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Clinical Development

Spartalizumab (PDR001), LAG525, capmatinib (INC280), canakinumab (ACZ885), ribociclib (LEE011)

Oncology Clinical Protocol CPDR001J2201 / NCT03484923

A randomized, open-label, phase II open platform study evaluating the efficacy and safety of novel spartalizumab (PDR001) combinations in previously treated unresectable or metastatic melanoma

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List of abbreviations

aBC	Advanced breast cancer
ADA	Anti-drug antibodies
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANSM	Agence Nationale de Sécurité du Medicament
Anti-HCV	Antibody to Hepatitis C virus
ASMA	Anti-smooth muscle antibody
AST	Aspartate aminotransferase
AUC	Area under the curve
BCRP	Breast Cancer Resistance Protein
BICR	Blinded independent central review
BID	*bis in diem*/twice a day
BLRM	Bayesian logistic regression model
BOR	Best overall response
C1D1	Cycle 1 Day 1
CAPS	Cryopyrin-associated periodic syndromes
CBD	Cannabidiol
CD8	Cluster of differentiation 8
CD-transferrin	Carbohydrate-deficient transferrin
CI	Confidence interval
CMO & PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central nervous system
CPI	Checkpoint Inhibitor
CR	Complete response
CRF	Case report/record form
CRO	Contract research organization
CSR	Clinical study report
CT	Computed tomography
CTC	Common terminology criteria
[redacted]	[redacted]
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
C_{trough}	Trough concentration
CV	Coefficient of variation
C*x*D*y*	Cycle *x* day *y*
CYP	Cytochrome P450
DCR	Disease control rate
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DoR	Duration of response
EBV	Epstein-Barr virus
EC50	Concentration of a drug that gives half-maximal response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status

[redacted]

eCRF	Electronic case report/record form
ERCP	Endoscopic retrograde cholangio-pancreatography
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
EoT	End of treatment
EWOC	Escalation with overdose control
FDA	Food and Drug Administration
FFPE	Formalin fixed paraffin embedded
FSFV	First subject first visit
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
HA	Health Authority
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBV-DNA	Deoxyribonucleic acid of Hepatitis B virus
HCC	Hepatocellular carcinoma
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HCV RNA	Hepatitis C virus ribonucleic acid
HEV RNA	Hepatitis E virus ribonucleic acid
HGF	Hepatocyte growth factor
HIV	Human immunodeficiency virus
HR	Hormone receptor
[redacted]	[redacted]
HSV	Herpes simplex virus
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent ethics committee
IFN	Interferon
IG	Immunogenicity
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgE	Immunoglobulin E
IgM	Immunoglobulin M
IgM anti-HAV	Immunoglobulin M antibody to hepatitis A virus
IgM & IgG anti-CMV	Immunoglobulin M and immunoglobulin G antibodies to cytomegalovirus
IgM & IgG anti-EBV	Immunoglobulin M and immunoglobulin G antibodies to Epstein-Barr virus
IgM & IgG anti-HEV	Immunoglobulin M and immunoglobulin G antibodies to hepatitis E virus
IgM & IgG anti-HBc	Immunoglobulin M and immunoglobulin G antibodies to hepatitis B core
IgM & IgG anti-HSV	Immunoglobulin M and immunoglobulin G antibodies to Herpes simplex virus
IHC	Immunohistochemistry

[redacted]

IL	Interleukin
ILD	Interstitial lung disease
INR	International normalized ratio
[redacted]	[redacted]
IRB	Institutional review board
[redacted]	[redacted]
IRT	Interactive Response Technology
ITIM	Immunoreceptor tyrosine-based inhibition motif
i.v.	intravenous
Kd	Equilibrium dissociation constant
LAG-3	Lymphocyte-activation gene 3
LDH	Lactate dehydrogenase
LFTs	Liver function tests
LLN	Lower limit of normal
LSFV	Last subject first visit
MAPK	Mitogen-activated protein kinase
MATE	Multidrug and toxin extrusion protein
MCMC	Markov chain Monte Carlo
MCV	Mean corpuscular volume
MDSC	Myeloid-derived suppressor cells
MEK	Mitogen-activated protein kinase kinase
mg	milligram
MHC	Major histocompatibility complex
ml	milliliter
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAI	Non-Steroidal Aromatase Inhibitor
NSCLC	Non-small cell lung cancer
OCT	Organic cation transporter
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
pFBP	Proportion of subjects with an favorable biomarker profile
PFS	Progression-free survival
PHI	Protected health information
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
p.o.	*per os*/by mouth/orally
PP	Posterior probability
PPI	Proton pump inhibitors
PR	Partial response
PT	Prothrombin time
Q2W	Every two weeks
Q3W	Every three weeks
Q4W	Every four weeks

[redacted]

Q8W	Every eight weeks
QD	*quaque die*/every day/once a day
QTcF	Corrected QT interval using Fridericia's formula
RAP	The Report and Analysis Plan is a regulatory document which provides evidence of preplanned analyses
RCC	Renal cell carcinoma
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
RoW	Rest of World
RP2D	Recommended phase two dose
R Value	Division of the ALT value by the ALP value, using multiples of the ULN
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s.c.	Subcutaneous
SC	Steering Committee
SD	Stable disease
SJS	Stevens-Johnson syndrome
SOD	Sum of diameter
$T_{1/2}$	Elimination half-life
T3	Triiodothyronine
T4	Thyroxine
TdP	Torsades de Pointe
TCR	T cell receptor
TEN	Toxic Epidermal Necrolysis
THC	Tetrahydrocannabinol
TIL	Tumor infiltrating lymphocytes
TIGIT	T cell immunoglobulin and ITIM domain
TIM-3	T cell immunoglobulin and mucin-domain containing protein 3
TNF	Tumor necrosis factor
TnI	Troponin I
TnT	Troponin T
T_{reg}	Regulatory T cell
TSH	Thyroid-stimulating hormone
UNK	Unknown
ULN	Upper limit of normal
US/USA	United States of America
USM	Urgent Safety Measure
VISTA	V-domain Ig suppressor of T cell activation
WHO	World Health Organization
WNT	The WNT signaling pathways are a group of signal transduction pathways made of proteins that pass signals into a cell through cell surface receptors.

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: every 28 days)
Dosage	Dose of the study drug given to the subject 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.
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol) For non-randomized arm 1A, enrollment defines the point/time when consented subject is deemed eligible for treatment in this arm.
Investigational drug(s)/study drug(s)	The drug(s) whose properties are being tested in the study.
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations.
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	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized subject
Screen Failure	A subject 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
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first subject.
Study treatment	For this study, the study treatment is defined as the combination of spartalizumab (investigational drug common for all combination arms in this study) with another investigational drug (which is different in each combination arm).
Study treatment interruption	Includes any delay or withholding of study treatment for any reason as well as an interruption during an infusion of study treatment for any reason
Study treatment discontinuation	Point/time when subject permanently stops taking study treatment for any reason
Subject number (Subject No.)	A unique identifying number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.

Treatment group / combination arm	A combination arm (also called treatment group within this document) defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

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Protocol summary

Title	A randomized, open-label, phase II open platform study evaluating the efficacy and safety of novel spartalizumab (PDR001) combinations in previously treated unresectable or metastatic melanoma
Brief title	Study of efficacy and safety of novel spartalizumab combinations in patients with previously treated unresectable or metastatic melanoma
Sponsor and phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Subjects who have failed to respond, or progressed while being on standard treatment for unresectable or metastatic melanoma which include targeted therapy (for patients with ^{V600}*BRAF*-mutant melanoma only) and/or immune checkpoint inhibitors (e.g. pembrolizumab, or nivolumab with or without ipilimumab) will be enrolled in this study. As of today, patients who have failed these standard therapies have very limited treatment options. The mechanisms of primary and acquired resistance to checkpoint inhibitors treatment are not well understood and are mainly due to a combination of intrinsic or extrinsic resistance mechanisms. The combinations tested in this study aim to alter the tumor and/or microenvironment in favorable way to overcome treatment resistance and restore T cell function. Considering the high number of potential targets and available compounds, an open platform design is applied for this study. Using the anti-PD-1 antibody spartalizumab as backbone, this study will evaluate novel compounds, which may help alter the tumor microenvironment through different mechanisms which may potentially reverse resistance to immune checkpoint blockade and restore T cell function. **LAG525** Although the PD-1/PD-L1 checkpoint axis plays a critical inhibitory role, secondary inhibitory immune checkpoints such as LAG-3 may also play a vital role leading to T cell dysfunction. Inhibition of LAG-3 with LAG525 may help restore T cell function. **Capmatinib** Neutrophils recruited to the tumor microenvironment play an immunosuppressive role, restraining T cell expansion, effector functions and contribute to resistance to immune therapy. In cancer patients, high serum levels of the c-MET ligand HGF correlated with increasing neutrophil counts and poor responses to checkpoint blockade therapies. Inhibition of c-MET with the capmatinib may help restore T cell function. **Canakinumab** Cytokines like IL-1β, derived from the tumor microenvironment and secreted by malignant cells, promotes tumor cell proliferation, increases invasiveness and dampens anti-tumor immune response, in part by recruiting inhibitory neutrophils. Inhibition of IL-1β with the IL-1β antagonist canakinumab may help restore T cell function. **Ribociclib** D-cyclin-CDK4/6-p16-pRb pathway is often up-regulated in melanoma but the cytostatic action of CDK4/6 inhibitors have only shown modest clinical benefit when used as single agent. The cytotoxic T cell-mediated clearance of tumor cells, along with the efficacy of CDK4/6 inhibition on tumor growth, have been shown to be further enhanced with immune checkpoint blockade. Given the magnitude of immune modulatory effects observed from CDK4/6 inhibitors, the combination of CDK4/6 inhibitors with check point inhibitors such as anti PD-1/PD-L1 may help to overcome resistance to anti PD-1/PD-L1.
Primary objective and key secondary objective	**Primary:** To evaluate the efficacy of each combination arm, as measured by confirmed objective response rate (ORR) **Key secondary:** To evaluate the efficacy of each combination arm in terms of duration of response (DoR)
Secondary objectives	• To evaluate the efficacy of each combination arm as measured by progression-free survival (PFS) and disease control rate (DCR) as per local RECIST v1.1 assessment • To evaluate overall survival (OS) of each combination arm • To characterize the safety and tolerability of each combination arm through the incidence and severity of AEs including changes in laboratory values, vital

	signs, cardiac assessment and dose interruptions, reductions, and permanent discontinuations of study treatment • To characterize the prevalence and incidence of immunogenicity of spartalizumab, LAG525 and canakinumab in each combination arm, through the prevalence of anti-drug antibodies (ADA) at baseline and ADA incidence on treatment • To evaluate changes from baseline in levels and phenotype of T cell populations in the tumor and tumor microenvironment, assessing the proportion of subjects with a favorable biomarker profile (pFBP)
Study design	This is a randomized, open-label, two-part, multi-center, open platform phase II study to assess the efficacy and safety of the anti-PD-1 antibody spartalizumab in combination with novel agents in previously treated unresectable or metastatic melanoma. A non-randomized single-arm (Arm 1A) has been added with protocol amendment 5 to assess the efficacy and safety of spartalizumab in combination with LAG525 in subjects with previously treated unresectable or metastatic LAG-3 positive melanoma, based on encouraging results from arm 1. The study consists of a selection phase (Part 1) and an expansion phase (Part 2). **- Randomized section of the study** **Part 1 : Selection phase** The randomized section of this study started with the following three initial combination arms: • Arm 1: LAG525 600 mg i.v. Q4W and spartalizumab 400 mg i.v. Q4W o Declared futile at interim analysis 2 • Arm 2: Capmatinib 400 mg p.o. BID and spartalizumab 400 mg i.v. Q4W o Declared futile at interim analysis 1 • Arm 3: Canakinumab 300 mg s.c. Q4W. and spartalizumab 400 mg i.v. Q4W o Declared futile at interim analysis 1 With protocol amendment 3, a fourth combination arm (Arm 4) was added: • Arm 4: Ribociclib 600 mg p.o. QD on Days 1-21 of a 28-day cycle and spartalizumab 400 mg i.v. Q4W o Declared futile at interim analysis 3 As dose regimens for new additional combinations with spartalizumab become established, new combination arms will be added under the same master protocol through protocol amendments. Eligible subjects will be randomized with equal probability to the arms. A maximum of 10 arms may be active at any given time under this master protocol, and any arms active in part 1 will continue to be randomized with equal probability. At each interim analysis, it will be determined (1) which arm is declared efficacious and will be expanded to part 2, (2) and which arms will continue enrollment in part 1 (up to 45 subjects) or (3) will be dropped for futility, taking into account all available efficacy, safety, and biomarker data. **Part 2 : Expansion phase** In the randomized section of the study, only combination arms that have met the pre-specified protocol criteria in part 1 will be eligible for opening of subject's enrollment in part 2. Exact randomization strategies for the arm(s) in part 2 of the study compared to arms still open for enrollment in part 1 will be determined at the time of the selection of the arm(s) that will be expanded in part 2. At any time during the study, subjects deemed eligible after the completion of screening procedures will be randomized to any open arms in both part 1 and part 2 for which the subject meets the eligibility criteria using an Interactive Response Technology (IRT) system. For each arm, randomization will be stratified by baseline LDH. Stratification will occur based on baseline LDH (≤ ULN vs. LDH > ULN). In both parts, crossover or re-randomization of subjects to other combination arms, including better performing arms, is not allowed. The first four arms evaluated in the randomized section of the study will enroll approximately a maximum of 230 subjects in total (for both parts of the study): approximately a maximum of 180 subjects in the selection phase (if all four combination arms enroll the maximum of 45 subjects each) and approximately 50

	subjects in the expansion phase (assuming that only one of the four initial combination arms will be expanded). **- Non-randomized section of the study** Arm 1A will enroll up to approximately 100 subjects in total with LAG-3 positive melanoma: 20 subjects in part 1 and up to approximately 80 subjects in part 2. Study treatment in Arm 1A will be: LAG525 600 mg i.v. Q4W and spartalizumab 400 mg i.v. Q4W. Two interim analyses for futility will be conducted for arm1A: based on data from 20 subjects treated in Part 1 and from 20 additional subjects treated in part 2 (i.e. 40 subjects in total combined with part 1 subjects).
Population	Randomized section of the study: Adult (≥ 18 years) patients with unresectable or metastatic melanoma previously treated with anti-PD-1/PD-L1 single-agent or in combination with anti-CTLA-4 therapy (^{V600}*BRAF* mutant patients must also have received prior ^{V600}*BRAF* inhibitor therapy, either single-agent or in combination with a MEK inhibitor) Non-randomized section of the study (Arm 1A): Adult (≥ 18 years) patients with LAG-3 positive unresectable or metastatic melanoma previously treated with anti-PD-1/PD-L1 (as monotherapy or in combination with ipilimumab) as last therapy prior to enrollment (^{V600}*BRAF* mutant patients must also have received prior ^{V600}*BRAF* inhibitor therapy, as monotherapy or in combination with a MEK inhibitor).
Key inclusion criteria	**Randomized section of the study** Key inclusion criteria are listed below, please refer to the protocol for the full list of inclusion criteria: • Histologically confirmed unresectable or metastatic stage IIIB/C/D or IV melanoma using AJCC edition 8 • Previously treated for unresectable or metastatic melanoma (refer to Section 5.2.1 in the protocol for details) • ECOG performance status 0-2 • At least one measurable lesion per RECIST v1.1 • At least one lesion, suitable for sequential mandatory tumor biopsies (screening and on-treatment) in accordance with the biopsy guidelines specified in protocol. The same lesion must be biopsied sequentially. Note: this lesion cannot be used as a target lesion. • Screening tumor biopsy must fulfill the tissue quality criteria outlined in the protocol, as assessed by a local pathologist **Non-randomized section of the study** Key inclusion criteria for arm 1A are listed below, please refer to the protocol for the full list of applicable inclusion criteria: • Histologically confirmed unresectable or metastatic stage IIIB/C/D or IV melanoma according to AJCC Edition 8 • Previously treated for unresectable or metastatic melanoma (refer to Section 5.2.2 in the protocol for details) • ECOG performance status 0-1 • At least one measurable lesion per RECIST v1.1 • Subjects must have baseline tumor sample (fresh tumor biopsy or recent archival sample, as described in the protocol) that is positive for LAG-3 per central assessment at the Novartis-designated laboratory (Histogenex, Antwerp, Belgium)
Key exclusion criteria	Key exclusion criteria common to all combination arms are listed below, please refer to the protocol for the full list of common and arm-specific exclusion criteria: • Subjects with uveal or mucosal melanoma • Presence of clinically active or unstable brain metastasis at time of screening. Note: Subjects with previously unstable brain lesions who have been definitively treated with stereotactic radiation therapy, surgery or gamma knife therapy are eligible: • Subjects with brain lesions who are untreated (i.e. newly discovered brain lesions during screening) or received whole brain radiation must have documented stable disease as assessed by two consecutive assessments

	≥ 4 weeks apart and have not required steroids for at least ≥ 4 weeks prior to randomization/enrollment. • Use of any live vaccines against infectious diseases within 3 months before randomization/enrollment. • Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization/enrollment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease. • Active, known or suspected autoimmune disease or a documented history of autoimmune disease. Note: Subjects with vitiligo, controlled type I diabetes mellitus on stable insulin dose, residual autoimmune-related hypothyroidism only requiring hormone replacement or psoriasis not requiring systemic treatment or conditions not expected to recur in the absence of an external trigger are permitted. • Active infection requiring systemic therapy (i.e. antibiotics, anti-virals, high dose steroids, immunosuppressants, or any other systemic therapy) at the time of randomization/enrollment. • Prior allogenic bone marrow or solid organ transplant • History of known hypersensitivity to any of the investigational drugs used in this study • Known history or current interstitial lung disease or non-infectious pneumonitis • Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to start of study treatment; completely resected basal cell and squamous cell skin cancers and any completely resected carcinoma in situ • Known history of testing positive for Human Immunodeficiency Virus (HIV) infection • Active Hepatitis B infection (HBsAg positive). Note: Subjects with antecedent of Hepatitis B (anti-HBc positive, HBsAg and HBV-DNA negative) are eligible • Subject with positive test for hepatitis C virus (HCV) ribonucleic acid (RNA) • Prior systemic therapy for unresectable or metastatic melanoma with any investigational agent, or with any other agent, except anti-PD-1/PD-L1 and anti-CTLA-4 (and ^{V600}*BRAF* and MEK inhibitors if subject has ^{V600}*BRAF* mutant disease). Prior neoadjuvant and or adjuvant therapy for melanoma completed less than 6 months before the start of study treatment. • Medical history or current diagnosis of myocarditis • Cardiac troponin T or I (TnI) level > 2 x ULN at screening
Investigational and reference therapy	**Study treatment is defined as :** • <u>Arm 1 and Arm 1A:</u> LAG525 and spartalizumab • <u>Arm 2</u>: capmatinib and spartalizumab • <u>Arm 3:</u> canakinumab and spartalizumab • <u>Arm 4:</u> ribociclib and spartalizumab Investigational drugs will be administered as follows: • All arms: spartalizumab will be administered as 400 mg intravenous (i.v.) infusion over 30 minutes (up to 2 hours, if clinically indicated) every four weeks (Q4W). • Arm 1 and Arm 1A: LAG525 will be administered as 600 mg i.v. infusion over 30 minutes (up to 2 hours, if clinically indicated) Q4W. • Arm 2: The starting dose of capmatinib will be 400 mg p.o administered on a twice daily (BID) dosing (total daily dose: 800 mg) orally from Day 1 till Day 28 of each 28-day cycle. • Arm 3: canakinumab will be administered as 300 mg s.c. injection Q4W. • Arm 4: The starting dose of ribociclib will be 600 mg p.o administered once a day from Day 1 to Day 21 of each 28-day cycle.

Efficacy assessments	**Radiological tumor assessments by local RECIST v1.1** • At screening • During treatment: 12 weeks (± 7 days) after the date of randomization (or after the date of first dose of study treatment in arm 1A), then every 8 weeks (± 7 days) until 52 weeks after randomization/date of first dose of study treatment in arm 1A, and every 12 weeks (± 7 days) thereafter until disease progression per RECIST v1.1 (as assessed by the investigator), death, lost to follow-up or withdrawal of consent. • End of Treatment (EOT): Only to be done if a scan was not conducted within 30 days prior to end of study treatment. • Efficacy follow-up: If subject discontinued study treatment for reason other than disease progression per RECIST v1.1, efficacy follow-up must be continued on the same schedule as during treatment until disease progression per RECIST v1.1. **Survival follow up** Every 3 months after safety/efficacy follow-up period.
Safety assessments	• Physical examination • ECOG performance status • Weight and vital signs • 12-lead ECG • Laboratory assessments, including hematology, chemistry, thyroid function, coagulation, serology, urine and safety cytokines • Pregnancy testing for women of childbearing potential • Adverse events (AEs): severity, relationship to study treatment and seriousness • Immunogenicity: Testing for anti-drug antibodies (ADA) for spartalizumab, LAG525 and canakinumab
Other assessments	[redacted] • Biomarker tissue samples: • Baseline tumor sample: Mandatory newly or recently acquired tumor biopsy (as defined in protocol section 7.2.3.1.1) at screening and newly obtained tumor biopsy at 3-4 weeks on treatment for the evaluation of $CD8^+$ T cell infiltration and T cell activation, gene expression analysis and/or T cell repertoire/clonality. When screening for arm 1A, centralized LAG-3 status assessment will be performed on baseline tumor sample by the Novartis-designated laboratory (Histogenex, Antwerp, Belgium). [redacted]
Data analysis	**Interim analyses** **- Randomized section of the study** In part 1, the first interim analysis is planned for ORR once at least ten subjects have been randomized into each of the three initial treatment groups (arm 1, arm 2, arm 3), and have either completed two post-baseline tumor assessments or have discontinued study treatment. Subsequent interim analyses will be conducted approximately every five months thereafter. The first interim analysis for arm 4 (ribociclib and spartalizumab) will be synchonized with the subsequent planned interim analyses for the other arms and will occur when at least ten subjects have been randomized to that arm and have either completed two post-baseline tumor assessments or have discontinued study treatment. Enrollment and assessment at subsequent interim analyses for each treatment group will continue until the criteria for futility/advancement into the expansion phase have been met, or 45 subjects

[redacted]

	have been randomized into a treatment group. To determine whether treatment arms have the potential to demonstrate clinically meaningful response rates, arms will need to show that they cross a specific probability efficacy threshold P(ORR ≥ 20%) ≥ 70% during the selection phase to advance to the expansion phase. Conversely, treatment arms can also be shown to cross a specific futility probability threshold P(ORR ≤ 15%) ≥ 70% and consequently will be declared as futile and enrollment in those arms will be terminated. No formal interim analysis is planned for part 2. **- Non-randomized section of the study** In part 1, the first interim analysis planned for ORR will occur once all 20 subjects treated in arm 1A have either completed two post-baseline tumor assessments or have discontinued study treatment. In part 2, a second interim analysis will be conducted after 20 subjects are treated in expansion phase (i.e. 40 subjects in total for arm 1A including the 20 treated in the selection phase) and followed up for at least two post-baseline efficacy assessments or have discontinued study treatment. At each interim analysis, it will be determined if arm 1A will be further explored or dropped for futility. **Primary analysis** The primary analysis in each of the randomized and non-randomized section of this study will be performed once an expanded arm has fully enrolled and all subjects in that arm have at least 9 months of follow-up . Formal hypothesis testing of the primary endpoint will be performed at the primary analysis taking into account data from both the expansion and selection phases.
Key words	Unresectable melanoma, metastatic melanoma, advanced melanoma spartalizumab (PDR001), LAG525, capmatinib (INC280), canakinumab (ACZ885), ribociclib (LEE011), immunotherapy, platform study, LAG-3

Amendment 5 (26-Jun-2020)

Amendment rationale

As of the date of release of this amendment, 174 subjects have received study treatment in part 1 (45 in arm 1, 43 in arm 2, 42 in arm 3 and 44 in arm 4) and all arms have been declared futile. No arm has yet been expanded to part 2 of the study.

The main purpose of amendment 5 is to add a new non-randomized single-arm (Arm 1A) in this study to evaluate the efficacy and safety of spartalizumab and LAG525 combination in LAG-3 positive subjects with previously treated unresectable or metastatic melanoma. Preliminary data generated in Arm 1 support further investigation of the spartalizumab plus LAG525 combination in order to validate the hypothesis that this combination could be effective in subjects with LAG-3 positive melanoma.

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.

Major changes are:

- Addition of arm 1A as a non-randomized single-arm:
    - Section 2.2 is updated to add the non-randomized section of the study and include the rationale for adding arm 1A outside of the randomized design and for the selection of a higher targeted overall response rate for decision-making in this selected arm.
    - Section 2.4.1.1 is added to provide the rationale for targeting subjects with LAG-3 positive melanoma in arm 1A, based on findings in arm 1 following interim analysis 2 (IA2).
    - Section 3 is updated to indicate that the objectives and endpoints defined apply for all arms.
    - Section 4.1 is updated to add the non-randomized section of the study with the addition of arm 1A. Section was also updated to reflect that the randomized and non-randomized sections of this study share the same objectives for part 1 and part 2. Section 4.1.1 header is created to individualize the design for the randomized section of the study from the description for the design of the non-randomized section that has been added in the newly created Section 4.1.2. The title of Figure 4-1 and text in Section 4.1.1 are updated to clearly indicate that they apply for the randomized section of the study. A new Figure 4-2 is added to provide an overview of the study design for the non-randomized section.
    - Section 4.1.3 header is created to individualize the paragraph describing subject-level study design and indicate that it will be shared by the randomized and non-randomized sections of the study. Regardless of the study section and part they are randomized/enrolled into, each subject will undergo the same study periods described in the section and will have assessments performed as described in Table 7-2.
    - The text in Section 4.1.3 for the treatment period and the former Figure 4-2 describing subject level study design (re-numbered Figure 4-3), as well as

text in Section 6.1.1, Section 7.1, Table 7-1, Table 7-2, Section 10, are updated to reflect "randomization/enrollment" or "randomized/enrolled" where statements are applicable for subjects randomized and subjects enrolled in arm 1A.

- A statement is added in Section 4.1.3, Section 7.1, Table 7-2, Table 7-3, and Section 7.2.1.2 to indicate that the schedule of RECIST v1.1 tumor assessments in arm 1A should be calculated taking the date of first dose of study treatment as reference (as this arm is not randomized), whereas the reference for this calculation in randomized arms is the date of randomization. Section 7.2.1.1 is also updated to indicate that imaging assessments obtained after date of first dose of study treatment cannot be considered as baseline images.
- Section 4.2.1 header is created to individualize the paragraph on timing of interim analyses and design adaptations in the randomized section of the study. Former Figure 4-3 is re-numbered Figure 4-4 (no update in the figure). Section 4.2.2 is created to describe the independent timing of interim analyses and design adaptations in the non-randomized section of the study.
- Section 4.3 is updated to indicate that each section of the study (randomized and non-randomized) will have a different timing for the completion of the primary analysis. Indeed, primary analysis will occur once all subjects randomized/enrolled in an arm expanded in part 2 (whether in the randomized or non-randomized section) will have at least 9 months of follow-up. This will not occur at the same time for each arm expanded in part 2 across the two sections of the study.
- Section 5.2.1 header is created to individualize the inclusion criteria applicable for the arms assessed in the randomized section of the study (arms 1,2, 3, 4)
- Section 5.2.2 is created to describe all the inclusion criteria that subject must meet to be eligible for arm 1A. Some of the inclusion criteria for arm 1A are the same as for other arms (those criteria have the same criterion number in Section 5.2.1 and Section 5.2.2; Note that inclusion criterion #8a is not applicable for arm 1A, which leads to a gap in criteria numbering). The below inclusion criteria differ for arm 1A compared to other arms:
    - Inclusion criterion #4b is adding new requirements for prior anti-cancer therapies received and prior disease progression compared to inclusion criterion #4a: all subjects must have received an anti-PD-1 pembrolizumab or nivolumab) either as monotherapy or in combination with ipilimumab as the last systemic therapy prior to enrollment and must have confirmed disease progression as per RECIST v1.1 (confirmed on a subsequent scan, which can be the scan performed during screening) while on or after this therapy prior to enrollment. Those new requirements are added to better assess the efficacy of the combination partner of spartalizumab over anti-PD1 alone and to have a more homogeneous patient population. The criteria for confirmed progression is being implemented to ensure that progression to prior PD-1 therapy was not a pseudo-progression.

[redacted]

  - Inclusion criterion #5a is changing the requirement on ECOG performance status, that must be 0 or 1 for subject to be eligible to arm 1A. This change is intended to exclude patients with worst performance status that in most cases would not even reach the first and second post-baseline tumor assessments (approximatively 6% of the patients enrolled in the study so far had ECOG performance status of 2).
  - Inclusion criterion #7b is adding a new requirement for subjects to have a baseline tumor sample (either newly collected during screening, or archival sample meeting requirements defined in Section 7.2.3.1.1) that is LAG-3 positive per central assessment at the Novartis-designated laboratory (Histogenex, Antwerp, Belgium). This new requirement allows selection of a population of subjects with LAG-3 positive melanoma who may derive a higher clinical benefit from treatment with LAG525 and spartalizumab combination based on IA2 findings in arm 1.

- Exclusion criteria #2a, #3 and #6a in Section 5.3.1 (listing exclusion criteria common to all arms) have minor updates to indicate that the criteria apply prior to randomization/enrollment.
- Section 6.1, Table 6-1 and Table 7-2 are updated to include the study treatment regimen received by subjects enrolled into arm 1 A (LAG525 600 mg Q4W i.v. and spartalizumab 400 mg Q4W i.v.), which is the same as for arm 1.
- Section 6.5.2 is updated to indicate which paragraphs are applicable for the randomized section of the study and add reference to Section 4.1.1. A statement is also added for the non-randomized section of the study to indicate that assignment to arm 1A in IRT (in part 1 or part 2) will be systematic in IRT as long as subject fulfills the inclusion/exclusion criteria applicable for arm 1A, given the absence of randomization.
- Section 7.1.2.3 is updated to reflect that randomization stratification on LDH value applies only in the randomized section of the study.
- Section 7.2.2.5 is updated to indicate that the requirements for subject to be fasting for at least 12 hours overnight before each blood collection to obtain fasting glucose and for investigators to monitor the potential occurrence of auto-immune diabetes for arm 1 also apply for arm 1A, as both arms share the same study drugs.
- Section 7.2.2.5.1, Table 7-2 and Table 7-5 are updated to indicate that the requirement for cardiac troponin T (or I) monitoring for arm 1 also apply for arm 1A, as both arms share the same study drugs.
- Table 7-2 and Table 7-6 are updated to indicate that the schedule of ECGs for subjects treated in arm 1A will be the same as the schedule for arm 1, as both arms share the same study drugs.
- Table 7-2 and Table 7-8 are updated to indicate that the schedule for collection of blood samples for [redacted] immunogenicity analyses for arm 1A is the same as the schedule for arm 1 as both arms share the same study drugs.

[redacted]

- Table 7-1, Table 7-2, Section 7.1.2 and Table 7-12 are updated to indicate that, when screening for arm 1A, the study informed consent can be signed up to 35 days prior to planned enrollment date to allow prompt collection of the newly or recently obtained baseline tumor sample after consent is given (screening period for arm 1A extended accordingly to up to 35 days in Table 7-2). As eligibility to arm 1A is dependent upon LAG-3 status assessed centrally, sites are requested to submit the baseline tumor sample to the Novartis-designated laboratory (Histogenex, Antwerp, Belgium) as early as possible and at the latest 20 days prior to planned enrollment date to allow sufficient time for central assessment and reporting of LAG-3 status in a timely manner. All other screening assessments for arm 1A have to be performed according to the timelines applicable for all other arms as mentioned in Table 7-1. It is recommended to wait to receive the result of LAG-3 status to perform further screening assessments.
- Centralized assessment of LAG-3 status on mandatory baseline tumor sample is added in Table 7-2 and Section 7.2.3.1 as a screening assessment specifically for arm 1A and described within the newly created Section 7.2.3.1.2. As added in Section 7.1.2 and Section 7.2.3.1.2, a subject whose baseline tumor biopsy tissue sample does not allow central assessment of LAG-3 will be considered a screen failure, unless a new baseline tumor sample is submitted and assessed for LAG-3 before the end of the screening period. Sample must be reported as LAG-3 positive for subject to be eligible to arm 1A. Other biomarkers described in Section 7.2.3.1 will be analyzed only if subject is enrolled.
- Wording on description of biomarker analyses on tumor samples which was included in Section 7.2.3, Section 7.2.3.1.1, Section 7.2.3.1.3 and Section 7.2.3.1.4 has been condensed and moved to Section 7.2.3.1 to avoid redundant information across different sections as the randomized and non-randomized sections of the study share the same secondary [redacted] biomarker objectives for all mandatory, optional or archival tumor tissue samples. A statement has also been added that tumor samples, including from screen failed patients, may be also used to generate data to support development of future companion diagnostic tests.
- Section 7.2.3.1.1 and Table 7-12 are updated to indicate the specific requirements for mandatory baseline tumor sample for LAG-3 testing for arm 1A which are different than all other arms. Biopsy guidelines for the collection of a fresh tumor biopsy (at screening and on treatment) are the same for arm 1A as in the other arms, but are not a requirement for eligibility to arm 1A. Similarly, the tissue quality criteria described in Table 7-13 are only recommendations, but not a requirement for eligibility for arm 1A. These requirements allow the enrollment of a subject in arm 1A as long as the baseline tumor sample is reported LAG-3 positive (and provided all other eligibility criteria for arm 1A are met), even if the sample does not meet tissue quality criteria in Table 7-13. Local pathology review of the tissue quality criteria defined in Table 7-13 on baseline tumor sample prior to enrollment is not required when screening for arm 1A, as the assessment will be done centrally as part of LAG-3 testing. Submission of a formalin-fixed tissue in ethanol as baseline tumor sample would only be acceptable when

[redacted]

screening for arm 1A, although submission of FFPE tumor block remains the preferred option.

- Updated Section 8.6 to indicate that the DMC will review safety data from any arm expanded in part 2, whether in the randomized or non-randomized section of the study.
- Section 10 : Introduction paragraph is updated to clarify that Section 10 and all sub-sections refer by default to the randomized section of the study and the same will apply to the non-randomized section of the study (where only arm 1A will be analyzed), unless specified otherwise. It has been added that the date of first dose of study treatment will be used as reference date for non-randomized section. Sections 10.4.2.1, 10.7.1, 10.8.1 headers were created to individualize paragraphs applicable for the randomized section of the study from the newly added paragraphs specific to the non-randomized section of the study (added in Sections 10.4.2.2, 10.7.2 and 10.8.2). Section 10.4.4 is updated to indicate that sub-group efficacy analyses on LDH starta applies only for arms in the randomized section of the study. Tables numbering have been updated accordingly due to addition of the non-randomized section details.

The other main changes done, not specific to the addition of arm 1A, are the following:

- Addition of the outcome of IA2 and IA3 and specified the outcome for each study treatment arm in Section 4.1.1.
- Clarification on interim analyses performed in part 1 in the randomized section of the study: Section 4.2.1 and Section 10.7.1. are updated to clarify that interim analyses in part 1 of the randomized section of study will continue to be performed at the pre-defined frequency until a clinical decision (e.g. arm declared futile or efficacy probabilistic thresholds crossed) is made for each arm in part 1. Combination arms, even if declared futile, will be analyzed at subsequent interim analyses until all subjects have been reported at least once (i.e. had a minimum follow-up of 20 weeks). Additional descriptive analyses may be performed if required. This update will allow Novartis to report data for all subjects at least once (after they have reached a minimum of 20 weeks of follow-up) if needed for publication purpose before the primary or final analysis.
- Removed statement in Section 4.3 that results of primary analysis will be summarized in a primary CSR: Generation of a primary CSR is not a regulatory requirement, therefore Novartis may not generate a primary CSR for each primary analysis performed, in the case where several primary analyses are done if arm(s) are expanded in both the randomized and non-randomized section of the study.
- Allow end of study to be declared in case no arms are expanded in part 2 (in either randomized or non-randomized section of the study): Section 4.3 is updated to indicate that the end of study can be declared once all subjects randomized/enrolled have at least 15 months of follow-up (i.e. 15 months after last subject is randomized/enrolled, regardless of the study section/part). Indeed, the completion of the primary analysis in each study section is conditioned on the expansion of at least one combination arm in part 2. This update in the definition of end of study would allow declaring the end of study and completion of the final analysis and generation of the final CSR, with a sufficient follow-up for all subjects randomized/enrolled.

[redacted]

Section 4.3 is also updated to remove the statement that all available data from all subjects up to this cut-off date will be analyzed and summarized in a final CSR.

- Revision of some exclusion criteria that are common to all arms in Section 5.3.1 :
  - Exclusion criterion #4 (re-numbered #4a) is revised to exclude subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days (instead of 7 days) of randomization/enrollment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease. This change is done to allow subjects with adrenal replacement steroids to be enrolled in the study as they require steroid doses > 10mg in case of stress condition (including but not limited to minor dental surgeries, fever).
  - Exclusion criterion #6 (re-numbered #6a) is revised to exclude subjects with any active infection (bacterial, viral or of any other type) that would require systemic therapy (including, but not limited to, antibiotics, anti-virals, high dose steroids, immunosuppressants). This change ensures that subjects with any type of active infection (including coronavirus infection) requiring systemic therapy are excluded from enrollment to ensure subject's safety.
  - Exclusion criterion #12 (re-numbered #12a) is revised to correct that active hepatitis B infection is defined based on HBsAg positivity only and not based on positive testing for HBV-DNA.
  - Exclusion criterion #15 (re-numbered #15a) is revised to clarify that a woman should have had bilateral tubal ligation (at least six weeks before taking study treatment) to be considered not of child bearing potential.
  - Exclusion criterion #17a is updated to remove the list of examples of prior neoadjuvant and/or adjuvant therapy for melanoma, as the list is not exhaustive (minor update). Any prior neoadjuvant and/or adjuvant therapy for melanoma completed less than 6 months before the start of study treatment makes the subject ineligible for the study.
- Revision of the threshold AST/ALT values for potential drug-induced liver injury (DILI) cases and guidance on investigations which can be performed to rule out other causes for liver injury in Section 6.3.3.1 (applicable for all arms) to align with current best clinical practices and publications: for subjects with elevated AST or ALT or total bilirubin at baseline, [AST or ALT > 3.0 × baseline] OR [AST or ALT > 8.0 × ULN], whichever is lower, combined with [total bilirubin > 2.0 × baseline AND > 2.0 × ULN] will require further investigations to exclude any other cause before DILI is assumed as the cause of liver injury. Investigations have been detailed in Section 6.3.3.1 and a new Table 6-38 is added to provide guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed liver abnormalities. All cases confirmed on repeat testing meeting the laboratory criteria defined for potential DILI, with no other alternative cause for liver test abnormalities identified should be reported as SAE using the term "potential treatment-induced liver injury".

[redacted]

- Clarified in Table 7-2, Table 7-12 and Section 7.2.3.1.3 that the provision of an archival tumor sample collected prior to the start of any prior anti-PD-1/PD-L1 mono- or combination therapy is mandatory if such sample is available.
- Amended tissue quality criteria to indicate that mandatory tumor samples submitted should not contain abundant melanin pigmentation, in the footnote of Table 7-13, which was a leading cause for tumor samples not being evaluable for LAG-3 and other biomarker analyses.
- Emphasized in Section 8.3 that a female participant becoming pregnant must discontinue study treatment and must be proposed the pregnancy consent form to allow the investigator to collect and report information regarding the pregnancy if consent given. Section 8.3 is also updated to specify that female subjects providing consent for pregnancy follow-up will be contacted one month after the estimated date of delivery, and 3 and 12 months after the estimated date of delivery for live births only. This aligns with information provided in the current pregnancy follow-up consent form for pregnant participants and pregnant partners of male participants.
- Population of analysis used for the calculation of the proportion of subjects with a favorable biomarker profile (pFBP) has been slightly modified in Section 10.5.5.1 to include the evaluability on at least two of the biomarker parameters used to define a favorable biomarker profile.
- BOR definition for stable disease in Section 14.2.3.1 of the RECIST guidelines in Appendix 2 has been corrected to reflect the study protocol tumor assessment schedule. At time of this protocol amendment, there was no impact on previous analyses done since no tumor assessment had been performed between 6 and 11 weeks that qualified for a BOR stable disease.

The following editorial changes have also been made:

- New abbreviations added in the list of abbreviations
- List of abbreviations and Section 1.2.2.1 updated to reflect the new definition for ICH, International Council for Harmonization.
- Glossary of terms updated to indicate that for non-randomized arm 1A, enrollment defines the point/time when consented subject is deemed eligible for treatment in this arm.
- Protocol summary updated to align with the changes described above which are impacting protocol summary. Details on prior therapies to be received for subjects to be eligible to randomized arms have been removed from the section on key inclusion criteria and replaced by a reference to the corresponding protocol section, as requirements differ in randomized and non-randomized arms. Wording for primary analysis was also corrected in the protocol summary as it was not reflecting accurately the timing of primary analysis as described in Section 4.3.
- Section numbers are updated across the document to refer to the adequate sub-paragraph for randomized or non-randomized section of the study. Figure and Table numbers are updated across the document to account for the new figures and tables added.
- Clarified in Section 7.2.1. that central imaging is performed by an independent reviewer.

[redacted]

- The term "newly obtained tumor biopsy" is replaced across the document with "mandatory newly or recently obtained tumor biopsy" to account for the fact that the mandatory baseline sample to be provided at screening for all arms can be a fresh biopsy collected during screening or a recently collected tumor sample (as stated in Section 7.2.3.1.1)
- Corrected "Formalin-fixed block in ethanol" to "Formalin-fixed tissue in ethanol" in Table 7-12 as the tissue is fixed, not the block.
- Updated Section 9.4 to clarify that dates of screenings, randomizations/enrollments, screen failures and study treatment completion are also tracked using the IRT system, as this was omitted by error in this paragraph.
- Included the list of informed consents available for this study in Section 11.3. A separate main study consent will be used for arm 1A.
- Instructions in italic within the RECIST v1.1 guidelines in Appendix 2 (Section 14.2) have been removed, as those are instructions for Novartis teams when developing the protocol which were left in the appendix by error.

IRBs/IECs

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

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

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

[redacted]

Amendment 4 (24-Jan-2020)

Amendment rationale

As of the date of release of this amendment, 168 subjects have received study treatment in part 1 (45 in arm 1, 43 in arm 2, 42 in arm 3 and 38 in arm 4) and enrollment is still ongoing in arm 4 in part 1 (part 2 of the study is not yet open).

The main purpose of amendment 4 is to amend ribociclib's dose modification guidelines for interstitial lung disease (ILD)/pneumonitis and Toxic Epidermal Necrolysis (TEN), following the observation of rare cases of ILD/pneumonitis in subjects receiving CDK4/6 inhibitors, and the reporting of TEN in the post-marketing setting in a well-documented literature case report (no case observed in the clinical trials). Therefore, this protocol amendment is implementing mandatory dose modification guidelines for investigators to interrupt ribociclib in case of ILD/pneumonitis grade 2 and to permanently discontinue ribociclib in case of ILD/pneumonitis of grade ≥ 3, and to discontinue ribociclib if TEN is diagnosed. Please refer to ribociclib (LEE011) Investigator Brochure Edition 14 for more information.

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.

Major changes are:

- Section 4.1 and protocol summary: Information has been added that enrollment in Part 1 is closed in the three initials arms (arms 1, 2 and 3) of the study.
- Section 4.2 and Section 10.7: Clarification has been added to indicate that combination arms will no longer be included in subsequent interim analyses after all subjects randomized in this arm had primary endpoint already reported in a previous interim analysis.
- Four exclusion criteria have been revised. Based on the current enrollment status in Arm 4 (i.e. 38 subjects randomized in Part 1 as of the date of release of this amendment), the changes in those exclusion criteria are not expected to affect the study population in Part 1:
    - Section 5.3.1 and protocol summary: Exclusion criterion #5 (re-numbered #5a) has been clarified to indicate that subjects with autoimmune conditions that are not expected to recur in the absence of an external trigger may be eligible.
    - Section 5.3.3: Exclusion criterion #28 (re-numbered #28a) has been corrected to remove the requirement to use central interpretation of triplicate ECGs at baseline, to align with section 7.2.2.6 stating that eligibility should be assessed by the investigator based on local interpretation of screening ECGs. It has also been clarified that the QTcF interval value (QT interval using Fridericia's correction) should be used at screening.
    - Section 5.3.3: Exclusion criterion #30 (re-numbered #30a) was revised to add uncorrected hypocalcemia as a risk factor for Torsades de Pointe and exclude subjects with such condition from receiving treatment with ribociclib, as low calcium levels can cause QT prolongation.

  - Section 5.3.3: Requirements on sodium and phosphorus values at screening were removed from exclusion criterion #33 (re-numbered #33a) as abnormal sodium or phosphorus levels have no impact on QT prolongation.

- Section 6.1.1.5: Recommendations were added for investigators on dosing of ribociclib if a visit has to be delayed within the allowed visit window. It has also been clarified that shortening the rest period to less than 7 days is not recommended.
- Section 6.3.1.3.2 and Section 6.3.1.4: Additional mandatory dose modification guideline has been added in Table 6-23 for the permanent discontinuation of capmatinib in the event of myocarditis of any grade or other cardiac events Grade ≥ 3 following the release of the INC280 Investigator Brochure Edition 11 describing a case of myocarditis observed in a subject treated with capmatinib and spartalizumab in PDR001J2201 study. A reference to Table 14-17 was also added within Table 6-12 (dose modifications for spartalizumab and LAG525) and Table 6-23 to refer investigators to recommended management guidelines for such cardiac events.
- Section 6.3.1.6: Mandatory dose modifications were added in Table 6-37 in case of interstitial lung disease/pneumonitis event for investigators to interrupt ribociclib for grade 2 events, or permanently discontinue ribociclib for grade ≥ 3 events following FDA recommendation for CDK4/6 inhibitors. Table 6-37 is also updated to clearly indicate that ribociclib must be permanently discontinued if Toxic Epidermal Necrolysis (TEN) is diagnosed.
- Section 6.4.2.2 and Section 6.4.3: Paragraphs regarding corticosteroids have been updated in order to allow for treatment of immune-related adverse events or in presence of stress conditions in patients with adrenal insufficiency higher doses of corticosteroids to be given for limited time as clinically necessary. A reference to Section 6.4.2.2 was also added in Section 6.4.3 paragraph on corticosteroids to ensure the investigator takes into account the specific restrictions on corticosteroids use during treatment with ribociclib in arm 4.
- Section 6.4.2.2 and Section 13: The list of medications to be used with caution during ribociclib treatment in Table 6-39 was updated with latest information available. The publication added in the footnote of Table 6-39 was added in the list of references in Section 13.
- Section 6.4.3: Apalutamide was added in the list of strong CYP3A4/5 inducers prohibited for use during ribociclib treatment in arm 4 in Table 6-42. This table was also updated to clarify that not only herbal preparations/medications but also dietary supplements known as strong inducers or inhibitors of CYP3A4/5 or with a known risk of QT prolongation are prohibited in arm 4.

The following editorial changes have also been made:

- Interstitial lung disease (ILD) was added in the list of abbreviations
- Section 6.3.1.6: The term “bi-weekly” in Table 6-35 was changed to “every 2 weeks” to avoid confusion and clarify that liver function tests should be monitored every 2 weeks (and not twice a week) in case of low-grade abnormalities in liver parameters.
- Section 6.6.4: It was clarified that destruction of study drugs at site is possible if allowed per local regulations and local Sponsor procedures and agreements.

[redacted]

- Section 7.1: Table 7-1 was revised to align the timing and allowed window for EOT visit assessments with Section 4.1, as clarification was previously provided that EOT visit should be scheduled within 7 days after the discontinuation of the last study drug (i.e. within 7 days after the last dose of the last study drug or after the date when decision was made to permanently discontinue both study drugs/the last study drug).
- Section 7.1.7 and Table 7-1 were revised to provide guidance to sites for the timing of 30-day safety follow-up visit in cases where the last dose of study drug was more than 30 days ago when the decision is taken to discontinue study treatment.
- Section 7.2.2.7.1: Table 7-11 was corrected to remove the second dose reference ID for C1D1 visit, which is not applicable for this visit.
- Correction of typographical errors across the document.

IRBs/IECs

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

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

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

[redacted]

Amendment 3 (29-Apr-2019)

Amendment rationale

As of the date of release of this amendment, 92 subjects have received study treatment in this study in part 1 (part 2 not yet open).

Amendment 3 is required in order to add a new combination arm for evaluation in this study (arm 4: ribociclib in combination with spartalizumab). D-cyclin-CDK4/6-p16-pRb pathway is often up-regulated in melanoma. Given the magnitude of immune modulatory effects observed from CDK4/6 inhibitors, the combination of CDK4/6 inhibitors with check point inhibitors such as anti PD-1/PD-L1 may help to overcome resistance to anti PD-1/PD-L1. The full rationale for addition of this new arm is provided in Section 2.4.4.

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.

Major changes are:

- Addition of arm 4 (ribociclib + spartalizumab) in this study:
  - Added Section 1.2.5 providing non-clinical data, clinical data [redacted] available to date on ribociclib given in combination with other agents.
  - Added Section 2.3.4 with rationale for dose and regimen selection for this new combination.
  - Added Section 2.4.4 with scientific rationale for choice of this new combination.
  - Added Section 2.6.4 with risks and benefits for this new combination.
  [redacted]
  - Updated Section 4.1 and Figure 4-1 to add arm 4 and reflect the revised sample size in Part 1 following the addition of this new combination arm.
  - Updated Section 4.2 to reflect changes in the timing of interim analyses with the addition of arm 4.
  - Added Section 5.3.3 with exclusion criteria specific to arm 4 to ensure subjects randomized in arm 4 do not have any contraindication to receive treatment with ribociclib.
  - Updated Section 6.1 and Table 6-1 to add the dose and regimen for ribociclib and spartalizumab in arm 4. Table 7-2 was also updated to indicate the starting dose and regimen for ribociclib administration in arm 4.
  - Added Section 6.1.1.5 with instructions to be provided to subjects randomized in arm 4 for oral intake of ribociclib during the study.
  - Updated Section 6.2 to indicate that dose re-escalation for ribociclib is not allowed.
  - Updated Section 6.3.1 to add ribociclib in the text and updated Table 6-2 to add quick reference to tables providing mandatory dose modifications for ribociclib in case of event suspected to be related to ribociclib.
  - Updated Section 6.3.1.1 and added Table 6-4 to indicate that dose reductions are allowed for ribociclib in case of adverse events and provide the dose levels for ribociclib allowed in the study and the dose reduction steps to be followed.
  - Updated Section 6.3.1.2 to add the maximum length of time allowed for ribociclib interruption.

[redacted]

- Added Section 6.3.1.6 and Table 6-34 to 6-37 to provide mandatory dose modifications to be followed for ribociclib in case of adverse events suspected to be related to ribociclib.
- Updated Section 6.3.3, Section 6.4, Section 7.1.7, Section 8.1.1 and Section 8.1.2 to indicate that AEs/SAEs must be followed and concomitant medications must be collected in eCRF up to 30 days after the last dose of ribociclib (in the case where this timepoint is later than 150 days after the last spartalizumab dose).
- Added Section 6.4.2.2 with concomitant medications to be used with caution during treatment with ribociclib of subjects randomized in arm 4 (including the addition of Table 6-39 providing a non-exhaustive list of those medications) and updated Section 6.4.3 to add prohibited concomitant medications for ribociclib (including the addition of Table 6-42 providing a non-exhaustive list of those medications).
- Updated Section 6.6 with information for ribociclib
- Revised Table 7-2 and Table 7-6 to add schedule of ECG assessments specific to arm 4.

- Updated chemistry laboratory parameters in Table 7-5 to add GGT in the parameters to be tested, as well as calcium corrected on serum albumin required at screening for all subjects (and then as clinically indicated), and indicate that fasting glucose must be obtained for subjects randomized in arm 4.
- Revised Section 10.3 to add ribociclib to the treatment calculation section
- Updated Section 10.4.2 and Table 10-3 to reflect new alpha calculations taking into account the addition of the ribociclib arm as well as the number of patients to be analyzed in the first interim analysis
- Revised Section 10.5.3.2 to include ribociclib to investigational drugs that will have an AESI list

- Updated Section 10.7 to capture the timing of the first interim analysis for the ribociclib and spartalizumab combination arm and specify that the 3 initial treatment groups mentioned refer to arm 1, arm 2 and arm 3.
- Updated Section 10.8 and Table 10-7 to capture the inclusion of the ribociclib and spartalizumab arm, the actual randomization of patients in the first interim analysis of the first three arms tested in this trial, and the number of patients to be randomized before the first interim analysis of the new combination arm

  - Section 13: Added references to new publications cited in the rationale sections added for ribociclib.
- Inclusion criterion #4 (Section 5.2, re-numbered #4a) and exclusion criterion #17 (Section 5.3.1, re-numbered #17a) have been revised in order to further ensure the enrollment of an homogenous study population and provide clarification to investigators on the requirements regarding prior therapies received in the metastatic setting and prior disease progression before study entry.
- Section 5.2: Inclusion criterion #9 (re-numbered #9a) has been updated to clarify that growth factors and/or transfusion support should not be administered within 14 days prior to screening blood draw.
- Section 5.3.1: Exclusion criterion #2 (re-numbered #2a) wording has been clarified, to clearly state that subjects with active/unstable brain metastases at time of screening are not eligible.
- Section 5.3.1: Exclusion criterion #19 (re-numbered #19a) has been updated to allow enrollment of subjects based on cardiac Troponin I testing (considered as more sensitive than Troponin T in some countries). Table 7-2 and Section 7.2.2.5.1 were updated accordingly and Table 7-5 has also been updated to indicate that Troponin I local testing is acceptable though central Troponin T testing is recommended.
- Updated Section 6.1.1.4 to provide additional instructions on canakinumab intravenous administration and sites of injection.
- Implementation of the most recent version for CTCAE grading guidelines (CTCAE v5.0) to ensure adequate grading of adverse events and comparability of safety profiles with future studies:
  - Section 1.2 and Section 2.6: Added a statement to clarify that adverse events (AEs) described in those sections for each study drug are described using CTCAE v4.03 grading, unless otherwise specified.
  - Section 5.2: Inclusion criterion #10 (re-numbered #10a) has been updated for treatment-related toxicities of prior anticancer therapies to be assessed using CTCAE v5.0 instead of v4.03.
  - Section 5.3.2: Exclusion criterion #27 (re-numbered #27a) has been updated to add the grading system to be used (CTCAE v5.0) for serum amylase.
  - Section 6.1.2: updated to specify that adverse events mentioned should be graded as per CTCAE v5.0.
  - Section 6.3.1 and Section 14.3 (Appendix 3): Tables 6-5 to 6-33 and Tables 14-10 to 14-17 have been updated to indicate that the grading system to be used is CTCAE v5.0. Definitions for each grade have been aligned with the definitions from CTCAE v5.0 for events for which definition was revised in CTCAE v5.0 compared to v4.03, i.e. creatinine alterations, abnormal liver tests (hepatic adverse events), amylase and lipase elevations, QTc prolongation.
  - Section 8.1.1 and Section 10.5.3 : Updated CTCAE version to be used for grading of adverse events in the study to CTCAE v5.0.
- Section 7.1.2: Added a statement that re-screened subjects are exempted to re-sign the optional pharmocogenetics ICF.
- Table 7-13: Added language to clarify that instructions for performing mandatory biopsies (e.g. size specifications, needle type, etc.) were intended as guidelines rather than strict requirements. Specifically the requirement for minimum total tissue volume

[redacted]

for mandatory newly collected tumor samples was removed, as the remaining guidelines are sufficient and tissue volume may be challenging to estimate for local pathologists.

- Section 7.2.3.1.1:
  - Added language to clarify the intent of the requirements and tissue quality criteria for mandatory biopsy collection. Specifically, it was clarified that for samples with >60% tumor content, total tissue area may be < 30 mm^2 but must be ≥15 mm^2 to expand the tissue quality criteria in Table 7-13.
  - Added a statement to allow mandatory screening biopsy requirement fulfillment from subjects who are re-screened or who recently had a biopsy as part of standard of care (including prior to signing of main study ICF).
- Section 8.7: Updated to implement a steering committee on the study.
- Section 14.3 (Appendix 3): Recommended management guidelines have been updated to align with published guidelines for the management of immune-related adverse events (Brahmer et al 2018) in case of occurrence of grade 2 immune-related liver abnormality results (Table 14-11), grade 3 or 4 immune-related pneumonitis (Table 14-14), immune-related symptomatic endocrinopathies and autoimmune diabetes grade 3 or 4 (Table 14-15) and infusion reaction or cytokine release syndrome of any grade (Table 14-16) suspected related to spartalizumab and/or LAG525.

The following editorial changes have also been made:

- Updated the protocol summary to reflect changes done in this protocol amendment
- Updated the list of abbreviations with new abbreviations added or missing abbreviations and removed abbreviations not used in the document
- Updated numbering of tables included in Section 6 and Section 7 of the protocol to reflect the addition of new tables in those sections relating to the addition of arm 4.
- Section 4.1 and Table 7-1: Updated to clarify that first dose of study treatment must be initiated within 3 days maximum after date of randomization.
- Section 4.1 and Section 7.1.5: Clarified that EOT visit should be scheduled within 7 days after last dose of last study drug or after the date when the decision was made to permanently discontinue both study drugs/the last study drug.
- Section 5.2: Clarified the protocol subsection for investigator reference (Section 7.2.3.1.1) in inclusion criteria #7 (re-numbered #7a) and #8 (re-numbered #8a).
- Section 6.3.1.1: Clarification was added that the BID dosing schedule applies only for capmatinib. Table 6-3 has also been updated to clearly indicate the number of tablets and dosage of tablets to be taken twice in a day for each dose level of capmatinib.
- Table 7-2 : An “X” was added in the row for “Disposition form”, which is also to be completed in eCRF in case of screen failure. The name of this form has been aligned with final name in eCRF.
- Section 7.2.2.1 and Section 7.2.2.6: Corrected that significant physical examination findings meeting the definition of AE, and new or worsened clinically significant findings on ECG, occurring after informed consent signature (and not after first dose of study treatment) must be recorded in the eCRF as AE.
- Section 7.2.2.5: Clarified the minimal fasting time and conditions to obtain fasting glucose at screening for all patients and for patients randomized in arm 1 and in arm 4.
- Table 7-7 and Table 7-8: Minor correction in dose reference ID programmed in the database from cycle 9 to avoid overlapping numbers.

[redacted]

[redacted]

- Section 7.2.3.1.1: Clarified that the tumor sample collected for mandatory on-treatment biopsy should be taken from the same anatomical location biopsied at screening, where medically feasible.
- Section 7.2.3.1.3: Added that, wherever possible, the guidelines and tissue quality criteria in Table 7-13 should be followed for optional biopsies.
- Throughout protocol, changed references from SAP Appendix to SAP Technical Appendix
- Section 10.4.2: Clarified assumption for number of patients enrolled in the selection phase
- Section 10.7: Clarified the timing of the 1st primary analysis
- Section 10.8: Clarified why the shrinkage estimator may be conservative and clarified the observed ORR from the other selection phase arms will be used in the calculation of the sample size in the expansion phase
- Section 10.8: Updated the timing of subsequent interim analyses in the selection phase, and the timing of the 1st primary ORR analysis after completion of expansion phase enrollment
- Correction of typographical errors and addition of the meaning of some abbreviations in the text across the document

IRBs/IECs/HA

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

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

[redacted]

Amendment 2 (06-Feb-2019)

Amendment rationale

As of the date of release of this amendment, 55 subjects have received study treatment in this study.

Amendment 2 is required to implement feedback from the French HA (Agence Nationale de Sécurité du Medicament, ANSM) after their review of protocol amendment 1. Rare cases of myocarditis and fatal heart failure have been reported in patients treated with checkpoint inhibitors alone and in combination (Varricchi et al 2017). As incidence of myocarditis is higher in immune checkpoint inhibitors combination trials, protocol amendment 2 is implementing precautionary on-treatment monitoring measures to optimize the detection of possible autoimmune myocarditis events in arm 1 combining spartalizumab and LAG525. Guidelines for the management of myocarditis events (of any grade) have also been revised.

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.

Major changes are:

- Section 6.3.1.3.2 (Table 6-11) and section 14.3 (Table 14-17 in Appendix 3): Table 6-11 was updated to mandate the permanent discontinuation of spartalizumab (in all arms) and LAG525 (in Arm 1) if myocarditis of any grade occurs. Recommended management guidelines in Table 14-17 were updated to recommend urgent cardiology consult to initiate high dose systemic corticosteroids in case of myocarditis events of any grade. References to published guidelines for the management of immune-related adverse events, including myocarditis, in patients treated with immune checkpoint inhibitor therapy (Brahmer et al 2018, Mahmood et al 2018) have been included in Table 14-17.
- Table 7-2 and Section 7.2.2.5: Table 7-2 and Table 7-5 were updated to add the monitoring of cardiac Troponin T level for patients randomized in Arm 1 during the first 2 months of study treatment (at C1D15, C2D1 and C3D1).
- Section 7.2.2.5.1 was added to provide guidance on specific monitoring of cardiac troponin T for patients randomized in Arm 1 with additional safety assessments to be performed in case of troponin T increase (Central electrocardiogram ECG assessment and local echocardiogram, Troponin T repeat, and cardiologist consultation if ECG or echocardiogram are abnormal and suggestive of myocarditis).

The following editorial changes have also been made:

- Section 5.3.2: Correction of the numbering of arm-specific exclusion criteria for continuity of numbering with common exclusion criteria.
- Table 14-9 in Section 14.2.3.2.9: correction of a typo.

IRBs/IECs/HA

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

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

[redacted]

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

[redacted]

Amendment 1 (24-Jul-2018)

Amendment rationale

As of 24-Jul-2018, the study has not started in any of the participating countries/sites.

Amendment 1 is required to implement specific feedback received from the US Food and Drug Administration (FDA), the Medicines and Healthcare products Regulatory Agency (MHRA), the German Paul -Ehrlich Institute (PEI) and the French health authority (Agence Nationale de Sécurité du Medicament, ANSM) upon review of the protocol, as well as additional changes.

Major changes are intended to:

- Clarify inclusion criterion #4 and add a new exclusion criterion # 17 to further define and homogenize the study population.
- Extend the time frame for exclusion of the use of any live vaccines before randomization in the common exclusion criterion #3 from 4 weeks to 3 months. This is based on the recommendation in the canakinumab Investigator's Brochure (IB) Edition 16 which stipulates that patients should complete all immunizations 3 months prior to initiating canakinumab therapy.
- Add two common exclusion criteria to exclude patients with medical history or current diagnosis of myocarditis or with elevated cardiac Troponin T at screening. Myocarditis is an immune mediated adverse event which has been associated with immune checkpoint inhibitors (CPIs), it is a rare event with an estimated incidence of less than 1% (Norwood TG et al, 2017). In the absence of consensus guidelines for cardiovascular monitoring and management for patients treated with CPI to date, a risk minimization approach is thus implemented with these changes as regards to the potential increased incidence of myocarditis when combining spartalizumab and LAG525 for early detection of myocarditis.
- Include two additional criteria in Section 6.1.5.1 for continuation of study treatment beyond disease progression per RECIST v1.1 to further clarify the population of patients who would potentially benefit from continuing treatment beyond progression per RECIST v1.1.
- Provide additional dose modification guidelines in Table 6-6 for the permanent discontinuation of spartalizumab (and LAG525 in Arm 1) in the event of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). After the recent occurrence of a case of SJS in a study with spartalizumab in combination with another investigational agent, the dose modification guidelines for protocols using spartalizumab were updated to mandate permanent discontinuation of study treatment for patients who experience SJS or TEN. This change has been part of an Urgent Safety Measure (USM) released on 15 June 2018. This protocol amendment is now formalizing these changes in Table 6-6. Additional instructions are also provided to investigators on spartalizumab/LAG525 dose modifications to be implemented in case of skin events (other than rash) possibly related to spartalizumab/LAG525.
- Update section 6.3.1 on dose modifications for spartalizumab and LAG525 and management guidelines in Appendix 3 to align with latest published consensus guidelines on the clinical management of suspected immune-related toxicities.
- Remove the requirements for ECGs at C1D1 visit and on treatment visits for patients randomized in Arm 3, as regular QT assessment is not required with monoclonal antibodies as regards to their low potential for QT prolongation. Patients in Arm 3 will

only be required to have an ECG assessment at End of Treatment visit (in addition to the ECG performed at screening), and if clinically indicated during study treatment. ECG assessment has been retained on Day 1 of the first 3 cycles for Arm 1, but at pre-dose only (post-dose ECG removed), to monitor for potential immune-related cardiac events.

- Add the collection of additional [redacted] immunogenicity (IG) samples for spartalizumab (all Arms), LAG525 (Arm 1) and canakinumab (Arm 3) at pre-dose every 3 months from Cycle 6 through end of treatment to monitor immunogenicity and related drug exposure throughout the treatment period.
- Provide additional guidelines in Section 7.2.2.1 for the monitoring of patients treated in Arm 2 with capmatinib. Investigators are asked to monitor any clinical signs indicative of neural toxicity to align with the potential risk for central nervous system (CNS) toxicity described in capmatinib (INC280) IB Edition 9.
- Remove visceral metastases as allowable lesion location sites for mandatory biopsies (at screening and on treatment between C1D21 and C2D1) (*this is applicable to France only*).
- Clarify that "Progression of malignancy" should be reported as a SAE in this study if the investigator suspects that the study treatment accelerates disease progression.
- Implement an independent Safety Data Monitoring Committee (DMC) during expansion phase (Part 2) of the study who will review relevant safety data on a regular basis and will provide recommendations on the continuation of the study.

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.

Major changes are:

- Section 5.2: Inclusion criterion #4 has been revised to clarify that all patients must have had objective disease progression while on or following prior anti-PD-1/PD-L1 therapy (administered alone or in combination with anti-CTLA4 therapy) and that this progression must have occurred within 12 weeks before randomization in this study. This criterion also provides the minimal time frame which must have elapsed between the last dose of those prior anti-cancer therapies and randomization.
- Section 5.3.1: Exclusion criterion #3 has been revised to exclude the use of any live vaccines within 3 months prior to randomization (instead of 4 weeks). Exclusion criterion #17 has been added to clarify that subjects who received any other systemic therapy for unresectable or metastatic melanoma than the ones listed in inclusion criterion # 4 are not eligible to the study. Two common exclusion criteria # 18 and 19 have also been added to exclude patients with medical history or current diagnosis of myocarditis or with elevated cardiac Troponin T level > 2 x ULN at screening.
- Section 6.1.5.1: Two additional criteria have been added for the investigator to confirm that a patient does not have any symptoms or signs indicative of disease progression and does not have a rapidly progressing disease before being allowed to continue study treatment beyond RECIST v1.1 disease progression.
- Table 6-6 in Section 6.3.1.3.2 and Table 14-12 in Appendix 3: A mandatory instruction has been added in Table 6-6 to permanently discontinue spartalizumab (and LAG525 for arm 1 patients) in the event of Stevens-Johnson syndrome or toxic epidermal necrolysis, and a recommendation to hospitalize the patient and have an urgent

[redacted]

dermatology consultation if such event occurs has been added in Table 14-12 (Appendix 3). Further instructions are also added in case of skin events (other than rash).

- Table 6-10: A recommendation to permanently discontinue spartalizumab/LAG525 has been added in case of recurring infusion reaction (despite adequate prophylactic measures).
- Section 6.3.1.3.2, Table 6-11 and Table 14-17 in Appendix 3: Provided clarification to investigators on the description of frequent manifestations of immune-related adverse events and added further description of rare immune-related adverse events observed with anti-PD-1/PD-L1 class agents for information of investigators. Additional instructions to investigators on spartalizumab/LAG525 dose modifications to be implemented in case of rare immune-related adverse events possibly related to spartalizumab/LAG525 have been added in Table 6-11, as well as recommendations on the management of those rare immune-related adverse events in Table 14-17.
- Table 7-2 and Table 7-6: Post-dose ECGs at C1D1 and C3D1 are no longer required for patients randomized in Arm 1 and ECGs at C1D1, C2D1 and C3D1 visits (pre- and post-dose) are no longer required for patients randomized in Arm 3 (unless clinically indicated).
- Table 7-2, Table 7-7, Table 7-8 and Table 7-10: Collection of [redacted] IG samples for spartalizumab (all arms), LAG525 (Arm 1) and canakinumab (Arm 3) have been added at predose on day 1 of every 3 months from C6D1 through end of treatment.
- Section 7.2.2.1: Added that investigators should monitor the occurrence of any clinical signs indicative of neural toxicity as part of the physical examination at Day 1 of each cycle for patients receiving capmatinib in Arm 2, and a neurological examination should be performed as clinically indicated.
- Section 7.2.2.5: Table 7-5 has been updated to add testing of cardiac Troponin T (TnT) level at screening for all patients.
- Section 7.2.3.1.1: Removed visceral lesions as allowable sites for mandatory biopsies (this is applicable to France only).
- Section 8.1.1: Clarified that “Progression of malignancy” should be reported as SAE if the investigator suspects that the study treatment accelerates disease progression.
- Section 8.6: Added description for the Safety DMC reviewing safety data during expansion phase (Part 2) of this study.

Other changes are:

- Section 1.2.1.2: Corrected the global number of patients treated with spartalizumab single agent or in combination to align with the numbers in the PDR001 IB Edition 7.1 (used as a source for data presented for spartalizumab in the background section of this protocol).
- Section 5.3.1 and Section 5.3.2: Clarified that time of randomization should be the reference for evaluation of subject’s eligibility in the study as regards to exclusion criteria #2, #3, #4, #6, #21, #25 and #27 as this is a randomized study.
- Section 5.3.1: Exclusion criterion #12 has been revised to exclude patients with positive test result for HBV-DNA at screening (which is also indicative of active HBV infection).
- Section 5.3.1: Exclusion criterion #16 has been revised to correct the time frame requirement for mandatory use of condoms for male participants from 30 days to 7 days after the last dose of study treatment. Indeed, recent studies have shown that monoclonal antibodies do not disseminate into semen and hence do not require the prolonged use of

[redacted]

condoms after the last dose. Capmatinib (INC280) is a small molecule and is able to disseminate into semen but has not shown to be genotoxic in preclinical studies (refer to INC280 IB Edition 9). Guidelines on birth control requirements for non-genotoxic small molecules recommend the use of condoms for male participants for at least five times the half-life after the last dose of drug. As the half-life of capmatinib is ranging from 3.5 to 6.3 hours, the use of condoms for a period of 7 days after the last dose of study treatment is considered conservative enough to ensure a complete wash-out of capmatinib from the body.

- Section 5.3.2: Exclusion criterion #27 has been revised to correct an error and clarify that patients with serum amylase grade > 2 are not eligible for randomization in arm 2, while patients with serum amylase grade 1 or 2 are eligible only if asymptomatic (no signs or symptoms suggesting pancreatitis or pancreatic injury).
- Sections 6.1.1.1, 6.1.1.2, 6.1.1.4 and 6.3.1: The delay allowed for administration of spartalizumab, LAG525 and canakinumab dose at scheduled visits has been corrected to 4 days instead of 7 days to match the visit and dose administration window of +/- 4 days defined in Table 7-1.
- Table 6-2 has been corrected to update table numbering and remove the rows for neurological and ocular events, as there is no specific dose modifications for those events. Investigators should follow dose modifications for “Other adverse events”.
- Section 6.3.1: In dose modifications tables (from Table 6-4 to Table 6-32), the recommendation to ‘continue treatment at the same dose level’ in case of grade 1 or grade 2 events has been deleted from the “Mandatory dose modification” column, as this is a recommendation but not a mandatory dose modification.
- Section 6.3.1.3.2: Table 6-11 describing dose modifications for spartalizumab in case of hematological adverse events suspected to be related to spartalizumab has been deleted, as it was included in error as hematological events are rare with immuno-oncology therapies. Dose modifications to be followed for spartalizumab/LAG525 by investigators in case of hematological event are already covered by the table providing dose modifications in case of other adverse events suspected to be related to spartalizumab/LAG525 (newly numbered Table 6-11). Specific instructions have also been added in this table in case of autoimmune hemolytic anemia, hemolytic uremic syndrome or acquired hemophilia grade ≥3.
- Section 6.3.1.4: Wording has been corrected to match information provided in Section 6.2 that re-escalation of the dose of capmatinib after a previous reduction due to adverse event is allowed in this study, provided certain criteria (described in Section 6.2) are met.
- Section 6.5.2 and Section 7.1.2.3: Removed the requirement to use central laboratory LDH result for randomization stratification to align with Section 7.2.2.5 that allows the use of local LDH result (if an immediate clinical decision is required).
- Section 7.1.6 and Glossary of terms: The definition of Withdrawal of Consent has been updated to enforce the protection of patients’ rights on the use and confidentiality of their Personal Data (definition of Personal Data has been added to the Glossary of terms) and align with the latest regulatory framework as regards to the use of their Personal data for patients who withdraw their consent, depending on local applicable law. It has been clarified that no further Personal Data will be collected after consent is withdrawn (except in the specific situations described and depending on applicable local law).
- Section 7.2.2.7.1: Replaced instructions provided for the processing of [redacted] IG samples by a reference to the central lab manual to avoid discrepancies between lab manual and protocol and updated the volume of blood collected at each planned

[redacted]

timepoint for [redacted] IG analyses for each study drug to match the actual blood collection volumes.

- Table 7-11: Separated the entries for blood collections for PBMC flow cytometry and sequencing analyses to align with the collection methods in the laboratory manual which require two blood draws totaling 12.5 mL.
- Section 13: Addition of a new reference.
- In addition, editorial revisions, clarifications and corrections are made throughout the protocol to improve consistency and understanding.

IRBs/IECs/HA

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

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

All other changes described in this amended protocol require IRB/IEC/HA approval prior to implementation.

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

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Melanoma is the most aggressive form of all skin cancers. Worldwide, it is expected that over 232,000 people are diagnosed with cutaneous melanoma each year and more than 55,000 people are expected to die of this disease annually. Usually melanoma is diagnosed at an early stage in which surgical excision is curative in most cases. The management of patients with unresectable or metastatic melanoma is more difficult, although recent advances have led to important improvements of clinical outcomes for this population.

The primary systemic therapy approaches for patients with unresectable or metastatic melanoma are (1) checkpoint inhibitor immunotherapy (anti-PD-1 monotherapy or in combination with anti-CTLA-4 therapy) or (2) targeted therapy with ^{V600}*BRAF* and MEK inhibitors (e.g. dabrafenib and trametinib) for melanomas harboring a ^{V600}*BRAF* mutation (NCCN Guidelines® Melanoma Version 1 2018; Cutaneous Melanoma: ESMO Guideline Committee 2015). The optimal sequencing of targeted therapy and checkpoint inhibitor therapy in ^{V600}*BRAF*-mutant melanoma has not been definitively established and is under investigation in study EA6134 [NCT02224781]. In clinical practice, the choice of treatment is driven by the tempo of disease, presence or absence of symptoms, medical history, comorbidities and other factors (e.g. patient preference).

As of today, patients who do not respond to, or progress on, the approved treatments have very limited treatment options, and there is no established standard of care. Guidelines recommend enrollment in a clinical trial, treatment with ipilimumab (anti-CTLA-4), chemotherapy, or high-dose interleukin-2 (IL-2) for selected patients (NCCN Guidelines® Melanoma Version 1 2018). Based on retrospective data from 47 patients treated in the pivotal phase III study KEYNOTE-006, single-agent checkpoint inhibitor therapy with ipilimumab has limited anti-tumor activity following failure of pembrolizumab (anti-PD-1) with a reported objective response rate (ORR) of 16% (Zimmer et al 2017). As a result, most patients are enrolled in clinical studies as there is an urgent need for new treatment options for patients who failed the available standard therapies.

Patients enrolled in this study have failed previous therapies including immune checkpoint inhibitors. The mechanisms of primary and acquired resistance to checkpoint inhibitors treatment are not well understood and are mainly due to a combination of intrinsic or extrinsic resistance mechanisms (see Section 2.1). The combinations tested in this study aim to alter the tumor and/or microenvironment in favorable way to overcome treatment resistance and restore T cell function.

1.2 Introduction to investigational treatments

In subsections providing clinical experience with each study drug, all adverse events (AEs) described are graded per Common Terminology Criteria for Adverse Events (CTCAE) v4.03, unless otherwise specified.

1.2.1 Overview of spartalizumab

Spartalizumab (PDR001) is a high-affinity, ligand-blocking, humanized immunoglobulin G4 (IgG4) monoclonal antibody directed against the human programmed cell death 1 (PD-1) receptor.

[redacted]

1.2.1.1 Non-clinical experience with spartalizumab

Spartalizumab binds specifically and with high affinity to human PD-1 and enhances IL-2 production in lymphocyte stimulation assays *in-vitro*. Spartalizumab does not cross-react with rodent PD-1. However, toxicology studies performed in cynomolgus monkeys showed acceptable cross reactivity with monkey PD-1. Repeat administration of spartalizumab to cynomolgus monkeys was tolerated at all doses tested up to 100 mg/kg/week for 5 weeks in the GLP toxicology single-agent study. No drug-related in-life, mortality, organ weight changes, or macroscopic findings were noted.

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

1.2.1.2 Clinical experience with spartalizumab

As of 19-Jan-2018, a total of 517 patients were exposed to spartalizumab single-agent every two weeks (Q2W), every three weeks (Q3W) or every four weeks (Q4W), and 722 patients were exposed to spartalizumab in combination with other agents in multiple tumor types including unresectable and metastatic melanoma. Based on the available pharmacokinetics (PK) and safety data, two recommended phase two doses (RP2D) for spartalizumab single-agent have been declared: spartalizumab 400 mg Q4W or 300 mg spartalizumab Q3W.

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

1.2.1.2.1 Clinical experience with spartalizumab single-agent in advanced melanoma

Data is available from a phase I/II, open-label, dose escalation/expansion study in advanced solid tumors [CPDR001X2101]. As of November 13, 2017, 61 patients with cutaneous and non-cutaneous melanoma received 400 mg spartalizumab Q4W. Out of the 61 patients, 36% were treatment-naïve and 20% had two or more prior therapies. Spartalizumab was well tolerated with a manageable safety profile. The most common treatment-related AEs (all grades, ≥5%) were fatigue (15%), decreased appetite (11%), hypothyroidism (8%), rash (8%), asthenia (7%), and vitiligo (7%).

Anti-tumor activity observed was as expected given the level of prior treatment and high proportion of patients with PD-L1 negative melanoma. ORR using RECIST v1.1 was 26% (16/61), including 1 complete response (CR). 41 patients (67%) had baseline PD-L1 data: 63% were PD-L1 negative (tumor proportion score <1%). ORR was 40% (6/15) for PD-L1 positive and 19% (5/26) for PD-L1 negative patients.

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

1.2.1.2.2 Clinical pharmacokinetics of spartalizumab

Following administration of spartalizumab via a 30 minute intravenous (i.v.) infusion in study [CPDR001X2101], approximately dose-proportional increases in spartalizumab exposure were observed from 1 mg/kg to 10 mg/kg as suggested by an approximately 10-fold increase in exposure for a 10-fold increase in dose. Moderate accumulation (1.0~3.0-fold) of spartalizumab was observed, as exposure in Cycle 3 was relatively higher than that in Cycle 1 following a Q2W or Q4W regimen. Pharmacokinetic (PK) variability was low to moderate as illustrated by inter-subject variability (e.g. 15.4 to 46.5% for C_{max} during Cycle 1). The observed median half-life for spartalizumab ranges from 10.0 to 23.2 days.

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

[redacted]

1.2.2 Overview of LAG525

LAG525 is a high-affinity, ligand-blocking, humanized anti-LAG-3 immunoglobulin G4 (IgG4) monoclonal 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.*

1.2.2.1 Non-clinical experience with LAG525

In Biacore assays, binding to mouse or rat LAG-3 proteins was undetectable demonstrating that LAG525 is not mouse or rat cross-reactive. LAG525 binds specifically and with high affinity to human LAG-3. The equilibrium dissociation constant (KD) 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 LAG-3 expressing human embryonic kidney (HEK 293) cells, LAG525 was binding 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 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 assays 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.

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 (DDI) 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 ABC 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 at doses of 6 mg/kg, 25 mg/kg, 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 mg/kg and 100 mg/kg) were noted in males but these changes were not adverse.

[redacted]

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 day 43 and/or day 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 Council for 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.

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

1.2.2.2 Clinical experience with LAG525

Clinical data is available from study [CLAG525X2101C]: An open-label, multicenter Phase I/II study to determine the safety and efficacy of LAG525 single-agent and in combination with spartalizumab in patients with advanced solid tumors. The study consists of dose-escalation parts for LAG525 single-agent, and LAG525 in combination with spartalizumab. During dose-escalation, 134 patients were treated with LAG525 single-agent, and 121 patients were treated with the combination of LAG525 and spartalizumab (data cut-off October 18, 2017).

1.2.2.2.1 Clinical experience with LAG525 single-agent

The preliminary safety information was summarized from the ongoing single-agent dose escalation part of the study (N=134) using a data cut-off of October 18, 2017.

Four dose limiting toxicities (DLT) were reported and included grade 3 events of localized intra-abdominal fluid collection (1 mg/kg Q2W), vomiting (5 mg/kg Q2W), elevated lipase (5 mg/kg Q2W) and grade 4 acute kidney injury (10 mg/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-tumor activity, and selection of a RP2D was not informed by anti-tumor activity. The RP2D 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 sLAG3 detected in blood samples was utilized as a pharmacodynamic (PD) marker for target engagement. Based on the trial simulation of the PK/PD model, 400 mg LAG525 Q3W and 800 mg LAG525 Q4W were selected as RP2D for LAG525 single agent (data on file). Simulation of the population PK model for LAG525 showed comparable inter-subject 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 single-agent RP2D.

Adverse events (AEs) of all grades and regardless of relationship to study treatment were reported in 132/134 subjects (98.5%) overall, with the most frequently reported (in >20% of subjects) AEs being fatigue and nausea (26.1% each), constipation (24.6%), decreased appetite (23.9%), abdominal pain and anemia (23.1% each), dyspnea and vomiting (20.9% each), which are consistent with AEs commonly reported for subjects with advanced solid malignancies. The safety profile appeared similar across different dose levels and schedules. Of the 134 subjects 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 subjects were anemia (14 subjects, 10.4%) and dyspnea (7 subjects, 5.2%). Seventy-six of the 134 treated (56.7%) experienced AEs (all grades) suspected to be related to study treatment. In this subject group, the following grade 3 or 4 AEs were reported (10 subjects, 7.5%): decreased appetite and vomiting (3 subjects each); fatigue, nausea, amylase increased, lipase increased (2 subjects each); abdominal pain, anemia, blood creatinine increased and hyperuricemia (1 subject each).

Serious adverse events (SAEs), all grades, and regardless of relationship to study treatment, were reported in 53 subjects (39.6%). The majority of SAEs (49 out of 53 subjects who experienced SAEs) were Grade 3/4 in severity. Among the 53 subjects who experienced SAEs, 18 events among 7 subjects were suspected related to study treatment including intra-abdominal fluid collection (1 patient, 1 mg/kg Q2W, DLT), abdominal pain and melena (1 patient, 3 mg/kg Q2W), infection and vomiting, (1 patient, 5 mg/kg Q2W, DLT), increased lipase and diarrhea (1 patient, 5 mg/kg Q2W, DLT), diarrhea (1 patient, 5 mg/kg Q2W), and nausea, vomiting, anorexia, fatigue, and failure to thrive (1 patient, 240mg Q2W). One patient experienced multiple SAEs suspected 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 10 mg/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.

Single-agent LAG525 demonstrated only minimal anti-tumor activity in solid tumors. No RECIST v1.1 responses were seen at any dose level but some subjects (papillary renal cell carcinoma [RCC], non-small cell lung cancer [NSCLC], ovarian granulosa tumor, thymoma) experienced prolonged stable disease.

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

1.2.2.2.2 Clinical experience with LAG525 in combination with spartalizumab

For the combination rationale of LAG525 with spartalizumab please refer to Section 2.4.1.

As of October 18, 2017, 186 subjects have been treated with LAG525 in combination with spartalizumab in the combination part of study [CLAG525X2101C]. 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 with a Q3W and 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 7.2 to 23.8 days, which is similar to the results from the ongoing [CPDR001X2101] study. There are no human PK data generated to date.

Four subjects experienced DLT which included grade 3 hyperglycemia (80 mg LAG525 Q2W and 400 mg spartalizumab Q4W), grade 4 autoimmune hepatitis and grade 3 fatigue (1000 mg LAG525 Q4W and 400 mg spartalizumab, Q4W), grade 3 brain tumor edema (600 mg LAG525 Q3W and 300 mg spartalizumab Q3W), and grade 3 pneumonitis (400 mg LAG525 and 400 mg spartalizumab, Q4W).

The preliminary safety information was summarized from the ongoing combination part of the study using a data cut-off of October 19, 2017. AEs of all grades and regardless of relationship to study treatment were reported in 171 subjects (91.9%) overall, with the most frequently reported (in >20% of subjects) AEs being fatigue (27.4%), nausea (27.4%), and diarrhea (21.0%). Grade 3/4 AEs regardless of relationship to study treatment were reported in 79 subjects (42.5%). The frequency of each grade 3/4 AEs was below 10%. The most frequently reported AEs occurring in 2 or more subjects included anemia (5.9%), asthenia (2.7%), fatigue (2.2%), dyspnea (2.2%), nausea (1.6%), vomiting (1.6%), decreased appetite (1.1%), abdominal pain (1.1%), and back pain (1.1%). Of the 186 subjects with the combination, 110 (59.1%) experienced AEs (all grades) suspected to be related to study treatment. In this subject group, the following grade 3/4 AEs were reported (16 subjects, 8.6%): fatigue, diarrhea, asthenia, anemia, aspartate aminotransferase increased, alanine aminotransferase increased, amylase increased, headache, cough, hyperglycemia, pneumonitis, polyarthritis (1 subject each), hypophosphatemia, lipase increased (2 subject each). Serious adverse events (SAEs), all grades, regardless of relationship to study drug, were reported in 65 subjects (34.9%). The majority of these subjects (53 out of 65) experienced SAEs that were Grade 3/4 in severity. Among the 65 subjects who experienced SAEs, 17 events in 12 subjects were suspected related to study treatment. SAEs, all grades, regardless of relationship, occurring in more than 2 subjects were pyrexia (6 subjects), dyspnea, fatigue, nausea (4 subjects each), acute kidney injury, colitis, hypercalcemia, pain, pleural effusion and vomiting (2 subjects each). 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 [CLAG525X2101C] included 5 subjects with advanced and heavily pre-treated triple negative breast cancer (TNBC). Two of these subjects showed durable partial response (PR) with both subjects being on treatment for over a year (data on file). Anti-tumor activity was also reported in other solid tumors. One subject with thymoma achieved a complete response (CR) and 11/100 evaluable subjects with a variety of solid tumors had a confirmed PR. The majority of subjects with confirmed PR have durable responses. Several prolonged stable disease (SD) were observed. The study is ongoing and these data are therefore preliminary and may be subject to change.

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

1.2.2.2.3 Clinical Pharmacokinetics of LAG525

The preliminary pharmacokinetics of LAG525 have been characterized from 100 patients in single-agent and 101 patients in combination in the clinical study [CLAG525X2101C] (data cut-off date of March 20, 2017).

[redacted]

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., C_{max} or AUC_{last}) on cycle 3 was relatively higher than that on cycle 1 indicating moderate accumulation of LAG525. Between-subject 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. Comparing to a typical monoclonal antibody 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 (i.v.). 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 (DDI) are not anticipated for LAG525 because it is not expected to interact with drug metabolizing enzymes or transporters. Preliminary analysis of immunogenicity in subjects on the [CLAG525X2101C] study suggests the presence of ADAs in some subjects. 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.

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

1.2.3 Overview of capmatinib

Capmatinib (INC280) is a small ATP (adenosine triphosphate) competitive, reversible inhibitor of the c-MET receptor tyrosine kinase.

1.2.3.1 Non-clinical experience with capmatinib

Capmatinib possesses potent inhibitory activity against the c-MET kinase *in vitro* and is highly specific for c-MET with > 10,000-fold selectivity over several other human kinases tested. Potent activity of blocking c-MET activation has been observed in cell-based biochemical and functional assays that measure c-MET-mediated signal transduction, as well as c-MET-dependent cell proliferation, survival, and migration. In c-MET–dependent mouse tumor models (including lung cancer models), capmatinib exhibits dose-dependent anti-tumor activity and causes tumor regression at well tolerated doses that exceeded IC90 coverage (Liu et al 2011). Importantly, plasma levels of capmatinib correlate with both, the dose administered and the extent of tumor growth inhibition *in vivo*. In c-MET/HGF-driven mouse xenograft tumor models, oral dosing of capmatinib demonstrated significant *in vivo* activity in blocking both c-MET phosphorylation and tumor growth. Collectively, the data

suggest that capmatinib possesses potent *in vitro* and *in vivo* biological and pharmacologic activities.

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

1.2.3.2 Clinical experience with capmatinib

As of the cut-off date (September 28, 2017), a total of 1109 cancer patients and 158 non-cancer subjects have received capmatinib. A total of 622 patients with solid tumors have been treated with capmatinib single-agent, and 487 patients have been treated with capmatinib in combination with other agents.

1.2.3.2.1 Clinical experience with capmatinib single-agent

Capmatinib single-agent data is available from the reference study [CINC280X2102]: a phase I dose escalation study in patients with c-MET dependent advanced solid tumors with an expansion part in hepatocellular carcinoma (HCC), gastric cancer, NSCLC, RCC and other solid tumors.

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

1.2.3.2.2 Clinical experience of capmatinib in combination with spartalizumab

For the combination rationale of capmatinib with spartalizumab please refer to Section 2.4.2.

Capmatinib in combination with spartalizumab is currently being evaluated in the open-label phase Ib/II study in patients with advanced HCC [CINC280X2108]. As of the data cut-off (25-Sep-2017), 20 patients were enrolled and treated with capmatinib in combination with spartalizumab within the dose escalation part of the study, using three dose levels (200 mg bid, 300 mg BID and 400 mg BID) of capmatinib in combination with 300 mg spartalizumab Q3W. The expansion part has not started yet.

The median age of patients was 62.5 years (range 47 to 78 years). 16 patients were male and 4 were females. Eleven patients (55%) had an ECOG performance status of 0 at baseline; 9 patients (45%) had an ECOG performance status of 1. 13 patients (65%) were still receiving treatment and 7 patients (35%) had discontinued treatment. The reasons for end of treatment were progressive disease (4 patients, [20%]), adverse event (1 patient, [5%]), subject/guardian decision (1 patient, [5%]), and death (1 patient, [5%], due to underlying disease).

Nineteen patients (95%) experienced AEs of any grade, regardless of causality. The most common AEs were edema peripheral (10 patients, [50%]), nausea (7 patients, [35%]), blood creatinine increased and fatigue (each in 6 patients, [30%]), and rash (5 patients, [25%]). The most frequent AEs suspected to be related to study treatment were edema peripheral (9 patients, [45%]), fatigue, rash (each in 5 patients, [25%]), blood creatinine increased, nausea, vomiting (each in 4 patients, [20%]). Seven patients (35%) had grade 3/4 AEs suspected to be related to study treatment: nausea (2 patients, [10%]), edema peripheral, ALT increased, diarrhea, stomatitis, hypotension, platelet count decreased, acute myocardial infarction, unstable angina, blood bilirubin increased, dehydration, and neutropenia (each in 1 patient, [5%]). Six SAEs regardless of causality have been reported for 4 (20%) patients. Three patients (15%) experienced the following SAEs suspected of being related to study treatment: unstable angina pectoris, diarrhea, dehydration, and chronic obstructive pulmonary disease (COPD) exacerbation.

[redacted]

There were no DLT observed in cohort 1 (capmatinib 200 mg BID with spartalizumab 300 mg Q3W) and cohort 2 (capmatinib 300 mg BID with spartalizumab 300 mg Q3W). One patient in cohort 3 using capmatinib 400 mg BID in combination with 300 mg Q3W spartalizumab experienced Grade 3 diarrhea, suspected to be related to study treatment, which was considered a DLT. The dose of spartalizumab 300 mg i.v. Q3W and capmatinib 400 mg BID is currently under evaluation.

Capmatinib in combination with nivolumab in NSCLC

The phase II [CEGF816X2201C] study is currently enrolling patients with Epidermal growth factor receptor (EGFR) wild-type NSCLC to receive the combination of capmatinib with the approved anti-PD-1 antibody nivolumab. As of February 1, 2017, 9 patients had been enrolled in safety monitoring cohorts and treated with capmatinib 400 mg p.o. BID in tablet formulation plus nivolumab 3 mg/kg i.v. every 2 weeks, on 28-day cycles. The most commonly reported adverse events (occurring in 2 or more patients), regardless of CTCAE grade, that were suspected to be related to study treatment were nausea (n=7, 77.8%), diarrhea (n =5, 55.6%), increased amylase (n=4, 44.4%), vomiting (n=4, 44.4%), asthenia (n=3, 33.3%), fatigue (n=3, 33.3%), arthralgia, increased blood creatinine, decreased appetite, increased lipase, and peripheral edema (n=2 each, 22.2%). Four patients (44.4%) experienced at least one Grade ≥3 adverse event that was suspected to be related to study treatment. These events included asymptomatic increased lipase (n=2, 22.2%) and increased amylase, asthenia, lethargy, somnolence, and vomiting (n=1 each, 11.1%). One patient had a dose reduction of capmatinib during the first cycle of treatment. Based on these data, the decision was made to continue with expansion enrollment using capmatinib 400 mg p.o. BID tablet plus nivolumab 3 mg/kg i.v. every 2 weeks.

1.2.3.2.3 Clinical pharmacokinetics of capmatinib

After oral administration, capmatinib was rapidly absorbed with the median time to reach maximum drug concentration (T_{max}) ranging from 1 to 2 hours for tablets and from 1 to 4 hours for capsules. The elimination half-life estimated from ranged from 3.5 to 6.3 hours across the cohorts. Accumulation in capmatinib exposure following repeated administration of 400 mg BID tablets is low, with geometric mean accumulation ratio of 1.4-fold. Steady state capmatinib exposure is expected to be reached by the third day of consecutive BID dosing. The mean plasma exposure increase is roughly dose proportional for capmatinib tablet from 200 mg BID to 400 mg BID.

Based on the tablet PK and safety data, the dosage of capmatinib 400 mg BID in tablet form has been declared as the RP2D. Capmatinib can be administered without regard to food, and caution is advised with proton pump inhibitors (PPI) as exposure may be decreased. Capmatinib is not a CYP3A4 inhibitor, but a moderate CYP1A2 inhibitor. Capmatinib is an inhibitor of P-gp as well as BCRP transporters, with clinically relevant DDI potential. The concurrent use of strong CYP3A4 inducers with capmatinib should be avoided. Based on the available data, capmatinib does not show a risk of QT prolongation.

For more information, please refer to the current [capmatinib Investigator's Brochure].

1.2.4 Overview of canakinumab

Canakinumab (ACZ885, ILARIS®) is a high-affinity human anti-interleukin-1β (IL-1β) monoclonal antibody that belongs to the IgG1/κ isotype subclass.

1.2.4.1 Non-clinical experience with canakinumab

Canakinumab neutralizes the bioactivity of human IL-1β by preventing its binding to the IL-1β receptor. Canakinumab specifically binds human IL-1β with a Kd of 40-60 picomolar and has no cross-reactivity with human IL-1α (IL-1F1), human IL-1 receptor antagonist (IL-1Ra, IL-1F3) or other members of the IL-1 family (IL-1F4-IL-1F9). Canakinumab is selective for human and marmoset IL-1β (IL-1F2) but does not bind to mouse, rat, rabbit, rhesus, or cynomolgus monkey IL-1β. Because canakinumab does not react with rodent IL-1β, the *in vivo* activity of canakinumab was demonstrated in models on inflammation induced by human IL-1β in rodents. Canakinumab inhibited the IL-1β induced effect.

An extensive program of toxicology studies was performed. The marmoset monkey was characterized as an appropriate model to predict human safety. Regarding toxicokinetics, exposure to canakinumab was demonstrated. Following i.v. or s.c. administration, canakinumab was well tolerated in marmosets at all dose levels investigated without any relevant adverse findings. No anti-drug antibodies were detected. Long-term animal studies have not been performed to evaluate the carcinogenic potential of canakinumab. The mutagenic potential of canakinumab was not evaluated. No significant treatment-related effects were observed with respect to male or female fertility in a mouse model using a murine analog of canakinumab.

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

1.2.4.2 Clinical experience with canakinumab

1.2.4.2.1 Clinical experience with canakinumab single-agent

As of June 20, 2017 a total of 15,902 patients had been enrolled in Novartis sponsored interventional canakinumab studies. Canakinumab has demonstrated efficacy in a variety of non-oncologic indications: cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), tumor necrosis factor receptor associated periodic syndrome (TRAPS), hyper immunoglobulin D syndrome (HIDS), mevalonate kinase deficiency (MKD), systemic juvenile idiopathic arthritis (SJIA).

A recent large randomized phase III study (CANTOS) has demonstrated a clinically and statistically significant effect of canakinumab 150 mg and 300 mg every 3 months versus matching placebo in reducing the risk of major adverse cardiovascular events (MACE) (Ridker et al 2017a). The results of the CANTOS study also reported that inhibition of IL-1β dose dependently reduced the occurrence of lung cancers in post myocardial infarction patients with elevated high-sensitivity CRP (hsCRP) suggesting an anti-tumor effect with canakinumab treatment (Ridker et al 2017b). A phase III study evaluating the efficacy and safety of adjuvant canakinumab versus placebo in NSCLC is ongoing (EUDRACT number 2017-004011-39).

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

1.2.4.2.2 Clinical experience with canakinumab in combination with spartalizumab

For the combination rationale of canakinumab with spartalizumab please refer to Section 2.4.3.

Data for the combination of canakinumab with spartalizumab is available from a phase Ib, open-label, multi-center study [CPDR001X2103]. As of the data cut-off (July 31, 2017), 16 patients were enrolled and treated in the dose escalation part of the study, using three dose levels: 100 mg canakinumab s.c. Q8W, 300 mg canakinumab Q8W and 600 mg

canakinumab Q8W in combination with 400 mg Q4W spartalizumab. Fifteen patients (94%) experienced AEs of any grade, regardless of causality. The most common AEs were decreased appetite (6 patients, [37%]), fatigue (5 patients, [31%]), anemia and dyspnea (each in 4 patients, [25%]), and back pain, dizziness and nausea (each in 3 patients, [18%]). The majority of AEs were Grade 1/2. Six (37%) experienced AEs of any grade, suspected to be related to study treatment. The most frequent AEs suspected to be related to study treatment were fatigue (5 patients, [18%]) and decreased appetite (2 patients, [12%]). Seven patients (44%) experienced Grade 3/4 AEs regardless of causality (each 1 patient [6.3%]): anemia, dyspnea, back pain, urinary tract infection, acute respiratory failure, aspartate aminotransferase increased, cancer pain, cystitis, herpes zoster. No patient had a Grade 3/4 AEs that was suspected to be related to study treatment. Eight SAEs have been reported for 5 (31%) patients with none suspected of being related to study treatment.

There were no DLT observed and the Phase I of the study is ongoing.

1.2.4.2.3 Clinical pharmacokinetics of canakinumab

During the development of canakinumab, four drug formulations were investigated. Bioavailability and absorption rate constants of the product types were similar, ranging from 63-76% and 0.28-0.38 d-1., respectively. The peak serum canakinumab concentration (C_{max}) occurred approximately 7 days following single s.c. administration of 150 mg canakinumab in adult CAPS subjects. Exposure parameters (such as AUC and C_{max}) increased in proportion to dose over the dose range of 0.3 to 10 mg/kg as intravenous infusions or from 150 to 600 mg as subcutaneous injection. The serum clearance (CL) and volume of distribution of canakinumab varied according to body weight (6.01 L/day and 0.174 L/day in a typical CAPS patient weighing 70 kg). The mean terminal half-life was 26 days. After accounting for body weight differences, no clinically significant differences in the PK properties of canakinumab were observed between CAPS, TRAPS, HIDS/MKD, FMF, SJIA and gouty arthritis subjects. There was no indication of accelerated clearance or time-dependent change in the PK properties of canakinumab following repeated administration.

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

1.2.5 Overview of ribociclib

1.2.5.1 Non-clinical experience with ribociclib

Ribociclib inhibits the CDK4/ Cyclin D (CCND1) and CDK6/CCND3 enzyme complexes with IC_{50} values of 0.01 and 0.039 µM in biochemical assays, respectively, while showing a high degree of selectivity for CDK4/6 versus other cyclin-dependent kinases. In more than 40 pRb-positive cell lines derived from diverse cancer types, ribociclib inhibited Retinoblastoma protein (pRb) phosphorylation and interfered with G1 to S phase cell cycle progression.

Ribociclib has demonstrated *in vivo* anti-tumor activity in subsets of tumor xenograft models including but not limited to breast, melanoma, neuroblastoma, malignant rhabdoid, lung, pancreas and hematological malignancies. In addition, ribociclib has shown anti-tumor activity when combined with targeted agents which inhibit signaling pathways known to regulate D-cyclin levels, including inhibitors of the RAF, mitogen-activated protein kinase kinase (MEK), phosphoinositide 3-kinase (PIK3) and mammalian target of rapamycin (mTOR) pathways.

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

[redacted]

1.2.5.2 Clinical experience with ribociclib

Ribociclib is being investigated in patients with advanced breast cancer (aBC) and other solid tumors in multiple clinical trials at different phases of development. Three large phase III studies in patients with aBC have led to regulatory approvals in the USA and EU.

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

1.2.5.2.1 Clinical experience with ribociclib in combination with endocrine agents

Clinical Safety:

Clinical safety of ribociclib with endocrine agents such as letrozole, tamoxifen, exemestane, fulvestrant, and goserelin has been evaluated in several combination trials. The safety profile of ribociclib in combination with Non-Steroidal Aromatase Inhibitor (NSAI) (+/- goserelin) was investigated in two phase III trials in aBC (MONALEESA-2 [CLEE011A2301] and MONALEESA-7 [CLEE011E2301]).

Study [CLEE011A2301] is a phase III, multicenter study of the combination of ribociclib or placebo with letrozole in postmenopausal women with HR-positive, HER2-negative advanced (metastatic or loco regionally recurrent) breast cancer. In total, 668 patients were randomized; 334 patients each to the ribociclib plus letrozole arm and the placebo plus letrozole arm. Median duration of follow up at the second overall survival interim analysis (data cut-off 02-Jan-2017) was 26.4 months. As of January 2017, the most commonly (≥ 30%) reported AEs in ribociclib plus letrozole group, irrespective of causality were: neutropenia (64.1%), nausea (53.3%), fatigue (41.3%), diarrhea (38.3%), alopecia (34.4%), vomiting (33.5%), and arthralgia (33.2%). The incidence of Serious Adverse Events (SAE)s was 25.4% and 15.5% in the ribociclib plus letrozole and placebo plus letrozole arms, respectively. The trial reported 12 (3.6 %) patients with at least one > 480 ms post-baseline QTcF for the ribociclib arm, and 2 (0.6 %) patients with at least one > 480 ms post-baseline QTcF in the placebo arm. One case of sudden death has been observed in a context of grade 3 hypokalemia and grade 2 QTcF prolongation. Permanent discontinuations due to AEs were reported in 16.8% of patients receiving ribociclib plus letrozole and 3.9% in patients receiving placebo plus letrozole. The most common AEs leading to treatment discontinuation of ribociclib in patients receiving ribociclib plus letrozole were ALT increased (4.5%), AST increased (2.7%), vomiting (2.4%) based on data cut off of 04-Jan-2017.

For a comprehensive review of the safety profile of ribociclib in combination with endocrine agents, please refer to the current [ribociclib Investigator's Brochure].

Clinical Efficacy:

Efficacy of ribociclib with endocrine agents has been evaluated in three published phase III combination trials in patients with aBC, two of them evaluating the combination of ribociclib with NSAI (+/- goserelin).

Key efficacy results:

Study [CLEE011A2301] met its primary objective at the primary analysis (29 Jan 2016 data cut off), with compelling evidence of clinical benefit in patients with HR-positive, HER2-negative advanced breast cancer. A 44.4% estimated risk reduction in ribociclib plus letrozole treated patients was evident in the primary PFS endpoint as per investigator assessment (HR=0.556, 95% CI: 0.429, 0.720; one sided p-value $=3.29\times10^{-6}$). Updated PFS analyses (02 Jan 2017 data cut off) demonstrated continued treatment benefit for patients

receiving ribociclib and letrozole vs placebo and letrozole (hazard ratio=0.568; 95% CI: 0.457–0.704; p=9.63×10–8;). Median PFS was prolonged by 9.3 months, from 16.0 months (95% CI: 13.4–18.2) in the placebo arm to 25.3 months (95% CI: 23.0–30.3) in the ribociclib arm. The 24-month PFS rates were 54.7% in ribociclib plus letrozole arm vs 35.9% in the placebo plus letrozole arm. As of 02-Jan-2017 cut off, overall survival data remain immature, with 15.0% vs 19.8% of patient deaths in the ribociclib plus letrozole vs placebo plus letrozole arm (hazard ratio=0.746; 95% CI: 0.517–1.078; p=0.059).

For more details, please refer to the current [ribociclib Investigator's Brochure].

1.2.5.2.2 Clinical experience with ribociclib in combination with spartalizumab

[NCT03294694] is an open-label phase I dose escalation study with primary objective to determine the safety, tolerability, maximum-tolerated dose (MTD) and recommended phase 2 dose (RP2D) of the combination of ribociclib and spartalizumab in metastatic HR-positive breast cancer and advanced ovarian cancer. Nine women with breast cancer and one woman with ovarian carcinoma participated in the dose escalation portion of the trial. The median age was 57 years (50-70 years); all 10 (100%) had ECOG PS of 0 or 1; all patients had metastatic disease. The median number of prior therapies for metastatic breast cancer was 2 (range 0-4). The median number of prior cytotoxic chemotherapies for metastatic breast or ovarian disease was 4 or more (range 0-4+). Eight of the nine participants with breast cancer (89%) had prior exposure to a CDK4/6 inhibitor in any setting.

Three subjects were enrolled to Dose Level 1 (400mg p.o. QD ribociclib + 400 mg i.v. Q4W spartalizumab) and no DLTs were observed. Three subjects were enrolled to Dose Level 2 (600mg p.o QD ribociclib + 400mg i.v. Q4W spartalizumab) and no DLTs were observed. Four additional subjects were enrolled to this dose level; one was deemed unevaluable due to drug compliance issues and was replaced. Among these three evaluable subjects, one subject experienced a DLT of grade 3 atrial flutter and grade 3 atrial fibrillation, which were determined to be possibly related to both ribociclib and spartalizumab. Based on this information, a Maximum Tolerated Dose (MTD) of 600mg p.o QD ribociclib in combination with 400mg i.v. Q4W spartalizumab was declared.

A full listing of all grade toxicity determined to be possibly, probably, or definitely related to either ribociclib or spartalizumab are outlined here: alanine aminotransferase increased (6 patients, 60%), aspartate aminotransferase increased (3 patients, 30%), atrial fibrillation, atrial flutter, blood bilirubin increased, hyperglycemia, platelet count decreased, white blood cell count decreased (all reported in 1 patient, 10%).

One of ten participants experienced a best response per RECIST 1.1 of SD for <16 weeks; 8 had a best response of progressive disease; one participant was not evaluable per RECIST 1.1 but experienced clinical progression; one participant was not evaluable for a response assessment altogether. Nine participants were removed from treatment due to progressive disease; one was removed for unacceptable toxicity.

Overall the combination demonstrated a favorable safety and tolerability profile. An expansion cohort of the doublet later opened for ovarian participants, as well as a safety run-in with the addition of fulvestrant for breast participants that lead to a dose expansion cohort.

1.2.5.2.3 Clinical pharmacokinetics of ribociclib

The clinical pharmacokinetics (PK) of ribociclib have been evaluated in a phase I study in patients with advanced solid tumors or lymphomas [CLEE011X2101]. Following oral dosing, ribociclib was rapidly absorbed with median Tmax ranging from 1 to 4 hours.

[redacted]

The T1/2 accumulation for ribociclib was 32.0 hours and the mean CL/F (apparent total body clearance of drug from the plasma) was 25.5 L/hr at steady-state at 600 mg in patients with advanced cancer. Ribociclib is mainly eliminated via hepatic clearance (extensive hepatic metabolism via CYP3A), with renal clearance playing a lesser role in humans.

Concomitant use of ribociclib with strong CYP3A4 inhibitors or strong CYP3A4 inducers should be avoided as ribociclib exposure may be markedly affected. Concurrent use of sensitive CYP3A4 substrates with a narrow therapeutic index should be avoided. Concurrent use of CYP1A2 substrates is not expected to lead to clinically important drug-drug interaction (DDI).

No apparent drug-drug interaction (DDI) was observed between ribociclib and the combination partner letrozole or anastrozole based on PK data in the MONALEESA-2 and -7 trials. Based on the population PK analysis, concomitant use of letrozole or anastrozole had no impact on ribociclib exposure.

Food does not affect the PK of ribociclib administered as a capsule or tablet formulation; therefore ribociclib capsules or tablets can be taken without regard to meals [CLEE011A2111, CLEE011A2103].

Refer to the current [ribociclib Investigator's Brochure] for additional details.

2 Rationale

2.1 Study rationale and purpose

Patients eligible for this study failed to respond, or progressed while being on standard treatment for unresectable or metastatic melanoma which include either targeted therapy (for patients with ^{V600}*BRAF*-mutant melanoma) and/or immune checkpoint inhibitors (e.g. pembrolizumab, nivolumab with or without ipilimumab) due to either primary or acquired resistance (Kim et al 2016, Sharma et al 2017, Jenkins et al 2018).

Patients with primary resistance to treatment with checkpoint inhibitors do not respond because of a combination of intrinsic or extrinsic tumor-cell resistance mechanisms. Intrinsic mechanisms may include lack of antigen expression, loss of HLA (human leukocyte antigen) or B2M (Beta-2-Microglobulin) expression, alterations in antigen processing, alterations in signaling pathways (e.g. MAPK, PI3K, WNT, IFN), and constitutive PD-L1 expression. Extrinsic mechanisms may include expression of inhibitory immune checkpoints (e.g. CTLA-4, PD-1, VISTA, TIM-3, LAG-3), T cell exhaustion, immune suppressive cells (e.g. T_{reg}, MDSC, macrophages), and cytokines and metabolites release into the tumor microenvironment (e.g. CSF-1, tryptophan, TGF-β, adenosine) (Kim et al 2016, Sharma et al 2017, Jenkins et al 2018).

Approximately one third of patients with metastatic melanoma who have responded to checkpoint inhibitor therapy with anti-CTLA-4 or anti-PD-1 will eventually progress due to an acquired resistance. Although not well-understood, potential mechanisms for acquired resistance include loss of T cell function, lack of T cell recognition by downregulation of tumor antigen presentation and development of escape mutation variants in the cancer (Kim et al 2016, Sharma et al 2017, Jenkins et al 2018).

Considering the importance of the inhibitory effect of the PD-1/PD-L1 axis as described above, there is rationale to use an anti-PD-1 antibody even in patients who have received previous checkpoint inhibitor therapy. Furthermore, the established anti-tumor activity of anti-PD-1/PD-L1 checkpoint inhibitors as monotherapy in a wide spectrum of cancers

together with its favorable toxicity profile provides a strong rationale for its use as a backbone for combination strategies. Although the PD-1/PD-L1 checkpoint axis plays a critical inhibitory role, secondary immune checkpoints such as LAG-3, TIGIT, and VISTA may also play a vital role leading to T cell dysfunction. As a result, targeting these inhibitory checkpoint inhibitors (e.g. with the anti-LAG-3 antibody LAG525) may restore T cell function (refer to the rationale for combining LAG525 with spartalizumab in Section 2.4.1).

Neutrophils recruited to T cell-inflamed microenvironments play an immunosuppressive role, restraining T cell expansion, effector functions and contribute to resistance to immune therapy. High blood neutrophil counts and neutrophil-to-lymphocyte ratios predict poor survival in cancer patients (Shen et al 2014, Templeton et al 2014) and poor outcome to checkpoint immunotherapy in melanoma patients (Ferrucci et al 2015, Gebhardt et al 2015). In cancer patients, high serum levels of the c-MET ligand HGF (hepatocyte growth factor) correlated with increasing neutrophil counts and poor responses to checkpoint blockade therapies (Glodde et al 2017). In addition, cytokines like IL-1β, derived from the tumor microenvironment and secreted by malignant cells, promotes tumor cell proliferation, increases invasiveness and dampens anti-tumor immune response, in part by recruiting inhibitory neutrophils (Apte et al 2006, Miller et al 2007). Therefore, inhibition of c-MET (e.g. with the c-MET inhibitor capmatinib) or the cytokine IL-1β (e.g. with the IL-1β antagonist canakinumab) may restore T cell function resulting in tumor response in a population with lack of treatment options as of today (refer to the rationale for combining capmatinib and canakinumab with spartalizumab in Section 2.4.2 and Section 2.4.3 respectively).

MDSC are a heterogeneous population of immature myeloid cells and represent another class of tumor infiltrating cells which are highly immunosuppressive. These cells contribute to tumor immune escape by inhibiting cytotoxic T cell proliferation and driving T regulatory cell induction. Cytokines such as IL-1β secreted by tumor cells have been shown to recruit MDSC to tumor microenvironment (Guo et al 2016). Therefore, strategies to suppress the MDSC population by various ways including inhibition of IL-1β may offer another approach to boost sensitivity to anti PD-1 therapy.

Using the anti-PD-1 antibody spartalizumab as backbone, this study will evaluate novel compounds, which may help alter the tumor microenvironment through different mechanisms which may potentially reverse resistance to immune checkpoint blockade and restore T cell function.

A specific rationale for each of the combinations tested in is provided in Section 2.4.

2.2 Rationale for the study design

Considering the importance of the inhibitory effect of the PD-1/PD-L1 axis as described in Section 2.1, the anti-PD-1 antibody spartalizumab will be used in combination with other compounds, which may help alter the tumor microenvironment favorably to potentially reverse the primary or acquired resistance to checkpoint inhibitor blockade. As outlined in Section 2.1, there are multiple intrinsic and extrinsic resistance mechanisms, which can be targeted to restore T cell activity against the tumor.

Considering the high number of potential targets and available compounds, an open platform design is applied for this study. In general, platform designs allow for simultaneous assessment of multiple treatments within a single disease under one master protocol (Ventz et al 2017, Saville et al 2016). An open platform design starts with a predefined fixed number of treatment arms but as new suitable treatments become available during the course of the

trial new treatment arms can be added. Those new arms are added based on evolving scientific rationale (e.g. mechanism of action), preclinical data and if an acceptable safety profile has been established. Furthermore, platform designs offer adaptive features such as dropping treatment arms for futility and declaring one or more treatments efficacious. A protocol amendment will be needed each time a new arm is added to the study.

The platform study design methodology has been successfully applied as an accelerated mechanism to evaluate multiple compounds in various diseases, and has been successfully implemented in recent clinical studies (e.g. I-SPY2, STAMPEDE, AML15, AML16) (Ventz et al 2017, Saville et al 2016, Renfro 2017, Berry et al 2015, Woodcock et al 2017).

The randomized section of this study is designed as a randomized, open-label, two-part, multi-center, open platform phase II study to assess the efficacy and safety of novel combinations using the anti-PD-1 antibody spartalizumab as a backbone in previously treated unresectable or metastatic melanoma. The primary endpoint is confirmed objective response rate (ORR) in each combination arm with supportive key secondary endpoint of duration of response (DoR) using RECIST v1.1. A study design using those endpoints has been utilized as primary means of efficacy evaluation in disease settings with no available therapies or in settings where currently available therapy does not provide sufficient evidence of benefit. Since there are no available therapies for patients eligible for this study (who failed to respond, or progressed while being on standard treatment for unresectable or metastatic melanoma), the targeted response rate of 25% is deemed to be clinically meaningful and transformative in this patient population and warrants further development.

The non-randomized section of this study is designed to assess the efficacy and safety of spartalizumab combined with LAG525 treatment in subjects with previously treated unresectable or metastatic LAG-3 positive melanoma. The primary and key secondary endpoints are similar to the randomized section of this study. The targeted ORR of 30% chosen in this arm 1A is deemed to be clinically meaningful and transformative in this selected subject population, where the ORR would be expected to be higher than in a non-selected population, and warrants further development.

The two sections of the study (randomized and non-randomized) consists of two parts each:

- Part 1 (selection phase) to evaluate the preliminary efficacy in terms of ORR of spartalizumab in combination with novel agents and to identify combination arm(s) that will be expanded to part 2 using Bayesian statistical methodology. Bayesian approach is ideally suited for repeated assessment of efficacy data that accrues during the course of the study and provides basis for probabilistic decision rules that can incorporate prior information.
- Part 2 (expansion phase) to obtain more precise estimate(s) of ORR in combination arm(s) selected for expansion, as well as further investigate their efficacy and safety.

The exploratory ‘selection’ process in Part 1 will be based on the confirmed ORR observed in each of treatment combination arms that will be compared against predefined efficacy thresholds (discussed in Section 10.4.2.1 for randomized section of this study and in Section 10.4.2.2 for the non-randomized section) and probabilistic decision rules (also presented in Section 10.4.2) to drop arms for futility or advance arms to part 2 will be applied. Hypothesis testing approach will be applied after completion of part 2 within each of the arms that were expanded to confirm efficacy in those arms (Section 10.4.2). Although, no formal comparison among treatment arms is planned, a randomized design is being used in the randomized section of this study. Randomization removes the potential of bias in allocation of patients in treatment combination arms and ensures comparability of arms in terms of

[redacted]

importance of baseline prognostic factors (like baseline level of lactate dehydrogenase [LDH]) that allows for meaningful side-by-side comparisons.

At the time of protocol amendment 5, no arms were enrolling in the randomized section of this study (refer to Section 4.1.1). The new arm 1A evaluating the combination of spartalizumab with LAG525 is being added as a single arm in the non-randomized section of this study. Given the selected LAG3-positive population in non-randomized section, the targeted clinically relevant ORR and the ORR corresponding to the null hypothesis will be slightly higher than in the randomized section of this study.

The study design as proposed is expected to provide initial preliminary evidence of benefit by showing a clinically meaningful magnitude of response rate, which - based on recent experience with anti-PD-1 inhibitors - should serve as an appropriate surrogate to predict clinical benefit.

It is expected that the suggested study design will allow early identification of successful combinations while reducing patient exposure to futile treatments.

2.3 Rationale for dose and regimen selection

2.3.1 LAG525 in combination with spartalizumab

In the phase I/II study [CLAG525X2101C], patients with a variety of advanced solid tumors have been treated at multiple dose levels of single-agent LAG525 or LAG525 in combination with spartalizumab. Overall, single-agent LAG525 and LAG525 in combination with spartalizumab were tolerated with safety profiles similar to those of other approved checkpoint inhibitors. A maximum tolerated dose was not identified for LAG525. Anti-tumor activity was not observed with LAG525 single agent but was seen at several dose levels of LAG525 in combination with spartalizumab. There was no clear pattern between dose and anti-tumor activity. Therefore, a PK/PD modeling was used to support determination of the RP2D. 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 patients [Justification for RP2D report]. Based on the trial simulation of the PK/PD model, two RP2Ds were declared for the combination: 400 mg LAG525 Q3W in combination with 300 mg spartalizumab Q3W and 800 mg LAG525 Q4W in combination with spartalizumab 400 mg Q4W.

An alternate dose regimen of 600 mg LAG525 Q4W in combination with spartalizumab 400 mg Q4W was chosen for this study. Even though the LAG525 dose is lower than the recommended dose regimen of 800 mg Q4W, the predicted tumor target (LAG-3) suppression is similar to the higher dose schedule (88% vs. 92%).

2.3.2 Capmatinib in combination with spartalizumab

In the phase 1b/II study [CINC280X2108], patients with hepatocellular carcinoma (HCC) have been treated at multiple dose levels with the combination of capmatinib and spartalizumab or spartalizumab single-agent. Based on the observed DLT rate (as described in Section 1.2.3.2.2), the BLRM-EWOC model used in this study supports a dose of 400 mg capmatinib BID in combination with 300 mg spartalizumab Q3W. In the current study the alternate dosing regimen of 400 mg capmatinib BID in combination with spartalizumab 400 mg Q4W will be used. PK and safety data across dose levels in study [CPDR001X2101] supported the declaration of two RP2Ds, 300 mg Q3W and 400 mg Q4W, for spartalizumab as single-agent. Based on the population PK model simulations, both regimens are expected

to achieve similar exposure range at steady-state and achieve a mean steady-state C_{trough} value higher than the *in vitro* EC50 for antigen-stimulated IL-2 production, a translational biomarker for PD-1 blockade [Summary of phase I clinical safety, pharmacokinetic (PK) and pharmacodynamics (PD) data].

2.3.3 Canakinumab in combination with spartalizumab

Data for the combination of canakinumab with spartalizumab is available from a Phase Ib, open-label, multi-center study [CPDR001X2103].

From data available as of July 31, 2017 (as described in Section 1.2.4.2.1), there were no DLT observed and the Phase I of the study is ongoing. The dose level of canakinumab 600 mg Q8W in combination with spartalizumab 400 mg Q4W was declared as the RP2D. In the current study an alternate dose regimen of canakinumab 300 mg Q4W in combination with spartalizumab 400 mg Q4W will be used to align the dosing schedules. Based on the population PK model simulations the canakinumab 300 mg Q4W regimen is predicted to achieve similar exposure as the canakinumab 600 mg Q8W. Based on the available safety data across the doses tested the alternate dose regimen is expected to be well tolerated.

2.3.4 Ribociclib in combination with spartalizumab

The dose (oral administration of 600 mg daily) and regimen (days 1-21 of a 28 day cycle) of ribociclib was selected for this study since this dose and regimen were shown to be tolerable when combined with endocrine therapy in clinical trials in patients with HR-positive, HER2-negative advanced BC (see Section 1.2.5.2). A phase I study of the CDK4/6 inhibitor ribociclib in combination with the PD-1 inhibitor spartalizumab in patients with metastatic hormone receptor-positive breast cancer and metastatic ovarian cancer is currently ongoing [NCT03294694]. Based on the information from the dose-finding cohort, a MTD of 600 mg p.o QD ribociclib in combination with 400mg i.v. Q4W spartalizumab was declared. An expansion cohort of the doublet later opened for ovarian participants. Furthermore, a safety run-in with the addition of fulvestrant for breast cancer participants was initiated that led to a dose expansion cohort. Other doses and/or regimens of ribociclib in combination with spartalizumab may be explored in this study in the future.

2.4 Rationale for choice of combination drugs

2.4.1 Rationale for LAG525 in combination with spartalizumab

LAG-3 and PD-1 function at multiple levels to control T cell homeostasis, activation, and differentiation. Furthermore, they contribute to cell extrinsic regulation by controlling T_{reg} cell homeostasis and function, and mitigating dendritic cell differentiation and function. As a result, simultaneous blockade of LAG-3 and PD-1 may synergistically restore T cell activation and enhance anti-tumor immunity (Woo et al 2012, Ascierto et al 2017).

In vivo studies have demonstrated a synergistic effect in anti-tumor activity of the dual blockade of the LAG-3 and PD-1 co-inhibitory receptors when compared to the inhibition of either checkpoint alone. $CD4^+$ and $CD8^+$ TIL from Sa1N fibrosarcoma, MC38 colon carcinoma and B16 melanoma have previously been shown to co-express PD-1 and LAG-3.

Combined LAG-3 and PD-1 blockade led to rapid and complete regression of established tumors in 70% of Sa1N fibrosarcoma and 80% of MC38 colon carcinoma within 50 days of the initiation of therapy. Using the maximum likelihood model, this demonstrated synergy

of co-blockade over single agent activity. Both TIL and lymphocytes from draining lymph nodes harvested from treated mice had increased numbers of $CD8^{+}IFN\gamma^{+}$ TIL, further supporting the anti-tumor role of co-blockade (Woo et al 2012). Further, data from dual LAG-3/PD-1 knockout mice experiments show that compared to wild type, the dual knockout mice developed an early onset (4 weeks of age) lethal autoimmune condition that resulted in approximately 80% of the mice moribund by approximately 10 weeks. The major histopathologic manifestations included diffuse fibrosis, lymphohistiocytic endocarditis, myocarditis and pancreatitis. In contrast, LAG-3 and PD-1 single knockout mice lacked any disease manifestations or histopathology over this period of observation. These results show that the PD-1 and LAG-3 pathways synergistically regulate immune self-reactivity (Woo et al 2012).

Taken together, these preclinical data demonstrate that co-blockade of the PD-1 and LAG-3 pathways leads to synergistic anti-tumor activity superior to blockade of either inhibitory protein alone (Woo et al 2012). Recently, clinical data showed that patients treated with the anti-LAG-3 antibody BMS-986016 in combination with the anti-PD-1 antibody nivolumab is well tolerated with a safety profile similar to nivolumab monotherapy and provides encouraging efficacy in a heavily pre-treated, advanced melanoma population. Higher response rates correlated with higher LAG-3 expression, irrespective of PD-L1 expression status (Ascierto et al 2017).

2.4.1.1 Rationale for targeting subjects with LAG-3 positive melanoma in arm 1A

The combination of LAG525 and spartalizumab has been explored in arm 1 within the CPDR001J2201 study in unselected metastatic melanoma patients who had progressed on prior anti-PD(L)-1 therapy, alone or in combination. Data from the first 35 patients enrolled in arm 1 were analyzed as part of the second interim analysis (IA2) and the safety profile of spartalizumab plus LAG525 (arm 1) was consistent with the safety profile of the individual drugs. The most common adverse events in arm 1 (>20%) were nausea (31.4%) and asthenia (22.9%). One subject reported multiple organ dysfunction syndrome as AE leading to treatment discontinuation and death. The main reason for treatment discontinuation was disease progression (57.1%). The ORR based on local radiology review per RECIST v1.1 was 8.6% (95% CI:1.8, 23.1) with 3 confirmed responders. The observed responses were durable with 2 responders ongoing for 7.4 months at the time of data cut off. The 3rd responder had brain metastasis and high LDH levels at enrollment and reported a duration of response of 3.7 months. LAG-3 status was determined for baseline tumor samples collected during screening using immunohistochemistry (IHC) analysis. Of the baseline biopsy samples from the 3 clinical responders, 2 samples were positive for LAG-3 and 1 sample was not evaluable for LAG-3 IHC evaluation but had high *LAG3* gene expression as analyzed by Nanostring. With only 4 of 35 patients total with positive LAG-3 tumor status, correlative analyses were limited in arm 1 hence further exploration is warranted to confirm these findings. Taken together, the preliminary data support further investigation to validate the hypothesis that the spartalizumab plus LAG525 combination could be effective in patients with positive LAG-3 tumor status. A centralized IHC assay will be used to select patients for arm 1A using a $\geq$ 5% threshold for positive LAG-3 staining in order to enroll the same patient population where an enrichment in response was observed in arm 1 during IA2.

[redacted]

2.4.2 Rationale for capmatinib in combination with spartalizumab

Stromal release of HGF and increased expression of its receptor c-MET are found in many solid tumors including melanoma (Sierra et al 2011; Etnyre et al 2014). c-MET is a receptor tyrosine kinase encoded by the MET proto-oncogene that activates several intracellular signaling pathways including RAS-MAPK, PI3K-AKT, RAC1, and PAK. As a result, c-MET signaling regulates proliferation, cell survival, and migration in development, tissue regeneration, and tumorigenesis. Further, several studies reported immunosuppressive roles for the HGF/c-MET axis such as an impairment of dendritic cell functions and the induction of T cell tolerance (Benkhoucha et al 2010, Okunishi et al 2005). High blood neutrophil counts and neutrophil-to-lymphocyte ratios predict poor survival in cancer patients and poor outcomes to checkpoint inhibitor therapy in melanoma (Ferrucci et al 2015). Current clinical studies aim to evaluate the c-MET inhibitors in cancers with deregulated c-MET signaling

A multitude of effects of HGF/c-MET signaling on identity and function of immune cells has been reported in the preclinical literature (Molnarfi et al 2015). A common theme is the modulation of dendritic cell function by HGF towards a "tolerogenic" phenotype. Therefore, inhibition of c-MET signaling on dendritic cells is expected to improve their T cell stimulatory activity, suggesting that capmatinib has the potential to enhance the efficacy of immunotherapies such as checkpoint blockade by anti-PD-1 antibodies. Indeed, a recent preclinical study showed that inhibition of c-MET with capmatinib or genetic knockout can enhance T cell mediated anti-tumor immunity in a variety of treatment regimens and mouse models (Glodde et al 2017). The proposed mechanism in this report is different from the dendritic cell hypothesis and based on a c-MET dependent reactive neutrophil response: when T cells attack and kill tumor cells, the ensuing tissue damage triggers a repair response that involves secretion of HGF by the tumor-associated stroma. As a consequence, neutrophils with immunosuppressive properties are mobilized and migrate to the tumor, dampening the T cell response. This negative feedback can be prevented by capmatinib.

Both of these preclinical hypotheses suggest that inhibition of c-MET on immune cells may be beneficial for T cell mediated anti-tumor immunity.

In order to independently reproduce these results, the combination of anti-PD-1 and capmatinib was tested in two syngeneic mouse models at Novartis [RD-2017-00370 draft report]: the widely used MC38 colon cancer model was tested, which was originally generated by chemical mutagenesis and bears a high mutation burden. Combination treatment led to increased T cell infiltration in the short term, and an improved anti-tumor immune response with a higher cure rate than either single agent in the long term. MC38 cells were not sensitive to capmatinib *in vitro*. The *in vivo* studies were extended in a second model that was generated at Novartis in a genetically engineered mouse strain with error-prone DNA replication, which also leads to a high mutation burden. Again, addition of capmatinib to anti-PD-1 therapy led to an increased cure rate, while the c-MET inhibitor was largely inactive on its own.

Besides these direct functional data in mouse models, the reported immunosuppressive effects of HGF/MET on dendritic cells (summarized above) further support the rationale for combining anti-PD-1 and capmatinib, because both agents have the potential to enhance T cell mediated anti-tumor immunity through complementary mechanisms. While inhibition of HGF/c-MET signaling is expected to enhance antigen presentation and T cell stimulation by dendritic cells, anti-PD-1 antibodies will prevent suppression of T cell function through PD-L1 expressed on tumor cells or other immune cells.

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2.4.3 Rationale for canakinumab in combination with spartalizumab

The IL-1 family consists of agonistic and antagonistic molecules as well as receptors. The two major agonistic proteins are IL-1α and IL-1β. IL-1β is not present under homeostatic conditions, but is induced and secreted upon inflammatory signals (Voronov et al 2014).

Solid tumors in which IL-1β has been shown to be upregulated include breast, colon, lung, head and neck cancers and melanoma, and patients with IL-1β producing tumors have generally a poor prognosis (Lewis et al 2006). Secreted IL-1β, derived from the tumor microenvironment and secreted by malignant cells, promotes tumor cell proliferation, increases invasiveness and dampens anti-tumor immune response, in part by recruiting inhibitory neutrophils (Apte et al 2006, Miller et al 2007). In addition, IL-1β derived from inflammasome activation or cancer cell lines expressing high IL-1β promote generation and infiltration of immunosuppressive myeloid cells such as myeloid-derived suppressor cells (MDSC) and tumor-associated macrophages (TAMs) into tumor microenvironments (Guo et al 2016, Lechner et al 2010). Such cells were found to be enriched and activated in melanoma, hindering anti-tumor immune responses and leading to the tumor progression (Umansky et al 2014, Martens et al 2014). Experimentally, inhibition of IL-1β results in a decrease in tumor burden and metastasis (Voronov et al 2003) and also reduced the recruitment of myeloid cells in preclinical breast cancer models (Guo et al 2016). Importantly, reducing MDSC levels were also shown to increase sensitivity to anti-PD-1 therapy syngeneic mouse tumor models (lung and renal cell cancer) (Orillion et al 2017).

Canakinumab is a high-affinity human monoclonal antibody against interleukin-1β (IL-1β). Recent results from a large randomized, double-blind phase III study of canakinumab in patients with cardiovascular disease showed that canakinumab reduced the occurrence of lung cancers (Ridker et al 2017b). By inhibiting the pro-inflammatory cytokine IL-1β, canakinumab may alter the inflammation in the tumor microenvironment in a positive way, which in combination with spartalizumab could overcome resistance.

2.4.4 Rationale for ribociclib in combination with spartalizumab

The cyclin D-CDK 4/6-p16^{INK4}-pRb signaling pathway plays a key role in mammalian cell proliferation, where D cyclins bind to and activate CDK4/6, which phosphorylates pRb and drives progression of the cell cycle at the G1/S phase transition checkpoint (Ortega et al 2002, Shapiro 2006). The majority of cancers (~80%) maintain a functional pRb and alter the positive and negative regulators of CDK4/6 to increase activity of these kinases (Ortega et al 2002, Shapiro 2006). Copy number variation or overexpression in at least one component of the cyclin D-CDK4/6 pathway is seen in approximately 75% of melanoma (Young et al 2014).

Pharmacological inhibition of CDK4/6 in vitro are cytostatic causing downregulation of E2F target genes, loss of proliferation markers and cell cycle arrest in G1. However, only modest clinical benefit was observed in the unselected early clinical phase trials of single agent CDK4/6 inhibitors. Based on these findings, synergistic combinations with CDK4/6 inhibitors are being explored to amplify the efficacy of CDK4/6 inhibitors. CDK4/6 inhibitors can induce senescence and senescent cells are associated with activation of the innate and adaptive immune system as they secrete a collection of inflammatory cytokines, chemokines and proteinases, collectively referred to as the senescence associated secretory phenotype (SASP) (Xue et al 2007). Additionally, CDK4/6 inhibitors have shown to increase cancer cell presentation of tumor neoantigens on major histocompatibility complex (MHC) class I molecules. CDK4/6 inhibitors have also been shown to suppress the

proliferation of immunosuppressive regulatory T cells, increase nuclear levels of NFAT and increased transcriptional activity resulting in a change in the cytokine milieu within the tumor microenvironment and increased effector T cell activity (Deng et al 2018).

The cytotoxic T cell-mediated clearance of tumor cells, along with the efficacy of CDK4/6 inhibition on tumor growth, have been shown to be further enhanced with immune checkpoint blockade (Schaer et al 2018, Jerby-Arnon et al 2018, Goel et al 2017). Furthermore, CDK4 was implicated in a tumor cell resistance program including T cell exclusion and immune evasion and CDK4/6-inhibition was shown to repress the program and overcome resistance to anti-PD1 therapy (Jerby-Arnon et al 2018). Given the magnitude of immune modulatory effects observed from CDK4/6 inhibitors, the combination of CDK4/6 inhibitors with check point inhibitors such as anti PD1/PDL1 offers a novel treatment strategy in patients with relapsed/ refractory melanoma.

2.5 Rationale for choice of comparators drugs

Not applicable.

2.6 Risks and benefits

Subjects enrolled in this study have not responded to, or progressed on, the approved treatments for unresectable or metastatic melanoma (e.g. checkpoint inhibitors and/or targeted therapy) and have very limited treatment options. There is no established standard of care for this population. The combinations tested in this study may help alter the tumor microenvironment through different mechanisms which may potentially reverse the observed intrinsic and extrinsic resistance mechanisms (Section 2.1).

Specific risks for each compound and combination are discussed below. Implementation of dose modification and stopping rules, appropriate adverse event management, adherence to the protocol specific procedures and eligibility criteria, and close clinical monitoring (as mandated by the protocol) may further minimize the risk to subjects. As in any clinical study, there may be unforeseen risks with any of the combinations studied, which could be serious.

AE grades indicated in the subsections below for each study combination are using CTCAE v4.03, unless otherwise specified.

2.6.1 LAG525 and spartalizumab

Immune checkpoint inhibitors like LAG525 and spartalizumab may be associated with the occurrence of immune-mediated adverse events (irAEs). In general, irAEs can potentially involve every organ system with gastrointestinal (colitis), dermatologic, hepatic (hepatitis), pulmonary (pneumonitis), renal (nephritis) and endocrine toxicities (hypothyroidism, hyperthyroidism, type I diabetes, hypophysitis including hypopituitarism and adrenal insufficiency) being typically among the most frequent side effects. Other immune mediated AEs may rarely include the nervous system (e.g., encephalitis, Guillain-Barre syndrome, and myasthenia gravis), eye (e.g., uveitis), musculo-skeletal system (e.g., myositis, arthritis), cardiovascular system (e.g., vasculitis, myocarditis) or blood system (e.g., anemia). These side effects are generally manageable and reversible with dose interruption and administration of corticosteroids. 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 irAE may also occur after discontinuation of study treatment (Puzanov et al 2017). While the incidence of immune-related adverse events with

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single-agent anti PD-1 has been well characterized there may be a higher incidence of immune related adverse events with combination immune therapies, including the combination of LAG525 with spartalizumab. In addition, monoclonal antibodies such as spartalizumab and LAG525 can be associated with infusion-related reactions, which can be severe in some cases; these are often immediate and usually occur within minutes of the exposure to the study drug.

Combining immune checkpoint inhibitors targeting distinct inhibitory pathways demonstrated greater anti-tumor activity than each of the single-agents alone. In preclinical models, dual blockade of LAG-3 and PD-1 eradicated established melanoma and colon adenocarcinoma tumors that were largely resistant to single agent 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 [CCLAG525X2101C], treatment with LAG525 single agent and in combination with spartalizumab was well tolerated. LAG525 and spartalizumab showed promising efficacy, with RECIST responses across all dosage groups.

2.6.2 Capmatinib and spartalizumab

In rat and monkey studies, reversible pancreatic acinar cell vacuolation and/or apoptosis without inflammation were observed with capmatinib. Elevations in lipase and/or amylase were also seen during clinical development. When capmatinib is administered as a single agent, severe pancreatic events are reported in a number of patients. In study [CINC280A2201] study, grade 3/4 AEs of increased amylase suspected to be related to study treatment have been reported in 1 patient (0.5%) and Grade 3/4 increase in lipase suspected to be related to study treatment occurred in 9 patients (4.1%). Based on the current available data, a direct toxic effect of capmatinib on pancreas could not be definitively identified. Routine periodic clinical evaluations including serum amylase and lipase will be performed in this study. Further, patients with elevated amylase and/or lipase are excluded from this study.

The safety of the combination of capmatinib with spartalizumab is generally consistent with the single-agent experience for both compounds. No unexpected adverse events as compared with single agent data were observed.

In preclinical models, the combination treatment led to increased T cell infiltration in the short term, and an improved anti-tumor immune response with a higher cure rate than either single agent in the long term. Besides these direct functional data in mouse models, the reported immunosuppressive effects of HGF/MET on dendritic cells further support the rationale for combining anti-PD-1 and capmatinib, because both agents have the potential to enhance T cell-mediated anti-tumor immunity through complementary mechanisms.

It is hypothesized that the combination of capmatinib with spartalizumab may reverse resistance to checkpoint inhibitor therapy and restore T cell activity against the tumor in the subjects enrolled, which have very limited options.

2.6.3 Canakinumab and spartalizumab

Canakinumab is approved for the treatment of several inflammatory disorders in many countries and is marketed under the trade name ILARIS®. No dose-limiting toxicities of canakinumab have been observed in subjects receiving doses of up to 600 mg i.v. Q4W for

26 weeks (or with chronic dosing of up to 300 mg s.c. Q4W for over 2 years. Due to the mode of action of all inhibitors of the IL-1 pathway, infection is an important concern. As a result, subjects will be closely monitored for signs or symptoms of infection and appropriate treatment instituted in a timely manner (see Section 6.4.1). Monoclonal antibodies such as spartalizumab can be associated with infusion-related reactions, which can be severe in some cases; these are often immediate and usually occur within minutes of the exposure to the study drug.

The combination of canakinumab with spartalizumab was well tolerated (see Section 1.2.4.2.2). The most frequent AEs suspected to be related to study treatment were fatigue and decreased appetite. No patient had a Grade 3/4 AE that was suspected to be related to study treatment. There were no DLT observed.

It is hypothesized that the combination of canakinumab with spartalizumab may reverse resistance to checkpoint inhibitor therapy and restore T cell activity against the tumor in the subjects enrolled, which have very limited options.

2.6.4 Ribociclib and spartalizumab

Based on clinical data, treatment of ribociclib in combination with NSAI appears tolerable and toxicities of the treatment are expected to be manageable and reversible with treatment interruption, ribociclib dose reduction, or discontinuation. The 600 mg dose of ribociclib in combination with an NSAI has been investigated in the MONALEESA-2 and MONALEESA-7 Phase III studies in post- and premenopausal women with aBC respectively. Further details can be found in the latest [ribociclib Investigator's Brochure].

A phase I study of the CDK4/6 inhibitor ribociclib in combination with the PD-1 inhibitor spartalizumab in patients with metastatic hormone receptor-positive breast cancer and metastatic ovarian cancer is currently ongoing (NCT03294694). Based on the information from the dose finding cohort, a MTD of 600 mg p.o. QD ribociclib in combination with 400mg i.v. Q4W spartalizumab was declared. An expansion cohort of the doublet later opened for ovarian participants. Furthermore, a safety run-in with the addition of fulvestrant for breast cancer participants was initiated that led to a dose expansion cohort.

Patients in this study where ribociclib will be given in combination with spartalizumab will be carefully monitored for key toxicities that have been observed with ribociclib (refer to the current [ribociclib Investigator's Brochure]) and spartalizumab, and risks will be further minimized by adherence to inclusion/exclusion selection criteria, avoidance of prohibited medications, close safety monitoring and dose modification guidelines.

As per the inclusion/exclusion selection criteria, 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 must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below. These are applicable to all arms.

Table 3-1 Objectives and related endpoints

Primary objective	Endpoint	Analysis
To evaluate the efficacy of each combination arm, as measured by confirmed objective response rate (ORR)	Confirmed ORR using RECIST v1.1, per local assessment	Refer to Section 10.4
Key secondary objective	**Endpoint**	**Analysis**
To evaluate the efficacy of each combination arm in terms of duration of response (DoR)	DoR using RECIST v1.1, per local assessment	Refer to Section 10.5.1
Other secondary objectives	**Endpoint**	**Analysis**
To evaluate the efficacy of each combination arm as measured by progression-free survival (PFS) and disease control rate (DCR)	PFS and DCR, assessed using RECIST v1.1, per local assessment	Refer to Section 10.5.2
To evaluate the overall survival (OS) of each combination arm	Overall survival (OS)	Refer to Section 10.5.2
To characterize the safety and tolerability of each combination arm	Safety: Incidence and severity of AEs including changes in laboratory values, vital signs and cardiac assessment. Tolerability: Dose interruptions, reductions, and permanent discontinuations of study treatments	Refer to Section 10.5.3
To characterize the prevalence and incidence of immunogenicity of spartalizumab, LAG525 and canakinumab in each combination arm	Anti-drug antibodies (ADA) prevalence at baseline and ADA incidence on treatment	Refer to Section 10.5.4
To evaluate changes in levels and phenotype of T cell populations in the tumor and tumor microenvironment after treatment with combination therapies	Proportion of subjects with a favorable biomarker profile (pFBP), as defined by changes in numbers of cells expressing the $CD8^+$ T cell marker and/or T cell activation marker(s), T cell clonality and/or gene expression in tumor biopsy samples collected at baseline (screening) and compared to on treatment (3-4 weeks) samples	Refer to Section 10.5.5

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4 Study design

4.1 Description of study design

This is a randomized, open-label, multi-center, two-part, open platform phase II study to assess the efficacy and safety of the anti-PD-1 antibody spartalizumab in combination with novel agents in previously treated unresectable or metastatic melanoma. A non-randomized arm 1A has been added with protocol amendment 5 based on findings in arm 1 at IA2. Arm 1A is assessing the efficacy and safety of spartalizumab in combination with LAG525 in subjects with previously treated unresectable or metastatic LAG-3 positive melanoma.

This study consists of two parts, applicable for both randomized and non-randomized sections of the study:

- Part 1 : Selection phase

The primary objective of part 1 is to evaluate the preliminary ORR of spartalizumab in combination with novel agents in patients with previously treated unresectable or metastatic melanoma.

- Part 2 : Expansion phase

The primary objective for part 2 is to further characterize ORR of spartalizumab in combination with novel agents with relevant preliminary activity, as determined in part 1, for patients with previously treated unresectable or metastatic melanoma.

4.1.1 Randomized section of the study

At any time during the study, subjects deemed eligible after the completion of screening procedures will be randomized into any of the combination arms open to enrollment in the randomized section of this study (in either part 1 or part 2) for which the subject meets the eligibility criteria as described in Section 5 using an Interactive Response Technology (IRT) system. For each arm, randomization will be stratified by baseline level of lactate dehydrogenase (LDH). Stratification will occur with subjects with baseline LDH ≤ ULN (upper limit of normal), and subjects with baseline LDH > ULN.

Crossover or re-randomization of subjects to other combination arms, including better performing arms, is not allowed.

The first four arms evaluated in the randomized section of this study will enroll approximately a maximum of 230 subjects in total (for both parts of the study): approximately a maximum of 180 subjects in the selection phase (if all four combination arms enroll the maximum of 45 subjects) and approximately 50 subjects in the expansion phase (assuming that only one of the four initial combination arms will be expanded). If additional arms are expanded, then the maximum sample size will increase accordingly.

Part 1: Selection phase

The randomized section of this study started with the following three initial combination arms among which eligible subjects will be randomized with equal probability:

- **Arm 1:** LAG525 600 mg i.v. Q4W and spartalizumab 400 mg i.v. Q4W
  - Declared futile at interim analysis 2

[redacted]

- **Arm 2:** capmatinib 400 mg p.o BID and spartalizumab 400 mg i.v. Q4W
  - Declared futile at interim analysis 1
- **Arm 3:** canakinumab 300 mg s.c. Q4W and spartalizumab 400 mg i.v. Q4W
  - Declared futile at interim analysis 1

With protocol amendment 3, a fourth combination arm (Arm 4) was added:

- **Arm 4:** ribociclib 600 mg p.o QD on Days 1 to 21 of a 28-day cycle and spartalizumab 400 mg i.v. Q4W
  - Declared futile at interim analysis 3

After approval of protocol amendment 3 at each respective study site, eligible subjects will be randomized with equal probability across any of the four arms that are still open to enrollment within the selection phase.

As dose regimens for additional new combinations with spartalizumab become established, new combination arms will be added under the same master protocol through protocol amendments. A maximum of 10 arms may be active (open to enrollment) at any given time under this master protocol, and any arms active in part 1 will continue to be randomized with equal probability.

At each interim analysis, it will be determined which arm(s) (1) is declared efficacious and will be expanded to part 2, (2) will continue enrollment in part 1 (up to a maximum of 45 subjects enrolled in a given arm) or (3) will be dropped for futility, taking into account all available efficacy, safety and biomarker data. If a combination arm can be expanded to part 2, the exact sample size for part 2 will be determined at that time when the decision to expand this arm is taken (refer to Section 10.8.1 for further details on sample size considerations). The timing of interim analyses and the criteria used for decision-making at each interim analysis are detailed in Section 4.2.1and Section 10.

The maximum sample size for the first four arms in part 1 is approximately 180 subjects. However, based on simulations of sample size detailed in Section 10.8.1, it is expected that approximately 92-121 subjects will be enrolled in the first four arms during the selection phase.

Arm 1 (LAG525 plus spartalizumab) did not meet the efficacy nor the futility criterion at interim analysis 1, and enrollment was continued until the maximum of 45 subjects were randomized, and the arm was declared futile at interim analysis 2. However, findings supporting a potentially enriched response in subjects with LAG-3 positive tumor in arm1, warrant further development of the LAG525 plus spartalizumab combination in a LAG-3 positive selected patient population (refer to the rationale for arm 1A in Section 2.4.1.1).

Arm 2 (capmatinib plus spartalizumab) and arm 3 (canakinumab plus spartalizumab) were declared futile based on protocol specific criteria at interim analysis 1 and enrollment was consequently stopped for these arms. Arm 4 (ribociclib plus spartalizumab) was declared futile at interim analysis 3 after the enrollment in this arm was stopped at 44 subjects due to COVID-19 situation.

[redacted]

Part 2: Expansion phase

Only combinations arms that have met the pre-specified criteria defined in Section 4.2 and Section 10 will be opened for enrollment in part 2.

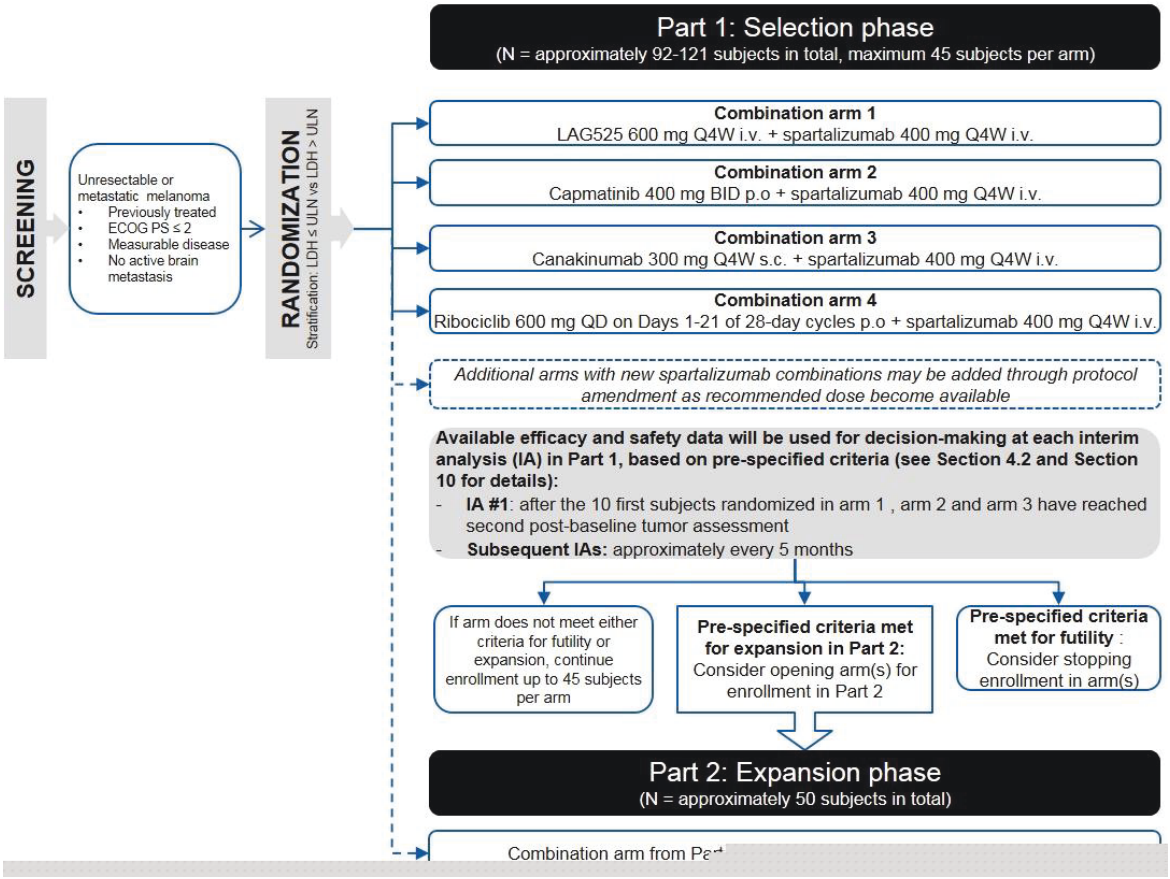
Exact randomization strategies in the situation when there is one (or more) arms open for enrollment in part 2 and there are still arms open for enrollment in part 1 will be determined at the time of the selection of the arm that will be expanded in part 2. Four factors will be considered at the time of opening an arm in part 2 to determine the exact randomization strategy and those are the following:

- Number of subjects enrolled in part 1 for the arm that meets criteria for expansion in part 2
- Number of subjects that will need to be enrolled in part 2 to have sufficient predictive power and alpha control
- Observed effect size (ORR) for the arm that meets criteria for expansion in part 2
- Observed effect size of other arms which are open for enrollment in part 1

Based on the sample size assumptions detailed in Section 10.8.1 and the assumption that only one of the four initial arms will meet the criteria for efficacy and will be expanded to part 2, it is expected that approximately 50 subjects will be enrolled in the expansion phase.

The study design for the randomized section of this study is schematized in Figure 4-1.

Figure 4-1 Overview of study design for randomized section of the study



4.1.2 Non-randomized section of the study

Subjects meeting the eligibility criteria for arm 1A, as described in Section 5, after the completion of screening procedures will be enrolled in this arm (in either part 1 or part 2) using the same Interactive Response Technology (IRT) system as used for the randomized section of the study.

Arm 1A will enroll up to approximately 100 subjects in total with LAG-3 positive melanoma (for both parts of the study) unless further exploration of this arm is stopped after 1st or 2nd interim analysis: 20 subjects in the selection phase and up to approximately 80 subjects in the expansion phase.

Part 1: Selection phase

After approval of protocol amendment 5, the following non-randomized combination arm will be opened for enrollment in part 1:

- **Arm 1A:** LAG525 600 mg i.v. Q4W and spartalizumab 400 mg i.v. Q4W, assessed in a population selected based on the LAG-3 status of their tumor.

Twenty (20) subjects will be treated in arm 1A in part 1. One interim analysis on these 20 subjects will be conducted as described in Section 4.2.2 to determine whether the efficacy probabilistic threshold is crossed for arm 1A and thus arm 1A may be expanded to part 2 or be dropped for futility.

Part 2: Expansion phase

Arm 1A will be opened for enrollment in part 2 only if the pre-specified criterion defined in Section 4.2.2 and Section 10.4.2.2 for this arm is met.

Based on the sample size assumptions detailed in Section 10.8.2, it is expected that up to approximately 80 subjects will be treated in arm 1A in the expansion phase, unless further exploration of this arm is stopped after 2nd interim analysis.

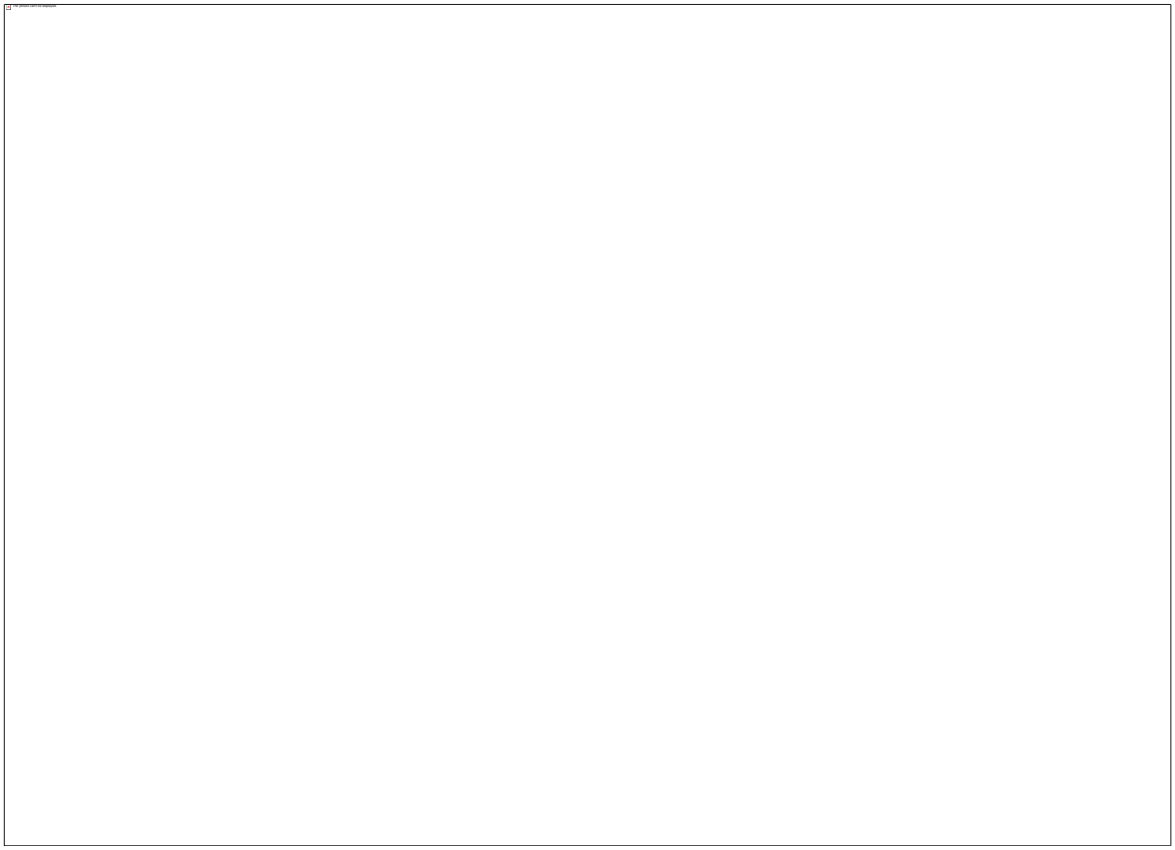
A second interim analysis will be conducted based on data from 20 additional subjects treated in expansion phase (i.e. 40 subjects in total combined with part 1 subjects) as described in Section 10.4.2.2 to support and inform decision-making on whether the arm 1A will be further explored or dropped for futility.

Enrollment may be held after 20 subjects are treated in part 2 until the outcome of the 2nd interim analysis is available.

Novartis may decide at any time during the study to prematurely stop enrollment in arm 1A for any reason.The study design for the non-randomized section of the study is schematized in Figure 4-2.

[redacted]

Figure 4-2 Overview of study design for non-randomized section of the study



4.1.3 Subject-level study design (common to randomized and non-randomized sections of the study)

Subjects in both part 1 and part 2 will undergo the same study periods as described below and in Figure 4-3 and will have assessments performed as described in Table 7-2:

Screening period

Subjects must sign the provided IRB/EC approved study informed consent form (ICF) prior to any study specific screening procedure. Refer to Section 7.1.2 for details on screening procedures and timing.

Treatment period

The treatment period begins when the first dose of study treatment is administered to the subject (on Day 1 of Cycle 1 [C1D1]), maximum 3 days after date of randomization/enrollment.

After randomization in one of the open arms (or enrollment in arm 1A) in part 1 or part 2, subjects will receive the study treatment corresponding to their arm on a 28-day cycle basis as described in Section 6 until disease progression per RECIST v1.1 by local assessment, unacceptable toxicity, start of subsequent anti-cancer therapy, withdrawal of consent, investigator's decision, lost to follow-up, death, or study is terminated by the sponsor. Subjects will be followed as per the schedule of assessments defined in Section 7.

The first RECIST v1.1 tumor assessment is scheduled 12 weeks after the date of randomization (or after the date of first dose of study treatment in arm 1A) and subsequent tumor assessments are detailed in Section 7.2.1.

Subjects may continue study treatment beyond disease progression by RECIST v1.1 if considered to be in the best interest of the subject and as long as all the protocol-specific criteria defined in Section 6.1.5.1 are met. In this case, the subject will continue assessments as defined in Section 7.

End of Treatment

Subjects should be scheduled for an End of Treatment (EoT) visit (refer to Section 7.1.5 for assessments to be performed) within 7 days after permanent discontinuation of study treatment for any reason (i.e. within 7 days after the last dose of the last study drug or after the date when decision was made to permanently discontinue both study drugs/the last study drug).

Safety follow-up

After study treatment discontinuation, all subjects must be followed for safety evaluations up to 150 days after the last dose of study treatment as outlined in Section 7.1.7.

Efficacy follow-up

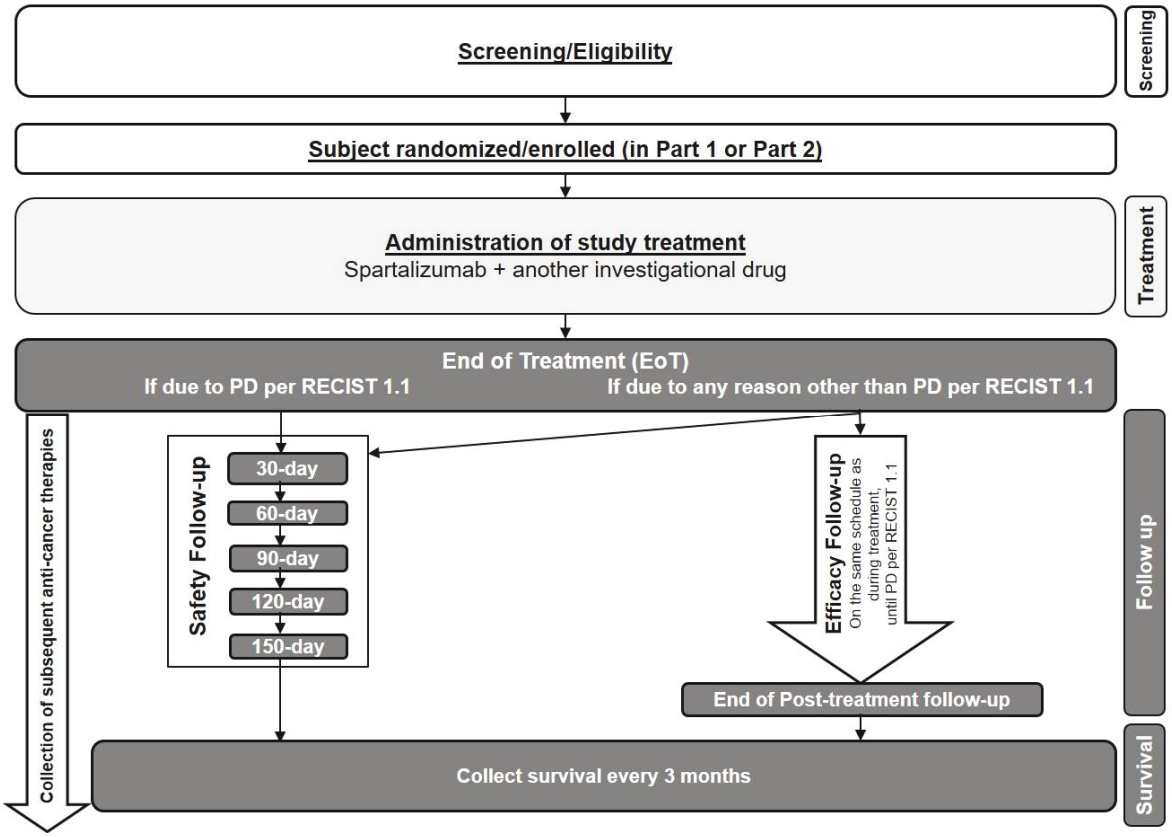
In parallel with the safety follow up, subjects who have permanently discontinued study treatment for any reason other than disease progression by RECIST v1.1 will continue tumor assessments as outlined in Section 7.1.8 until documented disease progression per RECIST v1.1 by local assessment, withdrawal of consent, lost to follow-up, death, or study is terminated by the sponsor. Every effort will be made to continue collection of tumor assessments even after start of another anti-cancer therapy for subjects that have not progressed.

Survival follow-up

Survival status and all subsequent anti-cancer therapies initiated after study treatment discontinuation (radiotherapies, surgeries and medications, including regimen number, names of all medications received within each regimen and start/end dates for each medication) will be collected as outlined in Section 7.1.9 until death, withdrawal of consent, lost to follow-up or end of study.

[redacted]

Figure 4-3 Overview of study design at subject level.



4.2 Timing of interim analyses and design adaptations

4.2.1 Randomized section of the study

The first interim analysis will be conducted in part 1 after approximately 10 subjects have been enrolled in each of the first three arms (arm 1, arm 2 and arm 3) and have completed the second post-baseline tumor assessment or have discontinued study treatment prior to completing the second post-baseline tumor assessment. The requirement to have at least 10 subjects in each arm is based on simulations showing that 10 is the minimal number of subjects to be able to declare futility as per decision rules presented below and also in Section 10.4.2.1.

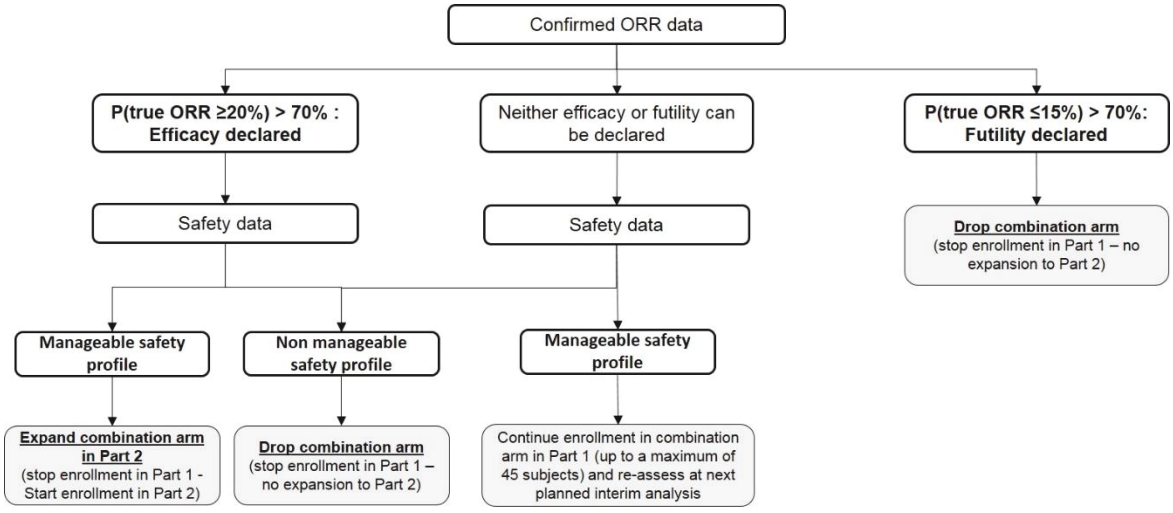
Subsequent interim analyses in part 1 will be conducted approximately every 20 weeks thereafter (since the first post-baseline assessment occurs at week 12, and the next post-baseline assessment occurs 8 weeks later) until sufficient subjects have been enrolled to assess if a combination is futile or meets the criteria for expansion in part 2. The first interim analysis for arm 4 (ribociclib and spartalizumab) will be synchronized with the subsequent planned interim analyses for the other arms and will occur when at least 10 subjects have been randomized to that arm and have either completed two post-baseline tumor assessments or have discontinued study treatment. Each interim analysis will be linked to a clinical decision point. Although the formal interim decisions rules and statistical thresholds (described in the paragraph below and in Section 10) are based on the observed confirmed ORR, all available efficacy, safety and biomarker data will be considered at each decision point to determine arms which are (1) considered futile, (2) will be expanded in part 2, or

(3) will continue enrollment in part 1 (until a maximum of 45 subjects). [redacted] Figure 4-4 presents pre-specified criteria for decision-making.

Statistical thresholds for efficacy and futility to be used at each interim analysis are defined as P(true ORR ≥ 20%) ≥ 70% and P(true ORR ≤ 15%) ≥ 70%, respectively. These statistical thresholds were chosen based on simulations so that clinically meaningful ORR thresholds of 10% for futility and 25% for efficacy are achieved with high probability (as presented in Table 10-10 in Section 10.8). The targeted ORR of 25% is deemed to be transformative in this population, since treatments are very limited for subjects who have not responded to, or progressed on the approved therapies for unresectable or metastatic melanoma. The probabilities will be calculated at each decision point for each arm based on observed confirmed ORR. Further details are provided in Section 10.4.2.1.

No interim analysis is planned for part 2.

Figure 4-4 Pre-specified criteria for decision making at each decision point (interim analysis) in part 1 to determine expansion in part 2 or drop of a combination arm



Of note, interim analyses will continue to be performed in the randomized section of the study at the pre-defined frequency until a clinical decision (e.g. arm declared futile or efficacy probabilistic thresholds crossed) on each arm in part 1 has been made. Even if declared futile, combination arms will be analyzed at subsequent interim analyses until all subjects have been reported at least once (i.e. had a minimum follow-up of 20 weeks). Additional descriptive analyses may be performed if required.

4.2.2 Non-randomized section of the study

The first interim analysis will occur in part 1 once all 20 subjects have been treated in arm 1A (in part 1) and followed up for at least two post-baseline efficacy assessments or have discontinued study treatment.

If arm 1A is expanded in part 2, the second interim analysis will be conducted once 20 additional subjects (i.e. 40 subjects in total combined with part 1 subjects) have been treated in the expansion phase and followed up for at least two post-baseline efficacy assessments or have discontinued study treatment.

[redacted]

Each interim analysis will be linked to a clinical decision point. Although the formal interim decisions rules and statistical thresholds (described in the paragraph below and in Section 10) are based on the observed confirmed ORR, all available data will be considered at this decision point to determine if the arm 1A is (1) considered futile, or (2) the efficacy probabilistic threshold is crossed and arm 1A may be expanded in part 2/may continue enrollment in part 2 at time of first interim analysis/2nd interim analysis respectively.

Statistical thresholds for efficacy and futility to be used is defined as P(true ORR $\geq$ 20%) > 70% and P(true ORR $\geq$ 20%) $\leq$ 70%, respectively. These statistical thresholds were chosen so that there is a sufficient efficacy signal observed before advancing this arm to the expansion phase and to ensure that if the true underlying ORR is 30% (clinically meaningful ORR) then the probability of crossing the threshold is sufficiently large (as presented in Section 10.4.2.2). The targeted ORR of 30% is deemed to be clinically meaningful and transformative in this selected patient population, where the ORR would be expected to be higher than in a non-selected population. The probabilities will be calculated based on observed confirmed ORR. Further details are provided in Section 10.4.2.2.

4.3 Definition of end of study

Timing of the randomized and non-randomized primary analysis is directly driven by the enrollment of the expansion arm of each section, and the primary analysis of each section will be run once the expanded arm has fully enrolled and also after all patients randomized/enrolled in that arm had at least 9 months of follow-up. This timing would allow for a potential minimum duration of response of 6 months for all subjects randomized/enrolled, assuming no delayed response. The exact timing of the randomized primary analysis could be revisited if more than one arm ends up being expanded.

Following the cut-off date for the primary analysis, the study will remain open. Ongoing subjects will continue to receive study treatment and will be followed as per the schedule of assessments, as long as subjects derive benefit from the combination arms in the opinion of the investigator.

The end of study is defined as the earliest occurrence of one of the following:

- All subjects have died or discontinued from the study
- Another clinical study (i.e. rollover study) becomes available that can continue to provide the appropriate combination treatment in this subject population and all subjects ongoing are eligible to be transferred to that clinical study
- All subjects randomized/enrolled in the study have at least 15 months of follow-up (i.e. 15 months after last subject is randomized/enrolled). For subjects still receiving study treatment at the time of end of study, every effort will be made to continue provision of study treatment outside this study through an alternative setting (e.g. Novartis managed access program) to subjects who in the opinion of the investigator are still deriving clinical benefit.

The final analysis and the generation of the final CSR will occur at the end of the study.

The timing of primary and final analyses and the definition of end of study will be updated, should new arms be added through protocol amendment or if more than one arm is expanded to part 2.

[redacted]

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the subject should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a discontinued or withdrawn subject. 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 subject's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

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

5.2 Inclusion criteria

5.2.1 Inclusion criteria for arms 1, 2, 3, 4

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

1. Written informed consent must be obtained prior to any screening procedures.
2. Male or female must be ≥ 18 years of age at time of providing informed consent.
3. Histologically confirmed unresectable or metastatic stage IIIB/C/D or IV melanoma using AJCC Edition 8 (refer to Appendix 1)

4a. Previously treated for unresectable or metastatic melanoma:

- Subjects with ^{V600}*BRAF* wild-type disease:
  - Subjects must have received prior systemic therapy for unresectable or metastatic melanoma with anti-PD-1/PD-L1. Additionally, subjects may have received anti-CTLA-4 as a single agent or in combination with anti-PD-1/PD-L1, irrespective of the sequence. No additional systemic treatment is allowed for advanced or metastatic melanoma
  - A maximum of two prior lines of systemic therapies for unresectable or metastatic melanoma are allowed.
  - The last dose of prior therapy (anti-PD-1, anti-PD-L1 or anti-CTLA-4) must have been received more than four weeks before randomization.
- Subjects with ^{V600}*BRAF* mutant disease:
  - Subjects must have received prior systemic therapy for unresectable or metastatic melanoma with anti-PD-1/PD-L1, and ^{V600}*BRAF* inhibitor. Additionally, subjects may have received anti-CTLA-4 as a single agent or in combination with anti-PD-1/PD-L1, or MEK inhibitor (in combination with ^{V600}*BRAF* inhibitor or as a single agent), irrespective of the sequence. No additional systemic treatment is allowed for advanced or metastatic melanoma
  - A maximum of three prior lines of systemic therapies for unresectable or metastatic melanoma are allowed

- The last dose of prior therapy must have been received more than 4 weeks (for anti-PD-1, anti-PD-L1 or anti-CTLA-4) or more than 2 weeks (for ^{V600}*BRAF* or MEK inhibitor) prior to randomization

- For all subjects with ^{V600}*BRAF* wild-type disease and with ^{V600}*BRAF* mutant disease: Subject must have documented disease progression as per RECIST v1.1 while on/after the last therapy received prior to study entry and while on/after treatment with anti-PD1/PD-L1. The last progression must have occured within 12 weeks prior to randomization in the study

5. ECOG performance status 0-2
6. At least one measurable lesion per RECIST v1.1 (refer to Appendix 2)

7a. At least one lesion, suitable for sequential mandatory tumor biopsies (screening and on-treatment) in accordance with the biopsy guidelines specified in protocol Section 7.2.3.1.1. The same lesion must be biopsied sequentially. Note: this lesion cannot be used as a target lesion.

8a. Screening tumor biopsy must fulfill the tissue quality criteria outlined in Section 7.2.3.1.1, as assessed by a local pathologist

9a. Subject must meet the following laboratory values at the screening visit in the absence of growth factors and/or transfusion support within 14 days prior to screening blood draw:

Hematological

- Hemoglobin ≥ 9 g/dL
- Absolute neutrophil count ≥ 1.5×10^9/L
- Platelets ≥ 75×10^9/L

Renal

- Serum creatinine < 1.5 mg/dL

Hepatic

- Total bilirubin ≤ 1.5 × ULN (upper limit of normal)
- AST ≤ 3.0 × ULN, except for subjects with liver metastasis, who may only be included if AST ≤ 5.0 × ULN
- ALT ≤ 3.0 × ULN, except for subjects with liver metastasis, who may only be included if ALT ≤ 5.0 × ULN

10a. Subjects must have recovered from treatment-related toxicities of prior anticancer therapies to grade ≤ 1 (CTCAE v 5.0).

5.2.2 Inclusion criteria for arm 1A (LAG525/spartalizumab)

Subjects eligible for inclusion in arm 1A in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained prior to any screening procedures.
2. Male or female must be ≥ 18 years of age at time of providing informed consent.
3. Histologically confirmed unresectable or metastatic stage IIIB/C/D or IV melanoma according to AJCC Edition 8 (refer to Appendix 1)

4b. Previously treated for unresectable or metastatic melanoma:

- All subjects must have received anti-PD-1 checkpoint inhibitor therapy (ie. pembrolizumab or nivolumab) either as monotherapy or in combination with ipilimumab as the last systemic therapy prior to enrollment and must have confirmed disease progression as per RECIST v1.1 (confirmed on a subsequent

scan, which can be the scan performed during screening) while on or after this therapy prior to enrollment.

- Subjects with ^{V600}*BRAF* wild-type disease must have received no more than 2 prior systemic therapies including prior anti-PD-1/PD-L1 (as monotherapy or in combination with ipilimumab)
- Subjects with ^{V600}*BRAF* mutant disease must have received no more than 3 prior systemic therapies including anti-PD-1/PD-L1 (as monotherapy or in combination with ipilimumab), and ^{V600}*BRAF* inhibitor (as monotherapy or in combination with a MEK inhibitor)
- The last dose of anti-PD-1 based therapy must have been received more than four weeks prior to first dose of study treatment.
- The last documented disease progression must have occured within 12 weeks prior to first dose of study treatment
- No additional systemic treatment is allowed for advanced or metastatic melanoma (this includes for example tumor infiltrating lymphocyte therapy)

5a. ECOG performance status 0-1

6. At least one measurable lesion per RECIST v1.1 (refer to Appendix 2)

7b. Subjects must have baseline tumor sample (fresh tumor biopsy or recent archival sample, as described in Section 7.2.3.1.1) that is positive for LAG-3 per central assessment at the Novartis-designated laboratory (Histogenex, Antwerp, Belgium)

9a. Subject must meet the following laboratory values at the screening visit in the absence of growth factors and/or transfusion support within 14 days prior to screening blood draw:

Hematological

- Hemoglobin ≥ 9 g/dL
- Absolute neutrophil count ≥ 1.5×10^9/L
- Platelets ≥ 75×10^9/L

Renal

- Serum creatinine < 1.5 mg/dL

Hepatic

- Total bilirubin ≤ 1.5 × ULN (upper limit of normal)
- AST ≤ 3.0 × ULN, except for subjects with liver metastasis, who may only be included if AST ≤ 5.0 × ULN
- ALT ≤ 3.0 × ULN, except for subjects with liver metastasis, who may only be included if ALT ≤ 5.0 × ULN

10a. Subjects must have recovered from treatment-related toxicities of prior anticancer therapies to grade ≤ 1 (CTCAE v 5.0).

5.3 Exclusion criteria

5.3.1 Exclusion criteria for all arms

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

1. Subjects with uveal or mucosal melanoma

2a. Presence of clinically active or unstable brain metastasis at time of screening. Note: Subjects with previously unstable brain lesions who have been definitively treated with stereotactic radiation therapy, surgery or gamma knife therapy are eligible.

[redacted]

- Subjects with brain lesions who are untreated (including newly discovered brain lesions during screening) or received whole brain radiation must have documented stable disease as assessed by two consecutive assessments ≥ 4 weeks apart and have not required steroids for at least ≥ 4 weeks prior to randomization/enrollment.

3. Use of any live vaccines against infectious diseases within 3 months before randomization/enrollment.

4a. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization/enrollment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

5a. Active, known or suspected autoimmune disease or a documented history of autoimmune disease. Note: Subjects with vitiligo, controlled type I diabetes mellitus on stable insulin dose, residual autoimmune-related hypothyroidism only requiring hormone replacement or psoriasis not requiring systemic treatment or conditions not expected to recur in the absence of an external trigger are permitted.

6a. Active infection requiring systemic therapy (i.e. antibiotics, anti-virals, high dose steroids, immunosuppressants, or any other systemic therapy) at time of randomization/enrollment.

7. Prior allogenic bone marrow or solid organ transplant

8. History of known hypersensitivity to any of the investigational drugs used in this study

9. Known history or current interstitial lung disease or non-infectious pneumonitis

10. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to start of study treatment; completely resected basal cell and squamous cell skin cancers and any completely resected carcinoma in situ

11. Known history of testing positive for Human Immunodeficiency Virus (HIV) infection

12a. Active Hepatitis B infection (HBsAg positive). Note: Subjects with antecedent of Hepatitis B (anti-HBc positive, HBsAg and HBV-DNA negative) are eligible

13. Subject with positive test for hepatitis C virus (HCV) RNA

14. Pregnant or nursing (lactating) women confirmed by a positive hCG laboratory test within 72 hours prior to initiating study treatment. Note: Low levels of hCG may also be considered a tumor marker, therefore if low hCG levels are detected, another blood sample at least 4 days later must be taken to assess the kinetics of the increase and transvaginal ultrasound must be performed to rule out pregnancy.

15a. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 150-days after last dose of study treatment. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

[redacted]

- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

NOTE: In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Note: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or bilateral 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.

16. Sexually active males unless they use a condom during intercourse while on treatment and for 7 days after the last dose of study treatment and should not father a child in this period. A condom is required to be used by vasectomized men as well during intercourse in order to prevent delivery of the drug via semen.

17a. Prior systemic therapy for unresectable or metastatic melanoma with any investigational agent, or with any other agent, except anti-PD-1/PD-L1 and anti-CTLA-4 (and ^{V600}*BRAF* and MEK inhibitors if subject has ^{V600}*BRAF* mutant disease). Prior neoadjuvant and/or adjuvant therapy for melanoma completed less than 6 months before the start of study treatment.

18. Medical history or current diagnosis of myocarditis

19a. Cardiac Troponin T (TnT) or I (TnI) level > 2 x ULN at screening

5.3.2 Exclusion criteria specific for arm 2 (capmatinib/spartalizumab)

Subject must not meet **any** of the following criteria to be eligible for randomization in arm 2:

20. History or current diagnosis of ECG abnormalities indicating significant risk of safety for subjects participating in the study such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
    - History of familial long QT syndrome or known family history of 'Torsades de Pointes'
21. History of myocardial infarction, angina pectoris, coronary artery bypass graft (CABG) within 6 months prior to randomization.
22. Resting QTcF > 480 msec (as a mean of triplicate ECG)
23. Use of agents known to prolong the QT interval unless it can be permanently discontinued for the duration of study
24. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of capmatinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome).

[redacted]

25. Subjects receiving strong inducers of CYP3A4 that cannot be discontinued or switched at least 1 week prior to randomization and for the duration of the study
26. Serum lipase > ULN
27a. Serum amylase grade > 2 (CTCAE v5.0). Note: Subjects with grade 1 or grade 2 serum amylase elevations at the time of randomization are eligible for Arm 2 if they are confirmed to have no signs or symptoms suggesting pancreatitis or pancreatic injury (e.g., elevated P-amylase, abnormal imaging findings of pancreas, etc)

5.3.3 Exclusion criteria specific for arm 4 (ribociclib/spartalizumab)

Subject must not meet **any** of the following criteria to be eligible for randomization in arm 4:

28a. Standard 12-lead ECG values defined as the mean of the triplicate ECGs:

- QTcF interval at screening > 450 ms (QT interval using Fridericia's correction)
- Mean resting heart rate > 90 bpm (determined from the ECG)

29. Subject with a known hypersensitivity to any of the excipients of ribociclib (eg. ribociclib tablets coating contains soya lecithin, and therefore should not be taken by subjects who are allergic to peanuts or soya).

30a. Subject has clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality, including any of the following:

- History of documented myocardial infarction (MI), angina pectoris, symptomatic pericarditis, or coronary artery bypass graft (CABG) within 6 months prior to study entry
- Documented cardiomyopathy
- Left Ventricular Ejection Fraction (LVEF) < 50% as determined by the multiple gated acquisition (MUGA) scan or echocardiogram (testing is not mandatory)
- Long QT syndrome or 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 hypocalcemia, hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
  - Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued or replaced by safe alternative medication (e.g. within 5 half-lives or 7 days prior to starting study drug, whichever is longer)
  - Inability to determine the QTcF interval
- 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)
- Systolic blood pressure (SBP) >160 or <90 mmH

31. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of ribociclib (e.g., uncontrolled ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
32. Subject is currently receiving any of the following substances and cannot be discontinued 7 days prior to Cycle 1 Day 1:

[redacted]

- Concomitant medications, herbal supplements, and/or fruits (e.g. grapefruit, pomelos, star fruit, Seville oranges) and their juices that are strong inducers or inhibitors of CYP3A4/5;
- Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.

33a. Subject has the following laboratory values outside of normal limits (and uncorrected after the use of supplements) before the first dose of study drug:

- Potassium
- Magnesium
- Total calcium (corrected for serum albumin)

34. Subject has one of the following laboratory values before the first dose of study drug:

- Total bilirubin ≥ ULN (for subjects with Gilbert's syndrome: total bilirubin is > 3.0 × ULN or direct bilirubin > 1.5 × ULN).
- Aspartate transaminase (AST) ≥ 2.5 × ULN (for subjects with liver metastasis: AST is ≥ 5 × ULN)
- Alanine transaminase (ALT) ≥ 2.5 × ULN (for subjects with liver metastasis: ALT is ≥ 5 × ULN)

6 Treatment

6.1 Study treatment

For this study, the terms 'investigational drugs' and 'study drugs' refer to spartalizumab, LAG525, capmatinib, canakinumab and ribociclib.

Eligible subjects will be randomized into one of the following arms and will receive the study treatment, defined as spartalizumab in combination with another investigational drug as described below and in Table 6-1:

- **Arm 1:** LAG525 600 mg Q4W i.v. and spartalizumab 400 mg Q4W i.v.
- **Arm 2:** Capmatinib 400 mg BID p.o and spartalizumab 400 mg Q4W i.v.
- **Arm 3:** Canakinumab 300 mg Q4W s.c. and spartalizumab 400 mg Q4W i.v.
- **Arm 4:** Ribociclib 600 mg QD p.o on days 1 to 21 of a 28-day cycle and spartalizumab 400 mg Q4W i.v.

If a subject does not meet the specific eligibility criteria of an arm the subject will be randomized to an open arm he is eligible for with probability according to the active randomization block.

As dose-regimens for new combinations with spartalizumab become established and a RP2D has been determined, arm(s) will be added under the same master protocol upon protocol amendment. A maximum of 10 arms may be active at any given time under this master protocol.

Subjects eligible for enrollment in the non-randomized arm 1A will receive the following study treatment (also refer to Table 6-1):

- **Arm 1A:** LAG525 600 mg Q4W i.v. and spartalizumab 400 mg Q4W i.v.

[redacted]

All dosages prescribed and dispensed to subjects and all dose modifications (interruption, reduction/escalation, delay) during the study and the reason for the dose modification must be recorded in the eCRF (electronic Case Report Form).

Administration of i.v. investigational drugs (i.e. LAG525, spartalizumab) must take place during in-clinic visits as per the schedule defined in Section 7 and Table 6-1, in a facility with appropriate resuscitation equipment and a physician readily available during the period of drug administration.

Administration of s.c. investigational drugs (i.e. canakinumab) must take place during in-clinic visits as per the schedule defined in Section 7 and Table 6-1.

Oral investigational drugs (capmatinib, ribociclib) will be dispensed by sites to the subjects at study visits scheduled on Day 1 of each 28-day cycle, as per Table 7-2.

6.1.1 Dosing regimen

After randomization/enrollment, subjects will receive the study treatment corresponding to the arm they were randomized/enrolled into as per the dose and schedule of administration defined in Table 6-1 for each investigational drug.

Patient must start study treatment within 3 days after randomization/enrollment.

Each treatment cycle is 28 days.

In-clinic intravenous infusions and s.c. injections of investigational drugs must be scheduled according to the appropriate number of calendar days from the day of first study treatment administration on C1D1.

Table 6-1 Dose and schedule of administration for investigational drugs used in the study

Investigational drug	Arm	Route	Dose	Frequency and/or Regimen (28-day cycles)
Spartalizumab (PDR001)	All arms	i.v.	400 mg	Q4W, on Day 1 of each 28-day cycle
LAG525	Arm 1 and Arm 1A	i.v.	600 mg	Q4W, on Day 1 of each 28-day cycle
Capmatinib (INC280)	Arm 2	p.o.	400 mg	BID (total daily dose 800 mg)
Canakinumab (ACZ885)	Arm 3	s.c.	300 mg	Q4W, on Day 1 of every 28-day cycle
Ribociclib (LEE011)	Arm 4	p.o.	600 mg	QD, on Days 1-21 of each 28-day cycle

6.1.1.1 Spartalizumab

Spartalizumab will be administered via intravenous infusion over 30 minutes (up to 2 hours, if clinically indicated) Q4W (on Day 1 of each 28-day cycle). A dose may be delayed by up to four days. If a dose cannot be administered within the planned window then the dose on that cycle should be skipped.

Guidance on dose modification is provided in Section 6.3. Please refer to Section 6.3.1.2 for the maximum duration allowed for a dose interruption.

The safety assessments should be performed as outlined in Section 7 according to the actual day of infusion.

Patients should be monitored for potential infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever, for at least 2 hours

[redacted]

after the first two infusions. Patients should be instructed how to notify study personnel if symptoms of infusion reaction occur. The same may apply for the subsequent infusions if clinically indicated. Subjects should not receive pre-medication to prevent an infusion reaction before the first infusion of study treatment, in order to determine if pre-medication is necessary.

For premedication guidance after occurrence of potential infusion reactions, please refer to Section 6.1.2.

For further information on spartalizumab, refer to [PDR001J2201 Pharmacy Manual].

6.1.1.2 LAG525

LAG525 will be administered via intravenous infusion over 30 minutes (up to 2 hours, if clinically indicated) Q4W (on Day 1 of each 28-day cycle). A dose may be delayed by up to four days. If a dose cannot be administered within the planned window then the dose on that cycle should be skipped.

The LAG525 infusion should be given prior the spartalizumab infusion. The spartalizumab infusion should start at least 30 minutes and up to 4 hours maximum after the completion of LAG525 infusion. LAG525 must be administered using separate infusion materials (bag, lines, filters) from spartalizumab, however the same access site may be used for both infusions.

Guidance on dose modification is provided in Section 6.3. Please refer to Section 6.3.1.2 for the maximum duration allowed for a dose interruption.

Patients should be monitored for potential infusion-related reactions following LAG525 infusion in the same way as described for spartalizumab in Section 6.1.1.1.

For premedication guidance after occurrence of potential infusion reactions, please refer to Section 6.1.2.

For further information on LAG525, refer to [PDR001J2201 Pharmacy Manual].

6.1.1.3 Capmatinib

Capmatinib will be administered orally on a twice daily (BID) dosing schedule from Day 1 till Day 28 of each 28-day cycle. The starting dose of capmatinib will be 400 mg BID (total daily dose: 800 mg).

On days of co-administration of capmatinib with spartalizumab, subjects should be instructed to take the morning dose of capmatinib during the clinic visit, when instructed by site personnel. The sequence of administration of capmatinib and spartalizumab is left at the investigator's discretion.

[redacted]

Guidance on dose modification is provided in Section 6.3. Please refer to Section 6.3.1.2 for the maximum duration allowed for a dose interruption.

[redacted]

- Subjects should take capmatinib twice daily at approximately the same time each day in the morning and in the evening [redacted]. The morning and the evening doses should be taken 12 (± 4) hours apart, although 12-hour interval is highly recommended. If a dose is not taken within 4 hours of the planned dosing time, the missed dose should not be replaced.
- Capmatinib can be administered with or without food. Each dose of capmatinib is to be taken with a glass of water (at least 8 ounces – approximately 250 mL) and consumed over as short a time as possible (i.e. not slower than 1 tablet every 2 minutes).
- Subjects should be instructed to swallow the tablets whole and not to chew them.
- Subjects should be instructed not to make up for missed doses or partial doses (i.e. when the entire dose is not taken as instructed). A missed or partial dose will be defined as a case when the full dose is not taken within 4 hours of the scheduled twice daily dosing. If that occurs, then the dose (or part remaining dose) should not be taken and dosing should restart with the next scheduled dose. If vomiting occurs, no attempt should be made to replace the vomited dose before the next scheduled dose. Subjects should be instructed to inform the investigational site staff of any missed or delayed doses.
- During the whole duration of treatment with capmatinib, precautionary measures should be taken against ultraviolet exposure (e.g. sunscreen, protective clothing, avoid sun exposure or solarium).

6.1.1.4 Canakinumab

Canakinumab will be administered as subcutaneous injection in the abdomen, upper outer thigh or upper outer arm Q4W (on Day 1 of every 28-day cycle). To administer a target dose of ACZ885 of 300 mg, two separate subcutaneous injections (of 1.0 mL each) must be administered to the patient at a visit and should not be injected in the same site (e.g. if first injection was done in the thigh, the second injection should be done in the opposite thigh). Alternate injection sites should be used throughout the study. A dose may be delayed by up to four days. If a dose cannot be administered within the planned window then the dose on that cycle should be skipped.

The sequence of administration of canakinumab and spartalizumab is left at the investigator's discretion.

Guidance on dose modification is provided in Section 6.3. Please refer to Section 6.3.1.2 for the maximum duration allowed for a dose interruption.

For further information on canakinumab, refer to [PDR001J2201 Pharmacy Manual].

6.1.1.5 Ribociclib

Ribociclib will be administered orally once a day (QD) on Days 1-21 of each 28-day cycle. Days 22-28 will be a "rest period" from ribociclib. The starting dose of ribociclib will be 600 mg QD (total daily dose: 600 mg).

Ribociclib should be taken as follows:

- Ribociclib is dosed for the first 21 days out of each 28-day cycle. The visit schedule should be adhered to, as far as possible. If a cycle x day 1 visit has to be delayed for any reason (within the + 4 day window allowed from planned date per protocol), the rest period of the previous cycle (x-1) can be extended to a maximum of 11 days and the number of days of ribociclib dosing for the cycle x should be adjusted accordingly to

[redacted]

maintain the visit schedule (subject will receive ribociclib for a few days less than 21 days for this cycle). Shortening the rest period to less than 7 days is not recommended.

- Patients should be instructed to take ribociclib with a large glass of water (at least 8 ounces – approximately 250 mL) at the same time each day (Day 1 to 21 of each 28-day cycle). [redacted]
- On scheduled visit days at the clinic, subjects must be instructed to take their dose of ribociclib in the clinic, under the supervision of the investigator or designee, when instructed by site personnel. The sequence of administration of ribociclib and spartalizumab is left at the investigator's discretion. On all other days, subjects may take ribociclib at home. Ribociclib can be administered with or without food.
- [redacted] If a subject vomits within 4 hours of ribociclib dosing, it should be documented in the subject's source documents.
- On a day of chemistry panel, hepatic safety markers and/or lipid panel sampling, subjects must be fasting from all food and drink for at least 12 hours overnight. Water is allowed during all fasting periods; however coffee, tea and juice are not permitted during the fasting period.
- Patients should be instructed to swallow the ribociclib tablets whole and not to chew or crush them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose (no attempt should be made to replace the vomited dose). The occurrence and frequency of any vomiting during a treatment cycle must be documented.
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.
- Patients must avoid consumption of grapefruit, grapefruit hybrids, pomelos/pummelos, starfruit, Seville oranges or products containing their juice during the entire study and preferably 7 days before the first dose of study medications. These foods are known as CYP3A4 inhibitors and have a potential to increase exposure to ribociclib.

  Herbal or dietary supplements known as strong inhibitors or inducers of CYP3A4/5 or those with a known risk of QT prolongation are not permitted. Multivitamins are permitted.

6.1.2 Ancillary treatments for potential infusion reactions with spartalizumab or LAG525

Subjects should not receive pre-medication to prevent an infusion reaction before the first infusion of study treatment, in order to determine if pre-medication is necessary. If a subject experiences an infusion reaction, he/she may receive pre-medication on subsequent dosing days. The pre-medication should be chosen per institutional standard of care, at the discretion of the treating physician. Recommendations for management for infusion reactions can be found in Appendix 3.

[redacted]

Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. If a subject experiences a grade 3 (per CTCAE v5.0) anaphylactic/anaphylactoid reaction, the subject will be permanently discontinued from LAG525/spartalizumab.

The NCI-CTCAE v5.0 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.

Guidelines on management of infusion reactions are provided in Table 6-11 (Mandatory Dose Modifications).

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

Please refer to Section 6.3 for interruption and discontinuation criteria.

6.1.5 Treatment duration

All subjects will start study treatment on C1D1 and will receive study treatment on a 28-day cycle basis until disease progression per RECIST v1.1 (by local assessment), or unacceptable toxicity, start of a subsequent anti-cancer therapy, withdrawal of consent, investigator's decision, lost to follow-up, death, or study is terminated by the sponsor.

Subjects may continue study treatment beyond disease progression by RECIST v1.1 if they derive clinical benefit and if the protocol-specific criteria defined in Section 6.1.5.1 are met.

Subjects should be scheduled for an End of Treatment (EoT) visit within 7 days after permanent discontinuation of the last study drug for any reason to have EoT assessments performed as defined in Section 7.

6.1.5.1 Treatment beyond disease progression

Subjects who derive clinical benefit may continue study treatment beyond RECIST v1.1 disease progression until loss of clinical benefit, unacceptable toxicity, start of subsequent anti-cancer therapy, withdrawal of consent, physician's decision, lost to follow-up, death or study is terminated by sponsor, provided they meet all the following criteria:

- Absence of symptoms and signs (including worsening of clinically relevant laboratory values) indicating disease progression
- Absence of rapid progression of disease
- Continuation will not delay an imminent intervention to prevent serious complications of disease progression (e.g. CNS metastases)
- Subject exhibits adequate tolerance to study treatment
- Subject remains with stable performance status

All study procedures must continue as outlined in Section 7 for subjects who continue treatment beyond disease progression per RECIST v1.1. In case of clinical deterioration or suspicion of disease progression, a follow-up imaging assessment should be performed

[redacted]

promptly rather than waiting for the next scheduled assessment. Subjects who are no longer deriving clinical benefit will be discontinued.

6.2 Dose escalation guidelines

Dose escalations for spartalizumab, LAG525 and canakinumab are prohibited.

If the dose of ribociclib has been reduced per the mandatory dose modification (Section 6.3.1.6), no dose re-escalation is permitted.

If the dose of capmatinib has been reduced per the mandatory dose modification (Section 6.3.1.4), escalation to the previous dose level is permitted if the following criteria are met:

- A period of 4 weeks of treatment has passed since restarting dosing at the reduced dose level and there is no recurrence of the AE.
- The subject is deriving clinical benefit.

6.3 Dose modifications

6.3.1 Mandatory dose modification and dose delay

For subjects who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are mandated for treatment-related adverse events in order to manage subject safety and allow subjects to continue the study treatment.

Dose reductions are only allowed for capmatinib and ribociclib (refer to Section 6.3.1.1). Dose changes for spartalizumab, LAG525 and canakinumab are prohibited.

Table 6-2 summarizes the mandatory dose modifications for specific treatment-related adverse events. If the specific adverse event is not listed, the guideline for 'Other adverse events' must be followed. AEs are to be graded according to NCI-CTCAE v5 (ctep.cancer.gov) and all dose modifications should be based on the worst preceding toxicity. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-5 to Table 6-37 and in Section 6.3.1.5 or listed in Section 7.1.5.

The investigator must follow the dose modifications for the study drug suspected to be related to the event:

- If the event is suspected to be related to spartalizumab, the investigator must follow the dose modifications specific for spartalizumab.
- If the event is suspected to be related to LAG525 or capmatinib or canakinumab or ribociclib, the investigator must follow the dose modifications specific for the suspected study drug.
- If it cannot be distinguished which of the study drugs within the combination is suspected to be related to the event, the investigator must follow the dose modifications specific to both study drugs within the combination.

Recommended management guidelines for suspected immune-related adverse events are provided in Appendix 3 and can be amended according to the local or institutional guidelines.

Except for arm 1 where spartalizumab and LAG525 must be permanently discontinued at the same time, it is allowed for the other arms to discontinue one of the two study drugs within the combination. Permanent study treatment discontinuation is defined as the permanent discontinuation of both study drugs within the combination arm.

[redacted]

Scheduled dosing of spartalizumab, LAG525 and canakinumab may, at the discretion of the investigator, be delayed by up to 4 days if subjects present with conditions that require withholding of dose. Outside of this 4 day window, the dose will be considered missed. After a dose is missed, every effort should be made to return to the original schedule of administration.

Please refer to Section 6.3.1.2 for the maximum duration allowed for a dose interruption for each study drug.

[redacted]

Table 6-2 Reference of AE and specific dose management criteria

Adverse event	Spartalizumab/LAG525	capmatinib	canakinumab	ribociclib
Colitis/Diarrhea	Table 6-5	Table 6-18	Table 6-30	
Hepatic	Table 6-6	Table 6-15	Table 6-27	Table 6-35
Skin	Table 6-7	Table 6-19	Table 6-31	
Renal	Table 6-8	Table 6-14	Table 6-26	
Interstitial lung disease like events/Pneumonitis	Table 6-9	Table 6-20		
Endocrinopathies	Table 6-10			
Infusion reaction and cytokine release syndrome	Table 6-11			
Hematological	Table 6-12	Table 6-13	Table 6-25	Table 6-34
Pancreatitis, amylase and/or lipase elevations		Table 6-16	Table 6-28	
QTc prolongation		Table 6-17		Table 6-36
Vomiting/Nausea		Table 6-18		
Fatigue/Asthenia		Table 6-21	Table 6-32	
Peripheral edema		Table 6-22		
Infections			Table 6-24	
Hypertension			Table 6-29	
Other adverse events	Table 6-12	Table 6-23	Table 6-33	Table 6-37

6.3.1.1 Dose reductions

Dose reductions for spartalizumab, LAG525 and canakinumab are prohibited.

Dose reductions are only allowed for capmatinib and ribociclib. All dose reductions should be based on the worst preceding toxicity demonstrated at the last dose. Dose reduction must follow the dose reduction steps described in Table 6-3 for capmatinib and in Table 6-4 for ribociclib. For each subject, a maximum of 2 dose level modifications are allowed after which the subject must be discontinued from treatment with capmatinib/ribociclib (reduction below dose level -2 is not allowed: subjects on dose level -2 necessitating further dose reduction due to an adverse event must permanently discontinue capmatinib/ribociclib). Altering from BID dosing schedule for capmatinib is not allowed.

Table 6-3 Dose reduction steps for capmatinib

Capmatinib dose levels	Capmatinib daily dose
Starting dose level	400 mg BID (= 2 x 200 mg tablets twice in a day; 800 mg total daily dose)
Dose level -1	300 mg BID (= 2 x 150 mg tablets twice in a day; 600 mg total daily dose)
Dose level -2	200 mg BID (= 1 x 200 mg tablets twice in a day; 400 mg total daily dose)

Table 6-4 Dose reduction steps for ribociclib

Ribociclib dose levels	Ribociclib daily dose
Starting dose level	600 mg QD (= 3 x 200 mg tablets once in a day; 600 mg total daily dose)
Dose level -1	400 mg QD (= 2 x 200 mg tablets once in a day; 400 mg total daily dose)
Dose level -2	200 mg QD (= 1 x 200 mg tablets once in a day; 200 mg total daily dose)

[redacted]

6.3.1.2 Maximum duration of study drug(s) interruption

If the treatment with spartalizumab is interrupted for more than 12 weeks (counted from the time the AE reaches a grade that leads to spartalizumab interruption), spartalizumab must be permanently discontinued.

If the treatment with LAG525 is interrupted for more than 12 weeks (counted from the time the AE reaches a grade that leads to LAG525 interruption), LAG525 must be permanently discontinued.

If the treatment with capmatinib is interrupted for more than 3 consecutive weeks (counting from the first day when a dose was interrupted), then capmatinib must be permanently discontinued.

If the treatment with ribociclib is interrupted for more than 28 consecutive days due to ribociclib-related toxicity (counting from the first day when a dose was interrupted, including the 7 days of planned interruption of dosing between Day 22-28 of a cycle), then ribociclib must be permanently discontinued.

If the treatment with canakinumab is interrupted for more than 4 weeks (counted from the intended day of the next scheduled dose), canakinumab must be permanently discontinued.

6.3.1.3 Mandatory dose modification for spartalizumab and LAG525

No changes in dose of spartalizumab and LAG525 are allowed. Overall, subjects with AE suspected to be related to spartalizumab and LAG525 including those of potential immune-mediated etiology (irAEs) may need to interrupt or permanently discontinue spartalizumab or/and LAG525 as outlined below, in Section 6.3.1.3.2 and in Table 6-5 to Table 6-12 or as listed in Section 7.1.5.

In general, spartalizumab or/and LAG525 must be permanently discontinued in case of:

- Any life-threatening adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy)
- Persistent grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to ≤ Grade 1 within 12 weeks
- Inability to reduce the dose of steroids (for the management of irAEs) to ≤ 10 mg/day prednisone or equivalent within 12 weeks.
- Any severe or grade 3 recurring treatment-related adverse reaction
- Any grade 4 irAE

Note: the 12 week timeframe will begin from the time the irAE reaches a Grade that leads to spartalizumab/LAG525 interruption.

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

Steroids should be tapered slowly and based on response/recovery of clinical symptoms. Consider to complete tapering over a period of at least 4 weeks. Slower tapering of corticosteroids therapy may be recommended if the adverse event is not showing improvement. If dose level of ≤ 10 mg of prednisone (or equivalent) is achieved, spartalizumab or/and LAG525 can be restarted as indicated in Table 6-5 to Table 6-12.

[redacted]

6.3.1.3.2 Dose modification for potential immune-mediated adverse events (irAEs)

Adverse events of special interest include irAEs that are associated with spartalizumab/LAG525 treatment. An irAE may be experienced by subjects treated with spartalizumab or/and LAG525 due to their mechanism of action and predicted based on the reported experience with other checkpoint inhibitors that have a similar mechanism of action. 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 adequate management and resolution.

Immune-related adverse events may be of low grade and self-limited, most frequently involving the gastrointestinal tract (e.g. diarrhea/colitis), skin (e.g. rashes, pruritus), liver (e.g. hepatitis), lung (e.g. pneumonitis), kidneys (e.g. nephritis) and endocrine systems (e.g. hypothyroidism, hyperthyroidism, type I diabetes, hypophysitis including hypopituitarism and adrenal insufficiency). Other immune-related 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 patients 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 treatment discontinuation. Serological, immunological and histological assessments should be performed as deemed appropriate by the investigator, to verify the potential immune-mediated nature of the AE, and exclude neoplastic, infectious or metabolic origin of the AE.

Severe grade or persistent lower grade irAEs typically require treatment interruption or permanent discontinuation of treatment and administration of systemic steroids, and sometimes other immunosuppressive medications (i.e. TNFα antagonists, mycophenolate or tacrolimus, etc.). 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 to avoid recurrence or worsening of irAE (Section 6.3.1.3.1). The management of irAEs may further include initiation of antibiotics for prophylaxis against opportunistic infections.

Subjects 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. Subjects who experience a new or worsening irAE should be contacted and/or evaluated by the study site more frequently as applicable.

Table 6-5 Colitis/diarrhea suspected to be related to spartalizumab or spartalizumab/LAG525

Grade (CTCAE v5)	Mandatory dose modification
Grade 2	If diarrhea is grade 2, despite loperamide at 2 mg every 2 hours for > 48h: Interrupt spartalizumab/LAG525 until recovery to grade ≤ 1 • Restart spartalizumab/LAG525 at the same dose level

[redacted]

Grade (CTCAE v5)	Mandatory dose modification
Grade 3	1st occurrence Interrupt spartalizumab/LAG525 until recovery to grade ≤ 1 or baseline • Restart spartalizumab/LAG525 at the same dose level 2nd occurrence Permanently discontinue spartalizumab/LAG525
Grade 4	Permanently discontinue spartalizumab/LAG525

Table 6-6 Abnormal liver tests suspected to be related to spartalizumab or LAG525/spartalizumab

Grade (CTCAE v5)	Mandatory dose modification
Grade 2	Interrupt LAG525/spartalizumab until recovery to grade ≤ 1 or baseline • Restart spartalizumab/LAG525 at the same dose level Patients with baseline grade 2 AST/ALT values may continue spartalizumab/LAG525
Grade 3 or 4	Permanently discontinue spartalizumab/LAG525 Patients with baseline grade 2 AST/ALT values must permanently discontinue spartalizumab/LAG525 treatment if value increased to grade 3 with increase ≥ 2 × baseline

Table 6-7 Rash/skin events suspected to be related to spartalizumab or spartalizumab/LAG525

Grade (CTCAE v5)	Mandatory Dose Modifications
Grade 2 (e.g. rash 10 to 30% BSA, pruritus)	If tolerable: continue spartalizumab/LAG525 If intolerable (or in case of bullous dermatitis, acute generalized exanthematous pustulosis or Drug Reaction with Eosinophilia and Systemic Symptoms): interrupt spartalizumab/LAG525 until tolerable or recovery to grade ≤ 1 or baseline • Restart spartalizumab/LAG525 at the same dose level
Grade 3 (e.g. rash > 30% BSA, pruritus) Other severe cutaneous adverse reactions Bullous dermatitis	1st occurrence Interrupt spartalizumab/LAG525 until recovery to grade ≤ 1 or baseline • Restart spartalizumab/LAG525 treatment at the same dose level. For patients with severe cutaneous adverse reaction or bullous dermatitis, risk/benefit before resuming treatment should be carefully considered. 2nd occurrence Permanently discontinue spartalizumab/LAG525
Grade 4: Life-threatening	Permanently discontinue spartalizumab/LAG525
Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)	Permanently discontinue spartalizumab/LAG525

Table 6-8 Creatinine alterations suspected to be related to spartalizumab or spartalizumab/LAG525

Grade (CTCAE v5)	Mandatory Dose Modification
Grade 2 (> 1.5 - 3.0 x ULN, or >1.5-3.0 x baseline if baseline was elevated)	Interrupt spartalizumab/LAG525 until recovery to ≤ grade 1 or baseline • Restart spartalizumab/LAG525 at the same dose level
Grade 3 (> 3.0 - 6.0 x ULN; or >3x baseline if baseline was elevated)	Permanently discontinue spartalizumab/LAG525
Grade 4 (> 6.0 x ULN)	Permanently discontinue spartalizumab/LAG525

Table 6-9 Pneumonitis suspected to be related to spartalizumab or spartalizumab/LAG525

Grade (CTCAE v5)	Mandatory dose modification
Grade 2	1st occurrence Interrupt spartalizumab/LAG525 until recovery to grade ≤ 1 or baseline • Restart spartalizumab/LAG525 at the same dose level 2nd occurrence Permanently discontinue spartalizumab/LAG525
Grade 3 or 4	Permanently discontinue spartalizumab/LAG525

Table 6-10 Endocrinopathies suspected to be related to spartalizumab or spartalizumab/LAG525

Grade (CTCAE v5)	Mandatory dose modification
Symptomatic endocrinopathies (e.g. hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism)	Interrupt spartalizumab/LAG525 until recovery to mild or no symptoms, and controlled with hormone replacement therapy • Once recovered or controlled with hormone replacement, restart spartalizumab/LAG525 at the same dose level Hypothyroidism may be managed with replacement therapy without study treatment interruption (unless life-threatening) Permanently discontinue spartalizumab/LAG525 for any life-threatening endocrinopathies (i.e. hyperthyroidism, adrenal insufficiency, hypophysitis) or recurring severe/life-threatening events which cannot be controlled with replacement therapy
Autoimmune diabetes (Grade 3 or symptomatic hyperglycemia)	1st occurrence Interrupt spartalizumab/LAG525 until recovery to grade 1 or baseline • Restart spartalizumab/LAG525 at the same dose level 2nd occurrence Permanently discontinue spartalizumab/LAG525
Autoimmune diabetes (Grade 4 hyperglycemia or life-threatening complications)	Permanently discontinue spartalizumab/LAG525

Table 6-11 Infusion reactions and cytokine release syndrome suspected to be related to spartalizumab or spartalizumab/LAG525

Grade (CTCAE v5)	Mandatory dose modification
Grade 2	Permanently discontinue spartalizumab/LAG525 in case of recurring infusion reaction despite adequate premedication and prolonged infusion/slow infusion rate
Grade 3 or 4	Permanently discontinue spartalizumab/LAG525

Table 6-12 Other adverse events suspected to be related to spartalizumab or spartalizumab/LAG525

Grade (CTCAE v5)	Mandatory dose modification
Grade 3	1st occurrence Interrupt spartalizumab/LAG525 until recovery to ≤ grade 1 or baseline • Restart spartalizumab/LAG525 treatment at the same dose level 2nd occurrence Permanently discontinue spartalizumab/LAG525
Grade 4	Permanently discontinue spartalizumab/LAG525
Encephalitis (any Grade) or aseptic meningitis Guillain-Barre Severe peripheral or autonomic neuropathy, or transverse myelitis	Permanently discontinue spartalizumab/LAG525
Myasthenia gravis	Grade 2 • Interrupt spartalizumab/LAG525 until recovery to ≤ Grade 1 or baseline

Grade (CTCAE v5)	Mandatory dose modification
	Grade ≥3 • Permanently discontinue spartalizumab/LAG525
Myocarditis (any grade) or other cardiac events Grade ≥ 3	Permanently discontinue spartalizumab/LAG525 (refer to Table 14-17 for recommended management guidelines for those events)
Pancreatitis Amylase/lipase elevation	Grade 2 acute pancreatitis • Interrupt spartalizumab/LAG525 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	Permanently discontinue spartalizumab/LAG525
Ocular events	Grade 2 • Interrupt spartalizumab/LAG525 until recovery to ≤ Grade 1 or baseline Grade 3 and 4 • Permanently discontinue spartalizumab/LAG525

6.3.1.4 Mandatory dose modifications for capmatinib

All dose modifications should be based on the worst preceding toxicity. Capmatinib dose reduction must follow the dose reduction steps described in Table 6-3 in Section 6.3.1.1. Dose escalation after previous dose reduction due to an adverse event is allowed as described in Section 6.2.

Table 6-13 Hematological adverse events suspected to be related to capmatinib

Grade (CTCAE v5)	Mandatory dose modifications
Neutrophil count decreased (ANC)	
Grade 3	Interrupt capmatinib until recovery to grade ≤ 2 • If resolved ≤ 7 days, restart at the same dose level • If not resolved within 7 days, restart at reduced dose level
Grade 4	Interrupt capmatinib until recovery to ≤ grade 2, then restart at reduced dose level
Febrile neutropenia	Interrupt capmatinib • If resolved in ≤ 7 days, restart at reduced dose level • If not resolved within 7 days, permanently discontinue capmatinib
Thrombocytopenia	
Grade 3 without clinically significant bleeding	Continue capmatinib at the same dose level
Grade 3 with clinically significant bleeding	Interrupt capmatinib until recovery to grade ≤ 2 • If resolved ≤ 7 days, restart at the same dose level • If not resolved within 7 days, restart at reduced dose level
Grade 4	Interrupt capmatinib until recovery to grade ≤ 2, then restart at reduced dose level. If toxicity recurs, permanently discontinue capmatinib

Table 6-14 Creatinine alterations suspected to be related to capmatinib

Grade (CTCAE v5)	Mandatory dose modifications
Grade 2 (> 1.5 - 3.0 x ULN; or >1.5-3.0 x baseline if baseline was elevated) OR Grade 3 (> 3.0 - 6.0 x ULN; or >3x baseline if baseline was elevated)	Interrupt capmatinib until recovery to grade ≤ 1 or baseline • If resolved in ≤ 7 days: restart capmatinib at reduced dose level • If not resolved within 7 days, permanently discontinue capmatinib
Grade 4 (> 6.0 x ULN)	Permanently discontinue capmatinib

[redacted]

Table 6-15 Abnormal liver test results suspected to be related to capmatinib

Grade (CTCAE v5)	Mandatory dose modifications
Isolated total bilirubin elevation - For patient's whose baseline total bilirubin is ≤ ULN	
Grade 1 (>ULN - 1.5 x ULN)	Maintain dose level of capmatinib and monitor liver enzymes
Grade 2 (>1.5 - 3.0 x ULN)	Interrupt capmatinib until recovery to grade ≤ 1 • If resolved in ≤ 7 days, restart at the same dose level • If not resolved within 7 days, restart at reduced dose level
Grade 3 (>3.0 - 10.0 x ULN) [c]	Interrupt capmatinib until recovery to grade≤ 1, • If resolved in ≤ 7 days, restart at reduced dose level • If not resolved within 7 days, permanently discontinue capmatinib
Grade 4 (>10.0 x ULN)	Permanently discontinue capmatinib
Isolated total bilirubin elevation - For patient's whose baseline total bilirubin is > ULN [b]	
Grade 1 > 1.0 - 1.5 x baseline if baseline was abnormal	Maintain dose level of capmatinib and monitor liver enzymes.
Grade 2 >1.5 – 3.0 × above baseline if baseline was abnormal	Interrupt capmatinib until recovery to baseline • If resolved in ≤ 7 days, restart at the same dose level • If not resolved within 7 days, restart at reduced dose level
Grade 3 >3.0 -10x above baseline if baseline was abnormal	Interrupt capmatinib until recovery to baseline • If resolved in ≤ 7 days, resume treatment at reduced dose level • If not resolved within 7 days, permanently discontinue capmatinib
Grade 4 (> 10.0 × ULN) [b] if baseline was abnormal	Permanently discontinue capmatinib
Isolated AST or ALT elevation for patient's baseline AST/ALT are ≤ ULN	
Grade 1 and 2 (> ULN - 5.0 × ULN)	Maintain dose level of capmatinib
Grade 3 (> 5.0 – 20.0 × ULN)	Interrupt capmatinib until recovery to grade ≤ 1, • If resolved in ≤ 7 days, restart treatment at reduced dose level • If not resolved within 7 days, permanently discontinue capmatinib
Grade 4 (>20.0 × ULN)	Permanently discontinue capmatinib
Isolated AST or ALT elevation for patient's baseline AST or ALT are > ULN	
Grade 2 (> 3.0 – 5.0 × baseline value)	Interrupt capmatinib until recovery to grade ≤ 1 or baseline • If resolved in ≤ 7 days, restart at reduced dose level • If not resolved within 7 days, permanently discontinue capmatinib
Grade ≥ 3 (> 5.0 × baseline value)	Permanently discontinue capmatinib
Combined [a, d] elevations of AST or ALT and total bilirubin	
For patients with normal baseline ALT or AST or total bilirubin value: AST or ALT >3.0 × ULN combined with total bilirubin >2.0 × ULN without evidence of cholestasis [c] OR For patients with elevated baseline AST or ALT or total bilirubin value [AST or ALT>2 × baseline AND > 3.0 × ULN] OR [AST or ALT > 8.0 × ULN], combined with [total bilirubin >2x baseline] AND >2.0 × ULN without evidence of cholestasis [c]	Permanently discontinue capmatinib in the absence of signs of cholestasis, hemolysis, and alternative causes of the liver injury have been excluded (e.g., concomitant use of hepatotoxic drug(s), alcoholic hepatitis, etc.).
[a] 'Combined' defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold.	

Grade (CTCAE v5)	Mandatory dose modifications
[b] If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g. review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the Investigator. [c] 'Cholestasis' defined as: ALP elevation (> 2 x ULN and R value (ALT/ALP in x ULN) < 2) in patients without bone metastases, or elevation of ALP liver fraction in patients with bone metastases. Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestasis (R≤2), hepatocellular (R≥5), or mixed (R>2 and <5) liver injury. [d] If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g., discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start treatment either at the same dose or one dose lower if meeting a criterion for dose reduction.	

Table 6-16 Pancreatitis, amylase and lipase elevations suspected to be related to capmatinib

Grade (CTCAE v5)	Mandatory dose modification
Pancreatitis	
Grade ≥ 3	Permanently discontinue capmatinib
Asymptomatic amylase and/or lipase elevation	
Grade 3 (> 2.0 - 5.0 × ULN with signs or symptoms; >5.0 x ULN and asymptomatic)	Interrupt capmatinib until resolved to grade ≤ 2 • If resolved in ≤ 14 days, restart at same dose level • If not resolved within 14 days, restart at reduced dose level
Grade 4 (> 5.0 × ULN and with signs or symptoms)	Permanently discontinue capmatinib
Symptomatic elevations	
Any grade	Permanently discontinue capmatinib

Table 6-17 QTc prolongations suspected to be related to capmatinib (Further guidance is provided in Section 6.3.2)

Grade (CTCAE v5)	Mandatory dose modification
Grade 3 (Average QTcF ≥ 501 ms; >60ms change from baseline)	Interrupt capmatinib until resolved to grade ≤ 2, • If resolved ≤ 7 days, restart at the same dose level • If not resolved within 7 days, restart at reduced dose level
Grade 4 (Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Permanently discontinue capmatinib

Table 6-18 Diarrhea, vomiting or nausea suspected to be related to capmatinib

Grade (CTCAE v5)	Mandatory dose modification
Diarrhea	
Grade 2 (despite maximal anti-diarrheal medication)	Interrupt capmatinib until resolved to grade≤ 1, then restart at same dose level • If diarrhea returns as grade ≥ 2, interrupt capmatinib until resolved grade ≤ 1, then restart at reduced dose level
Grade 3 or 4 (despite maximal anti-diarrheal medication)	Interrupt capmatinib until resolved to grade ≤ 1, then restart at reduced dose level
Vomiting	
Grade 2 (despite standard anti-emetics)	Interrupt capmatinib until resolved to grade ≤ 1, then restart at same dose level

Grade (CTCAE v5)	Mandatory dose modification
	If vomiting returns as grade ≥ 2, interrupt capmatinib until resolved to grade≤ 1, then restart at reduced dose level
Grade 3 and 4 (despite standard anti-emetics)	Interrupt capmatinib until resolved to grade ≤ 1, then restart at reduced dose level
Nausea	
Grade 3 (despite standard anti-emetics)	Interrupt capmatinib until resolved to grade ≤ 1, then restart at reduced dose level

Table 6-19 Skin events suspected to be related to capmatinib

Grade (CTCAE v5)	Mandatory dose modification
Grade 3, despite skin toxicity therapy	Interrupt capmatinib until resolved to grade ≤ 1, • If resolved in ≤ 7 days, restart at reduced dose level • If not resolved within 7 days (despite appropriate skin toxicity therapy), permanently discontinue capmatinib
Grade 4, despite skin toxicity therapy	Permanently discontinue capmatinib
* During the whole duration of treatment with capmatinib, the patient is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing and avoid sunbathing or using a solarium extensively).	

Table 6-20 Pneumonitis or interstitial lung disease (ILD) suspected to be related to capmatinib

Grade (CTCAE v5)	Mandatory dose modification
Grade 1	Interrupt capmatinib during diagnostic workup for pneumonitis/ILD If ILD/pneumonitis is confirmed permanently discontinue capmatinib Restart at reduced dose level upon resolution • If pneumonitis does not resolve within 6 weeks, permanently discontinue capmatinib. 2nd recurrence Interrupt capmatinib until resolved, then restart at reduced dose level. • If pneumonitis does not resolve within 6 weeks, permanently discontinue capmatinib. 3rd recurrence Permanently discontinue capmatinib.
Grade 2	Interrupt capmatinib dose during diagnostic workup until improvement to ≤ grade1. If ILD/pneumonitis is confirmed permanently discontinue capmatinib If ILD/pneumonitis is NOT confirmed: • if symptoms resolve to ≤ grade 1 in ≤ 7 days, restart at reduced dose level • If symptoms do not resolve within 7 days or recur after dose reduction, permanently discontinue capmatinib.
Grade 3 or 4	Permanently discontinue capmatinib

Table 6-21 Fatigue/asthenia suspected to be related to capmatinib

Grade (CTCAE v5)	Mandatory dose modification
Grade 3	Interrupt capmatinib until resolved to Grade≤ 1 • If resolved in ≤ 7 days, restart at same dose level • If not resolved within 7 days, restart at reduced dose level
Grade 4	Permanently discontinue capmatinib

Table 6-22 Peripheral edema suspected to be related to capmatinib

Grade (CTCAE v5)	Mandatory dose modification
Grade 3	Interrupt capmatinib until resolved to grade ≤ 1, then restart at reduced dose level

[redacted]

Grade (CTCAE v5)	Mandatory dose modification
Grade 4	Permanently discontinue capmatinib

Table 6-23 Other adverse events suspected to be related to capmatinib

Grade (CTCAE v5)	Mandatory dose modification
Grade 1 or 2	Maintain dose level of capmatinib, consider initiating appropriate support medication For any intolerable grade 2 (e.g. limiting instrumental ADL), consider interrupting the dose until resolved to grade ≤ 1, then restart at reduced dose level
Grade 3	Interrupt capmatinib until resolved to grade ≤ 2, then restart at reduced dose level
Grade 4	Permanently discontinue capmatinib
Myocarditis (any grade) or other cardiac events Grade ≥ 3	Permanently discontinue capmatinib (refer to Table 14-17 for recommended management guidelines for those events)

6.3.1.5 Mandatory dose modifications for canakinumab

Table 6-24 Infections suspected to be related to canakinumab

Grade (CTCAE v5)	Mandatory dose modifications
Grade 3	Interrupt canakinumab until resolved to ≤ grade 2, then restart at the same dose level
Grade 4	Permanently discontinue canakinumab

Table 6-25 Hematological adverse events suspected to be related to canakinumab

Grade (CTCAE v5)	Mandatory dose modification
Neutropenia	
Grade 3 (ANC < 1000 - 500/mm^3)	Interrupt canakinumab until resolved to ≤ grade 2, then restart at the same dose level
Grade 4 (ANC < 500/mm^3)	Permanently discontinue canakinumab
Febrile neutropenia	
ANC <1.0 × 10^9/L, fever ≥ 38.5°C	Permanently discontinue canakinumab
Thrombocytopenia	
Grade 3 (< 50,000 - 25,000/mm^3)	Interrupt canakinumab until resolved to ≤ grade 1 • If resolved in ≤ 7 days, restart at same dose • If not resolved within 7 days, permanently discontinue canakinumab
Grade 4 (< 25,000/mm^3)	Permanently discontinue canakinumab

Table 6-26 Creatinine alterations suspected to be related to canakinumab

Grade (CTCAE v5)	Mandatory dose modification
Grade 3 (> 3.0 - 6.0 × ULN; or >3.0 x baseline if baseline was elevated)	Interrupt canakinumab until resolved to ≤ grade 2 or baseline • If resolved in ≤ 14 days, then restart at the same dose level • If not resolved within 14 days, permanently discontinue canakinumab
Grade 4 (> 6.0 x ULN)	Permanently discontinue canakinumab

Table 6-27 Hepatic adverse events suspected to be related to canakinumab

Grade (CTCAE v5)	Mandatory dose modifications
Isolated total Bilirubin elevation	
Grade 2 (> 1.5 - 3.0 × ULN; >1.5 - 3.0 x baseline if baseline was abnormal)	Interrupt canakinumab and monitor liver test[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 × ULN • If resolved in ≤ 14 days, restart at same dose level

Grade (CTCAE v5)	Mandatory dose modifications
	• If not resolved within 14 days, permanently discontinue canakinumab
Grade 3 (> 3.0 - 10.0 × ULN*; >3.0 - 10.0 x baseline if baseline was abnormal)	Interrupt canakinumab and monitor liver test[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 × ULN • If resolved in ≤ 14 days, then restart at the same dose level • If not resolved within 14 days, permanently discontinue canakinumab. The subject should be monitored weekly (including liver test[a]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
Grade 4 (> 10.0 × ULN*; >10.0 x baseline if baseline was abnormal)	Permanently discontinue canakinumab. The subject should be monitored weekly (including liver test[a]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
Isolated AST or ALT elevation	
Grade 2 (> 3.0 - 5.0 × ULN; >3.0 - 5.0 x baseline if baseline was abnormal)	Continue canakinumab at the same dose level Repeat liver test[a] within 48-72 hours; if abnormal values are confirmed upon the repeat test, then monitor liver test[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 × ULN
Grade 3 > 5.0 - 10.0 × ULN; >5.0 – 10 x baseline if baseline was abnormal	Interrupt canakinumab. Repeat liver test[a] within 48-72 hours; monitor liver test[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 × ULN. • If resolved in ≤ 28 days, restart canakinumab at same dose • If not resolved within 28 days, permanently discontinue canakinumab
> 10.0 - 20.0 × ULN' >10 - 20 x baseline if baseline was abnormal	Permanently discontinue canakinumab Repeat liver test[a] within 48-72 hours. Monitor liver test[a] weekly, or more frequently if clinically indicated, until resolved to ≤ baseline
Grade 4 (> 20.0 × ULN; >20.0 x baseline if baseline was abnormal)	Permanently discontinue canakinumab Repeat liver test[a] within 48-72; monitor liver test[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3 × ULN
Combined [b] elevations of AST or ALT and total bilirubin	
For subjects with normal baseline ALT and AST and total bilirubin value: AST or ALT >3.0 × ULN combined with total bilirubin >2.0 × ULN without evidence of cholestasis[c]	Permanently discontinue canakinumab Repeat liver test[a] within 48-72; monitor liver test[a] weekly or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks.

[a]Core liver tests consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 × ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 × ULN.)

[b] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold. If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction.

[c] "Cholestasis" defined as ALP elevation (>2.0 × ULN and R value <2) in subjects without bone metastasis, or elevation of ALP liver fraction in subjects 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 ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury.

* If total bilirubin > 3.0 × ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), continue treatment at the discretion of the investigator.

[redacted]

Table 6-28 Pancreatitis, amylase and/or lipase elevations suspected to be related to canakinumab

Grade (CTCAE v5)	Mandatory dose modification
Pancreatitis	
Grade ≥ 3	Permanently discontinue canakinumab
Asymptomatic amylase and/or lipase elevation[*]	
Grade 3 (> 2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic)	Interrupt canakinumab until resolved to grade≤ ,1 or baseline • If resolved in ≤ 7 days, restart at same dose level • If not resolved within 7 days, permanently discontinue canakinumab
Grade 4 (> 5.0 x ULN and with signs or symptoms)	Permanently discontinue canakinumab
[*]A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, subjects will be discontinued permanently from study treatment.	

Table 6-29 Hypertension suspected to be related to canakinumab

Grade (CTCAE v5)	Mandatory dose modification
Grade 3	Interrupt canakinumab until resolved ≤ grade 1, then restart at same dose level
Grade 4	Permanently discontinue canakinumab

Table 6-30 Diarrhea suspected to be related to canakinumab

Grade (CTCAE v5)	Mandatory dose modifications
Grade 2	Interrupt canakinumab until resolved to ≤ Grade1, then restart at same dose level
Grade 3	Permanently discontinue canakinumab
Grade 4	Permanently discontinue canakinumab

Table 6-31 Skin related toxicities suspected to be related to canakinumab

Grade (CTCAE v5)	Mandatory dose modification
Grade 3, despite skin toxicity therapy	Interrupt canakinumab until resolved to Grade≤ 1 • If resolved in ≤ 7 days, restart at same dose level • If not resolved within 7 days (despite appropriate skin toxicity therapy), permanently discontinue canakinumab
Grade 4, despite skin toxicity therapy	Permanently discontinue canakinumab

Table 6-32 Fatigue/asthenia suspected to be related to canakinumab

Grade (CTCAE v5)	Mandatory dose modifications
Grade 3	Interrupt canakinumab until resolved to ≤ grade1 • If resolved in ≤ 14 days, restart at same dose level • If not resolved within 14 days, permanently discontinue canakinumab

Table 6-33 Other adverse events suspected to be related to canakinumab

Grade (CTCAE v5)	Mandatory dose modification
Grade 3	Interrupt canakinumab until resolved to ≤ grade 1, restart at the same dose level
Grade 4, except alopecia	Permanently discontinue canakinumab

6.3.1.6 Mandatory dose modifications for ribociclib

Table 6-34 Hematological adverse events suspected to be related to ribociclib

Grade (CTCAE v5)	Mandatory dose modification
Thrombocytopenia	
Grade 2 (≥50 x 10^9/L – <75 x 10^9/L)	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib at the same dose.
Grade 3 (≥25 x 10^9/L – <50 x 10^9/L)	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib at the same dose level. If toxicity recurs at grade 3: temporary dose interruption until recovery to grade ≤1 and reduce ribociclib to the next lower dose level.
Grade 4 (<25 x 10^9/L)	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib at the next lower dose level. If toxicity recurs at grade 4: discontinue ribociclib
Absolute neutrophil count (ANC)	
Grade 3 (≥0.5 x 10^9/L – <1.0 x 10^9/L)	Dose interruption until recovery to ≥1.0 x 10^9/L. Re-initiate ribociclib at the same dose level. If toxicity recurs at grade 3: temporary dose interruption until recovery to ≥ 1.0 x 10^9/L. If resolved in ≤7 days, then maintain dose level. If resolved in >7 days, then reduce ribociclib dose to the next lower dose level.
Grade 4 (<0.5 x 10^9/L)	Dose interruption until recovery to ≥ 1.0 x 10^9/L. Re-initiate ribociclib at the next lower dose level.
Febrile neutropenia	
Grade 3 ANC <1.0 x 10^9/L with a single temperature of >38.3 ºC (101 ºF) or a sustained temperature of ≥38 ºC (100.4 ºF) for more than one hour	Dose interruption until improvement of ANC ≥ 1.0 x 10^9/L and no fever. Restart at the next lower dose level. If febrile neutropenia recurs, discontinue ribociclib.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib.
Anemia (Hemoglobin)	
Grade 3 (<8.0 g/dL)	Dose interruption until recovery to grade ≤ 2. Re-initiate ribociclib at the same dose.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib.

Table 6-35 Abnormal liver tests suspected to be related to ribociclib

Grade (CTCAE v5)	Mandatory dose modification
TOTAL BILIRUBIN without ALT/AST increase above baseline value	
Grade 1 (> ULN – 1.5 x ULN) (confirmed 48-72h later)	No dose adjustment required with LFTs monitored every 2 weeks
Grade 2 (> 1.5 – 3.0 x ULN)	Dose interruption of ribociclib If resolved to ≤ grade 1 in ≤ 21 days, then maintain dose level If resolved to ≤ grade 1 in > 21-28 days or toxicity recurs, then reduce to the next lower dose level Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption

[redacted]

	If toxicity recurs after two dose reductions, or recovery to ≤ grade 1 is > 28 days, discontinue ribociclib
Grade 3 (> 3.0 – 10.0 x ULN)	Dose interruption of ribociclib, until resolved to ≤ grade 1 , then reduce to the next lower dose level Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If resolved to ≤ grade 1 in > 28 days or toxicity recurs, discontinue ribociclib
Grade 4 (> 10.0 x ULN)	Discontinue ribociclib
Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of liver metastases, evidence of obstruction, such as elevated ALP and GGT typical of gallbladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤ 1 x ULN) due to hemolysis or Gilbert Syndrome, other pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.	
AST or ALT without bilirubin elevation > 2 x ULN	
Same grade as baseline or increase from baseline grade 0 to grade 1 (confirmed 48 – 72 h later)	No dose adjustment required with LFTs monitored per protocol if same grade as baseline or every 2 weeks in case of increase from baseline grade 0 to 1
Increase from baseline grade 0 or 1 to grade 2 (> 3.0 – 5.0 x ULN)	Dose interruption of ribociclib If resolved to ≤ baseline grade in ≤ 21 days, then maintain dose level If resolved to ≤ baseline grade in > 21 days or toxicity recurs, then reduce to the next lower dose level Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity recurs after two dose reductions or recovery to ≤ baseline grade is > 28 days, discontinue ribociclib
Increase from baseline grade 0 or 1 to grade 3 (> 5.0 – 20.0 x ULN)	Dose interruption of ribociclib until resolved to ≤ baseline grade, then reduce to the next lower dose level Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If recovery to ≤ baseline grade is > 28 days, discontinue ribociclib If toxicity recurs, discontinue ribociclib
Increase from baseline grade 2 to grade 3 (> 5.0 – 20.0 x ULN)	Dose interruption of ribociclib until resolved to ≤ baseline grade, then reduce to the next lower dose level Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity recurs after two dose reductions or recovery to ≤ baseline grade is > 28 days, discontinue ribociclib.
Grade 4 (> 20.0 x ULN)	Discontinue ribociclib
AST or ALT and concurrent Bilirubin	
For patients with normal ALT and AST and total bilirubin at baseline: AST or ALT >3.0 x ULN combined with total bilirubin > 2 x ULN without evidence of cholestasis OR For patient with elevated AST or ALT or total bilirubin at baseline: [AST or ALT >2 x baseline AND >3.0x ULN] OR [AST or ALT > 8.0 x ULN]- whichever is lower- **combined with** [total bilirubin > 2 x baseline AND >2.0 x ULN]	Discontinue ribociclib

[redacted]

Table 6-36 QTcF prolongation suspected to be related to ribociclib

Grade (CTCAE v5)	Mandatory dose modification
For All Grades	1. Check the quality of the ECG and the QT value and repeat if needed. 2. Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If outside of the normal range, interrupt ribociclib administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. 3. Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. 4. Check compliance with correct dose and administration of ribociclib. [redacted]
Grade 1* QTcF 450-480 ms	Perform steps 1-4 as directed in "For All Grades." No dose adjustment required.
Grade 2* QTcF 481-500 ms	Interrupt ribociclib. Perform steps 1-4 as directed in "For All Grades." Perform a repeat ECG within one hour of the first QTcF of ≥ 481 ms. Repeat ECG as clinically indicated until the QTcF returns to < 481 ms, Restart ribociclib with dose reduced by 1 dose level. If QTcF ≥ 481 ms recurs, ribociclib should be reduced again by 1 dose level. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 481 ms.
Grade 3* QTcF ≥ 501 ms; or > 60 ms change from baseline	Interrupt ribociclib. Perform steps 1-4 as directed in "For All Grades." Transmit ECG immediately and confirm prolongation/abnormalities with central assessment. Perform a repeat ECG within one hour of the first QTcF of ≥ 501 ms. If QTcF remains ≥ 501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to < 481 ms. • If QTcF returns to < 481 ms, ribociclib will be reduced by 1 dose level. • If QTcF remains ≥ 481 ms after performing steps 1-4 as directed in "For All Grades," discontinue ribociclib. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 501 ms If QTcF of ≥ 501 ms recurs, discontinue ribociclib.
Grade 4* Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of	Discontinue ribociclib. Perform steps 1-4 as directed in "For All Grades." • Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms.
*All values refer to the average of triplicate measurements if study protocol requires triplicate ECG collections.	

Table 6-37 Other adverse events suspected to be related to ribociclib

Consider performing an analysis of serum potassium, calcium, phosphorus, and magnesium for all adverse reactions, if indicated. If electrolyte values are outside of the normal range, interrupt ribociclib administration, correct electrolytes with supplements or appropriate therapy as soon as possible, and repeat electrolyte testing until documented normalization of the electrolytes.	
Grade (CTCAE v5)	**Mandatory dose modification**
Renal impairment (not due to other contributing factors)	
Grade 2 or higher	Discontinue ribociclib.
Interstitial lung disease/pneumonitis	
Grade 1 (asymptomatic)	No dose adjustment required. Initiate appropriate medical therapy and monitor as clinically indicated

[redacted]

Grade 2 (symptomatic)	Interrupt ribociclib dose until recovery to Grade ≤1, then resume ribociclib at the next lower dose level (An individualized benefit-risk assessment should be performed before resuming ribociclib).
Grade 3 or 4 (severe)	Discontinue ribociclib.
Other adverse events	
Grade 2	Dose interruption until recovery to grade ≤ 1. Initiate appropriate medical therapy and monitor. Re-initiate ribociclib at the same dose. If the same toxicity recurs at grade 2, interrupt ribociclib until recovery to grade ≤ 1. Re-initiate ribociclib at the next lower dose level.
Grade 3	Dose interruption until recovery to grade ≤ 1. Initiate appropriate medical therapy and monitor. Re-initiate ribociclib at the next lower dose level. If toxicity recurs at grade 2: temporary dose interruption until recovery to grade ≤ 1 and reduce ribociclib dose the next lower dose level. If toxicity recurs at grade 3, discontinue ribociclib.
Grade 4 (including Toxic Epidermal Necrolysis, TEN)	Discontinue ribociclib and treat with appropriate medical therapy.

6.3.2 Dose adjustments for QTcF prolongation suspected to be related to capmatinib

In case of QTcF >500 msec, (or QTcF prolongation >60 msec from baseline):

1. Assess the quality of the ECG recording and the QT value and repeat if needed
2. Interrupt capmatinib
3. Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming capmatinib.
4. Review concomitant medication associated with QT prolongation, including drugs with a 'Known', 'Possible', or 'Conditional' risk of Torsades de Pointes" (refer to qtdrugs.org), and drugs with the potential to increase the risk of study drug exposure related QT prolongation
5. Check capmatinib dosing schedule and treatment compliance

[redacted]

After confirming ECG reading at site, if QTcF > 500 msec

- Interrupt capmatinib
- Repeat ECG and confirm ECG diagnosis by a cardiologist or central ECG lab
- If QTcF confirmed > 500 msec:
  - Correct electrolytes, eliminate culprit concomitant treatments, and identify and address clinical conditions that could potentially prolong the QT interval.
  - Consult with a cardiologist (or qualified specialist)
  - Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 msec.
- After resolution to ≤ 480 msec, consider re-introducing capmatinib at reduced dose, and increase ECG monitoring for the next cycle(s):
  - If QTcF remains ≤ 500 msec after dose reduction, continue planned ECG monitoring during subsequent treatment
  - If QTcF recurs > 500 msec after dose reduction, discontinue subject from capmatinib.

[redacted]

6.3.3 Follow-up for toxicities

All subjects must be followed-up for AEs and SAEs for 150 days following the last dose of spartalizumab/LAG525, or up to 130 days after the last dose of canakinumab, or up to 30 days after the last dose of capmatinib or ribociclib, whichever is later. Suspected SAEs will continue to be collected beyond those timeframes. However, if the subject begins subsequent anti-cancer therapy before the 150-Day safety visit, the collection of new SAEs and AEs unrelated to study medication will stop and thereafter only suspected SAEs and suspected AEs will continue to be collected up to 150 days following the last dose of spartalizumab. If SAEs suspected to be related to study medication occur beyond Day 150, information should also be collected.

The emergence of irAEs may be anticipated based on the mechanism of action of checkpoint inhibitor therapies. Serologic, histologic (tumor sample) and immunological assessments should be performed as deemed appropriate by the Investigator to verify the immune-related nature of the AE and to exclude alternative explanations. Recommendations have been developed to assist investigators in assessing and managing the most frequently occurring irAEs (refer to Appendix 3). If cytokine release syndrome is suspected, the assessments outlined in Section 7.2.2.5 must be performed.

Subjects whose treatment is interrupted or permanently discontinued due to an irAE, AE or clinically significant laboratory value, must be followed-up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 30 days, and subsequently at approximately 30-day intervals (or more frequently if required by institutional practices, or if clinically indicated), until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary.

Refer to Section 6.3 and Appendix 3 for the follow-up evaluations recommended for selected toxicities.

6.3.3.1 Follow up on potential drug-induced liver injury cases (all arms)

Transaminase increase combined with total bilirubin increase may be indicative of potentially severe drug-induced liver injury (DILI), and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the subject's baseline AST/ALT and total bilirubin values; subjects meeting any of the following criteria will require further follow-up as outlined below:

- For subjects with normal ALT and AST and total bilirubin at baseline: AST or ALT > 3.0 × ULN combined with total bilirubin > 2.0 × ULN
- For subjects with elevated AST or ALT or total bilirubin at baseline: [AST or ALT > 3.0 × baseline] OR [AST or ALT > 8.0 × ULN], whichever is lower, combined with [total bilirubin > 2.0 × baseline AND > 2.0 × ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed as the cause of liver injury.

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

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

Evaluate status of liver metastasis (new or exacerbation) or vascular occlusion – e.g. using CT, MRI, or duplex sonography.

Perform relevant examinations (Ultrasound or MRI, ERCP) as appropriate, to rule out an extrahepatic cause of cholestasis, defined as an ALP elevation > 2.0 × ULN with R value < 2 in subjects without bone metastasis, or elevation of the liver-specific ALP isoenzyme in subjects 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 ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury.

Table 6-38 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

Table 6-38 Guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	• Ceruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

Other causes should also be considered based upon subjects' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; cardiovascular disease / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 diabetes / glycogenic hepatitis).

[redacted]

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" i.e. >50% likely, if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates probably

[redacted]

caused by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for liver test abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.1.2) and be reported as SAE using the term "potential treatment-induced liver injury". All events should be followed up with the outcome clearly documented.

6.4 Concomitant medications

The subject must be told to notify the investigational site about any new medications he/she takes after the start of the study treatment.

All medications (other than study treatment), including, surgeries, radiotherapies, or other medical procedures and significant non-drug therapies (blood transfusions, physical therapy, herbal/natural medications and) administered within 30 days prior to starting study treatment until 150 days following the last dose of spartalizumab/LAG525, or up to 130 days after the last dose of canakinumab, or up to 30 days after the last dose of capmatinib or ribociclib, whichever is later, must be recorded in the eCRF. If a new anti-cancer therapy is started then only medications relative to the suspected AE/SAE that are reported should be collected.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, the investigator should contact Novartis to determine if the subject should be discontinued from the study treatment or the study.

6.4.1 Permitted concomitant therapy

- In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrhea) and safety of the subject are allowed except those prohibited in Section 6.4.3.
- Limited-field palliative radiotherapy may be allowed (refer to Section 6.4.4) after documented discussion with Novartis.
- Immune-suppressive therapy (e.g. steroids) to treat (suspected) immune-mediated adverse events are allowed (see also Section 6.4.3).
- Treatment with bisphosphonates or denosumab for pre-existing bone metastases is allowed. If therapy needs to be initiated while on study, subjects should be evaluated for disease progression.
- Inactivated vaccines are allowed

6.4.2 Permitted concomitant therapy requiring caution and/or action

- Anticoagulation and anti-aggregation agents are permitted if the subjects 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.
- Anti-hypertensives are allowed as concomitant medications; however, because transient hypotension has occurred during infusions of monoclonal antibodies, consideration

should be given to withholding anti-hypertensive medications for 12 hours prior to infusion with spartalizumab and/or LAG525.

6.4.2.1 For subjects receiving capmatinib in combination arm 2

The following cautions should be taken:

- Capmatinib is a moderate CYP1A2 inhibitor. Co-administration of capmatinib increased sensitive CYP1A2 probe substrate (caffeine) AUC by 135%. The dose of CYP1A2 substrates with narrow therapeutic index may need to be reduced when used concurrently with capmatinib as capmatinib may increase their exposure. Consult the product information of concomitant drug for dose adjustment.
- Co-administration of capmatinib increased Pgp substrate (digoxin) exposure (AUC and C_{max} by 47% and 74%, respectively) and BCRP substrate (rosuvastatin) exposure (AUC and C_{max} by 108% and 204%, respectively). Monitor subjects closely for symptoms of increased exposure to Pgp or BCRP substrates. Consult the concomitant Pgp or BCRP substrate product information when considering dose adjustment.
- Co-administrating capmatinib with strong CYP3A4 inhibitor (itraconazole) increased capmatinib AUC by 40%. There is no change in capmatinib C_{max}. Execute caution when use strong CYP3A4 inhibitor concurrently with capmatinib.
- While the data on the concurrent use of PPI and food have to be considered preliminary as they have been generated in a small cohort of subjects of the study CINC280A2108, the decrease in exposure imposes caution on the use of PPI when capmatinib is taken.
- Short acting gastric acid modulators containing aluminum hydroxide and magnesium hydroxide, or calcium carbonate can be taken. However, it is recommended to take these drugs at least 3 hours before or 3 hours after administration of capmatinib. H2 receptor antagonists should be avoided. If subjects are using H2 receptor antagonists during the course of this study, subjects should not take capmatinib within 2 hours of taking H2 receptor antagonists. In addition, the next scheduled dose of capmatinib should be administered at least 8 hours after taking H2 receptor antagonists.
- Capmatinib is a weak to moderate inhibitor of CYP2C8, CYP2C9 and CYP2C19 *in vitro*. Substrates of CYP2C8, CYP2C9 and CYP2C19 with a narrow therapeutic window should be administered with caution.

Refer to Table 6-39 below for a list of the medications that require caution when concomitantly used with capmatinib.

Table 6-39 List of medications to be used with caution while on treatment with capmatinib (arm 2)

Mechanism of Interaction	Drug Name
Strong CYP3A inhibitor	ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak), indinavir/ritonavir, tipranavir/ritonavir, ritonavir, cobicistat, indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir, elvitegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, itraconazole, voriconazole, mibefradil, posaconazole, telithromycin, grapefruit juice, conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir, darunavir/ritonavir
CYP1A2 substrate with NTI	theophylline, tizanidine
CYP2C9 substrate with NTI	warfarin
CYP2C19 substrate with NTI	(S)-mephenytoin
P-gp substrates	afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, boceprevir, bosentan, carvedilol, carvedilol,

Mechanism of Interaction	Drug Name
	caspofungin, ceritinib, colchicine, cyclosporine, dabigatran, digoxin, doxepin, doxorubicin, eribulin, everolimus, fidaxomicin, fluvastatin, fosamprenavir, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, lapatinib, levetiracetam, linagliptin, losartan, maraviroc, mirabegron, naloxegol, nateglinide, nintedanib, olodaterol, pantoprazole, paroxetine, pazopanib, posaconazole, pravastatin, quinine, ranolazine, riociguat, risperidone, rivaroxaban, saquinavir, silodosin, simeprevir, sirolimus, sitagliptin, sorafenib, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole, atorvastatin, docetaxel, fentanyl, fexofenadine, linezolid, loperamide, nadolol, nevirapine, paclitaxel, proguanil, ritonavir, simvastatin, sofosbuvir, tacrolimus
BCRP substrates	atorvastatin, daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, paritaprevir, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sofosbuvir, sulfasalazine, tenofovir, topotecan, venetoclax
Proton pump inhibitor	omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole, dexlansoprazole
Short acting gastric acid modulator and H2 receptor antagonist	ranitidine, nizatidine, famotidine, cimetidine, aluminum hydroxide, aluminum carbonate, calcium hydroxide, calcium carbonate, bismuth subsalicylate
Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (Jan 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies" This may not be an exhaustive list, will be updated periodically. NTI: narrow therapeutic index	

6.4.2.2 For subjects receiving ribociclib in combination arm 4

Medications to be used with caution during treatment with ribociclib are listed below and in Table 6-40 (This list is not comprehensive and is only meant to be used as a guide. Please contact the medical monitor with any questions). These medications should be excluded from patient use if possible. If they must be given based on the investigator's judgment, then use with caution and consider a ribociclib interruption if the concomitant medication is only needed for a short time.

- Moderate inhibitors or inducers of CYP3A4/5 (may increase or decrease ribociclib exposure, respectively)
- Sensitive substrates of CYP3A4/5 that do not have narrow therapeutic index (ribociclib may increase exposure to these medications)
- Strong inhibitors of bile salt export pump (based on in vitro data co-administration with ribociclib may lead to intrahepatic cholestasis)
- Medications that carry a possible risk for QT prolongation (may precipitate QT prolongation and TdP)
- Sensitive substrates of the renal transporters MATE1/2 and OCT1/2 (ribociclib has a potential to increase exposure to substrates of these transporters, although no animal or clinical data are available to support these statements)
- Sensitive substrates of transporter BCRP (ribociclib has a potential to increase exposure to substrates of this transporter, although no animal or clinical data are available to support these statements)
- Corticosteroids: Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to lead to induction of CYP3A enzymes, thereby potentially reducing ribociclib drug exposure to sub-therapeutic levels. Systemic corticosteroid

treatment should be avoided during the study treatment with ribociclib, unless clinically required.

Topical applications (e.g. for rash), inhaled sprays (e.g. for obstructive airways diseases), eye drops or local injections (e.g. intra-articular) are allowed.

Table 6-40 List of medications to be used with caution during ribociclib treatment (arm 4)

Category	Drug Name
Moderate CYP3A4/5 inhibitors	Aprepitant, amprenavir, asafoetida resin (Ferula asafoetida), cimetidine, crizotinib, diltiazem, faldaprevir, imatinib, isavuconazole, netupitant, nilotinib, tofisopam, Schisandra sphenanthera (nan wu wei zi), verapamil
Moderate CYP3A4/5 inducers	Bosentan, dabrafenib, efavirenz, etravirine, genistein,lopinavir[5], modafinil, nafcillin,telotristat
Sensitive CYP3A4/5 substrates[1]	Alpha-dihydroergocryptine, apixaban, aprepitant, atorvastatin, avanafil, bosutinib, brotizolam, budesonide, buspirone, cannabinoids[6], cannabidiol[6], cobimetinib, darifenacin, dasatinib, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutnib, isavuconazole, ivabradine, ivacaftor, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, perospirone, quetiapine, ridaforolimus, rivaroxaban, sildenafil, simeprevir, ticagrelor, tilidine, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin
Bile salt export pump inhibitors	Alectinib, atorvastatin, bromocriptine, candesartan, clobetasol, clofaziminie, dabigatran, dipyridamole, glyburide, grazoprevir, ledipasvir, mifepristone,pioglitazone, reserpine, rifamycin, simeprevir, telmisartan, timcodar, troglitazone, velpatasvir
Medications that carry a possible risk for QT prolongation[2]	Alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine, asenapine, atazanavir, atomoxetine, bedaquiline, bendamustine, bortezomib, bosutinib, buprenorphine, cabozantinib, capecitabine, ceritinib, clomipramine, crizotinib, clozapine, cyamemazine (cyamepromazine), dabrafenib, dasatinib, degarilix, delamanid, desipramine, dexmedetomidine, dolasetron, efavirenz, eliglustat, epirubicin, eribulin mesylate, ezogabine(retigabine), famotidine, felbamate, fingolimod, flupentixol, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, ketanserin, lapatinib, lenvatinib, leuprolide, loperamide, lithium, melperone, midostaurin, mifepristone, mirabegron, mirtazapine, moexipril/HCTZ, necitumumab, , nilotinib, norfloxacin, nortriptyline, nusinersen, ofloxacin, olanzapineosimertinib, oxytocin, paliperidone, palonosetron, panabinostat, pasireotide, pazopanib, perflutren lipid microspheres, perphenazine, pilsicainide, pimavanserin, pipamperone, promethazine, prothipendyl, quetiapine, ranolazine, rilpivirine, risperidone, romidepsin, sertindole, sorafenib, sunitinib, tamoxifen, telavancin, tetrabenazine, tipiracil/trifluridine, tizanidine, tolterodine, toremifene, trimipramine, tropisetron, vardenafil, vemurafenib, venlafaxine, vorinostat, ziprasidone
MATE1/2 substrates[3]	Acyclovir, cephalexin, cimetidine, fexofenadine, ganciclovir, glycopyrronium, metformin, pindolol, plisicainide, ranitidine, topotecan, varenicline

OCT1/2 substrates[4]	Amantadine, carboplatin, cisplatin, cephalexin, cephradine, ipratropium, lamivudine, linagliptin, metformin, oxaliplatin, oxybutynin, phenformin, picoplatin, pilsicainide, pindolol, ranitidine, sorafenib, tropisetron, trospium, umeclidinium, zidovudine
BCRP substrates	Daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, sulfasalazine, sofosbuvir, tenofovir, topotecan, venetoclax

[1] Sensitive substrates include drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.
[2] The list provided is as of January 2018. Check https www crediblemeds.org/healthcare-providers/drug-list for the most updated list.
[3] MATE1 and MATE2 share considerable substrate specificity.
[4] OCT1 and OCT2 share considerable substrate specificity.
[5]Lopinavir and atazanavir are prohibited when combined with ritonavir (see Table 6-43)
[6] Based on data that exposure of cannabidiol (CBD), tetrahydrocannabinol (THC), 11-hydroxy THC, increased by ~2-3 folds when co-administered with ketoconazole (CYP3A4 inhibitor) (Stott et al 2013)
Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University "Clinically Relevant" Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

6.4.3 Prohibited concomitant therapy while receiving study drug(s)

The following concomitant therapies are prohibited for all subjects in all combination arms during the course of study treatment:

- Any other anti-cancer therapies (e.g. tumor infiltrating lymphocytes [TIL], checkpoint inhibitor therapy or other immunotherapies, chemotherapy, small molecules, other investigational drugs or devices,) or any other therapies that may be active against cancer or modulate the immune responses. For radiation please refer to Section 6.4.4.
- The use of systemic steroid therapy and other immunosuppressive drugs is not allowed except for the treatment of infusion reaction, immune related adverse events, imaging contrast dye allergy, substitution for adrenal insufficiency, or transient exacerbations of other underlying diseases such as chronic obstructive pulmonary disease (COPD). Please refer to Section 6.4.2.2 for specific cautions on corticosteroids use during treatment with ribociclib in arm 4.
- The use of live vaccines is not allowed through the whole duration of the study. Inactivated vaccines are allowed.
- For subjects in arm 2, co-administrating capmatinib with strong CYP3A4 inducer (rifampicin) decreased capmatinib AUC by 66% and C_{max} by 56%. Concurrent use of strong CYP3A4 inducers (refer to Table 6-41) is prohibited as decreased capmatinib exposure may lead to reduced efficacy.

Table 6-41 List of strong CYP3A4 inducers prohibited while on treatment with capmatinib (Arm 2)

Mechanism of Interaction	Drug Name
Strong CYP3A4 inducer	carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampicin, mitotane, St. John's wort (*Hypericum perforatum*)

[redacted]

Mechanism of Interaction	Drug Name
Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (Jan 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies" This may not be an exhaustive list, will be updated periodically.	

- For subjects in arm 2: As far as possible avoid co-administering drugs with a "Known", "Possible", or "Conditional" risk of QT prolongation and/or Torsades de Pointes (TdP) (refer to qtdrugs.org) during the course of the treatment with capmatinib:
  - If concomitant administration of drugs with a "Known risk of QT prolongation and/or TdP" (refer to Table 6-42) is required and cannot be avoided, study drug must be interrupted. If, based on the investigator assessment and clinical need, study treatment is resumed, close ECG monitoring is advised.
  - If during the course of the study, concomitant administration of a drug with "Possible risk" or "Conditional risk of QT prolongation and/or TdP" is required, based on the investigator assessment and clinical need, study treatment may be continued under close ECG monitoring to ensure subject safety.

A list of drugs associated with QT prolongation and/or TdP is available online at qtdrugs.org.

Table 6-42 Drugs with a known risk of QT prolongation and/or 'Torsades de Pointes' prohibited while on treatment with capmatinib

Class of medication	Drug Name
With Known risk of QT prolongation and/or 'Torsades de Pointes'	amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, grepafloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levomethadyl, levosulpiride, mesoridazine, methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, probucol, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, sulpiride, sultopride, terfenadine, terlipressin, terodiline, thioridazine, vandetanib
This may not be an exhaustive list. Check crediblemeds.org/healthcare-providers/drug-list for the most updated list.	

- **For subjects in arm 4,** co-administration of any medication listed below and in Table 6-43 with ribociclib is prohibited :
  - co-administration of strong inhibitors or inducers of CYP3A4/5 (may significantly increase or decrease ribociclib exposure, respectively).
  - co-administration of substrates of CYP3A4/5 with a narrow therapeutic index (ribociclib may increase exposure to these medications resulting in toxicity from these medications).
  - co-administration of medications with a known risk for QT prolongation and/or TdP (may precipitate QT prolongation and TdP in combination with ribociclib). As far as possible, avoid co-administration of QT prolonging drugs or any other drugs with the potential to increase the risk of drug-related QT prolongation (e.g., via a potential DDI that increases the exposure of ribociclib or the exposure of the QT prolonging drug). A definitive list of drugs with a known risk, possible risk, or conditional risk of QT prolongation and/or Torsades de Pointes (TdP) is available online at qtdrugs.org.
  - co-administration or ingestion of herbal medications/preparations or dietary supplements that are strong inhibitors or inducers of CYP3A4/5 or those with a

[redacted]

known risk of QT prolongation. These include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using these preparations/medications at least 7 days prior to first dose of study treatment.

Table 6-43 List of prohibited medications while on treatment with ribociclib (arm 4)

Category	Drug Name
Strong CYP3A4/5 inhibitors	Atazanavir/ritonavir, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, darunavir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir,ombitasvir/paritaprevir/dasabuvir/ritonavir (VIEKIRA PAK), posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole
Strong CYP3A4/5 inducers	Apalutamide, carbamazepine[3], enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin[3], rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[2,3]
CYP3A4/5 substrates with NTI[1]	Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, lomitapide[5], lovastatin, nicardipine, nisoldipine, pimozide, quinidine, simvastatin, sirolimus, tacrolimus
Medications with a known risk for QT prolongation[4]	Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, cocaine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, grepafloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levosulpiride, levomethadyl, mesoridazine methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, probucol, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, sulpiride, sultopride, terlipressin, terodiline, terfenadine, thioridazine, vandetanib
Herbal preparations/ medications or dietary supplements	Herbal preparations/medications or dietary supplements known as strong inducers or inhibitors of CYP3A4/5 or those with a known risk of QT prolongation are prohibited throughout the study. These include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh, and ginseng. Patients should stop using these herbal medications or dietary supplements 7 days prior to first dose of study drug.

[1] NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes) or drugs which have <2-fold difference in the minimum toxic concentrations and effective concentrations in the blood

[2] Herbal product

[3] P-gp inducer

[4] The list provided is as of December 2019. Check https www crediblemeds.org/healthcare-providers/drug-list for the most updated list.

[5] Drug has warning for risk of hepatotoxicity.

Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University "Clinically Relevant" Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

6.4.4 Radiotherapy

Limited-field palliative radiotherapy may be allowed after documented discussion with Novartis. Such local therapies administered during the study treatment must be recorded in the eCRF.

6.5 Subject numbering, treatment assignment or randomization

6.5.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. (7-digit number) consists of the Center Number (Center No.) (4-digit, as assigned by Novartis to the investigative site) with a sequential 3-digit subject number suffixed to it, so that each subject is numbered uniquely across the entire database.

Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available to the investigator.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the subject to register them into the IRT.

Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the subject is re-screened.

6.5.2 Treatment assignment or randomization

In the randomized section of the study, prior to dosing, all subjects who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms open to enrollment in part 1 and part 2 (Section 4.1.1 and Section 6.1). The investigator or his/her delegate will call or log on to the IRT and confirm that the subject fulfills all the inclusion/exclusion criteria for each arm. If the subject does not fulfill the inclusion/exclusion criteria specific to one or more arms, the IRT system will exclude those arms for randomization. For each arm , randomization will be stratified by baseline level of LDH (baseline LDH ≤ ULN and baseline LDH > ULN).

The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment arm assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These 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.

In the non-randomized section of the study, no randomization will be performed. Prior to dosing, all subjects who fulfill the inclusion/exclusion criteria applicable for arm 1A will be

enrolled via IRT and systematically assigned to this arm (in part 1 or part 2, refer to Section 4.1.2 and Section 6.1).

6.5.3 Treatment blinding

Not applicable.

6.6 Study drug preparation and dispensation

Study drug(s) will be dispensed to the subject by authorized site personnel only.

Administration of spartalizumab and LAG525 i.v. infusions must take place in a facility with appropriate resuscitation equipment available and a physician readily available during the period of drug administration. Clinical monitoring during and post infusion should be performed according to local practice and institutional guidelines, and as outlined in Section 6.1.

Capmatinib and ribociclib will be administered orally. Capmatinib or ribociclib tablets (in bottles), including instructions for administration, are dispensed by study personnel on an outpatient basis. Subjects will be provided with adequate supply of capmatinib or ribociclib for self-administration at home until at least their next scheduled visit. The investigator or responsible site personnel must instruct the subject or caregiver to take capmatinib or ribociclib as per protocol.

Canakinumab will be administered subcutaneously by site personnel.

Further instructions for the preparation and dispensation of spartalizumab, LAG525 and canakinumab are described in the [PDR001J2201 Pharmacy Manual].

6.6.1 Study treatment packaging and labeling

All study drugs will be provided as global clinical open supply and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

Spartalizumab will be supplied in vials containing 100 mg spartalizumab (PDR001) as a liquid concentrate solution for infusion.

LAG525 will be supplied in vial containing 100 mg LAG525 as a liquid concentrate solution for infusion.

Capmatinib (INC280) film-coated tablets for oral use will be supplied at 200 mg and 150 mg dosage strengths in bottles of 30 tablets to accommodate the initial dose as well as dose reduction steps.

Ribociclib (LEE011) film-coated tablets for oral use will be supplied at 200 mg dosage strength in bottles of 75 tablets to accommodate the initial dose as well as dose reduction steps.

Canakinumab will be supplied in vial containing 150 mg canakinumab (ACZ885) as a liquid solution for subcutaneous injection.

Study drugs labels will comply with the legal requirements of each country and will include storage conditions, a unique medication number (corresponding to study drug and strength). Responsible site personnel will identify the study drug package(s) to dispense by the medication number(s) assigned by IRT to the subject. Site personnel will add the subject number on the label. If the label has 2-parts (base plus tear-off label), immediately before

dispensing the package to the subject, site personnel will detach the outer part of the label from the package and affix it to the subject's source document.

6.6.2 Drug supply and storage

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

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each subject visit and information provided by the subject and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each subject visit.

Compliance will be assured by administration of the study treatment under the supervision of investigator or his/her designee.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Subjects will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

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

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate, or at site if allowed per local regulations and local Sponsor procedures and agreements.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-2 lists all of the assessments to be performed for all subjects (regardless of the study part, part 1 or part 2, they were randomized/enrolled into) and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the subject's source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column).

Additional assessments may be performed as clinically indicated.

[redacted]

No CRF will be used as a source document.

Study treatment will begin on C1D1 with the first administration of the assigned study treatment, depending on the arm the subject has been randomized/enrolled into.

Each treatment cycle is 28 days. All study visits, assessments and study treatment administration are to be scheduled according to the appropriate number of calendar days from the day of first study treatment administration on C1D1 (except for tumor assessments in randomized arms which have to be scheduled as per the scheduled number of weeks after the date of randomization) whenever possible as per the allowable visit window specified in Table 7-1 below. If one of the investigational drugs is interrupted or permanently discontinued, at any time during the study, all study visits and safety assessments should continue according to the appropriate number of calendar days from C1D1 as per the schedule of assessments, and efficacy assessments must continue as per the scheduled number of weeks from the date of randomization (or from the date of first dose of study treatment in arm 1A) as described in Table 7-2. Missed or rescheduled visits should not lead to automatic discontinuation.

Safety follow-up visits are to be scheduled according to the appropriate number of calendar days after the date of last dose of study drug administered (refer to Section 7.1.7).

Every effort must be made to follow the schedule of assessments within the windows outlined in the protocol.

[redacted]

The preferred sequence for assessments during study visits is ECG collection first, followed by vital signs, and blood sampling.

Table 7-1 Allowable visit windows

Visit name	Assessments	Window allowed
Screening	Physical examination (complete), Performance Status, weight, vital signs, hematology, chemistry, coagulation	≤ 14 days before C1D1
	Serum pregnancy test	≤ 72 hours before C1D1
	For Arm 1A: Collection/submission of newly or recently obtained baseline tumor biopsy sample (as defined in Section 7.2.3.1.1) for LAG-3 status central assessment	≤ 35 days before enrollment (tumor sample should be submitted as early as possible and at the latest 20 days prior to planned enrollment date to allow sufficient time for central testing)
	Other screening assessments	≤ 28 days before C1D1
C1D1	Administration of first dose of study treatment	Maximum 3 days after date of randomization/enrollment
	All visit assessments	NA (if screening laboratory assessments and physical examination were performed ≤ 72 hours before first dose of study treatment, they do not need to be repeated on C1D1)
Day 1 visit of all subsequent cycles	All visit assessments (except tumor assessment)	± 4 days
	Administration of i.v. and s.c. investigational drugs	± 4 days

[redacted]

Visit name	Assessments	Window allowed
During Treatment and Efficacy follow-up periods	Tumor assessments	± 7 days
[redacted]		
EoT	All assessments	+ 7 days after the discontinuation of the last study drug (i.e. within 7 days after the last dose of the last study drug or after the date when decision was made to permanently discontinue both study drugs/the last study drug) (tumor assessments do not need to be repeated if performed within 30 days prior to last study treatment administration)
30-day safety follow-up visit	All assessments	30 days (+ 7 days) after last dose of study treatment (if last dose was more than 30 days ago when the decision is taken to discontinue study treatment, then 30-day safety follow-up to be performed as soon as possible)
60-, 90-, 120-Day follow-up phone call/onsite visit	All assessments	± 7 days
150-Day follow-up visit	All assessments	+ 14 Days
Survival follow up	All assessments	± 14 days

[redacted]

Table 7-2 Visit evaluation schedule (applicable for all subjects, in both part 1 and part 2)

	Category	Protocol section	Screening period	Treatment Period (Cycle = 28 days)										Follow-up (FU) Period							
														Safety FU					Efficacy FU (Not applicable if EoT due to progression)		
			Screening	Cycle 1				Cycle 2	Cycle 3			Subsequent Cycles Day 1	End of Treatment (EoT)	30-day Safety FU	60-day Safety FU	90-day Safety FU	120-day Safety FU	150-day Safety FU	Efficacy FU	End of post-treatment FU	Survival
Day of cycle			**-28 (-35 for arm 1A) to -1**	**1**	**8**	**15**	**21**	**1**	**1**	**8**	**15**	**1**									
Obtain Informed Consent (ICF)																					
Study ICF	D	7.1.2, 11.3	X																		
[redacted]																					
Eligibility and subject's history																					
Demography	D	7.1.2.3	X																		
Inclusion/exclusion	D	5.2, 5.3	X																		
Relevant medical history	D	7.1.2.3	X																		
Diagnosis and extent of cancer, including ^{V600}*BRAF* status	D	7.1.2.3	X																		
HIV history	S	7.1.2.3	X																		
Prior anti-cancer therapies (medications, surgery, radiation)	D	7.1.2.3	X																		

[redacted]

	Category	Protocol section	Screening period	Treatment Period (Cycle = 28 days)										Follow-up (FU) Period							
														Safety FU					Efficacy FU (Not applicable if EoT due to progression)		
			Screening	Cycle 1				Cycle 2	Cycle 3			Subsequent Cycles Day 1	End of Treatment (EoT)	30-day Safety FU	60-day Safety FU	90-day Safety FU	120-day Safety FU	150-day Safety FU	Efficacy FU	End of post-treatment FU	Survival
Day of cycle			**-28 (-35 for arm 1A) to -1**	**1**	**8**	**15**	**21**	**1**	**1**	**8**	**15**	**1**									
Prior/concomitant medications	D	7.1.2.3, 6.4	From 30 days prior to starting study treatment until 150-Day safety follow-up or start of subsequent anti-cancer therapy, whichever occurs first. If subsequent anti-cancer therapy is started then only medications relative to the suspected AE/SAE that are reported should be collected. Investigator must ensure that no prohibited medication(s) (refer to Section 6.4.3) is given to the subject while on study treatment.																		
Subsequent anti-cancer therapy since discontinuation of study treatment	D	7.1.9											X								
Enrollment-Randomization																					
IRT Registration (after Study ICF signature)	S	6.5.1	X																		
IRT – Randomization/enrollment	S	6.5.2		X																	
Disposition form	D	7.1.5, 7.1.8	X										X							X	
Physical examination																					
Physical examination (complete)	S	7.2.2.1	X																		
Physical examination (short)	S	7.2.2.1		X				X	X			X	X	X							

[redacted]

	Category	Protocol section	Screening period	Treatment Period (Cycle = 28 days)										Follow-up (FU) Period							
														Safety FU					Efficacy FU (Not applicable if EoT due to progression)		
			Screening	Cycle 1				Cycle 2	Cycle 3			Subsequent Cycles Day 1	End of Treatment (EoT)	30-day Safety FU	60-day Safety FU	90-day Safety FU	120-day Safety FU	150-day Safety FU	Efficacy FU	End of post-treatment FU	Survival
Day of cycle			**-28 (-35 for arm 1A) to -1**	**1**	**8**	**15**	**21**	**1**	**1**	**8**	**15**	**1**									
Vital signs	D	7.2.2.2	X	X				X	X			X	X	X							
Height	D	7.2.2.3	X																		
Weight	D	7.2.2.3	X	X				X	X			X	X	X							
Performance status (ECOG)	D	7.2.2.4	X	X				X	X			X	X	X							
12-lead ECG (Arm 1, Arm 2, Arm 1A)	D	7.2.2.6	X	X				X	X				X								
12-lead ECG (Arm 3)	D	7.2.2.6	X	If clinically indicated									X								

[redacted]

	Category	Protocol section	Screening period	Treatment Period (Cycle = 28 days)									Follow-up (FU) Period							
													Safety FU					Efficacy FU (Not applicable if EoT due to progression)		
			Screening	Cycle 1				Cycle 2	Cycle 3			Subsequent Cycles Day 1	End of Treatment (EoT)	30-day Safety FU	60-day Safety FU	90-day Safety FU	120-day Safety FU	150-day Safety FU	Efficacy FU	End of post-treatment FU	Survival
Day of cycle			**-28 (-35 for arm 1A) to -1**	**1**	**8**	**15**	**21**	**1**	**1**	**8**	**15**	**1**								
12-lead ECG (Arm 4)	D	7.2.2.6	X	X		X		X	X		X	All subjects: at C4D1, C5D1, C6D1. Only for subjects with QTcF ≥ 481 ms at any time prior to cycle 7: Day 1 of all cycles from Cycle 7 until EoT	X								
Laboratory assessments																					
Hematology	D	7.2.2.5	X	X		X		X	X		X	X	X	X							
Chemistry	D	7.2.2.5	X	X		X		X	X		X	X	X	X							

[redacted]

	Category	Protocol section	Screening period	Treatment Period (Cycle = 28 days)										Follow-up (FU) Period							Survival
														Safety FU					Efficacy FU (Not applicable if EoT due to progression)		
			Screening	Cycle 1				Cycle 2	Cycle 3			Subsequent Cycles Day 1	End of Treatment (EoT)	30-day Safety FU	60-day Safety FU	90-day Safety FU	120-day Safety FU	150-day Safety FU	Efficacy FU	End of post-treatment FU	
Day of cycle			**-28 (-35 for arm 1A) to -1**	**1**	**8**	**15**	**21**	**1**	**1**	**8**	**15**	**1**									
Cardiac troponin T (or I)	D	7.2.2.5	X			Arms 1 and 1A only		Arms 1 and 1A only	Arms 1 and 1A only												
Coagulation	D	7.2.2.5	X	X		X		X	X		X	X	X	X							
Thyroid function - TSH	D	7.2.2.5	X					X	X			X	X	X							
Thyroid function - free T3 and Free T4	D	7.2.2.5	X					Only if TSH is abnormal													
Urinalysis - Local testing	S	7.2.2.5	X					X	X			X	X	X							
Serum pregnancy test - Local testing	S	7.2.2.5	X										X	X				X			
Urine pregnancy test - Local testing	S	7.2.2.5						X	X			X			X	X	X				
Hepatitis B and C Testing	D	7.2.2.5	X																		
Safety cytokines (for cytokine release syndrome)	D	7.2.2.5	X	Anytime when a suspected cytokine release syndrome occurs, immediately after the AE, and one week after occurrence of the AE																	

[redacted]

	Category	Protocol section	Screening period	Treatment Period (Cycle = 28 days)									Follow-up (FU) Period							
													Safety FU					Efficacy FU (Not applicable if EoT due to progression)		
			Screening	Cycle 1				Cycle 2	Cycle 3			Subsequent Cycles Day 1	End of Treatment (EoT)	30-day Safety FU	60-day Safety FU	90-day Safety FU	120-day Safety FU	150-day Safety FU	Efficacy FU	End of post-treatment FU	Survival
Day of cycle			**-28 (-35 for arm 1A) to -1**	**1**	**8**	**15**	**21**	**1**	**1**	**8**	**15**	**1**								
Local HIV testing, if required per local requirements	S	7.2.2.5	X																	
Tumor imaging and assessment per RECIST v1.1																				
CT/MRI scan (chest, abdomen, pelvis) with IV contrast enhancement	D	7.2.1	X	**During treatment:** 12 weeks (± 7 days) after the date of randomization (or after the date of first dose of study treatment in arm 1A), then every 8 weeks (± 7 days) until 52 weeks after randomization/date of first dose of study treatment in arm 1A then every 12 weeks until disease progression per RECIST v1.1. In case of continuation of study treatment beyond initial disease progression per RECIST v1.1: continue assessment with the same schedule. Refer to Section 6.1.5.1 and Section 7.2.1 for details. **End of Treatment (EOT):** Only to be done if a scan was not conducted within 30 days prior to end of study treatment. **Efficacy follow-up:** If subject discontinued study treatment for reason other than disease progression per RECIST v1.1, efficacy follow-up must be continued on the same schedule as during treatment until disease progression per RECIST v1.1. Refer to Section 7.2.1.2 for details on additional tumor assessments required for confirmation of response per RECIST 1.1 [redacted].									
Brain CT/MRI	D	7.2.1	X	If clinically indicated or if lesions were documented at screening, follow same schedule as CT/MRI of chest, abdomen, and pelvis.																
Whole-body bone scan	D	7.2.1	If clinically indicated																	

[redacted]

	Category	Protocol section	Screening period	Treatment Period (Cycle = 28 days)									Follow-up (FU) Period							
													Safety FU					Efficacy FU (Not applicable if EoT due to progression)		
			Screening	Cycle 1				Cycle 2	Cycle 3			Subsequent Cycles Day 1	End of Treatment (EoT)	30-day Safety FU	60-day Safety FU	90-day Safety FU	120-day Safety FU	150-day Safety FU	Efficacy FU	End of post-treatment FU	Survival
Day of cycle			**-28 (-35 for arm 1A) to -1**	**1**	**8**	**15**	**21**	**1**	**1**	**8**	**15**	**1**									
CT/MRI of other metastatic sites (e.g. neck)	D	7.2.1	If clinically indicated or if lesions were documented at screening, follow same schedule as CT/MRI of chest, abdomen, and pelvis.																	
Localized bone CT, MRI or X-ray	D	7.2.1	Only for lesions on whole body scan that are not visible on the chest, abdomen and pelvis scans. If lesions were documented at screening, follow same schedule as CT/MRI of chest, abdomen and pelvis																	
Color Digital Photography (including a metric ruler)	D	7.2.1	X	If clinically indicated or if cutaneous lesions were documented at screening, follow same schedule as CT/MRI of chest, abdomen, and pelvis.																
Collection of body fluid/tissue data	D	7.2.1	Record needle aspiration, biopsy or any other form of collection (e.g., paracentesis, puncture) performed for any clinically indicated reason																	
Safety																				
Adverse events (AEs)	D	8.1.1	Suspected AEs up to 150 days after last spartalizumab dose regardless of the start of subsequent anti-cancer therapy; non-suspected AEs up to 150 days after last spartalizumab dose or start of subsequent anti-cancer therapy, whichever is sooner.																	
Serious adverse events (SAEs)	D	8.1.2	Suspected SAEs up to 150 days after last spartalizumab dose and beyond, regardless of the start of subsequent anti-cancer therapy; non-suspected SAEs up to up to 150 days after last spartalizumab dose or start of subsequent anti-cancer therapy, whichever is sooner.																	

[redacted]

	Category	Protocol section	Screening period	Treatment Period (Cycle = 28 days)									Follow-up (FU) Period							
													Safety FU					Efficacy FU (Not applicable if EoT due to progression)		
			Screening	Cycle 1				Cycle 2	Cycle 3			Subsequent Cycles Day 1	End of Treatment (EoT)	30-day Safety FU	60-day Safety FU	90-day Safety FU	120-day Safety FU	150-day Safety FU	Efficacy FU	End of post-treatment FU	Survival
Day of cycle			**-28 (-35 for arm 1A) to -1**	**1**	**8**	**15**	**21**	**1**	**1**	**8**	**15**	**1**								
Arm 1 and Arm 1A: Immunogenicity (IG) sampling for spartalizumab (see Table 7-7) and LAG525 (see Table 7-8)	D	7.2.2.7		X				X	X			X – at C4D1, C5D1 and C6D1, then every 3 months (C9D1, C12D1, C15D1, etc)	X	X				X			
Arm 2 and Arm 4: Immunogenicity (IG) sampling for spartalizumab (see Table 7-7)	D	7.2.2.7		X				X	X			X – at C4D1, C5D1 and C6D1, then every 3 months (C9D1, C12D1, C15D1, etc)	X	X				X			

	Category	Protocol section	Screening period	Treatment Period (Cycle = 28 days)										Follow-up (FU) Period							Survival
														Safety FU					Efficacy FU (Not applicable if EoT due to progression)		
			Screening	Cycle 1				Cycle 2	Cycle 3			Subsequent Cycles Day 1	End of Treatment (EoT)	30-day Safety FU	60-day Safety FU	90-day Safety FU	120-day Safety FU	150-day Safety FU	Efficacy FU	End of post-treatment FU	
Day of cycle			**-28 (-35 for arm 1A) to -1**	**1**	**8**	**15**	**21**	**1**	**1**	**8**	**15**	**1**									
Arm 3: Immunogenicity (IG) sampling for spartalizumab (see Table 7-7) and canakinumab (see Table 7-10)	D	7.2.2.7		X				X	X			X – at C4D1, C5D1 and C6D1, then every 3 months (C9D1, C12D1, C15D1, etc)	X	X				X			
Safety follow-up	D	7.1.7												visit	visit or phone call	visit or phone call	visit or phone call	visit			
Tumor tissue samples																					
Mandatory newly or recently obtained tumor biopsy	D	7.2.3.1.1	X				Between C1D21 and C2D1 [redacted]														

[redacted]

	Category	Protocol section	Screening period	Treatment Period (Cycle = 28 days)									Follow-up (FU) Period							
													Safety FU					Efficacy FU (Not applicable if EoT due to progression)		
			Screening	Cycle 1				Cycle 2	Cycle 3			Subsequent Cycles Day 1	End of Treatment (EoT)	30-day Safety FU	60-day Safety FU	90-day Safety FU	120-day Safety FU	150-day Safety FU	Efficacy FU	End of post-treatment FU	Survival
Day of cycle			**-28 (-35 for arm 1A) to -1**	**1**	**8**	**15**	**21**	**1**	**1**	**8**	**15**	**1**								
Arm 1A only: Centralized assessment of LAG-3 status on baseline tumor sample	D	7.2.3.1.2	X																	
Mandatory, if available: Provision of archival FFPE block or slides from a tumor sample collected prior to start of any prior anti-PD-1/PD-L1 mono- or combination therapy	D	7.2.3.1.3		X																
[redacted]																				

[redacted]

	Category	Protocol section	Screening period	Treatment Period (Cycle = 28 days)									Follow-up (FU) Period							
													Safety FU					Efficacy FU (Not applicable if EoT due to progression)		
			Screening	Cycle 1				Cycle 2	Cycle 3			Subsequent Cycles Day 1	End of Treatment (EoT)	30-day Safety FU	60-day Safety FU	90-day Safety FU	120-day Safety FU	150-day Safety FU	Efficacy FU	End of post-treatment FU	Survival
Day of cycle			**-28 (-35 for arm 1A) to -1**	**1**	**8**	**15**	**21**	**1**	**1**	**8**	**15**	**1**									
[redacted]																					
Study treatment administration																					
All arms: spartalizumab infusion	D	6.1.1.1		400 mg i.v. Q4W																	
Arm 1 and Arm 1A: LAG525 infusion	D	6.1.1.2		600 mg i.v. Q4W																	
Arm 2: capmatinib administration	D	6.1.1.3		400 mg BID p.o.																	
Arm 3: canakinumab injection	D	6.1.1.4		300 mg s.c. Q4W																	

[redacted]

	Category	Protocol section	Screening period	Treatment Period (Cycle = 28 days)									Follow-up (FU) Period							
													Safety FU					Efficacy FU (Not applicable if EoT due to progression)		
			Screening	Cycle 1				Cycle 2	Cycle 3			Subsequent Cycles Day 1	End of Treatment (EoT)	30-day Safety FU	60-day Safety FU	90-day Safety FU	120-day Safety FU	150-day Safety FU	Efficacy FU	End of post-treatment FU	Survival
Day of cycle			**-28 (-35 for arm 1A) to -1**	**1**	**8**	**15**	**21**	**1**	**1**	**8**	**15**	**1**									
Arm 4: ribociclib administration	D	6.1.1.5		600 mg QD, on Days 1-21 of each 28-day cycle (Days 22-28 are a “rest period” from ribociclib)																	

[redacted]

[redacted]

	Category	Protocol section	Screening period	Treatment Period (Cycle = 28 days)									Follow-up (FU) Period							
													Safety FU					Efficacy FU (Not applicable if EoT due to progression)		
			Screening	Cycle 1				Cycle 2	Cycle 3			Subsequent Cycles Day 1	End of Treatment (EoT)	30-day Safety FU	60-day Safety FU	90-day Safety FU	120-day Safety FU	150-day Safety FU	Efficacy FU	End of post-treatment FU	Survival
Day of cycle			-28 (-35 for arm 1A) to -1	1	8	15	21	1	1	8	15	1									
[redacted]																					
Survival																					

[redacted]

	Category	Protocol section	Screening period	Treatment Period (Cycle = 28 days)									Follow-up (FU) Period							
													Safety FU					Efficacy FU (Not applicable if EoT due to progression)		
			Screening	Cycle 1				Cycle 2	Cycle 3			Subsequent Cycles Day 1	End of Treatment (EoT)	30-day Safety FU	60-day Safety FU	90-day Safety FU	120-day Safety FU	150-day Safety FU	Efficacy FU	End of post-treatment FU	Survival
Day of cycle			**-28 (-35 for arm 1A) to -1**	**1**	**8**	**15**	**21**	**1**	**1**	**8**	**15**	**1**								
Survival status	D	7.1.9																		Every 3 months

[redacted]

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 Screening

The screening period begins once written informed consent is provided and ends after 28 days (or after 35 days for subjects screened for Arm 1A) or when subject is randomized/enrolled, whichever comes first.

Screening assessments to confirm eligibility into the study, as described in Table 7-2, should be performed within 1 to 28 days prior to the first dose of study treatment, unless otherwise specified in Table 7-1.

Serum pregnancy test must be confirmed negative prior to the first dose of study treatment.

In the randomized section of the study, a subject whose baseline tumor biopsy tissue sample does not meet the tumor sample quality criteria outlined in Section 7.2.3.1.1 will be considered a screen failure. In the non-randomized section of the study, the collection of a baseline tumor sample should be performed as soon as possible after consent is obtained and submitted to Novartis- designated laboratory as early as possible and at the latest 20 days prior to planned enrollment date to allow sufficient time for receipt of central LAG-3 results and to complete screening assessments (refer to Section 7.2.3.1.1 and Section 7.2.3.1.2 for details). It is recommended to wait to receive the result of LAG-3 status to perform further screening assessments (as per allowed window defined in Table 7-1 for each assessment). A subject whose baseline tumor biopsy tissue sample does not allow central assessment of LAG-3 will be considered a screen failure, unless a new baseline tumor sample is submitted and assessed for LAG-3 before the end of the screening period. Sample must be reported as LAG-3 positive for subject to be eligible to arm 1A.

A subject 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 approximately 3 weeks of the original screening visit date. In this case, the subject will not be required to sign another ICF, and the original subject ID number assigned by the investigator will be used. In the event that the laboratory test(s) cannot be performed within 3 weeks of the original screening visit, or the re-test(s) do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the subject is considered a screen failure.

A new ICF will need to be signed if the investigator chooses to re-screen the subject after a subject has screen failed, however, the subject ID number will remain the same. All required screening activities (i.e. screening assessments required to confirm eligibility; however, the optional pharmocogenetics ICF does not need to be re-signed) must be performed when the subject is re-screened for participation in the study to satisfy the requirements defined in Table 7-1.

An individual subject may only be re-screened once for the study. Once the number of subjects screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the subjects who screen failed will not be permitted to re-screen.

[redacted]

7.1.2.1 Eligibility screening

Following registering in the IRT for screening, subject eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

7.1.2.2 Information to be collected on screening failures

Subjects who sign the study ICF but are subsequently found to be ineligible prior to randomization/enrollment will be considered a screen failure. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see SAE section for reporting details). If the subject fails to be randomized/enrolled, the IRT must be notified within 2 days of the screen fail that the subject was not randomized/enrolled.

Subjects who are randomized/enrolled and fail to start study treatment for any reason will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

7.1.2.3 Subject demographics and other baseline characteristics

The following data on subject characteristics will be collected at screening:

- Demographic information: age at consent, sex, ethnicity and race
- Relevant medical history (including medical conditions present at time of ICF signature)
- Melanoma histology, ^{V600}*BRAF* status and staging using AJCC staging edition 8 (refer to Appendix 1)
- All prior anti-cancer therapies (medications, surgeries, radiation)
- Prior and current concomitant medications: All medications and significant non-drug therapies taken within 30 days prior to the first dose of study treatment must be recorded in the eCRF. They will be updated on a continuous basis if there are any new changes to the medications.
- HIV history (If mandated per local requirements, a local HIV testing is to be done during screening)

In the randomized section of the study, the LDH value closest to the randomization date must be used in the IRT system for the stratification of randomization in each arm.

7.1.3 Run-in period

Not applicable.

7.1.4 Treatment period

After randomization/enrollment of the subject in an arm via the IRT system, the site personnel will have to report in the eCRF the arm in which the subject has been randomized/enrolled.

The treatment period begins when the first dose of study treatment is administered to the subject (on Day 1 of Cycle 1). Table 7-2 describes the assessments to be performed at each visit during treatment period (refer to Table 7-1 for windows of assessments).

[redacted]

Physical examination and laboratory assessments (hematology, chemistry and coagulation) performed as part of the screening evaluations will not require to be repeated on C1D1 prior to dosing if performed ≤ 72 hours prior to the first dose of study treatment.

In some circumstances (see Section 6.1.5.1), subjects may be allowed to continue to receive study treatment beyond disease progression as per RECIST v1.1 criteria. These subjects will continue assessments as outlined in Table 7-2 until discontinuation of study treatment.

7.1.5 Discontinuation of study treatment

Subjects who discontinue study treatment (i.e. when both investigational drugs are discontinued) at any time during the study for any reason should be scheduled for an End of Treatment (EoT) visit within 7 days after the discontinuation of the last study drug (i.e. within 7 days after the last dose of the last study drug or after the date when decision was made to permanently discontinue both study drugs/the last study drug), at which time all of the assessments for EoT will be performed as described in Table 7-2.

At this EoT visit, all dispensed investigational drugs should be reconciled and the adverse event and concomitant medications recorded in the eCRF.

In addition to mandatory permanent discontinuation of study treatment in case of unacceptable toxicity (as described in Section 6.3), study treatment must also be discontinued under the following circumstances:

- Pregnancy of the female subject
- Use of a prohibited concomitant therapy (refer to Section 6.4.3).
- Any other protocol deviation that results in a significant risk to the subject's safety

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

Subjects may voluntarily discontinue from the study treatment for any reason at any time. If a subject decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the subject's chart and in the eCRF.

All subjects who discontinue study treatment should return for the safety assessments indicated in Section 7.1.7, and if applicable, for the efficacy assessments indicated in Section 7.1.8.

Subjects should NOT be considered withdrawn from the study, unless they state an intention to withdraw consent for all study assessments including follow up (see Section 7.1.6) or become lost to follow-up for any other reason (see Section 7.1.10).

The investigator must also contact the IRT to register the subject's discontinuation from study treatment. Site personnel will also have to record the End of Treatment in the Disposition page in the eCRF.

Crossover or re-randomization of subjects to other arms, including better performing arms, is not allowed.

7.1.5.1 Replacement policy

Not applicable.

[redacted]

7.1.6 Withdrawal of consent

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

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

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

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 subject are not allowed unless safety findings require communicating or follow-up.

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

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

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

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

7.1.7 Follow up for safety evaluations (Safety follow up)

After study treatment discontinuation for any reason (except death), all subjects must be followed for safety evaluations as outlined in Table 7-2.

Due to the extended half-life of spartalizumab and LAG525 and the potential occurrence of side effects with checkpoint inhibitors, all subjects will be followed for safety up to 150 days after the last dose of spartalizumab or LAG525. In the case that spartalizumab is permanently discontinued, but the combination agent is continued (i.e capmatinib or canakinumab), subjects will have to be followed for safety evaluations up to 150 days following the last dose of spartalizumab/LAG525, or up to 130 days after the last dose of canakinumab, or up to 30 days after the last dose of capmatinib or ribociclib, whichever is longer. The 30-day safety follow-up visit should be scheduled 30 days after last dose of study treatment (if last dose was more than 30 days ago when the decision is taken to discontinue study treatment, then 30-day safety follow-up should be performed as soon as possible).

If a subsequent anti-cancer therapy is initiated, only adverse events suspected to be related to study treatment will be collected.

After the 30-day onsite safety follow-up visit, subjects will be followed (via telephone call or onsite visit if subject happens to be visiting the site) at 60, 90, 120 and 150 days after the last dose of spartalizumab/LAG525 (refer to Table 7-1 for visit windows). All safety

assessments should be completed as per Table 7-2. However, if the subject begins post treatment anti-cancer 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. Data collected should be recorded in the eCRF.

For female subjects of child bearing potential, a pregnancy test will be performed at the time points listed in Table 7-2. After the 30-Day Safety Follow-up visit, women of childbearing potential will perform at-home urine pregnancy testing every 30 days using kits provided until the 120-Day follow-up telephone call visit. Every effort must be made for the women of child bearing potential to return to the site for the 150-day Safety Follow-up visit for the final serum pregnancy test [redacted] samples. However, if the subject is unable to return then the subject will administer the urine pregnancy test at home using the kit provided. For all pregnancy tests performed at home, the site personnel will follow-up with the subject via telephone call to collect the date and the test results and document the information in the subject's source documents. If the subject returns to the site for the serum pregnancy test at the 150 day safety follow up the results must be documented in the subject's source documents.

Data collected for AEs/SAEs and concomitant medications must be recorded in the eCRF.

7.1.8 Follow-up for efficacy evaluations (Efficacy follow up)

In addition to safety follow up, subjects who discontinue study treatment for any reason other than documented disease progression as per RECIST v1.1 (per investigator assessment), death, lost to follow-up, or withdrawal of consent should continue tumor assessments as outlined in Section 7.2.1 until documented disease progression as per RECIST v1.1 (per investigator assessment), withdrawal of consent, lost to follow-up, death, or study is terminated by the sponsor. Every effort will be made to continue collection of tumor assessments even after the start of subsequent anti-cancer therapy for subjects that have not progressed.

Site personnel will have to record the End of Post-Treatment Follow up in the Disposition page in the eCRF at the end of efficacy follow-up, when subject meets one of the criteria described above.

7.1.9 Survival follow-up

Subjects will enter the survival follow-up period once they complete the safety follow-up and efficacy follow-up after study treatment discontinuation (whichever is longer). Subjects will then be contacted by telephone every 12 weeks (± 1 week) until death, withdrawal of consent, lost to follow-up or end of study to follow-up on their survival status. Any new anti-cancer therapies that have been started since study treatment was discontinued will also be collected (radiotherapies, surgeries and medications, including regimen number, names of all medications received within each regimen and start/end dates for each medication) and any change or new anti-cancer therapy initiated since the last telephone contact date will be captured in the eCRF.

7.1.10 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by

[redacted]

contacting the subject, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered lost to follow-up until due diligence has been completed. Subjects lost to follow up should be recorded as such in the Disposition eCRF page.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor response will be assessed locally and centrally according to the Novartis guideline version 3.2 (Appendix 2) based on RECIST 1.1 (Eisenhauer et al 2009). The imaging assessment collection plan is presented in Table 7-3. Details of the central review process will be described in the independent review charter.

Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis.

The local investigator's tumor assessment as per RECIST 1.1 will be used for primary endpoint analysis purposes and for treatment decision making. Blinded independent central review (BIRC) of the imaging data per RECIST 1.1 will be performed by the designated imaging CRO and results will be included for primary and final analyses as a supportive analysis. [redacted]

Information regarding prior interventions (e.g. radiotherapy), pre-existing radiographic findings that mimic metastatic disease at baseline/screening and prior interventions will be collected in the eCRF and transmitted electronically to the imaging CRO for review by the independent radiologist. Sites must ensure the data is entered in the eCRF prior to image submission to the CRO.

Information regarding cytology results (e.g. needle aspiration, biopsy or any other form of collection, paracentesis, puncture) obtained during the study for any clinically indicated reason will be also collected in the eCRF and transmitted electronically to the imaging CRO when applicable, for review by the independent radiologist. Sites must ensure the data is recorded in the eCRF prior to image submission to the CRO.

Clinical data such as physical exam, photography, biopsy results, pathology/histology and cytology results, as well as, information regarding prior interventions, pre-existing radiographic findings that could mimic metastatic disease at baseline/screening and on-study interventions will be transmitted electronically to the imaging CRO for review by an independent reviewer. Sites must ensure the data is entered in the eCRF prior to image submission to the CRO.

Table 7-3 Imaging Assessment Collection Plan

Procedure	Screening/Baseline Day -28 to Day -1)	During Treatment/Follow-up (± 7 days window)
Chest, abdomen and pelvis CT or MRI (with intravenous contrast enhancement) (for PET/CT please see Section 7.2.1.2)	Mandatory	**During treatment**: 12 weeks (± 7 days) after the date of randomization (or after the date of first dose of study treatment in arm 1A), then every 8 weeks (± 7 days) until 52 weeks after randomization/date of first dose of study treatment in arm 1A then every 12 weeks until disease progression per RECIST v1.1 by local assessment. **End of Treatment (EOT):** Only to be done if a scan

[redacted]

Procedure	Screening/Baseline Day -28 to Day -1)	During Treatment/Follow-up (± 7 days window)
		was not conducted within 30 days prior to end of study treatment. **Efficacy follow up**: subjects who discontinue study treatment for reason other than disease progression per RECIST v1.1 must continue to have scans performed on the same schedule as during treatment until disease progression per RECIST v1.1. In case of continuation of study treatment beyond initial disease progression per RECIST v1.1, follow the same schedule for scans as during treatment until criteria defined in Section 6.1.5.1 are met. Refer to Section 7.2.1.2 for details on additional tumor assessments required for confirmation of response per RECIST 1.1 [redacted].
Brain CT or MRI	Mandatory	If clinically indicated or if lesions were documented at screening, follow same schedule as CT/MRI of chest, abdomen, and pelvis.
Whole body bone scan	If clinically indicated	If clinically indicated
CT or MRI of other metastatic sites (e.g. neck)	If clinically indicated	If clinically indicated or if lesions were documented at screening, follow same schedule as CT/MRI of chest, abdomen, and pelvis.
Localized bone CT, MRI or X-ray	If clinically indicated	If clinically indicated or if lesions were documented at screening, follow same schedule as CT/MRI of chest, abdomen, and pelvis.
Color Digital photography (with metric ruler) of cutaneous lesions	Mandated for any cutaneous lesions present	If clinically indicated or if cutaneous lesions were documented at screening, follow same schedule as CT/MRI of chest, abdomen, and pelvis.

7.2.1.1 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 subject within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after randomization (or after the date of first dose of study treatment in arm 1A) cannot be considered baseline images. The following assessments are required at screening/baseline:

- Chest, abdomen and pelvis CT or MRI (with intravenous contrast enhancement)
- Brain CT or MRI
- Whole body bone scan, 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
- Color photography (with metric ruler) for any skin lesions present
- CT or MRI of other metastatic sites (e.g., neck), if clinically indicated

If a subject has a contraindication to intravenous CT 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

[redacted]

performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

Brain MRI or CT must be completed at screening. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable. If clinically indicated, a whole body bone scan must 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 must 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.

If skin lesions are present at screening, color photography should be acquired using a digital camera in clear focus, including a scale/ruler, in such a way that the size of the lesion(s) can be determined from the photograph.

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.

Any potential lesion that could mimic metastatic disease must be confirmed negative for melanoma as confirmed by biopsy/pathology and cannot be considered as measurable or non-measurable lesions.

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

7.2.1.2 Post-baseline imaging assessments

Imaging assessments as described in Table 7-3 should be performed at the time points specified using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 7-2). Imaging assessments for response evaluation will be performed 12 weeks (± 7 days) after the date of randomization (or after the date of first dose of study treatment in arm 1A), then every 8 weeks (± 7 days) until 52 weeks after randomization/date of first dose of study treatment in arm 1A, and every 12 weeks (± 7 days) thereafter until disease progression per RECIST 1.1 (as assessed by the investigator), death, lost to follow-up or withdrawal of consent. Imaging assessments should be scheduled using the randomization date (or after the date of first dose of study treatment in arm 1A) 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.

An additional tumor assessment must be performed to confirm response (complete response CR or partial response PR) as per RECIST v1.1, no less than 4 weeks after the criteria for response are first met.

For subjects who discontinue study treatment without disease progression per RECIST v1.1 (as assessed by the investigator), imaging assessments must be performed as part of efficacy follow up as described in Table 7-2 and Table 7-3 until disease progression per RECIST v1.1 (as assessed by the investigator), death, lost to follow-up or withdrawal of consent.

[redacted]

Every effort will be made to continue collection of tumor assessments even after the start of subsequent anti-cancer therapy for subjects that have not progressed.

For all subjects (including those who continue study treatment beyond disease progression per RECIST v1.1), at least two additional tumor assessments that are at least 4 weeks apart are recommended subsequent to disease progression per RECIST v1.1 [redacted] no less than 4 weeks after criteria for disease progression per RECIST v1.1 are first met. Tumor assessments after start of new anti-cancer therapy are recommended.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a subject, 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.

Any imaging exams submitted to the imaging CRO are expected to have a local RECIST v1.1 assessment completed and recorded in the eCRF. Scans done for safety and/or off protocol imaging should not be submitted to the imaging CRO and/or have a corresponding local RECIST v1.1 assessment.

Each lesion that is measured at baseline must be measured by the same method (either same imaging method or by photography, including a metric ruler) and when possible, by the same local radiologist/physician throughout the study so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Combined PET/CT with diagnostic CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of IV contrast media. At the discretion of the Investigators, PET scans may be performed to document progressive disease per RECIST v1.1. (Appendix 2).

All study imaging done for efficacy or for suspicion of progression, including assessments done after PD per RECIST v1.1 and any on protocol off-schedule imaging studies, must be submitted to the designated imaging CRO for quality control and central review.

7.2.2 Safety and tolerability assessments

Safety will be monitored as described in Table 7-2 by assessing physical examination, performance status, vital signs, weight, laboratory evaluations and ECG as specified below, as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

More frequent examinations may be performed at the investigator's discretion, if clinically indicated.

7.2.2.1 Physical examination

A complete physical examination will be performed at screening (and if clinically indicated thereafter) and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

[redacted]

A short physical exam will be performed as per schedule in Table 7-2 and will include the examination of general appearance. Based on the safety profiles of the study drugs, special attention should be given to any signs or symptoms suggestive for infections, pneumonitis or interstitial lung disease. Patients receiving capmatinib in Arm 2 should be monitored for any clinical signs indicative of neural toxicity, and a neurological examination should be performed as clinically indicated.

Information for all physical examinations must be included in the source documentation at the study site.

Clinically relevant findings that are present prior to signing informed consent must be recorded on the eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event (refer to Section 8) must be recorded in the eCRF as an adverse event.

7.2.2.2 Vital signs

Vitals signs will be collected as per the schedule in Table 7-2.

Vital signs include blood pressure (Systolic blood pressure [SBP] and diastolic blood pressure [DBP], supine position preferred when ECG is collected), pulse measurement, and body temperature.

7.2.2.3 Height and weight

Height will be measured at screening.

Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-2.

7.2.2.4 Performance status

ECOG Performance status scale will be used as described in Table 7-4.

Table 7-4 ECOG Performance Status

	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
5	Dead

7.2.2.5 Laboratory evaluations

A central laboratory will be used for analysis of all specimens listed in Table 7-5, except for urinalysis, HIV testing (to be performed only if required per local regulations) and urine/serum pregnancy tests, which will be performed locally. The laboratory assessments must be performed as per the schedule in Table 7-2.

At screening, all subjects must be fasting for at least 12 hours overnight before each blood collection to obtain fasting glucose.

[redacted]

Subjects randomized in Arm 1 or enrolled in Arm 1A (spartalizumab in combination with LAG525) and in Arm 4 (spartalizumab in combination with ribociclib) are required to be fasting for at least 12 hours overnight before each blood collection to obtain fasting glucose and investigators should monitor the potential occurrence of auto-immune diabetes (for Arm 1 and Arm 1A).

Note on fasting conditions: Subjects must be fasting from all food and drink. Water is allowed during all fasting periods; however coffee, tea and juice are not permitted during the fasting period.

Details on the collections, shipment of samples and reporting of results by the central laboratory will be provided to investigators in a separate Laboratory Manual.

Laboratory results from the central laboratory will be used to determine subject's eligibility (except for laboratory assessments performed locally). If an immediate clinical decision needs to be made, locally unscheduled testing may be performed and used to determine eligibility.

If local laboratory testing is performed during the study, the results of the local laboratory will be recorded in the eCRF if at least one of the following criteria is met:

- local results were used to determine subject's eligibility (including local LDH result used for stratification of randomization), or
- a treatment decision was made based on the local results, or
- local abnormal laboratory values or test results meet one of the criteria for adverse event(s), as defined in Section 8.1.1. In this case, local results supporting start/end date of adverse event and changes in grade should be recorded in the eCRF.

Sites will be requested to provide the local laboratory reference ranges and a copy of the laboratory certification to Novartis for all local laboratory results recorded in the eCRF.

Clinically significant laboratory abnormalities must be recorded as either medical history/current medical conditions or adverse events (if meeting the criteria for reporting as AE as defined in Section 8.1.1), as appropriate.

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

Table 7-5 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, Platelets, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other)
Chemistry	Albumin, Alkaline phosphatase, ALT , AST, GGT, LDH, Calcium, corrected calcium (corrected on serum albumin; mandatory at screening for all subjects, and then as clinically indicated), Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Total Bilirubin, Total Cholesterol, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (At screening: fasting glucose for all subjects; at subsequent time points: fasting glucose for subjects in Arm 1 and Arm 1A receiving LAG525 and for subjects in Arm 4 receiving ribociclib, non-fasting for other arms) Cardiac Troponin T (TnT) level must be tested at screening (for all patients), and then at C1D15, C2D1 and C3D1 for patients randomized into Arm 1 and Arm 1A only (also refer to Section 7.2.2.5.1 for monitoring guidance in Arm 1/Arm 1A). Central TnT testing is recommended, but if site is unable to assay TnT centrally (or locally), local Troponin I (TnI) is acceptable.
Urinalysis (local)	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen).

[redacted]

Test Category	Test Name
	If dipstick is abnormal, then perform local lab microscopic panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Thyroid function	At baseline: TSH, Free T3 and Free T4 At the subsequent visits, as indicated in Table 7-2: TSH only. If TSH is abnormal, central lab will test Free T3 and Free T4
Hepatitis serology	HBV-DNA, HbsAg, HbsAb, HbcAb, HCV RNA-PCR
Safety cytokines (for cytokine release syndrome)	IFN-γ, IL-6, IL-1 beta, TNF-α
HIV serology (local)	If required per local regulations: local HIV testing at screening
Pregnancy Test (local) for women of childbearing potential	At screening: A local serum pregnancy test must be performed ≤ 72 hours before first dose of study treatment. Local serum and urine pregnancy tests must then be performed as per Table 7-2

7.2.2.5.1 Troponin monitoring guidance

Cardiac enzyme Troponin T (or I) level must be tested at screening for all patients.

For patients randomized in Arm 1 and Arm 1A (spartalizumab + LAG525), additional cardiac troponin T (or I) assessments will be done during the first two months at C1D15, C2D1 and C3D1. If Troponin level is above ULN during the first two months, or if the level is above the screening value (if the screening value was 1-2 fold ULN), a central ECG assessment (as described in Section 7.2.2.6) and a local echocardiogram must be performed. If ECG and echocardiogram are normal, Troponin must be repeated the following day. However, if ECG or echocardiogram are abnormal and suggestive of myocarditis, a cardiologist must be consulted. Results of local echocardiogram (or any other local assessments performed for cardiac evaluation, as well as conclusions of any cardiologist consulted) will be documented in subject's source documents.

7.2.2.6 Electrocardiogram (ECG)

Standard 12 lead ECG (triplicate, unless otherwise stated) recording will be performed at each ECG collection time point as indicated in Table 7-6 using the ECG machine provided by central core ECG laboratory designated by Novartis.

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable assessment and according to the [ECG investigator manual].

The individual triplicate ECGs should be recorded approximately 2 minutes apart. The mean Fridericia QT correction formula (QTcF) value for each visit will be calculated from the triplicate ECGs for each subject and should be used for clinical decisions.

Subject's eligibility to the study should be assessed by the investigator based on the local interpretation of results from the triplicate ECG recordings performed on the machine provided. Clinically significant abnormalities present at screening should be reported as Medical History in the eCRF. Clinically significant findings must be discussed with Novartis prior to randomizing the subject in the study.

Interpretation of the ECG tracing must be made by a qualified physician. Each ECG tracing should be printed, labeled with the study number, subject number, date, and kept in the source documents at the study site.

[redacted]

New or worsened clinically significant findings occurring after informed consent is signed must be recorded as Adverse Events in the eCRF.

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.

If an unscheduled ECG is performed at an external medical facility, a copy of the ECG should be obtained and forwarded to the ECG core laboratory, and a copy kept in the source documents at the study site.

All ECGs performed during the study, including unscheduled triplicate ECGs with clinically relevant findings, 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.

Table 7-6 Central ECG collection plan

	Time				
Visit /Cycle	**Arm 1 and Arm 1A**	**Arm 2**	**Arm 3**	**Arm 4**	**ECG Type**
Screening	*Any time*	*Any time*	*Any time*	*Any time*	12 Lead, triplicate, central
C1D1	Pre-dose	Pre-dose	Not applicable	Pre-dose	12 Lead, triplicate, central
	Not applicable	Post dose: 4 hours after capmatinib administration	Not applicable	2h post-dose (± 15 min)	12 Lead, triplicate, central
	Not applicable	Not applicable	Not applicable	4 h post-dose (± 15 min)	12 Lead, triplicate, central
C1D15	Not applicable	Not applicable	Not applicable	Pre-dose	12 Lead, triplicate, central
	Not applicable	Not applicable	Not applicable	2h post-dose (± 15 min)	12 Lead, triplicate, central
	Not applicable	Not applicable	Not applicable	4 h post-dose (± 15 min)	12 Lead, triplicate, central
C2D1	Pre-dose (single)	Pre-dose (single)	Not applicable	Pre-dose (triplicate)	12 Lead, central
C3D1	Pre-dose	Pre-dose	Not applicable	Pre-dose	12 Lead, triplicate, central
	Not applicable	Post dose: 4 hours after capmatinib administration	Not applicable	2h post-dose (± 15 min)	12 Lead, triplicate, central
C3D15	Not applicable	Not applicable	Not applicable	Pre-dose	12 Lead, triplicate, central
	Not applicable	Not applicable	Not applicable	2h post-dose (± 15 min)	12 Lead, triplicate, central
C4D1	Not applicable	Not applicable	Not applicable	Pre-dose	12 Lead, triplicate, central
C5D1	Not applicable	Not applicable	Not applicable	Pre-dose	12 Lead, triplicate, central
C6D1	Not applicable	Not applicable	Not applicable	Pre-dose	12 Lead, triplicate, central

Visit /Cycle	Time				ECG Type
	Arm 1 and Arm 1A	Arm 2	Arm 3	Arm 4	
	Not applicable	Not applicable	Not applicable	2h post-dose (± 15 min)	12 Lead, triplicate, central
Day 1 of all other cycles (only for patients with QTcF ≥ 481 ms at any time prior to cycle 7)	Not applicable	Not applicable	Not applicable	Pre-dose	12 Lead, triplicate, central
Day 1 of cycle 9 and every third cycle (only for patients with QTcF ≥ 481 ms at any time prior to cycle 7)	Not applicable	Not applicable	Not applicable	2h post-dose (± 15 min)	12 Lead, triplicate, central
EoT	Anytime	Anytime	Anytime	Anytime	12 Lead, triplicate, central
Unscheduled	Anytime	Anytime	Anytime	Anytime	12 Lead, triplicate, central

7.2.2.7 [redacted] immunogenicity

7.2.2.7.1 [redacted] immunogenicity (IG) blood collection and handling

Blood samples for [redacted] IG analysis of spartalizumab, LAG525 and canakinumab will be collected according to the relevant time points described in Table 7-7, Table 7-8, Table 7-9, Table 7-10 and Table 7-11.

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Please refer to the CPDR001J2201 Central Lab Manual for instructions on processing of samples.

[redacted]

- A total of 3.5 mL of blood (serum) will be collected at specified time points for spartalizumab IG analysis.
- A total of 5 mL of blood (serum) will be collected at specified time points for LAG525 IG analysis.

[redacted]

- A total of 3.5 mL of blood (serum) will be collected at specified time points for canakinumab IG analysis.

The exact date and time of drug administration and blood draws for [redacted] IG assessment will be recorded in the eCRF.

[redacted]

If subject experience an SAE or an AE leading to the discontinuation of the study treatment. [redacted] If subjects experience suspected immunologically related AEs 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 of the occurrence. [redacted]

[redacted]

[redacted]

Table 7-7 Blood (serum) collection schedule for spartalizumab [redacted] immunogenicity samples (applicable for all subjects)

Cycle	Day	Scheduled Time Point [c]	Dose reference ID	[redacted]	IG Sample number	[redacted]
1	1	Pre-infusion C1D1[a]	1		301	
1	1	1 hr post end of C1D1 infusion (± 5 min)	1		-	
1	8	168 hr post C1D1 infusion (± 8 hr)	1		-	
1	15	336 hr post C1D1 infusion (± 24 hr)	1		-	
2	1	Pre-infusion C2D1 [a]	2		305	
2	1	1 hr post end of C2D1 infusion (± 5 min)	2		-	
3	1	Pre-infusion C3D1 [a]	3		307	
3	1	1 hr post end of C3D1infusion (± 5 min)	3		-	
3	8	168 hr post C3D1 infusion (± 8 hr)	3		-	
3	15	336 hr post C3D1 infusion (± 24 hr)	3		-	
4	1	Pre-infusion C4D1 [a]	4		311	
5	1	Pre-infusion C5D1 [a]	5		312	
6	1	Pre-infusion C6D1 [a]	6		313	
9, 12, 15, etc (every 3 months)	1	Pre-infusion [a]	101, 102, 103, etc		317, 318, 319, etc	

[redacted]

Cycle	Day	Scheduled Time Point [c]	Dose reference ID	[redacted]	IG Sample number	[redacted]
EOT	-	Anytime	N/A		314	
30-day safety follow-up visit		Anytime	N/A		315	
150-day safety follow-up visit [d]		Anytime	N/A		316	
-	-	Unscheduled [b]	N/A		3000+	

[a] Take samples within 30 min before the infusion begins
[redacted]
[c] Time is relative to the beginning of the infusion; it will be recorded as both days and hours on the eCRF but only as hours in the database (1 day = 24 hrs)
[d] for women with child bearing potential
Note 1: Immunogenicity samples are collected together with [redacted]. Blood samples are to be collected from the arm opposite from infusion site.
[redacted]

Table 7-8 Blood (serum) collection schedule for LAG525 [redacted] immunogenicity samples (only applicable for subjects enrolled in arm 1 and arm 1A)

Cycle	Day	Scheduled Time Point [c]	Dose reference ID	[redacted]	IG Sample number	[redacted]
1	1	Pre-infusion C1D1 [a]	11		501	
1	1	1 hr post end of C1D1 infusion (± 5 min)	11		-	
1	8	168 hr post C1D1 infusion (± 8 hr)	11		-	
1	15	336 hr post C1D1 infusion (± 24 hr)	11		-	
2	1	Pre-infusion C2D1 [a]	12		505	
2	1	1 hr post end of C2D1 infusion (± 5 min)	12		-	
3	1	Pre-infusion C3D1 [a]	13		507	
3	1	1 hr post end of C3D1 infusion (± 5 min)	13		-	
3	8	168 hr post C3D1 infusion (± 8 hr)	13		-	
3	15	336 hr post C3D1 infusion (± 24 hr)	13		-	
4	1	Pre-infusion C4D1 [a]	14		511	
5	1	Pre-infusion C5D1 [a]	15		512	
6	1	Pre-infusion C6D1 [a]	16		513	
9, 12, 15, etc (every 3 months)	1	Pre-infusion [a]	201, 202, 203, etc		515, 516, 517, etc	
EOT	-	Anytime	N/A		514	
-	-	Unscheduled [b]	N/A		5000+	

[redacted]

Cycle	Day	Scheduled Time Point [c]	Dose reference ID	[redacted]	IG Sample number	[redacted]

[a] Take samples within 30 min before the infusion begins
[redacted] Unscheduled IG blood samples will be uniquely, sequentially numbered 5000, 5001 etc.
[c] Time is relative to the beginning of the infusion; it will be recorded as both days and hours on the eCRF but only as hours in the database (1 day = 24 hrs)
Note 1: Immunogenicity samples are collected together with [redacted]. Blood samples are to be collected from the arm opposite from infusion site.
[redacted]

[redacted]

Table 7-10 Blood (serum) collection schedule for canakinumab [redacted] immunogenicity samples (only applicable for subjects enrolled in arm 3)

Cycle	Day	Scheduled Time Point	Dose reference ID	[redacted]	IG Sample number	[redacted]
1	1	Pre-dose C1D1 [a]	31		701	
1	8	168 hr post C1D1 dose (± 8 hr)	31		-	
1	15	336 hr post C1D1 dose (± 24 hr)	31		-	
2	1	Pre-dose C2D1 [a]	32		704	

[redacted]

Cycle	Day	Scheduled Time Point	Dose reference ID	[redacted]	IG Sample number	[redacted]
3	1	Pre-dose C3D1 [a]	33		705	
3	8	168 hr post C3D1 dose (± 8 hr)	33		-	
3	15	336 hr post C3D1 dose (± 24 hr)	33		-	
4	1	Pre-dose C4D1 [a]	34		708	
5	1	Pre-dose C5D1 [a]	35		709	
6	1	Pre-dose C6D1 [a]	36		710	
9, 12, 15, etc (every 3 months)	1	Pre-dose [a]	37, 38, 39, etc		712, 713, 714,etc	
EOT	-	Anytime	N/A		711	
-	-	Unscheduled [b]	N/A		7000+	

[a] Take samples within 30 min before the injection is administered.
[redacted]Unscheduled IG blood samples will be uniquely, sequentially numbered 7000, 7001 etc.
Note 1: Immunogenicity samples are collected together with [redacted]. Blood samples are to be collected from the arm opposite from infusion site.
[redacted]

[redacted]

[redacted]

7.2.2.7.2 Analytical method

Bioanalysis for [redacted] IG determination will employ validated assays:

The assay to quantify LAG525, capmatinib, spartalizumab and ribociclib will be validated LC-MS/MS (Liquid chromatography–mass spectrometry) methods respectively.

The assay to quantify canakinumab will be using a validated competitive ELISA method.

The assay to assess the IG against LAG525 and spartalizumab will be using validated homogeneous ELISA methods respectively.

The assay to assess the IG against canakinumab will be a validated Meso Scale Discovery (MSD) electrochemiluminescence assay.

7.2.3 Biomarkers

During the study, both blood and tumor samples will be collected for biomarker analyses as described in Table 7-12.

All assessments will be performed by a Novartis designated laboratory. Instructions for collection, storage and shipment of all biomarker samples will be provided in the laboratory manual. Required sample collection information must be entered in the eCRF and requisition forms.

While the goal of the biomarker study is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons. For example, there may be inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis. Alternatively, there may be insufficient efficacy to allow for correlative analyses. Therefore, depending on the results obtained during the study, collection/analysis of some samples may be omitted at the discretion of the sponsor.

Table 7-12 Biomarker sample collection plan

Sample Type	Volume	Visit	Time point
Tumor samples			
Mandatory, if available: Provision of archival formalin fixed paraffin embedded (FFPE) block or slides from a tumor sample collected prior to start of any prior anti-PD-1/PD-L1 mono- or combination therapy	FFPE block (preferred) or 15 archival slides *(leftover block can be returned upon request)*	C1D1	Any time

[redacted]

Sample Type	Volume	Visit	Time point
Mandatory Newly or recently obtained (as defined in Section 7.2.3.1.1) tumor biopsy	FFPE tumor block (Formalin-fixed tissue in ethanol is acceptable for arm 1A only)	Screening	Day -28 to Day -1 (for screening in arm 1A, sample can be collected from Day -35 and should be submitted as early as possible and at the latest by Day -20 for central LAG-3 assessment)
Mandatory Newly obtained tumor biopsy	FFPE tumor block	C1D21 +7 day window	Any time between C1D21 and C2D1, pre-dose

[redacted]

[redacted]

7.2.3.1 Biomarker assessments in tumor tissue

In the non-randomized section of the study, mandatory screening tumor samples will be centrally assessed to determine LAG-3 status for enrollment into arm 1A.

For all arms (randomized or non-randomized), biomarker analyses in mandatory tumor samples to assess changes in levels, phenotype and activation of T cell populations in the tumor and tumor microenvironment will support the decision making at each interim analysis as a part of the secondary objectives (Table 3-1). Secondary objective biomarker analyses may include but are not limited to $CD8^+$ T cell infiltration and T cell activation by IHC, gene expression analysis by Nanostring and/or T cell repertoire/clonality by TCR-sequencing [redacted] Analyses will be performed on an on-going basis, such that the data will be readily available for decision making purposes at each interim analysis.

[redacted]

7.2.3.1.1 Mandatory baseline and on-treatment tumor sample collections

Sequential tumor biopsies at screening and 3-4 weeks on treatment are mandatory. The same lesion should be biopsied sequentially whenever feasible. Biopsies of the target lesions are not allowed. A biopsy sample must be provided during screening prior to the first dose of study treatment and at 3 to 4 weeks on treatment (between C1D21 and C2D1). The biopsy guidelines for collection of biopsy specimens are described in Table 7-13.

In all arms except arm 1A: For the mandatory screening biopsy specimen, local pathology analysis is required to take place prior to randomization. If the tissue quality criteria listed in Table 7-13 are not met, the subject should be re-biopsied in order to meet eligibility requirements.

For arm 1A: Baseline tumor sample must be submitted directly to the Novartis-designated laboratory (Histogenex, Antwerp, Belgium) for central assessment of LAG-3 status. Local pathology review of tissue demonstrating that sample meets tissue quality criteria (Table 7-13) is not required for baseline sample (refer to Section 7.2.3.1.2 for details).

Table 7-13 Guidelines for mandatory biopsy collection (applicable for all arms) and tissue quality criteria (recommended for arm 1A, mandatory for other arms)

Biopsy guidelines	• Minimum three core samples per biopsy using an 18G or larger diameter needle or other biopsy method which results in tissue of comparable or larger size • Minimum size per tissue core should be ~10 mm in length and ~1 mm diameter
Tissue quality criteria*	• Minimum tumor content of 30%

[redacted]

• Minimum total tumor tissue area 30 mm^2

* Criteria are to be measured in one tissue section during local pathologist review. Total tumor tissue area excludes non-tumoral areas (i.e. necrosis, fatty, hemorrhagic tissue) and sample should not contain abundant melanin pigmentation. For samples with >60% tumor content, total tumor tissue area may be < 30 mm^2 but must be ≥15 mm^2.

Entire tissue sample (3 cores or comparably sized tissue sample, taken from the same lesion) should be submitted, embedded into a single block (or for arm 1A only, submission of formalin-fixed tissue in ethanol is also acceptable). Further instructions on the collection and submission of samples is found in the central laboratory manual.

Mandatory biopsies may be taken from cutaneous, subcutaneous, nodal or visceral lesions.

For France only: Mandatory biopsies should be taken from cutaneous, subcutaneous or nodal lesions.

CNS and bone metastasis are excluded for biopsy. Fine needle aspirates cannot be accepted.

For cases of re-screening OR if a biopsy was recently completed as part of standard of care (including before signing the main study ICF), the tissue sample can be submitted as baseline tumor sample as long as the following criteria are met:

- Recommended for arm 1A, mandatory for other arms: Biopsy date must be within 8 weeks of start of treatment
- Patient must not have received any therapy for unresectable or metastatic melanoma between collection of biopsy sample and start of study treatment
- Same lesion should be amenable for on-treatment biopsy
- Entire block must be available for submission
- Recommended for arm 1A, mandatory for other arms: Biopsy must meet tissue QC criteria (Table 7-13)

For the mandatory on-treatment biopsy specimen in all arms, every effort should be made to adhere with the biopsy guidelines and the resulting sample should meet the tissue quality criteria (Table 7-13). Where medically feasible, the on-treatment biopsy should be taken from the same anatomical location that was biopsied at baseline.

If the on-treatment biopsy is not taken, medical justification should be documented in the eCRF, i.e. the lesion shrank to an extent biopsy is no longer possible or there is a new or increased medical risk of biopsy since baseline, such as bleeding. If tissue quality criteria in Table 7-13 are not met for the on-treatment biopsy specimen, re-biopsy should be performed where medically feasible.

7.2.3.1.2 Mandatory central assessment of LAG-3 status for eligibility for arm 1A

Newly or recently obtained biopsy samples (as defined in Section 7.2.3.1.1) should be submitted directly to the Novartis-designated central testing laboratory (Histogenex, Antwerp, Belgium) for LAG-3 assessment as early as possible and at the latest 20 days prior to planned first treatment date (Day -20) to allow LAG-3 analysis and reporting of results within the 35-day screening period. The LAG-3 results will be reported directly to the clinical site and the sample must be reported as LAG-3 positive by the central lab for the subject to be eligible to arm 1A. Local LAG-3 results are not accepted for eligibility. Details for sample submission are found in the central laboratory manual.

To ensure tissue samples are evaluable for LAG-3 assessment, the tissue quality criteria in Table 7-13 should be followed and samples must not contain abundant melanin pigmentation.

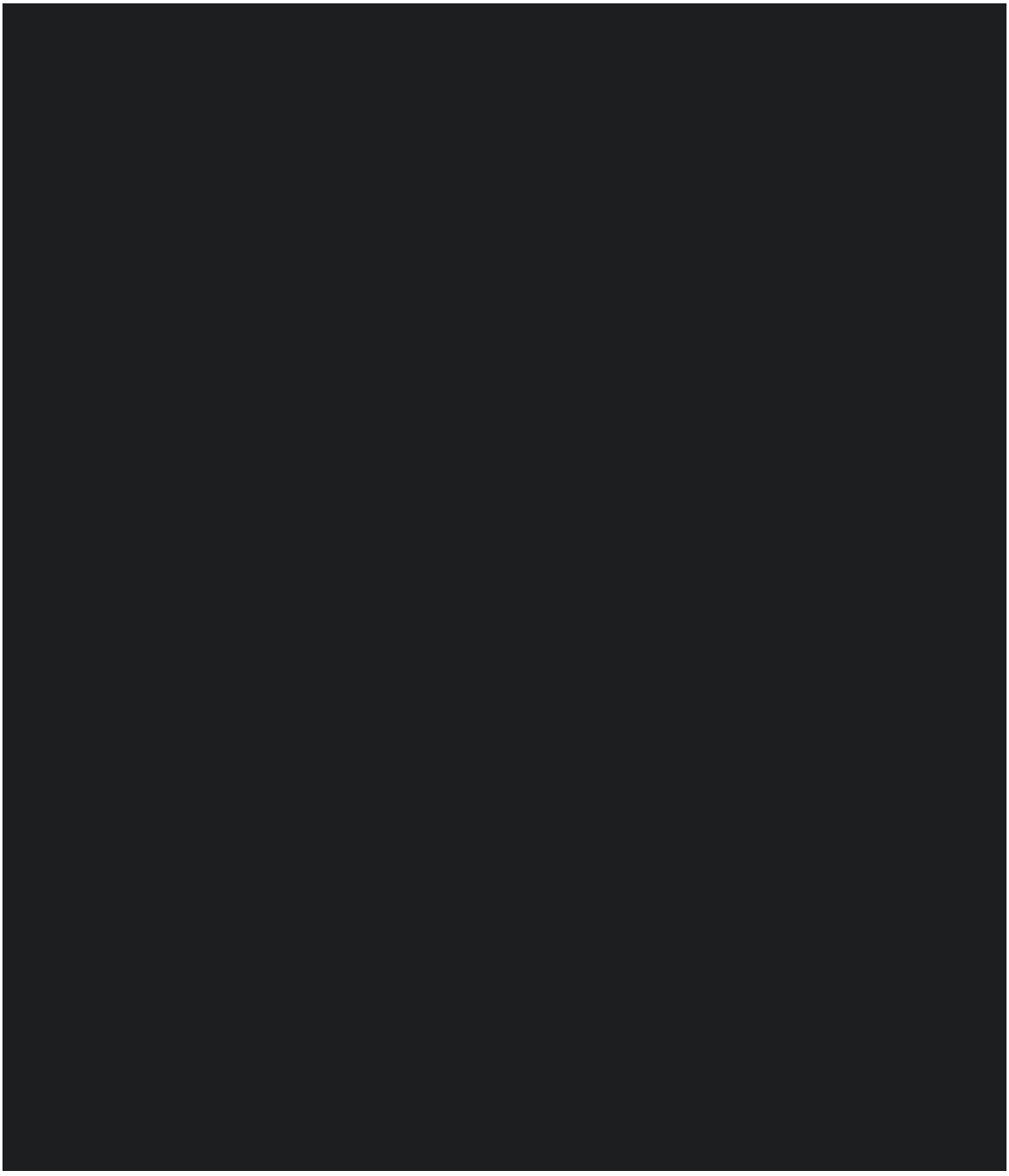
If the submitted sample is not evaluable for LAG-3 assesment for any reason at the Novartis-designated central laboratory (Histogenex, Antwerp, Belgium), another newly or recently obtained tumor biopsy (as defined in Section 7.2.3.1.1) will be requested. The sample must be centrally analyzed to determine LAG-3 status for eligibility before the end of the 35-day screening period or else the subject will be considered as a screen failure.

LAG-3 status will be assessed by immuohistochemistry by a qualified pathologist at the Novartis-designated central testing laboratory (Histogenex, Antwerp, Belgium). Samples which have ≥5% LAG-3 positive staining will be reported as positive for LAG-3 and samples with <5% LAG-3 positive staining will be reported as negative. Once LAG-3 testing is completed, the remainder of the tumor tissue sample will be analyzed for biomarkers for subjects enrolled as described in Section 7.2.3.1.

Upon request, samples determined to be LAG-3 negative will be returned to site. Some tissue material may be retained for potential companion diagnostic development.

[redacted]

[redacted]



8 Safety monitoring and reporting

8.1 Definition of adverse events and reporting requirements

8.1.1 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 subject or clinical investigation subject 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 subject 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 subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible). For serious adverse event refer to Section 8.1.2):

1. The Common Toxicity Criteria (CTC) AE grade: Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
2. Relationship to the study treatment. If the event is due to lack of efficacy or progression ofunderlying 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 arms, not on a single subject
3. 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 a SAE (see Section 8.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with each individual study drug, if the adverse event is considered related to study treatment. Action taken may include one or more of the following:
   - Dose not changed
   - Dose reduced/increased
   - Drug interrupted/withdrawn
6. Whether concomitant medication or non-drug therapy was given.
7. its outcome i.e., its recovery status or whether it was fatal

If the event worsens the event should be reported a second time in the eCRF 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 eCRF 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 subject.

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

Adverse event monitoring should be continued for at least 30 days after the last dose of capmatinib or ribociclib, or at least 130 days after the last dose of canakinumab, or at least

[redacted]

150 days after the last dose of spartalizumab/LAG525, whichever is longer. If a subject starts a subsequent anti-cancer therapy, then only adverse events suspected to be related to study treatment should be collected out to 150 days after discontinuation of 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 the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event, except if the investigator considers that progression of malignancy is related to study treatment.

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

Information about adverse drug reactions for the investigational drug can be found in the Investigator Brochure (IB) of each study drug.

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
- they require changes (reduction, delay or interruption/discontinuation) of study drug(s)

8.1.2 Serious adverse events

8.1.2.1 Definitions

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 a SAE refers to a reaction in which the subject 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

[redacted]

  - social reasons and respite care in the absence of any deterioration in the subject'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 subject 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 subject 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. Please refer to the ICH-E2D Guidelines.

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 (refer to Section 8.5).

8.1.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until at least 30 days after the last dose of capmatinib or ribociclib or at least 130 days after the last dose of canakinumab, or at least 150 days after the last dose of spartalizumab/LAG525, whichever is longer, must be reported to Novartis safety within 24 hours of learning of its occurrence. If a subject starts a subsequent anti-cancer therapy, then only SAE suspected to be related to study treatment should be collected out to 150 days after discontinuation of spartalizumab. SAE suspected to be related to 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.

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, a 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.

[redacted]

Suspected Unexpected Serious Adverse Reactions (SUSAR) 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 SAE experienced after the 150 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

For screen failures, SAE occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

8.2 Emergency unblinding of treatment assignment

Not applicable.

8.3 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 pregnancy consent form to allow the investigator to collect and report information regarding the pregnancy. To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. In consented subjects, 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. Follow-ups will be done one month after the estimated date of delivery and 3 and 12 months after the estimated date of delivery for live births only.

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 any 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.

8.4 Warnings and precautions

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

8.5 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, subject 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 recorded in the 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 8-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing 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.

8.6 Data Monitoring Committee

This study will include a safety data monitoring committee (DMC) to be activated when a combination arm (from the randomized or non-randomized section of the study) reaches Part 2 of the study (expansion phase) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess relevant safety data in the expansion phase of the study at defined intervals and recommend to the sponsor whether to continue, modify or terminate any or all combination arms in the expansion phase.

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

8.7 Steering Committee

The Steering Committee (SC) will be established comprising of investigators participating in the trial, i.e. not being members of the DMC, and Novartis/sponsor representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving 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 including authorship rules. The details of the role of the steering committee will be defined in the Steering Committee charter.

9 Data collection and management

9.1 Data confidentiality

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

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

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

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

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. During the study, the field monitor will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/CRA organization. Additionally, a central analytics organization may analyze data and identify risks and 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 subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the subject's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAE, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed

[redacted]

according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

9.3 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 Electronic Data Capture (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 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

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

9.4 Database management and quality control

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

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

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

Dates of screenings, randomizations/enrollments, screen failures and study treatment completion, as well as randomization codes and data about all study treatments dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis personnel (or designated CRO). The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and the treatment codes will be unblinded and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

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

[redacted]

10 Statistical methods and data analysis

By default Section 10 and all the sub-sections below refer to the randomized section of the study: the same analysis timing, definitions and analysis conventions apply to the non-randomized section of the study, unless specified otherwise. Only arm 1A (spartalizumab + LAG525) will be analyzed in the non-randomized section of the study. In the non-randomized section of the study, the date of first dose of study treatment is used as reference date instead of the randomization date.

For the selection phase (part 1) and expansion phase (part 2), efficacy, safety, and biomarker analysis will be conducted on all subject data at the time that each part is completed. The primary analysis of each randomized and non-randomized section will be performed once the expanded arm has fully enrolled and also after all patients randomized/enrolled had at least 9 months of follow-up. This timing would allow for a potential minimum duration of response of 6 months for all subjects randomized/enrolled, assuming no delayed response. The exact timing of the primary analysis of the randomized section of the study could be revisited if more than one arm is expanded to part 2.

The additional data for any subjects continuing to receive study treatment past this time, as allowed by the protocol, will be further summarized in a final study report once these subjects complete the study.

Categorical data will be presented as contingency tables (frequencies and percentages). For continuous data summary statistics of mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

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

10.1 Analysis sets

All below defined analysis sets will be used to analyze data from both the selection phase (part 1) and the expansion phase (part 2).

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned by randomization. According to the intent to treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure regardless of whether or not treatment was administered. This population will be the primary population for efficacy analysis.

For non-randomized section of the study, the full analysis set (FAS) will be identical to the safety set.

10.1.2 Safety set

The Safety Set includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

[redacted]

10.1.3 Per-Protocol set

Not applicable.

10.1.4 Dose-determining analysis set

Not applicable.

[redacted]

[redacted]

10.1.6 Other analysis sets

10.1.6.1 Biomarker analysis set

The biomarker analysis set, as it pertains to the secondary objective (Section 10.5.5), consists of all subjects in the safety set with an evaluable baseline tumor biopsy sample and at least one evaluable post-baseline tumor biopsy sample. [redacted]

10.2 Subject demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group and for all subjects in the FAS and the Safety Set.

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 at baseline will be summarized separately by system organ class and preferred term, by treatment group and for all subjects.

10.3 Treatments (study treatment, concomitant therapies, compliance)

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, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in months to spartalizumab, LAG525, capmatinib, canakinumab and ribociclib 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 duration of exposure will also be presented for the study treatment by treatment group.

The number of subjects with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized by treatment group and for all subjects, 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 and for all subjects.

10.4 Primary objective

The primary objective of this study is to evaluate the preliminary efficacy (in part 1) and efficacy (in part 2) of spartalizumab in combination with novel agents in subjects with previously treated unresectable or metastatic melanoma.

10.4.1 Variable

Objective response rate (ORR) is defined as the proportion of subjects with best overall response (BOR) of either confirmed complete response (CR) or confirmed partial response (PR), as per local review and according to RECIST v1.1 (see Appendix 2 for details).

[redacted]

ORR will be calculated based on the FAS. ORR and its 95% confidence interval will be presented by treatment group.

As a supportive analysis, ORR as per blinded independent central review (BICR) will be presented by treatment group; along with 95% confidence intervals (see Section 10.4.4).

10.4.2 Statistical hypothesis, model, and method of analysis

10.4.2.1 Randomized section of the study

Part 1: Selection Phase

No formal hypothesis testing will be conducted in part 1. The objective of this part of the study is to explore the anti-tumor activity of the combination of spartalizumab with novel agents as measured by ORR per RECIST v1.1, and to select an arm(s) with promising efficacy that will be advanced to the expansion phase.

To determine whether arms have the potential to demonstrate clinically meaningful response rates, arms will need to show that they cross a specific efficacy probability threshold during the selection phase to advance to the expansion phase. Conversely, arms can also be shown to cross a specific futility probability threshold and consequently will be declared as futile and enrollment in those arms will be terminated. These thresholds and probabilities are highlighted in Table 10-1.

Table 10-1 Probabilities thresholds used to declare efficacy or futility for an arm

Decision rule	Action
P(ORR ≤15%) ≥ 70%	Drop arm for futility
P(ORR ≥20%) ≥ 70%	Efficacy declared; Advance arm to expansion phase (part 2)

The futility decision rule was determined based on simulations such that arms with response rate that is not considered clinically meaningful (i.e. ORR < 10%) will be dropped with high probability (as illustrated in Table 10-10 in Section 10.8.1). Similarly, the decision criterion for advancement to the expansion phase was determined so that arms with clinically meaningful response rate that warrants further development (i.e. ORR>25%) will be advanced with high probability ('power') (see also Table 10-10).

To calculate these probabilities, a beta-binomial posterior distribution will be used as shown below:

$$p_i \sim beta(y_i + 1, n_i - y_i + 1)$$

where y_i are the number of confirmed responses in a combination arm (i), and n_i are the number of subjects enrolled in a combination arm (i). In calculation of the posterior distribution uninformed prior Beta[1,1] will be taken into account for each arrm. The posterior probability will be calculated separately for each arm based on the observed ORR based on RECIST v1.1 criteria at each decision point, i.e. at each interim analysis as described in Section 10.7.1.

No formal comparisons will be made between the combination arms for ORR in this 'selection' phase, instead each of the arms will be evaluated against efficacy and futility thresholds as presented above.

The final decision on whether an arm will be selected for advancement to the expansion phase will primarily be based on the observed ORR using decision rule described above but

other efficacy (in particular duration of response), safety, and biomarker data will be considered as well. Further considerations related to the design and execution of the selection phase will be captured in the SAP Technical Appendix.

Part 2: Expansion Phase

For the arms which show promise for efficacy in part 1 (based on pre-defined criteria), these arms may be expanded.

After completion of the expansion phase and within each arm separately, the following statistical hypothesis will be tested based on objective response rate (ORR):

- The null hypothesis is that the response rate is not clinically meaningful (≤ 10%).
- The alternative hypothesis is that the response rate is clinically meaningful (>10%). The target response rate that warrants further development is ≥ 25%

The null hypothesis will be formally rejected if the lower bound of exact 95% CI for ORR is above 10%. The primary analysis of ORR at the end of part 2 will be based on a combined pool of part 1 and part 2 data for given arm.

For example, assuming 24 subjects enrolled in an arm of interest in part 1 (see Section 10.8.1 for sample size estimates when true ORR = 0.25 in the selection phase), assuming this arm met criteria for expansion and finally assuming 50 subjects are enrolled in the expansion phase, then combined among 74 subjects enrolled in this arm in total and followed sufficiently, 14 or more responses need to be observed to reject the null hypothesis. With those 14 responders among 74 subjects, the point estimate for ORR will be 18.9% with an exact 95% confidence interval of (10.8%, 29.7%). Since the lower bound of the exact 95% CI will be > 10%, this leads to rejection of null hypothesis. The exact 95% CIs for potential observed ORR in 74 subjects are shown in Table 10-2:

Table 10-2 Exact binomial 95% confidence intervals around potential observed ORR for N=74

Number of responders	Observed ORR (%)	95% exact CI (%)
10	13.5	6.7, 23.5
11	14.9	7.7, 25.0
12	16.2	8.7, 26.6
13	17.6	9.7, 28.2
14	**18.9**	**10.8, 29.7**
15	20.3	11.8, 31.2
16	21.6	12.9, 32.7
17	23.0	14.0, 34.2
18	24.3	15.1, 35.7
19	**25.7**	**16.2, 37.2**
20	27.0	17.4, 38.6
21	28.4	18.5, 40.1
22	29.7	19.7, 41.5
23	31.1	20.8. 42.9
24	32.4	22.0, 44.3

Fifty subjects enrolled in the expansion phase considered in the example above also correspond to the number of subjects needed to ensure that the hypothesis to be tested after completion of part 2 has sufficient predictive power conditioned on the ORR observed in the selection phase (part 1) (see Section 10.8.1).

[redacted]

Alpha control considerations:

For each arm (treatment combination cohort) included in the study the potential for alpha inflation arises from the adaptive nature of the design and, in particular, from the presence of a selection process based on probabilistic decision rules described in Section 10.4.2.1.

To assess whether alpha is controlled for each combination treatment arm separately, simulations were conducted. Below in Table 10-3, simulation results for scenarios that include one or more arms with the true ORR of 0.10 corresponding to the null hypothesis threshold (see also Scenarios 1 and 2 in Section 10.8.1), are presented. Scenario 2 is investigated to assess a potential impact of shrinkage estimator on type I error inflation. In simulations, the focus was on assessing type I error for each of the 'null hypothesis' arm separately defined as the proportion of significant results after completion of part 2 for given arm (successful arm). The technical details for the simulations will be summarized in the SAP Appendix:

As shown in Table 10-3, for each of the 'null hypothesis' arms with the true ORR=0.10 the probability is less than 0.025 (ranging between 0. 0097 and 0. 0149) and therefore alpha is well-controlled. Even though there is no explicit alpha control measure used, alpha within each arm is still well-controlled due to the use of the futility criterion in the selection phase, as well as the adaptive nature of the sample size of part 2, based on the shrinkage estimator. Further simulation results for alpha for other scenarios and under a wide variety of samples sizes for the expansion arm will be presented in the SAP Technical Appendix.

Table 10-3 Type I error assessment: Probability of a successful result for scenario where the true ORR equals 0.10 for each arm and sample size of the expansion arm is 50 subjects

Scenario	Arm	True ORR	Probability of significant result
1	1	0.10	0. 0102
1	2	0.10	0. 0104
1	3	0.10	0. 0136
1	4	0.10	0.0097
2	1	0.10	0. 0101
2	2	0.10	0.0111
2	3	0.10	0.0149
2	4	0.25	NA*
3	1	0.10	0.0102
3	2	0.25	NA*
3	3	0.25	NA*
3	4	0.25	NA*
*NA=not applicable in the context of type I error assessment; applicable only to the arms with true ORR=0.10 corresponding to the null hypothesis			

Note: No type I error rate control measures will be used to address the testing across several treatment arms considering that each combination treatment included in the design represents a stand-alone scientific question of interest leading to a stand-alone null hypothesis independent of other arms and thus allowing for one specific claim of statistical significance for the given arm.

10.4.2.2 Non-randomized section of the study

Part 1: Selection Phase

[redacted]

No formal hypothesis testing will be conducted in part 1. The objective of this part of the study is to explore the anti-tumor activity of the combination of spartalizumab with LAG525 agent in subjects with LAG-3 positive melanoma as measured by ORR per RECIST v1.1, and to expand this new arm if it shows promising efficacy.

To determine whether the arm has the potential to demonstrate clinically meaningful response rate, a specific efficacy probabilistic threshold should be met during the selection phase to advance to the expansion phase. If not, the arm will be declared as futile and won't be expanded. These thresholds and probabilities are highlighted in Table 10-4.

Table 10-4 Probabilities thresholds used to declare efficacy or futility for arm 1A

Decision rule	Action
P(ORR ≥20%) ≤ 70%	Drop arm for futility
P(ORR ≥20%) > 70%	Efficacy signal - Consider advancing arm to expansion phase (part 2)

The efficacy probabilistic threshold and decision criterion was determined so that a sufficient signal of efficacy needs to be observed before advancing this arm to the expansion phase and to ensure that if the true underlying ORR is 30% (clinically meaningful ORR) then the probability of crossing the threshold is sufficiently large (refer to Table 10-12).

To calculate the posterior probabilities, a beta-binomial posterior distribution will be used as shown below:

$$p \sim beta(y+1, n-y+1)$$

Where y is the number of confirmed responses in arm 1A and n is the number of subjects treated. In calculation of the posterior distribution, uninformed prior Beta[1,1] will be taken into account. The posterior probability will be calculated based on the observed ORR using RECIST v1.1 criteria at interim analysis as described in Section 10.7.2.

The final decision on whether the arm will be selected for advancement to the expansion phase will primarily be based on the observed ORR using decision rule described above but other efficacy (in particular duration of response), safety, and biomarker data will be considered as well. Novartis may decide to not expand the arm despite the efficacy probability threshold crossed.

With 20 treated patients, 5 or more responders need to be observed to meet the efficacy probabilistic threshold as illustrated in Table 10-5.

Table 10-5 Posterior probability ORR≥20% given observed ORR at time of 1st interim analysis of selection phase

# of Responders out of 20	ORR observed (%)	PP(ORR≥20% | observed ORR) (%)
0	0	0.9
1	5	5.8
2	10	17.9
3	15	37.0
4	20	58.6
5	25	76.9
6	30	89.1
7	35	95.7
8	40	98.9

[redacted]

# of Responders out of 20	ORR observed (%)	PP(ORR≥20% | observed ORR) (%)
9	45	99.6
10	50	99.9

Part 2: Expansion Phase

If the pre-defined efficacy probabilistic threshold is met after the selection part, the arm 1A might be expanded.

A second interim analysis will be conducted including 20 additional patients treated in the expansion phase as described in Section 4.2.2, i.e. based on the total of 40 patients. The objective of this second interim analysis is to support and inform decision-making on whether arm 1A will be : (1) further explored (2) stopped for futility . To determine whether arm 1A has the potential to demonstrate clinically meaningful ORR, an efficacy probabilistic threshold same as in part 1 will need to be crossed (see Table 10-4). If not, the arm 1A will be declared futile and further exploration/enrollment will be stopped in this combination.With 40 subjects at time of 2nd interim analysis treated in arm 1A (combining part 1 and part 2), 9 responders will have to be observed to cross the efficacy probabilistic threshold (see Table 10-6 below).

Table 10-6 Posterior probability ORR≥20% given observed ORR at time of 2nd interim analysis in expansion phase

# of responders at 2nd IA out of 40 pts	ORR observed (%)	PP(ORR≥20% | observed ORR) (%)
5	12.5	14.4
6	15.0	26.1
7	17.5	40.7
8	20.0	56.2
9	22.5	70.4
10	25.9	81.8
Of note, 5 responders have to be seen at the 1st interim analysis to advance in the expansion and reach the point of 2nd interim analysis		

If efficacy probabilistic threshold is met at the 2nd interim analysis enrollment may continue in expansion up to approximately 80 subjects (i.e. 100 subjects in total adding the subjects in part 1).

After completion of the expansion phase, the following statistical hypothesis will be tested based on objective response rate (ORR):

- The null hypothesis: ORR ≤ 15%.
- The alternative hypothesis: ORR >15%

The null hypothesis will be formally rejected if the lower bound of exact 95% CI for ORR is above 15%. The primary analysis of ORR at the end of part 2 will be based on a combined pool of part 1 and part 2 data.

For example, assuming the scenario when 20 subjects are treated in part 1, efficacy probabilistic thresholds at 1st and 2nd interim analysis are met and the total of 80 subjects is treated in the expansion phase then among 100 subjects treated in this arm in total and followed sufficiently, 23 or more responses need to be observed to reject the null hypothesis. With those 23 responders among 100 subjects, the point estimate for ORR will be 23% with

an exact 95% confidence interval of (15.2, 32.5). The exact 95% CIs for potential observed ORR in 100 subjects are shown in Table 10-11 of Section 10.8.2.

10.4.3 Handling of missing values/censoring/discontinuations

For the computation of ORR, all confirmed responses (CR or PR) reported up to the analysis cut-off will be included. Subjects with no valid radiological assessment or unconfirmed responses will be considered as non-responders. Subjects who were non-responders before initiation of subsequent anti-cancer therapy will still be non-responders. In particular, subjects with CR or PR at the last radiological assessment prior to cut-off and no response at the previous assessment are by definition unconfirmed and will be considered as non-responders for the primary analysis.

10.4.4 Supportive and Sensitivity analyses

As a supportive analysis, ORR based on RECIST v1.1 criteria as per BICR will be analyzed with the same analysis conventions as the primary efficacy analysis, and the treatment effect will be summarized by the ORR with its 95% confidence interval using the Clopper-Pearson method.

As sensitivity analyses for ORR in the FAS, data from part 2 will be combined with data from part 1 to assess efficacy within the following sub-groups:

- LDH (≤ ULN vs. > ULN)
- ECOG PS (0 vs. 1 vs. 2)

10.5 Secondary objectives

The secondary objectives in this study are to evaluate efficacy in terms of duration of response (DoR), progression-free survival (PFS), disease control rate (DCR), and overall survival (OS) of spartalizumab in combination with novel agents in patients with previously treated unresectable or metastatic melanoma. DOR, PFS, and DCR will be based on investigator assessment and a BICR process will be conducted as a supportive analysis.

10.5.1 Key secondary objective

The key secondary objective is to determine duration of response treatment with spartalizumab in combination with novel agents in patients with previously treated unresectable or metastatic melanoma.

Duration of response (DOR) only applies to subjects whose best overall response is complete response (CR) or partial response (PR) according to RECIST v1.1, per local review.

The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to underlying cancer. Subjects continuing without progression or death due to underlying cancer will be censored at the date of their last adequate tumor assessment. DOR will be listed and summarized by treatment group for all subjects in the FAS with confirmed best overall response (BOR) of CR or PR.

10.5.2 Other secondary efficacy objectives

All secondary efficacy endpoints according to RECIST v1.1 will be based on tumor assessments as per local assessment.

[redacted]

Progression-free survival

Progression-free survival (PFS) is defined as the interval of time (in months) between the date of randomization to the date of event defined as the first documented disease progression (according to RECIST v1.1 criteria) or death due to any cause (whichever comes first). If a subject has not had an event before leaving study or initiation of subsequent anti-cancer therapy, progression-free survival is censored at the date of last adequate tumor assessment. Censoring of subjects who have not had an event before initiation of subsequent anti-cancer therapy corresponds to option F(2) presented in Table 14-9 in Appendix 2 and is used in this study in order to obtain PFS estimates that are not confounded by subsequent therapies.

PFS based on RECIST v1.1 will be analyzed in the FAS population. 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.

Disease Control Rate

Disease control rate (DCR) is defined as the proportion of subjects with best overall response of CR, PR, or SD according to RECIST v1.1 criteria and as per local review.

DCR will be calculated based on the FAS. DCR and its 95% confidence interval will be presented for each treatment group.

[redacted]

Overall Survival

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

OS will be analyzed in the FAS population. 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.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group. In addition, pooled safety analysis based on all subjects will be produced.

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

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

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.

Additional summaries will be displayed to report deaths, all AE, AE related to study treatment, all SAE and SAE related to study treatment collected up to 150 days after last administration of spartalizumab.

Safety will be assessed based on all treated subjects; toxicities will be defined by CTCAE v5. Incidence and severity of adverse events, causality attribution to drug, time to event onset, duration of the event, its resolution and concomitant medications administered will be recorded. Additional safety assessments will include laboratory safety assessment, vital signs, and cardiac assessment.

10.5.3.2 Adverse events

Summary tables for AE will include only AE that started or worsened during the on-treatment period, the treatment-emergent AE.

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 v5 grades), type of adverse event, and 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. The list of AESI will also include relevant events for spartalizumab, LAG525, capmatinib, canakinumab and ribociclib which will be defined in the SAP.

Project-specific AESI should be defined in the case retrieval strategy (CRS) with regular updates whenever necessary.

[redacted]

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

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

10.5.3.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) v5. 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 v5, results will be categorized as low/normal/high based on laboratory normal ranges.

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

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v5 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v5

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v5 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v5

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

[redacted]

10.5.3.4 Other safety data

ECG

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

Categorical Analysis of QT/QTc interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these subjects will be produced by treatment group.

Vital signs

Data on vital signs will be tabulated and listed, notable values will be flagged.

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

[redacted]

10.5.3.6 Tolerability

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

10.5.4 Immunogenicity

Immunogenicity will be characterized descriptively tabulating antidrug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment.

The impact of ADA on the occurrence of safety endpoints, efficacy endpoints, [redacted] may be assessed as appropriate. Further details will be provided in the SAP.

10.5.5 Biomarkers

Changes in levels, phenotype and/or activation of T cell populations in the tumor and tumor microenvironment will be analyzed on an on-going basis. Every effort will be made to make this data available for decision making purposes. Such analyses may include, but are not limited to $CD8^+$ T cell infiltration and T cell activation by IHC and gene expression analysis, and T cell repertoire/clonality by TCR-sequencing.

Biomarker-related hypotheses may be compared with results found in literature as well as verified with data derived from previous or concurrent clinical trials. [redacted]

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue the analysis of blood / fresh tumor biopsies due to either practical or strategic reasons (e.g., issues related to the quality and/or quantity of the samples or issues related to the assay). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and only the available data will be listed and potentially summarized.

10.5.5.1 Outline of the data analysis

The proposed data analysis is aligned with the secondary biomarker objectives of the protocol. Several biomarker parameters (Table 10-7) will be periodically analyzed for each subject.

Table 10-7 Parameter definitions for categorization of biomarker outcome at subject level

Biomarker parameter	Analysis	Criteria for favorable biomarker result
Number of tumor infiltrating T cells (TIL)	Changes of $CD8^+$ T cell numbers as assessed by IHC in tumor/ tumor microenvironment with treatment	Increase
Activation level of TIL	Change of T cell activation marker level(s) as assessed by IHC in tumor/tumor microenvironment with treatment	Increase
TIL repertoire/specificity of T cell response to tumor	TCR clonality changes as assessed by TCR-sequencing in tumor/tumor microenvironment with treatment	Increase

[redacted]

Biomarker parameter	Analysis	Criteria for favorable biomarker result
Changes in immune response gene expression signatures	Changes in expression of genes and/or gene signatures as assessed by mRNA analysis in tumor/tumor microenvironment with treatment	Defined per gene/gene signature

The following analyses may be used to determine the biomarker parameters for supporting the decision-making criteria to expand or not an arm in part 2:

- Assessment changes from baseline of the number of $CD8^+$ T cells present in the tumor and/or tumor microenvironment for spartalizumab in combination with novel agents
- Assessment of changes from baseline of T cell repertoire/clonality in the tumor and/or tumor microenvironment as assessed by TCR sequencing when combining spartalizumab with novel agents
- Assessment of changes from baseline of T cell activation markers as assessed by IHC present in the tumor and/or tumor microenvironment as assessed by IHC when combining spartalizumab with novel agents
- Assessment of changes from baseline of mRNA levels for expression of genes and/or gene signatures corresponding to immune activation in the tumor and/or tumor microenvironment

The overall biomarker result for each subject will be formulated according to the available biomarker data and by determining if each parameter is favorable or not according to the indicated criteria in Table 10-7. If an individual subject has two or more favorable parameters from Table 10-7 then that subject will be considered to have a favorable biomarker profile. For each arm, the proportion of subjects with a favorable biomarker profile (pFBP) are then defined as the number of subjects with favorable biomarker profiles divided by the number of subjects enrolled into the arm which are included in the "paired" biomarker analysis set for that particular interim analysis. The "paired" biomarker analysis set include all subjects in the safety set with an evaluable baseline tumor biopsy sample and at least one post-baseline tumor biopsy sample with evaluable results for 2 or more biomarker parameters listed in Table 10-7. If other biomarker data are available at the time of an interim analysis, these may also be considered. More details will be provided in the Statistical Analysis Plan or Biomarker Analysis Plan.

10.5.5.2 Data handling principles

Data preprocessing and transformations will be described in detail in the Programming Dataset Specifications document.

10.5.5.3 Data analysis principles

10.5.5.3.1 Analysis sets

Unless otherwise specified, all statistical analyses of biomarker data will be performed on subjects with biomarker data (Biomarker analysis set).

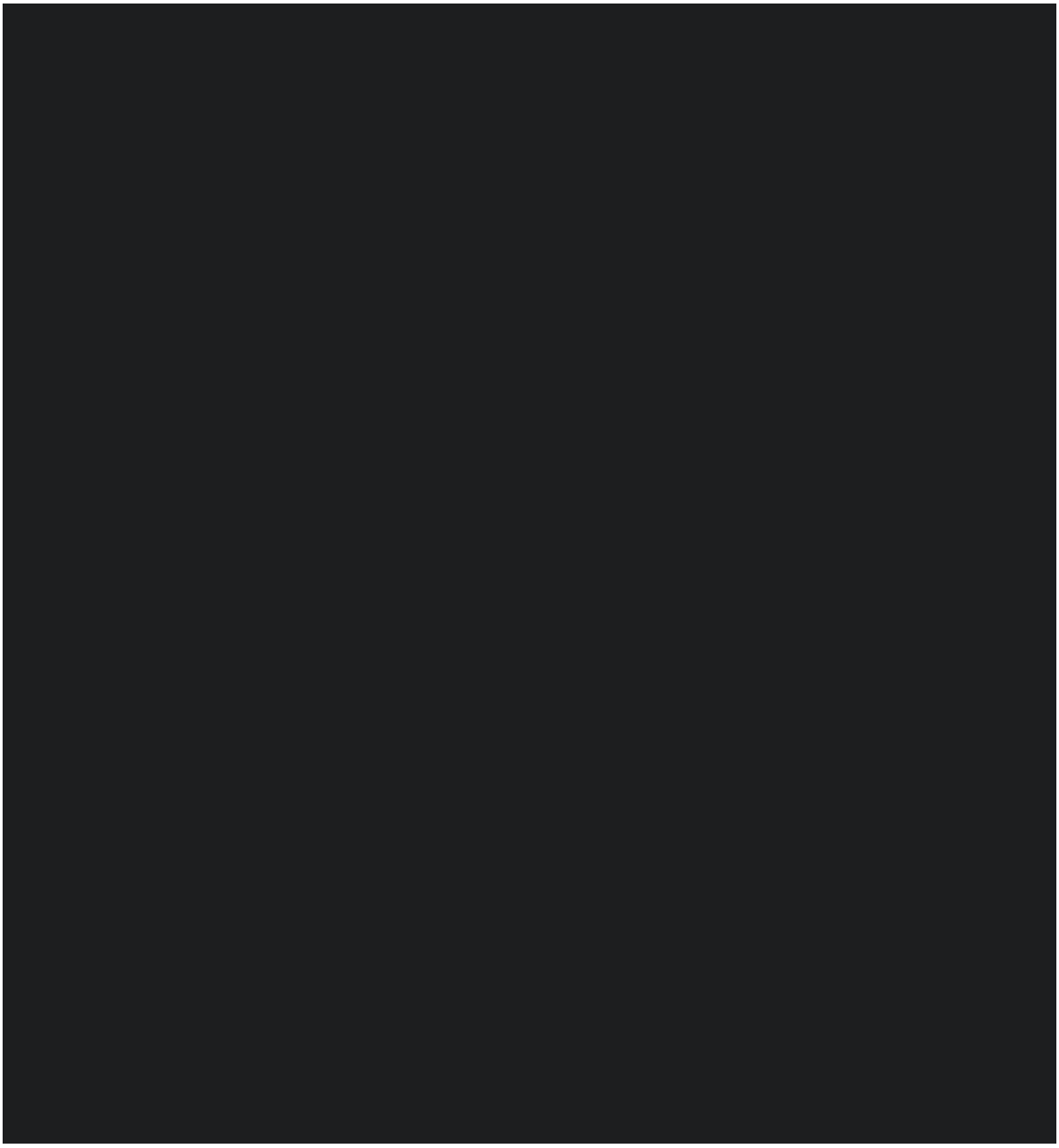
10.5.5.3.2 Basic tables, figures and listings

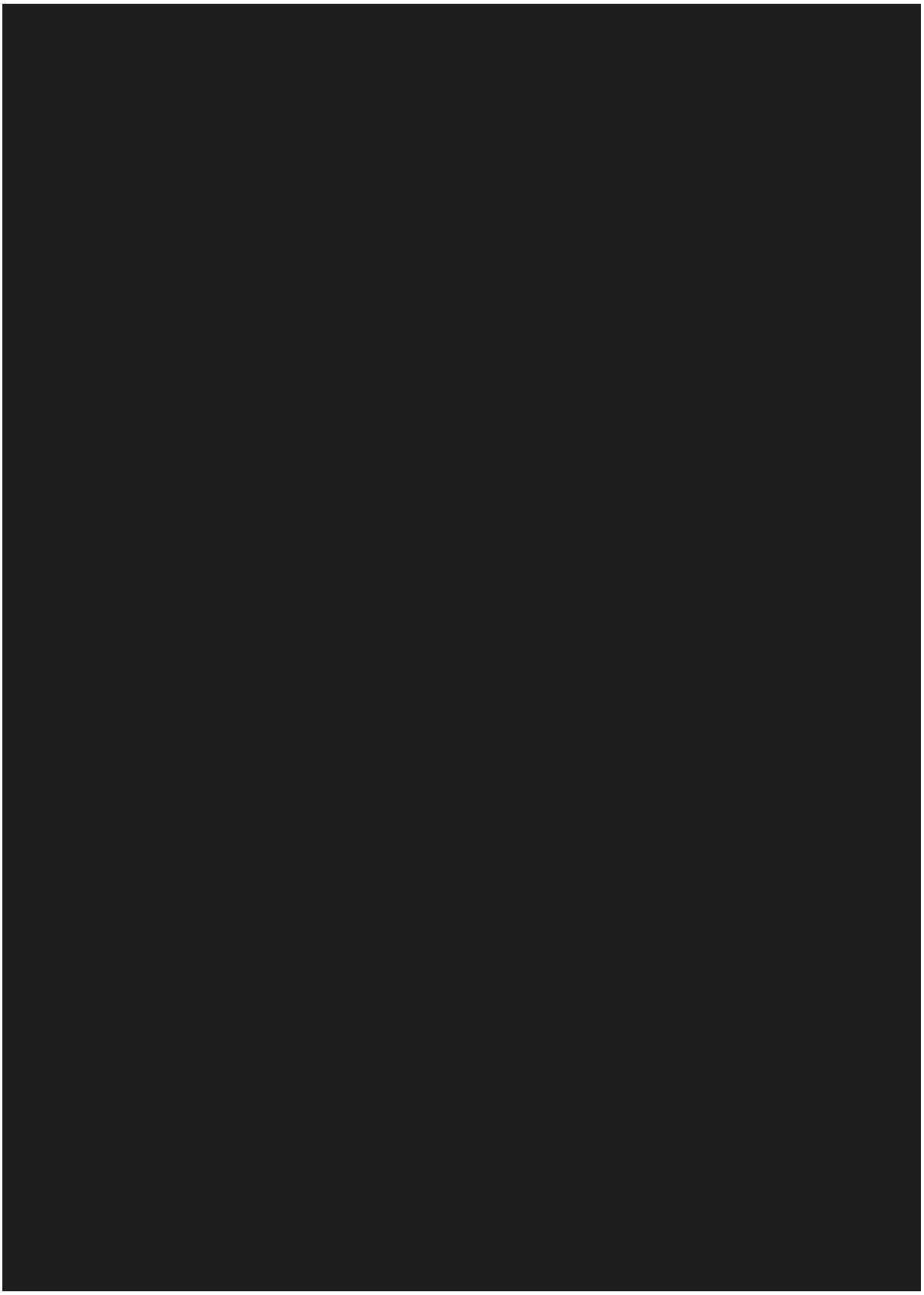
Unless otherwise stated, as project standard, all biomarker data collected will be listed and summarized. In the event of the collection of large biomarker data such as next generation sequencing, gene expression or protein expression panels, some pragmatic considerations

will be applied to limit output, as these may easily top thousands, if not tens of thousands of pages offering little to no scientific value.

Depending on the endpoint of interest, graphical displays such as box plots or strip plots may be used to assess the relationship of different biomarkers with clinical benefit. These may be separated by treatment arm and include either baseline or change from baseline values, where applicable.

For categorical markers such as mutation status, 2x2 contingency tables may be used to assess the relationship with clinical benefit and or Kaplan–Meier curves may be generated given the number of number of PFS events warrant such an assessment.





10.7 Interim analysis

10.7.1 Randomized section of the study

Part 1: Selection phase

As described in Section 4.2.1, the first interim analysis is planned for ORR once at least ten subjects have been randomized into each of the three initial treatment groups (arm 1, arm 2, arm 3), and have either completed two post-baseline tumor assessments or have discontinued study treatment. Subsequent interim analyses will be conducted approximately every five months thereafter since that is the scheduled timeframe to have two post-baseline scans. The first interim analysis for arm 4 (ribociclib and spartalizumab) will be synchonized with the subsequent planned interim analyses for the other arms and will occur when at least 10 subjects have been randomized to that arm, and have either completed two post-baseline tumor assessments or have discontinued study treatment. Enrollment and assessment at subsequent interim analyses for each treatment group will continue until the criteria for futility or advancement into the expansion phase have been met, or 45 subjects have been randomized into a treatment group using decision rules presented in Section 10.4.2.1.

Of note, interim analyses will continue to be performed in the randomized section of the study at the pre-defined frequency until a clinical decision (e.g. arm declared futile or efficacy probabilistic threshold crossed) on each arm in part 1 has been made. Even if declared futile, combination arms will be analyzed at subsequent interim analyses until all

subjects have been reported at least once (i.e. had a minimum follow-up of 20 weeks). Additional descriptive analyses may be performed if required.

Part 2: Expansion phase

No formal interim analysis is planned for this part of the trial. The first primary analysis will be performed once the first expanded arm has fully enrolled and also after all patients randomized had at least 9 months of follow-up. This timing would allow for a potential minimum duration of response of 6 months for all subjects randomized. Formal hypothesis testing of the primary endpoint (as described in Section 10.4.2.1) will be performed at the primary analysis. The final analysis will be performed at the end of the study as described in Section 4.3.

10.7.2 Non-randomized section of the study

Part 1 : Selection phase

As described in Section 4.2.2, there will be one interim analysis planned for ORR once all patients treated in arm 1A have either completed two post-baseline tumor assessments or have discontinued study treatment.

Part 2: Expansion phase

A 2nd interim analysis will be conducted once 40 patients have been treated within selection and expansion phases and have either completed two post-baseline tumor assessments or have discontinued study treatment.The primary analysis of this non-randomized section of the study will be performed once all patients treated in arm 1A had at least 9 months of follow-up. This timing would allow for a potential minimum duration of response of 6 months for all subjects enrolled. Formal hypothesis testing of the primary endpoint (as described in Section 10.4.2.2) will be performed at this primary analysis. The final analysis will be performed at the end of the study as described in Section 4.3.

10.8 Sample size calculation

10.8.1 Randomized section of the study

In this section, sample size will be presented based on specific potential scenarios for true ORR in the first four combination arms evaluated. In particular, for selection phase (part 1), since one can consider a wide variety of potential true ORR scenarios, the sample size will not be based on an exact calculation leading to one fixed number, but will instead be characterized by simulation based on average number of subjects enrolled into these arms under each individual scenario for true ORR. It is important to emphasize that the true underlying efficacy activity (in terms of ORR) of the four initial arms will have a substantial bearing on the total sample size needed in part 1. Subsequently, and given the adaptive nature of the study design, the sample size needed in expansion phase (part 2) to ensure sufficient power will depend on the ORR observed in part 1 and in particular on the rate observed in the arm that qualifies for expansion to part 2.

The sample size calculation for parts 1 and 2 were performed using SAS 9.4 software, based on the probabilities of first determining a efficacious treatment and a futile (non-efficacious) treatment in the selection phase (part 1), and then determining the number of subjects needed

to reject the null hypothesis (part 2). The following assumptions were made in the estimation of the required sample size:

Part 1: Selection phase:

Simulation based determination of the sample size needed for part 1 considers the following:

- The interim analyses will be performed with frequency described in Section 10.7.1.
- Decisions rules for declaring an efficacious or non-efficacious (futile) treatment described in Section 10.4.2.1 are used at each of the interim analyses
- Considers at least two interim analyses for the first three arms before the initiation of an interim analysis for arm 4 (ribociclib + spartalizumab)
- Takes into account the actual randomization in the first three arms for the first interim analysis (13 subjects for arm 1 [LAG525 + spartalizumab], 10 subjects for arm 2 [capmatinib + spartalizumab], and 12 subjects for arm 3 [canakinumab + spartalizumab])
- Allows for a random allotment of subjects (between 10 and 16) in arm 4 before the first interim analysis is conducted for that arm. Random allotment is necessary since the timing of the first interim analysis in this combination arm is controlled by the timing of the previous interim analyses before this arm begins randomization.
- Enrolling a cap of 45 subjects for combination arms that cannot be selected either to be an efficacious or non- efficacious treatment.
- An accrual rate of 8 subjects per month
- 1000 simulations for each scenario of true ORR

Taking into account the efficacy/futility criterions discussed in Section 10.4.2.1, below are results of simulations assuming a variety of scenarios for the 'true' underlying ORR. Table 10-10 below presents average sample size ('N') along with percentages for declaring 'futile' and 'promising/efficacious' combination arms.

Table 10-10 Simulation based sample size (N) with percentages for declaring 'futile' and 'efficacious' combination arms in the selection phase

Scenario	Arm	True ORR	Avg. N	Futility %	Efficacious %
1	1	0.10	31.6	75.35	4.57
	2	0.10	25.8	75.55	8.63
	3	0.10	27.7	72.91	11.53
	4	0.10	30.6	74.10	7.06
2	1	0.10	31.5	75.11	4.51
	2	0.10	25.9	75.77	8.59
	3	0.10	27.7	72.92	11.74
	4	0.25	26.5	5.99	71.24
3	1	0.10	32.6	75.11	4.29
	2	0.25	23.7	7.45	73.91
	3	0.25	21.6	5.40	78.86
	4	0.25	26.5	5.52	71.67
4	1	0.25	28.1	4.82	71.07
	2	0.05	19.5	97.38	0.97
	3	0.07	25.8	89.85	4.90
	4	0.15	32.7	38.17	21.91
5	1	0.25	29.2	4.40	69.59

[redacted]

Scenario	Arm	True ORR	Avg. N	Futility %	Efficacious %
	2	0.30	20.3	2.94	89.50
	3	0.35	15.7	0.67	97.62
	4	0.25	26.6	5.66	70.84
6	1	0.17	34.2	26.73	28.70
	2	0.19	27.6	22.24	44.67
	3	0.18	27.4	23.11	46.05
	4	0.16	31.7	33.27	26.97

The simulation results for part 1 demonstrate that in an efficacious arm with the true ORR of, for example 25%, the sample size will be approximately 22-29 subjects. In an arm with even higher efficacy, e.g. ORR of 35%, the sample size will be approximately 16 subjects since this arm will have a higher likelihood of being stopped earlier and declared as efficacious. On the other hand, an arm that is clearly futile, e.g. an arm with the true ORR of 5%, the sample size will be approximately 20 subjects. Based on the simulations results presented in Table 10-10, the expected average sample size in part 1 for all four arms together range between 92 and 121 subjects. The maximum sample size in part 1 for all four arms together is 180 subjects corresponding to the scenario when all four arms will be capped at 45 subjects.

The simulation results also demonstrate that decision rules described in Section 10.4.2.1 are adequate to detect efficacious and futile arms with high probabilities. For example, an arm with the true ORR of 25% will be declared as efficacious with approximately 70-79% probability. Similarly, an arm with the true ORR of, for example, 10% will be declared as futile with probability of 73-76% and declared as efficacious with probability of 4-12%. Of note, the probabilities for efficacy and futility estimated for each scenario and each arm do not add up to 100% since there is a possibility for each particular row in the table that given arm will fail to satisfy either of the criteria and its enrollment will subsequently be stopped using the cap of 45 subjects. Further simulation results for the selection phase will be summarized in the SAP Technical Appendix.

Part 2: Expansion phase

Considering the null hypothesis value of 10% and targeted response rate of 25% (see Section 10.4.2.1), the standard approach to sample size and power calculations that would not condition on part 1 result, would lead to the following sample sizes for part 2; n = 64, 49, 40, would provide power of 90%, 80%, and 70% respectively to reject the null hypothesis assuming the targeted response rate.

However, a more meaningful approach would be to utilize the information obtained in part 1 and then condition on the part 1 results to determine the sample size for part 2 with an adaptive approach. At the time when a decision to expand one ‘promising’ arm is taken (at any of the preplanned interim analyses as discussed in Section 4.2.1), the part 2 sample size for this ‘promising’ arm will be determined using a Bayesian predictive power approach. Predictive power is defined as probability of obtaining a statistically significant result based on the combined data from part 1 and part 2 for the selected ‘promising’ arm. The decision about the statistical significance is based on the lower bound of exact 95% CI for ORR as described in Section 10.4.2.1. The value used for conditioning in the predictive power calculation will be calculated on the basis of a shrinkage estimator of ORR. Use of the shrinkage estimator is considered conservative since it takes into account part 1 ORR results from all arms eligible for selection phase assessment (since at least one of the 1st 3 arms

could advance to part 2 before the 4th arm has enough subjects for assessment) and thus reduces bias of the ORR estimate of the 'promising' arm that might arise from the selection process that can lead to random high or random low values. The part 2 sample size for 'promising' arm will then be determined such that predictive power is at least 70%.

A more detailed description of steps needed to calculate the sample size of part 2 is provided below:

- Observed ORR for the 'promising' arm as well as observed ORR in the other selection phase eligible arms will be calculated
- Shrinkage estimator for the 'promising' arm as well as for the other selection phase eligible arms will be calculated based on 20000 iterations of the Markov chain Monte Carlo (MCMC).
- Shrinkage estimator for the 'promising' will be used as a value used for conditioning of the predictive power calculation
- Predictive power distribution is then formed based on the following:
  - Distribution of the observed ORR adjusted by the shrinkage estimator evaluated using MCMC
  - From this distribution, for a given number of responses and subjects in part 1, calculating the number of responses needed in part 2 to reject the null hypothesis for a predefined alpha at final analysis
  - For each sample of MCMC, the corresponding power is calculated. Predictive power is then the average of power over the MCMC samples.
- For the 'promising' arm, predictive power will be calculated for several sample size scenarios.
- The sample size for the efficacious arm to be enrolled in part 2 will be chosen such that the mean predictive power calculated from the 1000 simulations is at least 70%

Based on the simulation results (that will be further detailed in the SAP Technical Appendix, a sample size of 50 subjects in part 2 for the selected efficacious arm for which the true ORR is 25% is sufficient to achieve the predictive power of at least 70%.

In summary, a maximum of 230 subjects could be enrolled into the study, with approximately a maximum of 180 subjects in the selection phase (if all four combination arms enroll the maximum of 45 subjects) and approximately 50 subjects in the expansion phase (assuming that only one of the four initial combination arms will be expanded. However, based on the above assumptions and the current enrollment already in this trial, a total of approximately 142 to 171 subjects (approximately 92-121 subjects in part 1 for four arms and approximately 50 subjects in part 2 assuming just one expanded arm) will be expected to be enrolled in order to analyze data from the selection phase (part 1) and expansion phase (part 2) of this study. With this calculation, it is important to note that the true efficacy activity of the four initial arms will have a substantial bearing on the total sample size. For instance and considering the most extreme futility example, if all four arms meet the criterion for futility at the first interim analysis in part 1 and the fourth arm is assessed at its first interim analysis when 10 subjects are randomized to that arm, the total sample size of part 1 would be approximately 45, and no subjects would be enrolled into part 2. For another example, if the true efficacy activity is similar to scenario 5 presented in Table 10-10, for the case where the true ORR is 0.35 in part 1, only 16 subjects will be needed in part 1, and approximately 20 subjects will be needed in part 2 to have adequate predictive power.

[redacted]

Finally, this sample size takes into account only the three arms enrolled into the study. If more arms are eventually added to the study, then the sample size will increase accordingly.

Taking into account the first three initial arms and an enrollment rate of approximately 8 subjects per month, as well as 20 weeks to reach the second post-baseline assessment, the first interim analysis is expected to occur at approximately 9 months after the start of the study. Subsequent interim analyses will occurr approximately every 5 months afterwards until all arms either advance, stop, or reach the cap numbers of subjects in the selection phase. The first primary ORR analysis is estimated to occur approximately 28 months after the start of the study (taking into account the minimum follow-up time needed to assess DoR).

Shrinkage estimator

The estimates of ORR observed in part 1 can potentially be biased due to random high or random low values and thus the arm(s) to be expanded can potentially be selected based on a random-high ORR observed in part 1. Consequently the estimated sample size and power can potentially be affected as well. Therefore, a shrinkage estimator based on a hierarchical model that takes into account the ORR from all the combination arms will be used. The shrinkage estimator for ORR will be calculated using the observed ORR from each available arm at the time when an efficacious combination arm can be determined in part 1 so that predictive power can be determined.

For the shrinkage estimate the ORR for each treatment arm is determined by the hierarchical model of the logit of ORR:

$$shrinkage\ estimator = \frac{exp(beta0 + delta\{trt\})}{1 + exp(beta0 + delta\{trt\})}$$

where beta0 is the mean logit ORR amongst the treatment, and delta{trt} is the random effect of the hierarchical model between arms .

The prior distribution for beta0

$beta0 \sim normal\ (-1,\ var = 0.25)$

where -1 is the mean of the normal distribution with variance of 0.25. This is equivalent to median ORR rate of about 0.25.

For the random effects of the hierarchical model between treatments, the parameters to incorporate the random effects are shown below:

$$delta \sim normal(0, var = s2)$$

$$s2 \sim igamma(2, s = 1, upper = 2)$$

where 2 is the shape parameter of the inverse-gamma distribution and 1 is the scale parameter of the inverse-gamma distribution with truncation when the distribution reaches a value of 2.

With these priors, the shrinkage estimator model is developed with the following equations:

$$p_i \sim logistic(beta0 + delta)$$

$$r \sim binomial(n = N_i, p = p_i)$$

Parameters from the model to be used in the shrinkage estimator will be assessed using a Markov chain Monte Carlo (MCMC) method with 20000 iterations after a burn-in period of 2000 iterations.

Further considerations for the execution of the expansion phase will be presented in the SAP Appendix.

10.8.2 Non-randomized section of the study

Using a standard (naïve) sample size approach for a single stage study with ORR as the primary endpoint : to ensure 80% power to reject H0 ORR≤15% and considering clinically meaningful ORR of 30%, 80 subjects would be needed. However, given the proposed 3-stage design, the power and sample size calculations need to be adjusted as discussed below.

In arm 1A included in the non-randomized section of the study, 20 patients will be treated in the selection phase. If based on the data from those 20 patients the efficacy probabilistic threshold presented in Section 10.4.2.2 is met, up to 80 additional subjects will be treated in the arm 1A in the expansion phase (assuming the efficacy probabilistic threshold is met at the 2nd interim analysis as well).

The exact 95% CIs for various sample sizes and observed ORR are shown in Table 10-11 below.

Table 10-11 Exact binomial 95% confidence intervals for various sample size in expansion phase and observed ORR

Sample size ($N=N_{sel}+N_{exp}$)	No of responders	Observed ORR	95% exact CI (%)
50	11	22.0	11.5, 36.0
50	12	24.0	13.1, 38.2
50	13	26.0	14.6, 40.3
50	14	28.0	16.2, 42.5
50	15	30.0	17.9, 44.6
70	14	20.0	11.4, 31.3
70	15	21.4	12.5, 32.9
70	16	22.9	13.7, 34.5
70	17	24.3	14.8, 36.0
70	18	25.7	16.0, 37.6
100	20	20.0	12.7, 29.2
100	23	23.0	15.2, 32.5
100	25	25.0	16.9, 34.7
100	30	30.0	21.2, 40.0

Eighty patients treated in the expansion phase, resulting in 100 subjects in total when combining with subjects treated in the selection phase, provide sufficient power (>70%) to reject the null hypothesis of ORR ≤ 15% assuming the true ORR is 30% (refer to Table 10-12).

Taking into account the efficacy/futility criteria discussed in Section 10.4.2.2 of the protocol, the Table 10-12 below shows probability of crossing efficacy probabilistic threshold (being "efficacious") at first and second interim analysis and probability of a positive study with statistically significant result after completion of expansion phase (e.g. not stopped at

selection nor at 2nd interim analysis for futility and success criteria met at the end of expansion phase) under different underlying true ORR.

Table 10-12 Operating characteristics for different sample size in expansion and under true underlying ORR

Sample size			True ORR (%)	Efficacious (%) at 1st interim analysis in selection*	Efficacious (%) at 2nd interim analysis among 40 subjects **	Probability of positive study (power) *** at the end of expansion
Selection	Expansion	Total				
20	30	50	20	37.0	27.2	9.0
			25	58.5	52.1	30.7
			30	76.2	73.5	59.3
			40	94.9	94.7	93.2
20	60	80	20	37.0	27.2	10.6
			25	58.5	52.1	38.4
			30	76.2	**73.5**	68.7
			40	94.9	94.7	94.7
20	80	100	20	37.0	27.2	14.1
			25	58.5	52.1	45.0
			30	**76.2**	**73.5**	**72.1**
			40	94.9	94.7	94.7

* Post. Prob (ORR≥20% | observed ORR)>70%, under true ORR xx%

** Post.Prob (ORR≥20%| observed ORR)>70% at 2nd IA and efficacy threshold met at selection

*** Probability to cross efficacy thresholds at 1st IA in selection and 2nd IA in expansion and probability to reject H0 at the end of expansion over the combined selection and expansion treated subjects

The operating characteristics with 20 subjects treated in selection phase and 40 subjects at time of 2nd interim analysis demonstrate that decision rules described in Section 10.7.2 are adequate to meet efficacy probabilistic threshold with high probability:

- For example, if the true ORR is 30%, the efficacy probabilistic threshold will be crossed at the first interim analysis at the end of selection and qualify the arm for expansion with approximately 76% probability. Under the same underlying true ORR, the probability of crossing the efficacy probabilistic threshold at the 1st and 2nd interim analysis in selection and expansion parts is approximately 74%.
- When the true ORR is 20%, the efficacy probabilistic threshold will be crossed at the first interim analysis with approximately 37% (e.g futile with 63% probability) and with 27% at time of 2nd interim analysis (e.g. futile with 73% probability).

If the efficacy probabilistic thresholds are crossed at selection and 2nd interim analysis (e.g. at least 5 responders over 20 subjects in selection and at least 9 responders over 40 subjects in selection and expansion phases are observed), under a true ORR of 30%, the probability of rejecting null hypothesis at the end of the expansion with 80 patients in expansion phase (e.g. 100 patients in total) is approximately 72%. This sample size provides adequate power to reject H0 and robust results for safety to allow adequate risk-benefit assessment.

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

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

11.3 Informed consent procedures

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

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject 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 (i.e. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents. The date when a subject’s Informed Consent was actually obtained will be captured in their eCRFs.

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

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 subject informed consent and should be discussed with the subject 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 subject.

[redacted]

Women of child bearing potential should 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 requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

Male subjects 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.

The following informed consents 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. A separate main study consent is used for the non-randomized section of the study that includes only arm 1A.
- Pregnancy Outcomes Reporting Consent for female subjects or the female partners of any male subjects who took study treatment

[redacted]

11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult subjects are posted on novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LSLV), those for interventional clinical trials involving pediatric subjects within 6 months of study completion.

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

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to

[redacted]

present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

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

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

11.6 Study documentation, record keeping and retention of documents

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

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

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

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

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

[redacted]

11.7 Confidentiality of study documents and subject records

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

11.8 Audits and inspections

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

11.9 Financial disclosures

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

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for subject safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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14 Appendices

14.1 Appendix 1: AJCC Melanoma Staging System (Edition 8)

Refer to the full publication for further details (Gershenwald et al 2017).

Table 14-1 Definition of Primary Tumor (T)

T Category	Thickness	Ulceration status
TX Primary tumor thickness cannot be assessed (eg, diagnosis by curettage)		
T0 No evidence of primary tumor (eg, unknown primary or completely regressed melanoma)		
Tis (melanoma in situ)		
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm	With ulceration
	0.8-1.0 mm	With or without ulceration
T2	>1.0-2.0 mm	Unknown or unspecified
T2a	>1.0-2.0 mm	Without ulceration
T2b	>1.0-2.0 mm	With ulceration
T3	>2.0-4.0 mm	Unknown or unspecified
T3a	>2.0-4.0 mm	Without ulceration
T3b	>2.0-4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Table 14-2 Definition of Regional Lymph Node (N)

	Extent of regional lymph node and/or lymphatic metastasis	
N Category	No. of tumor-involved regional lymph nodes	Presence of in-transit, satellite, and/or microsatellite metastases
NX	Regional nodes not assessed (eg, sentinel lymph node [SLN] biopsy not performed, regional nodes previously removed for another reason); Exception: pathological N category is not required for T1 melanomas, use clinical N information	No
N0	No regional metastases detected	No
N1	One tumor-involved node or any number of in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (ie, detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or 3 tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or 3 clinically occult (ie, detected by SLN biopsy)	No
N2b	Two or 3, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with 2 or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (ie, detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or the presence of any number of matted nodes	No

[redacted]

	Extent of regional lymph node and/or lymphatic metastasis	
N Category	**No. of tumor-involved regional lymph nodes**	**Presence of in-transit, satellite, and/or microsatellite metastases**
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

Table 14-3 Definition of Distant Metastasis (M)

	M criteria	
M Category[b]	**Anatomic site**	**LDH level**
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated

CNS indicates central nervous system; LDH, lactate dehydrogenase. [b] Suffixes for M category: (0) LDH not elevated, (1) LDH elevated. No suffix is used if LDH is not recorded or is unspecified.

Table 14-4 AJCC pathological (pTNM) prognosis stage groups

When T is...	And N is...	And M is...	Then the pathological stage group is...
Tis	N0[a]	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N3c	M0	IIIC
T1a/b-T2a	N1a or N2a	M0	IIIA
T1a/b-T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID

[redacted]

When T is...	And N is...	And M is...	Then the pathological stage group is...
Any T, Tis	Any N	M1	IV

[a] Pathological stage 0 (melanoma in situ) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use clinical N information to assign their pathological stage.

14.2 Appendix 2: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival and Overall Survival (based on RECIST 1.1)

Harmonization of Efficacy Analysis of Solid Tumor Studies

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Document status:	Version 3.2: February 11, 2016 Version 3.1: November 29, 2011 Version 3: October 19, 2009 Version 2: January 18, 2007 Version 1: December 13, 2002
Release date:	11-Feb-2016
Authors (Version 3.2):	[redacted]
Authors (Version 3.1):	[redacted]
Authors (Version 3):	[redacted]
Authors (Version 2):	[redacted]
Authors (Version 1):	[redacted]

14.2.1 Introduction

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

The efficacy assessments described in Section 14.2.2 and the definition of best response in Section 14.2.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.2.3.2 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 14.2.4 of this guideline describes data handling and programming rules. This section

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is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

14.2.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000) and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009).

14.2.2.1 Definitions

14.2.2.1.1 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.

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

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14.2.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the subject 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 subjects be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how subjects with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 14.2.3.2.8.

14.2.2.1.3 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 anti-tumor effect of a treatment.
- For optimal evaluation of subjects, 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 subject 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

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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 subject 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.

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14.2.2.2 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).

14.2.2.2.1 Minimum target lesion size at baseline

- **Nodal target**: See Section 14.2.2.1.1.
- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 14.2.2.1.1.

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.

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

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 14-5) and non-target lesions (Table 14-6) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-7) as well as the presence or absence of new lesions.

14.2.2.3.1 Follow-up and recordings 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.

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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.

Non-nodal lesions

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

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

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

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

14.2.2.3.2 Determination of target lesion response

Table 14-5 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

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Response Criteria	Evaluation 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 14.2.2.2.	

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 14-5 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 subjects who have not achieved target response of CR. For subjects who have achieved CR, please refer to last bullet in this section.
- For those subjects 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.

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

14.2.2.3.3 Determination of non-target lesion response

Table 14-6 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].

1. 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..
2. 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)

[redacted]

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. ≥ 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 14.2.2.3.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.2.2.3.4 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
- 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 subject in which case the response should be UNK, as for any of this subject's assessment (see Section 14.2.2.3.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease).

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14.2.2.3.5 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 14-7.

Table 14-7 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 14.2.2.3.3.

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.

14.2.3 Efficacy definitions

The following definitions primarily relate to subjects who have measurable disease at baseline. Section 14.2.3.2.8 outlines the special considerations that need to be given to subjects with no measurable disease at baseline in order to apply the same concepts.

14.2.3.1 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 subject'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.

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

- CR = at least two determinations of CR at least 4 weeks apart before progression 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) > 11 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 11 weeks or early progression within the first 12 weeks)

The time durations specified in the SD/PD/UNK definitions above are based on the first 12-week tumor assessment frequency taking into account time windows for assessment. E.g. if the first assessment occurs at week 12 with a time window of +/- 7 days, a BOR of SD would require a SD or better response longer than 11 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 subject 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 subject has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

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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 subject. 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 subject 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 subject 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 overall lesion responses.

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

Overall response rate (ORR) is the proportion of subjects 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 subjects with a best overall response of CR or PR or SD. The objective of this endpoint is to summarize subjects 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 subjects 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 subjects 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 2001) and counts all subjects 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. Subjects 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

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disease control, subjects with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

14.2.3.2 Time to event variables

14.2.3.2.1 Progression-free survival

Usually in all Oncology studies, subjects 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 subject 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.

14.2.3.2.2 Overall survival

All subjects should be followed until death or until subject has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the subject was last seen alive / last known date subject 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 subject is not known to have died, survival will be censored at the date of last known date subject alive.

14.2.3.2.3 Time to progression

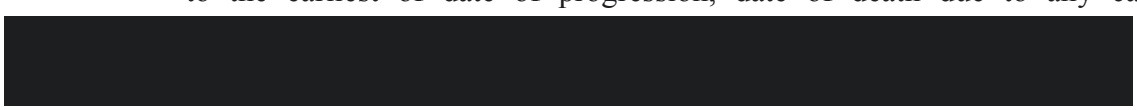
Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

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 subject has not had an event, time to progression is censored at the date of last adequate tumor assessment.

14.2.3.2.4 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 subjects who did not experience treatment failure will be censored at last adequate tumor assessment.

14.2.3.2.5 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 subjects: a good risk group and a poor risk group. Good risk subjects tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk subjects 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 subjects. Less potent agents induce a response mainly in good risk subjects only. This is described in more detail by (Morgan 1988).

It is recommended that an analysis of all subjects (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 subjects (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis, et al (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-subject analysis of these endpoints are not appropriate since the status of subjects throughout the study is usually taken into account in the analysis).

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

14.2.3.2.6 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.

[redacted]

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.2.3.2.5. It is recommended that an analysis of all subjects (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 subjects should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all subjects, subjects 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. FSFV to LSLV used for the analysis) for subjects 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 subject 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 FSFV to LSLV)
- at last adequate tumor assessment date otherwise. In this case subjects have not yet progressed so they theoretically still have a chance of responding

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

14.2.3.2.7 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:

[redacted]

- 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.

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 subject 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 subject 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) anti-cancer therapy or surgery.

14.2.3.2.8 Handling of subjects with non-measurable disease only at baseline

It is possible that subjects 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 subjects 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 subjects with measurable disease at baseline, subjects without measurable disease should also be incorporated in an appropriate manner. The overall response for subjects with non-measurable disease is derived slightly differently according to Table 14-8.

Table 14-8 Overall lesion response at each assessment: subjects with non-target disease only

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

[redacted]

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

[1] As defined in Section 14.2.2.3.

In general, the **non-CR/non-PD response** for these subjects is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response subjects 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 subjects 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 subjects with only non-measurable disease at baseline, handling subjects with a best response of CR as "responders" with respect to ORR and all other subjects as "non-responders".

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

14.2.3.2.9 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 subject being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 14.2.3.2.7, 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 14-9 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

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
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	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) 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 14.2.3.2.7
2. =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.2.3.2.7.
3. =The rare exception to this is if the subject 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 subjects 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 anti-cancer 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 anti-cancer therapy. It is strongly recommended that a tumor assessment is performed before the subject 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 14-8 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

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

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

14.2.4 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).

14.2.4.1 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).

[redacted]

14.2.4.2 End of treatment phase completion

Subjects **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 subjects 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 subject, 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.

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

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- 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 subject from trial.

14.2.4.3 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.

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

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

14.2.4.4 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

[redacted]

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 subjects with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

14.2.4.5 Programming rules

The following should be used for programming of efficacy results:

14.2.4.5.1 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.

14.2.4.5.2 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 14.2.3.2.7). 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.

[redacted]

14.2.4.5.3 Incomplete dates for last known date subject alive or death

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

14.2.4.5.4 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)'.

14.2.4.5.5 Study/project specific programming

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

14.2.4.5.6 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 14-8)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of subsequent anti-cancer therapy

* Adequate assessment is defined in Section 14.2.3.2.7. 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 subjects 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.

[redacted]

14.2.4.6 References (available upon request)

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[redacted]

14.3 Appendix 3: Recommended management of suspected immune-related adverse events related to spartalizumab and/or LAG525

Table 14-10 Recommended clinical management for suspected immune-related diarrhea/colitis

Diarrhea/colitis (NCI-CTCAE v5)	
Grade	**Recommended management**
Grade 1 (Increase of < 4 stools per day over baseline) mild increase in ostomy output compared to baseline. Grade 2 (Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL) and/or abdominal pain/ mucus or blood in stool.	• Diet & Hydration • Loperamide: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/d. Continue until free of diarrhea for 12h • Diarrhea > 24h: loperamide 2 mg every two hours; maximum 16 mg/d. Consider adding oral antibiotics. • Diarrhea > 48h: loperamide 2 mg every two hours; maximum 16 mg/d. Consider other second-line therapies for diarrhea (e.g. (octreotide, oral diphenoxylate) and oral antibiotics • If grade 2 and no improvement in 5 days: consider oral steroids • If grade 2 diarrhea persists > 1 week consider gastroenterologist consultation and endoscopy to evaluate for colitis • If grade 2 persists for 5 days and worsening of symptoms or diffuse ulcerations and bleeding seen on endoscopy, initiat steroids (0.5 - 1 mg/kg/d of prednisone or equivalent) and continue until symptoms improve to grade 1. • If no improvement occurs, manage as per grade 3. Steroids should be tapered slowly (see Section 6.3.1.3.1). • Sigmoidoscopy and biopsy can be considered and may assist in determining the duration of steroid taper based on the evidence of macroscopic and microscopic inflammation.
Grade 3 diarrhea: Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL; Grade 3 colitis: Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	• Clinical evaluation and hospitalization indicated; rule out bowel perforation and intravenous hydration. • Consider consultation with gastroenterologist and biopsy with endoscopy. • In addition to symptomatic treatment (diet, hydration, loperamide, antibiotics if indicated); initiate immediate treatment with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) is recommended. • When symptoms improve to ≤ grade 1, taper steroids slowly (see Section 6.3.1.3.1). Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding. • If no improvement in 2-3 d: consider initiating infliximab 5 mg/kg and continue steroids. Note: infliximab is contraindicated in patients with sepsis or a perforation. Upon symptomatic relief initiate a prolonged steroid taper over 6 to 8 weeks. • If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100

Diarrhea/colitis (NCI-CTCAE v5)	
Grade	**Recommended management**
	mg/d followed by a more prolonged taper and administer infliximab. • If symptoms persist despite the above treatment a surgical consult should be obtained.
Grade 4: Life-threatening consequences; urgent intervention indicated	Same as grade 3

Table 14-11 Recommended clinical management for suspected immune-related liver laboratory alterations

Abnormal liver tests (NCI-CTCAE v5)	
Grade	**Recommended management**
Grade 2: AST or ALT > 3 × ULN to ≤ 5.0x ULN; or if baseline abnormal >3.0 – 5.0 x baseline or bilirubin > 1.5 × ULN to ≤ 3 × ULN ; or if baseline abnormal >1.5 – 3.0 x baseline (if patient meets criteria for Hy's law refer to Section 6.3.3.1)	• 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

Abnormal liver tests (NCI-CTCAE v5)	
Grade	**Recommended management**
Grade 3 or 4: AST or ALT > 5.0 × ULN; or if baseline abnormal >5.0 x baseline. bilirubin > 3.0 × ULN; or if baseline abnormal >3.0 x baseline.	• Monitor hepatic laboratory tests more frequently (every 2-3 days) until returned to baseline values. • Consider viral serology (i.e. hepatitis A/B/C, CMV, and rule out other potential cause of liver injury such as concomitant medications or alcohol), consultation with hepatologist and liver biopsy to establish etiology of hepatic injury • If after 2-3 days new liver assessment shows worsening of laboratory test consider to initiate treatment with steroids prednisone 1-2 mg/kg/day or i.v. equivalents. • Add prophylactic antibiotics for opportunistic infections as appropriate • When symptoms/liver tests improve to grade ≤ 1, taper steroids over at least 4 weeks. • If serum transaminase levels or bilirubin do not decrease 48-72 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given as per institutional guidelines. • Infliximab is not recommended due to its potential for hepatotoxicity

Table 14-12 Recommended clinical management for suspected immune-related rash and other skin events

Rash and other skin Events (NCI-CTCAE v5)	
Grade	**Recommended management**
Grade 1: rash covering < 10% Body Surface Area (BSA)	• Initiate prophylactic and symptomatic treatment measures. • Consider use of topical corticosteroids or urea containing creams in combination with oral antipruritics or moderate strength topical steroid (hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream) • Reassess after 2 weeks.
Grade 2: 10-30% of BSA	• If tolerable, treat as per grade 1; • If intolerable, initiate systemic steroids (e.g. oral prednisolone 0.5-1 mg/kg/d) and consider dose interruption until tolerable or recovery to grade ≤ 1 or baseline • If symptoms persist or recur consider skin biopsy**.**
Grade 3: More than 30% of BSA	• Obtain a skin biopsy and dermatology consult. • Initiate systemic steroids with 1mg/kg/d of prednisone or equivalent.
Grade 4: Life-threatening	Same as grade 3; additional measures as per local institutional guidelines
Other skin events	
Stevens-Johnson syndrome, toxic epidermal necrolysis	• Hospitalization and urgent dermatology consultation • Institute supportive care immediately as per institutional guidelines

Table 14-13 Recommended clinical management for suspected immune-related nephritis

Nephritis (NCI-CTCAE v5)	
Grade	**Recommended management**
Grade 1: Creatinine > ULN to ≤ 1.5 × ULN); or if baseline abnormal >1 – 1.5 x baseline	• Monitor creatinine weekly • If creatinine return to baseline resume routine creatinine monitoring per protocol • Promote hydration and cessation of nephrotoxic drugs
Grade 2: Creatinine > 1.5 to ≤ 3 × ULN; or if baseline abnormal >1.5 – 3.0 x baseline	• Monitor creatinine every 2 to 3 days • Initiate 0.5 to 1 mg/kg/d prednisone or equivalents • If worsening or no improvement: 1 to 2 mg/kg/day prednisone or equivalents • Promote hydration and cessation of nephrotoxic drugs • Consult with specialist and consider renal biopsy
Grade 3: Creatinine >3.0 to ≤ 6.0 × ULN; or if baseline abnormal >3.0 – 6.0 x baseline	• Monitor creatinine every 1 to 2 days • Start 1 to 2 mg/kg/day prednisone or equivalents • Consult with nephrologist and consider renal biopsy
Grade 4: Creatinine > 6.0 × ULN	• Monitor creatinine daily • Initiate steroids with 1 to 2 mg/kg/d prednisone or equivalent • Consult with nephrologist and consider renal biopsy

Table 14-14 Recommended clinical management for suspected immune-related pneumonitis

Pneumonitis (NCI-CTCAE v5)	
Grade	**Recommended management**
Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated	• High-resolution CT with lung windows recommended, with serial imaging to monitor for resolution or progression. Repeat at least every 3 weeks • Monitor for symptoms every 2-3 days - Clinical evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse oximetry recommended • Consultation of pulmonologist recommended
Grade 2: Symptomatic-medical intervention indicated; limits instrumental ADLs	• Perform high-resolution CT with lung windows • Monitor symptoms daily, consider hospitalization • Clinical evaluation and laboratory work up for infection • Consult pulmonologist • Pulmonary function tests - if normal at baseline, repeat every 8 weeks • Bronchoscopy with biopsy and/or BAL recommended • Symptomatic therapy including corticosteroids if clinically indicated (1 to 2 mg/kg/d prednisone or equivalent as clinically indicated).
Grade 3: Severe symptoms; limits self-care ADLs; oxygen 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

Pneumonitis (NCI-CTCAE v5)	
Grade	**Recommended management**
Grade 4: Life- threatening respiratory compromise; urgent intervention required	• If no improvement within 48 hours, consider infliximab and/or other immune-suppressive therapy, or i.v. Ig as per local guidelines • Empiric antibiotics

Table 14-15 Recommended clinical management for suspected immune-related endocrinopathies

Endocrine events (NCI-CTCAE v5)	
Grade	**Recommended management**
Asymptomatic, intervention not indicated (e.g. hyperthyroidism or hypothyroidism)	• If TSH < 0.5 × LLN, or TSH > 2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated • Consider endocrinologist consult • If hypophysitis is considered, pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis) • Repeat labs in 1 to 3 weeks/MRI in 1 month if laboratory abnormalities persist but normal lab/pituitary scan
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 initiate
Autoimmune diabetes (Grade 3 or symptomatic hyperglycemia)	• 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)
Autoimmune diabetes (Grade 4 hyperglycemia or life-threatening complications)	Same as grade 3

Table 14-16 Recommended clinical management for suspected infusion reaction or cytokine release syndrome

Infusion reaction (NCI-CTCAE v5)	
Grade	**Recommended management**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. • Consider slowing infusion rate until recovery of symptoms • May continue spartalizumab

Grade 2
Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs
	• Stop infusion
	• 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 as medically indicated until the patient is deemed medically stable in the opinion of the investigator.
	• If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be re-premedicated for the next scheduled dose.
	• Patient may be premedicated 1.5h (± 30 minutes) prior to infusion with diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine) and acetaminophen 500-1000 mg p.o. (or equivalent dose of analgesic).
	• Consider permanent discontinuation of study treatment in case of recurring infusion reaction despite premedication and prolonged infusion

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 subject is deemed medically stable.
	• Hospitalization as indicated

Table 14-17 Recommended clinical management guidelines for suspected other potential immune-related events

Other (i.e. Autoimmune neuropathy, Demyelinating polyneuropathy, Guillain Barre, Myasthenia Gravis-like syndrome, non-infectious myocarditis, pericarditis, pancreatitis, encephalitis, and Grade 3 Fatigue with rapid onset in absence of disease progression) (NCI-CTCAE v5)	
Grade	**Recommended management**
Mild (Grade 1)	Provide symptomatic treatment
Moderate (Grade 2)	• Consider treatment interruption until recovery to ≤ grade 1 or baseline. • 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
Severe (Grade 3)	• Initiate systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg/d and other therapies as appropriate • Monitor closely and consult with a specialist
Grade 4	• Hospitalization and consult with specialist • Initiate systemic corticosteroids (prednisone a dose of 1-2 mg/kg/d or equivalent) and other therapies as appropriate
Encephalitis (any grade) 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/d prednisone equivalents.
Guillain-Barre Severe peripheral or autonomic neuropathy, or transverse myelitis	• Hospitalization and consult with specialist
Myasthenia gravis	• Consult with specialist • Consider pyridostigmine and systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg/d; other therapies as appropriate (e.g. IVIG) • Hospitalization in case of severe cases
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). Hospitalization as indicated
Pancreatitis Amylase/lipase elevation	• Evaluate for pancreatitis (clinical assessment, abdominal imaging and/or magnetic resonance cholangiopancreatography as appropriate) • Treatment may be continued in case of asymptomatic, isolated enzyme elevations without evidence for pancreatitis • Initiate steroids in case of ≥ grade 2 acute pancreatitis
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
Ocular events	• Consult with ophthalmologist