NOVARTIS

Clinical Development

LAG525

CLAG525B2101 / NCT03499899

A phase II open-label, randomized, three-arm, multicenter study of LAG525 given in combination with spartalizumab (PDR001), or with spartalizumab and carboplatin, or with carboplatin, as first or second line therapy in patients with advanced triple-negative breast cancer

Statistical Analysis Plan (SAP)
Amendment 2

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Document type: SAP Documentation

Document status: [redacted]

Release date: 07-Sep-2021

Number of pages: 63

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
7-Jun-2018	Prior to FSFV	Creation of final version	N/A - First version	NA
13-May-2020	Prior to DBL	Change of CTCAE version and subgroup analysis	1. added subgroup analysis for early relapsed patients 2. CTCAE version was changed to v5.0 3. Subgroup will be analyzed even if no arm meets the preliminary efficacy criteria	
7-Sep-2020	Prior to final DBL	Update to summarize Covid-19 PD and to include inconclusive samples for IG analsysis	1. Added summary of COVID-19 related protocol deviations 2. Added summary of subjects with ADA-inconclusive samples in the IG analysis 3. Changed study design figure per protocol amendment 4	Section 2.3.7 Section 2.11.1 Section 1.1

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List of abbreviations

ADA	Antidrug Antibodies
AE	Adverse event
AESI	Adverse Event of Specific Interest
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BMI	Body Mass Index
BOR	Best Overall Response
BRCA1/2	Breast Cancer 1/2 genes
CBR	Clinical Benefit Rate
CD8	Cluster of differentiation 8
CR	Complete Response
CRO	Contract Research Organization
CRS	Case Retrieval Strategy
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DBL	Database Lock
DI	Dose Intensity
DOR	Duration Of Response
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
FSFV	First Subject First Visit
IHC	Immunohistochemistry
LAG-3	Lymphocyte-Activation Gene 3
LSLV	Last Subject Last Visit
EOI	End of Infusion
EOT	End Of Treatment
ER	Estrogen Receptor
GFR	Glomerular Filtration Rate
HGLTs	High Level Group Terms
HLT	High Level Terms
i.e.	id est
IG	Immunogenicity
ITT	Intent-To-Treat
iRECIST	Immune-related RECIST

IRT	Interactive Response Technology
kg	killogram
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mL	milliliter
NCI	National Cancer Institute
NMQ	Novartis MedDRA Queries
o.d.	Once Daily
ORR	Overall Response Rate / Objective Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	Progressive Disease
PD-1	Programmed Death 1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PDI	Planned Dose Intensity
PFS	Progression-Free Survival
PgR	Progesterone receptor
PK	Pharmacokinetics
PR	Partial Response
PRO	Patient-reported Outcomes
PT	Preferred Term
qd	Qua'que di'e / once a day
RDI	Relative Dose Intensity
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
sd	Standard deviation
SD	Stable Disease
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SOD	Sum Of Diamaters
TA	Tumor Assessment
TBL	Total Bilirubin
TFLs	Tables, Figures, Listings
[redacted]	[redacted]
TNBC	Triple Negative Breast Cancer
TP	Time Point
TTR	Time To Response
ULN	Upper Limit of Normal
UNK	Unknown

WHO	World Health Organization
WHO-DD	WHO-Drug Dictionnary
WHO DRL	WHO Drug Reference Listing

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study reports (CSR, either CSR for the primary analysis or CSR for the final analysis) of study CLAG525B2101, a phase II, randomized, open-label, three-arm multicenter study of LAG525 given in combination with spartalizumab (PDR001), or with spartalizumab and carboplatin, or with carboplatin, as first or second line therapy in patients with advanced triple-negative breast cancer.

The content of this SAP is based on protocol CLAG525B2101 v04. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data. This SAP has been amended before the final close-out CSR for safety and PK analysis, for which no inferential analysis is planned.

1.1 Study design

This is a randomized, phase II , open-label, three-arm, multicenter study evaluating the safety and efficacy of LAG525 given in combination with spartalizumab, or LAG525 with spartalizumab and carboplatin, or LAG525 with carboplatin, as first or second line therapy in patients with advanced triple-negative breast cancer. Approximately 96 subjects will be randomized to one of the following treatment arms in 1:1:1 ratio:

- LAG525 + PDR001
- LAG525 + PDR001 + carboplatin
- LAG525 + carboplatin

Randomization will be stratified by the following factors:

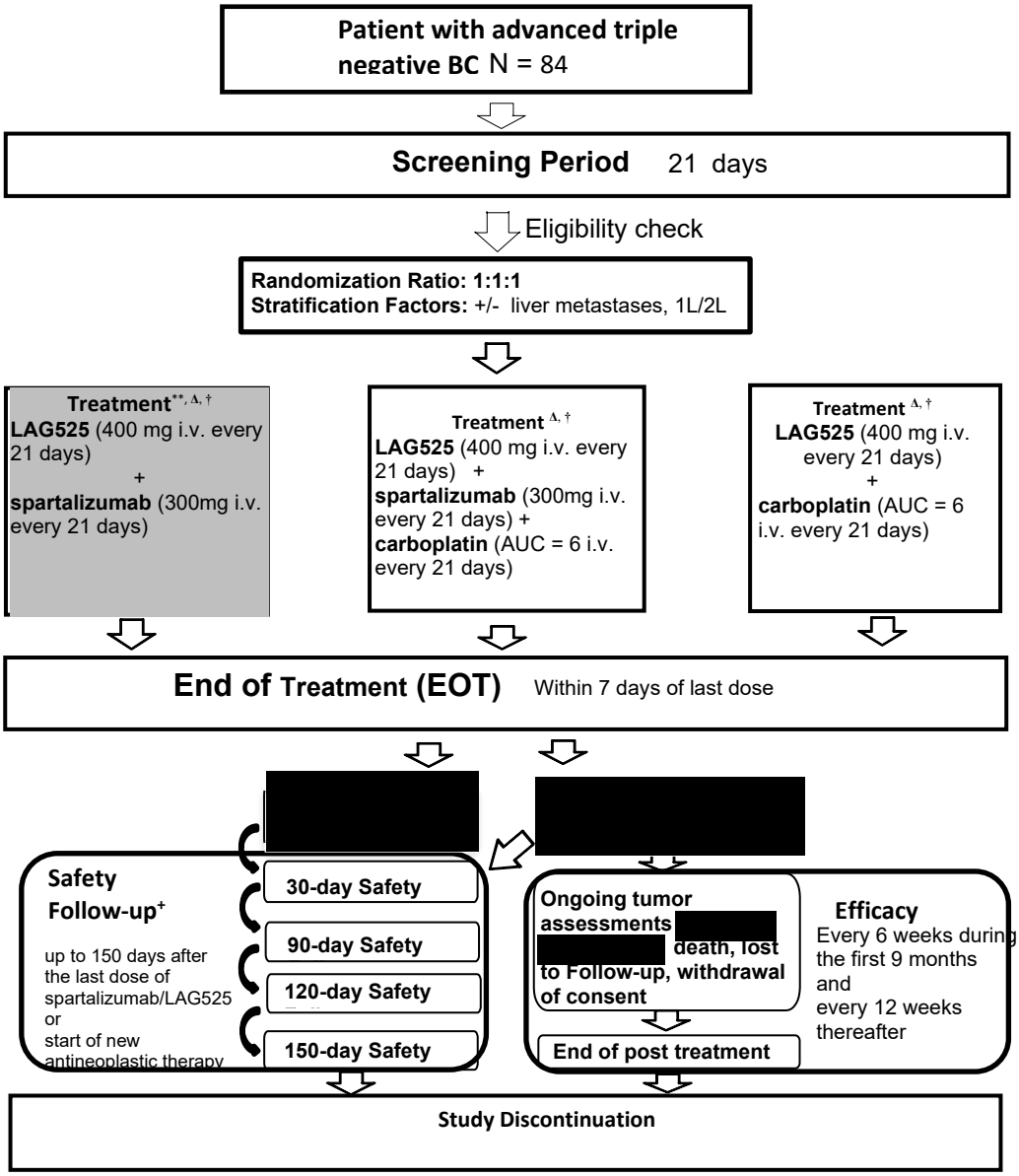
- Presence of liver metastasis (Yes / No)
- Line of therapy (First line: following disease progression after adjuvant or neoadjuvant therapy / Second line: following one disease progression in advanced or metastatic setting)

With protocol amendment 3, enrollment to treatment Arm 1 (LAG525 + PDR001) was prematurely closed. Novartis and the study steering committee decided to prematurely stop enrollment of subjects to Arm 1 after data review showed an increased treatment discontinuation rate due to progressive disease in Arm 1 as compared to Arms 2 and 3 (both containing carboplatin)

Overall response rate (ORR), as assessed by local investigators review of tumor response and using RECIST 1.1 criteria, is the primary endpoint in this study.

The primary analysis was conducted when all subjects have been followed for efficacy (tumor assessments) for at least 24 weeks or discontinued tumor assessments for any reason prior to 24 weeks. The primary analysis data will be summarized in the primary clinical study report (CSR). Any additional data for subjects continuing to receive study treatment past the data cut-off date for the primary CSR, as allowed by the protocol, will be reported in the final CSR on completion of the study.
No formal interim analysis is planned for this trial.

Figure 1-1 Study Design



[redacted]

**With protocol amendment 3, enrollment to treatment Arm 1 (LAG525 + spartalizumab) was prematurely closed

Δ Upon the release of protocol amendment #4, ongoing patients who will transfer into PTA program (roll over study or PSDS) only EOT visit will be performed but no safety, efficacy and survival follow-up

+ Patients who had stopped study treatment more than 150 days will be discontinued from the study – see Section 9.1.1 for details. Survival follow-up period is removed after protocol amendment #4 is approved

† with implementation of protocol amendment #4 for the remaining participants in the study all tumor assessments in the post-treatment follow-up period will be optional and will be left at the discretion of the investigator

1.2 Study objectives and endpoints

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

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the antitumor activity of the three treatment arms LAG525 + spartalizumab, LAG525 + spartalizumab + carboplatin and LAG525 + carboplatin, in subjects with advanced TNBC in first or second line of therapy, as measured by the objective response rate (ORR) per investigator's assessment according to RECIST v1.1.	• Overall response rate (ORR) per RECIST v1.1 per investigators' assessment
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the efficacy of the three treatment arms with respect to Duration of response (DOR), Time to response (TTR), Progression Free Survival (PFS) and Clinical benefit rate (CBR) per investigator's assessment according to RECIST v1.1	• Duration of response (DOR), Time to response (TTR), PFS and Clinical benefit rate (CBR) per investigators' assessment.
• To assess Overall Survival for each treatment arm	• Overall Survival (OS)
• To characterize the safety profile of each treatment arm	• Adverse events (AEs), serious AEs (SAEs), changes in hematology and chemistry values, vital signs, weight, ECOG performance status, electrocardiograms (ECGs), dose interruptions, reductions and dose intensity.
• To characterize the pharmacokinetics (PK) of LAG525, spartalizumab, and carboplatin in the three investigated combinations	• Pharmacokinetic parameters (e.g., Ctrough, Cmax, AUC)
• To assess immunogenicity of LAG525 and spartalizumab in the three investigated combinations	• Antidrug antibodies (ADA) prevalence at baseline and ADA incidence on treatment
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The primary analysis and final analysis will be performed by Novartis and/or a designated CRO. SAS version 9.3 or later and R version 3.2.3 or later software will be used to perform all data analyses and to generate tables, figures and listings.

Data included in the analysis

The analysis cut-off date for the primary analysis of study data was established after all randomized subjects have been followed for efficacy (tumor assessments) for at least 24 weeks or discontinued tumor assessments for any reason prior to 24 weeks. All statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

The analysis cut-off date for the final analysis of study data will be established at the end of the study, when all subjects have died or discontinued from the study, or another clinical study became available that can continue to provide study treatment in this subject population and all subjects ongoing are eligible to be transferred to that clinical study.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of subjects enrolled at centers, no center effect will be assessed.
Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment arm; a missing category will be included as applicable. Percentages will be calculated using the number of subjects in the relevant population or subgroup as the denominator.
Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment arm.

2.1.1 General definitions

Investigational drug and study treatment

Investigational drug will refer to LAG525 or spartalizumab (PDR001), combination partner will refer to carboplatin only, whereas study treatment will refer to LAG525 + spartalizumab, LAG525 + spartalizumab + carboplatin or LAG525 + carboplatin.

The term investigational treatment may also be referred to as ***study treatment*** which is used throughout this document.

Date of first administration of investigational drug / combination partner

The date of first administration of investigational drug / combination partner is defined as the first date when a non-zero dose of investigational drug / combination partner is administered and recorded on the 'Study treatment – LAG525/PDR001/carboplatin' eCRF pages. The date of first administration of study drug / combination partner will also be referred as start of investigational drug / combination partner.

Date of last administration of investigational drug / combination partner

The date of last administration of investigational drug / combination partner is defined as the last date when a nonzero dose of investigational drug / combination partner is administered and recorded on the 'Study treatment – LAG525/PDR001/carboplatin' eCRF pages. The date of last administration of investigational drug / combination partner will also be referred as end of investigational drug / combination partner.

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of study treatment was administered as per the 'Study treatment – LAG525/PDR001/carboplatin' eCRF pages. The date of first administration of study treatment will also be referred as ***start of study treatment***.

The date of first administration of study treatment is derived as the first date when a nonzero dose of any component of study treatment was administered as per the 'Study treatment – LAG525/PDR001/carboplatin' eCRF pages. (Example: if 1st dose of spartalizumab is administered on 05-Jan-2018, and 1st dose of LAG525 is administered on 03-Jan-2018, then the date of first administration of study treatment is on 03-Jan-2018).

Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a nonzero dose of study treatment was administered as per 'Study treatment – LAG525/PDR001/carboplatin' eCRF pages.

The date of last administration of study treatment is derived as the last date when a nonzero dose of any component of study treatment was administered as per 'Study treatment – LAG525/PDR001/carboplatin' eCRF pages. (Example: if the last spartalizumab dose is administered on 15-Apr-2018, and the last dose of LAG525 is administered on 17-Apr-2018, then the date of last administration of study treatment is on 17-Apr-2018).

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference start date for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, ECOG performance status, PK etc.) is the start of study treatment.

The reference start date for all other, non-safety assessments (i.e., tumor assessment, survival time, disease progression, tumor response) is the date of randomization.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Note: Some measurements may belong to safety measurement and to efficacy measurement ('death' is an efficacy endpoint, but it can also be included in the safety analysis). For safety, the 'study day' will be calculated relative to start of study treatment, while for efficacy overall survival will be derived relative to randomization date.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as “baseline” value or “baseline” assessment.

For safety evaluations, the last available assessment on or before the date of start of study treatment is taken for ”baseline” assessment.

In case time of assessment (e.g. pre-dose ECG) and time of treatment start is captured, the last available assessment before the treatment start date/time is used for baseline.

For safety parameters (e.g ECGs), where study requires multiple replicates per time point, the average of these measurements would be calculated for baseline (if not already available in the database).

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 value closest to normal should be considered as baseline.

If subjects have no value as defined above, the baseline result will be missing.

On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of subject’s informed consent to the day before first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date)
3. ***post-treatment period***: starting at day 31 after last administration of study treatment.

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period. Refer to Section 5.1.2 for imputation rules concerning AE start and stop dates.

For other safety data, the on-treatment period will start from the day after the date of first administration of study treatment, unless the time of assessment and time of treatment start is available on the day of study treatment start. For data where time of assessment (e.g. ECGs) and time of treatment start are captured, data collected on the day of first administration of study

treatment at a time before (after respectively) the time of first administration of study treatment will be considered on the pre-treatment period (on the on-treatment period respectively).

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs). However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Additional summaries will be displayed to report deaths, all AEs, AEs related to study treatment, all SAEs and SAEs related to study treatment collected up to 150 days after last administration of LAG525/spartalizumab or up to 30 days after the last dose of carboplatin whichever comes last..

Last contact date

The last contact date will be derived for subjects not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-1 Last contact date data sources

Source data	Conditions
Date of Randomization	No Condition
Last contact date/last date subject was known to be alive from Survival Follow-up page	Subject status is reported to be alive, lost to follow-up or unknown
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End dates from study treatment pages	Non-missing dose. Doses of 0 are allowed.
End of treatment date from disposition page at end of treatment	No condition.
Tumor (RECIST / iRECIST) assessment date	Result is not missing
Verification for treatment beyond RECIST1.1 PD	At least one non missing parameter value
Laboratory/PK/IG collection dates	Was sample taken? = 'Yes'.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date, unless the subject was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring if coming from Survival eCRF.

The last contact date will be used for censoring of subjects in the analysis of overall survival.

2.2 Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned by randomization. According to the intent to treat principle, subjects will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

Safety set

The Safety Set includes all subjects who received at least one dose of study treatment (i.e., at least one dose of any component of the study treatment, including incomplete infusion of spartalizumab, LAG525 or carboplatin). Subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

Pharmacokinetic analysis set (PAS)

The LAG525 pharmacokinetic analysis set (**PAS-LAG525**) includes all subjects who provide at least one evaluable LAG525 PK concentration. For a concentration to be evaluable, subjects are required to:

- Receive a planned dose of LAG525 prior to sampling.
- For pre-dose samples: have the sample collected prior to dosing on the assessment day and for samples post-C1D1 have the sample collected approximately 504 hr ± 24 hours after the previous dose.
- For end-of-infusion samples: have the sample collected 1 hour post end of infusion within ± 5 minutes of the scheduled time point;
- For 168 and 336 hours samples: have the sample collected 168, 336 hours post end of infusion within ± 24 hours of the scheduled timepoint.

The spartalizumab pharmacokinetic analysis set (**PAS-Spartalizumab**) includes all subjects who provide at least one evaluable Spartalizumab PK concentration. For a concentration to be evaluable, subjects are required to:

- Receive a planned dose of spartalizumab prior to sampling.
- For pre-dose samples: have the sample collected prior to dosing on the assessment day and for samples post-C1D1 have the sample collected approximately 504 hr ± 24 hours after the previous dose.
- For end-of-infusion samples: have the sample collected 1 hour post end of infusion within ± 5 minutes of the scheduled time point; have the sample collected 168, 336 hours post end of infusion within ± 24 hours of the scheduled timepoint.

The carboplatin pharmacokinetic analysis set (**PAS-carboplatin**) includes all subjects who provide at least one evaluable carboplatin PK concentration. For a concentration to be evaluable, subjects are required to:

- Receive a planned dose of carboplatin prior to sampling,

- For pre-dose samples, have the sample collected before the next dose administration within 30 minutes before the infusion begins
- For samples scheduled to be taken prior to End of Infusion (EOI), have the samples collected prior to EOI
- For end-of-infusion samples: have the sample collected 1, 2 and 3 hours post end of infusion: within ± 10 minutes of the scheduled time point

The PAS will be used for all PK analyses.

Immunogenicity (IG) analysis sets

The LAG525 **Immunogenicity prevalence set**includes all subjects in the Full analysis set with a determinant baseline LAG525 IG sample **or** at least one determinant post-baseline LAG525 IG sample.

The LAG525 **Immunogenicity incidence set** includes all subjects in the LAG525 Immunogenicity prevalence set with a determinant LAG525 baseline IG sample **and** at least one determinant LAG525 post-baseline IG sample.

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

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

See Section 2.11.1 for the definition of determinant.

Subject Classification:

Subjects may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-4.

Table 2-2 Subject classification based on protocol deviations and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written inform consent	Not applicable
Safety set	No written inform consent	No dose of any component of study treatment
PAS-LAG525	No written inform consent	No evaluable LAG525 PK concentration

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
PAS-Spartalizumab	No written inform consent	No evaluable spartalizumab PK concentration
PAS-carboplatin	No written inform consent	No evaluable carboplatin PK concentration
LAG525 IG prevalence set	No written inform consent	Subject not in the FAS No determinant baseline LAG525 IG sample and no determinant post-baseline LAG525 IG sample
LAG525 IG incidence set	No written inform consent	Subject not in the FAS No determinant baseline LAG525 IG sample No determinant post-baseline LAG525 IG sample
Spartalizumab IG prevalence set	No written inform consent	Subject not in the FAS No determinant baseline spartalizumab IG sample and no determinant post-baseline spartalizumab IG sample
Spartalizumab IG incidence set	No written inform consent	Subject not in the FAS No determinant baseline spartalizumab IG sample No determinant post-baseline spartalizumab IG sample

Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a subject withdraws full consent is recorded in the eCRF.

Additional data for which there is a separate informed consent, e.g. PK, [redacted] etc., collected in the clinical database without having obtained that consent will not be included in the analysis. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.2.1 Subgroup of interest

Efficacy

The primary efficacy endpoint ORR and the secondary endpoint DOR based on investigators' review of tumor assessments as per RECIST 1.1 will be summarized by the following subgroups to examine the homogeneity of treatment effect, provided that the primary efficacy analysis based on the FAS has shown a proof of preliminary efficacy for at least one treatment arm:

- Stratification factors: presence of liver metastasis (yes/no) and line of therapy (first line / second line) (based on randomization data from IRT)
- Age category (< 65 years, ≥ 65 years)
- Age category (< 50 years, ≥ 50 years)
- [redacted]
- Relapse free interval for the firstline patients (<12 month, ≥12 months) where realapse interval is defined as,

  the last dose date of prior adjuvant/neoadjuvant therapy - the progression date after the prior antineoplastic therapy+1
- Relapse free interval for the firstline patients (<6 months, 7-12 months, and >=12 months) where realapse interval is defined as,

  the last dose date of prior adjuvant/neoadjuvant therapy - the progression date after the prior antineoplastic therapy+1

For subgroup analysis, only point estimates by treatment arm and 95%-confidence intervals will be provided (see Section 2.5.4, Section 2.7.2, Section 2.8 for further analysis details). The objective of the efficacy subgroup analysis is to demonstrate homogeneity of treatment effect in the above subgroups.

Safety

Safety subgroup analyses will use the same method as for the analysis in the overall analysis set. Key safety analyses (overall summary of AEs and of AESIs, and AEs by PT) will be repeated on safety set in the following subgroups:

Age group (< 65 years, ≥ 65 years)The objective for carrying out these subgroup analyses is to identify potential safety issues that may be limited to a subgroup of subjects, or safety issues that are more commonly observed in a subgroup of subjects.

2.3 Subject disposition, demographics and other baseline characteristics

The Full Analysis Set (FAS) will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries will be reported by treatment arm and for all subjects and listings will be reported by treatment arm to assess baseline comparability. No inferential statistics will be provided.

2.3.1 Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment arm. Categorical data (e.g. gender, age groups: <65, ≥ 65 - < 85 and ≥ 85 years, race, ethnicity and ECOG performance status at baseline) will be summarized by frequency counts and percentages; the number and percentage of subjects with missing data will be provided. Continuous data (e.g. age, weight, height and body mass index (BMI)) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum). BMI (kg/m^2) will be calculated as weight[kg] / (height[m]^2) using height at screening and weight at baseline.

In addition, number of subjects treated will be summarized by age/gender combination and by race for each treatment arm in the Safety Set for DSUR reporting purposes.

2.3.2 Baseline stratification factors

The number (%) of subjects in each stratum (Presence of liver metastasis and Line of therapy) based on data obtained from the IRT system will be summarized overall and by treatment arm for the FAS. Discordances between the stratum recorded in IRT at the time of randomization and the actual stratum recorded in the clinical database through the data collected on eCRF will be cross-tabulated and listed.

2.3.3 Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: diagnosis of disease (Breast Cancer / Triple Negative Breast Cancer), primary site of cancer, predominant histology / cytology, histological grade, stage at initial diagnosis, time since initial diagnosis, time from initial diagnosis to first recurrence / progression (in months), time since most recent relapse/progression to randomization (in months), stage at time of study entry, presence/absence of target and non-target lesions, number and type of metastatic sites involved, sum of diameters (SOD) for target lesions (in mm), HER2 receptor status, estrogen receptor (ER) status and progesterone receptor (PgR) status.
Note: Presence/absence of target and non-target lesions will be based on the data collected on RECIST target/non-target lesion assessment eCRF pages. Metastatic sites will be based on diagnosis page.

2.3.4 Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF will be summarized and listed by treatment arm. The summaries will be presented by primary system organ class (SOC), preferred term (PT) and treatment arm. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

2.3.5 Other

Other categorical data (e.g. BRCA mutation status, PD-L1 status groups and LAG-3 status group: positive and negative based on relevant thereshold(s), CD8+ values) will be summarized by frequency counts and percentages; the number and percentage of subjects with missing data will be provided: see section 2.13 for further details.

[redacted]

2.3.6 Subject disposition

Enrollment by country and center will be summarized for all screened subjects and also by treatment arm using the FAS. The number (%) of randomized subjects included in the FAS will be presented overall and by treatment arm. The number (%) of screened and not-randomized subjects and the reasons for screening failure will also be displayed. The number (%) of subjects in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment group.

The following summaries will be provided (with % based on the total number of FAS subjects):

- Number (%) of subjects who were randomized (based on data from IRT system)
- Number (%) of subjects who were randomized but not treated (based on 'Study treatment' eCRF pages not completed for any study treatment component)
- Primary reason for not being treated (based on the 'Treatment disposition' eCRF page eCRF page)
- Number (%) of subjects who were treated (based on 'Study treatment' eCRF pages of each study treatment component completed with non-zero dose administered)
- Number (%) of subjects who are still on-treatment (based on the 'Treatment disposition' eCRF page not completed);
- Number (%) of subjects who discontinued the study treatment phase (based on the 'Treatment disposition' eCRF page)
- Primary reason for study treatment phase discontinuation (based on the 'Disposition' eCRF page for 'Treatment disposition')
- Primary reason for discontinuation of each study drug (based on the 'Disposition' eCRF page for LAG525/PDR001/carboplatin)
- Number (%) of subjects who have entered the post-treatment follow-up (based on the 'Subject status at EOT' eCRF page);

- Number (%) of subjects who have discontinued from the post-treatment follow-up (based on the 'Post-treatment follow-up disposition' eCRF page);
- Reasons for discontinuation from the post-treatment follow-up (based on 'Post-treatment follow-up disposition' eCRF page);
- Number (%) of subjects who have entered the survival follow-up (based on the 'Subject status' eCRF page at EOT, safety follow-up visits or at the end of Post-treatment follow-up).

2.3.7 Protocol deviations

The number (%) of subjects in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Data Handling Plan) overall and by treatment arm for the FAS. Major protocol deviations leading to exclusion from analysis sets will be tabulated separately overall and by treatment arm. All protocol deviations will be listed.

In addition to the pre-defined standard protocol deviation terms, 6 new protocol deviations and the corresponding relationship (health status related vs. site lockdown, patient concerns, etc.) to the COVID-19 pandemic have been defined in alignment with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (December 2020) and "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic" (April 2020) from EMA as listed below.

- Missing visits
- Changes in procedures and assessments
- Planned visits not done at sites
- Changes in drug supply method
- Treatment not given
- Patient discontinuation due to COVID-19 situation

The number and percentage of patients with any protocol deviations in the FAS will be summarized by COVID-19 relationship (related or not-related) and by treatment arm in the post-text table. A cross-tabulation of COVID-19 related protocol deviation vs. corresponding detailed relationship will also be produced by treatment arm. The detailed relationship is listed as below:

- COVID-19 health status related
- COVID-19 situation: Site issue
- COVID-19 situation: Lockdown / Quarantine of patient
- COVID-19 situation: Patient concern
- COVID-19 situation: Drug supply issue
- COVID-19 situation: Other

2.3.8 Analysis sets

The number (%) of subjects in each analysis set (defined in Section 2.2) will be summarized by treatment arm and stratum.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure, average cycle dose and actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment arm, separately for each component of study treatment. The duration of exposure will also be presented for the study treatment (LAG525 + spartalizumab, LAG525 + spartalizumab + carboplatin or LAG525 + carboplatin). Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of subjects in each interval. The number (%) of subjects who have dose reductions (for carboplatin), interruptions, and the reasons, will be summarized by treatment arm.

Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to LAG525, spartalizumab or carboplatin (as applicable depending on the treatment arm):

Duration of exposure to study treatment (weeks) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1.

The last date of exposure to study treatment is the latest of the last dates of exposure to LAG525, spartalizumab or carboplatin (as applicable depending on the treatment arm) (see Table 2-5).

Summary of duration of exposure of study treatment in appropriate time units will include categorical summaries (< 3 weeks, at least 3 weeks, at least 6 weeks, etc.) and continuous summaries (i.e. mean, standard deviation etc.) using appropriate units of time. Summary of cycles received will include categorical summaries (at least 1 cycle, at least 3 cycles, at least 5 cycles and etc).

Duration of exposure to LAG525, spartalizumab and carboplatin

Duration of exposure to LAG525 (weeks) = (last date of exposure to LAG525) – (date of first administration of LAG525) + 1.

Duration of exposure to spartalizumab (weeks) = (last date of exposure to spartalizumab) – (date of first administration of spartalizumab) + 1.

Duration of exposure to carboplatin (weeks) = (last date of exposure to carboplatin) – (date of first administration of carboplatin) + 1.

Table 2-3 Definition of last date of exposure of study drug

Study drug	Definition of last date of exposure of study drug	Example

LAG525 spartalizumab carboplatin	The planned end date of the last cycle in which the last non-zero dose of the investigational drug was last administered (i.e last date of administration + (planned interval duration-1day)) Note : If the subject died or was lost to follow-up before the derived last date, the last date of exposure to investigational drug is the date of death or the date of last contact, respectively. If the derived last date of exposure goes beyond the data cut-off date, it should be truncated to the date of data cut-off.	In a once every 3 weeks administration, the last date of exposure is the date of administration in the last cycle + 20 days

Summary of duration of exposure of LAG525, spartalizumab and carboplatin will include categorical summaries based on 21-day intervals (< 3 weeks, at least 3 weeks, at least 6 weeks, etc.) and using descriptive statistics (mean, standard deviation etc).

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment components.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the 'Study treatment – LAG525/PDR001/carboplatin' eCRF pages.

For subjects who did not take any drug component the cumulative dose for that component is by definition equal to zero.

For LAG525 and spartalizumab, the planned cumulative dose and actual cumulative dose will be expressed in mg.

For carboplatin, they will be expressed as calculated AUC (mg/mL x min). To that end the prescribed / administered dose in mg will be used to calculate the AUC using Calvert's formula based on the derived GFR value. Calvert's formula is given as:

- Carboplatin dosage (mg) = AUC (mg/mL x min) x [GFR (mL/min) + 25]

And the back-calculation for AUC is

- AUC (mg/mL x min) = Carboplatin dose (mg) / [GFR (mL/min) + 25]

For the calculation of GFR, creatinine value in the dabatase with a measurement time closest to the dosing date and the subject's age and weight at the creatinine collection time will be used with the Cockcroft & Gault formula. If the interval between the measurement time and dosing time is the same before and after dose, the measurement corresponding to the time before dose will be used. Cockcroft & Gault's formula (Cockroft and Gault 1976) is given as:

- Male GFR (mL/min) = [140 – age (years)] x weight (kg) x 1.23 / sCr (µmol/L)
- Female GFR (mL/min) = [140 – age (years)] x weight (kg) x 1.04 / sCr (µmol/L)

OR

- Male GFR (mL/min) = [140 – age (years)] x weight (kg) / [72 x sCr (mg/dL)]
- Female GFR (mL/min) = [140 – age (years)] x weight (kg) x 0.85 / [72 x sCr (mg/dL)]

Note: The planned dose of carboplatin is per AUC 6 in general, but could be lower if the corresponding dose (mg) was higher than 900 mg (maximum dose in mg allowed as per the protocol). Hence if for a subject the first carboplatin dose prescribed was capped at 900 mg, the prescribed carboplatin dose (AUC) will be back calculated and will be used as planned dose in AUC to compute the planned cumulative dose.

Dose intensity and relative dose intensity

Dose intensity (DI) for subjects with non-zero duration of exposure is defined as follows:

For LAG525 and spartalizumab, DI (mg / cycle) = Actual Cumulative dose (mg) / Duration of exposure to study treatment (cycle),

For carboplatin, DI (AUC / cycle) = Actual Cumulative dose (AUC) / Duration of exposure to study treatment (cycle),

where Duration of exposure to study treatment (cycle) = Duration of exposure to study treatment (day) / 21. It will be rounded up to the nearest cycle if the last date of exposure to study treatment is replaced by the cut-off date: e.g. 66 days will be rounded to 4 cycles.

If for example, the duration of exposure to spartalizumab is 6 weeks and the subject receives two injections of spartalizumab 300 mg:

DI (mg/cycle) = Actual Cumulative dose (mg) / Duration of exposure (cycle)

= 600 (mg) / (42/21) (cycle) = 300 (mg/cycle)

For subjects who did not take any drug component the DI for that component is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

For LAG525 and spartalizumab, PDI (mg / cycle) = Planned Cumulative dose (mg) / Duration of exposure (cycle). PDI (mg / cycle) is 400 mg/cycle for LAG525 and 300 mg/cycle for spartalizumab.

For carboplatin, PDI (AUC / cycle) = Planned Cumulative dose (AUC) / Duration of exposure (cycle).

Note: PDI (AUC / cycle) is AUC 6/cycle for carboplatin in general, but could be lower if the corresponding dose (mg) was higher than 900 mg. Hence if for a subject the first carboplatin dose prescribed is 900 mg, the prescribed carboplatin dose (AUC) will be back calculated and will be used as PDI per cycle for that subject.

Relative dose intensity (RDI) is defined as follows:

For LAG525 and spartalizumab, RDI = DI (mg / cycle) / PDI (mg / cycle).

For carboplatin, RDI = DI (AUC / cycle) / PDI (AUC / cycle).

DI and RDI will be summarized separately for each of the study treatment components, but using the duration of exposure of each of the components.

Some examples are given below on how to compute duration of exposure (cycle), planned/actual cumulative dose, PDI, DI and RDI in Table 2-6 and Table 2-7 for LAG525 and in Table 2-8 and Table 2-9 for carboplatin. For spartalizumab refer to LAG525 examples.

Table 2-4 Example 1 of LAG525 dose administration and exposure

Record number	Start/End Date	Dose Administered (mg)	Dose Stopped or Paused, Dose Interrupted?	Dose Permanently Discontinued	Reason
1	13Jun2018	400	No	No	
2	04Jul2018	400	No	No	
3	25Jul2018	400	No	No	
4	15Aug2018	0	Yes	No	AE

Duration of exposure (day) = (23Aug2018 = data cut-off date since LAG525 was not permanently discontinued) – (13Jun2018) + 1 = 72 days

Duration of exposure (cycle) for 72 days = 4 cycles (rounded from 3.4 cycles)

Planned cumulative dose (for 72 days, 4 cycles) = 1600 mg

Actual cumulative dose (for 72 days, 4 cycles) = 1200 mg

Dose intensity = (actual cumulative dose / duration of exposure in cycles) = 1200 mg / 4 cycles = 300 mg / cycle

Planned dose intensity = (planned cumulative dose / duration of exposure in cycle) = 1600 mg / 4 cycles = 400 mg / cycle

Relative dose intensity = (DI / PDI) x 100 = (300 mg/cycle) / (400 mg/cycle) x 100 = 75%

Table 2-5 Example 2 of LAG525 dose administration and exposure

Record number	Start/End Date	Dose Administered (mg)	Dose Stopped or Paused, Dose Interrupted?	Dose Permanently Discontinued	Reason
1	13Jun2018	400	No	No	
2	04Jul2018	400	No	No	
3	25Jul2018	400	No	No	
4	15Aug2018	0	Yes	Yes	AE / AE

Duration of exposure (days) = (25Jul2018 + 20 days since LAG525 was permanently discontinued) – (13Jun2018) + 1 = 63 days

Duration of exposure (cycle) for 63 days = 3 cycles

Planned cumulative dose (for 63 days, 3 cycles) = 1200 mg

Actual cumulative dose (for 63 days, 3 cycles) = 1200 mg

Dose intensity = (actual cumulative dose / duration of exposure in cycle) = 1200 mg / 3 cycles = 400 mg / cycle

Planned dose intensity = (planned cumulative dose / duration of exposure in cycle) = 1200 mg / 3 cycles = 400 mg / cycle

Relative dose intensity = (DI / PDI) x 100 = (400 mg/cycle) / (400 mg/cycle) x 100 = 100%

Table 2-6 Example 1 of carboplatin dose administration and exposure

Record number	Start/ End Date	Dose Prescribed (mg)	Dose Administered (mg)	Dose Prescribed (AUC)	Dose Administered (AUC)	Dose Permanently Discontinued
1	13Jun2018	800	800	6	6	No
2	04Jul2018	650	800	5	6	No
3	25Jul2018	650	650	5	5	No
4	15Aug2018	0	0	0	0	Yes

Duration of exposure (days) = (25Jul2018 + 20 days since carboplatin was permanently discontinued) – (13Jun2018) + 1 = 63 days

Duration of exposure (cycle) for 63 days = 3 cycles

Planned cumulative dose (for 63 days, 3 cycles) = 18 AUC

Actual cumulative dose (for 63 days, 3 cycles) = 17 AUC

Dose intensity = (actual cumulative dose / duration of exposure in cycle) = 17 AUC / 3 cycles = 5.7 AUC / cycle

Planned dose intensity = (planned cumulative dose / duration of exposure in cycle) = 18 AUC / 3 cycles = 6 AUC / cycle

Relative dose intensity = (DI / PDI) x 100 = (17 AUC/cycle) / (18 AUC/cycle) x 100 = 94.4%

Table 2-7 Example 2 of carboplatin dose administration and exposure

Record number	Start/ End Date	Dose Prescribed (mg)	Dose Administered (mg)	Dose Prescribed (AUC)	Dose Administered (AUC)	Dose Permanently Discontinued
1	13Jun2018	900	900	5.9	5.9	No
2	04Jul2018	900	900	5.9	5.9	No
3	25Jul2018	750	750	5	5	No
4	15Aug2018	0	0	0	0	Yes

Duration of exposure (days) = (25Jul2018 + 20 days since carboplatin was permanently discontinued) – (13Jun2018) + 1 = 63 days

Duration of exposure (cycle) for 63 days = 3 cycles

Planned cumulative dose (for 63 days, 3 cycles) = 5.9 x 3 AUC = 17.7 AUC, as dose prescribed is 900 mg, the planned dose is the planned dose prescribed (AUC)

Actual cumulative dose (for 63 days, 3 cycles) = 15.8 AUC

Dose intensity = (actual cumulative dose / duration of exposure in cycle) = 15.8 AUC / 3 cycles = 5.3 AUC / cycle

Planned dose intensity = (planned cumulative dose / duration of exposure in cycle) = 17.7 AUC / 3 cycles = 5.9 AUC / cycle

Relative dose intensity = (DI / PDI) x 100 = (15.8 AUC/cycle) / (17.7 AUC/cycle) x 100 = 89.3%

Dose reductions or interruptions

The number of subjects who have dose reductions, administration stopped/paused during infusion or interruptions, and the reasons, will be summarized separately for each of the study treatment components.

'Dose changed', 'Dose interrupted', "Was drug administration stopped or paused" fields from the 'Study treatment' eCRF pages for each study treatment component will be used to determine the dose reductions, dose interruptions and administration stopped /paused, respectively.

The corresponding fields 'Reason for change' and 'Reason for administration stopped or paused' will be used to summarize the reasons.

A dose change is either 'change in prescribed dose level' or 'dosing error' where actual dose administered is different from the prescribed dose.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption are entered on consecutive dose administrations with different reasons, separate interruptions will be counted. However, if the reason is the same in this mentioned multiple entries on consecutive dose administrations, then it will be counted as one interruption.

Reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level. Any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the eCRF, number of reductions will be derived programmatically based on the change and the direction of the change.

Note: No dose reductions are permitted for LAG525 or spartalizumab.

For carboplatin, it is considered as a reduction only if the difference between the previous prescribed dose in AUC and the current prescribed dose in AUC is greater than 15% of the previous prescribed dose in AUC.

Notes:

- A prescribed dose reduction lower than the previous prescribed dose, but where the administered dose is 0 mg or higher than the prescribed dose, will not be counted as a dose reduction: see records 10 and 11 in Table 2-10.
- A decrease in dose from the protocol planned starting dose or a decrease from the previous non-zero dose will be counted as a dose reduction even if this decrease has been directly preceded by an interruption: see record 8 in Table 2-10.

- If the dose decrease is followed by an interruption, with the dose resuming at the same level prior to the interruption, the second dose decrease or change in dosing frequency will not be counted as dose reduction: see record 6 in Table 2-10.
- If, due to a dosing error, a subject receives higher than protocol planned starting dose and moves down to the planned starting dose then this is not a dose reduction: see record 3 in Table 2-10. However if the change is directly from a higher than planned starting dose down to a lower than protocol planned starting dose, then this is a dose reduction.
- If, due to a dosing error, a subject receives lower than previous non-zero dose and resumes later at the protocol specified dose reduction, then lower dose received due to dosing error and protocol specified dose reduction are dose reductions.
- If, due to a dosing error, a subject receives lower than previous non-zero dose and resumes later at lower than previous non-zero dose, then 2 dose reductions will be counted.

Table 2-8 Examples of possible dose changes for carboplatin and dose reduction outcome

Record number	Prescribed dose (AUC)	Administered dose (AUC)	Counted as a dose reduction (Yes/No)	Comment
1	6	6	No	
2	6.5	6.5	No	Dose increased by error
3	6	6	No	Correcting dosing error
4	5	5	Yes	Prescribed dose reduction (e.g. due to AE)
5	0	0	No	Dose interruption
6	5	5	No	Resume previous dose
7	0	0	No	Dose interruption
8	5	4	No	Dosing error (not a prescribed dose reduction)
9	5	5	No	Correcting dosing error in row 8
10	4	0	No	Prescribed dose reduction (e.g. due to AE) but not administered due to dosing error
11	4	5	No	Prescribed dose reduction (e.g. due to AE) but not administered due to dosing error
12	4	4	Yes	Prescribed dose reduction (e.g. due to AE) and row 11 was not counted as a dose reduction (administered dose was 5 by error)

Treatment beyond RECIST progression

The number of subjects who continue treatment beyond RECIST1.1 progression according to local investigators assessment based on protocol specified criteria will be summarized. It includes all subjects who received any study treatment (i.e. at least one dose of LAG525, spartalizumab or carboplatin (including incomplete infusion)) after RECIST1.1 progression assessed by local investigators. Those subjects will be identified using the field "Will the subject continue treatment beyond disease progression as per RECIST1.1?" on the Verification for Treatment Beyond RECIST1.1 PD eCRF pages.

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of subjects who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery (excluding biopsy procedures) will be summarized by treatment arm. Prior anti-neoplastic medications will be summarized by therapy type (e.g. chemotherapy, hormonal therapy, etc.), setting (e.g. adjuvant, metastatic, etc.) and also by lowest ATC class, preferred term and treatment. Summaries will include total number of regimens, best response and time from last treatment to progression for the last therapy. The medication therapy type of any combination therapy will be classified based on the following order: immunotherapy, chemotherapy, biologic therapy (other than immunotherapy), targeted therapy, hormonal therapy. For example, a combination therapy of chemotherapy and biologic therapy will be classified as 'chemotherapy'. For radiotherapy, time since last radiotherapy, locations and setting of last therapy will be summarized. For prior surgery, time since last surgery, procedure and residual disease of last therapy will be summarized.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.

Anti-neoplastic medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHO-DD); Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and medications will be summarized by ATC class, preferred term, overall and by treatment group by means of frequency counts and percentages using FAS.

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a subject coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the WHO Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Concomitant non-drug therapies/procedures will be coded using MedDRA and summarized by SOC and preferred term. Concomitant medications with immunosuppressive intent (agents to treat suspected irAEs) will be summarized by lowest ATC class and preferred term using frequency counts and percentages. Concomitant medications with immunosuppressive intent will be programmatically flagged using a pre-specified list from the clinical team.

All concomitant systemic corticosteroids will be summarized by lowest ATC class and preferred term using frequency counts and percentages. Additionally, the cumulative number of days while on study treatment that a subject took any systemic corticosteroid will be summarized. Systemic corticosteroids) will be programmatically flagged using a pre-specified list from the clinical team.

All summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

Additional summaries will be provided to report medications starting between 31 days after last dose of study treatment and up to 150 days after last administration of LAG525/spartalizumab.

All reported concomitant therapies will be listed. Any concomitant therapies starting more than 150 days after the last dose of LAG525 or spartalizumab, or 30 days after last dose of study treatment whichever comes last, will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

2.5 Analysis of the primary objective

The primary objective is to to assess the antitumor activity of the three treatment arms LAG525 + spartalizumab, LAG525 + spartalizumab + carboplatin and LAG525 + carboplatin, in subjects with advanced TNBC in first or second line of therapy, as measured by the objective response rate (ORR) per investigator's assessment according to RECIST v1.1.

2.5.1 Primary endpoint

The primary endpoint of the study is ORR defined as the proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST 1.1 (see Appendix 3 of the study protocol). ORR will be calculated based on the FAS using local investigators review of tumor assessment data. Tumor assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) will be considered in the assessment of BOR. Treatment with bisphosphonates or denosumab for pre-existing painful bone metastases and limited-field palliative radiotherapy is permitted as per protocol, and will not be considered as new antineoplastic therapy.

BOR is defined as the best response recorded from the randomization date until disease progression as per RECIST 1.1. Complete and partial responses must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

The BOR for each subject is determined from the sequence of overall (lesion) responses according to the following rules:

CR = at least two determinations of CR at least 4 weeks apart before progression

PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR)

SD = at least one SD assessment (or better) > 5 weeks after randomization (and not qualifying for CR or PR).

PD = progression ≤ 13 weeks after randomization (and not qualifying for CR, PR or SD).

UNK = all other cases (i.e., not qualifying for confirmed CR or PR and without SD after more than 5 weeks or early progression within the first 13 weeks)

2.5.2 Statistical hypothesis, model, and method of analysis

The primary objective of the study is to assess the anti-tumor activity of the three treatment arms LAG525 + spartalizumab, LAG525 + spartalizumab + carboplatin and LAG525 + carboplatin, in subjects with advanced TNBC in first or second line of therapy, as measured by ORR per investigator's assessment according to RECIST v1.1. ORR based on RECIST1.1 will be calculated based on the FAS and according to the treatment group assigned at randomization following the Intent-To-Treat (ITT) principle.

In a randomized phase III study of carboplatin compared to docetaxel for subjects with metastatic or recurrent locally advanced triple negative breast cancer or *BRCA1/2* breast cancer, including 188 subjects randomized to carboplatin, the ORR with carboplatin in first line was 31.4% [Tutt et al 2014]. In the phase II clinical trial of platinum monotherapy in metastatic TNBC, with 86 subjects treated by carboplatin or cisplatin in first (69 subjects) or second line (17 subjects) the ORR was 25.6%. Specifically in second line, the ORR with cisplatin alone (9 subjects) was 22.2% and no subject responded in second line out of the 8 subjects treated by carboplatin [Isakoff et al 2015]. Based on cisplatin response rate in second line and considering that differences in population treated by the two drugs may explain the lower response rate observed with carboplatin, the ORR with carboplatin in second line is assumed around 20%.

Hence, based on those published results and assuming a similar proportion of subjects enrolled in first line and second line of therapy, the response rate with single agent carboplatin in subjects with advanced TNBC in 1st and 2nd line overall is expected to be 25%. A 10% absolute improvement in the response rate to 35% is considered a minimum clinically meaningful improvement in this study population. Therefore, proof of preliminary efficacy in each treatment group will be declared if both of the following conditions are met:

- the mean of the posterior distribution of ORR is at least 35%

and

- the posterior probability that the ORR is ≥ 25% is at least 0.9

The posterior distribution of ORR will be derived from the prior distribution and all available data from the subjects included in the FAS. A minimally informative unimodal Beta prior [Neuenschwander et al 2008] will be used for ORR in each arm (see Appendix 2 of study protocol for further details). All available data from the subjects included in the FAS will be used to derive posterior distribution of ORR by treatment arm.

The study will be positive if the proof of preliminary efficacy is declared for any treatment group.

ORR will be summarized using descriptive statistics (N, %) by treatment group along with the two-sided exact binomial 95% confidence interval [Clopper and Pearson 1934].

2.5.3 Handling of missing values/censoring/discontinuations

Subjects with unknown or missing BOR as per RECIST 1.1 will be counted as failures. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the best overall response must be "Unknown" unless progression is reported. If a complete response is not confirmed, the best overall response must be "Unknown" unless it occurs after the first 5 weeks (stable disease), or confirmed partial response or progression is reported. If a partial response is not confirmed, the best overall response must be "Unknown" unless it occurs after the first 5 weeks (stable disease) or progression is reported. For the computation of ORR, these subjects with unknown BOR will be included in the FAS and will be counted as 'failures'.

Only tumor assessments performed on or before the start of a new antineoplastic treatment other than study drug(s) (not considering palliative radiotherapy) will be considered in the assessment of BOR.

2.5.4 Supportive analyses

A sensitivity analysis considering subjects with unconfirmed PR or CR as responders may be performed if large delayed treatment effect is observed (i.e. with PR or CR at the last assessment prior to the cut-off date and ongoing in efficacy follow-up).

Timing of all tumor assessments will be depicted graphically for investigators' review of tumor assessments and displayed by treatment arm.

Subgroup analysis for ORR

The primary endpoint of ORR will be summarized using descriptive statistics (N, %) for the subgroups specified in Section 2.2.1 based on the primary analysis source (i.e., investigator assessment) and the same conventions as for the primary analysis.

[redacted]

Reasons for "Unknown" BOR

Subjects with 'unknown' BOR will be summarized by reason for having unknown status. The following reasons will be used:

- No valid post-baseline assessment

- All post-baseline assessments have overall lesion response UNK
- New anti-neoplastic therapy started before first post-baseline assessment
- SD too early
- PD too late

Note 1: A SD is considered as "SD too early" if the SD is documented within first 5 weeks after randomization date (i.e. until Day 35 included).

Note 2: A PD is considered as "PD too late" if the first documentation of PD is recorded more than 13 weeks after randomization date (.i.e. from Day 92 included) with no qualifying CR, PR or SD in between.

Note 3: Special (and rare) cases where BOR is "unknown" due to both too early SD and too late PD will be classified as "SD too early".

Waterfall plot to depict anti-tumor activity

Waterfall graphs will be used to depict the anti-tumor activity. These plots will display the best percentage change from baseline in the sum of diameters of all target lesions for each subject. Only subjects with measurable disease at baseline will be included in the waterfall graphs. Special consideration is needed for assessments where the target lesion response is CR, PR or SD, but the appearance of a new lesion or a worsening of non-target lesions results in an overall lesion response of PD. As a conservative approach, such assessments will not be considered for display as bars in the graph, since the percentage change in the sum of diameters of target lesions reflects the non-PD target lesion response, but the overall lesion response is PD. A subject with only such assessments will be represented by a special symbol (e.g. ✶) in the waterfall graph. Assessments with "unknown" target lesion response and assessments with unknown overall response will be excluded from the waterfall plots. Subjects without any valid assessments will be completely excluded from the graphs.

The total number of subjects displayed in the graph will be shown and this number will be used as the denominator for calculating the percentages of subjects with tumor shrinkage and tumor growth. Footnote will explain the reason for excluding some subjects (due to absence of any valid assessment).

All possible assessment scenarios are described in Table 2-11.

Table 2-9 Inclusion/exclusion of assessments used in waterfall graph

	Criteria for inclusion/exclusion			Possible sources of contradictions	
case	Target response	Overall lesion response	Include in waterfall?	Non-target response	New lesion?
1	CR/PR/SD	PD	Yes but as ✶ only	PD	any
2	CR/PR/SD	PD	Yes but as ✶ only	any	Yes
3	UNK	UNK or PD	No	any	any
4	CR/PR/SD	UNK	No	UNK	No
5	CR/PR/SD	CR/PR/SD	Yes as a bar	SD/IR	No
6	PD	PD	Yes as a bar	any	any

Percentage change from baseline in the sum of diameters of all target lesions over the time will be displayed for individual subjects.

2.6 Analysis of the key secondary objective

Not applicable

2.7 Analysis of secondary efficacy objective(s)

The secondary efficacy objectives are:

- To assess the efficacy of the three treatment arms with respect to Duration of response (DOR), Time to response (TTR), Progression Free Survival (PFS) and Clinical benefit rate (CBR) per investigator's assessment according to RECIST v1.1
- To assess Overall Survival for each treatment arm

2.7.1 Secondary endpoints

Duration of response (DOR)

Duration of response only applies to subjects whose best overall response is complete response (CR) or partial response (PR) according to RECIST 1.1 based on local investigators' review of tumor assessment data. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to underlying cancer. Subjects continuing without progression or death due to underlying cancer will be censored at the date of their last adequate tumor assessment using the censoring rule described for PFS analysis (see Section 2.7.3).

Time to response (TTR)

Time to response (CR or PR) is the time from date of randomization to first documented response of CR or PR (which must be confirmed subsequently using local investigators' review of tumor assessment data and according to RECIST 1.1). The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed).

All subjects in the FAS will be included in the time to response calculation. Subjects who did not achieve a confirmed PR or CR will be censored at:

- the maximum follow-up time (i.e. FSFV - LSLV used for the analysis) for subjects who had a PFS event (i.e. either progressed or died due to any cause);
- the last adequate tumor assessment date for all other subjects.

Progression-Free Survival (PFS)

PFS is defined as time from date of randomization to the date of event defined as the first documented progression or death due to any cause. PFS will be assessed via local review of tumor assessments according to RECIST 1.1 (see Appendix 3 of study protocol for further details). The analysis will be based on FAS and will include all data observed up-to the cut-off

date. PFS will be censored at the date of the last adequate tumor assessment if no PFS event is observed prior to the analysis cut-off date or before the start of the new anticancer therapy date, whichever is earlier (see Section 2.7.3 for additional details regarding censoring rules and determination of date of last adequate tumor assessment).

Discontinuation due to disease progression (collected on the 'Treatment disposition' and 'Post treatment follow up disposition' eCRF pages) without supporting objective evidence satisfying progression criteria per RECIST 1.1 will not be considered disease progression for PFS derivation. Clinical deterioration will not be considered as a qualifying event for progression.

Clinical benefit rate (CBR)

CBR is defined as the proportion of subjects with a best overall response (BOR) of confirmed CR or PR, or SD lasting 24 weeks or longer, according to RECIST 1.1 criteria. A subject will be considered to have SD for 24 weeks or longer if a SD response is recorded at (24-1) weeks or later from randomization, allowing for the ±1 week visit window for tumor assessments. CBR will be calculated using the FAS based on the investigators' tumor assessments.

Overall Survival (OS)

Overall Survival is defined as the time from date of randomization to date of death due to any cause. All deaths occurring on or before the cut-off date in the FAS will be used in the OS analysis. If a subject is not known to have died, then OS will be censored at the latest date the subject was known to be alive (on or before the cut-off date).

2.7.2 Statistical hypothesis, model, and method of analysis

Duration of response

DOR based on RECIST 1.1 will be listed and summarized by treatment group for all subjects in the FAS with confirmed BOR of CR or PR. DoR will be analyzed in the FAS population according to the treatment groups assigned at randomization. The DoR distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians [Brookmeyer and Crowley 1982] will be presented for each treatment group only if a sufficient number of responses is observed. DoR will also be summarized for the subgroups specified in Section 2.2.1.

Time to response

TTR will be listed and summarized by treatment group. TTR will be analyzed in the FAS population according to the treatment groups assigned at randomization. The TTR distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians [Brookmeyer and Crowley 1982] will be presented for each treatment group only if a sufficient number of responses is observed. A responders-only analysis will also be performed in this case.

Progression-Free Survival

PFS will be analyzed in the FAS population according to the treatment group assigned at randomization and including all data observed up to the cut-off date. The survival distribution

of PFS will be estimated using the Kaplan-Meier method. The results will be plotted graphically by treatment arm using Kaplan-Meier curves. The medians of PFS and 95% confidence intervals of the medians [Brookmeyer and Crowley 1982], along with the proportion of subjects event-free at 3, 6, 12 and 18 months and the associated 95% confidence intervals, will be presented for each treatment group.

Censoring pattern of PFS

Number of subjects with a PFS event and number of subects censored for the PFS analysis will be summarized. In addition, a summary of reasons for PFS censoring will be provided by treatment arm based on the following reasons:

1: Ongoing without event
2: Lost to follow-up
3: Withdrew consent
4: Adequate assessment no longer available
5: Initiation of new cancer therapy prior to progression
6: Event after >=2 missing tumor assessments

The PFS censoring reasons are defined in the following way.

If the time interval between the last adequate tumor assessment (TA) date and the earliest of the following dates is smaller or equal to interval of 2 missing tumor assessments:

1. Analysis cut-off date,
2. Start date of further anti-neoplastic therapy,
3. Date of consent withdrawal,
4. Visit date of study treatment discontinuation or end of post-treatment follow-up discontinuation due to lost to follow-up.

Then the PFS censoring reason will be:

1. ‘Ongoing’,
2. ‘New cancer therapy added’,
3. ‘Withdrew consent’,
4. ‘Lost to follow-up’,

If the time interval is larger than the interval of 2 missing tumor assessments with no event observed. then the PFS censoring reason will always default to ‘Adequate assessment no longer available’. If the time interval between the last adequate tumor assessment date and the PFS event date is larger than the interval of 2 missing tumor assessments then the subect will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments'.

These summaries on censoring reasons will be produced for PFS by investigators’ assessment. The censoring patterns will be compared between treatment arms.

As a supportive analysis, the same type of analysis will be done for PFS, without censoring the data of tumor assessments after the start a the new anticancer therapy.

Clinical benefit rate

CBR based on RECIST 1.1 will be calculated based on the FAS and according to the ITT principle. CBR and its two-sided exact binomial 95% confidence interval [Clopper and Pearson 1934] will be presented by treatment group.

Overall Survival

OS will be analyzed in the FAS population according to the treatment group assigned at randomization and including all data observed up to the cut-off date. The survival distribution of OS will be estimated using the Kaplan-Meier method. The medians of OS and 95% confidence intervals of the medians [Brookmeyer and Crowley 1982], along with the proportion of subjects alive at 3, 6, 12 and 18 months and the associated 95% confidence intervals, will be presented for each treatment group.

Censoring pattern of OS

The pattern of censored data will be examined between the treatment arms: reasons for censoring ('Alive' or 'Lost to follow-up') and death cause will be summarized by treatment arm. In addition, survival status, reason for censoring and death cause will be listed. Subjects not known to have died will be censored for 'Lost to follow-up' if the time between their last contact date and the analysis cut-off date is longer than the protocol specified interval between the survival follow-up assessments plus 2 weeks, i.e., 15 weeks for this study.

Duration of follow-up for PFS/OS

Study follow-up will be summarized using the following methods: summary of duration between randomization and cut-off date, and follow-up times for PFS/OS, which are defined as follows:

- Duration between randomization and data cut-off date = (Cut-off date – Date of randomization + 1) / 30.4375 (months). This item will be summarized overall.
- Follow-up time = (Date of event or censoring – Date of randomization + 1) / 30.4375 (months) regardless of censoring. Date of censoring is defined as the last adequate tumor assessment date for PFS or last contact date for OS. This item will be summarized by treatment arm.

All summaries will be reported in months. Date of censoring is the same as defined for the PFS and OS analysis.

In addition, median time to censoring will be computed by reversing censoring variable and performing Kaplan-Meier analysis.

2.7.3 Handling of missing values/censoring/discontinuations

PFS and DOR will be censored at the date of the last adequate tumor assessment if no PFS event is observed prior to the analysis cut-off date or before the start of the new anticancer therapy date, whichever is earlier.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment will be used. If no post-baseline assessments

are available (before an event or a censoring reason occurred) then the date of randomization will be used.

In particular, PFS and DOR will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after a new anticancer therapy is administered; the event occurred after two or more missing tumor assessments. The term "missing adequate tumor assessment" is defined as a TA not performed or tumor assessment with overall lesion response of "UNK". The rule to determine number of missing TAs is based on the time interval between the date of last adequate tumor assessment and the date of an event. If the interval is greater than twice the protocol-specified interval between the TAs and 2 times the protocol-allowed time window around assessments, then the number of missing assessments will be 2 or more.

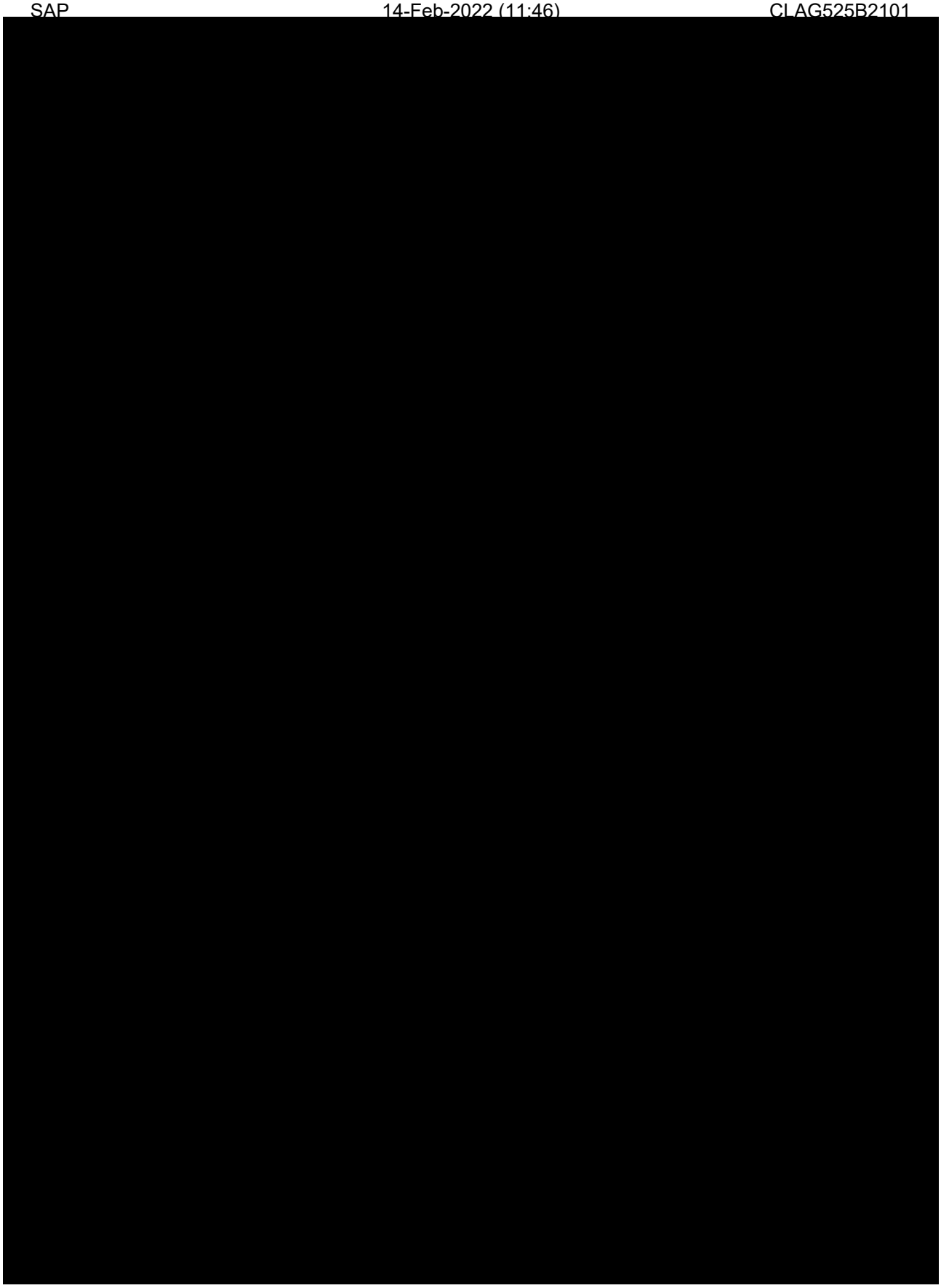
Refer to Table 2-12 for censoring and event date options and outcomes for PFS and DOR.

Table 2-10 Outcome and event/censor dates for PFS/DOR analysis

Situation	Date	Outcome
No baseline assessment	Date of randomization	Censored
Progression or death at or before next scheduled assessment	Date of progression (or death)	Progressed
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	Date of last adequate assessment	Censored
New anticancer therapy given prior to protocol defined progression	Date of last adequate assessment on or prior to starting new anti-cancer therapy	Censored
Death before first PD assessment	Date of death	Progressed

For Overall Survival, if a subject is not known to have died at the time of analysis cut-off, then OS will be censored at the date of last known date subject was alive, i.e., last contact date (see Section 2.1).

[redacted]



2.9 Safety analyses

All safety analyses will be based on the safety set.

2.9.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on treatment period. Additional summaries will be displayed to report all AEs, AEs related to study treatment, all SAEs and SAEs related to study treatment collected up to 150 days after last administration of LAG525/spartalizumab or up to 30 days after the last dose of carboplatin whichever comes last. All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject 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 the LAG525 + PDR001 + carboplatin arm, then on their frequency in the LAG525 + PDR001 arm and LAG525 + carboplatin arm.

The following adverse event summaries will be produced by treatment arm: overview of adverse events (number and % of subjects with any AE, treatment-related AE, SAE, treatment-related SAE, fatal SAE, treatment-related fatal SAE, AE leading to discontinuation, treatment-related AE leading to discontinuation, AE leading to dose adjustment/interruption, AE requring additional therapy), 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 adjustment/interruption, requiring additional therapy, requiring immunosuppressive medication, requiring systemic corticosteroid (> 10 mg of prednisone or equivalent), and leading to fatal outcome. Concomitant medications with immunosuppressive intent and systemic corticosteroids (>10 mg of prednisone or equivalent) will be programmatically flagged using a pre-specified list from the clinical team.

In addition, a summary of serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term). For the legal requirements of ClinicalTrials.gov and EudraCT at the time of the CSR for the final analysis, two required tables on on-treatment adverse events which are not serious adverse events with an incidence greater than 5% and on-treatment serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same subject, 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 / treatment-related SAE / non SAE has to be checked in a block e.g., among AEs 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 treatment-related SAEs and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.9.1.1 Adverse events of special interest / grouping of AEs

Adverse Events of Special Interest (AESI) consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical or safety interest in connection with the study compound. All definitions of AESI for LAG525 and spartalizumab will be stored in their respective Case Retrieval Strategy (CRS) sheet with clear versioning and reference to the MedDRA version used. If a CRS update is necessary, the final version needs to be available in a reasonable time ahead of the DBL. The CRS version will be included as a footnote of the AESI tables.

Data analysis of AESIs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound LAG525 or spartalizumab. 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.

AESI for LAG525 will be based on the most recent version of the dSPP and CRS for LAG525.

Based on the current version of the dSPP and spartalizumab CRS, AESI for spartalizumab are:

- Endocrinopathies
- Pneumonitis
- Colitis
- Hepatitis
- Nephritis
- Encephalitis
- Rash
- Infusion reaction
- Other immune disorders

For each specified AESI, number and percentage of subjects with at least one event of the AESI occurring during on treatment period will be summarized.

Summaries of these AESIs will be provided by treatment arm, (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death, requiring immunosuppressive medication etc.). If sufficient number of events occurred, analysis of time to first occurrence will be applied.

Additional summaries will be provided to report all AESIs, AESIs related to study treatment, all serious AESIs and serious AESIs related to study treatment collected during the on-treatment period and up to 150 days after last administration of LAG525/spartalizumab or up to 30 days after the last dose of carboplatin whichever comes last.

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

Time to first occurrence of AESIs

Time to first occurrence of an AESI is defined as time from start of study treatment to the date of first occurrence of first event within an AESI, i.e. time in days is calculated as (start date of first occurrence of event) – (start of study treatment) +1.

In the absence of an event during the on-treatment period, the censoring date applied will be **the earliest** of the following dates:

- death date
- new anticancer antineoplastic therapy start date (not considering palliative radiotherapy),
- end date of on-treatment period
- data cut-off date
- withdrawal of informed consent date.

The corresponding censoring reason will be used: death, new anti cancer therapy, treatment discontinuation, ongoing at cut-off date or consent withdrawal.

The following AESIs will be considered for time to first occurence analysis: Endocrinopathies, Colitis and Rash.

Failure curves (ascending Kaplan-Meier curves) will be constructed by treatment arm. Median together with 95% confidence interval as well as 25th percentile and 75th percentile will be presented for each treatment arm.

In addition, the median time to occurrence for the subset of subjects who experienced the event of interest will be calculated. Simple descriptive statistics, median, min and max as well as 25th percentile and 75th percentile, will be presented.

2.9.2 Deaths

Separate summaries for on-treatment and all deaths (including post-treatment death) will be produced by treatment arm, system organ class and preferred term. Additional summary will be displayed to report all deaths up to 150 days after last administration of LAG525/spartalizumab or up to 30 days after the last dose of carboplatin whichever comes last.

All deaths will be listed, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

2.9.3 Laboratory data

Laboratory data from all sources (central and local laboratories) 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 2.1.1).

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTC grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTC grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities

Magnesium data from Q2 lab analyzed between 05-Jun-2018 and 09-Jul-2018 and between 22-Nov-2018 and 02-Jan-2019 were excluded because the vendor (Q2 Solutions) identified an issue with serum magnesium (Mg) test results that were analyzed during these two time period. A carryover effect from assays run prior to the Mg tests on those days resulted in an increase of measured Mg test results. Hence, the Mg test results reported during these times may have been inaccurately increased and therefore should be considered as unreliable.

For the biochemistry data, two versions of the tables will be produced. One version will include all data and another version will exlude unreliable magnesium data.

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP). The number (%) of subjects with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized:

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN (potential Hy's law)

Potential Hy's Law events are defined as those subjects with concurrent occurrence of AST or ALT > 3xULN and TBL > 2xULN and ALP < 2xULN in the same assessment sample during the on-treatment period. Further medical review has to be conducted to assess potential confounding factor such as, liver metastates, liver function at baseline etc.

A figure displaying time course of hepatic function tests (ALT, AST, TBL, ALP) in subjects with potential Hy's law will be displayed in the Safety Set. Additonally, evaluation of drug-induced serious hepatotoxicity (eDISH) plots will be produced to display ALT and AST values by TBL values in units of ULN.

2.9.4 Other safety data

2.9.4.1 ECG and cardiac imaging data

At scheduled visits, triplicate 12-lead ECG's will be performed. ECG machines will automatically calculate heart rate and measures of PR, QRS, QT, and QTcF intervals. ECG data will be read and interpreted centrally.

Unscheduled safety ECG's may be performed at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECG's with clinically significant findings should be collected in triplicate.

Clinically significant abnormalities observed from single 12-lead ECGs collected at the study site are not part of the data analysis described below, but must be reported as adverse events.

ECHO/MUGAs will be performed to assess cardiac ejection fraction. The same procedure (either ECHO or MUGA) should be performed at baseline, follow-up visits if clinically indicated, and at EOT. All ECHO/MUGA assessments will be read and interpreted locally.

Data handling

In case the study requires ECG replicates at any assessment, the average of the ECG parameters at that assessment should be used in the analyses.

Data analysis

The number and percentage of subjects with notable ECG values will be presented by treatment arm.

- QT, QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

A listing of all ECG assessments will be produced by treatment arm and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

For left ventricular ejection fraction (LVEF), a shift table using CTC grades for 'Ejection fraction - decrease' as defined per CTCAE version 5.0 to compare baseline to the worst on-treatment value will be provided:

CTCAE	**0**	**1**	**2**	**3**	**4**

Ejection fraction - decrease	-	-	Resting ejection fraction (EF) 50 - 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; ≥20% drop from baseline	Resting ejection fraction (EF) <20%

2.9.4.2 Vital signs

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

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-13 below.

Table 2-11 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	below normal value
Weight (kg)	increase > 10% from Baseline	decrease > 10% from Baseline
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%

The number and percentage of subjects with notable vital sign values (high/low) will be presented by treatment arm. Descriptive statistics will be tabulated for baseline, at each post-baseline time point and changes from baseline at each post-baseline time point for each vital sign measure. Figures of change from baseline in systolic and diastolic blood pressure values over time will be displayed via boxplots based on time windows.

A listing of all vital sign assessments will be produced by treatment arm and notable values will be flagged. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.9.4.3 ECOG performance status

The ECOG PS scale (Table 2-14 will be used to assess physical health of subjects, ranging from 0 (most active) to 5 (least active):

Table 2-12 ECOG Performance Scale

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

Frequency counts and percentages of subjects in each score category will be provided by treatment arm and time point in subjects of the safety set.

2.10 Pharmacokinetic endpoints

The secondary objective for PK is to to characterize the PK of LAG525, spartalizumab, and carboplatin in the three investigated combinations.

PK parameters

The PK parameters which may be calculated using the PK sampling in cycle 1 and cycle 3, as appropriate, are shown in Table 2-15 The PK parameters are derived based on the non-compartmental methods using Phoenix WinNonlin® software version 6.4.

Table 2-13 Non-compartmental PK parameters for LAG525, spartalizumab and carboplatin

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUC0-t	AUC0-t is the area under the plasma (or serum or blood) concentration-time curve to a defined point in time. For LAG525/spartalizumab AUC0-t = AUC0-504h and for carboplatin AUC0-t = AUC0-3h (amount x time x volume-1)
Cmin or Ctrough	The minimum observed plasma or serum drug concentration (mass x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
Race	Accumulation ratio calculated as AUC0-t on Cycle 3 / AUC0-t on Cycle 1

Descriptive statistics (n, arithmetic mean, CV% mean, standard deviation (SD), median, geometric mean, CV% geo-mean, minimum and maximum) will be presented by treatment for Pharmacokinetic analysis set for all PK parameters defined in Table 2-15 except Tmax, where only n, median, minimum and maximum will be presented.

All individual PK parameters will be listed by treatment using the Safety set.

PK concentrations

Descriptive statistics (n, m (number of non-zero concentrations), arithmetic mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) for LAG525, spartalizumab and carboplatin concentration will be presented at each scheduled time point by treatment for the Pharmacokinetic analysis set.

Individual concentration-time profiles for LAG525, spartalizumab and carboplatin concentrations with median will be displayed graphically by treatment for Safety set on the semi-log view. In addition, the mean (+/- SD) and geometric mean concentration-time profiles for LAG525, spartalizumab and carboplatin by treatment over time will be displayed graphically for Pharmacokinetic analysis set on the linear and semi-log view.

All individual plasma concentration data for LAG525, spartalizumab and carboplatin will be listed by treatment for the Safety set.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ) (< 0.25 µg/mL for spartalizumab, <5 µg/mL for LAG525, < 1 ng/mL for carboplatin ultrafiltrate and < 100 ng/mL for carboplatin plasma) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK data will not be imputed and will be treated as missing.

2.11 PD and PK/PD analyses

The secondary PD objective is to assess immunogenicity of LAG525 and spartalizumab in the three investigated combinations.

[redacted]

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 and are further characterized in the neutralization assay to indicate the presence of neutralizing antibodies (NAb). 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 and respective drug (i.e. LAG525 or spartalizumab) 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) and ADA-positive NAb samples, both overall and by time point (including baseline). For summaries by time point, the denominator is the number of subjects 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 Subject ADA status

Subect ADA status will be defined for both investiganional drugs LAG525 and spartalizumab, based on their respective sample ADA status and respective PK concentrations. Any IG sample collected after 150 days of the last dose of the respective drug (i.e. LAG525 or spartalizumab) will not be used for summaries or derivations and will only be included in the listing.

Subject ADA status is defined as follows:

- *Treatment-induced ADA-positive subject*: subject with ADA-negative sample at baseline and at least one treatment-induced ADA-positive sample.
- *Treatment-boosted ADA-positive subject*: subject with ADA-positive sample at baseline and at least one treatment-boosted ADA-positive sample.
- *Treatment-unaffected ADA-positive subject*: subject 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 subject*: subject with ADA-positive sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.
- *ADA-negative subject*: subject with ADA-negative sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.
- *Inconclusive subject*: subject who does not qualify as treatment-induced ADA-positive, treatment-boosted ADA-positive, treatment-unaffected ADA-positive, treatment-reduced ADA-positive, or ADA-negative.

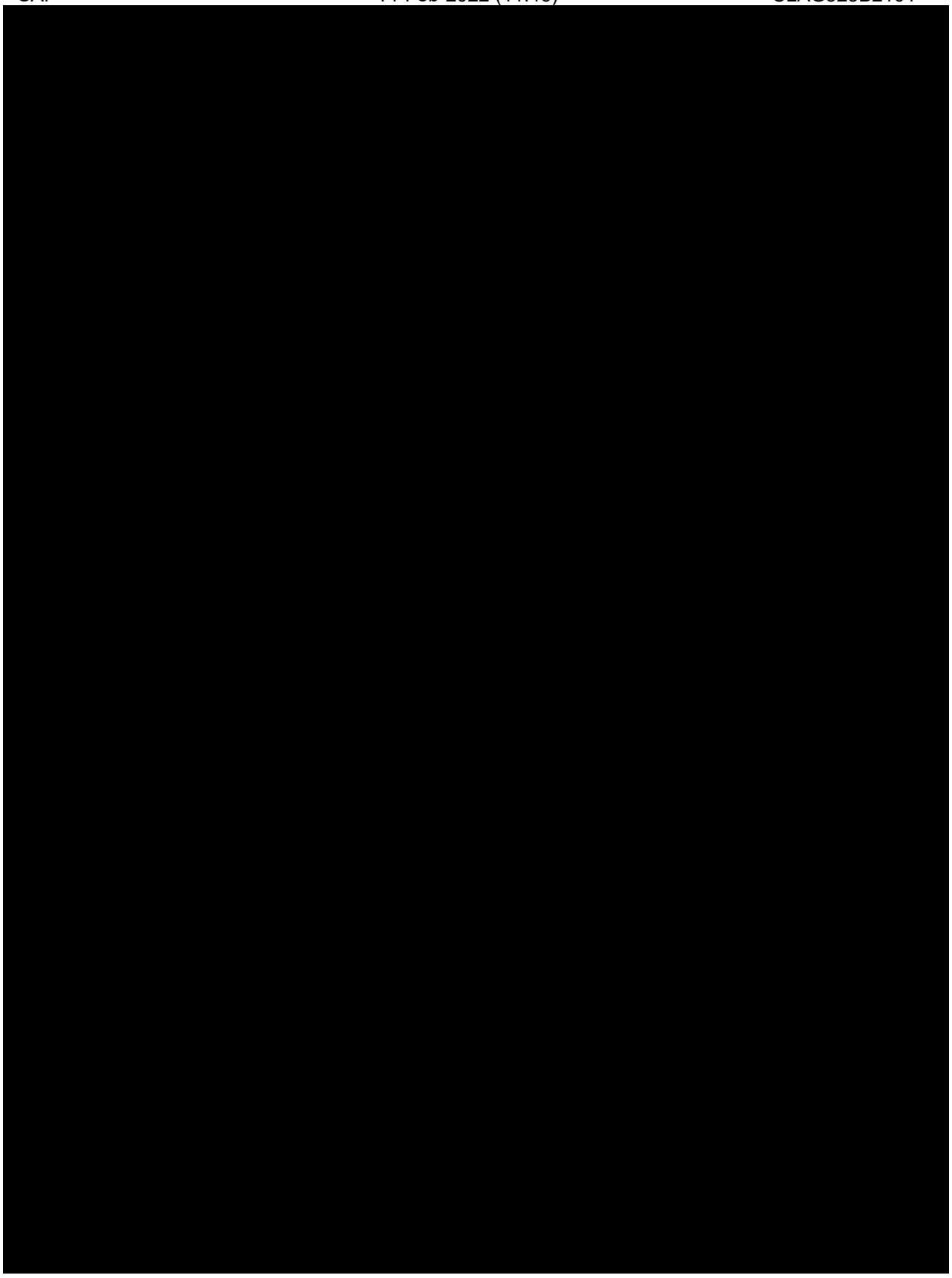
The following summaries of ADA subject status (n and %) will be provided using *Immunogenicity incidence set*:

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

Listings will be provided of subject ADA status.

2.12 Patient-reported outcomes

Not applicable.



2.15 Interim analysis

No formal interim analysis is planned for this trial. The primary analysis of the study data will be reported in the primary CSR based on all subjects' data up to the time when all subjects have been followed for efficacy (tumor assessments) for at least 24 weeks or discontinued tumor assessments for any reason prior to 24 weeks. Any additional data (e.g., DoR, OS, safety) for subjects continuing to receive study treatment past the data cut-off date for the primary CSR, as allowed by the protocol, will be reported in the final analysis on completion of the study.

3 Sample size calculation

3.1 Primary analysis

The sample size calculation is based on the primary variable ORR considering the statistical model, hypothesis and method of analysis detailed in Section 2.5. Proof of preliminary efficacy (PPE) for each drug combination (study arm) will be declared if both of the following conditions are met:

- the mean of the posterior distribution of ORR is at least 35%

and

- the posterior probability that the ORR is ≥ 25% is at least 0.9

Approximately 32 subjects will be enrolled in each arm for a total of approximately 96 subjects. In a given arm of 32 subjects, the type-I error rate is 8% while the probability of declaring proof of preliminary efficacy (PPE) is at least 80% for ORR ≥ 45% (Table 3-1).

Table 3-1 Operating characteristics with 32 subjects in each arm

True ORR	Probability of declaring PPE in each arm (12 or more responders)	Probability of missing PPE (11 or less responders) in each arm
25 %	0.079	0.921
30 %	0.228	0.772
35 %	0.448	0.552
40%	0.675	0.325
45 %	0.847	0.153

3.2 Power for analysis of key secondary variables

Not applicable.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of the dose end date for a given study treatment component:

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the subject is considered as on-going:

The subject should be treated as on-going and the cut-off date should be used as the dose end date.

Note: Scenario 1 should not be applicable for final CSR. All subjects should have EOT page complete before the Database lock for Final CSR

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Subjects with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

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

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period* After imputation, compare the imputed end date with the start date of that specific record: if imputed end date before start date then impute to start date
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period* (if same year as partial end date)

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period* (if same month and year as partial end date)

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent 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, 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) if the overall response at that assessment is CR/PR/SD/UNK. 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 a previous and following assessment is 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.

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Note: The latest available MedDRA version at the time of the analyses should be used. The MedDRA version used should be specified in the footnote of relevant tables.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

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).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 5.0 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAEv5.0, 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 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Table 5-3 CTC grades for laboratory values in Novartis Oncology (based on CTCAE v5.0 – Nov 2017)

				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 ↓	10^9/L	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	< 1.0 x 10^9/L
WBC (Leukocytosis)	10^9/L	WBC			-	-	> 100 x 10^9/L	-
Hemoglobin (Anemia)	g/L	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	< 100 - 80 g/L < 6.2 - 4.9 mmol/L	< 80 g/L < 4.9 mmol/L	-
Hemoglobin ↑	g/L	HGB			Increase >0-20 g/L above ULN	Increase >20-40 g/L above ULN	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 ↓	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↓	10^9/L	LYM		≥1.5x10^9/L	< 1.5 - 0.8 x 10^9/L	< 0.8 - 0.5 x 10^9/L	< 0.5 - 0.2 x 10^9/L	< 0.2 x 10^9/L
Lymphocytes ↑	10^9/L	LYM			-	> 4 - 20 x 10^9/L	> 20 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 ↑	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↑	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 (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 (Hyperuricemia)	umol/L	URATE	**150 - 470 umol/L** or 2.5 – 8 mg/dL *(59.48 x mg/dL = umol/L)*	Defined by clinical criteria only in CTCAE V5				

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

				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 (Hypophosphatemia)	mmol/L	PHOS	**0.97 – 1.45 mmol/L** or 3.0 - 4.5 mg/dL *(0.32 x mg/dL = mmol/L)*	Defined by clinical criteria only in CTCAE V5				
Calcium (corrected) (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) (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 (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 (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) (Hyperglycemia)	mmol/L	GLUCSN	**<7.8 mmol/L** or <140 mg/dL *(0.05551 x mg/dL = mmol/L)*	Defined by clinical criteria only in CTCAE V5				
Glucose (fasting) (Hyperglycemia)	mmol/L	GLUCSF	**3.9 – 5.8 mmol/L** or 70 - 105 mg/dL *(0.05551 x mg/dL = mmol/L)*					
Glucose (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 (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 (Hypokalemia)	mmol/L	K		≥ LLN	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Sodium (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 (Hyponatremia)	mmol/L	SODIUM		≥ LLN	< LLN - 130 mmol/L	< 129 - 125 mmol/L	< 124 - 120 mmol/L	< 120 mmol/L
Triglyceride ↑	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↑	1	INR	**0.8 – 1.2**	≤ 1.2	> 1.2- 1.5	> 1.5- 2.5	> 2.5	-
Activated partial thromboplastin time↑	sec	APTT	**25 - 35 sec**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Fibrinogen ↓	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.
Clinical criteria such as 'asymptomatic' or 'Life-threatening consequences' are not considered for determination of LAB CTC grades. Concomitant usage of therapy is also not considered.
Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, ≥ 1.5 x 109 /L (lymphocytes) and ≥ 2 x 109 /L (neutrophils) are considered as LAB CTC grade 0
The comparison with baseline is not considered for derivation of LAB CTC grades

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

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)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, 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 will be assigned as described above for grading.

5.4 Statistical models

5.4.1 Primary analysis

Analysis of Binary Data

Dual-criterion based Proof of Concept designs

The two criteria to assess the proof of preliminary efficacy (PPE) in each treatment group are thus:

- Clinical relevance: posterior mean ≥ 35%
- Bayesian statistical significance: pr(ORR ≥ 25% | data) ≥ 0.90

Let p_i denote the ORR for treatment group i and which follows a beta prior distribution Beta [a,b], where a>0, b>0. Let y_i out of n_i subjects be responders. Therefore, the posterior distribution of p_i is Beta($a+ y_i$, $b+ n_i-y_i$) [Spiegelhalter et al. 2004].

A minimally informative unimodal Beta prior [Neuenschwander et al. 2008] Beta [0.35/(1-0.35),1] will be used. The parameters were chosen so that the mean of the prior distribution is equal to 0.35, which ensures that the clinical relevance criterion is met, if the observed ORR is exactly equal to 35%.

The efficacy criteria will be assessed based on the actual number of subjects enrolled in the study. For example, if the total number of subjects is 32 in a given treatment group, the first efficacy criterion requires that at least 12 subjects are responders. In that case, the posterior distribution is Beta (0.35/(1-0.35)+12 , 1+32-12) and the posterior probability pr(ORR ≥ 25% | data) = 0.939.

For further details, see Appendix 2 of the study protocol.

Confidence interval for response rate

Responses will be summarized in terms of percentage rates with 95% confidence intervals using exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table [Clopper and Pearson 1934].

Analysis of time to events Data

Kaplan-Meier estimates

An estimate of the survival function in each treatment group will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

Treatment of ties

The STRATA statement in LIFETEST procedure will be used to analyze time to event data with ties.

5.4.2 Key secondary analysis

Not applicable

5.5 Rule of exclusion criteria of analysis sets

Not applicable.

[redacted]

6 Reference

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