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Novartis Research and Development

LAG525

Clinical Trial Protocol 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

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Table of contents

List of tables

List of figures

List of abbreviations

γ-GT	Gamma-glutamyl transferase
ABC/BC/LABC/MBC	Advanced Breast Cancer/Breast Cancer/Locally Advanced Breast Cancer/Metastatic Breast Cancer
ACTH	Adrenocorticotropic hormone
ADA	anti-drug antibody
ADC	Antibody-Drug conjugates
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	Area Under the Curve
AUClast	Area under the plasma concentration-time curve from time zero to time of last measurable concentration
AUCtau	Area under plasma concentration-time curve over dosing interval
BAL	Bronchoalveaolar lavage
BOR	Best Overall Response
CBR	Clinical Benefit Rate
CHO	Chinese Hamster Ovary
Cmax	Maximum Concentration
CMV	Cytomegalovirus
CNS	Central Nervous System
CR/iCR	Complete Response/Immune-related complete response
CRF/eCRF	Case Report/Record Form (paper or electronic)
CSR	Clinical study report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DDS	Dose Determining analysis Set
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DOR/iDOR	Duration of Response/ Immune related Duration of Response
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
EBV	Epstein-Barr Virus
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group

EDC	Electronic Data Capture
EEA	European Economic Area
EMA	European Medicines Agency
EOI	End of Infusion
EOT	End of Treatment
EPR	Early progression rate
ER	Estrogen Receptor
eSAE	Electronic Serious Adverse Event
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPFV	First Patient First Visit
FSH	Follicle Stimulating Hormone
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GDPR	General Data Protection Requirements
GGT	Gamma-Glutamyl-Transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
hr/hrs	Hour(s)
HA	Health Authority
HBcAb	Hepatitis B core Antibody
HBsAb	Hepatitis B surface Antibody
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C Virus
HIV	human immunodeficiency virus
HNSTD	Highest Non-Severely Toxic Dose
HSV	Herpes Simplex Virus
i.v.	Intravenous
IB	Investigator's Brochure
IC50	Half maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
[redacted]	[redacted]
IEC	Independent Ethics Committee
IFN	Interferon
Ig	Immunoglobulin
IG	Immunogenicity
IL-2	Interleukin 2

irAE	Immune Related Adverse Event
IRB	Institutional Review Board
[redacted]	[redacted]
IRT	Interactive Response Technology
ITT	Intent To Treat principle
IUD	Intra-uterine device
iUPD	Immune related-Unconfirmed Progressive Disease
LAG-3	Lymphocyte-Activation Gene 3
LFT	Liver function test
LH	Luteinizing hormone
LLQ	lower limit of quantification
LPLV	Last Patient Last Visit
mAb	Monoclonal Antibody
MedDRA	Medical dictionary for regulatory activities
MHC	Major Histocompatibility Complex
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
ORR/iORR	Overall Response Rate/immune related overall response rate
OS	Overall Survival
PA	Posteroanterior
PARP	Poly(ADP-ribose) polymerase
PAS	Pharmacokinetic Analysis Set
PBMC	Peripheral Blood Mononuclear Cells
PD	pharmacodynamic(s)
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PFS/iPFS	Progression Free Survival/immune related progression free survival
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PR	Progesterone Receptor
PR/iPR	Partial Response/immune related partial response
PSDS	Post Study Drug Supply
PTA	Post-Trial Access
Q2W/Q3W/Q4W	Every 2/3/4 weeks
R Value	ALT/ALP x ULN
RBC	red blood cell(s)
RCC	Renal Cell Carcinoma

RDC	Remote Data Capture
RDE	Recommended Doses for Expansion
RECIST	Response Evaluation Criteria in Solid Tumors
RoW	Rest of the World
RP2D	Recommended phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SEB	Staphylococcal Enterotoxin B
SOD	Sum of Diameter
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	total bilirubin
TIL	Tumor-Infiltrating Lymphocytes
TNBC	Triple Negative Breast Cancer
TnI/cTnI	Troponin I / cardiac Troponin I
TnT/cTnT	Troponin T / cardiac Troponin T
TSH	Thyroid Stimulation Hormone
TTF	Time to Treatment Failure
TTP	Time to progression
TTR/iTTR	Time To Response/immune related time to response
ULN	Upper limit of normal
UNK	Unknown
US	United States
USPI	United States Prescribing Information
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Investigational drug/treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial participants, regardless of randomization group, rescue medication, active drug run-ins etc.)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal Data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples

Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized participant.
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the participant came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or background therapy(ies)
Study treatment discontinuation	When the participant permanently stops taking study treatment prior to the defined study treatment completion date
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study Consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer, and does not allow any further collection of personal data

Amendment 4 (15-Feb-2021)

At the time of amendment 4, 20 participants have been randomized to treatment Arm 1, 34 participants have been randomized to treatment Arm 2, and 34 participants have been randomized to treatment Arm 3. Of the 88 randomized participants, 85 participants have discontinued the study treatment. Three participants are still receiving treatment in Arm 2 (LAG525 + spartalizumab + carboplatin), 3 participants are in safety follow-up (of which one is still in efficacy follow-up) and 12 are in survival follow-up.

Amendment rationale

The primary efficacy analysis was performed with a data cut-off date of 27-Feb-2020. None of the three treatment arms met the proof of preliminary efficacy (PPE) criteria of a mean of the posterior distribution of ORR $\geq$ 35% and a posterior probability of (ORR $\geq$ 25%) > 90%. No new safety signals were identified for any of the treatment arms.

Based on these results and together with an increasingly crowded treatment landscape in metastatic TNBC, Novartis decided to not further develop LAG525 in TNBC. This decision is not due to safety concerns.

The main purpose of this amendment is to: 1) define the duration of the follow-up period and 2) clarify the trial discontinuation rules for participants who are still ongoing in the trial as to whether they are eligible for a Post Trial Access (PTA) program i.e. rollover protocol or a post study drug supply (PSDS).

The following modifications were incorporated:

- The survival follow-up period will be removed and participants who are currently in survival follow-up can discontinue from the study with approval of amendment 4.
- The post treatment follow-up period will be limited to the safety follow-up period of 150 days after the last dose of LAG525 and/or spartalizumab (whichever was stopped last). If carboplatin was stopped more than 150 days after LAG525 and/or spartalizumab, the participant can be discontinued 30 days after the last dose of carboplatin.
- The end of study definition was revised to clarify that participants who have discontinued their study treatment for at least 150 days will be discontinued from the study.
- Tumor and blood samples at the time of disease progression were removed.
- The clinical information for LAG525 and spartalizumab (PDR001) were updated based on the spartalizumab IB v 9.0 released on 11-May-2020 and LAG525 IB v 6.0 released on 18-Feb-2020.
- Language was updated to align with the latest protocol template (OneCTP version 3.0) and provide mitigation action plan in case of public health emergencies such as Covid-19 pandemic.

The benefit/risk assessment indentified no additional risks related to the COVID-19 pandemic; hence, no changes were made.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through font for deletions and underline for insertions. The following sections have been changed in the amended protocol:

- List of abbreviations, glossary of terms, protocol summary and the whole protocol were revised to comply with the latest protocol template (OneCTP version 3.0).
- Protocol summary: efficacy assessment section was updated to specify that tumor assessments during the post-treatment efficacy follow-up period are now optional.
- Section 1.1.3.1.2: updated based on the IB LAG525 edition 6.0 released on the 18-Feb-2020.
- Section 1.1.3.2.2: updated based on the IB PDR001 edition 9.0 released on the 11-May-2020.
- Section 1.1.3.3.2: updated based on the IB LAG525 edition 6.0 released on the 18-Feb-2020 and on the IB PDR001 edition 9.0 released on the 11-May-2020.
- Figure 3.1: revised to clarify that participants still receiving study treatment will be moved into a Post-Trial Access program (PTA), that participants who have stopped study treatment for more than 150 days will be discontinued from the study, and that efficacy assessments in the post-treatment efficacy follow-up period are now optional.
- Section 4.6: new section added to describe disruption procedures in case of a Public Health emergency.
- Section 6.1.5: paragraphs added to include PTA information and procedures.
- Section 7: was updated as per the latest protocol template to provide a list of all ICFs used in the study and to include the possibility to conduct an informed consent discussion and signature remotely in case of public emergencies (if allowed by local health authorities).
- Table 8-1: was updated to indicate that efficacy assessments are optional during the post treatment follow-up period, to clarify that EOT visit is the last visit for participants who will transition into the PTA, to define the length of follow-up to 150 days after last study treatment dose, [redacted] and to clarify that survival follow-up period is removed.
- Section 8.3.1 and Table 8.2: were updated to clarify that during the efficacy follow-up post-treatment tumor assessments are now optional.
- [redacted]
- Section 9.1.1: was amended to add a new rule for study discontinuation; participants will be discontinued if it has been at least 150 days since their last dose of study treatment and to specify that efficacy assessments during the follow-up period are optional.
- Section 9.1.2: was updated to add the latest protocol template language on withdrawal of consent.
- Section 9.1.3: was updated to clarify that due diligence should be performed until the end of the study before confirmation that a participant is lost to follow-up.

- Section 9.2: was revised to clarify the definition of end of study.
- Section 9.2.2: was revised to notify that efficacy assessment in the post-treatment efficacy follow-up will be optional and participants in efficacy follow-up for at least 150 days after the last study treatment dose will be discontinued from the study.
- Section 9.2.3: was amended to indicate that the survival follow-up period will be removed upon approval of protocol amendment 4.
- Section 10.1.4: was updated to add the latest language on pregnancy reporting.

IRBs/IECs

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

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 3 (28-Mar-2019)

As of release of amendment 3, 19 subjects have been randomized to treatment Arm 1, 21subjects have been randomized to treatment Arm 2, and 21 subjects have been randomized to treatment Arm 3 and 2 patients were in screening.

Amendment rationale

The main purpose of this amendment is to stop enrollment to treatment Arm 1 (LAG525 + spartalizumab combination). 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).

Additionally, the following modifications were incorporated:

- The total number of subjects to be enrolled was changed from approximately 96 to approximately 84 as enrollment to arm 1 was closed prematurely.
- To clarify in inclusion criterion 9 that the most recently analyzed biopsy should be from locally recurrent or metastatic site.
- To clarify language in exclusion criterion 1 to specify that no prior "immune checkpoint inhibitors" are allowed as anticancer treatment, such as anti-LAG-3, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibody (any line of therapy). The prior expression "immunotherapy" was less precise.
- To correct exclusion criterion 19 by removing pneumococcal vaccine from the list of live vaccines as it was incorrectly added.
- In Section 6.2.2 it was specified that the restriction of less than 10 mg/day prednisone or equivalent is only related to the replacement-dose steroids in the setting of adrenal insufficiency.
- To clarify in Table 8-1 that a Central Laboratory Pregnancy test 72 hours prior to screening is only required for premenopausal woman.
- To add in Section 8.3.1 "Efficacy assessment (imaging)" that tumor assessment per RECIST 1.1 should also continue after start of subsequent anti-cancer therapy [redacted], in order to obtain additional information for supportive analyses.
- To modify postmenopausal definition in Section 8.4.3 to align with exclusion criterion 23.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions. The following sections have been changed in the amended protocol:

- In applicable sections, a statement was added that enrollment to treatment arm 1 was closed prematurely and figure 3-1 was also updated accordingly. The total number of subjects was also revised accordingly (from ~96 to ~84).
- In exclusion criterion 1 "immunotherapy" was replaced by "immune checkpoint inhibitors".

- Clarification was made to inclusion criterion 9 and Section 8-2 that the most recently analyzed biopsy should be from locally recurrent or metastatic site.
- Exclusion criterion 19 was corrected by removing pneumococcal vaccine from the list of live vaccines.
- Table 6-3 in Section 6.5.1.2.1 was corrected by separating the drug management for diarrhea/colitis Grade 1 versus Grade 2.
- Section 6.1.3 and Section 6.3.2 were amended that subjects will be randomized to treatment arms 2 and 3 in a ratio 1:1.
- Section 6.2.2 was revised to specify that the restriction of less than 10 mg/day prednisone or equivalent is only related to the replacement-dose steroids in the setting of adrenal insufficiency.
- To clarify in Table 8-1 that the screening Central Laboratory Pregnancy test is only required for premenopausal woman.
- Section 8.3.1, Figure 3-1, Table 8-1, Section 9.1.1 and Section 9.2.2 were updated to highlight that tumor assessment per RECIST 1.1 should also continue after start of subsequent antineoplastic therapy [redacted].
- Postmenopausal definition in Section 8.4.3 was modified to be in alignment with exclusion criterion 23
- Tables 8-7 and 8-8 were revised with the correct dose reference identifications and sample numbers when applicable.

IRB Section

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Amendment 2 (05-Oct-2018)

As of the release of this amendment, 4 subjects have received study treatment in the trial.

Amendment rationale

The purpose of this amendment is to implement Health Authority feedback as well as updates to the Novartis standard protocol language for PDR001-related protocols. An increased risk of potentially fatal autoimmune myocarditis was observed in non-Novartis clinical trials with the combination of anti-LAG-3 and PD-1 inhibitors. Therefore, measures to optimize detection of possible autoimmune myocarditis have been included.

- To add two exclusion criteria to exclude patients with medical history or current diagnosis of myocarditis (exclusion criterion 10.ii) or with elevated cardiac Troponin T (cTnT) or Troponin I (cTnI) above 2 x ULN at screening (exclusion criterion 10.iii).
- To add Section 8.4.2.2 on cardiac Troponin monitoring during the first 2 months of the study to monitor the risk of potentially fatal autoimmune myocarditis.
- To clarify the diagnosis and management of immune-mediated myocarditis in Table 6-10 as part of the risk minimization approach.
- To clarify in exclusion criterion 18 that additionally to obtaining known HIV history at screening, HIV testing may be mandated per local requirements/regulations (e.g. Health Authority (HA), EC/IRB).
- To remove standard chest X-ray (posteroanterior view) to screen for pneumonitis, as chest CT is already required during screening and is more sensitive to diagnose pneumonitis.
- To clarify in Section 6.2.2 that the use of live vaccines is not allowed through the whole duration of the study and that there are no prohibited therapies during the post-treatment follow-up period.
- To add Section 6.2.3 related to treatments for potential infusion reactions in order to provide guidelines for management of such events.
- To add flexibility for subjects to be re-screened once for criteria other than laboratory abnormalities and to clarify the rules for re-testing and re-screening.
- To clarify that “Progression of malignancy” should be reported as an AE/SAE in this study if the investigator suspects that the study treatment accelerates disease progression.
- To implement version 5.0 of the NCI-CTCAE grading system throughout the protocol.
- To use consistently the word “advanced” to describe the study indication as it includes both loco-regional recurrent and metastatic TNBC.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions. The following sections have been changed in the amended protocol:

- List of abbreviations was updated
- Section 5-2 was updated to revise exclusion criteria 10 and 18 as described in the amendment rationale

- Sections 6.2.2 and 6.5.1.2.3 were revised to avoid redundancies
- Section 6.2.3 was added to provide guidelines for management of potential infusion reactions
- Section 6.5.1.2: Tables 6-3 to 6-10 were updated according to the new version of the CTCAE grading system v5.0. Table 6-10 was also revised to clarify the dose interruption and re-initiation of LAG525 and spartalizumab in case of myocarditis
- Section 8: Table 8-1 was modified to replace MUGA scans with cardiac MRI scans throughout the study and remove chest X-ray at screening. HIV testing at screening if required by local requirements/regulations was added and table was modified to indicate at which visits cardiac Troponin is to be measured for the subjects
- Section 8.1 was updated to add flexibility for subjects to be re-screened once for criteria other than laboratory abnormalities and to clarify the rules for re-testing and re-screening.
- Section 8.4.1: Table 8-5 was updated to add testing of cTnT/TnI and possibility to perform local HIV testing when required per local regulations
- Section 8.4.2.1 was revised to replace MUGA scans with cardiac MRI scans
- Section 8.4.2.2 was added to described the troponin monitoring guideline
- Section 8.4.4 was revised to remove chest X-ray at screening
- Section 8.5.1: Table 8-7 and Table 8-8 were revised to be consistent with the footnotes and the dose ID numbers were modified in Table 8-7
- Section 9.1.4 was updated to clarify reasons for early termination to be consistent with the latest version of the Novartis Standard Language for Protocols
- Section 10.1.1 was updated to clarify that disease progression should be reported as an SAE if the investigator considers that progression of malignancy is accelerated by study treatment
- Section 15 was updated to include the references related to immune-mediated myocarditis and its management with glucocorticoids
- All the protocol including sections 1.1.3.2, 4.5.2, 6.1, 6.2 and 6.5 including Tables 6-3 to 6-10 was modified to be consistent with the latest version of the Novartis PDR001 compound Standard Language for Protocols
- In addition, revisions to the protocol were made to be consistent with the latest version of the Novartis Standard Language for Protocols and to correct typos including in section releated to protocol amendment 1 changes.

IRB Section

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The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1 (18-Jun-2018)

Amendment rationale

At the time of this amendment, no subjects have received study treatment in the trial and the original protocol has not been initiated at any study center globally.

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

[redacted]

- To align withdrawal of consent (WoC) language with the European Economic Area (EEA) General Data Protection Regulation (GDPR).
- To specify in exclusion criterion 1 that any type of prior anticancer immunotherapy is not allowed. Change in wording for this exclusion criteria improves clarity.
- To revise inclusion criterion 9 clarifying that the biopsy is needed from the advanced setting.
- To clarify in exclusion criterion 2 that patients who received platinum or mitomycin in the advanced setting are not eligible.
- To specify inclusion criterion 4: Adequate bone marrow and organ function will be assessed by central laboratory to standardize eligibility across all sites.
- To clarify in an additional exclusion criterion that pregnant or nursing (lactating) women are excluded from the study.
- To clarify that blood samples for PK analysis can be taken from any vein except from the site (e.g. port) or same arm that is used for drug infusion. The PK samples must not be taken from the same arm or site used for drug infusion because this would confound the PK data.
- To specify that assessment of pregnancy status for study eligibility must be ascertained by central laboratory because pregnant woman are excluded from this study.

[redacted]

- To clarify the time window for collection of end of infusion (EOI) samples for carboplatin (Table 8-8) from “2 min prior to EOI” to “EOI (±5 minutes)”. This change makes sampling more practical for the sites, still ensuring collection of valid samples for analysis.
- To clarify that central pre-dose ECG at C1D1 and C3D1 can be used for local interpretation

The following amendments were requested by Health Authorities:

- To describe that subjects who have radiographically progressed per RECIST 1.1 but are judged to derive clinical benefit from continued study treatment will be re-consented in a separate ICF before they continue receiving the investigational drugs. This will ensure subjects and investigators carefully consider the benefits of continued study treatment over seeking alternative treatment, potentially forgoing approved therapies if available, or choosing no further treatment.
- To extend the period until when efficacy assessments are performed every 6 weeks from 6 months to 9 months to increase the chance of capturing progression early.
- To revise exclusion criterion 15 and include patients with stable CNS metastasis into the study.
- To specify an early safety review after the first 8 subjects are enrolled on each the carboplatin, spartalizumab and LAG525 and the carboplatin and LAG525 arm and have completed their first 3-week treatment cycle to ensure there is no safety issue with the combination of these agents.
- To provide guidance on dose management of carboplatin in case of nephrotoxicity. LAG525 and spartalizumab carry the risk for immune mediated nephritis, a rare immune-related adverse event associated with immune checkpoint blockade. Carboplatin is also associated with nephrotoxicity. In patients with impaired renal function, dosage of carboplatin should be reduced as per local labeling for carboplatin and hematologic nadirs and renal function monitored.
- To include body temperature for vital sign monitoring.
- Specify in exclusion criterion 5, that patients with CTCAE grade 2 toxicity or higher due to prior cancer therapy will be excluded (except alopecia).

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions. The following sections have been changed in the amended protocol:

- List of abbreviations was updated
- Glossary of terms: personal data was added and withdrawal of consent was modified
- Protocol summary: key inclusion and exclusion criteria were updated to reflect changes made in the protocol amendment
- Section 3, figure 3-1, Section 8.3.1, Table 8-1, Table 8-2 and Section 9.1.1: the period until when efficacy assessments are performed every 6 weeks was extended from 6 months to 9 months
- Section 5.1:
  - inclusion criterion 4 was modified to clarify that it is assessed by central laboratory
  - inclusion criterion 9 was revised to clarify that the biopsy is needed from the advanced setting
- Section 5.2:
  - exclusion criterion 1 was modified to specify that any type of prior anticancer immunotherapy is not allowed

  - exclusion criterion 2 was edited to clarify the exclusion surrounding the previous use of platinum and mitomycin
  - exclusion criterion 5 was updated to exclude patients with CTCAE grade 2 toxicity or higher due to prior cancer therapy (except alopecia)
  - exclusion criteria 10 was edited to use the word “randomization” consistently in the exclusion criteria
  - exclusion criterion 15 was modified to include patients with stable CNS metastasis
  - exclusion criterion 25 was added to exclude pregnant or nursing (lactating) women from entering the study
- Section 6.1.5.1, Section 7 and Table 8-1 were modified to add re-consenting language as a condition for subject to receive treatment beyond progression
- Section 6.5.1.2, Table 6-6: guidance on dose management of carboplatin in case of nephrotoxicity was added
- Section 8.1, Section 8.2, Table 8-1 and Table 8-5 were updated to indicated that serum pregnancy test is to be performed by central laboratory
- Section 8.2 and Table 8-3: body temperature was added in vital signs assessment
- Section 8.3.1, clarification was provided on imaging assessments for subjects who continue study treatment beyond initial disease progression as per RECIST 1.1
- Table 8-6, Section 8.4.2 and Section 12.5.2. clarified that central pre-dose ECG C1D1 and C3D1 can be used for local interpretation
- Section 8.5.1.1.1, Table 8-7 and Table 8-8 clarification on site to use for withdrawal of blood PK/IG sampling was provided
- Table 8-8: window of +/- 5 minutes was added to PK blood sampling at the end of the infusion
- [redacted]
- [redacted]
- Section 9.1.2, language for withdrawal of consent was modified
- Section 10.2, an early safety review after the first 8 subjects have completed their first study treatment cycle on each the carboplatin, spartalizumab and LAG525 and the carboplatin and LAG525 arm was added
- Section 12.4.2, clarification was added regarding ORR descriptive statistics
- Section 12.5.1 clarification was added regarding treatment groups
- Section 12.6.1 reference to Appendix 4 was added and confidence intervals used for ORR and DOR by line of therapy were clarified
- [redacted]

IRB Section

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

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	LAG525B2101
Full Title	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
Brief title	A study of efficacy and safety of LAG525 in combination with spartalizumab, or with spartalizumab and carboplatin, or with carboplatin, in patients with advanced triple-negative breast cancer.
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to assess the efficacy, safety, and PK characteristics of the following three combinations: i) LAG525 + spartalizumab; ii) LAG525 + spartalizumab + carboplatin, and iii) LAG525 + carboplatin in participants with advanced TNBC and up to one prior line of systemic treatment for metastatic disease. A thorough biomarker strategy to address key aspects of tumor immunogenicity will be implemented in the study. LAG525 and spartalizumab are two immuno-agents targeting different immune checkpoints, and have been tested as single agents and in combination. To further enhance the efficacy of checkpoint inhibition, carboplatin will be given with LAG525 or with LAG525 and spartalizumab, based on the observation that the addition of chemotherapy can change the tumor microenvironment to be more favorable to immune response.
Primary Objective(s)	To assess the antitumor activity of the three treatment arms LAG525 + spartalizumab, LAG525 + spartalizumab + carboplatin and LAG525 + carboplatin, in participants with advanced TNBC in first or second line of therapy, as measured by the overall response rate (ORR) per investigator's assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
Secondary Objectives	• 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 • To characterize the safety profile of each treatment arm • To characterize the pharmacokinetics (PK) of LAG525, spartalizumab, and carboplatin in the three investigated combinations To assess immunogenicity of LAG525 and spartalizumab in the three investigated combinations
Study design	This is a phase 2, randomized, open-label, 3-arm, multicenter global study. With protocol amendment 3, enrollment to treatment Arm 1 (LAG525 + spartalizumab) was prematurely closed and subsequent enrolled participants will be randomized to Arms 2 and 3 only.
Study population	The study will include approximately 84 adult participants (after amendment 3) with advanced (loco-regionally recurrent not amenable to curative therapy or metastatic) TNBC which progressed after adjuvant or one prior line of systemic therapy for metastatic disease and never received prior treatment with an immune checkpoint inhibitor.

Key Inclusion criteria	• Patient is an adult ≥ 18 years old at the time of informed consent • Patient has advanced (loco-regionally recurrent not amenable to curative therapy or metastatic) breast cancer. • Patient must have measurable disease, i.e., at least one measurable lesion as per RECIST 1.1 criteria (Tumor lesions previously irradiated or subjected to other loco-regional therapy will only be considered measurable if disease progression at the treated site after completion of therapy is clearly documented) • Patient progressed after adjuvant or 1 prior systemic treatment in the metastatic setting. Patients with de novo metastatic disease are eligible if they received 1 prior line of therapy • Patient must have received prior systemic treatment that included taxane-based chemotherapy for adjuvant or metastatic disease • Patient must have a site of disease amenable to biopsy, and must be willing to undergo a new tumor biopsy at screening and during therapy on this study, the latter if medically feasible. Patients with an available archival tumor tissue do not need to perform a tumor biopsy at screening if patient has not received anti-cancer therapy since the biopsy was taken. • Patient has histologically and/or cytologically confirmed diagnosis of advanced TNBC (based on most recently analyzed biopsy from locally recurrent or metastatic site, local lab) meeting the following criteria: HER2 negative in situ hybridization test or an IHC status of 0 or 1+, and ER and PR expression is <1 percent as determined by immunohistochemistry (IHC) For the full inclusion criteria, please refer to Section 5.1.
Key Exclusion criteria	• Patient has received prior immune checkpoint inhibitors as anticancer treatment such as anti-LAG-3, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibody (any line of therapy). • Patient received prior neoadjuvant or adjuvant therapy with a platinum agent or mitomycin and experienced recurrence within 12 months after the end of the platinum-based or mitomycin containing therapy, or received platinum or mitomycin for metastatic disease. • Patient has had major surgery within 14 days prior to starting study treatment or has not recovered to grade 1 or less from major side effects. • Patient with presence of CTCAE grade 2 toxicity or higher due to prior cancer therapy. Exception to this criterion: patients with any grade of alopecia are allowed to enter the study. • Patient has received radiotherapy ≤ 4 weeks prior to randomization (≤ 2 weeks for limited field radiation for palliation), and has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia). • Patient has a known hypersensitivity to other monoclonal antibodies (mAbs), platinum-containing compounds, or to any of the excipients of LAG525, spartalizumab, or carboplatin. • Patient has symptomatic central nervous system (CNS) metastases, or CNS metastases that require local CNS-directed therapy (such as radiotherapy or surgery), or increasing doses of corticosteroids within the 2 weeks prior to first dose of study treatment. Patients with treated brain metastases should be neurologically stable and without CNS progression for at least 12 weeks prior to randomization and have

	discontinued corticosteroid treatment (with the exception of < 10 mg/day of prednisone or equivalent for an indication other than CNS metastases) for at least 4 weeks before first dose of any study treatment. For the full exclusion criteria, please refer to Section 5.2
Study treatment	Investigational drugs: LAG525, spartalizumab (PDR001) Combination drug: carboplatin
Efficacy assessments	Tumor assessments by investigator's assessment per RECIST 1.1 [redacted] every 6 weeks during the first 9 months and every 12 weeks thereafter. • Upon the approval of amendment 4, the tumor assessments during the post treatment efficacy follow-up period will now be optional and will be left at the discretion of the investigator. • Survival status every 12 weeks. Upon the approval of amendment 4, survival follow up is no longer required.
Pharmacokinetic assessments	• Calculation of PK parameters for LAG525, spartalizumab and carboplatin
Key safety assessments	• Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs. • Tolerability: Dose interruptions
Other assessments	Pharmacokinetics, Immunogenicity [redacted]
Data analysis	The primary analysis will be done when all participants 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 efficacy endpoint, ORR, will be determined based on local tumor assessment following RECIST 1.1 guidelines. The primary efficacy analysis will assess the antitumor activity of each treatment arm based on their respective posterior mean and posterior distribution of ORR. Analysis will be done in the Full Analysis Set according to the randomized treatment group. The safety of each combination will be assessed mainly from the frequency of adverse events and the number of laboratory values that fall outside of pre-determined ranges.
Key words	checkpoint inhibition, LAG525, spartalizumab (PDR001), carboplatin, triple-negative breast cancer, phase 2

1 Introduction

1.1 Background

1.1.1 Overview of disease pathogenesis, epidemiology and current treatment

Triple-negative breast cancer (TNBC) is an aggressive clinical subset of breast cancer (BC) defined by the lack of estrogen receptors (ERs) and progesterone receptors (PRs) and by human epidermal growth factor receptor 2 (HER2)-negative status. TNBC accounts for 15% to 20% of newly diagnosed breast cancer (BC) cases Kohler et al 2015. Given deficiency in molecular targets and lack of approved targeted therapies, chemotherapy remains the treatment of choice for subjects with TNBC. Despite a high initial sensitivity to chemotherapy, subjects with TNBC suffer high relapse rates after adjuvant therapy, rapid progression and short survival in the metastatic setting with a median overall survival (OS) of 9-12 months Liedtke et al 2008. Treatment of TNBC remains challenging and new therapeutic options are needed.

Standard systemic treatment for early stage breast cancer consists of anthracycline- and taxane-based combination chemotherapy. For the treatment of recurrent TNBC; however, no specific recommendations or treatment standards exist NCCN 2017; Cardoso et al 2017. Recently, several studies have demonstrated the efficacy of carboplatin and cisplatin particularly in mTNBC Isakoff et al 2015; Tutt et al 2014. Platinum agents have particular utility in TNBC tumor cells because they have a decreased DNA repair capacity Quinn et al 2003.

Genomic profiling studies revealed that TNBC is a heterogeneous disease with distinct molecular subtypes that each have a distinct prognosis Burstein et al 2015. Genomic features of those TNBC subtypes include activation of molecular pathways that may be actionable by molecularly targeted or immune-based approaches Burstein et al 2015; Denkert et al 2017.

Some molecular features of TNBC such as homologous recombination deficiency and high genomic instability may predict sensitivity to DNA repair inhibitors, including poly (ADP-ribose) polymerase-1 (PARP) inhibitors. PARP inhibitors (talazoparib, veliparib, olaparib) are in development for the treatment of BRCA-mutant and TNBC, which share similar molecular characteristics, and have shown promising results. In a randomized phase 3 trial, the PARP inhibitor olaparib monotherapy was compared with single-agent chemotherapy of the physician's choice (capecitabine, eribulin, or vinorelbine) in subjects with a germline BRCA mutation and HER2–negative metastatic breast cancer. Median progression-free survival (PFS) was significantly longer in the olaparib group than in the standard therapy group (7.0 months vs. 4.2 months) Robson et al 2017. Most recently, this study Robson et al 2017 led to FDA approval of the PARP inhibitor olaparib for the treatment of subjects with BRCA-mutated mBC (Lynparza® USPI 2018).

Several antibody-drug conjugates (ADC) are in clinical development for TNBC. For instance, a tumor-associated calcium signal transducer 2 known as TROP-2 or epithelial glycoprotein-1 antigen expressed in most TNBCs, may be a potential target. Sacituzumab govitecan, an antibody-drug conjugate targeting Trop-2 has shown promising activity in heavily pre-treated TNBC Bardia et al 2017. Encouraging results were also seen in the study of another ADC, glembatumumab vedotin in advanced glycoprotein NMB (gpNMB)–expressing breast cancer

which included a subset of TNBC. Glembatumumab vedotin is an ADC that combines a monoclonal antibody against the tumor-associated antigen gpNMB and a potent microtubule inhibitor monomethyl auristatin E (MMAE) Yardley et al 2015.

1.1.2 Immunotherapy

Since it has been recognized that immune escape is a hallmark of cancer Hanahan and Weinberg 2011, recent research has been focused on treatments to reengage the host immune system to attack and eradicate established tumors. The goal of immunotherapy in cancer is to sustain or rescue an existing tumor antigen-specific immune response capable of eradicating the disease. Tumors have complex mechanisms by which they alter antigen processing and presentation within their microenvironments, as well as the activation process of an immune response that shields the tumor from immune surveillance and suppresses surrounding leukocytes. Consequently, tumor antigen-specific CD8+ and CD4+ T cells isolated from human tumors often display impaired effector function manifested by ineffective cytotoxicity and impaired cytokine secretion. A critical feature of immune activation is that the ultimate response is tightly regulated by a balance between immunostimulatory and immunosuppressive mechanisms. Antigen specific T cells have an intrinsic mechanism to regulate their activation through the balance in expression of a series of membrane receptors categorized into co-stimulatory (e.g., 41BB, GITR) and co-inhibitory-"immune checkpoint" (e.g., CTLA-4, PD1, LAG-3) receptors Leen et al 2007. The overexpression of immune checkpoint receptors on various cells within the tumor microenvironment comprises a multifactorial suppressive signal to prevent a strong T-cell–mediated response.

A clinical blockade of immunosuppressive checkpoint receptors is therefore a promising approach to overcome immune suppression and induce tumor regression. Checkpoint inhibitors have been successfully introduced to clinical practice with the approvals of the antagonists to the CTLA-4 checkpoint (ipilimumab, BMS), PD-1 (e.g., nivolumab [BMS] and pembrolizumab [Merck]) and PD-L1 (atezolizumab [Genentech]).

Importantly, TNBC has been shown to be more immunogenic than other Advanced Breast Cancer (ABC) subtypes. Tumor infiltrating lymphocytes (TILs) are seen at higher level in TNBCs compared with HR-positive breast cancers Loi et al 2014; Ono et al 2012; Denkert 2014; Loi et al 2015 suggesting an immune response to tumor-associated antigens. Furthermore, TNBC is characterized by high rates of genetic mutations (due to genomic instability), which implicates production of more neoantigens and increased immunogenicity Banerji et al 2012. Additionally, given that the binding of inhibitory molecule PD-L1 in tumor microenvironment to PD-1 on T cells is a major mechanism of tumor immune evasion, it is notable that TNBC is characterized by higher expression of PD-L1 compared to HR-positive breast cancers Mittendorf et al 2014.

An improved understanding of the immunogenicity of TNBC has led to clinical studies of several immunotherapeutic agents. Several studies of single-agent immunotherapy in subjects with TNBC demonstrated notable responses. Specifically, in a Phase 1 study of a PD-1 inhibitor (pembrolizumab), the Overall Response Rate (ORR) among 27 evaluable subjects (any line of therapy) was 18.5% Nanda et al 2016. In a Phase 1 study of a programmed cell death ligand (PD-L1) antibody (atezolizumab), the ORR was 26% in first-line subjects but less than 10% in second and later lines of treatment Schmid et al 2017. In a Phase 2 study of a PD-1 inhibitor

(pembrolizumab) as monotherapy in third or later lines of 170 subjects with mTNBC, the ORR was 5% and subjects had a durable response with a DOR of 6.3 months Adams et al 2017.

Although the immune checkpoint blockade generally results in similar enhanced anti-tumor T-cell activation, those effects are mediated by distinct pathways and they demonstrate enhanced activity in combination. Combinations of immunotherapy approaches suggest that synergistic blockade of co-inhibitory receptors demonstrates greater antitumor activity than the single-agent. This has been demonstrated with the combination of a CTLA-4 inhibitor (ipilimumab) and a PD-1 inhibitor (nivolumab) that was more active than either single agent in advanced melanoma Wolchok et al 2013. Also, there is increasing evidence that cytotoxic agents influence the tumor-host environment and consequently the combination of immunotherapy with cytotoxic agents may synergize to increase the therapeutic efficacy Zitvogel et al 2013. At present, combinations of immune checkpoint inhibitors with and without chemotherapy are being investigated in different settings to further improve the clinical outcome for subjects with mTNBC.

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

1.1.3.1 Overview of LAG525

LAG525 is a high-affinity, ligand-blocking, humanized anti-LAG-3 immunoglobulin G4 (IgG4) antibody (stabilized hinge, S228P) directed against the Lymphocyte-Activation Gene 3 (LAG-3) immune checkpoint receptor on T-cells. LAG525 blocks LAG-3 from binding to its known ligand Major Histocompatibility Complex (MHC) Class II. LAG525 is cross-reactive to cynomolgus monkey LAG-3, equipotent to human LAG-3 and it shows functional activity *in vitro* and *in vivo.*

1.1.3.1.1 Non-clinical experience with LAG525

LAG525 binds specifically and with high affinity to human LAG-3. In BIACore assays binding to mouse or rat LAG-3 proteins were undetectable demonstrating that LAG525 is not mouse or rat cross-reactive. The equilibrium dissociation constant (K_D) value for LAG525 binding to human LAG-3 was 0.109±0.008 nM. In cell binding assays with human LAG-3 expressing Chinese Hamster Ovary (CHO) cells and cynomolgus monkey LAG-3 expressing human embryonic kidney (HEK 293) cells, LAG525 binds to human LAG-3 and cyno LAG-3 expressing cells with a comparable affinity of 1.9 nM and 2.3 nM, respectively. Given that LAG525 does not cross-react with rat or mouse LAG-3 but cross-reacts with cynomolgus monkey LAG-3, it cannot be evaluated in murine tumor models, making cynomolgus monkey a relevant species and the only species for toxicology studies. There was no tissue cross reactivity observed in good laboratory practice (GLP) studies with both human and cynomolgus monkey tissues specifically to assess the potential for off target binding.

Inhibition of LAG-3 binding to ligand MHC class II by LAG525 was demonstrated in cell binding assay with MHC class II expressing Daudi cells. LAG525 inhibited the binding of human LAG-3 to MHC class II with an IC50 of 5.5 nM. Additional support for LAG525 blockade of MHC class II was provided by hydrogen/deuterium exchange mass spectrometry

epitope mapping studies and crystallography. For more details, please consult the most recent edition of the [LAG525 Investigator's Brochure].

No specific non-clinical absorption or bioavailability studies were conducted for LAG525. No specific studies were conducted to study LAG525 metabolism as classical drug metabolic elimination does not represent an important clearance mechanism for monoclonal antibodies (mAbs). The majority of monoclonal antibody elimination occurs via intracellular catabolism.

No specific drug–drug interactions studies were conducted for LAG525. LAG525 is a mAb, and is not metabolized by Cytochrome P450 (CYP450) enzymes, or transported by P-glycoprotein (Pgp) or related ATP-binding cassette membrane transporters.

The non-clinical toxicology of LAG525 was evaluated in a five-week GLP toxicology study in cynomolgus monkeys with safety pharmacology endpoints and an 8 week recovery. There were no severely toxic events in any animals. The functional effects on the major physiological systems (e.g., cardiovascular, respiratory, and central nervous systems) were evaluated within the context of the 5-week GLP general toxicology study, there were no LAG525-related effects on any of these parameters. There were no effects of LAG525 on electrocardiogram (ECG) results, blood pressure, or respiration rate. Repeat administration of LAG525 to monkeys (3/sex/main and 2/sex/recovery groups) at doses of 6, 25, and 100 mg/kg was well tolerated at all doses tested with the exception of a hypersensitivity reaction after the third dose in a single female animal treated with 6 mg/kg. It was confirmed that this animal was positive for the presence of anti-drug antibodies (ADA). Mild increases in fibrinogen (100 mg/kg) and minimal increases in globulin (25 and 100 mg/kg) were noted in males but these changes were not adverse.

ADA-dependent hypersensitivity was also observed in the 14-week study with LAG525 in three of six animals treated with LAG525 at the dose of 25 mg/kg/week. Hypersensitivity-related clinical reactions (ataxia, hypoactive behavior, excessive salivation, and vomitus) were seen in two animals, which resulted in mortality in one animal and a significant reduction in exposure to LAG525 in the other, due to anti-LAG525 antibodies. Anti-LAG525 antibodies generally correlated with reduced exposure on Days 43 and/or 92 in animals that developed anti-LAG525 antibodies.

The effect of LAG525 on lymphocytes was tested on blood samples taken from treated and control animals. A minimal but statistically significant increase in proliferating CD4+ T cells (staining for both CD4 and Ki67 proliferation marker) was observed in animals given LAG525 at 100 mg/kg/week compared to control animals, similar to observed pharmacology results with LAG-3 blockade in previously reported pre-clinical studies Huard et al 1994; Workman et al 2004.

In accordance with International Conference on Harmonization (ICH) S6 (R1), no genotoxicity or mutagenicity studies are planned with LAG525. No carcinogenicity, reproductive toxicity and juvenile toxicity studies have been performed to date with LAG525.

1.1.3.1.2 Clinical experience with LAG525

Data is available from study [CLAG525X2101C]: An open-label, multicenter Phase I/II study to determine the safety and efficacy of LAG525 as a single agent and in combination with spartalizumab (PDR001) in participants with advanced solid tumor malignancies. The study

consists of dose-escalation parts for LAG525 as single agent, and LAG525 in combination with spartalizumab. During dose-escalation, 134 participants were treated with LAG525 single agent, and 356 participants were treated with the combination of LAG525 and spartalizumab (data cut-off date of 05-Mar-2019).

The preliminary pharmacokinetics of LAG525 have been characterized from 134 participants in single-agent and 356 participants in combination in the clinical study [CLAG525X2101C] (data cut-off date of 14-Feb-2019).

Following a 30-minute intravenous infusion of LAG525 in single-agent cohorts and in combination cohorts with spartalizumab, approximately dose-proportional increases in LAG525 exposure (Cycle 1 AUC_{last}) were observed from 1 mg/kg to 15 mg/kg as suggested by an approximate 20-fold increase in exposure with a 15-fold increase in dose. Based on preliminary data, exposure (e.g., Cmax or AUClast) on cycle 3 was relatively higher than that on cycle 1 indicating moderate accumulation of LAG525. Between participant PK variability was low to moderate. Based on a preliminary population pharmacokinetic model, doses at 240 mg and above were well described by a linear, two compartment model. The population estimated median terminal half-life for a typical patient was 17 days. Compared to a typical mAb half-life, a relatively short half-life was observed at low dose levels of LAG525 potentially due to soluble target (sLAG-3) mediated drug disposition in the blood circulation.

No specific assessment of absorption has been performed as LAG525 is administered intravenously. The distribution of LAG525 is typical of a monoclonal antibody, mainly into the central compartment. The expected metabolic pathway of LAG525 is degradation to small peptides and individual amino acids. PK drug-drug interactions (DDIs) are not anticipated for LAG525 because it is not expected to interact with drug metabolizing enzymes or transporters.

Preliminary analysis of immunogenicity in participants on the [CLAG525X2101C] study suggests the presence of anti-drug antibodies in some participants. This finding is expected following treatment with a therapeutic antibody. No formal immunogenicity assessment has been completed as yet with LAG525.

Preliminary exposure response relationships were explored on the heterogeneous patient population in study [CLAG525X2101C]. Exposure-safety analysis did not reveal a relationship between LAG525 exposure (observed or model-predicted) and the occurrence of grade 2+ AEs (regardless of relationship to drug or related to drug). Exposure-efficacy analysis also showed no relationship between LAG525 exposure and efficacy, whether in monotherapy or in combination with spartalizumab, though the reason may be due to the heterogeneous patient population.

The preliminary safety information was summarized from the ongoing single-agent dose escalation part of the study (N=134; data cut-off date: 05-Mar-2019). Four dose limiting toxicities (DLTs) were reported and included Grade 3 events of localized intra-abdominal fluid collection (1mg/kg at every two weeks; Q2W), vomiting (5mg/kg Q2W), elevated lipase (5mg/kg Q2W) and grade 4 acute kidney injury (10mg/kg Q4W). A Maximum Tolerated Dose (MTD) was not identified for LAG525. Furthermore, safety events occurred without a clear dose relationship. There was no clear pattern between dose and anti-tumoral activity, and selection of a recommended phase 2 dose (RP2D) was not informed by anti-tumor activity. The recommended phase II dose selection was therefore supported by a modeling approach to

estimate target engagement based on LAG525 PK and soluble LAG-3 (sLAG-3) from patient blood samples. sLAG-3 is shed from membrane-bound LAG-3, and circulating sLAG-3 detected in blood samples was utilized as a pharmacodynamic (PD) marker for target engagement. Based on the trial simulation of the PKPD model, the dose of 400 mg LAG525 Q3W was considered to be appropriate for RDE (Recommended Doses for Expansion)/RP2Ds for single-agent LAG525 in a 3-weekly regimen (Q3W), and 800 mg LAG 525 Q4W for single-agent LAG525 in a 4-weekly regimen (data on file).

Simulation of the population PK model for LAG525 showed comparable inter-participant variability for both fixed/flat and body weight scaled dosing for all dosing regimens (Q2W, Q3W, and Q4W). In such cases, it is suggested in the literature that a fixed dosing approach is preferable Bai et al 2012; Wang et al 2009, and therefore only fixed dosing schedules were considered in the PKPD analysis described above for selecting the LAG525 RP2D.

Adverse events (AEs) of all grades and regardless of relationship to study treatment were reported in 132/134 participants (98.5%) overall, with the most frequently reported (in >20% of participants) AEs being fatigue (26.9%) and nausea (26.1%), constipation, anemia and decreased appetite (24.6% each), abdominal pain and dyspnea (22.4% each) and vomiting (20.9%), which are consistent with AEs commonly reported for participants with advanced solid malignancies.

The safety profile appeared similar across different dose levels and schedules.

Of the 134 participants treated, 75 (56.0%) experienced grade 3/4 AEs regardless of relationship to study treatment. The most frequently reported grade 3/4 AEs occurring in 5% or more of participants were anemia (15 participants, 11.2%) and dyspnea (7 participants, 5.2%).

Seventy-five of the 134 treated (56.0%) experienced AEs (all grades) suspected to be related to study treatment. In this participant group, the following Gr 3 or 4 AEs were reported (9 participants, 6.7%): vomiting (3 participants), fatigue, nausea, amylase increased, lipase increased (2 participants each), decreased appetite, abdominal pain, anemia, blood creatinine increased, and hyperuricemia (1 participant each).

Serious adverse events (SAEs), all grades, and regardless of relationship to study treatment, were reported in 52 participants (38.8%). The majority of SAEs (47 out of 52 participants who experienced SAEs) were Grade 3 or 4 in severity. Among the 52 participants who experienced SAEs, 7 participants were suspected to be related to study treatment including intra-abdominal fluid collection (1 patient, 1mg/kg Q2W, DLT), abdominal pain and melena (1 participant, 3mg/kg Q2W), infection and vomiting, (1 patient, 5mg/kg Q2W, DLT), increased lipase, increased amylase and diarrhea (1 participant 5mg/kg Q2W, DLT), diarrhea (1 patient, 5mg/kg Q2W), and nausea, vomiting, anorexia, and fatigue, (1 patient, 240mg Q2W). One patient experienced multiple SAEs suspected to be related to study treatment which included acute kidney injury (DLT), tumor lysis syndrome, vomiting (worsening), multiple organ failure, and metabolic acidosis. This patient was treated with LAG525 at a dose of 10mg/kg Q4W and presented with acute kidney injury 26 days after the first and only dose of LAG525. The patient rapidly deteriorated in hospital and died 3 days after admission. An autopsy showed widespread metastatic disease consistent with the underlying diagnosis of cancer. The events (acute kidney injury, vomiting, metabolic acidosis and tumor lysis syndrome) were considered possibly related to LAG525.

For further details please refer to the latest [LAG525 Investigator's Brochure].

Single-agent LAG525 demonstrated only minimal activity in solid tumors. No RECIST responses were seen at any dose level but some participants (RCC, NSCLC, ovarian granulosa tumor, thymoma) experienced prolonged stable disease.

1.1.3.2 Overview of spartalizumab (PDR001)

Spartalizumab (PDR001) is a monoclonal antibody (mAb) directed against human Programmed Death-1 (PD-1), a critical immune checkpoint receptor that is expressed on CD4 and CD8 T cells upon activation (Freeman 2008). Engagement of PD-1 by its ligands, PD-L1 and PD-L2, transduces a signal that inhibits T-cell proliferation, cytokine production, and cytolytic function (Riley 2009). During tumorigenesis, cancer cells from a wide range of tumor types exploit immune checkpoint pathways, such as PD-1/PD-L1, to avoid detection by the adaptive immune system (Murphy 2011). Inhibitors of immunological checkpoints, including PD-1 and PD-L1 mAb's, have demonstrated significant antitumor activity in patients with various solid tumors.

For further details please refer to the latest PDR001 [Investigator's Brochure].

1.1.3.2.1 Non-clinical experience with spartalizumab

Spartalizumab (PDR001) is a high-affinity, ligand-blocking, humanized immunoglobulin G4 (IgG4) antibody directed against PD-1 that blocks the binding of PD-L1 and PD-L2, and enhances Interleukin 2 (IL-2) production in ex-vivo lymphocyte stimulation assays.

It does not cross-react with rodent PD-1; therefore, toxicology studies were performed only in cynomolgus monkeys where there was acceptable cross-reactivity with monkey PD-1. Repeat administration of spartalizumab to monkeys was tolerated at all doses tested up to 100 mg/kg/week for 5 weeks in the GLP toxicology single-agent study. No test article-related in-life, mortality, organ weight changes, or macroscopic findings were noted. There were no spartalizumab-related effects seen in any of the safety pharmacology endpoints assessed (cardiovascular, neurobehavioral, and respiratory). Macrophage infiltrates into the splenic white pulp were observed in animals given 100 mg/kg/week and mononuclear cell infiltrates, often associated with fibrosis, around the injection site blood vessel (saphenous vein) in a few animals given ≥25 mg/kg/week. These spartalizumab-related microscopic changes were fully reversible after an eight week recovery. Additionally, mostly low grade mononuclear infiltrates in the vascular and perivascular space in several tissues of main and recovery treated animals and in recovery controls were observed but with a slightly higher incidence in treated animals. No evidence of parenchymal damage was associated with the vascular/perivascular changes in any of the organs examined and the changes were not associated with any frank tissue injury. Dose-proportional exposure to spartalizumab in each dose group was confirmed. Anti-drug antibodies (ADA) to spartalizumab were observed in some spartalizumab treated cynomolgus monkeys. A trend of reduced drug exposure was observed in these ADA-positive animals. Based on the toxicology studies with spartalizumab as a single-agent, the Highest Non-Severely Toxic Dose (HNSTD) dose is 100 mg/kg.

For further details, please refer to the latest PDR001 [Investigator's Brochure].

1.1.3.2.2 Clinical experience with spartalizumab

Spartalizumab is currently being studied alone or in combination with other agents in ongoing phase I/Ib/II/III clinical trials. The preliminary toxicity profile appears to be similar to that of marketed inhibitors of PD-1 including the type, severity and frequency of occurrence of immune-mediated adverse events.

As of the safety cut-off of 26-Mar-2020, approximately 1702 participants have been treated with spartalizumab across 17 Novartis sponsored clinical studies as described in spartalizumab IB. Of these, a total of 562 participants were exposed to spartalizumab single agent.

The available safety data from these clinical studies indicate that spartalizumab is generally well tolerated. In the dose escalation phase of the first-in-man study [CPDR001X2101] in participants with advanced solid tumors, no Dose Limiting Toxicities were reported. The preliminarily identified safety risks associated with spartalizumab are consistent with and characteristic of agents that inhibit the PD-1 receptor, and an advanced cancer population investigated in the respective trials. Severe immune-related adverse events (irAEs) were infrequent and typically manageable with dose interruption and use of immunosuppressive treatment or other supportive therapy as clinically indicated; discontinuations due to irAEs were rare.

Based on pooled safety data from four studies comprising 562 participants treated with single agent spartalizumab across different regimen (400 mg Q4W [n=427], 300 mg Q3W [n=59] and 1-10 mg/kg Q2W or Q4W [n=76]) and various advanced solid tumors types (i.e. mainly non-small cell lung cancer (NSCLC), melanoma, triple negative breast cancer (TNBC), anaplastic thyroid carcinoma, neuroendocrine tumors and nasopharyngeal carcinoma), the most common AEs (>10%), all grades, regardless of relationship with study treatment included: fatigue (26.7%), decreased appetite (23.7%), anemia (23.5%), dyspnea (22.4%), nausea (21.2%), pyrexia (20.6%), cough (20.3%), diarrhea (18%), constipation (18%), vomiting (15.8%), asthenia (14.8%) and abdominal pain (12.3%), pruritus (11.4%), weight decrease (11.2%), AST increase (10.7%), peripheral oedema and rash (10% each). Most common AEs (>3%), all grades, suspected to be study drug related included fatigue (13.3%), decreased appetitive (7.1%), pruritus (7.1%), diarrhea (6.6%), nausea (6.0%), rash (6.0%), asthenia (5.5%), pyrexia (5.2%), anemia (4.8%) and AST increase (4.6%).

Most common SAEs (>1%), all grades, regardless of relationship with study treatment were dyspnea (4.8%), pneumonia (3.6%), abdominal pain (2.8%), pleural effusion (2.7%), pyrexia (2.7%), sepsis (2.1%), pneumonitis (2.1%), hypercalcemia (2.0%), anemia (1.6%), back pain (1.4%), respiratory failure (1.4%), cellulitis (1.2%) vomiting (1.2%), hyponatremia (1,2%), and fatigue, diarrhea, cardiac arrest, pneumonia aspiration, spinal cord compression (1.1% each). Pneumonitis (1.8%) is the only SAE suspected to be study drug related that occurred in more than 1% of participants.

AEs of special interest (AESI) for spartalizumab include endocrinopathies, colitis, skin reactions, hepatitis, nephritis, pneumonitis and other immune-related AEs (irAEs), and infusion reactions.

For further details, please refer to the latest version of the PDR001 [Investigator's Brochure], as well as Section 4.5 (Risks and Benefits) and Section 6.5 (Dose escalation and dose modification) of the protocol.

1.1.3.3 Overview of the combination of LAG525 and spartalizumab

1.1.3.3.1 Non-clinical experience with the combination of LAG525 and spartalizumab

In preclinical studies, in syngeneic tumor murine models (MC38 colorectal cancer, Sa1N fibrosarcoma and B16 melanoma) inhibition of either LAG-3 or PD-1 resulted in reduced tumor growth with only occasional tumor responses Woo et al 2012. In striking contrast, 70% and 80% of the Sa1N- and MC38-inoculated mice, respectively, were tumor-free after 50 days following combinatorial anti-LAG-3/anti-PD-1 immunotherapy indicating that simultaneous blockade of both checkpoints may have synergistic antitumor activity.

Combination activity of spartalizumab and LAG525 was tested in vitro in Staphylococcal Enterotoxin B (SEB)-stimulated peripheral blood mononuclear cells (PBMCs) assay and measured by enhanced IL-2 response. Combined blockade of the PD-1 and LAG-3 pathways with spartalizumab and LAG525, respectively, enhances the activated T cell response as measured by IL-2 secretion over either agent alone, and supports the rationale to block both PD-1 and LAG-3 in cancer, where enhanced anti-tumor activity is the desired outcome.

LAG525 and spartalizumab in combination were tested in 5 week GLP toxicology study. For more details, please consult the most recent edition of the [LAG525 Investigator's Brochure]. Neither spartalizumab nor LAG525 behaved differently in this combination study compared to their toxicokinetic (TK) characteristics after first dose in their single-agent GLP toxicity studies. For animals without notable ADA, the TK for spartalizumab and LAG525 was as expected for a typical IgG in this species. The low-dose combination (18/6 mg/kg spartalizumab and LAG525 respectively) was well tolerated. At the high-dose combination (18 mg/kg of both agents), hypersensitivity reactions were observed in one animal out of four after the fourth dose (recovered) and two animals after the fifth dose.

Pharmacodynamic activity of LAG525 and spartalizumab combination was confirmed in ex-vivo SEB stimulation assay with whole blood samples in the presence of LAG525 and spartalizumab. Blood taken from control animals demonstrated the augmentation of IL-2 release higher than blood taken from animals treated with LAG525 and spartalizumab indicating the target (LAG-3 and PD-1) engagement *in vivo*. For the assay details, please consult the most recent edition of the [LAG525 Investigator's Brochure]. When the above difference was not observed, the presence of ADAs was confirmed.

In the combination toxicology study there were no additional effects seen attributable to target biology of either agent and thus no effect on recommended starting doses in clinic as estimated from single agent studies can be expected.

1.1.3.3.2 Clinical experience with the combination of LAG525 and spartalizumab

In the combination part of study [CLAG525X2101C], 356 participants have been treated with LAG525 in combination with spartalizumab (Data cut-off date of 05-Mar-2019). LAG525 doses ranged from 0.3 mg/kg to 1000 mg, and spartalizumab doses ranged from 1 mg/kg to 400

mg. The combination was tested in a Q3Wand a Q4W schedule. Spartalizumab or LAG525 in the combination showed comparable PK to the single agent data at the same dose levels from the ongoing [CPDR001X2101] and [CLAG525X2101C] studies. The observed median half-life for spartalizumab ranged from 7.24 to 23.7 days, which is similar to the results from the ongoing [CPDR001X2101] study. There are no human pharmacodynamic data generated to date.

Four participants experienced DLTs which included Gr3 hyperglycemia (80mg LAG525 Q2W and 400mg spartalizumab Q4W), Gr4 autoimmune hepatitis and Gr3 fatigue (1000mg LAG525 Q4W and 400mg spartalizumab, Q4W), Gr3 brain tumor edema (600mg LAG525 Q3W and 300mg spartalizumab Q3W), and Gr3 pneumonitis (400mg LAG525 and 400mg spartalizumab, Q4W).

The preliminary safety information was summarized from the ongoing combination part of the study (data cutoff date: 05-Mar-2019). AEs of all grades and regardless of relationship to study treatment were reported in 352 participants (98.9%) overall, with the most frequently reported (in >20% of participants) AEs being nausea (28.4%), fatigue (27.0%), decreased appetite (22.5%), diarrhea (21.3%) and dyspnea (21.1%).

Grade 3/4 AEs regardless of relationship to study treatment were reported in 177 participants (49.7%). The frequency of each grade 3/4 AE was below 10%. The most frequently reported AEs occurring in 2 or more participants included anemia (6.2%), asthenia (4.2%), dyspnea (3.3%), fatigue (1.4%), vomiting (1.1%), decreased appetite (1.1%), abdominal pain (1.1%), arthralgia (1.1%) and back pain (1.1%).

Of the 356 participants with the combination, 232 (65.2%) experienced AEs (all grades) suspected to be related to study treatment. In this participant group, the following Gr 3 or 4 AEs were reported (33 participants, 9.3%): fatigue, hypothyroidism, maculopapular rash, arthralgia, anemia, hyponatremia (1 participant each), diarrhea, (2 participants each) aspartate aminotransferase increased, alanine aminotransferase increased and hypophosphatemia (3 participants each), asthenia (4 participants) lipase increased (5 participants).

Serious adverse events (SAEs), all grades, regardless of relationship to study drug, were reported in 150 participants (42.1%). The majority of these participants (124 out of 150) experienced SAEs that were Grade 3 or 4 in severity. Among the 150 participants who experienced SAEs, 19 participants experienced events that were suspected to be related to study treatment. SAE, all grades, regardless of relationship, occurring in more than 2 participants were dyspnea (14 participants), pleural effusion (9 participants) pyrexia (9 participants),pneumonitis (6 participants), abdominal pain, acute kidney injury, pain in extremity, pneumonia (5 participants each), ascites, back pain, colitis, fatigue, nausea, hypercalcemia, sepsis (4 participants each). The safety profile appeared similar across different dose groups. For more details, please refer to the most recent edition of the [LAG525 Investigator's Brochure].

Clinical review of the triplicate ECGs collected during the [CLAG525X2101C] study was not indicative of QTc prolongation by either LAG525 alone or in combination with spartalizumab. Overall, single-agent LAG525 and combination of LAG525 plus spartalizumab were tolerated with safety profiles similar to those of other marketed checkpoint inhibitors.

The combination part of the ongoing [CLAG525X2101C] study included 5 participants with advanced and heavily pre-treated TNBC. Preliminary indicate that two of these participants showed durable PRs with treatment for over a year (data on file).

Anti-tumoral activity was also seen in other solid tumors. Preliminary data indicate that one participant with thymoma achieved a CR and 11/100 evaluable participants with a variety of solid tumors had a confirmed PR. The majority of participants with confirmed PR had durable responses. Several cases of prolonged SD were observed.

Responses were observed across several dose levels of LAG525 in combination with spartalizumab. There was no clear pattern between dose and anti-tumoral activity. Therefore, a PKPD modeling approach was used to describe LAG525 PK and sLAG-3 data, and to further support determination of the RP2D. As mentioned earlier, the pharmacological criterion chosen to guide the selection was the ability to achieve 90% suppression of the target (LAG-3) expressed in the tumor in > 90% of participants. Based on the trial simulation of the PKPD model, the 400 mg LAG525 Q3W dose was selected as the RP2D for both single-agent LAG525 and in combination with spartalizumab in a 3-weekly regimen. A total of 23 participants have been treated with a Q3W schedule, of which 4 participants received the dose of 400 mg LAG525 and 300 mg spartalizumab during the escalation.

1.1.3.4 Overview of carboplatin

Carboplatin is a derivative of cisplatin which was the first platinum salt to be used in the treatment of malignancies. Carboplatin has a similar mechanism of action to cisplatin, but differs in terms of structure and has less toxicity. It reacts with intracellular DNA by forming platinum complexes, thereby inhibiting replication and transcription and leading to cell death (USPI for Paraplatin®).

Platinum agents have particular utility in TNBC tumor cells which have a decreased DNA repair capacity Quinn et al 2003. Accordingly, high pathologic complete response (pCR) rates have been observed among *BRCA1* carriers treated with cisplatin in the preoperative setting Byrski et al 2010 and high response rates (RRs) were also observed among one small cohort of *BRCA1* carriers treated with cisplatin in the metastatic setting Byrski et al 2012.

Preclinical studies demonstrated that sporadic TNBC often has similar features as *BRCA1/2*-mutated cancers, including harboring DNA repair defects that might predispose to platinum sensitivity Hastak et al 2010. Several clinical trials confirmed the activity of carboplatin in TNBC, showing that the addition of neoadjuvant carboplatin to anthracycline/taxane or anthracycline-free chemotherapy improved pathologic complete response (pCR) in early-stage TNBC, both in sporadic and in *BRCA*-mutated cancers von Minckwitz et al 2014; Sikov et al 2015; Sharma et al 2017; Silver et al 2010; Ryan et al 2009 and Rugo et al 2013.

Recently, several studies have demonstrated the meaningful activity of platinum-based chemotherapy for TNBC Isakoff et al 2015; Tutt et al 2014. In the multicenter phase II clinical trial of single agent platinum in metastatic TNBC Isakoff et al 2015, 86 subjects received first- or second-line cisplatin (75 mg/m2) or carboplatin (AUC 6) by physician's choice once every 3 weeks. The overall response rate (ORR) was 25.6%, including three complete responses and 19 partial responses. The ORR was 29% in first line, and 12% in second line mTNBC Isakoff et al 2015. The larger TNT study Tutt et al 2014, a randomized phase III trial, compared carboplatin with docetaxel, both as single agents, in 376 subjects with mTNBC or *BRCA1/2* breast cancer. Using carboplatin in first line TNBC yielded an ORR of 31%; the PFS was 3.1 months (95% CI: 2.5-4.2 months). The study showed no evidence of superior response to carboplatin compared to docetaxel in unselected TNBC subjects, with lower incidence of AE with carboplatin Tutt et al 2014.

Bone marrow suppression is the dose-limiting toxicity of carboplatin. The most frequent AEs in a cohort of patients with ovarian cancer receiving single-agent carboplatin as second line treatment were myelotoxicity (thrombocytopenia, neutropenia, anemia), and nausea and vomiting. Carboplatin has limited nephrotoxic and ototoxic potential; peripheral neurotoxicity is infrequent (US label Paraplatin®). In the TBCRC009 trial, single-agent carboplatin had generally mild toxicity in mTNBC, with fatigue, nausea, electrolyte abnormalities, and hematologic toxicity among the most common adverse events: Thrombocytopenia occurred in 49% of subjects, anemia in 65%, neutropenia in 35%, hypomagnesemia in 23%, and anorexia in 9%. Grade 3 and 4 adverse events were rare. Grade 3 and 4 adverse events occurring in at least 5% of all subjects included fatigue, neutropenia, dyspnea, anemia, hyperglycemia, and hyponatremia Isakoff et al 2015.

Carboplatin is administered as infusion therapy. The major route of elimination of carboplatin is renal excretion. A mathematical formula incorporating the glomerular filtration rate (GFR) and carboplatin target area under the concentration versus time curve (AUC in mg/mL•min) is commonly used to determine the initial dose, since it allows compensation for subject variations in pretreatment renal function.

Single agent carboplatin is included in the NCCN and other national guidelines as a reasonable option for the treatment of subjects with ABC in all lines of therapy. In particular, ESMO guidelines highlighted the benefit of a mild toxicity profile of carboplatin for subjects with TNBC Cardoso et al 2017. The NCCN-recommended dose is AUC 6 i.v. on day 1 of each cycle, based on the TBCRC009 study Isakoff et al 2015; NCCN 2017.

For more details, please refer to the local prescribing information for carboplatin.

1.2 Purpose

LAG525 and spartalizumab, two immuno-agents targeting different immune checkpoints, have been tested as single agents and in combination. It is expected that the addition of a chemotherapy agent, carboplatin, will further enhance the efficacy by making the tumor more immuno-reactive or by altering the tumor microenvironment to achieve an optimal anti-tumor immune response.

The goals of this Phase II study are to assess efficacy/safety of the following IO/IO combination ± carboplatin: i) LAG525 + spartalizumab; ii) LAG525 + spartalizumab + carboplatin, and ii)

LAG525 + carboplatin in participants with advanced TNBC and up to one prior line of systemic treatment for metastatic disease. With protocol amendment 3, enrollment to Arm 1 (LAG525 + spartalizumab) was prematurely closed.

[redacted]

2 Objectives and endpoints

Objectives and related endpoints are described in Table 2-1 below. With protocol amendment 3, enrollment to treatment Arm 1 (LAG525 + spartalizumab) was prematurely closed and all subsequent enrolled participants will be randomized to Arms 2 and 3 only.

Table 2-1 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 participants with advanced TNBC in first or second line of therapy, as measured by the overall 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]

Objective(s)	Endpoint(s)
[redacted]	

3 Study design

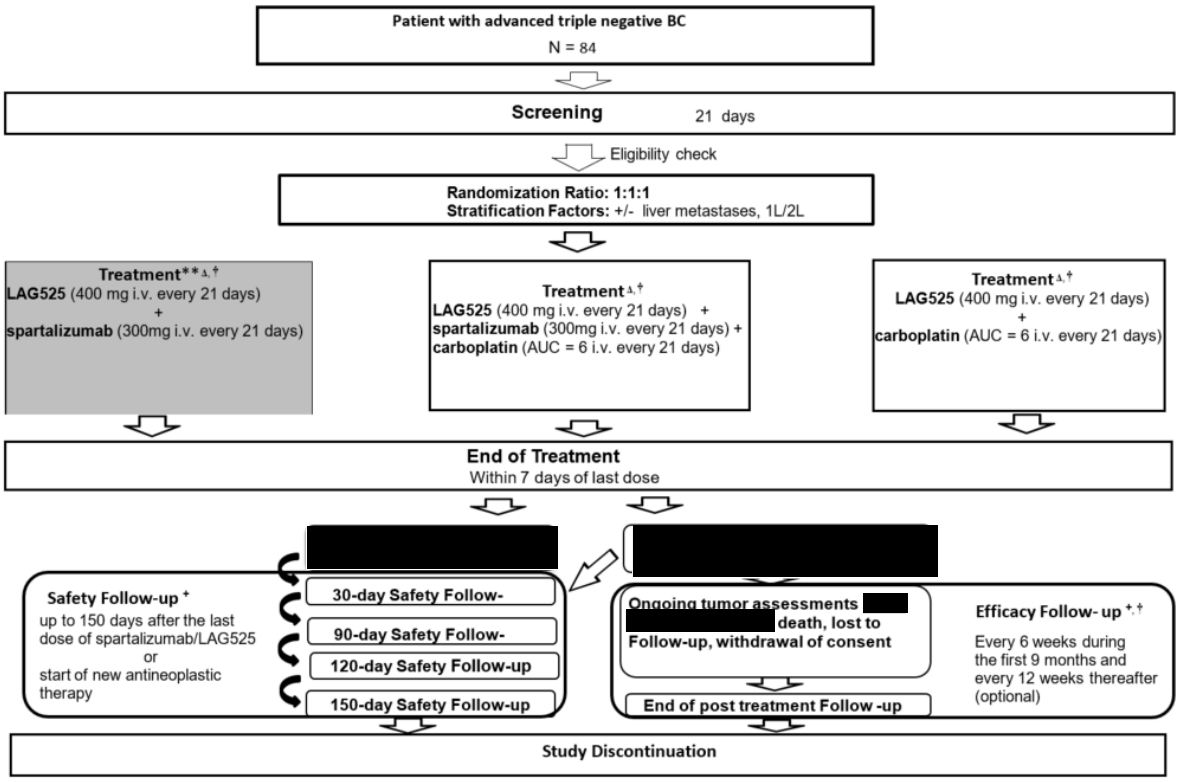
This is a phase II, open-label, randomized, three-arm, multicenter global study in participants with advanced (loco-regionally recurrent not amenable to curative therapy or metastatic) TNBC which progressed after adjuvant or one prior line of systemic therapy for metastatic disease.

With protocol amendment 3, enrollment to treatment Arm 1 (LAG525 + spartalizumab) was prematurely closed and subsequent enrolled participants will be randomized to Arms 2 and 3 only.

The study objective is to assess efficacy and safety of the following IO/IO ± carboplatin combinations (Figure 3-1):

- Arm 1: LAG525 + spartalizumab (enrollment of this arm is closed with protocol amendment 3)
- Arm 2: LAG525 + spartalizumab + carboplatin
- Arm 3: LAG525 + carboplatin

Figure 3-1 Study Design



*[redacted]

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

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

+ Participants who had stopped study treatment for 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

4 Rationale

4.1 Rationale for study design

There is a high unmet medical need for new therapeutic approaches to manage advanced TNBC. Immunotherapy has gained much interest as an option due to the promising results seen in clinical studies of the PD-1 inhibitor pembrolizumab Nanda et al 2016; Adams et al 2017 and the PD-L1 inhibitor atezolizumab Schmid et al 2017 in patients with TNBC. Yet, the main limitation of single agent immune checkpoint blockade is that only a subset of participants respond, due to the complexity of anti-cancer immune surveillance and therefore inadequacy of engaging only one component of the immune system to overcome immune suppression in the tumor microenvironment and mount an effective immune response. Combining different

checkpoint receptor blockades achieves distinct effects on the immune response Anderson et al 2016. Beyond combinations of PD-1 and CTLA-1 inhibitors that have demonstrated superior activity compared to monotherapy Wolchok et al 2013, new co-inhibitory receptors are investigated as potential targets to broaden the therapeutic repertoire Anderson et al 2016.

LAG-3 is a co-inhibitory receptor that may cooperate with PD-1 to inhibit immune responses Anderson et al 2016. In preclinical studies, the combined inhibition of PD-1 and LAG-3 checkpoints synergistically enhances antitumor responses over inhibition of either checkpoint alone Woo et al 2012. CD8+LAG-3+PD-1+ T cells from participants with ovarian cancer had impaired function in ex vivo assays compared with LAG-3+PD-1− or LAG-3−PD-1− subsets, but they restored their functions after the dual blockade of PD1 and LAG-3 Matsuzaki et al 2010. These data suggest that combined inhibition of LAG-3 and PD-1 in the clinic may have significant anti-tumor activity.

Combining immunotherapy agents with chemotherapeutic agents may provide an additional benefit to achieve additive or synergistic clinical activity Zitvogel et al 2013, Emens and Middleton 2015. Chemotherapy can change the tumor microenvironment to be more favorable to immune response. Importantly, it can induce immunogenic cell death, which facilitates the efficient antigen presentation Kroemer et al 2013. This has been shown to trigger potent T cell responses in preclinical models Pfirschke et al 2016; Lu et al 2017. Checkpoint inhibitors (anti-PD-1, anti-PD-L1, anti-CTLA4) have been also tested in combination with chemotherapy in NSCLC and melanoma in clinical settings and the results appeared to be promising Robert et al 2011; Lynch et al 2012; Reck et al 2013; Antonia et al 2014. A number of combinations of immune checkpoint inhibitors (anti-PD-1/pembrolizumab, anti-PD-L1/atezolizumab) with chemotherapy are in Phase III clinical trials in patients with newly diagnosed or advanced TNBC.

This is an open-label, phase II study of the three combinations, LAG525 + spartalizumab (Arm 1), LAG525 + spartalizumab + carboplatin (Arm 2), and LAG525 + carboplatin (Arm 3) in participants with advanced TNBC in first or second line therapy. Enrollment to treatment Arm 1 (LAG525 + spartalizumab) was prematurely closed with protocol amendment 3. Subsequent enrolled participants will be randomized 1:1 to either Arm 2 or Arm 3. The randomization will be stratified by the presence or absence of liver metastasis and by line of therapy, i.e. first line (following disease progression after adjuvant or neoadjuvant therapy) or second line (following one disease progression in advanced or metastatic setting).

The study will be conducted in patients with TNBC which is more immunogenic than other BC subtypes, has higher expression of PD-L1 and increased infiltration by TILs Loi et al 2014; Mittendorf et al 2014. These characteristics are considered among prerequisites for immune therapy, i.e., immune checkpoint inhibition to be effective in rescuing the existing anti-tumor immune response Dammeijer et al 2017. It was therefore plausible to assume that TNBC will be responsive to combination therapy with LAG525 + spartalizumab. With protocol amendment 3, enrollment to treatment Arm 1 (LAG525 + spartalizumab) was prematurely closed. The reason for this closure was a higher treatment discontinuation rate due to progressive disease in Arm 1 as compared to the treatment arms containing carboplatin (Arms 2 and 3). At study entry, TNBC status will be confirmed in the most recent biopsy because in up to 15% of participants initially diagnosed with TNBC, the hormone receptor status in the metastasis may shift to

positive, making those participants eligible for other treatment options Aurilio et al 2014. The threshold of ER and PR expression is <1 percent as determined by immunohistochemistry (IHC), following the recommendation of the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Hammond et al 2010.

4.1.1 Rationale for Arm 3 (LAG525 + carboplatin)

In Arm 3, LAG525 will be combined with chemotherapy, without the co-inhibitory effect of a PD-1 inhibitor. LAG-3 is associated with T cell regulation and represents a potential target for modulating T cell responses cancer on its own Anderson et al 2016. In the clinical study [CLAG525X2101C], LAG525 has demonstrated only minimal efficacy as single-agent but when co-inhibited with spartalizumab clinical responses were observed. LAG-3 blockade has also been shown to synergize with anti-tumor vaccination to improve tumor-specific immune response, supporting a direct role for LAG-3 in regulating CD8+ T cells Grosso et al 2007.

While LAG-3 plays a critical role in attenuating the effector function of PD-$1^{+}CD8^{+}$ infiltrating T cells, as has been demonstrated in tumor models, its blockade is effective during early events of T cell activation, probably via its binding to MHC class II Demeure et al 2001 After antigen encounter within tolerizing environments such as tumor, self-antigen or chronic infection, antigen-specific CD8 T cells differentiate into different subpopulations defined by LAG-3 and PD-1 expression, with each group having a distinct function and phenotype Grosso et al 2009. Signaling through the PD-1 and LAG-3 pathways have distinct functional consequences to CD8 T cells and manipulation of both antigen and cytokine signaling can influence CD8 tolerance through LAG-3 and PD-1 Grosso et al 2009.

As chemotherapy sensitizes the tumor to immune check point blockade therapy Pfirschke et al 2016, we hypothesize that it will create an environment early during T cell activation (e.g., increased antigen concentration, antigen availability) that will favor the arising of LAG-3+CD8+ T cells which will require only LAG-3 inhibition to differentiate into tumor antigen specific effector cells. In this environment, LAG-3 inhibition may be sufficient to obtain a clinical response, without the need of additional PD-1 checkpoint blockade.

4.1.2 Rationale for stratification by liver metastasis

The randomization will be stratified by the presence or absence of liver metastasis to account for the differential prognosis. Breast cancer patients, including those with TNBC, who have visceral metastasis generally have a worse outcome than patients with non-visceral metastasis, and the presence of liver metastasis in particular was an independent poor prognostic factor Pierga et al 2004; Kim et al 2013; Kassam et al 2009. Additionally, recent trials suggested organ-specific tumor responses in patients treated with immune checkpoint inhibitors in various diseases and demonstrated a poorer response rate in patients with liver metastasis compared to patients with other visceral metastasis.

For instance, in the study of pembrolizumab as monotherapy in participants with advanced TNBC Adams et al 2017, the response rate was lower in participants with visceral metastasis (ORR 2% vs 11% in participants with no visceral metastases); no participants with liver metastases had a response. Similarly, in lung cancer patients treated with PD-1 and PD-L1 inhibitors, no responses were seen in patients with liver metastases while all clinical responders had primarily intrathoracic disease or CNS involvement Pallai et al 2016. Nishino et al

evaluated irRECIST1.1 and standard RECIST1.1 responses in patients with advanced NSCLC patients treated with nivolumab and observed less responses in liver lesions Nishino et al 2016. In patients with advanced or metastatic melanoma treated with pembrolizumab or nivolumab, patients with liver metastases were less likely to respond to treatment Ribas et al 2016; Goldinger et al 2016. It was hypothesized that the liver has an intrinsic immune suppressive microenvironment Tagliamonte et al 2016; Buonaguro et al 2013, which may help tumors to escape from anti-tumor immune attacks during therapy with immune checkpoint inhibitors.

4.1.3 Rationale for stratification by line of therapy

The randomization will be stratified by line of therapy, i.e., first or second line, to account for the differential efficacy of first and second line therapy.

The data from published studies suggest that, for participants with mTNBC, the benefits from chemotherapy as well as from immunotherapy are higher in first line compared to second or later lines of therapy. In the TBCRC009 study, platinum (carboplatin or cisplatin) alone achieved an ORR of 29.0% in first line, and 11.8% in second line Isakoff et al 2015. Similarly, in a study of cetuximab with cisplatin versus cisplatin alone in participants with mTNBC, the response rate in the cisplatin alone arm as higher in first line (12%) versus second line (6%) of therapy Baselga et al 2013. In a phase 1 expansion cohort of single-agent atezolizumab in participants with mTNBC, the ORR was 26% for participant in first line and below 10% for participants in second or later lines Schmid et al 2017.

4.2 Rationale for dose/regimen and duration of treatment

The combination of LAG525 and spartalizumab has shown promising results in pre-clinical assays and responses were observed in clinical studies of spartalizumab alone ([CPDR001X2101]) and the combination of LAG525 and spartalizumab ([CLAG525X2101C]), particularly in participants with TNBC. For the combination, RDEs were established for use in three-weekly (q3w) and 4-weekly (q4w) regimens. The RDEs are 400 mg LAG525 + 300 mg spartalizumab (q3w) and 800 mg LAG525 + 400 mg spartalizumab q4w. In this study, a cycle is defined as 3 weeks (21 days) to match the approved schedule of carboplatin which is administered in cycles of three weeks (q3w), and doses will be 400 mg LAG525 and 300 mg spartalizumab.

Carboplatin will be dosed per AUC 6 i.v. on day 1 of each cycle, as recommended for single-agent and combination regimens for the treatment of participants with breast cancer NCCN 2017. Single-agent carboplatin at the AUC 6 dose has a well-known and manageable safety profile as demonstrated in clinical studies (see Section 1.1.3.4).

The present study will not include a dose escalation part because recently, carboplatin (dosed per AUC5 and AUC6) has been tested as combination partner with checkpoint inhibitors pembrolizumab or atezolizuamb in NSCLC studies and the combinations were found to have an acceptable safety profile Langer et al 2016; Herbst et al 2016. Of note, the incidence of myelotoxicity was not different between platinum-containing chemotherapy with or without pembrolizumab Keytruda® US prescribing information 2017.

Based on available safety data from these combination studies of carboplatin with checkpoint inhibitors, it is expected that there will be no significant overlap in the safety profile of

carboplatin and LAG525/spartalizumab. The protocol provides guidelines for dose modifications for each drug if toxicities occur in individual participants.

4.3 Rationale for choice of combination drugs

Carboplatin has been chosen as combination drug given its proven efficacy in TNBC and its generally mild safety profile (see also Section 1.1.3.4).

In the randomized phase III TNT trial the activity of single-agent carboplatin was tested against a standard chemotherapy with single-agent docetaxel in 376 TNBC participants including *BRCA1/2* mutation carriers Tutt et al 2014. In unselected TNBC participants, there was no significant difference in ORR, PFS, or OS between carboplatin and docetaxel. However, participants with *BRCA1/2* mutation who received carboplatin (n=48) had a significantly higher ORR (68% vs 33%) and better PFS (6.8 months vs 3.1 months) compared to participants with wild type *BRCA1/2* Tutt et al 2014.

Many participants with TNBC have germ line mutations in the *BRCA1/2* genes, which result in decreased DNA repair capacity Peshkin et al 2010**.** The functional link between the BRCA1/2 pathway and platinum response in TNBC was demonstrated in the TBCRC009 phase II trial of platinum monotherapy Isakoff et al 2015. Furthermore, in this trial, responses among those who did not carry mutations were associated with the presence of tumor genomic instability patterns characteristic of *BRCA1/2*-mutant tumors. Similarly, Watkins J, et al. Watkins et al 2015 analyzed a cohort of 126 TNBC participants and demonstrated the positive association between allelic imbalance, a form of genomic instability, in *BRCA* mutant and non-mutant tumors and specific sensitivity to carboplatin response.

Homologous recombination deficiency (HRD) status has been proposed to subclassify TNBC tumors, including *BRCA1/2* nonmutated tumors more likely to respond to platinum-containing therapy Telli et al 2016. However, HRD measure had no predictive performance for carboplatin benefit in the TNT trial with only modest increase in efficacy in HRD high participants vs low (38.2% vs 29.2, P=NS) Tutt et al 2014; Tutt et al 2016.

Sporadic *BRCA* wild-type TNBCs may display molecular features of homologous DNA recombination deficiency (BRCA-like phenotype) and harbor alterations in a diverse set of DNA repair genes (eg, *ATM, RAD51*). This suggested that the DNA-damaging platinum chemotherapy drugs would have broad activity in TNBC, in the germline *BRCA*-mutant subset and beyond.

While the main mechanism of action of platinum agents is believed to be the induction of cancer cell apoptosis as a response to their covalent binding to DNA, recent studies indicated that cellular molecules other than DNA may potentially act as targets, and that part of the antitumor effects of platinum drugs occurs through modulation of the immune system Hato et al 2014. These immunogenic effects include modulation of STAT signaling Lesterhuis et al 2011; induction of an immunogenic type of cancer cell death through exposure of calreticulin and release of ATP and high-mobility group protein box-1 (HMGB-1) Kroemer et al 2013; Tesniere et al 2010; and enhancement of the effector immune response through modulation of programmed death receptor 1-ligand and mannose-6-phosphate receptor expression Liu et al 2010.

The described above immunogenic momentum of platinum chemotherapy is being explored recently in the combination with immune checkpoint blockade. There is a good rationale to combine platinum compounds with checkpoint-blocking antibodies: Platinum can provide immunogenic cell death (ICD) (in case of oxaliplatin or cisplatin based chemoradiation), tumor cell sensitization to CTL lysis, and downregulation of PD-Ls. In several studies conducted in patients with advanced NSCLC, the combination of a checkpoint inhibitor, atezolizumab or pembrolizumab, with platinum-based chemotherapy demonstrated increased efficacy over the chemotherapy alone Lynch et al 2012; Reck et al 2017.

Specific studies to investigate drug-drug interactions (DDI) between LAG525 and/or spartalizumab with carboplatin have not been conducted. Monoclonal antibodies such as spartalizumab and LAG525 are eliminated through protein catabolism and target-mediated disposition, whereas carboplatin is mainly eliminated via the renal route of elimination. Therefore, the potential for drug-drug interaction between the two antibodies and carboplatin is considered low.

Nevertheless, PK of carboplatin, LAG525 and spartalizumab will be characterized in this study, so that DDI, if any, between the combination partners, can be explored (Section 12.5.3). As spartalizumab and LAG525 are intended to be used in combination with chemotherapy, this evaluation is particularly important since chemotherapeutic agents have narrow therapeutic range FDA DDI guidance 2012.

The safety of carboplatin is well established. Combination studies of carboplatin with checkpoint inhibitors have not led to new safety signals compared to the known toxicities of each agent alone (see Section 4.2).

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

4.5.1 Potential benefits to clinical trial participants

To date, immune checkpoint inhibitors suppressing the programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T lymphocyte associated protein 4 (CTLA-4) pathways have demonstrated significant clinical efficacy in multiple tumor types, combined with a tolerable and manageable safety profile, supporting recent regulatory approvals of mAbs against PD-1/PD-L1 and CTLA-1 in various indications including melanoma, non-small cell lung cancer, head and neck cancer, bladder cancer, renal cancer, Merkel Cell Carcinoma, and classical Hodgkin's lymphoma Opdivo® USPI 2018, Keytruda® USPI 2017, Yervoy® USPI 2018, Tecentriq® USPI 2017. LAG525 and spartalizumab are humanized IgG4 monoclonal antibodies which due to their respective mechanisms of action, are considered as immune checkpoint inhibitors.

TNBC has been shown to be more immunogenic than other BC subtypes and clinical studies of several immunotherapeutic agents demonstrated notable responses, albeit limited to few participants Nanda et al 2016; Schmid et al 2017; Adams et al 2017.

Combining immune checkpoint inhibitors targeting distinct inhibitory pathways like CTLA-4, PD-1 and LAG-3 demonstrated greater antitumor activity than each of the single-agents alone, e.g., in preclinical models dual anti-LAG-3/anti-PD-1 antibody treatment eradicated established melanoma and colon adenocarcinoma tumors that were largely resistant to single antibody treatment Woo et al 2012. Similarly, concurrent blocking of CTLA-4 and PD-1 pathways achieved clinical activity in advanced melanoma patients that was distinct from published monotherapy data, with rapid and deep tumor regressions in a substantial number of patients Wolchok et al 2013.

In study [CLAG525X2101C], the combination of LAG525 and spartalizumab has shown an efficacy signal with durable responses in 2 out of 5 heavily pretreated TNBC participants. The combination was well tolerated.

The addition of a chemotherapeutic agent has a dual effect of rendering tumor cells more antigenic to the immune system and at the same time stimulating the immune response, and will further enhance the therapeutic effect Zitvogel et al 2013.

In summary, it is expected that due to the synergistic effects, each of the tested combination regimens, LAG525 + spartalizumab, LAG + spartalizumab + carboplatin, and LAG525 + carboplatin, will increase the clinical benefit to participants with TNBC who have limited options in the advanced disease setting.

4.5.2 Potential risks to clinical trial participants

Immune checkpoint inhibitors may be associated with the occurrence of immune-mediated adverse events (irAEs). In general, irAEs can potentially involve every organ system but gastrointestinal (GI) (e.g. diarrhea, colitis), dermatologic (e.g. rash, pruritus), hepatic (e.g. hepatitis), pulmonary (e.g. pneumonitis), renal (e.g. nephritis) and endocrine toxicities (e.g. hypothyroidism, hyperthyroidism, type I diabetes, hypophysitis including hypopituitarism and adrenal insufficiency) are being typically the most frequent side effects. Other immune-mediated AEs may rarely include the nervous system (e.g., encephalitis, Guillain-Barre syndrome, myasthenia gravis), eye (e.g., uveitis, vision changes), musculo-skeletal system (e.g., myositis, arthritis), pancreas (e.g. pancreatitis), cardiovascular system (e.g., vasculitis, myocarditis) or blood system (e.g., anemia, cytopenias), and severe skin reactions such as toxic epidermonecrolysis or Steven Johnson syndrome. Furthermore, complications in participants with bone marrow or solid organ transplant have been reported (e.g. organ rejection, severe graft-versus-host disease). These side effects are generally manageable and reversible with dose interruption and administration of corticosteroids and/or other immuno-suppressants. However, fatal events have been reported in some cases with checkpoint inhibitor compounds; some events like endocrinopathies may further require life-long hormonal replacement. While most events are expected to occur during treatment, onset may be delayed and irAEs may also occur after discontinuation of study treatment (Spain et al 2016; Hofmann et al 2016; Champiat et al 2016; Brahmer et al 2018 and Haanen et al 2017). In addition, mAb's can be associated with infusion-related reactions some of which can be severe; these are often immediate and usually occur within minutes of the exposure to the study drug. Therefore, infusions should take place in a facility with appropriate resuscitation equipment available at the bedside and a physician readily available, and participants monitored for respective signs

and symptoms. Participants who experience severe or life-threatening irAEs or infusion reactions may need to permanently discontinue spartalizumab and/or LAG525.

In studies of spartalizumab [CPDR001X2101] and of LAG525 alone and in combination with spartalizumab [CLAG525X2101C], the drugs were well tolerated with safety profiles similar to those of other marketed checkpoint inhibitors. A MTD was not identified for either LAG525 or spartalizumab.

The available data suggests that LAG525 and spartalizumab have a safety profile comparable to other immune checkpoint inhibitors. It is therefore important to be vigilant and carefully identify AEs that may be suggestive of potential immune-mediated AEs, as their appearance may be sub-clinical (for example an asymptomatic laboratory abnormality), and early diagnosis is critical for appropriate management and to possibly prevent complications. Serological, immunological and histological assessments (such as biopsy of the affected tissue) should be performed as deemed appropriate by the investigator to verify the potential immune-mediated nature of the AE and to exclude alternative diagnoses or disease progression. Response to corticosteroids, if indicated, may contribute to the identification of an AE as irAE.

Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including identification and management of study-drug induced adverse events, are provided in Section 6.5.1.1 and Section 6.5.1.2. The risks to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures as well as close clinical monitoring.

Appropriate eligibility criteria and specific dose modification and stopping rules, along with adverse event management guidelines (provided in Section 6.5), are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in same section. There may be unforeseen risks with LAG525 and spartalizumab in combination with carboplatin, which could be serious. Refer also to preclinical toxicity and/or clinical data found in the latest [LAG525 and PDR001 Investigator's Brochures].

Novartis considers the potential risks of the combination regimens with LAG525, spartalizumab, and carboplatin are justified by the anticipated benefits that may be afforded to participants.

In addition, prior to enrollment, this protocol will undergo appropriate review by local and regional governance bodies including ethic committees and drug regulatory bodies.

4.5.3 Risks related to study procedures

Study related risks include, but are not limited to collection of fresh tumor samples, blood collections, and the different imaging methods included. Please refer to the study consent form for more information.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities (i.e. pandemic, epidemic or natural disaster), mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and

permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

The study will include patients with advanced (loco-regionally recurrent not amenable to curative therapy or metastatic) TNBC which progressed after adjuvant or one prior line of systemic therapy for metastatic disease and never received prior treatment with an immune-checkpoint inhibitor.

Participants enrolled in this study are not permitted to participate in additional parallel investigational clinical studies. The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Patient is an adult ≥ 18 years old at the time of informed consent, and has signed informed consent before any trial related activities and according to local guidelines
2. Patient has advanced (loco-regionally recurrent not amenable to curative therapy or metastatic) breast cancer.
3. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
4. Patient has adequate bone marrow and organ function as defined by the following laboratory values (as assessed by central laboratory for eligibility):
   - Absolute neutrophil count ≥ 1.5×10^9/L
   - Platelets ≥ 100×10^9/L
   - Hemoglobin ≥ 9.0 g/dL
   - Creatinine clearance (calculated using Cockcroft-Gault formula, or measured) ≥ 40 mL/min
   - Alanine aminotransferase (ALT) < 3 x ULN, except for patients that have tumor involvement of the liver, who may only be included if ALT ≤5.0 x ULN who are excluded if ALT > 5 x ULN
   - Aspartate aminotransferase (AST) < 3 x ULN, except for patients that have tumor involvement of the liver, who may only be included if AST ≤5.0 x ULN who are excluded if AST > 5 x ULN
   - Total serum bilirubin < 1.5 ULN; or total bilirubin ≤ 3.0 × ULN with direct bilirubin within normal range of the central laboratory in patients with well documented Gilbert's Syndrome
5. Patient must have measurable disease, i.e., at least one measurable lesion as per RECIST 1.1 criteria (Tumor lesions previously irradiated or subjected to other loco-regional therapy will only be considered measurable if disease progression at the treated site after completion of therapy is clearly documented).
6. Patient progressed after adjuvant or 1 prior systemic treatment in the advanced setting. Patients with *de novo* metastatic disease are eligible if they received 1 prior line of therapy.
7. Patient must have received prior systemic treatment that included taxane-based chemotherapy for adjuvant or metastatic disease.
8. Patient must have a site of disease amenable to biopsy, and must be willing to undergo a new tumor biopsy at screening and during therapy on this study, the latter if medically feasible. Patients with an available archival tumor tissue do not need to perform a tumor biopsy at screening if patient has not received anti-cancer therapy since the biopsy was taken.
9. Patient has histologically and/or cytologically confirmed diagnosis of advanced TNBC (based on most recently analyzed biopsy from locally recurrent or metastatic site, local lab) meeting the following criteria: HER2 negative in situ hybridization test or an IHC status of 0 or 1+, and ER and PR expression is <1 percent as determined by immunohistochemistry (IHC) Hammond et al 2010.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Patient has received prior immune checkpoint inhibitors as anticancer treatment, such as anti-LAG-3, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibody (any line of therapy).
2. Patient received prior neoadjuvant or adjuvant therapy with a platinum agent or mitomycin and experienced recurrence within 12 months after the end of the platinum-based or mitomycin containing therapy, or received platinum or mitomycin for advanced disease.
3. Patient is concurrently using other anti-cancer therapy.
4. Patient has had major surgery within 14 days prior to starting study treatment or has not recovered to grade 1 or less from major side effects.
5. Patient with presence of CTCAE grade 2 toxicity or higher due to prior cancer therapy. Exception: Patients with any grade of alopecia are allowed to enter the study.
6. Patient has received radiotherapy ≤ 4 weeks prior to randomization (≤ 2 weeks for limited field radiation for palliation), and has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia).
7. Patient has a known hypersensitivity to other monoclonal antibodies, platinum-containing compounds, or to any of the excipients of LAG525, spartalizumab, or carboplatin.
8. Patient with history of Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis, or a history of severe hypersensitivity reactions, which in the opinion of the investigator may pose an increased risk of serious infusion reaction.
9. History of acute pancreatitis within 1 year of screening or past medical history of chronic pancreatitis.
10. Clinically significant cardiac disease or impaired cardiac function, including any of the following: Cardiac or cardiac repolarization abnormality, including any of the following:
    i. History of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG) within 6 months prior to randomization
    ii. History or current diagnosis of myocarditis
    iii. Cardiac troponin T (TnT) or I (TnI) elevated > 2 x ULN at screening. Repeat Troponin test if values are between >1 and 2 x ULN
        - Patients with a screening or repeat levels ≤ 1 x ULN may be included.
        - If repeat Troponin levels are > 1 and < 2 x ULN, patient can be included at the investigator's discretion after cardiac assessment
        - Repeat assessment should be performed the following day if possible but may be later.
    iv. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block) or uncontrolled hypertension
    v. QTcF > 470 msec on screening central ECG or long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:

- Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
- Concomitant medication(s) known to cause Torsades de Pointe" per www.qtdrugs.org that cannot be discontinued or replaced by safe alternative medication. (within 5 half-lives or 7 days prior to starting study drug)
- Inability to determine the QTcF interval

11. Patient has active, known or suspected autoimmune disease or immune deficiency. Patients with vitiligo, type I diabetes on stable insulin, residual hypothyroidism only requiring hormone replacement, psoriasis not requiring systemic treatment or conditions not expected to recur in the absence of an external trigger should not be excluded.
12. History of allogenic bone marrow or solid organ transplant.
13. History of or current interstitial lung disease or pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).
14. Patient has a concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected carcinoma in situ of any type.
15. Patient has presence of symptomatic central nervous system (CNS) metastases, or CNS metastases that require local CNS-directed therapy (such as radiotherapy or surgery), or increasing doses of corticosteroids within the 2 weeks prior to first dose of study treatment. Patients with treated brain metastases should be neurologically stable and without CNS progression for at least 12 weeks prior to randomization and have discontinued corticosteroid treatment (with the exception of < 10 mg/day of prednisone or equivalent for an indication other than CNS metastases) for at least 4 weeks before first dose of any study treatment.
16. Patient has carcinomatous meningitis
17. Patient has clinically significant active bleeding or history thereof within four weeks prior to randomization.
18. Patient has active infection requiring systemic antibiotic therapy. Patients requiring systemic antibiotics for infection must have completed therapy before screening is initiated.
    - Patient has a known history of HIV infection (testing not mandatory).

    Note: As per local regulations or requirements (e.g. HA, EC/IRB), HIV testing during screening may be mandated.

    - Patients with active Hepatitis B infection (HBsAg positive) or hepatitis C infection.

    Note: Patients with antecedent of Hepatitis B (anti-HBc positive, HBsAg and HBV-DNA negative) are eligible.

    - Patients with positive test for hepatitis C ribonucleic acid (HCV RNA).

    Note: Patients in whom HCV infection resolved spontaneously (positive HCV antibodies without detectable HCV-RNA) or those that achieved a sustained virological response after antiviral treatment and show absence of detectable HCV RNA ≥ 6 months (with the

use of IFN-free regimes) or ≥ 12 months (with the use of IFN-based regimes) after cessation of antiviral treatment are eligible.

19. Patient received any live vaccine against infectious disease (e.g., varicella, yellow fever vaccine) within 4 weeks of initiation of study treatment
20. Patient is currently receiving or has received systemic corticosteroids or any immunosuppressive therapy (≥ 10mg/day prednisone or equivalent) within 7 days prior to starting study drug (other than replacement-dose steroids in the setting of adrenal insufficiency), or who have not fully recovered from side effects of such treatment. Topical, inhaled, nasal and ophthalmic steroids are allowed.
21. Patient has any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns, compliance with clinical study procedures or interpretation of study results
22. Participation in an interventional, investigational study within 2 weeks prior to the first dose of study treatment
23. Women of child-bearing potential defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during study treatment and for 6 months after the last dose of any study treatment. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS)

    Women are considered postmenopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
24. Sexually active males unwilling to use a condom during intercourse while taking study treatment, and up for 6 months after stopping study treatment. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above.
25. Pregnant or nursing (lactating) women confirmed by a positive hCG central laboratory test within 72 hours prior to initiating study treatment.

6 Treatment

6.1 Study treatment

For this study, the investigational drugs are LAG525 and spartalizumab (PDR001). The study treatment was defined as LAG525 and spartalizumab or LAG525 with or without spartalizumab in combination with carboplatin. With protocol amendment 3, enrollment to Arm 1 (LAG525 + spartalizumab) was prematurely closed. Subsequent enrolled participants will be randomized to either Arm 2 (LAG525 + spartalizumab + carboplatin) or Arm 3 (LAG525 + carboplatin).

All drugs will be administered as infusion.

Infusion must take place in a facility with appropriate resuscitation equipment available at the bedside and a physician readily available during the period of drug administration. The participant should be closely observed for potential infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever and the vital signs should be monitored more frequently if clinically indicated, during infusions and for at least 2 hours after the last infusion for the first 2 cycles. The same close observation may be applied for the subsequent cycles if medically indicated.

All dosages prescribed and administered to participants and all dose interruptions and changes during the study must be recorded on the appropriate electronic Case Report Form (eCRF) page.

6.1.1 Investigational and control drugs

LAG525 and spartalizumab will be supplied by Novartis Drug Supply Management or its designee in vials as a liquid formulation for infusion.

Carboplatin packaging and labeling will be performed according to locally available supplies of carboplatin.

Table 6-1 Investigational and combination drug

Investigational/ Combination Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
LAG525 100mg	Concentrate for solution for infusion	Intravenous use	Open-label patient specific; vials	Sponsor global
spartalizumab 100mg	Concentrate for solution for infusion	Intravenous use	Open-label patient specific; vials	Sponsor global
carboplatin 10mg/mL	Concentrate for solution for infusion	Intravenous use	Open-label bulk supply; vials	Local

6.1.1.1 Treatment regimen

The recommended dose for the combination of LAG525 + spartalizumab and single agent dose of LAG525 have already been established ([CLAG525X2101C], Section 4.2) and will remain

constant at the established RDE (LAG525 400mg and spartalizumab 300mg both i.v. every 21 days).

Carboplatin will be dosed per AUC 6 given intravenously on day 1 of every 3-week cycle.

All drugs should be given on the same day.

Table 6-2 Dosing regimen

Dose Level	LAG525 (i.v.) mg	spartalizumab (i.v.) mg	carboplatin (i.v.)
Starting Dose	400mg Q3W	300mg Q3W	AUC 6 Q3W

6.1.1.2 LAG525 and LAG525 + spartalizumab administration

LAG525 and spartalizumab will be administered via i.v. infusion over 30 minutes once every 3 weeks. Infusions of each antibody can be extended to up to 2 hours if clinically indicated.

For participants who receive both drugs, they will be administered separately in the same fashion with at least a 30-min break between the two antibody infusions.

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

6.1.1.3 Carboplatin administration

Carboplatin will be administered every three weeks via i.v. infusion over 15 to 60 minutes once LAG525 and spartalizumab infusions are completed. A break of 30 minutes must be observed between any infusions. Any pre-medications should be administered as per local standard practice.

The dose of carboplatin will be adjusted in order to not exceed 900 mg corresponding to a GFR (based on the Calvert formula) capped at 125 mL/min FDA guidance 2010.

Doses subsequent to the initial dose administered at Cycle 1 Day 1 should be adjusted according to the local prescribing information for carboplatin.

6.1.2 Additional study treatments

No additional treatment beyond the investigational drugs LAG525 and spartalizumab and the combination drug carboplatin is included in this trial.

6.1.3 Treatment arms/group

Participants were assigned at Cycle 1 Day 1 visit to one of the following 3 treatment arms in a ratio of 1:1:1:

- LAG525+spartalizumab (Arm 1)
- LAG525+spartalizumab+carboplatin (Arm 2)
- LAG525+carboplatin (Arm 3)

Starting with protocol amendment 3, participants will be assigned at Cycle 1 Day 1 visit to Arm 2 or Arm 3 in a ratio of 1:1.

Treatment crossover from one arm to another arm will not be permitted in this study.

6.1.4 Guidelines for continuation of treatment

Please refer also to Sections 6.5.1 and 6.5.2.

6.1.5 Treatment duration

Study treatment will continue until the participant experiences one of the following: disease progression per investigator's assessment by RECIST 1.1 (if not meeting the criteria for treatment continuation beyond disease progression as stipulated in Section 6.1.5.1) [redacted], unacceptable toxicity, pregnancy, treatment is discontinued at the discretion of the investigator or the participant, start of a new anti-neoplastic therapy, withdrawal of consent, lost to follow-up, death, or study is terminated by the sponsor.

The investigator may decide to stop carboplatin after 6 cycles, even if the above criteria are not met.

Participants who continue to derive clinical benefit from the treatment based on the investigator's evaluation may receive post-trial access (PTA). PTA means the provision of treatment to trial participants following their completion of this trial (EOT visit will be required prior to PTA). PTA will be provided until one of the following is met: participant no longer derives clinical benefit, investigator discontinues treatment, launch or reimbursement (where applicable), treatment fails to achieve registration in the trial participant's country, or the clinical program is discontinued for any other reason

Mechanisms for provision of PTA may include an extension phase to this study, a separate extension protocol, a rollover protocol, provision of the Novartis investigational product in a non-trial setting (known as post-study drug supply [PSDS]) when no further safety or efficacy data are required, or any other mechanism appropriate for the country.

The PTA mechanism must comply with local laws and regulations in the participating trial countries. If Novartis discontinues the PTA for this trial, Novartis will work with investigators to transition participants onto locally available alternative treatment, or standard of care.

6.1.5.1 Treatment beyond disease progression

Emerging clinical data indicate that participants may derive benefit from continuing treatment with immunotherapy despite initial evidence of disease progression.

Participants who received at least one dose of IO compound LAG525 and/or spartalizumab will be permitted to continue study treatment beyond initial disease progression per RECIST 1.1 [redacted], unacceptable toxicity, pregnancy, treatment is discontinued at the

discretion of the investigator or the participant, start of a new anti-neoplastic therapy, withdrawal of consent, lost to follow-up, death, or study is terminated by the sponsor, provided they meet all of the following criteria:

1. Additional informed consent for treatment beyond disease progression per RECIST 1.1 is provided by the participant
2. [redacted]
3. the continuation of treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g. CNS metastases)
4. participant exhibits adequate tolerance to study treatment
5. participant performance status is stable

Participants who meet the above criteria should continue study treatment beyond initial disease progression per RECIST 1.1 and continue all study procedures as outlined in Section 8.The reasons for the participant continuing treatment will be documented in the eCRF.

In case of clinical deterioration or suspicion of disease progression, a follow-up imaging assessment should be performed promptly rather than waiting for the next scheduled assessment. Participants that are no longer deriving clinical benefit [redacted] must be discontinued.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

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

- Medications to prevent or treat nausea or vomiting.
- Anti-diarrheal medications (e.g., loperamide) for participants who develop diarrhea.
- Pain medication to allow the participant to be as comfortable as possible.
- Treatment with bisphosphonates or denosumab and/or limited-field palliative radiotherapy or surgery for pre-existing painful bone metastases is permitted. Participants requiring initiation of such treatment during the course of the study must be evaluated for disease progression. Radiotherapy like any concomitant medication must be listed on the CRF. LAG525/spartalizumab should be held for ≥1 week prior to radiotherapy or surgery, and may be resumed ≥2 weeks after radiation or surgery, provided the participant has recovered from radiation or surgery related toxicity. Caution is advised for radiation to fields that include lung tissue because of the potential increased risk of pneumonitis when lung radiotherapy is used during therapy with checkpoint inhibitors.
- Immunosuppressive agents to treat suspected irAEs.
- Hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF), thrombopoietin mimetics or erythroid stimulating agents as per local or published guidelines; in case of anemia, thrombocytopenia or neutropenia, potential immune-mediated etiology should be ruled out.
- Nutritional support or appetite stimulants.
- Oxygen therapy and blood products or transfusions.

- Inactivated vaccines.

The participant must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications, procedures and significant non-drug therapies (including physical therapy, herbal/natural medications, and blood transfusions) administered after the participant was enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies or procedures pages.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis/sponsor medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis/sponsor to determine if the participant should continue participation in the study.

Please refer to Section 6.2.2 for prohibited medication.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Anticoagulation and anti-aggregation agents are permitted if the participants are already at stable doses for > 2 weeks at time of first dose and International Normalized Ratio (INR) should be monitored as clinically indicated per investigator's discretion. However, ongoing anticoagulant therapy should be temporarily discontinued to allow tumor sample according to the institutional guidelines.

In cases of isolated brain progression or other local progression, participants may receive palliative radiotherapy or surgery. In addition, localized, palliative radiotherapy for preexisting bone/liver metastases is permitted. LAG525/spartalizumab should be held for ≥1 week prior to radiotherapy or surgery. LAG525/spartalizumab may be resumed ≥2 weeks after radiation or surgery, provided the participant has recovered from radiation or surgery related toxicity. Chemotherapy should be held based on institutional guidelines. If palliative radiotherapy or surgery is initiated after start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be assessed and documented. In case of continuation of study treatment beyond disease progression by RECIST 1.1, the participant will continue assessments as defined in Section 8.

6.2.2 Prohibited medication

During the course of the study, participants must not receive other antineoplastic therapies (e.g. investigational drugs, devices, chemotherapy, immunotherapies) except those specified in the protocol or any other therapies that may be active against cancer or modulate the immune responses. However, limited-field palliative radiotherapy may be allowed as concomitant therapy (see above).

The use of systemic steroid therapy and other immunosuppressive drugs is not allowed except for the treatment of infusion reaction, irAEs, and for prophylaxis against imaging contrast dye allergy, standard pre-medication for chemotherapy or replacement-dose steroids in the setting of adrenal insufficiency (provided the replacement dose for adrenal insufficiency is < 10 mg/day prednisone or equivalent), or transient exacerbations of other underlying diseases such as COPD requiring treatment.

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

There are no prohibited therapies during the post-treatment follow-up period.

6.2.3 Treatments for potential infusion reactions with spartalizumab or LAG525

If a participant experiences an infusion reaction, he/she may receive pre-medication in subsequent cycles where the infusion of LAG525 and/or spartalizumab is administered. The pre-medication should be chosen per institutional standard of care, at the discretion of the treating physician.

Acute allergic reactions should be treated per institutional standard of care. This includes any therapy necessary to restore normal cardiopulmonary status in the event of anaphylactic/anaphylactoid reactions.

If a participant experiences a Grade 3 or higher infusion reaction or anaphylactic/anaphylactoid reaction, the participant will permanently discontinue LAG525/spartalizumab treatment. Further guidelines on management of LAG525/spartalizumab infusion reactions are provided in Table 6-9.

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

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is first enrolled for screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the participant to register them into the IRT. Once assigned, the Participant No. must not be reused for any other participant and the Participant No. for that individual must not be changed, even if the participant is re-screened. If the participant fails to be randomized or start treatment for any reason, the reason will be entered into the Disposition page.

IRT must be notified within 2 days that the participant was not randomized.

6.3.2 Treatment assignment, randomization

Participants were assigned to one of the three treatment arms in a ratio of 1:1:1. Starting with protocol amendment 3, participants will be assigned to Arm 2 and Arm 3 only in a ratio of 1:1 (Section 3 and Section 6.1).

Randomization will be stratified by the presence of liver metastasis and line of therapy (first line or second line).

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A participant randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of participant numbers to randomization numbers. Random permuted blocks scheme will be used for this study. The randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

Prior to dosing, all participants who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant. The randomization number will not be communicated to the caller.

6.4 Treatment blinding

Treatment will be open to participants, investigator staff, persons performing the assessments, and the Novartis representatives from the Clinical Trial Team.

6.5 Dose escalation and dose modification

Study treatment dose escalation is not permitted.

6.5.1 Dose modifications

For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions (LAG525 and spartalizumab and carboplatin) and/or reductions (carboplatin) are either recommended or mandated in order to allow participants to continue the study treatment.

Dose modification recommendations are made for each of the study drugs (for compound specific toxicities). Participants who discontinue a drug of the combination regimens (or two drugs of the triplet) for toxicity and continue on the other drug(s) may remain on study.

The following sections address the specific instructions for mandatory dose modifications and recommended management for adverse events considered suspected to be related to LAG525 and/or spartalizumab and/or carboplatin. These modifications/interruptions must be recorded on the Study Treatment form in EDC system.

The investigators should try to exclude any other etiology and try to identify the most likely drug of the combination to cause the AE.

If the causality of the suspected AE is difficult to determine, the investigator should assume that there is contribution from all drugs (LAG525, spartalizumab, carboplatin).

6.5.1.1 LAG525 and spartalizumab dose interruptions

Dose interruption for LAG525 and spartalizumab includes delaying or withholding the treatment for any reason (e.g., AE) as well as an interruption of treatments during an infusion. The dose may be interrupted for up to 12 weeks (counted from the time the irAE reaches a grade that leads to LAG525/spartalizumab interruption). If a participant requires a dose interruption of spartalizumab and/or LAG525 of more than 12 weeks, then the participant must discontinue the study drug which was interrupted.

If an AE occurs that requires interruption of LAG525/spartalizumab or carboplatin, then treatment for all drugs should be delayed up to a maximum of 2 weeks. If after a maximum of a 2 week delay, the AE has resolved to allow administration of LAG525/spartalizumab or carboplatin, but not both, the permitted study medication should be resumed. Treatment with just the permitted study medication can continue until the AE has resolved to allow resumption of treatment with all prescribed study drugs. However, carboplatin can be interrupted for a maximum of 42 days, and LAG525/spartalizumab can be interrupted for a maximum of 12 weeks. If the participant progresses during the dose interruption, or there is no rationale/clinical benefit of continuing therapy, the participant should be discontinued any time earlier.

Dose management for specific potentially immune-related AEs is summarized in Table 6-3, Table 6-4, Table 6-5, Table 6-6, Table 6-7, Table 6-8, Table 6-9 and Table 6-10. In case of any other AE that is not listed in the guidance tables and thought to be related to study drugs, and whether or not the AE is deemed to be immune related, treatment should be interrupted and restarted only after the toxicity has been resolved to grade 1 or lower. Deviations to mandatory dose interruptions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in below tables or listed in Section 9.1.1.

6.5.1.2 Dose interruption requirements for potential immune-mediated adverse events

6.5.1.2.1 Identification of and management requirements for AEs of potential immune-mediated etiology (irAE)

Adverse events of special interest (AESIs) include AEs of a potential immune-mediated etiology (irAE) that are associated with spartalizumab/LAG525 treatment. Investigators must be vigilant and carefully identify AEs that may be suggestive of potential irAEs as their appearance may be sub-clinical and early diagnosis is critical for its adequate management and resolution. Collaboration with disease-specific subspecialties is encouraged; corticosteroids are the mainstay of treatment for most irAEs.

An irAE may be of low grade and self-limited, frequently involving the GI tract (i.e., diarrhea/colitis), skin (i.e., rashes, pruritus), liver (i.e., hepatitis), lung (i.e., pneumonitis), kidneys (i.e., nephritis) and endocrine systems (i.e. hypothyroidism, hyperthyroidism, type I

diabetes, hypophysitis including hypopituitarism and adrenal insufficiency). Other immune-mediated AEs may rarely include the nervous system (e.g. encephalitis, Guillain-Barre syndrome, myasthenia gravis), eye (e.g. uveitis, vision changes), musculo-skeletal system (e.g. myositis, arthritis), pancreas (e.g. pancreatitis), cardio-vascular system (e.g. vasculitis, myocarditis) or blood system (e.g. anemia, cytopenias), and severe skin reactions such as toxic epidermal necrolysis or Stevens Johnson syndrome. Furthermore, complications in participants with bone marrow or solid organ transplant have been reported (e.g. organ rejection, severe graft-versus-host disease). However, nearly all organs can be affected by immune-mediated toxicities. IrAEs often occur relatively early (mostly within weeks to 3 months after treatment initiation), however, may develop at any time during treatment (even after several months), and may also occur after the treatment discontinuation. Serological, immunological and histological assessments should be performed as deemed appropriate by the investigator, to verify the potential immune-related nature of the AE, and exclude a neoplastic, infectious or metabolic origin of the AE.

Severe grade or persistent lower grade irAEs typically require interrupting or permanently discontinuing treatment and administration of systemic steroids, and sometimes other immunosuppressive medications (e.g., tumor necrosis factor alpha (TNFa) antagonists, mycophenolate or tacrolimus). Early recognition and work-up of irAEs and initiation of treatment are critical to reduce the risk of complications, since the majority of irAEs are reversible with the use of steroids and other immune suppressants. Some events like endocrinopathies may require life-long hormonal replacement. Tapering of steroids should not be too rapid (i.e. > 4 weeks) to avoid recurrence or worsening of irAEs. The management of irAEs may further include initiation of antibiotics for prophylaxis against opportunistic infections.

Participants should be instructed to return to the study site as soon as possible (instead of waiting for their next scheduled visit) if they experience symptoms consistent with an irAE. Participants who experience a new or worsening irAE should be contacted and/or evaluated by the study site more frequently.

Based on experience and published guidelines on the management of irAEs in patients treated with immune checkpoint inhibitors (Brahmer et al 2018; Haanen et al 2017; NCCN 2018) instructions have been developed how to manage irAEs that may occur in participants receiving checkpoint inhibitors, such as spartalizumab and/or LAG525. Dose modification requirements and AE management guidelines for the potential irAEs are provided in the following tables: diarrhea/colitis (Table 6-3), hepatitis (liver laboratory alterations) (Table 6-4), skin (rash) (Table 6-5), nephritis (Table 6-6), pneumonitis (Table 6-7), endocrinopathies (Table 6-8), encephalitis and other potential immune-related AEs (Table 6-10). In addition, guidance for management of spartalizumab/LAG525 infusion-related reaction is provided in (Table 6-9).

Under the category of OTHERS (Table 6-10) are included several irAE of interest that must be managed specifically and for which no specific guidance are provided in the table below. OTHERS include (but is not restricted to) the following events : Autoimmune neuropathy, demyelinating polyneuropathy, Guillain-Barre syndrome, myasthenia gravis-like syndrome, non-infectious myocarditis, non-infectious pericarditis, pancreatitis and, rapid onset of Grade 3 fatigue in the absence of disease progression.

Participants receiving spartalizumab and/or LAG525, may experience other irAEs than those listed in this document, therefore all AEs of unknown etiology associated with drug exposure should be evaluated to determine if it is possibly immune-related. In cases where the specific irAE is not listed in the tables below, the investigator should follow the guidance in Section 6.5.1.1. Investigators are encouraged to contact the Sponsor as needed to discuss cases that warrant separate discussion outside of the scope of the current instructions.

The dosing modification requirements are mandatory; however, the AE management guidelines are recommendations and can be modified according to the local practices.

General dose modification instructions:

No changes in dose of spartalizumab and/or LAG525 are allowed.

Overall AEs are to be graded according to NCI-CTCAE v5.0 **(**https://ctep.cancer.gov**)**. All dose interruptions and the reason for the dose interruption must be documented in the eCRF.

Overall, participants with AEs suspected to be related to spartalizumab or LAG525 including those of potential immune-mediated etiology (irAE) may need to interrupt or permanently discontinue study treatment as outlined in Section 6.5.

Permanently discontinue spartalizumab/LAG525 for any of the following:

1. Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy).
2. Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. The 12 weeks' timeframe will begin from the time the irAE reaches a grade that leads to spartalizumab and or LAG525 interruption.
3. Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 12 weeks after last dose of spartalizumab/LAG525.
4. Any severe or Grade 3 treatment-related adverse reaction that recurs.

Table 6-3 Criteria for dose interruption and re-initiation of LAG525 and spartalizumab treatment for potential immune-related diarrhea/colitis

Diarrhea/Colitis (NCI-CTCAE v5.0)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1 (Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline)	• Symptomatic treatment (loperamide, hydration, diet) • Monitor closely	• May continue spartalizumab/LAG525 treatment
Grade 2 (Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL)	• Consult with GI specialist • Stool evaluation, imaging and endoscopy as clinically indicated • Symptomatic treatment (loperamide, hydration, diet) • Commence steroids (0.5-1mg/kg per day of prednisone or i.v. equivalent) until symptoms improve	• Interrupt spartalizumab/LAG525 until diarrhea recovers to Grade ≤1 or baseline

Diarrhea/Colitis (NCI-CTCAE v5.0)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
and/or abdominal pain/ mucus or blood in stool.	to Grade 1, particularly in case of persisting/worsening symptoms, ulcerations or bleeding seen on endoscopy, or blood in stool. If no improvement occurs within days, manage as per Grade 3. • Slowly taper steroids once symptoms improve to Grade 1 (ie. Over 4-6 weeks)	
Grade 3 Diarrhea: Increase of ≥7 stools per day over baseline;; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL; Grade 3 Colitis: Severe abdominal pain; peritoneal signs	• Consider hospitalization; rule out bowel perforation and initiate i.v. hydration as needed. • Consultation with gastroenterologist and consider endoscopy and biopsy. • In addition to symptomatic treatment initiate treatment with i.v. steroids (1 to 2 mg/kg/d of methylprednisolone or equivalent) • Consider antibiotics as appropriate • If no improvement in 2-3 days: consider initiating infliximab 5mg/kg and continue steroids. (Infliximab is contraindicated in participants with sepsis/ perforation). • Slowly taper steroids once symptoms improve to Grade 1 (4 to 6 weeks) • If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab.	• Interrupt spartalizumab/LAG525 until diarrhea/colitis recovers to Grade ≤1 or baseline
Grade 4: Life-threatening consequences; urgent intervention indicated	• Same as Grade 3	• Permanently discontinue spartalizumab/LAG525

Table 6-4 Criteria for dose interruption and re-initiation of LAG525 and spartalizumab treatment for potential immune-related liver laboratory alterations

Abnormal liver function tests		
Severity	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 2: AST or ALT >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal or bilirubin >1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal (if participant meets criteria for potential drug-induced liver injury (DILI) cases refer to Section 6.5.2.1)	• Monitor hepatic laboratory tests more frequently (every 2-3 days) until returned to baseline values • Rule-out alternative causes (e.g. concomitant medications, infection, disease progression) • Consider prednisone (0.5-1 mg/kg/d) if liver tests worsen and/or significant symptoms	• Interrupt spartalizumab/LAG525 treatment until recovery to Grade ≤1 or baseline • Once recovered restart spartalizumab/LAG525 treatment at the same dose and schedule • Participants with baseline grade 2 AST/ALT value (>3.0-5.0 ULN) may continue spartalizumab/LAG525 treatment
Grade 3 or 4: AST or ALT >5.0xULN and/or bilirubin > 3.0x ULN	• Monitor hepatic laboratory tests more frequently (every 2-3 days) until returned to baseline values. • Consult with hepatologist; consider hospitalization and liver biopsy to establish etiology • Initiate treatment with steroids (prednisone 1-2 mg/kg/d or i.v. equivalent) • Add prophylactic antibiotics for opportunistic infections as appropriate • Once symptoms/liver tests improve to Grade ≤1, taper steroids over at least 4 weeks • If no improvement or steroid refractory	• Permanently discontinue spartalizumab/LAG525 • Participants with baseline grade 2 AST/ALT value (>3.0-5.0 ULN) will discontinue spartalizumab/LAG525 treatment if value increased to grade 3 with increase >=2x baseline, or to grade 4

Abnormal liver function tests		
Severity	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
	after 3 days, consider oral mycophenolate as per local treatment guidance • Infliximab is not recommended due to its hepatotoxicity potential	

* Send viral serology looking for hepatitis A, B, C & CMV and rule out any potential cause of liver injury (i.e., alcohol, other medications, etc.) Note: For additional information on follow-up of potential drug induced liver injury cases, refer to Section 6.5.2.1.

Table 6-5 Criteria for dose interruption and re-initiation of LAG525 and spartalizumab treatment for potential immune-related skin events

Skin Events (NCI-CTCAE v5.0)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1 (e.g. Rash, pruritus) covering < 10% Body Surface Area (BSA)	• Initiate prophylactic and symptomatic treatment measures. • Consider mild/moderate potency topical steroids or urea containing creams in combination with oral antipruritics • Reassess after 2 weeks	• Continue spartalizumab/LAG525 treatment
Grade 2 (e.g. Rash, pruritus): 10-30% of BSA	• Consider initiating systemic steroids (e.g., oral prednisolone 0.5-1mg/kg daily) and consider dose interruption • In addition, treat with topical emollients, oral antihistamines, and medium/high-potency topical steroids • If symptoms persist or recur consider skin biopsy	• Consider dose interruption • In case of bullous dermatitis, acute generalized exanthematous pustulosis or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), interrupt spartalizumab/LAG525 until recovery to Grade ≤1 or baseline
Grade 3 (e.g. Rash, pruritus): More than 30% of BSA,	• Consult with dermatologist and consider skin biopsy	• Interrupt spartalizumab/LAG525 until recovery to Grade ≤1 or baseline

Skin Events (NCI-CTCAE v5.0)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Other severe cutaneous adverse reactions Bullous dermatitis	• Initiate systemic steroids (1mg/kg/d prednisolone or i.v. equivalent); consider increasing if no improvement • High-potency topical steroids • Topical emollients, oral antihistamines as indicated • Consider gamma-aminobutyric acid (GABA) agonists or aprepitant in case of severe pruritus	• For participants with severe cutaneous adverse reaction or bullous dermatitis, risk/benefit before resuming treatment should be carefully considered.
Grade 4: Life-threatening	• Urgent dermatologic consultation and additional measures as per local guidelines.	• Permanently discontinue spartalizumab/LAG525
Stevens-Johnson syndrome, toxic epidermal necrolysis	• Hospitalization and urgent dermatology consultation • institute supportive care immediately as per institutional guidelines	• Permanently discontinue spartalizumab/LAG525

Table 6-6 Criteria for dose interruption and re-initiation of LAG525 and spartalizumab treatment for potential immune-related nephritis*

Nephritis (NCI-CTCAE v5.0)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1: Creatinine >ULN to ≤1.5x ULN	• Monitor creatinine weekly • Rule-out other causes (e.g. fluids, medications, i.v. contrast) • Promote hydration and cessation of nephrotoxic drugs	• Continue spartalizumab/LAG525 treatment
Grade 2: Creatinine >1.5 - 3.0 x baseline; >1.5 to ≤ 3.0 x ULN	• Monitor creatinine every 2 to 3 days and consult with nephrologist • Rule-out other causes (e.g. fluids, medications, i.v.contrast)	• Interrupt spartalizumab/LAG525 until serum creatinine recovers to ≤ Grade 1 or baseline

Nephritis (NCI-CTCAE v5.0)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
	• Initiate 0.5 to 1 mg/kg/day prednisone or equivalents if other causes are ruled out • If worsening or no improvement: 1 to 2 mg/kg/day prednisone equivalents • Promote hydration and cessation of nephrotoxic drugs • Consider renal biopsy	
Grade 3: Creatinine >3.0 x baseline; >3.0 to <6 x ULN	• Monitor creatinine every 1 to 2 days and consider hospitalization • Consult with nephrologist and consider renal biopsy • Start 1 to 2 mg/kg/day prednisone equivalents • Once event improves to Grade ≤1, slowly taper steroids over at least 4-6 weeks	• Permanently discontinue spartalizumab/LAG525
Grade 4: Creatinine > 6.0 x ULN	• Same as Grade 3 • hospital for close monitoring and management as per institutional guidelines	• Permanently discontinue spartalizumab/LAG525

*In participants with impaired renal function, dosage of carboplatin should be reduced as per local labeling for carboplatin and hematologic nadirs and renal function monitored.

Table 6-7 Criteria for dose interruption and re-initiation of LAG525 and spartalizumab treatment for potential immune-related pneumonitis

Pneumonitis (NCI-CTCAE v5.0)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated	• Chest imaging/CT scan; repeat imaging in 3-4 weeks or as clinically indicated • Monitor symptoms every 2-3 days, clinical evaluation and laboratory work-up for infection; pulse oximetry • Consultation with pulmonologist recommended	• Consider interruption of spartalizumab/LAG525

Pneumonitis (NCI-CTCAE v5.0)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 2: Symptomatic-medical intervention indicated; limits instrumental ADLs	• Chest imaging/CT scan; repeat imaging in 3-4 weeks or as clinically indicated • Monitor symptoms daily, consider hospitalization • Clinical evaluation and laboratory work up for infection, pulse oximetry • Consult pulmonologist • Pulmonary function tests • Bronchoscopy with biopsy and/or BAL recommended to rule out infection and/or disease progression/lung • Initiate steroids (1 to 2 mg/kg/day prednisone or equivalent). • Consider empirical antibiotics • If no improvement within 2-3 days, or worsening, treat as grade 3	• Interrupt spartalizumab/LAG525 until recovery to Grade ≤1 or baseline • Permanently discontinue spartalizumab/LAG525 treatment in case of recurring grade 2 pneumonitis
Grade 3: Severe symptoms; limits self-care ADLs; oxygen indicated Grade 4: Life-threatening respiratory compromise, urgent intervention indicated	• Hospitalization and pulmonary and infectious disease consultation • Methylprednisolone (1-2 mg/kg/d or equivalent) until symptoms improve to Grade ≤1, then slow taper over ≥4-6 weeks • If no improvement within 48 hours, consider infliximab and/or other immune-suppressive therapy, or i.v. Ig as per local guidelines • Empiric antibiotics	• Permanently discontinue spartalizumab/LAG525

Table 6-8 Criteria for dose interruption and re-initiation of LAG525 and spartalizumab treatment for potential immune-related endocrine events

Endocrine events (NCI-CTCAE v5.0)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Asymptomatic (grade 1), intervention not indicated (e.g.,		• Continue spartalizumab/LAG525 treatment

Endocrine events (NCI-CTCAE v5.0)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
hyperthyroidism or hypothyroidism)		
Symptomatic endocrinopathy (e.g., hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism)	• Endocrinology consultation • Rule out infection/sepsis and other alternative causes with appropriate cultures and imaging • Evaluate hormone levels (e.g. ACTH, cortisol, FSH/LH, TSH, free T4, testosterone/estrogen), metabolic panel (e.g. Na, K, CO2, glucose), and imaging (e.g. brain MRI) as clinically indicated • Initiate hormone replacement therapy as appropriate • Consider steroids (methylprednisolone 1 to 2 mg/kg/d or equivalent) in case of sever hypophysitis or thyrotoxicosis • Replacement of appropriate hormones may be required as the steroid dose is tapered • Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis • Consider a beta-blocker in case of severe hyper-thyroidism. • Consider hospitalization (e.g. in case of severe adrenal insufficiency/crisis), fluid replacement, and other supportive measures as clinically be initiated	• Interrupt spartalizumab/LAG525 until symptomatic recovery to mild (i.e., grade 1) or no symptoms, and controlled with hormone replacement therapy • Hypothyroidism may be managed with replacement therapy without treatment interruption (unless life-threatening) • Permanently discontinue for life-threatening (Grade 4) endocrinopathies (i.e., hyperthyroidism, adrenal insufficiency, hypophysitis) or recurring severe/life-threatening events not controlled by hormone replacement therapy

Endocrine events (NCI-CTCAE v5.0)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Autoimmune diabetes (Grade 3 or symptomatic hyperglycemia) Autoimmune diabetes (Grade 4 hyperglycemia or life-threatening complications)	• Initiate anti-glycemic therapy (i.e., insulin) as medically indicated and monitor glucose levels regularly until metabolic control is achieved • Evaluate for ketoacidosis as medically indicated • Consultation with endocrinologist • Consider hospitalization (e.g. in case of ketoacidosis)	• Interrupt spartalizumab/LAG525 until recovery to grade 1 or baseline • Permanently discontinue spartalizumab/LAG525 in case of recurring severe/life-threatening events not controlled by anti-glycemic therapy

Table 6-9 Criteria for dose interruption and re-initiation of LAG525 and spartalizumab treatment for infusion-related reactions

Infusion reaction (NCI-CTCAE v5.0)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs/pulse oximetry as medically indicated until the participant is deemed medically stable in the opinion of the investigator • Consider slowing infusion rate until recovery of symptoms	• Continue spartalizumab/LAG525

Grade 2
Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, i.v. fluids); prophylactic medications indicated for < =24 hrs
	• Stop Infusion and keep line open
	• Additional medical therapy as per local institutional guidelines that may include:
	  • i.v. fluids
	  • Antihistamines
	  • NSAIDS
	  • Acetaminophen
	  • Narcotics
	  • Oxygen and corticosteroids as indicated
	• Increase monitoring of vital signs/pulse oximetry as medically indicated until the
		• Permanently discontinue spartalizumab/LAG525 in case of recurring infusion reaction despite adequate premedication and prolonged infusion/slow infusion rate

Infusion reaction (NCI-CTCAE v5.0)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**

	participant is deemed medically stable.
	• If symptoms resolve, the infusion may be restarted at 50% of the original infusion rate
	• Premedicate participants approximately 1.5 hrs prior to next infusion of spartalizumab/LAG525 with:
	  • Diphenhydramine (50 mg po or equivalent)
	  • Acetaminophen (500-1000 mg po or equivalent)
	  • Or as per local institutional guidelines	

Grade 3:
Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)
 	
Grade 4:
Life-threatening; pressor or ventilatory support indicated
	• Stop Infusion
	• Additional medical therapy as per local institutional guidelines that may include:
	  • i.v. fluids
	  • Antihistamines
	  • NSAIDS
	  • Acetaminophen
	  • Narcotics
	  • Oxygen
	  • Corticosteroids
	  • Epinephrine
	• Close monitoring of vital signs, pulse oximetry and ECG as medically indicated until the participant is deemed medically stable.
	• Hospitalization as indicated
		• Permanently discontinue spartalizumab/LAG525

Table 6-10 Criteria for dose interruption and re-initiation of LAG525 and spartalizumab treatment for "other" potential immune-related AEs of special interest

Other immune mediated events- including but not limited to Autoimmune neuropathy, Demyelinating polyneuropathy, Guillain-Barre syndrome, Myasthenia gravis- like syndrome, Non-infectious myocarditis, pericarditis, pancreatitis, and Grade 3 Fatigue with rapid onset in absence of disease progression, encephalitis, vasculitis, myositis, hemolytic anemia, uveitis		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Mild (Grade 1)	• Provide symptomatic treatment evaluate/monitor adequately	• Continue spartalizumab/LAG525
Moderate (Grade 2)	• Ensure adequate evaluation to confirm etiology or exclude other causes • Provide symptomatic treatment • Systemic corticosteroids may be indicated • Consider biopsy for confirmation of diagnosis. • A specialist should be consulted	• Consider interruption of spartalizumab/LAG525 until recovery to ≤ Grade 1 or baseline
Severe (Grade 3)	• Initiate systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg/d or equivalent) and other therapies as appropriate • Monitor closely and consult with a specialist	• Interrupt spartalizumab/LAG525 until recovery to ≤ Grade 1 or baseline • May restart spartalizumab/LAG525 treatment at the same dose and schedule 2nd occurrence: • Permanently discontinue spartalizumab/LAG525
Grade 4	• Hospitalization and consult with specialist	• Permanently discontinue spartalizumab/LAG525
Guillain-Barre Severe peripheral or autonomic neuropathy, or transverse myelitis	• Hospitalization and consult with specialist	• Permanently discontinue spartalizumab/LAG525
Encephalitis or aseptic meningitis	• Rule out infectious or other causes of moderate to severe neurologic deterioration, and consult with specialist • If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents	• Permanently discontinue spartalizumab/LAG525
Myasthenia gravis	• Consult with specialist	Grade 2

Other immune mediated events- including but not limited to Autoimmune neuropathy, Demyelinating polyneuropathy, Guillain-Barre syndrome, Myasthenia gravis- like syndrome, Non-infectious myocarditis, pericarditis, pancreatitis, and Grade 3 Fatigue with rapid onset in absence of disease progression, encephalitis, vasculitis, myositis, hemolytic anemia, uveitis		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
	• Consider pyridostigmine and systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg/d; other therapies as appropriate (e.g. i.v. Ig) • Hospitalization in case of severe cases	• Interrupt PDR001 until recovery to ≤ Grade 1 or baseline Grade ≥3 • Permanently discontinue spartalizumab/LAG525
Myocarditis any grade, or cardiac event grade>=3	Urgent cardiology consult is essential to initiate high dose systemic corticosteroids (prednisone or equivalent) (Mahmood et al 2018, Brahmer et al 2018)	• Permanently discontinue spartalizumab/LAG525
Pancreatitis Amylase/lipase elevation	• Evaluate for pancreatitis (clinical assessment, abdominal imaging and/or MRCP as appropriate) • PDR001 may be continued in case of asymptomatic, isolated enzyme elevations without evidence for pancreatitis • Initiate steroids in case of ≥ grade 2 acute pancreatitis	Grade 2 acute pancreatitis: • Interrupt PDR001 until recovery to ≤ Grade 1 or baseline Grade ≥3 acute pancreatitis: • Permanently discontinue spartalizumab/LAG525
Autoimmune hemolytic anemia, hemolytic uremic syndrome, or acquired hemophilia grade ≥3	• Consult with specialist Consider systemic corticosteroids and other therapies as appropriate (e.g. transfusion) per local institutional guidelines	• Permanently discontinue spartalizumab/LAG525
Ocular events	Consult with ophthalmologist	Grade 2 • Interrupt PDR001 until recovery to ≤ Grade 1 or baseline Grade 3 and 4 • Permanently discontinue spartalizumab/LAG525

6.5.1.2.2 Guidance for corticosteroids tapering for management of immune-related AEs

Consultation with disease-specific experts is recommended. Steroids must be tapered slowly and based on response/recovery of clinical symptoms.

Consider complete tapering over a period of at least 4 weeks (sometime 6-8 weeks or longer) to prevent recurrent irAEs. Slower tapering or re-escalation of corticosteroids therapy may be needed if the adverse event is not showing improvement. Once corticosteroid tapering is achieved at a level of 10 mg of prednisone/day (or equivalent) or less, spartalizumab/LAG525 can be restarted as indicated in the dose modification tables. If the dose of prednisone or equivalent cannot be reduced to less than 10 mg/day before the administration of next dose of study treatment, then LAG 525/spartalizumab must be held (note: next dose can be delayed up to 12 weeks).

6.5.1.3 Dose modifications for carboplatin

The local prescribing information should be used for carboplatin dose modifications for the management of myelotoxicity and in participants with impaired kidney function.

6.5.2 Follow-up for toxicities

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

Participants with transaminase increase combined with total bilirubin (TBL) increase may be indicative of potential DILI, and should be considered as clinically important events.

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

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

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

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

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

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR, and alkaline phosphatase.

2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, and history of any pre-existing liver conditions or risk factors, should be collected.

3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.

4. Obtain PK sample, as close as possible to last dose of, if PK analysis is performed in the study.

5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", and thus, meet the definition of SAE and should be reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Study treatment will be dispensed at the site/clinic under the supervision of the investigator and/or study personnel. Records of study medication used, dosages administered, intervals between visits and the completion of the study will be captured in the Drug Accountability Form as well as in IRT. Pharmacokinetic parameters (measures of treatment exposure) will be determined in all participants as detailed in pharmacokinetics section.

6.6.2 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section. Only qualified and trained personnel to the preparation procedure will handle, prepare and dispense the study drug as described in Pharmacy Manual.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the

instructions specified on the labels and in the [Investigator's Brochure]. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis/sponsor CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

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

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

Dosing and treatment schedule will be performed according to Section 6.1.

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

Additional dosing guidelines for fasting glucose sampling:

On Day 1 of Cycles 1 and 3, a pre-dose fasting (overnight) glucose sample will be collected. The participant must be fasting overnight for at least 10 hours prior to the blood collection for fasting glucose but can freely drink water. A pre-dose pharmacokinetic sample will also be drawn at the same time. After these blood samples, the participant should have a light breakfast prior being administered the study treatment infusions.

Additional dosing guidelines for pharmacokinetic sampling:

On days with pharmacokinetic sampling (Cycle 1 Day 1, Day 8 and Day 15, Cycle 2 Day 1 and Day 8, Cycle 3 Day 1, Day 8 and Day 15, Day 1 of Cycles 4 to 7, End of Treatment visit), the participant does not have to fast overnight unless they are also having a fasting plasma glucose sample taken. The pre-dose sample should be drawn just before study treatment dosing. The sampling time of the pre-dose PK sample and the dosing time of study treatment infusions must be precisely recorded in the eCRF.

7 Informed consent procedures

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

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consent forms are included in this study:

- Main study consent, which also includes:
  - A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study
- Pregnancy Outcomes Reporting Consents for female subjects or the female partners of any male subjects who took study treatment
- Patient participation beyond disease progression

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

Participants who will continue study treatment beyond initial disease progression as per RECIST 1.1 criteria have to be re-consented. These participants must sign a new, witnessed IRB/IEC-approved informed consent form which will detail alternative available therapies.

As per section 4.6, during a Public Health emergency as declared by Local or Regional authorities (i.e. pandemic, epidemic or natural disaster), that may challenge the ability to obtain

a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference), if allowable by a local Heath Authority. Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments and indicates with an "X", the visits when they are to be performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in Table 8-1 or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Table 8-1 Assessment Schedule

Period	**Screening**	**Treatment**									**End of Treatment (EOT)**	**Follow-up[3]**						
Visit Name	**Screening**	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 1 Day 15**	**Cycle 2 Day 1**	**Cycle 2 Day 8**	**Cycle 3 Day 1**	**Cycle 3 Day 8**	**Cycle 3 Day 15**	**Subseq. cycles Day 1**	**End of Treatment (EOT)**	**30 day Safety F-up**	**60 day Safety F-up**	**90 day Safety F-up**	**120 day Safety F-up**	**150 day Safety F-up**	**End Post Treatment Follow-up**	**Survival F-up[4]**
Days	**-21 to -1**	**1**	**8 ±1**	**15 ±1**	**22 ±1**	**29 ±1**	**43 ±1**	**50 ±1**	**57 ±1**	**- ±3**	**-**	**- -0 +7**	**- ±7**	**- ±7**	**- ±7**	**- -0 +14**	**-**	**-**
Informed consent	X																	
IRT registration	X										X							
IRT randomization		X																
Treatment beyond progression ICF		for participants who meet the criteria outlined in Section 6.1.5.1																
Demography	X																	
Inclusion / Exclusion criteria	X																	
Medical history/current medical conditions	X																	
BRCA status if known	X																	
Locally confirmed TNBC status in advanced setting	X																	

Period	**Screening**	**Treatment**									**End of Treatment (EOT)**	**Follow-up[3]**						
Visit Name	**Screening**	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 1 Day 15**	**Cycle 2 Day 1**	**Cycle 2 Day 8**	**Cycle 3 Day 1**	**Cycle 3 Day 8**	**Cycle 3 Day 15**	**Subseq. cycles Day 1**	**End of Treatment (EOT)**	**30 day Safety F-up**	**60 day Safety F-up**	**90 day Safety F-up**	**120 day Safety F-up**	**150 day Safety F-up**	**End Post Treatment Follow-up**	**Survival F-up[4]**
Days	**-21 to -1**	**1**	**8 ±1**	**15 ±1**	**22 ±1**	**29 ±1**	**43 ±1**	**50 ±1**	**57 ±1**	**- ±3**	**-**	**- -0 +7**	**- ±7**	**- ±7**	**- ±7**	**- -0 +14**	**-**	**-**
Diagnosis and extent of cancer	X																	
Prior/concomitant medications	From 30d prior to starting study treatment until 150d safety follow-up or start of new antineoplastic medication, whichever is sooner. If new antineoplastic medication is started, only medications relative to the suspected AEs/SAEs should be collected.																	
Antineoplastic therapies (prior/since discontinuation of study treatment)	X										X	X	X	X	X	X	X	
Physical Examination	S	S			S		S			S	S							
Performance status	X	X			X		X			X	X	X						
Body Height	X																	
Body Weight	X	X			X		X			X	X							
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X						
Hematology	X	X	X	X	X	X	X			X	X	X						
Chemistry	X	X	X	X	X	X	X			X	X	X						
Thyroid Panel-TSH	X				X		X			X	X	X						
Thyroid Panel-Free T3; Free T4	X	Only if TSH is abnormal																

Period	**Screening**	**Treatment**									**End of Treatment (EOT)**	**Follow-up[3]**						
Visit Name	**Screening**	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 1 Day 15**	**Cycle 2 Day 1**	**Cycle 2 Day 8**	**Cycle 3 Day 1**	**Cycle 3 Day 8**	**Cycle 3 Day 15**	**Subseq. cycles Day 1**	**End of Treatment (EOT)**	**30 day Safety F-up**	**60 day Safety F-up**	**90 day Safety F-up**	**120 day Safety F-up**	**150 day Safety F-up**	**End Post Treatment Follow-up**	**Survival F-up[4]**
Days	**-21 to -1**	**1**	**8 ±1**	**15 ±1**	**22 ±1**	**29 ±1**	**43 ±1**	**50 ±1**	**57 ±1**	**- ±3**	**-**	**- -0 +7**	**- ±7**	**- ±7**	**- ±7**	**- -0 +14**	**-**	**-**
Hepatitis testing	X	If clinically indicated perform testing as needed																
Local HIV testing, if required per local requirements/regulations	S																	
Cytokines for safety	X	Anytime when a suspected cytokine release syndrome occurs, immediately after the AE, and one week after occurrence of the AE																
Coagulation	X	X			X		X			X	X	X						
Cardiac Troponin	X			X		X	X		X									
Urinalysis (macroscopic)	S				S		S			S	S							
Urinalysis (microscopic)	Any time dipstick urinalysis is abnormal																	
Pregnancy Test (serum)[1]	≤72 hours before first dose of study treatment										X	X				X		
Pregnancy test (urine)					S		S			S			S	S	S			

Period	**Screening**	**Treatment**									**End of Treatment (EOT)**	**Follow-up[3]**						
Visit Name	**Screening**	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 1 Day 15**	**Cycle 2 Day 1**	**Cycle 2 Day 8**	**Cycle 3 Day 1**	**Cycle 3 Day 8**	**Cycle 3 Day 15**	**Subseq. cycles Day 1**	**End of Treatment (EOT)**	**30 day Safety F-up**	**60 day Safety F-up**	**90 day Safety F-up**	**120 day Safety F-up**	**150 day Safety F-up**	**End Post Treatment Follow-up**	**Survival F-up[4]**
Days	**-21 to -1**	**1**	**8 ±1**	**15 ±1**	**22 ±1**	**29 ±1**	**43 ±1**	**50 ±1**	**57 ±1**	**- ±3**	**-**	**- -0 +7**	**- ±7**	**- ±7**	**- ±7**	**- -0 +14**	**-**	**-**
Tumor evaluation (CT scan/MRI/Bone scan)	-28 to -1	Every 6 weeks (+/- 1 week) for the first 9 months and every 12 weeks (+/- 1 week) thereafter, [redacted]. See Table 8-2 for imaging collection plan and Section 8.3.1. Upon the approval of amendment 4, the tumor assessments during the post-treatment efficacy follow-up period will be now optional and will be left at the discretion of the investigator.																
Chest X-ray		If clinically indicated																
ECG (Central)	At least 72 hours prior randomization	X					X				X							
ECG (Local)		S			S		S			On Day 1 of every 2 cycles after cycle 3								
Cardiac imaging (MRI/ECHO)	X	If clinically indicated									X							
Adverse Events	Suspected AE up to Day 150; non-suspected AE up to Day 150 or start of new post treatment anti-neoplastic medication, whichever is sooner. See Appendix 1 (Safety follow-up diagram)																	
Serious Adverse Events	Suspected SAE up to Day 150 and beyond; non-suspected SAE up to Day 150 or start of new post treatment anti-neoplastic medication, whichever is sooner. See Appendix 1 (Safety follow-up diagram)																	

[redacted]

Period	**Screening**	**Treatment**									**End of Treatment (EOT)**	**Follow-up[3]**						
Visit Name	**Screening**	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 1 Day 15**	**Cycle 2 Day 1**	**Cycle 2 Day 8**	**Cycle 3 Day 1**	**Cycle 3 Day 8**	**Cycle 3 Day 15**	**Subseq. cycles Day 1**	**End of Treatment (EOT)**	**30 day Safety F-up**	**60 day Safety F-up**	**90 day Safety F-up**	**120 day Safety F-up**	**150 day Safety F-up**	**End Post Treatment Follow-up**	**Survival F-up[4]**
Days	**-21 to -1**	**1**	**8 ±1**	**15 ±1**	**22 ±1**	**29 ±1**	**43 ±1**	**50 ±1**	**57 ±1**	**- ±3**	**-**	**- -0 +7**	**- ±7**	**- ±7**	**- ±7**	**- -0 +14**	**-**	**-**
[redacted]																		
Newly obtained tumor sample[2]	X																	
[redacted]																		
LAG525 infusion		Day 1 of each cycle (21 days) until EOT																

Period	**Screening**	**Treatment**									**End of Treatment (EOT)**	**Follow-up[3]**						
Visit Name	**Screening**	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 1 Day 15**	**Cycle 2 Day 1**	**Cycle 2 Day 8**	**Cycle 3 Day 1**	**Cycle 3 Day 8**	**Cycle 3 Day 15**	**Subseq. cycles Day 1**	**End of Treatment (EOT)**	**30 day Safety F-up**	**60 day Safety F-up**	**90 day Safety F-up**	**120 day Safety F-up**	**150 day Safety F-up**	**End Post Treatment Follow-up**	**Survival F-up[4]**
Days	**-21 to -1**	**1**	**8 ±1**	**15 ±1**	**22 ±1**	**29 ±1**	**43 ±1**	**50 ±1**	**57 ±1**	**- ±3**	**-**	**- -0 +7**	**- ±7**	**- ±7**	**- ±7**	**- -0 +14**	**-**	**-**
spartalizumab infusion		Day 1 of each cycle (21 days) until EOT																
carboplatin infusion		Day 1 of each cycle (21 days) until EOT																
PK sampling		At C1D1, C1D8, C1D15, C2D1, C2D8, C3D1, C3D8, C3D15, Day 1 of Cycles 4 to 7, EOT -See Table 8-7 and Table 8-8 for PK collection log																
Immunogenicity (IG) sampling		On Day 1 of Cycles 1 to 7, EOT - See Table 8-7 for immunogenicity sampling plan																
Participant's disposition	X										X						X	
Efficacy followup[3]																	X	
Safety followup visit[3]												X				X		
Safety follow-up Call[3]													S	S	S			
Survival followup[3,4]																		

S =Assessment to be recorded in the source documentation only
X = assessment to be recorded in the clinical database or received electronically from a vendor
[1] by Central Laboratory, unless participant is postmenopausal (see Exclusion Criterion 23 for definition of postmenopausal status)

[2] If new tumor sample cannot be obtained, archival tumor sample obtained maximum 6 months prior to start of study treatment is acceptable providing the participant has not received antineoplastic therapy since then.

[3] For ongoing participants 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.

[4] Follow-up duration is limited to 150 days after the last dose of LAG525 and/or spartalizumab (whichever was stopped last). If carboplatin was stopped more than 150 days after LAG525 and/or spartalizumab, the participant can be discontinued 30 days after the last dose of carboplatin. Survival follow-up period is removed after Protocol Amendment #4 is approved.

8.1 Screening

All study participants must be thoroughly informed about all aspects of the study, including the study treatment, visit schedule, required evaluations, and all regulatory requirements for informed consent. Written informed consent must be obtained before any study specific assessments are performed, including screening. If the participant is unable to read, an impartial witness should be present during the entire informed consent discussion.

For details of screening assessments, refer to Table 8-1.

The screening assessments must be performed within 21 days of first dose of study treatment to confirm participant's eligibility with the exception of the central serum pregnancy test which must be conducted within 72 hours prior to start of study treatment.

For participants who may have had procedures previously performed as part of the participant's routine disease care (prior to signing study informed consent), the following procedures can be used providing a proper documentation in participant's file is available:

Participants will also be asked to participate in an optional tumor tissue collection at disease progression. If so, the participant will have to sign an additional consent within the main informed consent form.

A participant who has a laboratory test result(s) that does not satisfy the entrance criteria may have the test(s) repeated. These test(s) may be repeated as soon as the investigator believes the re-test result(s) is/are likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within 21 days of screening period. In this case, the participant will not be required to sign another ICF, and the original participant ID number assigned by the investigator will be used. In the event that the laboratory test(s) cannot be performed within 21 days of screening period or the re-test(s) do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the participant is considered a screen failure.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, however, the participant ID number will remain the same. All required screening activities must be performed when the participant is re-screened for participation in the study to satisfy the requirements defined in Table 8-1. An individual participant may only be re-screened once for the study. Once the number of participants screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the participants who screen failed will not be permitted to re-screen.

8.1.1 Eligibility screening

Following registering in the IRT for screening, participant eligibility will be checked according to study inclusion and exclusion criteria as described in Section 5 once all screening procedures

are completed. A list of procedures to be performed during the 21-day screening period is summarized in Table 8-1.

Results of all screening/baseline evaluations must be reviewed by the investigator or his/her designee prior to start study treatment of each participant to ensure that all inclusion and exclusion criteria have been satisfied.

The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE section for reporting details). If a screen failure participant experiences an AE which does not meet SAE criteria, details about the AE will be recorded only in the investigator's source documents. If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g., participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

The following participant demographics and baseline characteristics are to be collected on all participants on the eCRF:

- Demography including age, sex, race and ethnicity (as per local regulations)
- Height, weight
- Medical history/current medical condition (including BRCA mutation status, if available) present before signing the informed consent. Investigators will have the discretion to record abnormal test findings on the appropriate CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.
- Confirmed TNBC status in advanced setting
- Diagnosis and extent of cancer
- Prior and concomitant medication: all medications and significant non-drug therapies taken within 4 weeks prior to first dose of study treatment as well as during study treatment.
- Prior antineoplastic therapy
- [redacted]

Furthermore, the following assessments will be performed to assess the eligibility of the participant:

- Vital signs including body temperature, blood pressure and pulse
- ECOG performance status
- ECG
- Cardiac imaging
- Tumor evaluation
- Laboratory evaluations (e.g., hematology, coagulation, biochemistry, thyroid function, urinalysis)

In addition a serum pregnancy test will be performed for women with childbearing potential by central laboratory and the result will automatically be transferred to Novartis.

Participants will be stratified at randomization according to: Absence or presence of liver metastasis and line of therapy (first or second line) in the advanced setting.

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

8.3 Efficacy

8.3.1 Efficacy assessment (imaging)

Tumor response will be assessed locally according to the Novartis guideline version 3.1 (Section 16.3 Appendix 3) based on RECIST 1.1 Eisenhauer et al 2009 [redacted]. The imaging assessment collection plan is presented in Table 8-2.

The local investigator's assessment will be used for the primary endpoint analysis (RECIST 1.1) and for treatment decision making based on secondary [redacted] efficacy endpoints (RECIST 1.1 [redacted]).

Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. Central review of the imaging data may be performed if deemed necessary. Please refer to the site imaging operations manual for additional information on image acquisition and data collection by the imaging CRO.

Table 8-2 Imaging Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest, abdomen and pelvis CT or MRI (with intravenous contrast enhancement)	Mandated	Mandated during treatment period, every 6 weeks (+/- 1 week) for the first 9 months and every 12 weeks (+/- 1 week) thereafter. With amendment #4 the imaging assements during the efficacy follow-up period will be optional and will be left at the investigator's discretion.
Brain CT or MRI	Mandated	If clinically indicated
Whole body bone scan	Mandated	If clinically indicated
Localized bone CT, MRI or x-ray	For any lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Color photography (with scale/ruler)	For any skin lesions present	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis

Procedure	Screening/Baseline	During Treatment/Follow-up
CT or MRI of other metastatic sites (e.g., neck)	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis

Baseline imaging assessments

Imaging assessments will be performed at screening/baseline within 28 days of start of treatment (Day -28 to Day -1 prior to Cycle 1 Day 1).

Any imaging assessments already completed during the regular work-up of the participant within 28 days prior to start of treatment, including before signing the main study ICF (Informed Consent Form), can be considered as the baseline images for this study. Any imaging assessments obtained after randomization cannot be considered baseline images. The following assessments are required at screening/baseline:

- Chest, abdomen and pelvis CT or MRI
- Brain CT or MRI
- Whole body bone scan
- Localized bone CT, MRI or x-ray, for any lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI
- CT or MRI of other metastatic sites (e.g., neck), if clinically indicated

If a participant is known to have a contraindication to CT intravenous (IV) contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts, however if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

A whole body bone scan should be performed per institutional standard of care (e.g., Tc-99 bone scan, whole body bone MRI, Fluorodeoxyglucose positron emission tomography (FDG-PET) or sodium fluoride (NaF) PET). Localized CT, MRI or X-rays should be acquired for all skeletal lesions identified on the screening whole body bone scan, which are not visible on the chest, abdomen and pelvis CT/MRI.

If clinically indicated, CT or MRI of other areas (e.g., neck) of disease as appropriate should be performed.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

Chest x-rays and ultrasound should not be used to measure tumor lesions.

Post-baseline imaging assessments

Imaging assessments as described in Table 8-2 should be performed using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 8-1). Imaging assessments for response evaluation will be performed every 6 weeks (+/- 7 days) during the first 9 months, and every 12 weeks (+/- 7 days) thereafter as outlined below. Imaging assessments should be scheduled using the randomization date as the reference

date (not the date of the previous tumor assessment), and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments performed.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a participant, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

Each lesion that is measured at baseline must be measured by the same method and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. If an unscheduled imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule. If the suspicion is confirmed, a complete imaging assessment as per Table 8-2 needs to be done as soon as possible. If the progression is not confirmed, an individual imaging procedure will not need to be repeated at the next scheduled imaging if it has been done within 4 weeks.

Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of i.v. contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (Section 16.3 Appendix 3).

An additional tumor assessment must be performed to confirm response (CR or PR) no less than 4 weeks after the criteria for response are first met.

For participants who discontinue study treatment for reasons other than documented disease progression per RECIST 1.1, death, lost to follow-up, or withdrawal of consent, tumor assessments must continue to be performed every 6 weeks in the first 9 months and every 12 weeks thereafter, until documented disease progression per RECIST 1.1 per investigator, death, lost to follow-up, or withdrawal of consent. Even after the start of subsequent anti-cancer therapy, every effort will be made to continue tumor assessments until disease progression, death, withdrawal of consent or loss to follow-up.

For participants who continue study treatment beyond initial RECIST 1.1. PD, [redacted] or discontinuation of study treatment (whichever occurs first) as outlined in Table 8-2.

For participants who discontinue study treatment [redacted], continuation of tumor assessments [redacted].

Upon the approval of amendment 4 by Institutional review board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities, the tumor assessments during the post-treatment efficacy follow-up period will be optional and will be left at the discretion of the investigator.

8.3.2 Appropriateness of efficacy assessments

Tumor response will be assessed locally according to the Novartis guideline version 3.1 (Section 16.3 Appendix 3) based on RECIST 1.1 Eisenhauer et al 2009 [redacted]

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

Table 8-3 Assessments & Specifications

Assessment	Specification
Physical examination	At screening, a complete physical examination will be performed including the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. Additionally include examination of breasts and loco-regional lymph nodes. If indicated based on medical history and/or symptoms, rectal, external genitalia and pelvic exams will be performed. A short physical exam will be performed at all visits as indicated above (see Table 8-1) during treatment except where a complete physical examination is required (see above). It will include at least the examination of general appearance and vital signs (body temperature, blood pressure [SBP and DBP] and pulse). If indicated based on symptoms, additional exams will be performed. Information for all physical examinations must be included in the source documentation at the study site and additionally reported in appropriate CRF page for blood pressure (SBP and DBP), vital signs, height and weight. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital sign	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 8-1.

Performance status:

ECOG Performance status scale will be used as described in Table 8-4.

Table 8-4 ECOG Performance Status

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

8.4.1 Laboratory evaluations

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

Table 8-5 Laboratory Assessments (Central and Local)

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands *(absolute values preferred , %s are acceptable)*
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatinine clearance, Creatine kinase, Direct Bilirubin, Indirect Bilirubin if Total Bilirubin > grade 1, Total Bilirubin, Total Cholesterol, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting)[1], Cardiac Troponin T (cTnT) recommended or Troponin I (cTnI) if unable to assay TnT[2]
Urinalysis (local)	Local Laboratory: Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) Local laboratory Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Thyroid	At baseline: TSH (Thyroid Stimulation Hormone), Free T3 and Free T4 At the subsequent visits as indicated in Table 8-1: TSH only. If TSH is abnormal, central lab will test Free T3 and Free T4
Hepatitis markers	HBV-DNA, HBsAg, HBsAb, HBcAb, HCV RNA-PCR (baseline)
HIV serology (local)	If required per local regulations: local HIV testing at screening
Cytokines	IFN-γ, IL-6, IL-1,TNF-α
Pregnancy Test	A central laboratory serum pregnancy hCG test must be performed at screening within 72 hours before first dose of study treatment, at EOT, at 30-day and 150-Day safety follow-up. A local laboratory urine pregnancy test must be performed at day 1 of every cycle beginning with cycle 2, and at home every 30-days after 30-day safety follow-up visit until120-day follow-up.

[1] Glucose (fasting) will be evaluated on Cycle 1 Day 1 and Cycle 3 Day 1, other visits do not require fasting state

[2] Troponin will be tested locally as outlined in Section 8.4.2.2.

Lab parameters will be evaluated by a central laboratory except for urinalysis, HIV testing (to be performed only if required per local regulations), urine pregnancy tests and troponin levels, which will be performed locally. Please refer to [Central Laboratory Manual] for details.

Local laboratory assessments may be performed if medically indicated or when the treating physician cannot wait for central laboratory results for decision making. In this particular situation, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel with local analysis.

Samples for safety cytokine panel at screening will be stored below -70°C by central laboratory and analyzed only if post-screening samples are received.

8.4.2 Electrocardiogram (ECG)

In this study local and central ECG will be used, depending on the time point and purpose.

The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

At screening, eligibility will be based on the average of triplicate ECGs (central read). In order to ensure ECG evaluation is received from the central laboratory for eligibility assessment, it is advisable to perform the ECG at least 72 hours prior to the scheduled randomization date.

A standard 12 lead ECG will be conducted prior to dosing on day 1 of cycles as indicated in Table 8-1. The ECG will be assessed locally to confirm participant safety. Any abnormality will be documented in the AE pages of the eCRF.

Standard triplicate 12 lead ECG will be performed on C1D1 and C3D1, pre-dose and post-dose, and submitted for central read. Any unscheduled ECG and the EoT ECG will be submitted for central read to ensure that any ECG-related AEs are assessed and confirmed centrally. Standard triplicate 12 lead ECG will be performed after the participant has been resting for 5-10 min prior to each time point. Triplicate ECGs should be taken approximately 2 minutes apart.

Table 8-6 Local and Central ECG collection plan

Cycle	Day	Time	ECG Type
Screening		at least 72 hrs prior to randomization	12 Lead, triplicate, central
1	1	Pre-dose After completion of infusions (±10 min)	12 Lead, local (pre-dose)* and 12 Lead, triplicate, central (pre- and post- dose)
2	1	Pre-dose	12 Lead, local
3	1	Pre-dose After completion of infusions (±10 min)	12 Lead, local (pre-dose)* and 12 Lead, triplicate, central (pre- and post- dose)
Every 2 cycles after the third cycle (odd numbered cycles)	1	Pre-dose	12 Lead, local
EOT		Anytime	12 Lead, triplicate, central
Unscheduled or Unplanned sample (as clinically indicated)		Anytime	12 Lead, triplicate, central
For any study arm, pre-dose is before start of infusion of the first drug, post-dose is after infusion of the last drug *if central 12 Lead ECG was performed it can be used for local interpretation (read and signed by investigator)			

Triplicate 12 Lead ECGs are to be collected with ECG machines supplied by the ECG central laboratory.

Single 12 Lead ECGs are collected at the study site using an ECG machine for safety assessment in real time by a qualified physician to ensure participant safety. The original ECGs appropriately signed must be collected and archived at the study site. Only clinically significant abnormalities must be reported as adverse events.

In the event that a QTcF value of > 470 ms is observed, or if an unscheduled ECG is performed for safety reasons, it is recommended to collect a time-matched PK sample and record the time and date of the last study drug intake to determine the drug exposure.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant

findings should be collected in triplicate. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.

All ECGs, including unscheduled triplicate safety ECGs with clinically relevant findings, collected during the study should be transmitted to the central core ECG laboratory for review.

The results of the centrally assessed ECGs are automatically transferred into the clinical database.

8.4.2.1 Cardiac imaging - MRI or echocardiography (ECHO)

Cardiac imaging will be done at screening, during the study treatment period if clinically indicated and at the end of treatment visit.

8.4.2.2 Troponin monitoring guidance

Cardiac enzyme troponin-T or I will be performed at screening. Troponin T assessment is recommended (Troponin I to be used if unable to assay TnT).

Additional safety assessments must be done during the first 2 months as outlined in Table 8-1. If Troponin level is above ULN during the first 2 months, or if level is above the screening value (if value was 1-2 fold ULN), echocardiogram and ECG must be performed. If ECG and ECHO are normal, Troponin must be repeated the following day. However if either ECG or ECHO are abnormal and suggestive of myocarditis, a cardiologist must be consulted.

8.4.3 Pregnancy and assessments of fertility

A condom is required for all sexually active male participants treated with carboplatin (Arm 2 and Arm 3) to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants should not donate sperm for the time period as defined per exclusion criteria 24 (Section 5).

All premenopausal women who are not surgically sterile will have pregnancy testing as follows. Additional pregnancy testing might be performed if requested by local requirements.

- At screening, a serum pregnancy testing will be performed within 72 hours of first dose of study treatment on all female participants of childbearing potential as defined per exclusion criteria 25.
- During study treatment, urine pregnancy tests will be performed on Day 1 of each cycle at the clinic/investigator's site. Any positive urine test needs to be confirmed with a serum test. If positive, the participant must be discontinued from the study treatment.
- At end of treatment visit, 30day and 150day safety follow-up visits, a serum pregnancy test will be performed.

Assessments of Fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following case:

1. Surgical bilateral oophorectomy without a hysterectomy

In the absence of the above medical documentation, follicle stimulating hormone (FSH) testing is required of any female participant, regardless of reported reproductive/menopausal status at screening/baseline.

8.4.4 Other safety evaluations

Chest X-ray

Standard chest X-ray (posteroanterior (PA) view) will be performed as per Table 8-1 if clinically indicated.

8.5 Additional assessments

8.5.1 Pharmacokinetics

8.5.1.1 Pharmacokinetics (PK) and Immunogenicity (IG)

PK and IG samples will be collected at the visits defined in the assessment schedule. Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment. Blood samples for LAG525 and spartalizumab PK and IG evaluation will be collected from all participants who receive at least one dose of LAG525 and spartalizumab. Blood samples for carboplatin PK evaluation will be collected from all participants who receive at least one dose of carboplatin. Time points of blood sample collection for LAG525 and spartalizumab PK and IG and for carboplatin PK will be collected from C1D1 to C7D1 as outlined in Table 8-7 and Table 8-8 (Section 8.5.1.1), respectively.

The exact date and clock times of drug administration PK and IG blood draw will be recorded on the appropriate eCRF. If participants experience a SAE or an AE leading to the discontinuation of the study treatment, an unscheduled PK blood sample should be obtained as close as possible to the event occurrence. If participants experience suspected immunologically related AE such as infusion-related reaction, hypersensitivity, cytokine release syndrome and anaphylaxis, an unscheduled IG blood sample should be obtained as close as possible to the event occurrence. The date and time of the last dose and the time of PK blood draw should be recorded. [redacted]

8.5.1.1.1 Pharmacokinetic and Immunogenicity blood collection and handling

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in any vein except from the site of infusion (e.g. port) or from the same arm that is used for drug infusion. A total of 3.5 mL of blood will be collected for PK analysis in serum and a total of 5 mL for IG analysis in serum for LAG525 at each designated sampling timepoint. For time points when sampling of LAG525 (mAb) PK and IG coincide, 8.5 mL of blood will be collected in total for both IG and LAG525 PK. A total of 2.5 mL of blood will be collected for PK analysis in serum, and a total of 3.5 mL for IG analysis in serum for spartalizumab at each designated sampling timepoint. For time points when sampling of spartalizumab (mAb) PK and IG coincide, 6 mL of blood will be collected in total for both IG and spartalizumab PK. After clotting, the resulting serum will be separated in aliquots and will be stored frozen until analysis.

Another 4 mL of blood at each designed timepoint will be collected for the PK analysis of carboplatin.

Refer to the [CLAG525B2101 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

Table 8-7 Schedule of blood collection log for LAG525 and spartalizumab pharmacokinetics (PK) and immunogenicity (IG)

Scheduled timepoints for PK and immunogenicity sampling (hours)			Dose Reference Identification (ID) For LAG525		Sample number for LAG525		Dose Reference Identification (ID) for spartalizumab		Sample number for spartalizumab	
Cycle	**Day**	**Scheduled time (hours)[a]**	**Dose ID following sampling**	**Dose ID prior to sampling***	**PK**	**IG[b]**	**Dose ID following sampling**	**Dose ID prior to sampling***	**PK**	**IG**
1	1	pre-infusion[g]	101		101	401	201		201	501
1	1	1 hr (± 5 min) post - EOI	101		102		201		202	
1	8	168 hr (±24h)	101		103		201		203	
1	15	336 hr (±24h)	101		104		201		204	
2	1	pre-infusion[g] (i.e., 504 hr (±24h) post-C1D1 dose)	102	101	105	402	202	201	205	502
2	8	168 hr (±24h)	102		106		202		206	
3	1	pre-infusion[g] (i.e., 504 hr (±24h) post C2D1 dose)	103	102	107	403	203	202	207	503
3	1	1 hr (± 5 min) post - EOI	103		108		203		208	
3	8	168 hr (±24h)	103		109		203		209	
3	15	336 hr (±24h)	103		110		203		210	
4	1	pre-infusion[g] (i.e., 504 hr (±24h) post-C3D1 dose)	104	103	111	404	204	203	211	504

Scheduled timepoints for PK and immunogenicity sampling (hours)			Dose Reference Identification (ID) For LAG525		Sample number for LAG525		Dose Reference Identification (ID) for spartalizumab		Sample number for spartalizumab	
Cycle	**Day**	**Scheduled time (hours)[a]**	**Dose ID following sampling**	**Dose ID prior to sampling***	**PK**	**IG[b]**	**Dose ID following sampling**	**Dose ID prior to sampling***	**PK**	**IG**
5	1	pre-infusion[g] (i.e., 504 hr (±24h) post-C4D1 dose)	105	104	112	405	205	204	212	505
6	1	pre-infusion[g] (i.e., 504 hr (±24h) post-C5D1 dose)	106	105	113	406	206	205	213	506
7	1	pre-infusion[g] (i.e., 504 hrs (±24h) post-C6D1 dose)	107	106	114	407	207	206	214	507
EOT					1000	5000			3000	6000
Unscheduled					1001+[c]	5001+[d]			3001+[e]	6001+[f]

EOI = End of infusion for each compound * These dose reference IDs refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK samples [a] Time is relative to the beginning of the infusion for each compound unless otherwise indicated [b] IG samples are being collected together with PK samples at the same time. [c] PK sample numbers for any unscheduled PK collection will start with 1001 for LAG525. [d] IG sample numbers for any unscheduled IG collection will start with 5001 for LAG525. [e] PK sample numbers for any unscheduled PK collection will start with 3001 for spartalizumab. [f] IG sample numbers for any unscheduled IG collection will start with 6001 for spartalizumab. [g] Take PK samples within 30 min before the each compound infusion begins.

Note:PK/IG blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in any vein except from the site of infusion (e.g. port) or from the same arm that is used for drug infusion.

Table 8-8 Schedule for blood collection for carboplatin pharmacokinetic (PK) blood collection log

Scheduled timepoints for PK and (hours)			Dose Reference Identification (ID)		PK (plasma) sample number	PK (plasma ultra filtrate) sample number
Cycle	**Day**	**Scheduled time (hours)**	**Dose ID following sampling**	**Dose ID prior to sampling***		
1	1	Pre-infusion[a]	301		301	601
1	1	EOI (±5 minutes)	301		302	602
1	1	1 hr (±10 minutes) post-EOI	301		303	603

Scheduled timepoints for PK and (hours)			Dose Reference Identification (ID)		PK (plasma) sample number	PK (plasma ultra filtrate) sample number
Cycle	**Day**	**Scheduled time (hours)**	**Dose ID following sampling**	**Dose ID prior to sampling***		
1	1	2 hr (±10 minutes) post-EOI	301		304	604
1	1	3 hr (±10 minutes) post-EOI	301		305	605
3	1	Pre-infusion[a]	302	31	306	606
3	1	EOI (±5 minutes)	302		307	607
3	1	1 hr (±10 minutes) post-EOI	302		308	608
3	1	2 hr (±10 minutes) post-EOI	302		309	609
3	1	3 hr (±10 minutes) post-EOI	302		310	610
4	1	Pre-infusion[a]	303	32	311	611
Unscheduled					7001+[b]	8001+[c]

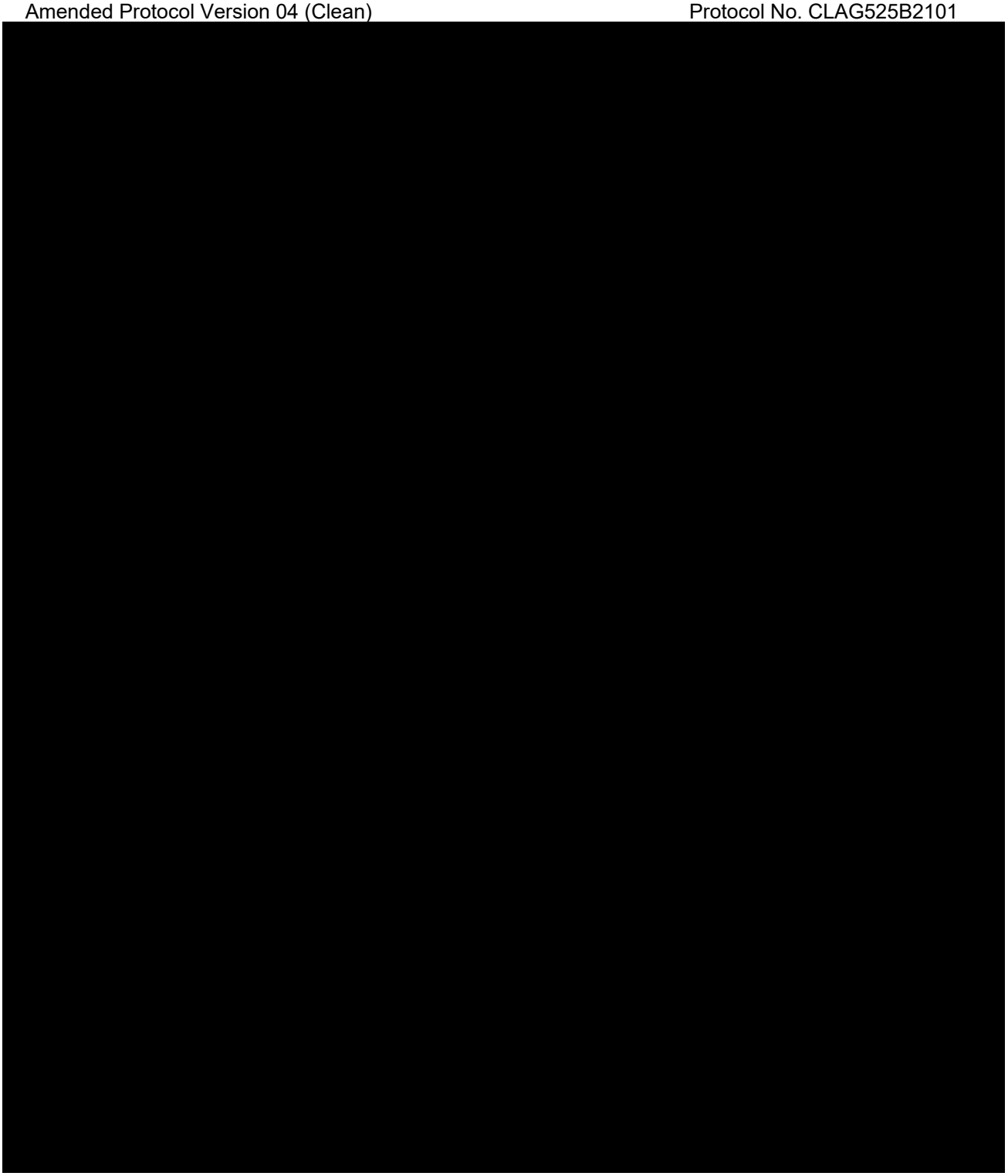
EOI = end of infusion * These dose reference IDs refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK sample [a] Take PK samples within 30 min before the carboplatin infusion begins [b] Sample numbers for any unscheduled plasma collection will start with 7001. [C] Sample numbers for any unscheduled plasma ultra filtrate collection will start with 8001. Note: PK blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in any vein except from the site of infusion (e.g. port) or from the same arm that is used for drug infusion. Plasma ultrafiltration involves separation of free from protein-bound microsolute in small volumes (0.15 – 1.0 mL) of serum, plasma, and other biological samples.

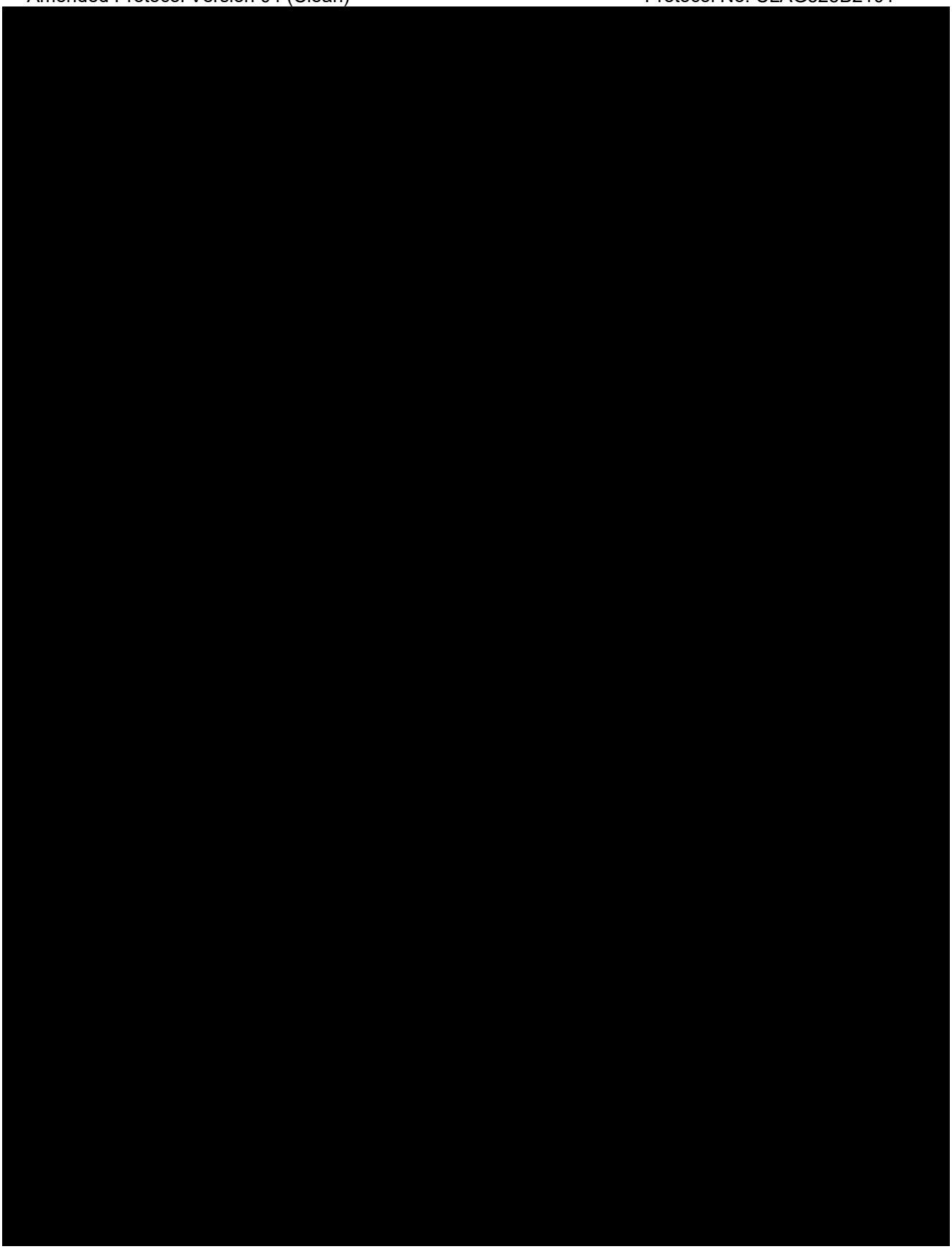
8.5.1.1.2 Analytical method

The validated analytical method for the quantification of LAG525 in human serum consists of trypsin digestion and solid phase extraction as sample clean-up. Prior to mass spectrometric detection, a reverse phase liquid chromatography step is incorporated to reduce sample complexity. The triple quadrupole mass spectrometer is set-up in tandem mode. LAG525 is quantified via detection on of a surrogate peptide. Using a sample volume of 50 µL of human serum, the validated LC-MS/MS LAG525 assay has an estimated LLOQ of 0.25 µg/mL.

Spartalizumab (PDR001) is quantified in human serum using a sample preparation method consisting of protein precipitation and tryptic digestion. The assay consists of a reduced phase liquid chromatography step prior to triple quadrupole mass spectrometry detection. Spartalizumab is quantified via detection on of a surrogate peptide. The validated method has an estimated LLOQ of 0.25 µg/mL, using 25 µL of human serum.

Carboplatin is measured via an Inductively Coupled Plasma Mass Spectrometer using the ratio response of platinium (Pt) to its internal standard. Carboplatin is measured both in ultrafiltrate (estimated LLOQ 1 ng/mL) and plasma (estimated LLOQ 100 ng/mL).





[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Participants may voluntarily discontinue from the study treatment for any reason at any time.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Adverse event requiring permanent discontinuation of study treatment as per Section 6.5.
- Progressive disease per RECIST 1.1 [redacted] (see criteria in Section 6.1.5.1 for continuation of treatment beyond disease progression by RECIST 1.1)
- Protocol deviation that results in significant risk to participant’s safety
- Use of prohibited treatment as per Section 6.2.2.
- Pregnancy (Pregnancy will be followed for outcome)

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant’s premature discontinuation of study treatment and record this information.

The investigator must also contact the IRT to register the participant’s discontinuation from study treatment.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdrawal of informed consent Section 9.1.2). **Where possible, they should return for the assessments indicated** in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation for reasons [redacted], death, lost to follow-up, or withdrawal of consent, at a minimum, the following data should be collected at clinic visits or via telephone/email contact:

- new antineoplastic therapy
- new / concomitant treatments
- adverse events/Serious Adverse Events
- tumor assessments must continue to be performed every 6 weeks (+/- 7 days) if discontinuation occurs within the first 9 months, and every 12 weeks (+/- 7 days) thereafter [redacted], death, lost to follow-up or withdrawal of consent.
- with implementation of protocol amendment #4, all tumor assessments during the post-treatment efficacy follow-up period will be optional for the remaining participants in the study and will be left at the discretion of the investigator. Moreover, participants who had stopped LAG525 and/or spartalizumab 150 days ago (whichever was stopped last) or who had stopped carboplatin more than 150 days after LAG525 and/or spartalizumab will be discontinued from the study (either immediately or for those who had received carboplatin 30 days after the last dose of carboplatin).

In some circumstances participants may be allowed to continue to receive study treatment beyond disease progression as per RECIST criteria. These participants will continue assessments as outlined in the assessments section, and will complete the EOT visit only after permanent discontinuation of study treatment. End of treatment is not considered as the end of the study.

9.1.2 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent and record this information.

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

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

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

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

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

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible (instructions will be provided to the investigator for contacting the participant, when the participant should stop taking drug and when the participant should come for a final visit) and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

The primary analysis will be conducted when all participants 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). Following the cut-off date for the analysis reported in the primary CSR, the study will remain open. Ongoing participants will continue to receive study treatment and be followed as per the schedule of assessments, as long as participants derive benefit from study treatment.

The end of study is defined as the earliest occurrence of one of the following: (1) all participants have died or (2) discontinued from the study, or (3) another clinical study becomes available that can continue to provide study treatment in this participant population and all ongoing participants are eligible to be transferred to that clinical study. All participants who have stopped their study treatment for at least 150 days after the last dose of LAG525 and/or spartalizumab (whichever was stopped last) will be discontinued from the study. If carboplatin was stopped more than 150 days after LAG525 and/or spartalizumab, the participant can be discontinued 30 days after the last dose of carboplatin.

At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to participants who in the opinion of the Investigator are still deriving clinical benefit. The final analysis will occur at the end of the study. Any additional data for participants continuing to receive study treatment past the data cutoff date for the primary CSR, as allowed by the protocol, will be reported in the final CSR on completion of the study.

9.2.1 Follow up for safety evaluations

All participants must be followed for safety up to 150 days after the last dose of LAG525 and/or spartalizumab whichever was stopped last. After the 30-day onsite safety follow-up visit, participants will be followed (via telephone call or onsite visit if participant happens to be visiting the site) at 60 (+/- 7), 90 (+/-7), 120 (+/-7) and 150 (+14) days after the last dose of LAG525 and/or spartalizumab (whichever was stopped last). If carboplatin is stopped more than 150 days after LAG525 and/or spartalizumab, only the 30-day safety follow-up visit needs to be performed.

All safety assessments should be completed as per Table 8-1. However, if the participant begins post treatment antineoplastic medication before the 150-Day safety follow-up visit the collection of new SAEs and AEs unrelated to study medication will stop and thereafter only suspected AEs and suspected SAEs will continue to be collected up to Day 150. Suspected SAEs will continue to be collected beyond the 150-Day safety visit (see Section 16.1 Appendix 1). Data collected should be added to the appropriate eCRF pages. For female participants of child bearing potential, a pregnancy test will be performed at the time points listed in Table 8-1.

9.2.2 Follow up for efficacy evaluations

Participants who discontinue study treatment for reasons [redacted], death, lost to follow-up or withdrawal of consent, should continue tumor assessment [redacted], death, lost to follow-up or withdrawal of consent at the same intervals as per Table 8-2.

Upon the approval of amendment 4 by Institutional review board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities, the tumor assessments will be optional and will be left at the discretion of the investigator. Participants who are in efficacy follow-up for at least 150 days after the last dose of study treatment can be discontinued from the study.

9.2.3 Survival follow up

Participants will enter the survival follow-up period once they complete the safety follow-up period and efficacy follow-up period after treatment discontinuation (whichever is longer). Participants will then be contacted by telephone every 12 weeks to follow-up on their survival status. Any new antineoplastic therapies that have been started since the last contact date will also be collected during these phone calls.

The survival follow-up period will be removed and participant that are currently in survival follow-up can discontinue from the study at the time of the approval of amendment 4 by Institutional review board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a participant or clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The Common Toxicity Criteria (CTC) AE grade (version 5.0).

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

2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality

will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant

3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes an SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken with study treatment.

All adverse events must be treated appropriately. Action taken with study treatment may include one or more of the following:

- Dose not changed
- Dose Reduced (only for carboplatin)
- Drug interrupted/withdrawn

6. its outcome
   a. not recovered/not resolved;
   b. recovered/resolved;
   c. recovered/resolved with sequelae;
   d. fatal; or unknown

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

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least:

- 150 days following the last dose of LAG525 and/or spartalizumab
- until the start of a new post treatment antineoplastic medication if sooner than the 150 days mentioned above. If a participant starts a post treatment antineoplastic therapy, then only adverse events suspected to be related to study treatment should be collected out to 150 days after discontinuation of LAG525 and/or spartalizumab
- 30 days after discontinuation of carboplatin if the participant continued carboplatin more than 150 days after the last dose of LAG525 and/or spartalizumab.

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

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (RECIST 1.1 [redacted] guidelines), should not be reported as a serious adverse event, except if the investigator considers that progression of malignancy is related to acceleration of tumour growth due to study treatment. Newly emerging clinical evidence indicates that a very small number of participants treated with immune checkpoint inhibitors may develop tumor growth acceleration. This is termed hyperprogression or hyperprogressive disease (Champiat et al 2017) and is distinct from pseudoprogression. If the investigator suspects that treatment with spartalizumab or LAG525 accelerates tumor growth it should be reported as an SAE. Note: Progressive disease which occurs as the result of treatment failure/resistance to the treatment is not an AE or SAE and should not be recorded as such.

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

Information about adverse drug reactions for LAG525 and spartalizumab can be found in the Investigator's Brochures. For carboplatin adverse drug reactions, please refer to the local label.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

10.1.1.1 Adverse Events of Special Interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the latest [Investigator Brochure].

- Endocrinopathies (Hypothyroidism, hyperthyroidism, diabetes, hypophysitis and hypopituitarism, adrenal insufficiency)
- Pneumonitis
- Colitis
- Hepatitis
- Nephritis
- Encephalitis
- Rash
- Other immune-mediated events
- Infusion reactions

For Adverse events related to carboplatin refer to the local product label.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of an SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent must be reported to Novartis safety within 24 hours of learning of its occurrence and until:

- at least 150 days following the last dose of LAG525 and/or spartalizumab
- the start of a new post treatment antineoplastic medication if sooner than the 150 days mentioned above
- 30 days after discontinuation of carboplatin if the participant continued carboplatin more than 150 days after the last dose of LAG525 and/or spartalizumab.

If a participant starts a post treatment antineoplastic therapy, then only SAEs suspected to be related to study treatment should be collected out to 150 days after discontinuation of LAG525 and/or spartalizumab. SAEs suspected to be related to LAG525 and/or spartalizumab will continue to be collected beyond the 150-Day safety visit.

Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

SAEs will be collected on all participants having signed an ICF and until reporting period is completed as described above. For participants who fail the screening, SAEs will be collected until the time the participant is deemed a Screen Failure.

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, an oncology Chief Medical Office and Participant Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the reporting period described above should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign the pregnancy consent form to allow the Study Doctor to ask about her pregnancy. To ensure participant safety, each pregnancy occurring after

signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

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

The collection of this information could last for up to delivery or several months after delivery if applicable following the birth.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the, respective sections.

10.2 Additional Safety Monitoring

In addition to the ongoing safety monitoring throughout the study, a safety review will occur after the first 8 participants on each the carboplatin, spartalizumab and LAG525 and the carboplatin and LAG525 arm have completed their first 3-week treatment cycle. This safety review will be performed by a Novartis review team including at least a clinician and a safety representative.

10.2.1 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the trial, and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

11 Data Collection and Database management

11.1 Data collection

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

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

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

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical

Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Dates of screenings, randomizations and screen failures, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

[redacted]

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis or delegated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis or delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

With protocol amendment 3, enrollment to treatment Arm 1 (LAG525 + spartalizumab) was prematurely closed. Participant data from Arm 1 will still contribute to the efficacy and safety objectives of the trial as per the analysis defined in this section.

The primary analysis of the study data will be reported in the primary CSR based on all participants' data up to the time when all participants 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 participants 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.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

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

The **Safety Set** includes all participants 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). Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

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

- receive a planned dose of LAG525 prior to sampling
- for pre-dose samples, have the sample collected before the next dose administration
- for end-of-infusion samples, have the sample collected 1 hour (± 5 min) post end of infusion

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

- receive a planned dose of spartalizumab prior to sampling
- for pre-dose samples, have the sample collected before the next dose administration
- for end-of-infusion samples, have the sample collected 1 hour (± 5 min) post end of infusion

The carboplatin pharmacokinetic analysis set (**PAS-carboplatin**) includes all participants who provide at least one evaluable carboplatin PK concentration. For a concentration to be evaluable, participants 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
- for samples scheduled to be taken prior to End of Infusion (EOI), have the samples collected prior to EOI
- for post-EOI samples, have the samples collected post EOI. The PAS will be used for all PK analyses.

[redacted]

Additional details, including definition of determinant, will be provided in the SAP.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS. In addition, number of participants treated will be summarized by age/gender combination and by race for each treatment arm in the Safety Set for DSUR reporting purposes.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class, preferred term, and treatment group.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum, and maximum will be presented.

The duration of exposure in weeks to LAG525, spartalizumab and carboplatin (as applicable) as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set.

The number of participants with dose adjustments (reductions in the case of carboplatin, interruption, or permanent discontinuation) and the reasons will be summarized by treatment group, and all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

12.4 Analysis of the primary endpoint(s)

The primary objective is to assess the antitumor activity of the three combinations LAG525 + spartalizumab, LAG525 + spartalizumab + carboplatin, and LAG525 + carboplatin, in participants with advanced TNBC in first or second line of therapy.

12.4.1 Definition of primary endpoint(s)

The primary efficacy variable is the overall response rate (ORR) defined as the proportion of participants with best overall response (BOR) of complete response (CR) or partial response (PR), as per local review and according to RECIST 1.1 (see Section 16.3 Appendix 3 for details).

BOR is defined as the best response recorded from the randomization date until disease progression as per RECIST 1.1. If any new antineoplastic therapy is taken while on study, any subsequent assessments will be excluded from the best overall response determination. 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 participant 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)

12.4.2 Statistical model, hypothesis, 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 participants 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 Intent-To-Treat (ITT) principle.

In a randomized phase III study of carboplatin compared to docetaxel for participants with metastatic or recurrent locally advanced triple negative breast cancer or *BRCA1/2* breast cancer, including 188 participants 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 participants treated by carboplatin or cisplatin in first (69 participants) or second line (17 participants) the ORR was 25.6%. Specifically in second line, the ORR with cisplatin alone (9 participants) was 22.2% and no participant responded in second line out of the 8 participants 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 participants enrolled in first line and second line of therapy, the response rate with single agent carboplatin in participants with advanced TNBC in 1st and 2nd line overall is expected to be 25% Isakoff et al 2015, Tutt et al 2014. 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 participants included in the FAS. A minimally informative unimodal Beta prior Neuenschwander et al 2008 will be used for ORR in each arm (see Section 16.3 Appendix 3 for further details).

Additionally, ORR will be summarized by treatment group along with the two-sided exact binomial 95% confidence interval Clopper CJ and Pearson 1934.

Waterfall graphs, which display the best percentage change from baseline in the sum of diameters of all target lesions for each participant with measurable disease at baseline, will be used to depict the anti-tumor activity of each treatment group.

12.4.3 Handling of missing values/censoring/discontinuations

Participants 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. For the computation of ORR, these participants 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) will be considered in the assessment of BOR.

12.4.4 Sensitivity and Supportive analyses

Supportive and sensitivity analyses will be conducted to support the primary objective, if appropriate, and the details of these analyses will be defined in the SAP.

12.5 Analysis of secondary endpoints

The secondary objectives are:

- To assess the efficacy of each treatment arm 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

- To characterize the safety profile of each treatment arm
- To characterize the pharmacokinetics (PK) of LAG525, spartalizumab and carboplatin in the three investigated combinations
- To assess immunogenicity of LAG525 and spartalizumab in the three investigated combinations

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Clinical benefit rate (CBR) is defined as the proportion of participants with a best overall response of complete response (CR) or partial response (PR) or an overall lesion response of stable disease (SD), lasting for a duration of at least 24 weeks. CR, PR and SD are defined as per local review according to RECIST 1.1 (see Section 16.3 Appendix 3 for details). CBR will be evaluated according to RECIST 1.1 (see Section 16.3 Appendix 3 for details).

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 CJ and Pearson 1934 will be presented by treatment group.

Time to response (TTR) is defined as the time from the date of randomization to the first documented response of either complete response (CR) or partial response (PR), which must be subsequently confirmed (i.e., the start date of response, not the date when response was confirmed).

TTR will be evaluated according to RECIST 1.1 (see Section 16.3 Appendix 3 for details).

All participants in the FAS will be included in TTR calculations. Participants without a confirmed CR or PR will be censored at the study-maximum follow-up time (i.e., LPLV-FPFV) for participants with a PFS event (i.e., disease progression or death due to any cause), or at the date of the last adequate tumor assessment for participants without a PFS event. 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 will be presented for each treatment group only if a sufficient number of responses is observed.

Duration of response (DOR) only applies to participants whose best overall response is complete response (CR) or partial response (PR) based on tumor response data per local review. DOR will be evaluated according to RECIST 1.1 (see Section 16.3 Appendix 3 for details).

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. Participants continuing without progression or death due to underlying cancer will be censored at the date of their last adequate tumor assessment. DOR based on RECIST 1.1 will be listed and summarized by treatment group for all participants 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 will be presented for each treatment group only if a sufficient number of responses is observed.

Progression-Free Survival (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 according to RECIST 1.1 (see Section 16.3 Appendix 3 for further details). PFS will be censored if no PFS event is observed before the earliest of (i) the analysis cut-off date, and (ii) the date when a new anti-neoplastic therapy is started. The censoring date will be the date of the last adequate tumor assessment prior to cut-off/start of new anti-neoplastic therapy.

PFS will be analyzed in the FAS population according to the treatment groups. The PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group.

Overall Survival (OS) is defined as the time from date of randomization to date of death due to any cause. If a participant is not known to have died, then OS will be censored at the latest date the participant was known to be alive (on or before the cut-off date). OS will be analyzed in the FAS population according to the treatment groups. The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group.

12.5.2 Safety endpoints

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

Safety summaries (tables, figures) will 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).

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

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

- Pre-treatment period: from day of participant's informed consent to the day before first dose of study medication
- On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
- Post-treatment period: starting at day 31 after last dose of study medication.

If dates are incomplete in a way that clear assignment to pre-, on-, or post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period. Additional details to address incomplete AE and/or dosing dates will be addressed in the SAP.

Adverse events

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs.

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.

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

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment, up to 150 days after last administration of LAG525/spartalizumab or up to 30 days after the last dose of carboplatin whichever comes last, and post-treatment) will be summarized.

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

Vital signs

Data on vital signs will be tabulated based on notable vital sign values. All vital signs data will be listed by treatment group, participant and visit/time, notable values will be flagged.

12-lead ECG

12-lead ECGs including PR, QRS, QT and QTcF will be obtained for each participant during the study. ECG data will be read and interpreted centrally.

All ECG data will be listed by treatment group, participant and visit/time, abnormalities will be flagged. Categorical analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, participant, and visit/time.

Grading of laboratory 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.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE version 5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

The following listings/summaries will be generated separately for hematology and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE version 5.0 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE version 5.0

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE version 5.0 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE version 5.0,

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

[redacted]

Other safety evaluations

Other safety data (e.g., cardiac imaging) will be summarized or listed as appropriate.

12.5.3 Pharmacokinetics

The respective PAS for each study drug will be used in the pharmacokinetic data analysis.

Drug concentration values below the lower limit of quantitation (LLOQ) will be displayed in listings as zero with a flag and handled as zero in the calculations for mean, CV for mean, standard deviation, minimum, median, maximum, but handled as missing for the calculation of the geometric means and their CV.

Descriptive statistics (n, m (number of non-zero concentrations), mean, CV%, SD, median, geometric mean, geometric CV%, minimum and maximum) for spartalizumab, LAG525 and carboplatin concentrations will be presented at each scheduled timepoint and visit by treatment group.

All spartalizumab, LAG525 and carboplatin concentration data will be displayed graphically and by treatment group and visit.

PK parameters may be calculated using the PK sampling in cycle 1 and cycle 3, as appropriate. The descriptive statistics (n, mean, CV%, standard deviation (SD), median, geometric mean, geometric CV%, minimum and maximum) will be presented for all PK parameters for spartalizumab, LAG525 and carboplatin by treatment group for both cycle 1 and cycle 3 defined in Table 12-1 except Tmax, where only n, median, minimum and maximum will be presented.

Table 12-1 Non-compartmental pharmacokinetic parameters for spartalizumab, LAG525 and carboplatin

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (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)

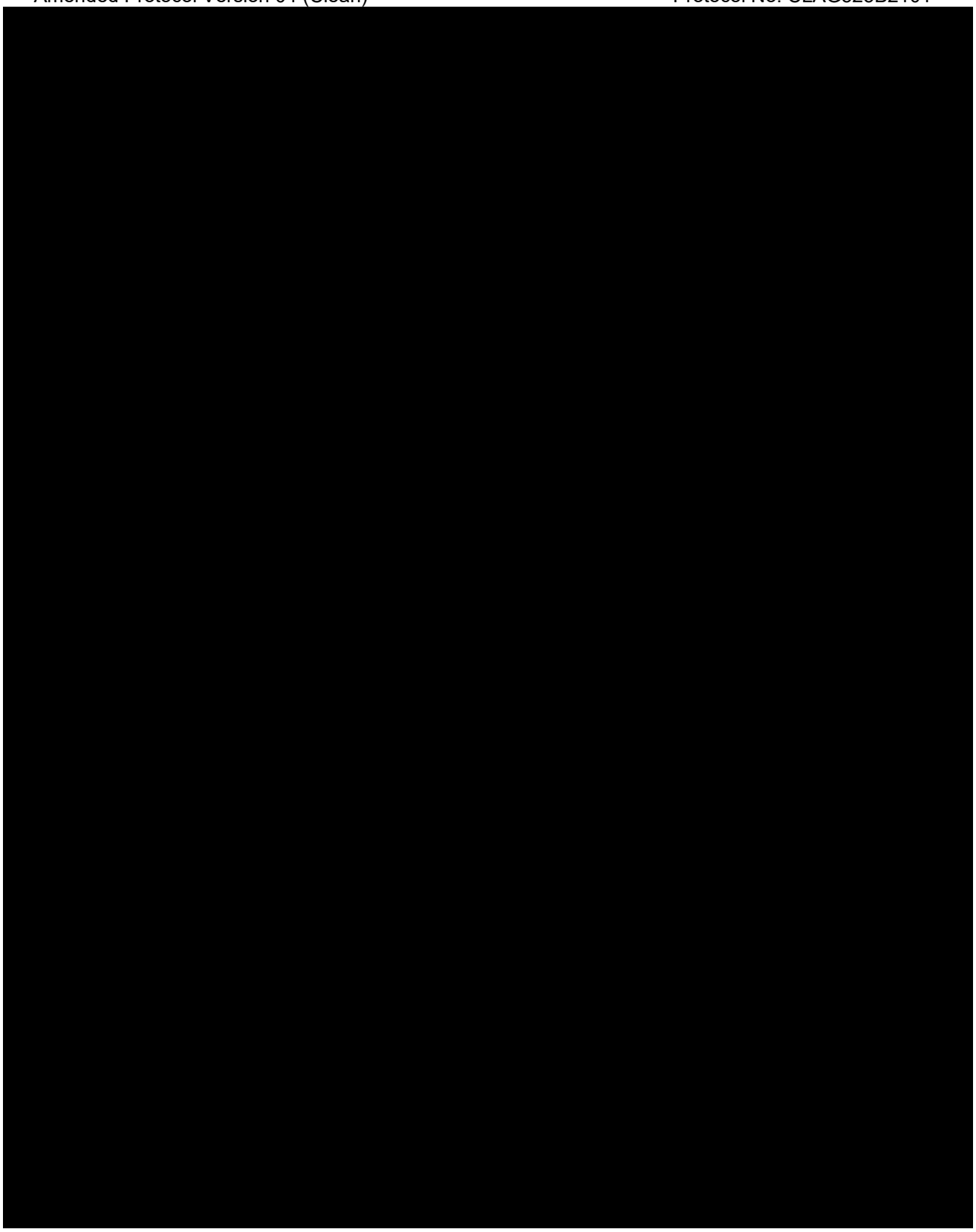
12.5.3.1 Data handling principles

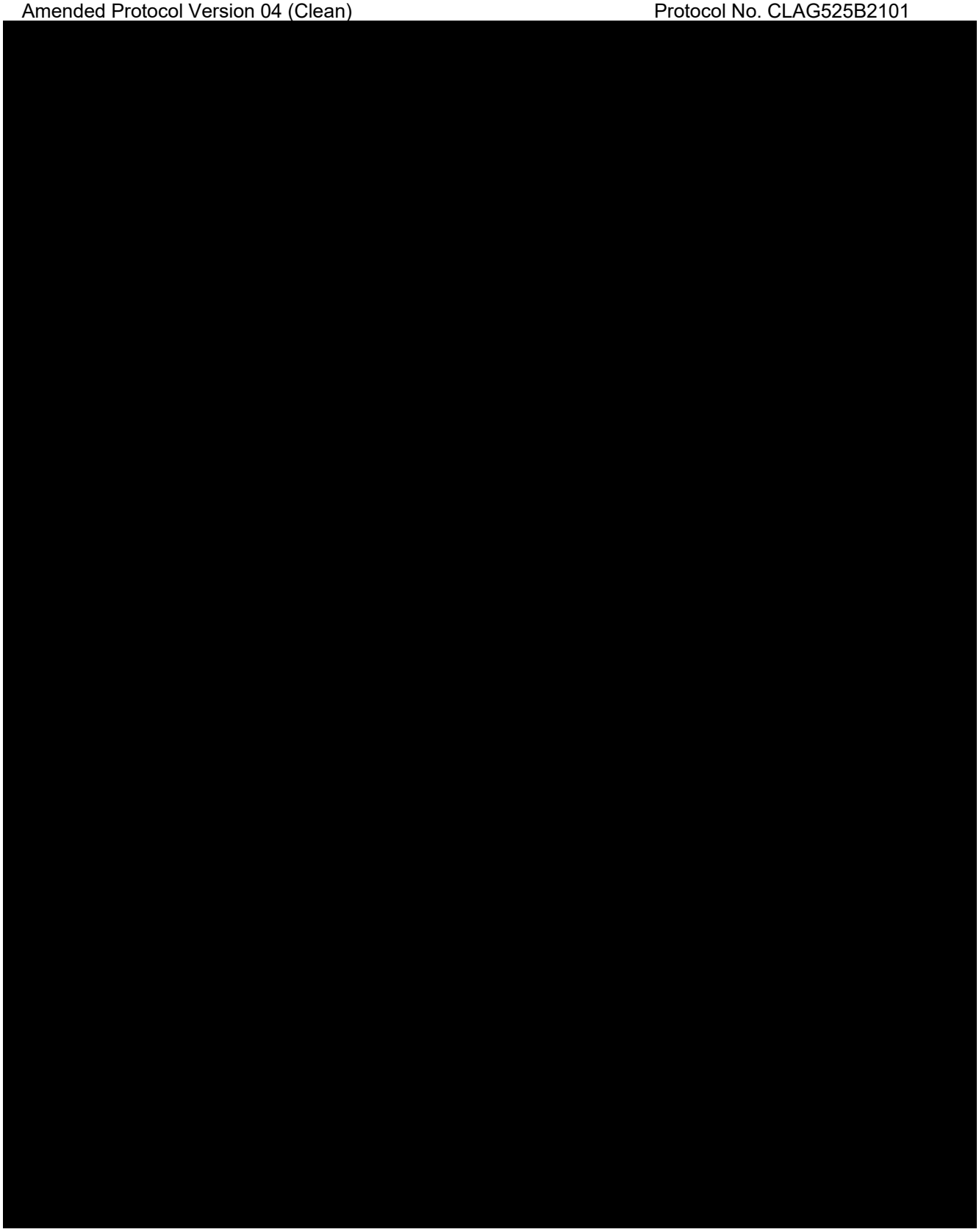
Missing values for any PK parameters or concentrations will not be imputed and will be treated as missing.

Below the limit of quantitation (BLQ) values will be set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. BLQ values will be treated as missing for the calculation of the geometric means and geometric CV%.

12.5.4 Immunogenicity

Immunogenicity will be characterized descriptively by tabulating anti-drug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment. Additional details will be specified in the SAP.





12.7 Interim analyses

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 participants' data up to the time when all participants 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 participants continuing to receive study treatment past the data cutoff date for the primary CSR, as allowed by the protocol, will be reported in the Final analysis on completion of the study.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size calculation is based on the primary variable ORR considering the statistical model, hypothesis and method of analysis detailed in Section 12.4.2. 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 participants were planned to be enrolled in each arm for a total of approximately 96 participants. In a given arm of 32 participants, 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 12-2). With protocol amendment 3, enrollment to treatment Arm 1 (LAG525 + spartalizumab) was prematurely closed. Therefore, approximately 84 participants will be enrolled (approximately 20 participants in Arm 1, and 32 participants per arm for Arms 2 and 3).

Table 12-2 Operating characteristics with 32 participants 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

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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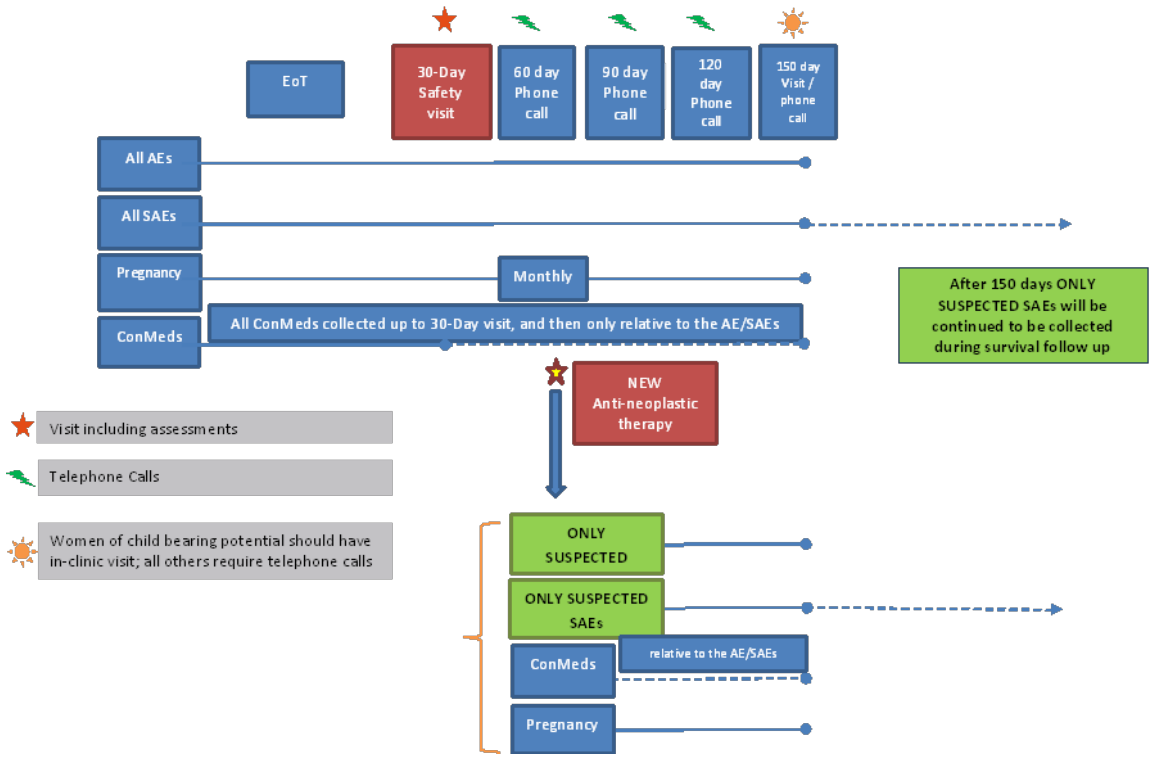
16 Appendices

16.1 Appendix 1: Safety follow-up diagram

Figure 16-1 Safety follow-up diagram



16.2 Appendix 2: Statistical considerations

The primary endpoint is the overall response rate (ORR). The analysis of the primary endpoint, which is Bayesian, uses a binomial sampling and a Beta prior distribution.

Based on clinical discussions and available literature, the null value for the ORR was set to 25%. Moreover, a minimum ORR improvement of 10% was considered necessary to justify further development (see Section 12.4.2 for information on published data available to help elicit the 25% and 35% targets).

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

- Clinical relevance: posterior mean $\geq 35\%$
- Bayesian statistical significance: $pr(ORR \geq 25\% \mid data) \geq 0.90$

The first criterion is met if the posterior mean ORR is at least 35% which is the minimum ORR of clinical interest. The second criterion provides reasonable evidence that the posterior ORR is better than the null value of 25%. Both criteria need to be met by at least one treatment group in order to meet the primary objective of the study.

Each analysis by treatment group is performed separately using a Beta-binomial model as follows:

Let us assume that y_i out of n_i patients have a response as per ORR in treatment group i (either LAG525 + spartalizumab, LAG525 + spartalizumab + carboplatin or LAG525 + spartalizumab + carboplatin).

The likelihood function is $y_i \sim Bin(n_i, p_i)$ where p_i denotes the ORR for treatment group i.

Assume p_i follows a beta prior distribution: $[p_i] \sim Beta(a_i, b_i)$, where $a_i > 0$, $b_i > 0$

The posterior distribution of p_i is therefore: $[p_i \mid y_i] \sim Beta(a_i + y_i, b_i + n_i - y_i)$

A minimally informative prior with unimodal Beta(0.35/(1-0.35),1) distribution is used. The prior parameters are chosen so that the prior mean for ORR is equal to 35%. This ensures that the clinical relevance criterion is met, if the observed ORR is exactly equal to 35%.

With the two criteria stated above the minimally required sample size is 32.

To better understand the design, operating characteristics for various true ORR were assessed using simulations as follows:

- Generate 100,000 trials with ORR results (yes / no) for n_i participants per treatment group, where the ORR follows a binomial distribution $y_i \sim Bin(n_i, p_i)$.
- Evaluate for each of these simulated trials whether the PPE criteria are met.
- The probability of declaring preliminary efficacy is the average number of trials meeting PPE over the 100,000 sampled trials.

The operating characteristics presented in Section 12.8.1 of the protocol consider n_i=32, with varying p_i from 0.25 to 0.45. Operating characteristics for additional sample sizes of 36 and 40 participants by treatment group were also assessed and full results are presented in the Table 16-1 hereafter:

Table 16-1 Operating characteristics with 32, 36 or 40 participants in each arm

Number of participants	True ORR	Probability of declaring PPE in each arm	Probability of missing PPE in each arm
32	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
36	25 %	0.092	0.908
	30 %	0.263	0.737
	35 %	0.507	0.493
	40%	0.738	0.262
	45 %	0.893	0.107
40	25 %	0.102	0.898
	30 %	0.296	0.704
	35 %	0.559	0.441
	40%	0.787	0.213
	45 %	0.924	0.076

Based on the Operating Characteristics the minimal sample size of 32 participants by treatment group was considered as adequate.

16.3 Appendix 3: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival, and Overall Survival (based on RECIST 1.1)

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Glossary

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

16.3.1 Introduction

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

The efficacy assessments described in Section 16.3.2 and the definition of best response in Section 16.3.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.3.3.2 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 16.3.4 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

16.3.2 Efficacy assessments

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

16.3.2.1 Definitions

16.3.2.1.1 Disease measurability

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

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

For patients without measurable disease see Section 16.3.3.2.8.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ^{3}15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ^{3}10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

- Cystic lesions:
- Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ^{3} 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

16.3.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 16.3.3.2.8.

16.3.2.2 Methods of tumor measurement - general guidelines

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

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

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow-up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Physical exams: Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10mm size, and can be assessed using calipers.
- Ultrasound: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- Endoscopy and laparoscopy: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

16.3.2.3 Baseline documentation of target and non-target lesions

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

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

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 16.3.2.1.1.
- **Nodal target**: See Section 16.3.2.1.1.

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

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as

a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

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

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 16-2) and non-target lesions (Table 16-3) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-4) as well as the presence or absence of new lesions.

16.3.2.4.1 Follow-up and recording of lesions

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

16.3.2.4.1.1 Non-nodal lesions

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

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

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

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

16.3.2.4.1.2 Nodal lesions

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

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

for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

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

16.3.2.4.2 Determination of target lesion response

Table 16-2 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm [2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]
• SOD for CR may not be zero when nodal lesions are part of target lesions	
• Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR • In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 16.3.2.2).	

Notes on target lesion response

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

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 16-2 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who

have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.

- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- Nodal lesion decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.

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

- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which

have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

16.3.2.4.3 Determination of non-target lesion response

Table 16-3 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline[2.]
• The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the investigator or central reviewer does prevail. • It is recommended that the investigator and/or central reviewer should use expert judgment to assign a Non-UNK response wherever possible (see notes section for more details)	

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.
- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ³ 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the

extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 16.3.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

16.3.2.4.4 New lesions

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

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion

1. If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 16.3.2.5).

- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ³ 10 mm for the first time in the study plus 5 mm absolute increase. **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 16.3.2.2.

16.3.2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 16-4.

Table 16-4 Overall lesion response at each assessment

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

This overall lesion response also applies when there are no non-target lesions identified at baseline.
Once confirmed PR was achieved, all these assessments are considered PR.
As defined in Section 16.3.2.4.

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

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

16.3.3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 16.3.3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

16.3.3.1 Best overall response

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

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

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

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

- For non-randomized trials where response is the primary endpoint, confirmation is needed.
- For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

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

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required

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

The time durations specified in the SD/PD/UNK definitions above are defaults based on a 6 week tumor assessment frequency. However these may be modified for specific indications which are more or less aggressive. In addition, it is envisaged that the time duration may also take into account assessment windows. E.g. if the assessment occurs every 6 weeks with a time window of +/- 7 days, a BOR of SD would require a SD or better response longer than 5 weeks after randomization/start of treatment.

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

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (³30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ³20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

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

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

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

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

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

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

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

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

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD. The objective of this endpoint is to summarize patients with signs of "activity" defined as either shrinkage of tumor (regardless of duration) or slowing down of tumor growth.

Clinical benefit rate (CBR) is the proportion of patients with a best overall response of CR or PR , or an overall lesion response of SD or Non-CR/Non-PD which lasts for a minimum time duration (with a default of at least 24 weeks in breast cancer studies). This endpoint measures signs of activity taking into account duration of disease stabilization.

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

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

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

16.3.3.2 Time to event variables

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

16.3.3.2.1 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

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

PFS rate at x weeks is an additional measure used to quantify PFS endpoint. It is recommended that a Kaplan Meier estimate is used to assess this endpoint.

16.3.3.2.2 Overall survival

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

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

16.3.3.2.3 Time to progression

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

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

16.3.3.2.4 PFS2

A recent EMA guidance (EMA 2012) recommends a substitute end point intermediate to PFS and OS called PFS2, a surrogate for OS when OS cannot be measured reliably, which assesses the impact of the experimental therapy on next-line treatment. The main purpose of this endpoint is to assess long term maintenance strategies, particularly of resensitizing agents and where it is necessary to examine the overall "field of influence".

PFS2, which could be termed PFS deferred, PFS delayed, tandem PFS, or PFS version 2.0, is the time from date of randomization/start of treatment to the date of event defined as the first documented progression on next-line treatment or death from any cause. The censoring rules for this endpoint will incorporate the same principles as those considered for PFS in this

document, and in addition may involve other considerations which will need to be detailed in the protocol.

Please note that data collection for the PFS2 is limited to the date of progression and not specific read of the tumor assessments.

It is strongly recommended that the teams consult regulatory agencies for scientific advice given the limited experience with the use of this endpoint in regulatory setting in light of methodological issues w.r.t. censoring foreseen.

16.3.3.2.5 Time to treatment failure

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

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

16.3.3.2.6 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988).

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

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

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

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

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

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

16.3.3.2.7 Time to response

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

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 16.3.3.2.5. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

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

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

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

Assessment date

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

CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

In the calculation of the assessment date for time to event variables, any unscheduled assessment should be treated similarly to other evaluations.

Start dates

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

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

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

End dates

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

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 16.3.3.2.8).

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

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

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

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

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

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with non-measurable disease is derived slightly differently according to Table 16-5.

Table 16-5 Overall lesion response at each assessment: patients with non-target disease only

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

[1] As defined in Section 16.3.2.4.

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

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

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

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

16.3.3.2.10 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression

event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 16.3.3.2.7, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics April 2005) as a reference, the following analyses can be considered:

Table 16-6 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after exactly one missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after two or more missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	Ignore the new anticancer therapy and follow situations above (ITT approach) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

[1] =Definitions can be found in Section 16.3.3.2.7.
[2] =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.3.3.2.7.
[3] =The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

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

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

- (C1) taking the actual progression or death date, in the case of only one missing assessment.

- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

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

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

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1) (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

Option (2), i.e. censoring at last adequate assessment may be used as a sensitivity analysis. If a high censoring rate due to start of new cancer therapy is expected, a window of approximately 8 weeks performed after the start of new cancer therapy can be used to calculate the date of the event or censoring. This should be clearly specified in the analysis plan.

In some specific settings, local treatments (e.g. radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/DoR analysis. For example, palliative radiotherapy given in the trial for analgesic purposes or for lytic lesions at risk of fracture will not be considered as cancer therapy for the assessment of BOR and PFS analyses. The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DoR analysis.

The protocol should state that tumor assessments will be performed every x weeks until radiological progression irrespective of initiation of new antineoplastic therapy. It is strongly recommended that a tumor assessment is performed before the patient is switched to a new cancer therapy.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 16-6 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly

followed from baseline, immediately before or on the date of the last adequate tumor assessment.

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

16.3.4 Data handling and programming rules

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

16.3.4.1 Study/project specific decisions

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

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

16.3.4.2 End of treatment phase completion

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

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

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

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Participant/guardian decision
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment

- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

Death is a reason which "*must*" lead to discontinuation of patient from trial.

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

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

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

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Participant/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

16.3.4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

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

16.3.4.5 Programming rules

The following should be used for programming of efficacy results:

16.3.4.5.1 Calculation of 'time to event' variables

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

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

16.3.4.5.2 Incomplete assessment dates

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

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 16.3.3.2.7). 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.

16.3.4.5.3 Incomplete dates for last known date patient alive or death

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

16.3.4.5.4 Non-target lesion response

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

16.3.4.5.5 Study/project specific programming

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

16.3.4.5.6 Censoring reason

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

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

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

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 16-6)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

* Adequate assessment is defined in Section 16.3.3.2.7. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

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

16.3.5 References (available upon request)

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

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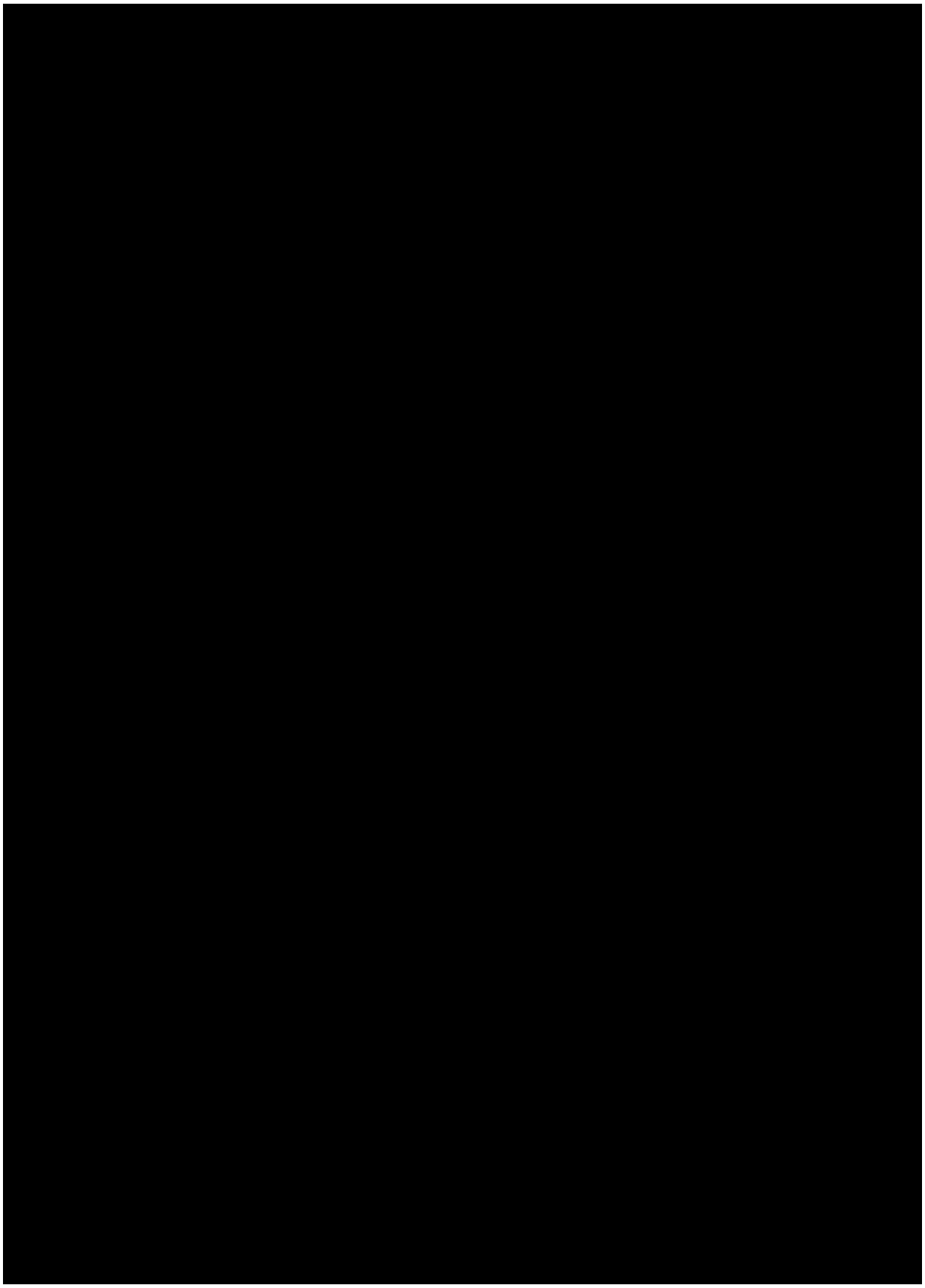

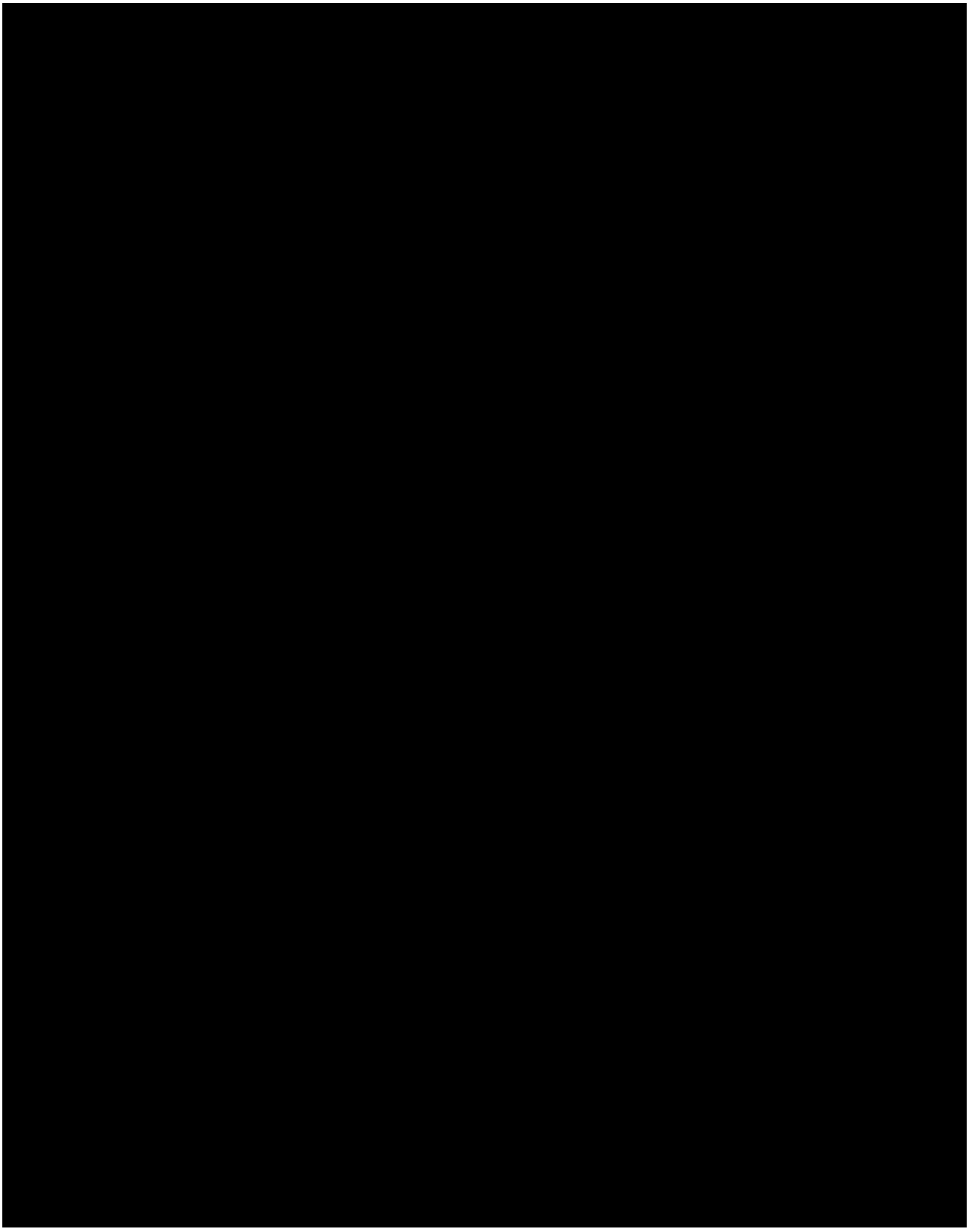

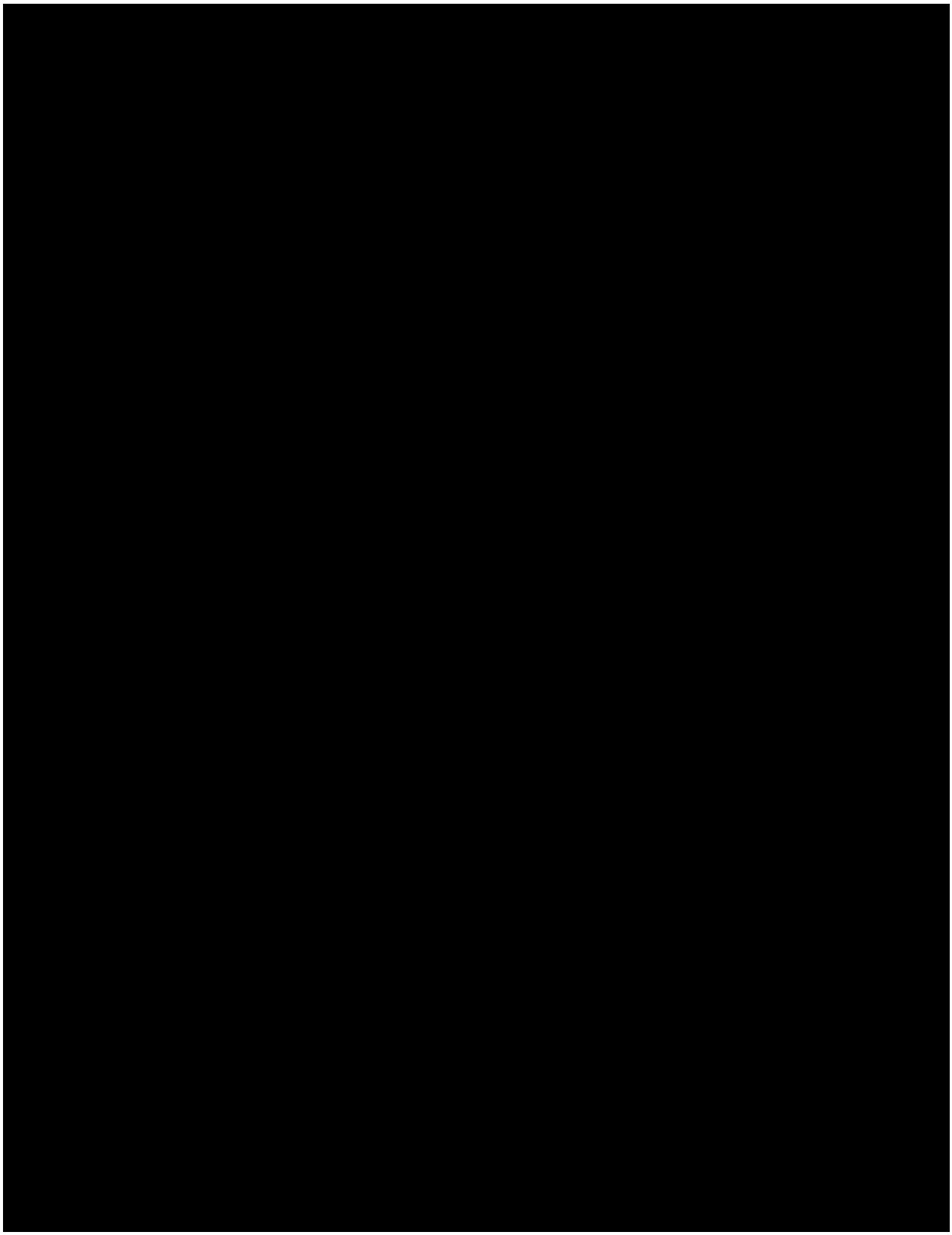

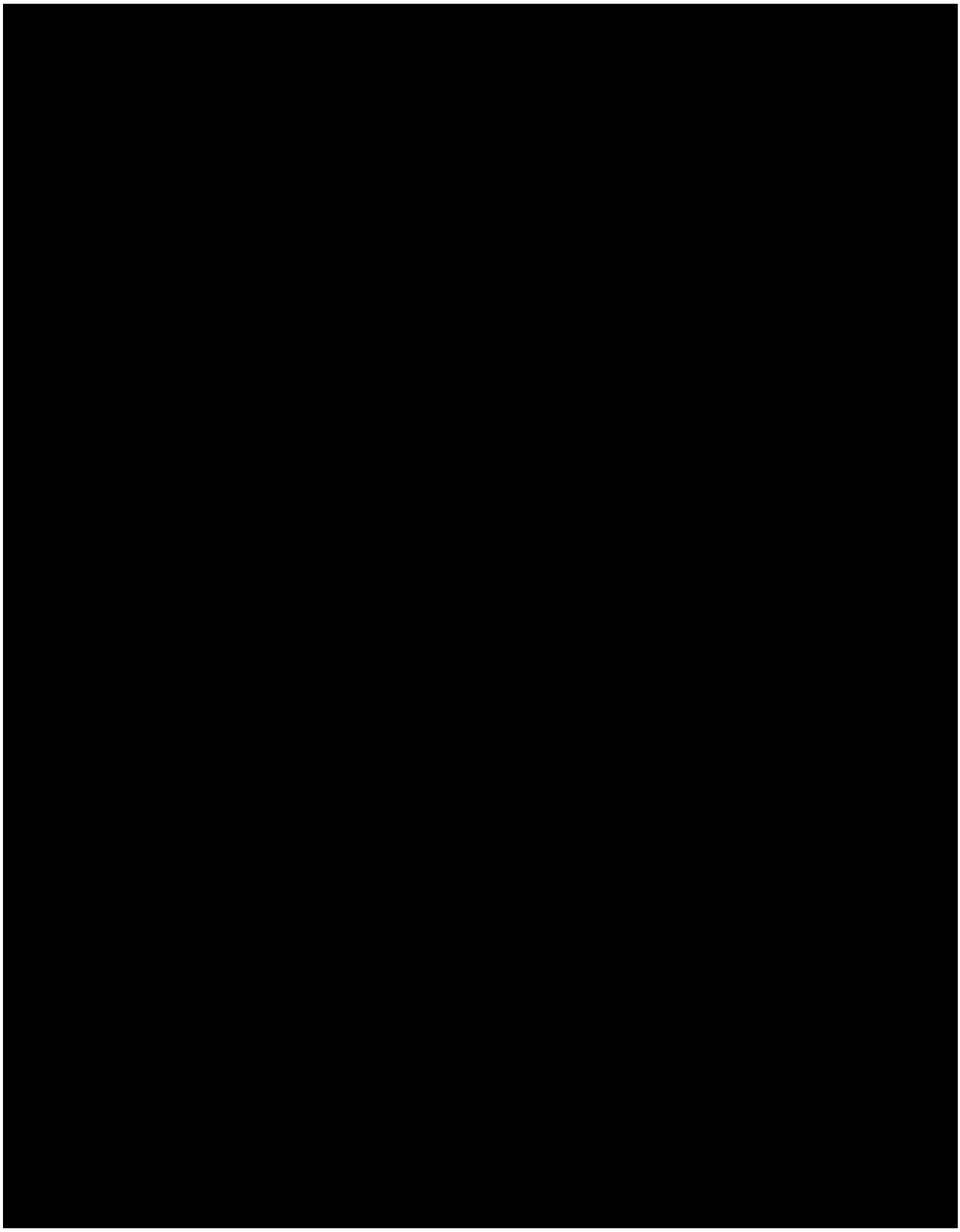

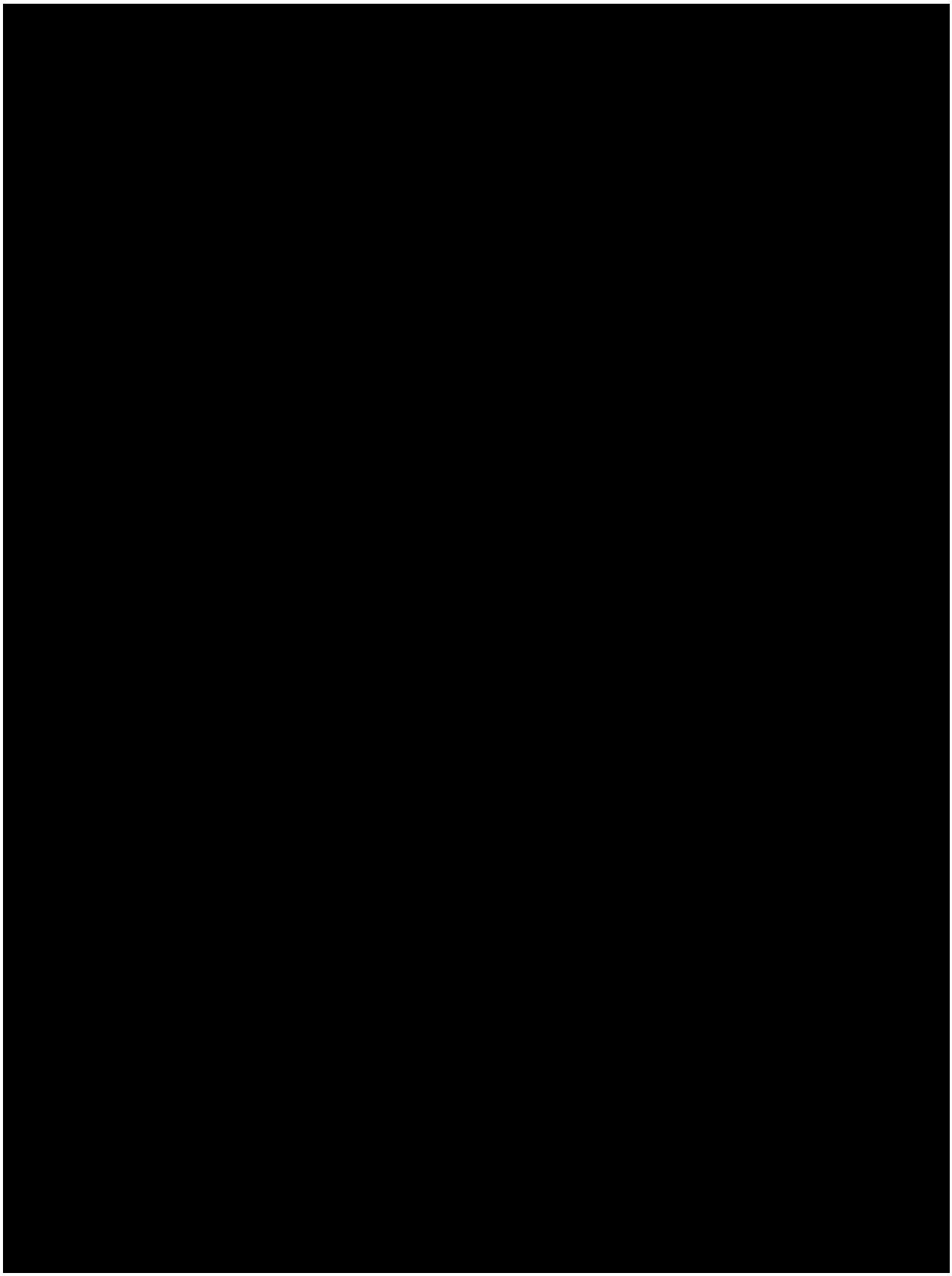

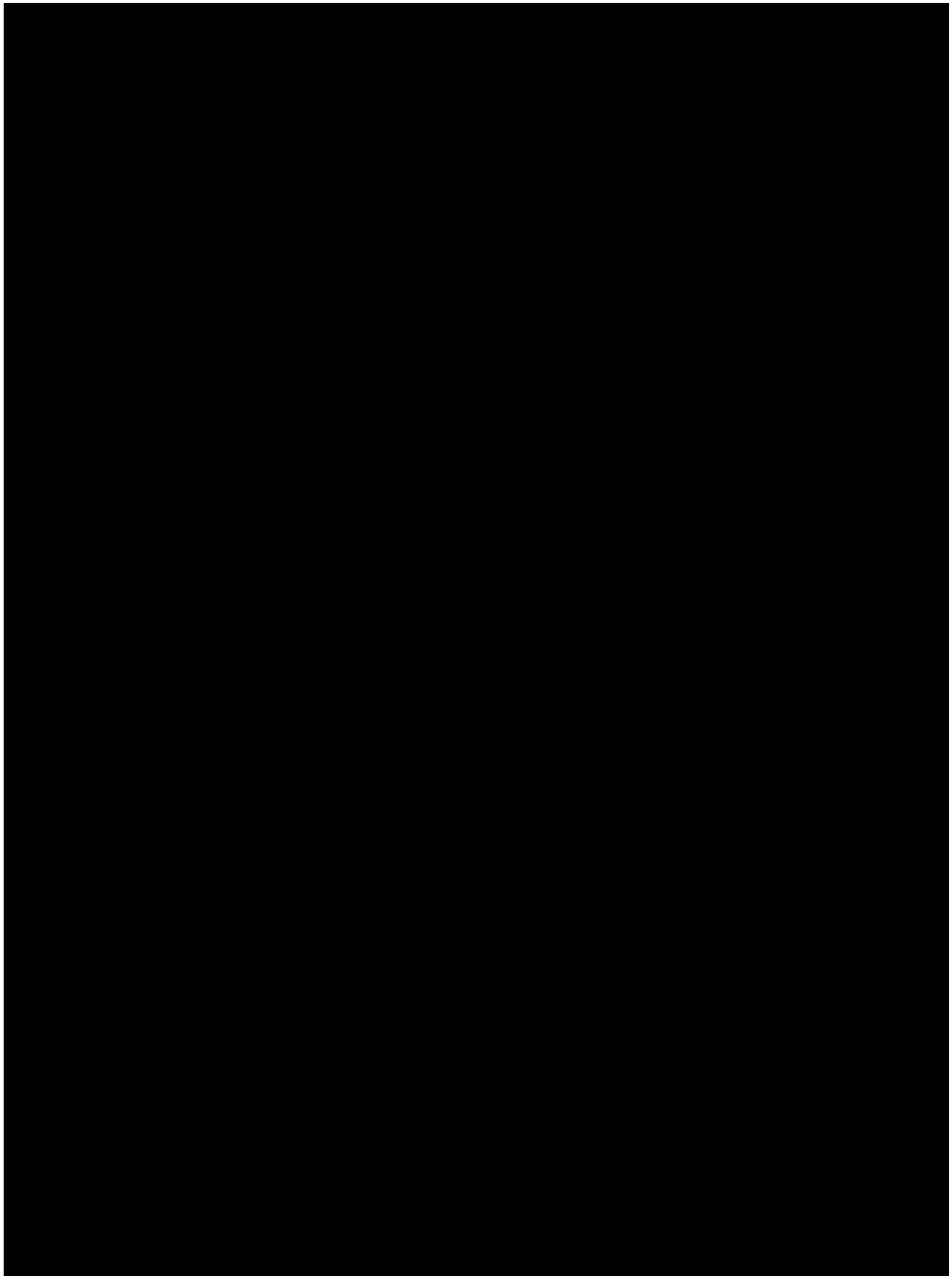

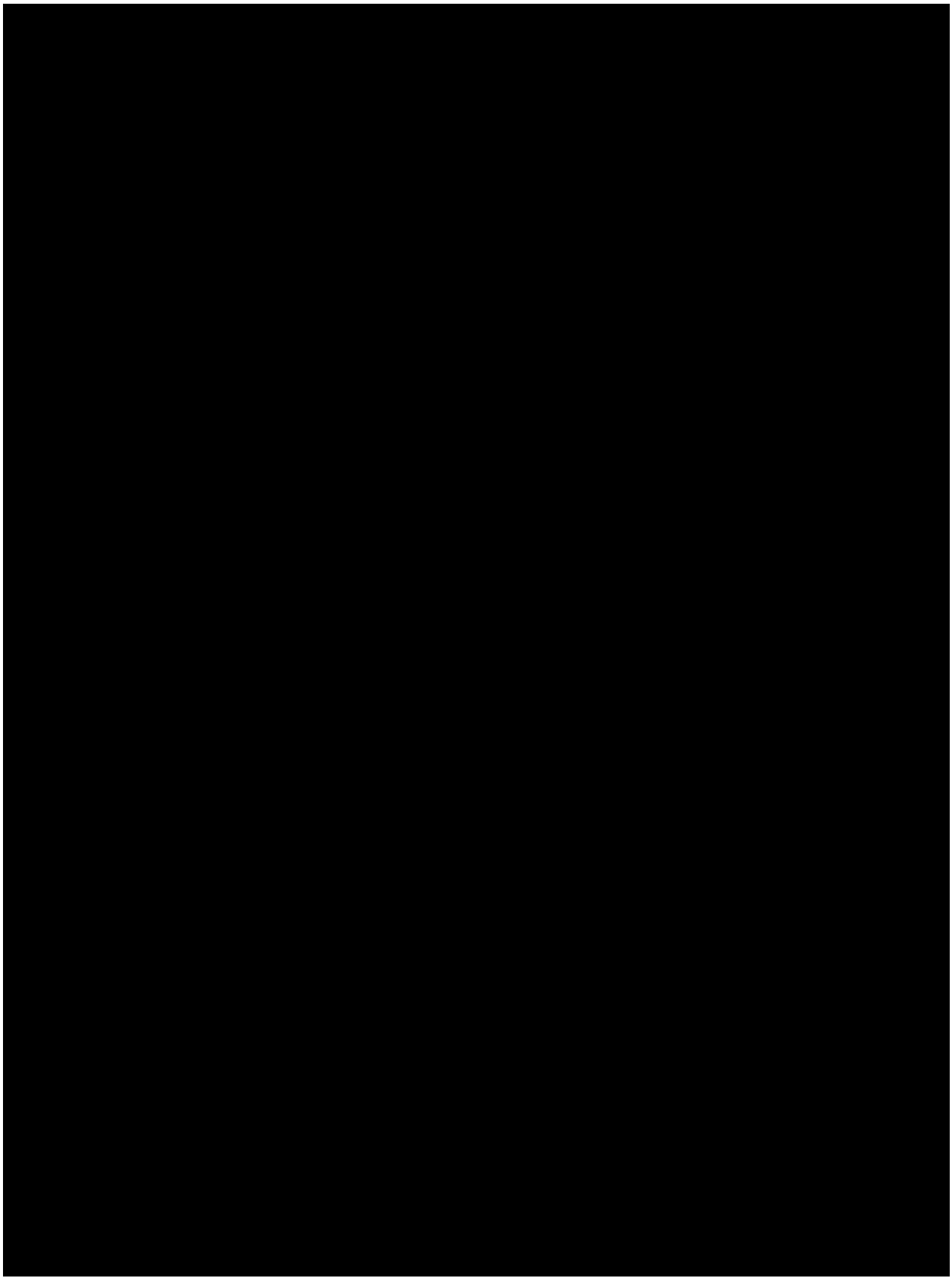

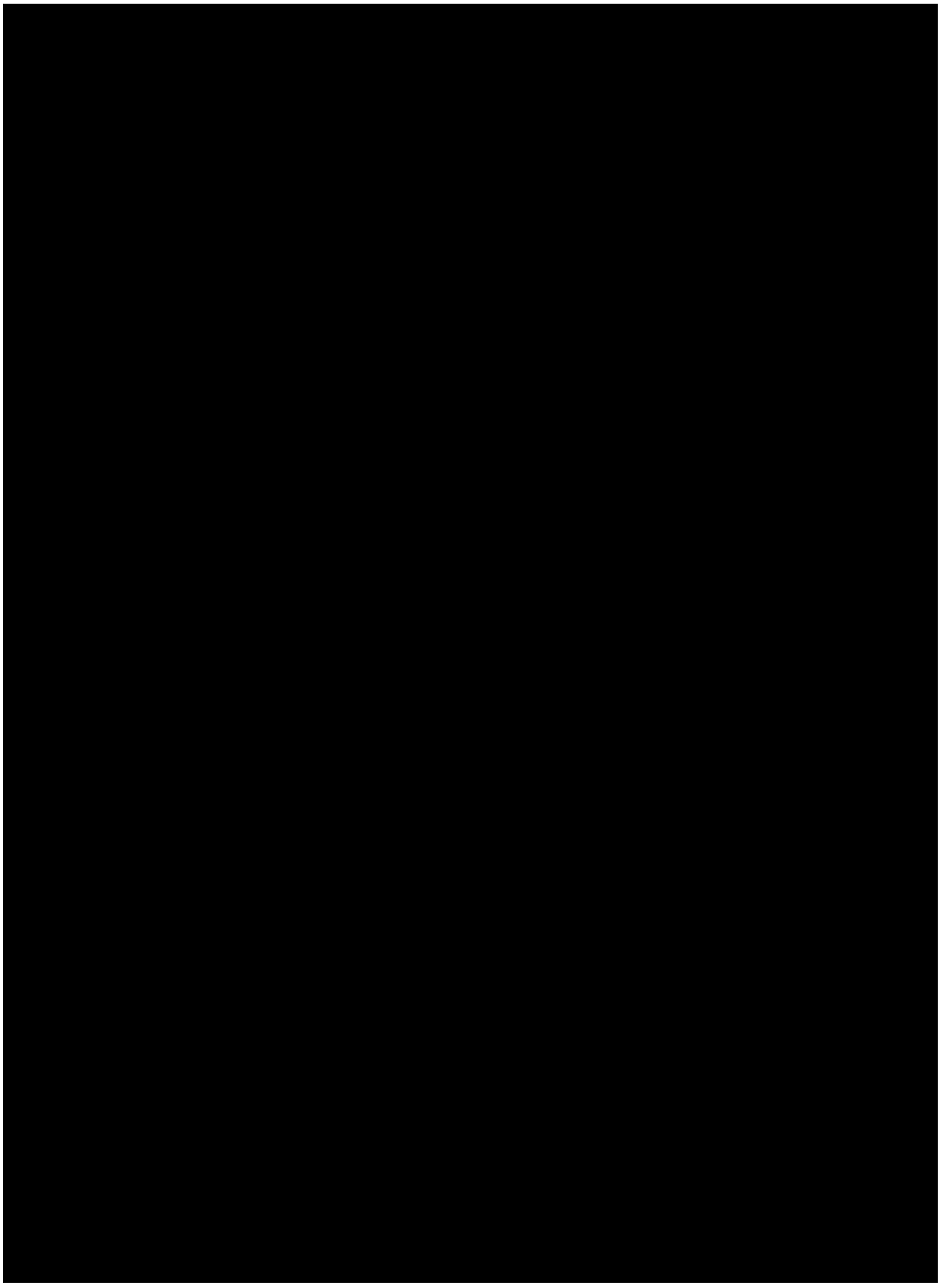

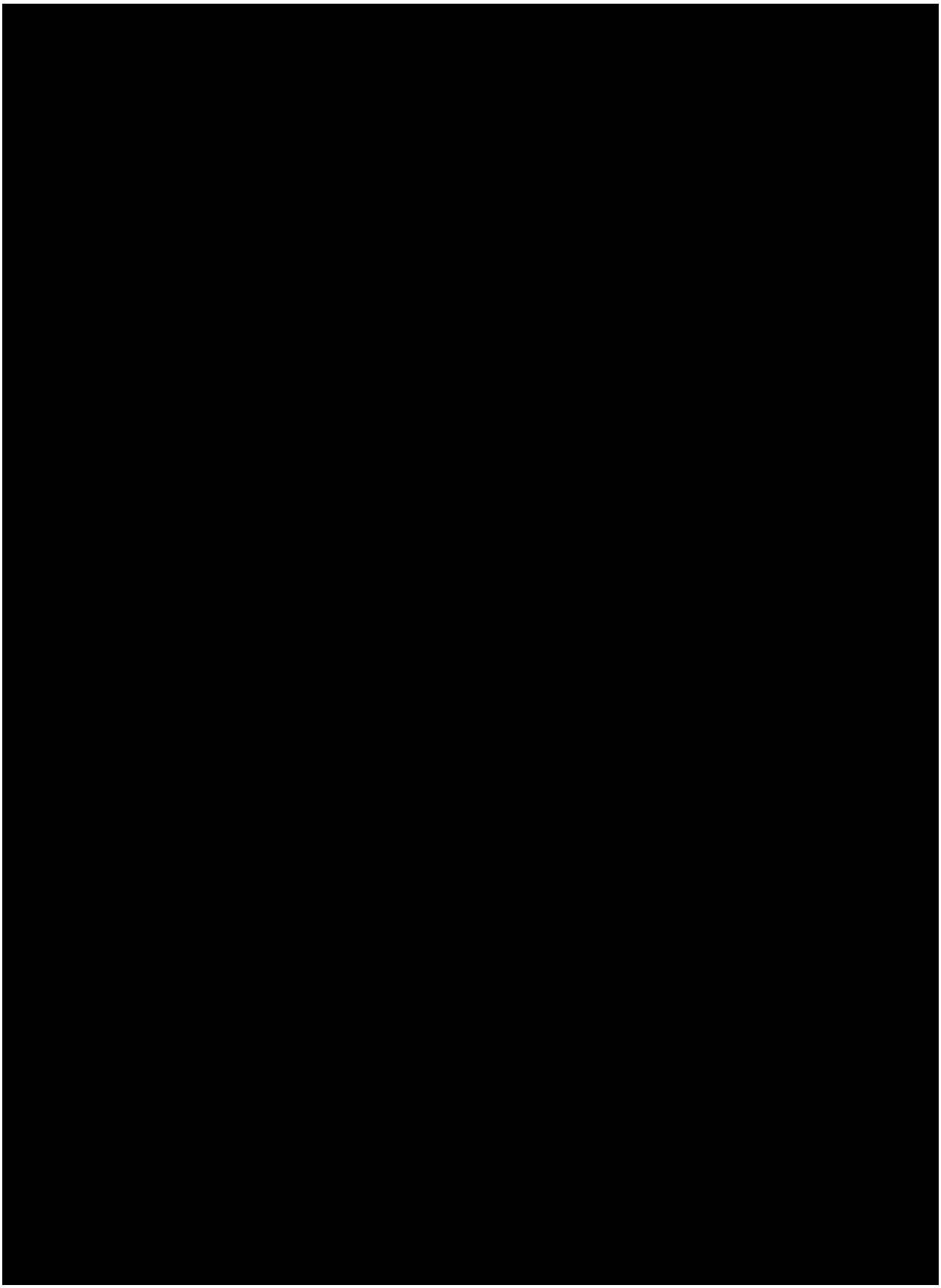

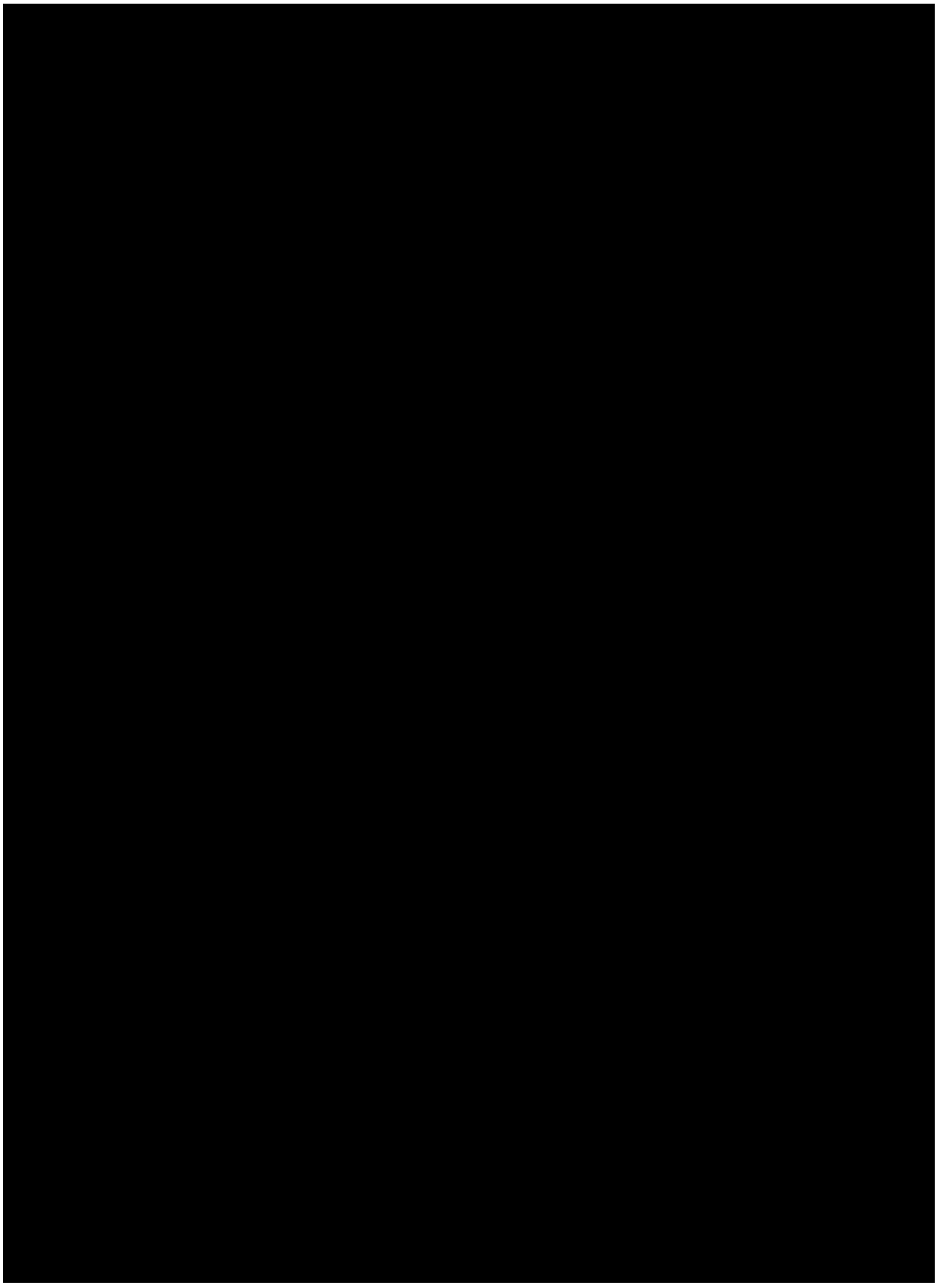

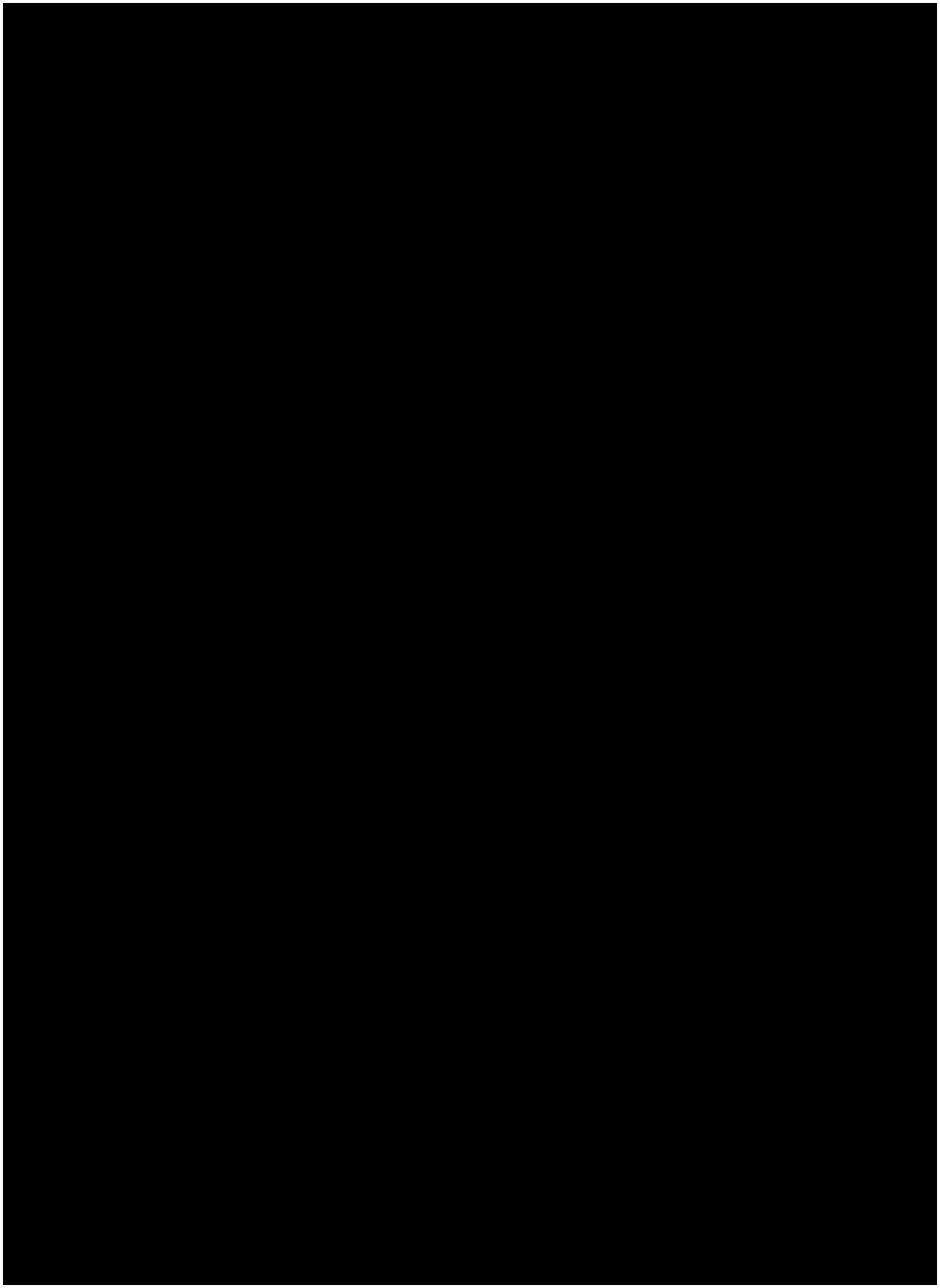

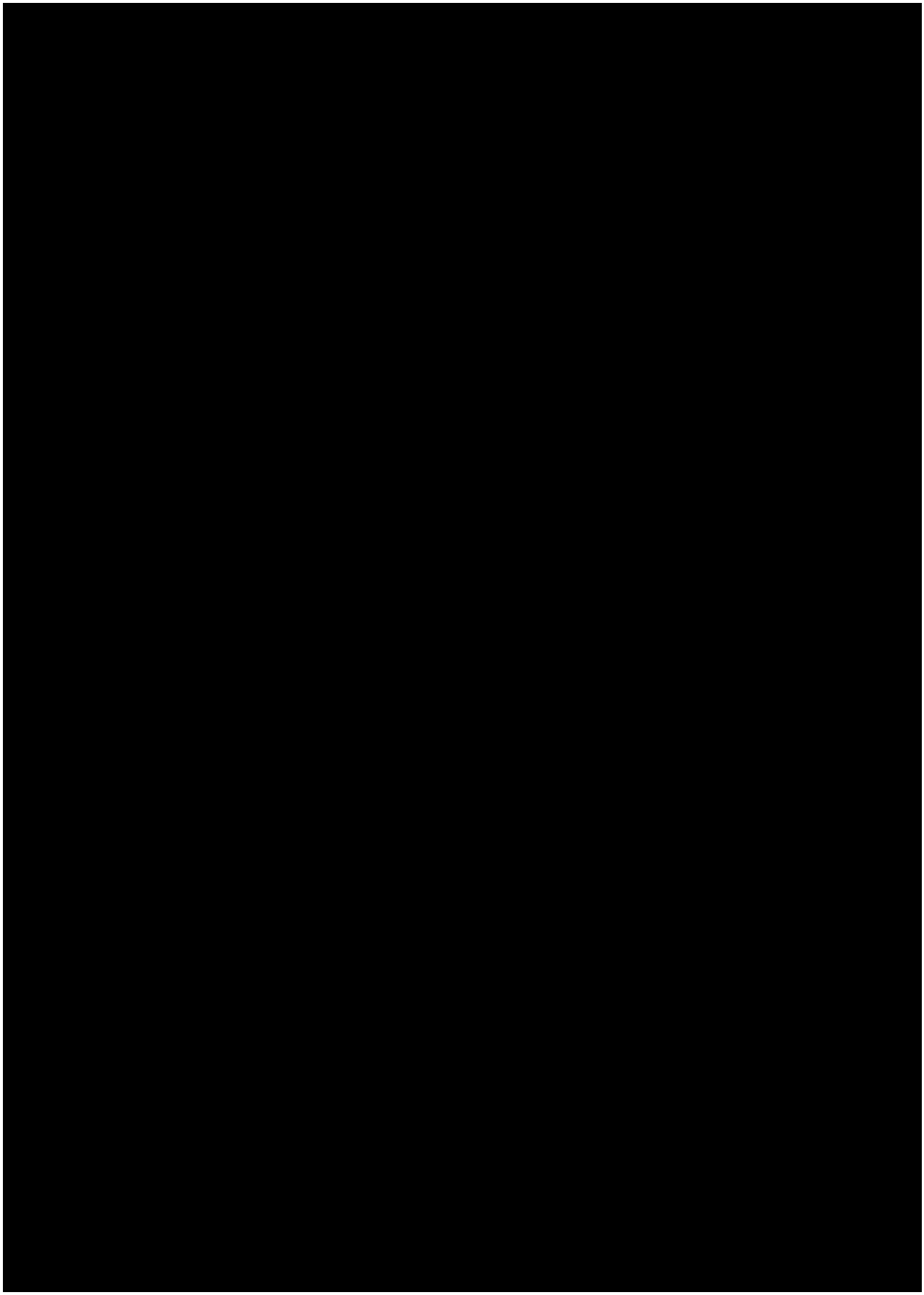

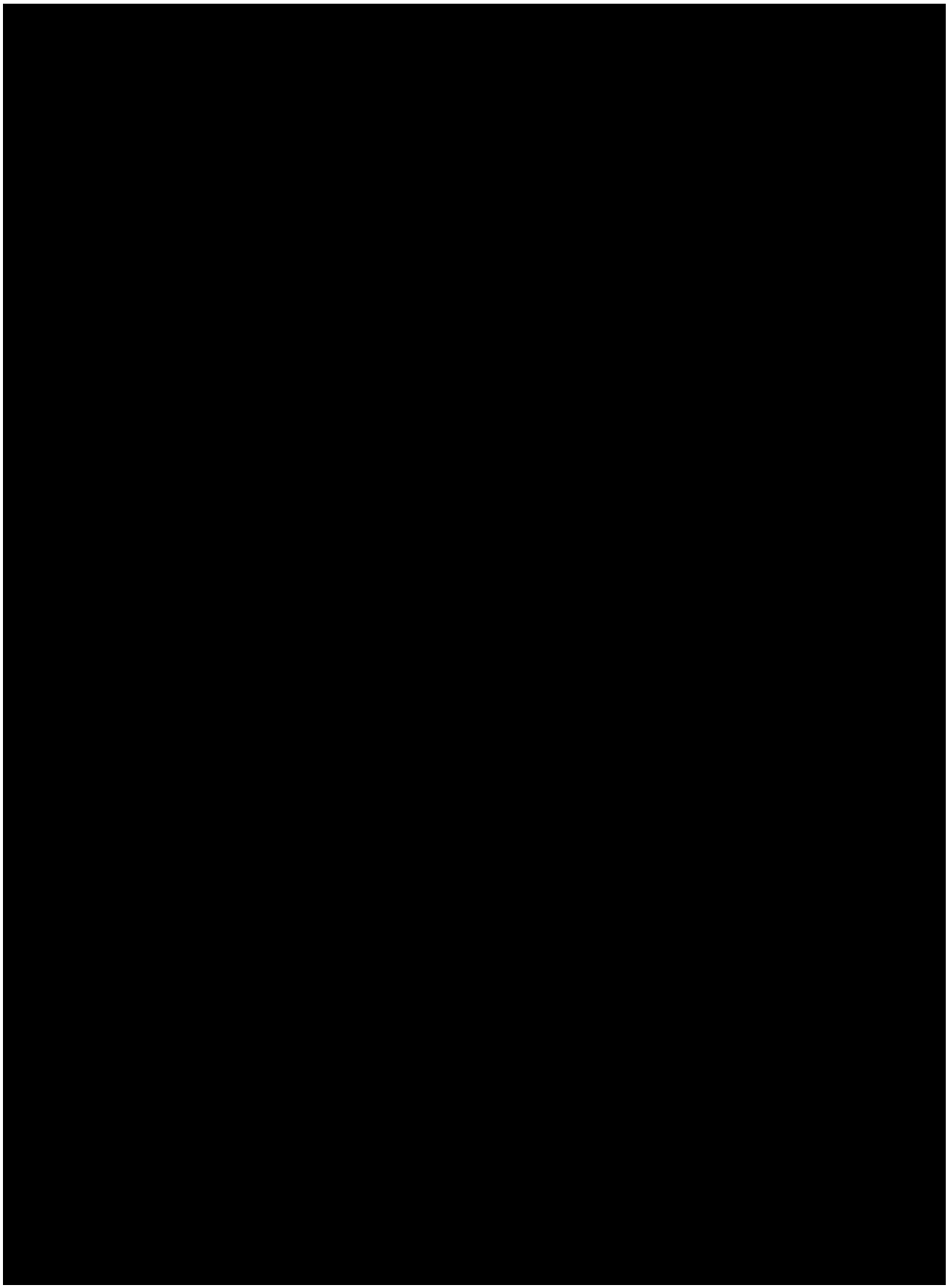

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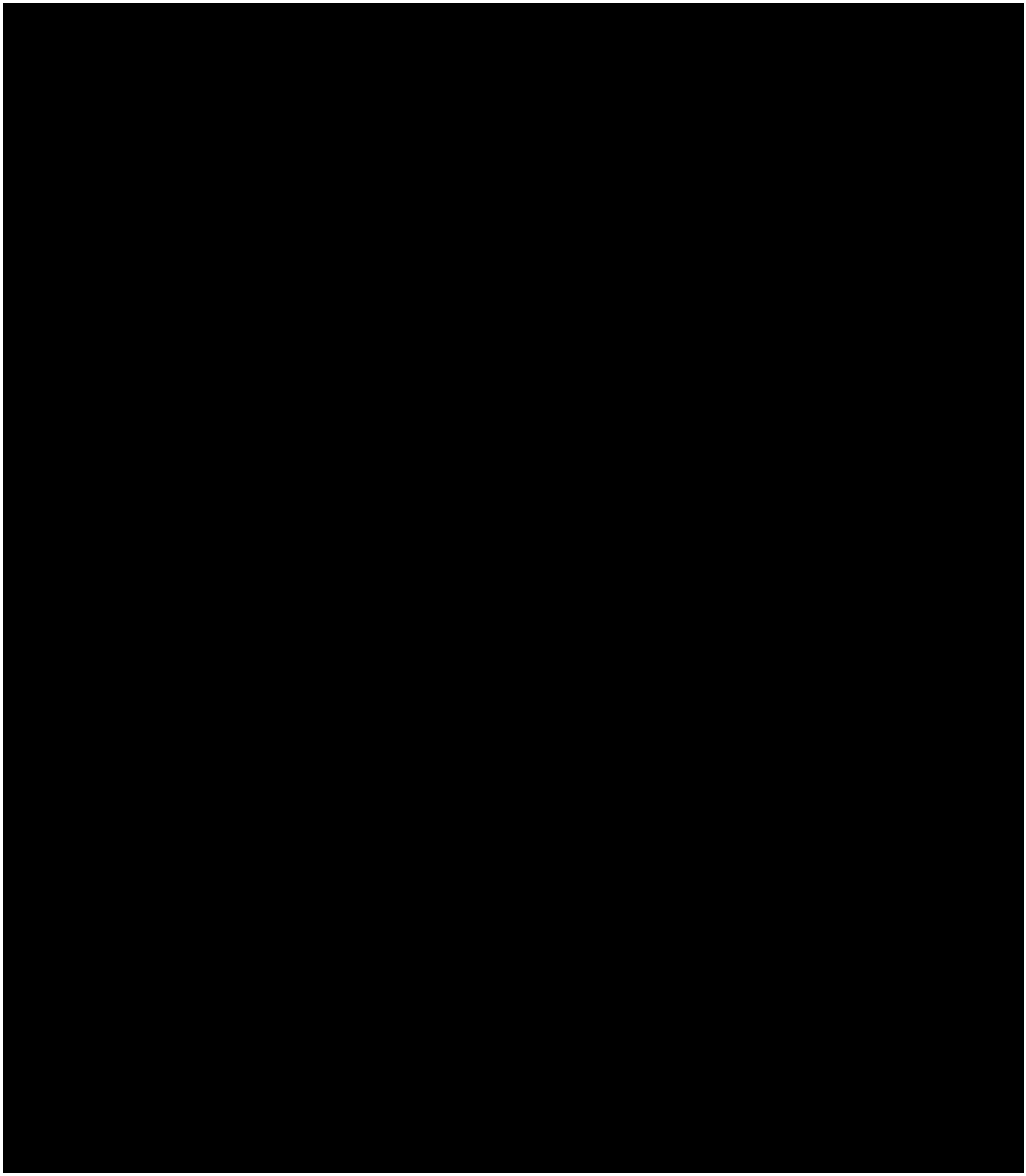

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