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NIS793

Clinical Trial Protocol CNIS793B12301 [daNIS-2] / NCT04935359

A randomized, double-blind, phase III study comparing NIS793 in combination with gemcitabine and nab-paclitaxel versus placebo combined with gemcitabine and nab-paclitaxel for first line treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC)

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ADA	Anti-drug Antibody
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
ANC	absolute neutrophil count
APTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
ASMA	Anti-Smooth Muscle Antibody
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATM	A-T mutated
AUC	Area under the curve
BLQ	Below the limit of quantitation
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
BRCA1/2	Breast Cancer gene 1/2
CA-19-9	Carbohydrate Antigen 19-9
CD-transferrin	Carbohydrate-Deficient Transferrin
CD8	Cluster of Differentiation 8
CDKN2	Cyclin Dependent Kinase Inhibitor 2
CCI	CCI [redacted]
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance (PK)
Cmax	Maximum drug concentration after dose administration
Cmin	Minimum drug concentration after dose administration
CMV	Cytomegalovirus
CNS	Central Nervous System
CO	Country Organization
COA	Clinical Outcome Assessment
COVID-19	Coronavirus disease 2019
CR	Complete Response
CRF	Case Report/Record Form (paper or electronic)
CCI	[redacted]
CSF	Colony-Stimulating Factor
CSR	Clinical study report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI	[redacted]
Ctrough(ss)	Trough Concentrations (steady state)
CV	Coefficient of variation
CYP2C8	Cytochrom P450 2C8

CYP3A4	Cytochrom P450 3A4
D5W	Dextrose 5% in Water
DCR	Disease Control Rate
DDS	Dose-determining set
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of Response
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECLIA	Electrochemiluminescent assay
ECM	Extracellular Matrix
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report/record form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
EM(E)A	European Medicines (Evaluation) Agency
EOI	End of Infusion
EOT	End of Treatment
EPCAM	Epithelial cellular adhesion molecule
CCI	[redacted]
CCI	[redacted]
EQ-VAS	EuroQol visual analogue scale
ERCP	Endoscopic Retrograde Cholangiopancreatography
eSAE	Electronic Serious Adverse Event
ESMO	European Society for Medical Oncology
EWOC	Escalation with Overdose Control
CCI	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FFPE	Formalin-Fixed Paraffin-Embedded
FIH	First-in-human
FPFV	First Patient First Visit
Free T3	Free Triiodothyronine
Free T4	Free Thyroxine
G-CSF	Granulocyte Colony-Stimulating Factor
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GFR	Glomerular Filtration Rate
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
h	Hour

HAV	Hepatitis A Virus
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HEV	Hepatitis E Virus
HgbA1c	Glycated Hemoglobin
HIV	Human immunodeficiency virus
HR	Hazard Ratio
CCI [redacted]	[redacted]
HSV	Herpes Simplex Virus
i.v.	intravenous
[redacted]	[redacted]
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICI	Immune checkpoint inhibitor
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	Interferon gamma
IG	Immunogenicity
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IL-1	Interleukin-1
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LFT	Liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
LPLV	Last patient last visit
mAb	monoclonal antibody
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mg/kg	milligram per kilogram
mg/m2	milligram per square meter
mg/mL	Milligram per milliliter

MID	Minimally important differences
mL	milliliter(s)
MLH1	MutL homolog 1
mm3	Cubic millimeter
mOS	Median Overall Survival
MRI	Magnetic Resonance Imaging
MSH2	MutS Homolog 2
MSH6	MutS Homolog 6
MSI-H	Microsatellite Instability-High
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next-generation sequencing
NIH	National Institutes of Health
NIS-PAS	NIS793 Pharmacokinetic analysis set
NTproBNP	N-terminal pro-brain natriuretic peptide
NTRK	Neurotrophic Tropomyosin-Related Kinase
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
PA3	Protocol amendment 3
PALB2	Partner and localizer of BRCA2
PAS	Pharmacokinetic analysis set
PCR	Protein creatinine ratio
CCI	CCI
PD (per RECIST)	Progression of Disease
PD-L1	Programmed Death-Ligand 1
PDAC/mPDAC	Pancreatic Ductal Adenocarcinoma/metastatic PDAC
PET	Positron Emission Tomography
PFS	Progression-free Survival
CCI	
CCI	
PK	Pharmacokinetic(s)
PMS2	PMS1 Homolog 2
PR	Partial Response
CCI	
CCI	
CCI	
CCI	
PSC	Pancreatic stellate cells
PSDS	Post-study drug supply
PS&PV	Patient Safety & Pharmacovigilance
PT	prothrombin time
PTA	Post Trial Access
PTT	Partial thromboplastin time

Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QMS	Quality Management System
QTc	Corrected QT Interval
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RD	Recommended dose
RDE	Recommended dose for expansion
RECIST	Response Evaluation Criteria In Solid Tumors
RMST	Restricted mean survival time
RNA	Ribonucleic Acid
RP3D	Recommended phase 3 dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARS-COVID-19	Severe acute respiratory syndrome Coronavirus disease 2019
SC	Steering Committee
SD	Standard deviation
SD (per RECIST)	Stable Disease
SJS	Stevens Johnson Syndrome
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SPC	Summary of Product Characteristics
SRT	Safety review team
STK11	Serine/Threonine Kinase 11
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEN	Toxic Epidermal Necrolysis/Lyell Syndrome
TGFβ	Transforming Growth Factor β
Tmax	Time to reach maximum drug concentration after dose administration
TMB	Tumor mutational burden
TNF	Tumor necrosis factor
TP53	Tumor protein p53
TSH	Thyroid Stimulating Hormone
TTR	Time to Response
UK	United Kingdom
ULN	Upper limit of normal
USPI	United States Prescribing Information
VAS	Visual analogue scale
vs.	Versus
WHO	World Health Organization
WOCBP	Women of Child-Bearing 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
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
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 drug (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 drug 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.
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.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Off-site healthcare Professional	A qualified healthcare professional, such as include those used in the study e.g. Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.

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.
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.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
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.
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	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
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
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
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.

Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
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 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 3 (18-Aug-2023)

Enrollment for the randomized part was completed on 18-Apr-2023 with a total of 490 subjects randomized and 21 enrolled in the safety run-in part.

Amendment rationale

As of 07-Jul-2023, treatment with NIS793/placebo was stopped based upon the DMC's recommendation CCI observed in the investigational treatment arm (NIS793 + gemcitabine + nab-paclitaxel). The trial was unblinded and subjects were allowed to continue with standard of care (SOC) chemotherapy (gemcitabine + nab-paclitaxel) per investigator assessment. As of 10-Aug-2023, 154 subjects were still receiving standard of care chemotherapy (gemcitabine + nab-paclitaxel) all in the randomized part, and no patients are receiving NIS793/placebo in the study.

This protocol amendment has been implemented to reduce the assessment burden for ongoing subjects, redefine the study completion date, incorporate updates to protocol per template language, and amend the planned data analysis milestones. In addition, the following changes are implemented:

Changes to the protocol

Changes to specific sections of the protocol are shown in the tracked changes version of the protocol using strike through red font for deletions and red underline for insertions.


CCI

IRBs/IECs

- A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities
- The changes described in this amended protocol require IRB/IEC approval prior to implementation
- The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment

Amendment 2 (13-Apr-2023)

As of 13-Apr-2023, 752 participants have been screened to the Randomized part with 468 participants randomized. In addition, twenty- one participants were previously enrolled to the Safety Run-in part.

Amendment rationale

In light of the most recently released NIS793 IB Ed 8, this protocol amendment is to update the relevant sections to reflect the changes made in the IB including the schedule of cardiac assessments (echocardiogram/cardiac imaging; ECG and cardiac specific enzymes, Troponin-I and NTproBNP; providing clearer guidance to investigators for collection and reporting of all relevant data in case of a cardiac AE to help with better characterization of a potential cardiac risk) and the most recent updates from NIS793 studies. In addition it includes clarifications to the most frequent questions received from participating countries. Please, refer to IB section 7.4.2.1 about cardiac disorders within the most recent version of NIS793 IB.

The protocol amendment will also incorporate the following changes:

- Changes and additional clarifications as described in the list of changes below
- Clarify the protocol text based on questions received from participating countries

Changes to the protocol

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CCI


CCI

IRBs/IECs

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- The changes described in this amended protocol require IRB/IEC approval prior to implementation.
- The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1 (08-Nov-2021)

Amendment rationale

As of 08-Nov-2021, three out of 149 sites had been initiated and three participants have been screened to the Safety Run-in part with one patient enrolled. Approximately 10 participants will be enrolled to the Safety Run-in part, and 480 participants will be enrolled to the Randomized part. There are approximately 29 countries and 149 sites participating in the trial.

The purpose of this amendment is to clarify the protocol text based on the questions received from health authorities, ethics committees/IRBs, and participating countries:

- Clarification to exclusion criterion #11 to specify where history of HCV with a confirmation of a cure is acceptable for study entry.
- Update to allow global or local sourcing of Placebo (i.e., 5% dextrose in water) for NIS793 (randomized part) and update to dosage form of gemcitabine and nab-paclitaxel.
- Update to overview of NIS793 with most recent safety data from CNIS793X2101 and CNIS793B12201 studies
- Amendment 1 also includes minor editorial changes and additional clarifications as described in the list of changes below.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.


CCI

IRBs/IECs

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

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

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

Protocol summary

Protocol number	CNIS793B12301
Full Title	A randomized, double-blind, phase III study, comparing NIS793 in combination with gemcitabine and nab-paclitaxel versus (vs.) placebo combined with gemcitabine and nab-paclitaxel for first line treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC)
Brief title	Study of efficacy and safety of NIS793 in combination with standard of care (SOC) chemotherapy in first-line metastatic pancreatic ductal adenocarcinoma (mPDAC)
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug; Biological
Study type	Interventional
Purpose	The purpose of this study is to evaluate the efficacy and safety of NIS793 in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel and placebo in first-line mPDAC. This study aims to explore whether blockade of Transforming Growth Factor β (TGFβ) in combination with gemcitabine/nab-paclitaxel can reduce fibrosis in PDAC, restore chemo-sensitivity and ultimately lead to improvements in overall survival (OS) and other clinically relevant outcomes. A safety run-in part will be conducted before opening a randomized part to confirm the recommended phase 3 dose (RP3D) of NIS793 in combination with SOC anti-cancer therapy.
Primary Objective(s)	**Safety run-in part:** The primary objective of the safety run-in part is to confirm the recommended phase 3 dose (RP3D) of NIS793 in combination with gemcitabine and nab-paclitaxel (SOC). **Randomized part:** The primary objective of the randomized part is to compare OS in participants with mPDAC treated as the first line treatment with the combination of NIS793, gemcitabine and nab-paclitaxel to the combination of placebo with gemcitabine and nab-paclitaxel. The primary clinical question of interest of the randomized part is to estimate the treatment effect on the primary endpoint of OS of NIS793 in combination with gemcitabine and nab-paclitaxel (arm A) compared to placebo in combination with gemcitabine and nab-paclitaxel (arm B) for the target population, regardless of discontinuation from study treatment, or start of a new subsequent antineoplastic therapy.
Secondary Objectives	**Safety run-in part**: To evaluate: • Safety and tolerability of NIS793 in combination with gemcitabine and nab-paclitaxel • Preliminary anti-tumor activity of NIS793 in combination with gemcitabine and nab-paclitaxel • Pharmacokinetics (PK) of NIS793 in combination with gemcitabine and nab-paclitaxel **Randomized part**: • To evaluate the efficacy (progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), duration of response (DOR), time to response (TTR)) in participants treated as the first line treatment of NIS793 in combination with gemcitabine and nab-paclitaxel versus placebo plus gemcitabine and nab-paclitaxel • To evaluate safety and tolerability in each treatment arm • To explore PK of NIS793 in combination with gemcitabine and nab-paclitaxel • To characterize the incidence of immunogenicity of NIS793 in combination with gemcitabine/nab-paclitaxel

Study design	This is a multicenter, double-blind, two-arm, randomized phase III study that will have two parts: a safety run-in part and a 2-arm randomized part. The study will be conducted in multiple geographical regions. **Safety run-in part:** Approximately 10 participants will be enrolled at the starting dose to achieve at least 6 evaluable patients; however, if the starting dose is not recommended and a lower dose level is tested, 10 additional participants will be enrolled **Randomized part:** Approximatively 480 participants will be recruited and randomized (1:1 ratio) to the two treatment arms (~240/per arm). Participants will be stratified at randomization by performance status (0 vs. 1), presence of liver metastasis (yes vs. no), and region (North America, Europe, and Australia vs. other countries). As of 07-Jul-2023, study participants will no longer receive NIS793/placebo. Participants may continue to receive gemcitabine and nab-paclitaxel per investigator's assessment.
Rationale	This study will recruit participants with previously untreated mPDAC who have a poor prognosis and limited treatment options. The OS 5 year-rate is below 10% with currently approved chemotherapies, thus highlighting the need for innovative therapeutic options. Based on in vitro and in vivo preclinical, translational, and preliminary clinical data, it is expected that the addition of TGFβ-blockade to chemotherapy can reduce intratumoral fibrosis, improve chemosensitivity and allow a more robust anti-tumor response.
Study population	The study in both Safety run-in and Randomized part will include adult participants with mPDAC who have not received any prior systemic anti-cancer treatment for metastatic disease.
Key Inclusion criteria	Applicable for both Safety run-in and Randomized part • Participants aged ≥18 years with histologically or cytologically confirmed (based on local assessment and per local guidelines) mPDAC eligible for treatment in the first line setting and not amenable for potentially curative surgery • Presence of at least one measurable lesion assessed by Computerized Tomography (CT) and/or Magnetic Resonance Imaging (MRI) according to RECIST 1.1 • Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1 • Adequate organ function (assessed by central laboratory for eligibility) • Participants must have recovered from treatment-related toxicities of prior anticancer therapies to grade ≤ 1 (CTCAE v 5.0) at time of screening, except alopecia.
Key Exclusion criteria	Applicable for both Safety run-in and Randomized part • Previous systemic anti-cancer treatment for metastatic PDAC • Pancreatic neuroendocrine (islet) or acinar tumors • Participants with known status of microsatellite instability-high (MSI-H) or mismatch repair-deficient pancreatic cancer (if status is not already available, testing is not required at screening). • 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. • Radiation therapy 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). • Impaired cardiac function or clinically significant cardio-vascular disease • Use of hematopoietic growth factors or transfusion support ≤ 2 weeks prior to start of study treatment. • 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. • Serious non-healing wounds. • 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 indicated • Pre-existing peripheral neuropathy > grade 1 (CTCAE v5.0)

Study treatment	**Safety run-in:** combination of NIS793, gemcitabine and nab-paclitaxel **Randomized part:** Participants will be randomized to one of two treatment arms: • Investigational arm (Arm A): combination of NIS793, gemcitabine and nab-paclitaxel • Control arm (Arm B): combination of placebo, gemcitabine and nab-paclitaxel A cycle of treatment is defined as 28 days. As of 07-Jul-2023, participants will no longer receive NIS793/placebo. Participants may continue to receive gemcitabine and nab-paclitaxel per investigator's assessment.
Efficacy assessments	Applicable for both Safety run-in and Randomized part: Radiological tumor assessment by Investigator per RECIST 1.1 at screening, every 8 weeks for first year, then every 12 weeks. Survival assessments every 8 weeks after safety and efficacy follow-up periods.
Pharmacokinetic assessments	**Safety run-in:** PK parameters including e.g. maximum drug concentration after dose administration (Cmax) and trough concentrations (Ctrough), for NIS793 in combination with gemcitabine and nab-paclitaxel **Randomized part:** For participants CCI : • NIS793 serum concentrations over time and derived PK parameters (e.g. Cmax, area under the curve (AUC)) For participants CCI • PK parameters including Cmax, Ctrough and trough concentrations (steady state) ($Trough_{ss}$) for NIS793 Post implementation of protocol amendment 3, PK samples will no longer be collected.
Key safety assessments	**Safety run-in and Randomized part:** Physical examination ECOG performance status Vital signs, body weight Laboratory assessments Electrocardiogram (ECG), Cardiac imaging / enzymes Monthly pregnancy testing for women of childbearing potential, Adverse events (AEs) severity and relationship to study treatment and seriousness Post implementation of protocol amendment 3, refer to Table 8-2b for a list of applicable assessments.
CCI	

	CCI [redacted]
Data analysis	**Safety Run-in part:** The primary endpoint for the safety run-in part is the incidence of dose-limiting toxicity (DLT) during the DLT evaluation period. 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 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. For the treatment arm NIS793+SOC, the DLT evaluation period for each cohort is one cycle of treatment (i.e, approximately 4 weeks or 28 days). **Randomized part:** The following null and alternative hypothesis will be tested to address the primary efficacy objective for OS of arm A vs. arm B: $H_{01}:\theta_1 \geq 1$ vs. $H_{A1}:\theta_1 < 1$ where θ_1 is the OS hazard ratio (HR) of arm A vs. arm B. The null hypothesis will be tested with a stratified log-rank test at an overall one-sided 2.5% significance level. The stratification will be based on the randomization stratification factors: ECOG PS (0 vs. 1); liver metastasis (yes vs. no); region at enrollment (North America, Europe and Australia vs. other countries). CCI [redacted] Analyses will be based on the full analysis set (FAS) population according to the randomized treatment group and strata assigned at randomization. The hazard ratio for OS will be calculated, along with its 95% confidence interval (CI), from a stratified Cox model using the same stratification factors as for the log-rank test. The OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% CIs of the medians will be presented for each treatment group. The hazard ratio for OS will be calculated, along with its 95% CI, from a stratified Cox model using the same stratification factors as for the log-rank test. Secondary endpoints: To control the overall type I error, a hierarchical testing for secondary endpoints will be performed. If the primary comparison of OS is significant, the following tests of secondary endpoints will then be conducted each at a one-sided 2.5% level of significance: 1. PFS by investigator per RECIST 1.1 by stratified log-rank test 2. ORR per RECIST 1.1 by Cochran–Mantel–Haenszel chi-square test The PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% CIs of the medians will be presented for each treatment group. The hazard ratio for PFS will also be calculated, along with its 95% CI, using a stratified Cox model for the same stratification factors. The tumor related efficacy variables (ORR, DCR, TTR and DOR based on RECIST 1.1 will also be compared between the two treatment arms. ORR, DCR and their 95% CI will be presented by treatment arm. The distribution functions of TTR and DOR will be estimated using the Kaplan-Meier method. The median TTR and DOR along with their 95% CIs will be presented by treatment arm. Post implementation of protocol amendment 3, CCI [redacted] no hypothesis testing will be performed. The final analysis will occur as defined in Section 9.3. Accumulated data may be analyzed at any time prior to the final analysis to evaluate endpoints related to the safety of study participants.
Key words	NIS793, gemcitabine, nab-paclitaxel, mPDAC, TGFβ, Phase III

1 Introduction

1.1 Background

Pancreatic ductal adenocarcinoma (PDAC) represents a significant public health burden, (American Cancer Society 2023 Cancer Facts & Figures), with a 5-year survival rate of approximately 2.9% (Sohal et al 2020). In the absence of improvements in early diagnosis and treatment, PDAC will likely become the second leading cause of death worldwide by 2030 (Rahib et al 2014). There are two recommended first-line chemotherapy treatments for metastatic PDAC, FOLFIRINOX (a combination of 5-fluorouracil, folinic acid, irinotecan plus oxaliplatin) or gemcitabine plus nab-paclitaxel and the reported median overall survival (mOS) for both regimens is less than 12 months (Lambert et al 2017; Conroy et al 2011; Tempero et al 2019; Van Cutsem et al 2020). FOLFIRINOX is usually reserved for patients with good performance status (e.g., ECOG performance status 0-1) due to the toxicity associated with this combination regimen. Unlike other common cancers, survival gains have only improved slightly for advanced pancreatic cancer patients over the past decades and additional treatments are urgently needed (Sohal et al 2020).

One of the reasons for the poor response to therapeutic treatments in PDAC has been attributed to the extensive stromal response in this indication. PDAC displays in fact the most prominent desmoplastic reaction of all epithelial tumors (Erkan et al 2012; Neesse et al 2015), characterized by an abundance of activated stroma and progressive accumulation of extracellular matrix (ECM) proteins such as hyaluronic acid, which altogether contribute to tissue structural rigidity and poor perfusion. These structural aberrations significantly reduce penetration of macromolecules, hindering the tumor intake of therapeutics (Provenzano et al 2012; Feig et al 2012). Intra-tumoral fibrosis in PDAC is known to correlate with poor survival even after resection (Watanabe et al 2003; Erkan et al 2008). New agents targeting the desmoplastic tumor microenvironment may therefore represent an opportunity to establish novel therapeutic paradigms in the treatment of PDAC (Neesse et al 2015).

In this context, TGFβ-blockade offers the potential to address some of the aberrations of the PDAC microenvironment, due to its pleiotropic effects on stroma. In particular, TGFβ plays a pivotal role in the activation of pancreatic stellate cells (PSC), the most abundant type of fibroblasts in the pancreas and the chief organizers of the desmoplastic reaction (Apte et al 2004). As the expression of TGFβ increases throughout disease progression, so does the conversion of stellate cells into myofibroblasts, as well as the fibrotic response. Notably, studies have shown that TGFβ signaling components are often genetically silenced in the pancreatic cancer cells, disabling the tumor intrinsic suppressive activity of TGFβ and cooperating instead with other genetic alterations to promote tumor initiation and malignant progression (Jakowlew 2006; Neuzillet et al 2014). These molecular alterations likely represent a mechanism for pancreatic cancer cells to grow and spread in an overly high TGFβ microenvironment (Ciardiello et al 2020).

1.1.1 Overview of NIS793

NIS793 is an investigational recombinant human anti-TGFβ IgG2 monoclonal antibody (mAb). NIS793 has been initially evaluated in the first-in-human CNIS793X2101 study in adult patients with solid malignancies. In this study 120 patients 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 at the dose of 0.3 mg/kg/100 mg Q3W;
- NIS793/spartalizumab at the dose of 0.3-30 mg/kg/300 mg Q3W;
- NIS793/spartalizumab at the dose of 20-30 mg/kg Q2W/400 mg Q4W;
- NIS793/spartalizumab at the dose of 2100 mg/300 mg Q3W.

No patients experienced a dose limiting toxicity (DLT). NIS793 30 mg/kg Q3W in combination with spartalizumab 300 mg Q3W was the determined recommended dose for expansion (RDE), which translates to 2100 mg NIS793 and 300 mg spartalizumab Q3W flat-based dose. NIS793 20 mg/kg Q2W in combination with spartalizumab 400 mg Q4W was declared an alternative RDE, which translates to 1400 mg NIS793 Q2W and 400 mg 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-Jun-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%), 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, secondary to dyspnoea and 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.

The PK of NIS793 have been characterized in the CNIS793X2101 study (clinical cut-off date of 18-Jun-2021). Following administration of NIS793 via a 30-minute intravenous infusion, approximately a dose-proportional increase in NIS793 exposure [i.e., Cycle 1 max serum concentration (Cmax) and AUClast] was observed from 0.3 mg/kg to 30 mg/kg. Moderate

accumulation (approximately up to 2.0-fold) of NIS793 was observed based on the ratio of AUClast and Cmax on cycle 3 versus cycle 1. PK variability was low to moderate as illustrated by between subject variability [coefficient of variation % (CV%)] (e.g., 12.9 to 58.3 % for Cmax).

Based on preliminary population PK analysis, the estimated terminal half-life is approximately 18 days (95% confidence interval: 9 to 30 day), the systemic clearance is 9 mL/h with inter-individual variability of 31% and the volume of distribution at steady state is 5.1 L, consistent with the values typical for a monoclonal antibody. There was no significant difference in PK observed among various tumor types. For ongoing studies, 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 and the safety data from ongoing studies, does not impact the benefit-risk profile of NIS793 in combination with standard of care therapies for treatment of mPDAC subjects in this study. Please refer to NIS793 IB for further updated information and details.

1.2 Purpose

The purpose of the Safety run-in part is to assess the recommended phase 3 dose (RP3D) of NIS793 in combination with SOC anti-cancer therapy.

The purpose of the randomized part of this phase III study is to assess the efficacy and safety of NIS793 in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel and placebo in untreated mPDAC.

This phase III study aims to explore whether blockade of TGFβ in combination with standard of care (SOC) chemotherapy gemcitabine/nab-paclitaxel in the first line treatment of mPDAC can reduce fibrosis in PDAC, restore chemosensitivity and ultimately lead to improvements in overall survival and other clinically relevant outcomes.

As of 7-Jul-2023, the administration of NIS793/placebo was stopped based upon the DMC's recommendation CCI [redacted] in the investigational treatment arm (NIS793 + gemcitabine + nab-paclitaxel).

Despite the study not being able to address its primary objective for the randomized part, the DMC encouraged the continuing administration of gemcitabine/nab-paclitaxel to all subjects per Investigator's assessment, and the collection of additional follow-up data to better characterize the safety of NIS793 in combination with gemcitabine/nab-paclitaxel.

2 Objectives, endpoints and estimands

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 3 dose (RP3D) of NIS793 in combination with gemcitabine and nab-paclitaxel (SOC). • **Randomized part**: To compare OS in participants with mPDAC treated as the first line treatment with the combination of NIS793, gemcitabine and nab-paclitaxel to the combination of placebo with gemcitabine and nab-paclitaxel.	• **Safety run-in part**: Incidence of DLTs during the first cycle (4 weeks) of treatment • **Randomized part**: Overall Survival (OS)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
Safety run-in part: • To evaluate safety and tolerability of NIS793 in combination with gemcitabine and nab-paclitaxel	**Safety run-in part:** • Safety: Incidence and severity of AEs including changes in laboratory parameters, vital signs, body weight and cardiac assessments • Tolerability: Dose interruptions, reductions and dose intensity
• Pharmacokinetics (PK) of NIS793 in combination with gemcitabine and nab-paclitaxel	• PK parameters including e.g. Cmax and Ctrough for NIS793 in combination with gemcitabine and nab-paclitaxel
• Preliminary anti-tumor activity of NIS793 in combination with gemcitabine and nab-paclitaxel	• 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 OS
Randomized part: • To evaluate the efficacy (PFS, ORR, DCR, DOR, TTR) in participants treated as the first line treatment of NIS793 in combination with gemcitabine and nab-paclitaxel versus placebo plus gemcitabine and nab-paclitaxel	**Randomized part:** • PFS, ORR, DCR, DOR and TTR by Investigator's assessment per RECIST 1.1
• To evaluate safety and tolerability in each treatment arm	• Incidence and severity of AEs and SAEs, changes in laboratory parameters, vital signs, body weight and cardiac assessments; dose interruptions, reductions and dose intensity
• To explore pharmacokinetics (PK) of NIS793 in combination with gemcitabine and nab-paclitaxel	• CCI [redacted], NIS793 serum concentrations over time and derived PK parameters (e.g. Cmax, AUC) • For participants CCI [redacted], PK parameters including Cmax, Ctrough and $C_{trough_{ss}}$ for NIS793
• To characterize the incidence of immunogenicity of NIS793 in combination with gemcitabine/nab-paclitaxel	• Anti-drug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI [redacted]	

Objective(s)	Endpoint(s)
	

2.1 Primary estimands

The primary estimand is specified for the randomized part only.

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).

The primary scientific question of interest is to estimate the treatment effect on the primary endpoint of overall survival of NIS793 in combination with gemcitabine and nab-paclitaxel (arm A) compared to placebo in combination with gemcitabine and nab-paclitaxel (arm B) for the target population, regardless of discontinuation from study treatment, or start of a new subsequent antineoplastic therapy.

The primary estimand is described by the following five attributes:

1. Population: all randomized participants with mPDAC treated with the first line treatment. Further details on the population characteristics are provided in the eligibility criteria.
2. Treatment: randomized treatments, i.e. NIS793 in combination with gemcitabine/nab-paclitaxel or placebo and gemcitabine/nab-paclitaxel with or without any new subsequent

antineoplastic therapy as needed. Further details about treatments are provided in Section 6.1.

3. Variable: overall survival (OS) defined as the time from the date of randomization to the date of death due to any cause.
4. Handling of remaining intercurrent events:
   - Discontinuation of study treatment for any reason:

OS will take into account all deaths irrespective of the study treatment discontinuation (treatment policy strategy)

- Any unforeseen intercurrent events (e.g., Coronavirus disease 2019 (COVID-19) -related events):

OS will take into account all deaths irrespective of any unforseen intercurrent events (treatment policy strategy)

5. Summary measure: hazard ratio (HR) for OS between the two treatment arms A and C.

2.2 Key secondary estimands

There are no secondary key estimands for this study.

3 Study design

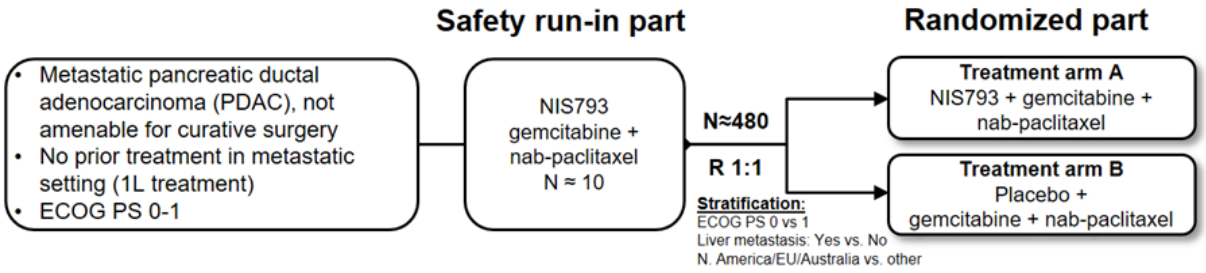
This is a randomized, double-blind, multicenter two-arm, phase III study that has two parts: a safety run-in part and a 2-arm randomized part. The study will be conducted in multiple geographical regions.

The study is expected to enroll approximately 10 participants in the safety run-in part and approximately 480 participants in the randomized part.

The decision to open the randomized part of the study will be based on dose confirmation and available safety, relevant PK, and other clinical and laboratory data from the safety run-in part.

An overview of the study design is depicted in Figure 3-1.

Figure 3-1 Study design



Safety run-in part

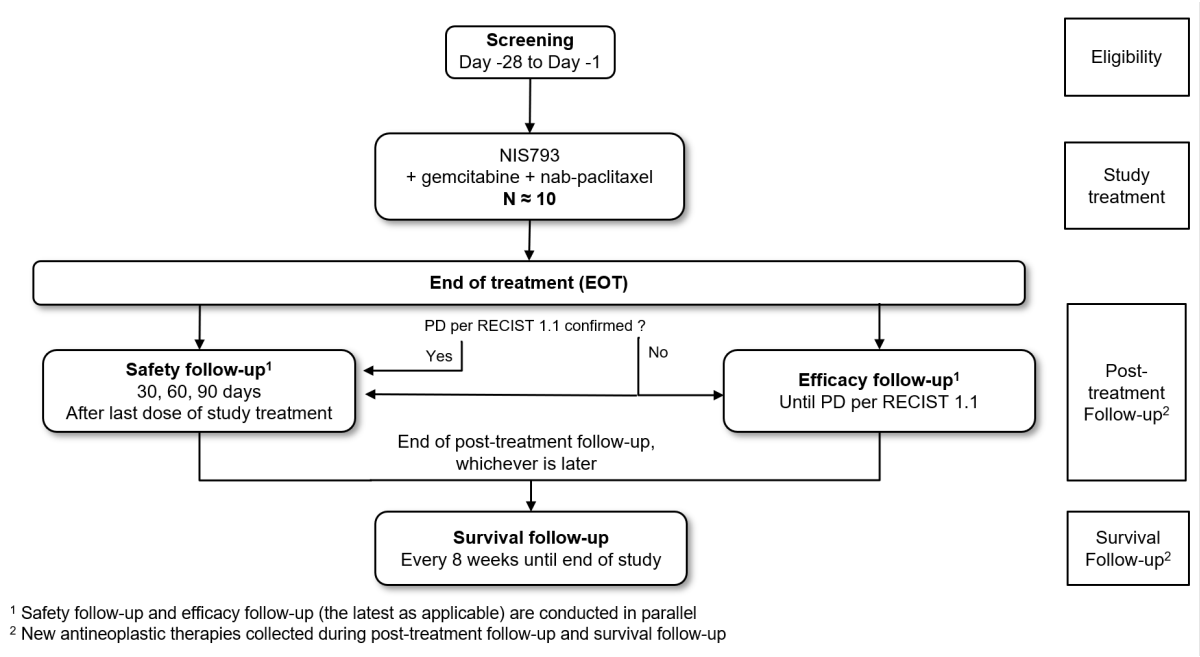
An open-label **safety run-in part** will be conducted to confirm RP3D of NIS793 in combination with gemcitabine and nab-paclitaxel. The safety run-in part will start with one treatment regimen – NIS793 (2100 mg every 2 weeks (Q2W)) in combination with gemcitabine and nab-

paclitaxel. Up to approximately 10 participants will be enrolled at each dose level to have at least 6 evaluable participants for the newly investigated treatment regimen during the dose limiting toxicities (DLT) assessment period. DLT assessment period is defined as first cycle (i.e. 28 days, or 4 weeks) of dosing of the study treatment. If the starting dose is not considered tolerable and the NIS793 dose is de-escalated to -1 dose level (2100 mg every 4 weeks (Q4W)), then an additional 10 participants will be enrolled in a cohort at the lower dose level. If the lower dose is not considered safe, the study will be terminated.

Dose confirmation will be guided by an adaptive 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 patients 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 (European Medicines Agency (EMA) 2007) and it constitutes an important aspect of the FDA's Critical Path Initiative (Food and Drug Administration (FDA) 2004).

For a diagram of the study flow in the safety run-in part, see Figure 3-2. Patients will undergo safety and efficacy assessments during screening, treatment, and follow-up as outlined in Table 8-2a visit evaluation schedule.

Figure 3-2 Study flow - Safety run-in part



[1] Safety follow-up and efficacy follow-up (the latest as applicable) are conducted in parallel
[2] New antineoplastic therapies collected during post-treatment follow-up and survival follow-up

Randomized part

The randomized part will enroll approximately 480 participants randomized 1:1 to the two treatment arms (~240/arm). Participants will be stratified at randomization by ECOG performance status (0 vs. 1), presence of liver metastasis (yes vs. no), and region (North America, Europe and Australia vs. other countries).

Participants will be randomized to one of two treatment arms:

- Investigational arm (Arm A): combination of NIS793, gemcitabine and nab-paclitaxel
- Control arm (Arm B): combination of placebo, gemcitabine and nab-paclitaxel

Crossover will not be allowed during the study duration.

This is a superiority study that will compare Arm A to Arm B to support the primary objective.

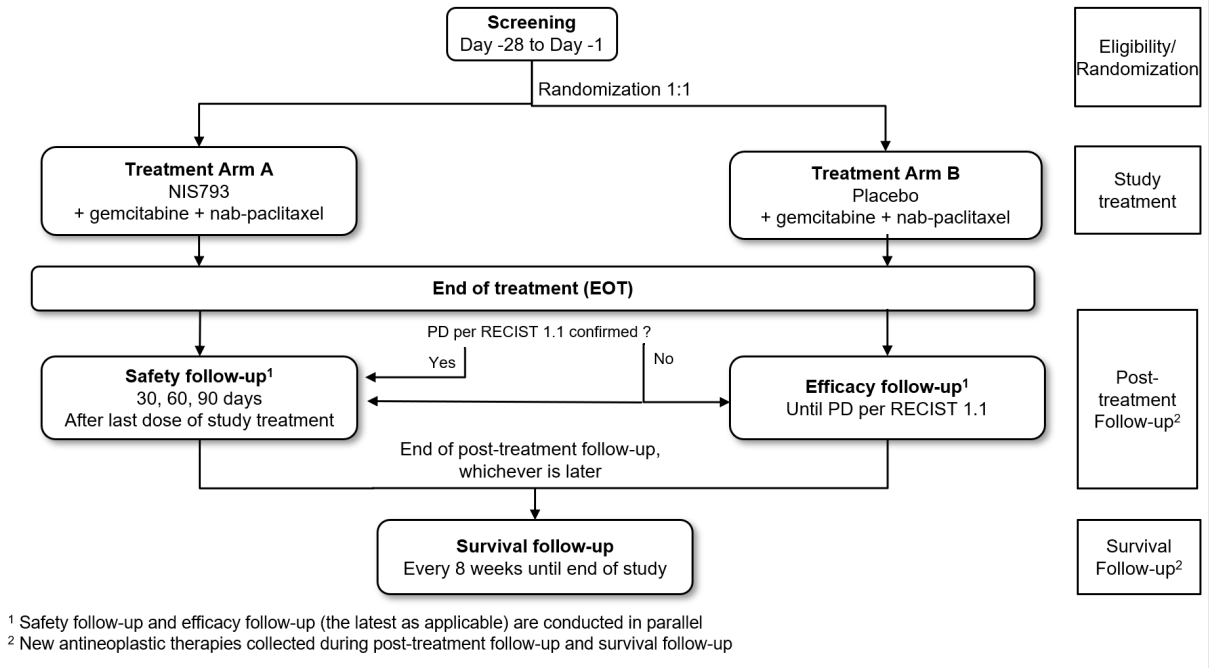
The study treatment is administered as a 28-day treatment cycle. NIS793 will be administered at a flat dose as confirmed in the safety run-in part on day 1 and 15 (e.g., 2100 mg intravenous (i.v.) Q2W or 2100 mg i.v. Q4W, if Q2W is considered as not tolerable in safety run in part) . Gemcitabine (1000 mg/m² on days 1, 8 and 15) and nab-paclitaxel (125 mg/m² on days 1, 8 and 15) will be given as per label.

Participants will be treated with study treatment until unacceptable toxicity, disease progression per RECIST 1.1, withdrawal of consent/opposition to use data/biological samples, or any other condition of treatment discontinuation conditions specified in the protocol, whichever is earlier.

As of 7-Jul-2023, the administration of NIS793/placebo was stopped for all subjects following the recommendation from DMC.

For a diagram of the study flow in the randomized part, see Figure 3-3. Patients will undergo safety and efficacy assessments during screening, treatment, and follow-up as outlined in Table 8-2a visit evaluation schedule.

Figure 3-3 Study flow - Randomized part



At the investigator's direction and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedure according to the assessment schedule in Table 8-2a (Note: Post protocol amendment 3, Table 8-2b must be followed), performed at a remote location. Procedures will be performed remotely under the oversight of the Investigator, who retains accountability for the oversight and all efficacy and safety decisions with delegation of tasks to an off-site healthcare professional. Novartis has the right to decide at any time what can and cannot be performed remotely.

4 Rationale

4.1 Rationale for study design

This prospective, randomized, double-blinded, multi-center, parallel, two-arm phase III study has been designed to evaluate the safety and efficacy of the investigational anti-TGFβ mAb, NIS793, in combination with the approved regimen of gemcitabine and nab-paclitaxel, in participants with previously untreated mPDAC. A Safety run-in part will be conducted before opening the randomized part to confirm the recommended phase 3 dose (RP3D) of NIS793 in combination with anti-cancer therapy.

This study will recruit participants with previously untreated mPDAC who in general have poor prognosis with available treatment options (Section 1.1 and Section 1.2). The OS 5 year-rate is below 10% with currently approved chemotherapies, thus highlighting the need for innovative therapeutic options (Sohal et al 2020).

Mouse models of pancreatic cancer have been poorly responsive to single agent TGFβ blockade, however the stromal modulating properties of TGFβ blockade indicate that it may

synergize in appropriately designed combination strategies (Greco et al 2015; Ostapoff et al 2014).

Based on in vitro and in vivo preclinical, translational, and preliminary clinical data it is expected that the addition of TGFβ-blockade to chemotherapy can improve chemosensitivity and allow a more robust anti-tumor response.

Table 4-1 Rationale for study design

Study Design Aspects	Rationale
Parallel two-arm design	This parallel study design will assess the efficacy of Arm A as compared to the control Arm B. The primary endpoint of interest is OS . OS is an acceptable primary endpoint for this indication.
Choice of background therapy	Gemcitabine/nab-paclitaxel, is a globally approved chemotherapy regimen for the first-line treatment of mPDAC (see Section 4.1.1).
Double Blinding	This is to reduce operational bias in assessments of efficacy, safety and PRO outcomes.
Randomization (strata, allocation ratio)	Participants will be randomized with a 1:1 ratio. The randomization will be stratified by ECOG performance status (0 vs. 1), presence of liver metastasis (yes vs. no), and region (North America, Europe, and Australia vs. other countries) due the expected difference in clinical outcomes between participants in these groups (Von Hoff et al 2013; Conroy et al 2011)
New visit schedule post implementation of protocol amendment 3	Protocol amendment 3 will allow participants to continue the study following a less intense safety and efficacy assessment, aligned with standard of care.

4.1.1 Rationale for choice of background therapy

The combination of gemcitabine plus nab-paclitaxel, an approved chemotherapy regimen for the treatment of first-line mPDAC, was chosen as backbone therapy in this study based on its tolerability profile and its use is recommended by clinical guidelines (National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO)) in this setting. The dose and regimen selected for this study are in accordance with each product labeling.

4.2 Rationale for dose/regimen and duration of treatment

In this study, the preliminary selection of NIS793 dose and regimen was based on available clinical safety, efficacy and PK information from clinical trial CNIS793X2101 and prescribing information for chemotherapy drugs gemcitabine and nab-paclitaxel. CNIS793B12201 is a randomized, parallel three-arm, open-label, multi-center, phase II study to evaluate the efficacy and safety of NIS793 with and without spartalizumab in combination with gemcitabine and nab-paclitaxel in participants with first-line mPDAC. The study is expected to enroll at least 156 participants. The study is currently ongoing and enrolled the first participant on the 16-Oct-2020 in the Safety Run-in part (enrolling at least 6 evaluable participants) to assess the safety and tolerability of NIS793 in combination with spartalizumab and SOC gemcitabine and nab-paclitaxel. CCI

CCI

In CNIS793X2101 study, the NIS793 recommended dose for expansion (RDE) was declared as 30 mg/kg every 3 weeks (Q3W) of NIS793 (equivalent to 2100 mg NIS793 Q3W as a fixed dose) in combination with spartalizumab 300 mg Q3W. However, the Phase II (CNIS793B12201) and this study will explore the maximum safe dose for NIS793 of 2100 mg Q2W, evaluated in CNIS793X2101. As of 18-May-2021, 11 participants (100%), who received NIS793 at a dose of 30 mg/kg Q2W in a combination with spartalizumab (CNIS793X2101), reported 59 AEs of any grades; of these, there were 12 grade ≥ 3 AEs experienced by 5 participants (45.5%) (n=3 participants experienced anaemia; n=1 participant experienced abdominal pain, rash, vomiting, asthenia, dyspnea, blood bilirubin, hypokalemia pain in extremity, paresthesia each). For more details, please refer to NIS793 IB. In addition, accumulation of total TGFβ-1 levels under treatment with NIS793 at the dose of 30 mg/kg Q2W indicated that there was sustained target engagement in systemic circulation over the dosing period, although there was no clear pattern between systemic exposure of NIS793 and/or dose and clinical efficacy. Overall, due to the sustained target engagement and the absence of safety concerns in patients who received NIS793 at 30 mg/kg Q2W, a flat dose of 2100 mg Q2W was selected to maximize the probability of successful treatment in mPDAC a highly desmoplastic tumor resistant to chemotherapy, where other ECM-targeted agents have previously failed.

Population PK analysis on the concentration data from the dose escalation phase of the study CNIS793X2101 was used to describe the PK of NIS793 including the impact of weight as a covariate on clearance and volume of distribution. Although body weight was a covariate on clearance, the predicted exposures at steady state between weight-based and fixed dosing regimens were comparable across different body weight categories. This analysis supports the use of fixed or flat dosing on a mg basis irrespective of participant body weight, as weight-based dosing does not decrease inter-individual variability.

Approved doses for gemcitabine (1000 mg/m^2) and nab-paclitaxel (125 mg/m^2) will be administered on days 1, 8, and 15 of each 4 week-cycle (refer to locally approved prescribing information).

4.3 Rationale for choice of combinations

This phase III study aims at exploring whether the NIS793-mediated reduction of intratumoral fibrosis through TGFβ inhibition in a highly desmoplastic, immune-excluded tumor such as mPDAC can relieve resistance to chemotherapy.

NIS793 will be combined with gemcitabine plus nab-paclitaxel, an approved chemotherapy regimen for the treatment of first-line mPDAC (Cascinu et al 2010; Sohal et al 2020).

4.4 CCI

CCI

CCI

4.5 Risks and benefits

Participants enrolled in this study are patients with mPDAC for which current available treatments (i.e. combination chemotherapy) are associated with limited efficacy with a median OS of less than 12 months (Conroy et al 2011; Von Hoff et al 2013), highlighting the significant unmet medical need in this disease.

The blockade of TGFβ with NIS793 in combination with SOC chemotherapy, gemcitabine and nab-paclitaxel, is expected to reduce fibrosis, enhancing the antitumor effect of chemotherapy and ultimately leading to improved overall survival of patients with mPDAC.

The investigational agent NIS793 will be combined with gemcitabine and nab-paclitaxel, an approved chemotherapy regimen for the treatment of first-line mPDAC with a well-characterized safety profile.

Based upon the available pre-clinical and clinical safety information for NIS793 clinical development programs and the known mechanism of action of the three study drugs and the known safety profile of SOC drugs, the combination of NIS793 with SOC may result in potential overlapping toxicity namely, neutropenia, febrile neutropenia, hypersensitivity reactions, infusion reactions, diarrhea, hypertension, hemorrhage, cardiac disorders, and skin reactions. Details regarding these adverse events are provided in the NIS793 Investigator Brochure along with guidance to investigators. Risk minimization and management measures include appropriate eligibility criteria (Section 5.1 and Section 5.2), well defined dose-limiting toxicity criteria, regular safety assessments including physical examination and investigations, and dose modification and management guidance for individual toxicities in the study protocol (Section 6.5).

All participants enrolled will be closely monitored for any adverse events while on study treatment and for an appropriate duration after the end of study treatment. The safety profile of this combination regimen will be defined on the basis of an ongoing review of the safety data.

Overall, based on the preliminary tolerability and target engagement observed in the NIS793 FIH study, CNIS793X2101, and the currently available safety data from ongoing studies, benefit-risk profile of the combination of NIS793 and gemcitabine/nab-paclitaxel are considered acceptable for treatment of participants with first-line mPDAC being evaluated in this study.

In addition, an iDMC will review available data at defined intervals to guarantee participants' safety.

Women of childbearing 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 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.

4.6 Rationale for Public Health Emergency mitigation procedures

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

5 Study Population

The study will include adult participants with mPDAC who have not received any prior systemic anti-cancer treatment for metastatic disease.

The investigator or designee must ensure that only participants who meet all the following inclusion criteria and none of the exclusion criteria are enrolled 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 (based on local assessment and per local guidelines) metastatic pancreatic ductal adenocarcinoma (mPDAC) eligible for treatment in the first line setting and not amenable for potentially curative surgery
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 0-1
6. Adequate organ function as defined by the following laboratory values (assessed by central laboratory for eligibility)
   - Absolute neutrophil count ≥ 1.5×10^9/L

- Platelets count ≥ 100 × 10^9/L
- Hemoglobin ≥ 9 g/dL
- Calculated creatinine clearance ≥ 60 mL/min (by using Cockcroft-Gault equation)
- Albumin ≥ 3 g/dL
- Prothrombin time (PT)/international normalized ratio (INR) and partial thromboplastin time (PTT) ≤ 1.5 x ULN (upper limit of normal). Participants requiring therapeutic anticoagulants are eligible if coagulation parameters are within therapeutic range.
- Total bilirubin ≤ 1.5 X ULN
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x ULN (≤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. Woman 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. Participants must have recovered from treatment-related toxicities of prior anticancer therapies to grade ≤ 1 (CTCAE v 5.0) at 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. Previous systemic anti-cancer treatment for metastatic PDAC

   Note: Previous neo-/adjuvant anti-cancer therapy for non-metastatic PDAC with last dose administered ≥6 months before the start of study treatment are allowed, providing that the treatment did not include anti-TGFβ antibody or TGFβ-targeting drug, or any of the study drugs for the disease under investigation (gemcitabine and nab-paclitaxel).
2. Pancreatic neuroendocrine (islet) or acinar tumors.
3. Participants with known status of microsatellite instability-high (MSI-H) or mismatch repair-deficient pancreatic cancer (if status is not already available, testing is not required at screening).
4. Presence of symptomatic central nervous system (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.
5. Known history of severe allergy or hypersensitivity to any of the study drugs or their 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 nab-paclitaxel and gemcitabine local prescribing information (e.g., Summary of Product Characteristics [SPC], United States Prescribing Information [USPI], etc.).
6. Participant is currently receiving any of the prohibited medications as outlined in Section 6.2.2 or in the nab-paclitaxel and gemcitabine local prescribing information, and

these cannot be discontinued ≥ 7 days or 5 half-lives, whichever is longer, before the first dose of that drug

7. 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.
8. Radiation therapy 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)
9. 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 < 3 months prior to study entry
   - Left ventricular ejection fraction <50%
   - Elevated cardiac enzymes (troponin I) elevation >2xULN
   - Cardiac valvulopathy ≥grade 2
   - Uncontrolled hypertension defined by a systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg
10. 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)
11. Active or chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections.

    Note: Patients with a history of hepatitis C virus (HCV) infection must have been treated with confirmation of cure, to be considered as eligible
12. 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: Participants with localized condition unlikely to lead to a systemic infection (e.g. chronic nail fungal infection) are eligible.
13. Use of hematopoietic growth factors or transfusion support ≤ 2 weeks prior to start of study treatment
14. 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
15. Serious non-healing wounds
16. Pre-existing peripheral neuropathy > grade 1 (CTCAE v5.0)
17. 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.
18. Any significant medical condition, laboratory abnormality or psychiatric or social condition that would constitute unacceptable safety risks to the patients, contraindicate patient participation in the clinical study, limit the patient's ability to comply with study requirements, or compromise patient's compliance with the protocol and all requirements of the study as stated in the Informed Consent Form (ICF). Significant medical conditions

include but are not limited to known history or current interstitial lung disease or non-infectious pneumonitis, 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 clinically significant deep vein thrombosis, pulmonary embolism or other clinically significant thromboembolic event.

19. Pregnant or breast-feeding (lactating) women, or women who plan to become pregnant or breast-feed during the study treatment and/or safety follow-up.
20. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are willing to use highly effective methods of contraception during treatment and for 90 days after stopping NIS793. Contraception use during treatment and after stopping SOC 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 contraception 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.

    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).

21. 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

6 Treatment

6.1 Study treatment

For this study, the investigational drug is NIS793, an anti-TGFß human monoclonal antibody. The study treatment is the combination of NIS793, gemcitabine and nab-paclitaxel versus the combination of placebo, gemcitabine and nab-paclitaxel.

Note: As of 7-Jul-2023, NIS793/placebo is no longer being administered.

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.

The study drugs will be administered at the recommended dose (RD) and/or per label as follows:

Safety run-in part:

- NIS793 at 2100 mg (Days 1 and 15)
- Gemcitabine at 1000 mg/m² (Days 1, 8 and 15)
- Nab-paclitaxel at 125 mg/m² (Days 1, 8 and 15)

Randomized part:

- NIS793 at 2100 mg or placebo (Days 1 and 15) assuming this is the confirmed RP3D in the safety run-in part or NIS793 at 2100 mg on Day 1 if dose level -1 is the confirmed RP3D in the safety run-in
- Gemcitabine at 1000 mg/m² (Days 1, 8 and 15)
- Nab-paclitaxel at 125 mg/m² (Days 1, 8 and 15)

Refer to Figure 6-1 for sequence of drug dispensing and to Section 6.7.2 for drug prescribing and administration information.

During the first two infusions (normally during the first cycle), participants should be closely observed and vital signs should be monitored more frequently if clinically indicated, during and for at least 2 hours after infusion of NIS793. No other treatment like pre-medications for subsequent chemotherapy will be allowed during this period. The same approach for observation and monitoring may be applied for subsequent cycles of NIS793 or placebo infusion, if medically indicated.

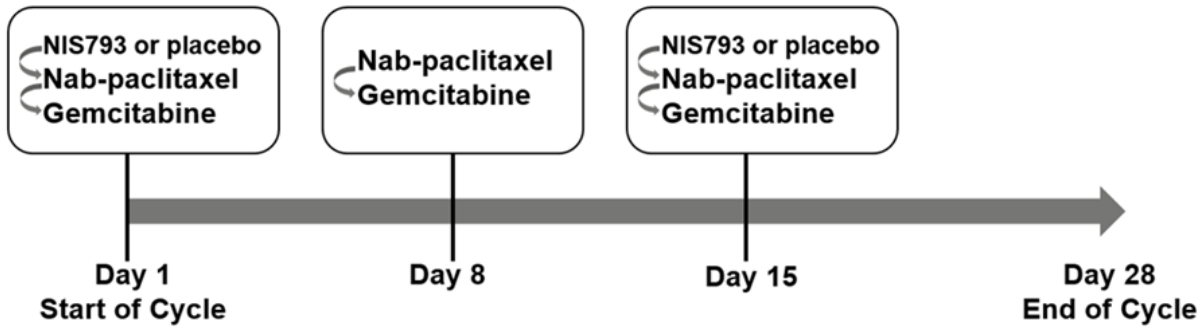
All dosages prescribed and administered to participants and all dose interruptions and changes during the study must be recorded on the study treatment electronic case report/record form (eCRF).

The generic version of gemcitabine and nab-paclitaxel if commercially available can be used according to local practice and local regulation.

Table 6-1 Study treatment drugs

Study treatment Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Drug sourcing: Sponsor (global or local)
NIS793 (100 mg/mL*)	Concentrate for solution for infusion (Liquid in Vial)	i.v.	Unblinded participant kits Infusion bag is blinded in the randomized part	Global
Placebo for NIS793 (randomized part only)	Dextrose 5% in water (D5W) solution	i.v.	Unblinded participant kits Infusion bag is blinded	Global or local
Gemcitabine	Per locally approved formulation	i.v.	Open label; vials	Global or local
Nab-paclitaxel	Per locally approved formulation	i.v.	Open label; vials	Global or local
* The fill volume of 7 mL/vial is used in the Safety Run-in part and the fill volume of 10.5 mL/vial is used in the Randomized part.				

Figure 6-1 Study drug administration



Arrows indicate the sequence of administration of study drugs.

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

Participants in the **safety run-in part** will be assigned at cycle 1 day 1 to the following treatment regimen:

- Combination of NIS793, gemcitabine and nab-paclitaxel.

Participants in the **randomized part** will be assigned at cycle 1 day 1 to one of the following 2 treatment arms/groups in a ratio of 1:1:

- Investigational arm (Arm A): combination of NIS793, gemcitabine and nab-paclitaxel
- Control arm (Arm B): combination of placebo, gemcitabine and nab-paclitaxel

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

- NIS793 at 2100 mg or placebo (Days 1 and 15) assuming this is the confirmed RP3D in the safety run-in part, or NIS793 at 2100 mg on Day 1 if dose level -1 is the confirmed RP3D in the safety run-in part
- Gemcitabine at 1000 mg/m² (Days 1, 8 and 15)
- Nab-paclitaxel at 125 mg/m² (Days 1, 8, and 15)

Crossover will not be allowed during the study duration.

6.1.4 Treatment duration

Participants will continue to receive study treatment until RECIST 1.1 disease progression is radiologically documented by investigator assessment, unacceptable toxicity that precludes further treatment, treatment is discontinued at the discretion of the investigator or the participant, participant withdrawal of consent/opposition to use data/biological samples, pregnancy, lost to follow-up, or death (Section 9.1).

If the investigational treatment (NIS793 or placebo) is interrupted or delayed for > 8 weeks due to toxicity that is suspected to be related to treatment, the applicable treatment will be permanently discontinued if the AE doesn't resolve to ≤ Grade 1 or baseline within 8 weeks.

If treatment with NIS793 is permanently discontinued due to unacceptable toxicities, the investigator can continue SOC treatment until RECIST 1.1 disease progression as per investigator, as long as the participant is continuing to benefit from the SOC treatment as assessed by the investigator, and is tolerating the treatment and no other treatment is required. As of 07-Jul-2023, study participants will no longer receive NIS793/placebo. Refer to Section 9.3 for details on study completion.

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.

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

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

6.2.1 Concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care (such as anti-emetics, anti-diarrheal) and safety of the participant are allowed except when specifically prohibited (Section 6.2.2).

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

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate case report/record forms (CRFs).

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 randomizing a participant or allowing a new medication to be started. If the participant is already enrolled and is being treated with a prohibited medication, 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 (granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF) or erythroid stimulating agents)** are allowed as concomitant medications if prescribed according to accepted clinical guidelines (ASCO, NCCN, ESMO, etc.).
- **Anticoagulation therapy** is permitted and should be clearly documented.
- **Anti-hypertensives** are allowed as concomitant medications.
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines are allowed. It is recommended if possible: to get vaccination for SARS-COVID-19 before the start of the study treatment and outside the dose-limiting toxicity period; to avoid vaccination on a day of study treatment dosing, meaning on Days 1, 8 and 15 of a cycle and on the same location as administration of other injectable drugs.
- Decision to vaccinate study participants with SARS-CoV-2 vaccine should be based on the investigator's assessment of an individual benefit-risk and should follow the local Health Authorities and/or institutional guidelines. Also please refer to the prescribing information for the SARS-CoV-2 vaccine to be used.
- To optimize the immune response of the participant to the vaccine, we also recommend allowing 1-2 weeks break from study treatment before and after administering the vaccine with no or minimal disruption to the chemotherapy schedule, if possible.
- Palliative radiation is permitted. It should not be delivered to a target lesion if avoidable. If palliative radiotherapy is initiated after start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out.
- Participants with metastatic disease to the 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 imaging modalities to exclude disease progression; if disease progression is documented, the participant should discontinue study treatment. No drug-drug interaction is expected between NIS793 and bone-stabilizing agents.
- The metabolism of paclitaxel is catalyzed by cytochrome P450 2C8 (CYP2C8) and cytochrome P450 3A4 (CYP3A4). As per label, caution should be exercised when

administering nab-paclitaxel concomitantly with medicines known to either inhibit or induce CYP2C8 or CYP3A4 (refer to Section 16.4).

- Concomitant administration of study treatments could result in drug-drug interactions (DDIs)that could potentially lead to reduced activity or enhanced toxicity of the concomitant medications and/or gemcitabine and/or nab-paclitaxel.
- Please note that all lists in Section 16.4 are not comprehensive. Please refer to regularly updated 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).

6.2.2 Prohibited medication

- During the course of the study, participants must not receive **other additional investigational drugs, devices, chemotherapy, or any other therapies** that may be active against cancer.
- Use of live vaccines against infectious diseases within 4 weeks of initiation of study treatment and through the duration of study is not allowed.
- Use of prohibited medications as per local prescribing information for the SOC anti-cancer therapies is NOT allowed after the start of study treatment.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is first enrolled for screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial. 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 (Center No.) (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 ICF, the participant is assigned to the next sequential Participant No. available.

The investigator or designated staff will contact the interactive response technology (IRT) and provide the requested identifying information for the participant to register them into the IRT.

Once assigned, the Participant No. must not be reused for any other participant and the Participant No. for that individual must not be changed. If the participant fails to be enrolled or randomized or start treatment for any reason, the reason will be entered into the appropriate eCRF.

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 (refer to Section 8.1).

6.3.2 Treatment assignment, randomization

All participants entering the screening phase 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 part**, no randomization will be performed. All eligible participants will be assigned to treatment of NIS793 in combination with gemcitabine and nab-paclitaxel.

In the **Randomized part**, approximatively 480 eligible participants will be randomized *via* IRT in a 1:1 ratio to one of the following treatment arms:

- Arm A: NIS793 in combination with gemcitabine and nab-paclitaxel
- Arm B: placebo in combination with gemcitabine and nab-paclitaxel

Randomization will be stratified during screening by ECOG PS (0 vs. 1), presence of liver metastasis (yes vs. no) and region at enrollment (N. America + Europe + Australia vs. other countries).

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

The randomization number will not be communicated to the caller. The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. 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. Random permuted blocks scheme will be used for this study. The randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers.

A separate medication randomization list will be produced by or under the responsibility of Novartis Global Clinical Supplies (GCS) using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

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

The study treatment phase begins on Cycle 1, Day 1 with the first administration of study treatment. Cycle 1 Day 1 should occur no later than 3 days after registration into IRT system.

6.3.2.1 Replacement policy

Safety run-in part

Participants will not be replaced during the safety run-in part. However, if a participant is considered as non-evaluable for the Dose Determining Set (DDS), enrollment of a new participant to the current cohort will be considered if there is 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 cohort.

Randomized part

During the randomized part, no replacements will be needed.

6.4 Treatment blinding

Note: The trial was unblinded on 7-Jul-2023 following DMC's recommendation to stop administration of NIS793/placebo CCI .

The safety run-in part is open label. For the randomized part, the participants, investigator staff, persons performing the assessments, and Novartis clinical team will remain blind to the identity of the treatment from the time of randomization until database lock.

CCI

The following methods will be used to maintain the blind:

1. Randomization data will be kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the following exceptions:
   - an independent analysis team who need to prepare safety and efficacy CCI reports for the DMC and
   - the bioanalyst for PK analysis (to avoid the unnecessary analysis of placebo samples)
   - These personnel will not be involved in any other trial activities.
2. Open label supply of NIS793 will be provided at sites to the unblinded site pharmacist in order to prepare study drug and to conceal treatment code from participants and the investigator staff performing the assessments.
3. Data with unblinding potential, such as PK concentrations collected after the randomization visit, will be kept blinded until the time of final database lock.

The randomization codes associated with participants from whom PK samples are taken will be disclosed to PK analyst who will keep PK results confidential until data base lock.

Unblinding will occur in the case of participant emergencies (Section 6.6.2) and at the conclusion of the study.

Unblinding a single participant at a site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site. As a result, the participant should be discontinued from the study treatment.

Except in these cases, documented approval by the Novartis study physician is required prior to unblinding a participant's treatment assignment. In case of unblinding, all data is required to be captured in the eCRF prior to unblinding. Data after unblinding will continue to be collected as per protocol. The date of any unblinding and the reason will also be collected.

IMPORTANT: Due to the difference in preparation methods between the active and placebo treatments, an unblinded pharmacist/designee who is independent of the investigational staff will be required. Appropriate measures must be taken by the unblinded pharmacist to ensure

that the investigational staff remains blinded throughout the study. The unblinded pharmacist must not administer the drug to the participant nor have any contact with the study participants. Please refer to the Pharmacist Instruction Manual and Section 6.7.1.1.

Table 6-2 Blinding levels

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	CCI
Participants	B	B	UI	
Site staff	B	B	UI	
Unblinded site staff (see text for details)	UI	UI	UI	
Drug Supply and Randomization Office	UI	UI	NA	
Unblinded sponsor staff (see text for details)	UI	UI	UI	
Statistician/statistical programmer/data analysts	B	B	B	
CCI				
All other sponsor staff not identified above	B	B	B	

B Remains blinded; **NA** Not applicable; UI Allowed to be unblinded on individual patient level

6.5 Dose escalation and dose modification

Dose escalations for NIS793, gemcitabine and nab-paclitaxel are prohibited.

Investigational treatment dose modifications and interruptions are given in Section 6.5.4.

6.5.1 Dose escalation guidelines

6.5.1.1 Starting dose

The starting dose for NIS793 will be 2100 mg Q2W in combination with gemcitabine and nab-paclitaxel for the safety run-in part (Section 6.5.1.2). In case dose de-escalation is required, a lower dose level is defined as 2100 mg Q4W. No de-escalation is planned for the other components (gemcitabine and nab-paclitaxel) of the combination study regimen.

6.5.1.2 Provisional dose levels

Table 6-3 describes the starting dose and the dose levels that may be evaluated during this trial.

Table 6-3 Provisional dose levels

Dose level	Proposed daily dose	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	Proposed daily dose	Increment from previous dose
*Dose level -1 represents treatment dose for next cohort if starting dose is not considered safe. No dose reduction below dose level -1 is permitted for this study. • Gemcitabine is administered at 1000 mg/m^2 on Day 1, Day 8 and Day 15 of each 28-day cycle • Nab-paclitaxel is administered at 125 mg/m^2 Day 1, Day 8 and Day 15 of each 28-day cycle		

6.5.2 Guidelines for dose confirmation and determination of RP3D

For the purpose of dose confirmation, approximately 10 participants will be enrolled to achieve at least 6 evaluable participants during the DLT period in **Safety Run-in part**. The evaluable criteria are defined in DDS, and the evaluable patients will be included in the DDS. Participants must complete a minimum of 28 days (4 weeks) of dosing of study treatment with the minimum safety evaluation and drug exposure or have had a DLT within the first 28 days of study treatment to be considered evaluable for recommended dose decisions (refer to Section 6.5.3 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 16.1. The adaptive Bayesian methodology provides an estimate of the risk of DLT to future patients at all dose levels of the combination and incorporates all DLT information at all dose levels for this estimation.

Dose confirmation of NIS793 2100 mg Q2W in combination with SOC will occur if the following conditions are met in the **Safety Run-in part**:

- At least six evaluable participants treated at this dose and regimen
- The dose is considered safe by BLRM
- It is the dose recommended for participants after review of all clinical data by Safety Review Team (SRT) Meeting

If one of the conditions specified above is not satisfied in either regimen, dose confirmation cannot be declared and additional 10 participants (to achieve at least 6 evaluable participants) will be enrolled for the regimen at the lower dose level (dose level – 1). Dose level – 1 of NIS793 in combination with SOC anti-cancer therapy is 2100 mg Q4W. The same criteria of DLT assessments are applied for this new dose level. If dose confirmation cannot be declared on this lower dose, NIS793 in combination with SOC anti-cancer therapy will be considered as not tolerable and, the randomized part cannot start.

6.5.2.1 Implementation of dose confirmation 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 and CCI information will be evaluated by the Investigators who enrolled participants and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. Drug administration at the next lower dose level or in the randomized 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 SRT, steering committee (SC), and all participating investigators. Additional communication in a form of teleconference, webcast, or investigator meeting may be implemented if needed.

6.5.3 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 or 4 weeks) of the treatment with NIS793 in combination with gemcitabine/nab-paclitaxel and meets any of the criteria included in Table 6-4. The National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 5 will be used for all grading.

The investigator must notify the sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities (refer to Section 10.1.3 for notification guidelines).

Table 6-4 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 > 14 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/mm3)
Hepatobiliary	Grade 4 bilirubin elevation For patients 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 patients 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
Infusion related reaction	Grade ≥ 3 infusion related reaction
Infections	Grade 4

TOXICITY	**DLT CRITERIA** (NCI CTCAE v5.0 will be used for grading)
Pancreatitis	Symptomatic serum amylase or lipase elevation, medical intervention required Grade ≥ 3 pancreatitis
Peripheral neuropathy	Grade ≥ 3
Hemorrhage/ Bleeding	Grade ≥ 3
Ocular disorders	Grade ≥ 3 conjunctivitis, blepharitis, vision blurred
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

The SOC anti-cancer therapy will include combination of gemcitabine and nab-paclitaxel. 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.

6.5.4 Dose modifications

Note: As of 7-Jul-2023, NIS793/placebo is no longer being administered.

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

For participants in the Safety Run-in part beyond the first 28 days period and for participants in the Randomized part, refer to Table 6-5 for NIS793. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-5 or listed in Section 16.2 and Section 16.3.

Study treatments administration may be delayed due to toxicities. All dosing may resume once the AE has resolved to Grade 1 or baseline.

For adverse events assessed as related to SOC drugs, the local prescribing information or local/institutional dose interruption or reduction guidelines for adverse drug reactions of SOC anti-cancer therapy should be followed.

These dose changes must be recorded on the appropriate CRF.

6.5.4.1 Dose modification and dose Interruption for NIS793

Note: As of 7-Jul-2023, NIS793/placebo is no longer being administered.

No dose reductions are allowed for NIS793 in the **Randomized part** and beyond the first 28 days period of the **Safety Run-in part.** Increasing the dosing interval from Q2W to Q4W is allowed under circumstances described in Table 6-5.

Dose interruption for NIS793 is permitted if adverse drug reaction is suspected to be related to NIS793. Treatment may be resumed once the AE has resolved as described in Table 6-5.

If causal relationship for adverse drug reaction is suspected to be related to NIS793 and Gemcitabine/Nab-paclitaxel, the investigator should use clinical judgement for determining dose modifications per Table 6-5 for NIS793 and per locally approved label or institutional guidelines of Gemcitabine and Nab-paclitaxel.

Treatment can be resumed with Gemcitabine and Nab-paclitaxel with or without NIS793 at investigator's discretion. If NIS793 is interrupted or delayed for > 8 weeks due to toxicity that is suspected to be related to treatment, study treatment should be permanently discontinued.

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 infusion (EOI), 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 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 slower rate of infusion, and despite pre-medication, permanently discontinue NIS793.
Grade 3 or Grade 4	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	
Ocular (e.g. Conjunctivitis, Blepharitis, blurred vision)	
Grade 1	May continue NIS793. Consider ophthalmology consultation.
Grade 2	ophthalmology consultation.

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
	Upon resolution to ≤ Grade 1 consider resuming NIS793 in consultation with ophthalmologist.
Grade 3	• Interrupt NIS793. • Ophthalmology consultation. • Upon resolution to ≤ Grade 1 consider resuming NIS793 in consultation with ophthalmologist.
Grade 4	Permanently discontinue NIS793.
Cardiovascular	
Myocarditis Grade ≥ 2	Permanently discontinue NIS793.
Cardiac Valvulopathy & Other Cardiac Toxicity	
Grade 2	Interrupt NIS793. Repeat echocardiogram and assess cardiac function. Once resolved to Grade ≤ 1 or baseline, consider readministration of NIS793, if benefit outweighs the potential risk.
Grade ≥ 3	Permanently discontinue NIS793
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 NIS793. Repeat liver function tests (LFTs) within 48-72 hours, then monitor LFTs weekly until recovery to grade ≤1 or to baseline. Then resume NIS793 at the same dose interval if resolved in ≤ 14 days; if resolved in > 14 days, consider administration Q4W instead of Q2W.
AST or ALT >10.0 – 20.0 x ULN	Interrupt NIS793. 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 NIS793
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 NIS793. 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, increasing dosing from Q2W to Q4W.
ALT/AST > 3.0 x baseline AND >10 x ULN	Interrupt NIS793. 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 NIS793.
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 NIS793. Assess if case is drug induced liver injury (DILI). If DILI confirmed, permanently discontinue NIS793. For additional information on follow-up of potential drug induced liver injury cases, refer to Section 6.5.5.1. If no DILI confirmed, interrupt NIS793, treat the identified cause according to institutional guidelines.

Worst toxicity CTCAE[a] grade	**Recommended Dose Modification**
	Repeat LFTs within 48-72 hours, then monitor weekly, until enzyme levels resolve to ≤grade 1 or baseline. After recovery, re-administration of NIS793 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.
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 Alkaline Phosphatase (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 NIS793. 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 NIS793 at the same dose regimen.
Grade 3 (>3.0 – 10 ULN)	Interrupt NIS793. 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 foot-note regarding alternative cause/s of bilirubin elevation).
Grade 4 (> 10 x ULN)	See footnote*. Otherwise, permanently discontinue NIS793. If alternative cause/s is identified and managed, and bilirubin resolves to ≤ grade 1 or to baseline, resume NIS793 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 NIS793. If levels do not resolve to ≤ Grade 2 within ≤ 14 days after the initial report, interrupt NIS793. Upon resolution to ≤ Grade 2, consider resuming NIS793.
Renal	
Serum creatinine	
Grade 2	Interrupt NIS793. Manage per institutional practice. Upon resolution to ≤ Grade 1, consider resuming NIS793.

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Grade 3 or Grade 4	Permanently discontinue NIS793.
Endocrine	
Hyperthyroidism	
Grade 2	Consider continuing NIS793 and management according to institutional practice.
Grade 3	Interrupt NIS793. Upon resolution to Grade ≤ 1 with appropriate management, consider resuming NIS793 without dose modification.
Grade 4	Must discontinue and manage according to local/institutional guidance.
Other endocrine disorders	
Grade 2 and Grade 3	Interrupt NIS793. Upon resolution to Grade ≤ 1 with appropriate management, consider resuming NIS793.
Grade 4	Permanently discontinue NIS793 and manage according to local/institutional guidance.
Dermatology (rash)	
Grade 1	Continue NIS793. Consider topical steroids, antihistamines, topical emollients
Grade 2	Consider interrupting NIS793. Topical or oral steroids, antihistamines. If NIS793 is held and resolution to ≤ Grade 1, resume NIS793.
Grade 3	Interrupt NIS793. Manage per institutional practice. After resolution to ≤ Grade 1, consider resuming NIS793 after consultation with dermatologist.
Grade 4 or Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	Permanently discontinue NIS793 and manage according to local/institutional guidance.
Hematology	
Neutropenia	
Grade 3	Interrupt NIS793 until resolved to ≤ Grade 1 or baseline, then resume NIS793
Grade 4	Interrupt NIS793 • If resolved in ≤ 7 days, maintain NIS793 • If resolved in >7 days, permanently discontinue NIS793
Febrile neutropenia	
Grade 3	Interrupt NIS793. Upon resolution of fever and improvement of neutropenia to ≤ Grade 1 or baseline, resume NIS793.
Grade 4	Permanently discontinue NIS793
Thrombocytopenia	
Grade 3	Interrupt NIS793. Upon resolution to ≤ Grade 2 or baseline, resume NIS793.

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
	For Grade 3 associated with major bleeding, permanently discontinue NIS793.
Grade 4	Permanently discontinue NIS793.
Anemia	
Grade 3 or Grade 4	Interrupt NIS793. Upon resolution to ≤ Grade 2 or baseline within ≤ 7 days, resume NIS793.
Other laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	
Grade 3 or Grade 4	Interrupt NIS793. Upon resolution to ≤ Grade 1, resume NIS793 without dose modification. 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 NIS793.
Other non-laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	
Grade 2	Consider NIS793 interruption. Upon resolution to ≤ Grade 1, consider resuming NIS793.
Grade 3	Interrupt NIS793. Upon resolution to ≤ Grade 1, resuming NIS793 must be discussed with the relevant medical expert.
Grade 4	Permanently discontinue NIS793.
All dose modifications should be based on the worst preceding toxicity. [a] Common Toxicity Criteria for Adverse Events (CTCAE v5) *Note: 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. **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.	

6.5.4.2 Dose modification and dose Interruption for gemcitabine/nab-paclitaxel

As a guiding principle, it is highly recommended to consider maintaining compliance to full dose chemotherapy. PDAC is a difficult to treat tumor characterized by a prominent desmoplastic reaction which contributes to tissue structural rigidity and poor perfusion. This leads to a reduced penetration of macromolecules, such chemotherapy. Beside the expected benefit of TGFβ inhibition (decreasing tumor angiogenesis, increasing anti-tumor immune response, and inhibiting tumor growth), NIS793 is also expected to restore or modulate the

tumor microenvironment. Therefore, maintaining the highest dose of chemotherapy, if safety allows and in compliance with approved labels, should be considered.

Discussion with Novartis medical monitor is recommended in case of questions of chemo dose adjustments.

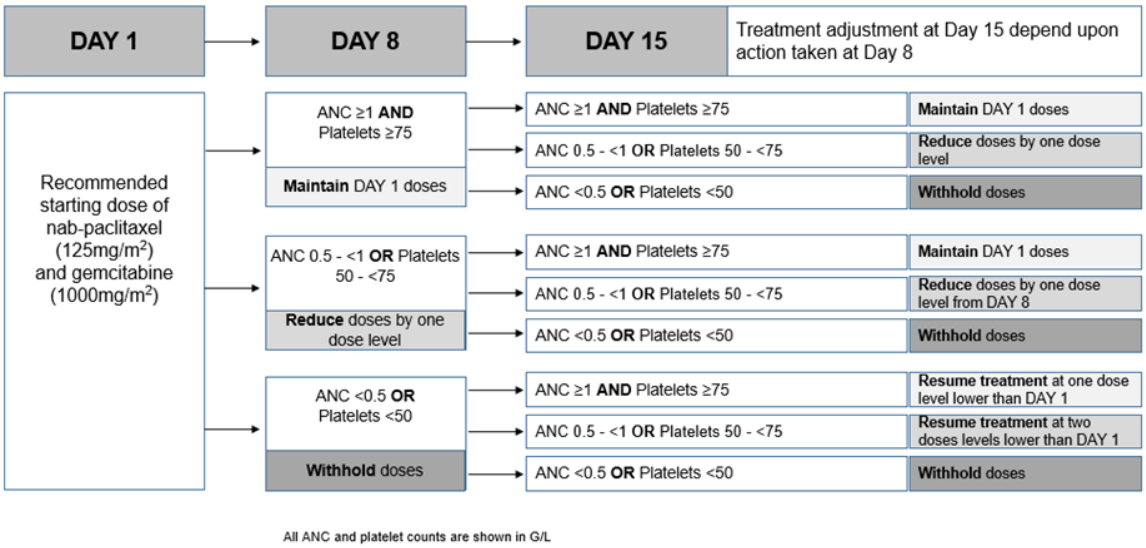
For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions, and/or reductions are either recommended or mandated in order to allow participants to continue the study treatment.

- **Dose reductions and dose interruptions** are allowed for gemcitabine/nab-paclitaxel. Instruction as per locally approved label or institutional guidelines should be followed.
- **Dose reductions** are allowed for gemcitabine/nab-paclitaxel and should follow the dose reduction steps described in Table 6-6. For each participant, a maximum of two dose level reductions for gemcitabine/nab-paclitaxel is allowed after which the participant must be discontinued.
- **Dose interruptions** due to toxicities are permitted for all study treatments. Dosing of each study treatment may resume once the AE has resolved, as described in Table 6-5, Figure 6-1 and Table 6-7. For gemcitabine/nab-paclitaxel, recommended dose modifications are provided in Figure 6-1 and Table 6-7 and are meant to be used for guidance (based on most recent updated gemcitabine/nab-paclitaxel Summary of Product Characteristics (SmPC or USPI). 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).
- Study treatments administration may be delayed due to toxicities. All dosing may resume once the AE has resolved to ≤ Grade 1 or baseline.
- Treatment should be resumed with Gemcitabine and Nab-paclitaxel as soon as the toxicity is improved following labels or institutional guidelines, with or without NIS793 at investigator's discretion (please refer to Section 6.5.4.1 for NIS793)

Table 6-6 Dose reduction for nab-paclitaxel and gemcitabine

	Nab-paclitaxel	Gemcitabine
Dose Level 1 (starting dose)	125 mg/m^2	1000 mg/m^2
Dose Level -1	100 mg/m^2	800 mg/m^2
Dose Level -2	75 mg/m^2	600 mg/m^2

Figure 6-2 Dose modifications of gemcitabine/nab-paclitaxel for hematological toxicities suspected to be related to gemcitabine/nab-paclitaxel



At Day 1, gemcitabine/nab-paclitaxel should not be administered if absolute neutrophil count (ANC) is < 1.5 G/L **OR** platelets are <100 G/L.

Table 6-7 Dose modifications of gemcitabine/nab-paclitaxel for non-hematological toxicities suspected to be related to gemcitabine/nab-paclitaxel

Worst toxicity CTCAE Grade	Recommended dose modification
Pneumonitis Grade≥ 2	• Discontinue gemcitabine and nab-paclitaxel promptly. • Treatment with steroids should be initiated as per local guidelines.
Nervous system Peripheral neuropathy Grade 3 or Grade 4	• Withhold nab-paclitaxel until improvement to ≤ Grade1. • Resume nab-paclitaxel to next lower dose level. • Dose of gemcitabine remains unchanged.
Cutaneous toxicity Grade 2 or Grade 3	• Reduce gemcitabine and nab-paclitaxel to next lower dose level. • Discontinue study treatment and discontinue participant from the study if toxicity persists.
Gastrointestinal toxicity Mucositis or diarrhea Grade 3 or Grade 4	• Withhold gemcitabine and nab-paclitaxel until improves to ≤ Grade 1. • Resume doses at next lower dose level.

6.5.5 Follow-up for toxicities

Participants must be followed-up for AEs and SAEs for 30 days after last dose of SOC chemotherapies and up to 90 days after last dose of NIS793, whichever is later.

Suspected SAEs will continue to be collected beyond those timeframes. However, if the participant begins subsequent anti-cancer therapy before the 90-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 90 days following the last dose of

study treatment. If SAEs suspected to be related to study medication occur beyond Day 90, 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.

If CCI is suspected, the assessments outlined in Section 8 must be performed.

Refer to Section 16.2 and Section 16.3 for the follow-up evaluations recommended for selected toxicities.

6.5.5.1 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), PT/INR, ALP, albumin, and creatine kinase. 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 ($R \leq 2$), hepatocellular ($R \geq 5$), 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 6-8 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

Table 6-8 Guidance to rule out possible alternative causes of observed LFT abnormalities

Disease	Assessment
Hepatitis A (HAV), B (HBV), C (HCV), E (HEV) virus	• Immunoglobulin M (IgM) anti-HAV; Hepatitis B virus surface antigen (HbsAg), IgM & Immunoglobulin G (IgG) anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Epstein-Barr Virus (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, Immunoglobulin E (IgE), (Immunoglobulin A) IgA
Alcoholic hepatitis	• Ethanol history, GGT, Mean Corpuscular Volume (MCV), Carbohydrate-Deficient transferrin (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).

Obtain PK and IG samples to determine exposure and immunogenicity to study treatment (Section 8.5.3 for more details).

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.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

NIS793 (or placebo), gemcitabine and nab-paclitaxel will be administered at the investigational site following the schedule in Table 8-2a and Table 8-2b, post implementation of protocol amendment 3. Note: administration of NIS793 (or placebo) was stopped as of 07-Jul-2023.

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.

Infusions will be administered in the clinic. This information must be captured in the source document, the appropriate CRFs and in the Drug Accountability Log.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all participants treated with NIS793, as detailed in pharmacokinetics Section 8.5.3.

6.6.2 Emergency breaking of assigned treatment code

Note: Post DMC recommendation, treatment codes have been released.

Emergency code breaks must only be undertaken when it is required to treat the participant safely.

Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the investigator to select the participant's next treatment regimen, and after discussion and agreement with the sponsor.

Most often, discontinuation from study treatment and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

Study treatment must be discontinued once emergency unblinding has occurred.

6.7 Preparation and dispensation

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

For NIS793 preparation prior to administration, please refer to NIS793B12301 Pharmacy Manual.

A unique medication number is printed on the study medication label. Investigator staff will identify the study medication kits to dispense to the participant by contacting IRT and obtaining the medication number(s). Note: As of 7-Jul-2023, NIS793/placebo is no longer being administered.

For gemcitabine and nab-paclitaxel preparation and administration, please refer to locally approved labels.

Study treatment gemcitabine and nab-paclitaxel, will be sourced as local commercial supply (in the locally approved formulation and packaging configuration) and labeled in the country when possible.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

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

Important note: To maintain the blind, an unblinded pharmacist/designee who is independent of the investigational staff will be required.

The Unblinded Pharmacist will be responsible for (1) receiving, handling and storing the investigational products, (2) preparing the investigational products according to the specifications in the Pharmacy Manual, (3) completing the relevant investigational product documentation, and (4) maintaining the blind in the study.

The appropriate measures must be taken by the unblinded pharmacist to ensure that the investigational staff remains blinded throughout the study. The unblinded pharmacist must not administer the drug to the participant nor have any contact with the study participants. Discussions between unblinded and blinded staff that may lead to unintentional sharing of treatment information are prohibited.

Please refer to the Pharmacist Instruction Manual.

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

The investigator or designated site staff must maintain an accurate record of the shipment, preparation, and administration 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 to the Novartis address provided in the investigator folder at each site.

6.7.2 Instruction for prescribing and taking study treatment

The dose and treatment schedule of each study treatment used in this study is described in Section 3.

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

Post DMC recommendation to stop administration of NIS793/placebo, no kits of study treatment were further dispensed by IRT as of 7-Jul-2023.

NIS793 or placebo is to be administered first, followed by dextrose solution flush. Finally, nab-paclitaxel is to be administered before gemcitabine. For more detail, refer to study pharmacy manual.

6.7.2.1 NIS793

Note: As of 7-Jul-2023, NIS793/placebo is no longer being administered.

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. Due to the difference in preparation methods between the active and placebo treatments, the preparation of infusion bags must be performed by an unblinded pharmacist who is independent of the investigational staff, while staff administrating the drug must be blinded. Please refer to Section 6.4, Section 6.7.1.1 and Pharmacist Instruction Manual.

NIS793 or placebo will be administered intravenously as a 30 minutes 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 and for at least 2 hours after the first two NIS793 infusions. The same may apply for 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 study pharmacy manual.

6.7.2.2 Gemcitabine and nab-paclitaxel

For instructions on preparation and dispensing of gemcitabine and nab-paclitaxel, refer to product labeling and the local guidance.

7 Informed consent procedures

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol).

The process of obtaining informed consent must be documented in the participant source documents. The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. A copy of the ICF(s) must be provided to the participant or their legally authorized representative. The ICF will contain a separate section that addresses the use of remaining mandatory samples for CCI [redacted]. The Investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for additional research. Participants who decline to participate in this CCI [redacted] will document this.

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), institutional review board (IRB)/independent ethics committee (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.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and also 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:
  - CCI
  - CCI
- As applicable:
  - Pregnancy follow-up model informed consent for pregnant participant or
  - Pregnancy follow-up model informed consent female partner for the pregnant partners of any male participants who took study treatment
  - Female partner info sheet for female partners of male study participants to inform them about the use of contraception

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

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities (i.e., pandemic, epidemic, or natural disaster) that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference) if allowable by a local 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 8-2a (Note: Post protocol amendment 3, Table 8-2b must be followed) lists all assessments to be performed for all participants for safety run-in and randomized part (unless otherwise noted in the table). 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. Additional assessments may be performed as clinically indicated.

All data obtained from these assessments must be supported in the participant’s source documentation. No CRF will be used as a source document. CCI

Study treatment will begin on C1D1 with the first administration of the assigned study treatment, depending on the cohort or 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 for the randomized part) whenever possible as per the allowable visit window specified in Table 8-1 below. If any one of the investigational drugs is temporarily interrupted or permanently discontinued, at any time during the study, safety and efficacy assessments should continue according to the schedule of assessments as described in Table 8-2a (Note: Post protocol amendment 3, Table 8-2b must be followed).

Participants who discontinue from study treatment are to return for the EOT 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.

Safety follow-up visits are to be scheduled according to the appropriate number of calendar days after the date of last dose of study drug administered. The 30-Day safety follow-up visit assessments should be performed on-site. The remaining safety follow-up visits (day 60, 90) may be performed remotely (e.g., telephone, videoconference) unless clinically indicated to be performed on-site.

Missed or rescheduled visits should not lead to automatic discontinuation.

Assessments which are indicated to be performed at Screening and on C1D1, only need to be repeated at C1D1 if the Screening assessment was done more than 7 days earlier, unless otherwise indicated in Table 8-1, Table 8-2a and Table 8-2b.

Laboratory and 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.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities (i.e., pandemic, epidemic, or natural disaster) that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local Health Authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g. teleconsultation) or visits by site staff / off-site healthcare professional(s) staff to the participant's home, can replace certain protocol assessments except for study treatment administration, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remains responsible for the evaluation of the data collected.

Table 8-1 Visit windows

Screening	Day -28 to Day -1
Serum pregnancy test	≤ 72 hours prior first dose of study treatment Note: Assessment done ≤ 72 hours prior to first dose of study treatment are permitted to be used as Cycle 1 Day 1 assessment and do not need to be repeated
All other screening assessments	Day -28 to Day -1
Physical examination, performance status, weight, vital signs Hematology, chemistry, urinalysis	**Note:** Assessment done ≤ 7 days of first dose of study treatment are permitted to be used as Cycle 1 Day 1 assessment and do not need to be repeated
Cycle 1 Day 1 Assessments and study treatment administration	Within 3 days after drug assignment or randomization in IRT
Cycle 1 Day 8, Cycle 1 Day 15, Day 1, Day 8 and Day 15 of subsequent cycles Assessments and study treatment administration	± 3 days
Cardiac assessments (echocardiogram, cardiac enzymes and ECG)	Cycle 3 Day 1 and Day 1 of every 2 cycles : ± 7 days
CCI	
PRO assessments	- 2 days (except screening)
Tumor assessments (during treatment/efficacy follow-up)	± 7 days
end of treatment (EoT)	Within 7 days of last dose of study treatment or within 7 days of the decision of discontinuation of 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 (on-site) 60-, 90-Day **safety follow-up** visit remote / onsite	± 7 days
Post treatment efficacy follow-up	± 7 days
Survival follow-up	±7 days

Table 8-2a CCI

Note: THIS TABLE IS NO LONGER EFFECTIVE POST PA3 APPROVAL. For applicable assessments refer to Table 8-2b.


CCI


CCI


CCI


CCI


CCI


CCI


CCI


CCI

Table 8-2b Assessment Schedule, post implementation of protocol amendment 3

CCI [redacted]

Period	**28 days Treatment**									**End of treatment**	**Safety follow-up**	**Post treatment efficacy follow-up**	**Survival follow-up**
Cycle	**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**						
Visit Name	**Cycle 1**			**Cycle 2**			**Cycle 3**			**End of treatment (EOT)**	**30 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 8 weeks)**
Days	1	8	15	1	8	15	1	8	15	-	30	-	-
Informed consent	X												
Prior/concomitant procedures and significant non-drug therapies	Continuous												
Physical Examination	S			S			S			S	S		
Performance status (ECOG) (Randomized part)	X			X			X			X	X		
Height													
Weight	X			X			X				X		
Vital Signs	X			X			X			X	X		
Hematology	X	X	X	X	X	X	X	X	X	X	X		
Chemistry	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	X			X			X			X	X		
Thyroid Panel	As clinically indicated												
Coagulation	As clinically indicated												
HgbA1c (Glycated hemoglobin)	As clinically indicated												
Pregnancy Test (WOCBP)	Refer to the drug label for gemcitabine and nab-paclitaxel												
Tumor marker CA-19-9	Every 8 weeks (C3D1, C5D1 etc. until week 52), then every 12 weeks									X		Same schedule as during treatment	
Troponin I and NTproBNP	As clinically indicated												
12-lead ECG	As clinically indicated												

Period	**28 days Treatment**									**End of treatment**	**Safety follow-up**	**Post treatment efficacy follow-up**	**Survival follow-up**
Cycle	**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**						
Visit Name	**Cycle 1**			**Cycle 2**			**Cycle 3**			**End of treatment (EOT)**	**30 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 8 weeks)**
Days	1	8	15	1	8	15	1	8	15	-	30	-	-
Cardiac imaging (echocardiogram)	As clinically indicated												
Chest, abdomen and pelvis CT (or MRI) and tumor evaluation as per RECIST (with intravenous contrast enhancement)[1]	Every 8 weeks (C3D1, C5D1 etc. until week 52), then every 12 weeks + EOT (If a scan was not conducted within 30 days prior to end of study treatment)											Same schedule as during treatment	
Brain CT or MRI[1]	As clinically indicated											As clinically indicated	
Whole body bone scan[1]	As clinically indicated											As clinically indicated	
Localized bone CT, MRI or X-ray[1]	As clinically indicated											As clinically indicated	
Other metastatic sites CT or MRI[1]	As clinically indicated											As clinically indicated	
Adverse Events	All AEs till end of safety follow-up period. Only suspected / study treatment-related AEs will be reported after the start of new anti-cancer therapy and until the end of the Safety Follow-Up period.												
Serious Adverse Events	All AEs till end of safety follow-up period. Only study treatment-related SAEs will be reported after the end of safety follow-up or after the start of new anti-cancer therapy, whichever is the earliest, until the end of survival follow-up; After the Safety Follow-up Period, and in the post-treatment efficacy follow-up period, report only treatment-related SAEs until the start of a new anti-neoplastic therapy												
Gemcitabine and nab-paclitaxel administration	X	X	X	X	X	X	X	X	X				
Antineoplastic therapies since discontinuation of study treatment										X	X	X	X
Survival contact													X
Disposition										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

Period	**28 days Treatment**									**End of treatment**	**Safety follow-up**	**Post treatment efficacy follow-up**	**Survival follow-up**
Cycle	**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**						
Visit Name	**Cycle 1**			**Cycle 2**			**Cycle 3**			**End of treatment (EOT)**	**30 days**	**Post treatment efficacy follow-up**	**Survival follow-up (every 8 weeks)**
Days	1	8	15	1	8	15	1	8	15	-	30	-	-
[1] Refer to Section 8.3.1 for further details on efficacy assessments													

8.1 Screening

The study IRB/IEC approved ICF must be signed and dated before any screening procedures are performed, except for laboratory and imaging 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 8-2a). Screening assessments must be repeated if performed outside of the specified screening window (Table 8-1). 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 the screening window (Day -28 to Day -1), 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. In such cases, a new ICF must be signed; new participant identifier 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 registration in IRT for screening, participant eligibility will be checked once all screening procedures are completed. The eligibility check will be registered 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 ICF and are subsequently found to be ineligible prior to treatment or enrollment in the Safety run-in part, or treatment or randomization in the Randomized part will be considered a screen failure. If the participant fails to be randomized, IRT must be notified within 2 days of the screen fail that the participant was not randomized. The reason for screen failure should be recorded on the appropriate CRF. 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 phase (see Section 10.1.3 for SAE reporting details). Data and samples collected from participants prior to screen failure may still be analyzed.

Participants who sign an inform consent and are eligible, and participants who are enrolled (Safety run-in part) or randomized (Randomized part) but fail to start treatment for any reason, e.g. participants randomized in error (Randomized part), will be considered an early terminator. In case of early termination from the study, the reason should be recorded on the appropriate CRF and participants should be followed up for efficacy, PROs (randomized part only), and survival.

Note: Post implementation of protocol amendment 3, PROs will no longer be collected from participants in the randomized part of the study.

8.2 Participant demographics/other baseline characteristics

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

Participant demographics: age, sex, race/predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) and will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded. Participant race / ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

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

- Germline mutation information should also be recorded when available for the following genes: A-T mutated (ATM), Breast Cancer gene 1 (BRCA1), Breast Cancer gene 2 (BRCA2), cyclin dependent kinase inhibitor 2 (CDKN2), epithelial cellular adhesion molecule (EPCAM), partner and localizer of BRCA2 (PALB2), serine/threonine kinase 11 (STK11), tumor protein p53 (TP53), microsatellite instability (MSI) status (MutS Homolog 2 (MSH2), MutL Homolog 1 (MLH1), MutS Homolog 6 (MSH6), PMS1 Homolog 2 (PMS2)) and Neurotrophic Tropomyosin-Related Kinase (NTRK) fusion status.
- Cancer characteristics including diagnosis, history, extent of cancer, prior anticancer treatments (medications, radiation, surgeries), date of progression prior to study entry.
- Other assessments will be completed for the purpose of determining eligibility for inclusion in the study as reported in Table 8-2a (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 medications and significant non-drug therapies taken within 30 days prior to the first dose of study treatment must be recorded in the eCRF. They will be updated on a continuous basis if there are any new changes to the medications.
- Tumor imaging assessments – Refer to Table 8-3.

8.3 Efficacy

8.3.1 Tumor imaging

Tumor response will be assessed locally by the investigator according to the Novartis guideline version 3.2 based on RECIST 1.1 (Section 16.5). The imaging collection plan is presented in Table 8-3 . The local investigator's assessment will be used for secondary endpoint analysis (RECIST 1.1) and for treatment decision making based on secondary efficacy endpoints (RECIST 1.1).

Tumor assessments on study treatment should be scheduled using the date of randomization (randomized part of the study) and C1D1 date (safety run-in part of the study) as the reference date and continued regardless of study treatment interruption and unscheduled assessments.

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 tumor 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. Combined Positron Emission Tomography (PET)/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of i.v. contrast media. At the discretion of the investigators, fluorodeoxyglucose-positron emission tomography (FDG-PET) scans may be performed to document progressive disease per RECIST 1.1.

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.

The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

Table 8-3 Imaging assessment collection plan

Procedure	Screening/ Baseline	Post baseline (during Treatment)	Efficacy follow up
CT of chest, abdomen and pelvis (with i.v.contrast enhancement)	Mandated	Every 8 weeks (C3D1, C5D1 etc. until week 52) then every 12 weeks thereafter until progression of disease (PD) as per RECIST 1.1. **EOT:** must be done if previous scan was not conducted within 30 days of the end of study treatment, unless there is prior documented PD per RECIST 1.1, or unless entering into efficacy follow-up whereby the imaging schedule should continue to be followed	Efficacy Follow-up for progression: continue tumor assessments using the same schedule until PD (per RECIST 1.1), withdrawal of consent/opposition to use data/biological samples, pregnancy, lost to follow up, or death (regardless of start of new anti-neoplastic therapy).
Brain CT or MRI	If clinically indicated	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen

Procedure	Screening/ Baseline	Post baseline (during Treatment)	Efficacy follow up
Whole body bone scan	If clinically indicated	If clinically indicated	If clinically indicated
CT scan or MRI of other metastatic sites (e.g., neck, etc.)	Only if clinically indicated	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen
Localized bone CT scan, MRI or x-ray (for any skeletal lesions identified on the whole body bone scan that are not visible on the chest/abdomen , if applicable, CT or MRI)	Only if clinically indicated	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen

8.3.1.1 Baseline imaging assessments

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

Any imaging assessments already completed during the regular routine of the participant within 28 days prior to start of treatment, including before signing the main study ICF, can be considered the baseline images for this study. Any imaging assessments obtained after enrollment cannot be considered baseline images.

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.

8.3.1.2 Post baseline imaging assessments

Post baseline imaging assessments are imaging assessments completed during the study treatment until EOT.

Imaging assessments for response evaluation will be performed every 8 weeks (C3D1, C5D1 until week 52 and then every 12 weeks thereafter) until disease progression per RECIST 1.1, death, lost to follow-up, pregnancy, withdrawal of consent/opposition to use data/biological samples.

8.3.1.3 End of treatment imaging assessments

At EOT, imaging assessments will be done for all participants provided the last imaging assessment was not conducted within 30 days prior to the end of study treatment, unless there is prior documented RECIST 1.1 PD, or unless participant will enter into efficacy follow-up.

8.3.1.4 Efficacy follow-up imaging assessments

All participants who discontinue study treatment **without** prior documented disease progression RECIST 1.1 as per investigator will continue these efficacy imaging assessments, in the efficacy follow-up phase, until documented disease progression by RECIST 1.1 as per

investigator, withdrawal of consent/opposition to use data/biological samples, pregnancy, lost to follow up, or death irrespective of start of new anti-neoplastic therapy.

8.3.2 Survival assessments

All participants will be followed for survival status every 8 weeks regardless of treatment discontinuation reason (see Section 9.3.3 for more details).

8.3.3 Appropriateness of efficacy assessments

The measurements are standard based on the Novartis guideline version 3.2 based on RECIST 1.1 (Section 16.5).

8.4 Safety

During treatment (for both safety run-in and randomized part)

Safety will be monitored by assessing physical examination, ECOG Performance Status, vital signs, body weight, ECG, laboratory assessments, pregnancy tests, as well as collecting adverse events at every visit. For details on AE collection and reporting, refer to Section 10. All safety assessments should be completed as per Table 8-2a (post implementation of protocol amendment 3, Table 8-2b must be followed).

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities (i.e., pandemic, epidemic, or natural disaster) that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 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.

Post treatment discontinuation (for both safety run-in and randomized part)

All safety assessments (including pregnancy test for female participants of child bearing potential) should be completed as per Table 8-2a (post implementation of protocol amendment 3, Table 8-2b must be followed).

All AEs and SAEs will be reported until the end of post-treatment safety follow-up.

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

After the end of safety follow-up, only SAEs suspected to be related to study treatment will be collected until the end of survival follow-up (Section 10.1.3).

Data collected should be added to the appropriate eCRF.

8.4.1 Laboratory evaluations

Central safety laboratories will be used for the analysis of scheduled hematology, chemistry, and other blood specimens (Table 8-4). 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, chemistry, 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.

Laboratory safety (hematology, chemistry, thyroid, coagulation) samples, except those to assess eligibility, may be collected locally in China according to the local regulations.

More frequent timepoints 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 phase 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 (study drug interruption, re-initiation, and/or termination). In those cases, local laboratory testing may be performed. Under exceptional circumstances eligibility may be assessed with local laboratory values only after consultation with the study medical lead. 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.

- 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). For sites in China that are unable to test all macroscopic urinalysis parameters at local labs as defined in this protocol, a sample should be collected locally by site for macroscopic testing as well as a sample collected and sent to central lab for microscopic testing.

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

If participants cannot visit the site for protocol-specified safety laboratory assessments, an alternative laboratory (local) collection site may be used.

If at any time a participant has laboratory parameters obtained from a local laboratory due to inability to have an on-site visit, 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.

Note: Post implementation of protocol amendment 3, refer to Table 8-2b for a list of applicable assessments.

Table 8-4 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, Hematocrit, Platelets, Erythrocytes, Leukocytes, Erythrocyte Cell with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands in percentage or absolute), Ery. Mean Corpuscular Hemoglobin, Ery. Mean Corpuscular Hemoglobin Concentration, Ery. Mean Corpuscular Volume
Chemistry	Albumin, ALT, AST, calcium (at screening, calcium corrected for albumin will be tested in addition to calcium), creatinine, creatinine clearance, creatine kinase, total bilirubin, direct and indirect bilirubin, urea nitrogen or urea, magnesium, potassium, sodium, fasting glucose, phosphate (inorganic phosphorus), alkaline phosphatase, amylase, lipase, GGT, lactate dehydrogenase (LDH), uric acid
Thyroid	At baseline: Thyrotropin (TSH), Free Triiodothyronine (Free T3) and Free Thyroxine (Free T4) At the subsequent visits, as indicated in Table 8-2a: Thyrotropin (TSH) only. If TSH is abnormal, central lab will test Free Triiodothyronine (Free T3) and Free Thyroxine (Free T4)
Coagulation	PT, INR, Activated partial thromboplastin time (APTT)
Hepatitis	Hepatitis B Virus DNA, Hepatitis B Virus Surface Antigen, Hepatitis B Virus Surface Antibody, Hepatitis B Virus Core Antibody, Hepatitis C Virus ribonucleic Acid (RNA) (baseline)
CCI	
HIV (local, where locally required)	Testing by local laboratory if required by local regulations
Urinalysis	Local laboratory: Macroscopic panel (Dipstick) (color, bilirubin, occult blood, macroscopic blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) If dipstick is abnormal, then perform central loboratory Microscopic panel (Erythrocytes, Leukocytes, casts, crystals, bacteria, epithelial cells) Urine culture only if clinically indicated
Additional tests	HgbA1c Troponin I and NTproBNP (N-terminal pro-brain natriuretic peptide) Carbohydrate antigen 19-9 (CA 19-9)
Serum pregnancy (local)	At screening visit (at the local laboratory) ≤ 72 hours prior first dose of study treatment, EOT and 30-Day safety follow-up visit If local requirements dictate otherwise, local regulations should be followed
Urine pregnancy (local)	Day 1 of every cycle and 60-, 90-Day safety follow-up Local testing If local requirements dictate otherwise, local regulations should be followed

8.4.1.1 CCI

CCI

CCI

8.4.1.2 Laboratory testing

Hematology, chemistry, thyroid function tests, coagulation, urinalysis and infectious disease marker tests are to be performed according to the visit schedule (Table 8-2a; post implementation of protocol amendment 3, Table 8-2b must be followed). Laboratory assessment 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 laboratory hematology testing may also be performed as medically necessary. Additional results from unscheduled hematology lab evaluations should be recorded on the appropriate eCRF.

Estimate of glomerular filtration rate (GFR) (via estimated creatinine clearance rate) will be done centrally using Cockcroft-Gault formula:

Figure 8-1 Estimated creatinine clearance rate using Cockcroft-Gault formula

Estimated creatinine clearance rate (eC_{Cr}) using Cockcroft-Gault formula

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

When serum creatinine is measured in µmol/L:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where *Constant* is *1.23* for men and *1.04* for women.

8.4.2 Performance status

The performance status will be assessed according to the ECOG performance status scale as specified in Table 8-5 (Oken et al 1982) following the schedule given in Table 8-2a.

Table 8-5 ECOG performance status

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

8.4.3 Electrocardiogram (ECG)

Post implementation of protocol amendment 3, ECG will be performed as clinically indicated.

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 8-2b.

The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

Standard 12-lead ECGs are to be performed with ECG machines available at the site at screening, Cycle 3 Day 1 (preferably before study treatment administration), then day 1 of every 2 cycles during treatment or earlier if clinically indicated and/or cardiac enzymes ≥2xULN, and at EOT.

For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. The individual ECGs should be recorded approximately 2 minutes apart. In that case, the mean QT interval corrected by Fridericia's formula (QTcF) value will be calculated from the triplicate ECGs for each participant.

Any identifier details must be redacted e.g. participant initials, date of birth.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or Aes as appropriate.

Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate CRF. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as Aes.

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

8.4.3.1 Cardiac imaging – echocardiogram

Post implementation of protocol amendment 3, cardiac imaging will be performed as clinically indicated.

Cardiac imaging (echocardiogram), will be performed at screening to determine cardiac function and morphology at baseline. Thereafter, echocardiogram will be performed at Cycle 3 Day 1 (preferably before study treatment administration), then day 1 of every 2 cycles during treatment, or earlier if clinically indicated and/or if cardiac enzymes are elevated*, and at EOT.

*Cardiac enzymes elevated: ≥ 2x ULN (if normal at screening), or ≥ 2x baseline (if baseline value was elevated).

Other methods for cardiac imaging (such as CT/MRI) may be used in case echocardiogram is not available. MUGA is not allowed.

8.4.3.2 Cardiac enzymes

Post implementation of protocol amendment 3, cardiac enzymes will be collected as clinically indicated.

Cardiac specific enzymes, Troponin I and NTproBNP, will be performed at screening, C3D1 (preferably before study treatment administration) and day 1 of every 2 cycles during treatment or earlier if clinically indicated, and at EOT.

8.4.4 Pregnancy and assessments of fertility

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

At screening, a serum pregnancy test must be performed within 72 hours before the first dose of study treatment. Monthly urine pregnancy tests will then be required to be performed on day 1 of every cycle beginning with Cycle 2, followed by serum pregnancy test at the EOT visit and 30-Day Safety follow-up visit.

Note: Post implementation of protocol amendment 3, refer to Table 8-2b for a list of applicable assessments.

If the participant is not coming to the clinic at the 60-Day and 90-Day safety follow-up timepoints, a urine pregnancy test may be performed at home or at a local doctor's office, 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 EOT 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).

8.4.5 Physical examination

Physical examination will be performed according to Table 8-2a (post implementation of protocol amendment 3, Table 8-2b must be followed).

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 and neurological.

At Cycle 2 Day 1 and onwards, a focused physical examination will be performed (it will include the examination of general appearance, vital signs, lymph nodes, lungs, abdomen, heart). If indicated based on symptoms, additional exams will be performed.

Only during safety run-in a focused physical examination will be performed at Cycle 1 Day 8-Day 15 and at Cycle 2 Day 8-Day 15.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that were 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 informed consent which meet the definition of an AE must be recorded as an AE (see Section 10.1).

8.4.6 Vital signs

Vital signs include systolic and diastolic 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 8-2a and Table 8-2b.

8.4.7 Height and weight

Height will be measured at screening.

Body weight (in indoor clothing, preferably without shoes) will be measured at screening and at subsequent timepoints as specified in Table 8-2a and Table 8-2b.

8.4.8 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.5 Additional assessments

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities (i.e., pandemic, epidemic, or natural disaster) that limits or prevents on-site study visits, additional assessments CCI may be collected locally, depending on local regulations and capability.

8.5.1 Clinical Outcome Assessments (COAs)

CCI

CCI

8.5.1.1 CCI

8.5.1.2 CCI

8.5.1.3 CCI

8.5.1.4 CCI

CCI

8.5.1.5 CCI

CCI

8.5.1.6 CCI

CCI

8.5.2 CCI

8.5.2.1 CCI

CCI

8.5.3 Pharmacokinetics

Post implementation of protocol amendment 3, PK[redacted]/IG samples will no longer be collected.

To assess PK, [redacted] and immunogenicity (IG) of NIS793, blood samples will be collected from all participants of the study to determine serum level of NIS793, [redacted] and anti-NIS793 antibody.

All participants who have evaluable PK data will be included in the PK data analysis. [redacted], PK parameters will be determined using non-compartmental method(s) using Phoenix WinNoinlin version 6.4 or above (Pharsight, Mountain View, CA). PK parameters for NIS793 in participants with [redacted] will be estimated and reported, when applicable. A population pharmacokinetic analysis for NIS793 may be conducted as well (e.g. to provide PK parameters for subsequent PK[redacted] analysis), the report will be provided separately if performed. PK samples will be collected at the visits defined in the Assessment Schedule. Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment. For more information, see the potential use of residual samples in Section 8.5.3.1.

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

8.5.3.1 Pharmacokinetic blood collection and handling

Refer to the study laboratory manual for detailed instructions for the collection, handling, and shipment of PK, IG and [redacted] samples.

On days and timepoints when PK/IG/[redacted], biochemistry or other blood sampling are to be performed in parallel, the PK/IG/[redacted] sample must be drawn first. For post-dose or end of infusion (EOI) PK/[redacted] samples, only the time window specified in the blood collection log tables are allowed, while other pre-dose PK/IG/[redacted] 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.

To assess PK of NIS793, blood samples will be collected from all participants in **safety run-in part** (Table 8-6) and **randomized part** (Table 8-7).

In the **randomized part**, approximately 30 participants enrolled for treatment (approximately 15 per treatment arm)[redacted] hese samples may be collected locally in accordance with local regulation.

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 institutional guidelines. At the specified timepoints, blood draws in the volume specified in the blood collection log tables will be collected.

[redacted]

CCI

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

IG samples associated with NIS793 are to be collected together with PK samples.

Post implementation of protocol amendment 3, PK/CCI/IG samples will no longer be collected; refer to Table 8-2b for a list of applicable assessments.

Table 8-6 Pharmacokinetic blood collection log – NIS793 (safety run-in part)

Treatment Period or Cycle	Day	Schedule Time Point	NIS793 analytes	CCI
1	1	Pre-dose[a]/0 h	PK and IG	
1	1	EOI (+ 1 h)	PK	
1	15	Pre-dose[a]/0 h	PK and IG	
2	1	Pre-dose[a]/0 h	PK and IG	
3	1	Pre-dose[a]/0 h	PK and IG	
3	1	EOI (+ 1 h)	PK	
3	15	Pre-dose[a]/0 h	PK and IG	
4	1	Pre-dose[a]/0 h	PK and IG	
6	1	Pre-dose[a]/0 h	PK and IG	
12	1	Pre-dose[a]/0 h	PK and IG	
18	1	Pre-dose[a]/0 h	PK and IG	
24	1	Pre-dose[a]/0 h	PK and IG	
EOT	-	-	PK and IG	
30-Day Safety follow-up	-	-	PK and IG	
60-Day and 90-Day Safety follow-up / End of safety follow up[b]	-	-	PK and IG	
Unscheduled[c]	-	-	PK and IG	PD

EOI, end of infusion for NIS793; IG, immunogenicity; CCI; PK, pharmacokinetic
a Pre-dose blood samples should be collected prior to start of NIS793 infusion
b NIS793: PK, IG and CCI samples on days 60 and 90 of safety follow- up will be mandatory if the safety follow-up is performed on site; these samples will not be collected if safety follow-up is performed remotely
c Unscheduled PK, CCI CCI and IG samples will be collected in the event of a clinically significant AE (such as infusion reaction/anaphylaxis/DILI) or if immunogenicity is suspected

Table 8-7 Pharmacokinetic blood collection log – NIS793 (randomized part)

Treatment Period or Cycle	Day	Scheduled Time Point	NIS793 analytes	CCI
1	1	Pre-dose[a]/0 h	PK and IG	
1	1	EOI (+ 1 h)	PK	
2	1	Pre-dose[a]/0 h	PK and IG	
3	1	Pre-dose[a]/0 h	PK and IG	
3	1	EOI (+ 1 h)	PK	
4	1	Pre-dose[a]/0 h	PK and IG	

Treatment Period or Cycle	Day	Scheduled Time Point	NIS793 analytes	CCI
6	1	Pre-dose[a]/0 h	PK and IG	
12	1	Pre-dose[a]/0 h	PK and IG	
18	1	Pre-dose[a]/0 h	PK and IG	
24	1	Pre-dose[a]/0 h	PK and IG	
EOT	-	-	PK and IG	
30-Day Safety follow-up	-	-	PK and IG	
60-Day and 90-Day Safety follow-up / End of safety follow up[b]	-	-	PK and IG	
Unscheduled[c]	-	-	PK and IG	

EOI, end of infusion for NIS793; IG, immunogenicity; CCI ; PK, pharmacokinetic
a Pre-dose blood samples should be collected prior to start of NIS793 infusion
b NIS793: PK, IG and CCI samples on days 60 and 90 of safety follow-up will be mandatory if the safety follow-up is performed on site; these samples will not be collected if safety follow-up is performed remotely;
c Unscheduled PK, CCI and IG samples will be collected in the event of a clinically significant AE (such as infusion reaction/anaphylaxis/DILI) or if immunogenicity is suspected

Table 8-8 CCI

CCI

8.5.3.2 Analytical method

8.5.3.2.1 NIS793

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

CCI 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 (ADA) and neutralizing antibodies (nAb) 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.

8.5.4 CCI

Table 8-9 CCI

CCI

CCI

8.5.4.1 CCI

8.5.4.1.1 CCI

CCI

CCI

8.5.4.1.2 CCI

CCI

8.5.4.2 CCI

CCI

CCI

8.5.4.3 Additional biomarker assessments

Additional biomarker assessment related to exploratory objectives of this study may also be performed based on scientific rationale and sample availability. These studies are hypothesis generating (i.e. discovery based research) and optional to the participant.

8.5.4.4 Optional Additional Research

If the participant agrees, by signing the optional consent for Additional Research, biological samples and data that remain after analysis is completed may be kept for up to 15 years to be used for additional research to help better understand how the study treatment works, learn more about the disease, improve the way clinical studies are conducted, or to help develop ways to detect, monitor or treat human diseases. A decision to perform such exploratory research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as assay availability.

8.5.5 CCI

CCI

CCI

CCI

8.5.6 Alcohol consumption

Information on alcohol consumption will be collected during screening for all participants.

8.5.7 Smoking history

Information on smoking history will be collected during screening for all participants.

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation and 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) 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
- Adverse event or laboratory abnormalities requiring permanent discontinuation of study treatment
- Progressive disease per RECIST 1.1 as per investigator 's assessment,
- Protocol deviation that results in significant risk to participant's safety
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment
- Any situation in which continued study participation might result in a safety risk to the participant
- Following emergency unblinding
- Study terminated by Sponsor

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.

Participants who discontinue from study treatment agree to return for the EOT and follow-up visits indicated in the Assessment Schedule (refer to Section 8).

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

After 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
- AEs / SAEs

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, tumor assessments must continue to be performed every 8 weeks until 52 weeks then every 12 weeks until documented disease progression per Investigator, death, lost to follow-up, discontinuation from study or withdrawal/opposition to use data/biological samples.

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatments, and further protocol-required assessments or follow-up, for any reason. If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and 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 followed 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 data 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.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

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

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

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.3 Study completion and post-study treatment

Following the recommendation to stop administration of NIS793/placebo, the DMC encouraged the continuing administration of gemcitabine/nab-paclitaxel to all subjects per Investigator's assessment, and the collection of additional follow-up data to better characterize the safety of NIS793 in combination with gemcitabine/nab-paclitaxel.

Study will be considered complete when each participant has completed at least 12 months of follow-up from randomization date, died, withdrawn consent, or lost to follow-up, whichever occurs earliest or, in the event of an early study termination. At which time, any study participant continuing with standard of care chemotherapy (gemcitabine + nab-paclitaxel) will be transitioned off the study and LPLV will be achieved.

At the time of the end of this study, participants continuing to derive clinical benefit from the standard of care chemotherapy (gemcitabine + nab-paclitaxel) 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.

For participants who transfer to another clinical study or an alternative treatment option to continue provision of study treatment, the follow-up for safety, efficacy and survival will not be performed.

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

9.3.1 Post-treatment efficacy follow-up

In parallel with safety follow-up, participants who discontinue study treatment without prior documented disease progression RECIST 1.1 as per investigator will continue efficacy imaging assessments as outlined in Section 8.3.1 until documented disease progression by RECIST 1.1 as per investigator, withdrawal of consent/opposition to use data/biological samples, pregnancy, lost to follow up, or death irrespective of start of new anti-neoplastic therapy.

If a participant starts a new anti-neoplastic therapy prior to progression, tumor assessments should continue per the planned visit schedule (Table 8-2a, post implementation of protocol amendment 3 Table 8-2b must be followed) until disease progression is documented. In addition, all new antineoplastic therapies given after the last dose of study treatment, will be recorded in the eCRF. If participants refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine if the participant had disease progression.

9.3.2 Safety follow-up

All participants must have safety evaluations after the last administration of study treatment (30 days after last dose of SOC chemotherapies gemcitabine/nab-paclitaxel and up to 90 days after NIS793, whichever is later). The 30-Day safety follow-up visit assessments should be performed on-site. The remaining safety follow-up visits (day 60, 90) may be performed remotely (e.g., phone call, videoconference) unless clinically indicated to be performed on-site. Concomitant medications will be collected until the 90-day safety follow-up has been completed or the start of a new antineoplastic therapy, whichever occurs first.

Post implementation of protocol amendment 3, refer to Table 8-2b for a list of applicable assessments.

Data collected should be added to the relevant CRF. For female participants of childbearing potential, pregnancy tests will be performed as outlined in Section 8.4.4.

9.3.3 Survival follow-up

All participants will be followed for survival status every 8 weeks after completion of the safety follow-up and efficacy follow-up (as applicable) until death, lost to follow-up, withdrawal of consent/opposition to use data/biological samples or end of study. Participants will be contacted remotely (e.g., telephone, videoconference) or in person during a visit to the site if applicable. Additional survival assessments may be performed outside the 8 weeks follow-up schedule if a survival update is required for an interim assessment to meet safety or regulatory needs.

Survival information will be documented in the source documents and appropriate eCRFs.

Any new antineoplastic therapies that have been started since the last contact date will also be collected during these remote calls (including start date, stop date, and date of progression if any).

9.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

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

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

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 AEs.

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.

AEs must be recorded in AE eCRF 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. AEs will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 to 5 will be used to characterize the severity of the AE.
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 (recovery status or 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.

Conditions which developed or worsened after signing informed consent (including during the screening period) should be recorded on the AE CRF for the participant.

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

AE monitoring for all participants should be continued for 30 days after last dose of SOC chemotherapies and up to 90 days after last dose of NIS793, whichever is later.

Following the completion of the 30 days safety follow-up period, if a new post-treatment antineoplastic therapy is initiated, only AEs suspected to be related to study treatment will be collected in the Adverse Events CRF.

Once an AE is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (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 (as per RECIST criteria for solid tumors), should not be reported as a SAE, 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 AEs 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.

10.1.1.1 Adverse events of special interest (AESI)

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 and known mechanism of action of the drug and potential overlapping toxicity of NIS793, gemcitabine and nab-paclitaxel, following adverse events are considered of special interest in this trial population:

- CCI
- Neutropenia ≥ Grade 3
- Febrile Neutropenia
- CCI

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

10.1.2 Serious adverse events

An SAE is defined as any AE [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 an event 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 SAE 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 until the end of safety follow-up (30 days after last dose of

SOC chemotherapies and up to 90 days after NIS793, whichever is later) 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 electronic serious adverse event (eSAE) with paper backup SAE Report 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*). The 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 Novartis associate from Patient Safety and Pharmacovigilance (PS & PV) Department 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 European 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.The primary mechanism for reporting an SAE to Novartis will be the electronic data collection tool. If the electronic system is unavailable, then the site will use the paper SAE data collection tool to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form or by telephone.

10.1.4 Pregnancy reporting

Pregnancies

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 Patient Safety and Pharmacovigilance (PS&PV). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment for any 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.

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 (European Medicines Agency (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. Study treatment errors and uses outside of what is foreseen in the protocol, 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.

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

Other than the safety monitoring noted in this protocol, there is no 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 16.2 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-8 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 16-9 and Table 16-10 Repeat liver chemistry tests (i.e. ALT, AST, total bilirubin, 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 6.5.4)
- 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, urinary tract infection (UTI), extreme exercise, 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 as summarized in Table 16-11 and Table 16-12.

10.3 Committees

10.3.1 Data Monitoring Committee

This study will include a data monitoring committee (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 be constituted prior to the randomization of the first participant in the randomized part. The DMC will review at defined intervals the safety data as well as the efficacy and safety data CCI of the double-blind, randomized, placebo-controlled part of the study. The kick-off meeting of the DMC and Independent Statistician will be held prior to FPFV. Thereafter, the DMC will meet two times a year to review accumulating safety data until study is unblinded. Further meetings may be scheduled in consultation between the DMC and the Sponsor to discuss safety data as required. DMC will recommend to the sponsor whether to continue, modify or terminate the trial. Additional details on the conduct of CCI can be found in Section 12.7.

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.

10.3.2 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.

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

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

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site. Data collected by third parties (such as safety laboratory, CCI) will be sent electronically to Novartis.

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 (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Safety laboratory assessments, pharmacokinetic (PK), CCI immunogenicity (IG) and CCI drawn during the course of the study will be collected from the investigator sites and sent to the Novartis designated central laboratory for processing. The laboratory results will be sent electronically to Novartis.

PRO questionnaire data will be collected by a contracted third party vendor and will be sent to Novartis electronically.

CCI

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

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate (at the time of final analysis), it will be locked **and the treatment codes will be unblinded** 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. 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 GCP, 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. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, 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 ICF 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

Note: As of 7-Jul-2023, NIS793/placebo is no longer being administered CCI [redacted].

Data from participating centers in this protocol will be combined, so that an adequate number of participants will be available for analysis. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum will be presented. For selected parameters, distributions (e.g., 25th and 75th percentiles) may also be presented. All summaries, listings, figures and analyses will be performed for all participants in the Safety Run-in part and Randomized part separately. All the analyses will be performed for Randomized part by treatment arms, unless otherwise specified. Additional summaries by participant subgroups may be produced as relevant for selected endpoints.

Screen failure participants are those who signed the informed consent, but never started the study treatment for any reason or have been randomized. For these participants, the collected eCRF data will not be included in any analyses, but reasons for not being randomized will be reported in the CSR as a separate listing.

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.

12.1 Analysis sets

A participant is considered to be enrolled into the study if they have signed the main study informed consent. Only participants who have signed main study informed consent will be included in the analysis data sets.

12.1.1 Full analysis set

Safety Run-in Part

For each 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.

Randomized Part

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

12.1.2 Safety set

Safety Run-in part

The Safety set 1 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)).

Randomized part

The Safety set 2 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 **Randomized 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

Applicable only for the Safety Run-In part

The DDS consists of all participants in the **Safety Run-in part** who met the minimum exposure criterion and have sufficient safety evaluations or experienced a DLT during the first 4 weeks of treatment.

A participant is considered to have met the minimum exposure criterion if the participant has received 2 doses of NIS793 (2100 mg Q2W) for the first cycle or 1 dose of NIS793 (2100mg Q4W for the lower dose cohort), and at least 66% of planned dose of chemotherapy (the planned dose consists of 3 doses of gemcitabine (1000 mg/m^2 Days 1, 8, and 15), and 3 doses of nab-paclitaxel (125 mg/m^2 Days 1, 8, and 15)).

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 both the Sponsor and Investigators to have enough safety data to conclude a DLT did not occur.

12.1.4 Pharmacokinetic analysis set

For the **randomized part**, one Pharmacokinetic analysis set (PAS) will be considered for planned treatments.

The PAS includes all participants who provided at least one evaluable PK concentration. For a concentration to be evaluable, participants are required to:

- Receive at least one dose (complete infusion) of the planned treatment prior to sampling
- Provide at least one valid PK concentration
- For pre-dose samples, have the sample collected before the next dose administration
- For end-of-infusion samples, have the sample collected within 1 hour post infusion

Participants may be excluded from the assessment of PK parameters if available data is insufficient. These participants will be identified at the time of analysis. More details will be defined in the SAP.

12.1.5 Immunogenicity analysis set

For the **randomization part**, the immunogenicity set 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.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment group for all the participants for the FAS and Safety set.

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

12.3 Treatments

The Safety set 1 and 2 will be used for the analyses below.

Categorical data will be summarized as frequencies and percentages. For continuous data, mean, SD, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure to NIS793 or placebo as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set.

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

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

12.4 Analysis supporting primary objectives

The primary objective is to evaluate and compare OS of NIS793, gemcitabine and nab-paclitaxel (Arm A) versus the placebo, gemcitabine and nab-paclitaxel (Arm B). The analysis will be performed on the FAS.

12.4.1 Definition of primary endpoint(s)

Safety run-in part

The primary endpoint for the safety run-in part is incidence of DLT during first cycle (i.e, 28 days, or (4 weeks) of treatments for NIS793, gemcitabine and nab-paclitaxel).

Randomized part

The clinical question of interest is to estimate the treatment effect of combination of NIS793, gemcitabine and nab-paclitaxel (arm A) compared to placebo, gemcitabine and nab-paclitaxel (arm B) for the target population on the primary endpoint. The definition of the corresponding primary estimand for the randomized phase is detailed in Section 2.1. The primary endpoint is overall survival (OS), defined as the time from the date of randomization to the date of death due to any cause. If a participant is not known to have died, then OS will be censored at the latest date the participant was known to be alive (on or before the analysis cut-off date).

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 28 days.

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 16.1.

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 cohort 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:

CCI

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 [CCI]) at that dosing regimen is less than CCI %.

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.

Randomized part:

The following null and alternative hypothesis will be tested to address the primary efficacy objective for OS of arm A vs arm B:

$H_{01}:\theta_1 \geq 1$ vs. $H_{A1}:\theta_1 < 1$

where θ_1 is the OS hazard ratio of arm A vs. arm B. The null hypothesis will be tested with a stratified log-rank test at an overall one-sided 2.5% significance level. The stratification will be based on the randomization stratification factors: ECOG PS (0 vs. 1); liver metastasis (yes vs. no); region at enrollment (North America, Europe and Australia vs. other countries).

CCI

Analyses will be based on the FAS population according to the randomized treatment group and strata assigned at randomization. The OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% Cis of the medians will be presented for each treatment group. The hazard ratio for OS will be calculated, along with its 95% CI, from a stratified Cox model using the same stratification factors as for the log-rank test.

12.4.3 Handling of intercurrent events of primary estimand

The different intercurrent events and the handling strategies are explained in the following:

1. Discontinuation of study treatment for any reason: OS will take into account all deaths irrespective of the study treatment discontinuation reasons (treatment policy strategy)
2. Any unforeseen intercurrent events (e.g., COVID-19 pandemic related events): OS will take into account all deaths irrespective of any unforeseen intercurrent events (treatment policy strategy)

12.4.4 Handling of missing values not related to intercurrent event

In the primary analysis, if a participant is not known to have died, then OS will be censored at the latest date the participant is known to be alive on or before to the analysis cut-off date.

12.4.5 Sensitivity analyses

Sensitivity analyses for the primary endpoint will be performed in order to provide evidence that results seen from the primary analysis for the primary endpoint are robust. The following sensitivity analysis will be performed for the OS, to assess the robustness of the estimation if there are some delayed treatment effects leading to non-proportional hazards which deviate from the proportional hazards assumptions specified in the primary analysis.

In the presence of non-proportional hazards, a modestly weighted log-rank test (Magirr, Burman 2019) will be considered a preferable alternative to HR for the estimation of treatment effect since no proportional hazards assumption is assumed for this method.

Additional sensitivity analyses may include other methods that provide alternative tests and treatment effect estimates in the presence of non-proportional hazards, e.g. weighted log-rank test with Fleming-Harrington class of weight, difference in the restricted mean survival time (RMST) (Uno et al 2014), landmark analyses, or piece-wise Cox regression to obtain HR by period. Details of all these analyses will be outlined in the SAP.

12.4.6 CCI

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

12.5.1.1 Analysis of other secondary efficacy endpoints

Safety run-in part:

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

- 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)

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.

Randomized part:

For the randomized part, the secondary objectives for the randomized part are to compare PFS, ORR and other tumor related efficacy (DCR, TTR and DOR) based on RECIST 1.1 of NIS793, gemcitabine and nab-paclitaxel (Arm A) vs. the placebo, gemcitabine and nab-paclitaxel (Arm B).

The following analyses are applicable to both parts unless otherwise noted.

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

Progression-free Survival (PFS)

PFS is defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause. PFS will be assessed via local review according to RECIST 1.1. PFS will be censored if no PFS event is observed before the analysis cut-off date. The censoring date will be the date of the last adequate tumor assessment prior to the analysis cut-off.

Censoring rules for PFS will be further detailed in the SAP.

For both parts, the PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% Cis of the medians will be presented for each treatment group.

For the randomized part only, PFS will be analyzed in the FAS population according to the randomized treatment group and strata assigned at randomization. The PFS will be formally tested by using stratified log-rank test in the FAS if primary endpoint of OS is statistically significant (Section 12.4.2). The hazard ratio for PFS will be calculated, along with its 95% CI, using a stratified Cox model.

Overall response rate (ORR)

For both parts, ORR is defined as the proportion of participants with a best overall response (BOR) of complete response (CR) or partial response (PR) as per local review that is subsequently confirmed. ORR will be evaluated according to RECIST 1.1 (Section 16.5). ORR based on RECIST 1.1 will be calculated based on the FAS. The ORR and its 95% CI will be presented by treatment groups.

For the randomized part, the ORR will be formally tested by using Cochran- Mantel–Haenszel chi-square test stratified by the randomization stratification factors if primary endpoint of OS is statistically significant (Section 12.4.2). The ORR and its 95% CI will be presented by treatment groups.

Disease Control Rate (DCR)

DCR is the proportion of patients with a BOR 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 (see Section 16.5 for details). DCR based on RECIST 1.1 will be calculated based on the FAS. DCR and its 95% CI will be presented by treatment group.

Time to response (TTR)

TTR is defined as duration of time between the date of randomization and the date of first documented response of either CR or PR, which must be subsequently confirmed (although date of initial response is used, not date of confirmation). TTR will be evaluated according to RECIST 1.1.

All participants in the FAS will be included in TTR calculations. Participants without a confirmed CR or PR will be censored at the time of PFS event (i.e., disease progression or death due to any cause) for participants with a PFS event (i.e., disease progression or death due to any cause), or at the date of the last adequate tumor assessment for participants without a PFS event. TTR will be listed and summarized by treatment group based on RECIST 1.1. The distribution function of TTR will be estimated using the Kaplan-Meier method. The median TTR along with 95% Cis will be presented by treatment arm.

Duration of response (DOR)

DOR is defined as the duration of time between the date of first documented response (CR or PR) and the date of first documented progression or death due to any cause (this is a modified definition from the one defined in the Section 16.5).

DOR only applies to participants whose BOR is CR or PR based on tumor response data per local review. DOR will be evaluated according to RECIST 1.1. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to any cause. Participants continuing without progression or death (event) due to any cause will be censored at the date of their last adequate tumor assessment. DOR based on RECIST 1.1 will be listed and summarized by treatment group for all participants in the FAS with confirmed BOR of CR or PR, as well as for the subgroup of FAS participants with confirmed BOR of CR only. Participants who never achieved a BOR of CR or PR will be excluded from the analysis. The distribution function of DOR will be estimated using the Kaplan-Meier method. The median DOR along with 95% Cis will be presented by treatment arm.

12.5.2 Safety endpoints

12.5.2.1 Analysis set and grouping for the analyses

For all safety analyses in this study, the safety set 1 will be used for safety run-in part. Results will be presented for all the following safety endpoints.

For all safety analyses, safety set 2 will be used for randomized part. Results will be presented by treatment arm for all the following safety endpoints.

All listings will be presented by treatment group and tables will be presented by treatment group and all participants.

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

1. pre-treatment period: from day of participant's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication up to 30 days after the date of last actual administration of any study medication
3. post-treatment period: starting at day 31 after last dose of study medication.

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

Adverse events (AEs)

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

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.

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 90 days after last administration of NIS793. Further details will be included in the SAP.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE v5.0 grades), type of adverse event, and relation to study treatment.

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

All reported 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 starting during the pre-treatment and post-treatment period will be flagged.

Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE v5.0 grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE v5.0 Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v5.0, results will be categorized as low/normal/high based on laboratory normal ranges. If required, for certain laboratory parameter, values lower than lower limit of normal (LLN) or higher than upper limit of normal (ULN) may further be summarized into categories based on multiples of LLN or ULN respectively.

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 v5.0 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v5.0

- Worst post-baseline CTCAE v5.0 grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v5.0 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v5.0

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

In addition to the above mentioned tables and listings, other analyses if needed, for example figures plotting time course of raw or change in laboratory tests over time or box plots may be specified in the SAP.

Other safety data

Data from other tests, such as ECG, vital signs, and body weight, will be listed and summarized accordingly. Notable values will be flagged in the listing. Definitions of notably abnormal results will be specified in the SAP.

ECG

12-lead ECGs including PR, QRS, QT, and QTcF intervals and heart rate will be obtained for each participant during the study. ECG data will be read and interpreted locally. Categorical analysis of QT/corrected QT interval (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.

Vital signs

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

Body weight

Body weight and changes from baseline weight will be summarized by treatment and visit/time.

12.5.3 Pharmacokinetics

For **safety run-in part**, PK summary statistics will be based on the NIS793 pharmacokinetic analysis set (NIS-PAS).

NIS793 concentration data will be listed by treatment, participant, and visit/sampling timepoint. Descriptive summary statistics will be provided by treatment and visit/sampling timepoint, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, coefficient of variation (CV) (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations.

CCI [redacted] in the **randomized part** of the study the descriptive statistics (n, mean, CV%, SD, median, geometric mean, geometric CV%, minimum and maximum) will be presented for PK parameters for NIS793 when applicable. PK parameters (e.g. AUC, minimum drug concentration after dose administration (Cmin), Cmax, time to reach maximum drug concentration after dose administration (Tmax)) will be estimated and reported at appropriate timepoints, when derivation of selective PK parameters is feasible (see Table 12-1). For participants CCI [redacted], the descriptive statistics (n, mean, CV%, SD, median, geometric mean, geometric CV%, minimum and maximum) will be presented for PK parameters (e.g. Cmax, Ctrough and Ctroughss) and will be reported at appropriate timepoints.

The PK parameters in the Table 12-1 will be estimated and reported, when applicable. 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})

12.5.4 Immunogenicity

Immunogenicity will be characterized descriptively by tabulating ADA prevalence at baseline, ADA incidence on-treatment and Nab ADA prevalence (refer to Section 12.1.5 for additional details). The impact of immunogenicity on PK, safety, and efficacy may be explored. Further details will be specified in the SAP.

12.6 CCI

12.6.1 CCI

12.6.1.1 CCI

12.6.1.2 CCI

12.6.2 CCI

12.6.3 CCI

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12.6.5 CCI

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12.7 CCI

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Table 12-2 CCI

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12.8 CCI

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12.8.1 CCI

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Table 12-3 CCI

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Table 12-4 CCI

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 GCP, 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 ICF, 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.

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 standard operating procedures (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
- 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.

15 References

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16 Appendices

16.1 CCI

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16.1.1 CCI

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16.1.1.2 CCI

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16.1.1.3 CCI

16.1.1.4 CCI

16.1.1.5 CCI

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Table 16-1 CCI

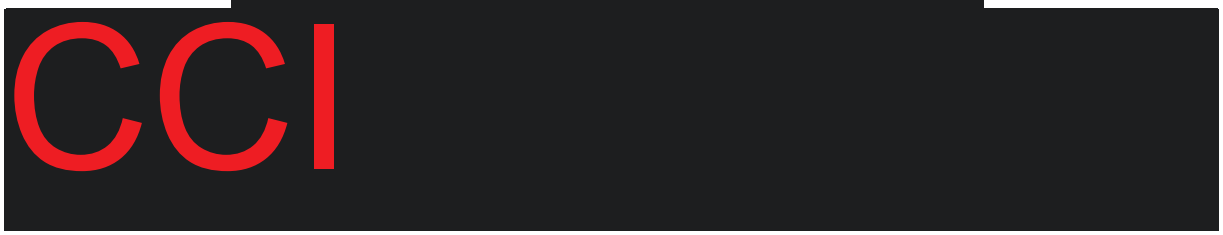

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Table 16-2 CCI

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Table 16-3 CCI

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16.1.1.6 CCI

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Table 16-4 CCI

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Table 16-5 CCI

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16.1.1.7 CCI

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Table 16-6 CCI

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16.1.2 Hypothetical on-study scenarios

To illustrate the performance of the BLRM model used to guide dose escalation, hypothetical dose escalations scenarios are presented in Table 16-7. In each scenario, the table displays the next dose level with the mean expected probability of dose limited toxicity P(DLT) and the probability of having excessive toxicity P(excessive toxicity) at that dose level. Note that next dose level could be the same dose level. If P(excessive toxicity) is ≥ 25%, then the next dose level does not meet EWOC and no more patients should be enrolled at this dose level and a new cohort should be opened at a lower dose level. The hypothetical scenarios considered various cases with 10 evaluable patients or 6 evaluable patients. Scenario 1, 5, and 6 are cases such that the starting dose is considered safe to proceed (meet EWOC), while scenario 2, and 7 are cases such that starting dose is not considered safe (does not meet EWOC). In those cases, cohort 2 will be opened at a lower dose level (scenario 3, 4, 8, and 9). If cohort 2 is considered unsafe to proceed, no more patients will be opened.

Table 16-7 Hypothetical dose escalation scenarios

Scenario	Cohort	NIS793 dose schedule*	Number of Evaluable patients	DLTs	Next dose level (NDL) NIS793 dose schedule*	Median P(DLT)	P(excessive toxicity)
1	Cohort1	2100 mg Q2W	10	3	2100 mg Q2W	0.218	0.200
2	Cohort1	2100 mg Q2W	10	4	2100 mg Q4W	0.175	0.086
3	Cohort1	2100 mg Q2W	10	4			
	Cohort2	2100 mg Q4W	10	1	2100 mg Q4W	0.148	0.016
4	Cohort1	2100 mg Q2W	10	4			
	Cohort2	2100 mg Q4W	10	2	2100 mg Q4W	0.185	0.044

Scenario	Cohort	NIS793 dose schedule*	Number of Evaluable patients	DLTs	Next dose level (NDL) NIS793 dose schedule*	Median P(DLT)	P(excessive toxicity)
5	Cohort1	2100 mg Q2W	6	1	2100 mg Q2W	0.106	0.054
6	Cohort1	2100 mg Q2W	6	2	2100 mg Q4W	0.211	0.225
7	Cohort1	2100 mg Q2W	6	3	2100 mg Q4W	0.189	0.149
8	Cohort1	2100 mg Q2W	6	3			
	Cohort2	2100mg Q4W	6	1	2100 mg Q4W	0.178	0.081
9	Cohort1	2100 mg Q2W	6	3			
	Cohort2	2100 mg Q4W	6	2	2100 mg Q4W	0.237	0.212

* NIS793 2100mg Q2W or 2100mg Q4W in combination with fixed dose of nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 (Day 1, 8, 15 of each cycle)

16.1.3 References (available upon request)

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16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-8 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)

	Definition/ threshold
	• 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 16-9 Follow up requirements for liver laboratory triggers with ALT, AST, TBL

	ALT	Total bilirubin (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	• Refer Table 6-5 for dose modifications • Measure ALT, AST, ALP, GGT, TBL, 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	• Refer Table 6-5 for dose modifications • Measure ALT, AST, ALP, GGT, TBL, 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	
	If normal at baseline:	Normal or elevated		

	ALT	Total bilirubin (TBL)	Liver Symptoms	Action
	ALT > 3 x ULN			
	If elevated at baseline: ALT > 2 x baseline AND > 3 x ULN		Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 16-10 Follow up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (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.

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-11 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50 % **+OR if <18 years old, eGFR ≤ 35 mL/min/1.73 m^2**	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ ORProtein-creatinine **ratio** (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	Assess and document • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

[+] Corresponds to KDIGO criteria for Acute Kidney Injury

Table 16-12 Renal Event Follow Up

Assess, document and record in CRF
• Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells, Blood pressure and body weight, Serum creatinine, blood urea nitrogen (BUN), electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid
• Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF
Monitor patient regularly (frequency at investigator's discretion) until:
• Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) or
• Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.Analysis of urine markers in samples collected over the course of the DIN event

16.4 Appendix 4: List of concomitant medications

The list of CYP450 substrates and list of CYP450 inhibitors / inducers 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. This list is only meant to be used as a guidance.

Table 16-13 List of CYP substrates, inhibitors and inducers of CYP3A4, and inhibitors of CYP2C8 to be used with caution

Category	Drug name
CYP3A4 substrates which are known or potential auto perpetrators	clarithromycin, conivaptan, encorafenib, erythromysin, diltiazem, mifepriston, ribociclib, telthromycin, troleandomycin, verapamil
Strong CYP3A4 inhibitors	ceritinib, clarithromysin, 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[1], carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifapentine, rifampin (rifampicin), St John's wort (*Hypericum perforatum*)[1]
Strong and moderate CYP2C8 inhibitors	clopidogrel (strong), deferasirox (moderate), gemfibrozil (strong), letermovir (moderate), teriflunomide (moderate)

[1]Herbal product. This list of CYP450 inhibitors and inducers 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 (September 2021).

16.5 Appendix 5: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival, and Overall Survival (based on RECIST 1.1)

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Glossary

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

16.5.1 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 16.5.3 and the definition of best response in Section 16.5.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.5.3.2 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 16.5.4 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.

16.5.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria by Therasse et al (2000) and revised RECIST guidelines (version 1.1) by Eisenhauer et al (2009).

16.5.2.1 Definitions

16.5.2.1.1 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 16.5.3.2.8.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥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.

16.5.2.1.2 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 16.5.3.2.8.

16.5.2.2 Methods of tumor measurement - general guidelines

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

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

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.

- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Physical exams: Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10mm size, and can be assessed using calipers.
- Ultrasound: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- Endoscopy and laparoscopy: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

16.5.2.3 Baseline documentation of target and non-target lesions

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

- Target lesions: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target

lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 16.5.2.1.1.
- **Nodal target**: See Section 16.5.2.1.1.

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

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

16.5.2.4 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 16-14) and non-target lesions (Table 16-15) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-16) as well as the presence or absence of new lesions.

16.5.2.4.1 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.

16.5.2.4.2 Determination of target lesion response

Table 16-14 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	

Response Criteria	Evaluation 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 16.5.2.2).	

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 16-14 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 CRF 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 CRF, 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.

16.5.2.4.3 Determination of non-target lesion response

Table 16-15 Response criteria for non-target lesions

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

Response Criteria	Evaluation of non-target lesions
[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. ³ 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 16.5.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

16.5.2.4.4 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 16.5.2.5).

- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ³ 10 mm for the first time in the study plus 5 mm absolute increase. **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 16.5.2.2.

16.5.2.5 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 16-16.

Table 16-16 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 16.5.2.4.			

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.

16.5.3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 16.5.3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

16.5.3.1 Best overall response

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

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or

supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

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

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

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

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

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

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

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

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until

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

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

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

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

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

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

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

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

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

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

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

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

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

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent 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).

16.5.3.2 Time to event variables

16.5.3.2.1 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.

16.5.3.2.2 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.

16.5.3.2.3 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.

16.5.3.2.4 PFS2

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

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

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

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

16.5.3.2.5 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.

16.5.3.2.6 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.

16.5.3.2.7 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 16.5.3.2.5. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

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

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

16.5.3.2.8 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

- 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 16.5.3.2.8).

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.

16.5.3.2.9 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 16-17.

Table 16-17 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 16.5.2.4.		

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.

16.5.3.2.10 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 16.5.3.2.7, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 16-18 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

Situation		Options for end-date (progression or censoring)[1] **(1) = default unless specified differently in the protocol or RAP**	Outcome
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 16.5.3.2.7.			
[2.] =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.5.3.2.7.			
[3.] =The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.			

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

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

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

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

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may

be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

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

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

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

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

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 16-18 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.

16.5.4 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).

16.5.4.1 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).

16.5.4.2 End of treatment phase completion

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

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

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Participant/guardian decision
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

Death is a reason which "*must*" lead to discontinuation of patient from trial.

16.5.4.3 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision

- Pregnancy
- Protocol deviation
- Technical problems
- Participant/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

16.5.4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

16.5.4.5 Programming rules

The following should be used for programming of efficacy results:

16.5.4.5.1 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.

16.5.4.5.2 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 16.5.3.2.7. If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

16.5.4.5.3 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

16.5.4.5.4 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

16.5.4.5.5 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

16.5.4.5.6 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 16-18)
- 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 16.5.3.2.7. 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

16.5.5 References (available upon request)

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