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NIS793

Clinical Trial Protocol CNIS793E12201 / NCT04952753

daNIS-3: An open-label, multi-center, phase II platform study evaluating the efficacy and safety of NIS793 and other new investigational drug combinations with standard of care (SOC) anti-cancer therapy for the second line treatment of metastatic colorectal cancer (mCRC)

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List of abbreviations

5-FU	5-fluorouracil
ADA	Anti Drug Antibodies
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
ANC	Absolute Neutrophil Count
ANP	Anti-neoplastic
ASMA	Anti-smooth muscle antibody
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BLRM	Bayesian Logistic Regression Model
BUN	Blood Urea Nitrogen
BYOD	Bring Your Own Device
CA-19-9	Carbohydrate Antigen 19-9
CEA	Carcinoembryonic Antigen
CK	Creatine Kinase
CMO&PS	Chief Medical Office and Patient Safety
CMS	Consensus Molecular Subtypes
CCI	[redacted]
COVID-19	Coronavirus Infectious Disease 2019
CR	Complete Response
CRC	Colorectal Cancer
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computerized Tomography
CCI	[redacted]
CTT	Clinical Trial Team
CV	Coefficient of Variation
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DDS	Dose Determining Set
DILI	drug induced liver injury
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
dMMR	mismatch repair-deficient
DOR	Duration Of Response
DPD	Partial Dipyrimidine Dehydrogenase
ECG	Electrocardiogram
ECLIA	Electrochemiluminescent Assay
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

EGFR	Epidermal Growth Factor Receptor
ELISA	Enzyme-linked immunosorbent assay
EOI	End of Infusion
CCI [redacted]	[redacted]
[redacted]	[redacted]
EOT	End of Treatment
ERCP	Endoscopic retrograde cholangiopancreatography
eSAE	Electronic Serious Adverse Event
ESMO	European Society for Medical Oncology
CCI [redacted]	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First In Human
FOLFIRI	Folinic acid, fluorouracil, and irinotecan
FOLFOX	Folinic acid, fluorouracil, and oxaliplatin
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
h	Hour
HBsAg	Hepatitis B virus surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
HR	Hazard Ratio
CCI [redacted]	[redacted]
iCPD	Immune Confirmed Progressive Disease
CCI [redacted]	[redacted]
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	Immunogenicity
IN	Investigator Notification
INR	International Normalized Ratio
CCI [redacted]	[redacted]
[redacted]	[redacted]
irAE	Immune Related Adverse Event
IRB	Institutional Review Board
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IRT	Interactive Response Technology
CCI [redacted]	[redacted]

IUD	Intra Uterine Device
iUPD	Immune Unconfirmed Progressive Disease
IUS	Intra Uterine System
LC-MS	Liquid Chromatography-Mass Spectrometry
LDH	lactate dehydrogenase
LFT	Liver function test
LLOQ	Lower Limit Of Quantification
LPLV	Last patient last visit
LVEF	Left Ventricular Ejection Fraction
mAb	monoclonal Antibody
mCRC	Metastatic Colorectal Cancer
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MRI	Magnetic resonance imaging
MSI-H	Microsatellite instability-high
MSS	microsatellites stable
MUGA	Multigated acquisition scan
NCA	Non-compartmental Analysis
NT-proBNP	N-Terminal-pro-B-type Natriuretic Peptide
OHP	Off-site Healthcare Professional
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PBMC	Peripheral Blood Mononuclear Cells
PD	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PoC	Proof of Concept
PR	Partial Response
CCI	[redacted]
PT	prothrombin time
PTT	Partial Thromboplastin Time
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RAP	The Report and Analysis Plan
RDE	Recommended Dose for Expansion
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended phase 2 dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics

SOC	Standard Of Care
SOD	Sum of Diameters
SRI	Safety Run-in
SRT	Safety Review Team
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TEN	Toxic epidermal necrolysis
TGF-β	Transforming growth factor beta
TME	Tumor Microenvironment
TTF	Time to treatment failure
TTP	Time To Progression
TTR	Time To Response
ULN	upper limit of normal
UPCR	Urine protein/creatinine ratio
UTI	Urinary Tract Infection
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
WoC	Withdrawal of Consent
WOCBP	Women of childbearing potential

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
CCI	
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study intervention (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study intervention administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant .
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to Novartis and other oversight authorities, as appropriate
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study

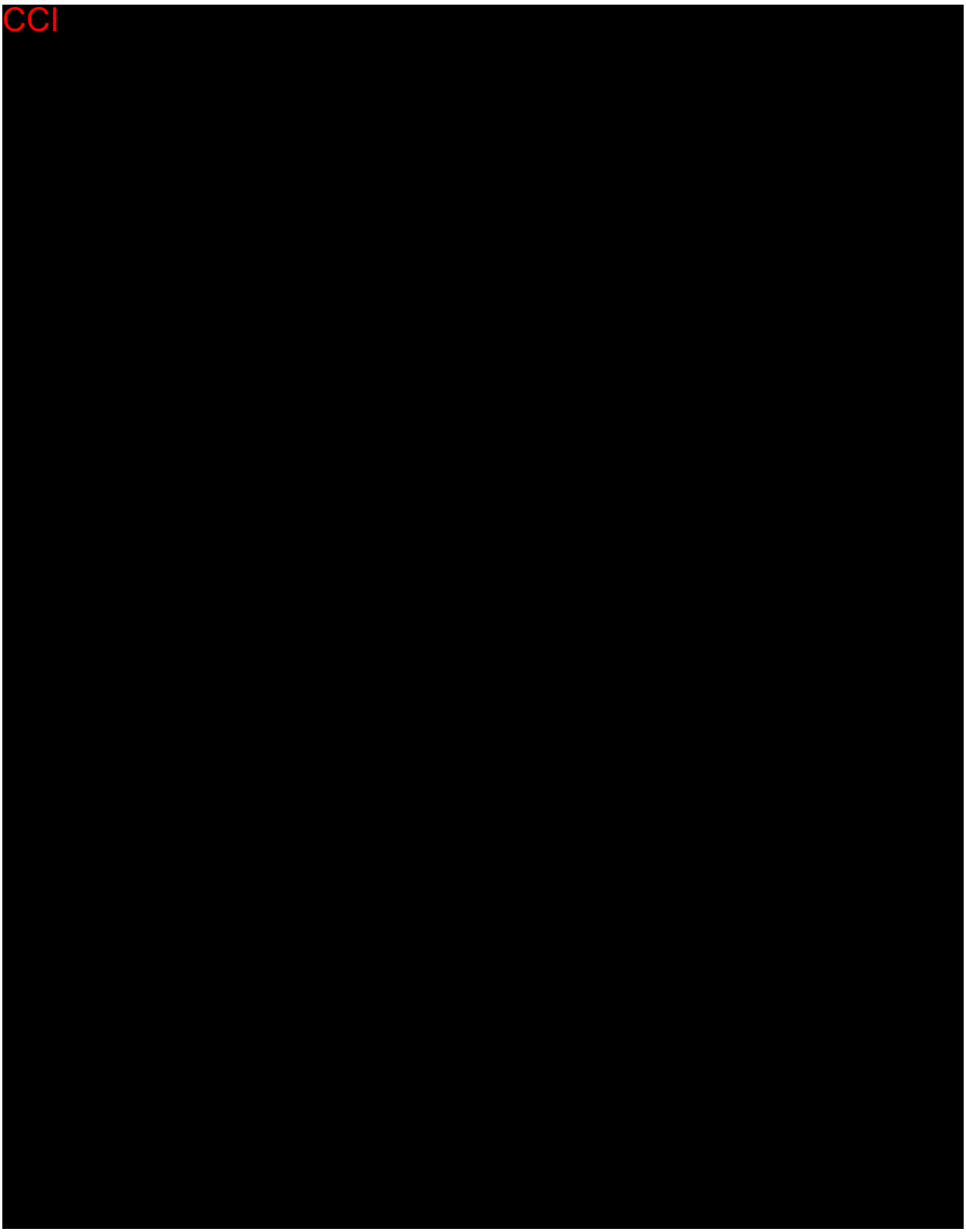
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
CCI	
Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued, and no further assessments are planned
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the Investigator will conduct the trial, but is for example a home or another appropriate location
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy

Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the Investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/ or biological samples AND no longer wishes to receive study treatment AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

Amendment 4 (11-Mar-2024)

Amendment rationale

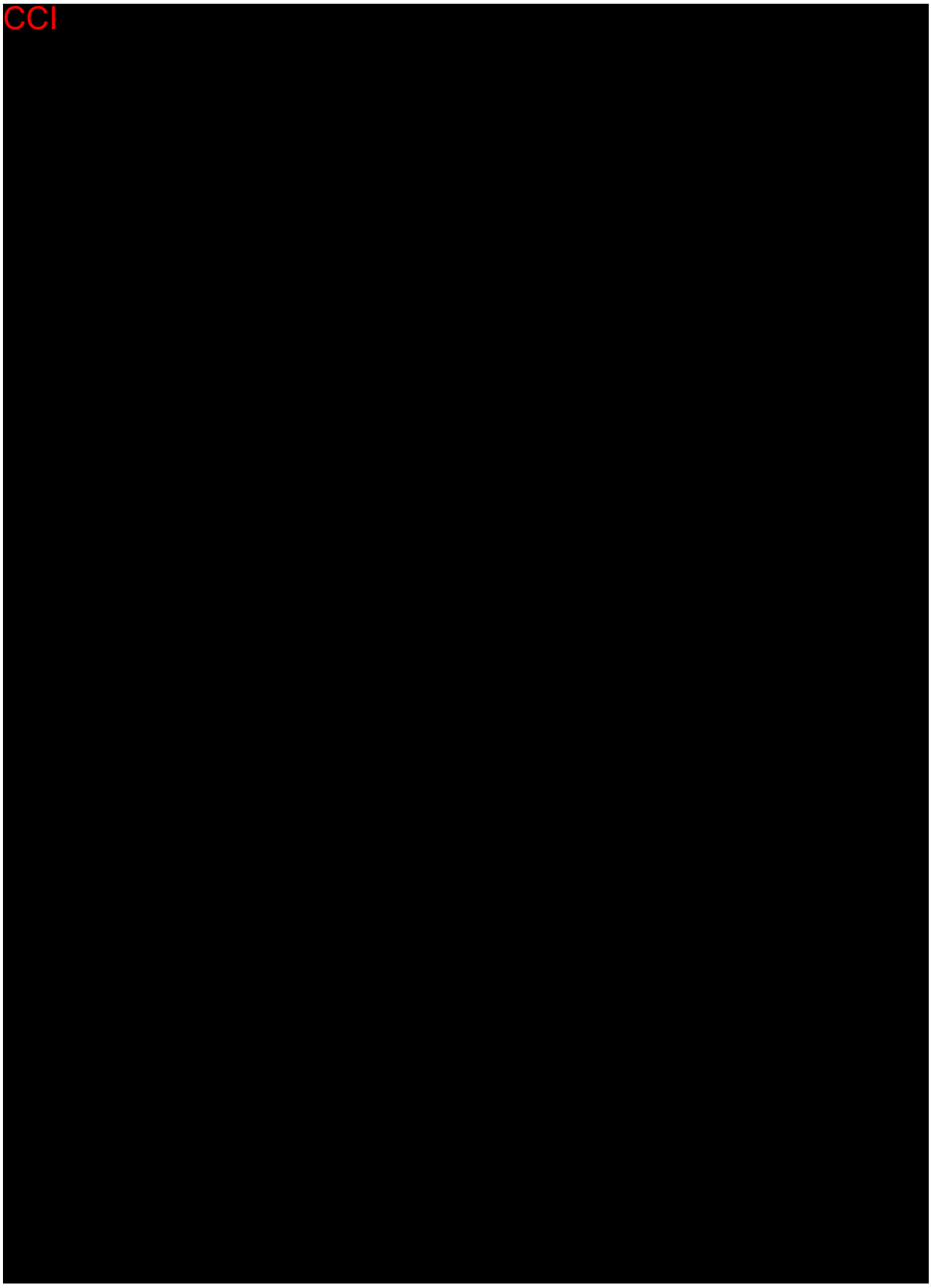
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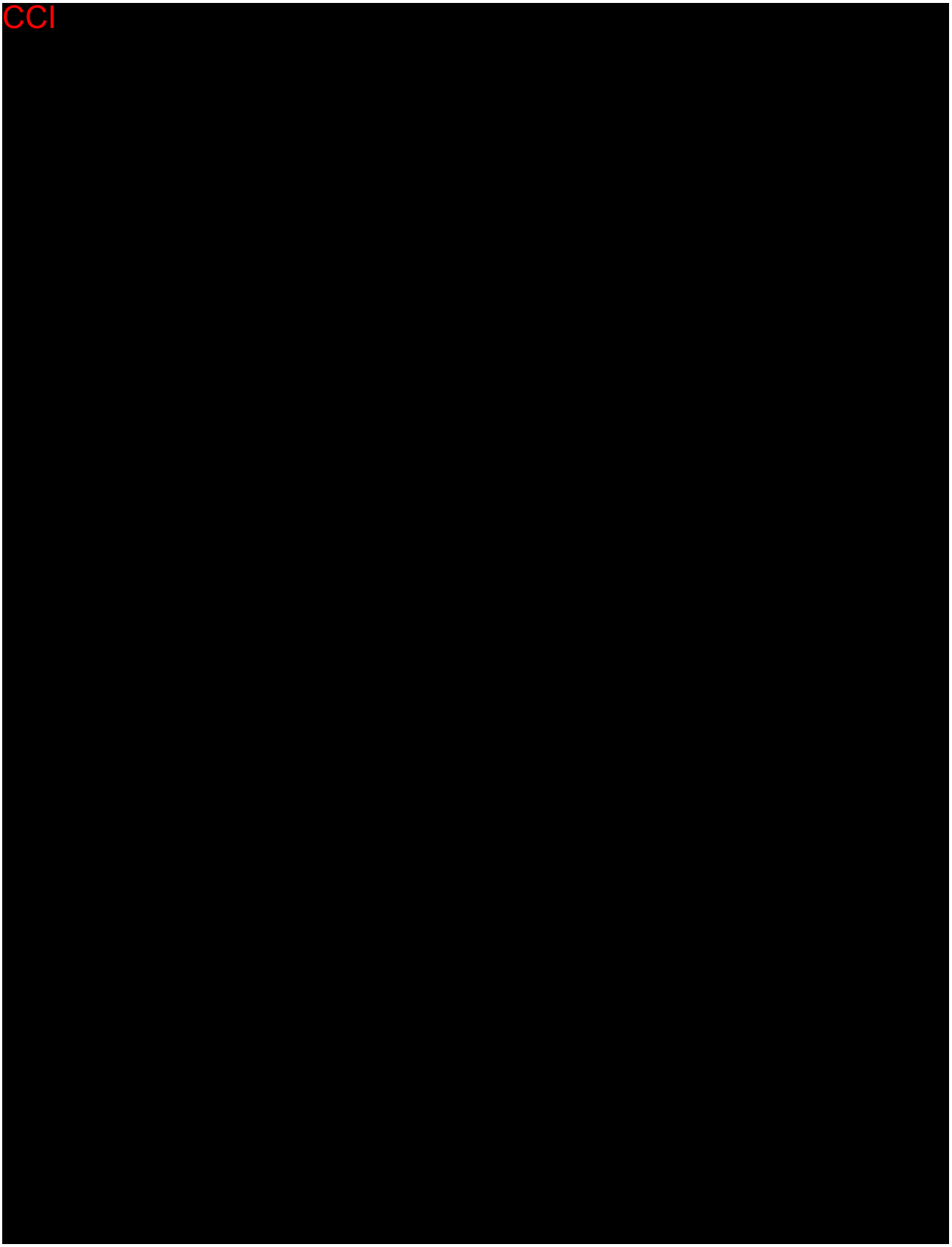
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Review requirements by IRB/ IEC and Health Authorities

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.

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

Amendment 3 (30-May-2023) – Withdrawn on 01-Sep-2023

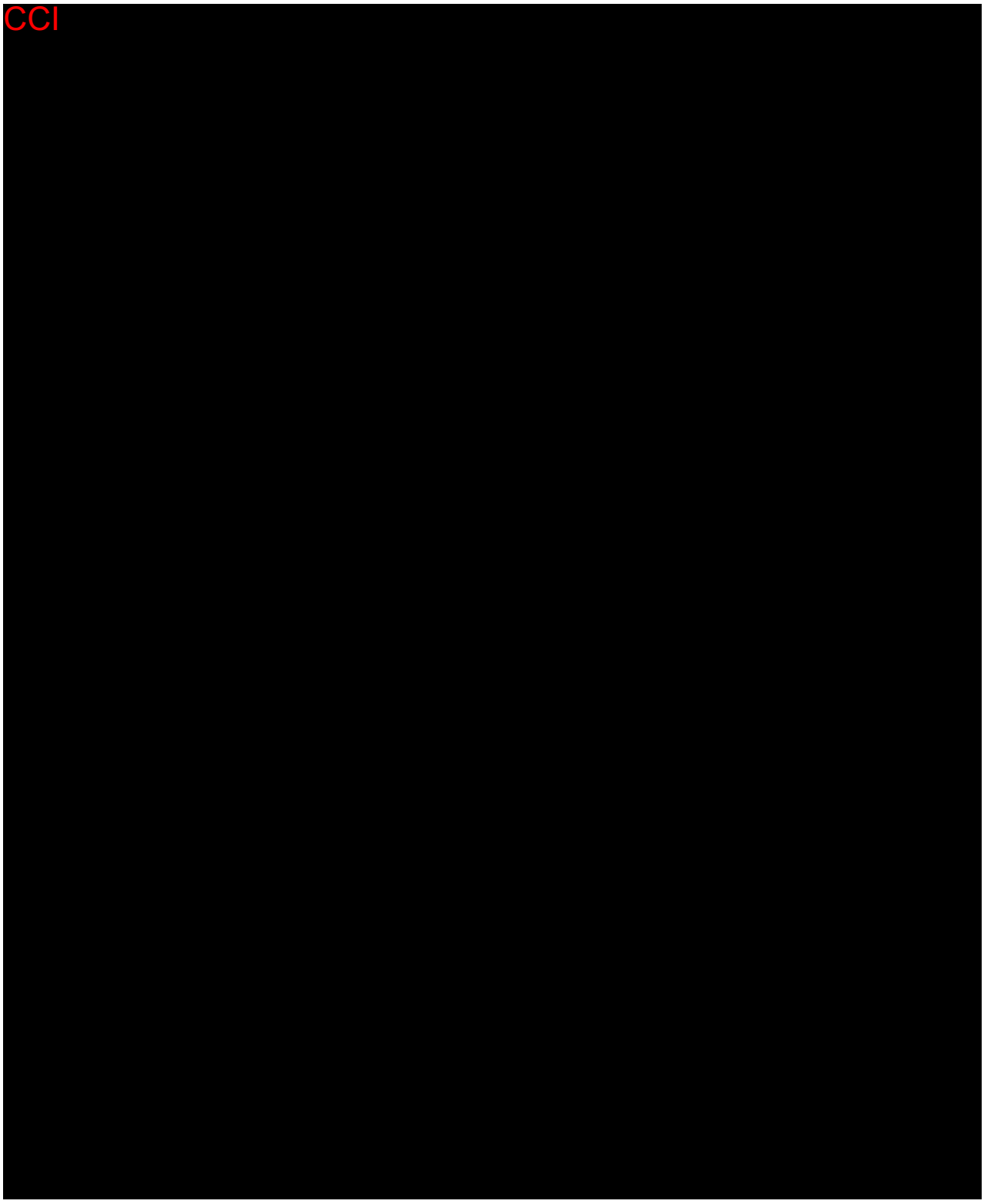
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Amendment 2 (20-Sep-2022)

Amendment rationale

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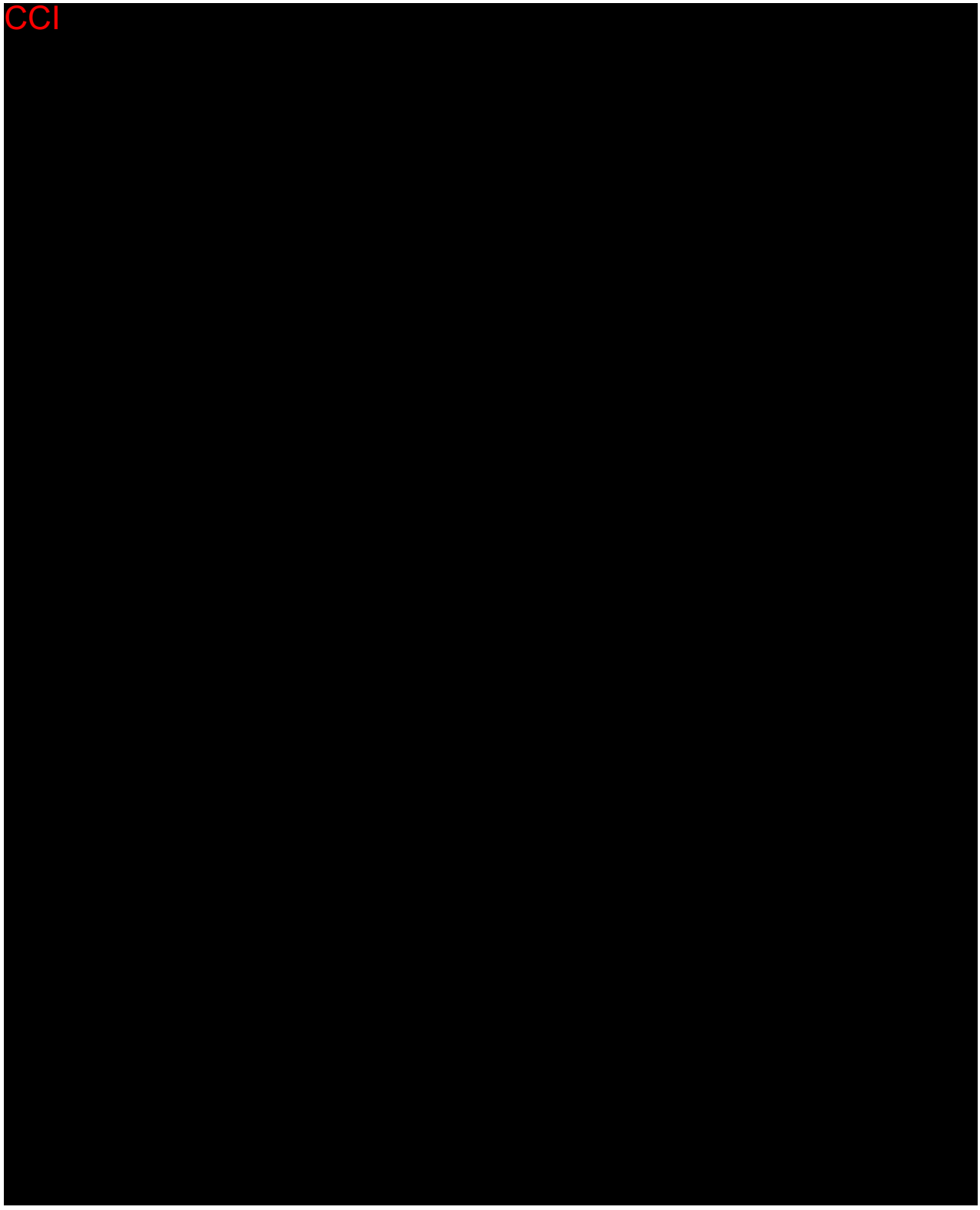
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Amendment 1 (25-Nov-2021)

Amendment rationale

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CCI

[redacted]

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

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Protocol summary

Protocol number	CNIS793E12201
Full Title	daNIS-3: An open-label, multi-center, phase II platform study evaluating the efficacy and safety of NIS793 and other new investigational drug combinations with standard of care (SOC) anti-cancer therapy for the second line treatment of metastatic colorectal cancer (mCRC)
Brief title	Study of NIS793 and other novel investigational combinations with SOC anti-cancer therapy for the second line treatment of mCRC
Sponsor and Clinical phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the preliminary efficacy and safety of NIS793 and other novel investigational combinations with SOC anti-cancer therapy vs SOC anti-cancer therapy for the second line treatment of mCRC. The SOC anti-cancer therapy in this study will include combination of bevacizumab with either modified FOLFOX6 (mFOLFOX6) or FOLFIRI chemotherapy regimens. This study aims to explore whether different mechanisms of action may reverse resistance and improve responsiveness to the currently considered SOC anti-cancer therapy in the second line mCRC setting. In each investigational arm, a Safety run-in part will be conducted before opening the expansion part to confirm the recommended phase 2 dose (RP2D) for a combination of any investigational drug with SOC anti-cancer therapy unless the dose has been confirmed externally to this trial. The Investigational arm #1 will study the combination of anti-transforming growth factor β (TGF-β) monoclonal antibody, NIS793 with SOC anti-cancer therapy. The purpose of this arm is to evaluate the safety and compare the preliminary efficacy of NIS793 in combination with SOC anti-cancer therapy vs SOC anti-cancer therapy for the second line treatment of mCRC. The investigational arm #2 will study the combination NIS793, tislelizumab (an anti-PD-1 monoclonal antibody) in combination with SOC anti-cancer therapy. The purpose of adding this arm is to evaluate the safety and compare the preliminary efficacy of NIS793 and tislelizumab in combination with SOC anti-cancer therapy vs SOC anti-cancer therapy for the second line treatment of mCRC.
Primary Objective(s)	**Safety Run-in (SRI) part**: To confirm the recommended phase 2 dose (RP2D) of NIS793 or NIS793+tislelizumab in combination with SOC anti-cancer therapy **Expansion part**: To evaluate preliminary efficacy of NIS793 or NIS793+tislelizumab in combination with SOC anti-cancer therapy versus SOC anti-cancer therapy in terms of progression-free survival (PFS) by Investigator assessment per RECIST 1.1
Secondary Objectives	**Safety Run-In (SRI)**: ● To evaluate safety and tolerability of NIS793 or NIS793+tislelizumab in combination with SOC anti-cancer therapy (bevacizumab with either mFOLFOX6 or FOLFIRI) in each investigational arm. ● To evaluate preliminary efficacy: PFS, overall response rate (ORR), disease control rate (DCR), duration of response (DOR), time to response (TTR) by Investigator assessment per RECIST 1.1 and overall survival (OS) of NIS793 or NIS793+tislelizumab in combination with SOC anti-cancer therapy in each investigational arm. ● To assess Pharmacokinetics (PK) of NIS793 and NIS793+tislelizumab in each investigational arm. ● To characterize the immunogenicity of NIS793 and tislelizumab in each investigational arm. **Expansion part:** ● To evaluate efficacy (ORR, DCR, DOR, TTR, OS) by Investigator assessment per RECIST 1.1 in each investigational arm and control arm.

	● To evaluate safety and tolerability in each investigational arm and control arm. ● To assess PK of NIS793 or tislelizumab in each investigational arm . ● To characterize the immunogenicity of NIS793 or NIS793+tislelizumab in each investigational arm.
Study design	This is an open-label, multi-center, phase II platform study. The platform design of this study is adaptive to allow flexibility in the introduction of additional treatment arms with new investigational drugs in combination with SOC anti-cancer therapy for the second line treatment of mCRC. The study will include control arm that will enroll participants treated with SOC anti-cancer therapy (bevacizumab with mFOLFOX6 or FOLFIRI) for the second line treatment of mCRC. Each investigational arm will include a combination of an investigational drug and the SOC anti-cancer therapy. Investigational arm #1 will include combination of NIS793 with SOC anti-cancer therapy. Investigational arm #2 will include combination of NIS793 with tislelizumab and SOC anti-cancer therapy. Combinations of other investigational drug(s) with SOC anti-cancer therapy may be added later by protocol amendment as new investigational arms (i.e, investigational arm #3, etc.). Each investigational arm will start with a Safety run-in (SRI) followed by an Expansion part. The SRI and Expansion parts will run independently for each SOC anti-cancer therapy, mFOLFOX6 or FOLFIRI with bevacizumab. The purpose of SRI is to confirm the dose of investigational drug with SOC anti-cancer therapy. Each SRI will enroll up to ● approximately 20 participants to have at least 12 evaluable participants (6 treated by NIS793 [or any other new investigational drug] + mFOLFOX6 + bevacizumab and 6 by NIS793 [or any other new investigational drug] + FOLFIRI + bevacizumab) Each expansion will enroll ● approximately 75 participants in each treatment arm and each investigational arm may have its concurrent control. The decision to open the expansion part of the study will be based on dose confirmation of investigational drug(s) with available safety, relevant PK and other relevant clinical and laboratory data from the safety run-in part. CCI [redacted]
Rationale	This study will recruit participants with microsatellites stable (MSS) metastatic colorectal cancer treated with second line treatment, who have a poor prognosis and limited treatment options. The OS 5 year rate with current treatment strategies is below 15%, thus highlighting the need for innovative therapeutic options. Different investigational drugs may be added to SOC anti-cancer therapy to try to enhance its efficacy. Based on in vitro and in vivo preclinical, translational and preliminary clinical data, it is expected that the addition of TGF-β blockade by NIS793, to chemotherapy and anti-VEGF treatment can relieve the resistance and improve responsiveness to these treatments in the first investigational arm (arm #1) and also that the addition of TGF-β blockade by NIS793, to chemotherapy, immunotherapy and anti-VEGF treatment can relieve tumor resistance and improve responsiveness to these treatments in the second investigational arm (arm #2).
Study population	The study will include adult participants with MSS metastatic colorectal cancer treated with second line treatment.
Key Inclusion criteria	● Participants aged 18 or older with histologically or cytologically confirmed (by local laboratory and local clinical guidelines) metastatic colorectal adenocarcinoma that is not amenable to potentially curative surgery in the opinion of the Investigator and progressed on or within 6 months after the last dose of one prior line of systemic anti-cancer therapy administered for metastatic disease. ● Presence of at least one measurable lesion assessed by CT and/or MRI according to RECIST 1.1. ● Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1. ● Adequate organ function (assessed by central laboratory for eligibility).
Key Exclusion criteria	● Previously administered systemic immunotherapy (e.g. anti-PD-1, anti-PD-L1/-L2, anti-CTLA-4 antibody) or TGF-β targeted therapies.

	● Microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) (mandatory, locally performed), BRAFV600 mutation positive colorectal cancer. ● Known complete or partial dipyrimidine dehydrogenase (DPD) enzyme deficiency (testing for DPD enzyme deficiency is not mandatory unless required by local regulations and can be conducted at a local laboratory). ● For participants treated with irinotecan: Known history or clinical evidence of reduced UGT1A1 activity (testing for UGT1A1 status is not mandatory unless required by local regulations and can be conducted at a local laboratory). ● Participants who have not recovered from a major surgery performed prior to start of study treatment or have had a major surgery within 4 weeks prior to start of study treatment. ● Impaired cardiac function or clinically significant cardio-vascular disease. ● Participants with conditions that are considered to have a high risk of clinically significant gastrointestinal tract bleeding or any other condition associated with or history of significant bleeding. ● Stroke or transient ischemic attack, or other ischemic event, or thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 3 months before start of study treatment. ● Active, known, or suspected autoimmune disease or a documented history of autoimmune disease ● Pregnant or breast-feeding women. ● Women of childbearing potential, unless willing to use highly effective contraception methods during treatment and after stopping study treatments as required.
Study treatment	The study treatment for the control arm in this study is SOC anti-cancer therapy (bevacizumab with mFOLFOX6 or FOLFIRI). Selection of FOLFIRI or mFOLFOX6 will be based on prior exposure to oxaliplatin or irinotecan. ● Participants who received oxaliplatin as first line therapy will be treated with FOLFIRI ● Participants who received irinotecan as first line therapy will be treated with mFOLFOX6 The study treatment for the investigational arm #1 is NIS793 with SOC anti-cancer therapy and for the investigational arm #2 is NIS793 with tislelizumab and SOC anti-cancer therapy. Additional investigational drugs and/ or additional combinations as separate investigational arms may be included following a protocol amendment(s). All study drugs are administered IV, based on a 28-day treatment cycle. CCI [redacted].
Efficacy assessments	Radiological tumor assessment by Investigator as per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) for all particpants in investigational arms #1 and #2 and Immune Response Evaluation Criteria in Solid Tumors (iRECIST) for participants treated with investigational arm #2 at screening and for all participants in arms #1 and #2 at screening in case of concurrent randomization, every 8 weeks for the first year, then every 12 weeks thereafter until disease progression, death, lost to follow-up or withdrawal of consent. ● Participants who enter efficacy follow-up will follow the same schedule as in the treatment period. ● Survival follow-up: every 12 weeks after the completion of safety and efficacy follow-up. CCI [redacted]
Pharmacokinetic (PK)/ Pharmacodynamic (PD/ /Immunogenicity (IG) assessments	● Pharmacokinetics (PK) of NIS793 and tislelizumab in combination with SOC anti-cancer therapy ● Incidence of antidrug antibodies (ADA; anti-NIS793, anti-tislelizumab at baseline and during the treatment CCI [redacted].
Key safety assessments	● Physical examination ● ECOG Performance Status

	● Vitals signs, body weight ● Laboratory assessments ● Electrocardiograms (ECGs), cardiac imaging/enzymes ● Pregnancy testing for women of childbearing potential (WOCBP) ● Adverse events monitoring (DLT, severity, relationship to study treatment and seriousness) CCI [redacted].
CCI [redacted]	
Data analysis	For each investigational arm, the study data will be analyzed and reported based on all participants' data of the safety run-in and expansion parts at the time when all participants have potentially reached the primary analysis timepoint. This timepoint can be arm-specific, therefore a single primary Clinical Study Report (CSR), or several CSRs may be prepared which may include more than one investigational arm. The additional data for any participants still on study past the data cutoff date for the primary Clinical Study Report (CSR), as allowed by the protocol, will be further summarized in a final CSR once these participants complete the study. The primary endpoint for the safety run-in part is the incidence of dose-limiting toxicity (DLT) during the DLT evaluation period. Dose confirmation will be guided by an adaptive Bayesian logistic regression model (BLRM) based on any DLTs observed. For the Expansion part, the primary endpoint for each investigational arm is PFS by Investigator's assessment per RECIST 1.1. For each investigational arm, the primary comparison is for each investigational arm and the combined control arm. All secondary analyses will be reported for the adequate population (i.e., FAS, Safety Set) by treatment arms. CCI [redacted].
Key words	NIS793, metastatic colorectal cancer, colorectal cancer, transforming growth factor beta (TGF-β), anti PD-1 monoclonal antibody

1 Introduction

1.1 Background

Colorectal cancer (CRC) is the 3rd most commonly diagnosed cancer in the world (1.8 million cases estimated) and the second highest cause of cancer death (881,000 deaths estimated). Higher incidence rates are observed in Australia, New Zealand, Europe and North America, whereas the lowest rates are found in Africa and South Central Asia. CRC is more frequent in males than in females (Bray et al 2018). Of newly diagnosed CRC patients, 75% have localized disease that is treated by surgical resection while 25% present with unresectable metastatic disease. Furthermore, approximately 30% of patients with localized CRC develop metastatic disease recurrence after the surgical removal of the tumor (Gill et al 2007). CRC death rates have declined progressively since mid-1980s in the United States and in many other western countries due to early detection and removal of colonic polyps, detection of CRCs at an earlier stage, and more effective primary and adjuvant treatments. In contrast, a worrying rise in patients presenting with colorectal cancer, younger than 50 years has been observed, especially rectal and left sided colon cancer (SEER Cancer Stat Facts: Colorectal Cancer 2019, Kasi et al 2019).

Colorectal cancer was one of the first solid tumors to be molecularly characterized with several genes and pathways implicated in tumor initiation and growth. The increasing understanding of molecular drivers and tumor-microenvironment interactions in CRC have produced major advances in drug development of targeted therapies and immunotherapies that have led to substantial improvements in the management and treatment of metastatic CRC (mCRC) over the last two decades. The median overall survival (OS) of patients diagnosed with unresectable mCRC has increased from approximately 12 months to >30 months with the integration of multiple cytotoxic agents and targeted therapies (Fakih 2015). The initial therapy for mCRC involves a cytotoxic backbone of a combination chemotherapy regimen, combining a fluoropyrimidine (e.g. 5-fluorouracil (5-FU), capecitabine) with oxaliplatin ("FOLFOX"/"CAPOX" regimens) (de Gramont et al 2000, Braun et al 2003), or irinotecan ("FOLFIRI" regimen) (André et al 1999, Fuchs et al 2007). Trials comparing 1st line treatment strategies demonstrated similar efficacy outcomes regardless of whether irinotecan or oxaliplatin was combined with fluoropyrimidine (Tournigand et al 2004). Therefore, the choice of the primary treatment regimen is commonly based on the physician's and patient's preferences and whether the patient has already received an adjuvant oxaliplatin-containing regimen (Schmoll and Stein 2014, Benson et al 2021).

Bevacizumab (an anti-vascular-endothelial growth factor [VEGF] monoclonal antibody [mAb]), cetuximab (anti-epidermal growth factor receptor [EGFR] mAb), and panitumumab (anti-EGFR mAb) are targeted therapies currently approved and used for the first line treatment of mCRC in combination with backbone chemotherapies (Hurwitz et al 2004, Saltz et al 2008, Van Cutsem et al 2009, Van Cutsem et al 2016). The anti-EGFR therapies are restricted to patients with RAS-wildtype tumors (oncogenic mutations in RAS are found in more than 50% of colorectal tumors (Dienstmann et al 2018)) while bevacizumab can be administered regardless of RAS mutation status. Either bevacizumab, cetuximab or panitumumab with combination chemotherapy (e.g., FOLFOX, capecitabine and oxaliplatin [CAPOX] or FOLFIRI) are reasonable options for the first line treatment of patients with RAS (KRAS/NRAS)-wildtype mCRC (Van Cutsem et al 2016). Sidedness of the tumor in the

metastatic setting is increasingly being recognized as a predictive marker of response of anti-EGFR drugs with a greater effect of chemotherapy plus EGFR therapy in patients with left sided tumors (Arnold et al 2017, Benson et al 2021).

For the second line of treatment of mCRC, the chemotherapy backbone is switched such that if a patient is treated in the first line setting with FOLFOX/CAPOX-based regimens, FOLFIRI is used in the second line treatment, and vice versa. Multiple studies have demonstrated the overall survival benefit of adding bevacizumab to the second line chemotherapy for patients who had progressed on a first line fluoropyrimidine containing regimen (Giantonio et al 2007); this benefit was also found in the second line treatment setting, in patients previously treated with a bevacizumab-containing regimen as first line treatment (Bennouna et al 2013, Masi et al 2015). In these studies, the benefit for bevacizumab was maintained regardless of KRAS mutation status. Addition of bevacizumab is accompanied by a moderate increase in overall toxicity with an absolute increase in incidence of grade 3/4 hypertension, bleeding, thromboembolic events, gastrointestinal perforation, fistulas/intra-abdominal abscess, and proteinuria (Saltz et al 2008). Patients with mCRC, after first line treatment, still have an important unmet medical need to improve current survival outcomes where median PFS is approximately 6 months and median overall survival (OS) is approximately 12 months with current available treatments (Bazarbashi et al 2019).

Regorafenib (a multitargeted tyrosine-kinase inhibitor) and TAS-102 (Lonsurf® ,combination of trifluridine and tipiracil, an oral anti-metabolite) are drugs that have demonstrated median OS benefit, but still OS remains below 8 months in heavily pretreated patients with at least 2 previous lines of therapy (Grothey et al 2013, Mayer et al 2015).

Additional therapies available for second-line therapy include immune checkpoint inhibitors which are indicated for the treatment of second/third line mCRC (pembrolizumab or nivolumab as a single agent, or nivolumab in combination with ipilimumab), for previously-treated, microsatellite instability–high or mismatch repair-deficient (MSI-H/dMMR) mCRC (Overman et al 2018a, Benson et al 2021). In Keynote-177 study, pembrolizumab demonstrated clinically meaningful and statistically significant improvement in PFS versus chemotherapy as first-line therapy for patients with MSI-H/dMMR mCRC, with fewer treatment-related adverse events (aEs) observed that supported FDA and EMA approval for use in these patients (Andre et al 2020). However, single agent checkpoint inhibitors have not demonstrated meaningful clinical activity for patients with proficient mismatch repair (pMMR) CRC (Overman et al 2018b).

BRAF-mutation V600E, that occurs in approximately 10% of mCRC patients, identifies a subgroup of patients with poor prognosis. The phase III BEACON trial demonstrated better OS with the triplet combination (encorafenib, binimetinib and cetuximab) and the doublet (encorafenib and cetuximab) vs Investigator's choice (cetuximab and irinotecan or cetuximab with FOLFIRI) for previously treated patients (Kopetz et al 2019). Based on these data, the FDA and EMA approved the combination of encorafenib and cetuximab for the treatment of previously treated patients with mCRC with a BRAF V600E mutation.

HER2 amplification or overexpression occurs in approximately 2-6% of unselected patients with mCRC and results from the MyPathway phase II study combining trastuzumab and pertuzumab for heavily pretreated patients showed preliminary efficacy results that were more pronounced in the RAS wild type subgroup (MericBernstam et al 2019). MET amplifications

and genomic rearrangements in kinases like ALK, ROS1, NTRK, and RET are also being investigated as druggable targets in CRC (Pagani et al 2019).

In 2014, on the basis of gene expression, colorectal cancer was classified into four molecular subtypes (consensus molecular subtypes CMS). The gene or pathways implicated are unique to each CMS; CMS 1 MSI-immune, CMS 2 canonical, CMS 3 metabolic and CMS 4 mesenchymal. CMS 4 tumors show upregulation of genes implicated in epithelial mesenchymal transition (EMT) and signatures associated with the activation of transforming growth factor β (TGF-β) pathway, angiogenesis, matrix remodeling pathways and complement inflammatory system. Right sided colorectal cancers are more often MSI-immune and metabolic tumors (Guinney et al 2015). Although tumor-sidedness and mutation status of tumors are important factors that currently guide selection of systemic treatments (NCCN Colon Cancer v15 2021), work is ongoing in clinical trials to explore the use of CMS classification subtyping as a prognostic or predictive marker.

Continuous updates in guidelines and treatment algorithms, including different sequences and combinations of chemotherapy, anti-VEGF and anti-EGFR agents, targeted drugs, immunotherapy, etc., have led to significant improvements in clinical outcomes for mCRC patients and median overall survival has doubled to 3 years but still, patients with mCRC ultimately progress and succumb to the disease (Dekker et al 2019). The 5-year relative survival percentage is still only 14.3% in the US (SEER Cancer Stat Facts: Colorectal Cancer 2019). New therapeutic options that are better tolerated guided with more accurate biomarkers are needed to improve outcomes both in the first- and second-line therapy setting for patients with mCRC (Soleimani et al 2019).

There are many possible innate and acquired molecular resistance mechanisms and treatment escape in mCRC. Specifically, to anti-angiogenesis therapies, hypoxia plays an important role in tumor resistance to chemotherapeutic agents favoring more aggressive metastatic disease and hence worse prognosis (Frentzas et al 2016, Comunanza and Bussolino 2017). Integrins activation plays a critical role in resistance to anti-angiogenic therapy (Giannelli et al 2014). CRC patient relapsing following chemotherapy indicated increased expression levels of HIF-1α/TGF-β2/GLI2, highlighting a potential biomarker and therapeutic target for chemotherapy resistance in colorectal cancer. This provides a valid rationale for combination of anti-TGFβ with anti-angiogenic therapy in CRC (Neuzillet et al 2015, Comunanza and Bussolino 2017, Tang et al 2018). The metastatic process has been extensively investigated but has yet to be linked with specific genetic alterations of epithelial CRC cells. Nevertheless, it has become clear that one of the key issues relies on tumor microenvironment (TME) (Derynck et al 2020). Therefore, blockage of cancer immunity and tumor-promoting inflammation have become hallmarks of cancer. The TME plays a critical role at the different stages of the disease from a physiological colonic epithelium to an adenomatous polyp and eventually to a mCRC. The TME confers to a CRC cell survival, immune evasion and a favorable environment to grow and metastasize (Van der Jeught et al 2018). TGF-β pathway plays a critical role in immune regulations, stromal cell activation and fibrosis. It has been recognized that alteration and aberrant regulation of TGF-β pathway plays a crucial role in the initiation, proliferation, inflammation and invasiveness of CRC. Moreover, various studies have shown that TGF-β is responsible for reducing drug sensitivity and recurrence in patients with cancer supporting the therapeutic potency of TGF-β inhibitors in combination with other treatments in this setting (Soleimani et al 2019).

As these inhibitors are mainly targeting the tumor microenvironment with little or dual effect on cancer cell proliferation, they should be used in combination with cytotoxic agents to kill these latter cells. In addition chemotherapy can induce TGF-β activity, possibly promoting metastatic progression, and high levels of TGF-β are associated with resistance to anti-cancer treatments, then, combined TGF-β inhibition may enhance tumor sensitivity to chemotherapy (Biswas et al 2007, Drabsch and ten Dijke 2012). Furthermore, there is increasing evidence showing that cytotoxic chemotherapy exerts its effect in malignant tumors not only through its classical mechanism of action but through its ability to stimulate anti-tumor immune effect releasing neoantigens and DAMPS (damage associated molecular patterns) causing also immunogenic death of tumor cells (Opzoomer et al 2019). In addition, several preclinical studies have shown that TGF-β may play a role in the acquired resistance to anti-angiogenic therapy (Haibe et al 2020).

The vast majority of patients with mCRC have microsatellite stable (MSS) tumors where benefit from single-agent immune checkpoint inhibitors is rather limited. Combination strategies of programmed cell death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte associated protein 4 (CTLA4) inhibition or chemotherapy have failed so far to improve efficacy in this setting (Nguyen et al 2020). Recently, it was reported that transforming growth factor-beta (TGF-β) signaling pathway participated in cancer immune escape and immune checkpoint inhibitor resistance. TGF-β is a versatile molecule which could bi-directionally regulate the initiation and progression of cancer. Furthermore, TGF-β has a multifaceted influence on the tumor immune microenvironment. Increasing evidence suggests that the excessive secretion of TGF-β in tumor closely relates to increased pro-tumor immune elements, restrained tumor-killing effect of tumor infiltrating lymphocytes (TIL), as well as limited infiltration of immune effector cells (Bai et al 2019). TGF-β is consequently implicated in T-cell exclusion and is associated with resistance to immune checkpoint blockade (PD-1 or PDL-1) (Van der Jeught et al 2018). In addition, preclinically, TGF-β blockade together with programmed cell death-1 (PD-1) inhibition acts synergistically in tumor models. All these support exploring TGF-β as a valid target for the treatment of metastatic colorectal cancer. Therefore, TGF-β might be a valuable target for cancer treatment and the dual-blockade of TGF-β/immune checkpoints would have a synergistic effect.

1.1.1 Overview of NIS793

NIS793 is an investigational recombinant human anti-TGF-β IgG2 mAb.

1.1.1.1 Non-clinical experience

CCI [redacted]

For the non-clinical toxicology of NIS793, refer to NIS793 Investigator's Brochure.

Although the role of TGF-β in the tumor microenvironment is multifaceted, emerging evidence points to TGF-β as a pivotal activator of myofibroblasts in the tumor microenvironment, inciting the progressive accumulation of collagen and extracellular matrix, a phenomenon,

referred to as desmoplastic reaction. Overall, the mechanical alterations secondary to the induction of the desmoplastic reaction can significantly shape the course of cancer disease, promoting cancer cell aggressive behaviors and contributing to resistance to chemotherapeutic drugs and immunomodulatory agents (Cremasco and Chang 2020). Studies in human colorectal cancer (CRC) cell lines have indicated that, TGF-β1 leads to chemoresistance, primarily through EMT (Mao et al 2017). Abundant desmoplasia and poor tissue perfusion or hypovascularity are thought to impede drug delivery in tumors with increased epithelial-to-mesenchymal transition. Increased intratumoural gemcitabine levels in pancreatic cancer animal models through modulation of stromal components by various pharmacological approaches, has resulted in suggesting that the tumor stroma may act as a physical barrier for drug delivery. Blocking hedgehog pathway demonstrated stromal depletion, significantly increased microvessel density and patency, and improved drug delivery in a KPC murine models (Olive et al 2009). Functional and preclinical experiments, performed in murine and human specimen, indicated that the blocking cancer associated fibroblast metabolic pathway enhances the antiproliferative effects of chemotherapy drug gemcitabine (Hessmann et al 2018).

Furthermore, notable reduction in the numbers of myofibroblasts in mice treated with NIS793 was accompanied by an increase in the number of tumor-infiltrating T cells, as determined by FACS assessment of tumor disaggregates. NIS793 was also shown to significantly augment the overall response to PD1-blockade in mice, leading to greater tumor regression and extended survival as compared to a PD-1 alone (Grauel et al 2020).

1.1.1.2 Clinical experience

As of the safety data cut-off date, 18-May-2021, a total of 129 patients have been treated with NIS793 across the two Novartis-sponsored clinical studies.

As of 18-May-2021, NIS793 is being evaluated in the ongoing first-in-human CNIS793X2101 study in adult patients with solid malignancies. In this study 120 patients have received at least one dose of NIS793. Eleven patients received NIS793 0.3-1 mg/kg Q3W as a single agent, and 109 patients received NIS793 in combination with a PD-1 targeting monoclonal antibody (mAB) spartalizumab: NIS793/spartalizumab 0.3 mg/kg/100 mg Q3W; 0.3-30 mg/kg/300 mg Q3W; 20-30 mg/kg Q2W/400 mg Q4W; and 2100 mg/300 mg Q3W.

No patients experienced a dose limiting toxicity (DLT). NIS793 30mg/kg Q3W in combination with spartalizumab 300mg Q3W was determined recommended dose for expansion (RDE), which translates to 2100mg NIS793 and 300mg spartalizumab Q3W flat-based dose. NIS793 20mg/kg Q2W in combination with spartalizumab 400mg Q4W was declared alternative RDE, which translates to 1400mg NIS793 Q2W and 400mg spartalizumab Q4W as a flat-based dose. All 120 patients (100%) have discontinued study treatment. The main reason for permanent discontinuation of study treatment was progressive disease in 102 patients (85.0%). Other reasons for permanent discontinuation of study treatment were adverse events (aEs) in seven (5.8%) patients, subject/guardian decision in six (5.0%) patients, and death in five (4.2%) patients.

One hundred and nineteen patients (99.2%) reported one or more aEs of any grade, regardless of causality. The most frequently reported aEs regardless of causality, were anaemia (29.2%), fatigue (28.3%), decreased appetite and nausea (each 25.8%), pyrexia (23.3%), and vomiting (22.5%).

Sixty-nine patients (57.5%) reported one or more aEs of grade 3 or higher, regardless of causality, during the course of the study. The most frequent grade 3 or higher AE regardless of causality were anaemia (17.5%), blood bilirubin increased and hyponatraemia (each 5.8%), and hypokalaemia (5.0%).

Sixty patients (50.0%) reported one or more aEs suspected to be study drug related during the course of the study until the cut-off date (18-May-2021). The most frequently reported aEs considered suspected to be study treatment related were rash (13.3%), pruritus (8.3%), fatigue (7.5%), nausea (6.7%), and decreased appetite, pyrexia and rash maculo-papular (each 5.0%). Fourteen patients (11.7%) reported grade 3 or higher aEs suspected to be study drug related. These were rash (3.3%), hyponatremia (1.7%), and pruritus, decreased appetite, amylase increased, diarrhoea, drug eruption, hepatic enzyme increased, hyperglycaemia, lipase increased, adrenal insufficiency, and haematuria (each 0.8%). Two patients (1.7%) had fatal AE events due to underlying disease, unrelated to study treatment dyspnoea and unrelated hepatic failure, the latter due to the presence of liver metastases. Fifty-three patients (44.2%) experienced at least one serious adverse event (SAE) regardless of causality while on study treatment. Thirteen patients reported SAEs suspected to be related to study treatment. One (10%) of the 11 patients treated with NIS-793 monotherapy experienced grade 3 or higher AE decreased appetite, and TEAE of all grades were experienced by 6 (54.5%) patients. For additional details on safety of NIS793 refer to the NIS793 Investigator's Brochure.

CCI [redacted]

As of 26-Mar-2021, NIS793 is being evaluated in phase II study CNIS793B12201, with and without spartalizumab in combination with SOC chemotherapy gemcitabine and nab-paclitaxel or SOC alone in participants with previously untreated metastatic pancreatic cancer, and 9 patients have been enrolled and treated in the safety run-in part with NIS793 2100 mg Q2W and spartalizumab 400 mg Q4W in combination with gemcitabine 1000 mg/m^2 Days 1, 8 and 15 and nab-paclitaxel 125 mg/m^2 Days 1, 8 and 15. The randomized part of the study was not opened at the time of data cut-off. As of 26-Mar-2021, five patients were ongoing on treatment and four patients have discontinued the study treatment. The primary reason for discontinuation was disease progression (3 patients), one patient discontinued due to AE. Out of nine patients, one patient experienced a DLT of grade 3 colitis. This DLT affected a 67-year-old male patient with first line metastatic pancreatic ductal adenocarcinoma (mPDAC). metastatic to the liver

with no significant medical history. The patient first presented at day 2 with G1 loose stools related to study treatment that recovered in 10 days. At day 17, the patient had G3 diarrhea with blood and G3 colitis formally diagnosed by sigmoidoscopy, both related to NIS793 and spartalizumab, leading to study treatment discontinuation. After two boluses of high-dose steroids, events of diarrhea and colitis resolved.

All nine patients reported one or more aEs of any grade and seven patients reported one or more aEs grade ≥ 3 (regardless of causality) during the study until the clinical data cut-off date, 26-Mar-2021. The most frequently reported aEs regardless of causality, any grade, were pyrexia (6 patients), nausea and rash (5 patients each), diarrhoea, fatigue and neutropenia (4 patients each), and asthenia and hypophosphataemia (3 patients each). The most frequent grade ≥ 3 aEs regardless of causality were neutropenia, neutrophil count decreased, rash maculo-papular, abdominal pain, colitis, diarrhoea haemorrhagic, gastritis haemorrhagic, ileal perforation, and back pain (1 patient each).

All nine patients reported one or more aEs suspected to be study drug related during the study. The most frequently reported aEs suspected to be study treatment related were nausea and rash (5 patients each), diarrhoea (4 patients), asthenia, fatigue, neutropenia and pyrexia (3 patients each), and alanine aminotransferase (ALT) increased, anaemia, aspartate aminotransferase (AST) increased, epistaxis, gingival bleeding, gingival swelling, neutrophil count decreased, rash maculo-papular and thrombocytopenia (2 patients each). Four patients reported grade 3/4 aEs suspected to be study treatment related: G3 neutrophil count decreased, G3 haemorrhagic gastritis, G3 hepatobiliary disorders, G3 rash maculopapular, G3 colitis, G3 diarrhoea haemorrhagic, and G4 neutropenia. Five patients experienced at least one SAE regardless of causality while on study treatment. Two SAEs were reported suspected to be related to study treatment, both for the same patient: G3 colitis and G3 diarrhoea haemorrhagic. For more details refer to the latest edition of the NIS793 Investigator's Brochure.

Based on the clinical experience with NIS793 from the ongoing first-in-human study CNIS793X2101, safety data from ongoing study CNIS793B12201, the safety profile of NIS793 is considered acceptable for continued clinical development.

Please refer to NIS793 IB for further updated information and details.

1.1.2 Overview of Tislelizumab

Tislelizumab (also known as BGB-A317 and VDT482) is a humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) against human programmed cell death-1 (PD-1) that is approved by China's Food and Drug Administration (CFDA) in different indications including Hodgkin's lymphoma, urothelial carcinoma, hepatocellular carcinoma, and squamous, non-squamous non-small cell lung cancer, and BLA for esophageal squamous cell carcinoma (ESCC) is accepted by FDA. Tislelizumab is being developed for treatment of human malignancies in multiple organs and tissues and is being investigated either as monotherapy or in combination with other therapies. As of 20-May-2021, 9 clinical studies with tislelizumab have been completed and 33 global and regional studies are ongoing.

1.1.2.1 Non-clinical experience

Tislelizumab binds to the extracellular domain of human PD-1 CCI [redacted]. It has either low or no antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), or complement-dependent cytotoxicity (CDC) effects in humans (Labrijn et al 2009, Zhang et al 2018).

Refer to the latest edition of tislelizumab Investigator's Brochure for additional details.

1.1.2.2 Clinical experience

As of 20-May-2021, 33 studies with tislelizumab are ongoing and 9 studies have been completed. Of the 33 ongoing studies, 15 have preliminary safety and efficacy data available in the Investigator's Brochure ed 9: CCI [redacted]. Additionally, there are 18 ongoing studies that do not have clinical data presented in this version of the IB. Based on pooled data from 2596 patients across 12 clinical studies, CCI [redacted] Refer to the latest edition of tislelizumab Investigator's Brochure for more detailed information on the compound.

1.1.2.2.1 Pooled safety data of monotherapy studies

Based on pooled analysis of 1992 patients with solid tumors treated in 7 tislelizumab monotherapy studies, CCI [redacted].

Refer to the tislelizumab Investigator's Brochure for additional details regarding safety data of tislelizumab.

1.1.2.2.2 Efficacy data of tislelizumab monotherapy

As of 20-May-2021, efficacy data of tislelizumab monotherapy in solid tumors are available from completed phase 1 study BGB-A317-001, completed phase 1/2 study BGB-A317-102, and completed phase 2 studies BGB-A317-203, BGB-A317-204, as well as ongoing phase 2 studies BGB-A317-207 and BGB-A317-208. CCI [redacted]

Refer to the tislelizumab Investigator's Brochure for additional details regarding efficacy data of tislelizumab.

1.1.2.2.3 Safety data of tislelizumab in combination studies

Based on pooled analysis of 544 patients treated, as of 20-May-2021, with tislelizumab in combination with chemotherapy in studies BGB-A317-205, BGB-A317-206, BGB-A317-304, and BGB-A317-307, CCI [redacted].

Refer to the tislelizumab Investigator's Brochure for additional details regarding safety data of tislelizumab.

In summary, combination of tislelizumab with chemotherapy was generally well tolerated and has tolerability profile consistent with the known PD-1 inhibitors in combination with chemotherapy.

1.1.2.2.4 Efficacy data of tislelizumab in combination therapy

Efficacy data is available from phase 3 studies BGB-A317-304, and BGB-A317-307, phase 2 studies BGB-A317-205, and BGB-A317-206, and phase 1/2 studies BGB-900-101, BGB-900-103, and phase 1a/1b BGB-A317/BGB-290_Study_001 of tislelizumab in combination with targeted therapies or chemotherapies.

CCI [redacted]

Refer to the tislelizumab Investigator's Brochure for additional details regarding efficacy data of tislelizumab.

1.2 Purpose

Despite recent improvements achieved using different strategies combining chemotherapy with targeted agents, treatment options for second line mCRC have modest efficacy in MSS metastatic CRC (median progression free survival ranges from 2.5 to 7.4 months and median overall survival from 9.2 to 14.3 months) (Leal et al 2017) and are often associated with toxicities. As such, mCRC remains an aggressive malignancy with a poor prognosis and clear need for more effective and safe therapies.

The purpose of this open-label phase II platform study is to evaluate safety and preliminary efficacy of NIS793 and other new investigational combinations [added later via protocol amendment(s)] in combination with SOC anti-cancer therapy versus SOC for the second line treatment of mCRC. The SOC anti-cancer therapy will include combination of bevacizumab with either mFOLFOX6 or FOLFIRI chemotherapy regimens as per Investigator's choice and based on prior exposure to oxaliplatin or irinotecan. This study will evaluate novel compounds, which may, through different mechanisms, potentially reverse resistance to the currently considered standard of care anti-cancer treatment in the second line mCRC setting.

In each investigational arm, the Safety run-in (SRI) part will be conducted before opening the Expansion part to confirm the recommended phase 2 dose (RP2D) for a combination of any investigational drug with SOC anti-cancer therapy unless the dose has been confirmed externally to this trial.

The first investigational arm of this study (Investigational arm #1) will explore the combination of NIS793 with SOC anti-cancer therapy. The purpose of the investigational arm #1 is to evaluate the safety and compare the preliminary efficacy of NIS793 in combination with SOC anti-cancer therapy vs SOC anti-cancer therapy for the second line treatment of mCRC.

The second investigational arm of this study will study (Investigational arm #2) the combination NIS793, tislelizumab in combination with SOC anti-cancer therapy. The purpose of adding the investigational arm #2 is to evaluate the safety and compare the preliminary efficacy of NIS793 and tislelizumab in combination with SOC anti-cancer therapy vs SOC anti-cancer therapy for the second line treatment of mCRC.

CCI [redacted].

2 Objectives, endpoints and estimands

The investigational arm #1 will include treatment with NIS793 + SOC anti-cancer therapy. Investigational arm #2 will include treatment with NIS793+tislelizumab+SOC anti-cancer therapy.

Combinations of other investigational drug(s) with SOC anti-cancer therapy may be added later by protocol amendment as new investigational arms (i.e., investigational arm #3, etc).

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• **Safety run-in part** To confirm the recommended phase 2 dose (RP2D) of each investigational arm (NIS793 or NIS793+tislelizumab or any investigational drug(s) in combination with SOC) (SOC: either modified FOLFOX6 + bevacizumab or FOLFIRI+ bevacizumab chemotherapy regimen)	• **Safety Run-in part:** • Incidence of DLTs during the first treatment cycle (4 weeks) of treatment

Objective(s)	Endpoint(s)
● **Expansion part:** To evaluate preliminary efficacy of each investigational arm (NIS793 or NIS793+tislelizumab or any investigational drug(s) in combination with SOC anti-cancer therapy) versus control arm (SOC anti-cancer therapy) in terms of progression-free survival (PFS) by Investigator's assessment per RECIST 1.1	● **Expansion part:** ● Progression-free survival (PFS) by Investigator's assessment per RECIST 1.1
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● **Safety run-in part:** To characterize the safety and tolerability of each investigational arm (NIS793 or NIS793+tislelizumab or any investigational drug(s) in combination with SOC)	● **Safety run-in part:** ● Safety: Incidence and severity of aEs including changes in laboratory parameters, vital signs and ECG parameters ● Tolerability: Dose interruptions, reductions and dose intensity
● Preliminary anti-tumor activity of each investigational arm (NIS793 or NIS793+tislelizumab or any investigational drug(s) in combination with SOC)	● Progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), duration of response (DOR) and time to response (TTR) by Investigator's assessment per RECIST 1.1 and Overall survival (OS)
● To characterize the pharmacokinetics (PK) of each investigational treatment (NIS793 or NIS793+tislelizumab in combination with SOC)	● Drug concentrations in serum of each investigational treatment over time and derived PK parameters (e.g., Ctrough, Cmax)
● To characterize the immunogenicity of each investigational treatment (NIS793 or NIS793+tislelizumab in combination with SOC)	● Incidence of antidrug antibodies (ADA), prevalence at baseline and ADA incidence during the treatment for investigational treatment(s).
● **Expansion part:** To evaluate and compare efficacy of each investigational arm (NIS793 or NIS793+tislelizumab or any investigational drug(s) in combination with SOC) and control arm in terms of ORR, DCR, DOR, TTR by Investigator's assessment per RECIST 1.1	● **Expansion part:** ORR, DCR, DOR, TTR by Investigator's assessment per RECIST 1.1
● To evaluate and compare the overall survival (OS) of each investigational arm and control arm (NIS793 or NIS793+tislelizumab or any investigational drug(s) in combination with SOC)	● OS
● Safety and tolerability	● Incidence and severity of aEs, changes in laboratory parameters, vital signs and ECG parameters; dose interruptions, reductions and dose intensity
● To characterize the PK of each investigational treatment (NIS793 or NIS793+tislelizumab in combination with SOC)	● Drug concentrations in serum of each investigational treatment over time and derived PK parameters (e.g., Ctrough, Cmax)
● To characterize the immunogenicity of each investigational treatment (NIS793 or NIS793+tislelizumab in combination with SOC)	● Incidence of antidrug antibodies (ADA), prevalence at baseline and ADA incidence during the treatment for investigational treatment(s).
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI [redacted]	

Objective(s)	Endpoint(s)
CCI	

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment). Primary estimand is defined only for the expansion part.The primary scientific question of interest is:

- What is the relative effect of each investigational treatment arm relative to the SOC anti-cancer therapy arm in prolonging PFS in the second line mCRC setting, regardless of study treatment discontinuations or start of a new subsequent antineoplastic therapy or prohibited medication which is not part of assigned study treatment strategy?

The primary estimand is described by the following five attributes:

1. **Population**: all participants with mCRC treated with the second line treatment. Further details on the population characteristics are provided in the eligibility criteria.
2. **Treatment**: investigational drug(s) in combination with SOC anti-cancer therapy and SOC alone with or without any new subsequent anti-neoplastic therapy or prohibited medication (refer to Section 6.2.2) post randomization/treatment as needed. The SOC anti-cancer therapy will include combination of bevacizumab with either modified FOLFOX6 or FOLFIRI depending on the prior first line treatment used by participants (refer to Section 3).

3. **Variable**: PFS defined as the time from the first date of randomization/treatment to the first documented progression as per RECIST 1.1 per Investigator or any-cause death.
4. **Handling of remaining intercurrent events**:
   - Discontinuation of study treatment for any reason: All PFS events will be included in the analysis irrespective of the study treatment discontinuation reasons (treatment policy strategy).
   - Any unforeseen intercurrent events (e.g., Coronavirus Infectious Disease 2019 (COVID-19) pandemic related events): All PFS events will be included in the analysis irrespective of any unforeseen intercurrent events (treatment policy strategy).
5. **Summary measure**: Hazard Ratio for PFS by Investigator per RECIST 1.1 between each investigational drug(s) in combination with SOC anti-cancer therapy arm vs SOC anti-cancer treatment arm, CCI [redacted].

Stratification factors considered for randomization are: the SOC regimen for treatments (modified FOLFOX6 or FOLFIRI) and the prior exposure to bevacizumab (yes/no).

2.2 Secondary estimands

Not applicable.

3 Study design

This is an open-label, multi-center, phase II platform study with control and investigational arms. Each investigational arm has a Safety run-in part (SRI) followed by an Expansion part (Figure 3-1).

The platform design of this study is adaptive to allow flexibility in the introduction of additional treatment arm(s) with new investigational drug(s) in combination with SOC anti-cancer therapy for the second line treatment of mCRC.

The study will include a Control arm that will enroll participants who will receive SOC anti-cancer therapy for the second line treatment of mCRC (Figure 3-2). The SOC anti-cancer therapy will include bevacizumab in combination with either modified FOLFOX6 or FOLFIRI (Section 6.1.3). The selection of FOLFIRI or modified FOLFOX6 will be based on prior exposure to oxaliplatin or irinotecan:

- Participants who received oxaliplatin as first line must be treated with FOLFIRI.
- Participants who received irinotecan as first line must be treated with modified FOLFOX6.

Each investigational arm will include a combination of an investigational drug and the SOC anti-cancer therapy (Figure 3-1 and Figure 3-2).

- Investigational arm #1 will include NIS793 in combination with SOC anti-cancer therapy.
- Investigational arm #2 will include NIS793 in combination with tislelizumab and SOC anti-cancer therapy.
- Additional arms may be added in future by protocol amendment(s).

Each investigational arm will start with a Safety run-in (SRI) unless the dose has been confirmed externally to this trial, followed by an Expansion part. The SRI and Expansion parts

will run independently for each SOC anti-cancer therapy, mFOLFOX6 or FOLFIRI with bevacizumab. The purpose of SRI is to confirm the dose of investigational drug with SOC anti-cancer therapy (Figure 3-2).

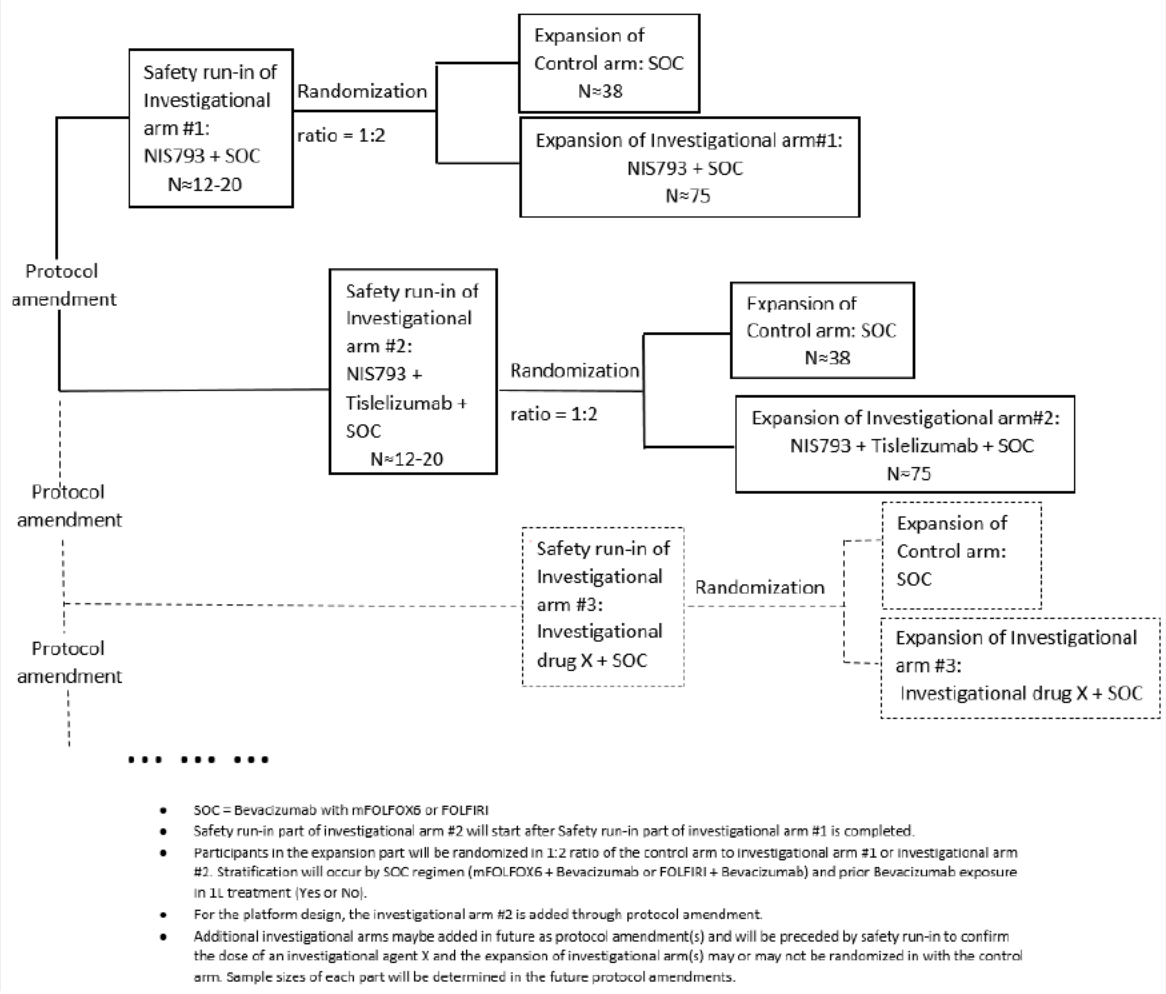
Enrollment in SRI part for investigational arm #2 and expansion part for investigational arm #1 is expected to begin once RP2D for NIS793 has been confirmed in the SRI part for investigational arm #1.

Other investigational drug(s) in combination with SOC anti-cancer therapy may be added later by protocol amendment as new investigational arms (i.e., investigational arm # 3, etc.).

CCI

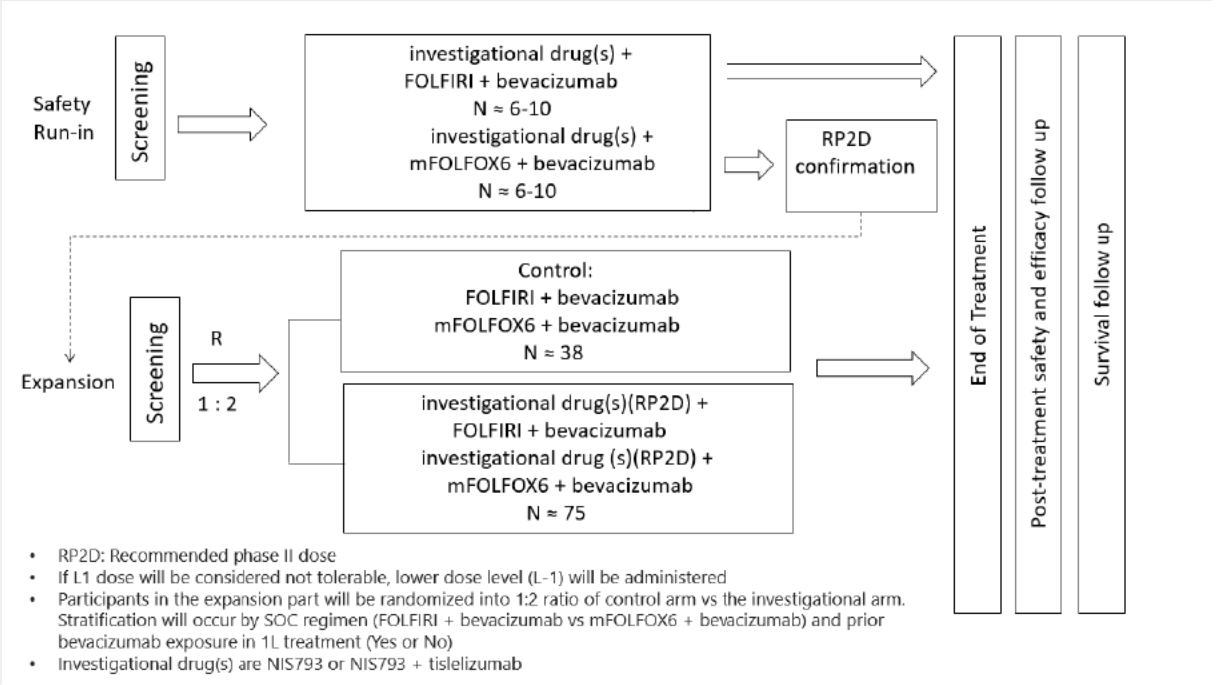
[redacted]

Figure 3-1 Overview of study design



The study flow of control arm, investigational arm #1, and arm #2 are provided in Figure 3-2.

Figure 3-2 Study flow of control and investigational arms



- RP2D: Recommended phase II dose
- If L1 dose will be considered not tolerable, lower dose level (L-1) will be administered
- Participants in the expansion part will be randomized into 1:2 ratio of control arm vs the investigational arm. Stratification will occur by SOC regimen (FOLFIRI + bevacizumab vs mFOLFOX6 + bevacizumab) and prior bevacizumab exposure in 1L treatment (Yes or No)
- Investigational drug(s) are NIS793 or NIS793 + tislelizumab

3.1 Safety run-in part

The **Safety run-in part** will be initiated to confirm RP2D of the investigational drug(s) with SOC anti-cancer therapy. Each safety run-in part will enroll approximately 20 participants to achieve at least 12 evaluable participants (10 participants enrolled in each group to achieve at least 6 evaluable participants) for each following regimen:

- Investigational drug(s) + modified FOLFOX6 + bevacizumab
- Investigational drug(s) + FOLFIRI + bevacizumab

At each dose level, at least 6 evaluable participants are required during the dose limiting toxicities (DLT) evaluation period. DLT evaluation period is defined as first cycle (i.e., 28 days, or 4 weeks) of dosing of the study treatment (Section 6.6.2).

Stratification will occur by SOC regimen (modified FOLFOX6 +bevacizumab or FOLFIRI + bevacizumab) due to the different safety profiles of the 2 regimens (Tournigand et al 2004) and prior exposure to bevacizumab (yes/no) (Figure 3-2).

If the starting dose (L1) is not considered safe, the dose will be de-escalated (L-1) (Table 6-2). An additional 10 participants will be enrolled at the lower dose level in that treatment regimen.

NIS793 dose may be modified in the event of aEs after the DLT evaluation period of 4 weeks according to the guidelines provided in Section 6.6.4.1.

RP2D for each investigational arm may be different for the combination with FOLFIRI and mFOLFOX6, depending on tolerability of the regimen. The RP2D for each regimen will be established when enrollment and DLT period for the respective regimen is complete, and totality of available safety, PK, and PD data has been analysed, interpreted and reviewed in the safety review meeting.

Dose confirmation will be guided by a Bayesian logistic regression model (BLRM) based on any DLTs observed for one cycle of treatment (i.e., 28 days, or 4 weeks). The adaptive BLRM will be guided by the Escalation with Overdose Control (EWOC) principle to control the probability of DLT in future participants on the study. BLRM is a well-established and widely used method to estimate the recommended dose for expansion (RDE) or maximal tolerable dose (MTD) in clinical trials in patients with cancer with small sample size. The use of Bayesian response adaptive models for small datasets has been endorsed by academic publications (Babb et al 1998, Neuenschwander et al 2008, Neuenschwander et al 2010, Natanegara et al 2014), by the European Medicines Agency (EMEA 2007) and it constitutes an important aspect of the FDA's Critical Path Initiative (FDA 2004).

3.2 Expansion part

The decision to open the **Expansion part** of the study will be based on dose confirmation of the investigational drug with available safety, relevant PK, and other relevant clinical and laboratory data from the SRI part (Figure 3-2). The expansion part will run independently for each SOC anti-cancer therapy, mFOLFOX6 or FOLFIRI with bevacizumab.

Each investigational arm will enroll approximately 75 participants. Each investigational arm will be randomized against a control arm in a 2:1 ratio resulting in approximately 38 patients receiving control, and a total of approximately 113 patients in each expansion.

Stratification will occur by SOC regimen (modified FOLFOX6 + bevacizumab or FOLFIRI + bevacizumab) due to the different safety profiles of the 2 SOC anti-cancer therapy regimens (Tournigand et al 2004) and prior exposure to bevacizumab (yes/no) (Figure 3-2).

Participants will be treated until unacceptable toxicity, disease progression per RECIST 1.1, withdrawal of consent, or any other condition of treatment discontinuation specified in the protocol. Treatment beyond PD per RECIST 1.1 is allowed until immune confirmed PD (iCPD) per iRECIST for participants treated in investigational arm #2, under conditions specified in Section 6.1.4.1.

Combinations of other investigational drug(s) with SOC anti-cancer therapy may be added later to this platform trial by protocol amendment as new investigational arms (i.e., investigational arm #3 etc.).

CCI [redacted].

Concurrent operation of expansion part of investigational arm #1 and SRI part of investigational arm #2

In the event that the SRI for investigational arm #2 is opened during the randomized expansion for investigational arm #1, participants will be assigned to SRI for investigational arm #2, investigational arm #1, or control by randomization. In this event, participants will be assigned to the SRI for investigational arm #2 or investigational arm #1 with equal weight, with the relative weights for investigational arm #1 and control remaining unchanged, resulting in a 2:2:1 randomization ratio.

Concurrent operation of expansion part of investigational arm #1 and expansion part of investigational arm #2

In the event that the randomized expansion for investigational arm #2 is opened during the randomized expansion for investigational arm #1, participants will be assigned to expansion for investigational arm #2, investigational arm #1, or control by randomization. In this event, participants will be assigned to the expansion for investigational arm #2 or investigational arm #1 with equal weight, with the relative weights for each investigational arm and its respective control remaining unchanged, resulting in a 1:1:1 randomization ratio.

Non-concurrent operation of expansion part of investigational arm #1 and investigational arm #2

In the event that no concurrent enrollment of randomized expansion for investigational arm #1 and investigational arm #2, participants will be assigned to each expansion with a 2:1 randomization ratio.

Participants will be randomized through the Interactive Response Technology (IRT) system depending on provided randomization ratio. Refer to Section 6.4.2 for details.

4 Rationale

4.1 Rationale for study design

This open-label, multi-center, phase II platform study aims at exploring whether the combination of investigational drugs with SOC anti-cancer therapy may potentially, through different mechanisms, reverse resistance to the currently considered standard of care anti-cancer therapy in the second line MSS mCRC setting.

Considering different potential targets and available compounds, a platform design is applied for this study. In general, platform designs allow for assessment of multiple treatments within a single disease under one master protocol (Saville and Berry 2016, Ventz et al 2017). A 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 numerous clinical studies (e.g., I-SPY2, STAMPEDE, AML 15, AML16) (Berry et al 2015, Saville and Berry 2016, Ventz et al 2017, Renfro and Sargent 2017, Woodcock and LaVange 2017).

Each investigational arm will include a combination of an investigational drug and SOC anti-cancer therapy and will start with a Safety run-in (SRI) followed by an Expansion part. The purpose of SRI is to confirm the dose of investigational drug with SOC anti-cancer therapy (refer to Figure 3-1), if a dose has not been confirmed externally to this trial.

Investigational arm #1 will include combination of NIS793 with SOC anti-cancer therapy. This choice is based on the hypothesis that the reduction of intratumoral fibrosis through TGF-β inhibition in mCRC can relieve resistance and improve responsiveness to chemotherapy and anti VEGF treatment (refer to Section 1).

Investigational arm #2 will include combination of NIS793 with tislelizumab and SOC anti-cancer therapy. This choice is based on the hypothesis that the reduction of intratumoral fibrosis and immune escape through TGF-β inhibition in mCRC can relieve resistance and improve responsiveness to chemotherapy, immunotherapy, and anti VEGF treatment (refer to Section 1).

Combinations of other investigational drug(s) with SOC anti-cancer therapy not currently outlined in this protocol may be added later by protocol amendment as new investigational arms (investigational arm #3, etc).

CCI [redacted].

Table 4-1 Study design rationale

Study design aspect	Rationale
Platform open- label study	The open-label platform design allows flexibility in adding new investigational treatment arms and allows assessment of multiple treatment arms when they become available during the course of the study for a single disease (mCRC, second line treatment). PFS is an adequate primary endpoint in this indication and the open-label design is an acceptable design for a proof-of-concept exploratory trial.
Randomization	The expansion part of each investigational arm and the control arm will start concurrently, and study participants will be randomized with a 1:2 ratio of control arm to the investigational arm by SOC regimen (FOLFIRI+bevacizumab vs mFOLFOX6+bevacizumab) and prior bevacizumab exposure in first line treatment (Yes vs No) (Figure 3-2). These two factors were chosen to balance previous treatments and the toxicity profile among treatment arms. In both parts of the study patients with MSI-high tumors (accounting for 5% of patients in the mCRC population) or those with BRAF mutation (10% prevalence) will be excluded from study participation due to different standard of care therapies for these patient populations.
Background therapy	Worldwide study conducted with mFOLFOX6 or FOLFIRI with bevacizumab, which is approved treatment in the second line treatment of mCRC (refer to Section 4.2).
New visit schedule post implementation of protocol amendment 4	Protocol amendment 4 will allow participants to continue the study following an updated safety and efficacy assessment, aligned with the SOC (refer to Table 8-4).

4.2 Rationale for choice of background therapy

Participants in the control arm and each investigational arm will receive SOC anti-cancer therapies. These will include the combination of bevacizumab with either mFOLFOX6 or FOLFIRI (refer to dose details in Section 6.1.3). These SOC anti-cancer therapies, recommended by clinical guidelines, were tested in large clinical trials and were demonstrated to improve OS, PFS, response, and other parameters of clinical benefit of treatment. SOC anti-cancer therapies will be administered and monitored according to local prescribing information and/or local institutional guidelines.

4.3 Rationale for dose/regimen and duration of treatment

NIS793

In this study, the selection of NIS793 dose and regimen is based on safety, efficacy, and PK information available from clinical trials CNIS793X2101 and CNIS793B12201, and prescribing information for 5-FU, irinotecan, oxaliplatin and bevacizumab. Every 2-week regimen (Q2W) for NIS793 i.v. is chosen to coordinate with the approved regimen of FOLFIRI or modified FOLFOX6 administered on days 1 and 15 of each 4 week-cycle (refer to locally approved labels and Section 6.1.3).

CCI

Tislelizumab

Tislelizumab will be administered at 300 mg Q4W in this study. While the 200 mg Q3W dose has been widely used in tislelizumab clinical development and shown clinical efficacy and acceptable safety, a Q4W regimen was designed to facilitate combination with agents with other cycle lengths. PK exposure-matching based on AUC was considered appropriate to establish a Q4W dose, consistent with FDA guidance (FDA/CDER 2021) on PK-based criteria for alternate dosing regimens of anti-PD-1 antibodies. CCI

4.4 Rationale for choice of control drugs (comparator) or combination drugs

In this platform protocol, the background therapy (SOC anti-cancer therapy) will be the same used as the control or comparator arm (Refer to Section 4.2).

In the investigational arm #1, the study will evaluate NIS793+SOC, and in the investigational arm #2, the study will evaluate NIS793+tislelizumab+SOC (Section 4.1).

The SOC used in this protocol for second line metastatic colorectal cancer is 5-FU, leucovorin, oxaliplatin or irinotecan (mFOLFOX 6 or FOLFIRI) and bevacizumab, approved and widely used chemotherapy regimens for the treatment of second-line mCRC. These particular chemotherapy regimens were chosen as background and comparator treatment based on their tolerability profile and their common use in this setting. The dose and the dose regimen to be used are in accordance with each product.

4.5 Purpose and timing of interim analyses/design adaptations

Safety review meetings for the safety run-in part will be conducted once sufficient number of participants have met the DLT evaluation criteria for each dose level (starting dose and lower dose level if de-escalated).

For the expansion part of the study, safety data will be reviewed by Data Monitoring Committee (DMC) on a regular basis. The safety data review will assess death during treatment, serious adverse events, Grade 3 or 4 adverse events and key laboratory abnormalities, and distribution of safety-related reasons for discontinuation. DMC may also perform benefit-risk assessment based on the totality of the data.

CCI [redacted]

The final analysis will occur after study completion as defined in Section 9.4. Accumulated data may be analyzed at any time prior to the final analysis to evaluate endpoints related to the safety of study participants.

4.6 Risks and benefits

The participants enrolled in this study will have MSS metastatic colorectal adenocarcinoma that is not amenable to potentially curative surgery and progressed on or within 6 months after the last dose of one prior systemic anticancer therapy administered for metastatic disease. Given the clinical characteristics, participants have fewer therapeutic options, and the established standard of care has limited benefit in this participant population (Dekker et al 2019, SEER Cancer Stat Facts: Colorectal Cancer 2019).

CCI [redacted]

CCI [redacted].

Also, all participants in this study in investigational and control arms will receive standard of care approved regimens as a backbone therapy, with a well characterized safety profile.

CCI [redacted] The safety profile of anti-PD-1, pembrolizumab plus mFOLFOX7 or FOLFIRI at standard doses in metastatic colorectal cancer was recently explored and considered manageable (Kim et al 2019). Similar experience was observed in study BGB-A316-205 combining tislelizumab with cisplatin and 5-fluorouracil **(**5-FU) in patient with esophageal cancers as well as combination of tislelizumab with oxaliplatin andcapacitabine in patients with gastric cancer (Xu et al 2020).

Based upon the available safety information from NIS793 and tislelizumab clinical development programs, the available preclinical data and known mechanism of action of these drugs and potential overlapping toxicity of all combination drugs, following adverse events are considered of special interest in this study population: Neutropenia/ febrile neutropenia, immunogenicity/ hypersensitivity reactions, infusion reactions, diarrhea, hypertension, haemorrhage, cardiac valvulopathy (symptomatic), renal toxicity, eyelid abnormality, skin reactions. In addition, the potential immune-related aEs considered to be AESIs with check-point inhibitors like tislelizumab, include, endocrinopathies, colitis, hepatitis, nephritis, and pneumonitis (please refer to Section 10.1.1.1 on adverse events of special interest (AESI). Details regarding these adverse events are provided in the NIS793 and tislelizumab Investigator's Brochures, along with guidance to Investigators.

CCI [redacted]

Women of child-bearing potential and sexually active males 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 participant will not reliably comply, they should not be entered or continue in the study.

Overall, the risk of drug-drug Interaction (DDI) between NIS793 (with or without tislelizumab) and 5-fluorouracil, leucovorin, oxaliplatin, irinotecan or bevacizumab is anticipated to be low.

Nevertheless, PK of NIS793 with and without tislelizumab, bevacizumab and irinotecan and SN-38 will be characterized in this study to assess the DDI, if any, between NIS793 and irinotecan or bevacizumab.

In addition, the safety data and benefit risk of the study treatment will be assessed on regular basis by a dedicated Novartis safety management team.

An independent DMC will be established to provide independent assessment of the safety of the study treatment, available PK, treatment efficacy and integrity of the ongoing study (Section 10.2.3). A Study Steering Committee will be established comprising Investigators and Novartis personnel participating in the trial to ensure scientific validity and transparent management of the trial according to the protocol (Section 10.2.4).

In participants who continue to receive NIS793 or tislelizumab or any other new investigational drug at dose level determined to be intolerable or above the RP2D in safety run in and in whom conditions for treatment discontinuation have not been met, the risk-benefit has to be considered before treatment continuation.

Overall, based on the preliminary safety profile, tolerability, target engagement, and response rates observed in the NIS793 FIH study, the expected benefit of the combinations of NIS793 with 5-FU, oxaliplatin or irinotecan and bevacizumab, with or without tislelizumab, are thought to outweigh the risk in participants with second line mCRC being evaluated in this study.

4.7 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity may be implemented. Notification of the Public health emergency as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures adapted to the situation must be submitted, if required, as per local regulations, Through a protocol amendment for approval by local or regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures.

5 Study Population

The study will include adult participants with MSS mCRC who have progressed on or within 6 months after one line of therapy for metastatic disease that included at least fluoropyrimidine (e.g., 5-FU, capecitabine) and oxaliplatin or irinotecan.

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

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study.
2. Age 18 years (or older, if required by local regulations) at the time of informed consent.
3. Histologically or cytologically confirmed (by local laboratory and local clinical guidelines) metastatic colorectal adenocarcinoma that is not amenable to potentially curative surgery in the opinion of the Investigator and progressed on or within 6 months after the last dose of one prior line of systemic anti-cancer therapy administered for metastatic disease.

   Note: Participants must have received at least two cycles of prior systemic anti-cancer therapy administered for metastatic disease. Prior line of systemic anti-cancer therapy for metastatic disease must include at least combination of fluoropyrimidine (e.g., 5-FU, capecitabine, S-1 etc) and oxaliplatin or irinotecan. Patients who received FOLFOXIRI as first line regimen are not eligible. Patients who received therapy including irinotecan as first line regimen must be eligible for modified FOLFOX6. Patients who received therapy including oxaliplatin as first line regimen must be eligible for FOLFIRI.

   Note: Prior systemic therapy administered as a radiosensitizer and maintenance therapy for the metastatic disease are not considered as separate line of treatment. Adjuvant or neoadjuvant chemotherapy (at least 8 weeks of treatment) is considered as one line of prior treatment if disease progression occurred within 6 months since the last dose of the therapy.
4. Presence of at least one measurable lesion assessed by CT and/or MRI according to RECIST 1.1.

   Note: Any lesion which has been subjected to percutaneous therapies or radiotherapy should not be considered measurable, unless the lesion has clearly progressed since the procedure.
5. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1.
6. Adequate organ function as defined by the following laboratory values (assessed by central laboratory for eligibility except where indicated (refer to Section 8.4.1)):
   - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
   - Platelets count $\geq 100 \times 10^9$/L
   - Hemoglobin ≥ 9 g/dL
   - Calculated creatinine clearance ≥ 60 mL/min (e.g., by using Cockcroft-Gault equation)
   - Albumin ≥ 3 g/dL
   - PT/INR and PTT $\leq$ 1.5 x ULN. Participants requiring therapeutic anticoagulants are eligible if coagulation parameters are within therapeutic range.
   - Total bilirubin $\leq$ 1.5 X ULN
   - Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase /serum glutamic pyruvic transaminase (ALT/SGPT) $\leq$ 3.0 x ULN ($\leq$5 x ULN in presence of liver metastasis). In participants with elevated ALT or AST, the values must be stable for at least 2 weeks and with no evidence of biliary obstruction by imaging.
7. Women of child-bearing potential must have negative pregnancy tests during the screening period and before starting study treatment.
8. Able to adhere to study visit schedule and other protocol requirements.
9. Participant must have recovered from treatment related toxicities of prior anticancer therapies to grade $\leq$1 (CTCAE v5.0) at the time of screening, except alopecia.

5.2 Exclusion criteria

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

1. Prior administration of anti-cancer immunotherapy (e.g., anti-PD-1, anti-PD-L1, anti-CTLA-4 antibody) or TGF-β targeted therapies.
2. Microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) (mandatory, locally performed), BRAFV600 mutation positive colorectal cancer (tests performed by local laboratory and per local guidelines).
3. Known complete or partial dipyrimidine dehydrogenase (DPD) enzyme deficiency (testing for DPD enzyme deficiency is not mandatory unless required by local regulations and can be conducted at a local laboratory).
4. **For participants treated with irinotecan:** Known history or clinical evidence of reduced UGT1A1 activity (testing for UGT1A1 status is not mandatory unless required by local regulations and can be conducted at a local laboratory).
5. Presence of symptomatic CNS metastases, or CNS metastases that requires directed therapy (such as focal radiotherapy or surgery) or increasing doses of corticosteroids 2 weeks prior to study entry. Participants with treated symptomatic brain metastases should be neurologically stable for 4 weeks post-treatment and prior to study entry, and at a dose of ≤ 10 mg per day prednisone or equivalent for at least 2 weeks before administration of any study treatment.
6. Known history of severe allergy or hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes (e.g., monoclonal antibodies), or contraindication to any of the study drugs as outlined in the 'Contraindications' or 'Warnings and Precautions' sections of the SOC local prescribing information (e.g., Summary of Product Characteristics [SmPC], United States Prescribing Information [USPI], etc.).
7. Participant is currently receiving other anti-cancer therapy (medication or radiotherapy) or received other investigational product within 30 days or 5 half-lives prior to initiation of study treatment, whichever is longer. **Note**: Participants that received bevacizumab, cetuximab or panitumumab as part of the first line therapy can be enrolled before the end of 5 half-lives of these drugs.
8. Participant is currently receiving any of the prohibited medications as outlined in the protocol or in the SOC anti-cancer therapy local prescribing information, and these cannot be discontinued ≥ 7 days or 5 half-lives, whichever is longer, before the first dose of study drug.
9. Participant has not recovered from a major surgery performed prior to start of study treatment or has had a major surgery within 4 weeks prior to start of study treatment.
10. Radiation therapy ≤ 4 weeks or brain-radiotherapy ≤ 4 weeks prior to start of study treatment (palliative radiotherapy to bone lesions allowed ≥ 2 weeks prior to start of study treatment).
11. Impaired cardiac function or clinically significant cardio-vascular disease, such as:
    - Congestive heart failure requiring treatment (NYHA grade ≥2), or clinically significant arrhythmia (including uncontrolled atrial flutter/fibrillation)
    - Acute myocardial infarction, unstable angina pectoris, coronary stenting, or bypass surgery <6 months prior to study entry

- LVEF < 50%
- Elevated cardiac enzymes troponin I > 2 x ULN
- Cardiac valvulopathy≥ grade 2
- Uncontrolled hypertension defined by a systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥100 mm Hg
- Medical history or current diagnosis of myocarditis

12. History of positive test for human immunodeficiency virus (HIV) infection (testing is not mandatory at screening, unless if required by local regulations, where the testing will be done by local laboratory (e.g., Czech Republic)).
13. Active or chronic hepatitis B virus (HBV) or hepatitis C virus infections. **Note**: Participants with a history of hepatitis C virus (HCV) infection must have been treated with confirmation of cure, to be considered as eligible.
14. Active untreated or uncontrolled systemic fungal, bacterial or viral infection (including COVID-19), which in the opinion of the Investigator places the study participant at an unacceptable risk. **Note:** Patients with localized condition unlikely to lead to a systemic infection e.g., chronic nail fungal infection, are eligible.
15. Use of hematopoietic growth factors or transfusion support ≤ 2 weeks prior to start of study treatment.
16. Participant has conditions that are considered to have a high risk of clinically significant gastrointestinal tract bleeding, or any other condition associated with or history of significant bleeding.
17. Serious non-healing wounds.
18. Stroke or transient ischemic attack, or other ischemic event, or thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 3 months before start of study treatment.
19. Concurrent malignancy other than the disease under investigation with exception of malignancy that was treated curatively and has not recurred within 2 years prior to the date of screening. Fully resected basal or squamous cell skin cancers and any carcinoma in situ are eligible.
20. Any significant medical condition, laboratory abnormality or psychiatric or social condition that would constitute unacceptable safety risks to the participants, contraindicate participant participation in the clinical study, limit the participant's ability to comply with study requirements, or compromise participant's compliance with the protocol and all requirements of the study as stated in the Informed Consent Form. Significant medical conditions include but are not limited to known history or current interstitial lung disease or non-infectious pneumonitis, chronic active hepatitis, liver cirrhosis or any other significant liver disease with moderate to severe hepatic impairment (Child-Pugh B or C), /ulcer/bone fracture, uncompensated/symptomatic hypothyroidism, requirement for hemodialysis or peritoneal dialysis, or uncontrolled significant deep vein thrombosis, pulmonary embolism or other clinical significant thromboembolic event.
21. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are willing to use highly effective methods of contraception during treatment with study drugs and for at least 90 days after stopping NIS793 and 120 days after stopping treatment with tislelizumab, whichever is latest. Contraception use

during treatment and after stopping Standard of Care chemotherapy should be followed per the local drug label requirements and guidelines. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. 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.
- Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
- Use of oral, (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.
- In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Note: Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age-appropriate history of vasomotor symptoms). Women are considered not of child-bearing potential if they are post-menopausal 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.

Note: Sexually active male participants and their partners who are women of childbearing potential should follow the contraception recommendations and any other precautionary measures as required by the local prescribing information for the SOC anti-cancer therapy.

Note: If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form (ICF).

22. Pregnant or breast-feeding women.
23. Use of any live/ attenuated vaccines against infectious diseases within 4 weeks of initiation of study treatment.
24. Active, known, or suspected autoimmune disease or a documented history of autoimmune disease, including ulcerative colitis and Crohn's disease (participants with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll).
25. Systemic chronic steroid therapy (>10 mg/day prednisone or equivalent) or any immunosuppressive therapy for >14 days within 7 days prior to planned date for first dose of study treatment. **Note**: Topical, inhaled, nasal and ophthalmic steroids are allowed. For

participants with adrenal insufficiency, replacement dose of >10 mg/day prednisone or equivalent are permitted.

26. History of allogeneic bone marrow or solid organ transplant

6 Treatment

6.1 Study treatment

For this study, in investigational arm #1, the investigational drug is NIS793, an anti-TGF-ß human monoclonal antibody. The study treatment is defined as SOC therapy for the control arm or as NIS793 with SOC therapy for investigational arm # 1.

For investigational arm # 2, tislelizumab and NIS793 will be the investigational drugs. The study treatment is defined as NIS793 with tislelizumab and SOC therapy for investigational arm #2.

Combinations of other investigational drug(s) with SOC anti-cancer therapy may be added later by protocol amendment as new investigational arms (i.e., investigational arm #3, etc.).

The SOC anti-cancer drugs used in the study are mFOLFOX6 or FOLFIRI administered with bevacizumab.

For all non-investigational drugs in the study, the local prescription information and local/institutional clinical practice are to be followed.

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded on the appropriate eCRF page.

CCI [redacted]

6.1.1 Investigational and control drugs

The treatment period begins on Cycle 1 Day 1. The duration of each treatment cycle is 28 days.

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

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)	Investigational control arm
NIS793 100 mg/ ml*	Concentrate for solution for infusion	Intravenous	Open label; vials	Sponsor (global)	Investigational arm #1, #2
Tislelizumab (VDT482) 100 mg/10 ml	Concentrate for solution for infusion	Intravenous	Open label; vials	Sponsor (global)	Investigational arm #2
5-Fluorouracil (5-FU)	Concentrate for solution for infusion	Intravenous	Open label; vials	Local	Investigational arm #1, #2 Control arm

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)	Investigational control arm
Leucovorin (folinic acid) (or levoleucovorin)	Concentrate for solution for infusion	Intravenous	Open label; vials	Local	Investigational arm #1, #2 Control arm
Irinotecan	Concentrate for solution for infusion	Intravenous	Open label; vials	Local	Investigational arm #1, #2 Control arm
Oxaliplatin	Powder/ Concentrate for solution for infusion	Intravenous	Open label; vials	Local	Investigational arm #1, #2 Control arm
Bevacizumab	Powder/ Concentrate for solution for infusion	Intravenous	Open label; vials	Local	Investigational arm #1, #2 Control arm
* The change of fill volume from 7 ml/vial to 10.5 ml/vial is expected during the study.					

NIS793 and tislelizumab (VDT482) will be supplied by Novartis or its designee in the form of solution for IV infusion as ready-to-use vials. Dispensing will be through IRT.

The standard of care therapies (5-fluorouracil, leucovorin, oxaliplatin, irinotecan and bevacizumab) will be provided locally by the study site, subsidiary or designee as commercially available in each participating country according to local practices and local regulations. Generic version of standard of care, if commercially available, can be used according to local practice and local regulation.

6.1.2 Additional study treatments

Additional study treatments include medication for anti-emetic prophylaxis (if needed and per institutional standard of care), which may include low dose corticosteroids, 5-HT3 receptor antagonists (e.g., granisetron, ondansetron) or other anti-emetic agents. The investigational site is responsible for sourcing any additional study treatments.

6.1.3 Treatment arms/group

The study will include:

- Control arm: SOC anti-cancer therapy (bevacizumab with mFOLFOX6 or FOLFIRI)
- Investigational arm: investigational drug(s) + SOC anti-cancer therapy
  - Investigational arm #1: NIS793 + SOC anti-cancer therapy
  - Investigational arm #2: NIS793 + tislelizumab + SOC anti-cancer therapy

Combinations of other investigational drug(s) with SOC anti-cancer therapy may be added later by protocol amendment as new investigational arms (i.e., investigational arm #3, etc).

All participants in the **Safety run-in part** and **Expansion parts** will be assigned to the study treatment at cycle 1 day 1.

Participants in each **Expansion part** will be assigned in a ratio of depending on different scenarios of concurrent operations refer to the Section 3.2.

In the **Safety run-in and Expansion parts**, the choice of the chemotherapy medications (mFOLFOX6 or FOLFIRI) will be determined by Investigator prior to allocation/ randomization based on prior treatment the study participant had received as the first line treatment for metastatic disease:

- Participants who received oxaliplatin as first line will be treated with FOLFIRI.
- Participants who received irinotecan as first line will be treated with mFOLFOX6.

The choice of chemotherapy cannot be changed afterward.

All study drugs are administered IV, based on a 28-day treatment cycle:

- NIS793 2100 mg on Days 1 and 15 of each 28-day cycle assuming this is the confirmed RP2D in safety run-in (or 2100 mg on Day 1 if dose level -1 of NIS793 is the confirmed RP2D in safety run-in)
- FOLFIRI + bevacizumab is administered on Days 1 and 15 of each 28-day cycle,
  - 5-Fluorouracil 400 mg/m^2 IV bolus followed by 2400 mg/m^2 as a 46-h continuous infusion
  - Leucovorin (folinic acid) 400 mg/m^2 IV (or levoleucovorin 200 mg/m^2 IV, where substitution is permissible per local regulations)
  - Irinotecan 180 mg/m^2 IV
  - Bevacizumab 5 mg/kg, or
- Modified FOLFOX6 + bevacizumab is administered on Days 1 and 15 of each 28-day cycle,
  - 5-Fluorouracil 400 mg/m^2 IV bolus followed by 2400 mg/m^2 as a 46-h continuous infusion
  - Leucovorin (folinic acid) 400 mg/m^2 IV (or levoleucovorin 200 mg/m^2 IV, where substitution is permissible per local regulations)
  - Oxaliplatin 85 mg/m^2 IV
  - Bevacizumab 5 mg/kg
- Tislelizumab 300 mg IV on day 1 of each 28-day cycle

6.1.4 Treatment duration

Participants will continue to receive study treatment until they experience unacceptable toxicity, disease progression as per RECIST 1.1, withdrawal of consent, or any other condition of treatment discontinuation specified in the protocol, and/or treatment is discontinued at the discretion of the Investigator or the participant (Section 9.1.1).

Treatment in investigational arm #2 is allowed beyond PD per RECIST 1.1 until immune confirmed PD (iCPD) per iRECIST under conditions specified in Section 6.1.4.1.Cross over treatment between any of the treatment arms will not be allowed.

If the investigational drug(s) (NIS793 and/or tislelizumab) is interrupted or delayed for > 8 weeks due to toxicity that is suspected to be related to treatment including potential immune-mediated adverse events (irAE), the applicable treatment will be permanently discontinued:

- if the AE doesn't resolve to < Grade 1 or baseline within 8 weeks and/or

- if the dose of steroids (for the management of irAE) remains > 10 mg/day prednisone or equivalent for > 8 weeks.

The 8-week timeframe will begin from the time the irAE reaches a grade that leads to NIS793 and/ or tislelizumab interruption. If treatment with SOC anti-cancer therapy is permanently discontinued in the NIS793+SOC treatment arm, the treatment with NIS793 must also be discontinued. If treatment with NIS793 and/ or tislelizumab is permanently discontinued due to unacceptable toxicities, the Investigator can continue tislelizumab and/or SOC anti-cancer therapy until RECIST 1.1 disease progression as per Investigator, as long as the participant is continuing to benefit from the SOC anti-cancer therapy as assessed by the Investigator, tolerating the treatment and no other anti-cancer treatment is immediately required.

CCI [redacted].

6.1.4.1 Treatment beyond disease progression

Based on the mechanism of action of immune checkpoint inhibitors (Billan et al 2020), participants may derive benefit from continuing study treatment despite initial evidence of disease progression.

Treatment beyond progression is not permitted for participants in investigational arm #1.

Participants in investigational arm #2 who derive clinical benefit as assessed by Investigator will be permitted to continue study treatment with tislelizumab with or without NIS793 and/or SOC beyond initial disease progression as per RECIST 1.1 and until immune confirmed PD (iCPD) per iRECIST, provided they meet all of the following criteria:

- Clinical benefit assessed by the Investigator
- Absence of immune confirmed PD (iCPD) by iRECIST
- Continuation of study treatment beyond initial RECIST 1.1 disease progression will not delay an imminent intervention to prevent serious complications of disease progression or prevent participants from receiving adequate care
- Participant performance status is stable
- Participant exhibits adequate tolerance to study treatment and has no unacceptable and irreversible toxicities related to study drugs

If tislelizumab is discontinued, treatment beyond RECIST 1.1 PD will not be allowed.

Participants who continue treatment beyond progression will have to continue to follow all study procedures as outlined in Section 8. Eligibility (as outlined above in this Section 6.1.4.1) for the participant continuing study treatment beyond RECIST 1.1 PD will be documented in the eCRF.

In case of clinical deterioration or suspicion of disease progression, a follow-up imaging assessment should be performed promptly rather than waiting for the next scheduled assessment.

Participants who are no longer deriving clinical benefit, have disease progression as per iRECIST, have unacceptable toxicity, or who meet other protocol discontinuation criteria, must be discontinued.

CCI [redacted].

6.2 Other treatment(s)

Participants should not receive pre-medication to prevent infusion reaction before the first infusion of study treatment, in order to determine if pre-medication is necessary. If a participant experiences an infusion reaction, he/she may receive pre-medication on subsequent dosing days. Guidelines on management of infusion reactions are provided in Table 6-5 for NIS793 and in Table 6-6 for tislelizumab.

Acute allergic reactions should be managed per institutional practice. In the event of anaphylactic/anaphylactoid reactions therapy necessary to restore normal cardiopulmonary status should be included. If a participant experiences a Grade ≥3 anaphylactic/anaphylactoid reaction, the participant will discontinue study treatment.

The CTCAE term "Infusion related reaction" should be used for study treatment related infusion reactions, unless the Investigator considers another term, such as "Allergic reaction," "Anaphylaxis," CCI [redacted]" more appropriate in a specific situation.

6.2.1 Concomitant therapy

In general, the use of any concomitant medication/therapy deemed necessary for the care of the participant (e.g., such as granulocyte colony-stimulating factor, premedication, antiemetic, antidiarrheal) is permitted except when specifically prohibited (Section 6.2.2).

The Investigator should instruct the participant to notify the study site about any new medications he/she takes after signing the informed consent. All medications including herbal/natural medications, surgeries, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) taken within 28 days prior to starting study treatment must be listed on the appropriate eCRF. Any other anti-cancer therapy (medication or radiotherapy), other investigational product received within 30 days or 5 half-lives prior to initiation of study treatment, whichever is longer must also be notified to the study site.

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

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

- Therapeutic treatment with **hematopoietic colony-stimulating growth factors (G-CSF or GM-CSF or erythroid stimulating agents)** are allowed as concomitant medications if prescribed according to accepted clinical guidelines (ASCO, NCCN, ESMO, etc.).

However, use of hematopoietic growth factors or transfusion support ≤ 2 weeks prior to start of study treatment is prohibited.

- **Anticoagulation therapy** is permitted and should be clearly documented. Elevated coagulation times have been reported in participants taking 5-FU concomitantly with warfarin. Caution should be used when warfarin is co-administered with 5-FU
- **Anti-hypertensives** are allowed as concomitant medications.
- **Palliative local radiation or surgical resection of a tumor and/or its metastases** during the study treatment are permitted after prior approval of Novartis medical monitor. For any surgery or radiotherapy initiated after the start of study treatment, the reason for its use must be clearly documented and cancer progression must be assessed and documented.
- Participants with disease metastatic to bone may receive **bone-stabilizing agents** such as bisphosphonates or monoclonal antibodies intended for this purpose. Participants requiring initiation of bone-stabilizing agents during the course of the study should be assessed by appropriate image modalities to exclude disease progression. No drug-drug interaction is expected between NIS793 and bone-stabilizing agents.
- Since oxaliplatin is eliminated primarily through the kidney, its clearance may be decreased by co-administration of potentially nephrotoxic compounds. Caution should be used when **nephrotoxic compounds** are co-administered with oxaliplatin.
- SARS-CoV-2 vaccines are allowed. It is recommended, if possible, to get vaccinated for SARS-COVID-19 before the start of the study treatment, and outside the dose-limiting toxicity period; to avoid vaccination on days of study treatment dosing, which are Days 1 to 3 and 15 to 17 of a cycle, and on the same location as administration of other injectable drugs. To optimize the immune response of the participant to the vaccine, if possible, allowing 1-2 weeks break from study treatment before and after the vaccine administration is recommended. No or minimal disruption to the chemotherapy schedule is required. Decision to vaccinate study participants with SARS-CoV-2 vaccine should be based on the Investigator's assessment of an individual benefit-risk, should follow the local Health Authorities and/or institutional guidelines. and the prescribing information for the SARS-CoV-2 vaccine to be used.

6.2.2 Prohibited medication

- During the course of the study, participants must not receive **any chemotherapy, therapies** that may be active against cancer or that are intended to modulate an immune response, **investigational drugs or devices** other than study therapy.
- Use of medications prohibited as per local prescribing information of the SOC anti-cancer therapies is NOT allowed after the start of the study treatment.
- Irinotecan and its active metabolite, SN-38, are metabolized via the human CYP450 3A4 isoenzyme (CYP3A4) and uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1), respectively. **Strong CYP3A4 inducers and strong CYP3A4 or UGT1A1 inhibitors** must not be co-administered with irinotecan (see Section 16.5.1 for more details).
- Use of hematopoietic growth factors or transfusion support ≤ 2 weeks prior to start of study treatment is prohibited.

- The use of **systemic steroid therapy** and other immunosuppressive drugs is not allowed, **with the exception of:**
  - Prophylactic use for participants with imaging contrast dye allergy.
  - Replacement-dose steroids (defined as > 10 mg/day of prednisone or equivalent dose of corticosteroids) in the setting of adrenal insufficiency.
  - For management of transient exacerbations of chronic inflammatory conditions such as COPD. Steroids must be reduced to ≤ 10 mg/day of prednisone or equivalent dose of corticosteroids prior to the next treatment with NIS793 with and without tislelizumab.
  - Short course of corticosteroids for chemotherapy-induced emesis prophylaxis and/or treatment according to local and institutional guidelines is allowed. The **treatment of study treatment-related infusion reactions or study treatment-related irAEs**. Steroids must be reduced to ≤10 mg/day of prednisone or equivalent dose of corticosteroids prior to the next study treatment administration.
- Topical, inhaled, nasal and ophthalmic steroids are allowed.
- The use of **live/ attenuated vaccines** against infectious diseases is not allowed within 4 weeks before initiation of study treatment and through the whole duration of the study. **Inactivated vaccines** are allowed.

6.3 Preparation and dispensation

Each study site will be supplied with investigational drugs (NIS793, tislelizumab) in packaging as described under investigational and control drugs section (Section 6.1.1).

For NIS793 preparation prior to administration, please refer to NIS793E12201 Pharmacy Manual for NIS793. For tislelizumab preparation prior to administration, please refer to NIS793E12201 Pharmacy Manual for Tislelizumab. A unique medication number is printed on the study medication label. Investigator staff will identify the study medication kits to dispense to the participant by contacting IRT and obtaining the medication number(s).

The investigational drug has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

Other new investigational drugs may be included and supplied following a protocol amendment.

For locally procured SOC anti-cancer therapies, according to the treatment assigned to the participant, investigator staff will select the medication to be dispensed to the participant. Site personnel will record the locally sourced supply dispensation into the participants' source document.

CCI [redacted]

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

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

SOC anti-cancer therapies will be handled according to package inserts or institutional guidelines.

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

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/ guidelines, Otherwise, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or the Novartis address provided in the Investigator folder at each site.

6.3.1.2 Handling of other treatment

Not applicable.

6.3.2 Instruction for prescribing and taking study treatment

The dose and treatment schedule of each study treatment used in this study is described in Section 6.1.3.

For the investigational drugs NIS793 and tislelizumab, separate bags and filters must be used for the infusions.

In **investigational arm #1**, NIS793 will be administered first by 30 minutes intravenous infusion (up to 1 hour if clinically indicated), followed by SOC therapy. During the first cycle, during and 2 hours after the administration of NIS793 participants will be observed closely and if clinically indicated, vital signs monitored more frequently before administering SOC.

In **investigational arm #2**, NIS793 will be administered first by 30 minutes infusion, followed by tislelizumab then SOC.

- NIS793 administration will be followed by dextrose solution flush and observation for approximately 2 hours during the first cycle before tislelizumab infusion.
- The initial infusion of tislelizumab (Cycle 1, Day 1) will be delivered over 60 minutes. After end of tislelizumab infusion, 1 hour of observation is required during first and second cycle before administering SOC. Approximately 30 minutes observation is required from cycle 3

onwards before administering SOC. During the infusion and observation period participants will be observed closely and vitals signs monitored more frequently if clinically indicated.

- If the initial infusion of tislelizumab (Cycle 1, Day 1) is well tolerated, then the subsequent infusions may be administered over 30 minutes, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug.

For more detail, refer to NIS793E12201 pharmacy manuals for NIS793, tislelizumab.

All kits of investigational drug(s) (NIS793 and tislelizumab) assigned by the IRT will be recorded in the IRT system.

CCI [redacted]

6.3.2.1 NIS793

NIS793 will be supplied in a vial as concentrate (liquid) for solution for infusion.

NIS793 (liquid) will be diluted into dextrose 5% in water (D5W) solution. Due to incompatibility, 0.9% sodium chloride must not be used. Please refer to the NIS793E12201 pharmacy manual.

NIS793 will be administered intravenously as a 30-minute infusion (up to 1 hour, if clinically indicated). Infusion must take place in a facility with appropriate resuscitation equipment available at the bedside, and a physician readily available during the period of drug administration.

Participants should be closely observed for potential infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever, and vital signs monitored more frequently if clinically indicated, during the infusion and for at least 2 hours after the first two NIS793 infusions. The same may apply for the subsequent NIS793 infusions if medically indicated. Participants should notify study personnel if symptoms of infusion reaction occur after any NIS793 infusion.

Further instructions for the preparation and dispensation of NIS793 are described in the NIS793E12201 pharmacy manual.

CCI [redacted]

6.3.2.2 SOC anti-cancer therapies; mFOLFOX6 or FOLFIRI and bevacizumab

For instructions on preparation and dispensing of mFOLFOX6 or FOLFIRI and bevacizumab, refer to product labeling and the local guidance.

6.3.2.3 Tislelizumab

Tislelizumab is a monoclonal antibody formulated for intravenous injection in a single-use vial (20R glass, United States Pharmacopeia [USP] type I), containing a total of 100 mg of antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in a single-use glass vial with a rubber stopper and capped by an aluminum flip-off seal cap.

The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature condition as specified on the label.

Refer to the NIS793E12201 Pharmacy Manual for Tislelizumab for details regarding intravenous administration, storage, accountability, and disposal. Please also refer to the Investigator's Brochure for other details regarding tislelizumab.

Tislelizumab 300 mg will be administered on Day 1 of each 28-day cycle (once every 4 weeks).

Tislelizumab will be administered by intravenous infusion through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the NIS793E12201 Pharmacy Manual for Tislelizumab.

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, participants must be monitored for at least 60 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a ≥ 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

Guidelines for dose modification, treatment interruption, or discontinuation and for the management of irAEs and infusion-related reactions are provided in detail in Section 6.6.4.2.

CCI [redacted].

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the Investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.4.2 Treatment assignment, randomization

All participants entering the screening period will be registered in the Interactive Response Technology (IRT) system. The Investigator or his/her delegate will then contact the IRT once all the inclusion/exclusion criteria have been assessed to confirm whether the participants will start study treatment or not.

In the **Safety run-in (SRI) part**, in the event that an SRI is open concurrently with the randomized expansion part of an investigational arm then randomization will be used to assign patients to the SRI vs. expansion. Otherwise, no randomization will be used to assign patients

to the SRI. All eligible participants will be administered investigational drug + modified FOLFOX6 or FOLFIRI + bevacizumab based on previous SOC therapy.

In the **Expansion part**, randomization will be performed via IRT for each investigational arm vs. control in a 2:1 ratio. Multiple expansion parts may run concurrently refer to the Section 3.2. Randomization will be stratified by treatment SOC anti-cancer therapy (FOLFIRI vs FOLFOX) and prior bevacizumab (yes vs no).

The IRT will assign a randomization number to the participant, which will be used to link the participant to investigational arms and control arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant 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 list will be produced under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

Additional investigational drugs and/ or additional combinations may be included in the expansion part following a protocol amendment. No randomization will be performed for these arms.

6.4.2.1 Replacement policy

Safety run-in part

If a participant is considered as non-evaluable for the Dose Determining Set (Section 12.1.3), enrollment of a new participant to the current arm will be considered if there are less than the required number of evaluable participants. Enrollment of new participants may be considered until at least the minimum number of 6 evaluable participants is achieved within the arm.

Expansion part

During the expansion part, no replacements will be needed.

6.5 Treatment blinding

Participants, Investigator site staff, persons performing the assessments, and the Novartis personnel will be unblinded to treatment assignment.

6.6 Dose de-escalation and dose modification

Dose escalation is not applicable.

Dose modifications and/or dose interruptions of investigational or other study treatment are provided in the following sections.

6.6.1 Dose de-escalation guidelines

6.6.1.1 Starting dose

In the Safety run-in part of the investigational arm #1 (NIS793 + SOC), the starting dose of NIS793 will be 2100 mg Q2W in combination with SOC anti-cancer therapy (Section 6.6.1.2). In case a dose de-escalation is required, a lower dose level is defined as 2100 mg Q4W (Table 6-2). No de-escalation is planned for the other components of the combination (chemotherapy or bevacizumab).

For the investigational arm #2 (NIS793 + tislelizumab + SOC), the starting dose for NIS793 will be either 2100 mg Q2W or Q4W, which is established in the safety run-in part of investigational arm #1 (NIS793+SOC) (Section 6.6.1.2). The dose of tislelizumab is 300 mg Q4W. If the starting dose of NIS793 will be 2100 mg Q2W and a dose de-escalation is required, a lower dose level for NIS793 will be defined as 2100 mg Q4W (Table 6-2). If the starting dose of NIS793 2100 mg Q4W is not tolerated, then no further dose de-escalation will be permitted. No de-escalation is planned for the other components of the combination (tislelizumab, chemotherapy, or bevacizumab).

Combinations of other investigational drug(s) with SOC anti-cancer therapy may be added later by protocol amendment as new investigational arms (e.g, investigational arm #3, etc).

6.6.1.2 Provisional dose levels

Table 6-2 describes the starting dose for NIS793 and the dose levels that may be evaluated during this trial in the safety run-in part.

Table 6-2 Provisional dose levels

Dose level	Proposed dose of NIS793	Increment from previous dose
1	2100 mg on Day 1 and 15 of every 28-day treatment cycle	starting dose
-1**	2100 mg on Day 1 of every 28-day treatment cycle	-50%

**Dose level -1 represents treatment dose if the starting dose is not considered safe. An additional 10 participants will be enrolled at the lower dose level in that treatment regimen. No dose reduction below dose level -1 is permitted for this study.

6.6.2 Guidelines for dose de-escalation and determination of RP2D

In **Safety run-in part,** for the purpose of dose confirmation for each treatment regimen approximately 10 participants will be enrolled to achieve at least 6 evaluable participants for each regimen during the dose limiting toxicity (DLT) period. The evaluable participant criteria are defined in Dose Determining Set (DDS), and the evaluable participants will be included in the DDS. To be considered evaluable for recommended dose decisions, participants must complete a minimum of 1 cycle of treatment (i.e., 28 days or 4 weeks) of dosing of study treatment with the minimum safety evaluation and drug exposure or have had a DLT within the first cycle of study treatment (refer to Section 12.1.3 for further details).

Bayesian logistic regression model (BLRM) for combinations using the escalation with overdose control (EWOC) criterion to evaluate the risk of DLT will guide the decision. The details of the BLRM are provided in Section 12.4 and Section 16.4. The adaptive Bayesian

methodology provides an estimate of all dose levels of the combination and incorporates all DLT information at all dose levels for this estimation.

In the safety run-in for investigational arm #1 (NIS793 + SOC) and also in the safety run-in for investigational arm #2 (NIS793 + tislelizumab + SOC), dose confirmation of NIS793 2100 mg Q2W or Q4W in combination with SOC will occur if the following conditions are met in the **Safety run-in part**:

- At least six evaluable participants are treated at this dose and regimen (6 evaluable participants for mFOLFOX6 + bevacizumab and another 6 for FOLFIRI + bevacizumab)
- The dose is considered safe by BLRM
- It is the dose recommended for participants after review of all relevant clinical data during the Safety Review Team (SRT) Meeting

If one of the conditions specified above is not satisfied in either regimen (mFOLFOX6 + bevacizumab or FOLFIRI + bevacizumab), dose confirmation cannot be declared and an additional approximately 10 participants (to achieve at least 6 evaluable participants) will be enrolled for the regimen at the lower dose level (dose level -1) if the starting dose is NIS793 2100 mg Q2W. Dose level -1 of NIS793 with or without tislelizumab in combination with SOC anti-cancer therapy is 2100 mg Q4W. The same criteria of DLT assessments are applied for this new lower dose level. If dose confirmation cannot be declared on this lower dose, NIS793, with or without tislelizumab, in combination with SOC anti-cancer therapy will be considered as not tolerable and the expansion part cannot start.

Combinations of other investigational drug(s) with SOC anti-cancer therapy may be added later by protocol amendment as new investigational arms (i.e., investigational arm #3, etc).

6.6.2.1 Implementation of dose de-escalation decisions

To implement the dose confirmation decision, the available toxicity information (including both DLT and adverse events and laboratory abnormalities that are not DLTs), and the available PK CCI information will be evaluated by the Investigators who enrolled participants and Novartis study personnel (including at least the study physician and a statistician) during a dose decision meeting by teleconference. Drug administration at the next lower dose level or in the **Expansion part** may not start until the Investigators receive written confirmation from Novartis indicating which dose regimen will be used.

Novartis will communicate the agreed dose decision in writing to the Safety Review Team (SRT), steering committee (SC), and all participating Investigators. Additional communication in a form of teleconference, webcast, or Investigator meeting may be implemented if needed.

6.6.3 Definitions of dose limiting toxicities (DLTs)

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first cycle (i.e., 28 days) of treatment with investigational drug(s) (NIS793 with or without tislelizumab) and SOC anti-cancer therapy regimens and meets any of the criteria included in Table-6-3 and Table 6-4 for investigational arm #2 in SRI. The National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 5.0 will be used for all grading AEs.

The Investigator must notify the sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities.

Table 6-3 Criteria for Defining Dose-Limiting Toxicities

TOXICITY	DLT CRITERIA (NCI CTCAE v5.0 will be used for grading)
Cardiac (including valvulopathy)	● Grade ≥ 3 cardiac events
Cutaneous reactions	● Grade ≥ 3
Gastrointestinal	● Grade 3 nausea and vomiting for > 3 days despite optimal anti-emetic therapy ● Grade 3 diarrhea for > 5 days despite optimal antidiarrheal treatment (which could include steroids) ● Grade 4 vomiting or diarrhea
Hematological	● Grade 4 neutropenia for > 7 consecutive days, or grade 4 febrile neutropenia ● Grade 4 anemia ● Grade 3 thrombocytopenia with clinically significant bleeding (i.e., life threatening and invasive intervention indicated) regardless of duration or requirement for transfusion, or grade 4 thrombocytopenia (<25,000/mm^3)
Hepatobiliary	● Grade 4 bilirubin elevation ● For participants with normal baseline AST, ALT and bilirubin values: ● AST or ALT > 8.0 × ULN; OR ● AST or ALT > 5.0 × ULN for more than 2 weeks; OR ● AST or ALT > 3.0 × ULN combined with total bilirubin > 2.0 × ULN without evidence of cholestasis ● For participants with abnormal baseline AST or ALT or abnormal baseline bilirubin value: ● ALT or AST > 3.0 x baseline value; OR ● ALT or AST > 3.0 x baseline (or > 8.0 x ULN), whichever occurs first, combined with total bilirubin > 2.0 x baseline and > 2.0 x ULN without evidence of cholestasis
Renal	● Grade ≥ 3 serum creatinine
Hypertension	● Grade 3 hypertension if it persists > 7 days despite optimal anti-hypertensive treatment ● Grade 4 hypertension of any duration
Pancreatitis	● Symptomatic serum amylase or lipase elevation, medical intervention required ● Grade ≥ 3 pancreatitis
Infusion related reaction	● Grade > 3 infusion related reaction
Infections	● Grade 4
Ocular disorders	● Grade ≥ 3 conjunctivitis, blepharitis, vision blurred
Hemorrhage/ Bleeding	● Grade ≥3 despite optimal treatment or Grade 4
Other AEs	Other clinically significant AEs: ● Grade ≥ 3 AEs that have not been previously identified for NIS793 or grade 4 AEs that have not been previously identified for SOC anticancer treatments ● Grade ≥ 3 AEs that are known to occur with NIS793 or grade 4 AEs that are known to occur with SOC anticancer treatments, but cannot be controlled using the recommended product-specific management guidelines (per local prescribing information), or leads to <50% of planned exposure of study medications ● Other clinically-significant AEs, including a single event or multiple occurrences of the same event that lead to a dosing delay of > 4 weeks should be considered as DLTs by the Investigators and the sponsor, even if not grade 3 or higher

TOXICITY	DLT CRITERIA (NCI CTCAE v5.0 will be used for grading)
The SOC anti-cancer therapy will include combination of bevacizumab with either modified FOLFOX6 or FOLFIRI. Events which will NOT be considered as DLT for the purpose of this protocol: Clinically insignificant laboratory values ≤ grade 2. For electrolyte abnormalities ≥ grade 3, the maximum allowable time limit for correction of to ≤ grade 1 is 72 hours.	

Table 6-4 Additional criteria for defining DLTs for investigational arm #2 in SRI

TOXICITY	DLT CRITERIA
Immune-related toxicities (except pneumonitis)	CTCAE Grade 3 immune-related toxicities that persist > 14 days with same severity despite treatment with corticosteroids Immune-related toxicities CTCAE Grade 4 of any duration Note: endocrinopathies managed with hormone replacement therapy are generally not considered DLT.
Pneumonitis (interstitial lung disease)	CTCAE Grade 2 pneumonitis if it persists > 7 days despite treatment with corticosteroids. Grade 3-4 pneumonitis of any duration
Other Adverse Events	Grade 3-4 infusion reaction Grade 4 events of any duration Other clinically significant toxicities, including a single event or multiple occurrences of the same event that lead to a dosing interruption of > 12 weeks should be considered to be DLTs by the Investigators and Novartis, even if not CTCAE Grade 3 or higher.

6.6.4 Dose modifications

For participants who do not tolerate the protocol-specified dosing regimen, dose interruptions and/or decreasing the dosing frequency for NIS793 from Q2W to Q4W are permitted to allow participants to continue the study treatment.

Refer to Table 6-5 for dose modifications for participants in the Safety run-in part beyond the first cycle (i.e, 28 days period), and for participants in the Expansion part. Permanent discontinuation of study treatment is mandatory for specific events indicated as such in Table 6-5 or listed in Section 6.6.4.2.

- No dose reductions are allowed for NIS793 in the Safety run-in or the Expansion part. Decreasing the dosing frequency from Q2W to Q4W is the only permitted dose modification for NIS793 and this is only allowed for participants enrolled in the SRI after the DLT evaluation period or for participants enrolled in the Expansion part under circumstances described in Section 6.6.4.1. Once NIS793 dosing frequency is decreased to 2100 mg Q4W, it cannot be increased to 2100 mg Q2W.
- Dose interruptions due to toxicities are permitted for all study treatments. Dose interruptions for NIS793 include dose delay or withholding the treatment for any reason. Dosing of each study treatment may resume once the AE has resolved, as described in Section 6.6.4.1, and the start of the cycle will be shifted accordingly. Instructions as per locally approved labels should prevail. All dose modifications, interruptions or discontinuations must be based on the worst toxicity graded according to CTCAE v5.0 (CTCAE 2017).
- If the Investigator considers that resuming therapy before the toxicity has resolved to Grade 1 or to resume therapy without dose reduction is in the best interest of the participant, this may be permitted following documented discussion with the Novartis medical monitor.

- Dose reductions and dose interruptions are allowed for SOC. Instructions as per locally approved label should be followed.

These dose changes must be recorded on the appropriate CRF.

CCI [redacted]

6.6.4.1 Dose modification and dose interruption for NIS793

- **No dose reductions** are allowed for NIS793. Increasing the dosing interval from Q2W to Q4W is allowed under circumstances described in Table 6-5. Once NIS793 dosing frequency is de-escalated to 2100 mg Q4W, it cannot be re-escalated to 2100 mg Q2W.
- **Dose interruption** due to toxicities is permitted. Dosing of study treatment may resume once the AE has resolved, as described in Table 6-5.

Table 6-5 Dose modifications of NIS793 for adverse drug reactions suspected to be related to NIS793

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Infusion reaction or hypersensitivity reaction	
Grade 1	Decrease infusion rate until recovery from the symptoms. If the infusion reaction happens after the end of the infusion, increase monitoring of vital signs until the participant is symptoms free. Administer subsequent NIS793 infusion at the same rate.
Grade 2	Stop infusion immediately and keep line open. Follow institutional guidelines for the management and follow-up of infusion reaction. Restart NIS793 infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion. If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, permanently discontinue study treatment.
Grade 3 or Grade 4	Stop NIS793 infusion immediately, and permanently discontinue study treatment. Provide supplemental oxygen, fluids, and other resuscitative measures as needed. Monitor vital signs (e.g., blood pressure, pulse, respiration, and temperature) every 15 ± 5 minutes until resolution.
CCI [redacted]	
Ocular (e.g., Conjuctivitis, Blepharitis, blurred vision)	
Grade 1	May continue study treatment. Consider ophthalmology consultation.
Grade 2	Ophthalmology consultation. Upon resolution to ≤ Grade 1 consider resuming study treatment in consultation with ophthalmologist.
Grade 3	Interrupt study treatment. Ophthalmology consultation. Upon resolution to ≤ Grade 1 consider resuming study treatment in consultation with ophthalmologist.
Grade 4	Permanently discontinue study treatment.

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Cardiovascular	
Myocarditis	
Grade ≥ 2	Permanently discontinue study treatment.
Cardiac Valvulopathy & Other Cardiac Toxicity	
Grade 2	Interrupt study treatment. Repeat echocardiogram and assess cardiac function. Once resolved, to Grade ≤ 1 or baseline, consider readministration of treatment, if benefit outweighs the potential risk.
Grade ≥ 3	Permanently discontinue study treatment.
Isolated AST and/or ALT elevation	
With normal AST and ALT at baseline:	
Grade 3: AST or ALT (>5.0 – 20.0) x ULN: AST or ALT >5.0 – 10.0 x ULN	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until recovery to Grade ≤ 1 or to baseline. Then resume treatment at the same dose interval If resolved in ≤ 14 days; if resolved in > 14 days, consider administration every 4 weeks (Q4W) instead of every 2 weeks (Q2W).
AST or ALT >10.0 – 20.0 x ULN	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until recovery to grade ≤1 or to baseline. Then increase dosing interval for NIS793 from Q2W to Q4W.
Grade 4: AST or ALT (>20 x ULN)	Permanently discontinue treatment.
With abnormal ALT/AST (up to grade 2 - ≤ 5.0 x ULN) at baseline:	
ALT/AST > 2.0 x baseline AND > 5.0 x ULN	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until recovery to baseline; Then resume same dose interval if resolved in ≤ 14 days; if resolved in > 14 days, increase dosing interval from Q2W to Q4W.
ALT/AST > 3.0 x baseline AND >10 x ULN	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor weekly until resolved to baseline; then increase dosing interval from Q2W to Q4W.
AST or ALT >20 x ULN (Grade 4)	Permanently discontinue treatment.
Concomitant elevation of AST and/or ALT and total bilirubin	
With normal AST/ALT and bilirubin at baseline:	
Grade 2 ALT and/or AST elevation (>3.0 x ULN) with bilirubin > 2.0 x ULN (unless Gilbert's syndrome)	Interrupt treatment. Assess if case is drug induced liver injury (DILI) - If DILI confirmed, permanently discontinue study treatment. For additional information on follow-up of potential drug induced liver injury cases, refer to Section 6.6.5.1. If no DILI confirmed, interrupt treatment, treat the identified cause according to institutional guidelines. Repeat LFTs within 48-72 hours, then monitor weekly, until enzyme levels resolve to ≤ Grade 1 or baseline. After recovery, re-administration of study treatment could be considered only if Investigator assesses benefit to outweigh the risk. Any decision regarding re-administration of study drugs and dose regimen should be discussed with the Sponsor.

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
With abnormal ALT/AST at baseline:	
ALT or AST >3.0 x baseline OR ALT or AST >8.0 x ULN [whichever is lower] combined with total bilirubin >2.0 x baseline AND >2.0 x ULN	Same as above.
Isolated total bilirubin elevation	
Any elevation > ULN	Fractionate bilirubin, evaluate for cholestatic liver injury (e.g., by testing ALP) or alternative causes of bilirubin elevation (e.g., disease progression [imaging]). Treat alternative causes according to institutional guidelines.
Grade 2 (>1.5 - 3.0 ULN)	Maintain treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline. If isolated bilirubin remains stable at Grade 2, continue treatment at the same dose regimen.
Grade 3 (>3.0 – 10 ULN)	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline. If resolved in ≤ 14 days, maintain dose regimen; if not resolved in 14 days, permanently discontinue NIS793. (Please see footnote regarding alternative cause/s of bilirubin elevation).
Grade 4 (> 10 x ULN)	See footnote**. Otherwise, permanently discontinue study treatment. If alternative cause/s is identified and managed, and bilirubin resolves to ≤ Grade 1 or to baseline, resume treatment at the same dose regimen.
**An isolated bilirubin elevation is not typical for DILI. Bilirubin can be elevated either as part of a “Hy’s law” constellation with a preceding elevation of ALT/AST, or as part of a cholestatic reaction with simultaneous elevation of other cholestatic parameters (ALP, GGT). Isolated bilirubin can be seen in conjunction with drugs that inhibit bilirubin conjugation or excretion, but both scenarios do not typically represent liver injury. Alternative causes of bilirubin elevation should therefore, be ruled out before basing dose modification decisions on bilirubin values alone.	
Asymptomatic amylase and/or lipase elevation[***]	
Grade 3, not associated with symptoms or clinical manifestations of pancreatitis***	May continue study treatment. If levels do not resolve to ≤ Grade 2 within ≤ 14 days after the initial report, hold study treatment. Upon resolution to ≤ Grade 2, consider resuming study treatment.
Renal	
Serum creatinine	
Grade 2	Interrupt study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1, consider resuming study treatment.
Grade 3 or Grade 4	Permanently discontinue study treatment.
Endocrine	
Hyperthyroidism	
Grade 2	Consider continuing study treatment and management according to institutional practice.
Grade 3	Interrupt study treatment. Upon resolution to Grade ≤ 1 with appropriate management, consider resuming study treatment without dose modification.
Grade 4	Must permanently discontinue and manage according to local/institutional guidance.

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Other endocrine disorders	
Grade 2 and Grade 3	Interrupt study treatment. Upon resolution to Grade ≤ 1 with appropriate management, consider resuming study treatment.
Grade 4	Permanently discontinue and manage according to local/institutional guidance.
Dermatology (rash)	
Grade 1	Continue study treatment. Consider topical steroids, antihistamines, topical emollients.
Grade 2	Consider interrupting study treatment. Topical or oral steroids, antihistamines. If study treatment is held and resolution to ≤ Grade 1, resume study treatment.
Grade 3	Interrupt study treatment. Manage per institutional practice. After resolution to ≤ Grade 1, consider resuming study treatment after consultation with dermatologist.
Grade 4 or Stevens-Johnson syndrome (SJS), or Lyell syndrome/ toxic epidermal necrolysis (TEN)	Permanently discontinue and manage according to local/ institutional guidance.
Hematology	
Neutropenia	
Grade 3	Interrupt study treatment. Upon resolution to ≤ Grade 2 or baseline within ≤ 7 days, resume study treatment.
Grade 4	Interrupt study treatment. If resolved in ≤ 7 days, maintain study treatment If resolved in > 7 days, permanently discontinue NIS793.
Febrile neutropenia	
Grade 3	Interrupt study treatment. Upon resolution of fever and improvement of neutropenia to ≤ Grade 2 or baseline, resume study treatment.
Grade 4	Permanently discontinue study treatment.
Thrombocytopenia	
Grade 3	Interrupt study treatment. Upon resolution to ≤ Grade 2 or baseline, resume study treatment. For Grade 3 associated with major bleeding, permanently discontinue study treatment.
Grade 4	Permanently discontinue study treatment.
Anemia	
Grade 3 or Grade 4	Interrupt study treatment. Upon resolution to ≤ Grade 2 or baseline within ≤ 7 days, resume study treatment.

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Other laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	
Grade 3 or Grade 4	Interrupt study treatment. Upon resolution to ≤ Grade 1, resume study treatment. Isolated Grade 4 electrolyte abnormalities not associated with clinical sequelae and corrected after appropriate management within 72 hours of their onset do not require discontinuation. In the case of Grade 4 electrolyte imbalances associated with clinical sequelae, or not resolved to ≤ Grade 1 within 72 hours despite appropriate management, permanently discontinue study treatment.
Other non-laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	
Grade 2	Consider study treatment interruption. Upon resolution to ≤ Grade 1, consider resuming study treatment.
Grade 3	Interrupt study treatment. Upon resolution to ≤ Grade 1, resuming study treatment must be discussed with the relevant medical expert.
Grade 4	Permanently discontinue study treatment.
All dose modifications should be based on the worst preceding toxicity. a Common Toxicity Criteria for Adverse Events (CTCAE v5) ***Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within one week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase.	

6.6.4.2 Dose modification and dose interruption for tislelizumab

No changes in dose or schedule of tislelizumab are allowed.

Tislelizumab treatment may be temporarily suspended if the patient experiences a toxicity that is considered related to tislelizumab and requires a dose to be withheld. Tislelizumab treatment should resume as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) and within 12 weeks after last dose of tislelizumab. If the administration of study drug can resume within ≤ 10 days, it should be administered in the current cycle. If the study drug needs to be withheld for > 10 days, it should be omitted from the current cycle and administration should continue at the start of the next cycle. If the patient is unable to resume tislelizumab within 12 weeks after the last dose of tislelizumab, then the patient should be discontinued from treatment. If the patient is not able to resume tislelizumab ≤ 12 weeks after the last dose for unforeseen non-drug-related reasons, continued treatment may be allowed if approved by the medical monitor.

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

An irAE may be low grade and self-limited, most frequently involving the GI tract (e.g., diarrhea/colitis), skin (e.g., rashes, pruritus), liver (e.g., immune mediated liver injury or liver laboratory alterations), 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-mediated AEs may rarely include

the nervous system (e.g., neuropathy, encephalitis, Guillain-Barre syndrome, myasthenia gravis), eye (e.g., uveitis, vision changes), musculo-skeletal system (e.g., rhabdomyolysis, myositis, arthritis, polymyalgia rheumatica), 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 epidermonecrolysis or Steven 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 the treatment discontinuation.

In general, identification and diagnosis of irAEs requires ruling out alternative causes/ etiology of the observed toxicity. The diagnostic work-up of a potential irAE should include, pertinent medical history and physical examination, standard biologic tests or as indicated by presenting signs and symptoms (e.g., blood cell count, liver, and renal function tests); relevant infection work-up (e.g., Clostridium difficile, parasite, cytomegalovirus for colitis, herpes simplex, herpes zoster for bullous dermatoses); directed serologic evaluations to help rule out other etiologies such as autoimmune conditions and/ or establish the diagnosis of an irAE; biopsy, if clinically considered necessary (e.g., is recommended for skin lesions, and can be considered for colitis, or renal injury). Imaging with computed tomography (CT) scan, X-Ray and/ or ultrasound, can be useful for example in diagnostic work-up of colitis, renal toxicities, pneumonitis, hepatitis and endocrinopathies. For further guidance it is recommended to refer to ESMO and ASCO guidelines for management of immune-related adverse events (Haanen et al 2017, Brahmer et al 2018).

Specific treatment modifications to manage tislelizumab-related toxicities, such as to irAEs and infusion-related reactions, are described in Appendix 6.

The following sections address the specific instructions for mandatory dose modifications and recommended management for adverse events considered suspected to be related to tislelizumab. These modifications/interruptions must be recorded on the Dosage Administration Record CRF.

6.6.4.2.1 Dose modification and management requirements for potential immune-related adverse events

Severe grade or persistent lower grade irAEs typically require interrupting or permanently discontinuing treatment and administration of systemic steroids, and sometimes other immunosuppressive medications (i.e., tumor necrosis factor alpha (TNFa) 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 (i.e., <4 weeks) to avoid recurrence or worsening of irAEs. The management of irAEs may further include initiation of antibiotics for prophylaxis against opportunistic infections.

Participants should be instructed to return to the study site as soon as possible (instead of waiting for their next scheduled visit) if they experience symptoms consistent with an irAE. Participants

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

Based on experience and published guidelines on the management of irAEs in participants treated with immune checkpoint inhibitors (Haanen et al 2017, Brahmer et al 2018), instructions have been developed how to manage irAEs that may occur in participants receiving tislelizumab. Dose modification requirements and AE management guidelines for the potential irAEs are provided in Appendix 6). In addition, guidance for management of tislelizumab infusion-related reactions is provided in Table 6-6.

Investigators are encouraged to contact Novartis as needed to discuss cases that warrant separate discussion outside of the scope of the current instructions.

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

6.6.4.2.2 Managing infusion-related reactions

Participants should be closely monitored for infusion-related reactions. Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available to treat severe and life-threatening infusion-related reactions.

Treatment modifications for symptoms of infusion-related reactions due to study drug(s), tislelizumab, is provided in Table 6-6 .

Table 6-6 Treatment modifications for symptoms of infusion-related reactions due to study drug(s)

NCI-CTCAE Grade	Treatment Modification for Tislelizumab
Grade 1 - mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 - moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, intravenous fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reaction has resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described below. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 – severe Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment.
Grade 4 – life threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment. Hospitalization is recommended.

Abbreviations: NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Event; NSAIDs, nonsteroidal anti-inflammatory drugs.

Once the tislelizumab infusion rate has been decreased by 50% or interrupted due to an infusion related reaction, the infusion rate must remain decreased for all subsequent infusions and be administered with premedication. If the participant has a second infusion-related reaction (≥ Grade 2) on the slower infusion rate, infusion should be discontinued, and the participant should be withdrawn from tislelizumab treatment.

NCI-CTCAE Grade 1 or 2 infusion reaction

Proper medical management should be instituted as indicated per the type of reaction. This includes, but is not limited to, an antihistamine (e.g., diphenhydramine or equivalent), antipyretic (e.g., paracetamol or equivalent), and if considered indicated, oral or intravenous glucocorticoids, epinephrine, bronchodilators, and oxygen. In the next cycle, participants should receive oral premedication with an antihistamine (e.g., diphenhydramine or equivalent) and an antipyretic (e.g., paracetamol or equivalent), and they should be closely monitored for clinical signs and symptoms of an infusion reaction.

NCI-CTCAE Grade 3 or 4 infusion reaction

Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes, but is not limited to, oral or intravenous antihistamines, antipyretics, glucocorticoids, epinephrine, bronchodilators, and oxygen.

Severe hypersensitivity reactions and flu-like symptoms

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice as described in the complete guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (UK) (Soar et al 2008). Participants should be instructed to report any delayed reactions to the Investigator immediately.

In the event of a systemic anaphylactic/anaphylactoid reaction the infusion must be immediately stopped, and the patient discontinued from the study. Systemic anaphylactic/anaphylactoid reactions typically manifest within minutes following administration of the drug/antigen and are characterized by respiratory distress; laryngeal edema; and/or intense bronchospasm; and often followed by vascular collapse or shock without antecedent respiratory difficulty; cutaneous manifestations such as pruritus and urticaria with/without edema; and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea.

The participant will be administered epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed. The patient should then be placed on monitor immediately, and the intensive care unit (ICU) should be alerted for possible transfer if needed.

For prophylaxis of flu-like symptoms, a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (i.e., 600 mg ibuprofen, 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of study drugs(s) infusion. Alternative treatments for fever (i.e., paracetamol) may be given to participants at the discretion of the Investigator.

6.6.5 Follow-up for toxicities

Participants must be followed-up for AEs and SAEs up to 30 days following the last dose of all study treatments.

Suspected SAEs will continue to be collected beyond those timeframes. However, if the participant begins subsequent anti-cancer therapy before the 30 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 30 days following the last dose of study treatment. If SAEs suspected to be related to study medication occur beyond Day 30, information should also be collected.Participants whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4 week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts (e.g. ophthalmologist, endocrinologist, dermatologist, psychiatrists) should be consulted as deemed necessary.

CCI [redacted].

Refer to Section 16.1 for the follow-up evaluations recommended for selected toxicities.

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

Participants with transaminase increase combined with total bilirubin increase may be indicative of potentially severe DILI. These events should be considered as clinically important 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 participant's baseline AST/ALT and total bilirubin value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- For participants with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT >3.0 x baseline] OR [ALT or AST > 8.0 x ULN], whichever occurs first, combined with [total bilirubin > 2.0 x baseline AND > 2.0 x 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, Gamma-glutamyl transferase (GGT), prothrombin time (PT)/International Normalized Ratio (INR), alkaline phosphatase, albumin, and creatine kinase (CK). If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended.

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, Endoscopic retrograde cholangiopancreatography (ERCP)) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis is defined as an ALP elevation > 2.0 x ULN with R value < 2 in participants without bone metastasis, or elevation of the liver-specific ALP isoenzyme in participants with bone metastasis.

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury.

Table 6-7 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed Liver Function Test (LFT) abnormalities.

Table 6-7 Guidance on specific assessments 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	Antinuclear antibodies (ANA) & Anti Smooth Muscle antibody (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)	Caeruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

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

CCI [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 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 LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

6.7 Additional treatment guidance

6.7.1 Treatment compliance

Study treatment will be administered at the investigational site following the schedule in Table 8-2 and Table 8-3. The date and time of all study treatment administrations during the study and any deviations from the protocol treatment schedule will be captured by the Investigator staff or delegates in the source document at each administration visit. All study treatments infused and returned must be recorded in the Drug Accountability Log.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all participants treated with NIS793, all participants treated with tislelizumab, all participants in SRI treated with bevacizumab or irinotecan, and select participants in Expansion part treated with bevacizumab or irinotecan, as detailed in pharmacokinetics section (Table 8-9).

CCI [redacted]

7 Informed consent procedures

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

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

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

Novartis will provide to Investigators in a separate document a proposed informed consent form that complies with the ICH E6 Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the Investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB) (and/or CDS for marketed drugs). This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the

investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed 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
  - CCI [redacted]
- As applicable, Pregnancy Outcome Reporting Consent for female participants or the female partners of any male participants who took study treatment

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

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

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

The study includes the option for the participant to have certain study procedures performed off-site by an off-site healthcare professional (OHP) instead of at the study site, for which a separate signature is required if the participant agrees. It is required as part of this protocol that the Investigator presents this option to the participant, as permitted by national and local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

As per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities (i.e., pandemic, epidemic, or natural disaster) that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The Assessment Schedule (Table 8-2 for Safety run-in part and Table 8-3 for expansion part) lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants in the Safety run-in part should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-2) or as close to the designated day/time as possible. Participants in the Expansion part should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-3) or as close to the designated day/time as possible.

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Study treatment will begin on Cycle 1 Day 1 (C1D1) with the first administration of the assigned study treatment depending on the arm the participant 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 which have to be scheduled as per the scheduled number of weeks after the date of randomization). Treatment cycles are intended to be 4 weeks (28 days), but the treatment can be delayed to manage toxicities according to the dose modification criteria in Section 6.6.4 and the locally approved label and local practice for the SOC anti-cancer therapies. In such cases, all study procedures (except for tumor assessments) will be completed at a later date corresponding to the delayed treatment.

Assessments which are indicated to be performed at Screening and on C1D1, only need to be repeated at C1D1 if the Screening assessment was more than 3 days earlier except as noted in Table 8-2 and Table 8-3.

Tumor assessments will be performed every 8 weeks for the first 52 weeks (~12 months) starting from date of randomization/ enrollment regardless of any treatment delays. Tumor assessments post Week 52 are specified in Table 8-5, and in Section 8.3. Radiological assessments performed as part of clinical standard of care prior to signing informed consent can be used if performed within the screening time window.

During the course of the study visits, test procedures should occur on schedule whenever possible as per allowable visit windows specified in Table 8-1 below.

Note: If any drug of the study treatment is temporarily interrupted or permanently discontinued at any time during the study, tumor assessments should continue according to the appropriate number of calendar days from randomization date as per the schedule of assessments.

Missed or rescheduled visits should not lead to automatic discontinuation. Participants who discontinue from study treatment are to return for the end of treatment visit as soon as possible and attend the follow-up visits as indicated in the Assessment Schedule.

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the CRF.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

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During a public health emergency, as defined in Section 4.7, alternative methods of providing continuing care may be implemented by the Investigator. If allowable by a local Health Authority, national and local regulations and depending on operational capabilities; phone calls, virtual contacts (e.g., tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant's home, can replace in person visits for certain protocol assessments such as safety monitoring, lab assessments, urine pregnancy test, COA etc. for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Allowable visit windows

Visit Name	Window
Screening	**Day -28 to Day -1**
● Physical examination, performance status, weight, vital signs ● Hematology, biochemistry, coagulation, urinalysis	● NOTE: Assessments done ≤ 7 days of first dose of study treatment are permitted to be used as Cycle 1 Day 1 labs/ assessments and do not need to be repeated.
● Serum pregnancy test	● ≤ 72 hours prior to first dose of study treatment
● All other screening assessments	● Day -28 to Day -1
Cycle 1 Day 1 Assessments and study treatment administration	Within 3 days after drug assignment or randomization in IRT
Day 15 of all cycles until EOT Assessments and study treatment administration	± 1 days
Day 1 of subsequent cycles Assessments and study treatment administration	± 3 days
Day 15 of cycles 3, 6, 9 until EOT and at 30 days safety follow-up, if applicable	
Eye examination including visual acuity and optical coherence tomography (For investigational arm #2 only)	± 7 days Refer to Section 8.4.3
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Tumor assessments (during treatment/efficacy follow-up)	± 7 days
End of Treatment (EOT)	Within 7 days after decision to discontinue study treatment 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	± 7 days
60-, 90-, 120-Day safety follow-up phone call / visit	± 7 days
Post treatment efficacy follow-up	± 7 days
Survival follow-up	± 7 days

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Table 8-2 Assessment Schedule, Safety run-in part

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Informed consent	X															
IRT Screening (after ICF signature)	X															
Demography	X															
Inclusion / Exclusion criteria	X															
Medical history/current medical conditions	X															

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Diagnosis and Extent of cancer (including MSI/dMMR (mandatory, local), BRAFV600 status (if applicable), RAS mutation status – (mandatory, local); DPD and UGT1A1 if applicable (local))	X															
Prior antineoplastic therapy (meds, surgery, radiation)	30 days prior to initiation of study treatment															

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Prior/concomitant medications/procedures and significant non-drug therapies[1]	X	continuous									X	X	X	X		
Concomitant antineoplastic radiotherapy[2]		continuous									X	X	X	X		
HBV, Hepatitis C Test	X															
HIV screen (mandatory, if required by local guidelines)	S															
IRT Enrollment		X														
Physical Examination	X[11]	X		X	X	X	X			X	X	X	X	X		

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Serum pregnancy (WOCBP)[3]																
Urine pregnancy (WOCBP)[3]	X[11]	X			X		X				X	X	X	X		
FSH (local and if applicable)	S[11]	S			S		S				S	S	S	S		
Vital Signs	X[11]	X		X	X	X	X			X	X	X	X	X		
Weight	within 72 hours before first dose									X						
Height		S			S		S				S	S	S	S		
Performance status (ECOG)	S															
Hematology	X[11]	X		X	X	X	X		X	X	X	X	X	X		
Biochemistry	X[11]	X		X	X	X	X		X	X	X	X	X	X		

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
HbA1c (Glycated hemoglobin)	X						C3D1 then every 3rd cycle (C6D1, C9D1.) and as clinically indicated			X			X			
Urinalysis	X[11]	X			X		X			X	X	X	X	X		
Eye examination including visual acuity and signs of intraocular inflammation (i.e., uveitis) (For investigational arm #2 only)	X (arm 1 and 2 in case of concurrent randomization)	X			X		X			X						

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Cardiac Enzymes (Troponin-I, NTproBNP)[13]	X						C3D1 then every 2nd cycle (C5D1, C7D1, C9D1,...) or earlier if clinically indicated and/ or cardiac enzymes≥2x ULN			X						
Troponin-I (For investigational arm #2 only)[13]		X			X		X									
Thyroid Panel	X	if clinically indicated								if clinically indicated	if clinically indicated					

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Coagulation	X	As clinically indicated and before any protocol defined biopsies								As clinically indicated and before any protocol defined biopsies	X	X	X	X		
CCI																
Tumor marker CA-19-9, CEA	X						Every 8 weeks (C3D1, C5D1, etc.) until week 52, then every 12 weeks								X	

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Tumor Evaluation using RECIST 1.1 (all participants), iRECIST (investigational arm #2) (CT or MRI of Chest, abdomen, pelvis I)[4]	X (arm 1 and 2 in case of concurrent randomization)						Every 8 weeks (C3D1, C5D1, etc.) until week 52, then every 12 weeks			X					X	
Brain CT or MRI[4]	if clinically indicated	if clinically indicated								if clinically indicated					if clinically indicated	
Whole body bone scan[4]	if clinically indicated	if clinically indicated								if clinically indicated					If clinically indicated	
Localized bone CT, MRI or X-ray[4]	if clinically indicated	if clinically indicated								if clinically indicated					if clinically indicated	
CT/ MRI of other metastatic sites[4]	if clinically indicated	if clinically indicated								if clinically indicated					if clinically indicated	

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
NIS793 administration (for participants on NIS793)[5]		X		X	X	X	Day 1 and 15 of C3 and subsequent cycles		X							
Tislelizumab administration (for participants in Investigational arm #2 only)		X			X		X									
5-Fluorouracil (5-FU) administration		X		X	X	X	Day 1 and 15 of C3 and subsequent cycles		X							
Leucovorin (folinic acid) (or levoleucovorin) administration		X		X	X	X	Day 1 and 15 of C3 and subsequent cycles		X							

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Irinotecan administration (for participants on FOLFIRI)		X		X	X	X	Day 1 and 15 of C3 and subsequent cycles		X							
Oxaliplatin administration (for participants on mFOLFOX6)		X		X	X	X	D1 and 15 of C3 and every subsequent cycle		X							
Bevacizumab administration		X		X	X	X	D1 and 15 of C3 and every subsequent cycle		X							
Adverse Events[6]	X	X														
Serious Adverse Events[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Antineoplastic therapies since discontinuation										X	X	X	X	X	X	X
ECG (12-lead)	X	if clinically indicated					if clinically indicated									
Echocardiogram	X	if clinically indicated					if clinically indicated									
CCI																

Period	Screening	28 days Treatment Cycle								End of treatment	Safety follow-up[9]				Post treatment efficacy follow-up	Survival Follow-up
Cycle		Cycle 1			Cycle 2		Cycle 3 (and subsequent cycles)									
Visit Name	Screening	Cycle 1			Cycle 2		Cycle 3 and subsequent cycles	Cycle 3		End of treatment (EOT)	30 days	60 days	90 days	120 days	Post treatment efficacy follow-up	Survival follow-up (every 12 weeks)
Days	-28 to -1	1	2	15	1	15	1	2	15	-	30	60	90	120	-	
CCI																

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
NIS793 PK sampling[8]		X		X			Day 1 of C3, C6, C12, C18, C24		C3D15	X		X	X			
NIS793 pharmacodynamic/ Total TGFβ1 sampling[8]		X		X			Day 1 of C3, C6, C12, C18, C24		C3D15	X		X	X			
NIS793 immunogenicity sampling[8]		X		X			Day 1 of C3, C6, C12, C18, C24		C3D15	X		X	X			
Tislelizumab PK sampling[8]		X	X	X	X		Day 1 of C3, C4, C6, 12, C18, 24	C3D2	C3D15	X				X		
Tislelizumab immunogenicity sampling[8]		X			X		Day 1 of C3, C4, C6, C12, C18, C24			X				X		

Period	Screening	28 days Treatment Cycle								End of treatment	Safety follow-up[9]				Post treatment efficacy follow-up	Survival Follow-up
Cycle		Cycle 1			Cycle 2		Cycle 3 (and subsequent cycles)									
Visit Name	Screening	Cycle 1			Cycle 2		Cycle 3 and subsequent cycles	Cycle 3		End of treatment (EOT)	30 days	60 days	90 days	120 days	Post treatment efficacy follow-up	Survival follow-up (every 12 weeks)
Days	-28 to -1	1	2	15	1	15	1	2	15	-	30	60	90	120	-	
CCI																

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
CCI																
IRT Discontinuation										X						
Survival follow up																X
Disposition	X									X					X	

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Within 30 days prior to start of study treatment until end of safety follow-up or start of new anti-neoplastic (ANP) medication, whichever is sooner. If new ANP medication is started then only medications relative to the suspected AEs/SAEs that are reportedshould be collected
[2] From start of study treatment until end of safety follow-up or start of new ANP medication, whichever is sooner. If new ANP medication is started then only medications relative to the suspected AEs/SAEs that are reported should be collected
[3] For women with child bearing potential status confirmed. Refer to Section 8.4 for further details
[4] Refer to Table 8-5 for further details on efficacy assessments. EOT imaging assessments will be done for participants without prior documented disease progression based on RECIST 1.1 (for participants in investigational arm #1 and the control arm) and using RECIST 1.1 and iRECIST (for participants in investigational arm #2) who do not enter the efficacy follow-up phase, provided the last imaging assessment was not conducted within 30 days prior to the end of study treatment.

Period	Screening	28 days Treatment Cycle								End of treatment	Safety follow-up[9]				Post treatment efficacy follow-up	Survival Follow-up
Cycle		Cycle 1			Cycle 2		Cycle 3 (and subsequent cycles)									
Visit Name	Screening	Cycle 1			Cycle 2		Cycle 3 and subsequent cycles	Cycle 3		End of treatment (EOT)	30 days	60 days	90 days	120 days	Post treatment efficacy follow-up	Survival follow-up (every 12 weeks)
Days	-28 to -1	1	2	15	1	15	1	2	15	-	30	60	90	120	-	

[5] Only of Day 1 of each cycle in case of dose de-escalation
[6] All AEs will be reported till end of safety follow up (F/U) period or if the new anti-cancer treatment started during the safety F/U, only AEs suspected to be related to study treatment will be reported, until the end of safety follow up period.
[7] All SAEs will be reported till end of safety F/U period or if the new anti-cancer treatment started during the safety F/U, only SAEs suspected to be related to study treatment will be reported. Only study treatment related SAEs will be reported after the end of safety F/U, until the end of survival F/U.
[8] CCI .
[9] 30-, 60-, 90-, and 120-day safety follow up visits are required for all participants in all arms.
[10] CCI
[11] Assessments need not be repeated at cycle 1 day 1 if performed at screening within 7 days of first dose of study treatment

Table 8-3 Assessment Schedule, Expansion part

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Informed consent	X															
IRT Screening (after ICF signature)	X															
Demography	X															
Inclusion / Exclusion criteria	X															
Medical history/current medical conditions	X															

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Diagnosis and Extent of cancer (including MSI/dMMR (mandatory, local), BRAFV600 status (if applicable), RAS mutation status – (mandatory, local); DPD enzyme and UGT1A1 if applicable (local))	X															
Prior antineoplastic therapy (meds, surgery, radiation)	30 days prior to initiation of study treatment															

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Prior/concomitant medications/procedures and significant non-drug therapies[1]	X	continuous									X	X	X	X		
Concomitant antineoplastic radiotherapy[2]		continuous									X	X	X	X		
HBV, Hepatitis C Test	X															
HIV screen (mandatory, if required by local guidelines)	S															
IRT Enrollment		X														
Physical Examination	S[11]	S			S		S				S	S	S	S		
Serum pregnancy (WOCBP)[3]	within 72 hours before dosing									X						
Urine pregnancy (WOCBP)[3]		S			S		S				S	S	S	S		

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
FSH (local and if applicable)	S															
Vital Signs	X[11]	X		X	X	X	X			X	X					
Weight	X[11]	X			X		X				X					
Height	X															
Performance status (ECOG)	X[11]	X		X	X	X	X			X	X					
Hematology	X[11]	X		X	X	X	X		X	X	X	X	X	X		
Biochemistry	X[11]	X		X	X	X	X		X	X	X	X	X	X		
HbA1c (Glycated hemoglobin)	X						C3D1 then every 3rd cycle (C6D1, C9D1.) and as clinically indicated			X			X			
Urinalysis	X[11]	X			X		X			X	X	X	X	X		

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Eye examination including visual acuity and signs of intraocular inflammation (i.e; uveitis) (For investigational arm #2 only)	X (for arm 1 and arm 2 in case of concurrent randmozation)	X			X		X			X						
Cardiac Enzymes (Troponin-I, NTproBNP)	X						C3D1 then every 3rd cycle (C6D1, C9D1.) and as clinically indicated				X			X		
Troponin-I (For investigational arm #2 only)		X			X		X									
Thyroid Panel	X	if clinically indicated								if clinically indicated	if clinically indicated					

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Coagulation	X[11]	As clinically indicated and before any protocol defined biopsies								As clinically indicated and before any protocol defined biopsies	X	X	X	X		
CCI																
Tumor marker CA-19-9, CEA	X						Every 8 weeks (C3D1, C5D1, etc.) until week 52, then every 12 weeks								X	
Tumor Evaluation using RECIST 1.1 (all participants), iRECIST (investigational arm #2) (CT or MRI of Chest, abdomen, pelvis I)[4]	X (arm 1 and 2 in case of concurrent randomization)						Every 8 weeks (C3D1, C5D1, etc.) until week 52, then every 12 weeks			X					X	

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Brain CT or MRI[4]	if clinically indicated	if clinically indicated								if clinically indicated					if clinically indicated	
Whole body bone scan[4]	if clinically indicated	if clinically indicated								if clinically indicated					If clinically indicated	
Localized bone CT, MRI or X-ray[4]	if clinically indicated	if clinically indicated								if clinically indicated					if clinically indicated	
CT/ MRI of other metastatic sites[4]	if clinically indicated	if clinically indicated								if clinically indicated					if clinically indicated	
NIS793 administration (for participants on NIS793)[5]		X		X	X	X	D1 and 15 of C3 and every subsequent cycle		X							
Tislelizumab administration (for participants in investigational arm #2 only)		X			X		X									
5-Fluorouracil (5-FU) administration		X		X	X	X	D1 and 15 of C3 and every subsequent cycle		X							

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Leucovorin (folinic acid) (or levoleucovorin) administration		X		X	X	X	D1 and 15 of C3 and every subsequent cycle		X							
Irinotecan administration (for participants on FOLFIRI)		X		X	X	X	D1 and 15 of C3 and every subsequent cycle		X							
Oxaliplatin administration (for participants on mFOLFOX6)		X		X	X	X	D1 and 15 of C3 and every subsequent cycle		X							
Bevacizumab administration		X		X	X	X	D1 and 15 of C3 and every subsequent cycle		X							
Adverse Events[6]	X	X														
Serious Adverse Events[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Antineoplastic therapies since discontinuation										X	X	X	X	X	X	X
ECG (12-lead)		X	if clinically indicated				if clinically indicated									
Echocardiogram		X	if clinically indicated				if clinically indicated									
CCI																

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
[redacted]																
NIS793 PK sampling[8]		X		X			Day 1 of C3, C6, C12, C18, C24		C3D15	X		X	X			
NIS793 pharmacodynamic/Total TGFβ1 sampling[8]		X		X			Day 1 of C3, C6, C12, C18, C24		C3D15	X		X	X			
NIS793 immunogenicity sampling[8]		X		X			Day 1 of C3, C6, C12, C18, C24		C3D15	X		X	X			
Tislelizumab PK sampling[8]		X	X	X	X		Day 1 of C3, C4, C6, 12, C18, 24	C3D2	C3D15	X				X		

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
Tislelizumab immunogenicity sampling[8]		X			X		Day 1 of C3, C4, C6, C12, C18, C24			X				X		

[redacted]

Period	**Screening**	**28 days Treatment Cycle**								**End of treatment**	**Safety follow-up[9]**				**Post treatment efficacy follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3 (and subsequent cycles)**									
Visit Name	**Screening**	**Cycle 1**			**Cycle 2**		**Cycle 3 and subsequent cycles**	**Cycle 3**		**End of treatment (EOT)**	**30 days**	**60 days**	**90 days**	**120 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**15**	**1**	**2**	**15**	**-**	**30**	**60**	**90**	**120**	**-**	
[redacted]																
IRT Discontinuation										X						
Survival follow up																X
Disposition	X									X					X	

Period	Screening	28 days Treatment Cycle								End of treatment	Safety follow-up[9]				Post treatment efficacy follow-up	Survival Follow-up
Cycle		Cycle 1			Cycle 2		Cycle 3 (and subsequent cycles)									
Visit Name	Screening	Cycle 1			Cycle 2		Cycle 3 and subsequent cycles	Cycle 3		End of treatment (EOT)	30 days	60 days	90 days	120 days	Post treatment efficacy follow-up	Survival follow-up (every 12 weeks)
Days	-28 to -1	1	2	15	1	15	1	2	15	-	30	60	90	120	-	

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] From 30 days prior to start of study treatment until end of safety follow-up or start of new anti-neoplastic (ANP) medication, whichever is sooner. If new ANP medication is started then only medications relative to the suspected AEs/SAEs that are reported should be collected
[2] From start of study treatment until end of safety follow-up or start of new ANP medication, whichever is sooner. If new ANP medication is started then only medications relative to the suspected AEs/SAEs that are reported should be collected
[3] For women with child bearing potential status confirmed. Refer to Section 8.4 for further details
[4] Refer to Table 8-5 for further details on efficacy assessments. EOT imaging assessments will be done for participants without prior documented disease progression based on RECIST 1.1 (for participants in investigational arm #1 and the control arm) and using RECIST 1.1 and iRECIST (for participants in investigational arm #2) who do not enter the efficacy follow-up phase, provided the last imaging assessment was not conducted within 30 days prior to the end of study treatment.
[5] Only of Day 1 of each cycle in case of dose de-escalation
[6] All AEs will be reported till end of safety follow up (F/U) period or if the new anti-cancer treatment started during the safety F/U, only AEs suspected to be related to study treatment will be reported, until the end of safety follow up period.
[7] All SAEs will be reported till end of safety F/U period or if the new anti-cancer treatment started during the safety F/U, only SAEs suspected to be related to study treatment will be reported. Only study treatment related SAEs will be reported after the end of safety F/U, until the end of survival F/U.
[8] CCI
[9] 30-, 60-, 90-, and 120-day safety follow up visits are required for all participants.
[10] CCI
[11] Assessments need not be repeated at cycle 1 day 1 if performed at screening within 7 days of first dose of study treatment

Table 8-4 Assessment Schedule, post protocol amendment 4 implementation

Period	**28 days Treatment Cycle**						**End of treatment**	**Safety follow-up[7]**
Cycle	**Cycle 1**		**Cycle 2**		**Cycle 3 (and subsequent cycles)**			
Visit Name	**Cycle 1**		**Cycle 2**		**Cycle 3**		**End of treatment (EOT)**	**30 days**
Days	**1**	**15**	**1**	**15**	**1**	**15**	**-**	**30**
Informed consent	X							
Prior/concomitant medications/procedures and significant non-drug therapies[1]	continuous							
Concomitant antineoplastic radiotherapy[2]	continuous							
Physical Examination	S[8]		S		S			S
Serum pregnancy (WOCBP)[3]							S	
Urine pregnancy (WOCBP)[3]	S		S		S			S
Vital Signs	X	X	X	X	X		X	X
Weight	X		X		X			X
Performance status (ECOG)	X	X	X	X	X		X	X
Hematology	X	X	X	X	X	X	X	X
Biochemistry	X	X	X	X	X	X	X	X
HbA1c (Glycated hemoglobin)	if clinically indicated (S)							
Urinalysis	As per local label or as clinically indicated (S)							
Eye examination including visual acuity and signs of intraocular inflammation (i.e; uveitis) (For investigational arm #2 only)	if clinically indicated (S)							
Cardiac Enzymes (Troponin-I, NTproBNP)[9]	if clinically indicated (S)							

Period	**28 days Treatment Cycle**						**End of treatment**	**Safety follow-up[7]**
Cycle	**Cycle 1**		**Cycle 2**		**Cycle 3 (and subsequent cycles)**			
Visit Name	**Cycle 1**		**Cycle 2**		**Cycle 3**		**End of treatment (EOT)**	**30 days**
Days	**1**	**15**	**1**	**15**	**1**	**15**	**-**	**30**
Troponin-I (For investigational arm #2 only)[9]	if clinically indicated (S)							
Thyroid Panel	if clinically indicated (S)							
Coagulation	if clinically indicated (S)							
CCI								
Tumor marker CA-19-9, CEA	if clinically indicated							
Tumor Evaluation using RECIST 1.1 (all participants)					Every 8 weeks (C3D1, C5D1, etc.) until week 52, then every 12 weeks		X	
Brain CT or MRI[4]	if clinically indicated							
Whole body bone scan[4]	if clinically indicated							
Localized bone CT, MRI or X-ray[4]	if clinically indicated							
CT/ MRI of other metastatic sites[4]	if clinically indicated							
5-Fluorouracil (5-FU) administration	X	X	X	X	D1 and 15 of C3 and every subsequent cycle	X		
Leucovorin (folinic acid) (or levoleucovorin) administration	X	X	X	X	D1 and 15 of C3 and every subsequent cycle	X		
Irinotecan administration (for participants on FOLFIRI)	X	X	X	X	D1 and 15 of C3 and every subsequent cycle	X		

Period	**28 days Treatment Cycle**						**End of treatment**	**Safety follow-up[7]**
Cycle	**Cycle 1**		**Cycle 2**		**Cycle 3 (and subsequent cycles)**			
Visit Name	**Cycle 1**		**Cycle 2**		**Cycle 3**		**End of treatment (EOT)**	**30 days**
Days	**1**	**15**	**1**	**15**	**1**	**15**	**-**	**30**
Oxaliplatin administration (for participants on mFOLFOX6)	X	X	X	X	D1 and 15 of C3 and every subsequent cycle	X		
Bevacizumab administration	X	X	X	X	D1 and 15 of C3 and every subsequent cycle	X		
Adverse Events[5]	X							
Serious Adverse Events[6]	X							
Antineoplastic therapies since discontinuation							X	X
ECG (12-lead)	if clinically indicated (S)							
Echocardiogram	if clinically indicated (S)							
IRT Discontinuation							X	
Disposition							X	

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] From 30 days prior to start of study treatment until end of safety follow-up or start of new anti-neoplastic (ANP) medication, whichever is sooner. If new ANP medication is started then only medications relative to the suspected AEs/SAEs that are reported should be collected
[2] From start of study treatment until end of safety follow-up or start of new ANP medication, whichever is sooner. If new ANP medication is started then only medications relative to the suspected AEs/SAEs that are reported should be collected
[3] For women with child bearing potential status confirmed. Refer to Section 8.4 for further details
[4] Refer to Table 8-5 for further details on efficacy assessments. EOT imaging assessments will be done for participants without prior documented disease progression based on RECIST 1.1 , provided the last imaging assessment was not conducted within 30 days prior to the end of study treatment.
[5] All AEs will be reported till end of safety follow up (F/U) period or if the new anti-cancer treatment started during the safety F/U, only AEs suspected to be related to study treatment will be reported, until the end of safety follow up period.
[6] All SAEs will be reported till end of safety F/U period or if the new anti-cancer treatment started during the safety F/U, only SAEs suspected to be related to study treatment will be reported. Only study treatment related SAEs will be reported after the end of safety F/U.
[7] A 30-day safety follow up visit is required for all participants.

Period	**28 days Treatment Cycle**						**End of treatment**	**Safety follow-up[7]**
Cycle	**Cycle 1**		**Cycle 2**		**Cycle 3 (and subsequent cycles)**			
Visit Name	**Cycle 1**		**Cycle 2**		**Cycle 3**		**End of treatment (EOT)**	**30 days**
Days	**1**	**15**	**1**	**15**	**1**	**15**	**-**	**30**

[8] Assessments need not be repeated at cycle 1 day 1 if performed at screening within 7 days of first dose of study treatment
[9] If Troponin-I test is not available, Troponin-T can be performed. However, for each participant same enzyme test should be performed throughout the study.

8.1 Screening

The study IRB/IEC approved informed consent form must be signed and dated before any screening procedures are performed, except for laboratory and radiological evaluations, which were performed as part of the participant's clinical standard of care within the acceptable screening window.Participants will be evaluated against study inclusion and exclusion criteria and safety assessments (refer to Table 8-2 for Safety run-in part, refer to Table 8-3 for Expansion part). Screening assessments must be repeated if performed outside of the specified screening window (Table 8-2 for Safety run-in part, Table 8-3 for Expansion part). Participants must meet **all** inclusion and **none** of the exclusion criteria at screening in order to be eligible for the study.

Laboratory test result(s) or symptoms that do not satisfy the eligibility criteria may be repeated or treated during the screening visit window. In the event that the repeated laboratory test(s) cannot be performed within 21 days, from the original screening visit, or do not meet the eligibility criteria, or other eligibility criteria have changed and are not met anymore, the participant is considered a screening failure.

Re-screening of a participant who has failed screening may be allowed only once. In such cases, a new ICF must be signed; new participant ID will be assigned. All required screening assessments must be repeated if they do not meet the allowed time window for screening when the participant is re-screened for participation in the study. An individual participant can only be re-screened once for the study.

8.1.1 Eligibility screening

Following registering in the IRT for screening, participant 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.

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to start treatment in **Safety run-in part** or **Expansion part** will be considered as screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious AE during the screening period (see Section 10.1.3 for SAE reporting details). If the participant fails to be enrolled/ randomized, the Interactive Response Technology (IRT) must be notified within 2 days of the screen fail that the participant was not enrolled/ randomized.

Participants who are enrolled/ randomized and fail to start treatment, e.g., participants enrolled/ randomized in error, will not be considered screen failures but will be considered early terminators. The reason for early termination should be recorded on the appropriate Case Report Form (eCRF), and participants should be followed up for efficacy/PRO and survival.

CCI [redacted]

8.2 Participant demographics/other baseline characteristics

Participant demographics: full date (only if required and permitted) or year of birth or age, sex, race/predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. In addition, MSI status will be recorded.

Where possible, the diagnosis and not symptoms should be recorded. Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, we need to assess the diversity of the study population as required by Health Authorities.

Additional data to be collected on **participant characteristics** at screening include:

- Cancer characteristics including diagnosis, history, extent of cancer, prior anticancer treatments (medications, radiation, surgeries), date of progression prior to study entry
- Mutation information should also be recorded for MSI/dMMR and RAS; when available for BRAFV600; forDPD enzyme and UGT1A if applicable.
- Other assessments will be completed for the purpose of determining eligibility for inclusion in the study as reported in Table 8-2 and Table 8-3 (e.g. ECOG Performance Status, complete physical examination, vital signs, hematology, blood chemistry, coagulation, urinalysis, serum pregnancy test for all female participants). Vital signs must include at minimum: systolic and diastolic blood pressure, pulse measurement, respiratory rate, and body temperature.
- Prior and current concomitant medications and surgical and medical procedures: All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study (within 30 days prior to the first dose of study treatment) must be documented. See the protocol Section 6.2.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.
- Tumor imaging assessments: Refer to Table 8-5.

8.3 Efficacy

8.3.1 Efficacy assessment

Tumor response will be assessed locally by the Investigator according to:

- the Novartis guideline version 3.2 (Section 16.2) based on RECIST 1.1 (Eisenhauer et al 2009) for all participants in investigational arms #1, #2 and the control arm(s).
- the Novartis guidelines version 1.1 (Section 16.7) based on iRECIST (Seymour et al 2017) for all participants in investigational arm # 2 and for all participants in arms #1 and #2 at screening in case of concurrent randomization.

The imaging assessment collection plan is presented in Table 8-5 .

The local Investigator's assessment will be used for endpoint analysis and for treatment decision making.

Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. Central review of the imaging data may be performed, if deemed necessary.

Information regarding prior interventions (e.g., radiotherapy), pre-existing radiographic findings that mimic metastatic disease at baseline/screening and prior interventions should be transmitted to the imaging CRO via the Baseline Clinical Formalong with the baseline images. Sites must ensure the data entered on the form is consistent with the data entered in the clinical database.

Information regarding cytology results should be transmitted to the imaging CRO via the Cytology Form for all visits, when applicable. Sites must ensure the data entered on the form is consistent with the data entered in the clinical database.

CCI [redacted]

Table 8-5 Local Imaging Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/ Efficacy Follow-up
CT/MRI of the chest, abdomen and pelvis (with intravenous contrast enhancement)	Mandated	Mandated every 8 weeks (+/- 7 days) until week 52, then every 12 weeks (+/ - 7 days).
Brain MRI or CT	If clinically indicated	For brain lesions identified at Screening, follow the same schedule as CT/MRI of the chest, abdomen, and pelvis. Otherwise, if clinically indicated.
Whole body bone scan	If clinically indicated	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	For any bone lesions identified at Screening, follow the same schedule as CT/MRI of the chest, abdomen, and pelvis. Otherwise, if clinically indicated.
CT/MRI of other metastatic sites (eg. neck)	If clinically indicated	If lesions were documented at Screening, follow same schedule as CT/MRI of chest, abdomen, and pelvis. Otherwise, if clinically indicated.

8.3.1.1 Baseline Imaging Assessments

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

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

- Chest, abdomen, and pelvis CT or MRI
- Brain CT or MRI, if clinically indicated
- 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
- CT or MRI of other metastatic sites (e.g., neck), if clinically indicated

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.

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

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

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

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

8.3.1.2 Post-baseline imaging assessments

Imaging assessments as described in Table 8-5 should be performed at the timepoints specified using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 8-1, Table 8-2, and Table 8-3; refer to Table 8-4 post implementation of protocol amendment 4). Imaging assessments for response evaluation will be performed every 8 weeks (+/- 7 days) until week 52, then every 12 weeks (+/- 7 days) thereafter until disease progression, death, lost to follow-up or withdrawal of consent/opposition to use data/biological samples.

If treatment with tislelizumab (in investigational arm #2) is continued beyond disease progression as per RECIST 1.1 (Section 6.1.4.1), a follow-up scan after the initial immune unconfirmed progressive disease (iUPD) per iRECIST should be done within 4 to 8 weeks, then tumor assessments will continue using the same schedule as outlined above until immune confirmed PD (iCPD) by iRECIST as assessed by the Investigator, death, lost to follow-up, withdrawal of consent/opposition to use data/biological samples or until start of new anti-neoplastic therapy. For participants who discontinue NIS793 and/or tislelizumab without iCPD, continuation of tumor assessments until iCPD by iRECIST assessed by the Investigator, death, lost to follow-up, withdrawal of consent/opposition to use data/biological samples or start of new anti-neoplastic therapy is recommended.

Imaging assessments should be scheduled using the randomization/enrollment date as the reference date (not the date of the previous tumor assessment) and should be performed regardless of whether study treatment is temporarily withheld, or unscheduled assessments are performed.

Additional imaging assessments may be performed at any time during the study at the Investigator's discretion to support the efficacy evaluations for a participant, as necessary.

Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

Each lesion that is measured at baseline must be measured by the same method and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. If an 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 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, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (Section 16.2).

All study imaging (including any off-schedule imaging studies) should be submitted to the designated imaging CRO for quality control.

CCI [redacted]

8.3.1.3 End of treatment imaging assessments

At end of treatment, imaging assessments will be done for participants without prior documented disease progression based on RECIST 1.1 (for participants in investigational arm #1 and the control arm) and using RECIST 1.1 and iRECIST (for participants in investigational arm #2) who do not enter the efficacy follow-up phase, provided the last imaging assessment was not conducted within 30 days prior to the end of study treatment.

CCI [redacted]

8.3.1.4 Efficacy follow-up imaging assessments

All participants who discontinue study treatment **without** prior documented disease progression based on RECIST 1.1 (investigational arm #1, control arm) or iRECIST (investigational arm #2) as per the Investigator will continue these efficacy imaging assessments in the efficacy follow-up phase until documented disease progression by RECIST 1.1 (investigational arm #1) or immune confirmed PD by iRECIST (investigational arm #2) as per Investigator, until withdrawal of consent/opposition to use data/biological samples, pregnancy, lost to follow up, start of new anti-neoplastic therapy, or death.

CCI [redacted]

8.3.2 Survival Assessments

All participants will be followed for survival status every 12 weeks regardless of treatment discontinuation reason for 2 years or until death, lost to follow-up, withdrawal of consent/opposition to use data/biological samples, or end of study, which ever occurs earlier. Additional survival assessments may be performed outside the 12 weeks follow-up schedule if a survival update is required for an interim assessment to meet safety or regulatory needs. Survival information can be obtained via phone, and information will be documented in the source documents and appropriate eCRFs.

Information on all subsequent therapies received for mCRC, if any, after study treatment has been completed, will be collected (including start date, stop date, and date of progression if any).

CCI [redacted]

8.4 Safety

Safety assessments are specified below in (Table 8-6) with the assessment schedule detailing when each assessment is to be performed (Table 8-2 and Table 8-3; refer to Table 8-4 post implementation of protocol amendment 4).

For details on AE collection and reporting, refer to AE Section 10.

As per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 2 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

- If participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).
- If participants cannot visit the site for protocol specified safety lab assessments conducted through central labs, local lab collection may be used.

Table 8-6 Physical Examination, vital signs, height and weight

Assessment	Specification
Physical examination	Physical examination will be performed according to Table 8-2 and Table 8-3; refer to Table 8-4 post implementation of protocol amendment 4. At Screening and Cycle 1 Day 1 prior to treatment, a complete physical examination will be performed and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. After Cycle 1 Day 1 onwards, a focused physical examination will be performed (e.g. examination of general appearance, lymph nodes, lungs, abdomen, heart, and examination of additional organs and systems based on signs and symptoms). 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 appropriate eCRF that captures medical history. Significant new findings that begin or worsen after signing informed consent which meet the definition of an AE must be recorded as an AE.
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, respiratory rate, and body temperature. Vital signs assessments will be performed as per schedule in Table 8-2 and Table 8-3; refer to Table 8-4 post implementation of protocol amendment 4.
Height and weight	Height in centimeters (cm or inch) and body weight (to the nearest 0.1 kilogram (kg) or lbs) in indoor clothing, but without shoes) will be measured as specified in Table 8-2 and Table 8-3; refer to Table 8-4 post implementation of protocol amendment 4.

Performance status:

The performance status will be assessed according to the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale as specified in Table 8-7 following the schedule given in Table 8-2 and Table 8-3.

CCI [redacted]

Table 8-7 Performance status

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

8.4.1 Laboratory evaluations

Central safety laboratories will be used for the analysis of scheduled hematology, biochemistry, and other blood specimens (Table 8-8). The laboratory evaluations should be assessed on the actual scheduled day, even if study drug is being withheld. The time windows for laboratory evaluations correspond to the visit time windows for each visit (Table 8-1). Laboratory assessments (hematology, biochemistry, coagulation, urinalysis) done ≤ 7 days of first dose of study treatment are permitted to be used as Cycle 1 Day 1 labs and do not need to be repeated.

More frequent time points should be added as deemed necessary per the Investigator's judgment to make sure toxicity profile is sufficiently characterized and dose modifications performed to safeguard the safety of the participant. Additional results from unscheduled laboratory evaluations should be recorded on the appropriate eCRF.

Laboratory values obtained during the screening period from the central laboratory will be used to assess eligibility. However, the site does not need to wait for the results of centrally-analyzed laboratory assessments when an immediate clinical decision needs to be made (e.g., study drug initiation, study drug interruption, re-initiation, and/or termination). In those cases, local laboratory testing may be performed. The Investigator is responsible for reviewing all laboratory reports for participants in the study and evaluating any abnormalities for clinical significance. For visits with safety laboratory assessment only, a participant on-site visit may not be required, as per the Investigator's discretion, and local laboratory testing may be performed.

If participants cannot visit the site for safety lab assessments conducted through central labs, local lab collection may be used during a Public Health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits.

Dipstick urinalysis (macroscopic panel) will be performed at the site (unless local institution policies dictate otherwise), and in the case of any out-of-range parameters, a urine sample will be sent to central laboratory for further analysis (microscopic panel and urine chemistry).

Details on the collection, sample shipment, and reporting of results by the central laboratory are provided in the Central Laboratory Manual and Flowchart.

If at any time a participant has laboratory parameters obtained from a local laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory. The results of the local laboratory will be recorded in the eCRF if any the following criteria are met:

- A treatment decision was made based on the local results, **or**
- There are no concomitant central results available, **or**
- Local lab results document an AE not reported by the central lab, **or**
- Local lab results document an AE where the severity is worse than the one reported by the central lab.

At any time during the study, up to safety follow-up, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the adverse event eCRF page. The severity of laboratory data will be graded using the Common Terminology Criteria for Adverse events (CTCAE v5.0). Additional analyses are left to the discretion of the Investigator.

CCI [redacted]

Table 8-8 Laboratory Assessment

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Erythrocytes, Leukocytes, Erythrocyte Cell Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other (absolute value preferred, %s are acceptable)
Biochemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphate, Sodium, Potassium, Serum Creatinine or calculated creatinine clearance (by using Cockcroft-Gault equation), Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Serum Bilirubin, Urea Nitrogen or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting), HbA1c (Glycated hemoglobin)
Cardiac Enzymes	Troponin I (if troponin-I test is not available, troponin-T can be performed; however, for each participant the same enzyme test should be performed throughout the study) and NT-proBNP (N-terminal-pro-B-type Natriuretic Peptide)
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Occult Blood, Macroscopic Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) If dipstick is abnormal, Microscopic Panel (Erythrocytes, Leukocytes, Casts, Crystals, Bacteria, Epithelial cells), and Urine Chemistry analysis of protein, creatinine, and urine protein/creatinine ratio (UPCR)
Coagulation	Prothrombin time (PT), International normalized ratio (INR), Activated partial Thromboplastin Time (APTT)
Thyroid	Triiodothyronine Free, Thyroxine Free Thyrotropin (TSH)
Hepatitis markers	Hepatitis B Virus DNA, Hepatitis B Virus Surface Antigen, Hepatitis B Virus Surface Antibody, Hepatitis B Virus Core Antibody, anti-HCV, Hepatitis C Virus RNA (baseline)
CCI [redacted]	[redacted]
Additional tests	CA 19-9, CEA
Pregnancy Test	At screening visit and EOT visit, serum pregnancy test Day 1 of every cycle beginning with Cycle 1 and Day 1 of each safety follow-up visit, urine pregnancy test If local requirements dictate otherwise, local regulations should be followed
Local tests	FSH if required (Section 8.4.4)

8.4.1.1 CCI [redacted]

[redacted]

8.4.2 Electrocardiogram (ECG)

ECGs will be locally collected and evaluated. Local single 12-lead ECGs should be recorded prior to the dose administration, after the participant has been resting for 5-10 min prior to the timepoints indicated in Table 8-2 and Table 8-3; refer to Table 8-4 post implementation of protocol amendment 4).

Additional, unscheduled, safety ECGs may be repeated at the discretion of the Investigator at any time during the study and as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study. Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate. Interpretation of the tracing must be made by a qualified physician and documented in the appropriate eCRF.

Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site. Clinically significant ECG abnormalities present at screening should be reported on the appropriate eCRF. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

The original ECGs on non-heat sensitive paper and a certified copy on non-heat sensitive paper, appropriately signed, must be archived at the study site.

8.4.2.1 Cardiac imaging - echocardiogram

Cardiac imaging (echocardiogram) will be performed at screening to determine cardiac function and morphology at baseline. Thereafter, echocardiogram will be performed if clinically indicated and/ or if cardiac enzymes are elevated: ≥ 2xULN (if normal at screening), or ≥ 2x baseline (if baseline value was elevated). Other methods for cardiac imaging could be used in case echocardiogram is not available in the center (for example, cardiac MRI or CT scan) (Refer to Table 8-2 and Table 8-3; refer to Table 8-4 post implentation of protocol amendment 4).

8.4.2.2 Cardiac enzymes

Cardiac specific enzymes, Troponin I and NTproBNP, will be performed for all patients at screening, C3D1 and day 1 of every third cycle during treatment duration or as clinically indicated, and at the 30-day safety follow-up visit after the last dose of study treatment (Table 8-2 and Table 8-3; refer to Table 8-4 post implementation of protocol amendment 4).

Although immune-related myocarditis is a rare complication of immune checkpoint inhibitors, troponin I will be assessed more frequently for all patients receiving tislelizumab at day 1 of every cycle to protect study participants (see Appendix 6 for guidelines for management of suspected immune-related myocarditis).

If Troponin-I test is not available, Troponin-T can be performed. However, for each participant the same enzyme test should be performed throughout the study.

CCI [redacted]

8.4.3 Ophthalmological assessment

Investigators should perform routine monitoring of visual acuity and signs of intraocular inflammation (i.e., uveitis) at screening, during study treatmentand at EOT. Assessments performed as SOC prior to obtaining written informed consent and within 28 days of randomization or first dose of study drug are acceptable as baseline (screeninng) assessments. Participants with ocular symptoms will be referred to and assesed by an opthalmologist, using slit lamp biomicroscopy as per practice by the assessing physician.

CCI [redacted]

8.4.4 Pregnancy and assessment of fertility

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner.

Pregnancy tests will be performed for women of childbearing potential. All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

A serum pregnancy test must be performed at screening and at EOT. At screening, a serum pregnancy test must be performed within 72 hours before the first dose of study treatment. A urine pregnancy test must be performed at every first visit of each cycle and during safety follow-up.

If the participant is unable to visit the clinic during the safety follow-up period, a pregnancy test may be performed at home or at a local doctor's office at each of the safety follow-up timepoints described above, and the results will be communicated to the site staff. These follow-up pregnancy tests will be recorded in the source documentation, not in the CRF.

If a positive pregnancy test is obtained in between study visits, the participant must immediately notify the Investigator. Male participants must notify the Investigator in case their partner becomes pregnant during the treatment period (Section 10.1.4).

In case of a positive urine pregnancy test, additional tests must be performed to confirm pregnancy and if confirmed, it requires immediate discontinuation of study treatment. See Section 10.1.4 for pregnancy reporting.

Local pregnancy test and associated results will not be collected on CRF.

If participants cannot visit the site to have serum pregnancy tests at the End of Treatment visit and 30-Day Safety follow-up visit during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

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Assessments of Fertility:

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

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile

In the absence of the above medical documentation, Follicle Stimulating Hormone (FSH) testing (local) is required of any female participant regardless of reported reproductive/ menopausal status at screening/ baseline.

8.5 Additional assessments




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8.5.2 Pharmacokinetics

In the investigational arm #1 (NIS793+SOC) and control arm (SOC), to assess PK, PD (TGFß-1), and immunogenicity (IG) of NIS793; PK, IG of bevacizumab; and PK of irinotecan, blood samples will be collected from participants in the safety run-in part and expansion part (Table 8-9).To assess PK, PD, and IG of NIS793, blood samples will be collected from all participants in the safety run-in part and expansion part to determine serum level of NIS793, total TGF-β1, and anti-NIS793 antibody, respectively.



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In the investigational arm #2 (NIS793+tislelizumab+SOC), PK and IG samples will be collected from participants in the Safety run-in and Expansion parts. Tislelizumab PK and IG samples will not be collected if end of safety follow-up visit (120 days following the last dose of study treatment) is performed via phone call. Time for collection of post-dose PK samples for tislelizumab is relative to the end of infusion of tislelizumab. All participants who have evaluable concentration data will be included in the PK data analysis. PK parameters will be determined using non-compartmental analysis (NCA) and/or population pharmacokinetic method(s) for NIS793. PK parameters such as those listed in Section 12.6.2.1 will be estimated and reported, when applicable. PK samples will be collected at the visits defined in the Assessment Schedule (Table 8-2 and Table 8-3; refer to Table 8-4 post implementation of protocol amendment 4). Refer to instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment.

The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

As per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, depending on local regulations and operational capabilities, visits by site staff/ home nursing staff for Pharmacokinetic sample collection can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

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8.5.2.1 Pharmacokinetic blood collection and handling

Refer to the study laboratory manual for detailed instructions for the collection, handling, and shipment on PK, PD, and IG samples.

On days and timepoints when PK/PD/IG, biochemistry or other blood sampling are to be performed in parallel, the PK/PD/IG samples must be drawn first. For post dose or end of infusion PK/PD samples, only the time window specified in the blood collection log tables is allowed, while other pre-dose PK/PD/IG samples may be obtained within 1 day from the scheduled date. Blood samples are to be collected from the arm contra-lateral to the infusion site. Alternatively, the infusion site will have to be flushed with 10 mL of saline.

All the blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein in accordance with the assessment schedule and instructional guidelines. At the specified timepoints described in Table 8-9, blood draws in the volume specified will be collected.

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On a day of PK collection and on a day of previous administration, the exact date and time of dosing, the date the sample was taken, and the actual time of sampling must be entered on the appropriate eCRF pages.

IG samples associated with NIS793, bevacizumab and tislelizumab are to be collected together with PK samples.

If needed, study drug administration and PK, PD, IG collections may be split over 2 days i.e. investigational drug(s) on day 1 and SOC chemotherapy on day 2. In this case, all PK, PD, IG samples must be collected at their designated times (i.e., related to the administration of the respective drug, e.g., 6 h post dose time point for irinotecan has to be sampled 6hs after FOLFIRI administration) as described in Table 8-9. Pre-dose samples for all study drugs have to be collected prior to NIS793 administration.

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Table 8-9 Pharmacokinetic, Pharmacodynamic, Immunogenicity blood collection log NIS793, bevacizumab, irinotecan and tislelizumab





8.5.2.2 Analytical method

8.5.2.2.1 NIS793

NIS793 will be determined in human serum using a validated enzyme-linked immunosorbent assay (ELISA).

Total TGF-β1 will be determined in human serum using a validated enhanced electrochemiluminescent assay (ECLIA).

A validated assay will be used to assess the anti-drug antibodies against NIS793.

The detailed method descriptions of all the assays will be included in the corresponding bioanalytical data report. All concentrations below the lower limit of quantification (LLOQ) or missing data will be labeled as such in the concentration data listing.





8.5.2.2.4 Tislelizumab

Tislelizumab concentrations in human serum will be determined using a validated ELISA.

A validated assay will be used to assess the anti-drug antibodies against tislelizumab.

The detailed method descriptions of all the assays will be included in the corresponding bioanalytical data report. All concentrations below the LLOQ or missing data will be labelled as such in the concentration data listing.

8.5.3 Biomarkers

Biomarker analyses will be used to investigate the effect of NIS793 with or without tislelizumab in combination with SOC anti-cancer therapy and SOC anti-cancer therapy alone CCI

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Table 8-10 Biomarker sample collection plan

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8.5.3.1 Biomarker assessments in tumor sample

8.5.3.1.1 Mandatory tumor requirement

For all participants in the study, archival or newly acquired biopsies (preferred) are required at screening. Archival samples must be obtained ≤ 12 months before the screening or a fresh tumor tissue biopsy should be obtained during the screening.

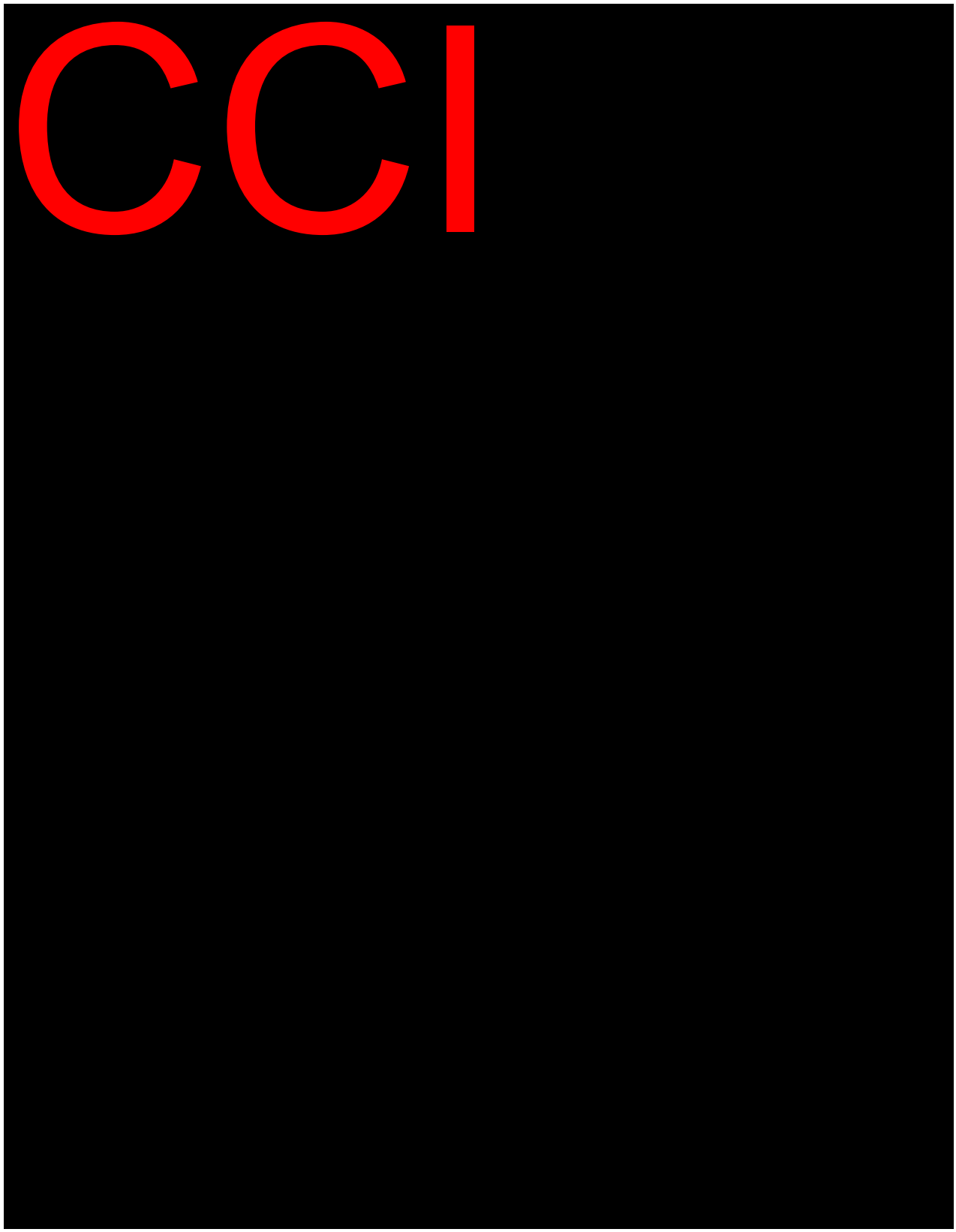
A minimum of a FFPE tissue block or 20 slides should be submitted in order to assess tumor biomarkers related to NIS793. If slides are being provided, only freshly cut slides are acceptable. Slide cut date must be provided on the requisition form. Bone is excluded as organ for biopsy location. Fine needle aspirates are not acceptable as sample types.

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8.5.3.2 Biomarker assessments in blood samples

All participants in the study are asked to provide mandatory plasma samples, collected at specific time points during treatment and at the time of disease progression, prior to initiation of new anti-cancer therapies. CCI


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9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the participant or the Investigator.

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

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which continued study participation might result in a safety risk to the participant
- Progressive disease per RECIST 1.1 as per Investigator's assessment.
- Death
- Any laboratory abnormalities that in the judgment of the Investigator, taking into consideration the participant’s overall status, prevents the participant from continuing participation in the study.

In some circumstances, participants may be allowed to continue to receive study treatment beyond disease progression per RECIST 1.1 criteria (Section 6.1.4.1). These participants will continue assessments as outlined in Section 8 and will complete the EOT visit only after permanent discontinuation from study treatment.

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

EOT visit must be scheduled within 7 days after decision to discontinue study treatment. The Investigator must also contact IRT to register the participant's discontinuation from study

treatment. Tumor assessments do not need to be repeated if performed within 30 days prior to last study treatment administration.

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (Table 8-2 and Table 8-3; refer to Table 8-4 post implementation of protocol amendment 4). If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

If a participant withdraws from treatment at a study visit, EOT assessments that are already part of that scheduled visit do not need to be repeated.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The Investigator must also contact the IRT to register the participant's discontinuation from study treatment.

For participants who discontinue from study treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples, the participant should enter the efficacy follow-up phase (Section 8.3.1.4). Tumor assessments must continue to be performed every 8 weeks until 52 weeks then every 12 weeks until documented disease progression per RECIST 1.1 as per Investigator assessment, death, lost to follow-up, discontinuation from study, or withdrawal of consent/opposition to use data/biological samples.

CCI [redacted]

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment and further protocol-required assessments or follow-up, for any reason.

9.1.3 Lost to follow-up

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

9.2 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use data and/or biological samples occurs when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be made as per local regulations (e.g., in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g., to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms. In this situation, the Investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/ exercise privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation. Study treatment must be discontinued, and no further assessments conducted.

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

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/ exercise data privacy rights should be made as detailed in the assessment table (Table 8-2 and Table 8-3; refer to Table 8-4 post implementation of protocol amendment 4).

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.3 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

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

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment. Investigator must contact the participant, the participant should stop taking study treatment, the participant should come in for a final visit, and should complete the safety follow up period. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or Novartis depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.4 Study completion and post-study treatment

Following the recommendation to stop administration of NIS793 and tislelizumab, the DMC encouraged continuing the administration of SOC therapy to all participants as per Investigator's assessment.

Participants continuing to derive clinical benefit from the SOC therapy in the opinion of the Investigator may continue such treatment outside of the study through an alternative setting at the Investigator's discretion according to local clinical practice.

The study will be considered complete when each participant discontinued the study, transitioned off to alternative treatments, died, withdrew consent, or is lost to follow-up, whichever occurs earliest or, in the event of an early study termination.

Post implementation of protocol amendment 4, the efficacy follow-up phase and survival follow-up phase will not be carried out.

Available data from all participants up to the final analysis cut-off date will be analyzed and summarized in a final CSR.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

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

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

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

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

1. Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a

lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant

3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment

All AEs must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/permanently discontinued

6. Its outcome (i.e., recovery status or whether it was fatal)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 AEs 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 participant.

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

AEs monitoring should be continued for at least 30 days after last dose of study treatment.

During the safety follow-up period, if a new post-treatment antineoplastic therapy is initiated only adverse events suspected to be related to study treatment will be collected in the Adverse Events CRF.

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 1.1 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.

AEs separate from the progression of malignancy (e.g., 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's Brochure (IB).

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

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10.1.1.1 Adverse events of special interest

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

Adverse events of special interest are defined on the basis of an ongoing review of the safety data.

Based upon the available safety information from NIS793 clinical development programs, the available preclinical data, known mechanism of action of the drug, and potential overlapping toxicity of all combination drugs, the following adverse events are considered of special interest in this trial population:

- Renal toxicity/serum creatinine ≥ Grade 2
- Neutropenia ≥ Grade3
- Febrile neutropenia
- Immunogenicity/Hypersensitivity reactions ≥ Grade3
- Infusion reactions ≥ Grade3
- Diarrhea ≥ Grade3
- Hypertension ≥ Grade3
- Haemorrhage ≥ Grade3
- Cardiac disorder (valvulopathy , cardiomyopathy ≥ Grade3)
- Skin reactions ≥ Grade3
- Eyelid abnormality (≥ Grade 2)
- In addition, the potential immune-related AEs considered to be AESI include: endocrinopathies, colitis, skin reactions, hepatitis, nephritis, pneumonitis, and infusion reaction.

Details regarding these adverse events are provided in NIS793 and Tislelizumab Investigator's Brochures. Potential emergent new AEs will be monitored during the course of the study.

AESI for any other investigational drug will be included by protocol amendment.

10.1.2 Serious adverse events

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

- Fatal
- life-threatening

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

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

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

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

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

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

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and up to 30 days after the last administration of study treatment (30 days for all) must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (**Note:** If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the eSAE form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

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 immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (**Note:** If more stringent, local regulations regarding reporting timelines prevail). 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.

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

SAE collection starts at time of main study informed consent whether the participant is a screen failure or not.

During the post-treatment safety follow-up period, if a participant starts a post-treatment antineoplastic therapy, then only SAEs suspected to be related to study treatment will be reported.

Any SAEs experienced after the end of the safety follow-up should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

Treatment-emergent elevations in AST or ALT (>3x ULN) in combination with total bilirubin >2x ULN or jaundice in the absence of cholestasis (defined as ALP < 2 ULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law). For this reason, a potential Hy's Law case requires expedited reporting, and will be handled as a serious unexpected adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even

before all other possible causes of liver injury have been excluded). Reporting should include all available information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

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10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery. The newborn will be followed up for up to 12 months after the due date, in case of live birth.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

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

Treatment error type	Document in Dosing CRF (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 an SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections (Section 10.1.1 and Section 10.1.2).

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Section 16.1 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-11 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-22 and Table 16-33 Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation.

These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.

- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate (refer to the dose modification Section 6.6.4).
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment Section 9.1), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include: Investigations based on Investigator's discretion like serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.2.2 Renal safety monitoring

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
- Any one of the following:
  - Urine protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol, OR
  - New onset dipstick proteinuria ≥ 3+, OR
  - New onset dipstick hematuria ≥ 3+ (after excluding menstruation, UTI, metastasis to renal tract/kidney or trauma)

Abnormal renal event findings must be confirmed after ≥24 hours but ≤ 5 days after first assessment.

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the Investigator or designated trial staff.

10.2.3 Data Monitoring Committee

A Data Monitoring Committee (DMC) is a group of professionals, experienced in clinical care and/or clinical research, assembled to provide additional safety oversight to a clinical study.

This study will include a DMC 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 review at defined intervals the safety data as well as the efficacy data from interim PFS analysis and some secondary analyses of each randomized Expansion part. The DMC meeting will be held approximately every 6 months. Additional DMC reviews may be performed if considered appropriate by DMC. DMC will recommend to the sponsor whether to continue, modify or terminate a trial. Additional details on the conduct of interim PFS and some secondary analyses can be found in Section 12.7.

Additionally, members of the DMC will be invited to join the SRT as observers. 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.

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10.2.4 Steering Committee

The Steering Committee (SC) will be established comprising Investigators participating in the trial, i.e., not being members of the DMC and Novartis representatives from the Clinical Trial Team (CTT).

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.

11 Data Collection and Database management

11.1 Data collection

Designated Investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the 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 (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

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

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

11.2 Database management and quality control

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

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

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

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

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e., eSource DDE or eCRFs) with the Investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/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 participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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

12 Data analysis and statistical methods

This section describes the data analyses used for the study. Treatment arms refers to both investigational arms and the control arm. The primary analysis of efficacy will be specific for each treatment arm. The secondary analyses described are applicable to all treatment arms unless otherwise specified. Additional data analyses will be described for new treatment arms in a future protocol amendment if different from the description below. Data from participating centers in this protocol will be combined, so that an adequate number of participants will be available for analysis.

For each treatment arm, the study data will be analyzed and reported based on all participants' data of the safety run-in and expansion parts at completion of the study as part of the final analysis. A single final CSR, which will include all treatment arms, will be prepared.

Analysis of all primary, secondary, and exploratory objectives will be carried out, unless otherwise specified.

All summaries, listings, figures and analyses will be performed for all participants in the Safety Run-in part and Expansion part separately. All the analyses will be performed by dose level and

by investigational arm separately for SOC with modified FOLFOX6 and with FOLFIRI) for the safety run-in part and by treatment arms for the Expansion part, unless otherwise specified. Additional summaries by participant subgroups may be produced as relevant for selected endpoints.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, distributions (e.g., 25th and 75th percentiles) may also be presented.

Screen failure participants, as described in Section 8.1, and the reasons for not starting the study treatment will be reported in a listing but will not be included in any analyses.

Details of the statistical analysis and data reporting will be provided in the Statistical Analysis Plan (SAP). Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

CCI [redacted]

12.1 Analysis sets

12.1.1 Full Analysis Set

Safety run-in Part

For the safety run-in part, the Full Analysis Set (FAS) comprises all participants that received any study drug. According to the intent to treat principle, participants will be analyzed according to the treatment(s) received.

Expansion Part

The Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned by randomization or treatment received (if not randomized). According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure.

12.1.2 Safety Set

Safety run-in part

The Safety set includes all participants who received at least one dose of study treatment [i.e., at least one dose of any drug of the study treatment (including incomplete infusion)].

Expansion part

The Safety set includes all participants who received at least one dose of study treatment (i.e., at least one dose of any drug of the study treatment (including incomplete infusion)). Participants in the **Expansion part** will be analyzed according to treatment received, where treatment received is defined as:

- the randomized treatment assigned if it was received at least once, or
- the first treatment received if the randomized treatment was never received.

All safety endpoints will be analyzed based on the safety sets.

12.1.3 Dose-Determining Set

Safety Run-In part

The Dose Determining Set (DDS) consists of all participants in the **Safety run-in part of each investigational arm** who met the minimum exposure criterion and have sufficient safety evaluations after 1 cycle (i.e., 4 weeks) of treatment or experienced a DLT during the first cycle of treatment.

A participant is considered to have met the minimum exposure criterion if the participant meets the minimum exposure criterion and has sufficient safety evaluations or experienced a DLT during the first cycle (4 weeks) of dosing. For investigational arm #1 NIS793+SOC, the minimum exposure criterion is the planned doses of NIS793 (2 dosing for Q2W, or 1 dosing for Q4W) and at least 1 dosing for SOC anti-cancer therapy within the first treatment cycle (i.e., 4 weeks) of study treatment. For investigational arm #2 NIS793+tislelizumab+SOC, the minimum exposure criterion is the planned doses of NIS793 (2 dosing for Q2W, or 1 dosing for Q4W), the planned dose of tislelizumab (1 dosing for tislelizumab), and at least 1 dosing for SOC anti-cancer therapy within the first treatment cycle (i.e., 4 weeks) of study treatment. If the participant did not receive the planned dosages due to DLT, the participant will be considered as meeting the minimum exposure criterion. The planned dosage for NIS793 is 2100 mg Q2W or 2100 mg Q4W (only applicable in case of a lower dose arm in **Safety run-in part**). The planned dosage for tislelizumab is 300 mg Q4W. The planned dosages for FOLFIRI or modified FOLFOX6 + bevacizumab are shown below:

- FOLFIRI + bevacizumab is administered on days 1 and 15 of each 28-day cycle:
  - 5-Fluorouracil 400 mg/m^2 i.v. bolus followed by 2400 mg/m^2 as a 46-h continuous infusion
  - Leucovorin (folinic acid) 400 mg/m^2 i.v. (or levoleucovorin 200 mg/m^2 i.v., where substitution is permissible per local regulations)
  - Irinotecan 180 mg/m^2 i.v.
  - Bevacizumab 5 mg/kg
- Modified FOLFOX6 + bevacizumab is administered on days 1 and 15 of each 28-day cycle:
  - 5-Fluorouracil 400 mg/m^2 i.v. bolus followed by 2400 mg/m^2 as a 46-h continuous infusion
  - Leucovorin (folinic acid) 400 mg/m^2 i.v. (or levoleucovorin 200 mg/m^2 i.v., where substitution is permissible per local regulations)
  - Oxaliplatin 85 mg/m^2 i.v.
  - Bevacizumab 5 mg/kg

Participants who do not experience a DLT during the first 4 weeks of treatment are considered to have sufficient safety evaluations if they have been observed for 4 weeks following the first dose and are considered by the Safety Review Team (SRT) to have sufficient safety data in the CRF and source document to conclude that a DLT did not occur. SRT will consist of Novartis

personnel and the Investigators whose sites have enrolled participants in the safety run in part. Additionally, members of the DMC will be invited to join the SRT as observers.

12.1.4 Pharmacokinetic Analysis Set

Individual Pharmacokinetic analysis sets (PAS) will be provided for NIS793 (NIS-PAS) and tislelizumab (TSL-PAS). CCI [redacted]. Each of the PAS includes all participants who provide an evaluable PK sample for this specific PAS and if **all** of the following conditions are satisfied:

- Participant receives at least one dose (complete infusion) of the planned treatments
- Participant provides at least one valid concentration
- For pre-dose samples, have the sample collected before the next dose administration

Participants may be removed from PK analysis on an individual basis depending on the number of available blood samples. These participants will be identified and justified at the time of analysis. The definition of an evaluable PK blood sample will be further specified in the statistical analysis plan (SAP).

CCI [redacted]

12.1.5 Immunogenicity Analysis Set

The immunogenicity (IG) set for each agent, i.e., tislelizumab, NIS793 CCI [redacted] includes two parts: IG prevalence set and IG incidence set:

- The IG prevalence set includes all participants in the FAS with a determinant baseline IG sample or at least one determinant post-baseline IG sample.
- The IG incidence set includes all participants in the IG prevalence set with a determinant baseline IG sample and at least one determinant post-baseline IG sample.

The definition of a determinant sample will be specified in the SAP.

CCI [redacted]

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively for participants in the **Safety run-in part** using the Safety Set and by treatment arm for participants in the **Expansion part** using the FAS.

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

12.3 Treatments

Safety sets will be used for the analyses below.

The duration of exposure to study treatment will be summarized by means of descriptive statistics using the safety set.

The duration of exposure will also be presented for each study drug, 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).

The number of participants with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized by treatment arm 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 summarized by anatomical therapeutic chemical classification system (ATC) term and treatment arm.

12.4 Analysis of the primary endpoint(s)/estimand(s)

12.4.1 Definition of primary endpoint(s)

Safety run-in part

The primary endpoint for the safety run-in part of each investigational arm is incidence of Dose Limiting Toxicities (DLT) during first cycle (i.e, 28 days, or 4 weeks) of treatments for

Investigational arm #1:

- NIS793 and SOC anti-cancer therapy (modified FOLFOX6 + bevacizumab)
- NIS793 and SOC anti-cancer therapy (FOLFIRI + bevacizumab)

Investigational arm #2:

- NIS793, tislelizumab and SOC anti-cancer therapy (modified FOLFOX6 + bevacizumab)
- NIS793, tislelizumab and SOC anti-cancer therapy (FOLFIRI + bevacizumab)

Expansion part

The primary estimand for the expansion part for each investigational arm is defined as in Section 2.1. For the primary estimand, the endpoint PFS is defined as the time from the date of randomization to the date of the first documented disease progression according to RECIST 1.1, or death due to any cause. PFS will be assessed via local review according to RECIST 1.1. Censoring conventions (i.e., handling of missing values, censoring, and discontinuations) are provided in Section 12.4.4.

12.4.2 Statistical model, hypothesis, and method of analysis

Safety run-in part

The primary endpoint for the safety run-in part is the incidence of DLT during first cycle (i.e 28 days or 4 weeks).

The decision on dose tolerability will be based on the totality of all relevant data from the ongoing study and a review of safety data from during the DLT evaluation period. A Bayesian logistic regression model (BLRM) for combinations using the escalation with overdose control (EWOC) criterion to evaluate the risk of DLT will guide the decision. The details on the BLRM statistical model and hypothetical dose confirmation scenarios are located in Section 16.4.

The assessment of patient risks will be based on summaries of the posterior distribution of DLT rates for each dose level of the respective regimen. After each arm of participants, the posterior

distribution for the risk of DLT for new participants at doses regimen of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT for each dose regimen lies within the following intervals:

- Under-dosing: [0, 0.16]
- Targeted toxicity: [0.16, 0.33]
- Excessive toxicity: [0.33, 1]

Dosing regimen decisions are guided by the escalation with overdose control (EWOC) principle (Rogatko et al 2007).

The possibility of excessive toxicity is of interest in this study as the objective is to confirm the safety of the proposed dose regimen. A dosing regimen may only be used for newly enrolled participants if the risk of excessive toxicity (within the interval [0.33, 1]) at that dosing regimen is less than 25%.

DLTs will be listed, and their incidence summarized by primary system organ class, preferred term and worst grade (CTCAE v5.0). Listings and summaries will be based on the DDS.

Expansion part

The primary efficacy analysis is to compare investigational arm #1 vs control and also to compare investigational arm #2 vs control. The primary analysis will compare the investigational arm against all patients randomized to control arms combined. There will be no formal hypothesis testing, and only descriptive analysis will be carried out.

For each investigational arm, the primary comparison is for each investigational arm vs a combined control arm.

The primary analysis of each investigational arm was planned to be performed approximately 16 months after the last patient randomized to that investigational arm. After the implementation of protocol amendment 4, only one (final) analysis will be carried out at the completion of the study.

The operating characteristics based on this analysis time are presented in Section 12.8.

The primary efficacy variable, PFS, will be analyzed at final analysis. There will be no formal hypothesis testing, and only descriptive analysis will be carried out.

The PFS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group.

12.4.3 Handling of remaining intercurrent events of primary estimand

For the analysis of NIS793 + SoC (investigational arm #1) vs SoC (control arm), the handling strategies for two intercurrent events are explained in the following:

- Discontinuation of study treatment for any reason: all PFS events will be included in the analysis irrespective of the study treatment discontinuation reasons (treatment policy strategy).

- Any unforeseen intercurrent events (e.g., COVID-19 pandemic related events): All PFS events will be included in the analysis irrespective of any unforeseen intercurrent events (treatment policy strategy).
- The handling strategies is same as described above for the primary analysis of NIS793 + tislelizumab + SoC (investigational arm #2) vs SoC (control arm).

12.4.4 Handling of missing values not related to intercurrent event

Safety run-in part

Participants who are ineligible for the DDS will be excluded from the primary analysis of DLT although their data will be used for all remaining analyses. Other missing data will simply be noted as missing on appropriate tables/listings.

Expansion part

If a PFS event is observed after two or more missing or non-adequate tumor assessments, then PFS will be censored at the last adequate tumor assessment before the PFS event. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used (see RECIST 1.1 in Section 16.2).

PFS events observed after the use of the new anti-cancer therapy will not be censored in the primary analysis. Additional sensitivity analysis might be performed with PFS censored after the use of new anti-cancer therapy.

Clinical progression without objective radiological evidence will not be considered as documented disease progression. Participants should be followed for documented progression after discontinuation of treatment for such clinical progression.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR, or SD before an event or a censoring reason has occurred. If no post-baseline assessments are available (before an event or a censoring reason occurred), the date of treatment randomization will be used.

More details will be provided in the SAP.

12.4.5 Sensitivity analyses for primary endpoint/estimand

12.4.5.1 Sensitivity analyses for primary endpoint of randomization

CCI [redacted]

12.4.6 Supplementary analysis

CCI [redacted]

12.5 Analysis of secondary endpoints/estimands

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

For the safety run-in part, the secondary efficacy endpoints are below:

- Progression-free survival (PFS) by Investigator per RECIST 1.1
- Overall response rate (ORR), disease control rate (DCR), duration of response (DOR), and time to response (TTR) by Investigator assessment as per RECIST 1.1
- Overall survival (OS)

For the expansion part, the secondary efficacy endpoints are the following:

- Overall response rate (ORR), disease control rate (DCR), duration of response (DOR) and time to response (TTR) by Investigator assessment as per RECIST 1.1
- Overall survival (OS)

The following analyses will be performed based on local investigator assessment and on FAS unless otherwise specified.

Overall response rate (ORR)

ORR is defined as the proportion of participants with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) as per Investigator assessment as per RECIST 1.1.

ORR will be calculated based on the data from the FAS and the corresponding 95% confidence intervals based on the exact binomial distribution (Clopper and Pearson 1934) will be presented.

Disease Control Rate (DCR)

DCR is defined as the percentage of participants with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) or stable disease (SD) as per Investigator assessment as per RECIST 1.1.

DCR will be calculated based on the data from the FAS and the corresponding 95% confidence intervals based on the exact binomial distribution (Clopper and Pearson 1934) will be presented.

Duration of response (DOR)

DOR is defined as the time from the date of first documented response (CR or PR) to the first documented progression per RECIST 1.1 or death due to any cause. If a participant with a CR or PR has no progression or death, the participant is censored at the date of last adequate tumor assessment.

DOR will be analyzed based on FAS for participants with confirmed BOR of CR or PR. Median DOR, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. KM estimates for DOR proportions at specific timepoints, along with 95% CI (Kalbfleisch 2002) will also be provided.

Time to response (TTR)

TTR is the time from the date of randomization to the date of event defined as the first documented response (CR or PR) per RECIST 1.1. If a participant has no response, the participant is censored at the date of last adequate tumor assessment.

TTR will be summarized using the Kaplan-Meier (KM) method, based on FAS. Median TTR, with corresponding 95% CI, and 25th and 75th percentiles will be presented. KM estimates for TTR proportions at specific timepoints, along with 95% CI will also be provided.

Overall survival (OS)

OS is defined as the time from the date of randomization to date of death due to any cause. If a participant is not known to have died by the date of the cut-off, OS will be censored at the last date the participant was known to be alive.

OS will be summarized using the Kaplan-Meier (KM) method, based on FAS. Median OS with corresponding 95% CI, and 25th and 75th percentiles will be presented. KM estimates for OS proportions at specific timepoints, along with 95% CI will also be provided. There will be no formal hypothesis testing, and only descriptive analysis will be carried out.

12.5.2 Safety endpoints

For the safety run-in part, summary tables and listings will be presented by dose regimen and arm using the safety set. For the expansion part, all listings and tables will be presented by treatment group. For all safety analyses, the safety set will be used.

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

1. Pre-treatment period: from day of participant's first informed consent to the day before first administration of any study treatment.
2. On-treatment period: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date),
3. Post-treatment period: starting at day 30+1 after the last administration of study treatment in the combination arm.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g., change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. 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 30 days after last administration of NIS793 or tislelizumab. Further details will be included in the SAP.

CCI [redacted].

Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment.

The number (and proportion) of participants with adverse events of special interest will be summarized by treatment.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

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

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

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

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

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

Vital signs

All vital signs data will be summarized by treatment and visit/time.

12-lead ECG

1. PR, QRS, QT, QTcF, RR, Heart Rate intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted (locally).
2. Categorical Analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented.

All ECG data will be summarized by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be summarized by treatment group, participant, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

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

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

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

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

For laboratory tests where grades are defined by CTCAE version 5.0:

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

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

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

In addition to the above-mentioned tables and listings, other exploratory analyses might be specified in the analysis plan.

Tolerability

Tolerability of study drug will be assessed by summarizing the number of and reasons for dose delays/interruptions and dose reductions. Dose intensity will also be tabulated for each component of the study treatment.

12.5.3 Pharmacokinetics

All PK data analysis and / or PK summary statistics will be based on the NIS-PAS and TSL-PAS. Descriptive summary statistics of NIS793 and tislelizumab concentration data will be provided by treatment and visit/sampling timepoint, including the frequency (n, %) of concentrations below the LLOQ and reported as zero for a safety-run in and a group with intensive sampling (approximately 20 participants).

Summary statistics will include mean (arithmetic and geometric), standard deviation, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations.

The PK parameters in the Table 12-1 will be calculated using non-compartmental methods using Phoenix WinNonlin (Pharsight, Mountain View, CA) software and reported, when applicable. Additional PK parameters may be estimated as needed. Descriptive summary statistics, for the PK parameters, will include: mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented. Missing data will not be imputed and will be treated as missing.

Table 12-1 Non-compartmental pharmacokinetic analysis

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume^{-1})
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume^{-1})
Cmax	The maximum (peak) observed serum/plasma drug concentration after dose administration (mass x volume^{-1})
Tmax	The time to reach maximum (peak) serum/plasma drug concentration after dose administration (time)
Ctrough	The lowest serum/plasma drug concentration reached by a drug before the next dose is administered (mass x volume^{-1})

12.5.3.1 Handling of missing values/censoring/discontinuations

Missing values for any PK parameters or concentrations will not be imputed and will be treated as missing. Below the limit of Quantitation (BLQ) values will be set to zero by the bioanalyst and will be displayed in the listings as zero and flagged. BLQ values will be treated as missing for the calculation of the geometric means and geometric CV%.

12.5.4 Immunogenicity

Descriptive summary statistics of ADA prevalence at baseline and ADA incidence on-treatment of investigational drugs will be provided by tabulating. Further details will be specified in the Statistical Analysis Plan (SAP).

12.6 Analysis of exploratory endpoints

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[redacted]

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12.7 Interim analyses

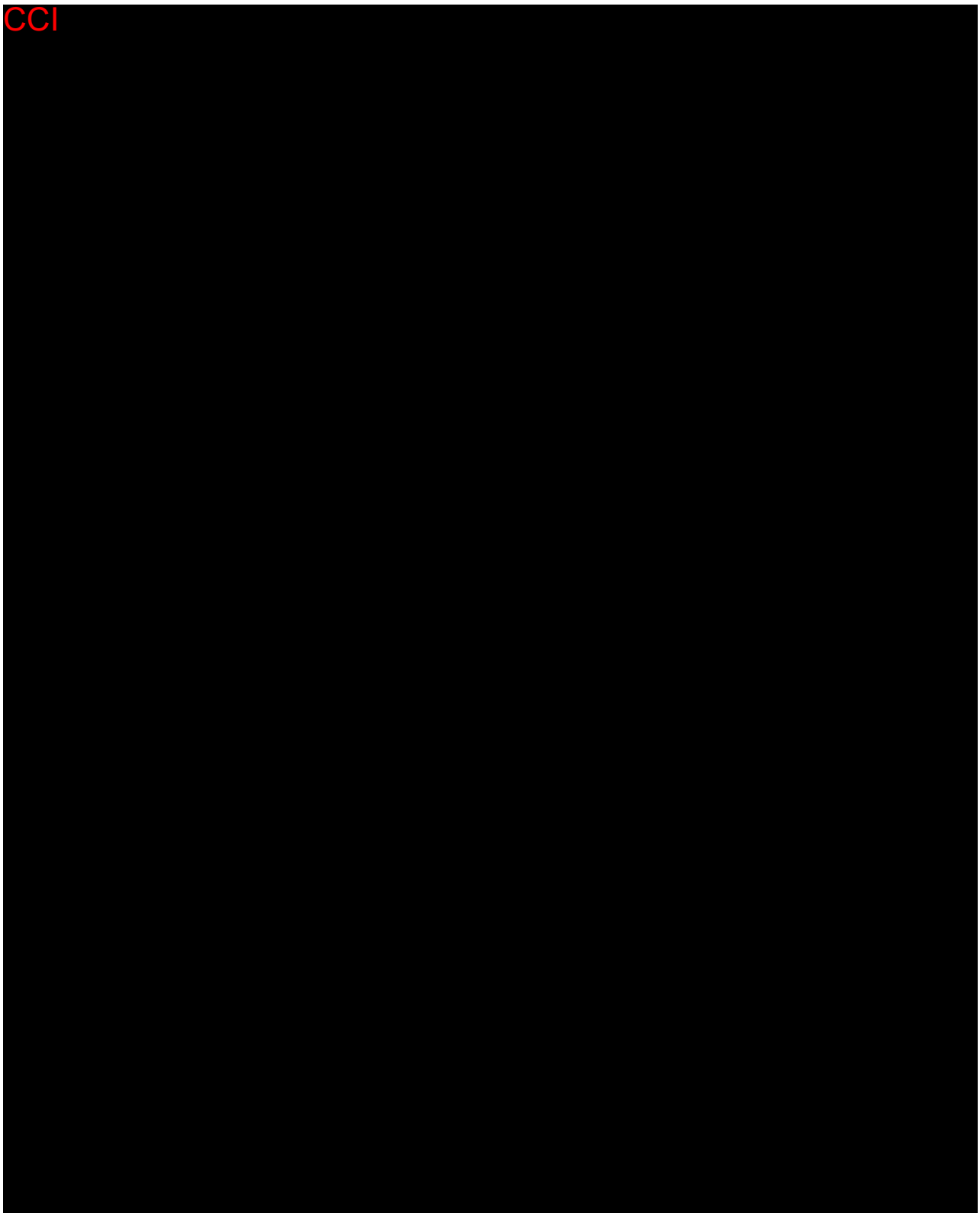
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12.8 Sample size calculation

12.8.1 Primary endpoint(s)

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13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

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

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

Summary results of primary and secondary endpoints will be disclosed based upon the global LPLV date, since multinational studies are locked and reported based upon the global LPLV.

Any data analysis carried out independently by the Investigator must be submitted to Novartis before publication or presentation. For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided.

13.4 Quality control and quality assurance

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

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

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

13.5 Participant engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter - after study start and at the end of study
- Plain language trial summary - after CSR publication

14 Protocol adherence

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

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

14.1 Protocol amendments

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

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

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

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References are available upon request.

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16 Appendices

16.1 Appendix 1: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity
If ALT or AST abnormal at baseline:	• ALT or AST > 3x baseline or > 300 U/L (whichever occurs first)

Table 16-2 Follow up requirements for liver laboratory triggers -ALT, AST, TBL

ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	**No change to study treatment** Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. Follow-up for symptoms.
If normal at baseline: ALT > 5 x ULN for more than two weeks **If elevated at baseline:** ALT > 3 x baseline and > 5 x ULN for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	**Interrupt study drug** Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. Follow-up for symptoms.
If normal at baseline: ALT > 8 x ULN	Normal	None	Initiate close monitoring and workup for competing etiologies.
ALT increase with bilirubin increase: **If normal at baseline:** ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline And > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.

ALT	TBL	Liver Symptoms	Action
If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline and > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 16-3 Follow up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Biliruin (isolated)		
>1.5 – 3.0 ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• Interrupt treatment • Repeat LFT within 48-72 hours • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF	Investigator discretion

Based on Investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.2 Appendix 2: Guidelines for response, duration of overall response, TTF, TTP, progression-free survival, and overall survival (based on RECIST 1.1)

16.2.1 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 16.2.2 and the definition of best response in Section 16.2.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.2.3.2 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 16.2.4 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

16.2.2 Efficacy assessments

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

16.2.2.1 Definitions

16.2.2.1.1 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.

For patients without measurable disease see Section 16.2.3.2.9.

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 patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

16.2.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g., in phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 16.2.3.2.9.

16.2.2.2 Methods of tumor measurement - general guidelines

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

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

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

- A change in methodology can be defined as either a change in contrast use (e.g., keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. However, another response assessment than the Novartis calculated UNK response may be accepted from the Investigator if a definitive response assessment can be justified, based on the available information.
- FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  - Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
  - Physical exams: Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10mm size, and can be assessed using calipers.
  - Ultrasound: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
  - Endoscopy and laparoscopy: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
  - Tumor markers: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g., CA-125 for ovarian

cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

16.2.2.3 Baseline documentation of target and non-target lesions

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

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

Minimum target lesion size at baseline:

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter.
- **Nodal target**: A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.
- **Non-target lesions**: All other lesions are considered non-target lesions, i.e., lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e., multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

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

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 16-4) and non-target lesions (Table 16-5) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-6) as well as the presence or absence of new lesions.

16.2.2.4.1 Follow-up and recording of lesions

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

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.

Nodal lesions:

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

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

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

16.2.2.4.2 Determination of target lesion response

Table 16-4 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm [2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

[1] SOD for CR may not be zero when nodal lesions are part of target lesions
[2] Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present, and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
[3] In exceptional circumstances an UNK response due to change in method could be over-ruled by the Investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 16.2.2.2).

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 16-4 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the

remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.

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

16.2.2.4.3 Determination of non-target lesion response

Table 16-5 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 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)

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 16.2.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

16.2.2.4.4 New lesions

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

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion.
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 16.2.2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥10 mm for the first time in the study plus 5 mm absolute increase. **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 16.2.2.2.

16.2.2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 16-6.

Table 16-6 Overall lesion response at each assessment

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

[1.] This overall lesion response also applies when there are no non-target lesions identified at baseline.

[2.] Once confirmed PR was achieved, all these assessments are considered PR.

[3.] As defined in Section 16.2.2.4

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

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

16.2.3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 16.2.3.2.9 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

16.2.3.1 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 patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

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

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

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

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

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required.
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required.
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).

- UNK = all other cases (i.e., not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks).

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

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

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

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

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

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

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

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

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

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

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

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

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

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

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

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

16.2.3.2 Time to event variables

16.2.3.2.1 Progression-free survival

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

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

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

16.2.3.2.2 Overall survival

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

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

16.2.3.2.3 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 patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

16.2.3.2.4 PFS2

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

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

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

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

16.2.3.2.5 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation

reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

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

16.2.3.2.6 Duration of response

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

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

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

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

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

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

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

16.2.3.2.7 Time to response

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

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 16.2.3.2.6. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

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

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

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

Assessment date

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

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

Start dates

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

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

End dates

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

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 16.2.3.2.8).

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

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

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

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

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

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with non-measurable disease is derived slightly differently according to Table 16-7.

Table 16-7 Overall lesion response at each assessment: patients with non-target disease only

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

[1] As defined in Section 16.2.2.4.

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

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

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

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

16.2.3.2.10 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 16.2.3.2.7, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) (FDA 2018). as a reference, the following analyses can be considered:

Table 16-8 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e., clinical progression based on Investigator claim	(1) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	(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 16.2.3.2.7.

[2.] =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.2.3.2.7.

[3.] =The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

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

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

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

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

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may

be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g., CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

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

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

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

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Additional suggestions for sensitivity analyses:

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g., by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 16-8 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.

16.2.4 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).

16.2.4.1 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).

16.2.4.2 End of treatment phase completion

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

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

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

Death is a reason which "*must*" lead to discontinuation of patient from trial.

16.2.4.3 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.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems

- Subject/guardian decision
- Death
- Progressive disease

Study terminated by the sponsor

16.2.4.4 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 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 respon ses may be re-evaluated by clinicians (based on local Investigator data recorded in eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the Investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the Investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the Investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

16.2.4.5 Programming rules

The following should be used for programming of efficacy results:

16.2.4.5.1 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.

16.2.4.5.2 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 16.2.3.2.7). 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.

Incomplete dates for last known date patient alive or death:

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

16.2.4.5.3 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

16.2.4.5.4 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

Censoring reason:

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

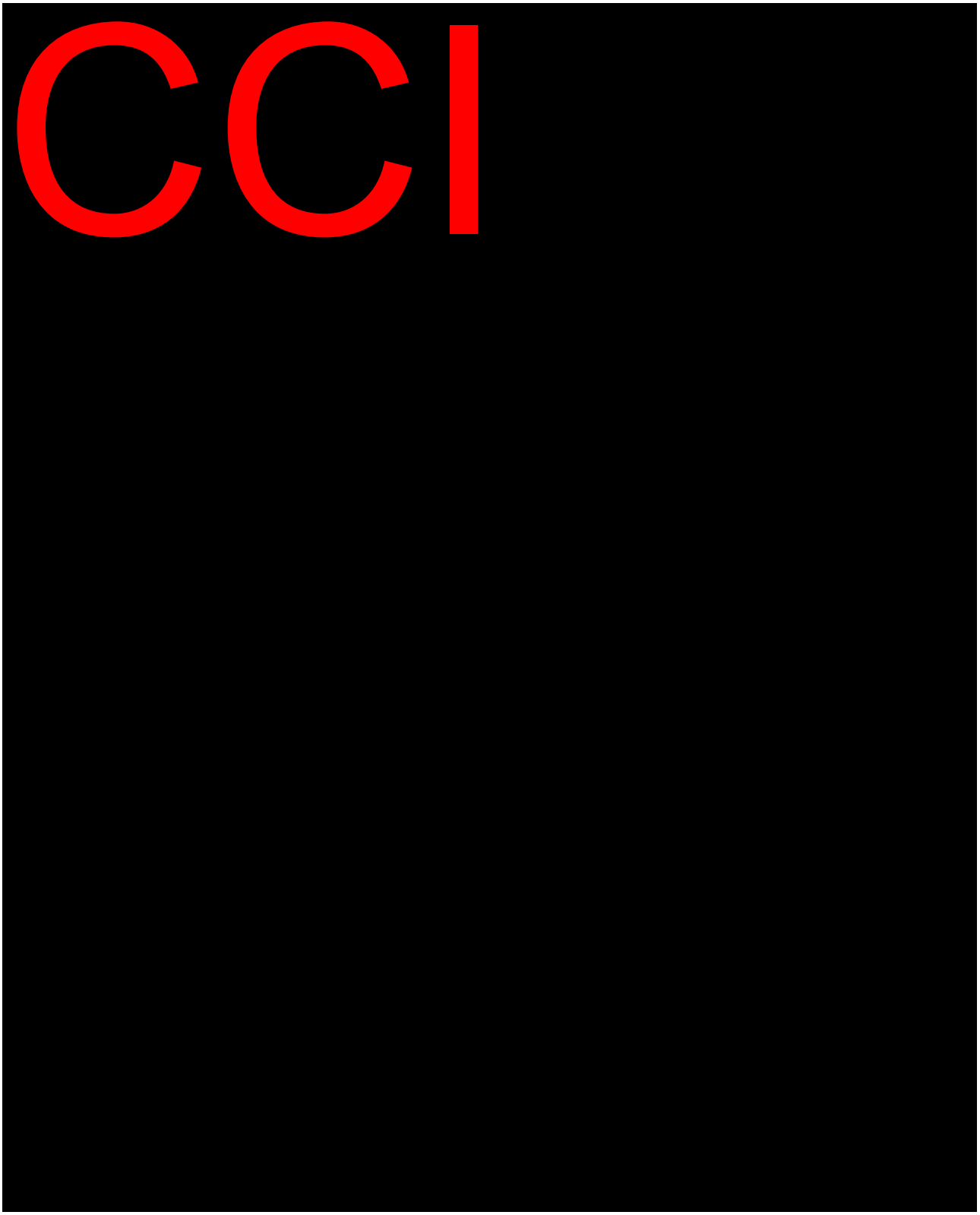
For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

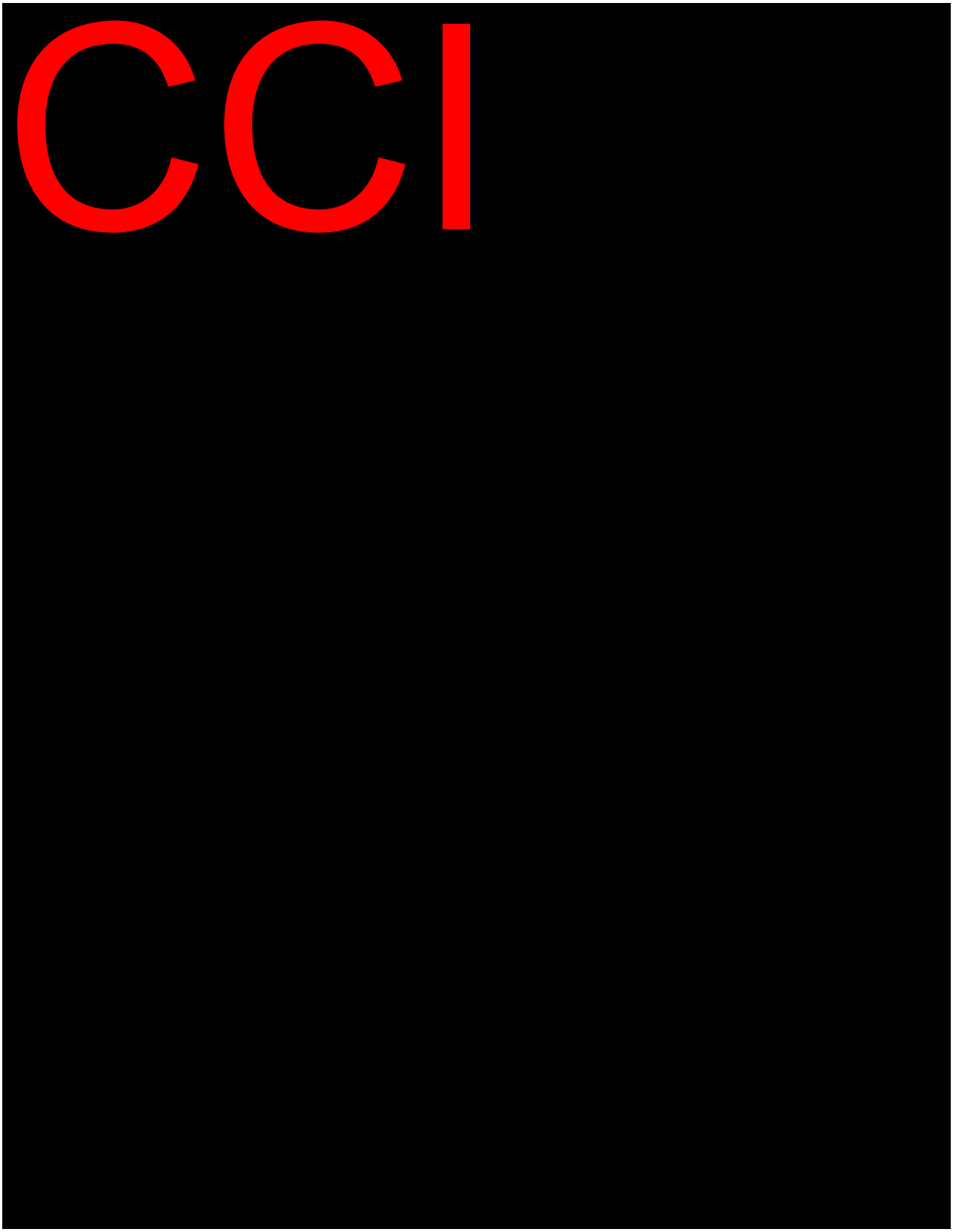
- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 16-8)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

* Adequate assessment is defined in Section 16.2.3.2.7. 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:

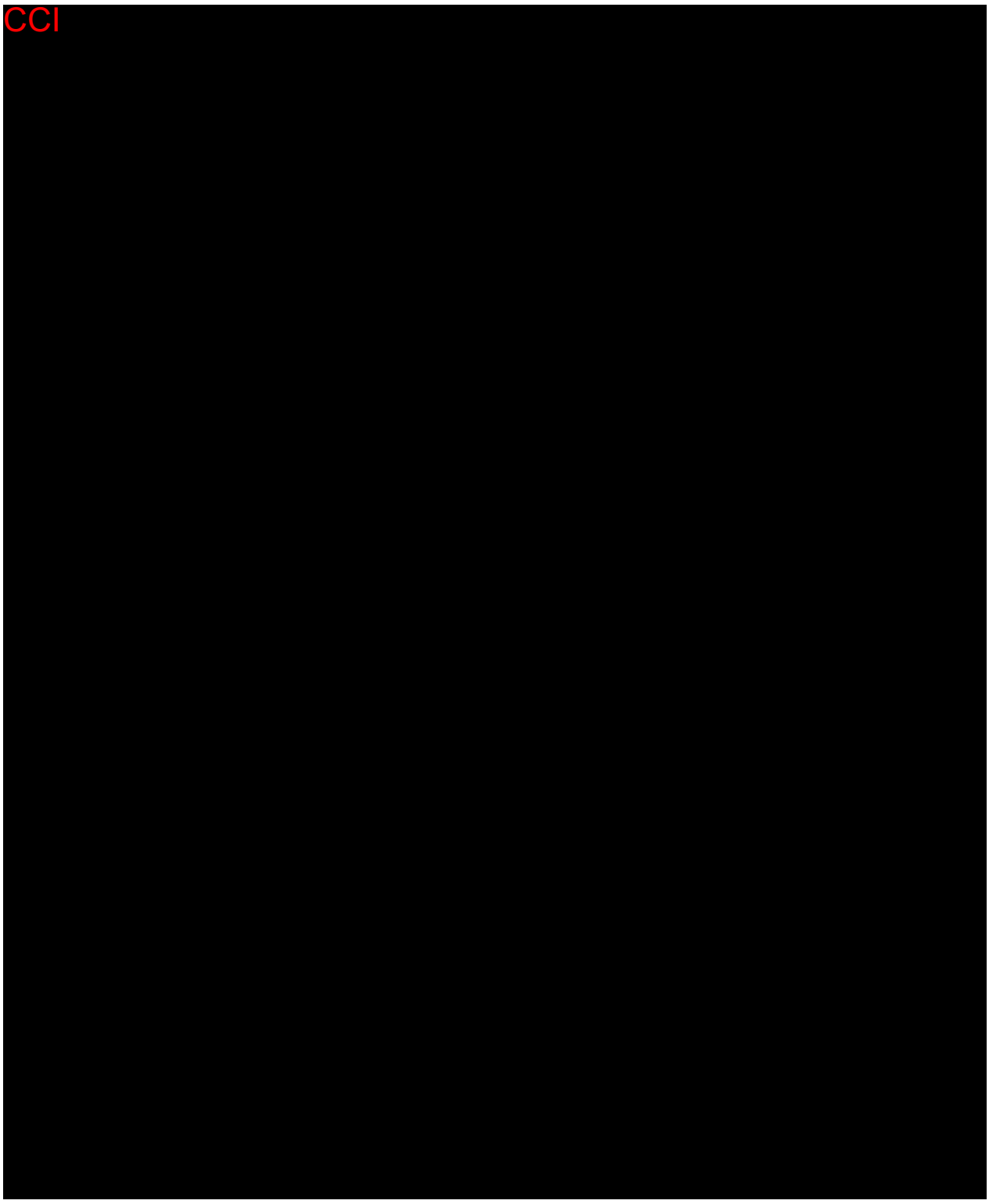
- This may be when there has been a definite decision to stop evaluation (e.g., reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g., withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

16.3 Appendix 3: CCI [redacted]




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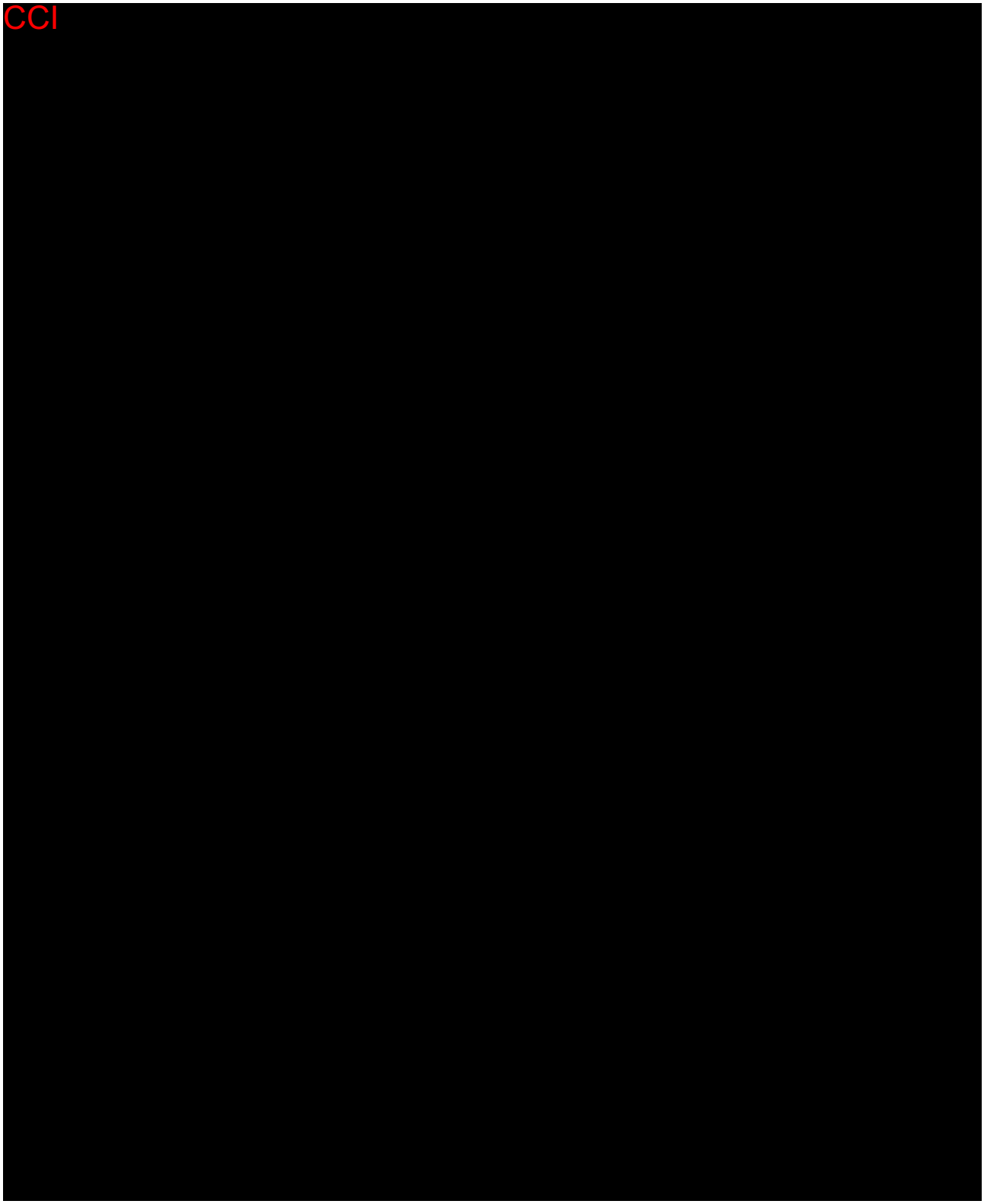
16.4 Appendix 4: CCI [redacted]



CCI

[redacted]

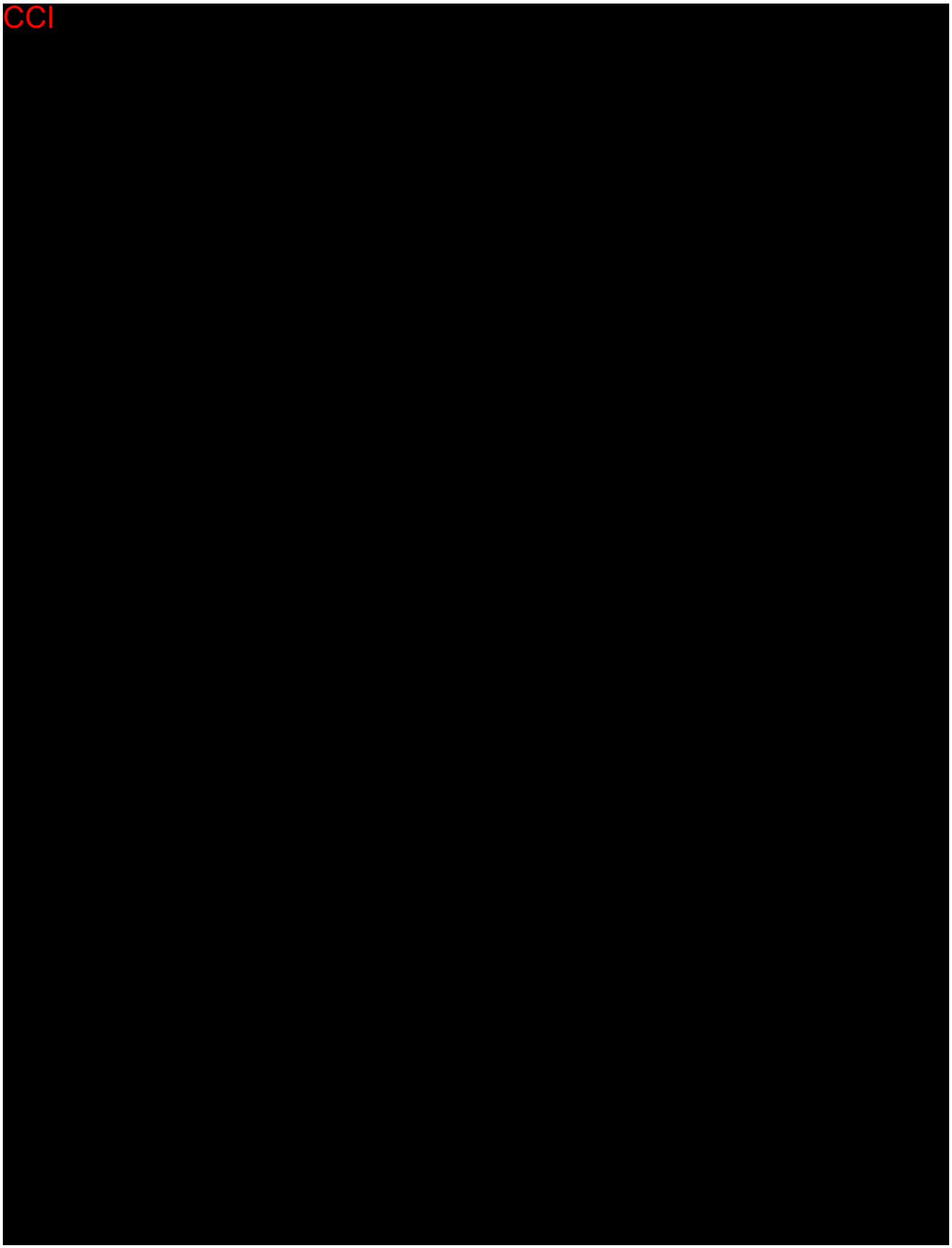
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16.5 Appendix 5

In general, the use of any concomitant medication deemed necessary for the care of the participant is permitted in this study, except as specifically prohibited below. Concomitant administration of study treatments could result in DDIs that could potentially lead to reduced activity or enhanced toxicity of the concomitant medications and/or bevacizumab and/or mFOLFOX6/ FOLFIRI. Please note that all lists in Appendix 5 are not comprehensive. Please refer to regular update online sources and the label of the concomitant drug to decide whether a drug is permitted (with caution) or prohibited based on Section 6.2.2 (prohibited Medications). In case of doubt, please contact the medical monitor with any questions.

16.5.1 Prohibited concomitant medications

Table 16-22 List of prohibited CYP3A4 inhibitors and inducers and UGT1A1 inhibitors

Category	Drug name
Strong CYP3A4 inhibitors	ceritinib, clarithromycin, conivaptan, grapefruit juice (citrus paradisi fruit juice, 240 mL TID), idealisib, itraconazole, ketoconazole, mibefradil, mifepristone, nefazodone, posaconazole, ribociclib, telithromycin, troleandomycin, voriconazole
Strong CYP3A4 inducers	apalutamide, avasimibe, carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifapentine, rifampin (rifampicin), St John's wort (*Hypericum perforatum*)[1]
UGT1A1 inhibitors	gemfibrozil, ketoconazole

[1] Herbal product
The list of CYP3A4 inhibitors / inducers and UGT1A1 inhibitors was adapted from Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: January 2021) which was compiled from the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling, and the University of Washington's Drug Interaction Database (//.druginteractionsolutions.org/).

16.6 Appendix 6: Immune-related adverse event evaluation and management

The recommendations below for the diagnosis and management of any immune-related AE (irAE) are intended as a guidance. This document should be used in conjunction with expert clinical judgement (by specialist physicians experienced in the treatment of cancer using immunological agents), and individual institutional guidelines or policies.

Criteria used to diagnose irAEs include blood tests, diagnostic imaging, histopathology, and microbiology assessments to exclude alternative causes such as infection, disease progression, and adverse effects of concomitant drugs. In addition to the results of these tests, the following factors should be considered when making an irAE diagnosis:

- What was the temporal relationship between initiation of tislelizumab and the AE?
- How did the patient respond to withdrawal of tislelizumab?
- Did the event recur when tislelizumab was reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is disease progression or an alternative diagnosis a more likely explanation?

When alternative explanations to autoimmune toxicity have been excluded, the irAE field associated with the AE in the eCRF should be checked. If further diagnostic evaluations change the assessment, the eCRF should be updated accordingly.

Table 16-23 Recommended diagnostic tests in the management of possible immune-related adverse events

Immune-related Toxicity	Diagnostic Evaluation Guideline
Thyroid Disorders	Scheduled and repeated thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss, and unexplained constitutional symptoms.
	Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath, or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including Dlco.
	Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.

Immune-related Toxicity	Diagnostic Evaluation Guideline
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, Clostridium difficile toxin, and cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain, or distension, consider colonoscopy with biopsy and surgical intervention as appropriate.
Eye Disorders	If a patient experiences acute, new onset, or worsening of eye inflammation; blurred vision; or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3 to 4; every 2 to 3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging (eg, ultrasound scan for metastases or thromboembolism). Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to a nephrologist for further management assistance.
Dermatology	Consider other causes by conducting a physical examination. Consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin, and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; DIco, diffusing capacity for carbon monoxide; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FBC, full blood count; HIV, human immunodeficiency virus; INR, international normalized ratio; LCI, liver cytosolic antigen; LFT, liver function test; LKM, liver kidney microsomal antibody; LP, liver pancreas antigen; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SLA, soluble liver antigen; SMA, smooth muscle antibody; T4, thyroxine; TFT, thyroid function tests; TSH, thyroid-stimulating hormone; UEC, urea electrolytes and creatinine.

16.6.1.1 Immune-related adverse event management algorithm

Immune-related AEs can escalate quickly. Study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention as appropriate is required.

Immune-related AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice, and contact the study medical monitor.

For some Grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the study medical monitor.

Steroid dosages in the table below are for oral or intravenous (methyl) prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory irAEs, consider use of steroid-sparing agents (e.g., mycophenolate mofetil [MMF]).

Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy.

Table 16-24 Treatment of suspected immune-related adverse events (irAE)

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Thyroid Disorders	1-2 Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker, and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with comorbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Hypophysitis	1-2 Mild-moderate symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4.	Continue study treatment.
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse intravenous methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinologist's advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to ≤ Grade 2. Discontinuation is usually not necessary.
Pneumonitis	1 Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider Pneumocystis infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.
	3-4 Severe or life-threatening symptoms: breathless at rest	Admit to a hospital and initiate treatment with intravenous methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological Toxicity	1 Mild symptoms	–	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe/life-threatening symptoms	Initiate treatment with oral prednisolone or intravenous methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
Colitis/Diarrhea	1 Mild symptoms: ≤ 3 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days, manage as a Grade 2 event.	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (nonenteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks. Consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate intravenous methylprednisolone 1-2 mg/kg/day.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Life-threatening symptoms	Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA Class III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Discontinue study treatment.
Skin reactions	1 Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: intravenous methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment) including Stevens-Johnson syndrome (all grades) or toxic epidermal necrolysis	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Permanently discontinue study treatment.
Hepatitis	1 ALT or AST > ULN to 3 x ULN	Check LFTs within 1 week and before the next dose; check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 ALT or AST >3 - 5 x ULN	Recheck LFTs every 48-72 hours. For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days, then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline Grade and prednisolone tapered to ≤ 10 mg.
	3 ALT or AST 5 - 20 x ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate intravenous (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	; Permanently discontinue study treatment.
	4 ALT or AST > 20 x ULN	Initiate intravenous methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Permanently discontinue study treatment.
	Worsening LFTs despite steroids: If on oral prednisolone, change to pulsed intravenous methylprednisolone. If on intravenous methylprednisolone, add mycophenolate mofetil (MMF) 500 to 1000 mg twice a day. If worsens on MMF, consider addition of tacrolimus. Duration and dose of steroid required will depend on severity of event.		

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Nephritis	1 Creatinine 1.5 x baseline or > ULN to 1.5 x ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5-3 x baseline or > 1.5-3 x ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3 x baseline or > 3-6 x ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate intravenous (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6 x ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia	1 Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
Ocular Toxicity	1 Asymptomatic eye examination/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate intravenous (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	2 Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2 and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	1 Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment, manage as a Grade 3 event.	Continue treatment or, if symptoms continue to worsen, hold study treatment until symptoms improve to baseline or Grade 0-1.
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ stomatitis	1 Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments, and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improve to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider intravenous corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ Rhabdomyolysis	1 Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2.	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3 x ULN or worse, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus intravenous (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve, add immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	For Grade 3: Hold study treatment until improved to Grade 0-1. Discontinue upon any evidence of myocardial involvement.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Myocarditis	< 2 Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing and including ECG, cardiac echo/MUGA, and/or other interventions per institutional guidelines; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2.	Hold study treatment. If a diagnosis of myocarditis is confirmed and considered immune-related, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or intravenous (methyl)prednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response, change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab, or anti-thymocyte globulin.	
	3 Severe symptoms with mild exertion		Note: The text here duplicates the text from the cell above. Adjust/merge as needed for page break. Hold study treatment. If a diagnosis of myocarditis is confirmed and considered immune related, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	4 Life-threatening		
Any recurrent immune-related adverse reaction (irAE) of grade 4 or grade 3			Permanently discontinue study treatment

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; ECG, electrocardiogram; INR, international normalized ratio;ir :immune-related; LFT, liver function test; MMF, mycophenolate mofetil; MUGA, multigated acquisition scan; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.a If clinically significant cardiac enzyme abnormalities are detected during laboratory assessment and serial cardiac enzyme assessments pose logistical hardship for the patient, then patient hospitalization should strongly be considered until immune-related myocarditis has been ruled out.

16.7 Appendix 7: iRECIST (version 1.1) guideline applicable for assessment of tumor response for immunotherapeutic trials in solid tumors

16.7.1 Introduction

This guideline provides the general principles and application of iRECIST (modified RECIST 1.1 for immune-based therapeutics) to assess tumor response and to derive efficacy endpoints in Novartis oncology immunotherapy clinical trials. This guideline is based on the publication: "iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics in solid tumors" by Seymour et al 2017.

This guideline will also refer to Novartis RECIST 1.1 (v3.2) for sections and derivations which are unchanged from RECIST 1.1.

This document is organized as follows:

- Section 16.7.2 describes the efficacy assessments: disease measurability, methods of tumor assessments, baseline documentation of target/non-target lesions, follow-up of target, non-target and new target/non-target lesions and evaluation of overall lesion response
- Section 16.7.3 provides the definitions and derivations of immune best overall response and time to event endpoints
- Section 16.7.4 provides the example scenarios

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16.7.2 Efficacy assessments

Tumor evaluations are done based on iRECIST criteria (Seymour et al 2017) and RECIST 1.1 guidelines (Eisenhauer et al 2009).

16.7.2.1 Disease measurability

The definition of disease measurability, classification of baseline lesions into target and non-target lesions, measurement and management of nodal disease, and calculation of sum of diameters (SOD) remains the same as RECIST 1.1. Please refer to Novartis RECIST 1.1 (v3.2) for details.

While there is no requirement to measure new lesions in RECIST 1.1, the new lesions identified at follow-up evaluations will be assessed and categorized as target or non-target in iRECIST using the same criteria of measurability as in RECIST 1.1. For additional details on handling of new lesions in iRECIST refer to Section 16.7.2.3.

16.7.2.2 Methods of tumor measurement

The methods used to measure tumors remain the same as RECIST 1.1. Please refer to Novartis RECIST v3.2 for details.

16.7.2.3 Target, non-target and new lesions

The methods used to classify lesions at baseline remains the same as RECIST 1.1. Please refer to Novartis RECIST 1.1 (v3.2) for details.

16.7.2.3.1 Target lesions

The selection of target lesions at baseline and their follow-up with the calculation of baseline/follow-up sum of diameters (SOD) should be performed as per RECIST 1.1.

16.7.2.3.2 Non-target lesions

The selection of non-target lesions at baseline and their follow-up with the assessment of lesion status should be performed as per RECIST 1.1 with the exception of the follow-up evaluations following unconfirmed progression based on these non-target lesions. Please refer to Section 16.7.2.4.2 for further details.

16.7.2.3.3 New lesions

A lesion not present at baseline and appearing at any follow-up evaluation time-point (TP) is considered a New Lesion. A new lesion will be considered as 'Newly appeared' at a follow-up evaluation TP if it appeared for the first time at that TP and did not exist prior to that TP. For all subsequent TP, this new lesion will be not considered as 'Newly appeared' and will be followed as a "Pre-existing" new lesion.

New lesions appearing at a follow-up evaluation TP will be classified either as New Lesion Target (NLT) or New Lesion Non-Target (NLNT) based on the TP when they were first identified using the same measurability criteria mentioned in RECIST 1.1. Once a new lesion is classified as NLT or NLNT, it should be followed as NLT and NLNT respectively at each subsequent TP regardless of change in size. New lesions do not have to resolve for subsequent overall response assessment of iSD or iPR provided the next assessment did not confirm progression (see Section 16.7.2.4).

16.7.2.3.4 New Lesions Target

All new measurable lesions up to a maximum of 5 new lesions (nodal+non-nodal) in total (and a maximum of 2 lesions per organ), representative of all involved organs should be identified as New Lesions Target (NLT). Each NLT should be uniquely and sequentially numbered, measured and recorded in the eCRF corresponding to "New Lesions Target". A sum of diameters (iSOD; long axis for non-nodal lesions, short axis for nodal) for all NLT will be calculated at each follow-up evaluation TP from the first appearance of a NLT. NLTs should not be included in the sum of diameter of the original target lesions identified at baseline.

16.7.2.3.5 New Lesions Non-target

All other new lesions which are not considered as new lesions-target at the corresponding evaluation TP will be considered as New Lesions Non-Target (NLNT). Multiple NLNTs involved in the same organ can be recorded as a single NLNT (i.e., multiple liver metastases). Each NLNT should be uniquely numbered in the appropriate eCRF. The lesion status of the NLNT at each follow-up evaluation compared to the "previous assessment" should be recorded at each follow-up evaluation TP.

16.7.2.4 Response evaluation

Response will be assessed using iRECIST based on (Seymour et al 2017). Response assigned using iRECIST will have a prefix of an 'i' (i.e., immune) (e.g. iCR for complete response) to differentiate them from RECIST 1.1 response.

The principles used to establish objective tumor response are largely unchanged from RECIST 1.1. The major change in iRECIST is the concept of unconfirmed disease progression (iUPD) and confirmed disease progression (iCPD). The response evaluation will remain the same for RECIST 1.1 and iRECIST up to the first iUPD timepoint.

Following are the key differences in response evaluation based on iRECIST compared to RECIST 1.1:

- Confirmation of disease progression is required per iRECIST. This leads to two separate response categories for overall response corresponding to progressive disease: unconfirmed progressive disease (iUPD) and confirmed progressive disease (iCPD); the rules for confirmation of disease progression are provided in Section 16.7.2.4.6.
- New lesions are to be separately followed and measured at subsequent evaluation TPs in iRECIST for response assessment.
- An iUPD can be followed by a complete (iCR) or partial response (iPR) or stable disease (iSD) or Non-iCR/Non-iUPD (for patients with only non-measurable disease at baseline) as overall response. If this happens, the bar (i.e., overall response) is "reset" and iUPD needs to re-occur per RECIST 1.1 followed by iCPD in order for the progression to be confirmed.

16.7.2.4.1 Target lesion response

The target lesion response will be assessed based on the criteria shown in Table 16-25.

Table 16-25 Determination of target lesion response by iRECIST

Time point (TP) response criteria	Applicable to Evaluation Time-points	Evaluation criteria
Immune Complete Response (iCR)	Any post-baseline evaluation TP prior to confirmation of progression (i.e., determination of overall lesion response of iCPD)	Same as CR criteria for target lesions by RECIST 1.1. iCR will be target lesion response at the next assessment if CR criteria per RECIST 1.1 is met and the overall response is reset after the previous assessment of overall response of iUPD*.
Immune Partial Response (iPR)	Any post-baseline evaluation TP prior to confirmation of progression (i.e., determination of overall lesion response of iCPD)	Same as PR criteria for target lesions by RECIST 1.1 (i.e,. reduction in target lesion SOD>=30% from baseline). iPR will be target lesion response at the next assessment if PR criteria per RECIST 1.1 is met and the overall response is reset after the previous assessment of overall response of iUPD*.
Immune Stable Disease (iSD)	Any post-baseline evaluation TP prior to confirmation of progression (i.e., determination of overall lesion response of iCPD)	Same as SD criteria for target lesions by RECIST 1.1 (i.e,. neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD) iSD will be target lesion response at the next assessment if SD criteria per RECIST 1.1 is met and the overall response is reset after the previous assessment of overall response of iUPD*.

Time point (TP) response criteria	Applicable to Evaluation Time-points	Evaluation criteria
Immune unconfirmed progressive disease (iUPD)	A post-baseline TP prior to iCPD where the previous adequate evaluation TP overall response was not iUPD	Same as PD criteria for target lesions by RECIST 1.1 (i.e., increase in target lesion SOD >=20% from nadir with an absolute increase of >=5mm). For iUPD after iCR, follow RECIST 1.1.
	A post-baseline TP prior to iCPD where the previous adequate evaluation TP overall response was iUPD	iUPD will remain iUPD provided the overall response is not reset and there is no confirmation of iUPD*.
Not Evaluable (NE)	Any post-baseline evaluation TP	Same as UNK (Unknown)/NE (Not evaluable) criteria for target lesions by RECIST 1.1

*For details on confirmation of progression (iCPD) and the reset of overall response after prior iUPD refer to Section 16.7.2.4.7.

For additional notes on target lesion response (e.g., reappearance of lesions, lesion split/coalesced etc.) refer to Novartis RECIST 1.1 (v3.2).

16.7.2.4.2 Non target lesion response

The non-target lesion response will be assessed based on the criteria shown in Table 16-26.

Table 16-26 Determination of non-target lesion response by iRECIST

Time point (TP) response criteria	Applicable to Evaluation Time-points	Evaluation criteria
Immune Complete Response (iCR)	Any post-baseline evaluation TP prior to confirmation of progression (i.e., determination of overall lesion response of iCPD)	Same as CR criteria for non-target lesions by RECIST 1.1 iCR will be non-target lesion response at the next assessment if CR criteria per RECIST1.1 is met and the overall response is reset after the previous assessment of overall response of iUPD*.
Immune Non-CR/non-UPD (Non-iCR/Non-iUPD)	Any post-baseline evaluation TP prior to confirmation of progression (i.e., determination of overall lesion response of iCPD)	Same as NON-CR/NON-PD criteria for non-target lesions by RECIST 1.1 Non-iCR/Non-iUPD will be non-target lesion response at the next assessment if the overall response is reset after the previous assessment of overall response of iUPD*.
Immune unconfirmed progressive disease (iUPD)	A post-baseline TP prior to iCPD where the previous adequate evaluation TP overall response was not iUPD	Same as PD criteria for non-target lesions by RECIST 1.1 (i.e., unequivocal progression of non-target lesions). For iUPD after iCR follow RECIST 1.1.
	A post-baseline TP prior to iCPD where the previous adequate evaluation TP overall response was iUPD	iUPD will remain iUPD provided the overall response is not reset and there is no confirmation of iUPD*
Not Evaluable (NE)	Any post-baseline evaluation TP	Same as UNK (Unknown)/NE (Not evaluable) criteria for non-target lesions by RECIST 1.1

*For details on confirmation of progression (iCPD) and the reset of overall response after prior iUPD refer to Section 16.7.2.4.7.

For additional notes on non-target lesion response (e.g., unequivocal progression etc.) refer to Novartis RECIST 1.1 (v3.2).

16.7.2.4.3 New lesion consideration in response

As mentioned in Section 16.7.2.3.3, the new lesions are classified as New Lesions Target (NLT) and New Lesions Non-Target (NLNT). Both NLT and NLNT will contribute to the overall response determination, however, will not be added to the SOD for baseline target lesions.

- A NLT or NLNT appearing for the first time at any post-baseline evaluation TP will result in an overall lesion response of iUPD unless it confirms disease progression which occurred at the previous TP. If it confirms disease progression which occurred at the previous TP, then overall lesion response will be iCPD.
- Recurrence of iUPD after return to iSD or better response following previous iUPD will be based on RECIST 1.1 principles. The new lesions would result in a new iUPD if:
  - New lesion appeared at that TP.
  - The pre-existing NLT met RECIST 1.1 criteria for PD i.e., 20% or more increase in iSOD from nadir with an absolute increase of ≥5mm. Nadir iSOD is obtained based on all previous TP assessments of NLT.
  - The pre-existing NLNT showed unequivocal worsening.
- New lesions do not have to resolve for a subsequent overall lesions response of iSD or iPR if there is a reset of overall response

16.7.2.4.4 New lesion-target (NLT) response

The new target lesion response will be applicable only from the time point of appearance of new target lesion(s) until the disappearance of the new target lesion(s). The new target lesion response will be assessed based on the criteria shown in Table 16-27.

Table 16-27 Determination of new lesion-target response by iRECIST

Time point (TP) response criteria	Applicable to Evaluation Time-points	Evaluation criteria
Immune unconfirmed progressive disease (iUPD)	A post-baseline TP from the appearance of new-target lesion and prior to iCPD, where the previous adequate evaluation TP overall response was not iUPD	A new target lesion appears at the current TP or pre-existing NLT met RECIST 1.1 PD criteria based on iSOD from new target lesions (At least 20% increase in iSOD relative to nadir or baseline with at least 5 mm absolute increase)
	A post-baseline TP from the appearance of new-target lesion and prior to iCPD, where the previous adequate evaluation TP overall response was iUPD	iUPD will remain iUPD provided there is no change in size of new target lesions and the overall response is not reset and there is no confirmation of iUPD*
Immune Stable Disease (iSD)	A post-baseline evaluation TP after the appearance of a new target lesion prior to iCPD	iSD will be new target lesion response at the next assessment following iUPD if there is change in size of new target lesions and the previous TP overall response of iUPD will be reset to iSD or better*

Time point (TP) response criteria	Applicable to Evaluation Time-points	Evaluation criteria
Immune Partial Response (iPR)	NA	
Immune Complete Response (iCR)	A post-baseline evaluation TP after the appearance of a new target lesion prior to iCPD	Disappearance of all new target lesions
Not Evaluable (NE)	A post-baseline evaluation TP after the appearance of a new target lesion	Same as UNK (Unknown)/NE (Not evaluable) criteria per RECIST 1.1

*For details on confirmation of progression (iCPD) and the reset of overall response after prior iUPD refer to Section 16.7.2.4.7.

16.7.2.4.5 New lesion-non-target response

The new non-target lesion response will be applicable only from the time point of appearance of new non-target lesion(s) until the disappearance of the new non-target lesion(s). The new non-target lesion response will be assessed based on the criteria shown in Table 16-28.

Table 16-28 Determination of new lesion-non-target response by iRECIST

Time point (TP) response criteria	Applicable to Evaluation Time-points	Evaluation criteria
Immune unconfirmed progressive disease (iUPD)	A post-baseline TP from the appearance of new non-target lesion and prior to iCPD. where the previous adequate evaluation TP overall response was not iUPD	A new non-target lesion appears at the current TP or pre-existing NLNT showed unequivocal worsening
	A post-baseline TP from the appearance of new non-target lesion and prior to iCPD, where the previous adequate evaluation TP overall response was iUPD	iUPD will remain iUPD provided there is no change in new non-target lesions and the overall response is not reset and there is no confirmation of iUPD*
Immune Non-CR/non-UPD (NON-iCR/NON-iUPD)	A post-baseline evaluation TP after the appearance of a new non-target lesion prior to iCPD	Non-iCR/Non-iUPD will be the new non-target lesion response if there is change in new non-target lesions and the previous overall response of iUPD will be reset to iSD or better*
Immune Complete Response (iCR)	A post-baseline evaluation TP after the appearance of a new non-target lesion prior to iCPD	Disappearance of all new non-target lesions
Not Evaluable (NE)	A post-baseline evaluation TP after appearance of a new non-target lesion	Same as UNK (Unknown)/NE (Not evaluable) criteria for non-target lesions by RECIST 1.1

*For details on confirmation of progression (iCPD) and the reset of overall response after prior iUPD refer to Section 16.7.2.4.7.

16.7.2.4.6 Confirmation of disease progression and reset of overall lesion response

Unlike RECIST 1.1, iRECIST requires confirmation of progression. A confirmatory scan should be performed at least 4 weeks after initial iUPD and no longer than 8 weeks after iUPD, provided the patient is clinically stable and does not require change of treatment. If progression is confirmed at the confirmatory scan, the overall lesion response will be iCPD. If the next

assessment after iUPD is not evaluable (NE), then the next adequate tumor assessment will be considered for the determination of iCPD.

Confirmation of progression requires either

- further worsening in the lesion category (i.e., target, non-target, new lesion) with existing iUPD

or

- a lesion category without prior iUPD met RECIST 1.1 criteria for progression.

Overall lesion response will be assessed as iCPD based on the following criteria if there is a further continued increase in tumor burden compared to the previous TP response of iUPD:

- If initial iUPD was due to Target lesions: further increase in target lesions of at least 5 mm* in the absolute value of SOD compared to the iUPD from previous TP.
- If initial iUPD was due to Non-Target lesions: Any increase in non-target lesions compared to the iUPD from previous TP.
- If initial iUPD was due to new lesions: Further increase in size of new lesion(s) (an increase of at least 5 mm* in iSOD of NLT or any increase in NLNT) compared to the iUPD from previous TP or appearance of additional new lesions at current TP.
- RECIST 1.1 criteria for PD was met in lesion categories (target or non-target or appearance of additional new lesions), where iUPD was not previously identified.

*Note: Sequential increases are additive; thus, a 4mm increase at one assessment, followed at the next assessment by a further 2mm increase meets the criteria for iCPD.

If progression (iUPD) was not confirmed at the next evaluation TP (i.e., no iCPD), then there are two scenarios for overall lesion response at the next evaluation TP as defined below:

- The overall lesion response is reset with response of iSD or better if it meets RECIST 1.1 criteria even if the new lesions do not resolve
- iUPD will remain at the next evaluation TP if there is no change in tumor burden or it meets PD per RECIST1.1 criteria
    - No change in tumor burden is defined as <5mm change in SOD/iSOD based on target/new-target lesions and no change in the status of non-target/new non-target lesions.

The overall lesion response is reset with a TP response of iSD or better if it meets RECIST 1.1 criteria (even if the new lesions do not resolve), after the previous evaluation TP response of iUPD, if it meets one of the below criteria compared to the TP, where prior iUPD was observed:

- Decrease of at least 5 mm in SOD based on target lesions
- Shrinkage in non-target lesions resulting in reduction of tumor burden
- Decrease of at least 5 mm in iSOD based on new target lesions
- Shrinkage in new non-target lesions resulting in reduction of tumor burden

After the overall lesion response is reset following iUPD, the target, non-target, new lesion target and new lesion non-target response evaluation will follow the criteria specified in Table 16-25, Table 16-26, Table 16-27, Table 16-28.

Note: Even if the overall lesion response is reset, all assessments including those assessments done prior to reset of response should be considered for determination of nadir, which will be used to determine the next occurrence of iUPD.

16.7.2.4.7 Overall lesion response

The overall lesion response for a post-baseline TP will be assessed as shown in Table 16-29.

Table 16-29 Overall lesion response for a time-point based on consideration of target lesions, non-target lesions and new lesions

Row	#Target lesion response*	Non-target lesion response*	New lesion response*		Overall TP response	
			Target†	Non-target††	No prior iUPD**	Prior iUPD**; ***
1	iCR	iCR	iCR	iCR	iCR	iCR
2	iCR	NON-iCR/NON-iUPD	iCR, iSD	iCR, NON-iCR/NON-iUPD	iPR	iPR
3	iPR	iCR, NON-iCR/NON-iUPD	iCR, iSD	iCR, NON-iCR/NON-iUPD	iPR	iPR as long as there is no iCPD
4	iSD	iCR, NON-iCR/NON-iUPD	iCR, iSD	iCR, NON-iCR/NON-iUPD	iSD	iSD as long as there is no iCPD
5	iUPD with no change or decrease from last TP	iUPD with no change or decrease from last TP	No iCPD due to new-target lesions	No iCPD due to new non-target lesions	NA	iUPD remains unless iCPD confirmed
6	iSD, iPR, iCR	iUPD	iUPD, iCR	iUPD, iCR	iUPD	Remains iUPD unless iCPD confirmed
7	iUPD	NON-iCR/NON-iUPD or iCR	iUPD, iCR	iUPD, iCR	iUPD	Remains iUPD unless iCPD confirmed
8	iUPD	iUPD	iUPD, iCR	iUPD, iCR	iUPD	Remains iUPD unless iCPD confirmed
9	Non-iUPD	Non-iUPD	iUPD	iUPD, NON-iCR/NON-iUPD, iCR	iUPD	Remains iUPD unless iCPD confirmed
10	Non-iUPD	Non-iUPD	iUPD, iSD, iCR	iUPD	iUPD	Remains iUPD unless iCPD confirmed

* Using RECIST 1.1 principles.

If no RECIST PD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD will be the same.

** in any lesion category.

*** previously identified in assessment immediately prior to this TP. If this is not the case then refer to column 'No prior iUPD'.

† Only applicable on/after the time point a new lesion-target appeared. If there are no new lesions-target consider new lesion-target response as if it is iCR.

†† Only applicable on/after the time point a new lesion-non-target appeared. If there are no new lesions-non-target consider new lesion-non-target response as if it is iCR.

If there are no baseline scans available, then the overall response at each assessment will be Not Evaluable (NE).

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 iCR.

For patients with only non-measurable disease at baseline, the overall response will be obtained based on Non-target response (refer to Table 16-26) and new lesions (Table 16-27, Table 16-28). Table 16-29 can be used for obtaining the overall response without considering the target lesion requirement in this situation.

16.7.2.5 Treatment continuation beyond RECIST 1.1 PD

Differentiating transient pseudo-progression from true progression, potentially requiring a change in therapy, can be challenging. Although early discontinuation of an effective drug is not desirable, continued long-term treatment with a non-effective drug past true progression might delay the initiation of potentially effective salvage therapy.

All decisions regarding continuation or discontinuation of therapy should be made by the Investigator in conjunction with the patient. It is recommended that clinical trials, which permit treatment beyond initial RECIST 1.1 defined progression (i.e., iUPD) should only allow patients who are clinically stable to continue on treatment until the next assessment (≥4 weeks later) and is still deriving benefit as per Investigator assessment. The next imaging assessment after RECIST 1.1 PD should ideally be no longer than 8 weeks later, to ensure that patients remain fit for salvage therapies. A longer timeframe before the next assessment may be reasonable if pseudo-progression is well described in the tumor type, especially if no effective salvage therapies are available and this should be justified in the trial protocol.

The imaging findings and the recommendation to continue treatment despite iUPD should be discussed with the patient before a decision is made about whether or not to continue therapy. Patients who have iUPD and are not clinically stable should be designated as not clinically stable in the case report form and it is recommended that the treatment should be withdrawn. The determination of clinical stability/benefit which would allow continuation of therapy will need to be made at the initial progression based on RECIST1.1 PD (iUPD by iRECIST) and at each subsequent assessment of iUPD.

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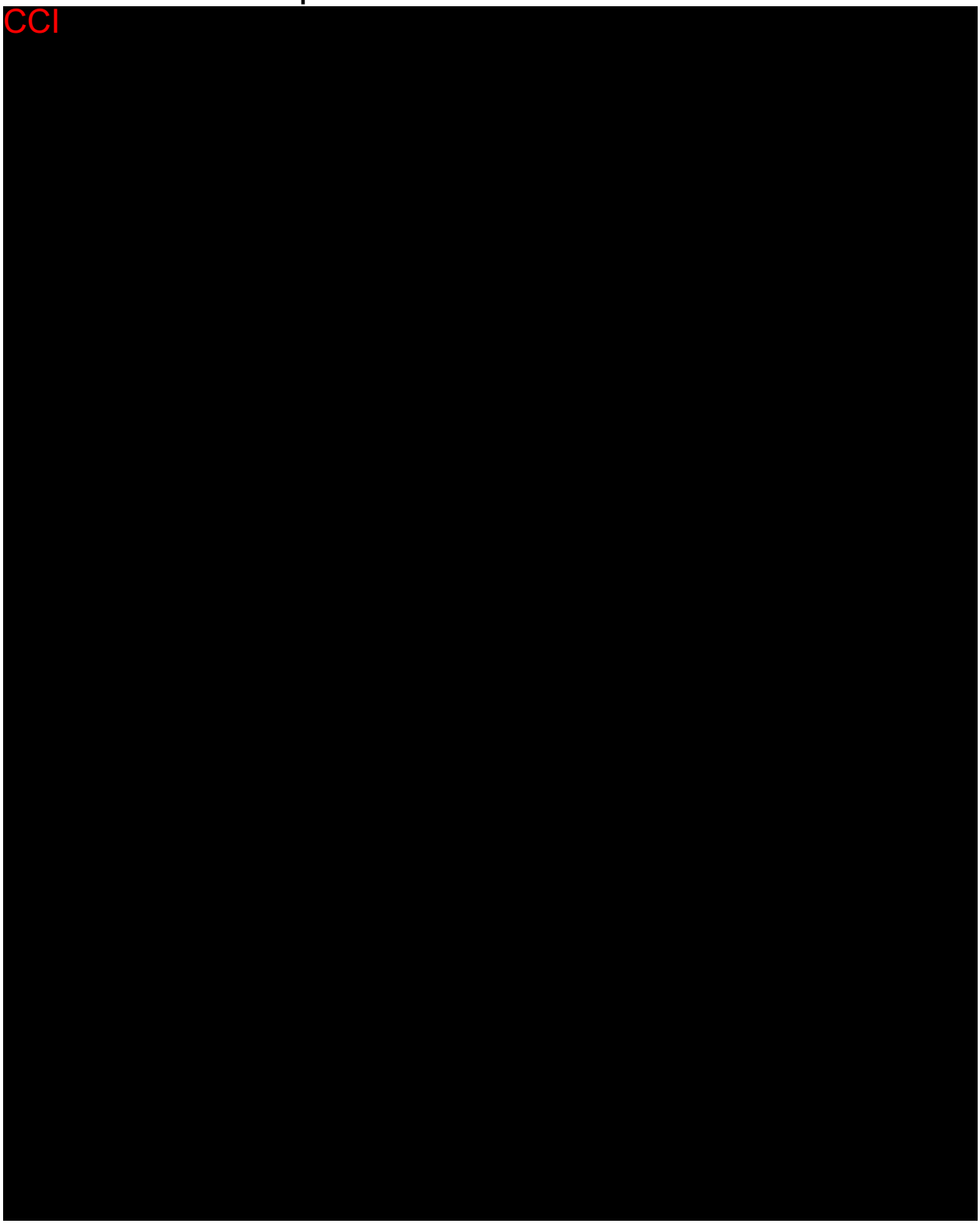
16.7.2.5.1 Guidance on assignment of clinical stability

An assignment of clinical stability generally requires that no worsening of performance status has occurred, that no clinically relevant increases in disease-related symptoms such as pain or dyspnea occur that are thought to be associated with disease progression (these symptoms are generally understood to mean a requirement for increased palliative intervention), and that no requirement for intensified management of disease-related symptoms exists, including increased analgesia, radiotherapy, or other palliative care.

16.7.3 Efficacy definitions

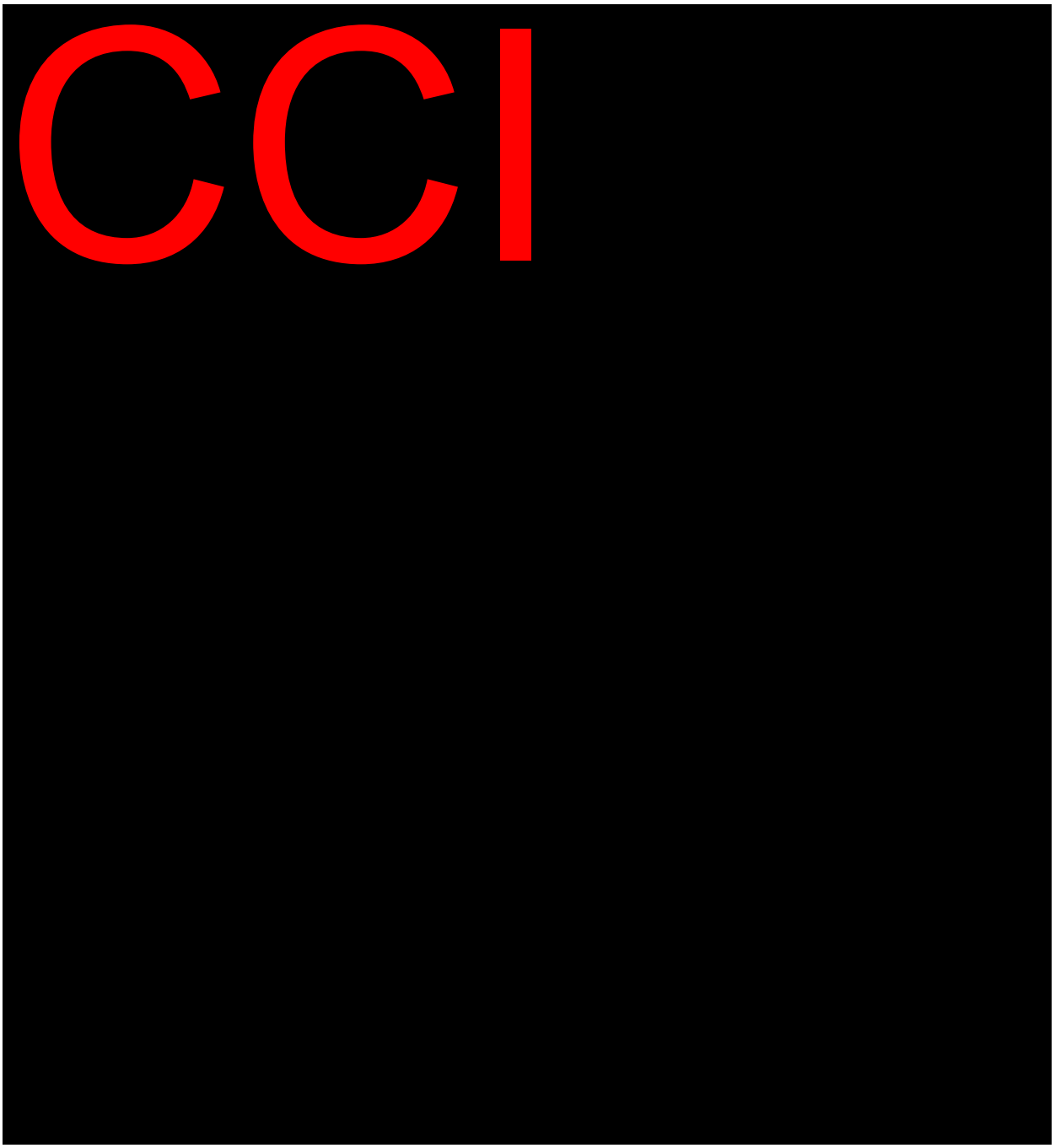
16.7.3.1 Best overall response

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16.7.3.2 Definition of endpoints



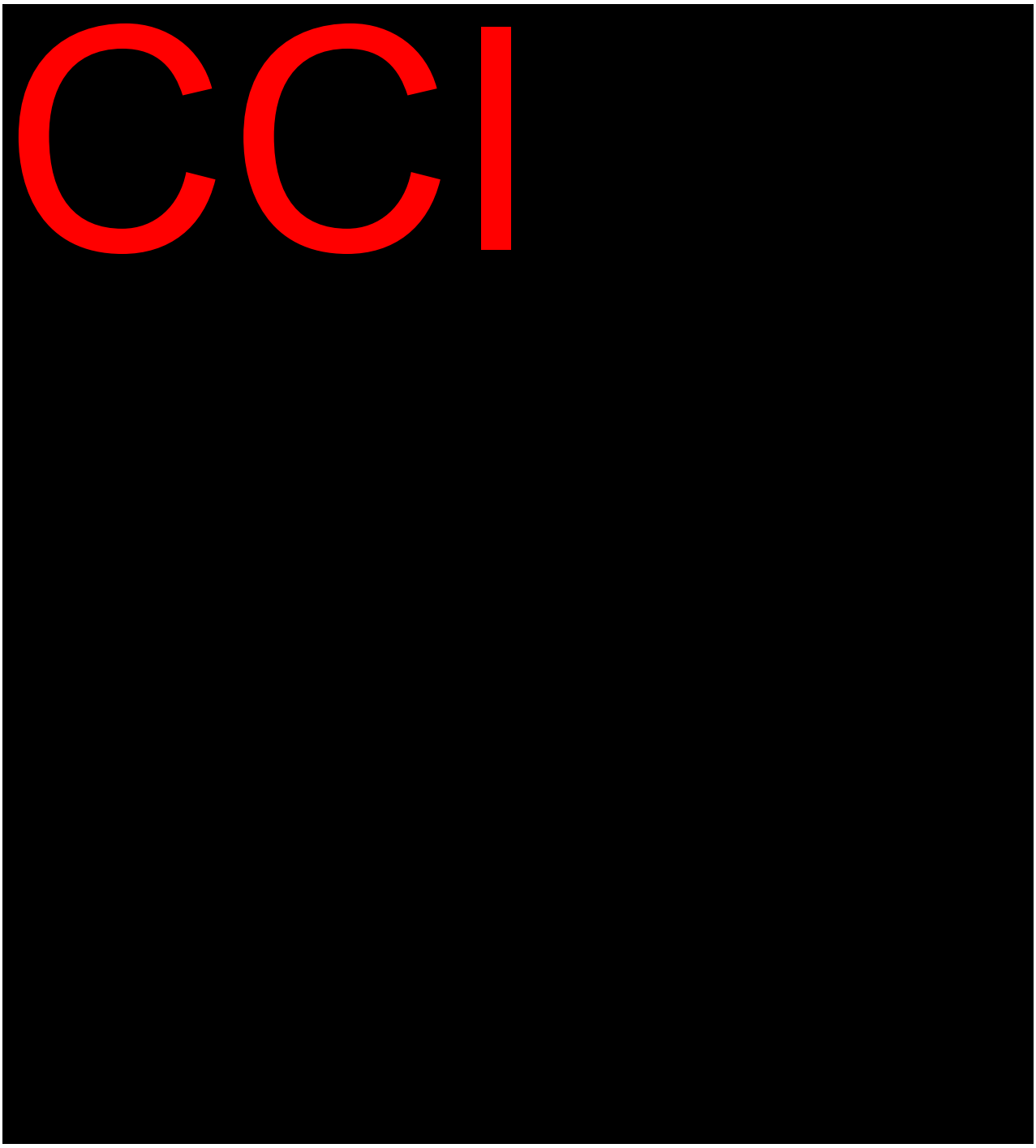

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