NOVARTIS

Clinical Development

LAG525

Protocol CLAG525X2101C / NCT02460224

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

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Table of contents

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[redacted]

[redacted]

List of figures

List of tables

[redacted]

List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AMI	Acute Myocardial Infarction
APC	Antigen Presenting Cell
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Curve
BLRM	Bayesian Logistic Regression Model
CDP	Clinical Development Plan
[redacted]	[redacted]
CMO&PS	Chief Medical Office and Patient Safety
CRC	Colorectal cancer
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
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
CV	Cardiovascular
DCR	Disease Control Rate
DDP	Dose Determining Pharmacokinetic Set
DDS	Dose-Determining Safety Set
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ER	Estrogen Receptor
eSAE	Electronic Serious Adverse Event
EWOC	Escalation With Overdose Control
FAS	Full Analysis Set
FIH	First In Human
FU	Follow Up
GDPR	General Data Protection Regulation
GEJ	Gastro-Esophageal Junction
GLP	Good Laboratory Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HED	human equivalent dose
HER2	Human Epidermal growth factor Receptor 2
HNSTD	highest non-severely toxic dose
i.v.	Intravenous(ly)
IEC	Independent Ethics Committee
[redacted]	[redacted]
IG	Immunogenicity
[redacted]	[redacted]
IL-6	Interleukin-6
IRB	Institutional Review Board
irAE	Immune Related Adverse Event
irRC	immune related Response Criteria

[redacted]

ITIM	Immunoreceptor Tyrosine-based Inhibitory Motif
KO	Knockout
LAG-3	Lymphocyte activation gene-3
LLOQ	Lower Limit Of Quantitation
LMWH	Low Molecular Weight Heparin
mAb(s)	monoclonal Antibody(ies)
MHC	Major Histocompatibility Complex
MSI-H	Microsatellite instability high
MTD	Maximum Tolerated Dose
NOAEL	No Observed Adverse Effect Level
NPC	Nasopharyngeal cancer
NSCLC	Non-Small Cell Lung Carcinoma
NYHA	New York Heart Association
ORR	Overall Response Rate
[redacted]	[redacted]
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamics
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PFS	Progression Free Survival
PK	Pharmacokinetics
PPS	Per Protocol Set
PR	Progesterone Receptor
Q2W	Every 2 weeks dosing schedule
Q3W	Every 3 weeks dosing schedule
Q4W	Every 4 weeks dosing schedule
RAP	Report and Analysis Plan
RCC	Renal Cell Cancer
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended phase two dose
SAE	Serious Adverse Event
SEC	Safety Event Categories
SJS	Stevens-Johnson syndrome
TCR	T Cell Receptor
TEN	Lyell syndrome/toxic epidermal necrolysis
TIL(s)	Tumor Infiltrating Lymphocyte(s)
[redacted]	[redacted]
TNBC	Triple Negative Breast Cancer
TTR	Time To Response
US	United States
WT	Wild type

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Sample	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.: q28 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
Patient Number (Patient No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Personal Data	Patient information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information, and biological samples.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression [redacted]
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; may or may not also be the point/time of premature patient withdrawal
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

[redacted]

Withdrawal of Study Consent	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data.

Protocol summary:

Protocol number	CLAG525X2101C
Title	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.
Brief title	Phase I/II study of single agent LAG525 or combination of LAG525 and PDR001 in patients with advanced malignancies.
Sponsor and Clinical Phase	Novartis Phase I/II
Investigation type	Monoclonal antibody
Study type	Interventional
Purpose and rationale	The purpose of this study is to characterize the safety, tolerability including determination of maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D), pharmacokinetics (PK), pharmacodynamics (PD) and anti-tumor activity of LAG525 as a single agent and in combination with PDR001, an antibody directed against PD-1 under investigation in a separate study ([PDR001X2101]). In addition, the safety, tolerability, pharmacokinetics and pharmacodynamics of single-agent LAG525 in Japanese patients will be evaluated and characterized. LAG-3 binds its ligand MHC Class II, and regulates T cell signaling. Blockade of LAG-3 has been shown to increase T cell proliferation and cytokine secretion, most notably IFN-γ. LAG-3 expression is also correlated with increased suppressive function in both FoxP3-positive natural regulatory T cells and induced FoxP3-negative regulatory cells. By blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2, PDR001 inhibits the PD-1 immune checkpoint, resulting in activation of an antitumor immune response by activating effector T-cells and inhibiting regulatory T-cells. Preclinical studies in the Sa1N fibrosarcoma and MC38 colon carcinoma models demonstrated tumor growth inhibition with anti-LAG-3 as a monotherapy with enhanced tumor growth inhibition observed with the combination of anti-LAG-3 and anti-PD-1 immunotherapy. Expression analysis in human tumor infiltrating lymphocytes (TILs) from cancer patients supports this conclusion, with LAG-3 and PD-1 co-expression identified on tolerized TILs in patients with ovarian cancer and microsatellite high colorectal carcinoma (MSI-H CRC).
Primary Objective(s)	**Phase I part** ● To estimate the RP2D or MTD for single agent LAG525 in all patients (including for Japanese patients) ● To estimate the RP2D or MTD for the combination of LAG525 and PDR001 **Phase II part** ● To estimate the overall response rate per RECIST V1.1 for single agent LAG525 as well as for the combination of LAG525 and PDR001

Secondary Objectives	● To characterize the safety and tolerability of single agent LAG525 given alone and in combination with PDR001 ● To characterize the pharmacokinetic profile of single agent LAG525 given alone and in combination with PDR001 ● To assess emergence of anti-LAG525, and anti-PDR001 antibodies following one or more intravenous (i.v.) infusions of single-agent LAG525 given alone or in combination with PDR001 ● To evaluate the preliminary antitumor activity of single agent LAG525 given alone or in combination with PDR001
Study design	This study has been designed as a phase I/II, multi-center, open-label study starting with a phase I dose escalation part (including a separate Japanese single-agent dose escalation arm) followed by a phase II part. Arm A: single agent LAG525 Arm B: combination of LAG525 and PDR001 Arm C: single agent LAG525 dose escalation in Japanese patients Data from the dose-escalation arms will be analyzed separately and pooled as appropriate. If the recommended dose of single agent LAG525 is the same in Arms A and C, patients enrolled in Japan may be recruited into the Phase II single agent part of the study. In addition, if the recommended dose of PDR001 for Japanese patients in the PDR001X1101 study is the same as that determined in study PDR001X2101, Japanese patients may also enter the combination parts of study LAG525X2101 at whichever dose is being tested at that time. Both PDR001 and LAG525 will be administered i.v. once every two weeks until a patient experiences unacceptable toxicity, progressive disease as per irRC or treatment is discontinued at the discretion of the investigator or the patient. In the combination cohort, the two antibodies will be administered separately with a break of 30 minutes between administrations. Infusions of each antibody can be extended to up to 2 hours if clinically indicated and the break between LAG525 and PDR001 antibody infusions can be up to 4 hours if clinically indicated. A cycle is defined as 28 days (21 days for patients on Q3W dosing schedule) for both monotherapy LAG525 and the combination of LAG525 and PDR001. For the combination arm, the first dose for the first two patients treated at each untested dose level will be staggered by 24 hours.
Population	The phase I part of the study will be conducted in adult patients with advanced solid tumors. The phase II part of the study, both single agent and combination arms, will be conducted in adult patients with melanoma, NSCLC and renal cancer with or without PD-1/PD-L1 treatment experience. The combination arm will also be conducted in patients with mesothelioma and TNBC with or without PD-1/PD-L1 treatment experience.

Inclusion criteria	1. Written informed consent must be obtained prior to any procedures. For ' Japan only: written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years. 2. Age ≥ 18 years 3. Phase I part: Patients with advanced/metastatic solid tumors, with measurable or non-measurable disease as determined by RECIST version 1.1 (refer to Appendix 1), who have progressed despite standard therapy or are intolerant of standard therapy, or for whom no standard therapy exists. 4. Phase II part: Patients with advanced/metastatic solid tumors, with at least one measurable lesion as determined by RECIST version 1.1, who have had disease progression. Additionally, the following must apply: a. NSCLC: i. Disease recurrence or progression during or after no more than one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease. Prior maintenance therapy is allowed (considered pemetrexed, erlotinib, bevacizumab). ii. Patients must have been tested for mutations affecting EGFR and/or ALK. (Patients with a known mutation in one gene need not be tested for the other). Patients with ALK or EGFR-positive NSCLC must have had recurrent or progressive disease after treatment with the corresponding inhibitor and no more than one platinum doublet-based chemotherapy, in any sequence. b. Melanoma: i. Patients with BRAF V600 mutation positive disease must have objective evidence of progression of disease after treatment with a BRAF inhibitor alone or in combination with other agents. ii. Patients with BRAF wild-type disease must have objective evidence of progression of disease but are not required to have received prior therapy. c. Renal: i. Patients must have objective evidence of progression of disease during or following at least one regimen of treatment for advanced renal cancer. d. Mesothelioma: i. Patients must have objective evidence of progression of disease during or following at least one prior line of systemic chemotherapy for advanced disease. e. TNBC: i. Patients must have objective evidence of progression of disease during or following no more than 2 prior lines of systemic chemotherapy for advanced disease. Patients must have received a prior taxane-containing regimen. 5. ECOG Performance Status ≤ 1. 6. Phase I Part: Patients enrolled in the Phase I part of the study must provide a new tumor biopsy at baseline and during treatment if medically feasible. Phase II part: Patients enrolled in the Phase II part of the study must provide a new tumor biopsy at baseline and during treatment, if medically feasible.
Exclusion criteria (selected)	1. Presence of symptomatic central nervous system (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 at least 4 weeks prior to study entry and off steroids for at least 2 weeks before administration of any study treatment. 2. History of severe hypersensitivity reactions to study treatment ingredients or other mAbs

	3. Patient with out-of-range laboratory values defined as: ● Creatinine clearance (calculated using Cockcroft-Gault formula, or measured) < 40 mL/min ● 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 ● Alanine aminotransferase (ALT) > 3 x ULN ● Aspartate aminotransferase (AST) > 3 x ULN ● Absolute neutrophil count (ANC) < 1.0 x 109/L ● Platelet count < 75 x 109/L ● Hemoglobin (Hgb) < 9 g/dL ● Potassium, magnesium, calcium or phosphate abnormality CTCAE > grade 2 4. Clinically significant cardiac disease or impaired cardiac function 5. Active, known or suspected autoimmune disease. Patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to an autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or other conditions not expected to recur are permitted to enroll. Patients previously exposed to anti-PD-1 / PD-L1 treatment who are adequately treated for skin rash or who are receiving replacement therapy for endocrinopathies should not be excluded. 6. Patients who required discontinuation of treatment due to treatment-related toxicities with prior therapy directed against the same target as the drug(s) under study in this protocol. 7. History of drug-induced pneumonitis or current pneumonitis 8. Active infection requiring systemic antibiotic therapy. Patients requiring systemic antibiotics for infection must have completed therapy before screening is initiated. 9. HIV infection. Testing for HIV status is not necessary unless clinically indicated 10. 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. 11. Malignant disease, other than that being treated in this study 12. 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. 13. a. Systemic anti-cancer therapy within 2 weeks of the first dose of study treatment. b. For cytotoxic agents that have major delayed toxicity, e.g. mitomycin C, nitrosoureas or more recent immunotherapies, 4 weeks is indicated as washout period. c. For patients receiving anticancer immunotherapies such as CTLA-4 antagonists, 8 weeks is indicated as the washout period. 14. Patients receiving chronic treatment with systemic steroid therapy (>10 mg/day prednisone or equivalent) within 7 days of the first dose of study treatment, other than replacement-dose steroids in the setting of adrenal insufficiency. Topical, inhaled, nasal and ophthalmic steroids are not prohibited. 15. Patients receiving systemic treatment with any immunosuppressive medication thought to interfere with the mechanism of action of the study drugs, other than replacement–dose corticosteroids in the setting of adrenal insufficiency. 16. Use of any live vaccines against infectious diseases within 4 weeks of initiation of study treatment. 17. Major surgery within 2 weeks of the first dose of study treatment.

	18. Radiotherapy within 2 weeks of the first dose of study drug, except for palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass. To allow evaluation of response to treatment, patients enrolled in the Phase II part must have remaining measurable disease that has not been irradiated. 19. Participation in an interventional, investigational study within 2 weeks prior to the first dose of study treatment. 20. Presence of ≥ CTCAE grade 2 toxicity (except alopecia, peripheral neuropathy and ototoxicity, which are excluded if ≥ CTCAE grade 3) due to prior cancer therapy. 21. Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GMCSF, M-CSF) ≤2 weeks prior to the first dose of study treatment 22. 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. 23. 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 LAG525 or PDR001. 24. 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	Tumor assessment per RECIST v1.1 and per irRC
Safety assessments	Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs
Other assessments	Serum PK parameters and immunogenicity.
Data analysis	The study data will be analyzed and reported based on all patients' data of the Phase I and Phase II parts up to the time when all patients have completed at least six cycles of treatment or discontinued the treatment. Patient data from dose escalation will be analyzed by Arm and from Phase II by Group. Study data may be pooled where appropriate.
Key words	Phase I/II, LAG525, PDR001, Checkpoint inhibitor, PD-1, PD-L1, LAG-3.

Amendment 10 (27-Jun-2019)

Amendment rationale

The primary purpose of this amendment is to revise the definition of 'end of study' to include the option for patients still on study treatment and who, in the opinion of the investigator, are still deriving clinical benefit at the time of end of study, to transfer to another study or to an alternative treatment option to continue providing study treatment to these patients.

[redacted]

Changes to the protocol

[redacted]

Section 4.1.3 and Section 4.3 was updated to include the addition of language to account for patients who would transfer into another study or an alternative treatment option to continue provision of study treatment.

Section 7.1.3 was updated to include the addition of language to specify that patients who transfer to another study or an alternative treatment option to continue provision of study treatment will complete end of treatment procedures.

Section 7.1.5 was updated to include the addition of language to specify that patients who transfer into another study or an alternative treatment setting to continue provision of study treatment will not complete the safety, disease progression [redacted].

[redacted]

Study status

As of 26-Mar-2019, 450 patients have been enrolled in this trial. Of the 450 patients, 255 patients have been treated in the dose escalation part, of which 134 received LAG525 single agent and 121 received LAG525 in combination with PDR001 and 235 patients that have been treated in the combination dose expansion part. As of 26-Mar-2019 there were 39 active patients. Ten of these patients were enrolled in the dose escalation part and 29 patients were enrolled in the dose expansion part.

[redacted]

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) 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.

Amendment 09 (16-Aug-2018)

Amendment rationale

The primary purpose of this amendment is to incorporate health authority-requested language requiring study treatment discontinuation in the event of Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN).

After the occurrence of a case of Stevens Johnson Syndrome (SJS) in a study with PDR001 in combination with another investigational agent, 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 15 June 2018. This protocol amendment is now formalizing these changes in the dose modification section and corresponding table describing the criteria for dose reduction/interruption and re-initiation of treatment for adverse drug reactions. Changes to other sections of the protocol have been made to align with the updated dose modification section.

In addition, the protocol has been revised to align with recently published guidelines on the clinical management of suspected immune-related toxicities.

Other modifications of the protocol are specified below:

- Withdrawal of study consent language has been updated to reflect the European Economic Area General Data Protocol Regulation (GDPR) requirements.
- [redacted]
- Clarify language regarding Progressive Disease in the End of Treatment disposition section. The criteria for progressive disease will include evaluation as per RECIST 1.1 and as determined clinically by the Investigator, in addition to per irRC.
- Language within the statistical analysis section of protocol was updated to add details and clarifications for reporting secondary safety and efficacy objectives. [redacted]
- Language within guideline for irRC has been updated to clarify the selection of new measurable lesions, and calculation of follow-up evaluations.

Study status:

The CLAG525X2101C study started enrollment on 17-June-2015. As of 21-Jun-2018, 255 patients have been treated in the Phase I study part and 212 patients have been treated in the Phase II study part which is currently ongoing. As anti-tumoral activity was not observed with LAG525 single agent but was seen at several dose levels of LAG525 in combination with PDR001, it was decided that only the combination portion Phase II expansion would be enrolled. This was not a consequence of any safety concern.

[redacted]

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.

Glossary of terms was updated to include the definition for Personal Data and Withdrawal of study consent.

Section 5.3 exclusion criteria was changed to align with updated recommended dose limiting toxicity table.

Section 6.2 and Table 6-4 was updated to align with recently published guidelines on the clinical management of suspected immune-related toxicities.

Section 6.3 and Table 6-5 was updated to align with recently published guidelines on the clinical management of suspected immune-related toxicities.

Section 6.3.5 was updated to include allowed dose of systemic steroid used for the management of other concurrent medical conditions.

Section 7.1.3 was updated to have progressive disease include per RECIST 1.1 or as determined clinically by the Investigator.

Section 7.1.4 was updated to differentiate sample use after a patient withdraws consent based on different regulations/laws around the world.

[redacted]

Table 7-6 footers were adjusted to clarify that the 1-hour post infusion sample should be taken at all dosing visits from Cycle 1 through Cycle 6 unless noted otherwise.

Section 8.3 was updated to note that if the mother consents outcome data will be collected for up to 12 months after the birth of the child.

Section 10.5.2 was updated to clarify data reporting for secondary efficacy objectives.

Section 10.5.3.1 was updated to clarify what analysis set will be used for safety analysis.

Section 10.5.3.2 was updated to clarify which adverse event summaries will be produced.

Section 14.2 was updated to clarify the selection of new measurable lesions and calculation of follow-up evaluations.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes in this amendment identified above as being related to the USM have already been implemented by a USM letter issued on 15 June 2018. These changes are required for patient safety (i.e. necessary to eliminate immediate hazards to the trial subjects ICH GCP 3.3.8). Therefore, they were required to have been implemented prior to IRB/IEC approval of this amendment.

[redacted]

All other 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.

[redacted]

Amendment 08 (21-Jun-2017)

Amendment rationale

The purpose of this amendment is to incorporate the following modifications:

- Addition of mesothelioma and triple negative breast cancer (TNBC) indications in the combination arm of the phase II part of the study, based on preliminary evidence of anti-tumor activity seen in these indications during the dose-escalation portion of CLAG525X2101C (As of 20Mar2017, 2 partial responses in mesothelioma and 2 partial responses in TNBC per RECIST), as well as activity reported in recent publications (Alley 2017; Nanda 2016) of other checkpoint inhibitors.
- To allow single-agent LAG525 patients to continue study treatment with LAG525 in combination with PDR001 upon disease progression after at least 4 cycles of LAG525 monotherapy treatment and to detail the required tests/samples to be collected. This modification to the protocol will: 1.) provide the opportunity for PDR001 treatment to a small number of patients who may not otherwise have access to a PD-1 inhibitor, and 2.) allow potentially more effective combination treatment with simultaneous LAG525 + PDR001 to patients who enrolled onto the LAG525 single-agent arm.
- Reduced PK blood sampling timepoints in order to minimize the number of blood samples collected for the Phase II patients.
- Inclusion criteria 5: ECOG performance status to ≤ 1 (changed from ≤ 2) in order to ensure that patients enrolling into phase II indications have a better opportunity to receive and tolerate therapy.
- Inclusion criteria 6: All phase II patients must provide a new tumor biopsy at baseline and during treatment, if medically feasible. The change from optional to mandatory biopsies is expected to increase the number of paired tumor specimens available for investigation of biomarkers relevant to anti-LAG-3 and anti-PD-1 therapy. [redacted]
- Exclusion criteria 3: Modified potassium, magnesium, calcium or phosphate abnormality to CTCAE > grade 2 (changed from grade 1) as these lab values tend to fluctuate with frequent assessment and may not reflect the patient's overall clinical status. Low-grade changes can be managed with supplementation, and are not intended to be the basis for exclusion from the clinical trial if the patient otherwise meets inclusion/exclusion criteria. Hemoglobin must not be < 9 g/dl (changed from < 8 g/dl) in order to potentially increase patients' ability to tolerate therapy.
- Exclusion criteria 14: provided washout and corticosteroid dose guidance, since this information was not provided previously.
- LDH laboratory test has been added for TNBC patients. In the single-agent pembrolizumab trial (Nanda 2016) reported that LDH ≥ 2 times the upper limit of normal was a poor prognostic indicator, and was associated with disease progression.

[redacted]

- Best overall response per was changed from 30 to 150 days due to delayed patient response.
- Section 1.2.3.2 was updated with current clinical experience for LAG525 and PDR001.

Study status:

The CLAG525X2101C study started enrollment on 17-June-2015. As of 31-May-2017, 254 patients have been treated, all in the Phase I dose escalation part. Dose escalation treatment is ongoing in all treatment arms. The single-agent Phase I dose escalation part enrolled 133 patients (119 in Arm A and 14 in Arm C)

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.

Sections 2.1, 2.2.3, 4.1, 5.1, 5.2 and 10 have been updated as described in the above rationale section for the addition of mesothelioma and TNBC.

Sections 4.1.3, 7.1.1.2; and Table 7-1 have been updated to collect BRCA status if known for TNBC patients.

Sections 5.2 and 5.3 Inclusion/Exclusion criteria have been updated as described in the above rationale.

Table 7-4 has been updated for LDH to be collected for TNBC patients.

Table 7-6 has been updated related to PK blood samples as described in the above rationale section

Section 7.2.4 has been updated per biopsy collection clarification Inclusion criteria 6.

Table 7-7 has been updated to note total volumes and remove tube types; also changed PBMCs to Whole Blood for RNA

Section 6.2.3.2.1, Table 7-1 and Section 7.2.3 has been updated as described in the above rationale section related to single-agent LAG525 patients being allowed to continue study treatment with LAG525 in combination with PDR001.

Section 14.1.17 best overall response has been updated as described in the above rationale.

Section 14.2 has been updated to provide additional details for new measurable lesions, unknown response and only non-measurable disease at baseline.

Study status:

The CLAG525X2101 study started enrollment on 17-June-2015. As of 31-May-2017, 254 patients had been treated, all in Phase I the dose escalation study part. Dose escalation is ongoing in all treatment arms.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

[redacted]

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**.**

[redacted]

Amendment 07 (09-Dec-2016)

Amendment rationale

The purpose of this amendment is to incorporate the following modifications requested by a regulatory authority:

- Added guidance for patients with hyperglycemia or other signs and symptoms of diabetes and diabetic ketoacidosis. In patients with severe hyperglycemia, the recommendation to omit the dose of LAG525 and PDR001 and manage as per Institutional guidelines until resolved to ≤ Gr 1 has been added. Additionally, patients without pre-existing diabetes or previously determined to be normoglycemic, but shown to have an abnormal random blood glucose at screening must have a fasting blood glucose test performed. Any subsequently diagnosed hyperglycemia should be managed appropriately as per Institutional guidelines.

[redacted]

- In addition, the following eligibility criteria in sections 5.2 and 5.3 were updated in this amendment: Inclusion criteria 4: clarifications on prior therapy requirements for Phase II patients to account for current standard of care. In response to the rapidly changing approach to treatment of patients with melanoma, the eligibility criterion has been changed to no longer require patients with melanoma to have received systemic therapy prior to being eligible for study enrolment. All patients with BRAF V600 mutant melanoma must have received a BRAF inhibitor.
- Inclusion criteria 6: Corrected formatting issue and clarified newly collected tumor biopsy is required at baseline for both Phase I and II if medically feasible.
- Exclusion criteria 1: Added additional guidance regarding patients with brain metastases to ensure suitability of patients to be enrolled.

[redacted]

- Exclusion criteria 5: Clarified that patients with prior anti-PD-1/PD-L1 treatment who are adequately treated for skin rash or replacement therapy for endocrinopathies should not be excluded
- Exclusion criteria 6: Added to exclude patients who discontinued prior checkpoint inhibitor therapy due to checkpoint inhibitor-related toxicity as these patients may be at higher risk of re-bound toxicity
- Exclusion criteria 18: Clarified that patients enrolled in the Phase II part must have remaining measurable disease that has not been irradiated.

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.

Section 1.2.2.2 Clinical experience with PDR001: Updated based on CPDR001X2101 trial.

[redacted]

Section 5.2 and 5.3 Inclusion/Exclusion Criteria has been updated as described in the rationale section above.

Section 6.1 Dosing regimen: Clarified guidance regarding resuming study treatment after dose interruptions to accommodate all potential dosing schedules.

Section 6.1.2 Ancillary Treatments: Added that if a patient experiences a Grade ≥3 anaphylactic/anaphylactoid reaction, the patient will be discontinued from the study.

Section 6.2.3 Guidelines for dose escalation: Clarified that the additional cohorts may be opened for additional pharmacodynamics data.

Table 6-4 Criteria for defining DLTs: Clarified DLT window for each Treatment Arm.

Section 6.3 Dose modifications: Adjusted guidance regarding resuming study treatment after dose interruptions.

Table 6-5 Recommended Dose Modifications: Added guidance for Type 1 Diabetes mellitus. Also clarified that decreasing the dose level or the dosing frequency is the recommendation for certain toxicities.

Section 6.3.3 Permitted concomitant therapy: Added guidance for certain hormone therapies as well as bisphosphonates to allow patients who may benefit from study treatment to enroll but who are dependent upon the therapies described for symptomatic disease control.

Section 6.3.4 Permitted concomitant therapy: Clarified concomitant therapy requirements apply to the DLT observation window (1 cycle for single agent, 2 cycles for combination treatment arms).

Table 7-1 Visit evaluation schedule: added and adjusted biomarker collections and removed 60 and 120 day safety follow up visits.

[redacted]

Section 4.1.3 and 7.1.5 Follow up period revised to align with the PDR001 program: removed 60 and 120 day post-treatment safety follow up. Also clarified that the follow up can be done by telephone or patient visit.

Section 7.2.1 Efficacy assessments: Clarified the scope of vendor for independent review of imaging data for imaging data in Phase II.

Table 7-2 Disease assessment collection plan: Added guidance on bone scans.

Table 7-4 Local clinical laboratory parameters collection plan: Added note regarding fasting glucose. Also revised collection of LDH to encompass all melanoma patients regardless of when they enroll.

Section 7.2.2.5.2 Clinical Chemistry: Added guidance on when glucose testing should be fasting or non-fasting.

[redacted]

Section 8.1.1 Adverse Event definitions and reporting: Clarified that after initiation of new post-treatment antineoplastic therapy, only AEs suspected to be related to study treatment will be collected in the safety follow up period.

Section 8.2.2 Serious Adverse Event reporting: Clarified that if a patient starts a post treatment antineoplastic therapy, only SAEs suspected to be related to study treatment will be collected in the safety follow up period.

Section 8.5 Data Monitoring Committee: Clarified that events through the DLT observation window (through Cycle 1 for Arms A and C, through Cycle 2 for Arm B) will be discussed at dose escalation teleconferences.

Section 10.1.4 Dose-Determining Analysis Set: The dose-determining set definition has been clarified to account for possible different dosing schedules for LAG525 and PDR001.

[redacted]

[redacted]

Section 11.5 Publication of study protocol and results: Added details regarding Novartis publication process

Study Status

The CLAG525X2101 study started enrollment on 17-June-2015. As of 25-Aug-2016, 117 patients had been treated, all in Phase I the dose escalation study part. Dose escalation is ongoing in all treatment arms.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) 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.

[redacted]

Amendment 06 (05-Jul-2016)

Amendment rationale

The purpose of this amendment is to incorporate changes related to the following: With the available PK data obtained from the single agent first-in-human study CPDR001X2101, an exploratory population PK (PopPK) analysis showed that the T1/2 of PDR001 in man is 20 [17, 23] days (mean [90% CI]). Using five times the upper bound of the confidence interval of the half-life of 23 days and an added safety margin, the protocol is amended to increase the duration of contraception and safety follow-up periods post PDR001 treatment from 90 days to 150 days. These changes are related to an Urgent Safety Measure communicated on 08-June-2016 to all investigators. For logistical simplicity, these changes are applicable for all patients in both the single-agent LAG525 and combination LAG525 + PDR001 study arms.

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 underlined for insertions.

- Safety follow-up period increased from 90 to 150 days following end of treatment in the following sections:
  - 4.1.3 Study Periods
  - 4.3 Definition of end of the study
  - 6.3.2 Follow-up for toxicities
  - Table 7-1 visit evaluation schedule
  - 7.1.5 Follow up periods
  - 8.1.1 Safety reporting
  - 8.2.2 Reporting (of SAEs)
  - 10.5.3 Safety objectives (definition of on-treatment and post-treatment periods)
- Section 7.2.2.5.7 Pregnancy and assessment of fertility and Table 7-1: Pregnancy testing added at 120 and 150 days following end of treatment.
- Exclusion Criteria 23 and 24: Requirement for women of child-bearing potential and sexually active males to use contraception increased from 90 to 150 days following end of treatment.
- Table 7-4 Local lab: LDH added for Phase 2 melanoma patients to align with other trials in the PDR001 program
- Protocol Summary Table: Population language corrected to align with body text

Study Status

The CLAG525X2101C study is currently ongoing in the Phase 1 study part.

[redacted]

IRB/IEC/HA Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) 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.

Amendment 05 (12-Apr-2016)

Amendment rationale

The purpose of this amendment is to incorporate the following modifications of the exclusion criteria requested by a regulatory authority:

- Exclusion Criteria 02: Revised to exclude patients with history of severe hypersensitivity reactions to study treatment ingredients or other mAbs
- Exclusion Criteria 07: Criterion added to exclude patients with a history of drug-induced pneumonitis or current pneumonitis
- Exclusion Criteria 23: Clarified the definition of women who are considered post-menopausal and not of child bearing potential

Additional changes to the protocol:

- Exclusion Criteria 13: Washout period requirements for anti-cancer therapies have been split for clarification. Four-week washout period requirement for recent immunotherapies has been added.
- Table 6-4: Clarified footnote regarding DLT observation window
- Section 6.1.2 and Table 6-5: Clarified wording regarding infusion reactions
- Table 7-1: Formatting corrected to clarify that capturing AEs and concomitant medications continues through the safety follow-up period
- Table 7-2: Clarified that bone scans or other disease assessment methods allowed per RECIST 1.1 may be used
- Section 10.1.4: Clarified minimum exposure for DDS for Q3W and Q4W schedule to align with Section 6.3.2
- Section 10.4.4, 10.7, 10.8, and 14.3.2: corrected wording to reference 12 Phase 2 groups

IRB/IEC/HA Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

[redacted]

Amendment 04 (12-Feb-2016)

Amendment Rationale

The purpose of this amendment is to include a Japanese dose escalation arm for single-agent LAG525 with the goal of informing subsequent clinical development opportunities in Japan.

The single agent dose escalation part of this study is already underway globally with the exception of Japan. At the time of writing this amendment patients are being treated with single-agent LAG525 at doses higher than the starting dose (1 mg/kg Q2W). In order to ensure that the safety and pharmacokinetic profiles of single-agent LAG525 are adequately characterized in Japanese patients at more than one LAG525 dose, a Japanese-specific dose escalation of single-agent LAG525 has been included in the protocol. The Japanese dose escalation will run separately from the ongoing dose escalation with a starting dose for single-agent LAG525 in Japanese patients of 1 mg/kg Q2W. Dose escalation decisions will be guided by a BLRM.

If the recommended dose of single agent LAG525 is the same in Arms A* and C**, patients enrolled in Japan may be recruited into the Phase II single agent part of the study. In addition, if the recommended dose of PDR001 for Japanese patients in the PDR001X1101 study is the same as that determined in study PDR001X2101, Japanese patients may also enter the combination parts of study LAG525X2101 at whichever dose is being tested at that time.

*Arm A: single-agent LAG525

**Arm C: single-agent LAG525 dose escalation in Japanese patients

Additional changes to the protocol:

The landscape of treatment with immunomodulatory therapy in oncology is evolving rapidly. In response to the growing number of patients with renal cancer receiving anti-PD-1/PD-L1 therapy, expansion arms have been added for patients with renal cancer who are refractory to or have relapsed following prior treatment with PD-1/PD-L1 inhibitors to explore whether LAG525 alone or in combination with PDR001 can overcome PD-1/PD-L1 resistance.

In order to provide more flexibility in the palliation of symptoms caused by some tumor lesions and allow patients to continue the study treatment, the prohibited concomitant therapy section was updated to allow localized radiotherapy for non-target lesions.

Because the determination of EGFR, ALK, or BRAF V600 status is not performed routinely as part of standard assessment of disease in all countries or study sites, this amendment includes the determination of these molecular parameters by a local laboratory, at screening, for patients with a tumor of unknown status. However, the test results will not be used for eligibility of enrollment.

List of 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 underlined for insertions.

- Section 1.2.2.2 Clinical Experience
  - Added a summary of PDR001X2101 study.
- Section 2.2: Rationale for the study design:

[redacted]

- Added a statement to include Japanese dose escalation arm for single-agent LAG525.
- A new section (Section 2.2.2) was created to describe Japanese dose escalation.
- Statement of recruitment of Japanese patients to the Phase II part was added to section 2.2.3.

- Section 3: Objectives and end points.
  - Primary objective was updated to include Japanese patients treated with single- agent LAG525.
- Section 4.1 Description of Study Design:
  - The study design was updated to include a separate Japanese dose escalation.
  - Figure 4-1 was updated to include a separate Japanese dose escalation arm with single-agent LAG525 (Arm C).
  - Updated treatment group after adding renal cell carcinoma pre-treated with PD-1/PD-L1 in the Phase II expansion part.
- Section 4.1.1 Phase I dose escalation.
  - Added single dose escalation arm (Arm C) for Japanese patients.
- Section 4.1.3 Study period
  - Added collection of EGFR, ALK, BRAF V600 status
- Section 5.2: Inclusion criteria.
  - Updated for Japan only: written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years age for Japanese patients.
- Section 5.3 Exclusion criteria
  - Removed one item in the exclusion criteria, which is prior PD-1 or PD-L1 directed therapy for renal cell carcinoma
  - Changed washout period from 6 weeks to 8 weeks for patients receiving anticancer immunotherapies such as CTLA-4 antagonists.
- Section 6.2. Dose escalation guidelines
  - Added Arm C throughout the section
- Section 6.2.3: Guidelines for dose escalation and determination of MTD/RP2D
  - Added Arm C to include Japan single agent dose escalation.
- Section 6.3.4 Permitted concomitant therapy requiring caution and/or action
  - Updated to allow all types of anti-coagulation be included as permitted concomitant therapy, not just warfarin and heparin
- Section 6.3.5 Prohibited concomitant therapy:
  - Clarified that limited-field palliative radiotherapy to non-target lesion(s) may be allowed after documented discussion with Novartis.
- Section 7.1 Study flow and visit schedule
  - Added wording to explain category “D” and “S” in Table 7-1
- Table 7-1 Visit evaluation schedule
  - Added collection of EGFR, ALK, BRAF V600 status

[redacted]

- Pregnancy test was updated to reflect that during the safety follow-up period, a pregnancy test can be performed at home if patients are not coming to the clinic for the safety follow up visits
- Added every 3 week dosing schedule to "study drug administration"

- Section 7.1.1.2 Patient demographics and other baseline characteristics
  - Clarified MSI, EGFR, ALK, or BRAF V600 status to be collected at baseline as appropriate.
- Section 7.1.2 Treatment period
  - A statement was added that for Japan only, patients enrolled in dose escalation are required to be hospitalized during the DLT evaluation period
- Section 7.1.5 Follow up period: 90-day safety follow up period
  - A statement was added to clarify that during the safety follow up period, if patients are not coming to the clinic for the safety follow-up visits, a pregnancy test may be conducted at home if patients are not coming to the clinic for the safety follow up.
- Table 7-2: Disease assessment collection plan
  - Table 7-2 was updated with detailed assessment collection plan.
- Section 7.2.2.5.7 Pregnancy and assessment of fertility
  - A statement was added to clarify that during the safety follow up period, if patients are not coming to the clinic for the safety follow-up visits, a pregnancy test may be conducted at home if patients are not coming to the clinic for the safety follow up visits
- Table 7-6: Pharmacokinetic blood collection log
  - Updated to provide specifications on some of the blood samples for Q2W, Q3W and Q4W schedules.
  - Footnote was updated that the sample collection may be stopped if sufficient data have been collected
- Section 8: Safety monitoring and reporting
  - Updated section 8 throughout to reflect eSAE reporting procedure at Novartis
- Section 10: Statistical Methods and data analysis.
  - Updated to include data analysis rules throughout the section; statistical hypothesis; model; and method of analysis for the Japanese-specific single agent LAG525 dose escalation.
- Section 14: Appendices.
  - Added a new Section14.4: "Statistical details of Phase I Bayesian logistic regression model (BLRM) in Japanese patients treated with single agent of LAG525".

[redacted]

IRB/IEC/HA Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) 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.

Amendment 03 (04-Dec-2016)

Amendment Rationale

The purpose of this amendment is to incorporate the following revision requested by a regulatory authority:

- To specify that if required by a Regulatory Authority, recruitment to combination dose levels will begin at dose level -1 (0.3 mg/kg LAG525 with 1 mg/kg PDR001) for patients from those countries.
- To specify that for the combination arm, the first dose for the first two patients treated at each untested dose level will be staggered by 24 hours.

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 underlined for insertions.

- Section 2.3 Rationale for dose and regimen selection
  - Specified that if required by a Regulatory Authority, recruitment to combination dose levels will begin at dose level -1 (0.3 mg/kg LAG525 with 1 mg/kg PDR001) for patients from those countries
- Section 4.1 Description of study design:
  - Specified that for the combination arm, the first dose for the first two patients treated at each untested dose level will be staggered by 24 hours.
  - Added that if required by a Regulatory Authority, recruitment to combination dose levels will begin at dose level -1 (0.3 mg/kg LAG525 with 1 mg/kg PDR001) for patients from those countries.
- Section 6.1.1 Dose regimen
  - Specified that for the combination arm, the first dose for the first two patients treated at each untested dose level will be staggered by 24 hours.
- Section 6.2.1 Starting dose rationale:
  - Added that if required by a Regulatory Authority, recruitment to combination dose levels will begin at dose level -1 (0.3 mg/kg LAG525 with 1 mg/kg PDR001) for patients from those countries
- Table 6-3 Provisional dose levels (Ph I Arm B: combinations of LAG525 and PDR001
  - Updated the footnote to specify that if required by a Regulatory Authority recruitment to combination dose levels will begin at dose level -1 (0.3 mg/kg LAG525 with 1 mg/kg PDR001) for patients from those countries
- Section 6.2.3 Guidelines for dose escalation and determination of MTD/RP2D
  - Added that if required by a Regulatory Authority, recruitment to combination dose levels will begin at dose level -1 (0.3 mg/kg LAG525 with 1 mg/kg PDR001) for patients from those countries
- Table 6-5 Recommended Dose Modifications for LAG525 and PDR001

[redacted]

- Added a footnote to Pancreatitis to explain: asymptomatic enzyme increases do not require delay of study treatment or dose reduction

[redacted]

- Section 7.2.2.5: Laboratory Evaluations
  - Clarified that cytokine release syndrome testing will be conducted centrally for sites not capable of local testing.

IRB/IEC/HA Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

[redacted]

Amendment 02 (14-Sep-2015)

Amendment Rationale

The goal of this amendment is as follows:

1. To focus the Phase II expansion on three main cancers: NSCLC, melanoma and renal cell carcinoma, both single agent and combination Phase II expansion will be conducted in cancers which are known to be responsive to single-agent PD-1 inhibition, to determine the efficacy of single-agent LAG525 and the combination of LAG525 with PDR001 in both the PD-1/PD-L1 pre-treated and naive settings.
   a. Expansion arms for patients in the PD-1/PD-L1 naïve setting will explore antitumor activity of single-agent LAG525 and the combination of LAG525 with PDR001.
   b. Expansion arms have been added for patients with NSCLC and melanoma who are refractory to or have relapsed following prior treatment with PD-1/PD-L1 inhibitors to explore whether LAG525 can overcome PD-1/PD-L1 resistance.
   c. [redacted]
2. Modify the inclusion criteria in the phase II part of the study for patients with NSCLC and melanoma who are naïve to PD-1/PD-L1 treatment, to align with study CPDR001X2101 where PDR001 is being tested as a single-agent in the same patient populations.
3. Allow the option to test alternate dosing (i.e. flat dosing) within single agent dose escalation and/or Phase II expansion if flat dosing is supported by emerging PK data generated during the study. Flat dosing may also be tested in the combination part of the study for both LAG525 and PDR001.
   a. Flat dosing decreases operational complexity with easier study drug preparation and may reduce the possibility of dosing errors.
4. Allow the option to test two doses of LAG525 during Phase II expansion
5. Allow collection of a blood sample for cytokine assessment (IL-6 [redacted]) for all patients at screening. This baseline sample will serve as a comparator for those patients who require follow-up assessment of cytokines (i.e. in case of an adverse event suspected to be cytokine release syndrome).
6. Clarification of certain exclusion criteria, and prohibited concomitant medications
7. Align the collection and analysis of [redacted] with preclinical evidence on the timing of immune response in tumor after therapy with PD-1 blocking antibodies [redacted]
8. Changed safety monitoring / reporting and follow up window from 30 days to 90 days throughout the document. During the safety follow up period, safety evaluations,

[redacted]

pregnancy test need to be performed on 30, 60 and 90 days after the last dose of the study drug.

9. To align this protocol with the latest Novartis guidelines for the prevention of pregnancies in participants in clinical trials and their partners, the exclusion criteria were updated to exclude sexually active male subjects who are not willing to use a condom during the study.

Additional Changes to the protocol

Section 2.2.2 Phase II:

- Updated patient populations to include those treated with prior PD-1 or PD-L1 inhibitors.

Section 2.3 Rationale for dose and regimen selection

- Introduced alternative dosing (flat dose [mg]) which may be implemented during the study

Section 4.1: Description of study design:

- Modified figure 4-1 study design
- Modified Arm A to include group 4 and 5 for the single dose expansion part
- Modified Arm B to include NSCLC and Melanoma patients who have received prior PD-1 or PD-L1. Removed patients with gastric, CRC, NPC and renal cell carcinoma with previous treatment of PD-1 / PD-L1.

Section 4.1.3 Study period

- Clarified biopsy requirements, i.e. in dose escalation part, it mandatory, in dose expansion part, it is optional.

Section 5.1 Patient population

- Updated patient populations in the expansion phase.

Section 5.2: Inclusion criteria

- Added detailed patient population criteria for the patients to be enrolled in the Phase II part of the study.
- [redacted]

Section 5.3: Exclusion criteria

- Added language about certain diseases /conditions that require steroid treatment are permitted to be enrolled
- RCC patients who have received prior PD-1/PD-L1 are now excluded from the Phase II expansion. Clarified that the topical use of steroids are not prohibited.
- Addition of exclusion criterion 24, which excludes sexually active male subjects who do not use a condom during intercourse

Section 6.1.1 Dosing regimen

- Clarified how to handle a dosing delay for PDR001 within the combination arm if clinically indicated (e.g. if an infusion reaction occurs after LAG525 administration).

[redacted]

Emphasized that the break between LAG525 and PDR001 infusions can be up to 4 hours if clinically indicated. If PDR001 cannot be administered safely within 4 hours after LAG525 administration, the dose must be omitted.

- Clarified there is a 7-day window for a dose delay of either single agent or combination treatment.
- Alternate dosing (i.e. a flat dose) may be implemented after at least one cohort has been tested using a weight-based dosing paradigm
- Introduced an option in the Phase II expansion to test 2 dose levels

Section 6.2.2 Provisional dose levels

- Modified Table 6-2 and Table 6-3 to add flat doses

Section 6.2.3

- Added flat dose in "mg" may be explored for single agent by opening new cohorts in the escalation part

Section 6.2.4

- Added DLT window for Q3W dosing schedule. It will 21 days for patients in Q3W dosing schedule.
- Clarified the duration of rash and/or photosensitivity should be 7 days instead of 14 days.

Section 6.3.1

- Removed the statement about maximum number of dose reductions allowed from Table 6-5 and placed the modified statement in the text, which allows more than 2 dose reductions of either drug if a patient is experiencing clinical benefit.

Section 6.3.2 Follow-up for toxicities

- Changed the follow-up window from 30 days up to 90 days. Safety evaluations will be conducted on 30, 60, and 90 days after the last doses of LAG525 and/or PDR001

Section 7.1 Study flow and visit schedule

- Added assessments for the cytokines IL-6 [redacted] at baseline
- Modified fresh tumor biopsy sample collection time, and changed the collection time point from cycle 2 to cycle 3.

Section 7.2.2.5.6 Cytokines

- Added baseline cytokines
- Added cytokine sample storage condition

Section 7.2.3 Pharmacokinetics and immunogenicity assessments

[redacted]

- Deleted the columns with dose reference ID
- Provided a footnote to analytes in Table 7-6.

[redacted]

Section 9.3 data collection

- Clarified PK and biomarker samples will be analyzed in central labs only, not in local labs.

Section 10: Statistical methods and data analysis

- Study groups were updated to reflect the new study design.
- Added alternative dose (flat dose in mg) and dosing schedule (Q4W) may be implemented during the study

Section 10.4.2 Statistical hypothesis, model, and method of analysis

- Clarified that DLT data from single agent LAG525 cohorts will be used in the BLRM for combo of LAG525 and PDR001
- Added BLRM for flat dosing
- Updated Phase II analysis

Section 10.8 sample size calculation

- Updated sample size justification for the phase II part

Section 14 Appendices

- Updated Appendix 14.3.2 for phase II statistical analysis

Amendment 01 (27-Apr-2015)

Amendment rationale

The purpose of this amendment is to incorporate the following revision requested by a regulatory authority:

- Revise the DLT criterion for thrombocytopenia to include CTCAE grade 3 thrombocytopenia with clinically significant bleeding as a DLT

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 underlined for insertions.

Section 6.2.4 Definitions of dose limiting toxicities (DLTs):

- Added grade 3 thrombocytopenia with clinically significant bleeding to hematology section of Table 6-4.

IRB/IEC/HA Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Immunotherapies that target immune checkpoints have recently shown strong efficacy and are emerging as key agents in cancer therapy. Antibodies targeting CTLA-4 (ipilimumab [BMS]) and PD-1 (e.g. nivolumab [BMS] and pembrolizumab [Merck]) demonstrate durable anti-tumor effects and an acceptable safety profile. While single agent treatments demonstrate promising efficacy, combinations of immunotherapy approaches suggest that synergistic blockade of co-inhibitory proteins demonstrates greater antitumor activity than the single agent (Wolchok 2013). Preclinical studies of the combination of PD-1 and LAG-3 demonstrate that simultaneous inhibition of both inhibitory receptors may have synergistic antitumor activity (Drake 2014; Woo 2012).

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).

Preclinical studies in the Sa1N fibrosarcoma and MC38 colon carcinoma models demonstrated tumor growth inhibition with anti-LAG-3 as a monotherapy with enhanced tumor growth inhibition observed with the combination of anti-LAG-3 and anti-PD-1 immunotherapy (Woo 2012). Expression analysis in human tumor infiltrating lymphocytes (TILs) from cancer patients supports this conclusion, with LAG-3 and PD-1 co-expression identified on tolerized TILs in patients with ovarian cancer and microsatellite high colorectal carcinoma (MSI-H CRC) (Chen 2014).

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

1.2.1 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 cynomolgus cross-reactive and shows functional activity.

1.2.1.1 Non-clinical experience with 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.

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.

[redacted]

1.2.1.2 Clinical experience with LAG525

This is the first in human (FIH) study for LAG525. Please refer to the [LAG525 Investigator's Brochure] for more details.

1.2.2 Overview of PDR001

PDR001 is a high-affinity, ligand-blocking, humanized anti-PD-1 IgG4 antibody (stabilized hinge, S228P) which blocks the binding of PD-L1 and PD-L2 to PD-1. PDR001 is cynomolgus cross-reactive and shows functional activity *in vitro* and *ex vivo*. For further details, please consult the most recent edition of the [PDR001 Investigator's Brochure].

1.2.2.1 Non-clinical experience PDR001

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 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.

[redacted]

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.

1.2.2.2 Clinical experience

The CPDR001X2101 study started enrollment on 27 April 2015 and is ongoing. As of 17 December 2015, a total of 58 patients had been treated in the study at the dose levels of 1, 3 and 10 mg/kg Q2W and 3 and 5 mg/kg Q4W. No patients have experienced a DLT. 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. 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].

1.2.3 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 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

As of a data cut-off date of 15-Nov-2016, a total of 198 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 106 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, 92 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.

2 Rationale

2.1 Study rationale and purpose

This is a FIH, phase I/II clinical study of single agent LAG525 and in combination with PDR001.

The goal of immunotherapy in cancer is to sustain or rescue an existing tumor antigen-specific immune response capable of eradicating the disease. Recent advances in cancer immunology revealed extensive interaction between the host immune system and the tumor suggesting that clinically evident tumors have evaded potentially effective antitumor responses. Tumor antigen-specific CD8+ and CD4+ T cells isolated from human tumors often display impaired effector function manifested by ineffective cytotoxicity and impaired cytokine secretion. The dysfunction of these tumor specific T cells is thought to result from the immunosuppressive tumor microenvironment and comprises T cell intrinsic and extrinsic mechanisms. T cell extrinsic mechanisms include suppressor cells (e.g. regulatory T cells (T_{reg}), myeloid derived suppressor cells, MDSC) and soluble cytokines (e.g. IL-10). T cell intrinsic suppression is coordinated via a series of membrane receptors on T cells which can be categorized into (1) those transducing negative activation signals (co-inhibitory receptors or “checkpoints” e.g. CTLA-4 or PD-1) and (2) those transducing positive signals for cell activation (co-stimulatory receptors, e.g. GITR, 41BB) (Leen 2007). The balance between the signals from co-stimulatory and co-inhibitory receptors controls T cell activation.

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).

Checkpoint inhibitors have been successfully introduced to clinical practice with the recent 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 which 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 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.

The purpose of this study is to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and anti-tumor activity of LAG525 as a single agent and in combination with PDR001, an antibody directed against PD-1 under investigation in a separate study [PDR001X2101]. PD-1 blockade has proven clinical efficacy in various disease settings, such as melanoma, non-small cell lung cancer (NSCLC), mesothelioma (Alley 2017), TNBC (Nanda 2016) and renal cell carcinoma.

Following determination of the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of LAG525 as a single agent, and of LAG525 in combination with PDR001, preliminary anti-tumor activity of single agent LAG525 and the combination of LAG525 and PDR001 will be assessed in melanoma, NSCLC, mesothelioma, TNBC and renal cancer in the expansion part. The RP2D will be determined from the collective experience in the clinic considering the safety data, pharmacokinetic data, pharmacodynamic data and any early antitumor activity observed along with the statistical inference from the Bayesian Logistic Regression Model (BLRM).

Expansion cohorts testing single agent LAG525 will open once the RP2D or MTD of single agent LAG525 is identified. Expansion cohorts testing the combination of LAG525 and PDR001 will open for enrollment once the RP2D or MTD of the combination is determined.

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Figure 2-1 Blockade of PD-1/PD-L1 and LAG-3 by PDR001 and LAG525

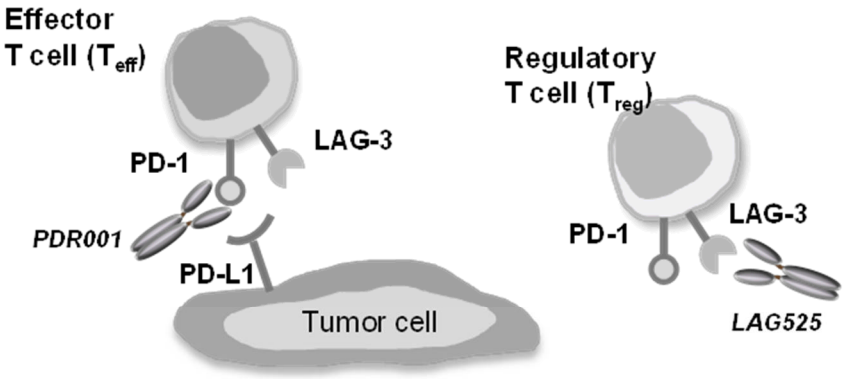


Figure 2-1 Blockade of PD-1/PDL-1 and LAG-3 by PDR001 and LAG525:
Simultaneously blocking two checkpoints may synergize for anti-tumor activity by targeting different cell types. PD-1 and LAG-3 are expressed on effector T cells as well as regulatory T cells. Blocking both checkpoints (with PDR001 and LAG525) may lead to enhanced T_{eff} cell and reduced T_{reg} cell activity. Differential expression of the checkpoints PD-1 and LAG-3 in different subsets of T cells remains an area of active investigation

2.2 Rationale for the study design

This is an open-label, phase I/II study of parallel cohorts with single-agent LAG525 or the combination of LAG525 and PDR001. The study consists of two parts: two parallel dose escalations with staggered starts in the Phase I part and Phase II cohorts at the maximum tolerated dose (MTD), or the recommended phase 2 dose (RP2D), if that is lower than the MTD, for the single agent arm and the combination arm in the Phase II part.

This study includes a Japanese dose escalation for single-agent LAG525 with the goal of informing subsequent clinical development opportunities in Japan (see Section 2.2.3).

2.2.1 Phase I

In the Phase I part, three dose escalations will be explored in advanced solid tumors: a single-agent dose escalation of LAG525 (Arm A), a separate single-agent dose escalation of LAG525 in Japanese patients (Arm C), and combination dose escalation of LAG525 and PDR001 (Arm B).

Dose escalation with combination of LAG525 and PDR001 will begin after the completion of at least the first two dose level cohorts of single agent LAG525. Then, the dose escalation arms (single agents and combination) may proceed in parallel. The design of the phase I part was chosen in order to establish the MTD/RP2D of LAG525 as a single agent and LAG525 in combination with PDR001 in patients with solid tumors amenable to immunotherapy. The dose escalation decision making will be guided by a Bayesian logistic regression model (BLRM) with overdose control (EWOC) principle based on DLT data in the context of available safety, PK and PD information. For details of the dose escalation, please refer to Section 6.2.

This open-label dose escalation study design using a BLRM is a well-established method to estimate the MTD, or identify a lower RP2D in cancer patients. The adaptive BLRM with EWOC principle controls the risk of DLT in future patients on study. The decisions on the single dose of LAG525 (during the single agent escalation) or in combination with PDR001 (during the combination escalation) are made by the Investigators and Novartis study personnel and will be based upon the dose identified to satisfy the EWOC criterion under the appropriate BLRM, patient tolerability and safety, PK and PD data available at the time of the decision Section 6.2.3.

2.2.2 Japanese single-agent dose escalation (Arm C)

The purpose of the Japanese dose escalation is to ensure that the safety and pharmacokinetic profiles of single-agent LAG525 are adequately characterized in Japanese patients at more than one LAG525 dose. The Japanese dose escalation for single-agent LAG525 will run separately from the ongoing dose escalation with a starting dose for single-agent LAG525 in Japanese patients of 1 mg/kg Q2W. Dose escalation decisions will be guided by a BLRM.

2.2.3 Phase II

Once the RP2D or MTD is determined for either single-agent LAG525 (Arm A) or the combination of LAG525 with PDR001 (Arm B), the respective phase II part of the study will begin. The primary objective of the phase II part is to estimate the preliminary anti-tumor activity of single agent LAG525 and in combination with PDR001.

The Phase II part of the study will be conducted in five diseases that are known to be potentially responsive to single-agent PD-1 inhibition: NSCLC, melanoma, mesothelioma, TNBC and renal cancer. The efficacy of single-agent LAG525 and the combination of LAG525 with PDR001 in these diseases will be assessed in both the PD-1/PD-L1 pre-treated and naive settings.

A Bayesian design will be used in order to estimate the overall response rate (ORR) in each disease area with single agent LAG525 or in combination with PDR001, evaluated at the RP2D of both single-agent LAG525 and the combination of LAG525 with PDR001 identified during phase I. The Phase II arms are designed to detect efficacy signals indicating a population where further study of either single-agent LAG525 or the combination of LAG525 with PDR001 is warranted. If the recommended dose of single-agent LAG525 is the same in Arms A and C, patients enrolled in Japan may be recruited to the Phase II single-agent part of the study. In addition if the recommended dose of PDR001 for Japanese patients in the PDR001X1101 study is the same as that determined in study PDR001X2101, Japanese patients may also enter the combination parts of study LAG525X2101 at which ever dose is being tested at that time.

2.3 Rationale for dose and regimen selection

The starting dose of LAG525 in the clinical setting was determined from toxicology studies as well as observed toxicity and efficacy from agents in the clinic with the similar mechanism of action of checkpoint inhibition (e.g. CTLA-4 and PD-1 inhibitors). The HNSTD dose from the cynomolgus monkey for LAG525 was 100 mg/kg. As LAG525 will be administered i.v., and it is generally accepted that antibody therapeutics allometrically scale according to body weight, the human equivalent dose (HED) of the HNSTD is 100 mg/kg. Based on the ICH S9 guidance,

[redacted]

a factor of six can be used to determine the maximum allowable starting dose, with an estimated maximum starting dose of 17 mg/kg administered weekly. LAG525 will be administered via i.v. infusion every 2 weeks, consistent with a schedule commonly used for humanized monoclonal antibodies with an expected half-life of approximately 10-20 days. Based on the pharmacologically active doses of 2-10 mg/kg in the clinic with agents having a similar mechanism of action (checkpoint inhibitors, CTLA-4 and PD-1 inhibitors, Topalian 2014, Wolchok 2013, Robert 2014) and with the intent to fully characterize the safety, pharmacokinetics, pharmacodynamics and preliminary efficacy at multiple dose levels, the starting dose of LAG525 is 1 mg/kg every 2 weeks. For the combination of LAG525 with PDR001 in dose escalation, the starting dose of PDR001 is 1 mg/kg and of LAG525 is 1 mg/kg administered intravenously once every 2 weeks and is based on the preclinical safety, tolerability, and PK data observed in the cynomolgus monkey with both PDR001 and LAG525 as described in Section 6.2.1. If required by a Regulatory Authority, recruitment to combination dose levels will begin at dose level -1 (0.3 mg/kg LAG525 with 1 mg/kg PDR001) for patients from those countries

For both LAG525 single agent and the combination of LAG525 with PDR001, alternative dosing (e.g. flat dose [mg]) and dosing schedules (e.g. less frequent dosing) may be implemented during the study based on emerging clinical toxicity and preliminary PK, PD and efficacy data.

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 TIL 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).

[redacted]

3 Objectives and end points

Objectives and related endpoints are described in Table 3-1 below and apply to all patients enrolled and treated unless otherwise stated.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Section 10.4.1
Phase I part: To estimate the RP2D or MTD for: ● Single-agent LAG525 (including Japanese patients) ● Combination of LAG525 and PDR001.	• The incidence of dose limiting toxicities (DLTs) during the first cycle of treatment with single agent LAG525. For the combination treatment of LAG525 and PDR001, the DLT window will be 2 cycles of the treatment.	
Phase II part: To estimate the overall response rate per RECIST V1.1 ● Single-agent LAG525 ● Combination of LAG525 and PDR001	• Overall response rate per "Response Evaluation Criteria in Solid Tumors (RECIST) V 1.1"	
Secondary		Section 10.5
Phase I and Phase II parts: • To characterize the safety and tolerability of single-agent LAG525 given alone and in combination with PDR001	• 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.	
• To characterize the pharmacokinetic profile of single-agent LAG525 given alone and in combination with PDR001	• Serum PK parameters (e.g. AUC, Cmax, Tmax, $t_{1/2}$ half-life)	
• To assess emergence of anti-LAG525, and anti-PDR001 antibodies following one or more intravenous (i.v.) infusions of single-agent LAG525 given alone or in combination with PDR001	• Presence and/ or concentration of anti-LAG525 and anti-PDR001 antibodies	

Objective	Endpoint	Analysis
Phase I part: ● To evaluate the preliminary antitumor activity of single-agent LAG525 given alone or in combination with PDR001	● ORR, progression free survival (PFS), duration of response (DOR) and disease control rate (DCR)	Section 10.5
Phase II part: ● To evaluate the preliminary antitumor activity of single-agent LAG525 given alone or in combination with PDR001	● ORR per immune related Response Criteria (irRC), PFS, DOR, DCR per RECIST V1.1 and per irRC	

[redacted]

[redacted]

4 Study design

4.1 Description of study design

This study is a phase I/II, multi-center, open-label study which consists of 2 dose escalation parts (Arms A and B) with a staggered start, each followed by an expansion part. The first escalation will be conducted with single-agent LAG525 in advanced solid tumors. Once the MTD/RP2D of single-agent LAG525 is determined, the study will continue with a Phase II expansion part with single-agent LAG525 in defined patient populations. The second dose escalation part will be performed with the combination of LAG525 and PDR001 in advanced solid tumors followed by a Phase II expansion part with the combination in defined patient populations. The dose escalation of the combination of LAG525 and PDR001 will not begin until a cohort of 3 mg/kg single-agent LAG525 has been completed. If the single-agent LAG525 dose of 3 mg/kg satisfies the EWOC criterion, the combination dose will begin with the planned starting dose as specified in Section 6.2.2. For the combination treatment arm, the first dose for the first two patients treated at each untested dose level will be staggered by 24 hours. If 3 mg/kg with single agent does not satisfy the EWOC criterion, or if required by a Regulatory authority, then the combination dose will begin with a lower dose level (please refer to Section 6.2.3 for details of the dose escalation process).

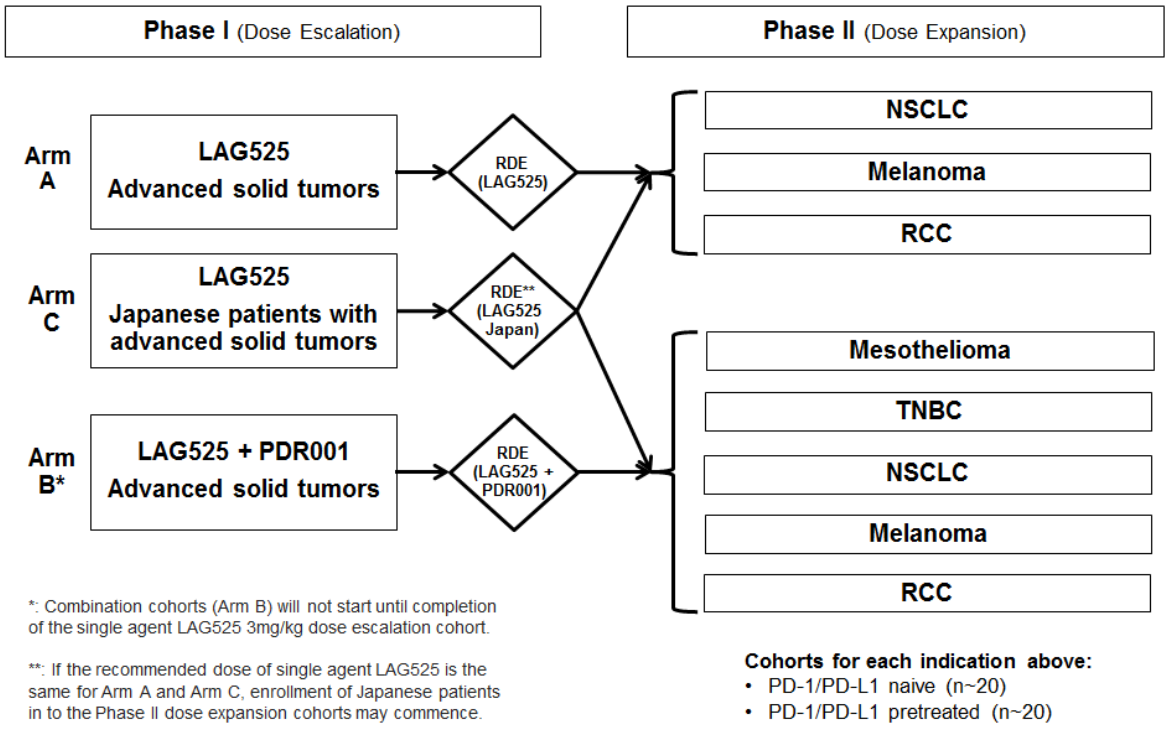
A separate Japanese dose escalation (Arm C) will be performed in order to ensure that the safety and pharmacokinetic profiles of single-agent LAG525 are adequately characterized in Japanese patients at more than one LAG525 dose. The Japanese dose escalation will run separately from the ongoing dose escalation with a starting dose for single-agent LAG525 in Japanese patients of 1 mg/kg Q2W. Dose escalation decisions will be guided by a BLRM. If the recommended dose of single agent LAG525 is the same in Arms A and C, patients enrolled in Japan may be recruited into the Phase II single-agent part of the study. In addition, if the recommended dose of PDR001 for Japanese patients on the PDR001X1101 study is the same as that determined in study PDR001X2101, patients in Japan may also enter the combination parts of the study at whichever dose is being tested at that time. After Japanese patients have enrolled in the combination dose escalation arm, and if during review of safety data (either in a Dose Escalation Meeting or during a regular safety review) Novartis and the enrolling Investigators consider the safety profile of Japanese patients treated in the combination arm to be potentially worse than that of patients treated in the rest of the world, an additional 3 to 6 Japanese patients may be recruited to a lower dose combination (previously studied in dose escalation) to further characterize the safety and tolerability of the combination in patients enrolled in Japan. If after review of safety data at the lower dose level, Novartis and the enrolling Investigators feel that re-escalation to a higher combination dose level is acceptable, Japanese patients may be treated at the same dose as patients in the rest of the world. If re-escalation is not acceptable, any additional Japanese patients recruited to the combination dose escalation will be treated at the lower dose. The combination dose escalation in the rest of the world may continue as planned.

Both PDR001 and LAG525 will be administered i.v. once every two weeks until a patient experiences unacceptable toxicity, progressive disease as per immune related Response Criteria (irRC) or treatment is discontinued at the discretion of the investigator or the patient. In the combination cohorts, the two antibodies will be administered separately with a break of 30

[redacted]

minutes between administrations. The study design is summarized in Figure 4-1. Alternative dosing schedules (e.g. less frequent dosing) may be implemented during the study based on clinical toxicity and preliminary PK, [redacted] and efficacy findings, including data from study PDR001X2101.

Figure 4-1 Study design



Note: In the single-agent LAG525 dose escalation (Arm A) at least 21 patients are required to define the RP2D; in the combination dose escalation (Arm B) at least 15 patients are required to define the RP2D and in the Japanese single-agent LAG525 dose escalation (Arm C) at least 12 patients are required to define the RP2D.

The primary clinical study report (CSR) will be based on all patients' data from both phase I and phase II parts, up to the time when all patients have completed at least six cycles of treatment or discontinued the treatment. Patients who are on study beyond cycle 6 may remain on treatment as per the protocol. Any additional data (after the data cut-off date for the primary CSR) will be further summarized at completion of the study, as defined in Section 4.3.

Study treatment group to be analyzed in Phase II expansion cohorts

Arm A: Single-agent LAG525 cohorts

- Group 1: single-agent LAG525, NSCLC (naïve to PD-1/PD-L1)
- Group 2: single-agent LAG525, Melanoma (naïve to PD1/PD-L1)
- Group 3: single-agent LAG525, Renal cancer (naïve to PD-1/PD-L1)
- Group 4: single-agent LAG525, NSCLC (pre-treated with PD-1/PD-L1)
- Group 5: single-agent LAG525, Melanoma (pre-treated with PD-1/PD-L1)
- Group 11: single-agent LAG525, Renal cancer (pre-treated with PD-1/PD-L1)

Arm B: Combination LAG525 + PDR001 cohorts

- Group 6: combination LAG525+PDR001, NSCLC (naïve to PD-1/PD-L1)
- Group 7: combination LAG525+PDR001, Melanoma (naïve to PD-1/PD-L1)
- Group 8: combination LAG525+PDR001, Renal cancer (naïve to PD-1/PD-L1)
- Group 9: combination LAG525+PDR001, NSCLC (pre-treated with PD-1/PD-L1)
- Group 10: combination LAG525+PDR001, Melanoma (pre-treated with PD-1/PD-L1)
- Group 12: combination LAG525+PDR001, Renal cancer (pre-treated with PD-1/PD-L1)
- Group 13: combination LAG525+PDR001, Mesothelioma (naïve to PD-1/PD-L1)
- Group 14: combination LAG525+PDR001, TNBC (naïve to PD-1/PD-L1)
- Group 15: combination LAG525+PDR001, Mesothelioma (pre-treated with PD-1/PD-L1)
- Group 16: combination LAG525+PDR001, TNBC (pre-treated with PD-1/PD-L1)

4.1.1 Phase I dose escalation

Single-agent LAG525 (Arm A)

During the phase I single-agent dose escalation, patients with any advanced solid tumor will be treated with single-agent LAG525 until the MTD is reached or a lower RP2D is established. At least 21 patients are required during dose escalation to define the MTD/RP2D.

Combination of LAG525 with PDR001 (Arm B)

During the phase I combination dose escalation, patients with any advanced solid tumor will be treated with LAG525 in combination with PDR001 until the MTD is reached or a lower RP2D is established. It is expected that an RP2D will be established before the MTD is reached. At least 15 patients are required during dose escalation to define the MTD/RP2D.

For all dose escalation arms, to assure that the RP2D does not exceed the MTD, the dose escalation will be guided by an adaptive Bayesian logistic regression model (BLRM) following the EWOC principle. For further details, please refer to Section 6.2.3.

[redacted]

Single-agent LAG525 in Japanese Patients (Arm C)

The Japanese dose escalation Arm C will be run separately from Arm A. At least 12 patients are required during dose escalation to define the MTD/RP2D. Dose escalation decisions will be guided by a separate BLRM to estimate the MTD /RP2D in Japanese patients (see Appendix 14.4).

4.1.2 Phase II expansion

Once the MTD and/or RP2D have been determined in the escalation parts, additional patients will be enrolled in the respective phase II expansion parts in order to assess the preliminary anti-tumor activity of single-agent LAG525 and LAG525 in combination with PDR001. Phase II Expansion cohorts testing single-agent LAG525 will open once the RP2D or MTD of single-agent LAG525 is identified. Phase II Expansion cohorts testing the combination of LAG525 and PDR001 will open for enrollment once the RP2D or MTD of the combination is determined. Novartis may elect not to initiate any given treatment arm based on emerging data (including but not limited to preliminary anti-tumor activity).

In the phase II part, patients will be assigned to different groups depending on the tumor type as shown in Figure 4-1. Please refer to Section 5.1 and Section 7.1.1 for further details. Each group will enroll approximately 20 patients, unless enrolling 20 patients to any of these groups is not logistically feasible, in which case enrollment may be stopped before 20 patients are treated in that group. Details of the sample size calculations leading to the patient numbers are provided in Section 10.8. The sample size in any group may be expanded to approximately 40 patients, if at least 3 patients (or if at least 2 patients for TNBC) have an objective response (PR or CR) per RECIST 1.1 or irRC in that group. A Bayesian design will be used in order to estimate ORR within each disease group (see Section 10.8 for details of sample size).

4.1.3 Study Periods

Screening period

The screening period begins once the patient has signed the study informed consent. Patients will be evaluated against study inclusion and exclusion criteria Section 5.2 and Section 5.3.

Status of MSI (high or low) for patients with CRC will be collected during screening. In addition, EGFR, ALK or BRAF V600 status is to be collected at baseline as appropriate. If known, BRCA status will be collected at baseline

[redacted]

Treatment period

The treatment period will begin on Cycle 1 Day 1. For the purpose of scheduling and evaluations, a treatment cycle will consist of 28 days (21 days for patients on Q3W dosing schedule).

[redacted]

Further details are provided in Table 7-1 and Section 7.1.2.

150-day follow-up (FU) period

Patients will be followed up for safety evaluations on 30, 90, and 150 days after the last dose of study treatment. Please refer to Table 7-1 and Section 7.1.5 for further details.

Disease progression FU

Patients who discontinue the study for any reasons other than disease progression as per irRC will be followed for progression of disease. Please refer to Section 7.1.5 for further details.

[redacted]

4.2 Timing of interim analyses and design adaptations

No formal interim analyses are planned. However, in the phase I part, the dose-escalation design foresees that decisions based on the current data will be taken before the end of the study. In the phase II part, the number of tumor responses will be monitored to determine if the enrollment in any group should be expanded from 20 to approximately 40 patients. Please refer to Section 10.7 for further details.

4.3 Definition of end of the study

The end of study will be when:

- 80% of the patients per disease group in the phase II part have completed the follow-up for disease progression or discontinued the study for any reason, and all patients have completed treatment and the 150 day safety follow-up period

or

- If the study is terminated early

or

- Another clinical study becomes available that can continue to provide study treatment in this patient population, and all patients ongoing are transferred to that clinical study.

At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative treatment option to patients who, in the opinion of the investigator, are still deriving clinical benefit.

See Section 10 Statistical Methods and Data Analysis for details of timing of the primary analysis and final reporting of data.

4.4 Early study termination

The study or any treatment group of 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

[redacted]

Treatment (EoT) visit and the assessments for EoT should be performed as described in Section 7.1.3 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 Patient population

In the phase I part of the study, both single and combination escalation will be conducted in all types of advanced solid tumors regardless of PD-1/PD-L1 treatment history**.**

In the phase II part of the study, both single agent and combination expansion arms will be conducted in patients with NSCLC, melanoma, and renal cancer as outlined in Figure 4-1. The combination arm will also be conducted in patients with mesothelioma and TNBC as outlined in Figure 4-1,

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.

5.2 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 procedures
   For Japan only: written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.
2. Age ≥ 18 years
3. Phase I part: Patients with advanced/metastatic solid tumors, with measurable or non-measurable disease as determined by RECIST version 1.1 (refer to Appendix 1), who have progressed despite standard therapy or are intolerant of standard therapy, or for whom no standard therapy exists.
4. Phase II part: Patients with advanced/metastatic solid tumors, with at least one measurable lesion as determined by RECIST version 1.1, who have had disease progression. Additionally, the following must apply:
   a. NSCLC:
      i. Disease recurrence or progression during or after no more than one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease. Prior maintenance therapy is allowed (considered pemetrexed, erlotinib, bevacizumab).
      ii. Patients must have been tested for mutations affecting EGFR and ALK. (Patients with a known mutation in one gene need not be tested for the other.) Patients with ALK or EGFR-positive NSCLC must have had recurrent or progressive disease after treatment with the corresponding inhibitor and no more than one platinum doublet-based chemotherapy, in any sequence.
   b. Melanoma:

[redacted]

i. Patients with BRAF V600 mutation-positive disease must have objective evidence of progression of disease after treatment with a BRAF inhibitor alone or in combination with other agents.
ii. Patients with BRAF wild-type disease must have objective evidence of progression of disease but are not required to have received prior therapy.

c. Renal:
i. Patients must have objective evidence of progression of disease during or following at least one regimen of treatment for advanced renal cancer.

d. Mesothelioma
i. Patients must have objective evidence of progression of disease during or following at least one prior line of systemic chemotherapy for advanced disease.

e. TNBC
i. Patients must have objective evidence of progression of disease during or following no more than 2 prior lines of systemic chemotherapy for advanced disease. Patients must have received a prior taxane-containing regimen.

5. ECOG Performance Status ≤ 1
6. Phase I Part: Patients enrolled in the Phase I part of the study must provide a new tumor biopsy at baseline and during treatment if medically feasible.

   Phase II part: Patients enrolled in the phase II part of the study must provide a new tumor biopsy at baseline and during treatment, if medically feasible.

5.3 Exclusion criteria

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

1. Presence of symptomatic central nervous system (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 at least 4 weeks prior to study entry and off steroids for at least 2 weeks before administration of any study treatment.
2. History of severe hypersensitivity reactions to study treatment ingredients or other mAbs
3. Patient with out-of-range laboratory values defined as:
   - Creatinine clearance (calculated using Cockcroft-Gault formula, or measured) < 40 mL/min
   - 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
   - Alanine aminotransferase (ALT) > 3 x ULN
   - Aspartate aminotransferase (AST) > 3 x ULN
   - Absolute neutrophil count (ANC) < 1.0 x 10^9/L
   - Platelet count < 75 x 10^9/L
   - Hemoglobin (Hgb) < 9 g/dL
   - Potassium, magnesium, calcium or phosphate abnormality CTCAE > grade 2

[redacted]

4. Clinically significant cardiac disease or impaired cardiac function, including any of the following:
   - Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (NYHA grade ≥ 2), uncontrolled hypertension or clinically significant arrhythmia
   - QTcF >470 msec on screening ECG or congenital long QT syndrome
   - Acute myocardial infarction or unstable angina pectoris < 3 months prior to study entry
5. Active, known or suspected autoimmune disease. Patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to an autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or other conditions not expected to recur, are permitted to enroll. Patients previously exposed to anti-PD-1 / PD-L1 treatment who are adequately treated for skin rash or who are receiving replacement therapy for endocrinopathies should not be excluded.
6. Patients who required discontinuation of treatment due to treatment-related toxicities with prior therapy directed against the same target as the drug(s) under study in this protocol.
7. History of drug-induced pneumonitis or current pneumonitis.
8. Active infection requiring systemic antibiotic therapy. Patients requiring systemic antibiotics for infection must have completed therapy before screening is initiated.
9. HIV infection. Testing for HIV status is not necessary unless clinically indicated.
10. 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.
11. Malignant disease, other than that being treated in this study. 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.
12. 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.
13. a. Systemic anti-cancer therapy within 2 weeks of the first dose of study treatment.

    b. For cytotoxic agents that have major delayed toxicity, e.g. mitomycin C, nitrosoureas or more recent immunotherapies, 4 weeks is indicated as washout period.

    c. For patients receiving a CTLA-4 antagonist or vaccine as anticancer therapy, 8 weeks is indicated as the washout period.
14. Patients receiving chronic treatment with systemic steroid therapy (> 10 mg/day prednisone or equivalent) within 7 days of the first dose of study treatment, other than replacement-dose steroids in the setting of adrenal insufficiency. Topical, inhaled, nasal and ophthalmic steroids are not prohibited.
15. Patients receiving systemic treatment with any immunosuppressive medication that would interfere with the action of the study drugs, other than replacement-dose corticosteroids in the setting of adrenal insufficiency.

[redacted]

16. Use of any live vaccines against infectious diseases within 4 weeks of initiation of study treatment.
17. Major surgery within 2 weeks of the first dose of study treatment (mediastinoscopy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery).
18. Radiotherapy within 2 weeks of the first dose of study drug, except for palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass. To allow evaluation of response to treatment, patients enrolled in the Phase II part must have remaining measurable disease that has not been irradiated.
19. Participation in an interventional, investigational study within 2 weeks prior to the first dose of study treatment.
20. Presence of CTCAE ≥ grade 2 toxicity (except alopecia, peripheral neuropathy and ototoxicity, which are excluded if ≥ CTCAE grade 3) due to prior cancer therapy.
21. Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GMCSF, M-CSF) ≤ 2 weeks prior to the first dose of study treatment. Patients must have completed therapy at least 2 weeks prior to the first dose of study treatment with any hematopoietic colony-stimulating growth factors. An erythroid stimulating agent is allowed as long as it was initiated at least 2 weeks prior to the first dose of study treatment.
22. 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.
23. 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 LAG525 and/or PDR001. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - 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
    - Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
    - 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.

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.

Women are considered post-menopausal and not of child bearing potential if they have had over 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (age appropriate (e.g. generally 40-59 years), history of vasomotor symptoms (e.g. hot flushes) in

[redacted]

the absence of other medical justification 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.

24. 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

For this study, the investigational drugs refer to LAG525 and PDR001. Both study drugs will be provided by Novartis. PDR001 will be supplied in lyophilized powder formulation. LAG525 will be supplied as a liquid formulation.

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**
LAG525	Liquid in vial for i.v. infusion	1 mg/kg (starting dose)	Every 2 weeks
PDR001	Powder for solution for infusion	1 mg/kg (starting dose)	Every 2 weeks

*Flat dosing may be tested based on the review of emerging PK data generated during the study
**Alternate dosing regimens may be implemented to assess a less frequent dosing regimen

For the combination arm of the study, the first dose for the first two patients treated at each untested dose level will be staggered by 24 hours. LAG525 and PDR001 will be administered via i.v. infusion over 30 minutes once every 2 weeks. They will be administered separately in the same fashion with at least a 30-min break between the two antibody infusions. Infusions of each antibody can be extended to up to 2 hours if clinically indicated and the break between LAG525 and PDR001 antibody infusions can be up to 4 hours if clinically indicated.

Both study drugs may be infused using the same i.v. access site. LAG525 will be given first followed by PDR001. The same administration sequence must be followed for all participants, i.e. LAG525 is infused first. If an infusion reaction occurs after administration of LAG525, the subsequent PDR001 infusion must be delayed until it is safe for the patient to receive PDR001 based on the clinical discretion of the investigator. The delay between LAG525 and PDR001 infusions can be up to 4 hours if clinically indicated. If PDR001 cannot be administered safely within 4 hours after LAG525 administration, the dose must be omitted.

A scheduled dose (of either single-agent LAG525 or the combination of LAG525 and PDR001) may be delayed to recover from an unresolved AE. If a patient requires a dose interruption of > 21 days from the intended day of the scheduled dose due to an unresolved AE related to study

drug(s), then the patient must be discontinued from the study, unless the patient is receiving clinical benefit and in the opinion of the investigator it is in the patient's best interest to remain on study. The patient may restart treatment after discussion with Novartis. Dose modifications should be followed described in Section 6.3.1 and Section 6.3.2.

If a significant number of patients require dose delays due to drug-related toxicities, the dosing regimen for the study may be changed to once every 21 or 28 days. This will be discussed in a dose escalation teleconference at the time of the proposed change and documented in the minutes of this meeting accordingly Section 6.2.3.1. Alternative dosing regimens (flat dose, mg) or a less frequent dosing regimen (e.g. Q3W or Q4W) may also be considered based on emerging clinical toxicity and preliminary PK [redacted] and efficacy data generated during the study. A treatment cycle is defined as 28 days (21 days for patients on Q3W dosing regimen) with the potential to extend the cycle an additional 7 days if necessary for recovery of toxicities, as described above. Missed doses will not be made up. The first dose of LAG525 or combination of LAG525 and PDR001 is Cycle 1 Day 1 which defines the patient's treatment cycles for the study.

Flat dosing may also be investigated in the combination part of the study for both LAG525 and PDR001.

Optional testing of two dose levels during phase II expansion

After a preliminary assessment of safety data in dose escalation, a decision may be made to investigate a second dose of LAG525 alone during the phase II expansion to further assess safety and efficacy. This would be performed in one disease setting. The two dose levels will be assigned in an alternating fashion to patients of the same disease group across all the sites in this global study. The number of patients required to be tested at this second dose level will be equivalent to the number of patients to be enrolled in this disease setting at the RP2D.

6.1.2 Ancillary treatments

Patients should not receive any pre-medications before the first infusion of the investigational drug LAG525 and/or PDR001. If a patient experienced an infusion reaction, he/she may receive pre-medications on subsequent dosing days after consultation with the Novartis Medical Monitor. Pre-medications should include but are not limited to paracetamol/acetaminophen and an antihistamine. The use of corticosteroid pre-medication will be at the discretion of the principal investigator in consultation with the Novartis Medical Monitor.

If ≥ 2 patients experience moderate to severe acute infusion reactions in a dose escalation cohort on C1D1 or if >25% of patients experience mild infusion reactions in the dose escalation, then mandatory primary prophylaxis regimens (i.e. before dosing on C1D1) will be instituted after discussion and agreement among principal investigators and Novartis. Prophylaxis regimens will include both paracetamol/acetaminophen and an antihistamine.

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. Such acute allergic reactions will be reported to the Sponsor in an expedited manner. These should be designated as reportable as a

[redacted]

SAE regardless of hospitalization as medically important events. Please refer to SAE reporting section for details.

Patients should be treated in a facility equipped for cardiopulmonary resuscitation. Appropriate resuscitation equipment should be available at the bedside and a physician readily available.

Guidelines on management of LAG525 or PDR001 infusion reactions are provided in Section 6.3.1 and Table 6-5.

The CTCAE category of "Infusion related reaction" should be used to describe LAG525 and/or PDR001 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 Treatment duration

A patient may continue treatment with LAG525 until the patient experiences unacceptable toxicity, confirmed disease progression per irRC and/or treatment is discontinued at the discretion of the investigator or the patient. Refer to Section 7.1.3 and Section 7.1.5.

If more than 2 consecutive doses of LAG525 or combination of LAG525 and PDR001 have to be skipped due to drug-related toxicities, then the drugs should be permanently discontinued. If a patient who misses more than 2 consecutive doses due to a drug-related toxicity is experiencing clinical benefit, and in the opinion of the investigator it is in the patient's best interest to remain on study, then the patient may continue the treatment(s) after discussion with Novartis.

6.2 Dose escalation guidelines

6.2.1 Starting dose rationale

Starting dose of LAG525 as a single agent (Arm A and Arm C)

The starting dose of LAG525 selected for this study is based on 4-week GLP toxicology studies performed in cynomolgus monkeys as LAG525 cross reacts with monkey LAG-3 but not rat or murine LAG-3. LAG525 is a monoclonal antibody that does not have agonist activity, and will be administered to patients with advanced malignancies; therefore the starting dose is based on the ICH S9 guidance. In the cynomolgus monkey study, the HNSTD dose was 100 mg/kg. The human equivalent dose (HED) of the HNSTD is 100 mg/kg. Based on the ICH S9 guidance, a factor of six can be used to determine the maximum allowable starting dose, with an estimated maximum starting dose of 17 mg/kg administered weekly. Based on the pharmacologically active doses of 2-10 mg/kg in the clinic with agents having a similar mechanism of action (checkpoint inhibitors, CTLA-4 and PD-1 inhibitors, Topalian 2014, Wolchok 2013, Robert 2014) and with the intent to fully characterize the safety, pharmacokinetics (PK), [redacted] and preliminary efficacy at multiple dose levels, the starting dose of LAG525 is 1 mg/kg every 2 weeks.

[redacted]

Starting dose of LAG525 and PDR001 combination (Arm B)

PDR001 cross reacts with monkey PD-1 and thus, the starting dose of PDR001 selected for this study is based on 4-week GLP toxicology studies performed in cynomolgus monkeys and prior clinical experience with nivolumab and pembrolizumab (Topalian 2014, Robert 2014). It is anticipated that PDR001 will have similar PK/PD properties to these comparators; PDR001 is expected to demonstrate antitumor activity at doses of 2-3 mg/kg dosed every 2-3 weeks. The HNSTD of PDR001 was 100 mg/kg, administered i.v., once weekly. The human equivalent dose (HED) of the HNSTD is 100 mg/kg. The maximum permitted starting dose in patients is 1/6 x 100 mg/kg, or 17 mg/kg administered weekly.

In order to evaluate the safety, PK [redacted], and antitumor activity of PDR001 in combination with LAG525 across a range of doses, the starting dose in the combination study is 1 mg/kg of PDR001 and 1 mg/kg of LAG525 i.v. administered every 2 weeks (Q2W). If required by a Regulatory Authority, recruitment to combination dose levels will begin at dose level -1 (0.3 mg/kg LAG525 with 1 mg/kg PDR001) for patients from those countries.

For details of dose escalation please refer to Section 6.2.3.

6.2.2 Provisional dose levels

There will be three dose escalation arms in this study; Table 6-2 and Table 6-3 describe the starting doses and the provisional dose levels of single-agent LAG525 and the combinations of LAG525 and PDR001, respectively, that may be evaluated during this trial. With the exception of starting dose level 1, actual dose levels will be determined based on available toxicity, pharmacokinetic [redacted] data, guided by the BLRM, following a discussion with participating Investigators during dose escalation teleconferences Section 6.2.3. Dose escalation will continue until one or more MTDs or/RP2Ds are determined.

Table 6-2 Provisional dose levels (Ph I Arm A and Arm C: single-agent LAG525)

Dose level	Proposed dose LAG525* Weight adjusted dose (Flat dose)****	Increment from previous dose
-1**	0.3 mg/kg (20 mg)***	-70%
1 (starting dose)	1 mg/kg (80 mg)***	0
2	3 mg/kg (240 mg)***	<300%
3	10 mg/kg (800 mg)***	< 333%

*It is possible for additional and/or intermediate dose levels to be added during the course of the study Cohorts may be added at any dose level below the MTD in order to better understand safety, PK [redacted] Multiple dose levels below the MTD may be evaluated simultaneously in order to obtain PK [redacted] data across a range of doses.
**Dose level -1 represents treatment doses for patients requiring a dose reduction from the starting dose level.
***Alternate dosing may be explored (i.e. flat dose, mg). If an alternate dosing regimen is used the dose may need to be adjusted to achieve an equivalent exposure per cycle.
****1 mg/kg corresponds to a flat dose of 80 mg

Table 6-3 Provisional dose levels (Ph I Arm B: combinations of LAG525 and PDR001)

Dose level	Proposed dose LAG525* Weight adjusted dose(flat dose)****	Proposed dose PDR001* Weight adjusted dose (Flat dose****)
-2**	0.3 mg/kg (20 mg)	0.3 mg/kg (20 mg)
-1**	0.3 mg/kg (20 mg)	1 mg/kg (80 mg)
1 (starting dose)	1 mg/kg (80 mg)	1 mg/kg (80 mg)
2	1 mg/kg (80 mg)	3 mg/kg (240mg)
3	3 mg/kg (240mg)	3 mg/kg (240mg)
4	3 mg/kg (240mg)	10 mg/kg (800 mg)
5	10 mg/kg (800 mg)	10 mg/kg (800 mg)

*It is possible for additional and/or intermediate dose levels to be added during the course of the study Cohorts may be added at any dose level below the MTD in order to better understand safety, PK [redacted]. Multiple dose levels below the MTD may be evaluated simultaneously in order to obtain PK [redacted] data across a range of doses.
**Dose level -2 and -1 represent treatment doses for patients requiring a dose reduction from starting dose level. If required by a Regulatory Authority, recruitment to combination dose levels will begin at dose level -1 (0.3 mg/kg LAG525 with 1 mg/kg PDR001) for patients from those countries.
***Alternate dosing may be explored (i.e. flat dose, mg). If an alternate dosing regimen is used the dose may need to be adjusted to achieve an equivalent exposure per cycle.
****1 mg/kg corresponds to a flat dose of 80 mg

6.2.3 Guidelines for dose escalation and determination of MTD/ RP2D

The maximum tolerated dose (MTD) is defined as:

- Arm A and Arm C (single-agent LAG525): for patients enrolled in the single agent arm with administration of single agent LAG525, the highest drug dosage that is unlikely (< 25% posterior probability) to cause DLT in 33% or more of the treated patients in the first cycle of study treatment under that schedule. The DLT window for **Arm A and C is one cycle (28 days, 21 days for patients on Q3W dosing schedule)**. Patients enrolled in this arm must receive at least two doses (Q2W schedule) of LAG525 to be considered evaluable for toxicity. For the Q3W and Q4W schedule, one dose must be received.
- Arm B (combination of LAG525 and PDR001): for patients enrolled in the combination treatment arm in the dose escalation part with administration of both LAG525 and PDR001, the highest combination drug doses that is unlikely (< 25% posterior probability) to cause DLT in 33% or more of the treated patients in the first two cycles of study treatment under that schedule. The DLT window for **Arm B is two cycles (56 days, 42 days for patients on Q3W dosing schedule).** Patients must receive at least three doses (Q2W schedule) of both study drugs during the first two cycles (DLT observation window) to be considered evaluable for toxicity. For the Q3W and Q4W schedule, patients must receive 2 doses of both study drugs during the first two cycles.

During the dose escalation of combination agents, only 1 of the 2 study drugs can be escalated at a time.

Adverse events and laboratory abnormalities considered to be DLTs are defined in Table 6-4.

For Arm B, since several combinations may correspond to this definition, more than one MTD may be identified with different doses of the study drugs. One (or more) of these MTDs or a suitable lower dose combination will then be selected as the RP2D(s).

The applied adaptive Bayesian methodology provides an estimate of the single-agent LAG525 and the combinations of LAG525 and PDR001 not exceeding the MTD. Typically the MTD is a tested dose (or combination) with maximum probability of targeted toxicity (DLT rate between 16% and <33%). The use of the EWOC principle limits the risk that a potential next dose will exceed the MTD Section 10.4.2.

For the purposes of dose escalation decisions, each cohort will consist of 3 to 6 newly enrolled patients who will be treated at the specified dose level in the arm of treatment (Arm A and C refers to single agent and Arm B refers to combination treatment). Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 patients may be enrolled at any dose level below the estimated MTD(s)/ RP2D(s) for further elaboration of safety, pharmacokinetic [redacted] parameters as required.

The dose escalation will proceed as follows:

- **Arm A (Single-agent LAG525):** The first cohort enrolled in the study will be treated with the starting dose of 1 mg/kg LAG525 as a single agent in Arm A. Once this cohort is complete and the dose escalation decision has been determined collectively between the Sponsor and the participating investigators to escalate, the second cohort in Arm A will open with 3 mg/kg. Once a cohort of 3 mg/kg is complete and demonstrated to satisfy the EWOC criterion (< 25% posterior probability to cause DLT in 33% or more of the treated patients in the first cycle of study treatment), combination dosing will begin (Arm B) at the planned starting dose. In the event that the single-agent LAG525 dose of 3 mg/kg does not satisfy the EWOC criterion, then combination dose escalation may only proceed at a dose level one level below the LAG525 dose deemed safe (i.e. combination dose level -1, 0.3 mg/kg LAG525 with 1 mg/kg PDR001).
- **Arm B (LAG525 and PDR001 combination):** The combination dose escalation (Arm B) will proceed provided that the single-agent LAG525 dose of 1 mg/kg did not exceed the MTD. The starting dose for the combination will be 1 mg/kg of LAG525 combined with 1 mg/kg of PDR001, unless the second dose level of single-agent LAG525 at 3 mg/kg is not tolerated or if required by a Regulatory Authority, in which case combination dose escalation will proceed at dose level -1 (0.3 mg/kg LAG525 with 1 mg/kg PDR001). The dose escalation of the combination Arm B will then proceed in parallel with the remaining dose escalation of Arm A.
- **Arm C (Japan single-agent LAG525):** The same guidelines will be applied to dose escalation of single-agent LAG525 in Japanese patients. The first cohort of patients enrolled in the Japanese sub-population will be treated with a starting dose of 1 mg/kg LAG525 Q2W as a single agent. Once this cohort is complete and the dose escalation decision has been determined collectively between the Sponsor and the participating investigators to escalate the dose, the second cohort will open at a dose of up to 3 mg/kg Q2W (or flat dose equivalent) that satisfies EWOC criterion. The dose escalation will then proceed until the RP2D or MTD is determined. The Japanese dose escalation Arm C will be run separately from Arm A. Dose escalation decisions will be guided by the BLRM to estimate the MTD / RP2D in Japanese patients in the context of available safety and PK information.

Arm A and Arm B in dose escalation may enroll patients in an alternating fashion if two cohorts in the arms are open in parallel. If only one cohort is open at a given time, patients will enroll only into the open cohort and enrollment will pause until an additional cohort in either arm is

[redacted]

opened for enrollment. Patients identified for enrollment in dose escalation will be assigned to the appropriate cohort by Novartis.

For the purposes of dose escalation decisions, patients can be considered evaluable in each arm after having met the following criteria:

- **Arm A and Arm C**: Patients must complete a minimum of 1 cycle of treatment with the minimum safety evaluation and drug exposure (at least two doses of LAG525) or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions.
- **Arm B**: Patients must complete a minimum of two cycles of treatment with the minimum safety evaluation and drug exposure (at least three doses of both study drugs) or have had a DLT within the first two cycles of treatment to be considered evaluable for dose escalation decisions.

Dose escalation decisions will be made by investigators and Novartis study personnel. For each arm, decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs, all CTCAE Grade $\geq$ 2 toxicity data during Cycle 1 (arm A and Arm C), and cycles 1 and 2 (arm B), PK, [redacted] data from evaluable patients. The recommended dose for the next cohort of subjects will be guided by the BLRM with EWOC principle (Section 2.2) and determined by a synthesis of all available data from the cohort.

The adaptive Bayesian methodology provides an estimate of all dose levels of LAG525 and PDR001 that do not exceed the MTD and incorporates all DLT information at all dose levels for this estimation. In general, the next dose will have the highest chance that the DLT rate will fall in the target interval [16-33%) and will always satisfy the EWOC principle. In all cases, the dose for the next cohort will not exceed a 333% (1/2 Log_{10}) increase from the previous dose. Smaller increases in dose may be recommended by the Investigators and Sponsor upon consideration of all of the available clinical data.

If the first 2 patients in a previously untested dose level experience a DLT, further enrollment to that cohort will stop and the BLRM will be updated with this new information. Re-evaluation of the available safety, PK, [redacted] data will occur. By incorporating information gained at the preceding dose levels, additional patients may be enrolled at this dose level or a lower dose level as agreed by Investigators and Novartis personnel and if the BLRM predicts that the risk that this dose exceeds the MTD remains below 25% (EWOC).

Dose escalation for each arm (Arm A and Arm C, single-agent LAG525 or Arm B, combination of LAG525 and PDR001) will continue until identification of the RP2D or the MTD of the single-agent or combination.

[redacted]

The MTD/RP2D will be determined if the following conditions are met:

1. at least 6 patients have been treated at this dose
2. this dose satisfies one of the following conditions:
   a. the posterior probability of targeted toxicity at this dose exceeds 50%, or
   b. minimum of 21 patients for the single agent Arm A or 15 patients for the combination Arm B, or 12 patients for the Japanese dose escalation Arm C have already been treated on the trial for this arm.
3. it is the dose recommended for patients, either per the model or by review of all clinical data by Novartis and Investigators in a dose-escalation teleconference, see Section 6.2.3.1.

To better understand the safety, tolerability, PK [redacted] of single-agent LAG525 or combinations of LAG525 and PDR001, additional cohorts of patients may be enrolled at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation.

If a decision is made to escalate to a higher dose level but one or more additional patient(s) treated at the preceding dose level experiences a DLT during the DLT window, then the BLRM will be updated with this new information before any additional patients are enrolled at that higher dose level. Subjects ongoing will continue treatment at their assigned dose levels.

If the circumstance arises that a MTD is not reached in either single agent LAG525 escalation or that of the combination, then the RP2D of that arm will be determined from a synthesis of all data available, including safety and tolerability, pharmacokinetic [redacted] assessments and any preliminary antitumor activity observations.

Change of schedule:

In the event of a change in dosing schedule, then a new BLRM will be used to evaluate this new schedule. This new BLRM will incorporate down-weighted existing dose escalation data in the prior distribution.

The starting dose for the new regimen will be determined based on the available data, including safety, and will be subject to the EWOC criterion under the newly constructed model. The new regimen will be less frequent than the Q2W schedule.

Change to flat dose:

Flat dosing (in mg) may be explored for single-agent LAG525 by opening a new cohort(s) in the escalation part of this study. The combination of LAG525 and PDR001 utilizing flat dosing may also be explored from the start of the combination dose escalation. Please refer to Table 6-2 and Table 6-3.

Additional BLRMs will be developed to evaluate the flat dosing for single-agent LAG525 and its combination with PDR001. Those BLRMs will incorporate down-weighted dose escalation data from the weight-based dosing cohorts in an informative prior distribution.

The starting dose for the flat dose will be determined based on the available data, including safety, and will be subject to the EWOC criterion under the newly constructed model. The equivalent weight based dose should have been tested and shown to satisfy the EWOC criterion.

[redacted]

6.2.3.1 Implementation of Dose Escalation Decisions

To implement dose escalation decisions, the available toxicity information (including all safety data, AEs Grade ≥ 2 and laboratory abnormalities that are not DLTs), the assessment of those doses satisfying the EWOC criterion from the BLRM, and the available PK [redacted] information will all be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. All occurrences of DLT will be discussed and agreed at the dose decision teleconference among participating investigators and Novartis study personnel.

Cohort enrollment and drug administration at the next higher dose level may not proceed until the investigator receives written confirmation from Novartis indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level with written confirmation of the next higher dose level to be tested.

6.2.3.2 Intra-Patient dose escalation

Intra-patient dose escalation is not permitted at any time within the first 4 cycles of treatment. After the 4th cycle is completed, individual patients may be considered for treatment at a dose of single agent LAG525 or in combination with PDR001, higher than the dose to which they were initially assigned. Only one of the study drugs will be escalated at any one time. Study drugs will be escalated as detailed in Section 6.2.2. In order for a patient to be treated at a higher dose of either single agent LAG525 or in combination with PDR001, he or she must have tolerated the lower dose combination for at least 4 cycles of therapy (e.g., he or she must not have experienced at the lower dose level originally assigned a toxicity of CTCAE grade ≥ 2 considered related to study drug). Moreover, the new, higher dose combination with which the patient is to be treated must be a dose combination that has completed evaluation in a dose-escalation meeting and satisfies the EWOC criterion under the Bayesian model given all available data.

There is no limit to the number of times a patient may have his or her dose of LAG525 increased as a single agent or in combination with PDR001. Any further increases after the initial intra-patient dose escalation are subject to the same rules as for the initial intra-patient escalation. Consultation with Novartis must occur prior to any intra-patient dose escalation occurring. These changes must be recorded on the Dosage Administration Record CRF.

6.2.3.2.1 Switch to LAG525 in combination with PDR001 for patients treated with LAG525 single-agent

Upon disease progression, patients assigned to LAG525 monotherapy during dose escalation may switch to LAG525 + PDR001 at a combination dose level that uses the patient's same LAG525 dose and has been determined safe and tolerable in previous dose escalation patients. If there is no combination dose level that includes the patient's LAG525 monotherapy dose, the patient may receive a lower dose level of LAG525 when switching to LAG525 in combination with PDR001; alternatively, the patient may switch to the LAG525 + PDR001 recommended Phase II dose, once the RP2D has been established. Patients switching to combination therapy must have completed at least 4 cycles of LAG525 monotherapy with no toxicity of CTCAE grade ≥ 2 considered related to study treatment.

PDR001 may be added to LAG525 treatment only after documented discussion and agreement between Novartis and the Investigator, based on each patient's condition and review of the planned dose and schedule.

Patients will start LAG525 in combination with PDR001 on Day 1 of the cycle during which the switch is made and patients will resume their standard scheduled visits per Table 7-1. For patients who switch from single-agent LAG525 to LAG525 in combination with PDR001, patients will resume the standard visit schedule; hematology/chemistry labs and vital signs will be collected on Days 8 and 15 as unscheduled assessments for the first cycle upon switch to the LAG525 in combination with PDR001. Cycle 1 will start based on the patient's first dose of the original LAG525 monotherapy. After switching to combination therapy, patients will continue to have efficacy assessments as per protocol; however, the response data from these patients will not be incorporated into the ORR. No additional biopsies will be required. For patients who switch from single-agent LAG525 to LAG525 in combination with PDR001, immunogenicity samples will be collected as unscheduled assessments (instead of their standard PK collection schedule) on Day 1 pre-dose for the first 6 cycles upon switch to the LAG525 in combination with PDR001, and PK blood samples will be collected on Days 1 (pre-infusion) and 8 as unscheduled assessments (instead of their standard PK collection schedule) for the first cycle upon switch to the LAG525 in combination with PDR001. Patients who switch from single agent LAG525 to LAG525 in combination with PDR001 will need to complete an additional End of Treatment Phase Disposition CRF, but the EOT tests/procedures are not required until discontinuation of LAG525 in combination with PDR001.

6.2.4 Definitions of dose-limiting toxicities (DLTs)

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value of CTCAE grade ≥ 3 assessed as having a suspected relationship to study drug, and unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first cycle of treatment with single agent LAG525 or within the first two cycles of treatment with the combination of LAG525 and PDR001, and meets any of the criteria included in Table 6-4.

DLT window:

- Arm A and Arm C with single agent LAG525: 28 days (one cycle) (21 days for patients on Q3W dosing schedule).
- Arm B with combination of LAG525 and PDR001: 56 days (two cycles) (42 days for patients on Q3W dosing schedule).

Emerging data from the new field of immune-immune combination studies suggest that some immune-related adverse events have a prolonged latency (Wolchok 2013). As such, the DLT window for the combination arm in this trial is extended to the length of two cycles or 56 days.

National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 4.03 will be used for all grading unless otherwise specified. For the purpose of dose-escalation decisions, DLTs will be considered and included in the BLRM.

[redacted]

The investigator must notify the Sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities. Prior to enrolling patients into a higher dose level, CTCAE grade ≥ 2 adverse events will be reviewed for all patients at the current dose level.

Table 6-4 Criteria for defining dose-limiting toxicities

During dose escalation, any Grade 3 or Grade 4 AEs related to study treatment occurring in cycle 1 (applies to dose escalation Arm A and Arm C) , and in cycles 1 and 2 (applies to dose escalation Arm B) are DLTs, EXCEPT:	
Fatigue	Grade 3 fatigue that resolves to ≤ Grade 1 within 7 days.
Fever, Infection	Grade 3 infection or fever, in the absence of neutropenia,that resolves within 7 days.
Hypertension	Grade 3 hypertension that resolves within 7 days after starting anti-hypertensive therapy.
Gastrointestinal	Grade 3 nausea and vomiting that resolves to ≤ Grade 1 within 48 hours of starting optimal anti-emetic therapy.
	Grade 3 diarrhea that resolves within 7 days after starting optimal anti-diarrhea treatment, where colitis is not suspected.
Hepatic	Grade 3 ALT or AST in the absence of significantly increased bilirubin that resolves to ≤ Grade 1 within 7 days.
Amylase and lipase	Asymptomatic Grade ≥ 3 amylase or lipase.
Dermatologic	Grade 3 non bullous rash without epidermal detachment that resolves to ≤ Grade 1 within 7 days of starting treatment.
Hematologic	Grade 3 neutropenia without fever or other clinical symptoms that resolves to ≤ Grade 1 within 7 days.
	Grade 3 thrombocytopenia without clinically significant bleeding.
	Grade 3 anemia that resolves within 7 days in the absence of transfusion.
	Lymphopenia of any grade is not a DLT.
Electrolytes	Grade 3 electrolyte abnormalities that resolve to ≤ Grade 1 within 7 days after starting supplementation.
Musculoskeletal	Grade 3 asymptomatic increase in creatine kinase that resolves within 14 days in the absence of evidence of cardiac involvement.
Immune-related toxicities*	In general, a Grade 3 immune-related AE that resolves to ≤ Grade 1 within 7 days of starting appropriate treatment is not a DLT.

The following Grade 2 AEs related to study treatment <u>are considered DLTs</u>:	
Ocular disorders	Grade 2 eye pain or reduction of visual acuity are DLTs if they do not respond to topical therapy and do not improve to Grade 1 severity within 2 weeks of the initiation of topical therapy, OR if they require systemic treatment.
Pneumonitis	Grade 2 pneumonitis is a DLT if it does not resolve to ≤ Grade 1 within 7 days of starting corticosteroids.
Myocarditis	Grade 2 myocarditis is a DLT.
Colitis	Grade 2 colitis is a DLT if it persists > 7 days despite treatment with corticosteroids.
Hepatic	Grade 2 ALT or AST accompanied by bilirubin >1.5 x ULN is a DLT.
Dermatologic	Grade 2 bullous disease that does not resolve to ≤ Grade 1 within 7 days of starting corticosteroids is a DLT.
Other adverse events	Other clinically significant toxicities, including a single event or multiple occurrences of the same event that lead to a dosing delay of > 7 days within the DLT window, may be considered to be DLTs by the Investigators and Novartis, even if not CTCAE grade 3 or higher. Infusion reactions will not be considered as dose limiting because they are idiosyncratic and not related to dose.
* Depending on the nature of the AE, there may be cases where immune-related Grade 2-3 AEs of any duration warrant declaration of a DLT and permanent study discontinuation (e.g. Stevens-Johnson Syndrome (SJS)). DLT determination not already outlined in this table will be made on a case-by-case basis after Investigator discussion with the Novartis Medical Monitor.	

6.3 Dose modifications

6.3.1 Dose modification and dose delay

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

- If a patient experiences an AE meeting the criteria for DLT as outlined in Section 6.2.4 (including events occurring after cycle 1 for Arm A and C or including events occurring after cycle 2 for Arm B), treatment should be withheld at the onset of the AE. Following resolution of the toxicity to grade 1 or to the patient's baseline value, the patient may resume study treatment after discussion with Novartis. If the investigator considers it to be in the patient's best interest to resume therapy before the toxicity has resolved to grade 1 or to the patient's baseline value, this may be permitted on a case by case basis after discussion with Novartis.
- 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

[redacted]

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 scheduled dose (of either single-agent LAG525 or the combination of LAG525 and PDR001) may be delayed to recover from an unresolved AE. If a patient requires a dose interruption of > 21 days from the intended day of the scheduled dose due to an AE related to study drug(s), then the patient must be discontinued from the study, unless the patient is receiving clinical benefit and in the opinion of the investigator it is in the patient's best interest to remain on study. The patient may restart treatment after discussion with Novartis.

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.

Table 6-5 outlines the recommended dose modifications for selected toxicities.

All interruptions or change to study drug administration must be recorded on the Dose Administration Record eCRF.

Table 6-5 Recommended Dose Modifications for LAG525 and PDR001

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Infusion reaction or hypersensitivity reaction	
Grade 1	Decrease infusion rate until recovery from the symptoms.
Grade 2	Stop infusion immediately, and keep line open. Follow institutional guidelines for the management and follow-up of infusion reaction. 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 permanently discontinue study treatment.
Grade 3 and Grade 4	Discontinue infusion immediately, and discontinue study treatment. Provide supplemental oxygen, fluids, and other resuscitative measures as needed. Monitor vital signs (e.g. blood pressure, pulse, respiration, and temperature) every 15 ± 5 minutes until resolution.
Cytokine Release Syndrome (CRS)	
Grade 2	See instructions for Grade 2 Infusion Reaction above.
Grade 3 or Grade 4	Discontinue study treatment. Follow-up CRS as per institutional guidelines. Take blood for cytokine measurements as specified in Section 8.4.1 – Laboratory evaluations.

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
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.
Pulmonary (pneumonitis)	
Grade 1	Consider study treatment hold. Manage per institutional practice. Consider resuming study treatment upon radiographic evidence of improvement.
Grade 2	Hold study treatment. Pulmonary and infection workup. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification.
Grade 3 or Grade 4	Discontinue study treatment.
Cardiovascular	
ECG QTc-Interval prolonged; hypertension	
Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 or baseline (hypertension, QTc) or < 30 msec difference from baseline (QTc) within ≤ 7 days, may resume study treatment without dose modification after discussion with the Novartis Medical Monitor. Baseline ECG refers to the ECG(s) collected at screening.
Grade 4	Discontinue study treatment.
Other cardiovascular disorders	
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, or Grade ≥ 3 other cardiac disorders related to study treatment	Discontinue study treatment.
Gastrointestinal	
Diarrhea/colitis*	
Grade 1	May continue study treatment without dose modification. Manage per institutional standard guidelines which should include anti-diarrheal treatment, consideration of corticosteroid therapy, and hydration.
Grade 2	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 modification after discussion with the Novartis Medical Monitor.

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Grade 3	Hold study treatment. GI consultation. Upon resolution to ≤ Grade 1 and tapering of steroid requirement to ≤ 10 mg prednisone per day, consider resuming study treatment after discussion with the Novartis Medical Monitor.
Grade 4	Discontinue study treatment.
AST and/or ALT elevation	
Grade 2 AST and/or ALT	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1 or baseline, consider resuming study treatment without dose modification.
Grade 2 transaminitis with bilirubin >1.5 x ULN (unless Gilbert's syndrome)	Discontinue study treatment.
Grade 3 AST and/or ALT	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.
Grade 4 AST and/or ALT	Discontinue study treatment.
Isolated total bilirubin elevation**	
Grade 2	Hold study treatment. Upon resolution to ≤ Grade 1 or baseline, may continue study treatment without dose modification.
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 1 or baseline, may consider resuming study treatment after discussion with the Novartis Medical Monitor.
Grade 4	See footnote**. Otherwise, discontinue study treatment.
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.
Pancreatitis	
Grade 2/radiologic evidence	Hold study treatment. Manage per 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.
Grade 3 or Grade 4	Discontinue study treatment.
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.

[redacted]

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
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	May resume therapy 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 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.
Dermatology (rash)	
Grade 1	Continue study treatment without dose modification. 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 study treatment. Manage per institutional practice. After resolution to ≤ Grade 1, consider resuming study treatment after discussion with the Novartis Medical Monitor.

[redacted]

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Bullous dermatitis	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. Grade 4 bullous dermatitis: discontinue study treatment
Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	Permanently 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	
Grade 3 or Grade 4	Hold study treatment. 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	
Grade 3	Hold study treatment. 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.
Lymphopenia	
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.

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
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.

All dose modifications should be based on the worst preceding toxicity.

[a] Common Toxicity Criteria for Adverse Events (CTCAE)

*Note: anti-diarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.

**Note: If Grade 3 or 4 hyper-bilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (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.

***Note: 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.

6.3.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, must be followed-up at least once a week (or more if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first.

The emergence of Immune-Related AE (irAE) may be anticipated based on the mechanism of action of immunomodulatory therapies.

An irAE is any clinically significant adverse event affecting any organ that is associated with study drug exposure, is consistent with an immune-mediated mechanism, and where alternative explanations have been investigated and ruled out or are considered to be unlikely. Serologic, histologic (tumor sample) and immunological assessments should be performed as deemed appropriate by the Investigator or specialist consultant to verify the immune-related nature of the AE. An empiric trial of corticosteroids may also contribute to understanding the etiology of a potential irAE.

Consensus management algorithms for irAEs have been developed and are available to assist investigators in assessing and managing irAEs (refer to Section 6.3.1 Dose modifications).

In case of a toxicity suspected to be a cytokine release syndrome, the assessments outlined in Section 7.2.2.5.6 must be performed.

All patients must be followed up for irAEs, AEs, and SAEs for 150 days following the last doses of LAG525 and/or PDR001.

6.3.3 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.

For patients with hormone resistant prostate cancer receiving luteinizing hormone-releasing hormone agonists or antagonists, or for patients with metastatic carcinoid tumors receiving somatostatin analogs to control symptoms of carcinoid syndrome, these treatments must have been initiated ≥4 weeks prior to first dose of study treatment and may be continued throughout the study.

Bisphosphonates are generally allowed for the management of bone metastases and osteoporosis. However, chronic concomitant bisphosphonate therapy for the prevention of bone metastasis is not permitted. If bisphosphonate therapy is to be started after the first dose of study drug, prior consultation and approval by Novartis is required and the reason for its use must be clearly documented.

Patients 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 and Concomitant Medications or the Surgical and Medical Procedures CRF. Prior antineoplastic therapies including medications, radiotherapy, and surgery are to be recorded on the separate Prior Antineoplastic Therapy eCRF during screening.

6.3.4 Permitted concomitant therapy requiring caution and/or action

Treatment with hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) may not be initiated during the DLT observation window (see Section 6.2.3) in the dose escalation part of the study, unless the patient has already experienced a DLT. Treatment with erythroid stimulating agents (ESAs) may not be initiated during the DLT observation window in the dose escalation part of the study, unless the patient has already experienced a DLT. If a patient is using ESA prior to enrollment (at least 2 weeks prior to the first dose of study treatment), they may continue at the same dose.

Anticoagulation is permitted if the patients are already at stable doses for >2 weeks at time of first dose and INR should be monitored as clinically indicated per investigator's discretion. However, ongoing anticoagulant therapy should be temporarily discontinued to allow tumor biopsy according to the institutional guidelines.

Antihypertensives are 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 infusion with the study drugs including LAG525 or its combination with PDR001.

6.3.5 Prohibited concomitant therapy

During the course of the study, patients may not receive other additional investigational drugs, agents, devices, chemotherapy, or any other therapies that may be active against cancer. However, 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 corresponding CRF. Additionally, no other therapeutic monoclonal antibodies and no immunosuppressive medication may be

administered while on this study. Denosumab may be used for the management of bone metastases.

The use of systemic steroid therapy (at doses greater than 10 mg/day prednisone or equivalent) and other immunosuppressive drugs is not allowed, with the exception of:

- Prophylactic use for patients with imaging contrast dye allergy.
- Replacement-dose steroids (defined as 10mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids) in the setting of adrenal insufficiency.
- Transient exacerbations of chronic inflammatory conditions such as COPD. Steroids must be reduced to 10 mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids prior to the next treatment with LAG525 and/or PDR001.
- Upon treatment of LAG525 and/or PDR001 infusion reactions or LAG525 and/or PDR001-related irAEs, steroids must be reduced to 10 mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids prior to the next treatment with LAG525 and/or PDR001.

Topical, inhaled, nasal and ophthalmic steroids are allowed. The use of live vaccines is not allowed through the whole duration of the study. Inactivated vaccines are allowed.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first pre-screened (if applicable) or when the patient is enrolled for screening. The subject number is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No. is 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.

6.4.2 Treatment assignment or randomization

The assignment of a patient to a particular cohort will be coordinated by the sponsor. No randomization will be performed in this study.

6.5 Study drug preparation and dispensation

LAG525 is supplied as liquid in vial (100 mg per vial). PDR001 100 mg is formulated as powder for solution for infusion. Further instructions for the preparation and dispensation of LAG525 and PDR001 are described in the [Pharmacy Manual].

All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

6.5.1 Study drug packaging and labeling

LAG525 100 mg liquid in vial.

PDR001 (100 mg powder for solution for infusion) will be supplied by Novartis to Investigator as open label bulk medication.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but will not supply information about the patient.

6.5.2 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, LAG525 and PDR001 should be stored according to the instructions specified on the drug labels.

6.5.3 Study drug compliance and accountability

6.5.3.1 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.

6.5.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment according to local institutional drug accountability processes. 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 monitor or to the Novartis address provided in the investigator folder at each site.

6.5.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

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. The table (“Category” column) indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S).

[redacted]

No CRF will be used as a source document.

Screening/baseline evaluations must be performed ≤ 21 days before Cycle 1 Day 1, except for baseline radiological evaluations which must be done within 28 days. Assessments required on Cycle 1 Day 1 that are performed as part of the screening evaluations and within 72 hours prior to the first dose of study treatment, do not need to be repeated on Cycle 1 Day 1. 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 +/- 7 days is allowed. If the infusion of LAG525 or its combination with PDR001 is delayed, the assessments will be shifted accordingly. On PK collection days the windows are provided in Section 7.2.3.

Radiological assessments must be performed +/- 7 days of the scheduled date of the assessment.

Table 7-1 Visit evaluation schedule

			Screening Phase	Treatment Phase														Follow-up		
Visit name	**Category**	**Protocol Section**	**Screening**	**Cycle 1**					**Cycle 2**		**Cycle 3**					**Subsequent cycles**	**EoT**	**Safety Follow-Up[g]**	**Disease Progression F/U**	
Day of cycle			**-21 to -1**	**1**	**2**	**8**	**11**	**15**	**1**	**15**	**1**	**2**	**8**	**11**	**15**	**1**				
Obtain Informed Consent	D	7.1.1	X																	
Demography	D	7.1.1.2	X																	
Inclusion/ exclusion criteria	D	5.2 / 5.3	X																	
Medical History	D	7.1.1.2	X																	
Diagnosis and extent of cancer	D	7.1.1.2	X																	
MSI status if applicable	D	7.1.1.2	X																	
EGFR, ALK, BRAF V600 status (if applicable) and BRCA (if known)	D	7.1.1.2	X																	
Prior antineoplastic therapy	D	7.1.1.2	X																	
Prior/concomitant medications	D	7.1.1.2	X	Continuous																
Physical examination	S	7.2.2.1	X	X		X		X	X	X	X					X	X			
Height	D	7.2.2.3	X																	
Weight	D	7.2.2.3	X	X					X		X					X	X			
Vital signs	D	7.2.2.2	X	X		X		X	X	X	X					X[h]	X			
Performance status	D	7.2.2.4	X														X			
Hematology	D	7.2.2.5.1	X	X		X		X	X	X	X					X[h]	X			
Chemistry	D	7.2.2.5.2	X	X		X		X	X	X	X					X[h]	X			
Coagulation	D	7.2.2.5.3	X																	

			Screening Phase	Treatment Phase														Follow-up		
Visit name	**Category**	**Protocol Section**	**Screening**	**Cycle 1**					**Cycle 2**		**Cycle 3**					**Subsequent cycles**	**EoT**	**Safety Follow-Up[g]**	**Disease Progression F/U**	[redacted]
Day of cycle			**-21 to -1**	**1**	**2**	**8**	**11**	**15**	**1**	**15**	**1**	**2**	**8**	**11**	**15**	**1**				
Urinalysis	D	7.2.2.5.4	X																	
Thyroid function	D	7.2.2.5.5	X	X					X		X					X	X			
Cytokines ([redacted]IL-6)	D	7.2.2.5.6	X	In case of a suspected cytokine release syndrome																
Pregnancy test	D	7.2.2.5.7	X						X		X					X	X			
	S	7.2.2.5.7																X[g]		
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5																X	X	X
[redacted]																				
Tumor evaluation as per RECIST 1.1 and as per irRC.	D	7.2.1	X	Every 8 weeks **± 1 week after Cycle 1 Day 1 until 40 weeks**, then every 12 weeks until progression of disease per irRC or patient withdrawal. For disease progression f/u, every 8 weeks ± 1 week until 40 weeks, then every 12 weeks ± 1 week until progression of disease per irRC, or lost to follow-up.																
ECG	D	7.2.2.6.1	X	X					X		X					X[a]	X[j]			
Adverse events	D	8	Continuous																	
[redacted]																				

[redacted]

			Screening Phase	Treatment Phase														Follow-up		
Visit name	**Category**	**Protocol Section**	**Screening**	**Cycle 1**					**Cycle 2**		**Cycle 3**					**Subsequent cycles**	**EoT**	**Safety Follow-Up[g]**	**Disease Progression F/U**	[redacted]
Day of cycle			**-21 to -1**	**1**	**2**	**8**	**11**	**15**	**1**	**15**	**1**	**2**	**8**	**11**	**15**	**1**				
Study Drug administration	D	6.1.1		i.v. every 2 weeks (potential alternative schedules, e.g., every 3 or 4 weeks).																
PK sampling[c]	D	7.2.3		X	X	X	X	X	X		X	X	X	X	X	X[a, i]	X[k]			
Immunogenicity (IG) sampling	D	7.2.3		X					X		X					X[a, i]	X			
[redacted]																				

a. Cycles 4-6 only.
b. Anytime from Cycle 3 Day 1 through Cycle 3 Day 15.
c. Japanese patients enrolled in dose escalation are required to be hospitalized during the DLT evaluation period
[redacted]
g. Safety evaluations for 150 days after the last dose of study treatment with contacts at 30-, 90-, and 150-day. Pregnancy tests every month until the 150-day safety follow-up; can be performed at home or at a local doctor's office if the patient is not coming to the clinic.
h. For patients who switch from single-agent LAG525 to LAG525 in combination with PDR001, patients will resume the standard visit schedule; hematology/chemistry labs and vital signs will be collected on Days 8 and 15 as unscheduled assessments for the first cycle upon switch to the LAG525 in combination with PDR001.
i. For patients who switch from single-agent LAG525 to LAG525 in combination with PDR001, immunogenicity samples will be collected as unscheduled assessments (instead of their standard PK collection schedule) on Day 1 pre-dose for the first 6 cycles upon switch to the LAG525 in combination with PDR001, and PK blood samples will be collected on Days 1 (pre-infusion) and 8 as unscheduled assessments (instead of their standard PK collection schedule) for the first cycle upon switch to the LAG525 in combination with PDR001.
j. After the primary CSR cut-off date is reached, EOT ECGs will be performed at the discretion of the investigator.
k. After the primary CSR cut-off date is reached, EOT PKs will not be performed.

[redacted]

7.1.1 Screening

The study IRB/IEC informed consent form must be signed and dated before any screening procedures are performed, except for laboratory and radiological evaluations 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. Patients are allowed to re-screen after abnormal labs or symptoms are corrected or treated.

7.1.1.1 Information to be collected on screening failures

A patient who signed an Informed Consent Form but failed to be started on treatment for any reason will be considered a screen failure. If patients are found not eligible after signing the main study consent, the patients will be considered as screening failures, and data will be handled in the same manner.

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 SAE during screening.

7.1.1.2 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, 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. For patients with CRC, the MSI status will be collected. If the MSI status determination is not performed routinely as part of the patient standard follow-up, it is requested to be determined locally during screening. In the phase II part of the study, for patients with NSCLC, the EGFR and ALK mutation status will be collected; for patients with melanoma, the BRAF V600 mutation status will be collected; for patients with TNBC, if known, the BRCA status will be collected. If the EGFR, ALK or BRAF V600 status is not known, it is requested to be determined locally during screening. These test results are not required to qualify for enrollment.

7.1.2 Treatment period

A treatment cycle is defined as 28 days for the purposes of scheduling procedures and evaluations (21 days for patients on Q3W dosing schedule). Please refer to Table 7-1 for details of the timing of required assessments and Section 7.1 for visit windows. Based on emerging available safety, PK, [redacted] and efficacy data generated during the study, the treatment cycle length may be switched to 21 days.

For Japan only, patients enrolled in dose escalation are required to be hospitalized during the DLT evaluation period.

Patients will be treated until they experience unacceptable toxicity, progressive disease per irRC and/or treatment is discontinued at the discretion of the investigator or the patient, as described in Section 7.1.3 and Section 4.3.

[redacted]

Patients may continue treatment with LAG525 or its combination with PDR001 until the patient experiences unacceptable toxicity that precludes any further treatment, disease progression, and/or treatment is discontinued at the discretion of the investigator or by patient request. Patients who have disease progression and have evidence of clinical benefit, such as disease shrinkage at other sites or symptomatic improvement, may continue treatment with LAG525 or its combination with PDR001. In addition, LAG525 or its combination with PDR001 treatment may be temporarily interrupted to permit local therapy for symptomatic metastases after disease progression has been documented. Patients who continue on treatment after disease progression should discontinue study treatment once they are no longer deriving benefit as assessed by the investigator.

7.1.3 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine 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 study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

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

- Adverse event
- Lost to follow-up
- Physician's decision
- Progressive disease per irRC, RECIST 1.1, or as determined clinically by the Investigator
- 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:

- Death
- Pregnancy

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.

[redacted]

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.1.5. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.6. If a patient discontinues study treatment, but continues study assessments, the patient remains on study until such time as he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be recorded on the Study Phase Completion Disposition CRF page.

Patients who transfer into another study or an alternative treatment option to continue provision of study treatment will perform the end of treatment procedures.

7.1.3.1 Replacement policy

Phase I dose escalation part:

Patients will not be replaced on study. However, if a patient is considered to be non-evaluable for the Dose Determining Set (DDS), enrollment of a new patient to the current cohort will be considered if there is less than the required number of evaluable patients. Enrollment of new patients may be considered until at least the minimum number or at most the maximum number of evaluable patients is achieved within the cohort. Minimum and maximum numbers of evaluable patients per cohort are defined in Section 6.2.3.

Phase II expansion part: during the phase II expansion part no replacements will be needed.

7.1.4 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 allow further collection of personal data

In this situation, the investigator should make reasonable effort (e.g. telephone, email, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information. Study treatment must be discontinued and no further assessments conducted. The data that would have been collected at subsequent visits will be considered missing.

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient's sample until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and the informed consent form.

For European Union and Rest of World: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.1.5 Follow up period

150-day safety follow up period

All patients must have safety evaluations 30 days, 90 days, and 150 days after the last dose of study treatment. The follow-up can be done by telephone call or a visit. 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 on-going 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.

Antineoplastic therapies since discontinuation of study drug will be collected during this follow-up period. 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.

For a female participant of child bearing potential, a pregnancy test will be performed on Days 30, 60, 90, 120 and 150 after stopping the study treatment. If the patient is not coming to the clinic for the safety follow-up visits, a pregnancy test will be performed at home or at a local doctor's office at each of the safety follow-up time points described above, and the results will be communicated to the site staff and will be recorded only in the source documentation, not in the CRF.

Disease progression follow up period

Patients who discontinue study treatment for any reason other than death, disease progression per irRC, lost to follow-up, consent withdrawal, start of new cancer therapy or study termination, also should return for tumor evaluation assessments every 8 weeks until 40 weeks, and then 12 weeks until progression of disease per irRC. 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.

Antineoplastic therapies since discontinuation of study drug will be collected during this follow-up period.

[redacted]

7.1.6 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

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

1. RECIST v1.1 (Appendix 1)
2. irRC (Appendix 2)

The local investigator's assessment will be used for the analysis of response according to both RECIST 1.1 and irRC, and for treatment decision making (study discontinuation due to PD as per irRC). Patients experiencing progressive disease per RECIST v. 1.1 criteria may continue to be treated according to irRC guidelines until progression is documented via irRC. Imaging data may be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. The local investigator's assessment will be used for the data analysis and for treatment decision making. Central review of the imaging data may be performed if deemed necessary.

At screening, all patients will undergo CT with i.v. contrast of the chest, abdomen and pelvis. 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. See Table 7-2 for further details.

Tumor assessments will be performed at the following time points:

- Screening
- Every 8 weeks ± 1 week after Cycle 1 Day 1 until 40 weeks, then every 12 weeks ± 1 week until progression of disease per irRC or patient withdrawal. After EOT, during disease progression f/u, every 8 weeks ± 1 week until 40 weeks, then every 12 weeks ± 1 week until progression of disease per irRC, or lost to follow-up.
- PR or CR, per both RECIST 1.1 and irRC, will be confirmed by a new assessment after at least 4 weeks. Also PD, as per irRC, needs to be confirmed after at least 4 weeks.
- At the End of Treatment, if a scan was not conducted within 30 days prior to End of Treatment

Disease progression follow-up should be performed as described in Section 7.1.5.

[redacted]

Table 7-2 Disease assessment collection plan

Procedure	Screening/Baseline	During Treatment/Follow-up
CT or MRI with contrast enhancement (Chest, Abdomen, Pelvis)	Mandated	Every 8 weeks ± 1 week after Cycle 1 Day 1 until 40 weeks, then every 12 weeks ± 1 week until progression of disease per irRC or patient withdrawal. After EOT, during disease progression f/u, every 8 weeks ± 1 week until 40 weeks, then every 12 weeks ± 1 week until progression of disease per irRC, or lost to follow-up
Brain CT or MRI with contrast	Mandated	If disease was detected at baseline, or if clinically indicated
Localized bone CT, MRI or x-ray	For any lesions identified on the bone scan that are not visible on the chest, abdomen and pelvis CT or MRI	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Whole body bone scan	If clinically indicated	If clinically indicated
Any other procedure allowed as per RECIST 1.1 guidelines and not conflicting with this section		

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing 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 according to Table 7-1.

At Screening and Cycle 1 Day 1, prior to LAG525 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 system. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

From Cycle 1 Day 8 onwards, a short physical examination will be performed. A short physical exam will include the examination of general appearance, vital signs (temperature, blood pressure [BP] and pulse) and body sites as directed by symptoms.

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

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) must be performed before dosing and as indicated in Table 7-1 as per institutional standards.

Vital signs should be assessed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the Investigator if medically indicated, and will be recorded as unscheduled assessment.

7.2.2.3 Height and weight

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

7.2.2.4 Performance status

Performance status is determined as indicated in Table 7-3.

Table 7-3 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

[redacted]

7.2.2.5 Laboratory evaluations

All laboratory parameters assessed for safety purposes will be evaluated locally (except cytokine release syndrome testing, which will be performed and analyzed centrally for sites not capable of local testing). Refer to Table 7-4 for a summary of the parameters to be evaluated according to Table 7-1. On dosing days of LAG525 or its combination with PDR001, samples for these parameters will be collected prior to the infusion of LAG525 or its combination.

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

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 7-4 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, White blood cells with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Calcium, Chloride, Creatinine, Glucose* Magnesium, Inorganic Phosphate, Potassium, Sodium, Total Bilirubin (also measure direct and indirect bilirubin if total bilirubin is > grade 1), Blood Urea Nitrogen (BUN) or Urea, amylase, and lipase. Additionally for melanoma and TNBC patients: LDH
Coagulation	Prothrombin time (PT) or International normalized ratio [INR]), activated partial thromboplastin time (APTT)
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, pH, Protein, Specific Gravity, White Blood Cells)
Thyroid	Total or free T4, TSH
Cytokines	[redacted] Interleukin-6 (IL-6)
*See Section 7.2.2.5.2 regarding fasting glucose testing	

7.2.2.5.1 Hematology

Hematology panel outlined in Table 7-4 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 7-4 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 7-4 will be performed as per the assessment schedule in Table 7-1.

7.2.2.5.4 Urinalysis

Urinalysis panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1.

7.2.2.5.5 Thyroid function

Thyroid function panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1.

7.2.2.5.6 Cytokines

The cytokine panel outlined in Table 7-4 will be performed on an as needed basis in case a patient has an adverse event suspected to include cytokine release syndrome. This assessment is in addition to the pharmacodynamic cytokine panels described in Section 7.2.4.3.2.

Baseline cytokine samples must be collected at screening for all patients. If a suspected cytokine release syndrome occurs, additional sample(s) must be collected at the following time points:

- within 5 hours after the occurrence of the adverse event
- One week after the occurrence of the adverse event.
- Samples collected for cytokine tests will be stored at -70^{0}C. The samples will be analyzed retrospectively in batches for those patients who experience an AE that is suspected to be cytokine release syndrome.

7.2.2.5.7 Pregnancy and assessment 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 Days 30, 60, 90, 120, and 150 after stopping the study treatment. If the patient is not coming to the clinic for the safety follow-up visits, a pregnancy test will be performed at home or at a local doctor's office at each of the safety follow-up time points described above, and the results will be communicated to the site staff and 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 7-5. 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 in the combination arm will be collected after the completion of the last dose of infusion.

Table 7-5 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. **A PK sample should be collected just after an ECG performed due to an unexpected cardiac signal.		

All ECGs will be independently reviewed by a central laboratory. Instructions for the collection and transmission of ECGs to the central ECG laboratory will be provided in the ECG Manual.

After the primary CSR cut-off date is reached, ECGs will be performed at the discretion of the investigator and will be recorded on an unscheduled CRF page. These ECGs will not be reviewed by the central laboratory.

Clinically significant abnormalities present at screening should be reported on the Medical History CRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page. All eligibility and patient management decisions should be made based on the local reading of the ECG.

7.2.3 Pharmacokinetics and immunogenicity assessments

The following PK parameters will be determined for LAG525 alone, LAG525 in combination with PDR001 and PDR001 in combination with LAG525 using non-compartmental methods: Cmax, Tmax, AUC0-tlast (AUC0-336h - Cycle 1 Day 1 and Cycle 3 Day 1), time to last measurable concentration (Tlast), t1/2, and the accumulation ratio of LAG525 and PDR001. [redacted].

The data will be analyzed- using WinNonlin Phoenix (Pharsight Corporation; Mountain View, CA). PK profiles to assess PK properties of single-agent LAG525 and LAG525 in combination

[redacted]

with PDR001 will be collected from all enrolled patients. Please refer to Table 7-6 for details on PK and immunogenicity (IG) sample collections. For patients who switch from single-agent LAG525 to LAG525 in combination with PDR001, immunogenicity samples will be collected as unscheduled assessments (instead of their standard PK collection schedule) on Day 1 pre-dose for the first 6 cycles upon switch to the LAG525 in combination with PDR001, and PK blood samples will be collected on Days 1 (pre-infusion) and 8 as unscheduled assessments (instead of their standard PK collection schedule) for the first cycle upon switch to the LAG525 in combination with PDR001.

If the dosing of Cycle 3 Day 1 is delayed, the PK sampling for PK profile should be delayed accordingly to match the scheduled time points for cycle 3 as outlined in Table 7-6. PK and IG samples will be collected also at the End of Treatment Visit and in the event of a clinically significant AE (such as infusion reaction/anaphylaxis) or if IG is suspected, at which time those samples could be used to measure any relevant biomarkers, to understand the infusion reaction/adverse event better. After the primary CSR data cut-off date is reached, no additional PK and IG samples will be collected for the patients still on-going on the study.

[redacted]

Table 7-6 Pharmacokinetic blood collection log for LAG525 alone, LAG525 in combination with PDR001 and PDR001 in combination with LAG525 in all patients[b]

Cycle	Day	Scheduled Time Point (h)[a, f]	Analytes[c d]
1	1	Pre-infusion of Cycle 1	mAb and IG
1	1	1h post infusion (± 5 min)	mAb
1	2[e]	24h post infusion (± 2h)*	mAb
1	8	168h post infusion (± 8h)*	mAb
1	11[e]	240h post infusion (± 24h)*	mAb
1	15	Q2W: Pre-infusion / 336h post infusion (±24h)* Q3W: 336h post infusion (±24h)* Q4W: 336h post infusion (±24h)*	mAb
2	1	Q2W: Pre-infusion* Q3W: Pre-infusion / 504h post infusion (±24h)* Q4W: Pre-infusion / 672h post infusion (±24h)*	mAb and IG
2	1[e]	1h post infusion (± 5 min)	mAb
3	1	Pre-infusion of Cycle 3	mAb and IG
3	1	1h post infusion (± 5 min)	mAb
3	2[e]	24h post infusion (± 2h)*	mAb
3	8	168h post infusion (± 8h)*	mAb
3	11[e]	240h post infusion (± 24h)*	mAb
3	15	Q2W: Pre-infusion / 336h post infusion (±24h) Q3W: 336h post infusion (±24h) Q4W: 336h post infusion (±24h) *	mAb

[redacted]

Cycle	Day	Scheduled Time Point (h)[a, f]	Analytes[c d]
4	1	Q2W: Pre-infusion Q3W: Pre-infusion / 504h post infusion (±24h) Q4W: Pre-infusion / 672h post infusion (±24h)*)	mAb and IG
5	1	Pre-infusion of Cycle 5	mAb and IG
5	1[e]	1h post infusion (± 5 min)	mAb
6	1	Pre-infusion of Cycle 6	mAb and IG
6	1[e]	1h post infusion (± 5 min)	mAb
EOT			mAb and IG
Unscheduled[g]			mAb and IG

[a.] Time points are taken from the infusion completion time.

[b.] PK samples are to be collected from the arm opposite from infusion site, or alternatively, infusion site will need to be flushed with 10 mL of saline.

[c.] Analytes for PK (mAb) will include LAG525 alone, LAG525 in combination with PDR001PDR001 in combination with LAG525, and analytes for IG will include LAG525 alone, LAG525 in combination with PDR001, PDR001 in combination with LAG525

[redacted]

[e.] PK samples to be collected at this timepoint for Phase I patients only

[f.] For LAG525 in combination with PDR001 patients, the 1-hour post infusion sample should be taken after each infusion

[g.] For patients who switch from single-agent LAG525 to LAG525 in combination with PDR001, immunogenicity samples will be collected as unscheduled assessments (instead of their standard PK collection schedule) on Day 1 pre-dose for the first 6 cycles upon switch to the LAG525 in combination with PDR001, and PK blood samples will be collected on Days 1 (pre-infusion) and 8 as unscheduled assessments (instead of their standard PK collection schedule) for the first cycle upon switch to the LAG525 in combination with PDR001.

*Collection of these samples may be stopped if sufficient data have been collected

7.2.3.1 Bioanalytics

Bioanalysis for pharmacokinetic studies will employ 2 validated assays:

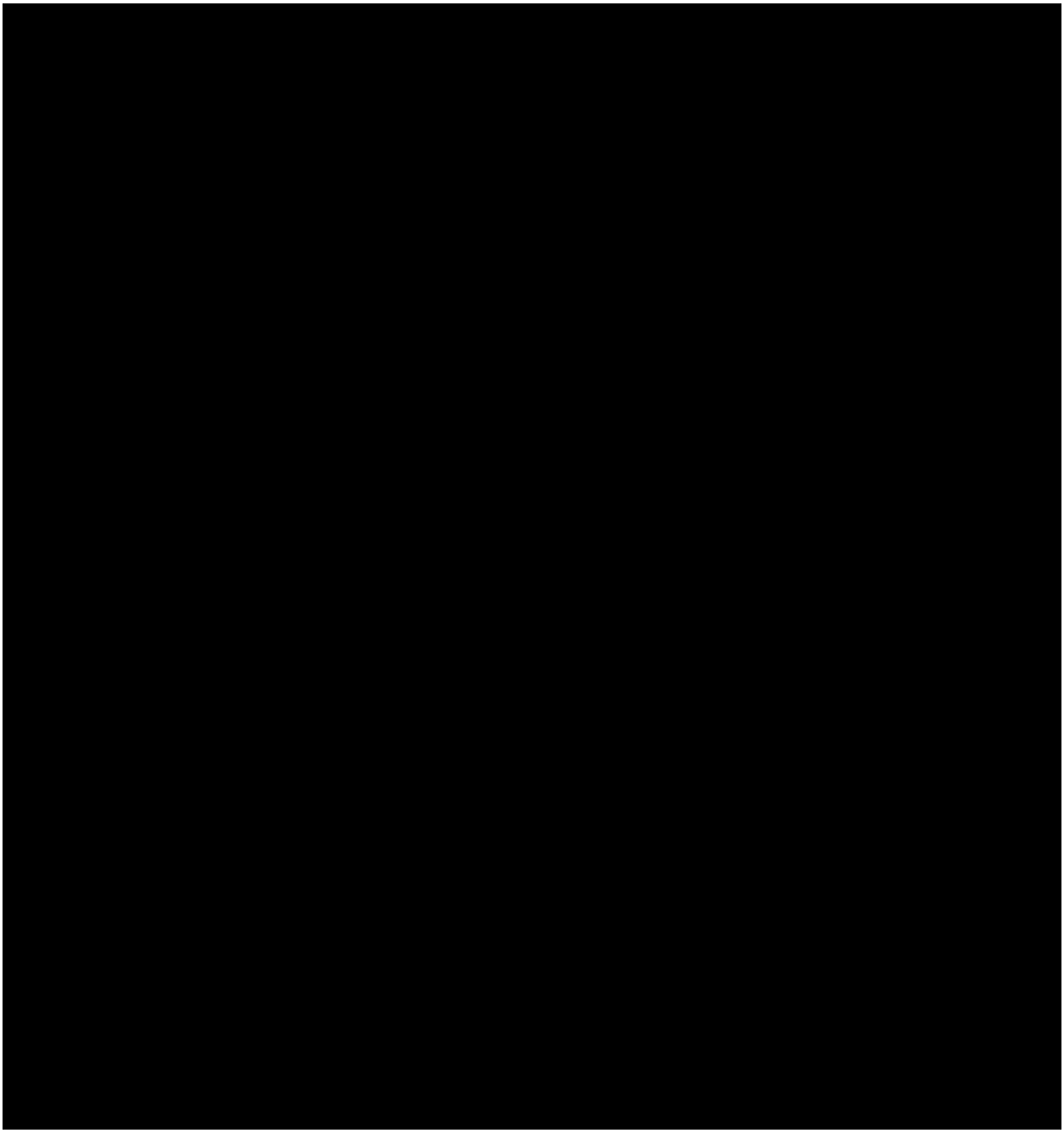
1. The assay to quantify LAG525 and PDR001 will be a validated LCMS.
2. The assay to quantify and assess the IG against LAG525 and PDR001 will be using a validated homogeneous ELISA.

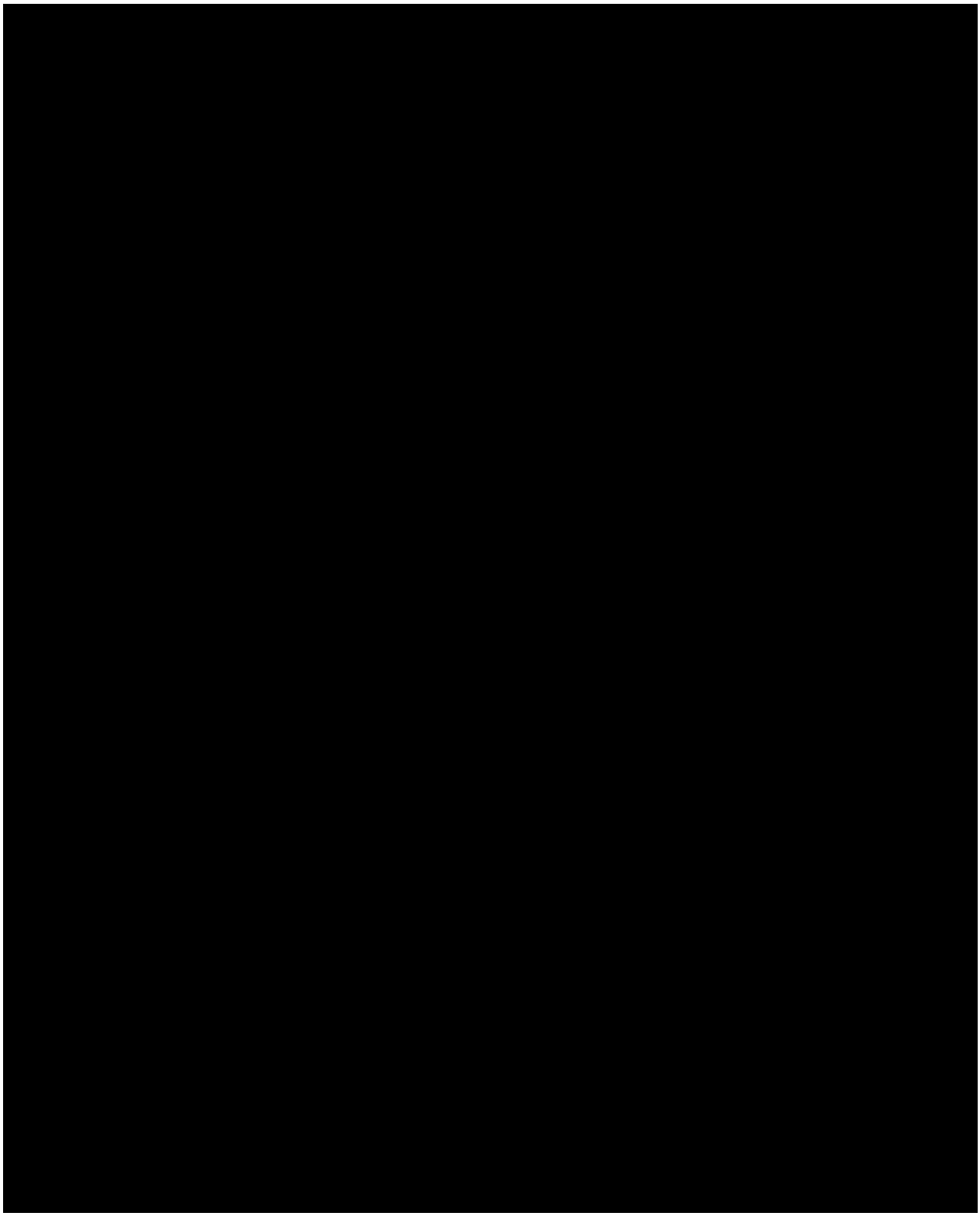
7.2.3.2 PK and immunogenicity sample handling, labeling, and shipping instructions

Blood samples should be collected from the arm opposite from the investigational drug infusion, or from another site. A total of 5 mL of blood will be collected at each time point. For time points when LAG525 or PDR001 (mAb) PK and IG are to be measured, a single blood sample will be collected for both IG and PK. After clotting and centrifugation, the resulting serum will be separated in aliquots and will be stored frozen until analysis. Please see the Laboratory Manual for detailed instructions about collection, handling and shipment of samples.

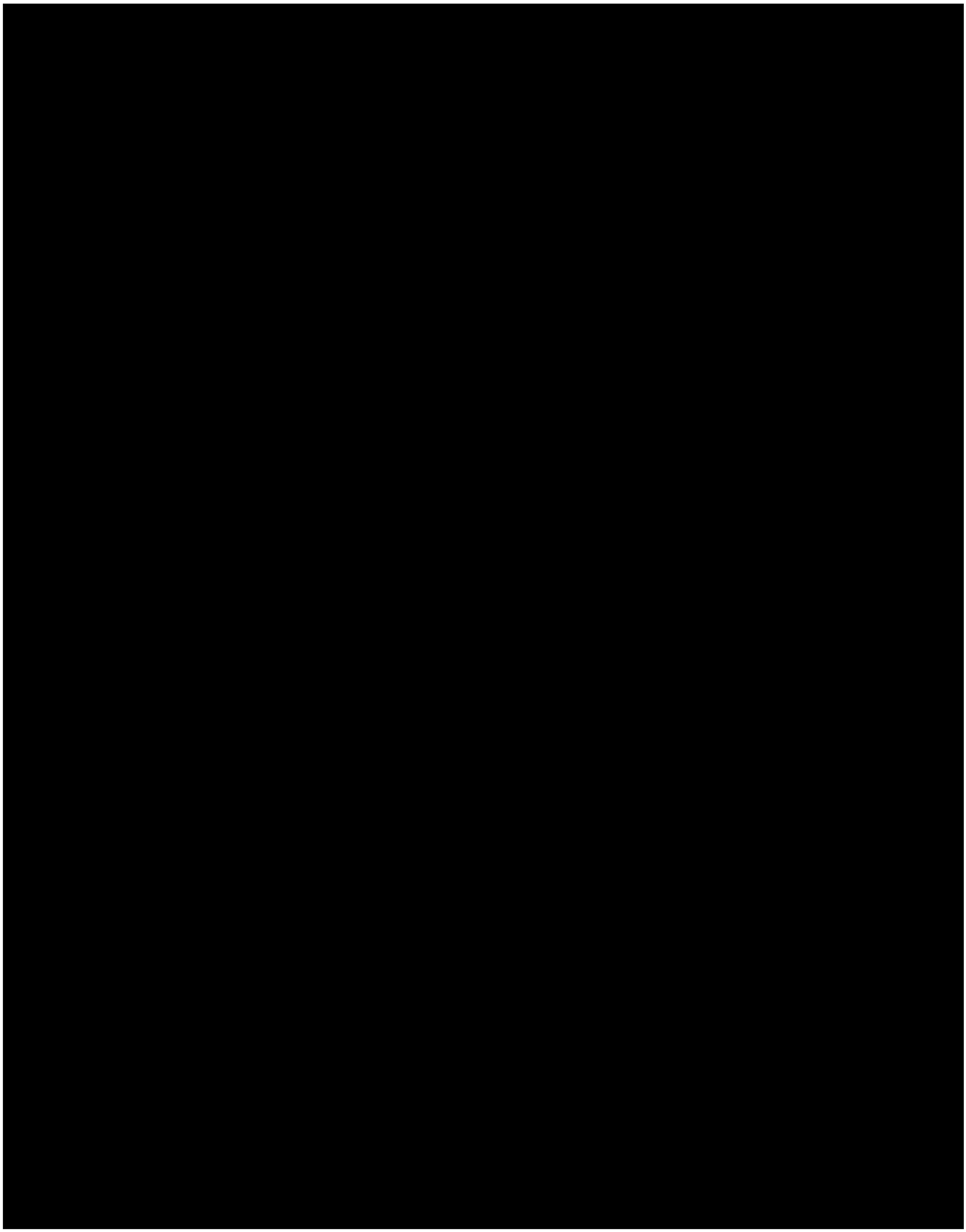
The actual collection date and time of each sample will be entered on the Pharmacokinetics/Immunogenicity Blood Collection eCRF pages.

[redacted]





[redacted]



[redacted]

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 of the patient's CRF. 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 but is collected as a seriousness criterion. Information about deaths will be collected through a Death form.

[redacted]

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:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. 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.

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 (for example, as per irRC or as per RECIST), 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.

[redacted]

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
- 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 *(specify what this includes)*
    - 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

Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST or irRC. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event.

Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

[redacted]

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

8.2.2 Reporting

For patients who sign the study ICF, SAE collection starts at time of main study informed consent 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 this 150 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE 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.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report 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 Report Form in English [For Japan: sites participating in FIH studies must complete the SAE report form in English], and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the 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 Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event 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 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. After the mother has provided consent, these data will be collected for up to 12 months after the birth of the child.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology 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 and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should 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.

8.4 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.

8.5 Data Monitoring Committee

A data monitoring board will not be used for this study. This is an open-label, Phase I-II study in which all patients receive either LAG525 or the combination of LAG525 with PDR001. Novartis will have access to the Safety Data on a regular basis. Novartis will host investigator teleconferences on a regular basis during the study. Further, during the phase I part of the study Novartis and the investigators will meet at the end of each treatment cohort to discuss and evaluate all of the gathered safety data. At the dose escalation teleconference the clinical course (safety information including both DLTs and all CTCAE Grade 2 or higher toxicity data during the DLT observation period, and PK data) for each patient in the current dose cohort will be described in detail. Updated safety data on other ongoing patients, including data in later cycles, will be discussed as well.

Dose escalation decisions will be based on a clinical synthesis of all relevant available data and not solely on DLT information. Selection of the actual dose for the next cohort of patients will be guided by the BLRM with EWOC, and a medical review of relevant clinical, PK and laboratory data. Novartis and the investigator parties must reach a consensus on whether to declare MTD, escalate the dose any further, or whether to de-escalate and/or recruit an additional cohort of patients at the current dose level Section 10.4.2, Section 10.7.

During the phase II part of the study Individual patient data will be reviewed on an ongoing basis. Overall response rate (ORR) per RECIST V1.1, ORR per irRC and aggregate safety data will be monitored quarterly by the study team across the duration of the trial. The data review and analysis will be based on the available investigator reported data in the clinical database at that time Section 10.7.

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 or at an investigator's meeting, 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.

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

For studies using Electronic Data Capture (EDC), 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.

PK and biomarker (blood, serum, plasma and/or tissue) samples obtained during the course of the study will be collected from the Investigator sites and analyzed by a Novartis designated laboratory, contracted central laboratories. ECG data collected during the study will be reviewed and processed centrally by a specialist CRO. During the course of the study, Novartis may decide to have a central review of the radiological assessments performed. In such case, the investigator’s staff will be instructed on how to send data from these radiological assessments to a Contract Research Organization (CRO) for central review when needed. 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 each analytical laboratory with the respective sample(s) by the field monitor or by the designated investigational site staff; and one copy will be retained at the investigational site.

9.4 Database management and quality control

For studies using eCRFs, 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 is required to respond promptly to queries and to make any necessary changes to the data.

[redacted]

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.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

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

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis. Data will be summarized using descriptive statistics (continuous data) and/or contingency table (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements and all relevant PK [redacted] measurements. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

The study data will be analyzed and reported based on all patients' data of the dose escalation and expansion parts up to the time when all patients have potentially completed at least six cycles of treatment or discontinued the study. Any additional data for patients continuing to receive study treatment past the data cutoff date for the primary Clinical Study Report, as allowed by the protocol, will be reported at completion of the study as defined in Section 4.3.

The following rules will be followed for reporting results unless stated otherwise:

- For the phase I part data will be analyzed by Arm and cohorts treated with the same dose or dose combination (dose levels and schedules) will be pooled into a single treatment group by Arm. All summaries, listings, figures and analyses will be performed by treatment group and Arm. Arms to be analyzed are:
  - Arm A: Single-agent LAG525
  - Arm B: Combination LAG525 + PDR001
  - Arm C: Single-agent LAG525 dose escalation in Japanese patients
- For the phase II, all summaries, listings, figures for primary efficacy analysis and safety analyses will be presented by disease group and/or by dose group for one or more disease groups whenever applicable. Patients from the expansion part will be classified according to the disease group to which they were assigned at baseline based on the disease type.
- The different groups to be analyzed are:
  - Group 1: single-agent LAG525, NSCLC (naïve to PD-1/PD-L1)
  - Group 2: single-agent LAG525, Melanoma (naïve to PD-1/PD-L1)
  - Group 3: single-agent LAG525, Renal cancer (naïve to PD-1/PD-L1)
  - Group 4: single-agent LAG525, NSCLC (pre-treated with PD-1/PD-L1)
  - Group 5: single-agent LAG525, Melanoma (pre-treated with PD-1/PD-L1)

- Group 11: single-agent LAG525, Renal cancer (pre-treated with PD-1/PD-L1)
- Group 6: combo LAG525+PDR001, NSCLC (naïve to PD-1/PD-L1)
- Group 7: combo LAG525+PDR001, Melanoma (naïve to PD-1/PD-L1)
- Group 8: combo LAG525+PDR001, Renal cancer (naïve to PD-1/PD-L1)
- Group 9: combo LAG525+PDR001, NSCLC (pre- treated with PD-1/PD-L1)
- Group 10: combo LAG525+PDR001, Melanoma (pre-treated with PD-1/PD-L1)
- Group 12: combo LAG525+PDR001, Renal cancer (pre-treated with PD-1/PD-L1)
- Group 13: combo LAG525+PDR001, Mesothelioma (naïve with PD-1/PD-L1
- Group 14: combo LAG525+PDR001, TNBC (naïve with PD-1/PD-L1)
- Group 15: combo LAG525+PDR001, Mesothelioma (pre-treated with PD-1/PD-L1)
- Group 16: combo LAG525+PDR001, TNBC (pre-treated with PD-1/PD-L1)

Patients in groups 1 to 5 and 11 will receive the recommended dose of single-agent LAG525; patients in groups 6 to 10 and 12 to 16 will receive the recommended combination doses of LAG525 and PDR001.

Note: patients from the dose escalation and the expansion will not be pooled in any analyses unless otherwise specified.

Alternative dosing (i.e. flat dose (mg) and/or dosing schedules (e.g. Q4W)) may be implemented during the study as described in Section 6.1.1. Patients treated with flat dosing (mg) or an alternative dosing schedule will be analyzed as separate treatment groups unless otherwise specified. Details on dose pooling will be provided in the reporting and analysis plan (RAP).

Screen failure patients are those who signed the informed consent, but never started the study treatment for any reason. For these patients, the eCRF data collected will not be included in analyses, but will be reported in the CSR as separate listings.

10.1 Analysis Sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who received at least one dose of assigned single-agent LAG525, or at least one full or partial dose of assigned combination of study drugs. Patients will be analyzed according to the planned treatment. The FAS will be used for all listings of raw data. Unless otherwise specified, the FAS will be the default analysis set used for all analyses.

10.1.2 Safety Set

The Safety Set includes all patients from the FAS who have received at least one dose of LAG525 or PDR001. Patients will be classified according to treatment received, where treatment received is defined as:

1. The treatment assigned if it was received at least once, or
2. The first treatment received when starting therapy with study treatment if the assigned treatment was never received.

[redacted]

The safety set will be used for the safety summary of the study.

10.1.3 Per-Protocol Set

The Per Protocol Set (PPS) consists of a subset of FAS patients in the phase II part who meet the following criteria:

- Presence of at least one measurable lesion according to RECIST 1.1 as per Appendix 1
- At least 2 post-baseline tumor assessments (unless disease progression is observed before that time)
- Have received the planned treatment
- Have not been pre- treated with PD-1 or PD-L1 inhibitors except patients in the pretreated groups, who must have previously received a PD-1- or PD-L1-directed therapy.

Patients will be classified according to planned treatment.

The PPS will be used in the phase II part of the study only and will define the patients used in the sensitivity analysis of the primary endpoint Section 10.4. If the PPS and the FAS are identical, then analyses described by the PPS below will not be performed.

10.1.4 Dose- Determining Analysis Set

Single-agent LAG525 escalation cohort

The dose-determining analysis set (DDS) consists of all patients from the safety set in the dose escalation part who either meet the minimum exposure criterion and have sufficient safety evaluations, or have experienced a DLT during Cycle 1.

A patient is considered to have met the minimum exposure criterion if having received at least two of the planned dose of LAG525 during Cycle 1 for the Q2W schedule or at least one planned dose of LAG525 during Cycle 1 for the Q3W and Q4W schedules. Patients who do not experience a DLT during the first cycle are considered to have sufficient safety evaluations if they have been observed for ≥ 28 days following the first dose (21 days for patients on Q3W dosing schedule), and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

For patients who switch from single agent LAG525 to combination with PDR001, the DLTs occurring after the switch will not be considered in the BLRM.

Combination of LAG525 and PDR001 dose escalation cohort

The dose-determining analysis set (DDS) consists of all patients from the safety set in the dose escalation part who either meet the minimum exposure criterion and have sufficient safety evaluations, or have experienced a DLT during the first two cycles.

A patient is considered to have met the minimum exposure criterion if both of the following criteria are met

1. The patient has received at least three doses of LAG525 during the first 2 cycles for the Q2W schedule or at least two doses of LAG525 during the first 2 cycles for the Q3W and Q4W schedules and

[redacted]

2. The patient has received at least three doses of PDR001 during the first 2 cycles for the Q2W schedule or at least two doses of PDR001 during the first 2 cycles for the Q3W and Q4W schedules

Patients who do not experience a DLT during the first two cycles are considered to have sufficient safety evaluations if they have been observed for ≥ 56 days following the first dose (42 days for patients on Q3W dosing schedule), and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

In the dose escalation part, patients who do not meet these minimum safety evaluation requirements will be regarded as ineligible for the DDS and an additional patient(s) may be recruited.

10.1.5 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who have at least one blood sample providing evaluable PK data. The PAS will be used for all PK analyses.

Note: Patients may be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. These patients will be identified at the time of analysis.

10.2 Patient demographics / other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be listed in detail.

Qualitative data (e.g. performance status) and quantitative data (e.g. weight) will be summarized by appropriate descriptive statistics for each treatment group in phase I and for each group in phase II.

10.3 Treatments (study treatment, concomitant therapies, compliance)

For each of LAG525 and PDR001, the actual dose and duration in days of treatment as well as the dose intensity (actual dose received/actual duration) and relative dose intensity (the ratio of dose intensity to planned dose/planned duration) will be listed and summarized by means of descriptive statistics by treatment group. Categories for relative dose intensity of LAG525 or PDR001 will be specified as < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of patients within each category will be presented by treatment group.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by patient and summarized by ATC term and treatment group.

The reason for discontinuation from treatment will be summarized and listed, along with dates of first and last dose of LAG525 and PDR001 (if applicable), duration of exposure to LAG525 and PDR001 (if applicable) and date of discontinuation for each patient.

Compliance with the protocol will be assessed by the number and proportion of patients with protocol deviations. Protocol deviations will be identified prior to database lock and will be listed and summarized.

10.4 Primary Objective

Phase I part:

To estimate the recommended phase 2 dose (RP2D) or the maximum tolerated dose (MTD) for single-agent LAG525 (including for Japanese patients) and for the combination of LAG525 and PDR001.

Phase II part:

To assess preliminary anti-tumor activity of single-agent LAG525 and combinations of LAG525 and PDR001.

10.4.1 Variable

Phase I

For the single-agent LAG525 dose escalation arm, the primary variable is the incidence of DLTs in the first cycle of treatment. For the combo dose escalation arm, the primary variable is the incidence of DLTs in the first two cycles of treatment. Estimation of the MTD(s)/RP2D(s) will be based upon the estimation by the BLRM of the probability of a DLT in the DLT window for patients in the dose-determining set. In addition, the dose-exposure relationship for LAG525 and PDR001 will be estimated and used to support dose decisions.

Phase II

The primary variable is the Overall Response Rate (ORR), defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR) based on local Investigator assessment, as defined in RECIST v1.1. Estimation of the true ORR in this part of the study will be based upon the observed ORR for patients in FAS, using a Bayesian analysis.

10.4.2 Statistical hypothesis, model, and method of analysis

Phase I

An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle will be used to make dose recommendations and estimate the MTD(s)/ RP2D(s) during the dose escalation part of the study. The BLRM will be fit on the dose-limiting toxicity data (i.e. absence or presence of DLT) during the DLT window accumulated throughout the dose escalation to model the dose-toxicity relationship. In the single-agent LAG525 dose escalation part, the dose-toxicity (DLT) relationship is described by the following 2-parameter BLRM:

$\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$, $\alpha_1>0$, $\beta_1>0$

where $\text{logit}(\pi_1(d_1))= \log(\pi_1(d_1)/(1-\pi_1(d_1)))$, and $\pi_1(d_1)$ is the probability of a DLT at dose d_1, where d_1 represents the Q2W dose of LAG525. Doses are rescaled as d_1/d_1^* with reference dose d_1^*=3 mg/kg of LAG525. As a consequence α_1 is equal to the odds of DLT rate at d_1^*. Note that for a dose equal to zero, the probability of toxicity is zero.

For Japanese patients, the same model as above will be applied to guide single agent dose escalation decisions. Currently available information about the dose-DLT relationships of single-agent LAG525 in Arm A will be used to derive informative priors for the BLRM parameters describing the dose-DLT relationships of this agent taking into consideration the heterogeneity between the global population and Japanese patients. For further details on the statistical model including the prior specification for the model parameters refer to in Appendix 14.4 (Appendix 4)

In the dose escalation for the combinations, the dose-toxicity (DLT) relationship is modeled by a 5-parameter BLRM as follows. Let $\pi_1(d_1)$ be the probability of DLT if LAG525 is given as a single agent at Q2W dose d_1, and $\pi_2(d_2)$ the probability of DLT if PDR001 is given as a single agent at Q2W dose of d_2. $\pi_{12}(d_1,d_2)$ denotes the probability of DLT if LAG525 is given in combination with PDR001 at Q2W dose d_1 of LAG525 and Q2W dose d_2 of PDR001. The possibility of synergism or antagonism between the safety profiles of the two drugs is captured in the model of odds of DLT rate with combination doses.

LAG525: $\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$

PDR001: $\text{logit}(\pi_2(d_2)) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$

$\text{Odds}(\pi_{12}(d_1,d_2))) = \pi_{12}(d_1,d_2)/(1- \pi_{12}(d_1,d_2))$

$= \exp(\eta(d_1/d_1^*)(d_2/d_2^*))(\pi_1(d_1)+ \pi_2(d_2) - \pi_1(d_1)\,\pi_2(d_2))/((1- \pi_1(d_1))(1- \pi_2(d_2))),$

where $\text{logit}(\pi.(d.)) = \log[\pi.(d.)/\{1- \pi.(d.)\}]$, $d_1^* = 3$ mg/kg and $d_2^* = 3$ mg/kg are the reference doses of LAG525 and PDR001 respectively, $\alpha_1, \alpha_2, \beta_1, \beta_2 > 0$ and $-\infty < \eta < \infty$ is the interaction coefficient.

At the time of each LAG525+PDR001 dose escalation analysis, DLT data up to, and including, the last completed cohort from the single agent dose escalation will be included in the LAG525+PDR001 BLRM. Single agent LAG525 data will be incorporated directly into the BLRM since this data comes from the same study. Single agent PDR001 data from study PDR001X2101 dose escalation will also be utilized. In order to account for between study variability, the DLT data obtained from PDR001X2101 will be discounted (e.g. using down-weighting approach).

The Bayesian approach requires the specification of prior distributions for the model parameters. The prior distributions for the BLRM are derived based on available pre-clinical data on LAG525 and PDR001 and also clinical data for nivolumab and pembrolizumab. For further details on the BLRM model including the prior specification for the model parameters, and examples of hypothetical decisions that may be followed during the dose escalation, refer to Appendix 14.3.1.

After each cohort of patients, the posterior distributions for the probabilities of DLT rates at different dose levels (or combinations) are obtained. Dose recommendation will be based on posterior summaries including the mean, median, standard deviation, 95%-credible interval, and the probability that the true DLT rate for each dose lies in one of the following categories:

- [0,16%] under-dosing
- [16%,33%] targeted toxicity
- [33%,100%] excessive toxicity

Dose recommendation will also be guided by the EWOC principle, which mandates the dose for the next cohort to have less than 25% chance of excessive toxicity. The final estimate of the MTD(s)/ RP2D(s) will also satisfy this condition.

In case of changes in dosing schedule during dose-escalation, a BLRM of the same functional form described in Appendix 14.3.1 will be used to estimate the dose-DLT relationship for each schedule based on a newly derived prior incorporating the historical trial data and the on-study data from previous schedule. At each time the model is updated, all available information on the dose-DLT relationship from all explored dosing schedules will be used. In order to account for between schedule variability in the assessment of a given dosing schedule, the DLT data obtained from other explored dosing schedules will be down-weighted. A similar approach will be taken in the event of a change from weight-based dosing to flat dosing. A new BLRM with the same functional form will be developed to evaluate the flat dose. All DLT data obtained from the weight-based dosing cohorts will be incorporated and down-weighted appropriately.

Phase II

A Bayesian design will be used in order to estimate ORR within each group as defined in Section 4.1, and it will be used to provide inferential summaries (e.g., mean, median, interval probabilities) in relation to the patient population.

Each group will enroll approximately 20 patients, and may be extended to 40 patients if at least 3 patients have an objective response for NSCLC, renal cancer, melanoma and mesothelioma, and at least 2 patients have an objective response for TNBC as the target ORR is lower for TNBC. The primary analysis will be performed when all patients have completed at least 6 cycles of treatment or discontinued prior to that time for any reason.

For a Bayesian design, a prior distribution for the parameter of interest, ORR, must be specified. For the current study, the prior clinical assumption for single-agent LAG525 and its combination with PDR001 in the selected patient populations is used in order to derive a minimally informative unimodal Beta prior distribution that reflects the level of uncertainty around ORR before starting the current trial. The prior mean ORR is conservatively set to be equal to 20% and the parameters of the minimally informative Beta prior distribution of ORR have been set up as follows:

- $a/(a+b) = 0.2$
- $a = 0.25$
- $b = 1.0$

At primary analysis, this prior distribution will be updated with all the data available from the patients in the FAS. See sample size estimation in section 10.8.

Single-agent LAG525 (groups 1 to 5 and group 11): Estimates of the ORR for each group along with mean, median, standard deviation, and 95% credible intervals and the interval probabilities for the true ORR lying within [0%, 10%], [10%, 20%], [20%, 30%], [30%, 50%] and [50%, 100%] will be presented.

If the observed ORR is equal to or greater than 20% for NSCLC and renal cancer (i.e. ≥ 8 responses (CR or PR) out of 40 patients) and 30% for melanoma (i.e. ≥ 12 responses [CR or

[redacted]

PR) out of 40 patients), then this will be considered as preliminary evidence of antitumor activity of single-agent LAG525 in the respective patient groups.

Note that for a sample size of n = 40,

- for NSCLC and renal cancer, if the observed ORR is 20% then the posterior probability of true ORR greater than 15% is 78.2%.
- for melanoma, if the observed ORR is 30% then the posterior probability of true ORR greater than 20% is 92.3%.

LAG525+PDR001 combination (groups 6 to 10 and groups 12 to 16): Estimates of the ORR for each group along with mean, median, standard deviation, and 95% credible intervals and the interval probabilities for the true ORR lying within [0%, 20%], [20%, 30%],[30%, 45%], [45%, 60%] and [60%, 100%] will be presented.

If the observed ORR is equal to or greater than 30% for NSCLC, mesothelioma and renal cancer (i.e. ≥ 12 responses (CR or PR) of out 40 patients), 20% for TNBC (i.e. ≥ 8 responses [CR or PR] of out 40 patients) and 45% for melanoma (i.e. ≥ 18 responses [CR or PR] of out 40 patients), then this will be considered as preliminary evidence of antitumor activity of LAG525+PDR001 in the respective patient group.

Note that for a sample size of n = 40,

- for NSCLC, mesothelioma and renal cancer, if the observed ORR is 30% then the posterior probability of true ORR greater than 20% is 92.3%.
- for TNBC, if the observed ORR is 20% then the posterior probability of true ORR greater than 10% is 96.6%.
- for melanoma, if the observed ORR is 45% then the posterior probability of true ORR greater than 30% is 97.2% (See Section 10.8).

10.4.3 Handling of missing values/censoring/discontinuations

Patients in the dose escalation part who are ineligible for the DDS will be excluded from the primary analysis, although their data will be used for all remaining analyses.

Patients in the phase II part who have BOR of Unknown (UNK) or not assessed (NA) will be considered as a treatment failure in the primary analysis of ORR. Patients with individual scans of UNK or NA will be handled according to RECIST 1.1 as per Appendix 1.

Other missing data will simply be noted as missing on appropriate tables/listings.

10.4.4 Supportive analyses

For the phase I part, dose-exposure relationships will be estimated for LAG525 and PDR001 via Bayesian linear models, in order to further guide the dose recommendation to targeted exposure of LAG525 and PDR001. Further details will be given in the RAP.

- From the estimation of the two dose-exposure models, the following posterior summaries will be derived for each dose combination: Mean, median, standard deviation and 95%-credible interval for the exposure of both drugs
- The probability that the true $AUC_{(0\text{-}336h)}$ after first dose of treatment achieves the target exposure.

[redacted]

For the phase II part, the primary analysis on ORR will be repeated using the PPS.

If there are a substantial number of patients receiving palliative radiotherapy, sensitivity analyses of ORR will be performed where the tumor response assessments are censored at the time of palliative radiotherapy. BOR is determined by the best response recorded between the date of first dose of treatment and date of objectively documented progression or date of subsequent anticancer therapy (including on-treatment palliative radiotherapy of non-target lesions), whichever occurs first.

In addition, a Bayesian hierarchical model will be applied to the overall response data from patients in the phase II part. Response rates π_j will be inferred for j = 1,…, 16, for groups 1 to 16 respectively.

For each group j, the number of responders follows a binomial distribution

$r_j \sim \text{Bin}(n_j, \pi_j)$

We further let the parameters $\theta_j = \log(\pi_j /(1-\pi_j))$ be either exchangeable with some of the other group parameters, or non-exchangeable with any of them. Based on the number of groups in the phase II part, we allow for two exchangeability distributions, which, for example, accounts for the case where some indication show no activity and some are promising.

Thus, for each group j three possibilities arise, with respective probabilities $p_j = (p_{j1}, p_{j2}, p_{j3})$, as follows:

1. With probability p_{j1} the parameter θ_j follows a normal distribution with exchangeability parameters μ_1 and τ_1:

$\theta_j \sim N(\mu_1,\tau_1^2)$

2. With probability p_{j2} , θ_j follows a normal distribution with exchangeability parameters $\mu_2 < \mu_1$ and τ_2:

$\theta_j \sim N(\mu_2,\tau_2^2)$

3. With remaining probability $p_{j3} = 1-p_{j1}-p_{j2}$, θ_j follows a weakly-informative prior distribution

$\theta_j \sim N(m_w,v_w)$

For the detailed specifications of m_w, v_w, the a-priori weights p_j (j=1,…,J), and the prior distributions for μ_1, τ_1, μ_2, and τ_2, see Appendix 14.3.2.

At completion of the study, the HM will be updated with all the data available from the patients in the FAS by group. All responses and progressions will be determined as per RECIST v1.1.

Single-agent LAG525 (groups 1 to 5 and group 11): For each of the groups where patients take the recommended dose of single agent LAG525, estimates of the ORR along with mean, median, standard deviation, and 95% credible intervals and the interval probabilities for the true ORR lying within [0%, 10%], [10%, 20%], [20%, 30%], [30%, 50%] and 50%, 100%] will be presented.

Success will be declared for the single agent LAG525 if **both** of the following two criteria are fulfilled:

[redacted]

a. the true ORR for the indication has posterior mean of at least 20%, and
b. there is at least 90% posterior probability that the true ORR exceeds 10%.

LAG525+PDR001 combination (groups 6 to 10 and groups 12 to 16): For each of the groups where patients take the recommended combination doses of LAG525+PDR001, estimates of the ORR along with mean, median, standard deviation, and 95% credible intervals and the interval probabilities for the true ORR lying within [0%, 20%], [20%, 30%],[30%, 45%], [45%, 60%] and [60%, 100%] will be presented.

Success will be declared for the combo of LAG525 and PDR001 if **both** of the following two criteria are fulfilled:

a. the true ORR for the indication has posterior mean of at least 30%, and
b. there is at least 90% posterior probability that the true ORR exceeds 20%.

Additional supportive [redacted] analyses will be conducted to support the primary objective, if appropriate, and the details of these analyses will be defined in the RAP.

10.5 Secondary Objectives

10.5.1 Key secondary objective(s)

Not applicable

10.5.2 Other secondary objectives

Analysis of efficacy endpoints will be performed separately for the single agent LAG525 arm and for the combo arm using the FAS.

Tumor response will be determined per local investigators' assessment. All efficacy secondary endpoints will be defined and analyzed based on tumor assessment by RECIST 1.1 and irRC as described in Appendix 14.1 and Appendix 14.2, respectively.

Efficacy endpoints will include ORR, PFS, DOR and DCR for phase I and phase II. In Phase II secondary endpoints BOR and ORR will be defined based on irRC only. Definitions for these endpoints are provided in Appendix 14.1.

For irRC the key difference from RECIST in the assessments of these endpoints is the requirement for confirmation of PD no less than 4 weeks after the criteria for PD are first met. The date of the first of these two assessments is then the date of confirmed progression. For patients who have ended treatment without a valid confirmation assessment, for the purposes of analysis the single assessment of PD will be treated as a confirmed PD. A single assessment of PD followed by a subsequent assessment of SD or better will be considered as a pseudo-progression, and will not be used for analysis.

Individual lesion measurements and overall response assessments will be listed by patient and assessment date. BOR, PFS, DOR and DCR will be listed by patient.

BOR and ORR will be summarized by treatment group for all patients treated in the phase I part. The following analyses will be presented by disease group for patients treated in the phase II part.

[redacted]

- BOR will be summarized
- ORR and DCR will be summarized with an accompanying [90%] exact binomial confidence interval (CI)
- For PFS the survival function will be estimated using the Kaplan-Meier (KM) product limit method and displayed graphically. Median duration, with a two-sided [90%] CI, and 25th and 75th percentiles (Brookmeyer et al 1982, Klein et al 1997) will be presented. KM estimates of survival proportions at specified time points, along with corresponding [90%] CIs (Greenwood's formula, Kalbfleisch et al 1980) will also be provided.
- For DOR, KM estimates may be provided if sufficient numbers of patients respond.

For patients switching from single-agent LAG525 to combination, efficacy endpoints (like BOR, ORR, PFS, etc.) will be censored at the time the patients start receiving PDR001. All efficacy assessments from these patients will be listed and the assessments performed under combination will be flagged.

Any additional analyses of efficacy endpoints will be described in the RAP.

10.5.3 Safety Objectives

10.5.3.1 Analysis set and grouping for the analyses

For summaries of DLTs, the DDS will be used. For all other safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. post-treatment period: starting at day 31 after last dose of study medication.

Safety summaries will primarily be based on all data from the on-treatment period. Following last administration of study medication, adverse events (including serious adverse events), and new antineoplastic therapies are collected for a period of 150 days. Following start of new antineoplastic therapy, only study treatment related adverse events will be collected. Select summaries of related adverse events will be produced for the overall period starting from the first dose of study treatment until the end of the post-treatment period.

For patients who switch from single-agent LAG525 to combination with PDR001, the on-treatment period will be defined from day of first dose of study medication to 30 days after the last dose of single-agent LAG525.

All safety assessments from these patients will be listed and the assessments performed under combination will be flagged.

10.5.3.2 Adverse events (AEs)

Primary summary tables for AEs have to include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs. Additional select summaries will be

produced using all related AEs that started or worsened during the combined on-treatment and post-treatment periods.

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of AE, relation to study treatment by treatment group.

Serious adverse events and non-serious adverse events will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- Frequency table for newly occurring on-treatment grades 3 or 4 (see below for details).
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- Listing of all clinically relevant laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the RAP.

10.5.3.4 Other safety data

ECG

- shift table baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs

Definitions of notably abnormal results will be specified in the RAP.

- shift table baseline to worst on-treatment result

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

[redacted]

10.5.3.6 Tolerability

Tolerability of study treatment will be assessed by summarizing the number of treatment dose interruptions and dose reductions. Reasons for dose interruptions and dose reductions will be listed by patient and summarized (Section 10.3).

10.5.3.7 Pharmacokinetics

The pharmacokinetic parameters that will be assessed are presented in Table 10-1.

Table 10-1 Pharmacokinetic Parameters to be analyzed

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL	The total body clearance of drug from the plasma (volume x time-1)
Vz	The apparent volume of distribution during terminal phase (associated with λz) (volume)
AR	Accumulation Ratio=Cmax (multiple Dose)/Cmax (single dose)

PAS will be used in all pharmacokinetic data analysis and PK summary statistics. PK data from Japanese patients treated on the single agent Japanese dose escalation (Arm C) will be analyzed separately.

Pharmacokinetic variables:

The following pharmacokinetic parameters will be determined by profile using non-compartmental method(s) for single agent LAG525, LAG525 in combination with PDR001and PDR001 in combination with LAG525:

- AUCinf, AUClast (AUC0-336h), Cmax, Tmax, T1/2, CL, Vz and accumulation ratio.

Biofluid concentrations will be expressed in mass per volume units. All concentrations below the limit of quantitation or missing data will be reported as such in the concentration data listings. Concentrations below the limit of quantitation will be treated as zero in summary statistics.

Descriptive statistics of all pharmacokinetic parameters will include arithmetic and geometric mean, median, SD, and CV, geometric CV, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. Since Tmax is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter.

Summary statistics will be presented for LAG525 serum concentrations at each scheduled time point. Descriptive graphical plots of individual serum concentration versus time profiles and mean concentration versus time profiles will be generated.

Missing concentration values will be reported as is in data listings. Concentration values below Lower limit of quantitation (LLOQ) will be handled as zero in summary statistics, and reported as is in data listings. Any missing pharmacokinetic parameter data will not be imputed.

[redacted]

Further analyses may be conducted using population PK approaches. [redacted] Any analyses performed will be specified either in the RAP prior to clinical database lock or in a stand-alone analysis plan document. All analyses will be reported either in the CSR or a stand-alone report.

Dose proportionality

The analysis of dose proportionality will be conducted for AUC and Cmax of single agent LAG525, LAG525 in combination with PDR001 and PDR001 in combination with LAG525 using a power model on log-transformed scale. The log-transformed PK parameters will each be regressed onto a fixed factor for log (dose). The 90% confidence interval (CI) of the slope for each PK parameter will be computed from the model and presented in a summary table.

[redacted]

[redacted]

10.7 Interim Analysis

No formal interim analyses are planned.

However, in phase I, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose

[redacted]

escalation part, the next dose will be chosen depending on the observed data (based on safety, tolerability, PK, PD and efficacy data, guided by the recommendations from the BLRM of DLT using EWOC, and recommendations from participating investigators). Details of this procedure and the process for communication with Investigators are provided in Section 6.2.3.

Data from patients in the phase II part will be reviewed on an ongoing basis to monitor the safety and tolerability of the RP2D in that part of the study. The sample size in any of the 16 groups (1 to 16) may be extended to approximately 40 patients, if at least 3 patients have a response (PR or CR) per RECIST 1.1 or irRC for NSCLC, melanoma, renal cancer and mesothelioma, and if at least 2 patients have a response (PR or CR) per RECIST 1.1 or irRC for TNBC. The Investigators and Novartis study personnel will make the decision based on a synthesis of all relevant data available including safety, PK [redacted] information.

10.8 Sample size calculation

Phase I

Cohorts of 3 to 6 evaluable patients will be enrolled in the dose-escalation part including at least six patients at the MTD(s)/ RP2D(s) level, as described in Section 6.2.3. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 patients may be enrolled at any dose level below the estimated MTD(s)/ RP2D(s) for further elaboration of safety and pharmacokinetic parameters as required. At least 21 patients are required to be treated in the single agent LAG525 dose escalation (Arm A), at least 12 patients are required to be treated in the Japanese dose escalation (Arm C), and at least 15 patients are required to be treated in the combo dose escalation (Arm B), for the model to have reasonable operating characteristics relating to estimation of the MTD.

Phase II

Approximately 20 patients will be initially enrolled to each of the groups 1 to 16. Any of the 16 groups may be extended to approximately 40 patients.

Single-agent LAG525 (groups 1 to 5 and group 11):

Assume that efficacy will be claimed for single agent LAG525 if observing an ORR of $\geq 20\%$ for NSCLC or renal cancer and $\geq 30\%$ for Melanoma, the operating characteristics of the design are provided in Table 10-2, including the probability of stopping the enrollment at 20 patients (fewer than 3 responses in the first 20 patients), and the probabilities to extend the enrollment to 40 patients and observe an ORR $\geq 20\%$ and $\geq 30\%$.

Specifically,

- If the true ORR is 10% for NSCLC or renal cancer (i.e. in the unacceptable efficacy range), the probability of observing an ORR $\geq 20\%$ is 3.8% ($< 5\%$).
- If the true ORR is 15% for melanoma (i.e. in the unacceptable efficacy range), the probability of observing an ORR $\geq 30\%$ is 1.2% ($< 5\%$).
- If the true ORR is 30% for NSCLC or renal cancer (i.e. in the clinically significant efficacy range), the probability of observing an ORR $\geq 20\%$ is 92.6%.

[redacted]

- If the true ORR is 40% for melanoma (i.e. in the clinically significant efficacy range), the probability of observing an ORR ≥ 30% is 92.8%.

Table 10-2 Operating characteristics of the design (single agent LAG525)

True ORR	Probability to observe <3 responses in first 20 patients	Groups 1,3,4 and 11: NSCLC and Renal cancer	Groups 2 & 5: Melanoma
		probability to observe an ORR ≥ 20% with 40 patients	probability to observe an ORR ≥ 30% with 40 patients
10%	67.7%	3.8%	< 0.1%
15%	40.5%	22.5%	1.2%
20%	20.6%	53.1%	8.7%
25%	9.1%	78.8%	28.4%
30%	3.5%	92.6%	55.8%
40%	0.4%	99.5%	92.8%

Combination LAG525+PDR001 (groups 6 to 10 and groups 12 to 16):

Assume that efficacy will be claimed for the combination of LAG525 + PDR001 if observing an ORR of ≥ 30% for NSCLC or renal cancer or mesothelioma, ≥ 20% for TNBC and ≥ 45% for melanoma, the operating characteristics of the design are provided in Table 10-3 and Table 10-4, including the probability of stopping the enrollment at 20 patients (fewer than 3 responses in the first 20 patients for NSCLC, renal cancer, melanoma and mesothelioma and fewer than 2 responses in the first 20 patients for TNBC), and the probabilities to extend the enrollment to 40 patients and observe an ORR ≥ 30% (for NSCLC, renal cancer, mesothelioma), 20% (for TNBC) and ≥ 45% % (for melanoma).

Specifically,

- If the true ORR is 15% for NSCLC, mesothelioma or renal cancer (i.e. in the unacceptable efficacy range), the probability of observing an ORR ≥ 30% is 1.2% (< 5%).
- If the true ORR is 30% for melanoma (i.e. in the unacceptable efficacy range), the probability of observing an ORR ≥ 45% is 3.2% (< 5%).
- If the true ORR is 40% for NSCLC, mesothelioma or renal cancer (i.e. in the clinically significant efficacy range), the probability of observing an ORR ≥ 30% is 92.8%.
- If the true ORR is 55% for melanoma (i.e. in the clinically significant efficacy range), the probability of observing an ORR ≥ 45% is 92.3%.
- If the true ORR is 10% for TNBC (i.e. in the unacceptable efficacy range), the probability of observing an ORR ≥ 20% is 4.1% (< 5%).
- If the true ORR is 30% for TNBC (i.e. in the clinically significant efficacy range), the probability of observing an ORR ≥ 20% is 94.2%.

Table 10-3 Operating characteristics of the design (LAG525+PDR001)

True ORR	Probability to observe <3 responses in first 20 patients	Groups 6,8,9,12,13,15: NSCLC, renal and mesothelioma probability to observe an ORR ≥ 30% with 40 patients	Groups 7 & 10: melanoma probability to observe an ORR ≥ 45% with 40 patients
15%	40.5%	1.2%	<0.1%
20%	20.6%	8.7%	<0.1%
30%	3.5%	55.8%	3.2%
40%	0.4%	92.8%	31.1%
45%	0.1%	98.2%	56.1%
55%	<0.1%	>99.9%	92.3%

Table 10-4 Operating characteristics of the design (LAG525 + PDR001)

True ORR	Probability to observe <2 responses in first 20 patients	Groups 14, 16: TNBC probability to observe an ORR ≥ 20% with 40 patients
10%	39.2%	4.1%
15%	17.6%	24.1%
20%	6.9%	55.7%
25%	2.4%	81.3%
30%	0.8%	94.2%
40%	0.1%	99.8%

10.9 Power for analysis of key secondary variables

Not applicable.

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/EC/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 or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

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.

[redacted]

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 is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. clinicaltrials.gov, before study start. In addition, results of interventional clinical trials in adult patients are posted on novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year

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of study completion (i.e., LPLV) and those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted.

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

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.

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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 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 (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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14 Appendices

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

Harmonization of Efficacy Analysis of Solid Tumor Studies

Document type:	TA Specific Guideline
Document status:	Version 3.1: 29-Nov-2011 Version 3:0: 19-Oct-2009 Version 2:0: 18-Jan-2007 Version 1:0: 13-Dec-2002
Release date:	29-Nov-2011
Authors (Version 3.1):	[redacted]
Authors (Version 3):	[redacted]
Authors (Version 2):	[redacted]
Authors (Version 1):	[redacted]

[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 multiforme
MRI	Magnetic resonance imaging
LPLV	Last patient last visit
[redacted]	[redacted]
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 noncystic 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/pulmonis, 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). Cytologic 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 cytologic 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.

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

[redacted]

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.

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.

[redacted]

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 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 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

[redacted]

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

[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).

[redacted]

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 150 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
- 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

[redacted]

- 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.

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:

[redacted]

- 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 timepoint 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

The protocol should state which of the following variables is used in that study.

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 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.

[redacted]

[redacted]

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 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).

[redacted]

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 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 randomization/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 [redacted]).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- 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

[redacted]

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. [redacted] 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
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.

[redacted]

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
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)

Situation	Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
[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.

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:

[redacted]

- **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
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment

[redacted]

- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

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 [redacted].

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 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.

[redacted]

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.

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 [redacted].

[redacted]

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

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

14.2 Appendix 2: Guidelines for immune-related response criteria (IrRC) using one-dimensional measurements (simulating RECIST 1.1)

14.2.1 Introduction

The currently used immune-related response criteria (irRC) uses unidimensional measurements to assess tumor response and it is an adaptation of the original irRC published by Wolchok (Wolchol et al. 2009 and Nishino et al. 2013).

The purpose of this document is to summarize the irRC guidelines in details focusing on differences in tumor response assessments between irRC and RECIST v1.1.

The primary difference between irRC and RECIST 1.1 is the definition of progressive disease. The definitions of baseline target/non target lesions, number of lesions selected at baseline, the criteria for lesion measurement method of evaluation of response and definition of response are the same for irRC and RECIST 1.1 and are available in the RECIST 1.1 guidelines (Appendix 14.1).

14.2.2 New Lesions and non-target lesions

In irRC a new lesion does not automatically indicate progressive disease.

New measurable lesions are added to the sum of diameters of the previously existing target lesions, and the sum of diameters is followed at each subsequent tumor assessment.

New measureable lesions are defined using the same criteria as for baseline target lesions in RECIST v1.1. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions. Up to five new measurable lesions (and a maximum of two per organ) are allowed in total and will be included in the overall tumor assessment.

Non-target lesions (baseline and new non-measurable lesions) are used primarily for determination of Complete Response (CR). The RECIST v1.1 definitions for the assessment of non-target lesions apply. A CR requires that all non-target lesions disappear (both those present at baseline and any new non-measurable lesions that have appeared during the study). If after worsening a non-target lesion becomes measurable, it should still be followed as a non-target lesion. Worsening of non-target lesions and new non-measurable lesions only indicate disease progression if there is unequivocal evidence of disease progression (Table 14-6).

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

To assess tumor response, the sum of diameters for all target lesions is calculated (at baseline and throughout the study). The diameters of any new measurable lesions are included in the sum of diameters at each assessment to provide the total tumor burden. At each assessment, percent change in the sum of diameters is calculated and compared to baseline or to nadir in order to evaluate the target lesion response (including new measurable lesions) (Section 14.2.4). This evaluation combined with the status of non-target lesions (baseline and new non-

measurable lesions) is then used to determinate the overall lesion response. The measurement thresholds for irPR and irPD assessment are the same as for RECIST v1.1 (Table 14-6).

14.2.4 Definitions of response categories and evaluation of overall lesion response

In irRC, the overall response is primarily based on target lesions (baseline and new measurable lesions). The non-target lesions only contribute to define irCR, and irPD in the case of unequivocal progression, as shown below in Table 14-6.

Like in RECIST 1.1, irCR and irPR must be confirmed at a new assessment after at least 4 weeks. Unlike RECIST 1.1, irPD also requires confirmation at a new assessment after at least 4 weeks.

The response categories are defined as follows:

- **Immune related Complete Response (irCR)**: Disappearance of all non-nodal target lesions and non-target lesions in two consecutive observations not less than 4 weeks apart. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm. (Sum of diameters may be greater than zero at the time of CR, if nodal lesions are included as target lesions).
- **Immune related Partial Response (irPR)**: At least a 30% decrease in the sum of diameters of all target lesions including new target lesions in two consecutive observations not less than 4 weeks apart, taking as reference the baseline sum of diameters.
- **Immune related Progressive Disease (irPD)**: At least a 20% increase in the sum of diameters of all measured target lesions including new measurable lesions. The irPD must be confirmed in a second evaluation not less than 4 weeks later, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline (nadir). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Worsening of non-target lesions (existing or new) only indicate PD when there is unequivocal evidence of progression, confirmed in a second evaluation not less than 4 weeks later.
- **Immune related Stable Disease (irSD)**: Neither a sufficient shrinkage to qualify for irPR or irCR, nor an increase in lesions which would qualify for irPD.
- **Unknown (UNK)**: Progression has not been documented and one or more target lesions or new measurable lesions observed at earlier assessment have not been/could not be assessed or have been assessed using a method significantly different from baseline (target lesions) or assessment of first occurrence (for new measurable lesions) that prevents reasonable comparison to the prior assessments.

Table 14-6 Overall response at each assessment

Measurable response Target and new measurable lesions (Tumor burden), * (%)	Non-measurable response Non-target lesions (both baseline and new non-measurable)	Overall response Using irRC
- 100	Absent	irCR[a]
- 100	Stable/not evaluated	irPR[a]
≤-30	Absent/Stable/not evaluated	irPR[a]
>-30 and<+20	Absent/Stable/not evaluated	irSD

≥+20	Any	irPD[a]
Any	Unequivocal progression	irPD[a]

*the diameter of new measurable lesions is included in the calculation of the sum of diameters.
[a] To be confirmed after at least 4 weeks.

If the evaluation of any of the target lesions could not be made during follow-up, the overall status must be 'unknown' unless progression was documented.

If the evaluation of any non-target lesions is not made, and all target lesions disappeared, irCR cannot be determined and overall response must be "irPR".

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 irCR.

14.2.5 Only non-measurable disease at baseline

For patients with only non-measurable disease at baseline, unequivocal progression of non-target lesions will constitute an irPD (i.e. worsening of the overall tumor burden which is substantial enough to lead to discontinuation or change of therapy). In addition, the appearance of new lesions (measurable or non-measurable) consistent with unequivocal progression taking into account the overall disease burden will constitute an irPD. The absence of all non-target lesions and no new lesions will qualify for irCR. Otherwise the overall response will be considered as irNon-CR/Non-PD (irNCRNPD) similar to RECIST 1.1. Confirmation of irPD and irCR as specified above in (Section 14.2.4) is required. If any baseline non-target lesion or a new lesion observed at an earlier post-baseline evaluation was not/could not be assessed at a later post-baseline tumor evaluation then the overall response will be irUNK. No confirmation is required for irNCRNPD.

14.2.6 Reference (available upon request)

Wolchok JD, Hoos A, O'Day S et al (2009) Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clin Cancer Res; 15:7412-20.

Nishino M, Giobbie-Hurder A, Gargano M, et al (2013) Developing a Common Language for Tumor Response to Immunotherapy: Immune-Related Response Criteria Using Unidimensional Measurements. Clin Cancer Res; 19:3936-3943.

14.3 Appendix 3: Statistical details of Phase I Bayesian logistic regression models (BLRM) and Phase II hierarchical models

14.3.1 Phase I BLRM

An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle will be used to make dose recommendations and estimate the maximum tolerated dose (MTD) and/or identify the recommended dose for Phase II (RP2D) during the dose escalation part of the study. The use of Bayesian response adaptive models for Phase I studies has been advocated by the EMEA guideline on small populations (2006) and by Rogatko (2007) and is one of the key elements of the FDA's Critical Path Initiative.

In the single-agent LAG525 dose escalation part, the dose-toxicity (DLT) relationship is described by the following 2-parameter BLRM:

$\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*), \qquad \alpha_1>0, \beta_1>0$

where $\text{logit}(\pi_1(d_1))= \log(\pi_1(d_1)/(1-\pi_1(d_1)))$, and $\pi_1(d_1)$ is the probability of a DLT at dose d_1, where d_1 represents the Q2W dose of LAG525. Doses are rescaled as d_1/d_1^* with reference dose d_1^*=3 mg/kg of LAG525. As a consequence α_1 is equal to the odds of DLT rate at d_1^*. Note that for a dose equal to zero, the probability of toxicity is zero.

In the dose escalation for the combinations, the dose-toxicity (DLT) relationship is modeled by a 5-parameter BLRM as follows. Let $\pi_1(d_1)$ be the probability of DLT if LAG525 is given as a single agent at Q2W dose d_1, and $\pi_2(d_2)$ the probability of DLT if PDR001 is given as a single agent at Q2W dose of d_2. $\pi_{12}(d_1,d_2)$ denotes the probability of DLT if LAG525 is given in combination with PDR001 at Q2W dose d_1 of LAG525 and Q2W dose d_2 of PDR001. The possibility of synergism or antagonism between the safety profiles of the two drugs is captured in the model of odds of DLT rate with combination doses.

LAG525: $\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$

PDR001: $\text{logit}(\pi_2(d_2)) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$

$\text{Odds}(\pi_{12}(d_1,d_2))) = \pi_{12}(d_1,d_2)/(1- \pi_{12}(d_1,d_2))$

$= \exp(\eta(d_1/d_1^*)(d_2/d_2^*))(\pi_1(d_1)+ \pi_2(d_2) - \pi_1(d_1)\,\pi_2(d_2))/((1- \pi_1(d_1))(1- \pi_2(d_2))),$

where $\text{logit}(\pi.(d.)) = \log[\pi.(d.)/\{1- \pi.(d.)\}]$, $d_1^* = 3$ mg/kg and $d_2^*= 3$ mg/kg are the reference doses of LAG525 and PDR001 respectively, $\alpha_1, \alpha_2, \beta_1, \beta_2 > 0$ and $-\infty < \eta < \infty$ is the interaction coefficient.

The Bayesian approach requires the specification of prior distributions for all model parameters. This section provides details of the statistical model, the derivation of prior distributions for the model parameters, and the properties of the adaptive design (dosing recommendations for hypothetical data scenarios and operating characteristics).

14.3.1.1 Prior specifications for single agent model parameters

Prior for PDR001 parameters (log(α_2), log(β_2)):

Because more clinical data are available on the class of anti-PD-1 antibody than the anti-LAG-3 antibody, we first derive the prior for single-agent PDR001. This prior will be checked based upon the available single agent data of PDR from CPDR001X2101 study.

This study uses a mixture prior consisting of two components, as specified in Table 14-7. Component 1 is the distribution derived based on PDR001 preclinical data and clinical data on Nivolumab and Pembrolizumab, and is also the component that reflects the low toxicity profile. The assigned weight for component 1 is 80%. Component 2 allows for a case assuming higher toxicity. The assigned weight for component 2 is 20%.

Table 14-7 Prior distribution of model parameters – phase I single agent PDR001

Parameter	Means	Standard deviations	Correlation	Weight
Component 1: priors for a low toxicity profile				
log(α_2), log(β_2)	-2.692, -1.26	1.0, 1.0	0	0.8
Component 2: priors for a more toxicity sensitive population				
log(α_2), log(β_2)	-2.3, 0	2, 1	0	0.2

Component 1:

For the intercept parameter log(α_2), the prior mean of -2.692 is derived based on the a-priori median of an assumed 6.3% DLT rate at the reference dose d_2*= 3 mg/kg. By setting the standard deviation of log(α_2) =1, the respective upper bound of the 95% a-priori interval of the DLT rate at dose 3 mg/kg is 32.5%, lower than 33%, which represents the a-priori assumption that 3 mg/kg of PDR001 is a safe dose.

For the log-slope parameter log(β_2), the prior mean of -1.26 and prior standard deviation of 1 have the following interpretation: when tripling the dose, the odds of having a DLT are multiplied by a factor of 3^{β}, i.e., by 1.4 for the median and approximately (1.0, 9.1) for the 95% interval. This reflects the a-priori assumption that the dose-DLT curve may be quite flat for the anti-PD1 antibody.

Component 2:

This weakly informative bivariate normal prior allows for a case with higher toxicity.

For the intercept parameter log(α_2), the prior mean of -2.3 is derived based on the a-priori median of an assumed 9.1% DLT rate at the reference dose d_2*= 3 mg/kg. By setting the standard deviation =2, the respective 95% a-priori interval at dose 3 mg/kg is wide (0.2%, 84%), which represents weak prior information.

For the log-slope parameter log(β_2), the prior mean of 0 and prior standard deviation of 1 allow for very flat to very steep slopes. Therefore, it is a weakly informative prior. The interpretation is as follows: when tripling the dose, the odds of having a DLT are multiplied by a factor of 3^{β}, i.e., by 3 for the median and (1.2, 2439.2) for the 95% interval.

For both components, the correlation between log(α_2) and log(β_2) is set to 0.

Prior for LAG525 parameters (log(α_1), log(β_1)):

Before observing any clinical data, the DLT profile of single-agent LAG525 is expected to be similar to that of single-agent PDR001. Therefore, it is reasonable to use the same mixture prior defined in Table 14-7 for (log(α_1), log(β_1)).

Table 14-8, Table 14-9 and Table 14-10 summarize the DLT rates of the associated prior distribution. The doses not meeting the overdose criteria are bold in the table, i.e. it is not eligible at the start of the study (under the prior).

Table 14-8 Summary of prior distribution of DLT rates – phase I single agent LAG525 (derived from the mixture prior in Table 14-7)

LAG525 dose (mg/kg Q2W)	Prior probabilities that Pr(DLT) is in interval:					Quantiles		
	[0, 0.16)	[0.16,0.33)	[0.33, 1]	Mean	SD	2.50%	50.00%	97.50%
0.3	0.939	0.047	0.014	0.049	0.076	0	0.024	0.252
1 (starting dose)	0.9	0.075	0.026	0.069	0.095	0.001	0.039	0.334
3	0.805	0.134	0.061	0.11	0.133	0.006	0.066	0.518
10	0.615	0.2	0.185	0.205	0.233	0.012	0.114	0.946

Table 14-9 Summary of prior distribution of DLT rates – phase I single agent LAG525 (derived from the Component 1 prior in Table 14-7)

LAG525 dose (mg/kg Q2W)	Prior probabilities that Pr(DLT) is in interval:					Quantiles		
	[0, 0.16)	[0.16,0.33)	[0.33, 1]	Mean	SD	2.50%	50.00%	97.50%
0.3	0.948	0.046	0.006	0.048	0.059	0	0.028	0.216
1 (starting dose)	0.918	0.071	0.011	0.064	0.069	0.004	0.041	0.257
3	0.849	0.127	0.024	0.09	0.084	0.009	0.064	0.327
10	0.683	0.211	0.106	0.151	0.154	0.013	0.1	0.603

Table 14-10 Summary of prior distribution of DLT rates – phase I single agent LAG525 (derived from the Component 2 prior in Table 14-7)

LAG525 dose (mg/kg Q2W)	Prior probabilities that Pr(DLT) is in interval:					Quantiles		
	[0, 0.16)	[0.16,0.33)	[0.33, 1]	Mean	SD	2.50%	50.00%	97.50%
0.3	0.898	0.053	0.048	0.056	0.129	0	0.006	0.496
1 (starting dose)	0.821	0.09	0.089	0.095	0.167	0	0.022	0.653
3	0.624	0.162	0.214	0.193	0.231	0.002	0.092	0.838
10	0.345	0.154	**0.501**	0.42	0.346	0.006	0.332	0.999

Note: bold values indicate doses not meeting the overdose criterion (less than 25% chance of excessive toxicity) with the prior information only.

To check the performance of the model, the document summarizes some hypothetical dose escalation scenarios. Details regarding dose recommendation are described in Section 10.4.2 of the protocol.

[redacted]

14.3.1.2 Hypothetical dose escalation scenarios for the single-agent LAG525 arm

In order to show how the Bayesian model performs, different hypothetical dose escalation scenarios were investigated. The design should make reasonable dose-recommendations during the clinical trial based on the observed DLTs for hypothetical dose escalation scenarios. During the study, the decision to dose escalate after completion of a given cohort and the actual dose chosen for the subsequent cohort will depend on the recommendation of the BLRM per EWOC principle, estimated/predicted exposure at each dose level, and medical review of available clinical and laboratory data.

Some hypothetical dose escalation scenarios to illustrate the dose escalation up to the fourth dose cohort are listed in Table 14-11. The maximum dose increment allowed in the scenarios did not exceed 334% as per escalation rules defined in Section 6.2.3. The recommended next dose level satisfied the EWOC principle.

Table 14-11 Hypothetical dose escalation scenarios for on-study decisions – phase I single agent LAG525

Scenario	LAG525 Dose level (mg/kg)	Npat	Ntox	Next Dose Level (NDL)	P(Target) NDL	P(Over) NDL	Median DLT rate (NDL)
1	1	4	0				
				3	0.101	0.026	0.054
2	1	4	1				
				3	0.264	0.108	0.121
3	1	4	2				
				1	0.365	0.221	0.19
4	1	4	0				
	3	3	0				
				10	0.146	0.108	0.079
5	1	4	0				
	3	3	1				
				3	0.215	0.055	0.098
6	1	4	0				
	3	3	2				
				1	0.21	0.036	0.089
7	1	4	0				
	3	6	0				
				10	0.126	0.084	0.068
8	1	4	0				
	3	6	1				
				10	0.241	0.193	0.137
9	1	4	0				
	3	6	2				
				3	0.338	0.089	0.142

Scenario	LAG525 Dose level (mg/kg)	Npat	Ntox	Next Dose Level (NDL)	P(Target) NDL	P(Over) NDL	Median DLT rate (NDL)
10	1	4	0				
	3	3	1				
	3	3	0				
				10	0.241	0.193	0.137
11	1	4	0				
	3	3	1				
	3	3	1				
				3	0.338	0.089	0.142
12	1	4	0				
	3	3	1				
	3	3	2				
				1	0.254	0.034	0.103
13	1	4	0				
	3	3	2				
	1	3	0				
				3	0.337	0.248	0.191
14	1	4	0				
	3	3	2				
	1	3	1				
				1	0.367	0.064	0.143
15	1	4	0				
	3	3	2				
	1	3	2				
				1	0.506	0.212	0.222
16	1	4	1				
	3	3	0				
				10	0.274	0.118	0.128
17	1	4	1				
	3	**3**	**1**				
				3	0.38	0.15	0.168
18	1	4	1				
	3	3	2				
				1	0.416	0.179	0.192
19	1	4	1				
	3	3	1				
	3	5	0				
				10	0.364	0.137	0.16

[redacted]

Scenario	LAG525 Dose level (mg/kg)	Npat	Ntox	Next Dose Level (NDL)	P(Target) NDL	P(Over) NDL	Median DLT rate (NDL)
20	1	4	1				
	3	3	1				
	3	5	1				
				3	0.463	0.102	0.175
21	1	4	1				
	3	3	1				
	3	5	2				
				1	0.445	0.082	0.166
22	1	3	0				
	3	5	2				
	1	3	1				
				3	0.479	0.182	0.201
23	1	3	0				
	3	5	2				
	1	3	1				
	1	4	0				
				3	0.429	0.128	0.173

Overall, the model is showing appropriate behaviors, in agreement with clinical sense and decision making process. The dose levels investigated correspond to the provisional dose levels specified in Section 6.2.2.

14.3.1.3 Prior specifications for LAG525 + PDR001 combination model parameters

The 5-parameter BLRM used to guide the dose escalation for the combination of LAG525+PDR001 will use DLT information from both dose escalation arms: patients receiving the single-agent LAG525 and patients receiving the LAG525+PDR001 combo. At each dose escalation meeting, data from the last completed single agent cohort will be incorporated directly into the model, without down-weighting. The available single agent data from CPDR001X2101 study will also be used to check the prior information for the BLRM model.

The prior distributions of model parameters for single-agent LAG525 and single-agent PDR001 have been derived in Section 14.3.1.1.

Prior for the interaction parameter η_{12}:

A normal prior distribution for the interaction parameter η_{12} is to be derived to reflect the current uncertainty about the toxicity profile of the combination of LAG525 and PDR001. The risk of significant positive interaction between LAG525 and PDR001 cannot be totally excluded. The interaction parameter η_{12} was chosen accordingly but with a degree of uncertainty in order to allow for the possibility that the interaction may be positive or negative. Therefore the following assumption is made for the interaction parameter:

[redacted]

- η_{12} is normally distributed and centered at log $(1.5)*(d_1/d_1^*)*(d_2/d_2^*)$, i.e. 50% increase in odds of DLT due to interaction compared to independence at the anticipated combination reference dose d_1^* and d_2^*.
- 97.5th percentile of η_{12} is log $(5)*(d_1/d_1^*)*(d_2/d_2^*)$, i.e.5-fold increase in odds of DLT due to interaction compared to independence at the combination reference dose d_1^* and d_2^*.

Therefore the prior mean for η_{12} is 0.405 and the prior standard deviation is 0.614. This allows for the potential of both synergism and antagonism between the safety profiles of the two drugs. Since the interaction is dose-dependent (see model definition in Section 10.4.2), the prior for the interaction parameter has a simple interpretation only at the anticipated combination reference dose of LAG525 = 3 mg/kg Q2W and PDR001 = 3 mg/kg Q2W.

Table 14-12 summarizes the prior distributions of the model parameters and Table 14-13 summarizes the corresponding prior distribution for the DLT rates at each provisional dose level.

Table 14-12 Prior distribution of model parameters – phase I LAG525 + PDR001

Parameters	Description	Means	Standard deviations	Correlation	Weight
$\log(\alpha_1),\log(\beta_1)$	LAG525 parameters	-2.692, -1.26	1.0, 1.0	0	0.8
		-2.3, 0	2, 1	0	0.2
$\log(\alpha_2),\log(\beta_2)$	PDR001 parameters	-2.692, -1.26	1.0, 1.0	0	0.8
		-2.3, 0	2, 1	0	0.2
η_{12}	Interaction LAG525-PDR001	0.405	0.614		

Table 14-13 Summary of prior distribution of DLT rates – phase I LAG525 + PDR001

LAG525 dose (mg/kg Q2W)	Prior probabilities that Pr(DLT) is in interval:					Quantiles		
	[0, 0.16)	[0.16,0.33)	[0.33, 1]	Mean	SD	2.50%	50.00%	97.50%
PDR001 = 0.3 mg/kg Q2W								
0.3	0.834	0.129	0.037	0.097	0.105	0.004	0.066	0.386
1	0.778	0.168	0.053	0.117	0.119	0.009	0.082	0.451
3	0.658	0.241	0.102	0.16	0.148	0.019	0.114	0.61
10	0.448	0.292	**0.261**	0.264	0.238	0.029	0.181	0.96
PDR001 = 1 mg/kg Q2W								
0.3	0.778	0.169	0.053	0.117	0.118	0.009	0.083	0.448
1	0.709	0.216	0.075	0.14	0.13	0.015	0.102	0.509
3	0.556	0.3	0.144	0.191	0.161	0.026	0.143	0.673
10	0.309	0.288	**0.403**	0.339	0.259	0.033	0.264	0.975
PDR001 = 3 mg/kg Q2W								
0.3	0.655	0.243	0.102	0.16	0.147	0.019	0.116	0.599
1	0.551	0.303	0.146	0.192	0.161	0.026	0.144	0.663
3	0.35	0.329	**0.321**	0.282	0.208	0.035	0.226	0.831
10	0.211	0.135	**0.654**	0.534	0.339	0.013	0.556	0.997

LAG525 dose (mg/kg Q2W)	Prior probabilities that Pr(DLT) is in interval:			Mean	SD	Quantiles		
	[0, 0.16)	[0.16,0.33)	[0.33, 1]			2.50%	50.00%	97.50%
PDR001 = 10 mg/kg Q2W								
0.3	0.438	0.298	**0.263**	0.266	0.236	0.029	0.184	0.957
1	0.302	0.287	**0.411**	0.341	0.258	0.033	0.268	0.972
3	0.208	0.137	**0.655**	0.535	0.339	0.013	0.561	0.997
10	0.21	0.04	**0.75**	0.71	0.398	0	0.981	1

Note: bold values indicate doses not meeting the overdose criterion (more than 25% chance of excessive toxicity) with the prior information only.

14.3.1.4 Hypothetical dose escalation scenarios for LAG525 + PDR001 combination arm

Table 14-14 shows on-study dosing recommendations for some hypothetical data scenarios.

Note that the next dose combination is selected in concordance with the provisional dose levels specified in Section 6.2.2 of the protocol wherever it is allowed, to mimic possible on-study escalation steps.

Table 14-14 Hypothetical dose escalation scenarios for on-study decisions – phase I LAG525 + PDR001

Scenario	Dose combination LAG525 (mg/kg Q2W) / PDR001 (mg/kg Q2W)	Npat	Ntox	Next dose combination (NDC)	P(target) NDC	P(over) NDC	Median DLT rate (NDC)
1	1/1	4	0	1/3	0.237	0.052	0.108
2	1/1	4	1	1/3	0.408	0.163	0.181
3	1/1	4	2	0.3/1	0.409	0.183	0.187
4*	1/0 (single agent cohort 1) 1/1	3 4	0 2	1/1	0.444	0.183	0.195
5	1/1 1/3	4 3	0 0	3/3	0.32	0.129	0.144
6	1/1 1/3	4 3	0 1	1/3	0.364	0.082	0.148
7	1/1 1/3	4 3	0 2	1/1	0.358	0.064	0.141
8	1/1 1/3	4 5	1 0	3/3	0.395	0.191	0.187
9	1/1 1/3	4 5	1 1	1/3	0.481	0.104	0.18

Scenario	Dose combination LAG525 (mg/kg Q2W) / PDR001 (mg/kg Q2W)	Npat	Ntox	Next dose combination (NDC)	P(target) NDC	P(over) NDC	Median DLT rate (NDC)
10	1/1 1/3	4 5	1 2	1/1	0.486	0.113	0.184
11	1/1 0.3/1	4 3	2 0	1/1	0.441	0.128	0.177
12	1/1 0.3/1	4 3	2 1	0.3/1	0.489	0.223	0.222
13	1/1 0.3/1	4 3	2 2	Stop			
14*	1/0 (single agent cohort 1) 1/1 0.3/1	3 4 3	0 2 2	0.3/0.3	0.495	0.241	0.231
15*	1/0 (single agent cohort 1) 3/0 (single agent cohort 2) 1/1 1/3	3 3 4 3	0 0 0 0	3/3	0.293	0.088	0.127
16*	1/0 (single agent cohort 1) 3/0 (single agent cohort 2) 1/1 1/3	3 3 4 3	0 0 0 1	3/3	0.4	0.235	0.205
17*	1/0 (single agent cohort 1) 3/0 (single agent cohort 2) 1/1 1/3	3 3 4 3	0 0 0 2	1/1	0.276	0.032	0.117
18*	1/0 (single agent cohort 1) 3/0 (single agent cohort 2) 1/1 1/3	3 3 4 3	0 1 1 1	1/3	0.526	0.189	0.217
19*	1/0 (single agent cohort 1) 3/0 (single agent cohort 2) 1/1 1/3	3 3 4 3	0 1 1 2	1/1	0.543	0.173	0.214

[redacted]

Scenario	Dose combination LAG525 (mg/kg Q2W) / PDR001 (mg/kg Q2W)	Npat	Ntox	Next dose combination (NDC)	P(target) NDC	P(over) NDC	Median DLT rate (NDC)
20*	1/0 (single agent cohort 1) 3/0 (single agent cohort 2) 1/1 1/3	3 3 4 3	0 0 1 1	1/3	0.466	0.15	0.188

[redacted]

Scenario	Dose combination LAG525 (mg/kg Q2W) / PDR001 (mg/kg Q2W)	Npat	Ntox	Next dose combination (NDC)	P(target) NDC	P(over) NDC	Median DLT rate (NDC)
21*	1/0 (single agent cohort 1) 3/0 (single agent cohort 2) 1/1 1/3	3 3 4 3	0 0 1 2	1/1	0.47	0.13	0.186
*PDR001 dose of 0 represents a single-agent LAG525 cohort. Data from patients receiving the single-agent LAG525 are incorporated directly into the model, without down-weighting Within Table 14-14, P(Target) NDC represents the probability that the true DLT rate for the dose lies in the target interval (16%, 33%) while P(Over) NDC represents the probability that the true DLT rate for the dose exceeds 33%.							

Within Table 14-14, it can be seen that the model generally leads to decisions that are in agreement with clinical sense. The dose levels investigated correspond to the provisional dose levels specified in Section 6.2.2.

14.3.1.5 Operating characteristics for LAG525 + PDR001 combination arm

Scenarios

In order to show how the design performs, 5 hypothetical scenarios were investigated:

1. For scenario 1, the odds of DLT are aligned with the prior information, i.e. the DLT rates for dose combinations are set to the median values derived from the prior.
2. For scenario 2, the odds of DLT are assumed to be 33% decrease from scenario 1
3. For scenario 3, the odds of DLT are assumed to be 25% increase from scenario 1
4. For scenario 4, the odds of DLT are assumed to be 2-folder increase from scenario 1
5. For Scenario 5, it was assumed all provisional combination doses are safe. The odds of DLT remain flat when the doses are escalated beyond 3 mg/kg of LAG525 and 3 mg/kg of PDR001.

The true probabilities used in the simulation are presented in the tables for each scenario above.

Scenario 1 – aligned with prior

Table 14-15 True underlying probabilities of DLT for Scenario 1

LAG525 (mg/kg, Q2W)	PDR001 (mg/kg, Q2W)			
	0.3	**1**	**3**	**10**
0.3	0.066	0.083	0.116	**0.184**
1	0.082	0.102	0.144	**0.268**
3	0.114	0.143	**0.226**	0.561
10	**0.181**	**0.264**	0.556	0.981
Bold values indicate dose combinations in the targeted toxicity interval [16%, 33%).				

Scenario 2 – Scenario 1 + 33% decrease in odds of DLT

Table 14-16 True underlying probabilities of DLT for Scenario 2

LAG525 (mg/kg, Q2W)	PDR001 (mg/kg, Q2W)			
	0.3	**1**	**3**	**10**
0.3	0.045	0.057	0.080	0.131
1	0.056	0.070	0.101	**0.196**
3	0.079	0.100	**0.163**	0.460
10	0.128	**0.193**	0.455	0.972
Bold values indicate dose combinations in the targeted toxicity interval [16%, 33%).				

Scenario 3 – Scenario 1 + 25% increase in odds of DLT

Table 14-17 True underlying probabilities of DLT for Scenario 3

LAG525 (mg/kg, Q2W)	PDR001 (mg/kg, Q2W)			
	0.3	**1**	**3**	**10**
0.3	0.081	0.102	0.141	**0.220**
1	0.100	0.124	**0.174**	**0.314**
3	0.139	**0.173**	**0.267**	0.615
10	**0.216**	**0.310**	0.610	0.985
Bold values indicate dose combinations in the targeted toxicity interval [16%, 33%).				

Scenario 4 - Scenario 1 + 2 folder increase in odds of DLT

Table 14-18 True underlying probabilities of DLT for Scenario 4

LAG525 (mg/kg, Q2W)	PDR001 (mg/kg, Q2W)			
	0.3	**1**	**3**	**10**
0.3	0.124	0.153	**0.208**	**0.311**
1	0.152	**0.185**	**0.252**	0.423
3	**0.205**	**0.250**	0.369	0.719
10	**0.307**	0.418	0.715	0.990
Bold values indicate dose combinations in the targeted toxicity interval [16%, 33%).				

Scenario 5 – Misspecification of DLT relationship

Table 14-19 represents the hypothetical scenario that all provisional combination doses are safe. The odds of DLT are set the same as in scenario 1 for lower dose combinations and remain flat when the doses are escalated beyond 3 mg/kg of LAG525 and 3 mg/kg of PDR001.

[redacted]

Table 14-19 True underlying probabilities of DLT for Scenario 5

LAG525 (mg/kg, Q2W)	PDR001 (mg/kg, Q2W)			
	0.3	**1**	**3**	**10**
0.3	0.066	0.083	0.116	**0.184**
1	0.082	0.102	0.144	**0.268**
3	0.114	0.143	**0.226**	**0.268**
10	**0.181**	**0.264**	**0.264**	**0.268**
Bold values indicate dose combinations in the targeted toxicity interval [16%, 33%).				

Simulation parameters:

1000 trials were used to simulate each scenario. The starting dose combination was chosen as 1 mg/kg for LAG525 and 1 mg/kg for PDR001, and the maximal dose to jump to was orthogonal, and follows the protocol specifications (Section 10.4.2 of the protocol). The number of patients to enroll in each cohort and stopping rules used to declare MTD were defined as:

- Maximum number of patients treated: 60
- Minimum cohort size: 3
- Minimum number of patients treated at a given dose combination in order to declare MTD: 6
- Posterior probability of targeted toxicity at this combination dose > 50% and is the highest among potential doses, or

Minimum number of patients treated in the trial: 15

Metrics

Operating characteristics were reviewed for the simulations to compare the relative performance under each true scenario. The metrics reviewed were:

1. Average proportion of patients receiving a target dose combination on study (I)
2. Average proportion of patients receiving a dose combination with true P(DLT) ≥ 33% on study (II)
3. Average proportion of patients receiving a dose combination with true P(DLT) < 16% on study (III)
4. Proportion of trials that were recommended a target dose combination as the MTD (correct final decision) (IV)
5. Proportion of trials that were recommended a dose combinations with true P(DLT) ≥ 33% as the MTD (patient risk) (V)
6. Proportion of trials that were recommended a dose combination with true P(DLT) < 16% as the MTD (VI)

Results

Table 14-20 below summarizes the simulated operating characteristics of the model for the 5 different scenarios studied, additionally showing the percentage of trials stopped before declaring MTD when all dose combinations were considered too toxic.

[redacted]

Table 14-20 Results

Scenario	Metric						
	I	II	III	IV	V	VI	Stopped
1	0.418	0.003	0.579	0.573	0	0.420	0.007
2	0.527	0.018	0.454	0.787	0.009	0.203	0.001
3	0.672	0.002	0.326	0.915	0	0.075	0.010
4	0.745	0.201	0.054	0.785	0.162	0.019	0.034
5	0.434	0	0.566	0.602	0	0.392	0.006

The simulated operating characteristics presented show that the combination model performs well under the hypothetical scenarios investigated.

The proportion of patients treated at overly toxic dose combinations (metric II) is very low for all the scenarios. The probability of identifying a dose with P (DLT) > 0.33 as MTD (metric V) is low for all scenarios.

In scenarios 2, 3 and 4, the probability that the identified MTD falls within the target interval (metric IV) is more than 78%, showing excellent targeting of MTD.

In scenarios 1, the underlying P (DLT) is low and below 0.33 for most dose combinations except 3/3, 3/10 and 10/3 for LAG525 in mg/kg / PDR001 in mg/kg; in scenario 5, none of the underlying P (DLT) is above 0.33. This explains why scenarios 1 and 5 have a relatively high proportion of patients receiving a dose with P (DLT) < 0.16 (metric III) and why the probability that the identified MTD falls within the under-dose interval (metric VI) is not very low.

The percentages of trials that were stopped when all dose combinations were considered too toxic are low (< 5%) in all scenarios.

In conclusion, the simulations performed illustrate that the model has good operating characteristics.

14.3.2 Prior specifications for phase II hierarchical model

As a supporting analysis, for patients in phase II part, the ORR for each of 16 groups is estimated using a hierarchical model with two exchangeable groups and one non-exchangeable group (see Section 10.4.4) and data from all 16 groups.

The model is given in Section 10.4.4 and the details of prior specifications are provided here. Three results will be used in the below specifications:

a. For a probability π, we construct a weakly-informative prior distribution on the logit-scale, i.e. for $\log(\pi/(1-\pi))$, as follows: the prior median is set to a plausible value m_π, and the "prior sample size" will be approximately one. For the latter, under a normal approximation, the resulting variance on the logit-scale is $v_\pi = 1/m_\pi + 1/(1- m_\pi)$. This leads to a weakly-informative normal prior distribution for $\log(\pi/(1-\pi))$ with mean m_π and variance v_π.
b. For exchangeable group-specific parameters $\theta_j = \log(\pi_j /(1-\pi_j))$, $\theta_j \sim N(\mu, \tau^2)$, let the prior distributions be $\mu \sim N(m_\mu, v_\mu)$ and $\tau \sim HN(s)$. Here, HN(s) denotes the half-normal distribution with scale parameter *s*.

c. Assume that the marginal (total) variance V(θ) as well as the scale parameter *s* are known, where the first defines the a-priori uncertainty for the indication parameters, and the second defines the a-priori degree of borrowing across groups. From these specifications, the prior variance of μ follows from the law of total variance

$V(\theta) = E(V(\theta|\mu,\tau) + V(E(\theta|\mu,\tau)) = E(\tau^2)+V(\mu) = s^2 + v_{\mu},.$

From this, the variance of μ is $v_\mu = V(\theta) - s^2$.Based on these results, we specified the prior distributions for parameters in the hierarchical model as follows:

1. The group-specific normal priors for the **non-exchangeable** case, defined by m_w and v_w were derived from (a) above. The prior median for the response probability was set as 0.2 (a limited treatment effect), and the corresponding variance was derived as described in (a) above. This results in

   $m_w = \text{logit}(0.2) = -1.386$, $v_w = 1/0.2 + 1/(1 - 0.2) = 2.5^2$
2. For the **exchangeable** cases, the specifications were as follows:
   2.1 Applying (b) above, τ_1 and τ_2 were given a half-normal distribution with scale 0.5, implying a prior 95%-interval for τ as (0.016, 1.12), which allows for small to large between-indication heterogeneity (Spiegelhalter 2004).
   2.2 μ_1 and μ_2 were given normal prior distributions. For μ_1, the mean of the prior distribution was set to logit(0.1) = –2.197 corresponding to no treatment effect. For μ_2, the mean was set to logit(0.3) = –0.847 corresponding to a substantial treatment effect.
   2.3 Assume θ_j belongs to the first exchangeability distribution. Applying (c) above, the total variance worth approximately one subject is 3.33^2. Since $\tau_1 \sim HN(0.5)$ the variance for the normal prior distribution for μ_1 becomes 3.296^2. The same approach was used to derive the variance for the normal prior distribution for μ_2, yielding a variance of 2.124^2.
3. Finally, for each group j, the **prior mixture weights** p_j were chosen as

   $p_j = (0.25, 0.25, 0.50)$, $j=1,\ldots,16$.

This means that each group has 25% prior probability to belong to the first exchangeability distribution, 25% probability to belong to the second exchangeability distribution, and 50% probability to be non-exchangeable with some (or all) of the other indications.

The prior distributions are summarized in Table 14-21, which also shows the prior medians and 95%-intervals for the response rates π_j.

Table 14-21 Prior distribution of hierarchical model parameters

Parameter	Prior distribution
μ_1	N(-2.197, 3.296^2)
μ_2	N(-0.847, 2.124^2)
τ_1	HN(scale=0.5)
τ_2	HN(scale=0.5)
m_w, v_w ,	−1.386, 2.5^2
$p_j = (p_{j1},p_{j2},p_{j3})$, j=1,…,12	(0.25, 0.25, 0.5)
	Median (2.5%, 97.5%)
π_i	0.2 (0.001, 0.98)

14.4 Appendix 4: Statistical details of Phase I Bayesian logistic regression model (BLRM) in Japanese patients treated with single agent of LAG525

This appendix provides details of the statistical model, the derivation of prior distributions from historical data of LAG525 from global patients, and the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios.

14.4.1 Statistical model

An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle will be used to make dose recommendations and estimate the maximum tolerated dose (MTD) and/or identify the recommended dose for expansion (RP2D) during the dose escalation part of the study. The use of Bayesian response adaptive models for Phase I studies has been advocated by the EMEA guideline on small populations (2006) and by Rogatko (2007) and is one of the key elements of the FDA's Critical Path Initiative.

Single agent LAG525 for Japanese patients: In the single-agent LAG525 dose escalation part, the dose-toxicity (DLT) relationship is described by the following 2-parameter BLRM:

$$\text{logit}(\pi(d)) = \log(\alpha) + \beta \log(d/d^*),\ \alpha>0,\ \beta>0$$

Where $logit(\pi(d)) = log(\frac{\pi(d)}{1-\pi(d)})$, and $\pi(d)$ is the probability of a DLT at dose d.

Doses are rescaled as d/d* with reference dose d*=3 mg/kg of LAG525. As a consequence α is equal to the odds of DLT rate at d*, and β (>0) is the increase in the log-odds of a DLT by a unit increase in log-dose. Note that for a dose equal to zero, the probability of toxicity is zero.

The Bayesian approach requires the specification of prior distributions for all model parameters. This section provides details of the statistical model, the derivation of prior distributions for the model parameters, and the properties of the adaptive design (dosing recommendations for hypothetical data scenarios and operating characteristics).

14.4.2 Prior specifications

The Bayesian approach requires the specification of prior distributions for all model parameters. A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the model parameters.

14.4.2.1 Prior distribution for the logistic parameters

A mixture prior distribution for the single-agent LAG525 model parameters was derived. It consists of a mixture of a meta-analytic-predictive (MAP) prior and a weakly informative prior corresponding to high toxicity to make the prior more robust. To obtain the mixture prior, 50% weight was assigned to the MAP prior, and 50% weight was assigned to the weakly informative prior.

14.4.2.1.1 Description of the MAP approach

The aim of the MAP approach is to derive a prior distribution for the logistic parameters ($\log(\alpha^*)$, $\log(\beta^*)$) of the new trial (eg., Japanese sub-population in the LAG525x2101 study) using DLT data from the ongoing dose-escalation in global patients (LAG525x2101 study).

Let r_{ds} and n_{ds} be the number of patients with a DLT, and the total number of patients at dose d in historical trial s ($s = 1, \ldots, S$). The corresponding probability of a DLT is π_{ds}. The model specifications for the derivation of the MAP prior are as follows:

$$r_{ds} \mid \pi_{ds} \sim \text{Bin}(\pi_{ds}, n_{ds})$$

$$\text{logit}(\pi_{ds}) = \log(\alpha_s) + \beta_s \log(d/d^*)$$

$$(log(\alpha_s), log(\beta_s)) \mid \mu, \psi \sim \text{BVN}(\mu, \psi), \qquad s = 1, \ldots, S$$

$$(log(\alpha^*), log(\beta^*)) \mid \mu, \psi \sim \text{BVN}(\mu, \psi)$$

Where $d^* = 3$ mg/kg and $S = 1$ in this study and refers to Arm A. The parameters $\mu = (\mu_1, \mu_2)$ and ψ are the mean and between-trial covariance matrix for the logistic parameters, the latter with standard deviations τ_1, τ_2, and correlation p. The parameters τ_1 and τ_2 quantify the degree of between trial heterogeneity. The main objective is to estimate the predictive distribution

$$(log(\alpha^*), log(\beta^*)) \mid (r_{ds}, n_{ds} : s = 1, \ldots, S)$$

based on DLT data from arm A. To do that, it is assumed:

- normal priors for μ_1 and μ_2,
- log-normal priors for τ_1 and τ_2, and
- a uniform prior for p.

Since the predictive distribution is not available analytically, the Markov Chain Monte Carlo (MCMC) method is used to simulate values from this distribution. This is implemented using WinBUGS 14.1.3. The sample from this distribution is approximated by a mixture of bivariate normal (BVN) distributions. BVN mixtures with increasing numbers of mixture components are fitted to the sample using the expectation-maximization (EM) algorithm (Dempster 1977). The optimal number of components of the mixture is then identified using the Akaike information criterion (AIC) (Akaike 1974).

14.4.2.1.2 Implementation of the MAP approach

For the MAP model, data from global patients treated in Arm A of the global study [CLAG525X2101C] was used (Table 14-22).

Table 14-22 Data from global patients in study CLAG525X2101C

Dose of LAG525 *	Dose of LAG525 (mg/kg,Q2w)	No of DLTs/No of evaluable patients
1 (mg/kg,Q2w)	1	1/12
3(mg/kg,Q2w)	3	0/11
5(mg/kg,Q2w)	5	2/4
10(mg/kg,Q2w)	10	0/4
3(mg/kg,Q4w)	1.5	0/5
5(mg/kg,Q4w)	2.5	0/3

Dose of LAG525 *	Dose of LAG525 (mg/kg,Q2w)	No of DLTs/No of evaluable patients
10(mg/kg,Q4w)	5	0/4
* Data cut-off date: 22 January, 2016		

Weakly informative priors are assumed for μ_1 and μ_2, with means corresponding to a risk of DLT at the reference dose of 10%, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_1 and τ_2 are assigned such that (1) their medians correspond to moderate between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Schmidli 2014). The prior distributions for the model used for deriving the MAP priors are specified in Table 14-23.

Table 14-23 Prior distributions for the parameters of the MAP model used to derive the prior

Parameter	Prior distribution
μ_1	N(mean = logit(0.10), sd = 2)
μ_2	N(mean = 0, sd=1)
τ_1	log-normal(mean = 0.25, sd = log(2)/1.96)
τ_2	log-normal(mean = 0.125, sd = log(2)/1.96)
ρ	uniform(-1,1)

14.4.2.1.3 Derivation of the weakly informative prior

A weakly informative BVN prior to allow higher toxicity than MAP prior is derived by assuming median probability of DLT at 3 mg/kg to be 20%, as well as a log-linear relationship between dose and the odds of DLT as defined in Section 14.4.1. This results in setting the mean of $\log(\alpha)$ equal to -1.386. The mean of $\log(\beta)$ is set to 0. Furthermore, setting standard deviation of $\log(\alpha) = 2$ and $\log(\beta) = 1$, and setting the correlation between $\log(\alpha)$ and $\log(\beta) = 0$ to complete the determination of this prior. See Table 14-24.

14.4.2.2 Summary of prior distributions

The prior distributions of the model parameters are summarized in Table 14-24.

Prior summaries for DLT rates are summarized at each provisional dose level in Table 14-25.

Table 14-24 Prior distribution of model parameters

Parameter	Mean	Standard deviations	Correlation	Weight
LAG525 MAP prior, BVN mixture (*log*(*α*), *log*(*β*)), weight = 50%				
BVN mixture 1	(-2.410 , -0.602)	(0.572 , 0.555)	-0.179	0.206
BVN mixture 2	(-2.988 , -1.050)	(0.719 , 0.747)	-0.272	0.180
BVN mixture 3	(-2.758 , 0.025)	(0.779 , 0.419)	-0.178	0.114
Weakly informative prior (*log*(*α*), *log*(*β*)), weight = 50%				
Weakly informative	(-1.386, 0)	(2, 1)	0	0.5

Table 14-25 Summary of prior distribution of DLT rates

PDR001 dose (mg/kg, Q2W)	Prior probabilities that P(DLT) is in interval:					Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33, 1]	Mean	SD	2.5%	50.0%	97.5%
0.3	0.905	0.046	0.050	0.062	0.134	0.000	0.017	0.534
1 (starting dose)	0.842	0.070	0.088	0.101	0.170	0.000	0.038	0.697
3	0.690	0.126	0.185	0.188	0.230	0.008	0.088	0.870
10	0.412	0.222	**0.367**	0.349	0.318	0.022	0.207	0.997

SD = standard deviation.
Bold values indicate dose(s) not meeting the EWOC principle with the prior information only.

14.4.3 BLRM design properties for hypothetical data scenarios

Table 14-26 shows on-study dosing recommendations for some hypothetical data scenarios. Note that the next dose is selected in concordance with the provisional dose levels specified in Section 6.2.2 of the protocol wherever it is allowed, to mimic possible on study escalation steps.

Table 14-26 Hypothetical dose escalation scenarios for on-study decisions – phase I single agent LAG525

Scenario	LAG525 Dose level (mg/kg)	Npat	Ntox	Next Dose Level (NDL)	P(Target) NDL	P(Over) NDL	Median DLT rate (NDL)
1	1	4	0	3	0.106	0.080	0.069
2	1	4	1	1	0.197	0.111	0.089
3	1	4	2	0.3	0.267	0.241	0.164
4	1	4	0				
	3	3	1	3	0.229	0.136	0.118
5	1	4	0				
	3	3	2	1	0.168	0.051	0.066
6	1	4	0				
	3	6	0	10	0.223	0.151	0.118
7	1	4	0				
	3	6	2	3	0.346	0.191	0.174
8	1	4	0				
	3	3	1				
	3	5	0	5	0.219	0.113	0.117
9	1	4	0				
	3	3	1				
	3	3	1	3	0.346	0.191	0.174
10	1	4	0				
	3	3	1				
	3	3	2	1	0.191	0.041	0.072
11	1	4	0				
	3	3	2				
	1	3	1	1	0.352	0.110	0.148

[redacted]

Scenario	LAG525 Dose level (mg/kg)	Npat	Ntox	Next Dose Level (NDL)	P(Target) NDL	P(Over) NDL	Median DLT rate (NDL)
12	1	4	0				
	3	3	2				
	1	3	2	0.3	0.274	0.092	0.113
13	1	4	1				
	1	5	0	3	0.199	0.134	0.110
14	1	4	1				
	1	3	2	0.3	0.321	0.194	0.166
15	1	4	1				
	1	5	0				
	3	4	0	10	0.315	0.144	0.148
16	1	5	0				
	3	4	0				
	10	3	0	10	0.184	0.033	0.090

Within Table 14-26, it can be seen that the model generally leads to decisions that are in agreement with clinical sense: progressive increase of the doses if no DLT is observed, enrolling of a new cohort at the same dose level when 1 DLT is reported, and de-escalation when more than 1 DLT is reported in a cohort. It is expected that the dose-DLT relationship in Japanese patients will be very similar to that observed outside Japan. Scenario 16 is a hypothetical scenario where the dose-DLT relationship is consistent between global and Japanese patients. In this case, the posterior weight for the prior components based on data from the global study [CLAG525X2101C] increases to from 50% to 70%, demonstrating support for the exchangeability of these two populations based on DLT data.

In addition, Table 14-26 shows also some examples for the unlikely case of dissimilarity in the dose-DLT relationship between Japanese and global patients. Scenario 5 is an example illustrating such dissimilarity. In this case, the posterior weight for the prior components based on data from the global study [CLAG525X2101C] reduces to 19%. Overall, in the case of dissimilarity, the model performs appropriately, leading to dose de-escalation.

14.4.3.1 Operating characteristics

In order to show how the proposed design performs under different true dose- DLT profiles, various hypothetical scenarios were investigated.

14.4.3.2 Simulation setup

Table 14-27 shows 4 dose-DLT scenarios, taking scenario 1 (true DLT rates equal to mean prior DLT rates) as the basis. Scenarios 2, 3 and 4 have increased DLT rates compared to scenario 1:

-Scenario 2: the odds of DLTs are 2-fold larger than the ones of scenario 1

-Scenario 3: the odds of DLTs are 3-fold larger than the ones of scenario 1

-Scenario 4: the odds of DLTs are 5-fold larger than the ones of scenario 1

The following table presents the true underlying probabilities of DLT for each scenario

Table 14-27 dose-DLT scenarios

Test scenarios	Assigning DLT probabilities to each dose level				Note
	0.3 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg	
1	0.062	0.101	**0.188**	0.349	True dose-DLT relationship based on prior mean DLT rates
2	0.117	**0.183**	**0.316**	0.517	2-fold odds inflation from test scenario 1
3	**0.165**	**0.252**	0.410	0.617	3-fold odds inflation from test scenario 1
4	**0.248**	0.360	0.537	0.728	5-fold odds inflation from test scenario 1
n-fold odds inflation: p1/(1-p1) = n*[p0/(1-p0)], p1=n*p0/(1-p0+n*p0), where p0 is a probability of test scenario 1					

- For each scenario data for 1000 trials were generated.
- Dose levels investigated: 0.3, 1 (starting dose), 3, 10 mg/kg
- Cohort size: 3, 4, 5, or 6 patients (randomly assigned with a uniform rate of 25%)
- Stopping rule/MTD selection criteria:
  - Maximum number of patients per a trial: 30 patients
  - Minimum number of patients per a trial: 12 patients
  - Minimum number of patients at MTD: 6 patients
  - Posterior probability of targeted toxicity at MTD: >50%

Table 14-28 Operating characteristics of BLRM-based dose escalation design

Profile	Parameter	PDR001 dose level (mg/kg)				stopped (toxicity) [2]	stopped (max N) [3]
		0.3	1	3	10		
1	True probability of DLT (%) [1]	6.2	10.1	18.8	34.9		
	Average # of patients recruited	0.45	6.8	6.84	3.09		
	Average # of DLTs	0.04	0.69	1.26	1.08		
	% of MTD selection	1.7	23.8	48.8	23.1	2.3	0.3
2	True probability of DLT (%) [1]	11.7	18.3	31.6	51.7		
	Average # of patients recruited	1.36	8.48	5.23	0.91		
	Average # of DLTs	0.16	1.60	1.64	0.47		
	% of MTD selection	8.5	46.5	31.2	3.1	10.4	0.3
3	True probability of DLT (%) [1]	16.5	25.2	41	61.7		
	Average # of patients recruited	2.19	8.69	3.66	0.32		
	Average # of DLTs	0.36	2.13	1.50	0.2		
	% of MTD selection	15.7	50.2	13.6	0.4	19.8	0.3
4	True probability of DLT (%) [1]	24.8	36.0	53.7	72.8		
	Average # of patients recruited	3.17	7.76	1.62	0.08		
	Average # of DLTs	0.77	2.86	0.84	0.06		
	% of MTD selection	24.5	23.2	2.4	0.0	49.7	0.2

[1] Bolding indicates doses with true probability of DLT within the target toxicity interval [16%, 33%).
[2] Proportion (%) that a trial is stopped since all dose levels are too toxic.
[3] Proportion (%) that a trial is stopped since the maximum number of patients is reached without selecting a MTD.

[redacted]

14.4.3.3 Results

The simulated operating characteristics presented show that the BLRM performs well under the hypothetical profiles investigated. Indeed, the simulations performed illustrate that the model has reasonable operating characteristics and the number of patients with DLT was limited through a trial. In scenario 1, the odds of DLT are aligned with the prior information. In this scenario, the simulations show that about 49% and 23% of chance for selecting MTD at 3mg/kg and 10mg/kg dose levels, respectively. Finally, in scenario 4, with 5-fold odds inflation from test scenario 1, the chance to stop the trial due to high toxicity of all dose levels is very high (49.7%) as expected since only 0.3 mg/kg dose has the underlying P (DLT) that is below 33%. The simulations show that there is about 23% of chance for selecting MTD at 1mg/kg dose level since the assumed P(DLT) for this dose lies very close to the upper boundary of at those doses the target interval, leading to a tendency for the model estimate of the probability of overdose to identify this as a dose not satisfying the EWOC criterion.

In conclusion, the simulations performed illustrate that the model has good operating characteristics under the 4 hypothetical profiles investigated.

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