NOVARTIS

Clinical Development

LAG525, PDR001

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

Statistical Analysis Plan (SAP)

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Table of Contents

List of tables

Document History – Changes compared to previous version of SAP.

Version	Date	Changes
1.0	27Jan2020	Draft
Amendment 1	07Jul2019	1. Added list of abbreviations and glossary terms. 2. Updated study design adding TNBC and Mesothelioma indications. 3. Removed single agent groups from Phase II part. 4. Updated the definition of DDS by adding specific wording for different dosing regimens. 5. Added the definitions for immunogenicity analysis sets. 6. Updated medical history section by adding more details on the analysis. 7. Added a subsection on analysis set exclusion. 8. Updated the definitions of last date of exposure for both monotherapy and combo therapy. 9. Updated definitions of duration of exposure and actual cumulative dose. 10. Removed the definitions of cumulative planned doses, percentage of days dosed and percentage of days at planned dose. 11. Removed the language about the primary bayesian analysis of ORR for single agent LAG525. 12. Added definitions of efficacy endpoints like BOR, ORR, DOR, PFS and TTR. 13. Updated language on the efficacy analysis will be done for all patients. Added language about efficacy analysis for patients who switched from single agent to combination. 14. Added language on safety summaries and patients who switched from single agent and combination. 15. Added language on data analysis for safety and laboratory data. 16. Clarified notable high or low values for vital signs. 17. Updated language about PK parameters and the PK analysis. 18. Added immunogenicity analysis section. 19. Added details about calculation of baseline in the appendix. 20. Added imputation rules in the appendix. 21. Added definitions and derivation rules for irRC in the appendix. 22. Removed languages on the construction of waterfall plots and cycle definition. 23. Updated the references.
Amendment 2	15Jul2019	Updated language for baseline calculations for efficacy assessments.
Amendment 3	29Oct2020	Clarified PPS
Amendment 4	21Jan2021	Section 2.11.1.1 – Removed from the definition of determinant samples the exclusion for the ADA-inconclusive sample Section 2.8.2.2 - Added information regarding lab conversion units for T4 and regarding the imputed units for the normal ranges.
Amendment 5	15Mar2021	Section 2.8.2.3 – Removed Listing of all clinically relevant laboratory data with values flagged; added tables for worst post-baseline

Version	Date	Changes
		hematology and biochemistry abnormalities based on CTC grades; removed from Table 2-4 ‘total protein’

List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Curve
AUCtau	Area Under the Curve for time 0 to tau
BHM	Bayesian Hierarchical Model
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dosage administration record
DCR	Disease Control Rate
DDP	Dose Determining Pharmacokinetic Set
DDS	Dose-Determining Safety Set
DI	Dose intensity
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
EWOC	Escalation With Overdose Control
FAS	Full Analysis Set
i.v.	Intravenous(ly)
ICF	Informed Consent Form
[redacted]	[redacted]
IG	Immunogenicity
[redacted]	[redacted]
IL-6	Interleukin-6
irRC	immune related Response Criteria
LAG-3	Lymphocyte activation gene-3
MTD	Maximum Tolerated Dose
NSCLC	Non-Small Cell Lung Carcinoma
ORR	Overall Response Rate
[redacted]	[redacted]
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamics
PDI	Planned dose intensity
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	Partial Response
PT	Preferred term
RAP	Report and Analysis Plan
RCC	Renal Cell Carcinoma
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended phase 2 dose
SAE(s)	Serious Adverse Event(s)
SOC	System organ class
SOD	Sum of diameters
SSD	Study Specific Document
TIL(s)	Tumor Infiltrating Lymphocyte(s)
[redacted]	[redacted]
TMTB	Total measurable disease burden
TNBC	Triple Negative Breast Cancer

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: 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 who enrolls in the study
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 and/or survival
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 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 a patient permanently discontinues study treatment for any reason
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. 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
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study LAG525X2101C that will be presented in the Clinical Study Report (CSR). The output shells (in-text and post-text) accompanying this document can be found in the TFL shells document. The specifications for derived variables and datasets can be found in the Programming Datasets Specifications (PDS) document. This version of the SAP is based on Protocol Amendment 10.

All changes to the planned analysis described in this document required before or after database lock will be made through an amendment or addendum, respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in the TFL shells document without the need to amend.

The SAP, TFL shells and PDS documents may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., MTD/RDE declaration, IB updates, abstracts, posters, presentations, manuscripts and management updates. Data used for these analyses will have a status aligned to the database lock guidance.

1.1 Study design

This study is a phase I/II, multi-center, open-label study which consists of 3 dose escalation parts (Arms A, B and C) with a staggered start, each followed by a Phase II part.

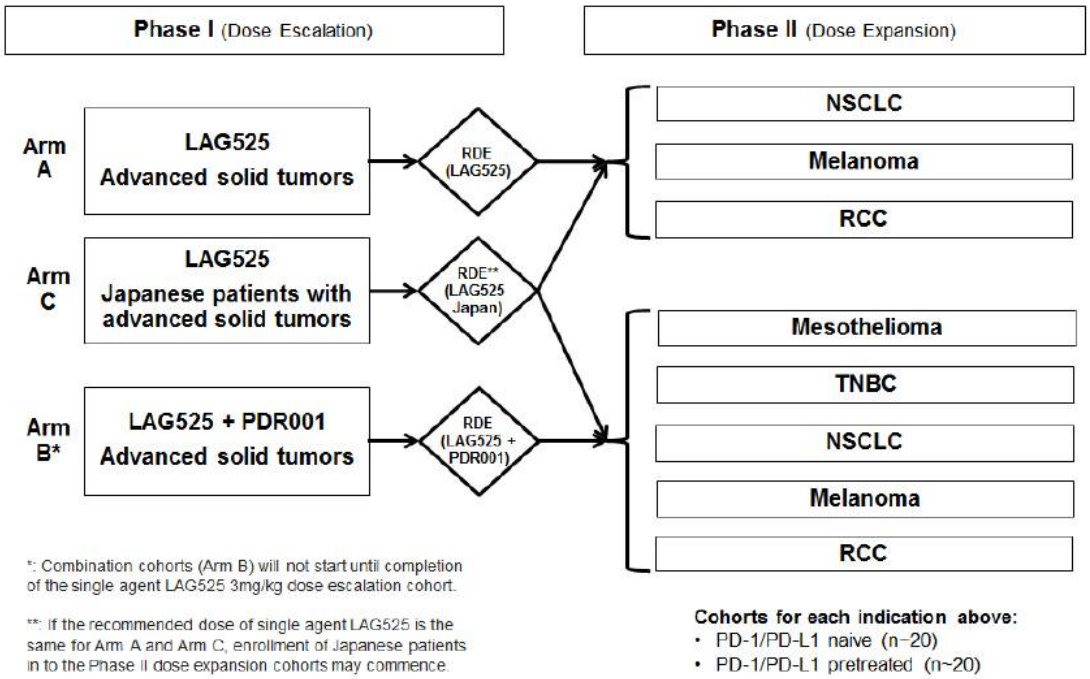
The first escalation is conducted with single-agent LAG525 in advanced solid tumors. The second dose escalation part is performed with the combination of LAG525 and PDR001 in advanced solid tumors. A separate Japanese dose escalation (Arm C) is performed in order to ensure that the safety and pharmacokinetic profiles of single-agent LAG525 are adequately characterized in Japanese patients at more than one LAG525 dose. Arms A and B are followed by a Phase II part after the determination of MTD/RP2D of single-agent LAG525 and combination of LAG525 and PDR001 respectively.

If the RP2D of single-agent LAG525 are the same in Arms A and C, patients enrolled in Japan could be recruited in Phase II single-agent part of the study. In addition, if the recommended dose of PDR001 for Japanese patients on the PDR001X1101 study are the same as that determined in study PDR001X2101, patients in Japan could also enter the combination parts of the study at whichever dose was being tested at that time.

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 (or less) 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;

The study design is summarized in Figure 1-1.

Figure 1-1



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 final clinical study report (CSR) will be based on all patients' data from both phase I and phase II parts.

As antitumor 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 of Phase II would be enrolled.

1.2 Objectives and endpoints

Objective	Endpoint
Primary	
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	
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 if 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
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

2 Statistical Methods

2.1 Data analysis general information

The statistical analysis of this study will be performed by Novartis personnel or a designated third party. A detailed description of the statistical analysis methods will be provided in Appendix 16.1.9 of the primary CSR. R version 2.13.2 (or later version), JAGS and WinBUGS version 1.4.3. will be used for Bayesian modeling. PK parameters will be calculated using non-compartmental methods available in *Phoenix* WinNonlin version 5.2. *SAS*® 9.3 or later (SAS Institute Inc., Cary, NC, USA) will be used in all other analyses.

The study data will be analyzed and reported (in a final CSR) based on all patients' data of the dose escalation and Phase II parts up to the time when all patients have potentially completed treatment or discontinued the study. The final CSR will include all outputs planned within TFL shells document.

Data from participating centers in this study protocol will be combined, so that an adequate number of patients will be available for analysis. No center effect will be assessed. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant pharmacokinetic (PK) [redacted] measurements using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for quantitative data and contingency tables (frequencies and percentages) for qualitative data.

Both pre and post intra patient dose escalation data will be listed and summarized together under the one dose level/treatment group.

The following rules will be applied 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 Phase II will be classified according to the disease group to which they were assigned at baseline based on the disease type.
- The study treatment groups that were analyzed in the Phase II combination LAG525 + PDR001 cohorts were
  - 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: combination LAG525+PDR001, Renal cancer (pre-treated with PD-1/PD-L1)
- Group 13: combo LAG525+PDR001, Mesothelioma (naïve to PD-1/PD-L1)
- Group 14: combo LAG525+PDR001, TNBC (naïve to 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)

For phase I, all summaries, listings, figures for primary efficacy analysis and safety analyses will be presented by dosing regimen whenever applicable. Data from Arm A and Arm C will be pooled for safety and efficacy data.

2.1.1 General definitions

Study drug and study treatment

For Arm A and C (monotherapy):

Study drug and study treatment both refer to LAG525 and are used interchangeably.

For Arm B (combo therapy):

Study drug refers to the individual compound i.e., LAG525 or PDR001. Study treatment refers to any combination of study drugs.

Date of first/last administration of study drug and study treatment

The date of first (last) administration of study treatment is derived as the first (last) date when a non-zero dose of any component of study treatment was administered and recorded on the Dosage Administration Record (DAR) eCRF. For the sake of simplicity, the date of first (last) administration of study treatment will also be referred as start (last) date of study treatment.

Study day

The study day for all assessments/events will be calculated using the start date of study treatment as reference. For assessments/events occurring on or after the start date of study treatment, study day will be calculated as:

Study day (days) = Event date – Start date of study treatment + 1.

Therefore, the first day of study treatment is study day 1.

For all assessment/events occurring prior to the start of the study treatment, study day will be negative and will be calculated as:

Study day (days) = Event date – Start date of study treatment.

Study day will be displayed in the data listings.

On-treatment assessment/event

An on-treatment assessment/event is defined as any assessment/event obtained in the time interval from the start date of study treatment until the last date of study treatment (i.e., including combination partner) + 30 days inclusive.

2.2 Analysis sets

The number (%) of patients in each of the defined analysis set will be summarized using the Full Analysis Set (FAS).

Full Analysis Set

The FAS comprises all patients who received at least one full or partial 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.

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.

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

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 Study Protocol Appendix 1
- At least 2 post-baseline tumor assessments (unless disease progression according to RECIST 1.1 is observed before that time)
- Have received the planned treatment

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. If the PPS and the FAS are identical, then analyses described by the PPS below will not be performed.

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 Q2W schedule or at least one planned dose of LAG525 during Cycle 1 for Q4W schedule. Patients who do not experience a DLT during the first cycle are considered to have sufficient safety evaluations if they have been observed for $\geq$ 28 days following the first dose, and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

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 planned doses of LAG525 during the first 2 cycles for the Q2W schedule or at least two planned doses LAG525 during the first 2 cycles for the Q3W schedule and Q4W schedules and

2. The patients has received at least three planned doses of PDR001 during the first 2 cycles for the Q2W schedule or at least two planned 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 $\geq$ 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 additional patient(s) may be recruited.

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.

Immunogenicity (IG) analysis sets

The Immunogenicity prevalence set includes all patients in the Full analysis set with a determinant baseline IG sample **or** at least one determinant post-baseline IG sample.

The Immunogenicity incidence set includes all patients in the Immunogenicity prevalence set with a determinant baseline IG sample **and** at least one determinant post-baseline IG sample.

The IG analysis sets will be different for LAG525 and PDR001.

See Section 2.11.1.1 for the definition of determinant.

2.3 Patient disposition, demographics and other baseline characteristics

Unless noted otherwise, summaries described in this section will be based on the FAS. Summaries will be produced by treatment group or dosing regimen as appropriate and overall summary. Data will be listed individually by patient based on the FAS.

2.3.1 Patient disposition

The FAS will be used for the patient disposition summary tables and listings. The following will be tabulated:

- Number (%) of patients who discontinued treatment (based on completion of the 'End of Treatment' page with discontinuation date and reason entered),
- Primary reasons for study treatment discontinuation (based on discontinuation reason entered in the 'End of Treatment' page),
- Number (%) of patients who discontinued from study (based on completion of the 'Study evaluation completion' page with discontinuation date and reason entered),
- Primary reasons for study evaluation completion (based on discontinuation reason entered in the 'Study evaluation completion' page).

2.3.2 Basic demographic and background data

All demographic and background data (e.g. age, gender, race) will be listed and summarized.

Qualitative variables (e.g. gender) will be summarized by means of contingency tables for each treatment group. Quantitative variables (i.e. age, weight, and BMI) will be summarized by appropriate descriptive statistics for each treatment group.

BMI and BSA are calculated using the following formulas:

- *BMI [kg/m2] = weight[kg] / (height[m]**2)*
- *BSA [m2] = 234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000*

2.3.3 Medical History

Medical history and ongoing conditions will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of reporting. The MedDRA version

used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings. Medical history and current (ongoing) medical conditions, including cancer-related conditions and symptoms will be listed.

2.3.4 Prior antineoplastic therapy

Prior anti-neoplastic therapy will be summarized for medication, radiotherapy and surgery. The number (%) of patients who received any prior anti-neoplastic medication, radiotherapy or surgery will be summarized separately.

The summary of prior anti-neoplastic medications include the total number of regimens (note: there can be more than one medication per regimen), immuno-oncology therapeutic class, setting at last medication, best response at last medication (defined to be the best response during the last treatment regimens recorded) and time (in months) from start of last medication to progression. The last medication is defined based on the last start date of all prior regimen components. Prior antineoplastic medications is also summarized by Anatomical Therapeutic Chemical (ATC) class, and preferred term.

The summary of prior anti-neoplastic radiotherapy will include the radiotherapy locations, (including all locations recorded for each patient), setting at last radiotherapy and method.

The summary of prior anti-neoplastic surgery will include the time (in months) between the last surgery (non-biopsy procedure) to start of study treatment.

2.3.5 Diagnosis and extent of cancer

The summary of diagnosis and extent of cancer (disease history) will include primary site of cancer, details of tumor histology/cytology, histological grade, stage at initial diagnosis, time (in months) from initial diagnosis of primary site to start of study treatment, time (in months) since most recent recurrence/relapse or progression to start of study treatment, time (in months) from initial diagnosis of primary site to first recurrence/relapse or progression, current stage of cancer, current extent of disease (metastatic sites) and types of lesions (target and non-target lesions) at baseline.

2.3.6 Analysis set exclusion

Patients will be excluded from the analysis sets based on the protocol deviations and specific non-protocol deviations entered in the database. All protocol deviations and non-protocol deviations leading to exclusion from specific analysis sets will be identified before database lock. Protocol and non-protocol deviations leading to exclusion from specific analysis sets and reasons for exclusion from populations will be tabulated/listed by treatment (Phase I) /indication and treatment (Phase II).

Table 2-1 displays non-protocol deviations leading to exclusion from analysis set definitions and Table 2-2 displays protocol deviations leading to exclusion from analysis set definitions.

Table 2-1 Non-protocol deviation leading to exclusion from analysis set definitions

Summary of non PD	Analysis set(s) to be excluded
No valid post-baseline safety assessment	SS

Summary of non PD	Analysis set(s) to be excluded
No administration of study treatment	FAS, SS, PPS, DDS, PAS, Immunogenicity prevalence set, Immunogenicity incidence set
1. Patient, who has not experienced DLT, was not observed for ≥ 28 days (for SA) and ≥ 56 days (for Q2W/Q4W Combo) and ≥ 42 days (for Q3W Combo) following the C1D1 or had not completed the required safety evaluations for Cycle 1 or 2. Patient who has not experienced DLT and has not received appropriate number planned doses in Cycle 1/Cycle 2 (See Section 2.2).	DDS
Patient did not have at least one measurable LAG525 concentration in cycle 1	PAS
No determinant IG sample at both baseline and post-baseline	Immunogenicity prevalence set
No determinant IG sample at baseline or post-baseline or both	Immunogenicity incidence set

Table 2-2 Protocol deviation leading to exclusion from analysis set definitions

Protocol Deviation ID (DVSPID)	Summary of PD	Analysis set(s) to be excluded
INCL01	Written informed consent must be obtained prior to screen procedures.	FAS, SS, PPS, DDS, PAS, Immunogenicity prevalence set, Immunogenicity incidence set
INCL04	In the Phase II part, patient does not have at least one tumor lesion meeting measurable disease criteria as determined by RECIST v1.1.	PPS
INCL05	In the Phase II part, patient was not a patient with either NSCLC, melanoma, TNBC, RCC or Mesothelioma.	PPS

2.4 Protocol deviations

The FAS will be used for the protocol deviation summary tables and listings. The frequency counts and percentage of patients with any CSR-reportable protocol deviation will be tabulated by the deviation category (entry criteria not satisfied; wrong treatment or incorrect dose; developed withdrawal criteria, but not withdrawn; took an excluded concomitant medication; others). The full list of protocol deviations are documented in the Study Specification Document (SSD).

2.5 Treatments (study treatment, rescue medication, other concomitant therapies, compliance)

Unless otherwise noted, the Safety set will be used for all treatment/medication data summaries and listings.

2.5.1 Study treatment

2.5.1.1 Dose intensity and exposure

For Arm A and C (monotherapy):

Last date of exposure to study treatment is:

- ✓ min(the last date of study treatment + 13 days, death date, data cut-off date) for Q2W schedule
- ✓ min(the last date of study treatment + 27 days, death date, data cut-off date) for Q4W schedule

For Arm B (combo therapy):

Last date of exposure to study treatment is:

- ✓ min(max(last date of PDR001 administration, last date of LAG525 administration) + 13 days, death date, data cut-off date) for Q2W schedule
- ✓ min(max(last date of PDR001 administration, last date of LAG525 administration) + 20 days, death date, data cut-off date) for Q3W schedule
- ✓ min(max(last date of PDR001 administration, last date of LAG525 administration) + 27 days, death date, data cut-off date) for Q4W schedule
- ✓ min(max(last date of PDR001 administration + 27 days, last date of LAG525 administration + 13 days), death date, data cut-off date) for LAG525 Q2W and PDR001 Q4W schedule

Definitions are as follows:

- Duration of exposure to study treatment (weeks): (last date of exposure to study treatment − first date of study treatment + 1)/7 (periods of interruption are not excluded)
- Duration of exposure to study drug (weeks): (last date of exposure to study drug − first date of study drug + 1)/7 (periods of interruption are not excluded)
- Actual cumulative dose (mg): total actual dose for the study drug over the duration for which the patient is on study treatment as documented in the DAR eCRF.

  The following algorithms will be used to calculate the actual dose per one infusion in mg:

  - ✓ For weight based dosing: Actual dose (mg) = (Calculated dose prescribed, mg) × (Total volume administrated, ml) / (Total volume constituted, ml)
  - ✓ For flat dosing: Actual dose(mg) = (Dose prescribed, mg) × (Total volume administrated, ml) / (Total volume constituted, ml)

These parameters used for calculation ('Calculated dose prescribed', 'Dose prescribed', 'Total volume constituted', 'Total volume administered') will be collected on the DAR eCRF page. For patients who did not take any of study treatment, the actual cumulative dose is by definition equal to zero. Actual cumulative dose will then be calculated as the sum of actual dose per one infusion for all infusions.

- Planned cumulative dose (mg): the total dose planned to be given as per the protocol up to the last date of study treatment administration. It is calculated in mg as:
  - ✓ For weight based dosing: Planned cumulative dose (mg) = sum of (Calculated dose prescribed, mg) for all infusions
  - ✓ For flat dosing: Planned cumulative dose (mg) = sum of (Dose prescribed, mg) for all infusions.

Similarly, 'Calculated dose prescribed' and 'Dose prescribed' will be collected on the DAR eCRF page. The planned cumulative dose is not summarized/listed. It is used for relative dose intensity calculations.

- DI (mg/day): actual cumulative dose (*mg*) / duration of exposure (days) for patients with non-zero duration of exposure.
- PDI (mg/day): planned cumulative dose (mg)/duration of exposure (days)

The dose intensity (DI) and planned dose intensity (PDI) will not be summarized/listed. They are used for relative dose intensity calculations.

- RDI (%): 100 × DI (mg/day)/PDI (mg/day)

The duration of exposure to study treatment will be summarized. In addition, RDI (including categories: <0.5, ≥0.5-<0.75, ≥0.75-<0.9, ≥0.9-<1.1, ≥1.1) will be summarized for each study drug.

2.5.1.2 Dose changes

All doses of the study drugs along with reasons for any dose change will be listed.

Dose interruption: Any dose interruption flagged in the DAR CRF page with a reason other than "as per protocol". Actual dose equal to zero between the first and last non-zero doses, following a non-zero actual dose.

Dose reduction: Any dose change flagged in the DAR CRF page with a reason other than "as per protocol". A non-zero actual dose that is less than the immediate previous non-zero actual dose (if not the first dose) and below the treatment planned dose.

Frequency counts and percentages of patients who have dose reductions or interruptions, and the corresponding reasons, will be provided for each study drug. The number of dose interruptions per patient, and the duration of dose interruptions (days) will be summarized for each study drug. Also, the number of dose reductions per patient and the duration of dose reductions (days) will be summarized for each study drug and treatment group.

2.5.2 Prior and Concomitant therapies

Concomitant therapies are defined as any medications (excluding study treatment, prior antineoplastic treatments) and significant non-drug therapies (including physical therapy and blood transfusions) administered in the study and are recorded in the Concomitant Medications/significant non-drug therapies eCRF. These therapies will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system.

Concomitant therapy and significant non-drug therapies prior to or after the start of the study drug will be listed by patient.

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 2.8.1). No imputation will be performed for concomitant medication end dates.

2.5.3 Compliance

Compliance is presented as the percentage of patients who took a predefined percentage (RDI categories: <0.5, 0.5-<0.75, 0.75- <0.9, 0.9-<1.1, ≥1.1) of the number of prescribed doses of study treatment. Details have been provided in Section 2.5.1.1.

2.6 Analysis of the primary variable(s)

2.6.1 Phase I: dose escalation part

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.

An adaptive BLRM guided by the Escalation with overdose control (EWOC) principle (Babb et al 1998) will be used to make dose recommendations and estimate the MTD(s)/RP2D(s) during the escalation parts of the study using DDS set. The methodology is described in detail in [CLAG525X2101C Amendment 10 Section 10.4.2].

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 Q2Wdose 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 [CLAG525X2101C Amendment 10 - Appendix 14.4].

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 $-\infty < \eta < \infty$.

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 down-weighted assuming substantial heterogeneity (Chen et al 2006, Neuenschwander et al 2010).

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 (Robert et al 2014, Deeks 2014). 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 [CLAG525X2101C Amendment 10 Appendix 14.3].

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 introduction of new dosing schedule during dose-escalation, a separate BLRM will be used. At each dose escalation, the model will be updated and 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 new dosing schedule, the DLT data obtained from other explored dosing schedules will be down-weighted assuming substantial

heterogeneity. Please see the Appendix 16.1.9 for additional details about the statistical methodology.

All tables and listings will be presented by treatment in which data from different Phase I cohorts treated with the same dose and schedule will be pooled in the CSR.

2.6.2 Phase II part

A Bayesian design will be used in order to estimate Overall Response Rate (ORR) within each group as defined in Section 2.1, 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.

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 (Neuenschwander et al 2008). 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:

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

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.

LAG525+PDR001 combination (groups 6 to 10 and Group 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 or renal cancer or mesothelioma (i.e. $\geq$ 12 responses (CR or PR) out of 40 patients), 20% for TNBC (i.e. $\geq$ 8 responses (CR or PR) out of 40 patients) and 45% for melanoma (i.e. $\geq$ 18 responses (CR or PR) out of 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%.

2.6.3 Supportive analysis

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

In addition, a Bayesian hierarchical model (BHM) will be applied to the overall response data from
patients in the phase II part. Response rates π_j will be inferred for j = 6,…, 16, for groups 6 to 16 respectively.

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

$r_j \sim Bin(n_j, \pi_j)$

We further let the parameters $\theta_j = \log(\pi_j /(1-\pi_j))$ be either exchangeable with other indication parameters, or non-exchangeable.

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

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

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

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 $p_{j2} = 1-p_{j1}$, 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, μ_2, τ_1 and τ_2, see [CLAG525X2101C Amendment 10 Appendix 14.3].

At completion of the study, the BHM will be updated with all the data available from the patients in the FAS by disease group. All responses and progressions will be determined as per RECIST 1.1.

LAG525+PDR001 combination (groups 6 to 10 and group 12 to 16): For each of the groups where patients took 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%.

2.6.3.1 Handling of missing values/censoring/discontinuations

Patients in the dose escalation part who are ineligible for the DDS will be excluded from the primary statistical 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 [CLAG525X2101C Amendment 10 Appendix 1].

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

2.7 Analysis of the secondary variables

2.7.1 Efficacy definitions

Best overall response (BOR)

The BOR is the best response recorded from the start of the treatment until disease progression/recurrence. For RECIST v1.1 and irRC, any assessments taken before the start of any further antineoplastic therapy will be considered in the assessment of BOR in recognition that response to immunotherapy may be delayed. For both RECIST v1.1 and irRC, if any alternative antineoplastic therapy is taken while on study, any subsequent assessments will be excluded from the BOR determination.

Per RECIST v1.1, CR and PR need to be confirmed with at least two determinations of CR or PR respectively at least 4 weeks apart before progression. In order to classify overall response as SD, a patient must have at least one SD assessment (or better) > 6 weeks after start date of study treatment. In order to classify overall response as PD, a patient must have progression < 12 weeks after start date of study treatment.

Per irRC, irCR, irPR and irPD need to be confirmed with at least two determinations of irCR or irPR or irPD, respectively at least 4 weeks apart. In order to classify overall response as irSD, the patient must have at least one SD assessment (or better) > 6 weeks after start date of study treatment.

Overall response rate (ORR) and Disease control rate (DCR)

ORR is the proportion of patients with a best overall response of CR or PR (RECIST v1.1) or of irCR or irPR (irRC). DCR is the proportion of patients with a best overall response of CR, PR, or SD (RECIST v1.1) or of irCR, irPR, or irSD (irRC). For phase I single agent and combination tables, NCRNPD (RECIST v1.1) or iNCRNPD (irRC) are included in the calculation of DCR.

Progression free survival (PFS)

For assessment per RECIST v1.1, PFS is the time from date of 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, PFS is censored at the date of last adequate tumor assessment ([CLAG525X2101C Amendment 10 Appendix 14.3]).

Duration of response (DOR)

DOR applies only to patients with a BOR of confirmed CR or PR (RECIST v1.1). For assessment per RECIST v1.1, DOR is defined as the time from the date of the first documented response (CR or PR) to the date of first documented progression, or death due to study indication.

Time to response (TTR)

TTR applies only to patients with a BOR of confirmed CR or PR (RECIST v1.1). For assessment per RECIST v1.1, TTR is the time between date of start of treatment until first documented response (CR or PR).

Use of alternative cancer therapy

For both RECIST v1.1 and irRC, if any alternative cancer therapy is taken other than palliative radiotherapy or biopsy any subsequent assessments will be excluded from the analysis of endpoints based on tumor response assessments.

Date of last contact

If the patient is not known to have died, the date of last contact will be used. All data excluding the biomarker date will be used to find the date of last contact.

2.7.2 Efficacy evaluation

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

Evaluation of tumor response will be based on investigator assessment according to RECIST v1.1 and irRC [CLAG525X2101C Amendment 10 Appendix 14.3].

Efficacy endpoints will include ORR, PFS, DOR and DCR as per RECIST V1.1 and per irRC, for phase I and phase II.

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. Best overall response per RECIST 1.1 and per irRC will be listed and tabulated.

For all efficacy parameters, data will be listed, summarized, or analyzed by treatment group for the phase I part, and by disease group (groups 6 to 10 and 12 to 16) for phase II patients treated at the MTD(s)/ RP2D(s).

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.

- 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 at least 10 patients respond in each dosing regimen/indication.

PFS, along with DOR and time to response (TTR) for patients who experience a CR or PR at any time on study, will be listed by patient. Median PFS time and the proportion of patients who are progression-free at 3, 6, 9, and 12 months will be estimated for each group.

For patients who switched from single agent LAG525 to combination with PDR001, the efficacy information will be censored at the date of last adequate assessment before the switch. All efficacy assessments after the switch will be listed and flagged.

2.7.3 Waterfall plot for best overall response and best percentage change from baseline for all target lesions for each patient

The waterfall plot per RECIST 1.1 for all patients is the sum of the longest diameter of all target lesions for each patient by treatment. The FAS will be used to depict anti-tumor activity by treatment.

2.8 Safety evaluation

The assessment of safety is based on the type and frequency of Adverse Events (AEs) as well as on the number of laboratory values that fall outside of pre-determined ranges (Common Toxicity Criteria for Adverse Events (CTCAE) grading limits or normal ranges as appropriate). Other safety data include electrocardiogram and vital signs.

The Safety set is used for summaries and listings of safety data with the exception of dose limiting toxicities (DLT) for which the DDS is used.

Differences between treatment received and intended treatment, if any, are provided in a listing.

The overall observation period is 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 are primarily 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 are collected. Select summaries of related adverse events are produced for the overall period starting from the first dose of study treatment until the end of the post-treatment period.

All safety assessments are listed and those collected during the post-treatment period are flagged.

For patients who switch from single-agent LAG525 to combination with PDR001, the on-treatment period is 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 are listed and the assessments performed under combination and those collected 30 days later than the last dose of single-agent are flagged separately.

2.8.1 Adverse events (AEs)

2.8.1.1 Data handling

Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) and assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, respectively.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

If CTCAE grading does not exist for an AE, grades 1, 2, 3, or 4 corresponding to the severity of mild, moderate, severe, and life-threatening, respectively, will be used. CTCAE grade 5 (death) is not used in this study. Death information will be collected on the "Death" eCRF pages.

2.8.1.2 Data analysis

Primary summary tables for AEs will include only AEs that started or worsened during the on-treatment period.

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and /or preferred tem, severity (based on CTCAE grades),

type of AE and 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 deaths are considered to be due to study indication.

All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study treatment, AE outcome etc. AEs starting during the pre or post-treatment periods will be flagged in the listings.

AEs will be summarized by number and percentage of patients having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. Occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in all patients.

The following adverse event summaries will be produced by treatment for AEs starting or worsening during the on-treatment period:

- Overview of adverse events and deaths (number and % of patients who died, with any AE, any SAE, any AE leading to dose reductions/interruptions, AE leading to discontinuation)
- AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment);
- Seriousness (SAEs, and non-SAEs);
- Leading to treatment discontinuation;
- Leading to dose interruption/adjustment;
- Requiring additional therapy;
- Dose limiting toxicities by PT

The following listings will be produced:

- All adverse events (safety set)

Deaths (CSR Outputs)

On-treatment deaths are summarized produced by preferred term.

All deaths will be listed for the safety set, deaths occurring after the on-treatment period will be flagged.

EudraCT and clinicaltrials.gov requirements for AEs and Deaths summaries

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on treatment-emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship, will be provided by SOC and PT.

2.8.1.3 Adverse events of special interest / grouping of AEs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound LAG525. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on-treatment period will be summarized.

Summaries of these AESIs will be provided by safety topic and treatment.

2.8.2 Laboratory data

2.8.2.1 CTC grading for laboratory parameters

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of laboratory CTC grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTC grades are given in Novartis internal criteria for CTC grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 is not applicable. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as sodium-low and sodium-high.

2.8.2.2 Imputation rules

CTC grading for blood differentials is based on absolute values.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential
xxx count = (WBC count) * (xxx %value / 100)
Same rule will be applied for normal ranges.

Corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:
Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL) - 4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium are as defined in the previous section.

For T4 when corresponding units are mcg/dL (microgram per deciliter) then it can be converted directly into ug/dL with no conversion factor applied (i.e. 1 mcg/dL = 1 ug/dL). For the units as pg/mL can be converted to ug/dL by dividing by 10000 (i.e. 1 pg/mL = 10^{-4} ug/dL)

For the laboratory parameters where the CTC grades depend on the normal ranges, when normal ranges are captured as 0 and 888888.xxx then the normal ranges and normal ranges indicator should not be present and the corresponding CTC grade should not be derived.

2.8.2.3 Data analysis

Laboratory data from all sources (central and local laboratories (as applicable)) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 2.8).

The following listing will be produced for the laboratory data:

- Listing of all CTC grade 3 or 4 laboratory toxicities

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

- Worst post-baseline hematology and biochemistry based on CTC grades

For laboratory tests where grades are defined by CTCAE 4.03:

- Shift tables using CTCAE 4.03 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE 4.03:

- Shift tables using the low/normal/high/ (low and high)

Table 2-3 and Table 2-4 list all laboratory parameters for which CTCAE grades are defined and for which CTCAE grades will be listed on local laboratoty normal ranges respectively.

Table 2-3 Laboratory parameters for which CTCAE grades are defined

Hematology and coagulation		Biochemistry	
White Blood Cells (WBC)	↑↓	Creatinine	↑
Hemoglobin	↓	Sodium	↑↓
Platelets counts	↓	Potassium	↑↓
Absolute Neutrophils	↓	Corrected calcium	↑↓
Absolute Lymphocytes	↑↓	Magnesium	↑↓
		Albumin	↓
		AST (SGOT)	↑
		ALT (SGPT)	↑
		Total Bilirubin	↑
		Inorganic Phosphorus	↓
		amylase	↑
		lipase	↑
		Alkaline phosphatase	↑
		Fasting Glucose	↑↓

↑ Indicates that CTC grade increases as the parameter increases.

↓ Indicates that CTC grade increases as the parameter decreases.

Table 2-4 Laboratory parameters (without CTCAE grades) for which lab reference ranges are defined

Hematology and coagulation	Biochemistry
Hematocrit	Blood urea nitrogen (BUN)
Absolute Basophils	Urea*
Absolute Eosinophils	
	Direct Bilirubin
Absolute Monocytes	Indirect Bilirubin
	T4
	T4FR
	TSH
	Chloride
	Bicarbonate
*Urea will be converted to BUN and reported as BUN.	

2.8.2.4 Hematology

Hematologic tests include: a complete blood count (CBC) consisting of a total white blood cell count (WBC) with differential (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), hematocrit, hemoglobin, and platelet count.

Differential counts will be converted to absolute values for CTC grade classification. For all the differential counts, percentages will be converted to absolute values, if necessary:

e.g. Absolute WBC diff (Wunit) = Absolute WBC (Wunit)*Relative WBCdiff(%)/100.

2.8.2.5 Biochemistry

Biochemistry includes the following parameters: urea or blood urea nitrogen (BUN), creatinine, sodium, potassium, corrected calcium, albumin, total bilirubin (also measure direct and indirect bilirubin if total bilirubin is > grade 1), alkaline phosphatase, AST (SGOT), ALT (SGPT), glucose, magnesium, chloride, bicarbonate, inorganic phosphorus (phosphate), amylase, and lipase.

2.8.2.6 Other clinical laboratory parameters

Coagulation includes the following parameters: Prothrombin time (PT) or international normalized ratio[INR], activated partial thromboplastin time (APTT).

Other parameters include thyroid function (total or free T4, TSH) and cytokines interleuklein 6 (IL-6) [redacted].

2.8.3 Vital signs, weight and physical examinations

Vital sign assessments are performed in order to characterize basic body function. The following parameters are collected: systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), body temperature (°C), and weight (kg).

Vital signs collected during on-treatment period will be summarized. Values measured during the post-treatment period will be flagged in the listings. The number and percentage of patients with notable vital sign values (high/low) will be presented by treatment. For analysis of vital signs, the clinically notable vital sign criteria are provided in Table 2-5.

Table 2-5 Criteria for notable vital sign values

Vital sign [unit]	Notable high value	Notable low value
Systolic blood pressure [mmHg]	≥180 mmHg with increase from baseline of ≥20 mmHg	≤90 mmHg with decrease from baseline of ≥20 mmHg
Diastolic blood pressure [mmHg]	≥105 mmHg with increase from baseline of ≥15 mmHg	≤50 mmHg with decrease from baseline of ≥15 mmHg
Pulse rate [bpm]	≥100 bpm with increase from baseline of >25%	≤50 bpm with decrease from baseline of >25%
Body temperature [°C]	≥ 39.1	--
Weight [kg]	≥10% increase from baseline	≥10% decrease from baseline

Vital signs shift table based on values classified as notable low, normal, notable high or notable (high and low) at baseline and worst post-baseline will be produced.

Descriptive statistics will be provided for baseline, for worst post-baseline value and change from baseline to worst post-baseline value for each vital sign measure.

Patients with any clinically notable vital sign value will be listed.

2.8.4 Electrocardiograms

2.8.4.1 ECG data descriptive statistics

The average of the ECG parameters at that assessment should be used in the analyses, if the average is associated with the nominal timepoint. If nominal timepoint is unavailable, the average will not be done and the individual values will be used. The following summaries will be provided for each applicable ECG parameter:

- Number (%) of patients having notable ECG values according to Table 2-6.

Table 2-6 Criteria for notable ECG values

ECG parameter	Criteria for ECG notable values
QT, QTcF, QTcB (ms)	Increase from baseline >30 ms to ≤60 ms, >60 ms New QT/QTc >450 to <=480ms; >480 to <=500 ms; >500 ms
HR (bpm)	Increase from baseline >25% and value >100 bpm Decrease from baseline >25% and value <50 bpm
PR (ms)	Increase from baseline >25% and value >200 ms New PR >200 ms
QRS (ms)	Increase from baseline >25% and value >120 ms New QRS >120 ms

Patients with any notable change from baseline for each QT/QTc interval will be listed.

2.8.5 Tolerability

Tolerability of study treatment will be assessed by summarizing the number of dose interruptions and dose reductions by treatment group. Reasons for dose interruption and dose reductions will be listed by patient and treatment group and summarized by treatment group. Relative dose intensity of study treatment (see Section 2.5.1) will be also be used to assess tolerability.

2.9 Pharmacokinetic data

All serum concentrations that are quantification (BLQ) set to zero in the bioanalytical data.

The PK parameters on Table 2-7 will be estimated and listed. All concentrations below the LLOQ , or any missing data, will be labeled as such in the concentration data . Concentrations below the LLOQ will be treated for summary statistics. The "zero" values will be excluded from geometric calculation.

PAS will be used in all pharmacokinetic data analysis and PK summary statistics, except dose-exposure analysis in Phase I.

The pharmacokinetic parameters that will be assessed are presented in Table 2-7.

Table 2-7 Pharmacokinetic Parameters to be analyzed

Variable	Definition (unit)
AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCtau*	The AUC from time zero to the end of the dosing interval, tau (mass x time x volume-1) as per Q2W (336 hours), Q3W (504 hours) and Q4W (672 hours) dosing regimen (ug*hr/mL or ug*day/mL)
Cmax	Maximum observed concentration after drug administration [mass x volume^{-1}] (ug/mL)
Tmax	Time to reach Cmax [time] (hours or days)
T1/2	Elimination half-life (hours or days)
T1/2,eff	Effective half-life based on accumulation (hr) = ln2 • tau/ ln(Racc / (Racc-1)) at cycle 3 after multiple dosing
Cav,ss	The average steady state concentration during multiple dosing which is determined as Cav,ss = AUCtau,ss/tau, for AUCtau and tau
Racc	Accumulation Ratio=AUClast at Cycle 3 /AUClast at Cycle 1

*AUCtau is defined as AUC0-336h, AUC0-504h and AUC0-672h for Q2W, Q3W and Q4W dosing regimen of LAG525 or PDR001, respectively.

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 noncompartmental method(s) for single agent LAG525, LAG525 in combination with PDR001 and PDR001 in combination with LAG525:

- AUClast (AUC0-336h, AUC0-504h and AUC0-672h), Cmax, Tmax, T1/2, T1/2,eff 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.

Further analyses may be conducted using population PK approaches. [redacted]

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. For LAG525 as a single agent and for LAG525 when in combination with PDR001 dose proportionality will be assessed for Cmax and AUC(0-336h) for Q2W regimen, and for Cmax and AUC(0-672h) for Q4W regimen respectively, only for Cycle 1 and 3 separately within the same output, considering every dose level except flat doses, when single agent, and flat dose levels only when in combination. For LAG525 when in combination with PDR001, for Q3W regimen, dose proportionality will be assessed for Cmax and AUC(0-504h) for Cycles 1 and 3 separately within the same output. For PDR001 when in combination with LAG525 dose

proportionality will be assessed for Cmax and AUC(0-336h) for Q2W, and for Cmax and AUC(0-672h) for Q4W, for Cycles 1 and 3 separately within the same output, considering flat dose levels only.

2.10 Biomarkers

[redacted]

Table 2-8 Biomarkers and purpose of analysis

Biomarker	Purpose of analysis
[redacted]	[redacted]

Biomarker	Purpose of analysis
Anti-LAG525/ anti-PDR001 antibodies	Assess emergence of anti-LAG525/anti-PDR001 antibodies following one or more intravenous (i.v.) infusions of LAG525/PDR001

[redacted]

Please see the next section for details on the analysis of emergence of anti-drug antibodies.

2.11 PD and PK/PD analysis

2.11.1 Immunogenicity

2.11.1.1 Sample ADA Status

Each IG sample is assessed in a three tiered anti-drug anti-body (ADA) testing approach. All IG samples are analyzed in the initial screening assay (first tier). Samples testing negative in the screening assay are not subject to a confirmatory assay. Samples testing positive in the screening assay are then subjected to the confirmatory assay to demonstrate that ADA are specific for the therapeutic protein product (second tier). The titer of confirmatory positive samples will be subsequently determined in the titration assay (third tier). Samples identified as positive in the confirmatory assay are considered ADA positive. Samples can test negative in either the screening or confirmatory assay but for analysis purposes they are not differentiated. The following properties of each sample will be provided in the source data:

- Result of assay according to pre-specified confirmatory cut point: ADA positive (yes) or ADA negative (no)
- Titer (for positive samples): numerical representation of the magnitude of ADA response
- Drug tolerance level: highest drug concentration that does not interfere in the ADA detection method
- Fold titer change (i.e. x-fold): threshold for determining treatment boosted

Determinant samples are defined as samples which are not unevaluable (where unevaluable = sample where assay is not available).

The following definitions apply only to determinant samples:

- ADA-negative sample: Determinant sample where assay is ADA negative and LAG525 (PDR001) PK concentration at the time of IG sample collection is less than the drug tolerance level.

- ADA-positive sample: Determinant sample where assay is ADA positive.
- ADA-inconclusive sample: Sample where assay is ADA negative and LAG525 (PDR001) PK concentration at the time of IG sample collection is greater than or equal to the drug tolerance level or missing.

The following definitions apply only to post-baseline ADA-positive samples with a corresponding determinant baseline sample. To be classified as treatment-boosted or treatment-unaffected, both the post-baseline and baseline titer must be non-missing:

- treatment-induced ADA-positive sample: ADA-positive sample post-baseline with ADA-negative sample at baseline.
- treatment-boosted ADA-positive sample: ADA-positive sample post-baseline with titer that is at least the fold titer change greater than the ADA-positive baseline titer.
- treatment-unaffected ADA-positive sample: ADA-positive sample post-baseline with titer that is less than the fold titer change greater than the ADA-positive baseline titer.

NOTE: PK concentrations which are flagged for exclusion will still be used to determine ADA-inconclusive and ADA-negative samples.

The following summaries of ADA sample status (n and %) will be provided using Immunogenicity prevalence set:

- ADA-positive samples (i.e. ADA prevalence), overall and by time point (including baseline). For summaries by time point, the denominator is the number of patients at that time point with a determinant sample.

Listings will be provided of sample ADA status (including titer for positive samples).

2.11.1.2 Patient ADA status

Any IG sample collected after 150 days of the last dose of LAG525 and/or PDR001 will not be used for summaries or derivations and will only be included in the listing.

Patient ADA status is defined as follows:

- Treatment-induced ADA-positive patient: patient with ADA-negative sample at baseline and at least one treatment-induced ADA-positive sample.
- Treatment-boosted ADA-positive patient: patient with ADA-positive sample at baseline and at least one treatment-boosted ADA-positive sample.
- Treatment-unaffected ADA-positive patient: patient with ADA-positive sample at baseline, no treatment-boosted ADA-positive samples, and at least one treatment-unaffected ADA-positive sample.
- Treatment-reduced ADA-positive patient: patient with ADA-positive sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.
- ADA-negative patient: patient with ADA-negative sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.

- Inconclusive patient: patient who does not qualify as treatment-induced ADA-positive, treatment-boosted ADA-positive, treatment-unaffected ADA-positive, treatment-reduced ADA-positive, or ADA-negative.

The following summaries of ADA patient status (n and %) will be provided using Immunogenicity incidence set:

- Treatment-boosted ADA-positive patients; denominator is the number of patients with ADA-positive sample at baseline.
- Treatment-induced ADA-positive patients; denominator is the number of patients with ADA-negative or ADA- inconclusive sample at baseline.
- ADA-inconclusive subjects: denominator is the number of subjects in Immunogenicity incidence set.
- ADA-negative patients: denominator is the number of patients in Immunogenicity incidence set.
- ADA-positive patients (i.e. ADA incidence): calculated as the number of treatment-boosted ADA-positive and treatment-induced ADA-positive patients; denominator is the number of patients in Immunogenicity incidence set.

Listings will be provided of patient ADA status.

2.12 Interim analyses

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 escalation part, the next dose will be chosen depending on the observed data (based on safety, tolerability, PK, [redacted] 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 of the study protocol.

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 10 groups (6 to 10 and 12 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 and PD information.

3 Sample size calculation

Please refer to Section 10.8 in the study protocol of LAG525X2101C study ([CLAG525X2101C Amendment 10 Section 10.8]).

4 Appendix

4.1 Baseline

Baseline is the result of an investigation describing the "true" state of the subject before start of study treatment administration.

Baseline (e.g. for laboratory parameters) is considered as the last non-missing assessment or value before start of the first treatment, unless otherwise stated under the related assessment.

For efficacy assessments/events, baseline is the last available and valid assessment performed or value measured within 28 days before the first treatment administration. If pre-treatment administration is not available, assessment within 7 days after first treatment administration can also be considered as baseline assessment.

Baseline could be within 28 days before first treatment administration or on the same day as first treatment administration if specified pre-dose (e.g., ECG). The baseline for measurements of height could be taken any day before first treatment.

If time is recorded for the first treatment dose and for a specific assessment performed the day of first dose, this assessment is considered as baseline only if it is actually performed before the first dose, as checked using both times.

If time is not recorded, a specific assessment performed the day of first dose administration is considered as baseline if, according to protocol, it should be performed before the first dose.

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) or collected for ECGs or vital signs, then the last value should be considered as baseline.

Patients with no data on a particular parameter before the first treatment administration will have a missing baseline for this parameter.

For ECG evaluations three serial 12-lead ECGs will be obtained on Cycle 1 Day 1 for each patient, prior to the first administration of study treatment (C1D1). In case the assessments prior to the first administration (C1D1) are missing, the evaluations done at screening will be used for baseline calculations. The average of the ECG measurements at nominal timepoint will serve as the patient's baseline value for post-dose comparisons.

4.2 Imputation rules

4.2.1 AE, ConMeds and safety assessment date imputation

Table 4-1 Imputation of start dates (AE, CM)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates
day, month	• If available year = year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY o Else set start date = study treatment start date. • If available year > year of study treatment start date then 01JanYYYY • If available year < year of study treatment start date then 01JulYYYY
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Any AEs and CMs with partial/missing dates will be displayed as such in the data listings. Any AEs and CMs which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided. No imputation will be performed for AEs and CMs end dates.

4.2.2 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent/first recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, and if the overall response at that assessment is CR/PR/SD/UNK, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT scan). Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. 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

previous and following assessment are not available, this assessment will not be used for any calculation.

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date, then the evaluation is considered post-cut-off date and will be excluded from analysis.

New anti-neoplastic therapy

Start date:

- If Day is missing, then impute to the max (treatment start date, first day of the month).
- If Day and month are missing then impute to the max (treatment start date, Jan 1).
- If Year, Month and Day are missing then impute to treatment start date.

End date:

No imputation.

Prior anti-neoplastic therapy

Start date:

The same rule which is applied to the imputation of AE/concomitant medication start date will be used, except that 'study treatment start date-1' should be used other than 'study treatment start date' when applicable in the imputation.

End date:

Imputed date = min (start date of study treatment, last day of the month), if day is missing;

Imputed date = min (start date of study treatment, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

Missing death date

For cases when either day is missing or both month and day are missing for the date of death, the following imputation rules will be implemented:

- If only day is missing, then impute max [(1 mmm-yyyy), min (last contact date + 1, cut-off date)].
- If both day and month are missing, then impute max [(1 Jan-yyyy, min (last contact date + 1, cut-off date)].

4.3 Definition and derivation rules for irRC

4.3.1 Total measurable disease burden

In irRC target and new measurable lesions are used to evaluate total measurable tumor burden (TMTB). TMTB is the sum of diameters (SOD) of all target and new measurable lesions. Similar to RECIST v1.1 where SOD of the target lesions is used for determination of target lesion response, for irRC TMTB is used for determination of target and new measurable lesion response.

4.3.1.1 Best percentage change from baseline in TMTB

Best percentage change from baseline in TMTB is defined as the percentage change from baseline to the smallest measured post-baseline TMTB occurring at or before the time of confirmed irPD.

4.3.2 Assessment of disease progression

To facilitate analysis, each assessment of progression is categorized as one of three types: pseudo progression, confirmed progression and unconfirmed progression.

4.3.2.1 Pseudo-progression

Patients with a single irPD, followed by an assessment of irSD or better will be considered to have a pseudo-progression (pPD). For the purposes of analysis, pseudo-progressions are not treated as progression events.

4.3.2.2 Confirmed progression

Confirmed progression 1 (type 1, cPD1) is declared if a patient has 2 consecutive tumor assessments at least 4 weeks (28 days) apart both showing disease progression. Assessments with an UNK response or PD assessments < 28 days after initial PD, are discarded.

The first PD is flagged as cPD1 while all subsequent PDs are flagged as xPD1.

The table below shows two hypothetical data scenarios and programming instructions.

Sequence of assessments	Instructions
1 irPD 2 irUNK 3 irPD (Assessment 1 + 30 days)	• Assessment 3 is ≥28 days after Assessment 1 • Assessment 3 represents confirmation of irPD at assessment 1 • Assessment 1 irPD is flagged cPD1 • Assessment 3 irPD is flagged xPD1
1 irSD 2 irPD 3 irPD (Assessment 2 + 20 days) 4 irPD (Assessment 2 + 30 days)	• Assessment 3 is < 28 days after Assessment 2 • Assessment 4 is ≥ 28 days after Assessment 2 • Assessment 4 represents confirmation of irPD at assessment 2 • Assessment 2 irPD is flagged cPD1 • Assessment 3 and 4 irPDs are flagged xPD1

Confirmed progression 2 (type 2, cPD2) is declared if a patient discontinues treatment following a single PD with no subsequent assessments ≥ 28 days later. Assessments with an UNK response or PD assessments < 4 weeks (28 days) after initial PD, are discarded. Discontinuation of treatment is obtained from EOT case report form.

The assessment is flagged as cPD2 and subsequent PDs (<28 days after first PD) are flagged as xPD2.

The table below shows two hypothetical data scenarios and programming instructions.

Sequence of assessments	Instructions
1 irSD 2 irPD - EOT	• Patient withdraws after initial progression (Assessment 2) without confirmation • Assessment 2 irPD is flagged as cPD2
1 irPD 2 irPD (Assessment 1 + 20 days) - EOT	• Assessment 2 irPD is <28 days after Assessment 1, so does not represent confirmation • However, patient has completed treatment • Assessment 1 irPD is flagged cPD2 • Assessment 2 irPD is flagged xPD2

4.3.2.3 Unconfirmed progression

Patients with a single irPD, and no assessment of irSD or better (assessment with an irUNK response or irPD assessments < 4 weeks after initial irPD, are discarded) continuing treatment at the time of the analysis will be considered as unconfirmed (uPD).

4.3.3 Best overall response

Assessment of BOR will be based on all assessments up to and including the first assessment of irPD (cPD1, cPD2, or uPD). Assessments made after start of new anti-cancer therapy, will be excluded.

BOR will be defined with the following hierarchy:

irCR	Two consecutive determinations of irCR ≥28 days (4 weeks) apart Non-consecutive assessments of irCR may also result in BOR of irCR if all intervening assessments are irUNK
irPR	Two determinations of irPR (or better) ≥28 days (4 weeks) apart The two determinations of irPR (or better) may be separated by one or more assessments of irSD, but may not be separated by an assessment of irPD
irSD	At least one irSD assessment (or better) > 42 days (6 weeks) after first treatment
irPD	Event flagged as cPD1, cPD2 or uPD ≤ 84 days (12 weeks) after first treatment
irUNK	All other cases

4.3.4 Time to event analyses:

4.3.4.1 Progression events

PDs flagged as pPD are not included in time to event analyses.

Patients are classified as follows:

0	No event (censored)
1	Confirmed PD (cPD1 or cPD2)
2	Unconfirmed PD (uPD)

For the primary analysis of time to event endpoints, both confirmed and unconfirmed progression will be included as progression events with date of progression being the date of the assessment flagged as cPD1, cPD2 or uPD according to the algorithm defined in Section 4.3.2.

A sensitivity analysis of time to event endpoints may be conducted in which patients with unconfirmed PD are treated as censored, with date of last adequate assessment = visit date for assessment flagged uPD.

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

Assessment date

Assessment date is defined as for RECIST v1.1 ([CLAG525X2101C Amendment 10 Appendix 14.1]).

Start date

Start date is as defined for RECIST v1.1 ([CLAG525X2101C Amendment 10 Appendix 14.1]).

End dates for time to event variables

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

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of death as recorded on death eCRF
- Date of progression as defined in Section 4.2.4.1.
- 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 progression 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 start of treatment is used.

Note: for sensitivity analyses of time to event endpoints ongoing Patients with an unconfirmed progression may be censored at time of last assessment.

4.3.4.3 Censoring reason

Censoring reason is derived as for RECIST v1.1 (Table 4-2).

Date of confirmed response

Response (irPR or irCR) should be confirmed by a second assessment no less than 4 weeks after the first assessment showing response. Date of response is then the date of the first of these two assessments. For confirmation of irCR the two assessments must be consecutive (intervening assessments of irUNK are permissible). For confirmation of irPR the two assessments do not need to be consecutive, but must not be separated by a pseudo-progression event.

The table below shows a hypothetical data scenarios with programming instructions.

Sequence of assessments	Instructions
1 irPR 2 irPD 3 irPR 4 irPR	• The first PR (assessment 1) is followed by a pseudo-progression (assessment 2) and is therefore not confirmed • Subsequently the Patient has a irPR (assessment 3) which is confirmed at the following assessment (assessment 4) • The BOR for this Patient is irPR, with date of confirmed irPR equal to the date of assessment 3

4.4 Event dates used in PFS and DOR

Based on definitions outlined in [CLAG525X2101C Amendment 10 Section 14.1.25], the following analyses can be considered:

Table 4-2 Options for event dates used in PFS and DOR

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

1. =Definitions can be found in [CLAG525X2101C Amendment 10 Section 14.1.25]

2. =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined [CLAG525X2101C Amendment 10 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.

4.5 CTCAE

Table 4-3 CTC grades for laboratory values in Novartis Oncology (based on CTCAE v4.03 – June 2010)

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Hematology								
WBC ↓ WBC [2] (Leukocytosis)	10^9/L 10^9/L	WBC WBC	**3.9 – 10.7 x 10^9/L**	≥ LLN	< LLN - 3.0 x 10^9/L -	< 3.0 – 2.0 x 10^9/L -	< 2.0 – 1.0 x 10^9/L > 100 x 10^9/L	< 1.0 x 10^9/L -
Hemoglobin [2] (Anemia) Hemoglobin ↑	g/L g/L	HGB HGB	**120 - 160 g/L** or 7.4 - 9.9 mmol/L (F) **140 - 170 g/L** or 8.7 – 10.6 mmol/L (M) *(16.113 x mmol/L = g/L)*	≥ LLN	< LLN - 100 g/L < LLN - 6.2 mmol/L Increase >0-20 g/L above ULN	< 100 - 80 g/L < 6.2 - 4.9 mmol/L Increase >20-40 g/L above ULN	< 80 g/L < 4.9 mmol/L Increase >40 g/L above ULN	- -
Platelets ↓	10^9/L	PLAT	**150 - 350 x 10^9/L**	≥ LLN	< LLN - 75.0 x 10^9/L	< 75.0 - 50.0 x 10^9/L	< 50.0 - 25.0 x 10^9/L	< 25.0 x 10^9/L
Neutrophils [3]↓	10^9/L	NEUT		≥2x10^9/L	< 2.0 - 1.5 x 10^9/L	< 1.5 - 1.0 x 10^9/L	< 1.0 - 0.5 x 10^9/L	< 0.5 x 10^9/L
Lymphocytes [3]↓ Lymphocytes ↑	10^9/L 10^9/L	LYM LYM		≥1.5x10^9/L	< 1.5 - 0.8 x 10^9/L -	< 0.8 - 0.5 x 10^9/L > 4 - 20 x 10^9/L	< 0.5 - 0.2 x 10^9/L > 20 x 10^9/L	< 0.2 x 10^9/L -
Biochemistry								
AST ↑	U/L	AST	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT ↑	U/L	ALT	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Total bilirubin ↑	umol/L	BILI	**5.1 – 20.5 umol/L** or 0.3 – 1.2 mg/dL *(17.1 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Alk. Phosphatase ↑	U/L	ALP	**36 - 92 U/L** or 0.5 - 1.5 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine [4]↑	umol/L	CREAT	**61.9 - 115 umol/L** or 0.7 – 1.3 mg/dL *(88.4 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Creatinine kinase [4]↑	U/L	CK	**30 - 170 U/L** or 0.5 – 2.83 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Albumin [2] (Hypoalbuminemia)	g/L	ALB	**35 - 55 g/L** or 3.5 to 5.5 g/dL	≥ LLN	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-
Total Cholesterol ↑	mmol/L	CHOL	**3.88 – 5.15 mmol/L** or 150 - 199 mg/dL *(38.67 x mg/dL = mmol/L)*	≤ ULN	> ULN - 7.75 mmol/L > ULN - 300 mg/dL	> 7.75 -10.34 mmol/L > 300 – 400 mg/dL	>10.34-12.92 mmol/L > 400 – 500 mg/dL	>12.92 mmol/L > 500 mg/dL
Lipase ↑	U/L	LIPASE	**<95 U/L** or <1.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Amylase ↑	U/L	AMYLASE	**0 - 130 U/L** or 0 – 2.17 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Uric acid [2] (Hyperuricemia)	umol/L	URATE	**150 - 470 umol/L** or 2.5 – 8 mg/dL *(59.48 x mg/dL = umol/L)*	≤ ULN	> ULN – 10 mg/dL > ULN – 595 umol/L	-	-	> 10 mg/dL > 595 umol/L

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

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

				CTC Grades[(1)]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Phosphorus[(2)] (Hypophosphatemia)	mmol/L	PHOS	**0.97 – 1.45 mmol/L** or 3.0 - 4.5 mg/dL *(0.32 x mg/dL = mmol/L)*	≥ LLN	< LLN - 2.5 mg/dL < LLN - 0.8 mmol/L	< 2.5 - 2.0 mg/dL < 0.8 - 0.6 mmol/L	< 2.0 - 1.0 mg/dL < 0.6 - 0.3 mmol/L	< 1.0 mg/dL < 0.3 mmol/L
Calcium (corrected) [(2)] (Hypercalcemia)	mmol/L	CACALC	**2.2 - 2.6 mmol/L** or 9 - 10.5 mg/dL *(0.2495 x mg/dL = mmol/L)*	≤ ULN	> ULN - 11.5 mg/dL > ULN - 2.9 mmol/L	> 11.5 - 12.5 mg/dL > 2.9 - 3.1 mmol/L	> 12.5 - 13.5 mg/dL > 3.1 - 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Calcium (corrected) [(2)] (Hypocalcemia)	mmol/L	CACALC		≥ LLN	< LLN - 8.0 mg/dL < LLN - 2.0 mmol/L	< 8.0 - 7.0 mg/dL < 2.0 - 1.75 mmol/L	< 7.0 - 6.0 mg/dL < 1.75 - 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Magnesium [(2)] (Hypermagnesemia)	mmol/L	MG	**0.62 – 0.99 mmol/L** or 1.5 – 2.4 mg/dL *(0.4114 x mg/dL = mmol/L)*	≤ ULN	> ULN - 3.0 mg/dL > ULN - 1.23 mmol/L	-	> 3.0 – 8.0 mg/dL > 1.23 – 3.3 mmol/L	> 8.0 mg/dL > 3.3 mmol/L
Magnesium [(2)] (Hypomagnesemia)	mmol/L	MG		≥ LLN	< LLN - 1.2 mg/dL < LLN - 0.5 mmol/L	< 1.2 - 0.9 mg/dL < 0.5 - 0.4 mmol/L	< 0.9 - 0.7 mg/dL < 0.4 - 0.3 mmol/L	< 0.7 mg/dL < 0.3 mmol/L
Glucose (non-fasting) [(2)] (Hyperglycemia)	mmol/L	GLUCSN	**<7.8 mmol/L** or <140 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	-	> ULN - 250 mg/dL > ULN - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose (fasting) [(2)] (Hyperglycemia)	mmol/L	GLUCSF	**3.9 – 5.8 mmol/L** or 70 - 105 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	> ULN - 160 mg/dL > ULN - 8.9 mmol/L	> 160 - 250 mg/dL > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose [(2)] (Hypoglycemia)	mmol/L	GLUCSN/ GLUCSF		≥ LLN	< LLN - 55 mg/dL < LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3.0 - 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Potassium [(2)] (Hyperkalemia)	mmol/L	K	**3.5 - 5.0 mmol/L** *(0.2558 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium [(2)] (Hypokalemia)	mmol/L	K		≥ LLN	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Sodium [(2)] (Hypernatremia)	mmol/L	SODIUM	**136 - 145 mmol/L** *(0.435 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Sodium [(2)] (Hyponatremia)	mmol/L	SODIUM		≥ LLN	< LLN - 130 mmol/L	-	< 130 - 120 mmol/L	< 120 mmol/L
Triglyceride [(2)] ↑	mmol/L	TRIG	**< 2.82 mmol/L** or < 250 mg/dL *(0.01129 x mg/dL = umol/L)*	< 150 < 1.71	≥ 150 - 300 mg/dL ≥ 1.71 – 3.42 mmol/L	> 300 - 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 - 1000 mg/dL > 5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L
Coagulation								
INR [(2)]↑	1	INR	**0.8 – 1.2**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Activated partial thromboplastin time[(2)]↑	sec	APTT	**25 - 35 sec**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Fibrinogen [(4)]↓	g/L	FIBRINO	**1.5 – 3.5 g/L** or 150 – 350 mg/dL *(0.01 x mg/dL = g/L)*	≥ LLN	< LLN - 0.75 x LLN	< 0.75 - 0.5 x LLN	< 0.5 - 0.25 x LLN	< 0.25 x LLN

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

(1) = **LAB CTC grades 1, 2, 3, 4 overrule the study specific (central or local) normal range criteria**, e.g. if ULN of Sodium is 151 mmol/L and the value is 151 mmol/L, CTC grade 2 is assigned although the value is ≤ ULN.
(2) = **Life-threatening consequences and/or hospitalization are <u>not</u> considered** for determination of LAB CTC grades 3 and 4. Concomitant usage of anticoagulation therapy (for INR and Fibrinogen) is not considered either.
(3) = Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, **≥ 1.5 x 10^9/L (lymphocytes) and ≥ 2 x 10^9/L (neutrophils) are considered as LAB CTC grade 0**
(4) = For Creatinine and Fibrinogen, the **comparison with baseline is <u>not</u> considered** for derivation of LAB CTC grades

5 References

Babb J, Rogatko A, Zacks S (1998) Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med.; 17 (10):1103-1120.

Brookmeyer, R., & Crowley, J. (1982). A Confidence Interval for the Median Survival Time. Biometrics, 38(1), 29-41. doi:10.2307/2530286

Chen M, Ibrahim J (2006) The Relationship Between the Power Prior and Hierarchical Models, Bayesian Analysis, 1, Number 3.

Deeks ED (2014) Nivolumab: A review of its use in patients with malignant melanoma. Drugs; 74:1233-39.

Kalbfleisch, J. & Prentice, R. (1980) The statistical analysis of failure time data, John Wiley & Sons, Inc., New York.

Klein J. & Moeschberger, M. (1997). Survival Analysis: Techniques for Censored and Truncated Data. Springer, 1431-8776.

Neuenschwander B, Branson M, Gsponer T (2008) Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med.; 27 (13):2420-39.

Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter D (2010) Summarizing historical information on controls in clinical trials. Clin Trials 2010 7: 5.

Neuenschwander B, Matano A, Tang Z, Roychoudhury S, Wandel S and Bailey S: A Bayesian Industry Approach to Phase I Combination Trials in Oncology in Zhao W and Yang H. Statistical Methods in Drug Combination Studies. Chapman & Hall/CRC, 2014.

Robert C, Ribas A, Wolchok JD, et al (2014) Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomized dosecomparison cohort of a phase 1 trial. Lancet; 384:1109-17.

Rup B, et al. (2015). Standardizing terms, definitions and concepts for describing and interpreting unwanted immunogenicity of biopharmaceuticals: recommendations of the Innovative Medicines Initiative ABIRISK consortium. Clinical and Experimental Immunology 181:385-400.

Shankar G, et al. (2014). Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides – harmonized terminology and tactical recommendations. The AAPS Journal 16:658-673.