on whether or not pre-specified criteria for stopping (for futility) or continuing enrollment (for early success) is met, each tumor cohort can enroll a minimum of 5 patients and a maximum of 30 patients during the course of the study. When at least 5 patients within a group have completed 24 weeks of treatment and have CBR data available, analysis for futility and early success (expansion) will commence to inform a "go/no-go" decision for that cohort. For tumor cohorts in which treatment is not declared futile and pre-specified CBR rate for early success is met, a "go" decision will be made to continue enrolling to a maximum of 30 patients for that cohort. Expanded tumor cohorts will continue to have ongoing analysis for futility to allow for early stopping in the event that observed 24 weeks CBR rates do not meet pre-specified final success criteria (see Section 10). For tumor cohorts in which treatment has not been declared futile, but criteria for expansion has not been met, enrollment will be paused at 10 patients until a "go/no-go" decision can be made based on information gleaned from the dynamic borrowing of CBR data across tumor cohorts (see Section 10). A "no-go" decision can be made for a tumor cohort if: 1) 24 week CBR rates of the first 5-10 patients show treatment to be futile and cohort will not expand; 2) subsequent analysis in a cohort that expanded fails to demonstrate continued evidence of activity such that 24 weeks CBR is not predicted to meet pre-specified criteria for final success (See Section 10).

Primary analysis for all stages will be intent-to-treat. Those patients who discontinue study treatment for any reason other than disease progression or treatment related toxicity may be replaced (at the discretion of Novartis), until at least 5 patients with 24 weeks of CBR data are accrued within a cohort. All patients enrolled into a tumor cohort prior to expansion must not have been exposed to prior immuno-oncology (IO) therapy as specified in exclusion criteria (Section 5.3).

Once a tumor cohort is selected for expansion, the cohort shall continue to enroll patients until the cohort enrolls a total of 30 patients.

In each expansion cohort, it is permissible to enroll patients that have received previous CPB therapy as follows:

- A maximum of 6 of the 30 patients enrolled into an expansion cohort may have received previous CPB therapy.
- All patients enrolled prior to expansion must be IO naive
- 24 of the 30 patients enrolled into each tumor cohort must be IO naive.
- In the event an expanded cohort does not enroll 30 patients, the previously treated patients must not comprise more than 20% of total number of patients enrolled in the cohort.
- The patients previously exposed to CPB therapy must satisfy all inclusion-exclusion criteria as set forth in sections 5.3 and 5.4

4.4 Timing of interim analyses

Given the adaptive enrollment model and signal finding nature of this study, frequent interim analyses may be required to inform futility, early success (go/no-go decisions), and final success declarations within the tumor cohorts. The first interim analysis for the primary endpoint will occur when one or more tumor cohorts have accrued 5 patients with 24 week CBR data. Subsequent interim analyses will occur when at least 10 additional patients enrolled to the study

[redacted]

have 24 week CBR data available AND at least 3 months have elapsed since the previous interim analysis cut off. Interim analyses for primary endpoint will continue at minimum 3 month intervals until end of study (provided at least 10 additional patients have 24 week CBR data at each interim analysis).

There is no plan for a formal interim analysis of safety or other secondary endpoints for this study. However, for publication or other purposes, interim data review of clean data will be performed as necessary. At these interim reviews, patient demographics/baseline characteristics, the primary and secondary endpoints as applicable, and all important safety endpoints will be summarized. No formal report will be issued for these data reviews.

4.5 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible for End of Treatment (EOT) visit and the same assessments for EOT should be performed as described in Section 7 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Definition of End of Study

Patient accrual to the study will end when all tumor cohorts have completed initial futility and expansion analysis AND all expanded cohorts have accrued 30 patients. The study will end when all enrolled patients have either discontinued or completed 2 years of study therapy AND 150 days of safety follow up.

5.2 Patient population

This study will be conducted in 35-210 patients with select solid tumors or hematological malignancies as outlined in Table 4-1. Tumor types may be excluded or added during the course of the study in the case of early futility or success based upon an interim analysis or at the discretion of Novartis.

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.3 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Written informed consent must be obtained prior to any screening procedures.
2. Patient is ≥ 18 years of age on the day of consenting to the study

[redacted]

3. Patient must have had at least one prior line of therapy for their disease and must not be beyond 4th progression/relapse of disease (5 maximum prior lines).
4. Patient has a pathology confirmed diagnosis of a solid tumor or lymphoma listed in Table 4-1 and measurable disease as per appropriate guidelines:
   - **All Solid Tumors: by RECIST 1.1 (Appendix 1)**
     - For advanced well differentiated neuroendocrine tumors, the following also apply:
       - Pathologically confirmed, well-differentiated (Grade 1 or Grade 2), advanced (unresectable or metastatic), neuroendocrine tumor
       - No history of and no active symptoms related to carcinoid syndrome
       - Patient has not had hepatic intra-arterial embolization within the last 6 months or cryoablation or radiofrequency ablation of hepatic metastases within 2 months of first dose
   - **Diffuse Large B-cell Lymphoma: by the Revised Response Criteria for Malignant Lymphoma (Cheson et al 2007) (Appendix 2)**
     - Relapsed/refractory disease as defined by relevant standardized response criteria (see Section 4)
     - Patients with prior autologous transplant are eligible
     - Patient has at least one measurable nodal lesion (≥2 cm). In case where the patient has no measurable nodal lesions ≥ 2 cm in the long axis at screening, then the patient must have at least one measurable extra-nodal lesion
5. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
6. Patient must have locally advanced or metastatic disease.

5.4 Exclusion criteria

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

1. Presence of symptomatic CNS metastases, or CNS metastases that require local CNS-directed therapy (such as radiotherapy or surgery), or increasing doses of corticosteroids within the prior 2 weeks. Patients with treated brain metastases should be neurologically stable (for 4 weeks post-treatment and prior to study enrollment) and off steroids for at least 2 weeks before administration of any study drug.
2. History of severe hypersensitivity reactions to other mAbs
3. Patient with out of range laboratory values:
   a. Creatinine clearance (calculated using Cockcroft-Gault formula, or measured) < 40 mL/min
   b. Total bilirubin > 1.5 x ULN, except for patients with Gilbert's syndrome who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN
   c. Alanine aminotransferase (ALT) > 3 x ULN, except for patients that have tumor involvement of the liver, who are excluded if ALT > 5 x ULN
   d. Aspartate aminotransferase (AST) > 3 x ULN, except for patients that have tumor involvement of the liver, who are excluded if AST > 5 x ULN

[redacted]

e. Absolute neutrophil count (ANC) < 1.0 x 10^9/L
f. Platelet count < 75 x 10^9/L
g. Hemoglobin < 9 g/dL

4. Impaired cardiac function or clinically significant cardiac disease, including any of the following:
   a. Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (NYHA Grade ≥ 2), uncontrolled hypertension or clinically significant arrhythmia
   b. QTcF > 470 msec on screening/baseline ECG or congenital long QT syndrome
   c. Acute myocardial infarction or unstable angina pectoris < 3 months prior to study entry
5. Active, known or suspected autoimmune disease or a documented history of autoimmune disease within three years prior to screening with exception of:
   a. Patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to an autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
6. If otherwise eligible for the IO sub-group, patients previously exposed to anti-PD-1/PD-L1 treatment who are adequately treated for skin rash or with replacement therapy for endocrinopathies should not be excluded
7. Active infection requiring systemic antibiotic therapy. Patients requiring systemic antibiotics for infection must have completed therapy before screening is initiated.
8. Known history of HIV infection. Testing for HIV status is not necessary unless clinically indicated
9. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Testing for HBV or HCV status is not necessary unless clinically indicated or the patient has a history of HBV or HCV infection.
10. Patient with second primary malignancy within < 3 years of first dose of study treatment. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma in situ of any type.
11. Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns, compliance with clinical study procedures or interpretation of study results.
12. Systemic anti-cancer therapy within 2 weeks of the first dose of study treatment. For cytotoxic agents that have major delayed toxicity, e.g. mitomycin C and nitrosoureas, 4 weeks is indicated as washout period.
13. Prior immunotherapy treatment with PD-1, PD-L1, CTLA-4, or LAG-3 antibodies, CAR-T therapy, gene therapies, and/or Provenge therapy.
    a. This exclusion does not apply to patients enrolled in the immunotherapy pre-exposed subgroup (n=6 per tumor type) in those cohorts that undergo expansion to 30 patients.

[redacted]

b. For patients in the immunotherapy pre-exposed subgroups:
   - Prior IO therapy with PD-1, PD-L1, or LAG-3 antibodies, within 4 weeks of first dose of study treatment
   - CTLA-4 antagonist or vaccine as anticancer therapy within 6 weeks of first dose of study treatment
   - Patients who discontinued prior anti-PD-1, PD-L1 or anti LAG-3 therapy due to therapy related toxicity
   - Patients with a history of any grade immune-related ocular adverse event.
   - Patients with a history of Grade ≥ 3 immune-related adverse event.
   - Patients with evidence of active noninfectious pneumonitis or history of interstitial lung disease.
   - Patients with risk of reactivation of hepatitis B or C.
   - Patients who are on endocrine replacement therapy should be stable on the dose.

14. Systemic chronic steroid therapy or any immunosuppressive therapy (>10mg/day prednisone or equivalent). Topical, inhaled, nasal and ophthalmic steroids are allowed.
15. Use of any live vaccines against infectious diseases within 4 weeks of initiation of study treatment.
16. Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) or erythroid stimulating agents ≤ 2 weeks prior to start of study drug. If erythroid stimulating agents were initiated more than 2 weeks prior to the first dose of study treatment and the patient is on a stable dose, they can be maintained.
17. Presence of CTCAE ≥ grade 2 toxicity (except peripheral neuropathy and ototoxicity, which are excluded if ≥ CTCAE grade 3) due to prior cancer therapy.
18. Allogeneic stem cell transplant recipients
19. Major surgery within 2 weeks of the first dose of study treatment (mediastinoscopy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery).
20. Participation in an interventional, investigational study within 2 weeks prior to the first dose of study treatment.
21. Pregnant or lactating women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
22. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 150 days after the last dose of PDR001 and LAG525. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

[redacted]

a. Highly effective contraception methods include:
b. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
c. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
d. Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject.
e. Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
f. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

23. Sexually active males unless they use a condom during intercourse while taking the drug and for 150 days after stopping study treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via seminal fluid.

6 Treatment

6.1 Study treatment

[redacted] All dosages prescribed and dispensed to patients and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
PDR001	[redacted]	[redacted]	Every 3 weeks (Q3W)
LAG525	LAG525 [redacted]	[redacted]	Every 3 weeks (Q3W)

[redacted]

[redacted]

6.1.2 Ancillary treatments

Patients should not receive pre-medication to prevent infusion reactions before the first infusion of study treatment, in order to determine if pre-medication is necessary. If a patient experiences an infusion reaction, he/she may receive pre-medication on subsequent dosing days. The pre-medication should be chosen per institutional standard of care, at the discretion of the treating physician. Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. If a patient experiences a Grade 3 anaphylactic/anaphylactoid reaction, the patient will be discontinued from the study. The patient may resume study treatment following documented discussion with the Novartis medical monitor.

Guidelines on management of infusion reactions are provided in Table 6-3.

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

6.1.3 Rescue medication

Not applicable

[redacted]

6.1.4 Guidelines for continuation of treatment

Please refer to Section 6.3 Dose modifications and Section 6.3.2 Follow up for toxicities.

6.1.5 Treatment duration

[redacted]

6.2 Dose escalation guidelines

Not applicable

6.3 Dose modifications

6.3.1 Dose modification and dose delay

Dose reductions are not permitted. PDR001 and LAG525 may be delayed due to toxicities. The dosing regimen may resume once the adverse event has resolved to grade 1 or baseline, and the start of the cycle will be shifted accordingly.

If the Investigator considers it to be in the patient's best interest to resume therapy before the toxicity has resolved to Grade 1this may be permitted, following documented discussion with the Novartis medical monitor.

Overall, irAEs that do not recover to ≤ Grade 1 or baseline at a dose of immunosuppression of ≤ 10 mg/day prednisone or equivalent (or as indicated in the Table 6-2) within 12 weeks after initiation of immunosuppressive therapy, PDR001 and LAG525 must be permanently discontinued. All interruptions or changes to study drug administration must be recorded on the Dose Administration Record eCRF.

If PDR001 and LAG525 treatment is interrupted for more than 12 weeks due to study treatment-related toxicities, then the study treatment should be permanently discontinued. If a patient who misses more than 12 weeks of study treatment has objective evidence of response (e.g. serum, urine, or marrow evidence of response that does not meet criteria for PR, or documented improvement in a physical exam finding), and in the opinion of the investigator it is in the patient's best interest to remain on study, then the patient may continue study treatment following documented approval from Novartis. Details are provided in Table 6-2 below.

Table 6-2 Maximum permitted missed doses prior to permanent discontinuation of study treatment

Study drug	Maximum permitted missed consecutive doses prior to permanent discontinuation of study treatment
[redacted]	

PDR001	3
LAG525	3

Patients who discontinue the study for a study related AE or a study-related abnormal laboratory value must be followed as described in Section 6.3.2. All interruptions or change to study drug administration must be recorded on the Dose Administration Record eCRF.

Dose delays for adverse events related to the study medication are summarized in Appendix 5. Generally, following resolution of the adverse event to Grade 1 or to the patient's baseline value, the patient may resume study treatment on the same dosing schedule, if there is no evidence of disease progression.

6.3.2 Follow-up for toxicities

The emergence of irAEs may be anticipated based on the mechanism of action of immunomodulatory therapies.

Serologic, histologic (tumor sample) and immunological assessments should be performed as deemed appropriate by the Investigator to verify the immune-related nature of the AE and to exclude alternative explanations. Management algorithms (Appendix 5) have been developed to assist investigators in assessing and managing the following groups of AEs: Gastrointestinal; Renal; Pulmonary; Hepatic; Endocrinopathy and Skin.

For subjects who do not tolerate the protocol-specified dosing schedule, dose or schedule adjustments are permitted in order to allow the subject to continue the study treatment. The following guidelines need to be applied:

- If a subject experiences an AE meeting the criteria for DLT, treatment must be withheld.
- For clinical management of suspected immune-related events, reference to consensus management guidelines is recommended such as those provided in the National Comprehensive Cancer Network (NCCN) Guidelines for the Management of Immunotherapy-Related Toxicities (available at : https://www.nccn.org/professionals/physician_gls/default.aspx#immunotherapy), the American Society for Clinical Oncology clinical practice guideline for Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy (Brahmer 2018) or the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Management of Toxicities from Immunotherapy (Haanen 2017). Note that in general, study treatment should be interrupted for grade 3 and 4 toxicities and for a subset of lower grade toxicities.
- Consider early referral to specialists with expertise in the diagnosis and management of immune-related AEs to thoroughly investigate events of uncertain etiology.
- Events not included in the study protocol or the reference guidance documents should be managed per institutional preference.
- A decision to resume treatment following the occurrence of a DLT, grade 3 or 4 or serious adverse suspected immune-related events, may be taken only after documented discussion with the Novartis medical monitor.

  Patients whose treatment is interrupted or permanently discontinued due to an irAE, AE or clinically significant laboratory value, must be followed-up at least once a week (or more

[redacted]

frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. All patients must be followed up for irAEs, AEs and SAEs for 150 days following the last dose of study treatment.

Table 6-3 outlines the recommended dose delays and follow-up evaluations for selected toxicities.

Table 6-3 Recommended Dose Delays and re-initiation of treatment for adverse drug reactions

Worst Toxicity CTCAE v4.03 Grade	**Recommended Dose Delays**
Cardiac disorders	
ECG QTc-Interval prolonged Grade 2 (except myocarditis)	Hold study treatment. Upon resolution to Grade ≤ 1 or baseline, may resume study treatment without dose modification after discussion with the Novartis Medical Monitor.
Grade 2 myocarditis,	Discontinue study treatment
Grade 3	Omit dose of LAG525 and PDR001until returned to CTCAE Grade ≤ 1 or < 30 msec difference from baseline. Baseline ECG refers to the ECG(s) collected at screening. May resume study treatment without modifications after discussion with Novartis Medical Monitor.
Grade 4	Discontinue study treatment.
Cardiac disorders – others	
Grade 1 and 2	Maintain dose level of LAG525 and PDR001.
Grade ≥ 3	Discontinue study treatment.
Skin toxicity	
Rash/photosensitivity Grade 1	Maintain dose level of LAG525 and PDR001and manage per institutional standard guidelines. (Topical steroids, antihistamines, topical emollients)
Grade 2	Consider holding study treatment. Topical or oral steroids, antihistamines. If study treatment is held and resolution to ≤ Grade 1, resume study treatment without dose modification.
Grade 3 or Grade 4	hold dose of LAG525 and PDR001 until returned to CTCAE Grade ≤ 1. Treat according to institutional practice which generally includes anti-histamine regimen, corticosteroid treatment (oral or topical) can be considered for symptomatic rash (e.g. pruritus). consider resuming therapy after expert consultation and documented discussion with Novartis Medical Monitor.
Bullous dermatitis	

Worst Toxicity CTCAE v4.03 Grade	**Recommended Dose Delays**
Stevens-Johnson Syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	Hold study treatment. Grade 1-2 bullous dermatitis: discussion with the Novartis Medical Monitor is required before considering resuming study treatment. Grade 3 bullous dermatitis: consider resuming therapy after expert consultation and documented discussion with the Novartis medical monitor Permanently discontinue study treatment.
GI disorders	
Diarrhea/Colitis Grade 1 Grade 2 & Grade 3 Grade 4	Note: anti-diarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea. Maintain dose level of LAG525 and PDR001and manage per institutional standard guidelines which should include corticosteroid therapy and anti-diarrheal treatment as needed consideration of corticosteroid therapy, and hydration. Hold study treatment. GI consultation. Upon resolution to ≤ Grade 1 and tapering of steroid requirement to ≤ 10 mg prednisone per day, resume study treatment without dose delay after discussion with the Novartis Medical Monitor. Discontinue study treatment
AST and/or ALT elevation Grade 2 AST and/or ALT Grade 2 transaminitis with bilirubin >1.5 x ULN (unless Gilbert's syndrome) Grade 3 AST and/or ALT Grade 4 AST and/or ALT **Isolated total bilirubin elevation** Grade 2	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1 or baseline, consider resuming study treatment without dose modification. Discontinue study treatment. Hold study treatment. Manage per institutional practices. Upon resolution to ≤ Grade 1 or baseline within 7 days, consider resuming study treatment without dose modification after discussion with the Novartis Medical Monitor. Otherwise, discontinue study treatment. Discontinue Study Treatment

[redacted]

Worst Toxicity CTCAE v4.03 Grade	Recommended Dose Delays
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 1 or baseline, may continue study treatment without dose modification. Hold study treatment. Upon resolution to ≤ Grade 1 or baseline, may consider resuming study treatment after discussion with the Novartis Medical Monitor.
Grade 4	Discontinue study treatment. Exception: If Grade 3 or 4 hyper-bilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then delay study treatment until resolved ≤ Grade 1, and resume study treatment at the discretion of the investigator.
Asymptomatic amylase and/or lipase elevation Grade 3 or Grade 4, not associated with symptoms or clinical manifestations of pancreatitis	Continue study treatment. If levels do not resolve to ≤ Grade 2 within ≤ 14 days after the initial report, hold study treatment. Upon resolution to ≤ Grade 2, may resume study treatment without dose modification, after discussion with the Novartis Medical Monitor. A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within one week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase.
Pancreatitis*	
Grade 1	Maintain dose level of LAG525 and PDR001and manage per institutional standard guidelines.
Grade 2/radiologic evidence	Omit dose of LAG525 and PDR001 until returned to CTCAE Grade ≤ 1. Treat according to institutional practice. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification, if no clinical evidence of pancreatitis and after discussion with the Novartis Medical Monitor. Discontinue study treatment
Grade 3 or Grade 4	Discontinue study treatment
Pulmonary disorders	
Pneumonitis	Omit LAG525 and PDR001 for any case of suspected pneumonitis.
Any Grade	Initiate institutional protocol for pneumonitis management which generally includes obtaining appropriate imaging (high resolution CT scan) and consider bronchoalveolar lavage if clinically indicated for biopsy. Treatment with high dose corticosteroid therapy is recommended. Concurrent corticosteroid and antibiotic therapy is recommended if infectious causes have not been ruled out.
Grade 1	Consider study treatment hold. Manage per institutional practice. Consider resuming study treatment upon radiographic evidence of improvement.

[redacted]

Worst Toxicity CTCAE v4.03 Grade	**Recommended Dose Delays**
Grade 2	Hold study treatment. Pulmonary and infection workup. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification.
Grade 3 or 4	Discontinue study treatment
Infusion reactions	
Grade 1	Decrease infusion rate until recovery of the symptoms.
Grade 2	Stop infusion immediately, and keep line open. Provide supplemental oxygen and fluids, as needed. Monitor vital signs (e.g., blood pressure, pulse, and temperature) every 15 ± 5 minutes until resolution. Administer medications for symptomatic relief as needed: Urticaria: Diphenhydramine (25 to 100 mg i.v.) as needed every 4 to 6 hours, or alternative as appropriate. Fever: Acetaminophen/paracetamol (650-1000 mg by mouth) as needed every 4 to 6 hours, or alternative as appropriate. Rigors: Meperidine 25 mg i.v. as needed every 6 hours or alternative as appropriate. Corticosteroids may be administered, as needed. **Resume infusion** once infusion reaction resolves (**within 8 hours of initial start of infusion**): Maintain dose level. Administer oral pre-medication (e.g.1000 mg of acetaminophen/paracetamol, 50-100 mg diphenhydramine hydrochloride or alternative antihistamine), within 60 minutes of restarting the infusion. Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion. - If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then discontinue patient from study treatment.
Grade 3 or 4	Discontinue infusion immediately, and permanently discontinue patient from study treatment. Provide supplemental oxygen, fluids, and other resuscitative measures as needed. Guidance provided above. Monitor vital signs (e.g., blood pressure, pulse, respiration, and temperature) every 15 ± 5 minutes until resolution.
Type 1 Diabetes mellitus	Monitor patients for hyperglycemia or other signs and symptoms of diabetes and diabetic ketoacidosis. Administer insulin for type 1 diabetes. In patients with severe hyperglycemia omit dose of LAG525 and PDR001 and manage as per Institutional guidelines until resolved to ≤ Gr 1
Cytokine Release Syndrome (CRS)	
Grade 2	See Instructions for Grade 2 Infusion Reactions.
Grade 3 or Grade 4	Discontinue study treatment Follow-up CRS as per institutional guidelines.

[redacted]

Worst Toxicity CTCAE v4.03 Grade	**Recommended Dose Delays**
Ocular (uveitis, eye pain, blurred vision)	
Grade 1	Continue study treatment without dose modification. Ophthalmology consultation.
Grade 2	Hold study treatment. Urgent ophthalmology consultation. Upon resolution to ≤ Grade 1 may consider resuming study treatment without dose reduction after discussion with the Novartis Medical Monitor and in consultation with ophthalmology.
Grade 3 or Grade 4	Discontinue study treatment. Urgent ophthalmology consultation.
Renal **Serum Creatinine**	
Grade 2	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification after discussion with the Novartis Medical Monitor.
Grade 3 or 4	Discontinue Study Treatment
Musculoskeletal	
Grade 2 or Grade 3	Hold study treatment. Consider resuming study treatment without dose modification upon resolution to ≤ Grade 1 with appropriate management.
Grade 4	**Discontinue study treatment** In some cases, resuming study treatment may be considered after discussion with the Novartis Medical Monitor and consultation with a rheumatologist.
Endocrine **Hypothyroidism or hyperthyroidism**	
Grade 2	May continue study treatment without dose modification. Management according to institutional practice.
Grade 3	**Hold Study Treatment** Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment without dose modification.
Grade 4	Hold Study Treatment. May resume study treatment following resolution or control with physiologic hormone replacement
Other Endocrine Disorders	
Grade 2 and Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment without dose modification.
Grade 4	Hold study treatment. Grade 4 treatment-related endocrinopathies, such as adrenal insufficiency, adrenocorticotropic hormone (ACTH) deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Novartis Medical Monitor.
Neurology	
Grade 1	Consider study treatment hold, particularly for clinical

[redacted]

Worst Toxicity CTCAE v4.03 Grade	**Recommended Dose Delays**
	suspicion of Guillain-Barre syndrome, encephalitis, aseptic meningitis, transverse myelitis, or peripheral neuropathy.
Grade 2	Hold study treatment. In some cases, resuming study treatment may be considered after discussion with the Novartis Medical Monitor.
Grade 3 or Grade 4	Discontinue study treatment.
Hematology	
Neutropenia (ANC)	
Grade 3 or Grade 4	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline within ≤ 7 days, resume study treatment without dose modification, after discussion with the Novartis Medical Monitor.
Febrile Neutropenia	Hold study treatment.
Grade 3 or Grade 4	Upon resolution of fever and improvement of neutropenia to ≤ Grade 2 or baseline, resume study treatment without dose modification, after discussion with the Novartis Medical Monitor.
Thrombocytopenia	Hold study treatment.
Grade 3	Upon resolution to ≤ Grade 2 or baseline, resume study treatment without dose modification. For Grade 3 associated with major bleeding, discontinue study treatment.
Grade 4	Discontinue study treatment.
Anemia	
Grade 3 or Grade 4	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline within ≤ 7 days, resume study treatment without dose modification.
Lymphoma	
Any Grade	Treatment-related lymphopenia does not require study treatment hold or discontinuation.
Other laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 1, resume study treatment without dose modification.
Grade 4	Isolated Grade 4 electrolyte abnormalities not associated with clinical sequelae and corrected after appropriate management within 72 hours of their onset do not require discontinuation. In the case of Grade 4 electrolyte imbalances associated with clinical sequelae, or not resolved to ≤ Grade 1 within 72 hours despite appropriate management, discontinue study treatment.
Other non-laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	
Grade 2	Consider study treatment hold, at Investigator discretion. Upon resolution to ≤ Grade 1, resume study treatment without dose modification.
Grade 3	Hold Study Treatment Upon resolution to ≤ Grade 1, resuming study treatment must be discussed with the Novartis Medical Monitor.
Grade 4	Discontinue Study Treatment

[redacted]

Worst Toxicity CTCAE v4.03 Grade	Recommended Dose Delays
In patients experiencing AE not meeting the criteria above of Grade ≥ 3, study drugs should be omitted until resolved to Grade ≤ 1 or baseline. If AE resolves to Grade ≤1 or baseline in 21 days or less, then treatment may restart with a less frequent dosing schedule after consultation with Novartis.	
All dose modifications should be based on the worst preceding toxicity. Once a dose has been administered less frequently it will not be administered more frequently at a later time even if there is no toxicity.	

6.3.2.1 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastases, or elevation of ALP liver fraction in patients with bone metastases.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term

[redacted]

"potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events are provided in Section 6. Refer to preclinical toxicity and or clinical data found in the [Investigator's Brochure].

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrhea) and safety of the patient are allowed.

The patient must be told to notify the investigational site about any new medications, herbal remedies and dietary supplements he/she takes after the start of the study treatment. All medications (other than study treatment) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Prior/Concomitant Medications or the Surgical and Medical Procedures eCRFs.

6.4.2 Permitted concomitant therapy requiring caution and/or action

If a patient is using erythropoiesis stimulating agents (ESAs) prior to enrollment (at least 2 weeks before start of study treatment), he/she may continue at the same dose.

Anticoagulation therapy is permitted if the patients are already at stable doses of warfarin or stable doses of low molecular weight heparin (LMWH) for > 2 weeks at time of first dose and International Normalized Ratio (INR) should be monitored as clinically indicated per investigator's discretion. However, ongoing anticoagulant therapy should be temporarily discontinued to allow tumor sample collection according to the institutional guidelines if applicable.

Anti-hypertensive therapy is allowed as concomitant medications; however, because transient hypotension has occurred during infusions of monoclonal antibodies, consideration should be given to withholding anti-hypertensive medications for 12 hours prior to the infusion of study drugs.

A brief (< 24 hours) course of steroids for prophylaxis against imaging contrast dye allergy is permitted for patients undergoing tumor assessments.

6.4.3 Prohibited concomitant therapy

As far as possible, avoid co-administering QT prolonging drugs. If during the course of the study, concomitant administration of drugs with a known potential to cause Torsades de Pointe is required and cannot be avoided, study drug must be interrupted until an assessment of the potential safety risk has been performed. A definitive list of drugs associated with QT

prolongation and/or TdP is available online at www.qtdrugs.org. If, based on the investigator assessment and clinical need study treatment is resumed, close ECG monitoring is advised.

Treatment with hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) may not be taken during the study.

During the course of the study, patients must not receive other additional investigational drugs, devices, chemotherapy, or any other therapies that may be active against cancer or modulate the immune responses.

Limited-field palliative radiotherapy to non-target lesion(s) may be allowed as concomitant therapy after documented discussion with Novartis. Such local therapies administered during the study treatment must be listed on the Concomitant Antineoplastic Therapy – Radiotherapy CRF. Additionally, no other therapeutic monoclonal antibodies and no immunosuppressive medication may be administered while on this study unless given for the management of immune toxicity.

The use of systemic steroid therapy and other immunosuppressive drugs is not allowed except for the treatment of infusion reaction, irAEs, for prophylaxis against imaging contrast dye allergy or replacement-dose steroids in the setting of adrenal insufficiency (providing this is < 10 mg/day prednisone or equivalent), or transient exacerbations of other underlying diseases such as chronic obstructive pulmonary disease (COPD) requiring treatment for < 3 weeks. Systemic corticosteroids required for the control of infusion reactions or irAEs must be tapered and be at non-immunosuppressive doses (< 10 mg/day of prednisone or equivalent) before the next study drug administration. If more than 10 mg/day prednisone is used, study treatment should be suspended. Topical, inhaled, nasal and ophthalmic steroids are allowed.

The use of live vaccines is not allowed through the duration of the study. Inactivated vaccines are allowed.

6.4.4 Use of Bisphosphonates and radiotherapy

6.4.4.1 Bisphosphonates

The use of bisphosphonates is allowed regardless of indication provided patients have been on stable doses optimally for at least 4 weeks prior to the start of treatment. Patients requiring initiation of bisphosphonate treatment during the course of the study should be assessed by appropriate image modalities to exclude disease progression; if disease progression is documented, the patient should discontinue study treatment.

6.4.4.2 Palliative radiotherapy

Palliative radiation is permitted if done solely for bone relief. It should not be delivered to a target lesion and it should not encompass more than 25% of irradiated bone marrow.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient

[redacted]

throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

6.5.2 Treatment assignment or randomization

Not applicable.

6.5.3 Treatment blinding

This is an open-label study.

6.6 Study drug preparation and dispensation

[redacted] Both PDR001 and LAG525 will be administered intravenously as a 30 minute infusion (up to 2 hour, if clinically indicated). Further instructions for the preparation and dispensation of LAG525 and PDR001 are described in the Pharmacy Manual(s). All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

6.6.1 Study treatment packaging and labeling

PDR001 100 mg powder for solution for infusion and/or liquid in vials and LAG525 100 mg liquid in vials will be supplied by Novartis to investigator as open-label bulk medication and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

PDR001 and LAG525 in different formulations and strengths can be used once they are approved.

Study treatment labels will comply with the legal requirements of each country and will include storage conditions and a unique medication number (corresponding to study treatment and strength).

If the label has 2-parts (base plus tear-off label), immediately before administering it to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document.

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, PDR001 and LAG525 should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure].

Table 6-4 Supply and storage of study treatments

Study treatments	Supply	Storage
PDR001	Centrally supplied by Novartis	Refer to study treatment label
LAG525	Centrally supplied by Novartis	Refer to study treatment label

[redacted]

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Study treatment will be administered to the patient by the study site staff at the study sites. Compliance will be assured by administration of the study treatment under the supervision of investigator or his/her designee. Information will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis or designee monitor or to the Novartis address provided in the investigator folder at each site.

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

No CRF will be used as a source document.

Screening/baseline evaluations must be performed ≤ 21 days before Cycle 1 Day 1. Assessments required on Cycle 1 Day 1 that are performed as part of the screening evaluations and within 4 days prior to the first dose of study treatment, do not need to be repeated on Cycle 1 Day 1 (except Pregnancy test which needs to be completed within 72 hours prior to the first dose). Laboratory and radiological assessments performed as part of standard of care prior to signing informed consent may be used if performed within the screening time window.

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. A visit window of +/- 4 days is allowed for visits and a window of +/- 7 days is allowed for radiological assessments.

[redacted]

For the 30-day and 150-day safety follow-up visits, a window of +7 days is allowed. For the 60-day, 90-day, and 120-day safety follow-up, a window of ± 14 days is allowed.

If the infusion of either study drug is delayed (see Section 6), the visit will be shifted accordingly.

[redacted]

Table 7-1 Visit evaluation schedule (Cycle Length is 21 days/ 3 weeks)

	Protocol Section	Screening	Cycle 1		Cycle 2		Cycle 3	Subsequent Cycles	End of study treatment (EoT)	Safety Follow up	
Visit Name		**1**	**2**	**3**	**4**	**5**	**6**	**7,8,9…**			
Day of cycle			**1**	**8**	**1**	**8**	**1**	**1**		**30, 90, & 150**	**60 & 120**
All Patients											
Obtain Informed Consent		x									
Demography		x									
Inclusion/exclusion criteria		x									
Medical History		x									
Diagnosis and extent of cancer		x									
Antineoplastic therapy		x							x	x	x
Physical examination	7.2.2.1	x	x	x	x	x	x	x	x		
ECOG Performance status	7.2.2.4	x	x		x		x	x	x		
Height	7.2.2.3	x									
Weight	7.2.2.3	x	x		x		x	x	x		
Vital signs	7.2.2.2	x	x		x		x	x	x		
Hematology	7.2.2.5.1	x	x	x	x	x	x	x	x		
Chemistry (including liver function tests)	7.2.2.5.2	x	x	x	x	x	x	x	x		
Thyroid function (Free T4 and TSH)	7.2.2.5.5	x	x		x		x	x	x		
Coagulation	7.2.2.5.3	x									
Urinalysis	7.2.2.5.4	x									
HIV, HBV, HCV		x									
Pregnancy test	7.2.2.5.6	x	x		x		x	x	x	x *	x *
ECG (See Table 7-4 for time points)	7.2.2.6.1	x	x		x		x	X(C4-C6 only)	x		
Cardiac imaging (MUGA/ECHO)	7.2.2.6.2	x									

[redacted]

	Protocol Section	Screening	Cycle 1		Cycle 2		Cycle 3	Subsequent Cycles	End of study treatment (EoT)	Safety Follow up	
Visit Name		**1**	**2**	**3**	**4**	**5**	**6**	**7,8,9…**			
Day of cycle			**1**	**8**	**1**	**8**	**1**	**1**		**30, 90, & 150**	**60 & 120**
Adverse events	8.1	Continuous									
Prior/concomitant medications	6.4	Continuous									
Surgical and medical procedures		Continuous									
Study Drug administration LAG525(Q3W)	6.1		x		x		x	x			
Study Drug Administration PDR001(Q3W)	6.1		x		x		x	x			
Imaging and radiological tumor assessment	7.2.1	x			Every 6 weeks starting at week 12 through week 24 and every 12 weeks thereafter						
Serum prostate-specific antigen (PSA) (Prostate cancer only)	7.2.1.1.1	x			Every 6 weeks starting at week 12 through week 24 and every 12 weeks thereafter						
Cancer Antigen-125 (ovarian cancer only)	7.2.1.1.2	x			Every 6 weeks starting at week 12 through week 24 and every 12 weeks thereafter						
Measurement of superficial disease (if present)	7.2.1.1.3	x			Every 6 weeks starting at week 12 through week 24 and every 12 weeks thereafter						
Lymphoma Patients Only											
Exam for enlarged spleen or liver	7.2.1.1.4	x			To confirm response of CR						
Measurement of superficial B symptoms	7.2.1.1.5	x	x		x		x	x			
PET scan	7.2.1.1.7	x			To confirm response of CR						
Bone Marrow Biopsy or aspirate	7.2.1.1.6				To confirm response of CR						

* Can be performed at home or at a local doctor's office if the patient is not coming to the clinic.

[redacted]

7.1.1 Molecular pre-screening

Not Applicable

7.1.2 Screening

All screening evaluations must be performed as closely as possible to the beginning of treatment and never more than 21 days prior to starting study drug.

The study IRB/IEC informed consent form must be signed and dated before any screening procedures are performed, except for evaluations (for example imaging assessments) performed as part of standard of care within the screening window. Patients will be evaluated against study inclusion and exclusion criteria and safety assessments. For details of assessments, refer to Table 7-1.

Screening assessments must be repeated if performed outside of the specified screening window Section 7.1. For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered ineligible and a screening failure.

A patient who has a laboratory test result(s) that does not satisfy the entrance criteria may have the test(s) repeated. These test(s) may be repeated to satisfy the entrance criteria, but should be completed within 21 days of the original screening visit date. In this case, the subject will not be required to sign another ICF, and the original patient ID number assigned by the investigator will be used. In the event that the laboratory test(s) cannot be performed within 21 days of the original screening visit, or the re-test(s) do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the patient is considered a screen failure, and must be discontinued from the study.

Disease assessments must be performed within 21 days of enrollment and will be assessed locally by the investigator. Patients who fail to start on treatment within 21 days of screening may be re-screened. A new ICF will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed, however, if the patient is rescreened a new patient ID will be assigned. All required screening activities must be performed when the patient is re-screened for participation in the study. An individual patient may only be re-screened once for the study. The Sponsor may close the study to further screening. In this case, the patients who screen failed will not be permitted to re-screen.

For details of assessments, refer to Table 7-1.

Upon signing the Informed Consent Form (ICF), a patient will be assigned a unique subject identifier for the study.

[redacted]

7.1.2.1 Eligibility screening

Once all screening procedures are completed, eligibility should be confirmed prior to the subject receiving the first dose of study drug.

7.1.2.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details).

7.1.2.3 Patient demographics and other baseline characteristics

Data to be collected will include general patient demographics, relevant medical history and current medical conditions, diagnosis and extent of tumor, details of prior anti-neoplastic treatments (including medications, radiations and surgeries), prior medication, procedures, significant non-drug therapies and any other assessments that are done for the purpose of determining eligibility for inclusion in the study.

7.1.3 Run-in period

Not applicable

7.1.4 Treatment period

A treatment cycle is defined as 21 days for the purposes of scheduling procedures and evaluations. Please refer to Table 7-1 for details of the timing of required assessments and Section 7.1 for visit windows.

Patients will receive study treatment for a maximum of 2 years, or until disease progression (assessed by investigator per RECIST 1.1 and the Revised Response Criteria for Malignant Lymphoma criteria (Cheson et al 2007) for lymphoma), unacceptable toxicity, death or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, start of a new anti-neoplastic therapy or at the discretion of the investigator or patient), otherwise known as End of Treatment.

Clinical experience indicates that objective responses to immunotherapy follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while other target lesions are regressing ("mixed response") (Wolchock 2009). Therefore, patients with disease progression, may remain on treatment, if the Investigator considers it to be in in the patient's best interest, and after documented discussion with the Novartis Medical Monitor.

These considerations should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment.

[redacted]

Patients with an unconfirmed progressive disease who show signs of clinical deterioration or toxicity will enter the 150-day safety follow-up period. Such deterioration will be assessed to have occurred after a clinical event that, in the investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the patient is not benefiting from study treatment and cannot be managed by the addition of supportive care.

7.1.5 Discontinuation of study treatment

Patients may voluntarily discontinue from the investigational treatment for any reason at any time. If a patient decides to discontinue, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue investigational treatment for a given patient if he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment may be discontinued if any of the following occur:

- Adverse event
- Lost to follow-up
- Physician's decision
- Progressive disease per defined response criteria
- Study terminated by the sponsor
- Subject/guardian decision
- Protocol deviations that result in significant risk to the patients' safety
- Technical problems

Patients will be withdrawn if any of the following occur:

- Pregnancy
- Death

At the time patients discontinue study treatment, a visit should be scheduled as soon as possible, and within 14 days of the last dose of study drug or within 14 days of the decision to permanently discontinue study treatment, at which time all of the assessments listed for the EOT visit will be performed (Table 7-1). If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit. An End of Treatment Phase Disposition CRF page should be completed, giving the date and reason for stopping the study treatment. End of treatment/Premature withdrawal visit is not considered as the end of the study.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 150 days following the last dose of study treatment.

[redacted]

7.1.5.1 Replacement policy

Those patients who discontinue study treatment for any reason other than disease progression or treatment related toxicity may be replaced at the discretion of Novartis, until a minimum of 5 patients with 24 weeks of CBR data are accrued within a cohort.

7.1.6 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

7.1.7 Follow up for safety evaluations

150-day safety follow up period

All patients must have safety evaluations for 30, 90 and 150 days after the last dose of study treatment. Antineoplastic therapies since discontinuation of study drug will be collected during this follow-up period. Concomitant medications will be collected until the 30-day safety follow-up has been completed or the start of a new antineoplastic therapy, whichever occurs first. Information related to AEs (including concomitant medication taken for ongoing AEs) will be collected for 150 days after the last dose of study drug. All AEs suspected to be related to study treatment should be followed up weekly or as clinically indicated until resolution or stabilization. Data collected should be added to the Adverse Events CRF, the antineoplastic therapies since discontinuation of study treatment CRF and the Concomitant Medications CRF.

For a female participant of childbearing potential, a urine pregnancy test will be performed on Day 30, 60, 90, 120 and 150 after stopping the study treatment. Please see Section 7.2.2 for details

If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine if the patient had disease progression.

[redacted]

7.1.8 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

The primary efficacy endpoint is clinical benefit rate as defined in Section 10.4. The secondary efficacy endpoint is overall response rate of PR or greater as defined in Section 10.5. Other secondary endpoints are time from the date of first dose to the date of first documented disease progression or relapse or death due to any cause, time from the date of first dose to the date of death due to any cause, time from the first documented response to the date first documented disease progression or relapse or death due to any cause, and other safety measurements as defined in Section 10. The local investigator's assessment will be used for the analysis and for treatment decision making.

Clinical suspicion of disease progression at any time will require assessment and confirmation to be performed promptly, rather than waiting for the next scheduled tumor assessment. In case of an unscheduled or delayed tumor assessment for any reason, subsequent disease assessments must be performed according to the originally planned schedule from baseline.

7.2.1.1 Radiological Tumor Assessment

At screening, all patients will undergo CT with i.v. contrast of the chest, abdomen and pelvis. Additionally, patients with lymphoma will also undergo CT with i.v. contrast of the neck and a PET scan. MRI should only be used to evaluate sites of disease that are not adequately imaged by CT. If a patient is intolerant of iodine-based contrast agents, CTs may be performed without contrast. MRI may be used to evaluate sites of disease where a CT without i.v. contrast is not adequate. Visible skin lesions and easily palpable subcutaneous tumors may be measured by physical examination using a ruler or calipers. Ultrasound should not be used to measure sites of disease.

No modality change would be allowed during the study when assessing overall tumor status. For subsequent scans in the same patient, the radiologist must account for all lesions that were present at screening and must use the same technique as used at screening. If possible, a single radiologist should perform all tumor response evaluations for an individual patient. Only in exceptional cases when during the study a patient develops intolerance to the CT scan contrast medium, a CT scan without contrast will be acceptable to avoid modality change.

Tumor assessments will be performed at the time points specified in Table 7-1.

[redacted]

Radiological disease assessments will be performed every 6 weeks (±7 days), starting 12 weeks after first dose of study drug and continuing through week 24. The frequency of radiological disease assessments will be reduced to every 12 weeks after patients have completed 24 weeks on treatment and will continue until confirmed disease progression. Solid tumor response will be determined locally according to RECIST 1.1 (Appendix 1). Lymphoma response will be determined locally according to Revised Response Criteria for Malignant Lymphoma, (Cheson et al 2007) (Appendix 2).

The local investigator's assessment will be used for the analysis of response and for treatment-making decisions. Clinical experience indicates that objective responses to immunotherapy follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while other target lesions are regressing ("mixed response") (Wolchock 2009). Therefore, patients with confirmed disease progression, may continue to receive treatment, beyond initial disease progression, if the Investigator considers it to be in in the patient's best interest to remain on the study, and after documented discussion with the Novartis Medical Monitor.

7.2.1.1.1 Prostate Specific Antigen (PSA) (prostate cancer only)

Prostate Specific Antigen (PSA) will be used in the assessment of prostate cancer at screening. Subsequent tumor assessments must be performed on the same schedule as radiological tumor assessments (see Table 7-1).

7.2.1.1.2 Cancer Antigen-125 (ovarian cancer only)

Cancer Antigen-125 (CA-125) will be used in the assessment of ovarian cancer at screening by revised GCIC criteria. Subsequent tumor assessments must be performed on the same schedule as radiological tumor assessments (see Table 7-1).

7.2.1.1.3 Physical examination for superficial disease (if applicable)

Clinical assessment of any existing superficial lesions (skin nodules and palpable lymph nodes) at screening and at each subsequent tumor assessment must be performed on the same schedule as radiological tumor assessments (see Table 7-1).

Skin lesions should be documented using a digital camera (color photography) in clear focus showing the ruler or calipers and the corresponding measurement in such a way that the size of the lesion(s) can be determined from the photograph. Skin photographs should be continued at subsequent tumor assessments for any lesions that were photographed at screening.

7.2.1.1.4 Enlarged spleen and liver (Lymphoma only)

The presence of enlarged spleen or liver before start of treatment on the basis of CT scan (or MRI scan) should be recorded on the corresponding eCRF at baseline, and reassessed if the patient has a radiological CR.

A maximum of four of the largest dominant measurable nodules representing all involved anatomic locations should be selected as splenic and hepatic index lesions to be measured.

[redacted]

All other splenic or hepatic nodules (both measurable and non-measurable) are considered as non-index lesions.

7.2.1.1.5 Physical examination for superficial disease and B symptoms (Lymphoma only)

Tumor assessment by physical examination and evaluation of disease related B symptoms (unexplained fever of ≥ 38°C; unexplained, recurrent drenching night sweats; or unexplained loss of >10% body weight within the previous 6 months) will be performed at screening and day 1 of every cycle (±4 days) until progression of disease or patient withdrawal. Refer to Appendix 2 for specifications and measurement.

Skin lesions should be documented using a digital camera (color photography) in clear focus showing the ruler or calipers and the corresponding measurement in such a way that the size of the lesion(s) can be determined from the photograph. Skin photographs should be continued at subsequent tumor assessments for any lesions that were photographed at screening.

7.2.1.1.6 Bone marrow assessment (Lymphoma only)

Information on the patient's bone marrow involvement based on documented history prior to study entry must be present in his/her source documents. Prior tumor bone marrow involvement should be entered on the corresponding eCRF.

Core bone marrow biopsy will not be performed at screening but is required to confirm complete responses (at the first occurrence of radiological and clinical evidence of CR) in patients with bone marrow tumor involvement prior to study treatment who achieve Complete Response based on clinical and radiological evidence. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). Bone marrow biopsy should be obtained no later than at the next visit immediately following clinical and radiological evidence of CR (i.e. < 28 days ± 7 days from the date of the radiological assessment, on which the CR is based on).

7.2.1.1.7 Positron emission tomography (PET)

All Lymphoma Patients will have a PET scan completed at screening and then a follow up scan to confirm a complete response to study treatment (see Table 7-1).

7.2.2 Safety and tolerability assessments

Safety will be monitored by physical examination, vital signs, body height and weight, performance status, hematology, chemistry, coagulation, urinalysis, thyroid function, pregnancy, ECG, cytokine testing, as well as collecting of the AEs at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

Physical examination will be performed at the time points indicated in Table 7-1.

[redacted]

At Screening and Cycle 1 Day 1, prior to study drug infusion, a complete physical examination will be performed and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

From Cycle 2 onwards, a short physical examination will be performed. A short physical exam will include the examination of general appearance, vital signs (blood pressure [BP] and pulse) and body sites as directed by symptoms.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) must be assessed prior to dosing and as indicated in Table 7-1.

7.2.2.3 Height and weight

Height in centimeters (cm) or inches and body weight (to the nearest 0.1 kilogram [kg], or to the nearest 0.1 pound, in indoor clothing, but without shoes) will be measured as indicated in Table 7-1.

7.2.2.4 Performance status

ECOG performance status will be assessed according to the time points in Table 7-1, using the criteria in Table 7-2.

Table 7-2 ECOG performance status

Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

7.2.2.5 Laboratory evaluations

All laboratory parameters assessed for safety purposes will be evaluated locally. Refer to Table 7-3 for a summary of the parameters to be evaluated according to Table 7-1. On days of dosing, samples for these parameters will be collected prior to the infusion of study drug.

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

[redacted]

Novartis will be provided with a copy of the laboratory certification and tabulation of the normal ranges for each parameter required. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

Table 7-3 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands *(absolute value preferred))*
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Total Bilirubin (also measure direct and indirect if total bilirubin is > grade 1), Blood Urea Nitrogen (BUN) or Urea, Amylase, Lipase, Glucose
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, pH, Protein, Specific Gravity, White Blood Cells)
Coagulation	Prothrombin time (PT) or, International normalized ratio [INR], Activated partial thromboplastin time (APTT)
Thyroid	Total or Free T4, TSH
Pregnancy Test	At screening, a serum test within 72 hours before the first dose. Day 1 of each cycle starting with Cycle 2, EOT, during the follow-up period on Day 30, 60, 90, 120 and 150 after stopping the study treatment serum or urine pregnancy test

7.2.2.5.1 Hematology

Hematology panel outlined in Table 7-3 will be performed as per the assessment schedule in Table 7-1.

7.2.2.5.2 Clinical chemistry

Clinical chemistry panel outlined in Table 7-3 will be performed as per the assessment schedule in Table 7-1. Patients without pre-existing diabetes or previously determined to be normoglycemic shown to have an abnormal random blood glucose at screening must have a fasting blood glucose test performed and any subsequently diagnosed hyperglycemia should be managed appropriately as per Institutional guidelines.

7.2.2.5.3 Coagulation

Coagulation panel outlined in Table 7-3 will be performed as per the assessment schedule in Table 7-1.

7.2.2.5.4 Urinalysis

Urinalysis panel outlined in Table 7-3 will be performed as per the assessment schedule in Table 7-1.

[redacted]

7.2.2.5.5 Thyroid function

Thyroid function panel outlined in Table 7-3 will be performed as per the assessment schedule in Table 7-1.

7.2.2.5.6 Pregnancy and assessments of fertility

Pregnancy tests will be performed for women of child bearing potential. At screening, a serum pregnancy test must be performed within 72 hours before the first dose. During the study (Day 1 of each cycle starting with Cycle 2) a serum or urine pregnancy test must be performed. At End of Treatment, a serum or urine pregnancy test must also be performed. Pregnancy test will also be performed during the follow-up period on Day 30, 60, 90, 120 and 150 after stopping the study treatment.

If the patient is not coming to the clinic during the safety follow-up, it can be performed at home or at a local doctor's office, and the results will be communicated to the site staff. These follow-up pregnancy tests will be recorded only in the source documentation, not in the CRF.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as per the assessment schedule in Table 7-1 and Table 7-4. Blood samples scheduled at the same time point should be taken after the ECGs are completed. The ECGs on C1D1, C2D1, C3D1, C4D1, C5D1 and C6D1 must be performed in triplicate. The post-dose ECGs will be collected after the completion of the last dose of infusion.

Table 7-4 12 Lead ECG collection plan

Cycle	Day	Time
Screening	-21 to -1	Anytime
1	1	*Pre-dose
1	1	*1h (±5 min) hour post dose
2	1	*Pre-dose
2	1	*1h (±5 min) hour post dose
3	1	*Pre-dose
3	1	*1h (±5 min) hour post dose
4	1	*Pre-dose
4	1	*1h (±5 min) hour post dose
5	1	*Pre-dose
5	1	*1h (±5 min) hour post dose
6	1	*Pre-dose
6	1	*1h (±5 min) hour post dose
EoT	-	Anytime
Unscheduled	-	Anytime
*ECGs Performed in triplicate.		

[redacted]

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

7.2.2.6.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

MUGA scan or echocardiogram (ECHO) will be used to assess LVEF at screening and during the treatment phase as clinically indicated to assess signs or symptoms of cardiotoxicity. In case of clinically significant abnormalities, they should be reported on the Adverse Events eCRF.

7.2.3 Pharmacokinetics

Not Applicable.

7.2.4 Biomarkers

Not Applicable.

7.2.4.1 Tumor Collection (Expansion Cohorts Only)

Not Applicable.

7.2.5 Resource utilization

Not applicable.

7.2.6 Patient reported outcomes

Not applicable.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant,

require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page. Adverse event monitoring should be continued for at least 150 days following the last dose of study treatment. After initiation of new post-treatment antineoplastic therapy, only AEs suspected to be related to study treatment will be collected in the Adverse Events CRF. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected through a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- The severity grade (CTCAE Grade 1-4)
- Its duration (Start and end dates)
- Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

[redacted]

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (RECIST or as per guidelines for hematological malignancies), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect

[redacted]

- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,

Note that hospitalizations for the following reasons should not be reported as serious adverse events:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 SAE Reporting

For patients who sign the study ICF, SAE collection will start upon signing whether the patient is a screen failure or not.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 150 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. If a patient starts a post treatment antineoplastic therapy, then only SAEs suspected to be related to study treatment will be reported.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 150 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site

Follow-up information is submitted in the same way as the original SAE . Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event

[redacted]

regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure and is thought to be related to the Novartis study treatment, an oncology Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

[redacted]

8.7 Steering Committee

Not applicable.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol, to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

[redacted]

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

[redacted] ECG data collected during the study will be reviewed and processed locally. Designated investigational site staff will enter the information required by the protocol into the appropriate eCRF and/or designated laboratory requisition forms. Field monitors will review the eCRFs and laboratory paper requisition forms for accuracy and completeness and instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to analytical laboratory with the respective sample(s) by the designated investigational site staff; and one copy will be retained at the investigational site.

9.4 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

[redacted]

[redacted]

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

All data will be analyzed by a designated CRO in collaboration with Novartis. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation. The data from all centers that participate in this study will be combined in the final safety and efficacy analysis.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) will include all patients who have received at least one dose of study drug.

FAS will be used for the analysis of efficacy endpoints.

10.1.2 Safety set

The Safety Set will include all patients who received at least one dose of study treatment and had at least one post-baseline safety assessment.

Please note: the statement that a patient had no adverse event (on the Adverse Event eCRF) constitutes a safety assessment.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be listed and summarized for all patients using the FAS. Categorical data, such as gender, race, etc., will be presented by frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical at baseline will be summarized for all enrolled patients.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study medication

Duration of study treatment exposure, cumulative dose and dose intensity will be summarized by the patient cohorts as above using the Safety Set. The number of patients with dose changes/interruptions will be presented along with reasons for the dose change/interruption. The safety set will be used for the tables and listings.

[redacted]

10.3.1 Concomitant therapies

Concomitant medications and significant non-drug therapies taken concurrently with the study drugs will be listed and summarized for the FAS by Anatomical Therapeutic Chemical Classification System (ATC) term, preferred term and treatment arm by means of frequency counts and percentages. These summaries will include medications starting on or after the start of study treatment (defined as cycle 1 day 1) or medications starting prior to the start of study treatment and continuing after the start of study treatment.

Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed. The safety set will be used for all above mentioned concomitant medication tables and listings.

10.4 Primary objective

The primary objective is to assess the clinical benefit of treatment with PDR001 + LAG525 at 24 weeks of treatment based on local investigator assessment.

For patients with solid tumors, the assessment criteria will be RECIST 1.1 and will include responses of CR or PR or SD. For lymphoma the Revised Response Criteria for Malignant Lymphoma (Cheson et al 2007) criteria will apply. Response criteria are included in the appendices.

For solid tumors, an assessment of CR or PR using RECIST 1.1 must be confirmed at least 4 weeks after initial observation. If the two assessments differ, the best overall response will be determined by Table 14-3 of Appendix 1.

For efficacy parameters, data will be listed, summarized, or analyzed by tumor cohort.

10.4.1 Variable

The primary efficacy variable is the clinical benefit rate (CBR) (e.g. defined as CR, PR or SD) at week 24 by RECIST 1.1 for solid tumors and the Revised Response Criteria for Malignant Lymphoma, (Cheson et al 2007), for Lymphoma.

10.4.2 Statistical hypothesis, model, and method of analysis

The study will enroll patients from 7 tumor cohorts.

These seven pre-specified tumor cohorts (also referred to as “groups”) are:

Group	Malignancy
1	Small cell lung cancer
2	Gastric/esophageal adenocarcinoma
3	Castration resistant prostate adenocarcinoma (CRPC)
4	Soft tissue sarcoma
5	Ovarian adenocarcinoma
6	Advanced well-differentiated neuroendocrine tumors*
7	Diffuse large B cell lymphoma (DLBCL)*

[redacted]

We let Y_i be the response indicator for the i^{th} subject, and let R_g be the assumed probability of response within a control population and $\pi_g = \Pr(Y_i = 1 \mid g_i = g)$ be the underlying probability of response for group g within the trial. We transform to the logit scale for modeling purposes. Let θ_g be the mean log odds treatment effect, i.e.:

$$\theta_g = \log\left(\frac{\pi_g}{1-\pi_g}\right) - \log\left(\frac{R_g}{1-R_g}\right)$$

Thus, θ_g is the group specific logistic regression coefficient for group g. The primary analysis is a set of group specific tests that $\theta_g>0$, meaning that the treatment is better than the assumed control rate for that group. Thus, we wish to test the set of hypotheses

$$H_{0g} : \theta_g \leq 0$$

$$H_{1g} : \theta_g > 0$$

We proceed in a Bayesian fashion, assigning a prior distribution (discussed below) and computing the posterior probability of H_{1g} within each group g. If, at the final analysis,

$$\Pr(\theta_g>0 \mid \text{data}) > 0.80$$

then group g will be declared a success. Hence, the final analysis produces a separate decision for each group. The trial allows for early stopping of groups for futility, described below. No early stopping for success is allowed.

The statistical design borrows information across subgroups with a hierarchical model. The hierarchical model allows dynamic borrowing of information between groups such that more borrowing occurs when the groups are consistent and less borrowing occurs when the groups differ. In this way, the model is a compromise between the extremes of a completely pooled analysis as opposed to a separate analysis in each group. We additionally incorporate a clustering mechanism that allows borrowing within clusters but treats clusters separately. This minimizes borrowing across groups that are quite different in terms of CBR effects.

The hierarchical model approach involves two stages. The goal of both stages is to allow the data to drive the amount of borrowing across groups. If the data indicate a large amount of borrowing is appropriate (due to similar results), the model will borrow more and thus increase the overall power of the trial within each group. In contrast, if the data indicate a small amount of borrowing is appropriate (due to dissimilar results) the model will adjust and each group will stand more on its own. This “dynamic” borrowing property is distinct from other approaches which use a fixed informative prior or apriori assume an amount of borrowing across groups. Here the approach includes two stages to identify the appropriate amount of borrowing based on the data.

The first stage of model places the groups into distinct clusters. The purpose of this stage is to minimize borrowing of information across groups that appear to be quite different. Thus, for example, should 2 of the groups appear similar while the others differ significantly, the model may place a large probability on two clusters, one containing the two similar groups with the

[redacted]

other containing the remaining groups. The model does not pick one particular clustering, but instead incorporates the uncertainty of the data in this determination, producing a probability distribution over the possible clustering. Thus, in our example, the model may consider it highly likely that the 2 similar groups are in one cluster with the remaining groups in another, but it would also retain lower probabilities on the possibility all groups are in one cluster (e.g. we are simply seeing differences in the two groups by chance) as well as other possibilities. The complete analysis averages over this uncertainty.

At the second stage, we place hierarchical models over the groups within each cluster (thus, conditional on the clustering, there is no borrowing of information across clusters, only within clusters). The hierarchical model assumes that the θ_g have an across groups distribution

$$\theta_g \sim N(\mu, \tau^2)$$

The across group mean μ and variance τ^2 are unknown, and hence have a prior distribution which is combined with the data to produce estimates of μ and τ^2.

The variance component τ controls the degree of borrowing among groups. Small values of τ result in a greater degree of borrowing while large values of τ correspond to less borrowing. The parameter τ is estimated using the data, so the observed between group variation is a key component of the model behavior.

Combined, the two stages allow groups with similar results to borrow information between them (they will have a high probability of being in the same cluster) while groups with different results with borrow far less information between them (they will have a low probability of being in the same cluster).

Details of the hierarchical model is provided in Appendix 4.

10.4.3 Evaluation of trial success and futility

Interim monitoring will occur once 5 subjects have CBR data available within a cohort. Interim analyses will continue every 3 months thereafter provided at least 10 subjects contribute new CBR data to the subsequent interim. Simulation studies in this document approximate this interim plan, as they are timed 12 weeks apart without any restrictions on the number of new observations within the analysis.

At each interim analysis, the groups will be evaluated for early futility and sample size expansion by comparing posterior quantities for the CBR to pre-specified early stopping criteria.

Table 10-1 Historical CBR for each group

Group Index	Tumor Type	Median PFS (mo.)	Hist. CBR (%)	Hypothetical Yearly Average Accrual (Subjects)
1	SCLC	1.5	6.25	20
2	Gastroesophageal	5	43.50	16
3	STS	6.2	51.10	13
4	Prostate	4	35.40	11
5	Ovarian	3	25.00	10

[redacted]

6	Advanced NET	5	43.50	7
7	DLBCL	3	25.00	6

Early Futility

If there is less than 20% probability that the response rate in a subgroup exceeds the historical rate R_g, then the group will stop enrollment early for futility. Formally, enrollment will stop early for futility if:

$$\Pr(\pi_g > R_g) < 0.20.$$

A group is only eligible for early stopping once a minimum of 5 patients have been evaluated for response in that group.

Early Success

If there is at least 70% probability that the response rate in a subgroup exceeds the historical rate, then the subgroup will stop enrollment early for success. Formally, enrollment will stop early for success if:

$$\Pr(\pi_g > R_g) > 0.70.$$

A minimum of 5 subjects will need to be evaluated prior to declaring a group to be efficacious. This eligibility remains effective until the next interim analysis is conducted, at which point eligibility is re-evaluated based on the currently available data and corresponding model outcomes.

Post-Expansion Futility

If there is less than a 60% probability that the clinical benefit rate in a group exceeds the historical rate, then the group will stop enrollment early for futility. Formally, enrollment will stop early for futility if:

$$\Pr(\pi g > Rg) < 0.60.$$

A group is only eligible for this post-expansion stopping criterion once the group has expanded to a sample size beyond 10 subjects enrolled. Note this post-expansion futility is a stricter futility rule than that used prior to sample size expansion.

Final Analysis

The final analysis will occur when both accrual and follow-up are complete for all groups. If, at the completion of the trial, there is at least 80% probability that the response rate in a group exceeds the historical rate, then the group will be considered a success. Formally:

$$\Pr(\pi_g > R_g) > 0.80.$$

10.4.4 Handling of missing values/censoring/discontinuations

A patient who has not progressed or died at the date of the analysis cut-off would have his/her PFS and OS censored at the time of the last adequate assessment before the cut-off date. Any

[redacted]

disease assessment indicating response status other than "unknown" or "not done" is considered an adequate response assessment.

10.4.5 Supportive and Sensitivity analyses

Not Applicable.

10.5 Secondary objectives

10.5.1 Secondary efficacy objectives

Tumor response will be determined per local investigators' assessment, according both RECIST 1.1 and the Revised Response Criteria for Malignant Lymphoma, (Cheson et al 2007). Response related efficacy assessments will be defined and analyzed based on both RECIST 1.1 and the Revised Response Criteria for Malignant Lymphoma, (Cheson et al 2007).

For all efficacy parameters, data will be listed, summarized, or analyzed by tumor group.

The secondary objectives of the study:

- To assess Overall Response (OR) of Partial Response (PR) or Complete Response (CR) based on local investigator assessment. For patients with solid tumors the assessment criteria will be RECIST 1.1 and will include responses of CR and/or PR. For lymphoma the Revised Response Criteria for Malignant Lymphoma (Cheson et al 2007) criteria will apply. Response criteria are included in the appendices. The overall response rate (ORR, PR plus CR) and its 95% exact confidence interval will be provided for each patient group. In the event where sample size in each patient group is small (<10), only ORR summary for entire study cohort will be presented
- To assess the following, based on local investigator assessment per RECIST 1.1 for solid tumors, or the Revised Response Criteria for Malignant Lymphoma (Cheson et al 2007) for lymphoma:
  - Time to Progression (TTP)
  - Time to Response (TTR)
  - Progression Free Survival (PFS)
  - Duration of Response (DOR)
- To assess safety and tolerability.

Time to progression (TTP) is defined as the time from the date of first dose to the date of first documented disease progression or relapse. Time to response (TTR) is defined as the time from the date of first dose to the date of first documented response of CR or PR. The secondary efficacy variable progression free survival (PFS) is defined as the time from the date of first dose to the date of first documented disease progression or relapse or death due to any cause during study medication or within 150 days from last dosing date.

PFS, TTP and TTR will be summarized and graphed using the Kaplan-Meier product-limit method for each patient group. Patients who drop-out without progression will be censored at

the time of last adequate assessment. The estimates of the 25th, median, 75th percentiles of the PFS and their 95% confidence intervals will be provided, if applicable.

The duration of response (DOR) applies only to patients whose best response was PR or CR. For patients with solid tumors the assessment criteria will be RECIST 1.1 and will include responses of CR and/or PR. For lymphoma the Revised Response Criteria for Malignant Lymphoma (Cheson et al 2007) will apply. The duration of response is defined as the time from the first documented response to the date first documented disease progression or relapse or death due to any cause. The duration of response will be summarized descriptively for each patient group.

10.5.2 Safety objectives

For all safety analyses, the safety set will be used. All listings and tables will be presented by patient groups.

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., electrocardiogram, vital signs) will be considered as appropriate. All safety data will be listed.

The safety summary tables will include only assessments collected no later than 150 days after study treatment discontinuation. Those collected later than 150 days after study treatment discontinuation will be flagged in listings.

10.5.2.1 Analysis set and grouping for the analyses

10.5.2.1.1 Adverse events (AEs)

All adverse events recorded during the study will be summarized. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, maximum severity (based on CTCAE v4.03), type of adverse event, relationship to the study treatment by tumor cohort. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and patient group.

Adverse events will be summarized by presenting the number and percentage of patients by system organ class and/or preferred term, the maximum severity (based on CTCAE v4.03) and treatment arm. Adverse events related to study treatment will also be summarized. In addition, adverse events of related nature may be analyzed by categories regrouping the relevant preferred terms, as appropriate.

10.5.2.1.2 Laboratory abnormalities

All laboratory values will be converted into SI units and the severity grade will be calculated using appropriate common terminology criteria (CTCAE v4.03).

A severity grade of 0 will be assigned when the value is within normal limits. For lab parameters for which severity grades are determined both through normal limits and absolute cut-offs, in the unlikely case when a local laboratory normal range overlaps into the higher (i.e. non-zero)

[redacted]

CTCAE grade, the laboratory value will still be taken as within normal limits and assigned a CTCAE grade of zero.

A listing of laboratory values will be provided by laboratory parameter, patient, and treatment arm. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory toxicities). Lab values collected later than 150 days after study treatment discontinuation will be flagged in the listings

The following by-group summaries will be generated separately for hematology, and biochemistry parameters:

- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

10.5.2.1.3 Other safety data

Summary statistics for data from other tests will be provided, notable values will be flagged, and any other information collected will be listed as appropriate.

Descriptive summary statistics will be provided for :

- Electrocardiograms: changes from baseline to last available ECG results
- Cardiac imaging: number and percentage of patients with notable LVEF values
- Vital signs: number and percentage of patients with at least one post-baseline vital sign abnormality
- ECOG performance status: shift table comparing baseline to worst post baseline ECOG performance status.
- All other safety related procedures as required
- Listings with flagged notable values and any other information collected will be provided as appropriate.

10.6 Exploratory objectives

Not applicable.

10.7 Interim analysis

Scheduled interim data reviews will occur for the primary endpoint of clinical benefit rate only as required by the Bayesian Hierarchical design. The first interim data review will be performed after the 5 subjects have CBR data available within a cohort. Interim analyses will continue every 3 months thereafter provided at least 10 subjects contribute new CBR data to the subsequent interim. At each interim analysis, the tumor cohorts will be evaluated for early

[redacted]

futility and early success by comparing posterior quantities for the response rate to pre-specified early stopping criteria.

There is no plan for a formal interim analysis of safety or other secondary endpoints for this study. However, for publication or other purposes, interim data review of clean data will be performed as necessary. At these interim reviews, patient demographics/baseline characteristics, the primary and secondary endpoints as applicable, and all important safety endpoints will be summarized. No formal report will be issued for these data reviews.

10.8 Sample size calculation

The sample size was chosen by the usual criteria of obtaining adequate power for the alternative hypothesis of interest as given in Sections 6.2.3 and 6.2.2 of Appendix 4. This hypothesis corresponds to a generally effective treatment across cohorts and incorporates variation in treatment effects to reflect the realistic expectation that treatment effects may differ by cohort. In this setting, analytical power calculations are not possible, but the design was simulated to obtain the power of the study as shown in the appendix. The sample sizes shown (minimum of 5 for futility stopping, minimum of 10 for early success and maximum of 24 as a cohort cap) achieve adequate power for the alternative hypothesis. The simulations included the expected variable accrual by simulating a Poisson process with expected accrual also shown in the appendix.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent

[redacted]

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept

at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis

[redacted]

and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations but not later than 10 working days.

[redacted]

13 References (available upon request)

Antonia SJ et al., Phase I/II study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032. J Clin Oncol 33, 2015 (suppl; abstr 7503)

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[redacted]

14 Appendices

14.1 Appendix 1: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival and Overall Survival (based on RECIST 1.1)

Harmonization of Efficacy Analysis of Solid Tumor Studies

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[redacted]

Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
GBM	Glioblastoma multiform
MRI	Magnetic resonance imaging
LPLV	Last patient last visit
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

[redacted]

14.1.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 14.1.2 and the definition of best response in Section 14.1.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.1.18 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 14.1.28 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

14.1.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

14.1.3 Definitions

14.1.4 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

Measurable disease - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 14.1.26.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.

[redacted]

- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- **Cystic lesions**:
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) 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.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonic, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

14.1.5 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 14.1.26.

14.1.6 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

[redacted]

- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

[redacted]

- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytological confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytological examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

14.1.7 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions**: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 14.1.4.
- **Nodal target**: See Section 14.1.4.

[redacted]

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

14.1.8 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment, response is evaluated first separately for the target (Table 14-1) and non-target lesions (Table 14-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-3) as well as the presence or absence of new lesions.

14.1.9 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

14.1.10 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial “partial volume” effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

[redacted]

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

14.1.11 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a "non-zero size" will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

14.1.12 Determination of target lesion response

Table 14-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm[2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

[1]. SOD for CR may not be zero when nodal lesions are part of target lesions
[2]. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
[3]. Methodology change See Section 14.1.6.

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to

[redacted]

change the 0 value, then the investigator/radiologist has to decide between the following three possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- **Missing measurements**: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- **Nodal lesion decrease to normal size**: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split**: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced**: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.

[redacted]

- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
  - Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
  - Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
  - Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

14.1.13 Determination of non-target lesion response

Table 14-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

[1]. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- **Unequivocal progression**: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD 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 CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the

[redacted]

extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.1.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.1.14 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- 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 first observation of the lesion.
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 14.1.15).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.1.6.

14.1.15 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 14-3.

Table 14-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[redacted]

[1]. This overall lesion response also applies when there are no non-target lesions identified at baseline.
[2]. Once confirmed PR was achieved, all these assessments are considered PR.
[3]. As defined in Section 14.1.8.

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

14.1.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.1.26 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.1.17 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- For non-randomized trials where response is the primary endpoint, confirmation is needed.
- For trials intended to support accelerated approval, confirmation is needed

[redacted]

- For all other trials, confirmation of response may be considered optional.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

[redacted]

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The time point for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

14.1.18 Time to event variables

14.1.19 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that

[redacted]

randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

14.1.20 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

14.1.21 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

14.1.22 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

14.1.23 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of

[redacted]

response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988).

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

14.1.24 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred, a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.1.23. It is recommended

[redacted]

that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

14.1.25 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

Start dates

For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.

[redacted]

- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.1.26).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

14.1.26 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-4.

Table 14-4 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD

[redacted]

Non-target lesions	New Lesions	Overall lesion response
Any	Yes	PD

[1] As defined in Section 14.1.8.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

14.1.27 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 14.1.25, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 14-5 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed

[redacted]

Situation		Options for end-date (progression or censoring)[1] **(1) = default unless specified differently in the protocol or RAP**	Outcome
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

[1].=Definitions can be found in Section 14.1.25
[2].=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.25.
[3].=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

[redacted]

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

14.1.28 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

14.1.29 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

14.1.30 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy

[redacted]

- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol

14.1.31 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

14.1.32 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response

[redacted]

at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

14.1.33 Programming rules

The following should be used for programming of efficacy results:

14.1.34 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

14.1.35 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 14.1.25). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

14.1.36 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

14.1.37 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

14.1.38 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

[redacted]

14.1.39 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 14-5)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 14.1.25. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

14.1.40 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791

Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, Vol.45: 228-47

Ellis S, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials 2008; 29: 456-465

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FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005

FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont. Clin Trials; 9: 11-18

Therasse P, Arbuck S, Eisenhauer E, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16

[redacted]

14.2 Appendix 2: Revised Response Criteria for Malignant Lymphoma, therapeutic response/outcome assessment in lymphoma studies (based on Cheson response criteria 2007)

[redacted]

List of Abbreviations

CMR	Complete metabolic response
CR	Complete response
CT	Computed tomography
DLBCL	Diffuse large B cell lymphoma
FDG	Fluorodeoxyglucose
FL	Follicular lymphoma
LDi	Longest transverse diameter of a lesion
MRI	Magnetic resonance imaging
NMR	No metabolic response
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PMD	Progressive metabolic disease
PMR	Partial metabolic response
PR	Partial response
PPD	Product of the Perpendicular Diameters
SD	Stable disease
SDi	Shortest axis perpendicular to LDi
SPD	Sum of the product of the perpendicular diameters for multiple lesions
SUV	Standard Uptake Value
5PS	PET Five Point Scale

Disease assessments will be based on the International Working Group response criteria (Cheson 1999), and the International Harmonization Project revised response criteria (Cheson et al 2007b). Further clarification on these criteria has been published by (Cheson 2007a).

1 Definitions and criteria for normalization

a. Definitions

i. Nodal vs extranodal lesion

A lesion is categorized based on the location as:

- **Nodal lesion**,
- **Extranodal lesion**, if it is located in organs other than lymph node or nodal mass, but including spleen and liver.

2 Measurability of Tumor Lesions at Baseline

All tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

a. Measurable Nodal and extranodal lesions

A lesion will be called **measurable** if it can be measured accurately in 2 perpendicular dimensions and:

[redacted]

- For nodal lesion, if the long axis is > 15 mm, regardless of the length of the short axis,
- For extranodal lesion, if the long and short axes are ≥ 10 mm.

Patients should have **at least one measurable nodal lesion greater than 20 mm** in the long axis.

In cases where the patient has no measurable nodal lesions greater than 20 mm in the long axis at Screening, then the patient must have at least one measurable extranodal lesion

b. Classification of lymph nodes

Lymph nodes are classified according to their size and/or relationship to the disease:

- A lymph node meeting the measurability requirement above will constitute a **measurable nodal lesion**.
- A lymph node not meeting the measurability requirement but with long axis ≥15 mm (e.g. short axis cannot be measured accurately) will constitute a **non-measurable nodal lesion**.
- A lymph node not meeting the measurability criteria but with a size of 11 mm to 15 mm in the long axis and ≥ 10 mm in the short axis will be checked for relationship to disease:
  - If it is thought to be disease related, it will constitute a **non-measurable nodal lesion**
  - If it is not thought to be disease related, it will constitute an **abnormal lymph node** but not a lesion.
- All other lymph nodes will be considered normal and will not constitute nodal lesions.

c. Criteria for normalization of lesions

The normalization of lesions is defined as follow:

- A measurable nodal lesion must become ≤ 15 mm in long axis to be considered normalized.
- A non-measurable nodal lesion must decrease to ≤ 10 mm in the short axis and be ≤ 15 mm in long axis to be considered normalized.
- An extranodal lesion must disappear completely (assigned a size of 0 mm x 0 mm) to be considered normalized.

3 Specification by methods of measurement

a. Measurement of lesions

All radiological measurements should be taken in two perpendicular dimensions and recorded in metric notation, using a ruler or calipers.

i. PET

Visual assessment currently is considered adequate for determining whether a PET scan is positive, and use of the standardized uptake value is not necessary.[1] In brief, a positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with

[redacted]

normal anatomy or physiology, without a specific standardized uptake value cutoff.[1] Other causes of false-positive scans should be ruled out. Exceptions include mild and diffusely increased FDG uptake at the site of moderate- or large-sized masses with an intensity that is lower than or equal to the mediastinal blood pool, hepatic or splenic nodules 1.5 cm with FDG uptake lower than the surrounding liver/spleen

ii. CT scan (or MRI)

For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at Screening and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If at Screening a patient is known to be allergic to CT contrast or develops allergy during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in an "Unknown" overall radiological response assessment. However, another overall radiological response than the Novartis calculated "Unknown" response may be accepted from the investigator if a definitive overall radiological response can be justified to be based on the available information.

In order to calculate the sum of the product of the diameters (SPD) of all index lesions (or extranodal lesions), their size must be entered throughout the study.

Actual lesion measurements should be entered on the corresponding eCRFs. If, during the course of the study, either of the perpendicular diameters of a lesion cannot be reliably measured because of its small size, it is recommended to enter the minimum limit of detection as the diameter size (e.g. 5 mm for spiral CT). In other cases when, during the course of the study, the diameter cannot be reliably measured for reasons other than its size (i.e. borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

If lesions become confluent over time, it is recommended to measure them as one lesion, report the overall diameters to one of the lesions and assign 0 mm x 0 mm to each of the other previously measured lesions. If a lesion splits during the study, each sub-lesion should be measured separately for all subsequent assessments and all sub-lesions contribute to the SPD.

iii. Bone marrow assessment

Documentation of status of bone marrow involvement by lymphoma based on prior bone marrow biopsy or aspirate findings is required at Screening for all patients.

[redacted]

If no such documentation is available then a bone marrow biopsy or aspirate should be performed at Screening.

If bone marrow involvement is assessed by biopsy, the biopsy sample should have a goal of > 20 mm unilateral core. If the biopsy sample is indeterminate by morphology (immunohistochemistry), then flow cytometry may be performed on bone marrow aspirate to confirm the findings.

iv. Physical examination and assessment of B-symptoms

Skin lesions, if the size is ≥ 20 mm in at least one diameter, must be histologically confirmed for lymphoma involvement (the investigational site must document the histological confirmation (yes or no) on the corresponding eCRF) and photographed including a ruler (color photography using digital camera). Tumor assessment will be performed and results will be recorded on the corresponding eCRF at Screening and at Day 1 of every cycle (±4 days) after first dose of study drug.

B-symptoms are of importance in determining prognosis and should resolve completely in patients who have achieved complete response. B-symptoms in lymphoma patients are disease related clinical symptoms and are not caused by anticancer therapy (or drug toxicity).

B-symptoms are defined as follows:

- Significant unexplained fever (≥ 38°C),
- Unexplained, recurrent drenching night sweats
- Unexplained loss of > 10% body weight within the previous 6 months, as assessed and reported (present vs. absent) by the Investigator.

4. Evaluation of Radiological Response

For the sake of simplicity, complete remission and complete response will both be referred to as complete response.

Definitions of Response for Lymphoma patients are listed in Table 4-1. To evaluate disease response to treatment, all index and non-index lesions will be followed and assessed throughout the study. At each assessment, response is evaluated separately for the **index lesions** (Table 4-1) and **non-index lesions** (Table 4-2) identified at Screening, then a combined overall radiological response is determined (Table 4-3).

Table 4-1 Response Definition for Lymphoma

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	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative

[redacted]

Response	Definition	Nodal Masses	Spleen. Liver	Bone Marrow
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 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	≥ 50% decrease in SPD of nodules (for single nodule in 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 a 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

a. Evaluation of Index Lesions (nodal and extranodal)

i. When index nodal lesions are not in complete response

The response for index lesions is evaluated by calculating the Sum of the Products of Diameters (SPD) of all index lesions (see Table 4-2), except when there is a Complete Response for index nodal lesions (i.e. complete normalization of all index nodal lesions) (see Section ii.).

Table 4-2 Radiological status based on SPD calculation for all index lesions

Response Criteria[1]	Evaluation of index lesions
Complete Response (CR)	See Table 4-4 below (not based on SPD calculation for all index lesions)
Partial Response (PR)	At least 50% decrease from Screening in the SPD of all index lesions
Stable Disease (SD)	Failure to attain the criteria needed for CR or PR and failure to fulfill the criteria for PD
Progressive Disease (PD)	At least a 50% increase from nadir[2] in the SPD of all index lesions

[1] At each assessment (if the index nodal lesions are not in CR status), the response status based on SPD calculation will be first assessed for meeting PD status criteria, then PR status and SD status.

[2] Nadir is defined as the smallest sum of the product of the diameters of all index lesions recorded so far, at or after Screening.

[redacted]

ii. When index nodal lesions are in complete response

When there is a Complete Response for index nodal lesions (i.e. complete normalization of all index nodal lesions as defined in Section v.: all index lesion ≤ 15 mm in long axis), the SPD for these index nodal lesions may not be equal to zero and therefore a calculation of a SPD for all index lesions may be misleading. Therefore, by default, a specific response for extranodal index lesions needs to be evaluated, based on the SPD calculation restricted to all index extranodal lesions only (see Table 4-3).

Table 4-3 Radiological response criteria for index extranodal lesions in case of CR in index nodal lesions

Response Criteria[1]	Evaluation of index extranodal lesions
Complete Response (CR)	Complete disappearance of all index extranodal lesions
Partial Response (PR)	At least 50% decrease from Screening in the SPD restricted to all index extranodal lesions
Stable Disease (SD)	Failure to attain the criteria needed for CR or PR and failure to fulfill the criteria for PD
Progressive Disease (PD)	At least a 50% increase from nadir[2] in the SPD restricted to all index extranodal lesions

[1] At each assessment, response will be first assessed for meeting CR status. If CR status is not met, response will be assessed for PD status, then PR status and SD status.
[2] Nadir is defined as the smallest sum of the product of the diameters restricted to all index extranodal lesions recorded so far, at or after Screening.

The algorithm for evaluating the response integrating index extranodal lesions and the SPD calculated on all index lesions (where appropriate) provides an overall response for index lesions.

iii. Evaluation of response for all index lesions

The evaluation of response for all index lesions is based on the combination of the response for index nodal lesions (CR or non-CR), the response for index extranodal and the status based on the SPD calculated on all index lesions (nodal and extranodal), as described in Table 4-4.

Table 4-4 Radiological response for index lesions

Response for index nodal lesions[1]	Response for index extranodal lesions[1]	Status based on SPD calculation for all index lesions	Response for index lesions
CR	CR	Not calculated	CR
CR	SD/ PR	Not calculated	PR
CR	PD	PD	PD
CR	PD	PR	PR
CR	PD	SD	SD
Non-CR	Not evaluated	PD	PD
Non-CR	Not evaluated	PR	PR
Non-CR	Not evaluated	SD	SD

[redacted]

Response for index nodal lesions[1]	Response for index extranodal lesions[1]	Status based on SPD calculation for all index lesions	Response for index lesions

[1] If no index nodal lesions are present at Screening, then index lesions response is equal to the index extranodal lesions response. A similar rule applied if no index extranodal lesions are present at Screening, then index lesions response is equal to the index nodal lesions response.

In case of missing measurements of any of the index lesions, the radiological response for index lesions at that assessment will be "Unknown (UNK)", unless progression was seen.

All lesions must have been measured with the same method as the one used at Screening, otherwise the radiological response for index lesions at that assessment will be "Unknown (UNK)".

iv. Evaluation of non-index lesions (including nodal, splenic and/or hepatic nodules and other extranodal lesions)

At each reassessment, a non-index lesion (or a group of non-index lesions) will be given one of the following designations:

- Normalization (non-index nodal lesion has regressed to normal size; non-index extranodal lesion is no longer present). Normalization of non-index nodal lesions should be determined based on their size at Screening.
- Improved, stable or worsened, but without unequivocal evidence of disease progression (non-index lesion is present but there is not sufficient worsening to declare PD based on the existing non-index lesions).
- Unequivocal evidence of disease progression (worsening of existing non-index lesions is sufficient to declare PD)
- Not assessed

Then, this status for each non-index lesion (or group of non-index lesions) will lead to a global response for non-index lesions (Table 4-5):

Table 4-5 Response criteria for non-index lesions (nodal, splenic and/or hepatic nodules and other extranodal lesions)

Response Criteria	Evaluation of non-index lesions
Complete Response (CR)	Complete normalization of all non-index nodal and extranodal lesions: Radiological regression to normal size of all lymph nodes and complete disappearance of all extranodal (including splenic and/or hepatic nodules) lesions
Stable Disease (SD)	Failure to attain the criteria needed for CR and failure to fulfill the criteria for PD
Progressive Disease (PD)	Unequivocal disease progression of any existing non-index lesions (nodal or extranodal)

In case of a missing status of any of the non-index lesions, the radiological response for non-index lesions at that assessment will be "Unknown (UNK)", unless progression was seen.

All lesions must have been measured with the same method as the one used at Screening, otherwise the radiological response for non-index lesions at that assessment will be "Unknown (UNK)".

[redacted]

v. New lesions

The appearance of

- any new nodal lesion ≥15 mm in any axis. New nodal lesion is defined by:
  - either a previously normal lymph node becoming > 15 mm in any axis,
  - or a previously identified abnormal lymph node showing an increase of at least 50% in the long axis,
  - as assessed by investigator

OR

- any discrete extranodal (including splenic and/or hepatic nodules) lesions reliably appearing on CT scan or MRI after Screening

is always considered as Progressive Disease (PD) and has to be recorded as a new lesion in the appropriate module of the eCRF. Determination of new lymphoma involvement in organs other than lymph nodes or liver or spleen should be confirmed histologically and the site must document that in a comment to the corresponding eCRF.

vi. Overall radiological response

Overall radiological response is calculated as shown in Table 4-6.

Table 4-6 Overall radiological response at each assessment

Index lesions	Non-index lesions[1]	New lesions	Overall radiological response
CR	CR	No	CR
CR	SD	No	PR
PR	CR or SD	No	PR
SD	CR or SD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1]If no non-index lesions are present at Screening, then this column is not used in evaluating overall radiological response.

If the evaluation of any of the index or non-index lesions identified at Screening could not be made during follow-up or if the index or non-index response is "Unknown (UNK)", the overall response status at that assessment must be "Unknown (UNK)" unless progression or a new lesion was seen.

vii. Evaluation of overall disease response

The evaluation of overall disease response at each assessment is a composite of the individual radiological responses (index and non-index lesions, new lesions), laboratory test (bone marrow) and clinical responses (lymphoma related clinical symptoms).

[redacted]

viii. Bone marrow re-assessment at time of radiological CR

In order to confirm a Complete disease response (CR), bone marrow biopsy or aspirate may be required when a radiological CR has been achieved. Details are provided in the Study Protocol. The infiltrate of lymphoma in bone marrow must have cleared on repeat bone marrow biopsy or aspirate. Patients who achieve a CR by other criteria but who have persistent morphologic positive or inconclusive bone marrow involvement will be considered partial responders. New or recurrent bone marrow involvement anytime during the follow up will be considered PD. Bone marrow biopsy or aspirate will be performed after the first assessment of CR or when clinically indicated.

The biopsy sample of bone marrow must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry.

ix. Overall disease response

If a patient has an overall radiological response of CR then this response must be confirmed by bone marrow biopsy or aspirate (if required as per the Study Protocol), presence of normal liver and spleen size, and evaluation of lymphoma related B-symptoms. The patient's overall response will be calculated as follows:

A patient will be deemed to have overall disease response of CR if bone marrow biopsy or aspirate becomes negative for tumor involvement (if the bone marrow was involved by lymphoma at Screening) and the liver and spleen are normal in size and there are no lymphoma related B-symptoms in addition to radiological CR.

If assessments of any of the following: lymphomatous infiltration of bone marrow (If required as per the Study Protocol), or evaluation of B-symptoms is not done, unknown or indeterminate or B-symptoms are still present when the overall radiological response is assessed as CR or the liver or spleen are enlarged, then the overall disease response will be assessed as PR until evaluation of these factors have shown normalized results and recorded on the corresponding eCRF.

For patients whose radiological response is anything other than CR, assessment of bone marrow, liver, spleen and B-symptoms will not be required in evaluating overall response and overall disease response is the same as radiological response. However any new or recurrent bone marrow involvement at any time during follow-up will be considered PD.

Of note, appearance of B-symptoms or enlarged spleen or liver will not in themselves constitute documentation of progression. They are however expected to be associated with progressive disease. Every effort should be made to document that evidence radiologically and report the corresponding tumor assessments. Such tumor assessments are expected to be performed within 2 months of appearance of B-symptoms or enlarged spleen or liver.

5. References (available upon request)

Cheson BD (2007a) The international harmonization project for response criteria in lymphoma clinical trials. Hematol Oncol Clin N Am 21:841-854.

[redacted]

Cheson BD (2009) The case against heavy PETing. J Clin Oncol 27:1742-1743.

Cheson BD, Horning SJ, Coiffier B, et al (1999) Report of an International Workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 17:1244-1253.

Cheson BD, Pfistner B, Juweid ME, et al (2007b) Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586.

FDA Guideline (2005) Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005.

[redacted]

14.3 Appendix 3: Eastern Cooperative Oncology Group (ECOG) performance status

Score	Performance status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

[redacted]

14.4 Appendix 4: Adaptive Basket Trial for Combination Immune-therapy in Patients with Advanced Solid and Lymphoma

1 Introduction

This document outlines the adaptive design framework to be used for a single-arm Phase II study for the investigation combination immune-therapy across multiple cancer subtypes.

Seven pre-specified tumor cohorts, (also referred to as "groups") are planned for the analysis:

- Small-cell lung cancer (SCLC)
- Soft tissue sarcoma (STS)
- Ovarian
- Diffuse large B-cell lymphoma (DLBCL)
- Gastroesophageal
- Prostate
- Advanced NET

The primary endpoint in each group is clinical benefit rate (CBR) assessed at 24 weeks. All patients will receive the experimental treatment.

The trial incorporates analyses based on a hierarchical model that allows for the possibility that the effect profile for the population of tumor types may be homogeneous or heterogeneous. There may be 'clusters' or subsets of tumor types – some in which the treatment is effective, and others not. The analysis borrows information, in a limited sense, from the tumor types that demonstrate similar CBR effects based on the trial data. The clustering used to characterize the distribution of tumor via a Dirichlet process prior (Escobar & West, 1995; Neal, 2000) is solely based on the observed CBRs. As described in Berry et al. [Berry, 2013], borrowing via a hierarchical model is a type of shrinkage estimation; it provides a formal mechanism by which extreme observations are shrunk toward the mean.

Prospectively, the model is developed by evaluating its performance from simulated trials. Hence, the false-positive rate can be controlled and power assessed. The advantages to borrowing are 1) increased precision of CBR estimates and 2) better decisions regarding CBRs.

2 Primary Analysis

We let Y_i be the response indicator for the i^{th} subject. We define $\pi_g = \Pr(Y_i = 1 \mid g_i = g)$ as the underlying probability of clinical benefit for group g for the experimental treatment and R_g as the assumed probability of clinical benefit for group g within the control population. We transform to the logit scale for modeling purposes. Let θ_g be the mean log odds treatment effect, i.e.:

$$\theta_g = \log\left(\frac{\pi_g}{1-\pi_g}\right) - \log\left(\frac{R_g}{1-R_g}\right).$$

Thus, θ_g is the logistic regression coefficient for the treatment within group g. The primary analysis is a set of group specific tests of $\theta_g > 0$, meaning that the treatment is better than the assumed control rate within that group. Thus, we wish to test the set of hypotheses

$$H_{0g} : \theta_g \leq 0,$$

$$H_{1g} : \theta_g > 0.$$

[redacted]

We proceed in a Bayesian fashion, assigning a prior distribution (discussed below) and computing the posterior probability of H_{1g} within each group g. If, at the final analysis,

$$\Pr(\theta_g>0 \mid \text{data}) > 0.80,$$

then group g will be declared a success. Hence, the final analysis produces a separate decision for each group. The trial allows for early stopping of groups for futility, described below. No early stopping for success is allowed.

3 Trial Logistics

For the primary population for which primary analyses, including the hierarchical modeling, will be conducted, the maximal sample size is 24 subjects per group. An additional 6 subjects per group may be enrolled in an exploratory population but will not be included in the primary analysis.

In simulations, interim analyses are conducted every 13 weeks, with the first interim analysis occurring once any group has 5 subjects with CBR data or 10 subjects are enrolled. In practice, interims will be spaced such that 3 months have elapsed since the previous interim AND at least 10 additional subjects contribute new CBR data to the next interim.

Interim decisions are driven by $\Pr(\theta_g>0 \mid \text{data})$, the probability that the treatment is better than control (this is the same probability that drives the final analysis).

At each interim, $\Pr(\theta_g>0 \mid \text{data})$ is computed for each group. If at any interim $\Pr(\theta_g>0 \mid \text{data})$ is too small (<0.20) the group is stopped for futility. To expand enrollment beyond 10 subjects, $\Pr(\theta_g>0 \mid \text{data})$ must be sufficiently large (>0.70) at the most recent interim. Note interims are not conducted at the time of enrolling the 11^{th} subject in a group, but rather the most recent interim results are used for expansion. If $\Pr(\theta_g>0 \mid \text{data})$ is not sufficiently large and 10 subjects are already enrolled in a group, the group will pause enrollment (it is not futile, simply not promising enough for more investigation). Should this probability reach the required level at a later interim analysis, enrollment may start again and the group sample size would then expand from 10 to 24 subjects. Once a group expands beyond 10 subjects, if at any future time $\Pr(\theta_g>0 \mid \text{data})$ shrinks sufficiently low (<0.60) the group is stopped for futility. Thus, should an expansion be started but the expansion data not be trending in the right direction (toward the needed 0.80 at the final analysis), the expansion will be halted. A minimum of 5 subjects with CBR data will be required in a group before it may discontinue enrollment for futility or expand from 10 to 24 subjects.

Enrollment will continue until no more subjects can be enrolled and all current subjects have completed 24 weeks of follow-up. This occurs when all groups have either stopped for futility, enrolled to 24 subjects, or enrolled to 10 subjects and are not expanding. The final analysis will occur once enrollment is complete and all subjects have been followed to their endpoint.

4 Statistical Modeling

We let Y_i be the response indicator for the i^{th} subject. We define $\pi_g = \Pr(Y_i = 1 \mid g_i = g)$ as the underlying probability of clinical benefit for group g for the experimental treatment and R_g as

[redacted]

the assumed probability of clinical benefit for group g within the control population. We transform to the logit scale for modeling purposes. Let θ_g be the mean log odds treatment effect, i.e.:

$$\theta_g = \log\left(\frac{\pi_g}{1-\pi_g}\right) - \log\left(\frac{R_g}{1-R_g}\right).$$

The statistical design borrows information across subgroups with a hierarchical model. The hierarchical model allows dynamic borrowing of information between groups such that more borrowing occurs when the groups are consistent and less borrowing occurs when the groups differ. In this way, the model is a compromise between the extremes of a completely pooled analysis as opposed to a separate analysis in each group. We additionally incorporate a clustering mechanism that allows borrowing within clusters but treats clusters separately. This minimizes borrowing across groups that are quite different in terms of CBR effects.

The purpose of such an analysis (discussed in more detail in the appendix) is to produce higher power or lower type I error in situations where we see some commonality (identical effects are not required) among the groups. The model will borrow more in situations where the groups appear similar than in situations where the groups appear different.

4.1 Hierarchical Model with Clustering

Our hierarchical approach involves two stages. The goal of both stages is to allow the data to drive the amount of borrowing across groups. If the data indicate a large amount of borrowing is appropriate (due to similar results), the model will borrow more and thus increase the overall power of the trial within each group. In contrast, if the data indicate a small amount of borrowing is appropriate (due to dissimilar results) the model will adjust and each group will stand more on its own. This "dynamic" borrowing property is distinct from other approaches which use a fixed informative prior or apriori assume an amount of borrowing across groups. Here the approach includes two stages to identify the appropriate amount of borrowing based on the data.

The first stage of model places the groups into distinct clusters. The purpose of this stage is to minimize borrowing of information across groups that appear to be quite different. Thus, for example, should 2 of the groups appear similar while the others differ significantly, the model may place a large probability on two clusters, one containing the two similar groups with the other containing the remaining groups. The model does not pick one particular clustering, but instead incorporates the uncertainty of the data in this determination, producing a probability distribution over the possible clusterings. Thus, in our example, the model may consider it highly likely that the 2 similar groups are in one cluster with the remaining groups in another, but it would also retain lower probabilities on the possibility all groups are in one cluster (e.g. we are simply seeing differences in the two groups by chance) as well as other possibilities. The complete analysis averages over this uncertainty. This clustering approach is implemented through a Dirichlet Process Mixture (DPM) model, described in the appendix.

At the second stage, we place hierarchical models over the groups within each cluster (thus, conditional on the clustering, there is no borrowing of information across clusters, only within clusters). The hierarchical model assumes that the θ_g have an across groups distribution

[redacted]

$$\theta_g \sim N(\mu, \tau^2)$$

The across groups mean μ and variance τ^2 are unknown, and hence have a prior distribution which is combined with the data to produce estimates of μ and τ^2.

The variance component τ controls the degree of borrowing among groups. Small values of τ result in a greater degree of borrowing while large values of τ correspond to less borrowing. The parameter τ is estimated using the data, so the observed between group variation is a key component of the model behavior.

Combined, the two stages allow groups with similar results to borrow information between them (they will have a high probability of being in the same cluster) while groups with different results with borrow far less information between them (they will have a low probability of being in the same cluster).

Details of the two stages may be found in the Appendix.

5 Evaluation of Trial Futility, Sample Size Expansion, and Success

Interim monitoring will occur once 5 subjects have CBR data available within a group or 10 subjects have been enrolled within a group. Interim analyses will continue every 3 months thereafter provided at least 10 subjects contribute new CBR data to the subsequent interim. Simulation studies in this document approximate this interim plan, as they are timed 13 weeks apart without any restrictions on the number of new observations within the analysis.

At each interim analysis, the groups will be evaluated for early futility and sample size expansion by comparing posterior quantities for the CBR to pre-specified early stopping criteria.

5.1 Early Futility

If there is less than 20% probability that the clinical benefit rate in a group exceeds the historical rate R_g, then the group will stop enrollment early for futility. Formally, enrollment will stop early for futility if:

$$\Pr(\pi_g > R_g) < 0.20.$$

A group is only eligible for early stopping once a minimum of 5 subjects has been evaluated for response in that group.

5.2 Sample Size Expansion

If there is at least 70% probability that the clinical benefit rate in a group exceeds the historical rate, then the group is eligible to expand its overall sample size from 10 to 24 subjects. Formally, a group is eligible to expand if, at the last conducted interim:

$$\Pr(\pi_g > R_g) > 0.70.$$

A group is only eligible for sample size expansion once a minimum of 5 subjects has been evaluated for CBR in that group. This eligibility remains effective until the next interim analysis is conducted, at which point eligibility is re-evaluated based on the currently available data and corresponding model outcomes.

[redacted]

5.3 Post-Expansion Futility

If there is less than a 60% probability that the clinical benefit rate in a group exceeds the historical rate, then the group will stop enrollment early for futility. Formally, enrollment will stop early for futility if:

$$\Pr(\pi g > Rg) < 0.60.$$

A group is only eligible for this post-expansion stopping criterion once the group has expanded to a sample size beyond 10 subjects enrolled. Note this post-expansion futility is a stricter futility rule than that used prior to sample size expansion.

5.4 Final Analysis

The final analysis will occur when both accrual and follow-up are complete in all groups. If, at the completion of the trial, there is at least 80% probability that the clinical benefit rate in a group exceeds the historical rate, then the group will be considered a success. Formally:

$$\Pr(\pi g > Rg) > 0.80.$$

6 Simulation

Extensive simulations have been conducted to develop and understand the performance of the adaptive design, the hierarchical model including clustering mechanism, interim monitoring, and decision criteria. We evaluated the design under a variety of possible "truths" for the underlying CBR within each group.

6.1 Simulation Assumptions

6.1.1 Trial Enrollment

The assumed average accrual is 124 subjects in 18 months across the 7 groups. The average group rate of accrual varies by group, with some groups enrolling at a faster rate than others. Hypothetical yearly accrual rates are provided in Table 1. It is anticipated that the yearly accrual rates will vary by group, but based on a different pattern across groups than that assumed for simulations. A Poisson distribution with these assumed mean rates dictate trial entry for simulated subjects. Hence, actual accrual rates within each simulated trial will vary from the mean based on this distributional assumption.

No dropouts are assumed for this simulation; hence, the final endpoint will be observed for every subject.

6.1.2 Historical Control Rates

The assumed control CBRs (R_g) vary by group and are provided in the below table. Many of these rates are not directly available in the literature. Rather, we have estimated the CBR based on estimates of the median PFS time (and assuming exponential PFS). The median PFS times and estimated historical CBR rates are shown in Table 1. Because these rates vary, a numbering scheme (1 through 7) is used in simulations and corresponding results to index the 7 groups.

[redacted]

Group Index	Tumor Type	Median PFS (mo)	Hist. CBR (%)	Hypothetical Yearly Average Accrual (Subjects)
1	SCLC	1.5	6.25	20
2	Gastroesophageal	5	43.50	16
3	STS	6.2	51.10	13
4	Prostate	4	35.40	11
5	Ovarian	3	25.00	10
6	Advanced NET	5	43.50	7
7	DLBCL	3	25.00	6

Table 1 – Historical CBR for each group

6.2.3 Treatment Clinical Benefit Rate Scenarios

Due to the borrowing nature of the model, the design is evaluated across six scenarios, which represent a variety of potential outcomes for the distribution of true CBRs across the groups. These include:

a. 'All Great' scenario: treatment is effective in all groups
b. 'All Null' scenario: the treatment has no effect for any group
c. 'Half' scenario: all odd-indexed groups are effective at the same level as 'All Great' while all even-indexed groups are ineffective at the historical CBRs
d. '2 Great' scenario: groups 2 and 5 are effective at the same level as 'All Great' while all other groups are ineffective at the historical CBRs
e. '2 Null' scenario: the same two groups (2 and 5) are ineffective at the historical CBRs while all other groups are effective at the same levels as those in the 'All Great' scenario
f. 'Mixed' scenario: varying levels of effectiveness across the groups, such that groups 2 and 5 are effective at the same level as 'All Great', groups 1, 4, and 7 have a moderate effect that is smaller, and groups 3 and 6 are ineffective

Since the control CBR differs across groups, we define the treatment effects for each scenario on the log-odds scale. A "great" effect is an increase of 0.7 on the log-odds scale. A "moderate" effect assumes an increase of 0.35 on the log-odds scale.

The assumed treatment rates for each scenario are shown in the table below and plotted in Figures 1-6. Values identical to the control are show in red, values associated with a great effect are shown in green, and values with a moderate level of effect more difficult to detect are shown in blue.

Group	Hist. CBR (%)	All Great	All Null	Half	2 Great	2 Null	Mixed
1	6.25	11.84	6.25	11.84	6.25	11.84	8.64
2	43.50	60.79	43.50	43.50	60.79	43.5	60.79
3	51.10	67.79	51.10	67.79	51.1	67.79	51.1
4	35.40	52.46	35.40	35.40	35.4	52.46	43.75
5	25.00	40.16	25.00	40.16	40.16	25	40.16
6	43.50	60.79	43.50	43.50	43.5	60.79	43.5
7	25.00	40.16	25.00	40.16	25	40.16	32.11

[redacted]

Table 2 – Treatment CBR profiles for each scenario by group

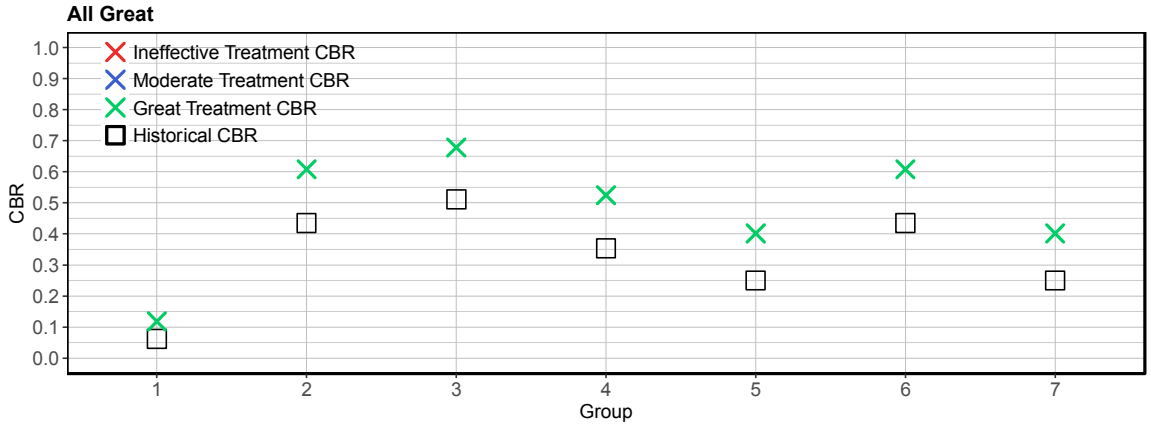

Figure 1 – Assumed CBRs for 'All Great'. All groups have an increase of 0.7 on the log-odds scale, indicated by green x's.

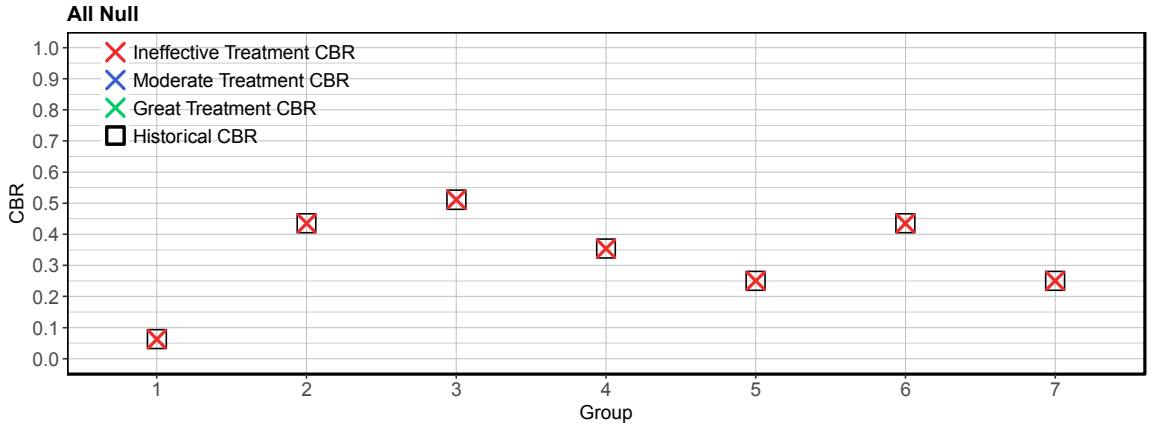

Figure 2 – Assumed CBRs for 'All Null'. No groups are effective, indicated by red x's.

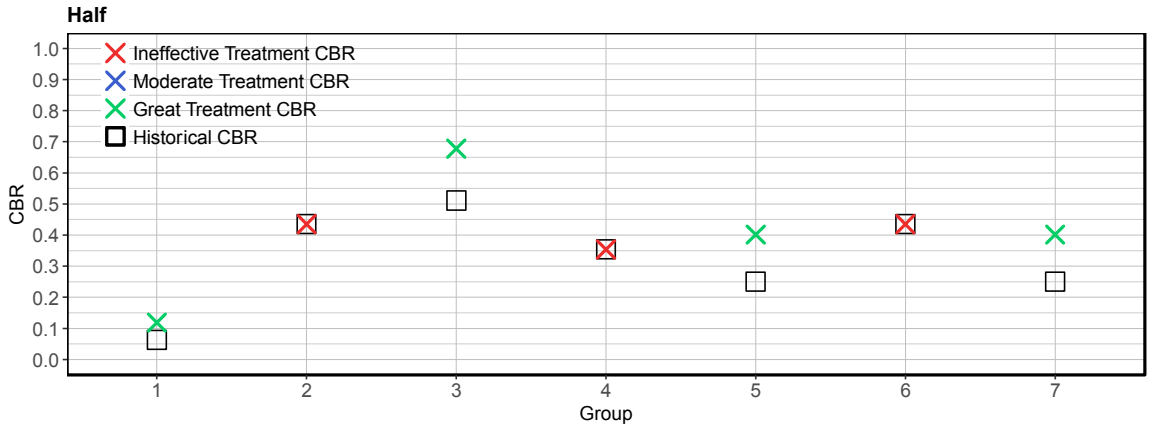

Figure 3 – Assumed CBRs for 'Half'. Odd numbered groups are effective, indicated by green x's, with log-odds increase of 0.7. Even numbered groups are ineffective, indicated by red x's.

[redacted]

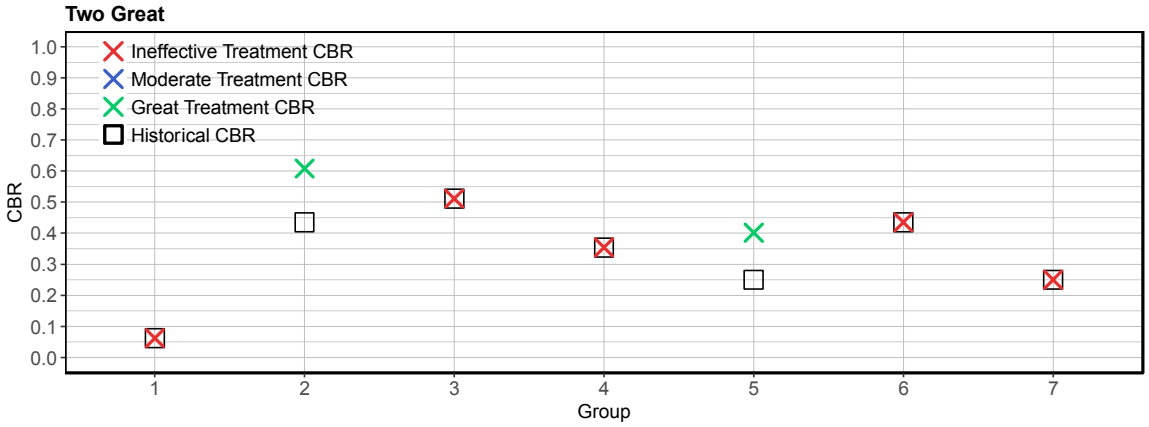

Figure 4 – Assumed CBRs for '2 Great'. Groups 2 and 5 are effective, indicated by green x's, with log-odds increase of 0.7. All other groups are ineffective, indicated by red x's.

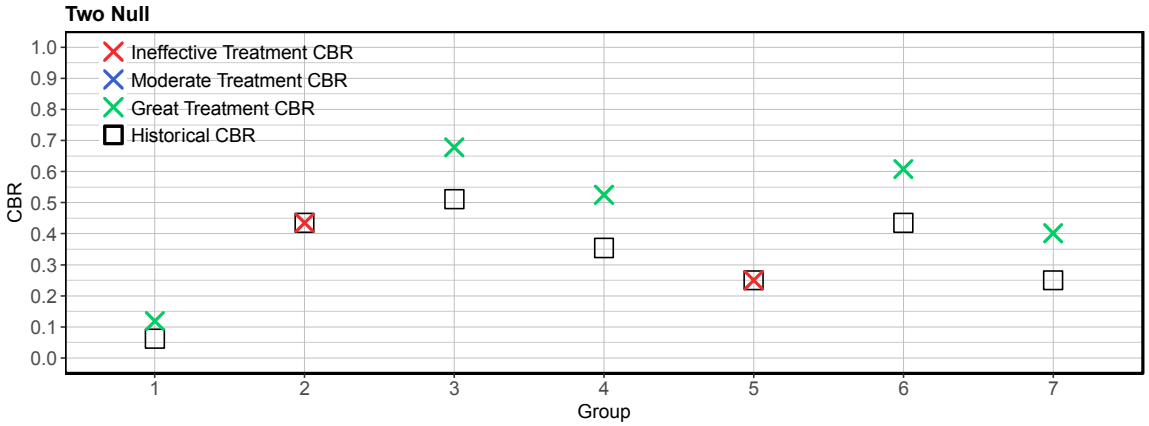

Figure 5 – Assumed CBRs for '2 Null'. Groups 2 and 5 are ineffective, indicated by red x's. All other groups are effective, indicated by green x's, with log-odds increase of 0.7.

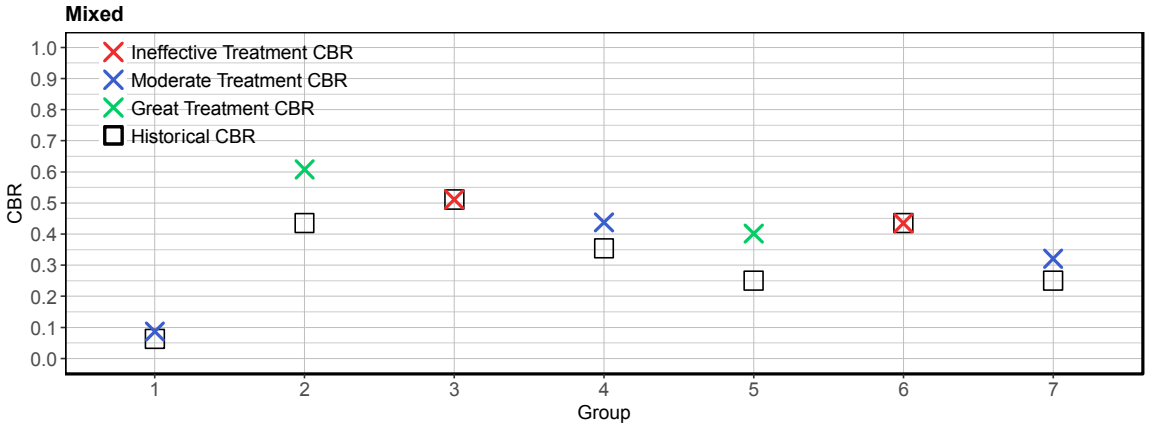

Figure 6 – Assumed CBRs for 'Mixed'. Groups 3 and 6 are ineffective, indicated by red x's, groups 2 and 5 are effective with log-odds increase of 0.7, indicated by green x's, and groups 1, 4, and 7 have moderate effect, log-odds increase of 0.35, indicated by blue x's.

[redacted]

6.2.4 Simulation Details

For each assumed scenario, 1,000 trials were simulated. For each analysis (i.e. each interim within each trial), posterior distributions were estimated via Markov chain Monte Carlo (MCMC) methods using 50,000 iterations, discarding the first 5,000 iterations as burn-in. The simulations were performed using custom software coded in C ++.

6.2.5 Simulation Output

For each scenario, overall descriptive measures are reported and include:

- Proportion of trials that declare each group successful at the final analysis
- Average number of correct and incorrect decisions
- Proportion of studies that expand each group to an overall sample size of 24
- Proportion of trials that expand 0, 1, 2, …, 7 groups
- The proportion of group expansions that declare success (averaging over groups)
- Average group sample size
- Average trial sample size
- Probability of stopping enrollment early for futility
- Average trial duration

In-depth information is also provided for one simulated example trial. This illustrates the flow and outcome of possible trials based on the pre-specified statistical decision rules.

These results are compared to an alternative design approach in which each group is independently analyzed, without the borrowing of the hierarchical model. This comparison helps illustrate the effect of the borrowing on the operating characteristics.

These results are also compared to an alternative design approach in which no early futility stopping prior to sample size expansion is conducted. This comparison elucidates the patient savings achieved with early futility testing.

6.3 Results

6.3.1 Probability of Group Success

We evaluated the probability of group success for each group in each of the six scenarios for the distribution of assumed true CBRs for each group. If the group is truly effective (great or moderate), this represents the power for detecting this effect in the group. For groups where the treatment is truly ineffective (null), declaring trial success represents a mistake. Our goal is to correctly classify the 7 groups into effective and ineffective groups.

Table 3 shows the probability of success by group. Entries in red represent groups where the treatment effect is 0 (e.g. the treatment is ineffective). Entries in green appear where the treatment is great, and thus indicate the power of the design. Entries appear in blue for a moderate effect, also indicating the power of the design. Results are provided in tabular and graphical format.

[redacted]

Group	Hist. CBR (%)	All Great	All Null	Half	2 Great	2 Null	Mixed
1	6.25	0.565	0.049	0.399	0.095	0.445	0.232
2	43.50	0.809	0.126	0.231	0.638	0.266	0.694
3	51.10	0.824	0.108	0.715	0.161	0.750	0.199
4	35.40	0.802	0.118	0.199	0.156	0.718	0.430
5	25.00	0.769	0.082	0.663	0.584	0.220	0.635
6	43.50	0.810	0.099	0.186	0.140	0.738	0.187
7	25.00	0.762	0.088	0.636	0.138	0.667	0.395

Table 3 – Probability of group success

The probability of trial success is dependent upon the historical control rates and distribution of true CBRs across the groups. When the treatment effects are the same across all groups (All Great, All Null), estimation efficiencies, due to borrowing, result in strong trial performance. In the All Null scenario the individual groups have less than a 13% chance of mistakenly declaring group success. In the All Great scenario, power generally ranges from 76.2%-82.4%. The groups that have a small historical control rate tend to have lower power. This is due to the selection of scenarios whereby power is assessed for detecting a 0.7 log-odds improvement, which is more difficult for lower historical control rates. In addition, the global type I error (proportion of trials that declare at least one group successful in the All Null scenario) is controlled at 0.431.

When the treatment effects vary across the groups, the amount of appropriate borrowing also varies, impacting the operating characteristics. Power is reduced and the probability of mistakenly classifying an ineffective group as effective is larger in these situations. For the scenarios simulated, the power varies considerably; from roughly 40%-75% while the largest probability of incorrectly declaring an ineffective group effective is 0.266.

In the 'Mixed' scenario, the moderate effects are difficult to detect. These groups typically have around 40% power.

[redacted]

Figure 7 – Probability of success in each group for each scenario.

For each trial, there are 7 decisions to be made regarding the success in a group. For a group that is truly effective (great or moderate), declaring success is a correct decision. For a group that is truly ineffective, declaring success is an incorrect decision. Table 4 shows the average number of correct and incorrect decisions per scenario, averaged across all groups. Table 5 provides additional detail about the tradeoff between detecting truly ineffective groups versus not detecting truly effective groups.

	All Great	**All Null**	**Half**	**2 Great**	**2 Null**	**Mixed**
Correct	5.3	6.3	4.8	5.5	4.8	4
Incorrect	1.7	0.7	2.2	1.5	2.2	3

Table 4 – Average number of correct and incorrect decisions

Subset	**Decision**	**All Great**	**All Null**	**Half**	**2 Great**	**2 Null**	**Mixed**
Effective	Final Success Met	5.3	NA	2.4	1.2	3.3	2.4
Effective	Final Success Not Met	1.7	NA	1.6	0.8	1.7	2.6
Ineffective	Final Success Met	NA	0.7	0.6	0.7	0.5	0.4
Ineffective	Final Success Not Met	NA	6.3	2.4	4.3	1.5	1.6

[redacted]

Table 5 – Average number of true effective and ineffective groups meeting success and not meeting success

6.3.2 Sample Size Expansion

The probability of expanding from an overall sample size of 10 to 24 is examined for each group within each scenario (Table 6, Figure 8). Groups that are in truth effective tend to have large probabilities of expanding to n=24 subjects (68%-90%). For scenarios in which there are only a few effective groups ('2 Great'), the probability of expanding those groups drops to 72%-74%. Likewise, the probability of expanding ineffective groups is largely dependent upon the distribution of effects across the groups. When no groups are effective, the model tends to correctly detect moderate effects as spurious 'highs' and down-weights those estimates leading to less chance of expanding to n=24.

Group	Hist. CBR (%)	All Great	All Null	Half	2 Great	2 Null	Mixed
1	6.25	0.688	0.196	0.574	0.302	0.636	0.475
2	43.50	0.863	0.385	0.511	0.744	0.530	0.782
3	51.10	0.901	0.357	0.820	0.439	0.854	0.488
4	35.40	0.875	0.332	0.488	0.409	0.831	0.628
5	25.00	0.857	0.303	0.777	0.721	0.501	0.764
6	43.50	0.891	0.324	0.481	0.415	0.843	0.470
7	25.00	0.859	0.290	0.766	0.391	0.788	0.608

Table 6 – Probability of expanding from 10 to 24 subjects.

[redacted]

Figure 8 – Probability of expanding from 10 to 24 subjects.

The proportion of trials that expand 0, 1, 2, …, 7 groups are reported (Table 7, Figure 9). When all groups are effective (All Great), typically 5-7 groups expand (on average, 5.934 groups expand). When no groups are effective (All Null), the likelihood of expanding multiple groups decreases greatly, with an average of 2.187 groups expanding.

Groups	All Great	All Null	Half	2 Great	2 Null	Mixed
Average	5.934	2.187	4.417	3.421	4.983	4.215
0	0	0.161	0.013	0.043	0.003	0.019
1	0.002	0.238	0.045	0.105	0.022	0.069
2	0.011	0.235	0.093	0.190	0.048	0.110
3	0.031	0.156	0.140	0.177	0.087	0.124
4	0.057	0.097	0.161	0.182	0.149	0.170
5	0.181	0.065	0.256	0.174	0.274	0.256
6	0.342	0.038	0.202	0.096	0.281	0.170
7	0.376	0.010	0.090	0.033	0.136	0.082

Table 7 – Number of Group Expansions (0, 1, 2,…,7)

[redacted]

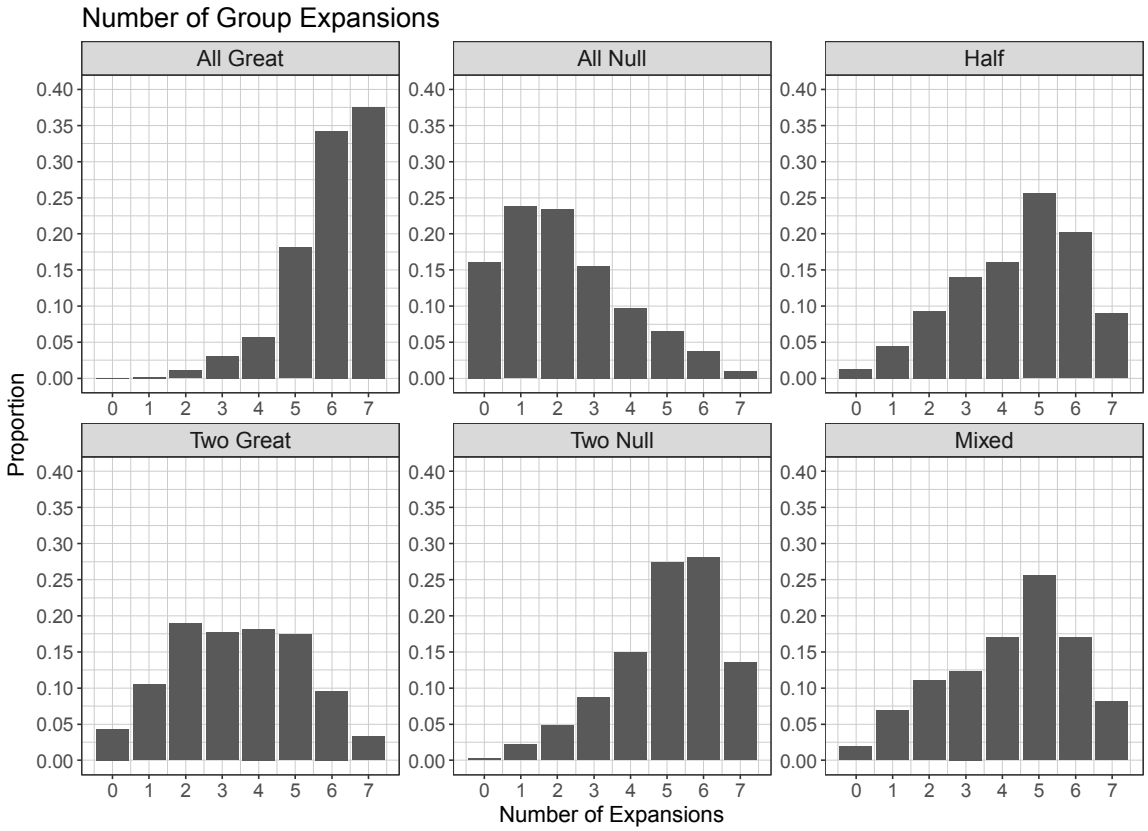

Figure 9 – Number of Group Expansions (0, 1, 2,…,7)

The proportion of group expansions that declare success, averaged over groups within each trial, is provided in Table 8.

Scenario	Proportion
All Great	0.899
All Null	0.306
Half	0.685
2 Great	0.559
2 Null	0.763
Mixed	0.657

Table 8 – Proportion of group expansions that declare success

6.3.3 Average Sample Size

The average sample size for each group and for each trial (summing over groups) within each scenario are provided in Tables 9 and 10, and graphically in Figure 10. In the 'All Great' scenario, each group is likely to expand and thus the average sample size is close to the maximum per group. In the 'All Null' scenario, the average sample size is smaller per group due to early futility stopping and the expansion criteria identifying when enrollment may expand from 10 to 24 subjects.

[redacted]

The average trial size varies from 94.3 subjects to 150.6 subjects. The average trial size reduces as the number of groups that stop enrollment for futility increase. The maximum trial sample size is 168 subjects (full enrollment of 24 subjects within each of 7 groups).

Group	Hist. CBR (%)	All Great	All Null	Half	2 Great	2 Null	Mixed
1	6.25	19.6	12.6	17.8	14.1	18.7	16.5
2	43.50	21.8	14.7	16.5	20.0	16.8	20.6
3	51.10	22.3	14.0	21.1	15.1	21.5	15.8
4	35.40	21.9	13.7	15.8	14.8	21.2	18.1
5	25.00	21.6	13.3	20.4	19.5	15.8	20.2
6	43.50	22.0	13.3	15.2	14.4	21.3	15.1
7	25.00	21.4	12.8	20.0	14.0	20.4	17.3

Table 9 – Average group sample size

Trial Sample Size	All Great	All Null	Half	2 Great	2 Null	Mixed
	150.6	94.3	126.9	111.9	135.6	123.6

Table 10 – Average trial sample size

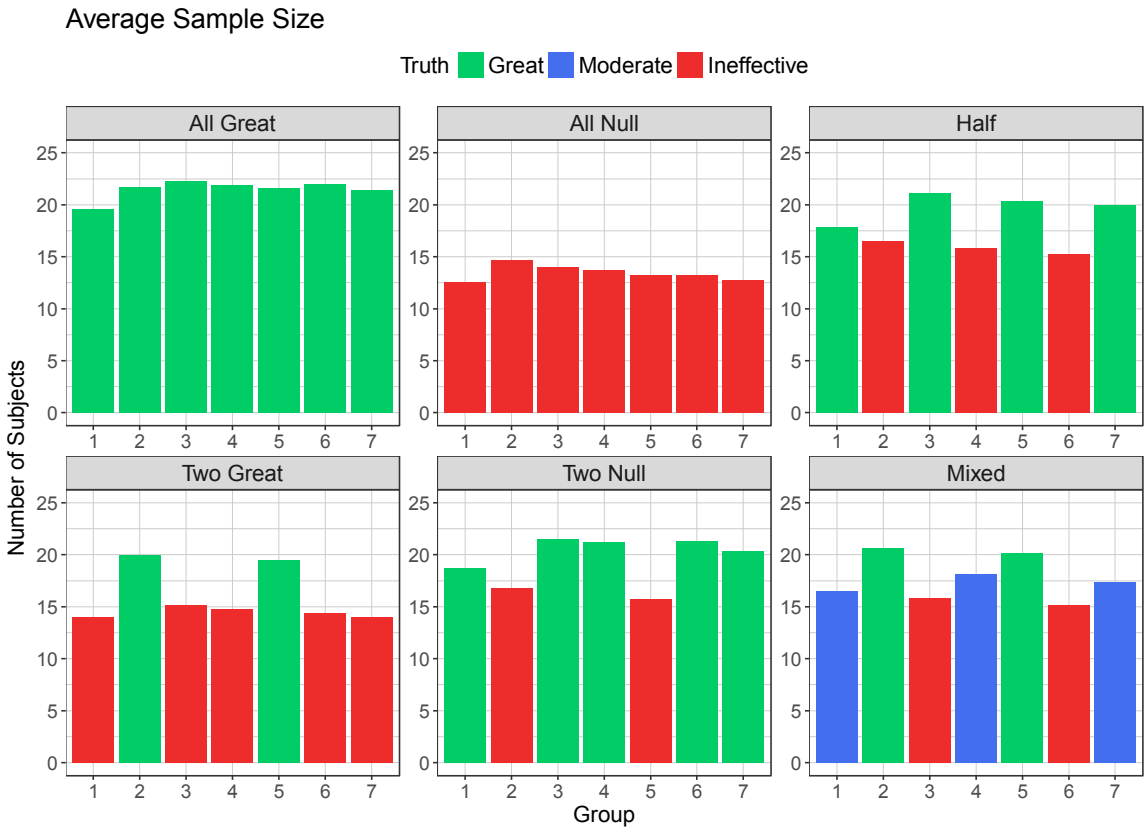

Figure 10 – Average group sample size

[redacted]

6.3.4 Early Futility

Table 11 and Figure 11 summarize the proportion of trials that stop early (either by futility before enrolling 10 subjects, by not meeting the expansion criteria, or by futility after expansion).

Group	Hist. CBR (%)	All Great	All Null	Half	2 Great	2 Null	Mixed
1	6.25	0.318	0.832	0.449	0.731	0.390	0.559
2	43.50	0.166	0.721	0.585	0.300	0.546	0.259
3	51.10	0.136	0.781	0.218	0.692	0.196	0.654
4	35.40	0.156	0.786	0.651	0.708	0.219	0.459
5	25.00	0.176	0.819	0.280	0.336	0.649	0.295
6	43.50	0.153	0.809	0.699	0.749	0.219	0.701
7	25.00	0.194	0.836	0.300	0.763	0.272	0.523

Table 11 – Probability of stopping early for futility

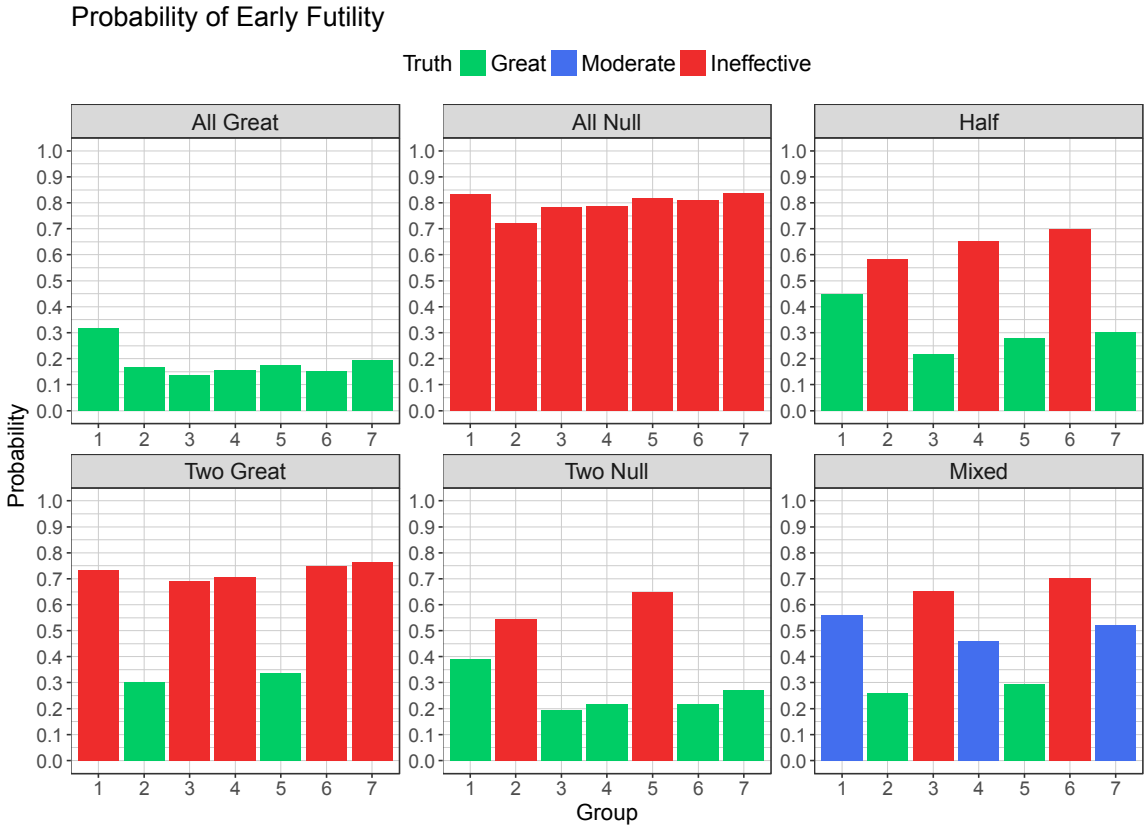

Figure 11 – Probability of stopping early for futility

6.3.5 Trial Duration

Based on the currently assumed hypothetical accrual rates, the average trial duration across scenarios ranges from 3.4 years to 4.6 years as shown in Table 12. The 'All Null' scenario tends

[redacted]

to have shorter trials due to many groups stopping early for futility. Duration is largely dependent upon accrual. The majority of the groups stop enrollment much earlier than the average values as described in Table 13. Due to the assumed non-constant accrual rate, slow-enrolling groups take extra time to enroll, thereby increasing the duration of the overall trial. In practice, faster or slower accrual rates (than those simulated) for all groups will largely impact these numbers.

All Great	All Null	Half	2 Great	2 Null	Mixed
4.6	3.4	4.4	3.7	4.6	4.1

Table 12 – Average trial duration in years

Number of Years from First Subject First Visit	Scenario					
	All Great	All Null	Half	2 Great	2 Null	Mixed
1	6.8	5.7	6.4	6.2	6.5	6.5
2	5.9	4.2	5.3	5	5.6	5.3
3	3.3	2.2	3.3	2.8	3.6	3.1
4	1.7	1	1.9	1.3	2.1	1.6
5	0.5	0.3	0.7	0.4	0.7	0.5
6	0.1	0	0.2	0.1	0.1	0.1

Table 13 – Average number of groups continuing to enroll subjects after 1, 2, 3, 4, 5, and 6 years

6.4 Example Trials

6.4.1 Overview

In this section, we present an example of the trial to illustrate the adaptive process.

The trial is described graphically in a series of plots. Each plot describes the current data at the time of the interim. The plots include the following features:

- Light gray bars represent the number of subjects enrolled.
- Dark gray bars represent the number of subjects with CBR data
- Bars may be outlined blue, yellow, red, or green. Blue indicates a group may continue to enroll; yellow indicates that enrollment has been paused for the group; red indicates a group has permanently stopped for futility; and green indicates a group has declared success.
- Vertical dashed lines are provided at 10 and 24 subjects.
- Text columns to the right of the plot display the following summary statistics for each group:
  - Pr(>Ctrl): The probability that the CBR exceeds that group's corresponding historical control based on the hierarchical model
  - Data: The observed number of events/the number of subjects with CBR data available
  - Obs. CBR: The observed CBR

[redacted]

  - Est. CBR: The model-estimated CBR
- Red/green diamonds at n=10 indicate whether a group has met its expansion threshold (no go/go). Once a group has expanded beyond n=10, this gate remains green.
- The historical control for each group is displayed on the left side in orange.

In the simulations, interims occur every 13 weeks. Hence, a large number of interims may occur per trial. For this example, we show results for a small number of select interims in order to highlight the features of the adaptive design.

6.4.2 Example Trial 1

6.4.2.1 Example Trial 1, Interim 1

The trial begins enrolling subjects across all groups. The first interim analysis (Figure 12) occurs at 31 weeks from the first subject enrolled. Decisions (for futility or sample size expansion) can only be made for groups that have at least 5 subjects with CBR data available. No groups have CBR data available from at least 5 subjects, and therefore, no groups can stop for futility or enroll beyond 10 subjects until the next interim analysis. Groups 2 and 3 have already enrolled 10 subjects and therefore pause enrollment. This enrollment pause will be re-evaluated at the next interim analysis.

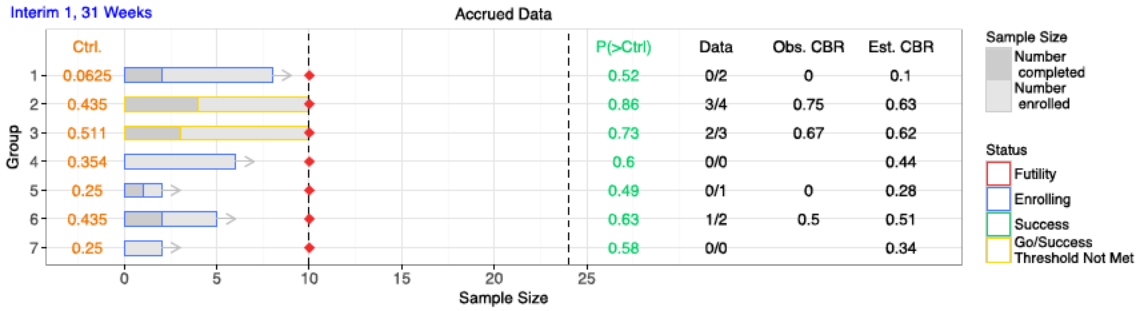

Figure 12 – Example trial 1, interim 1

6.4.2.2 Example Trial 1, Interim 2

The next interim as shown here occurs 13 weeks later at Week 44 (Figure 13). Groups 1, 2, and 3 each have at least 5 subjects with CBR data available. For Group 2, the hierarchical model estimates $\Pr(\pi_g > R_g \mid \text{data}) = 0.82$, which exceeds the 70% threshold for expansion; thus Group 2 is eligible to continue enrolling beyond 10 subjects (indicated by the green diamond on the plot). Groups 1 and 3 have 0/8 and 4/7 clinical benefit rates, respectively. The $\Pr(\pi_g > R_g \mid \text{data})$ is 0.38 and 0.65 for these groups, both below the 0.70 sample size expansion threshold and above the 0.20 futility threshold. These groups do not yet meet criteria for expansion or futility and thus must wait for additional data to become available before making decisions. Groups 4, 5, 6, and 7 don't yet have CBR data from at least 5 subjects and each continue to enroll subjects.

[redacted]

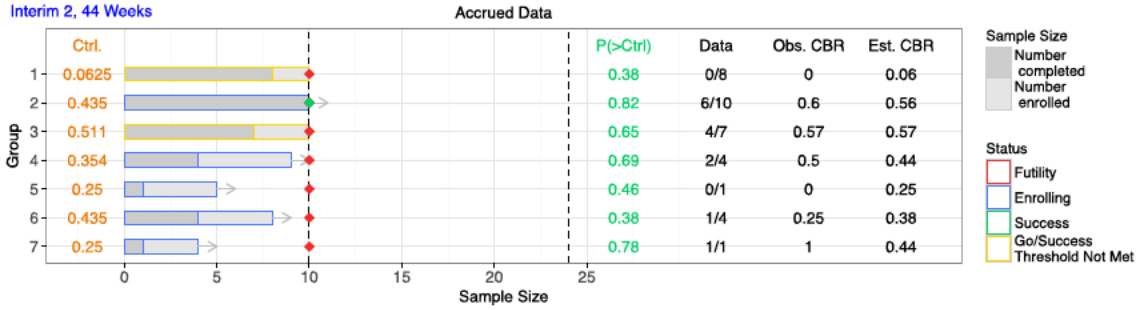

Figure 13 – Example trial 1, interim 2

6.4.2.3 Example Trial 1, Interim 3

Interim 3 occurs at 57 weeks. Groups 2 (which previously expanded its sample size) continues to enroll subjects. Groups 3 and 4 have clinical benefit rates of 7/10 and 4/6 respectively. The $\Pr(\pi_g > R_g \mid \text{data})$ is 0.90 and 0.92 for these groups, each above the 0.70 expansion threshold and are therefore eligible to enroll beyond 10 subjects. Group 1 has 0/8 subjects and with a $\Pr(\pi_g > R_g \mid \text{data}) = 0.43$ remains paused to further enrollment. Group 6 has a CBR of 1/5 and with a $\Pr(\pi_g > R_g \mid \text{data}) = 0.30$ also pauses further enrollment beyond its currently enrolled 10 subjects. Groups 5 and 7 still don't have CBR data from at least 5 subjects and each continue to enroll more subjects.

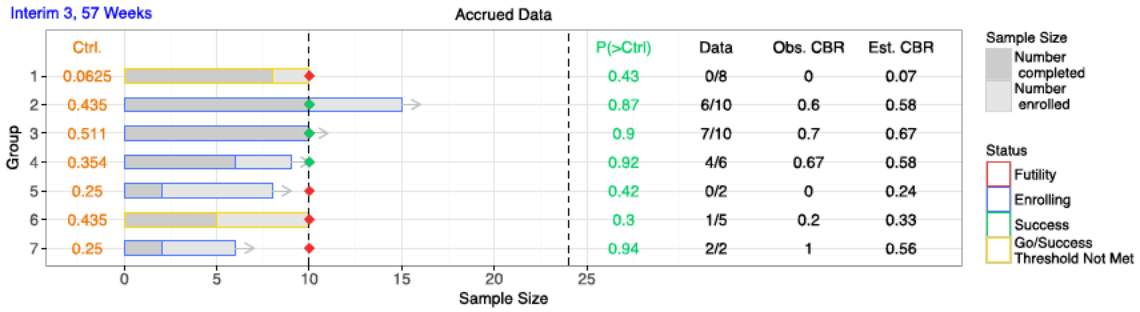

Figure 14 – Example trial 1, interim 3

6.4.2.4 Example Trial 1, Interim 4

Interim 4 occurs at 70 weeks. Now, groups 2 and 3 are each enrolling beyond 10 subjects. Group 4 which had previously been deemed eligible for expansion based on a CBR of 4/6 now has 10 subjects enrolled, a CBR of 4/9, and $\Pr(\pi_g > R_g \mid \text{data}) = 0.72$. It still meets the expansion threshold of 0.70 and therefore is still eligible to enroll beyond 10 subjects.

Group 5 has enrolled 9 subjects, has a CBR of 0/6, and a $\Pr(\pi_g > R_g \mid \text{data}) = 0.17$. This probability is below the early futility threshold and therefore stops enrollment for futility. Groups 1 and 6 still remained paused at 10 subjects enrolled. Group 7 has 9 subjects enrolled and with a CBR of 2/4 does not have sufficient CBR data available to make a decision about expansion. Therefore, enrollment will pause at 10 for Group 7 until the next interim at which point that decision can be assessed.

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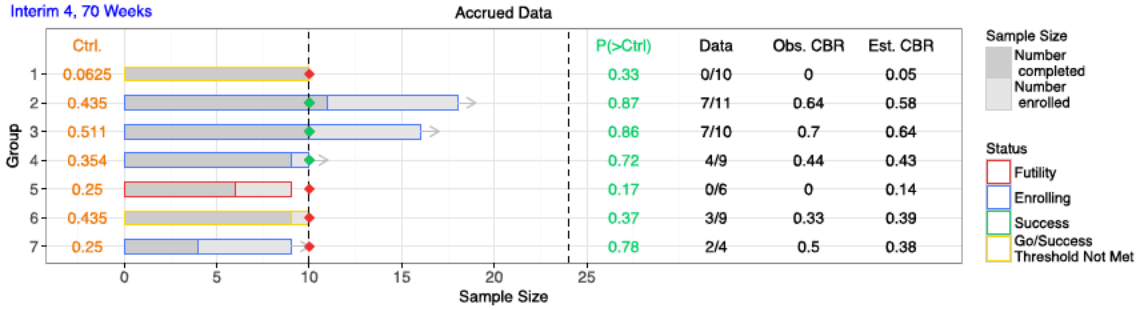


Figure 15 – Example trial 1, interim 4

6.4.2.5 Example Trial 1, Interim 5

Interim 5 occurs at 83 weeks. Groups 2, 3, and 4 continue to enroll beyond 10 subjects. In addition, Group 7 now has 1o subjects enrolled, a CBR of 3/7, and a $\Pr(\pi_g > R_g \mid \text{data}) = 0.81$ which is above the 0.70 expansion threshold and becomes eligible to also expand beyond 10 subjects.

Groups 1 and 6 have full follow-up on all subjects (0/10 and 4/10 respectively). Neither of these groups have sufficient evidence to expand beyond 10 subjects.

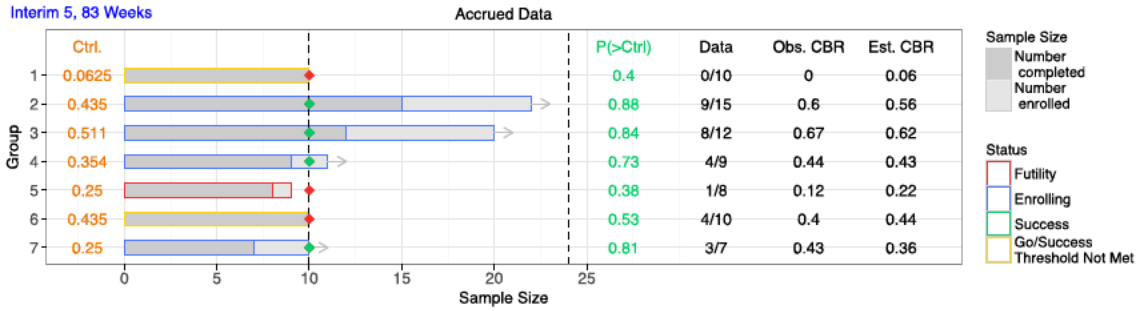


Figure 16 – Example trial 1, interim 5

6.4.2.6 Example Trial 1, Interim 8

Interims 6-7 are not shown here. We next show the results for interim 8 of the trial, which occurs at Week 122. At this point in the trial, Group 2 has complete CBR data for all 24 subjects. For this group, the $\Pr(\pi_g > R_g \mid \text{data}) = 0.87$ which meets the final success criteria based on a 0.80 threshold. Group 3 has fully enrolled all 24 subjects and is awaiting full follow-up prior to making a decision.

Groups 4 and 7 continue to enroll addition subjects while groups 1 and 6 remain paused to further enrollment.

[redacted]

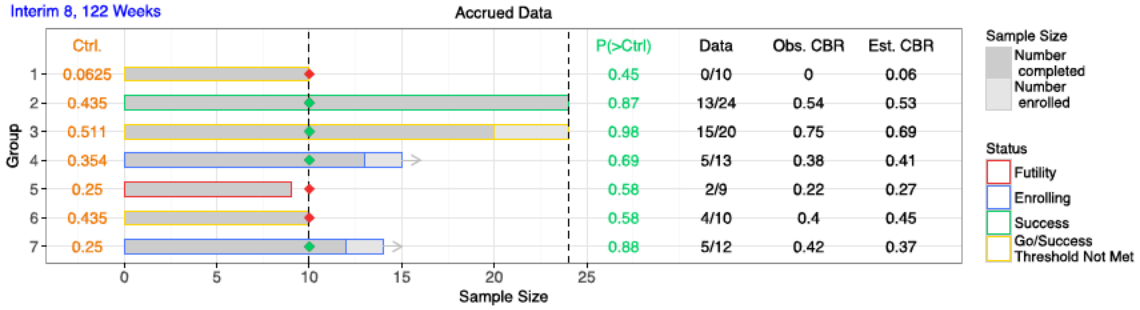


Figure 17 – Example trial 1, interim 8

6.4.2.7 Example Trial 1, Interim 10

Interim 9 is not shown here. We next show the results for interim 10 of the trial, which occurs at Week 148. Now Group 3 has complete CBR data for all 24 subjects. For Group 3, the CBR is 18/24 and the $\Pr(\pi_g > R_g \mid \text{data}) = 0.98$ which also meets the final success criteria based on a 0.80 threshold.

Group 4 has enrolled 19 subjects, has a CBR of 5/15, and a $\Pr(\pi_g > R_g \mid \text{data}) = 0.56$. This probability is below the 0.60 post-expansion futility criteria. Therefore, with CBR data not continuing to look promising, Group 4 stops for futility. Group 7 is the only group continuing to enroll subjects into the trial.

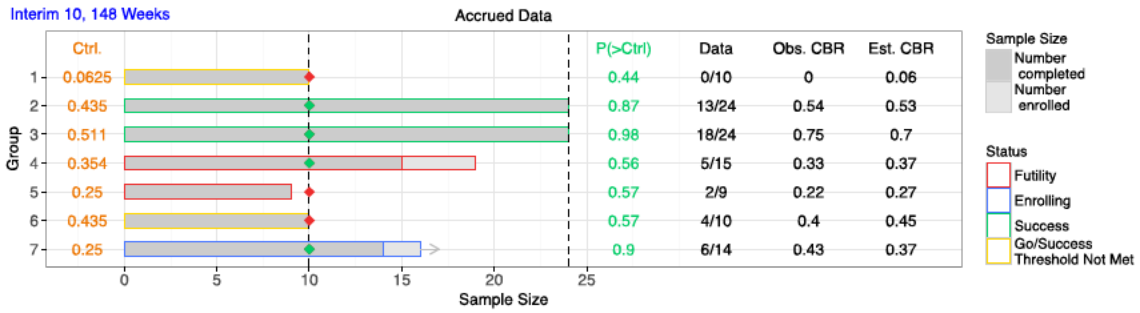


Figure 18 – Example trial 1, interim 10

6.4.2.8 Example Trial 1, Interim 16 (Final Analysis)

We skip the remaining interims and instead show Interim 16 which is the final analysis at 226 weeks. This occurs once enrollment has stopped for all groups and full 24-week follow-up has been achieved for all subjects in the trial. Group 7 now has a CBR of 10/24 and $\Pr(\pi_g > R_g \mid \text{data}) = 0.96$ which meets the final success criteria.

In total, groups 2, 3, and 7 each fully enrolled to 24 subjects and each met final success based on the 0.80 success threshold. Groups 1, 4, 5, and 6 either stopped early for futility or never had promising enough results to expand from 10 to 24 subjects.

[redacted]

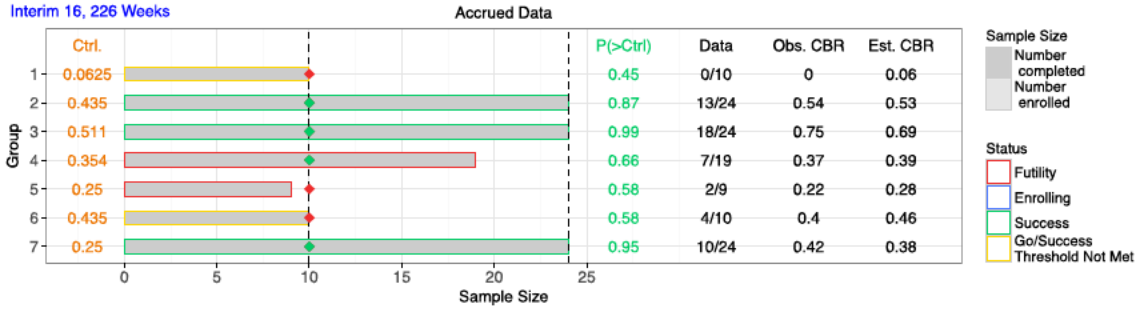


Figure 18 – Example trial 1, interim 16 (Final Analysis)

7 Modeling Details

Recall at the first stage the groups are clustered according to a Dirichlet Process Mixture Model.

The number of clusters is not assumed to be known in advance but will instead be inferred from the data using Dirichlet Process Mixtures (DPM). The DPM looks across all the possible clusterings of the groups and assigns a probability to each based on the data. The prior distribution in a DPM is governed by a parameter α. When α is small, the prior favors large clusters. As α tends to zero, the prior tends to place all its mass on a single cluster containing all the groups. As α increases, the prior places more mass on clusterings with a large number of clusters. As α becomes very large, the prior places all of its mass on having a separate cluster for each group (that is, no borrowing across groups). Thus, by specifying extreme values of the prior one could force the groups into one cluster or force the groups to be analyzed in separate clusters. Here we choose a moderate version of α=2 (common values might be anywhere between 0.5 and 5) and allow the data more control over the clustering.

The details of the prior are as follows. Let z_g represent the cluster to which group g belongs. Then $z_g \sim \text{Categorical}(p)$, where p is the vector such that p_k is the probability that a group belongs to cluster k and $\sum_{k=1}^{\infty} p_k = 1$. We construct p using a stick-breaking process:

$$p_k = \beta_k \prod_{i=1}^{k-1} (1 - \beta_i)$$

and

$\beta_k \sim \text{Beta}(1, \alpha)$.

A large value of α thus removes a very small amount of probability for p, resulting in many clusters, while a small value of α tends to produce probabilities near 1 for the first cluster.

Conditional on the clustering, we fit a hierarchical model which has an across groups distribution

$$\theta_g \sim N(\mu, \tau^2)$$

As discussed above, this across groups distribution states that within a cluster we expect to see some variation in the parameters, with that variation governed by τ. When τ is small, there is minimal variation across groups within a cluster, and thus within the cluster the model would

[redacted]

approach pooling. In contrast, when τ is large we expect large amount of across group variation, and thus even though the groups are in the same cluster the θ_g values may be quite different. Apriori we have no way of knowing τ, so we estimate it using the data combined with the prior distributions

$$\mu \sim N(0, 1.82)$$

and

$$\tau 2 \sim IG(3,0.5),$$

where *IG(α, β)* is the inverse gamma distribution defined by:

$$f(x|\alpha,\beta) = \frac{\beta^{\alpha} e^{-\beta/x}}{x^{\alpha+1}\Gamma(\alpha)}.$$

When the entire model is implemented (via Markov Chain Monte Carlo) we consider the full joint distribution of the clustering combined with the hierarchical model parameters. We average over the entire range of the uncertainty in the parameters to produce the posterior distribution for each group parameter θ_g, which is then used to drive the decisions in the design.

8 Comparison of Analysis Approaches: Hierarchical Borrowing versus Independent Analyses

The Bayesian hierarchical model-based analysis approach for the 7 groups is compared to instead conducting independent analyses for each of the groups. These analysis approaches are compared within the context of this exact trial design with identical futility and sample size expansion criteria. For independent analyses, the final success criteria are instead based on exact binomial tests at the 0.20 level. Note that this comparison does not compare the adaptive design to a standard fixed design. The adaptive features are included in both, the only change is the final analysis. Operating characteristics to compare these analysis approaches are provided.

8.1 Probability of Success

For effective groups, the probability of success is consistently higher across most scenarios relative to independent analyses.

Group	All Great	All Null	Half	3 Great	3 Null	Mixed
1	0.565/0.470	0.049/0.091	0.399/0.404	0.095/0.112	0.445/0.434	0.232/0.243
2	0.809/0.733	0.126/0.157	0.231/0.180	0.638/0.645	0.266/0.186	0.694/0.680
3	0.824/0.732	0.108/0.113	0.715/0.680	0.161/0.126	0.750/0.699	0.199/0.135
4	0.802/0.727	0.118/0.132	0.199/0.163	0.156/0.152	0.718/0.689	0.430/0.406
5	0.769/0.629	0.082/0.072	0.663/0.590	0.584/0.560	0.220/0.083	0.635/0.572
6	0.810/0.743	0.099/0.116	0.186/0.147	0.140/0.134	0.738/0.702	0.187/0.146
7	0.762/0.616	0.088/0.082	0.636/0.578	0.138/0.099	0.667/0.586	0.395/0.281

Table 17 – Probability of success (borrowing/independent analyses)

[redacted]

Figure 19 – Probability of success (borrowing versus independent analyses)

8.2 Mean Squared Error

The mean squared error (MSE) is a measure of the average vale of (estimate − truth)^2. It incorporates both the bias and variance associated with the estimate. The MSE values for the borrowing analysis are consistently lower than that of independent analyses.

Group	All Great	All Null	Half	3 Great	3 Null	Mixed
1	0.002/0.007	0.001/0.004	0.002/0.007	0.001/0.003	0.002/0.007	0.001/0.005
2	0.009/0.018	0.008/0.016	0.009/0.017	0.015/0.019	0.009/0.017	0.013/0.019
3	0.008/0.016	0.010/0.019	0.011/0.017	0.010/0.019	0.010/0.017	0.010/0.020
4	0.009/0.017	0.007/0.016	0.008/0.016	0.008/0.016	0.011/0.018	0.009/0.017
5	0.008/0.017	0.005/0.012	0.011/0.017	0.013/0.017	0.006/0.012	0.011/0.017
6	0.009/0.017	0.009/0.019	0.009/0.019	0.009/0.019	0.011/0.019	0.009/0.019
7	0.009/0.018	0.005/0.014	0.012/0.020	0.005/0.014	0.011/0.019	0.008/0.017

Table 18 – MSE (borrowing/independent analyses)

[redacted]

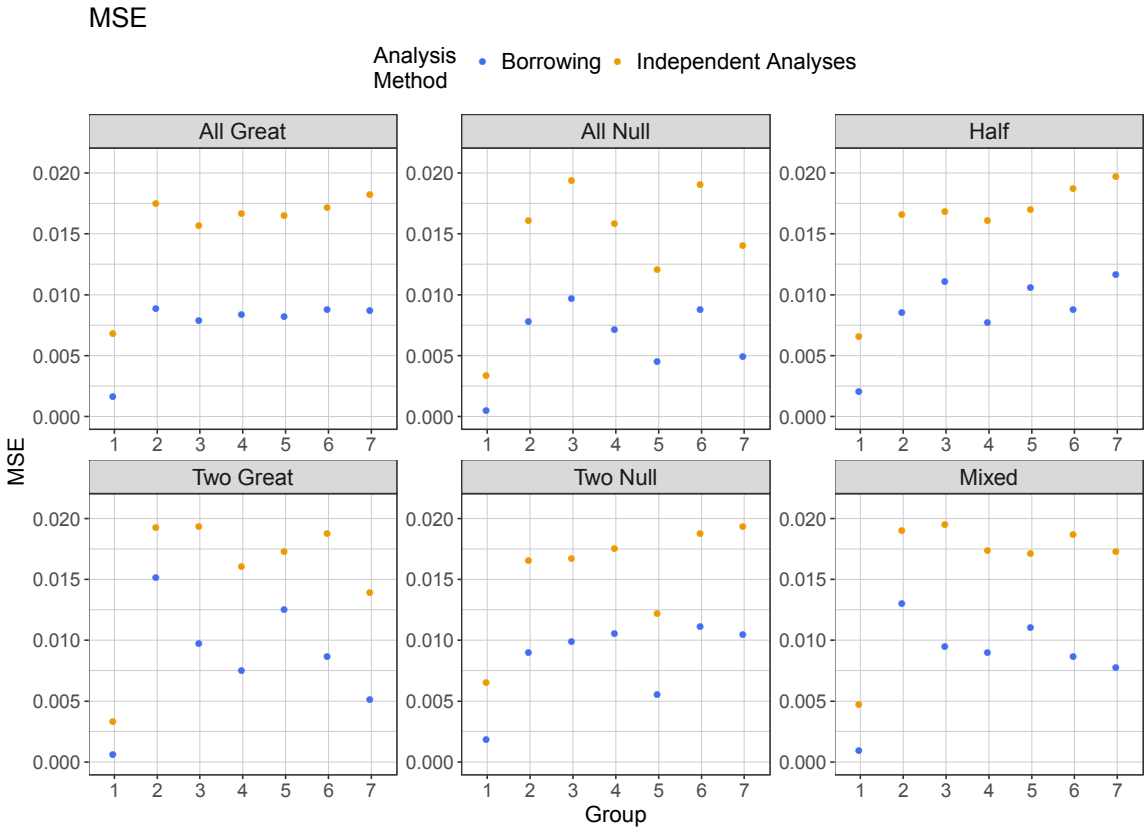


Figure 20 – MSE (borrowing versus independent analyses)

9 Comparison of Design Approaches: Planned Design with or without Early Futility prior to Sample Size Expansion

Simulated trial data has been applied to two designs:

1. The planned design as described in this report but with early futility prior to sample size expansion removed
2. The planned design as described in this report

The former approach describes the design (including sample size expansion and post-expansion futility stopping) but without early futility stopping prior to sample size expansion. If early futility stopping were permitted, a fraction of the trials (this varies based on the scenario and group) will halt enrollment earlier than it otherwise would have and prohibit those groups from ultimately meeting success. For groups that would otherwise have met success, the early futility leads to a missed success and reduction in power. While for groups that did not ultimately meet success, the early futility stopping provides a savings in patients and resources. Inherent in the futility stopping is a trade-off between power reduction and subject savings. The goal is to minimize any potential reduction in power while allowing the design to reduce its required sample size required to determine success in each group.

[redacted]

Figure 21 describes the probability of success for each group and scenario if no early futility were conducted. Green represents success and black represents not meeting success. Next, Figure 22 shows these same probabilities of success for the planned design as described in this report, when early futility is incorporated. For trials that originally did not meet success (black in Figure 21), a portion of them stop enrollment earlier due to early futility testing (pink in Figure 22) and represent patient savings. Across groups and scenarios, the percentage of trials with patient savings ranges from 0 to 16%. For trials that originally did meet success (green in Figure 21), a very small portion of them stop enrollment earlier due to early futility testing (red in Figure 22) and represent missed successes. The resulting power loss ranges from 0% to 0.7%. These simulations illustrate that early futility testing allows for the possibility of patient savings, particularly in null situations where treatment effectiveness is poor across many groups while loss in power is extremely low or nonexistent.

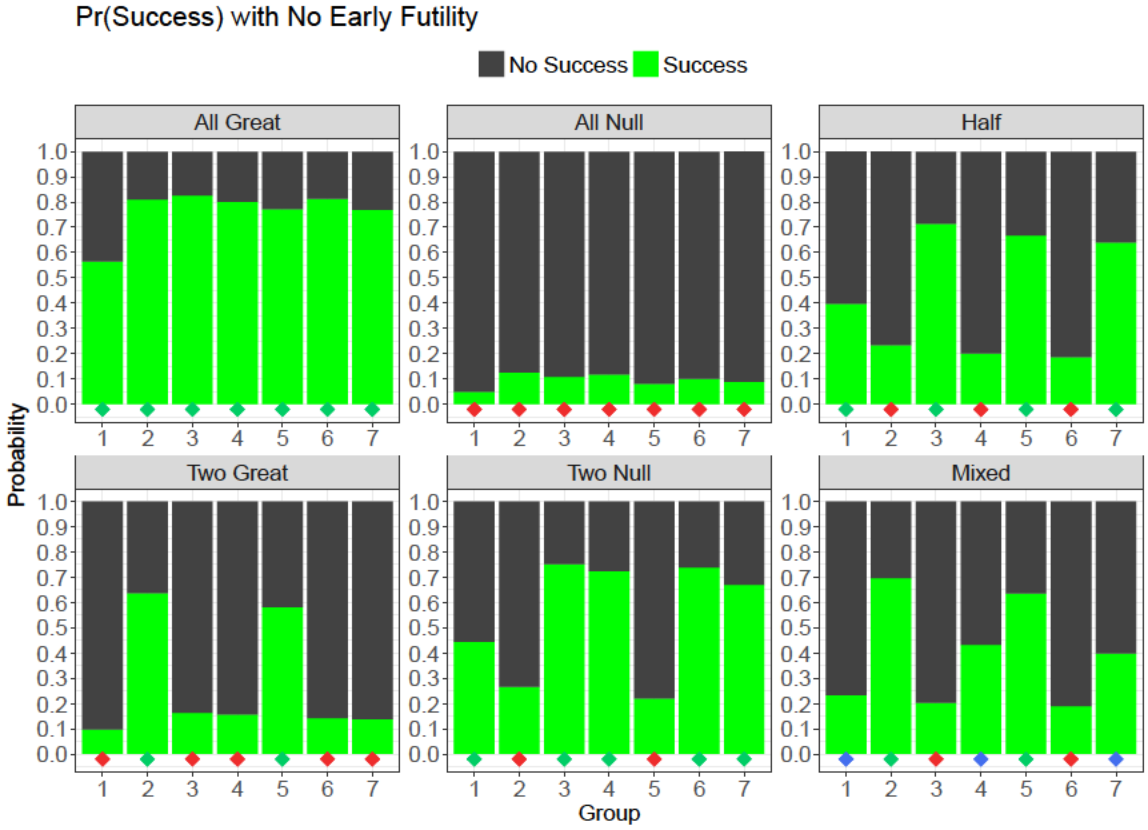


Figure 21 – Probability of success in each group for each scenario if no early futility were conducted. The green, blue, and red diamonds indicate whether in truth groups were effective, moderately effective, or not effective respectively.

[redacted]

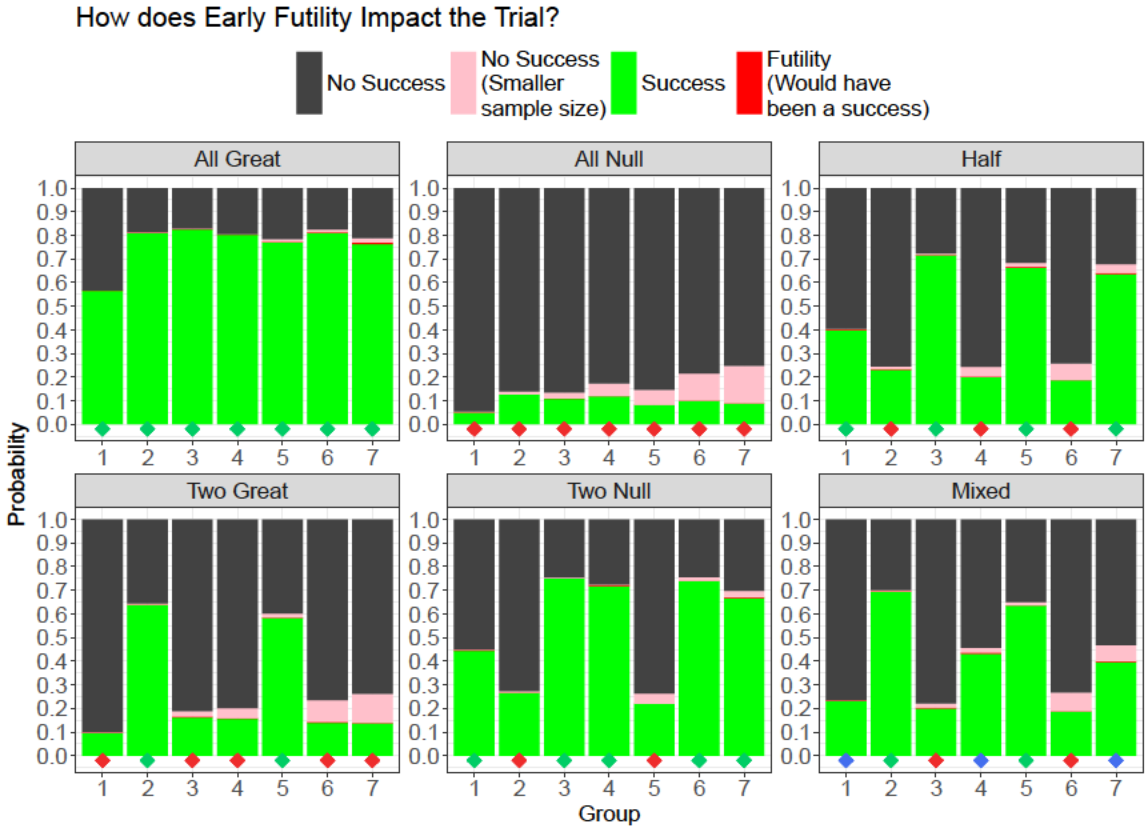


Figure 22 – Probability of success in each group for each scenario when early futility is conducted. This plot provides a comparison for overall performance of the planned design relative to one where early futility stopping prior to sample size expansion is not conducted. The green, blue, and red diamonds indicate whether in truth groups were effective, moderately effective, or not effective respectively.

10 References

Berry, S., Broglio, K, Groshen, S. Berry, D. (2013). Bayesian Hierarchical Modeling of Patient Subpopulations : Efficient Designs of Phase II Oncology Clinical Trials. Clinical Trials 10(5) 720-734.

Escobar, M., West, M. (1995) Bayesian Density Estimation and Inference Using Mixtures. Journal of the American Statistical Association, (90) 577-588.

Neal, R. (2000). Markov Chain Sampling Methods for Dirichlet Process Mixture Models. Journal of Computational and Graphical Statistics, (9) 249-265.

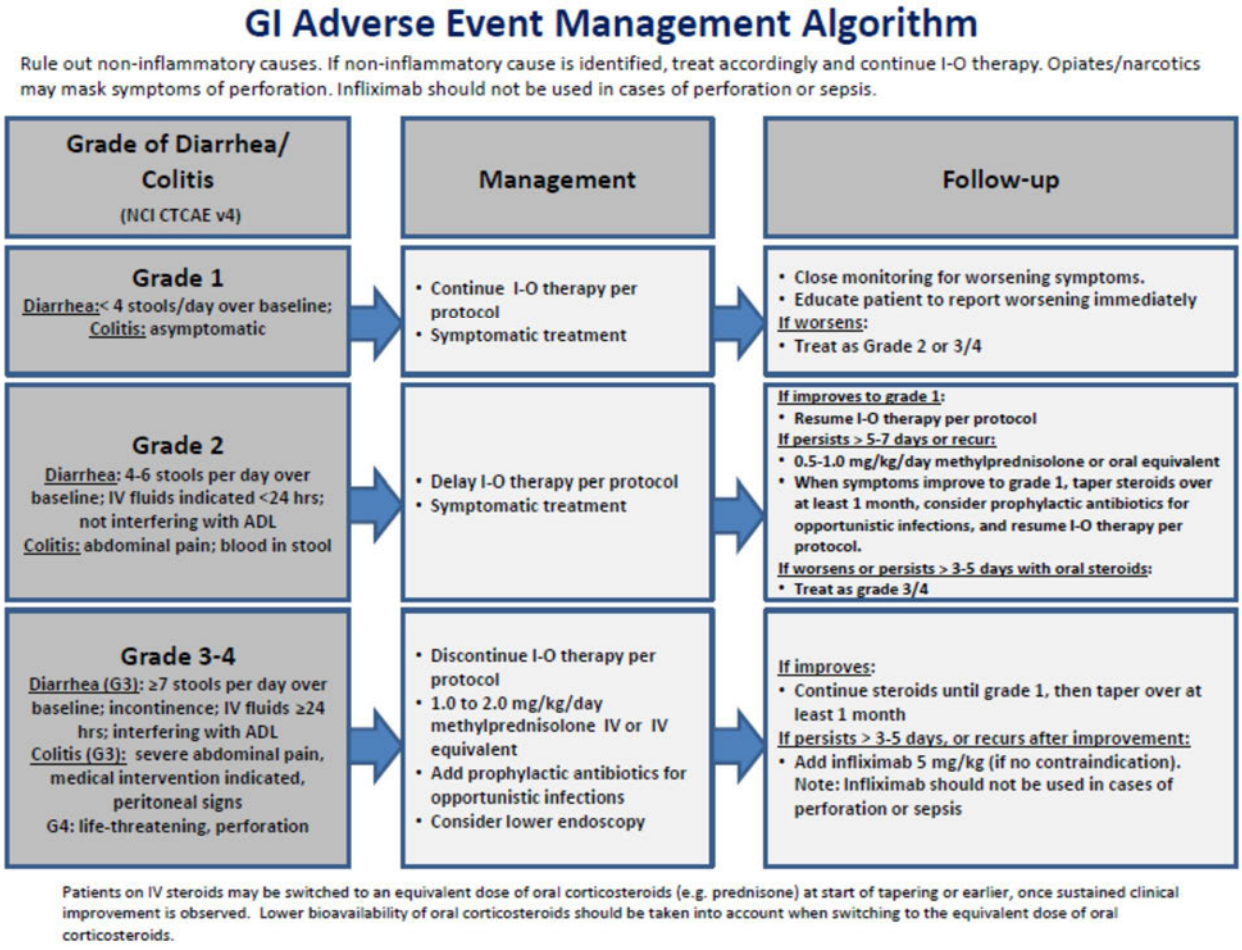
[redacted]

14.5 Appendix 5: Recommended management algorithms for suspected toxicities

These general guidelines for management of toxicities (Postow 2015) constitute guidance to the Investigator and are not intended to substitute institutional standard of care practice.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

14.5.1 GI adverse event management algorithm



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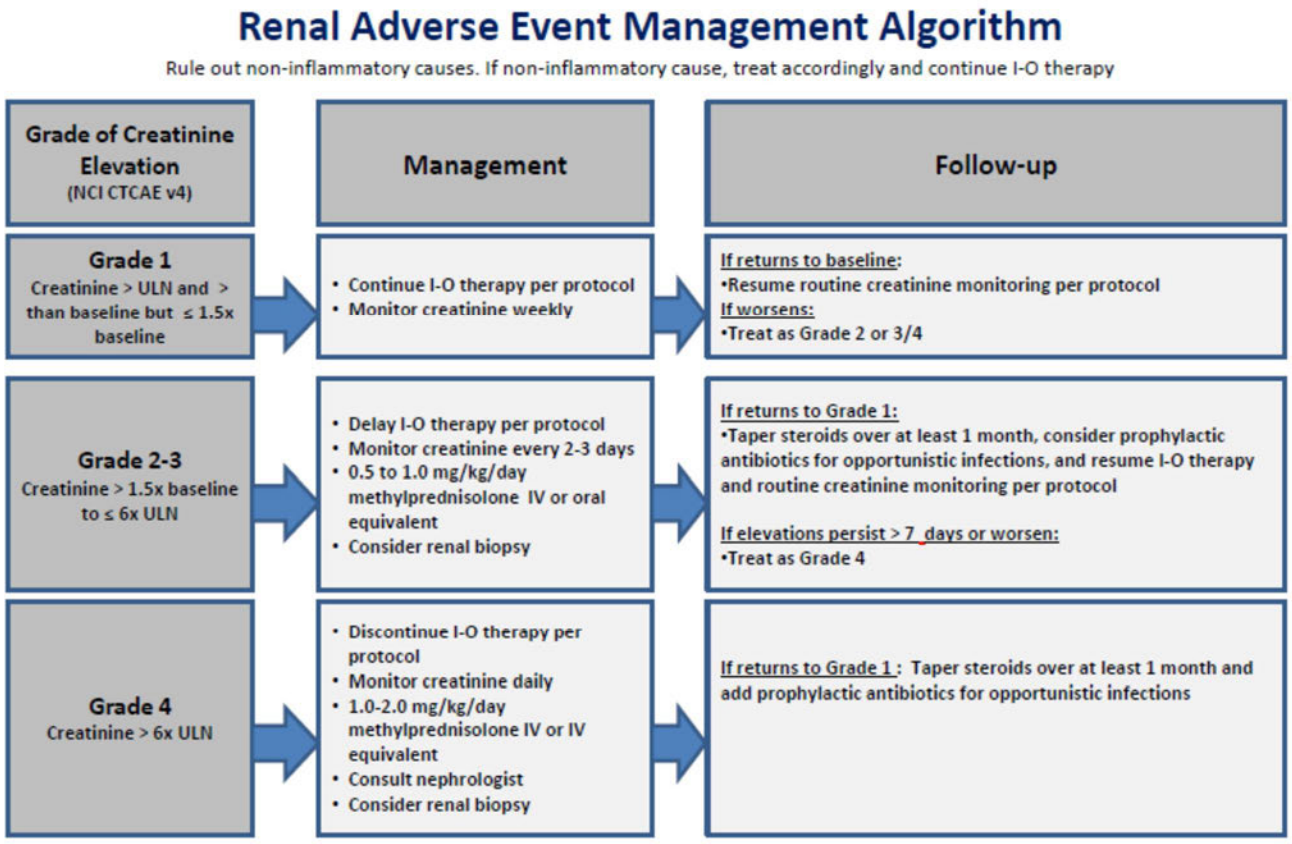
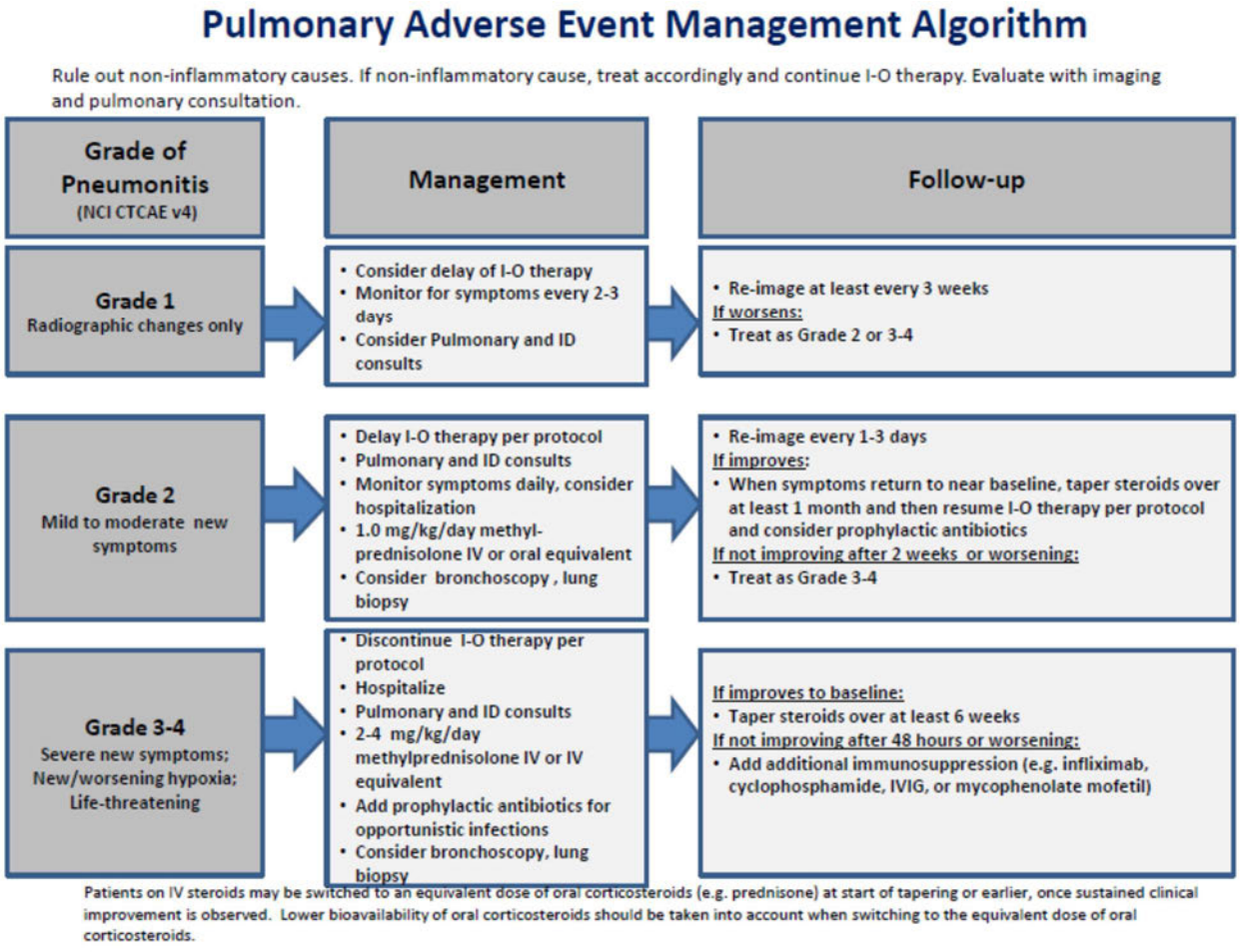
14.5.2 Renal adverse event management algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

[redacted]

14.5.3 Pulmonary adverse event management algorithm



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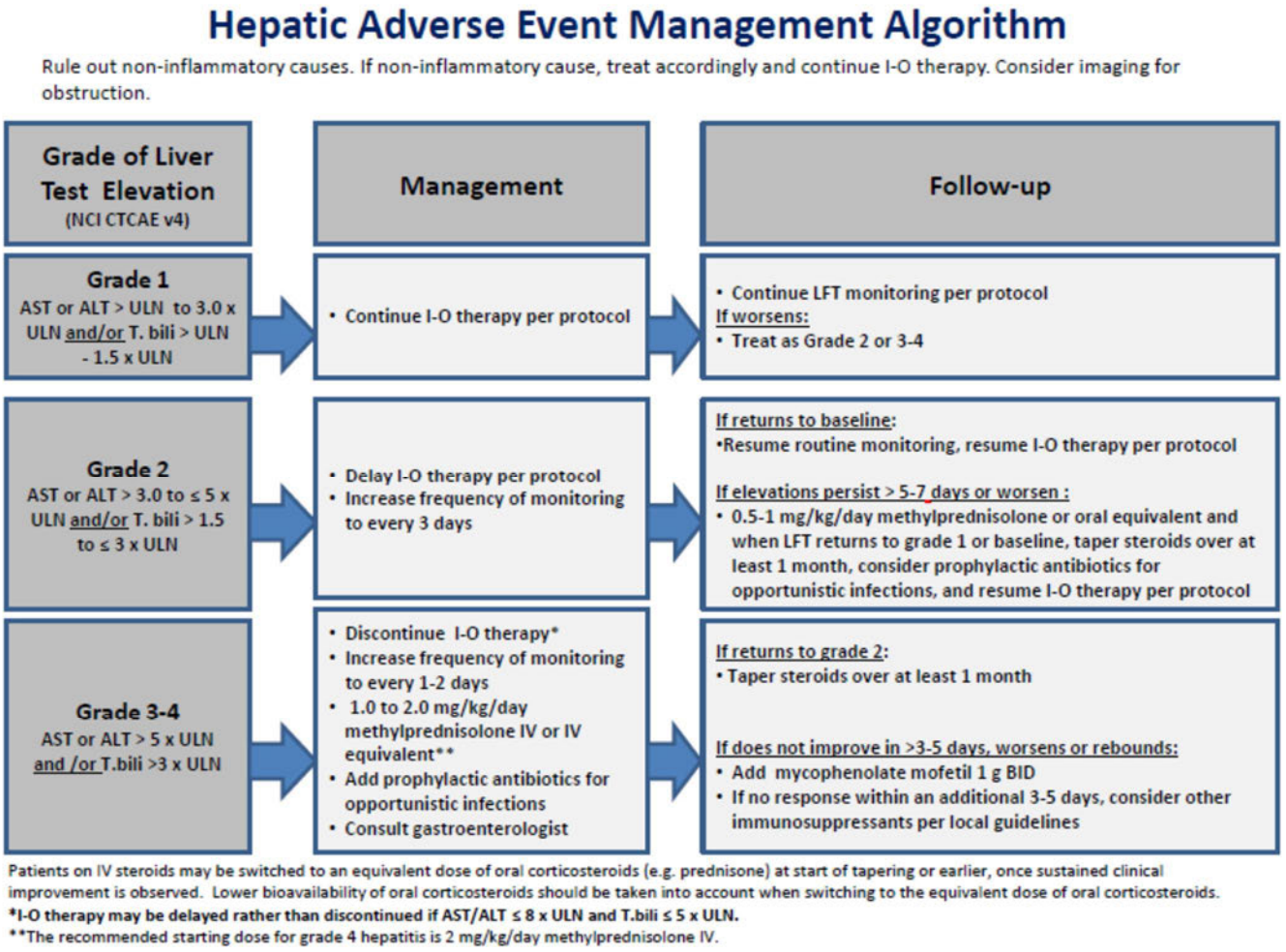
14.5.4 Hepatic adverse event management algorithm



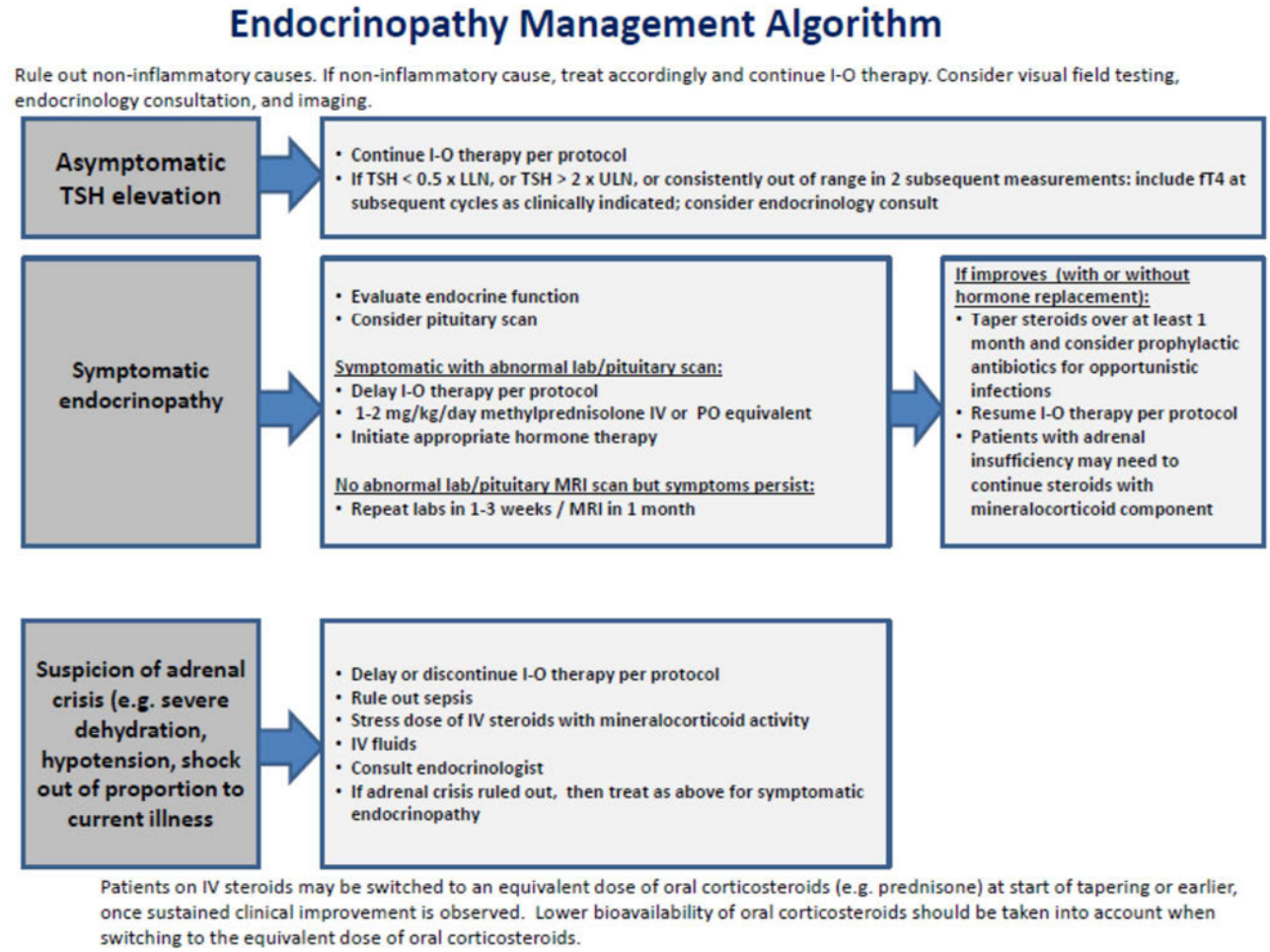
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**

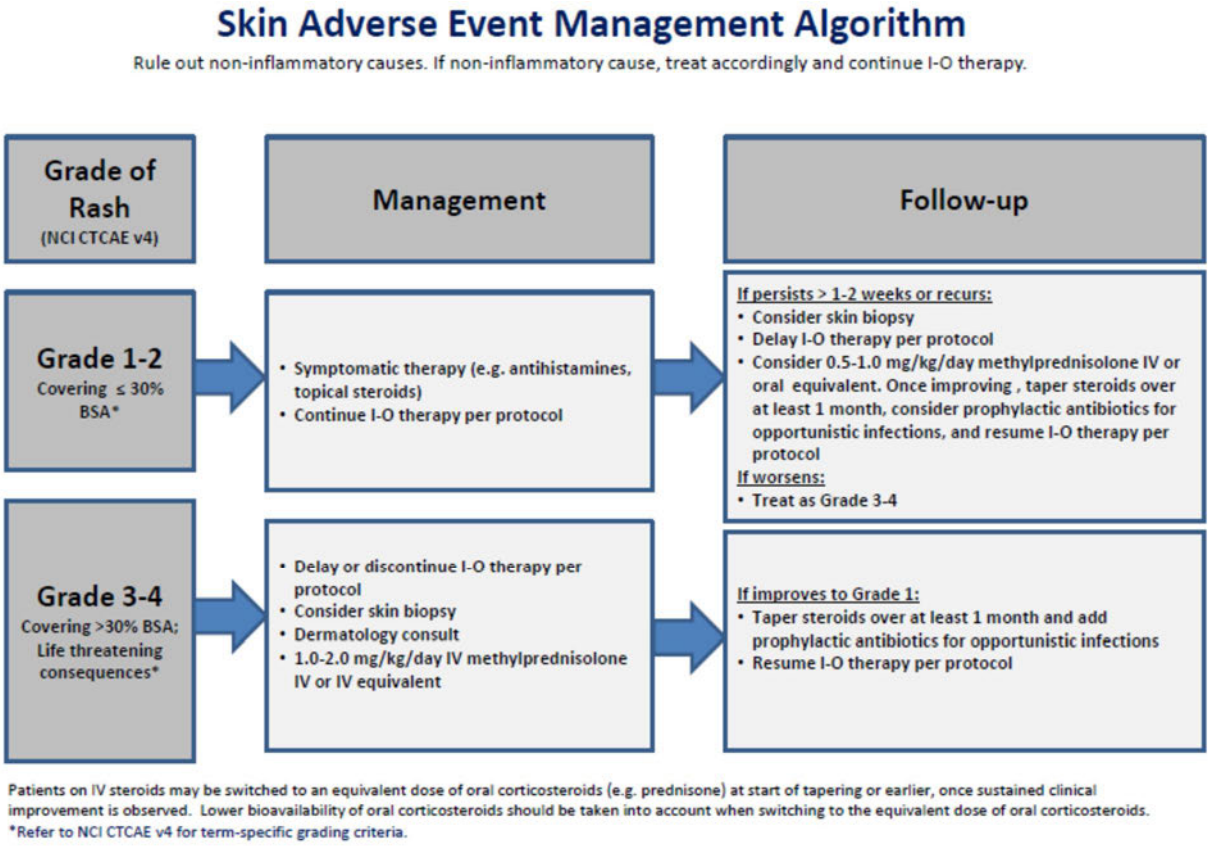
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

[redacted]

14.5.5 Endocrinopathy management algorithm



14.5.6 Skin adverse event management algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

[redacted]

14.5.7 References (available upon request)

Postow MA, Chesney J, Pavlick AC, et al (2015). nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med.;372(21):2006-17 (supplementary appendix).

[redacted]