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Novartis Research and Development

NIS793

Clinical Trial Protocol CNIS793B12201 / NCT04390763

A phase II, open label, randomized, parallel arm study of NIS793 (with and without spartalizumab) in combination with SOC chemotherapy gemcitabine/nab-paclitaxel, and gemcitabine/nab-paclitaxel alone in first-line metastatic pancreatic ductal adenocarcinoma (mPDAC)

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List of abbreviations

ADA	Antidrug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BLQ	Below the Limit of Quantitation
BOR	Best Overall Response
BUN	Blood Urea Nitrogen
BW	Body Weight
C-FAS	Complete Full Analysis Set
CK	Creatine Kinase
Cmax	Maximum observed drug concentration
CNS	Central Nervous System
CRF	Case Report/Record Form (paper or electronic)
CR	Complete Response
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DDS	Dose Determining Set
DILI	Drug-Induced Liver Injury
dFdU	2',2'-difluoro-deoxyuridine
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DOR	Duration of Response
ECG	Electrocardiogram
ECLIA	Enhanced Chemiluminescent Assay
ECM	Extra-cellular Matrix
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EoT	End of Treatment
ERCP	Endoscopic Retrograde Cholangiopancreatography
eSAE	Electronic Serious Adverse Event
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GLDH	Glutamate Dehydrogenase

GLP	Good Laboratory Practice
h	Hour
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
HR	Hazard Ratio
IA	Interim Analysis
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	Immunogenicity
[redacted]	[redacted]
IN	Investigator Notification
INR	International Normalized Ratio
IP	Intraperitoneal
irAE	Immune related Adverse Event
IRB	Institutional Review Board
IRT	Interactive Response Technology
KD	Constant of Dissociation
LC-MS/MS	Liquid Chromatography-Mass Spectrometry
LDH	Lactate Dehydrogenase
LFT	Liver function test
LLOQ	Lower Limit Of Quantification
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
mPDAC	Metastatic Pancreatic Ductal Adenocarcinoma
MSI	Microsatellite Instability
Nab	Neutralizing antibody
NOAEL	No Observed Adverse Event Level
NSCLC	Non-Small Cell Lung Cancer
NTproBNP	N-terminal pro b-type natriuretic peptide
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
[redacted]	[redacted]
PD	Progressive Disease
PD-1	Programmed Death-1
PDAC	Pancreatic Ductal Adenocarcinoma
PD-L1	Programmed Death-Ligand 1

PFS	Progression Free Survival
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
pM	picomolar
PR	Partial Response
PT	Prothrombin Time
QTcF	QT interval corrected by Fridericia's formula
RAP	The Report and Analysis Plan
RD	Recommended dose
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Stable Disease
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	Standard Of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1/2	Terminal half-life
TGFβ	Transforming Growth Factor β
TTP	Time To Progression
ULN	Upper Limit of Normal
vs	versus
WHO	World Health Organization
WoC	Withdrawal of Consent

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
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same 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)
Dosage	[redacted]
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Estimand	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 patients 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
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
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 number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized participant
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
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 (WoC) /	Withdrawal of consent from the study occurs only when a participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes

Opposition to use of data /biological samples	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. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Protocol summary

Protocol number	CNIS793B12201
Full Title	A phase II, open label, randomized, parallel arm study of NIS793 (with and without spartalizumab) in combination with SOC chemotherapy gemcitabine/nab-paclitaxel, and gemcitabine/nab-paclitaxel alone in first-line metastatic pancreatic ductal adenocarcinoma (mPDAC)
Brief title	Study of efficacy and safety of NIS793 (with and without spartalizumab) in combination with SOC chemotherapy in first-line metastatic pancreatic ductal adenocarcinoma (mPDAC)
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the efficacy and safety of NIS793 with and without spartalizumab in combination with SOC chemotherapy gemcitabine/nab-paclitaxel in first-line metastatic pancreatic ductal adenocarcinoma. The blockade of TGFβ with and without PD-1 in combination with chemotherapy may reduce fibrosis in PDAC, while restoring chemo-sensitivity and T-cell cytotoxic activity ultimately improving clinical response rate and durability in first-line mPDAC.
Primary Objective(s)	**Safety Run-in part:** To assess the safety and tolerability of NIS793 with spartalizumab in combination with gemcitabine/nab-paclitaxel. **Randomized part:** To evaluate the Progression Free Survival (PFS) per Investigator assessment of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel versus SOC chemotherapy gemcitabine/nab-paclitaxel.
Secondary Objectives	Randomized part: To evaluate the safety and tolerability of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel To assess the preliminary anti-tumor activity of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel To assess Overall Survival (OS) of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel To assess the CD8 and PD-L1 status of the participants at screening and on treatment versus gemcitabine/nab-paclitaxel To characterize the incidence of immunogenicity of NIS793 and spartalizumab in combination with gemcitabine/nab-paclitaxel To characterize the pharmacokinetics (PK) of NIS793, spartalizumab, gemcitabine/nab-paclitaxel in combination treatment or alone (gemcitabine/nab-paclitaxel)

Study design	This study consists of two parts: A **Safety Run-in part** of NIS793 with spartalizumab in combination with gemcitabine/nab-paclitaxel A **Randomized part** parallel arms of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel. Participants will be randomized in a 1:1:1 ratio. The Randomized part will be initiated following review of Safety Run-in part data (clinical, PK, and laboratory data) in a safety review meeting.
Study population	The study will include adult participants with metastatic pancreatic ductal adenocarcinoma (mPDAC) who have not received any prior systemic anti-cancer treatment for metastatic disease.
Key Inclusion criteria	Participants with histologically or cytologically confirmed treatment naïve metastatic adenocarcinoma of the pancreas with measurable disease per RECIST 1.1. Participants must have a site of disease amenable to biopsy, be candidate for tumor biopsy, and must be willing to undergo a tumor biopsy at screening and during therapy on the study. ECOG performance status ≤ 1
Key Exclusion criteria	Previous radiotherapy, surgery (note: placement of biliary stent is allowed), chemotherapy or investigational therapy for the treatment of metastatic disease. Participants having received previous chemotherapy in the adjuvant setting Participants with MSI-H pancreatic adenocarcinoma Participants with a diagnosis of pancreatic neuroendocrine tumors (NETs), acinar, or islet cell tumors Participants amenable to potentially curative resection Presence of symptomatic CNS metastases or CNS metastases that require local CNS-directed therapy History of severe hypersensitivity reactions to other monoclonal antibodies Malignant disease other than that being treated in the study Systemic chronic steroid therapy (>10mg/day prednisone or equivalent) or any immunosuppressive therapy Known history of testing positive for HIV infection Active HBV and HCV infection Use of any live vaccines against infectious diseases within 4 weeks of initiation of study treatment Active, known or suspected autoimmune disease History of or current pneumonitis or interstitial lung disease

Study treatment	**Safety Run-in part**: NIS793 i.v. 2100 mg (or 1400 mg in case dose level -1 is required) Q2W plus spartalizumab i.v. 400 mg Q4W plus nab-paclitaxel i.v. 125 mg/m2 plus gemcitabine i.v. 1000 mg/m2 **Randomized part** (participants will be treated at the dose confirmed to be safe after **Safety Run-in part**): **Arm 1**: NIS793 plus spartalizumab plus gemcitabine plus nab-paclitaxel **Arm 2**: NIS793 plus gemcitabine plus nab-paclitaxel **Arm 3**: gemcitabine plus nab-paclitaxel A cycle of treatment is defined as 28 days.
Efficacy assessments	Radiological tumor assessment by Investigator per RECIST 1.1 at screening, every 8 weeks for first year, then every 12 weeks. Survival assessments every 12 weeks after safety and efficacy follow-up period
Pharmacokinetic assessments	Concentrations and derived PK parameters of NIS793, spartalizumab, gemcitabine and nab-paclitaxel Antidrug antibodies (ADA) prevalence at baseline and ADA incidence on treatment (anti-NIS793 and anti-spartalizumab)
Key safety assessments	Physical examination ECOG performance status Vital signs Laboratory assessments ECGs Monthly pregnancy testing for women of childbearing potential Adverse events (AEs), severity, relationship to study treatment and seriousness
Other assessments	[redacted]
Data analysis	**Safety Run-in part** The primary safety objective is to assess the safety and tolerability of NIS793 with spartalizumab and gemcitabine/nab-paclitaxel and to identify the dose to be tested in Randomized part. The dose to be tested in Randomized part will be primarily assessed based on the incidence of dose limiting toxicities (DLTs). Safety and tolerability will be additionally evaluated based on the incidence of (serious) adverse events, changes in laboratory values, vital signs, ECGS and dose interruptions, reductions, and dose intensity. The decision to proceed with the Randomized part will be taken based on safety observed during Safety Run-in part. **Randomized part** The primary efficacy estimand is to characterize the anti-tumor activity of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel. The primary analysis may be performed when both or either of the following criteria are met: Approximately 60 participants (who comply with the FAS criteria) have experienced a PFS event (documented progression as per RECIST 1.1 or death due to any cause) in the NIS793 with spartalizumab and gemcitabine/nab-paclitaxel (Arm 1) and gemcitabine/nab-paclitaxel (Arm 3) arms.

Approximately 60 participants (who comply with the FAS criteria) have experienced a PFS event (documented progression as per RECIST 1.1 or death due to any cause) in the NIS793 with gemcitabine/nab-paclitaxel (Arm 2) and gemcitabine/nab-paclitaxel (Arm 3) arms.

Interim analysis of efficacy data may be conducted, prior to the primary analysis, to support decision making concerning the Sponsor's clinical development projects.

A Bayesian model will be used to estimate and provide inferential summaries of the PFS hazard ratio (HR). For each treatment comparison (Arm 1 vs Arm 3 and Arm 2 vs Arm 3), the PFS will be modeled using a two-piece hazard model, which allows to specify different HRs before and after the possible delayed effect. A weakly informative prior distribution will be assumed for Arms 1 and 2. A mixture prior distribution will be assumed for Arm 3, which consists of two components derived from a historical gemcitabine/nab-paclitaxel study.

At the time of the analysis, the model will be updated with all available data of participants in the Full Analysis Set (FAS), and the posterior distribution for the HR after the delayed effect will be estimated. Inferential summaries based on the posterior distribution will be presented, including median, mean, standard deviation and one-sided 90% credible interval.

[redacted] with spartalizumab and gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel and similarly, of NIS793 with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel.

The secondary endpoints safety, overall response rate (ORR), duration of response (DOR), time to progression (TTP), and overall survival (OS) will be analyzed based on FAS and presented by treatment arm.

Key words NIS793, spartalizumab, gemcitabine, nab-paclitaxel, mPDAC, TGFβ, PD-1, Phase II

Amendment 04 (April 2022)

Amendment rationale

The main purpose of this amendment is to allow for potential interim analysis (IA) where statistical analyses by treatment arm can be conducted. While study is open label, by treatment arm analyses were not allowed in previous protocol version. The IA will be used to support future NIS793 development and will have no impact on the current study design and conduct.

Further minor changes have been made to correct inconsistencies.

Study update

The CNIS793B12201 study started enrollment on 16-Oct-2020. As of 28-Mar-2022, 78 participants have been treated in the study: 11 participants in the Safety Run-in part and 67 in the Randomized part.

Changes to the protocol

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

Glossary of terms:

- Definition of Withdrawal of consent / Opposition to use of data /biological samples was updated in order to align with Section 9.1.2 Withdrawal of informed consent/Opposition to use data/biological samples.

Section 4.4 Purpose and timing of interim analyses/design adaptations:

- Addition of potential interim analysis in the Randomized part of the study.

Section 5.2 Exclusion criteria:

- Clarification that women are considered post-menopausal if they satisfy criteria at least six weeks prior to enrollment to the study.

Section 6.4 Treatment blinding:

- Addition of language that will allow statistical analysis by treatment arm in case of interim analysis.

Section 6.7.1 Handling of the study treatment and additional treatment:

- Wording was added to allow destruction of unused study treatment, drug labels and packaging at the site.

Section 10.1.3 SAE reporting:

- SAE reporting section was updated to clarify that initial and follow-up information about SAEs should be reported to Novartis immediately, without delay and under no circumstances later than 24h after obtaining knowledge of the event or follow-up information about the event.

Section 12 Data analysis and statistical methods:

- Addition of possibility for a primary clinical study report, prior to the end of the study.
- Adjustment of number of events for primary analysis from 60 to approximately 60 to provide more flexibility for timing of primary analysis.

Section 12.7 Interim analyses:

- Addition of potential interim analysis in the Randomized part of the study.

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.

Amendment 03 (April 2021)

Amendment rationale

The purpose of this amendment is to address the following:

- Based on emerging new NIS793-related preclinical safety findings of vascular inflammation and tubulo-interstitial nephritis observed in non-GLP toxicology studies in cynomolgus monkeys and rats, additional precautionary measures have been implemented (update of exclusion criteria for impaired cardiac function, addition of cardiac imaging and cardiac enzymes safety assessments and addition of urinalysis monitoring during treatment) to enhance cardio-vascular and renal risks mitigation.
- Additional clarification on the mitigation of risks already described in the NIS793 Investigator Brochure, was provided. Namely, exclusion criterion related to bleeding risk was added, and drug-induced liver injury (DILI) was included in the dose modification recommendation.
- To revise the primary estimands and introduce secondary estimands related to efficacy objectives (anti-tumor response, overall survival):
  - In the context of the COVID-19 pandemic, discontinuations due to COVID-19 were added as part of the intercurrent events for primary and secondary estimands.
  - Secondary estimands for efficacy objectives were introduced in order to further refine the clinical questions of interest.
- To account for the observed enrollment rate of the Safety Run-in part and potential impact of the COVID-19 pandemic on the study enrollment, and given the primary endpoint of the study, the enrollment rate of the Randomized part and time-to-first readout were re-assessed.
- In order to mitigate the risks for participant safety and data integrity due to disruptions (e.g. COVID-19), disruption proofing language was added throughout the protocol.
- [redacted]
- For consistency between both study treatments, spartalizumab and NIS793, the 2h observation period was aligned to the first cycle.
- Maximum permitted duration of study treatment interruption or delay, which will not lead to permanent treatment discontinuation, was extended to 12 weeks, to account for potential immune related toxicity and allow more time for recovery in case of toxicity.
- Further minor changes have been made to correct inconsistencies.

Study update

The CNIS793B12201 study started enrollment on 16-Oct-2020. As of 14-Apr-2021, 10 participants have been treated in the Safety Run-in part.

Changes to the protocol

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

Section 1.1.2.1.1 Non-clinical experience with NIS793:

- Section was updated to include new non-clinical toxicology and pharmacology data in rats and cynomolgus monkeys.

Section 2.1 Primary estimands:

- Wording was simplified to combine the clinical questions in one question.
- Treatment discontinuation related to COVID-19 was added as part of the intercurrent events. Changes were reflected across Section 12 Data analysis and statistical methods.

Section 2.2 Secondary estimands:

- Secondary estimands addressing efficacy objectives, as well as handling of intercurrent events, were introduced. Changes were reflected across Section 12 Data analysis and statistical methods.

Section 4.6 New section added: Rationale for Public Health Emergency mitigation procedures.

Section 5.2 Exclusion criteria:

- Cardiac function criteria was updated by adding requirements related to left ventricular ejection fraction, cardiac enzymes, valvulopathy, uncontrolled hypertension and myocarditis.
- Criterion was added to exclude participants with conditions that are considered to have a high risk of bleeding.

Table 6-1 Investigational and control drug:

- Correction was made to allow use of any locally available/approved formulation of gemcitabine and nab-paclitaxel.

Section 6.1.4 Treatment duration:

- Maximum permitted duration of study treatment interruption or delay, which will not lead to permanent treatment discontinuation, was extended to 12 weeks.

Section 6.3.2 Treatment assignment, randomization:

- Incorrect part of the sentence, that refers to study treatment blinding, was deleted.

Section 6.5.4 Dose modifications:

- Section was updated to allow NIS793 dose modification by increasing NIS793 dosing interval from Q2W to Q4W after adverse events as described in the Table 6-5.

Section 6.5.5.1 Follow up on potential drug-induces liver injury (DILI) cases:

- New section and Table 6-8 added.

Section 6.7.2 Instruction for prescribing and taking study treatment:

- Clarification that 1 hour follow-up post NIS793 infusion includes flush and observation, as per pharmacy manual.
- Spartalizumab and NIS793 2h observation period was aligned to the first cycle.

Section 7 Informed Consent Procedures:

- Paragraph was added to allow remote informed consent discussion during the study, in case of a Public Health emergency.

Section 8 Visit schedule and assessments:

- Addition of alternative methods of providing continuing care may be implemented by the Investigator during a Public Health emergency situation.

Table 8-2 Assessment schedule:

[redacted]

- Cardiac imaging (echochardiogram and CT/MRI) and cardiac enzymes assessments were added.
- Urinalysis monitoring during treatment was added.

Section 8.2 Participant demographics/other baseline characteristics:

- Addition of collection of race and ethnicity in order to identify variations in safety or efficacy.

[redacted]

Section 8.4 Safety:

- Paragraph was added to allow remote safety monitoring during the study, in case of Public Health emergency.

Section 8.4.6 Electrocardiogram (ECG):

- Reference to the ECG Manual was removed as ECG assessment is only local.

Table 8-5 Laboratory assessment:

- Troponin I and NTproBNP assessments were added.

Section 8.4.6.1 Cardiac imaging - echocardiogram or CT/MRI scan and Section 8.4.6.2 Cardiac enzymes:

- Sections were added in order to describe cardiac safety monitoring.

Table 8-6 Pharmacokinetic blood collection log - NIS793 and spartalizumab in Safety Run-in part and Randomized Arms 1 & 2:

- Addition of DILI as a reason for collection of unscheduled PK [redacted] G sample.

Table 8-7 Pharmacokinetic blood collection log – gemcitabine and nab-paclitaxel in Safety Run-in and Randomized part (all Arms):

- Collection window of Cycle 4 Day 2 PK samples was prolonged from 2h to 4h, to allow more flexibility in sample collection.
- Addition of DILI as a reason for collection of unscheduled PK sample.

[redacted]

Section 9.1.2 Withdrawal of informed consent/Opposition to use data/biological samples

- Withdrawal of informed consent was clarified to clearly differentiate withdrawal of informed consent and discontinuation from the study.

Section 10.1.4 Pregnancy reporting:

- Pregnancy outcomes will be collected for up to one year.

Section 12 Data analysis and statistical methods:

- Addition of secondary safety analysis and overall survival analysis as part of the primary analysis readout to better inform ongoing Phase III trial at the time of the primary analysis.

[redacted]

Section 12.2 Participant demographics and other baseline characteristics:

- Removal of duplication of language detailing categorical and continuous data presentation.

Section 12.3 Treatments:

- Redundant text was deleted.

Section 12.5.1.1 Handling of intercurrent events of secondary estimands:

- New section was added

Section 12.5.1.2 Handling of missing values not related to intercurrent events:

- New section was added

Section 12.8 Sample size calculation:

- Change in the accrual of participants in the Randomized part from 20 to 15 per month for the three arms, based on the accrual rate from the Safety Run-in part.

Table 12-2 Operating characteristics for scenarios with 100 participants, 60 events, and a 3-month delayed effect:

- Addition of information regarding the underlying assumptions for the simulation of scenarios.
- Correction of operating characteristics.

Appendix 5 Bayesian model set-up and prior specifications:

- Correction of Table 16-9 and addition of Table 16-10 and Table 16-11, accounting for additional scenarios as part of the sensitivity analysis.

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.

Amendment 02 (August 2020)

Amendment rationale

The purpose of this amendment is to address the following Health Authorities' request:

- To state that sexually active males have to use a condom while taking study treatment and for 180 days after stopping treatment.
- To include instruction to follow contraception recommendations and other precautionary measures required by locally approved SmPC of gemcitabine and nab-paclitaxel.

Study update

At the time of this amendment, this protocol is under review by Health Authorities of the participating countries and recruitment has not yet started.

Changes to the protocol

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

Section 5.2 Exclusion criteria:

- Change of the duration of contraception for sexually active males from 90 to 180 days after stopping study treatment.
- Simplified language for the duration of contraception for women of childbearing potential on study treatment.
- Added instruction to follow local prescribing information for SOC with regards to contraception and other precautionary measures.

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.

Amendment 01 (July 2020)

Amendment rationale

The purpose of this amendment is to address the following Health Authorities request:

- To revise the protocol so that Grade 3 diarrhea lasting for > 72 hours is a DLT.

Additional editorial changes have been made to clarify or correct the language in some sections.

Study update

At the time of this amendment this protocol is under review by Health Authorities of the participating countries and recruitment has not yet started.

Changes to the protocol

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

Section 5.2 Exclusion criteria

- Correction of a typo in renal exclusion criterion 4, from serum creatinine < ULN to serum creatinine > ULN.
- Correction of a typo in hepatic exclusion criterion 4 to clarify Gilbert's syndrome participants are <u>not</u> eligible for listed lab parameters.

Section 6.5.3 Definitions of dose limiting toxicities (DLTs)

- Table 6-3: Change of DLT definition for Grade 3 diarrhea from events lasting > 7 days to > 3 days.

Section 8 Visit schedule and assessments

- Update of Table 8-2 Assessment schedule to align ECG schedule with Section 8.4.6 and collection of Concomitant medications until 30 days safety follow-up as per Section 9.2.3

Section 8.5.1.1 Pharmacokinetic blood collection and handling

- Update of footnote in Table 8-7 to correct C1D1 pre-dose gemcitabine PK sample should be collected prior to nab-paclitaxel dosing

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.

1 Introduction

1.1 Background

1.1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1.1 Pancreatic ductal adenocarcinoma (PDAC)

Pancreatic ductal adenocarcinoma (PDAC) represents a significant public health burden, being the fourth-leading cause of cancer-related death, with an estimated 45,750 deaths and 56,770 new cases in 2019 in the US (American Cancer Society - Cancer facts & figures 2019). Despite progress in the management of PDAC, the overall 5-year survival rate for all stages combined is 8%, decreasing to 3% for patients presenting with advanced disease (American Cancer Society - Cancer facts & figures 2019). In the absence of improvements in early diagnosis and treatment, PDAC will likely become the second leading cause of death by 2030 (Akerberg et al 2017).

The development of effective chemotherapies in PDAC has been limited with only modest improvements in survival. Gemcitabine monotherapy was established as the standard of care (SOC) for first-line patients with advanced PDAC from 1997 to 2011 (Burris et al 1997). More recently, FOLFIRINOX, a combination of 5-fluorouracil, folinic acid, irinotecan plus oxaliplatin has demonstrated superiority to gemcitabine alone, with an overall survival (OS) of 11.1 months vs 6.7 months (Lambert et al 2017, Conroy et al 2011). However, due to toxicity associated with this combination regimen, FOLFIRINOX is reserved for patients with good performance status. The combination of gemcitabine plus nab-paclitaxel in advanced PDAC was shown to improve OS in comparison to gemcitabine alone, with an OS of 8.3 months vs 6.7 months, and a more favorable safety profile than FOLFIRINOX (Von Hoff et al 2013). Based on the above studies, FOLFIRINOX and gemcitabine plus nab-paclitaxel were approved as first-line treatment of advanced PDAC in 2011 and 2013, respectively. Despite these approved chemotherapies for the treatment of first-line PDAC, OS 5 year-rate remains below 10%, thus highlighting the need for innovative therapeutic options.

Checkpoint inhibitors have shown limited activity as monotherapy in PDAC with no objective response reported with BMS-936559, a PD-L1 antibody tested in advanced PDAC (Brahmer et al 2012) and disease control rate (DCR) of 6% with durvalumab monotherapy in a randomized phase 2 trial in second line metastatic PDAC (mPDAC) (O'Reilly et al 2019). Consistent with these results, the dMMR status that predicts response to PD-1/PD-L1 blockade in solid tumors has been reported to have a low incidence of 1.6% in PDAC (Le et al 2017).

One of the reasons for the poor response to therapeutic treatment 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 2011), characterized by an abundance of activated stroma and progressive accumulation of extracellular matrix proteins. While intra-tumoral fibrosis in PDAC is known to correlate with poor survival even after resection (Watanabe et al 2003, Erkan et al 2008), this dense tumor microenvironment also constitutes a mechanical obstacle to the penetration of therapies to the tumor parenchyma (Feig et al 2012). More recently, desmoplasia in PDAC has been also

associated with a state of immune exclusion, depicting the prevalent accumulation of tumor infiltrating immune cells within peritumoral regions and their paucity in the tumor core. Altogether, these attributes strongly contribute to the lack of efficacy of standard therapies, as well as immunotherapies in PDAC. New agents targeting the desmoplastic tumor microenvironment may therefore represent an opportunity to establish novel therapeutic paradigms in the treatment of PDAC.

In this context, TGFβ-blockade offers the potential to address some of the aberrations of the PDAC microenvironment, due to of 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. PCSs are quiescent in normal tissues, but upon activation, they adopt a myofibroblast-contractile phenotype, secreting and remodeling the stiff extracellular matrix characteristic of the PDAC microenvironment (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). Loss of function or truncating mutations of *TGFβRI*, *TGFβRII*, *Smad2*, and *Smad4* genes have all been reported in PDAC (Riggins et al 1997, Schutte et al 1996). Loss of 18q21 chromosome that harbors the *Smad4* gene, for example, is observed in 60% of pancreatic cancer (Hahn et al 1996a, Hahn et al 1996b) and has been suggested to promote KRAS-driven malignant transformation of pancreatic duct cells (Leung et al 2013). Smad4 inactivation also correlates with aggressive tumor cell behavior and is therefore associated with worse prognosis (Hahn et al 1996a, Blackford et al 2009). TGFβRII mutations are also common in PDAC, accounting for about 4-7% of pancreatic cancers (Lin and Feng 2005, Hansel et al 2003, Goggins et al 1998), while mutations in TGFβRI are found in 2% of them (Hansel et al 2003, Goggins et al 1998, Hahn et al 1996a, Achyut and Yang 2011). These molecular alterations likely represent a mechanism for pancreatic cancer cells to grow and spread in an overly high TGFβ microenvironment.

1.1.2 Introduction to investigational treatments

1.1.2.1 Overview of NIS793

NIS793 is a recombinant human anti-TGFβ IgG2 mAb that belongs to the IgG2/λ isotype subclass and binds TGFβ1 and TGFβ2 with high affinity and, to a lesser extent, TGFβ3.

1.1.2.1.1 Non-clinical experience with NIS793

The extracellular domains of the three TGFβ isoforms are highly conserved across human, cynomolgus monkey and rodents. Human and cynomolgus monkey share a 100% sequence identity for all three isoforms of TGFβ. Rodent TGFβ differs from the human/monkey by one amino acid for TGFβ1 and TGFβ3 and by 3 amino acids for TGFβ2. This results in a greater than 97% sequence identity among species.

For the non-clinical toxicology of NIS793, refer to NIS793 Investigator's Brochure. Briefly, before the first entry in humans, NIS793 was investigated in tissue cross-reactivity studies and in a 13-week rat toxicity study up to 10mg/kg/wk i.v. as well as in a 4-week cynomolgus monkey toxicity study up to 16mg/kg/wk i.v. both followed by 4-week recovery period. In the rat, minimal to mild non-adverse effects were observed in liver, kidney, bone, and eyelids, which could reflect inhibition of the tissue homeostatic effects of TGFβ with NIS793 (bone, eyelids). For the effects in liver and kidney, the relation to treatment and inhibition of TGFβ is not clear and could indicate incidental findings or an increase in normal rat specific background findings. In the monkey study, assessments of safety pharmacology endpoints were included. No adverse effects on cardiovascular, central nervous system or respiratory function were observed. Overall, no observed adverse event level (NOAEL) were set to 10mg/kg in the rat study and to 16mg/kg in the cynomolgus study.

In a rat non-GLP pharmacology model of lung fibrosis, valvulopathy in the heart was found at NIS793 at 30mg/kg intraperitoneal, every second day (IP, Q2D) after 14 days. The exposure levels in these animals were in the clinically relevant range. In currently evaluated 8-week dose range finding and tolerability studies in rats and monkeys, adverse findings were observed in the kidney (tubulo-interstitial nephritis with tubular hypertrophy/hyperplasia) and the vascular system (vascular inflammation, vascular necrosis and endothelial cell hyperplasia) of cynomolgus monkeys at 65 mg/kg/wk i.v., and in the heart (cardiac valvulopathy) of rats at 30 and 90 mg/kg/wk i.v.. Toxicokinetic and anti-drug antibody data are not yet available. Based on modeling and simulation projections of exposure in rats and monkeys, these findings likely occurred at exposure comparable to those achieved in participants in current oncology trials.

Preclinical studies in tumor-bearing mice have shown that NIS793 was sufficient to impair myofibroblast differentiation in the tumor microenvironment, supporting the hypothesis that TGFβ-blockade could represent a valid approach to target intratumoral fibrosis development. The observed reduction in the numbers of myofibroblasts in mice treated with NIS793 was accompanied by an increase in the number of tumor-infiltrating T cells, as determined by FACS assessment of tumor disaggregates. NIS793 was also shown to significantly augment the overall response to PD1-blockade in mice, leading to greater tumor regression and extended survival as compared to aPD-1 alone.

1.1.2.1.2 Clinical experience with NIS793

NIS793 is currently evaluated as a single agent and in combination with spartalizumab in CNIS793X2101 first-in-human study. As of clinical data cut-off date, 03-Jun-2019, a total of 43 participants have been treated with NIS793 (liquid or lyophilisate formulation) as a single agent (NIS793: 0.3-1 mg/kg Q3W) or in combination with spartalizumab (NIS793/spartalizumab: 0.3 mg/kg/100 mg Q3W and 0.3-30 mg/kg/300 mg Q3W). Four participants (9.3%) were ongoing. No participants experienced a dose limiting toxicity (DLT). Twenty nine participants discontinued study treatment (27 for progressive disease, one for adverse events (AEs) and one for death).

After the clinical cut-off date, 11 additional participants were treated with NIS793 Q2W regimen (20 and 30 mg/kg) in combination with spartalizumab (400 mg Q4W) and none of them experienced a dose limiting toxicity (DLT).

Forty-two participants (97.7%) reported one or more AEs of any grade and 22 participants (51.2%) reported one or more AEs grade 3/4 (regardless of causality) during the course of the study until the clinical data cut-off date, 03-Jun-2019. The most frequently reported AEs regardless of causality, any grade were fatigue: (16 participants, 37.2%), nausea (14 participants, 32.6%), vomiting (13 participants, 30.2%), constipation (12 participants, 27.9%), decreased appetite, anemia, dyspnoea, and pyrexia (each 10 participants, 23.3%). The most frequent grade 3/4 AEs regardless of causality were fatigue, anemia, and hypercalcemia (each three participants, 7.0%), and these were all grade 3. Grade 4 AEs reported were blood bilirubin increased, reduced general condition, and intracranial hemorrhage, which were all not suspected AEs. Twenty participants (46.5%) reported one or more AEs suspected to be study drug related during the course of the study until the cut-off date. The most frequently reported AEs considered suspected to be study treatment related were fatigue (six participants, 14%), rash (four participants, 9.3%), hypothyroidism, nausea and pruritus (each three participants, 7.0%). Reported AEs were all of lower grade (≤grade 2) with the exception of one AE drug eruption and one AE decreased appetite, both of grade 3. Nineteen participants (44.2%) experienced at least one serious adverse event (SAE) regardless of causality. Two of these SAEs were reported as suspected to be related to study treatment (grade 2 and 3 drug eruption); both events were reported in one participant treated with NIS793 0.3mg/kg + spartalizumab 300 mg Q3W.

As of clinical data cut-off date, the preliminary PK data of NIS793 have been characterized in the CNIS793X2101 study. Following administration of NIS793, dose-proportional increased exposure (i.e. Cycle 1 Cmax and AUClast) with moderate accumulation (~ 2.0-fold) between cycles 1 and 3 was observed.The recommended dose (RD) has been determined as NIS793 30 mg/kg Q3W in combination with spartalizumab which is comparable to a flat dose of 2100 mg (equivalent of 30 mg/kg when using body weight of 70 kg) NIS793 and 300 mg spartalizumab, Q3W in solid tumor participants.

For more details, please refer to NIS793 Investigator's Brochure.

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

1.1.2.2 Overview of spartalizumab

1.1.2.2.1 Non-clinical experience with spartalizumab

Spartalizumab binds specifically and with high affinity to human PD-1. In Biacore assays, the KD of spartalizumab on human PD-1 is 0.827 nM. The affinity of spartalizumab for cynomolgus PD-1 is 0.929 nM, nearly the same for human PD-1, as noted above.

Spartalizumab has been evaluated in a 5-week GLP toxicology study in cynomolgus monkeys (once weekly i.v. dosing at 0, 6, 25 or 100 mg/kg for a total of five doses) with safety pharmacology endpoints. Additional control and high dose animals were maintained for an eight week recovery period. There were no test article-related effects on in-life parameters, mortality, organ weight changes, or macroscopic findings. Test article related histopathological findings comprised macrophage infiltrates in the spleen (100 mg/kg/week) and low grade mononuclear infiltrates in the vascular and perivascular space (≥ 6 mg/kg/week). In a

subsequent 14-week GLP toxicology study in cynomolgus monkeys, doses of 25 and 100 mg/kg (once weekly i.v. dosing for a total of 14 doses) were well tolerated. Microscopic findings included mononuclear cell infiltrates in several tissues.

For further details, please refer to the Spartalizumab Investigator's Brochure.

1.1.2.2.2 Clinical experience with spartalizumab

The first in human phase I/II study CPDR001X2101 is ongoing in participants with advanced malignancies and has completed enrollment. The dose escalation part of the study evaluated dose levels of 1, 3 and 10 mg/kg every two weeks (Q2W) and 3 and 5 mg/kg every 4 weeks (Q4W). No participant experienced a dose limiting toxicity (DLT). The pharmacokinetics (PK) analysis of the dose escalation data using a population approach and the expected wide therapeutic index of PD-1 inhibitors support the use of flat dosing for spartalizumab of 400 mg Q4W or 300 mg Q3W. The expected spartalizumab Ctrough concentrations using either dosing regimen exceed the EC50 for PD-1 blockade by approximately 75-fold in an *ex vivo* assay in peripheral blood mononuclear cells (PBMCs). Based on the available PK and safety data, the recommended phase 2 dose (RP2D) of spartalizumab has been declared as 400 mg i.v. Q4W or 300 mg i.v. Q3W for combination treatment regimens for which this may be more convenient.

Spartalizumab is currently being studied alone or in combination with other agents in ongoing phase I - III clinical trials. The toxicity profile appears to be similar to that of marketed inhibitors of PD-1 including the type, severity and frequency of occurrence of immune-mediated AEs. As observed with other PD-1 inhibitors, immune-mediated toxicities are reversible in many cases. In some cases, they may require treatment with corticosteroids. Certain toxicities are expected to be lifelong and may require replacement therapy with hormones, for example in the case of hypothyroidism.

Overall, spartalizumab was well tolerated with a safety profile similar to those of other marketed anti-PD-1 antibodies. For further details, please refer to the Spartalizumab Investigator's Brochure.

1.1.2.3 Overview of gemcitabine

Gemcitabine is a pyrimidine analog which is metabolized to two active metabolites, gemcitabine diphosphate and gemcitabine triphosphate. The cytotoxic effects of gemcitabine are exerted through incorporation of gemcitabine triphosphate into DNA, resulting in inhibition of DNA synthesis and induction of apoptosis. Gemcitabine is cell-cycle phase specific (S and G1/S-phases) (Grindey et al 1990, Eli Lilly 1999).

Gemcitabine is rapidly metabolized by cytidine deaminases in liver, kidney, blood and other tissue (Gilbert et al 2006). Drug elimination is mediated through renal excretion. Within one week of administration 92% to 98% of the dose was recovered, almost entirely in the urine (Eli Lilly 1999).

The main toxicities of gemcitabine are elevated liver enzymes ((aspartate transaminase (AST) /aspartate aminotransaminase (ALT)) and alkaline phosphatase (ALP), nausea/vomiting, protein/hematuria, dyspnea, rash and myelosuppression (Moore et al 1992, Mertens et al 1993, Lund et al 1994).

Gemcitabine is approved for use alone or with other drugs in pancreatic cancer, ovarian cancer, non-small cell lung cancer (NSCLC) and breast cancer (NCCN 2019, ESMO Guidelines 2015).

Refer to local approved label for more details.

1.1.2.4 Overview of nab-paclitaxel

Nab-paclitaxel is a microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerisation. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or 'bundles' of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

The major route of elimination of nab-paclitaxel is hepatic and fecal (20% of the total dose administered). *In vitro* studies with human liver microsomes and tissue slices showed that paclitaxel in nab-paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by CYP2C8 and 2 minor metabolites, 3'-p-hydroxypaclitaxel and 6α, 3'-p-didydroxypaclitaxel, by CYP3A4. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

The main toxicities of nab-paclitaxel in combination with gemcitabine are fatigue, peripheral neuropathy, nausea/vomiting, alopecia, peripheral edema, diarrhea, pyrexia, appetite, rash, and dehydration (Von Hoff et al 2013).

Nab-paclitaxel is approved for use alone or with other drugs in pancreatic cancer, NSCLC and breast cancer (NCCN 2019, ESMO Guidelines 2015).

Refer to local approved label for more details.

1.1.2.5 Overview of the combination treatment

1.1.2.5.1 Non-clinical experience with the combination treatment

There is no non-clinical experience with NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel.

1.1.2.5.2 Clinical experience with the combination treatment

There is no clinical experience with NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel.

1.1.2.5.3 Potential for drug-drug interactions

No specific drug–drug interactions studies were conducted for NIS793. NIS793 is a mAb, not metabolized by cytochrome P450 (CYP450) enzymes, or transported by P-glycoprotein (P-gp) or related ABC membrane transporters. In a cellular assay, TGFβ has been shown to alter the expression of certain CYP450 enzymes (Müller et al 2000). Changes in expression of CYP450 enzymes with administration of NIS793 are unknown but considered unlikely. In addition, cytokines produced by activated lymphocytes may impact the levels of P-gp and the activity of CYP450 enzymes (Harvey and Morgan 2014, Dumais et al 2008, Renton 2005). The clinical

relevance of cytokines impacting levels of P-gp and CYP450 with administration of NIS793 is unknown but considered unlikely NIS793 Investigator's brochure.

Pharmacokinetic drug-drug interactions (DDIs) are not anticipated for spartalizumab because it is not expected to interact with drug metabolizing enzymes or transporters. To date, no dedicated DDI studies have been conducted with spartalizumab. Monoclonal antibodies such as spartalizumab are eliminated through protein catabolism, and not metabolized by CYP450 enzymes or transported by P-gp or related ABC membrane transporters. The risk of DDI has been evaluated in multiple combination clinical studies with spartalizumab and appears to be very low PDR001 Investigator's brochure; the experience with NIS793 to date appears to be similar NIS793 Investigator's brochure. In summary, the potential for DDI between antibodies used in combination is considered highly unlikely.

Paclitaxel is metabolized by CYP2C8 and CYP3A4. As per label, caution should be exercised when administering nab-paclitaxel concomitantly with medicines known to either inhibit or induce CYP2C8 or CYP3A4.

Overall, the risk of DDIs between NIS793/spartalizumab and gemcitabine/nab-paclitaxel is anticipated to be low. Nevertheless, PK of gemcitabine/nab-paclitaxel in the presence and absence of NIS793 or spartalizumab will be characterized in this study to assess the DDIs.

1.1.2.5.4 Expected overlapping toxicity

Based on available preclinical and clinical safety data described in Section 1.1.2.1 and Section 1.1.2.2, the combination of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel may have associated toxicities that may overlap (Table 1-1).

The AEs associated with NIS793 and spartalizumab are detailed in Section 6.5, in NIS793 Investigator's brochure, PDR001 Investigator's brochure, gemcitabine and nab-paclitaxel local labels.

All participants enrolled will be closely monitored for these potential overlapping toxicities as well as any unforeseen risk.

Table 1-1 Potential overlapping toxicities

Drug	Toxicities overlapping with NIS793/spartalizumab
Gemcitabine/nab-paclitaxel (see local drug label)	Hematological toxicity (e.g. anemia, thrombocytopenia, leucopenia, neutropenia, febrile neutropenia)
	Pulmonary toxicity (e.g. pneumonitis)
	Gastrointestinal toxicity (e.g. nausea, vomiting, diarrhea, decreased appetite)
	Hepatic toxicity (e.g. increase in LFTs (Liver function tests))
	Skin toxicity (e.g. maculopapular rash, rash, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis)
	Constitutional (e.g. fatigue, asthenia, pyrexia)
	Hypersensitivity reaction/infusion reaction
	Embryo-fetal toxicity

1.2 Purpose

The prognosis of mPDAC remains extremely poor despite approved therapies with a median OS of 8.5 months and overall response rate of 23% with gemcitabine/nab-paclitaxel (Von Hoff et al 2013). Few effective treatment options exist, highlighting the significant unmet medical need in this disease.

Pancreatic cancer is a highly desmoplastic tumor characterized by prominent deposition of collagen and extracellular matrix proteins such as hyaluronic acid, which altogether contribute to tissue structural rigidity and poor perfusion. These structural aberrations significantly reduce the penetration of macromolecules, hindering the tumor intake of therapeutics (Provenzano et al 2012). Activated stellate cells, the primary cell population responsible for the fibrotic response in PDAC, may further support the development of a chemoprotective microenvironment by directly scavenging drugs (Hessmann et al 2018), and through the secretion of factors that aid tumor cells escape the control of cytostatic and cytotoxic agents (Lotti et al 2013, Sun et al 2016, Nakasone et al 2012, Acharyya et al 2012, Hirata et al 2015).

In addition to conferring physiological resistance to chemotherapeutic drugs the stromal elements of the tumor microenvironment possess great immunomodulatory potential (Turley et al 2015), and can therefore play a critical role in the poor response to immunotherapies reported in PDAC. T cells poorly migrate in areas of densely packed collagen, moving along the tumor stroma interface, they can also rarely penetrate tumor cell islets. Extra-cellular matrix (ECM) molecules (e.g. Hyaluronic acid, thrombospondin, and Tenascin C) directly promote T-cell dysfunction. Thus, PDAC presents as an immune excluded tumor associated with resistance to immune checkpoint inhibitors.

High levels of TGFβ in the tumor microenvironment have been primarily linked to its tolerogenic potential in infiltrating immune cells. Moreover, TGFβ is also a key regulator of stromal cell activation and fibrosis in many pathological conditions (Pickup et al 2013). Recently, emerging data have identified TGFβ signaling in cancer-associated fibroblasts as well as a determinant of T-cell exclusion and poor response to immune checkpoints blockade (Mariathasan et al 2018, Tauriello et al 2018).

The purpose of this Phase II study is to assess the efficacy and safety of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel in untreated mPDAC. The overarching hypothesis is that blockade of TGFβ in combination with SOC chemotherapy gemcitabine/nab-paclitaxel can reduce fibrosis in PDAC, restoring chemo-sensitivity and unleashing T-cell infiltration and activation. Whether anti-PD-1 can then restore immunological competency in mPDAC when combined with TGFβ inhibition will also be tested. Ultimately, these therapeutic combinations could improve the clinical response rate and durability in first-line mPDAC.

2 Objectives and endpoints

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 assess the safety and tolerability of NIS793 + spartalizumab in combination with gemcitabine/nab-paclitaxel	• Incidence of DLTs during the first 4 weeks of treatment • Safety: Incidence and severity of treatment emergent AEs and SAEs, changes between baseline and post-baseline laboratory parameters, vital signs, and ECG parameters • Tolerability: Dose interruptions, reductions and dose intensity
Randomized part: • To evaluate the progression-free survival (PFS) of NIS793 with spartalizumab in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel • To evaluate the PFS of NIS793 with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel	• Progression-free survival based on Response Evaluation Criteria in Solid Tumors (RECIST1.1) as per local Investigator's review
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
Randomized part	
• To evaluate the safety and tolerability of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel	• Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs, dose interruptions, reductions, and dose intensity
• To assess the preliminary anti-tumor activity of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel	• Overall response rate (ORR), Duration of response (DOR), Time to Progression (TTP) RECIST 1.1 as per local Investigator's review
• To assess Overall Survival (OS) of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel	• Overall Survival (OS)
• To assess the CD8 and PD-L1 status of the participants at screening and on treatment versus gemcitabine/nab-paclitaxel	• Change from baseline in CD8 and PD-L1 IHC related markers
• To characterize the incidence of immunogenicity of NIS793 and spartalizumab in combination with gemcitabine/nab-paclitaxel	• Antidrug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment (anti-NIS793 and anti-spartalizumab)
• To characterize the pharmacokinetics (PK) of NIS793, spartalizumab, gemcitabine/nab-paclitaxel in combination treatment or alone (gemcitabine/nab-paclitaxel)	• Pharmacokinetic parameters (e.g. Ctrough, Cmax, AUClast) • PK concentration time profiles

2.1 Primary estimands

The primary clinical question of interest is:

- What is the effect of NIS793 plus gemcitabine/nab-paclitaxel with and without spartalizumab relative to gemcitabine/nab-paclitaxel in prolonging time to death or radiological progression in first line mPDAC,
  - regardless of whether participants switched to a new anti-cancer therapy that is not part of their assigned treatment strategy or/and
  - regardless of whether participants discontinued treatment (due to COVID-19 or any reason not related to new anti-cancer therapy)?

The justification for targeting these treatment effects is that we wish to estimate the relative effects of the treatment strategies in the presence of potentially a) a new anti-cancer therapy that is not a part of the assigned treatment strategy or/and b) a treatment discontinuation (due to COVID-19 or any reason not related to new anti-cancer therapy).

The primary estimands are described by the following attributes:

- **Population**: adult participants with mPDAC who have not received any systemic treatment for metastatic disease. Further details about the population are provided in Section 5.
- **Primary variable**: Progression Free Survival (PFS), defined as time from randomization to first documented progression as per RECIST 1.1 or any-cause death.
- **Treatments of interest**:

- Experimental treatments: NIS793 with spartalizumab and gemcitabine/nab-paclitaxel (**Arm 1**) and NIS793 with gemcitabine/nab-paclitaxel (**Arm 2**);
- Standard of Care (SOC): gemcitabine/nab-paclitaxel (**Arm 3**).

Further details about the investigational and control treatments are provided in Section 6.

- **Summary measure**: PFS hazard ratio of: a) NIS793 with spartalizumab and gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel and b) NIS793 with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel.

Handling of intercurrent events:

- New anti-cancer therapy initiated before observing PFS event will be handled using the treatment policy strategy, considering the new anti-cancer therapy as part of the treatment strategy. New anti-cancer therapy can refer to:
  1. The SOC administered in the trial. This case is applicable to participants of **Arms 1 and 2** switching to gemcitabine/nab-paclitaxel.
  2. Any anti-cancer therapy not administered in the trial, applicable to all three arms.
- Treatment discontinuation related to COVID-19 will be handled using the treatment policy strategy, meaning that the participant will continue to be followed for progression per RECIST 1.1;
- Treatment discontinuation for any reason not related to new anti-cancer therapy or to COVID-19 will be handled using the treatment policy strategy, meaning that the participant will continue to be followed for progression per RECIST 1.1.

Refer to Section 12.4.2 for more details on primary estimands.

2.2 Secondary estimands

The secondary clinical questions of interest are:

- What is the preliminary anti-tumor activity of NIS793 plus gemcitabine/nab-paclitaxel with and without spartalizumab relative to gemcitabine/nab-paclitaxel in first line mPDAC,
  - regardless of whether participants switched to a new anti-cancer therapy that is not part of their assigned treatment strategy or/and
  - regardless of whether participants discontinued treatment (due to COVID-19 or any reason not related to new anti-cancer therapy)?
- What is the overall survival (OS) of NIS793 plus gemcitabine/nab-paclitaxel with and without spartalizumab relative to gemcitabine/nab-paclitaxel in first line mPDAC,
  - regardless of whether participants switched to a new anti-cancer therapy that is not part of their assigned treatment strategy or/and
  - regardless of whether participants discontinued treatment (due to COVID-19 or any reason not related to new anti-cancer therapy)?

The justification for targeting these treatment effects is that we wish to estimate the relative effects of the treatment strategies in the presence of potentially a) a new anti-cancer therapy that is not a part of the assigned treatment strategy or/and b) a treatment discontinuation (due to COVID-19 or any reason not related to new anti-cancer therapy).

The secondary estimands are described by the following attributes:

1. **Population**: adult participants with mPDAC who have not received any systemic treatment for metastatic disease. Further details about the population are provided in Section 5.
2. **Primary variables**:
    - Best overall response (BOR) defined as the best response recorded from the start of the treatment until disease progression;
    - Duration of response (DOR) defined as the time from CR or PR to first documented progression as per RECIST 1.1 or any-cause death;
    - Time-to progression (TTP) defined as the time from randomization to first documented progression as per RECIST 1.1 or death due to underlying cancer;
    - OS defined as the time from randomization to death due to any cause.
3. **Treatments of interest**:
    - Experimental treatments: NIS793 with spartalizumab and gemcitabine/nab-paclitaxel (**Arm 1**) and NIS793 with gemcitabine/nab-paclitaxel (**Arm 2**);
    - SOC: gemcitabine/nab-paclitaxel (**Arm 3**).

Further details about the investigational and control treatments are provided in Section 6.

4. **Summary measures**:
    - Overall response rate in a) NIS793 with spartalizumab and gemcitabine/nab-paclitaxel b) NIS793 with gemcitabine/nab-paclitaxel and c) gemcitabine/nab-paclitaxel;
    - DOR, TTP, and OS hazard ratio of: a) NIS793 with spartalizumab and gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel and b) NIS793 with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel.

Handling of intercurrent events:

- New anti-cancer therapy initiated before observing the event of interest (related to anti-tumor activity and OS) will be handled using the treatment policy strategy, considering the new anti-cancer therapy as part of the initially assigned treatment strategy. New anti-cancer therapy can refer to:
    1. The SOC administered in the trial. This case is applicable to participants of **Arms 1** and **2** switching to gemcitabine/nab-paclitaxel;
    2. Any anti-cancer therapy not administered in the trial, applicable to all three arms.
- Treatment discontinuation related to COVID-19 will be handled using the treatment policy strategy, meaning that the participant will continue to be followed for the event of interest (related to anti-tumor activity and OS);
- Treatment discontinuation for any reason not related to new anti-cancer therapy or to COVID-19 will be handled using the treatment policy strategy, meaning that the participant will continue to be followed for the event of interest (related to anti-tumor activity and OS).

Refer to Section 12.5.1 for more details on secondary estimands.

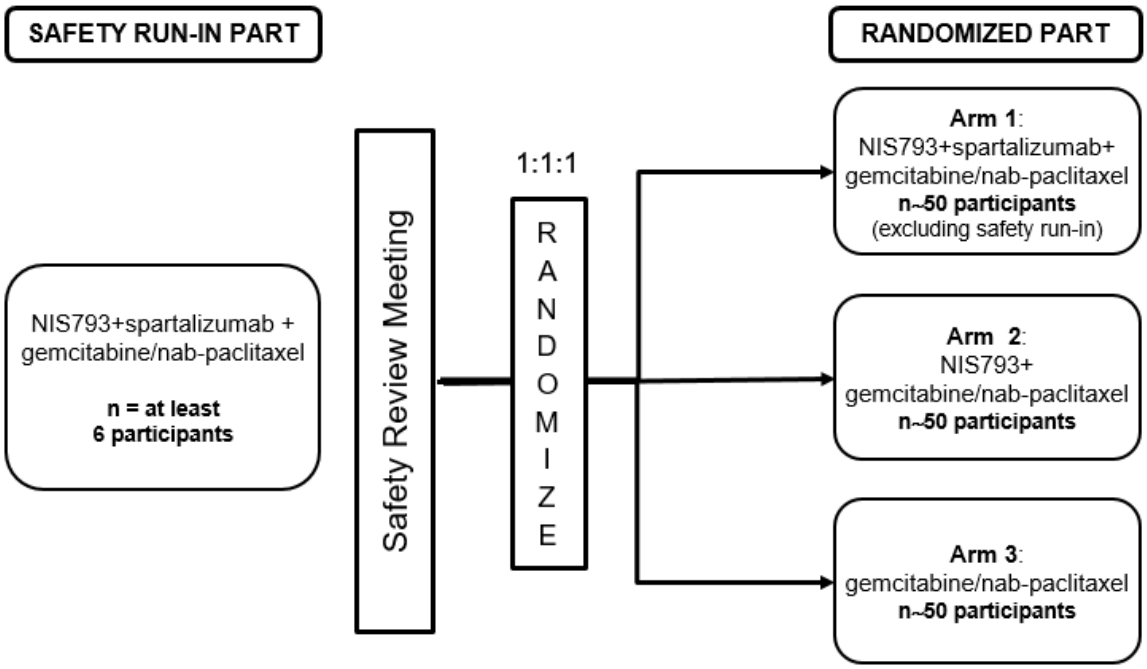
3 Study design

3.1 Description of study design

This is a randomized, parallel arms, open-label, multi-center, Phase II study to evaluate the efficacy and safety of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel in participants with first-line mPDAC.

The study is expected to enroll at least 156 participants. An overview of the study design is depicted in Figure 3-1.

Figure 3-1 Study design



Safety Run-in part

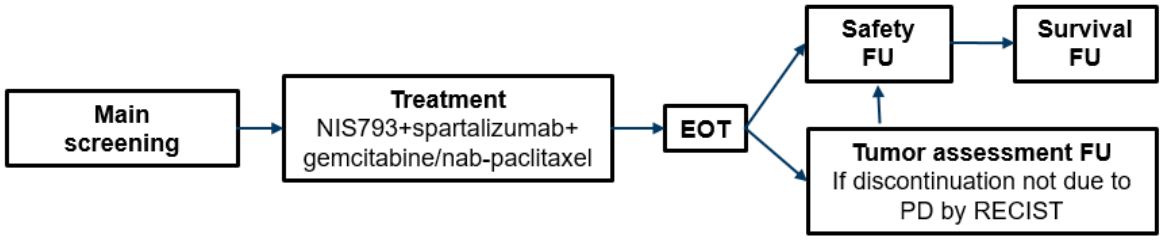
The study will start with a **Safety Run-in part** to assess the safety and tolerability of NIS793 in combination with spartalizumab and SOC gemcitabine/nab-paclitaxel. Doses defined for each study treatment, as part of this quadruplet will be administered in the **Randomized part** in the quadruplet/triplet/doublet-based treatment arms (refer to Figure 3-1). At least six participants will be enrolled in the **Safety Run-in part**.

NIS793 will be administered at a flat dose of 2100 mg every 2 weeks, spartalizumab at a flat dose of 400 mg every 4 weeks. 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.

A safety review meeting, as described in the Section 6.5.2.1, will take place when six enrolled participants have completed 4 weeks treatment, or discontinued earlier due to DLT. The dose decision will be guided by an algorithm specified in Section 6.5.2. If decision to modify the dosing regimen is made at this time, an additional safety review of the new dosing regimen will take place after six additional participants have been enrolled and completed 4 weeks treatment or have discontinued earlier due to DLT.

Refer to Figure 3-2 for an overview of the **Safety Run-in part** study flow.

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



EOT: end of treatment; FU: follow-up

Randomized part

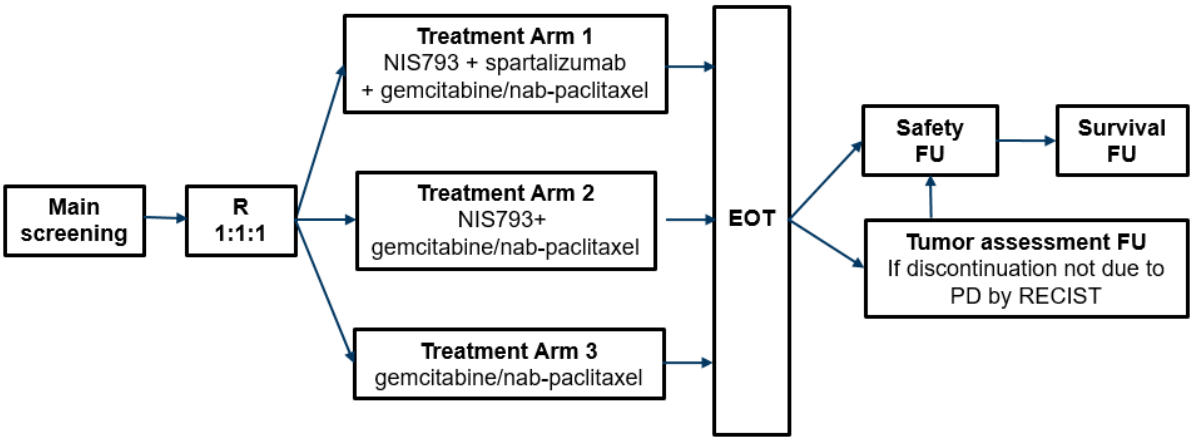
After the **Safety Run-in part** has been completed, the randomization part will open and approximately 150 participants will be randomized in a 1:1:1 ratio to one of the three treatment arms:

- **Arm 1:** NIS793 with spartalizumab and gemcitabine/nab-paclitaxel
- **Arm 2:** NIS793 with gemcitabine/nab-paclitaxel
- **Arm 3:** gemcitabine/nab-paclitaxel

Participants in any randomized arm will be treated according to each study treatment dose,including gemcitabine/nab-paclitaxel (dose label), declared to be safe in the **Safety Run-in part**.

Refer to Figure 3-3 for an overview of the study flow in **Randomized part**.

Figure 3-3 Study flow in Randomized part



R: randomization; EOT: end of treatment; FU: follow-up

4 Rationale

4.1 Rationale for study design

The design of this Phase II, parallel arms, open label study was chosen to characterize the clinical activity, safety and tolerability of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel in participants with previously untreated mPDAC.

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Participant population	The study will enroll previously untreated metastatic PDAC
Two-part study	The **Safety Run-in part** to assess the safety and tolerability of the combination NIS793 with spartalizumab and gemcitabine/nab-paclitaxel will precede the **Randomized part** that will assess the efficacy of the different combinations (refer to Figure 3-1)
Randomization (1:1:1 ratio)	Randomization will ensure reduction of treatment assignment bias. Participants will be randomized at 1:1:1 ratio
Comparator treatment	Worldwide study conducted with gemcitabine/nab-paclitaxel, which is approved chemotherapy in the first-line treatment of mPDAC

4.2 Rationale for dose/regimen and duration of treatment

In this study, the selection of the dose and regimen is based on the currently available preclinical and clinical safety, efficacy and PK, information from the first-in-human clinical trial CNIS793X2101 and labels for approved chemotherapy gemcitabine/nab-paclitaxel.

In CNIS793X2101 study, the NIS793 plus spartalizumab recommended dose (RD) has been determined as 2100 mg (equivalent of 30 mg/kg when using body weight of 70 kg) Q3W/300 mg Q3W in solid tumor participants.

In this study, Q2W regimen for NIS793 and Q4W regimen for spartalizumab i.v. are chosen to coordinate with the administration cycle of the chemotherapy (gemcitabine and nab-paclitaxel). NIS793 at 2100 mg Q2W plus spartalizumab at 400 mg Q4W will be evaluated. NIS793 was well tolerated in CNIS793X2101 study across all tested doses (0.3 to 30 mg/kg) and dosing regimens (Q2W and Q3W), with no significant safety signal detected during DLT period. Although there was no clear pattern between systemic exposure of NIS793 and/or dose and clinical efficacy, accumulation of total TGFβ-1 levels under treatment (Q3W or Q2W regimens) with NIS793 at the dose of 30 mg/kg Q2W supports sustained target engagement in systemic circulation over the dosing period. In addition, *in vitro* data (projected steady state trough level after 2100 mg NIS793 Q2W above IC_{90} concentration, RD-2019-00226), preclinical data (projected steady state trough level after 2100 mg NIS793 Q2W above concentration from preclinical efficacy study associated with high risk (~23%) of relapse to NIS793, RD-2019-00227; RD-2019-00228) generated for NIS793 and published data from M7824, another anti-TGFβ molecule (projected steady state trough level after 2100 mg NIS793 Q2W similar to that observed for M7824 (Strauss et al 2018)) further support CNIS793X2101-based assessment of RD. Overall, as no safety issues have been reported in participants who received NIS793 at 30 mg/kg Q2W, a flat dose of 2100 mg Q2W was selected to maximize the chances of seeing efficacy in PDAC, a highly desmoplastic tumor resistant to chemotherapy and immune checkpoint inhibitors, 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 characteristics of NIS793 including the impact of weight as a covariate on clearance and volume of distribution. The analysis suggested that the pharmacokinetics of NIS793 can be well described using a two compartment model with first order elimination from the central compartment. This is consistent with the observation that NIS793 PK appears dose proportional and time-independent based on the non-compartmental analyses. Although body weight (BW) is a covariate on clearance in the population PK model with the estimated exponent of 0.55 (CV%=40%) from the power model, the predicted exposure and trough (mean values and variability) concentration at steady state between weight-based and fixed dosing regimens were comparable across different BW 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.

The proposed starting dose and regimen for NIS793/spartalizumab will be the recommended dose of 2100 mg Q2W/400 mg Q4W, as outlined above.

Overall, the risk of DDI between NIS793 or spartalizumab and gemcitabine or nab-paclitaxel is anticipated to be low. Nevertheless, PK of any study treatment will be characterized in this study to assess the DDI, if any, between NIS793 or spartalizumab and gemcitabine or nab-paclitaxel.

The dose of 400 mg Q4W spartalizumab (RD from first in human spartalizumab study) will be used in combination with NIS793.

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 labels).

For treatment duration, refer to Section 6.1.4.

4.3 Rationale for choice of combination and comparator drugs

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

To this end, NIS793 will be combined with gemcitabine plus nab-paclitaxel, an approved chemotherapy regimen for the treatment of first-line mPDAC. This particular chemotherapy was chosen as a comparator treatment based on its tolerability profile and its common use in this setting. The dose and the dose regimen to be used are in accordance with each product labeling.

To test whether anti-PD-1 can further improve the benefits of TGFβ inhibition and restore anti-tumor immune responses, spartalizumab will be also tested in combination with NIS793 and gemcitabine/nab-paclitaxel.

4.4 Purpose and timing of interim analyses/design adaptations

Safety Run-in part

Refer to Section 12.7 for details on the **Safety Run-in** interim analysis (IA) for **Randomized part** dose decision.

Randomized part

IA of efficacy data of the Randomized part may be conducted to support decision making related to Sponsor's clinical development of NIS793. Additional supportive analyses of available clinical data may be considered if appropriate. The IA of the Randomized part data is not planned to support formal design adaptations in the current Phase II study.

4.5 Risks and benefits

Participants enrolled in this study are patients with previously untreated mPDAC for which treatment, even in the first-line setting, is associated with an extremely poor prognosis (Conroy et al 2011, Von Hoff et al 2013, Moore et al 2007). Preclinical studies supported TGFβ-blockade as a valid approach to target intratumoral fibrosis development. In addition based on the preliminary tolerability, target engagement, and response rates observed in the ongoing NIS793 FIH study, combinations of NIS793 with and without spartalizumab, and gemcitabine/nab-paclitaxel are thought to outweigh the risk in participants with first-line

mPDAC being evaluated in this study. This randomized study testing novel combinations of NIS793 with and without spartalizumab, in combination with SOC chemotherapy gemcitabine/nab-paclitaxel, offers the opportunity for those participants to be treated with a novel investigative therapy, however with no guarantee of improved benefit over SOC.

Appropriate eligibility criteria, specific dose modification, and stopping rules, are included in this protocol. Recommended guidelines for prophylactic or supportive management of expected toxicities, including study-drug induced AEs, are provided in Section 6.2.

The risk to participants in this study may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. In addition, a Data Monitoring Committee (DMC) will review available data at defined intervals to guarantee participants' safety. As with any clinical study, there may be unforeseen risks with any of the combinations studied that could be serious. Based on currently available data, potential overlapping toxicities between NIS793 and gemcitabine/nab-paclitaxel and between NIS793 with spartalizumab and gemcitabine/nab-paclitaxel are expected and are described in Section 1.1.2.5.4. For further detail, refer to the latest NIS793 Investigator's brochure and PDR001 Investigator's brochure and gemcitabine and nab-paclitaxel labels.

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 must 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 metastatic pancreatic ductal adenocarcinoma 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 and none of the exclusion criteria are offered treatment in the study.

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study.
2. Male or female ≥ 18 years of age at the time of informed consent.

   For Japan only: written consent is necessary both from the participant and his/her legal representative if he/she is under the age of 20 years.

3. Participants with histologically or cytologically confirmed treatment-naïve metastatic adenocarcinoma of the pancreas with measurable disease as per RECIST 1.1.
4. Participants must have a site of disease amenable to biopsy, and be candidate for tumor biopsy according to the treating institution's guidelines. Participants must be willing to undergo a tumor biopsy at screening and during therapy on the study. In the event a new biopsy cannot be safely performed at study entry, an archival sample (collected <6 months prior) may be substituted following documented discussion with Novartis.
5. ECOG performance status ≤ 1.

5.2 Exclusion criteria

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

1. Previous radiotherapy, surgery (with exception of placement of biliary stent, which is allowed), chemotherapy or any other investigational therapy for the treatment of metastatic pancreatic cancer. Participants having received previous chemotherapy in the adjuvant setting.
2. Participants amenable to potentially curative resection.
3. Participants with a diagnosis of pancreatic neuroendocrine tumors (NETs), acinar, or islet cell tumors.
4. Having out of range laboratory values defined as:

   Hematological:

   - Absolute neutrophil count (ANC) < 1.5 G/L
   - Platelet count < 100 G/L
   - Hemoglobin < 9 g/dL

   Coagulation:

   - PT/INR and PTT > 1.5 x ULN. Participants requiring therapeutic anticoagulants are eligible if coagulation parameters are within therapeutic range.

   Renal:

   - Serum creatinine > ULN or creatinine clearance (calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) formula [eGFR in mL/min per 1.73 m2 = 175 x SerumCr-1.154 x age-0.203 x 1.212 (if participant is black) x 0.742 (if female], or measured) < 60 mL/min.

Hepatic:

- Total bilirubin > 1.5 x ULN (any elevated bilirubin should be asymptomatic at enrollment) except for participants with Gilbert's syndrome who are not eligible if total bilirubin > 3 x ULN or direct bilirubin > 1.5 x ULN.
- Albumin < 2.5 g/dL.
- Aspartate transaminase (AST) > 3 x ULN, or AST > 5 x ULN for participants with metastatic disease in the liver.
- Alanine transaminase (ALT) > 3 x ULN, or ALT > 5 x ULN for participants with metastatic disease in the liver.

For participants with elevated ALT or AST at baseline, the values must be stable for 2 weeks and with no evidence of biliary obstruction by imaging.

5. Participants with MSI-H pancreatic adenocarcinoma.
6. Presence of symptomatic CNS metastases, or CNS metastases that require local CNS-directed therapy (such as 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.
7. History of severe hypersensitivity reactions to any ingredient of study drug(s) and other mAbs and/or their excipients.
8. The participant exhibits any of the events outlined in the contra-indications or special warnings and precautions sections of gemcitabine and nab-paclitaxel as per locally approved labels.
9. Impaired cardiac function or clinically significant cardiac disease, including any of the following:
    - Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (NYHA Grade ≥ 2), or clinically significant arrhythmia (including uncontrolled atrial flutter/fibrillation)
    - Acute myocardial infarction, unstable angina pectoris, coronary stenting, or bypass surgery < 6 months prior to study entry
    - Left ventricular ejection fraction < 50%
    - Elevated cardiac enzymes (troponin I) elevation > 2 x ULN
    - Cardiac valvulopathy ≥ Grade 2
    - Uncontrolled hypertension defined by a systolic blood pressure ≥ 160 mg and/or diastolic blood pressure ≥ 100 mg Hg
    - Medical history or current diagnosis of myocarditis
10. Known history of testing positive HIV infection.
11. Active HBV or HCV infection. Participants whose disease is controlled under antiviral therapy should not be excluded.
12. Malignant disease, other than that being treated in this study, except for malignancies treated curatively and that have not recurred in the past 2 years prior to study treatment; completely

resected basal cell and squamous cell skin cancers, and any completely resected carcinoma *in situ* are not excluded.

13. Active, known or suspected autoimmune disease. Participants with vitiligo, type I diabetes, residual hypothyroidism only requiring hormone replacement, psoriasis not requiring systemic treatment or conditions not expected to recur may be considered.
14. History of or current interstitial lung disease or pneumonitis grade ≥ 2.
15. Major surgery, open biopsy, or significant traumatic injury ≤ 4 weeks prior to start of study treatment.
16. Systemic chronic steroid therapy (>10mg/day prednisone or equivalent) or any other immunosuppressive therapy within 7 days of the first dose of study treatment. Topical, inhaled, nasal and ophthalmic steroids are allowed.
17. Use of any live vaccines against infectious diseases within 4 weeks of initiation of study treatment.
18. Use of hematopoietic growth factors or transfusion support ≤ 2 weeks prior to start of study treatment. If growth factors were initiated more than 2 weeks prior to the first dose of study treatment and the participant is on a stable dose, they can be maintained.
19. Any medical condition that would, in the Investigator's judgment, prevent the participant's participation in the clinical study due to safety concerns, compliance with clinical study procedures or interpretation of study results.
20. Pregnant or lactating women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human Chorionic Gonadotropin (hCG) laboratory test.
21. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for 180 days after stopping medication. 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 tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
    - Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months, or as per locally approved label, before taking study treatment.

Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 180 days after stopping study treatment. A condom is required for <u>all</u> sexually

active male participants to prevent them from fathering a child and to prevent delivery of study treatment *via* seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above. 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 anti-cancer SOC.

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).

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age-appropriate [generally age from 40 to 59 years], history of vasomotor symptoms [e.g. hot flush]) in the absence of other medical justification or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks prior to enrollment to study. 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 to be not of childbearing potential.

22. 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.

6 Treatment

6.1 Study treatment

For this study, the investigational drugs are NIS793, an anti-TGFβ human monoclonal antibody, and spartalizumab, an anti-PD-1 receptor recombinant humanized monoclonal antibody. The study treatment is NIS793 with and without spartalizumab plus SOC treatment of gemcitabine plus nab-paclitaxel.

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.

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 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 the infusions of NIS793 with and without spartalizumab. The same may be applied for the subsequent cycles of NIS793 with and without spartalizumab infusions if medical indicated.

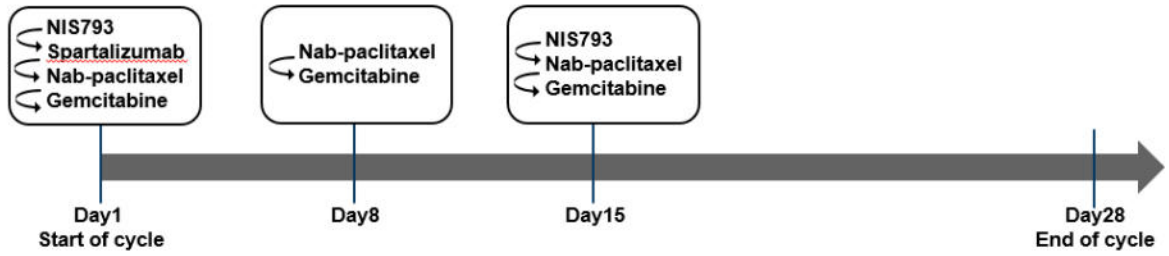
All dosages prescribed and administered to participants and all dose interruptions and changes during the study must be recorded on the study treatment eCRF (electronic Case Report/Record Form).

Table 6-1 Investigational and control drug

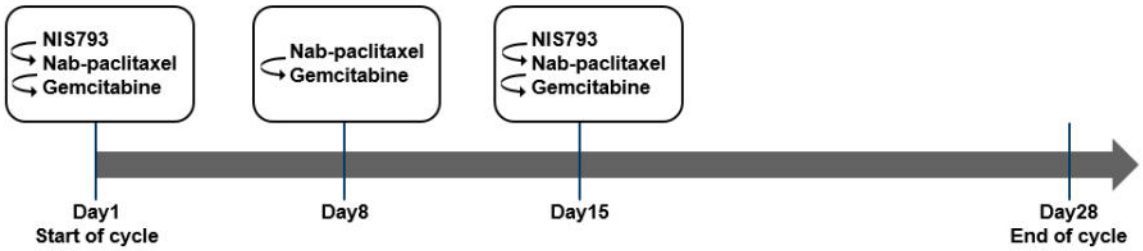
Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spartalizumab (PDR001) 100mg / 4mL	Concentrate for solution infusion (Liquid in Vial)	i.v. use	Open label participant kits	Sponsor (global)
Gemcitabine	Locally approved/available	i.v. use	Open label; vials	Local sourced
Nab-paclitaxel	Locally approved/available	i.v. use	Open label; vials	Local sourced

Figure 6-1 Study drug administration

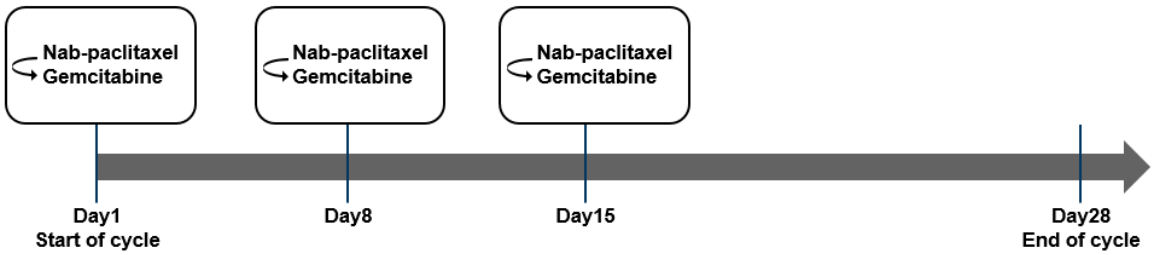
Safety Run-in part and Randomized Arm 1



Randomized Arm 2



Randomized Arm 3



Arrows indicate the sequence of administration of study drugs.

6.1.2 Additional study treatments

Not applicable.

6.1.3 Treatment arms

Safety Run-in part

All participants in the **Safety Run-in part** will be enrolled in a unique treatment arm of NIS793 with spartalizumab in combination with gemcitabine/nab-paclitaxel.

Randomized part

Participants will be randomized to one of the following three treatment arms in a "1:1:1" ratio

- **Arm 1**: NIS793 + spartalizumab + gemcitabine + nab-paclitaxel
- **Arm 2**: NIS793 + gemcitabine + nab-paclitaxel
- **Arm 3**: gemcitabine + nab-paclitaxel

6.1.4 Treatment duration

Participants will be treated until they experience unacceptable toxicity, disease progression per RECIST 1.1 as determined by Investigator (for exception please refer to Section 6.1.4.1), and/or treatment is discontinued at the discretion of the Investigator or the participant, or withdrawal of consent.

If study treatment (any drug) is interrupted or delayed for > 12 weeks due to toxicity that is suspected to be related to treatment, study treatment will be permanently discontinued. For participants who still derive clinical benefit, continuation of study treatment may be considered after discussion and documented approval from Novartis medical monitor.

6.1.4.1 Treatment beyond disease progression

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

Participants treated with NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel will be permitted to continue study treatment beyond initial disease progression as per RECIST 1.1. criteria provided they meet the following criteria:

- Clinical benefit assessed by the Investigator
- No rapid disease progression or evidence of clinical deterioration
- No unacceptable and irreversible toxicities related to study
- [redacted]
- Continuation of treatment beyond initial progression will not delay an imminent intervention to treat/prevent serious complications of disease progression, or prevent participants from receiving adequate care
- Participant performance status is stable

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

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

[redacted]

6.2 Other treatment(s)

Participants should not receive pre-medication to prevent infusion reaction before the first infusion of study treatment, in order to determine if pre-medication is necessary. If a participant experiences an infusion reaction, he/she may receive pre-medication on subsequent dosing days. The pre-medication should be chosen per institutional practice at the discretion of the treating physician.

Acute allergic reactions should be treated as needed per institutional practice or the dose modification guideline (Section 6.5.4). 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.

Guidelines on management of infusion reactions are provided in Table 6-5.

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

6.2.1 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.

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 Forms.

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 first study treatment dosing 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 (G-CSF or GM-CSF) and erythroid stimulating agents** may only be initiated after the **Safety Run-in**. If a participant is using an erythroid stimulating agent prior to enrollment (at least 2 weeks before start of study treatment), they may continue at the same dose.
- **Anticoagulation therapy** is permitted if the participants are already at stable doses for >2 weeks (with the exception of low molecular weight heparin) at time of first dose and adequate laboratory tests are performed as clinically indicated per Investigator's discretion and according to local practices. Participants who develop a new requirement for anticoagulant therapy during the conduct of the study may remain on study after documented discussion with the Novartis medical monitor. However, ongoing anticoagulant therapy should be temporarily discontinued to allow tumor sampling according to the institutional guidelines.
- **Anti-hypertensives** are allowed as concomitant medications. However, because transient hypotension has been reported during infusions, consideration should be given to withholding anti-hypertensive medications for 12 hours prior to infusion with study treatment.
- Participants with disease metastatic to bone may receive **bone-stabilizing agents** such as bisphosphonates or monoclonal antibodies intended for this purpose.
- Caution should be exercised when administering nab-paclitaxel concomitantly with **medicines known to inhibit or induce either CYP2C8 or CYP3A4** (refer to Appendix 3).

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 or that are intended to modulate an immune response.
- However, **limited-field palliative radiotherapy** to non-target lesion(s) may be allowed as concomitant therapy after documented discussion with Novartis. Such local therapies administered during the study treatment must be listed on the eCRF. Study treatment must be interrupted during radiotherapy.
- The use of **systemic steroid therapy** (at doses greater than 10 mg/day prednisone or equivalent) and other immunosuppressive drugs is not allowed, **with the exception of:**
  - Prophylactic use for participants with imaging contrast dye allergy.
  - Replacement-dose steroids (defined as 10 mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids) in the setting of adrenal insufficiency.
  - Transient exacerbations of chronic inflammatory conditions such as COPD. Steroids must be reduced to 10 mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids prior to the next treatment with NIS793 with and without spartalizumab.
  - Short course of systemic steroid therapy for early side effect of gemcitabine/nab-paclitaxel (e.g flu like syndrome) may be acceptable after documented discussion with Novartis.
- The **treatment of study treatment-related infusion reactions or study treatment-related irAEs**. Steroids must be reduced to ≤10 mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids prior to the next study treatment administration.
- **Topical, inhaled, nasal and ophthalmic steroids** are allowed.
- The use of **live vaccines** is not allowed through the whole duration of the study. **Inactivated vaccines** are allowed.

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 enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (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 informed consent form, the participant is assigned to the next sequential Participant No. available.

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

6.3.2 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 with spartalizumab and gemcitabine/nab-paclitaxel.

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

- Arm 1: NIS793 plus spartalizumab plus gemcitabine/nab-paclitaxel
- Arm 2: NIS793 plus gemcitabine/nab-paclitaxel
- Arm 3: gemcitabine/nab-paclitaxel

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 numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

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

6.4 Treatment blinding

Treatment will be open to participants, Investigator staff, persons performing the assessments, and Novartis. In order to minimize the potential impact of the treatment knowledge, until the IA (Section 4.4) or the primary analysis is conducted, whichever occurs first, no aggregated statistical analyses (efficacy or safety across the study) shall be performed by treatment (other than analyses as specified in the study protocol).

6.5 Dose evaluation and dose modification

6.5.1 Dose evaluation guidelines

6.5.1.1 Dosing regimen: Safety Run-in part

A cycle of treatment is defined as 28 days.

In **Safety Run-in part**, the study drugs (Dose level 1) will be administered at the RD and/or per label as follow:

[redacted]

- Spartalizumab at 400mg Q4W
- Gemcitabine at 1000mg/m^2 Day 1, Day 8 and Day 15
- Nab-paclitaxel at 125mg/m^2 Day 1, Day 8 and Day 15

6.5.1.2 Provisional dose levels

Table 6-2 Starting dose and dose level-1 that may be evaluated during the first 28 days period of the Safety Run-in part

	NIS793	Spartalizumab	Nab-paclitaxel	Gemcitabine
Dose Level 1 (Starting dose)	2100 mg Q2W	400 mg Q4W	125 mg/m^2	1000 mg/m^2
Dose Level -1	1400 mg Q2W	400 mg Q4W	125 mg/m^2	1000 mg/m^2

During the first 28 days period of the Safety Run-in part, the following rules apply:

- Dose level -1 (Table 6-2) represents the dose regimen that may be explored if dose de-escalation from the initial dose level is required.
- No dose de-escalation below dose level -1 is permitted.

Beyond the first 28 days period of the Safety Run-in part and in the Randomized part, the following rules apply:

- Participants will be treated with the doses declared safe at the safety review meeting (refer to Section 6.5.2.1).
- If dose modifications are required, please refer to Section 6.5.4.
- No re-escalation is permitted for any drug.

6.5.2 Guidelines for dose evaluation

For the purpose of dose evaluation, at least six participants will be treated in **Safety Run-in part**.

To be evaluable, participants must complete 4 weeks of treatment with the minimum safety evaluation and drug exposure or have a DLT within these 4 weeks of treatment for **Randomized part** dose regimen decision. Refer to Section 12.1.3 for more detail.

Novartis clinical team and Investigators will assess clinical, PK and laboratory data of all participants having received any treatment in the study before the safety review meeting to decide on the NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel dose regimen to be tested in **Randomized part**.

Dose confirmation of NIS793 2100 mg Q2W with spartalizumab 400 Q4W in combination with gemcitabine/nab-paclitaxel will occur if the following conditions are met in the **Safety Run-in part**:

- Six evaluable participants treated at this dose and regimen.
- No more than one DLT has been observed out of six evaluable participants.
- It is the dose recommended for participants after review of all clinical data by Novartis and Investigators in a safety review meeting.

If one of the conditions specified above is not satisfied, dose confirmation cannot be declared and a second cohort may be treated at NIS793 1400 mg Q2W with spartalizumab 400 Q4W in combination with gemcitabine 1000 mg/m^2 and nab-paclitaxel 125 mg/m^2. The same criteria are applied for this new dose and regimen. If dose confirmation cannot be declared on this lower dose, the **Randomized part** cannot start and the study will end.

6.5.2.1 Implementation of dose decision

To implement the dose decision, the available toxicity information as defined in Section 6.5.2 will be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. **Randomized part** may not start until the Investigators receive written confirmation from Novartis indicating which dose regimen will be used.

6.5.3 Definitions of dose limiting toxicities (DLTs)

A dose-limiting toxicity (DLT) is defined as an AE or abnormal laboratory value where the relationship to study treatment cannot be ruled out and is not clearly related solely to disease, disease progression, inter-current illness, or concomitant medications, occurs within the first 28 days of treatment with NIS793 with spartalizumab in combination with gemcitabine/nab-paclitaxel and meets any of the criteria included in Table 6-3. The National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 5.0 will be used for all grading. For the purpose of decision on dose to be tested in **Randomized part**, DLTs will be considered.

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

Table 6-3 Criteria for defining dose-limiting toxicities applicable during the DLT period (cycle 1 = 28 days) of the Safety Run-in part

The following considerations will apply to defining DLTs:	
Hepatic	Grade 4 bilirubin increase
	For participants with normal baseline AST and ALT values: AST or ALT > 8 x ULN ALT ≥ 5 x ULN persistent for > 14 days
	For participants with normal baseline AST, ALT and bilirubin values: AST or ALT > 3 x ULN combined with total bilirubin > 2 x ULN without evidence of cholestasis
	For participants with abnormal baseline AST or ALT value: ALT or AST > 3 x baseline value persistent for > 14 days ALT or AST > 2 x baseline value combined with total bilirubin > 2 x ULN
Hematology	Grade 4 anemia
	Grade 4 neutropenia (for > 14 consecutive days) or Grade 4 febrile neutropenia
	Grade 4 thrombocytopenia (for > 7 consecutive days)
	Grade 3 thrombocytopenia with clinically significant bleeding regardless of duration or requirement of platelet transfusion
Any Grade 3 or Grade 4 AEs (CTCAE version 5.0) related to study treatment occurring during Cycle 1 are DLTs, EXCEPT:	
Fatigue	Grade 3 fatigue that resolves to ≤ Grade 1 within 7 days.
Hypertension	Grade 3 hypertension that resolves within 7 days after starting anti-hypertensive therapy.
Gastrointestinal	Grade 3 nausea and vomiting that resolves to ≤ Grade 1 within 3 days of starting optimal anti-emetic therapy.
	Grade 3 diarrhea that resolves within 3 days after starting optimal anti-diarrhea treatment, where colitis is not suspected.
Dermatologic	Grade 3 non bullous rash without epidermal detachment that resolves to ≤ Grade 1 within 7 days of starting treatment.
Hematology	Lymphopenia of any grade is not a DLT.
Electrolytes	Grade 3 electrolyte abnormalities that resolve to ≤ Grade 1 within 7 days after starting supplementation.
Musculoskeletal	Grade 3 asymptomatic increase in creatine kinase that resolves within 14 days in the absence of evidence of cardiac involvement.
Immune-related toxicities*	Grade 3 immune-related AE that resolves to ≤ Grade 1 within 7 days of starting appropriate treatment is not a DLT, unless otherwise specified in this table.
The following Grade 2 AEs related to study treatment are considered DLTs:	
Ocular disorders	Grade 2 eye pain or reduction of visual acuity are DLTs if they do not respond to topical therapy and do not improve to Grade 1 severity within 2 weeks of the initiation of topical therapy, OR if they require systemic treatment.
Pneumonitis	Grade 2 pneumonitis is a DLT if it does not resolve to ≤ Grade 1 within 7 days of starting corticosteroids.
Myocarditis	Grade 2 myocarditis is a DLT.

Colitis	Grade 2 colitis is a DLT if it persists > 7 days despite treatment with corticosteroids.
Dermatologic	Grade 2 bullous disease that does not resolve to ≤ Grade 1 within 7 days of starting corticosteroids is a DLT.
Other adverse events	Other clinically significant toxicities, including a single event or multiple occurrences of the same event that lead to a dosing delay of > 14 days in cycle 1, may be considered to be DLTs by the Investigators and Novartis, even if not CTCAE Grade 3 or higher.

* Depending on the nature of the AE, there may be cases where immune-related Grade 2-3 AEs of any duration warrant declaration of a DLT and permanent study discontinuation (e.g. Stevens Johnson Syndrome (SJS)). DLT determination not already outlined in this table will be made on a case-by case basis after Investigator discussion with the Novartis Medical Monitor.

6.5.4 Dose modifications

For participants who do not tolerate the protocol-specified dosing regimen, 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, Table 6-6 and Table 6-7.

- **No dose reductions** are allowed for NIS793/spartalizumab in the **Randomized part** and beyond the first 28 days period of the **Safety Run-in part.** For NIS793, increasing the dosing interval from Q2W to Q4W is allowed under circumstances described in Table 6-5.
- **Dose reductions** are allowed for gemcitabine/nab-paclitaxel and should follow the dose reduction steps described in Table 6-4. 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, Table 6-6 and Table 6-7. For gemcitabine/nab-paclitaxel, recommended dose modifications are provided in Table 6-6 and Table 6-7 and are meant to be used for guidance. 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 (http://ctep.cancer.gov).
- For clinical management of suspected immune-related events, reference to consensus management guidelines is recommended such as those provided in the National Comprehensive Cancer Network (NCCN) Guidelines for the Management of Immunotherapy-Related Toxicities (available at : https://www.nccn.org/professionals/physician_gls/default.aspx#immunotherapy), the American Society for Clinical Oncology clinical practice guideline for Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy (Brahmer et al 2018) or the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Management of Toxicities from Immunotherapy (Haanen et al 2017). Note that in general, study treatment should be interrupted for grade 3 and 4 toxicities and for a subset of lower grade toxicities.

- Consider early referral to specialists with expertise in the diagnosis and management of immune-related AEs to thoroughly investigate events of uncertain etiology.
- Events not included in the study protocol or the reference guidance documents should be managed per institutional preference.
- Study treatments administration may be delayed due to toxicities. All dosing may resume once the AE has resolved to Grade 1 or baseline, and the start of the cycle will be shifted accordingly.
- If the Investigator considers it to be in the participant's best interest to resume therapy before the toxicity has resolved to Grade 1, or to resume without dose reduction, this may be permitted, following documented discussion with the Novartis medical monitor.

The dose changes must be recorded on the appropriate CRF.

Table 6-4 Dose reduction for nab-paclitaxel and gemcitabine applicable in the Safety Run-in part (after Cycle 1) and in the Randomized part (all Arms)

	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

Table 6-5 Dose modifications of NIS793 and spartalizumab for adverse drug reactions suspected to be related to NIS793/spartalizumab. Safety Run-in part (after Cycle 1) and Randomized part

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Infusion reaction or hypersensitivity reaction	
Grade 1	Decrease infusion rate until recovery from the symptoms.
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 slow rate of infusion, and despite oral pre-medication, then permanently discontinue study treatment.
Grade 3 or Grade 4	Discontinue infusion immediately, and discontinue study treatment. Provide supplemental oxygen, fluids, and other resuscitative measures as needed. Monitor vital signs (e.g. blood pressure, pulse, respiration, and temperature) every 15 ± 5 minutes until resolution.
Cytokine Release Syndrome (CRS)	
Grade 2	See instructions for Grade 2 Infusion Reaction above.
Grade 3 or Grade 4	Discontinue study treatment. Follow-up CRS as per institutional guidelines.

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Ocular (uveitis, eye pain, blurred vision)	
Grade 1	Continue study treatment without dose modification. Ophthalmology consultation.
Grade 2	Hold NIS793 and spartalizumab. Urgent ophthalmology consultation. Upon resolution to ≤ Grade 1 may consider resuming study treatment without dose reduction after discussion with the Novartis Medical Monitor and in consultation with ophthalmology.
Grade 3 or Grade 4	Discontinue study treatment. Urgent ophthalmology consultation.
Pulmonary (pneumonitis)	
Grade 1	Consider study treatment hold. Manage per institutional practice. Consider resuming study treatment upon radiographic evidence of improvement.
Grade 2	Hold study treatment. Pulmonary and infection workup. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification.
Grade 3 or Grade 4	Discontinue study treatment.
Cardiovascular	
ECG QTc-Interval prolonged; hypertension	
Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 or baseline (hypertension, QTc) or < 30 msec difference from baseline (QTc) within ≤ 7 days, may resume study treatment without dose modification after discussion with the Novartis Medical Monitor. Baseline ECG refers to the ECG(s) collected at screening.
Grade 4	Discontinue study treatment.
Other cardiovascular disorders	
Grade 2 (except myocarditis)	Hold study treatment. Upon resolution to Grade ≤ 1 or baseline, may resume study treatment without dose modification after discussion with the Novartis Medical Monitor.
Grade 2 myocarditis, or Grade ≥ 3 other cardiac disorders related to study treatment	Discontinue study treatment.
Cardiac valvulopathy	
Grade 2	Hold study treatment. Repeat echocardiogram and assess cardiac function. Once resolved to Grade ≤ 1 or baseline, consider re-administration of treatment, if benefit outweighs the potential risk.
Grade 3	Discontinue study treatment.
Gastrointestinal	
Diarrhea/colitis*	
Grade 1	May continue study treatment without dose modification. Manage per institutional standard guidelines which should include anti-diarrheal treatment, consideration of corticosteroid therapy, and hydration.

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Grade 2	Hold study treatment. GI consultation. Upon resolution to ≤ Grade 1 and tapering of steroid requirement to ≤ 10 mg prednisone per day, resume study treatment without dose modification after discussion with the Novartis Medical Monitor.
Grade 3	Hold study treatment. GI consultation. Upon resolution to ≤ Grade 1 and tapering of steroid requirement to ≤ 10 mg prednisone per day, consider resuming study treatment after discussion with the Novartis Medical Monitor.
Grade 4	Discontinue study treatment.
Isolated AST and/or ALT elevation	
Grade 2 AST and/or ALT	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1 or baseline, consider resuming study treatment without dose modification.
Grade 2 transaminitis with bilirubin >1.5 x ULN (unless Gilbert's syndrome)	Discontinue study treatment.
Grade 3 AST and/or ALT	Hold study treatment. Manage per institutional practices. Upon resolution to ≤ Grade 1 or baseline within 72 hours, consider resuming study treatment without dose modification after discussion with the Novartis Medical Monitor. If resolved in <=14 days, resume treatment without dose modification. If resolved in >14 days, consider dose modification of NIS793 with administration Q4W instead of Q2W, without any spartalizumab dose modification. Otherwise, discontinue study treatment.
Grade 4 AST and/or ALT	Discontinue study treatment.
Concomitant elevation of AST and/or ALT and total bilirubin	
With normal AST/ALT and bilirubin at baseline:	
Grade 2 ALT and/or AST elevation (>3.0 x ULN) with bilirubin > 2.0 x ULN (unless Gilbert's syndrome)	Hold study treatment. Assess if case is drug induced liver injury (DILI). • If no DILI confirmed, treat the identified cause according to institutional guidelines. Repeat LFTs within 48-72 hours, then monitor weekly, until enzyme levels resolve to ≤ Grade 1 or baseline. After recovery, re-administration of study treatment could be considered only if Investigator assesses benefit to outweigh the risk. Any decision regarding re-administration of study drugs and dose regimen (NIS793 only) should be discussed with the Novartis Medical Monitor. • If DILI confirmed, discontinue study treatment. For additional information on follow-up of potential DILI cases, refer to Section 6.5.5.1.
With abnormal ALT/AST at baseline:	

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
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[**/***]	
Grade 2	Hold study treatment. Upon resolution to ≤ Grade 1, may continue study treatment without dose modification.
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 1, may consider resuming study treatment after discussion with the Novartis Medical Monitor.
Grade 4	See footnote**/***. Otherwise, discontinue study treatment.
Asymptomatic amylase and/or lipase elevation[****]	
Grade 3, not associated with symptoms or clinical manifestations of pancreatitis****	Continue study treatment. If levels do not resolve to ≤ Grade 2 within ≤ 14 days after the initial report, hold study treatment. Upon resolution to ≤ Grade 2, may resume study treatment without dose modification, after discussion with the Novartis Medical Monitor.
Pancreatitis	
Grade 2/radiologic evidence	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification, if no clinical evidence of pancreatitis and after discussion with the Novartis Medical Monitor.
Grade 3 or Grade 4	Discontinue study treatment.
Renal	
Serum creatinine	
Grade 2	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification after discussion with the Novartis Medical Monitor.
Grade 3 or Grade 4	Discontinue study treatment.
Musculoskeletal	
Grade 2 or Grade 3	Hold study treatment. Consider resuming study treatment without dose modification upon resolution to ≤ Grade 1 with appropriate management.
Grade 4	Discontinue study treatment. In some cases, resuming study treatment may be considered after discussion with the Novartis Medical Monitor and consultation with a rheumatologist.
Endocrine	
Hypothyroidism or hyperthyroidism	
Grade 2	May continue study treatment without dose modification. Management according to institutional practice.
Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment without dose modification.

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Grade 4	May resume therapy following resolution or control with physiologic hormone replacement.
Other endocrine disorders	
Grade 2 and Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment without dose modification.
Grade 4	Hold study treatment. Grade 4 treatment-related endocrinopathies, such as adrenal insufficiency, adrenocorticotropic hormone (ACTH) deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Novartis Medical Monitor.
Neurology	
Grade 1	Consider study treatment hold, particularly for clinical suspicion of Guillain-Barre syndrome, encephalitis, aseptic meningitis, transverse myelitis, or peripheral neuropathy.
Grade 2	Hold study treatment. In some cases, resuming study treatment may be considered after discussion with the Novartis Medical Monitor.
Grade 3 or Grade 4	Discontinue study treatment.
Dermatology (rash)	
Grade 1	Continue study treatment without dose modification. Topical steroids, antihistamines, topical emollients
Grade 2	Consider holding study treatment. Topical or oral steroids, antihistamines. If study treatment is held and resolution to ≤ Grade 1, resume study treatment without dose modification.
Grade 3 or Grade 4	Hold study treatment. Manage per institutional practice. After resolution to ≤ Grade 1, consider resuming study treatment after discussion with the Novartis Medical Monitor.
Bullous dermatitis	Hold study treatment. Grade 1-2 bullous dermatitis: discussion with the Novartis Medical Monitor is required before considering resuming study treatment. Grade 3 bullous dermatitis: consider resuming therapy after expert consultation and documented discussion with the Novartis medical monitor. Grade 4 bullous dermatitis: discontinue study treatment
Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	Permanently discontinue study treatment

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Hematology	
Neutropenia	
Grade 3 or Grade 4	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline within ≤ 7 days, resume study treatment without dose modification, after discussion with the Novartis Medical Monitor.
Febrile neutropenia	
Grade 3 or Grade 4	Hold study treatment. Upon resolution of fever and improvement of neutropenia to ≤ Grade 2 or baseline, resume study treatment without dose modification, after discussion with the Novartis Medical Monitor.
Thrombocytopenia	
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline, resume study treatment without dose modification. For Grade 3 associated with major bleeding, discontinue study treatment.
Grade 4	Discontinue study treatment.
Anemia	
Grade 3 or Grade 4	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline within ≤ 7 days, resume study treatment without dose modification.
Lymphopenia	
Any grade	Treatment-related lymphopenia does not require study treatment hold or discontinuation.
Other laboratory adverse events, <u>not</u> specified elsewhere in table and <u>not</u> included in the consensus guidelines	
Grade 3 or Grade 4	Hold study treatment. Upon resolution to ≤ Grade 1, resume study treatment 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, discontinue study treatment.

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Other non-laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	
Grade 2	Consider study treatment hold, at Investigator discretion. Upon resolution to ≤ Grade 1, resume study treatment without dose modification.
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 1, resuming study treatment must be discussed with the Novartis Medical Monitor.
Grade 4	Discontinue study treatment.

All dose modifications should be based on the worst preceding toxicity.

[a] Common Toxicity Criteria for Adverse Events (CTCAE v5)

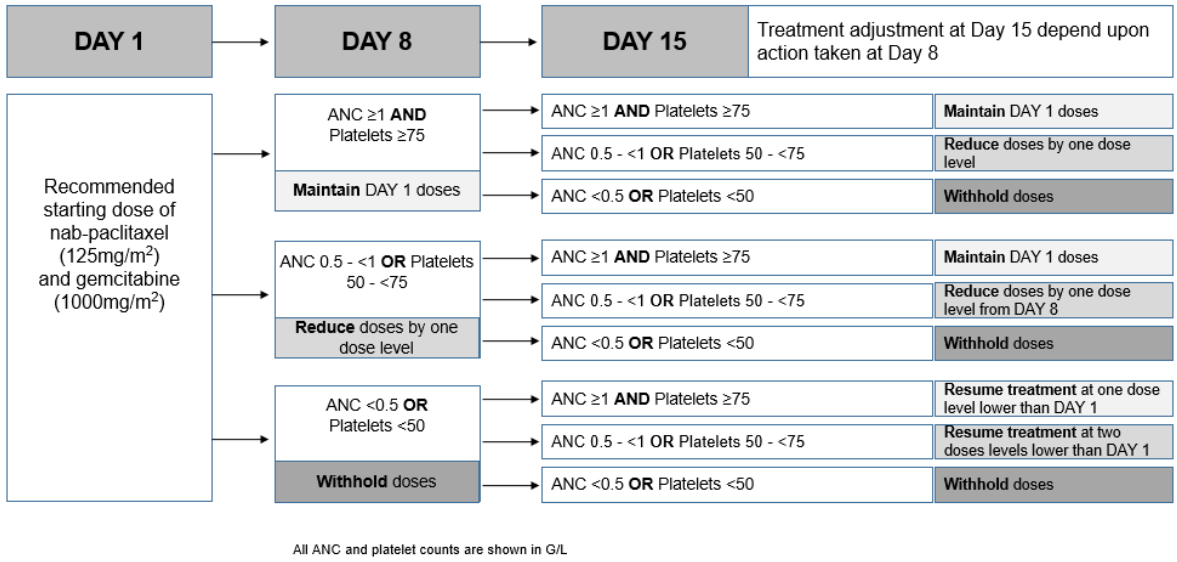
*Note: anti-diarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.

**Note: If Grade 3 or 4 hyper-bilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then delay study treatment until resolved ≤ Grade 1, and resume study treatment at the discretion of the Investigator.

***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.

Table 6-6 Dose modifications of gemcitabine/nab-paclitaxel for hematological toxicities suspected to be related to gemcitabine/nab-paclitaxel. Safety Run-in part (after Cycle 1) and Randomized part (as per locally approved labels)



All ANC and platelet counts are shown in G/L

- At Day 1, gemcitabine/nab-paclitaxel should not be administered if 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. Safety Run-in part (after the Cycle 1) and Randomized part (as per locally approved labels)

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 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 four weeks, and subsequently at approximately four weeks intervals, until resolution or stabilization of the event, whichever comes first. All participants must be followed for AEs and SAEs after discontinuation of study treatments.

The emergence of Immune-Related AE (irAE) may be anticipated based on the mechanism of action of immunomodulatory therapies.

An irAE is any clinically significant AE affecting any organ that is associated with study drug exposure, is consistent with an immune-mediated mechanism, and where alternative explanations have been investigated and ruled out or are considered to be unlikely. Serologic, histologic (tumor sample) and immunological assessments should be performed as deemed appropriate by the Investigator or specialist consultant to verify the immune-related nature of the AE. An empiric trial of corticosteroids may also contribute to understanding the etiology of a potential irAE.

Consensus management algorithms for irAEs have been developed and are available to assist Investigators in assessing and managing irAEs (refer to Section 6.5.4).

All participants must be followed-up for irAEs, AEs and SAEs as per Section 9.2.3.

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

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]

Other possible causes of abnormal liver tests should be considered and their role clarified before DILI is assumed as the cause of liver injury.

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

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, GGT (gamma-glutamyl transferase), GLDH (glutamate dehydrogenase), prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase. If available, testing of 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, B, C, E	• IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

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

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, spartalizumab, gemcitabine and nab-paclitaxel will be administered at the investigational site following the schedule in Table 8-2. 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.

6.7 Preparation and dispensation

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

For NIS793 and spartalizumab preparation prior to administration, please refer to NIS793B12201 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).

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

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

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

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

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

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

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.

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 3.1.

All kits of study treatment assigned by the IRT and locally supplied commercial drugs will be recorded in the IRT system.

For participants treated with both NIS793 and spartalizumab, separate bags and filters must be used for the infusions. NIS793 is to be administered first, followed by dextrose solution flush and observation for approximately 1 hour before spartalizumab infusion. After end of spartalizumab infusion, 2 hours of observation is needed during first cycle before dispensing of nab-paclitaxel and gemcitabine. Finally, nab-paclitaxel is to be administered before gemcitabine.

For more detail, refer to study pharmacy manual.

6.7.2.1 NIS793

NIS793 will be supplied in a vial as powder (lyophilisate) for solution for infusion. A concentrate (liquid) for solution for infusion may be used once available.

[redacted]

NIS793 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 of the first cycle of NIS793 infusion. The same may apply for the subsequent NIS793 infusions if medically indicated. Participants should notify study personnel if symptoms of infusion reaction occur after any NIS793 infusion.

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

6.7.2.2 Spartalizumab

Spartalizumab will be supplied in a vial as concentrate for solution for infusion. [redacted]

Spartalizumab will be administered intravenously as a 30 minutes infusion (up to 2 hours, 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 of the first cycle of spartalizumab infusion. The same may apply for the subsequent spartalizumab infusions if medically indicated. Participants should be further provided instructions to notify study personnel if symptoms of infusion reaction occur after any spartalizumab infusion.

Further instructions for the preparation and dispensation of spartalizumab are described in the study pharmacy manual.

6.7.2.3 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

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

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

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

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

Information about common side effects already known about the investigational drug can be found in the NIS793 Investigator's Brochure, the PDR001 Investigator’s Brochure, and gemcitabine and nab-paclitaxel locally approved labels. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, *via* an Investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

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 during the study due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Heath Authority.

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

The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment

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

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

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

8 Visit schedule and assessments

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

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-2) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed study treatments should be reconciled, and the AE and concomitant medications recorded on the CRF.

Assessments which are indicated to be performed at Screening and on C1D1, only need to be repeated at C1D1 if the Screening assessment was more than 3 days earlier.

Laboratory and radiological assessments performed as part of 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 and depending on operational capabilities, phone calls and virtual contacts (e.g. tele consult) can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Visit windows

Visit name	Window
Screening	Day -21 to Day -1
• Radiological evaluation	Day -28 to Day -1
• Pregnancy	Within 3 days prior first dose of study treatment
Cycle 1 Day 1	Within 7 days after drug assignment (**Safety Run-in part**) or randomization (**Randomized Part**) in IRT
Day 1 of subsequent cycles	+ 3 days
PK/IG [redacted] sampling	Refer to Table 8-6 and refer to Table 8-7
Tumor assessments	± 7 days
End of Treatment (EoT)	Within 14 days of last dose of study treatment OR Within 14 days of the decision of discontinuation of study treatment
Safety follow-up assessments	± 7 days

Table 8-2 Assessment schedule

Period	**Screening**	**Treatment**										**Follow-up**				
Visit Name	**Screening**	**C1**			**C2**			**C3 and subsequent cycles**			**EOT**	**Safety [1]**			**Disease progression**	**Survival**
Day of cycle	**-21 to -1**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**		**30 days**	**90 days**	**150 days**		
Obtain informed consent	X															
Participant History	X															
Demography	X															
Inclusion/exclusion criteria	X															
Relevant medical history/current medical history	X															
Diagnosis and extent of cancer	X															
Smoking and alcohol history	X															
MSI status	X															
Germline mutations panel	X															
Prior/concomitant medications and non-drug procedures	Continuous												Continuous			
Concomitant antineoplastic radiotherapy		Continuous														
Physical Exam	S	S	S	S	S	S	S	S	S	S	S					
Height	X															

Period	**Screening**	**Treatment**										**Follow-up**				
Visit Name	**Screening**	**C1**			**C2**			**C3 and subsequent cycles**			**EOT**	**Safety [1]**			**Disease progression**	**Survival**
Day of cycle	**-21 to -1**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**		**30 days**	**90 days**	**150 days**		
Weight	X	X			X			X			X					
Vital Signs	X	X	X	X	X	X	X	X	X	X	X					
Performance status	X	X	X	X	X	X	X	X	X	X	X					
Hematology	X	X	X	X	X	X	X	X	X	X	X					
Chemistry (full)	X	X			X			X			X					
Chemistry (alleviated)			X	X		X	X		X	X						
Urinalysis	X	X			X			X			X					
CA 19-9	X	X			X			X			X					
Troponin I and NTproBNP	X							C3D1, and D1 of every third cycle, or as clinically indicated			X					
Thyroid function (**for Safety Run-in part and Randomized Arms 1 & 2**)	X	X			X			X			X					
HBV, HCV, HIV	X															
Pregnancy Test	S	S			S			S			S	S (done monthly)				

Period	**Screening**	**Treatment**									**Follow-up**				
Visit Name	**Screening**	**C1**			**C2**			**C3 and subsequent cycles**			**EOT**	**Safety [1]**			**Disease progression**	**Survival**
Day of cycle	**-21 to -1**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**		**30 days**	**90 days**	**150 days**		
Tumor evaluation as per RECIST 1.1 [redacted]	X	During treatment: starting on Cycle 3 Day 1, every 8 weeks until week 52, and then every 12 weeks until progression of disease as per RECIST 1.1, death, lost to follow-up or withdrawal of consent.									X[3]				X[4]	
ECG	X	As clinically indicated, as outlined in Section 8.4.6														
Cardiac imaging (echocardiogram or CT/MRI)	X	As clinically indicated or if cardiac enzyme increase ≥ 2x ULN (if normal at screening), or ≥ 2x baseline (if baseline value was elevated).														
Adverse Events	Continuous															
Newly obtained tumor sample	X[2]							X[5] (anytime between C3D2 and C3D4)			X[6](optional)					
[redacted]																
PK Sampling		X (as per schedule outlined in Section 8.5.1.1)														
IG sampling		X (as per schedule outlined in Section 8.5.1.1)														

Period	**Screening**	**Treatment**										**Follow-up**				
Visit Name	**Screening**	**C1**			**C2**			**C3 and subsequent cycles**			**EOT**	**Safety [1]**			**Disease progression**	**Survival**
Day of cycle	**-21 to -1**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**		**30 days**	**90 days**	**150 days**		
NIS793 administration (**Safety Run-in part, and Randomized Arms 1 & 2**)		X		X	X		X	X		X						
Spartalizumab administration (**Safety Run-in part and Randomized Arm 1**)		X			X			X								
Gemcitabine & nab-paclitaxel administration (**Safety Run-in part, and all Randomized Arms**)		X	X	X	X	X	X	X	X	X						
IRT Registration/Randomization	X	X (study treatment dispensing)									X					

Period	**Screening**	**Treatment**										**Follow-up**				
Visit Name	**Screening**	**C1**			**C2**			**C3 and subsequent cycles**			**EOT**	**Safety [1]**			**Disease progression**	**Survival**
Day of cycle	**-21 to -1**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**		**30 days**	**90 days**	**150 days**		
Antineoplastic therapies since discontinuation												X	X	X	X	
Survival contact																X
Disposition	X										X				X	

1. Safety follow-up at: 30 days for all participants and 90 days for participants treated with NIS793 (Safety Run-in part and Randomized Arms 1 and 2) and 150 days for participants treated with spartalizumab (Safety Run-in part and Randomized Arm 1).

2. At screening, archival tumor sample < 6 months is acceptable.

3. If a scan was not conducted within 30 days prior to end of study treatment.

4. Every 8 weeks until week 52 from first dose, then every 12 weeks until progression of disease.

5. For participants discontinued between C2D15 and C3D1, biopsy should be collected at EoT visit.

6. For Safety Run-in part and Randomized Arms 1 and 2: Newly obtained tumor biopsy is optional for participants who clinically benefited from the study treatment.

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

8.1 Screening

Screening

The study IRB/IEC approved informed consent form must be signed and dated before any screening procedures are performed, except for laboratory and radiological evaluations, which were performed as part of the participant's clinical standard of care within the acceptable screening window.

Participants will be evaluated against study inclusion and exclusion criteria and safety assessments (refer to Table 8-2). 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 21 days, from the original screening visit, or do not meet the eligibility criteria, or other eligibility criteria have changed and are not met anymore, the participant is considered a screening failure.

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

8.1.1 Information to be collected on screening failures

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

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

8.2 Participant demographics/other baseline characteristics

Participant demographic (year of birth or age, sex, race/predominant ethnicity (if permitted)) and baseline characteristic data are to be collected on all participants. Relevant medical history/current medical condition present before signing the informed consent will be recorded. In addition, alcohol use history, smoking history and MSI status will be recorded. Germline mutation information should also be recorded for following genes: *ATM, BRCA1, BRCA2, CDKN2, MSH2, MLH1, MSH6, EPCAM, PALB2, STK11, TP53.*

Investigators will have the discretion to record abnormal test findings on the appropriate CRF, whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

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

Participant race and ethnicity are collected and analyzed to assess the diversity of the study population as required by certain Health Authorities and may be used to identify variations in safety or efficacy due to these factors.

8.3 Efficacy

8.3.1 Tumor imaging

Tumor response will be assessed locally according to two sets of criteria:

1. Novartis guideline version 3.1 (Appendix 1) based on RECIST 1.1 (Eisenhauer et al 2009) (All Arms).

[redacted]

The imaging assessment collection plan is presented in Table 8-3.

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

In addition, radiological assessments will be collected by an imaging Contract Research Organization (CRO) designated by Novartis, and may be assessed centrally in addition to the local assessment if deemed necessary.

Table 8-3 Imaging assessment collection plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest, abdomen and pelvis CT or MRI(with i.v. contrast enhancement)	Mandated	Mandated, every 8 weeks (+/- 7 days)
Brain CT or MRI	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Whole body bone scan	If clinically indicated	If clinically indicated

Procedure	Screening/Baseline	During Treatment/Follow-up
Localized bone CT, MRI or x-ray	For any lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
CT or MRI of other metastatic sites (e.g., neck)	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis

8.3.1.1 Baseline imaging assessments

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

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

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

If brain metastases are suspected at baseline, brain MRI or CT should be completed. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

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

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

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

8.3.1.2 Post-baseline imaging assessments

Imaging assessments as described in Table 8-3 should be performed using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 8-2). Imaging assessments for response evaluation will be performed every 8 weeks (+/- 7 days) during the first year, and every 12 weeks (+/- 7 days) thereafter until disease progression, death, lost to follow-up or withdrawal of consent.

Imaging assessments should be scheduled using the Cycle 1 Day 1 date as the reference date (not the date of the previous tumor assessment), and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments performed.

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

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

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

Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of IV contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (Appendix 1) [redacted]

8.3.2 Appropriateness of efficacy assessments

The efficacy assessments selected are standard for this indication/participant population. Additional information can be found in Appendix 1 and Appendix 2 (RECIST 1.1 [redacted]).

8.4 Safety

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

For details on AE collection and reporting, refer to Section 10.1.

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, regular phone or virtual calls can occur for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

8.4.1 Physical examination

Physical examination will be performed according to Table 8-2.

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.

After Cycle 1 Day 1 onwards, a short physical examination will be performed (it will include the examination of general appearance, vital signs).

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.

For Japan only: oxygen saturation (SpO2) will be measured by pulse oximetry for Japanese participants every time physical examination is performed as indicated in Table 8-2. The results of SpO2 will be recorded only in the source documentation.

8.4.2 Vital signs

Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.

Vital signs assessments will be performed as per schedule in Table 8-2.

8.4.3 Height and weight

Height will be measured at screening.

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

8.4.4 Performance status

The performance status will be assessed according to the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale as specified in Table 8-2 following the schedule given in Table 8-4.

Table 8-4 ECOG performance status

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

8.4.5 Laboratory evaluations

All laboratory parameters assessed for safety purposes described in Table 8-5 Laboratory assessment will be evaluated locally as per Table 8-2. Unscheduled assessment can be performed if clinically indicated.

The results of the laboratory tests performed locally will be recorded in the eCRF, unless differently specified in Table 8-2. Novartis must be provided with a copy of the normal ranges and certification of the all laboratories used to assess participants' safety during study conduct, when possible. The Investigator is responsible for reviewing all laboratory reports for participants in the study and evaluating any abnormalities for clinical significance.

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

Table 8-5 Laboratory assessment

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other (absolute value preferred , %s are acceptable)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, non-fasting Glucose
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Thyroid	T4 [free], TSH
Virology	HBV, HCV, HIV
Additional tests	CA 19-9, Troponin I and NTproBNP
Pregnancy Test	Serum / Urine pregnancy test

8.4.5.1 Hematology

Please refer to Table 8-5 Laboratory assessment for a list of tests to be performed and Table 8-2 for timing of assessments.

8.4.5.2 Chemistry

Please refer to Table 8-5 Laboratory assessment for a list of tests to be performed and Table 8-2 for timing of assessments.

At Day 1 of each cycle, full chemistry will be assessed.

At Day 8 and Day 15 of each cycle, alleviated chemistry tests will be done. Only Alkaline phosphatase, ALT, AST, Creatinine, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, and BUN or Urea will be assessed.

8.4.5.3 Urinalysis

Please refer to Table 8-5 Laboratory assessment for a list of tests to be performed and Table 8-2 for timing of assessments.

8.4.5.4 Thyroid

Thyroid panel outlined in Table 8-5 Laboratory assessment will be performed in the **Safety Run-in part** and in **Randomized part** in the NIS793 with and without spartalizumab (**Arms 1 and 2**) as per the assessment schedule in Table 8-2.

8.4.5.5 Virology

Virology panel outlined in Table 8-5 Laboratory assessment will be performed as per the assessment schedule in Table 8-2.

8.4.5.6 Additional tests

Carbohydrate antigen 19-9 (CA 19-9) outlined in Table 8-5 Laboratory assessment will be performed as per the assessment schedule in Table 8-2.

8.4.6 Electrocardiogram (ECG)

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The individual ECGs should be recorded approximately 2 minutes apart.

Standard 12 lead ECGs are to be performed with ECG machines available at the site at screening and as clinically indicated.

On day and timepoints coinciding with blood sample collection, the ECG should be taken prior to blood collection.

For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. In that case, the mean 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. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the Investigator.

8.4.6.1 Cardiac imaging - echocardiogram or CT/MRI scan

Cardiac imaging (either echocardiogram or CT/MRI), will be performed at screening to determine cardiac function and morphology at baseline. Thereafter, echocardiogram will be performed if clinically indicated and/or if cardiac enzymes are elevated:

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

8.4.6.2 Cardiac enzymes

Cardiac specific enzyme Troponin I and NTproBNP will be performed at screening, C3D1 and day 1 of every third cycle during treatment duration or as clinically indicated, and at EOT visit.

8.4.7 Pregnancy

A condom is required for all sexually active male participants to prevent them from fathering a child and to prevent delivery of study treatment *via* seminal fluid to their partner. In addition, male participants should not donate sperm for the time period specified in Section 5.2.

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

At screening, a serum pregnancy test must be performed within 3 days before the first dose. During the study (Day 1 of each cycle starting with Cycle 2) and at End of Treatment, a serum pregnancy test must be performed.

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

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.

8.4.8 Appropriateness of safety measurements

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

8.5 Additional assessments

8.5.1 Pharmacokinetics

To assess PK, [redacted] and immunogenicity (IG) of NIS793, blood samples will be collected from all participants in **Safety Run-in part** and **Randomized Arms 1 and 2** to determine serum level of NIS793, [redacted] and anti-NIS793 antibody.

To assess PK and IG of spartalizumab, blood samples will be collected from all participants in **Safety Run-in part** and **Randomized Arm 1** of the study to determine free spartalizumab concentration in serum, and anti-spartalizumab antibody level in serum.

To assess PK of gemcitabine and nab-paclitaxel, blood samples will be collected from all participants in **Safety Run-in part** and **all three Randomized arms** of the study. PK of gemcitabine, dFdU (2',2'-difluoro-deoxyuridine, the primary metabolite of gemcitabine), and total nab-paclitaxel will be determined in plasma.

All participants who have evaluable PK data will be included in the PK data analysis. PK parameters will be determined using non-compartmental method(s) for NIS793, spartalizumab, nab-paclitaxel, gemcitabine, and dFdU. PK parameters such as those listed in Table 12-1 will be estimated and reported, when applicable. [redacted] PK[redacted] analysis may be conducted based on preliminary data prior to data base lock, and nominal time instead of actual elapsed time may be used. 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 the next section.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emerging data. Moreover, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons. Therefore, depending on the results obtained during the study, sample collection analysis may be omitted at the discretion of Novartis.

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

8.5.1.1 Pharmacokinetic blood collection and handling

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

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]

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 and spartalizumab are to be collected together with PK samples.

Table 8-6 Pharmacokinetic blood collection log - NIS793 and spartalizumab in Safety Run-in part and Randomized Arms 1 & 2

Cycle	Day	Scheduled Timepoint (h)	NIS793 analytes	[redacted]	Spartalizumab analytes
1	1	Predose [a]	PK and IG		PK and IG
1	1	1h post dose (± 5min)	PK		PK
1	2	24h post dose (+ 24h)	PK		PK
1	8	168h post dose (± 8h)	PK		PK
1	15	336h (± 24h post dose) (pre-NIS793 dose)	PK		-
2	1	Predose [a]	PK and IG		PK and IG
3	1	Predose [a]	PK and IG		PK and IG
3	1	1h post dose§ (± 5min)	PK		PK
3	2	24h post dose (+ 48h)	PK		PK
3	8	168h post dose (± 8h)	PK		-
3	15	336h (± 24h post dose) (pre-NIS793 dose)	PK		-
4	1	Predose [a]	PK and IG		PK and IG
5	1	Predose [a]	PK and IG		PK and IG
6	1	Predose [a]	PK and IG		PK and IG
7	1	Predose [a]	PK and IG		PK and IG
8	1	Predose [a]	PK and IG		PK and IG
EOT		-	PK and IG		PK and IG
End of safety follow-up[c]		-	PK and IG		PK and IG
Unscheduled[b]		-	PK and IG		PK and IG

IG, immunogenicity

a Pre-dose blood samples should be collected prior to start of NIS793 and spartalizumab infusion

b Unscheduled PK 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.

c Samples will not be collected if end of safety follow up may be performed *via* phone call

Table 8-7 Pharmacokinetic blood collection log - gemcitabine and nab-paclitaxel in Safety Run-in part and Randomized part (all Arms)

Cycle	Day	Scheduled Timepoint (h)	PK (GEM)	PK (nPAC)
1	1	Predose (0h)[a]	x	x
1	1	End of n-PAC infusion (± 5 min)	-	x
1	1	End of GEM infusion (± 5 min)	x	x
1	1	2h post start of n-PAC infusion (+ 10 min)	x	x
1	1	3h post start of n-PAC infusion (+ 10 min)	x	x
1	1	5h post start of n-PAC infusion (+ 30 min)	x	x
1	2	24h post start of GEM infusion (+ 24 h)	x	x
4	1	Pre-dose (0h)[a]	x	x
4	1	End of n-PAC infusion (± 5 min)	-	x
4	1	End of GEM infusion (± 5 min)	x	x
4	1	2h post start of n-PAC infusion (+ 10 min)	x	x
4	1	3h post start of n-PAC infusion (+ 10 min)	x	x
4	1	5h post start of n-PAC infusion (+ 30 min)	x	x
4	2	24h post start of n-PAC infusion (+ 4 h)	x	x
EOT		-	x	x
End of safety follow-up[c]		-	x	x
Unscheduled[b]		-	x	x

GEM, gemcitabine

n-PAC, nab-paclitaxel

a Pre-dose blood sample should be collected after end of NIS793 and spartalizumab infusion AND prior to start of nab-paclitaxel infusion for nab-paclitaxel PK sample, and prior to start of nab-paclitaxel infusion for gemcitabine PK sample, respectively.

b Unscheduled PK and IG samples will be collected in the event of a clinically significant AE (such as infusion reaction/anaphylaxis/DILI) or if IG is suspected.

c Samples will not be collected if end of safety follow up may be performed *via* phone call

8.5.1.2 Analytical method

8.5.1.2.1 NIS793

NIS793 will be determined in human serum using a validated ELISA with a lower limit of quantification (LLOQ) at 150 ng/mL.

[redacted]

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

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

8.5.1.2.2 Spartalizumab

Quantitative determination of spartalizumab in human serum will be performed using a validated Liquid Chromatography-Mass Spectrometry (LC-MS/MS) assay with a LLOQ at 250 ng/mL.

Anti-drug antibodies against spartalizumab will be determined in human serum using a validated homogenous ELISA assay.

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

8.5.1.2.3 Gemcitabine

Plasma (Lithium Heparin) concentration of gemcitabine and dFdU will be determined by using a validated LC-MS/MS with anticipated LLOQs at 50.0 ng/mL for gemcitabine and 50.0 ng/mL for dFdU using human plasma.

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

8.5.1.2.4 Nab-paclitaxel

Plasma (Sodium Heparin) concentration of nab-paclitaxel will be determined using a validated High-Performance Liquid Chromatography/Electrospray Ionization Tandem Mass Spectrometry (HPLC-ESI-MS/MS) assay with a LLOQ at 5.00 ng/mL.

The detailed method description of the nab-paclitaxel assay will be included in the corresponding bioanalytical data report. All concentrations below the LLOQ or missing data will be labelled as such in the concentration data listing.

8.5.2 Biomarkers

Biomarker analyses will be used to investigate the effect of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel and gemcitabine/nab-paclitaxel alone at the molecular and cellular level as well as to determine how changes in the markers may relate to exposure and clinical outcomes.

[redacted]

The sample collection information must be entered on the appropriate sample collection eCRF page(s) and requisition form(s). Detailed instructions for the collection, processing, and shipment of biomarker samples are outlined in the laboratory manual for the study.

Sample(s) should be collected at the visit/timepoint(s) defined in the biomarker Table 8-8.

On C1D2-D3 and C3D2-D4, biomarker samples and PK samples should be collected at the same time.

Table 8-8 Biomarker sample collection plan

Sample Type	Visit/ Timepoint	Approx. volume	Marker	Purpose
Tumor Samples				
Newly obtained tumor sample *	[redacted]	**Newly obtained tumor sample:** 3-6 passes of a core needle biopsy **Archival tumor sample:** FFPE block (preferred) or a minimum of 15 slides cut no longer than 5 months prior to screening (4µm thickness)	[redacted]	[redacted]
[redacted]				

[redacted]

* Archival tumor & de-identified pathology report may be permitted if it meets the inclusion criteria outlined in Section 5.1.

** Biomarker samples to be collected at the same time as PK samples.

*** For participants who discontinued for any reason between C2D15 and C3D1, prior to the planned biopsy collection, the biopsy should be collected at the participants scheduled EoT visit instead, if feasible, and will be reported as unscheduled sample.

**** For Safety Run-in part and Randomized Arms 1 and 2: An optional newly obtained tumor biopsy is requested for participants who clinically benefited from the study treatment to study tumor resistance mechanisms.

8.5.2.1 Biomarker assessment in tumor samples

Newly obtained pre- and on-treatment paired tumor samples are required and are collected at screening and on-treatment as indicated in Table 8-8. An archival tumor and a copy of the corresponding de-identified pathology report may be submitted at the screening visit in place of a newly obtained biopsy provided the biopsy meets the criteria outlined in Section 5.1. Otherwise, a newly obtained biopsy at screening is required. If the participant discontinues between the Cycle 2 day 15 and Cycle 3 day 1 visit (for any reason), and the on-treatment biopsy has not already been taken, the biopsy should be collected prior EOT, if feasible. Additionally an optional newly obtained tumor sample is requested at EOT from participants who benefited from study treatment of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel i.e., stable disease (SD) for at least 6 months, PR, or CR.

In the event an inadequate tumor sample is received at screening following a new biopsy procedure (e.g. found to have low tumor content), an archival tumor may be requested to allow for the analysis described in Table 8-8. The archival tumor must meet specifications as described in Section 5.1.

[redacted]

Sequencing of immune and cancer related genes will be performed in tumor. Tumor may be sequenced at screening, on-treatment and EOT from participants who benefited from study treatment, i.e., stable disease (SD) for at least 6 months, PR, or CR.

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration 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.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Any situation in which study participation might result in a safety risk to the participant
- Death

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

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should not be considered withdrawn from the study unless they withdraw their consent (see Section 9.1.2). Where possible, they should return for the assessments indicated in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up Section 9.1.3. This contact should preferably be done according to the study visit schedule.

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

After study treatment discontinuation, 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 treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent as applicable, 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, or withdrawal of consent as applicable.

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

9.1.1.1 Replacement policy

Participants of the **Randomized part** will not be replaced on study. All treated participants will contribute to the final analyses. During **Safety Run-in part**, if a participant is considered to be non-evaluable for the Dose Determining Set (Section 12.1.3), enrollment of a new participant to the current cohort will be considered. Enrollment of new participants may be considered until six evaluable participants within a cohort are achieved.

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

Withdrawal of consent/opposition to use data occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

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 in writing (depending on local regulations) and recorded in the source documentation.

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

Where consent to the use of personal and coded data is not required 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 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.

9.1.3 Lost to follow-up

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

9.1.4 Early study termination by the sponsor

The study can be stopped 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 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.

9.2 Study completion and post-study treatment

Study completion is defined as when the end of study criteria are met, or, in the event of an early study termination decision, the date of that decision.

9.2.1 End of study

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

- All participants have discontinued study treatment and completed the safety follow-up and at least 80% of the participants have died, withdrawn consent or are lost to follow-up.
- Another study becomes available that can continue to provide participants' study treatment, and all participants ongoing are transferred to that clinical study and all discontinued participants have completed the safety follow-up period. Transfer of participants will only be allowed after primary endpoints (refer to Table 2-1) have been reached.
- The study is terminated early (Section 9.1.4). In such case the end of study will be when all participants have completed the treatment period and the safety follow-up period.

At the end of the study, every effort will be made to continue provision of study treatment outside the study through an alternative treatment option to subjects (or patients) who, in the opinion of the Investigator, are still deriving clinical benefit.

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

See Section 12 Data Analysis and statistical methods for details of timing of the primary analysis and final reporting of data.

9.2.2 Post-treatment follow-up

After treatment discontinuation, all participants will be followed for safety and survival, as described in Section 9.2.3 and Section 9.2.4.

Participants who discontinue study treatment for any reason other than death, disease progression per RECIST 1.1 while on treatment, clinical deterioration, lost to follow-up, consent withdrawal, study termination, also should return for tumor evaluation assessments. 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. Once the Follow up for Disease progression period ended, the End of Post treatment Phase disposition CRF should be completed.

In addition, participants who discontinue study treatment for any reason other than death, disease progression (radiological or clinical deterioration), lost to follow-up, withdrawal of consent or study termination should return for tumor evaluation assessments every 8 weeks until 52 weeks then every 12 weeks until confirmation of disease progression per RECIST 1.1, death, lost to follow-up, or withdrawal of consent. If a participant starts a new anti-neoplastic therapy prior to progression, tumor assessments should continue per the planned visit schedule (Table 8-2) 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.

9.2.3 Safety follow-up

All participants must have safety evaluations for 90 days after the last dose of NIS793, 150 days after the last dose of spartalizumab and 30 days after the last dose of gemcitabine and nab-paclitaxel, whichever is longer. The evaluations can be done by telephone call or visit for the 30-, 90-, and 150-day safety follow-up visits. Concomitant medications will be collected until the 30-day safety follow-up has been completed or the start of a new antineoplastic therapy, whichever occurs first. A PK and immunogenicity sample should be collected at the end of safety follow-up as described in Section 8.5.1. If the safety evaluation is conducted by phone, samples do not need to be collected.

Data collected should be added to the relevant CRF. For female participants of childbearing potential, pregnancy tests will be performed as outlined in Section 8.4.7.

9.2.4 Survival follow-up

After completion of the safety follow-up, participants will enter the survival follow-up period. Participants will be contacted by telephone every 12 weeks to follow-up their survival status. Any new antineoplastic therapies that have been started since the last contact date will also be collected during these phone calls.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a 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 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):

- 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.
- 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
- Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
- Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
- 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/withdrawn

6. Its outcome

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 CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

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

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

AE monitoring should be continued for at least 30 days for all participants, 90 days for participants treated with NIS793 and 150 days for participants treated with spartalizumab, following the last dose of study treatment.

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 permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Progression of maligna [redacted] ing fatal outcomes), if documented by use of appropriate method (as per RECIST [redacted] 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 (i.e. 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.

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

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

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (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 30 days for all participants, 90 days for participants treated with NIS793 and 150 days for participants treated with spartalizumab, following the last administration of study treatment, must be reported to Novartis safety immediately, without undue delay, but no 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 with paper back-up Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

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.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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

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

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

After the completion of the 30 days 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.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study

Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

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

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

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

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

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

10.2 Additional Safety Monitoring

10.2.1 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 assess at defined intervals the progress of a clinical trial, safety data (aggregated data and by treatment data), and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial.

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.

11 Data Collection and Database management

11.1 Data collection

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

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

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

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

11.2 Database management and quality control

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

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

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

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

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

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

12 Data analysis and statistical methods

Data from participating centers in this protocol will be combined, so that an adequate number of participants will be available for analysis.

The primary analysis may be conducted and results may be reported in a primary CSR when both or either of the following criteria are met:

- Approximately 60 participants (who comply with the FAS criteria) have experienced a PFS event (documented progression as per RECIST 1.1 or death due to any cause) in the NIS793 with spartalizumab and gemcitabine/nab-paclitaxel (**Arm 1**) and gemcitabine/nab-paclitaxel (**Arm 3**) arms.
- Approximately 60 participants (who comply with the FAS criteria) have experienced a PFS event (documented progression as per RECIST 1.1 or death due to any cause) in the NIS793 with gemcitabine/nab-paclitaxel (**Arm 2**) and gemcitabine/nab-paclitaxel (**Arm 3**) arms.

In case of primary CSR, any additional data for participants continuing to receive study treatment past the data cutoff date for the primary CSR, as allowed by the protocol, will be reported at completion of the study in a final CSR.

All summaries, listings, figures and analyses will be performed for all participants in the **Safety Run-in part** and by treatment arm for the **Randomized part**, unless otherwise specified. Additional summaries by participant subgroups may be produced as relevant for selected endpoints.

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

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

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

12.1 Analysis sets

12.1.1 Full Analysis Set

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.

Safety Run-in and Randomized parts

The Complete Full Analysis Set (C-FAS) comprises all participants from FAS and participants to whom study treatment has been assigned during the **Safety Run-in part** and 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)).

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

Safety Run-In part

The Dose Determining Set (DDS) consists of all participants in the **Safety Run-in part** who met the minimum exposure criterion and have sufficient safety evaluations after 4 weeks of treatment 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 or 1400 mg Q2W (only applicable in case of second cohort in **Safety Run-in part**)), 1 dose of spartalizumab (400 mg Q4W), 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

Randomized part

Five separate Pharmacokinetic analysis sets (PAS) will be considered. One for NIS793 (NIS-PAS), one for spartalizumab (PDR-PAS), one for gemcitabine (GEM-PAS), one for dFdU, the primary metabolite of gemcitabine (dFdU-PAS), and one for nab-paclitaxel (PAC-PAS). Each of the PAS includes all participants who provide an evaluable PK profile for this specific PAS. A profile is considered to be evaluable if **all** of the following conditions are satisfied:

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

Participants may be removed from PK analysis on an individual basis depending on the number of available blood samples. These participants will be identified at the time of analysis.

12.1.5 Immunogenicity Analysis Set

Randomized part

The immunogenicity (IG) 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 listed and summarized descriptively for participants in the **Safety Run-in part** using the C-FAS and by treatment arm for participants in the **Randomized part** using the FAS.

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

12.3 Treatments

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

The duration of exposure in weeks of NIS793, spartalizumab, gemcitabine, and nab-paclitaxel 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.

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

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

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by participant and summarized by anatomical therapeutic classification system (ATC) term and treatment arm.

12.4 Analysis of the primary endpoints/estimands

12.4.1 Safety endpoints

Safety Run-in part

The primary safety objective is to characterize the safety and tolerability of NIS793 with spartalizumab and gemcitabine/nab-paclitaxel and to identify the dose to be tested in **Randomized part** and in future studies of NIS793 with spartalizumab and gemcitabine/nab-paclitaxel.

12.4.1.1 Definition of primary endpoints

The primary endpoints will be evaluated based on the following criteria:

- Incidence of DLTs
- Incidence of AEs and SAEs
- Changes in laboratory values, vital signs, and ECGs
- Dose interruptions, reductions, and dose intensity

12.4.1.2 Statistical hypothesis, model, and method of analysis

For all safety analyses, safety set 1 will be used.

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

Pre-treatment period

- From day of participant's first informed consent to the day before first administration of any study drug.

On-treatment period

- From date of first administration of any study drug to 30 days after date of last actual administration of any study drug (including start and stop date).

Post-treatment period

- Starting at day 30+1 after the last administration of study treatment in the combination arm.

Safety summaries will primarily be based on all data from the on-treatment period. Following last administration of study treatment, AEs (including SAEs) will be collected for 30 days from last dose of gemcitabine/nab-paclitaxel, 90 days from the last dose of NIS793, and 150 days from the last dose of spartalizumab. New anti-cancer therapies will be collected until participant's death or lost to follow-up. Following start of new anti-cancer therapy, only

study treatment related AEs will be collected. Select summaries of related AEs will be produced for the combined on-treatment and post-treatment periods. Details will be specified in the SAP.

Dose-limiting toxicities

The dose to be tested in **Randomized part** will be decided based upon the percentage of DLTs during the first 4 weeks of treatment for participants in the DDS, along with the evaluation of additional safety, clinical, PK, [redacted] data.

Algorithmic based approach

For a dose to be declared safe, the targeted DLT rate should be below 33%. Occurrence of two or more DLTs out of six evaluable participants would trigger dose de-escalation or the end of study. For more details on the safety criteria refer to Section 6.5 and Appendix 4.

Reporting

DLTs will be listed and their incidence will be summarized by primary system organ class and worst grade (CTCAE version 5.0), using the DDS.

Adverse events

The number (and percentage) of participants with treatment emergent AEs (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 primary system organ class and preferred term
- by primary system organ class, preferred term, and maximum severity
- by Standardized MedDRA Query (SMQ) and preferred term

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

The number (and percentage) of participants with AEs of special interest (AESIs) will be summarized. A participant with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

SAEs, non-serious AEs, and AESIs during the on-treatment period will be tabulated.

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

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

Vital signs

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

Vital signs collected during on-treatment will be summarized. The number and percentage of participants with notable vital sign values will be presented for the safety set 1. A listing of participants with notable vital signs will be provided and values measured during the

post-treatment follow up will be flagged in the listing. Notable vital sign values criteria will be specified in the SAP.

12-lead 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. The average of the ECG parameters at each assessment should be used in the analyses.

ECGs collected during on-treatment will be summarized. The number and percentage of participants with notable ECG values will be presented. A listing of participants with notable ECGs will be provided and values measured during the post-treatment follow-up will be flagged in the listing. Notable ECG values criteria will be specified in the SAP.

Clinical Laboratory Evaluations

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

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

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

For laboratory tests where grades are not defined by CTCAE v5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

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

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v5.0 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 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.

Tolerability

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

12.4.1.3 Handling of missing values/censoring/discontinuations

Participant safety data will be reported up to the cut-off date, end of post-treatment (if discontinued), death, lost to follow-up, or withdrawal of consent as applicable, whichever happened first. Missing values will not be imputed and will be reported as such.

12.4.1.4 Sensitivity and Supportive analyses

Not applicable.

12.4.2 Efficacy estimands

Randomized part

The primary efficacy objective of this study is to characterize the difference in anti-tumor activity of:

a) NIS793 with spartalizumab and gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel and

b) NIS793 with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel,

by estimating the progression-free survival (PFS). Estimation of the hazard ratios (HRs) of the PFS and the corresponding credible intervals will be used to detect the magnitude of such anti-tumor activity difference.

12.4.2.1 Definition of primary estimand

PFS is defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS will be assessed *via* local review according to RECIST 1.1 (see Appendix 1 for further details). In the primary analysis, PFS will be censored at the date of the last adequate tumor assessment if no PFS event is observed prior to the analysis cut-off date. Handling of missing data (e.g., due to administrative censoring) is provided in Section 12.4.2.4.

12.4.2.2 Statistical hypothesis, model, and method of analysis

The same Bayesian model will be used to estimate and provide inferential summaries for both PFS HRs a) NIS793 with spartalizumab and gemcitabine/nab-paclitaxel (**Arm 1**) versus gemcitabine/nab-paclitaxel (**Arm 3**) and b) NIS793 with gemcitabine/nab-paclitaxel (**Arm 2**) versus gemcitabine/nab-paclitaxel (**Arm 3**). For each comparison, the PFS will be modeled using a two-piece hazard model, which allows specifying different hazard rates before and after the possible delayed effect for **Arms 1** and **2** and constant hazard rate for **Arm 3**. Models are presented for the first comparison (**Arm 1** vs **Arm 3**). The same assumptions apply to the second comparison (**Arm 2** vs **Arm 3**).

$$\lambda_t(t) = \lambda_1 + (\lambda_2 - \lambda_1)\left(\frac{1}{2} + \frac{1}{2}\tanh\big(s(t-v)\big)\right) \text{ and } \begin{cases} \lambda_1 = \mu * \eta \\ \lambda_2 = \mu/\eta \end{cases}$$

$$\lambda_c(t) = -\frac{\log(\mathrm{PFS(t)})}{\mathrm{t}},$$

where λ_t and λ_c are the hazard rates for **Arms 1** and **3**, respectively. Parameters λ_1 and λ_2 are the respective hazard rates before/after the delayed effect for **Arm 1**, μ is a type of average hazard and η is the divergence from this average in each period. The study year is depicted by t, $s = 15$ is a fixed slope parameter that dictates the speed with which the hazard changes from period 1 to period 2 and ν is the risk changing timepoint (i.e., the time to the delayed effect). The corresponding HR between **Arm 1** and **Arm 3** after the delayed effect is λ_2/λ_c.

The same weakly informative prior distribution will be assumed for **Arms 1** and **2**. A mixture prior distribution will be assumed for **Arm 3**, which consists of two components derived from a historical gemcitabine/nab-paclitaxel study. For further details, refer to Appendix 5.

At the time of the analysis, the model will be updated with all available data of participants in the FAS and the posterior distribution for the HR after the delayed effect will be estimated. Inferential summaries based on the posterior distribution will be presented, including median, mean, standard deviation, and one-sided 90% credible interval.

[redacted] with spartalizumab and gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel. Same criteria will be applied for NIS793 with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel.

12.4.2.3 Handling of remaining intercurrent events of primary estimand

The primary analysis will account for three intercurrent events as explained in the following:

- **Start of a new anti-cancer therapy prior to disease progression or death:** Tumor assessment data collected after discontinuation of study treatment and start of new anti-cancer therapy will be used to derive PFS.
- **Treatment discontinuation related to COVID-19**: Tumor assessment data collected after discontinuation of study treatment due to COVID-19 will be used to derive PFS.
- **Treatment discontinuation for any reason not related to new anti-cancer therapy or COVID-19:** Tumor assessment data collected after discontinuation of study treatment will be used to derive PFS.

12.4.2.4 Handling of missing values not related to intercurrent events

If a PFS event is observed after two or more missing or non-adequate tumor assessments, then PFS will be censored at the last adequate tumor assessment before the PFS event. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used (see RECIST 1.1 in Appendix 1).

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

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

More details will be provided in the SAP.

12.4.2.5 Sensitivity analysis for primary estimand

As a sensitivity efficacy analysis, PFS will be analyzed using a Cox model, without considering delayed effects, based on the FAS with the same analysis conventions as for the primary estimand. The treatment effect for each of the two comparisons will be summarized by the overall HR with its one-sided 90% confidence interval. Kaplan-Meier curves for PFS as well as medians along with their two-sided 95% confidence intervals will be presented for each treatment arm.

12.4.2.6 Supplementary analyses

A supplementary clinical question of interest is:

- What is the effect of NIS793 and gemcitabine/nab-paclitaxel with and without spartalizumab relative to gemcitabine/nab-paclitaxel in prolonging time to death or radiological progression in first line mPDAC, had a new anti-cancer therapy not been available or had participants not discontinued treatment due to COVID-19?

The justification for targeting these treatment effects is that we wish to estimate the relative effects of the treatment strategies in the absence of potentially a) a confounding effect of any new anti-cancer therapy that is not a part of the assigned treatment strategy or b) a treatment discontinuation due to COVID-19.

In this supplementary estimand, all four attributes, that is population, primary variable, treatments of interest, and summary measure will be the same as for the primary estimand.

Handling of intercurrent events:

- New anti-cancer therapy initiated before observing PFS event will be handled using the hypothetical strategy.
- Treatment discontinuation related to COVID-19 will be handled using the hypothetical strategy;
- Treatment discontinuation for any reason not related to new anti-cancer therapy or COVID-19 will be handled using the treatment policy strategy, as for the primary estimand.

Start of a new anti-cancer therapy prior to disease progression or death and treatment discontinuation due to COVID-19 will be analyzed considering two different options:

Option 1

PFS will be censored at the last adequate disease assessment before the start of new anti-neoplastic therapy or before discontinuing treatment due to COVID-19.

Option 2

Data from participants who switched to a new anti-cancer therapy or discontinued treatment due to COVID-19 will be imputed, simulating PFS times from a different model than the one described in Section 12.4.2.2. For the imputation, we will take into account the hazard rate of participants who remained into the study.

12.4.2.7 Supportive analyses

As a supportive efficacy analysis of the study, PFS will be analyzed for the first comparison (**Arm 1** vs **Arm 3**), based on the C-FAS, using the same analysis conventions as for the primary estimand. Participants from the **Safety Run-in part** will be analyzed together with **Arm 1**. For each arm separately, the Bayesian posterior estimate of median and one-sided 90% credible interval of HR will be presented using C-FAS. Similarly, for each arm separately, the median PFS per local review and the one-sided 90% confidence interval for HR of PFS will be presented, using C-FAS. The same analysis conventions as in the primary efficacy analysis will be applied.

12.5 Analysis of secondary endpoints/estimands

Randomized part

12.5.1 Efficacy estimands

The secondary efficacy objectives of this study are to assess the following:

- Anti-tumor activity of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel, based on overall response rate (ORR), duration of response (DOR), and time to progression (TTP)
- Overall survival (OS) of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel.

Overall response rate (ORR)

ORR is defined as the proportion of participants with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) as per Investigator assessment as per RECIST 1.1 (see Appendix 1).

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

Duration of response (DOR)

DOR is defined as the time from the date of first documented response (CR or PR) to the first documented progression per RECIST 1.1 or death due to any cause. If a participant with a CR or PR has no progression or death, the participant is censored at the date of last adequate tumor assessment. Definition of last adequate tumor assessment is provided in Appendix 1.

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

Time to progression (TTP)

TTP is the time from the date of randomization to the date of event defined as the first documented progression per RECIST 1.1 or death due to underlying cancer. If a participant has no progression or death, the participant is censored at the date of last adequate tumor assessment. Definition of last adequate tumor assessment is provided in Appendix 1.

TTP will be summarized using the Kaplan-Meier method, based on FAS. Median TTP, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. Kaplan-Meier estimates for TTP proportions at specific timepoints, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided.

Overall survival (OS)

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

OS will be summarized using the Kaplan-Meier method, based on FAS. Median OS, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. Kaplan-Meier estimates for OS proportions at specific timepoints, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided.

12.5.1.1 Handling of intercurrent events of secondary estimands

The secondary analyses will account for three intercurrent events as explained in the following:

- **Start of a new anti-cancer therapy prior to disease progression or death:** Tumor assessment data collected after discontinuation of study treatment and start of new anti-cancer therapy will be used to derive the secondary variables.
- **Treatment discontinuation related to COVID-19**: Tumor assessment data collected after discontinuation of study treatment due to COVID-19 will be used to derive the secondary variables.
- **Treatment discontinuation for any reason not related to new anti-cancer therapy or COVID-19:** Tumor assessment data collected after discontinuation of study treatment will be used to derive the secondary variables.

12.5.1.2 Handling of missing values not related to intercurrent events

For handling of missing values, censoring, and discontinuations refer to Section 12.4.2.4.

12.5.2 Safety endpoints

Randomized part

For all safety analyses, safety set 2 will be used. Results will be presented by treatment arm following the analyses as presented in Section 12.4.1.

12.5.3 Immunogenicity

Immunogenicity will be characterized descriptively by tabulating ADA prevalence at baseline and ADA incidence on-treatment. The impact of immunogenicity on PK, safety, and efficacy will be explored. Further details will be specified in the SAP.

12.5.4 Pharmacokinetics

All PK data analysis and PK summary statistics will be based on the NIS-PAS, PDR-PAS, GEM-PAS, dFdU-PAS, and PAC-PAS. PK parameters will be determined using non-compartmental method(s) for NIS793, spartalizumab, gemcitabine, dFdU, and nab-paclitaxel.

NIS793, spartalizumab, gemcitabine, dFdU, and nab-paclitaxel 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, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations.

The PK parameters in the Table 12-1 will be 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 parameters

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)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration time curve (time). Use qualifier for other half-lives
CL	The total body clearance of drug from the serum/plasma (volume x time-1)
Vz	The volume of distribution during terminal phase (associated with λz) (volume)

12.5.4.1 Handling of missing values/censoring/discontinuations

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

12.5.4.2 Population pharmacokinetic analysis

If data permit, a non-linear mixed-effects model may be applied to the NIS793 and/or spartalizumab and/or gemcitabine and/or dFdU and/or nab-paclitaxel concentration-time data to generate post hoc estimates of pharmacokinetic parameters to characterize the NIS793 and/or spartalizumab and/or gemcitabine and/or dFdU and/or nab-paclitaxel exposure. If there is sufficient data for analysis, the details of the population pharmacokinetic analyses will be provided in a separate reporting and analysis plan, and the results may be reported in a separate population pharmacokinetic report. Data from this and other studies may be pooled for analysis.

Data generated on hypothesis-free platforms will be reported separately (e.g. CSR addendum).

12.7 Interim analyses

Safety Run-in part

No formal IA is planned. However, the dose evaluation from the **Safety Run-in part** for NIS793 with spartalizumab and gemcitabine/nab-paclitaxel allows that decisions are taken based on the current data. More precisely, after each cohort in the dose evaluation, the decision to proceed with the **Randomized part**, de-escalate, or end the study will be based on review, by Novartis study personnel and Investigators, of available safety and tolerability information (including the DLT risk assessment) along with PK [redacted] data. Details of this procedure and the process for communication with Investigators are provided in Section 6.5.

Randomized part

IA of efficacy data may be conducted to support decision making concerning the Sponsor's clinical development projects. Additional supportive analyses of available clinical data may be considered if appropriate. Details on the IA may be provided in the CSR SAP or in a stand-alone SAP.

However, this IA is not planned to support formal design adaptations in the current phase II study.

The safety data will be monitored on a regular basis by the DMC (as defined in Section 10.2.1).

Further details will be provided in DMC charter and DMC SAP.

12.8 Sample size calculation

12.8.1 Primary endpoints

Safety Run-in part

No formal statistical power calculations to determine sample size were performed for this part of the study.

At least six participants will be enrolled in order to have six evaluable participants. Table 16-8 in Appendix 4 presents the probability of observing zero, one, or more than two DLTs out of six participants for different true DLT rates. In case of dose de-escalation to dose level -1 (Table 6-2), a second cohort will open and at least six more participants will be enrolled in order to have six evaluable participants.

Randomized part

Sample size calculation was based on simulations for various scenarios on treatment outcome, number of participants included, and number of events at the timepoint of the analysis using the Bayesian model defined in Section 12.4.2.2.

The evaluation of the success criteria was based on the HR of the PFS (NIS793 with spartalizumab and gemcitabine/nab-paclitaxel vs gemcitabine/nab-paclitaxel) after the timepoint of risk change in the assumed two-piece hazard model (HR2) used in the Bayesian model (in order to account for potential delayed effects). The same success criteria apply for the HR of the PFS of NIS793 with gemcitabine/nab-paclitaxel vs gemcitabine/nab-paclitaxel.

The success criteria used for the evaluation of the efficacy of the simulation samples are the following:

- At least 50% confidence level that HR2 $\leq$ 0.7
- At least 90% confidence level that HR2 < 1

Approximately 150 participants are expected to be treated in the study (additionally to those from the **Safety Run-in part**), randomized with ratio 1:1:1 (NIS793 with spartalizumab and gemcitabine/nab-paclitaxel (**Arm 1**): NIS793 with gemcitabine/nab-paclitaxel (**Arm 2**): gemcitabine/nab-paclitaxel (**Arm 3**)). In this calculation a 10% risk of dropout per participant year has been taken into consideration.

Regarding the enrolment plan of the study, we assume that 15 participants will be accrued per month in all three arms, until a total of 150 participants are treated in the study.

The reported median PFS for gemcitabine/nab-paclitaxel as first-line therapy for PDAC participants was 5.5 months in Von Hoff study (Von Hoff et al 2013). It was, therefore, assumed that the median PFS of gemcitabine/nab-paclitaxel ranged between 5 and 6 months. For the NIS793 treated arms, we expect an approximately 3-month delayed onset of clinical benefit due to immunotherapeutic compounds that will be referred to as delayed effect. Additionally, we expect around 50% reduction in the hazard rate of PFS, after the timepoint of risk change in the assumed two-piece hazard model.

For both comparisons, the same model assumptions are considered. Therefore, sample size calculations will be presented only for the first comparison and the same calculations will be applicable to the second comparison. Table 12-2 presents the operating characteristics of the Bayesian model with different outcome scenarios keeping stable the total sample size to 100 participants (for **Arms 1** and **3**), the number of total PFS events to 60 required at the timepoint of the analysis, and assuming a 3-month delayed effect for **Arm 1**. With this combination, reasonable operating characteristics can be achieved. Description of operating characteristics of alternative sample size and delayed effect assumptions can be found in Appendix 5.

Table 12-2 Operating characteristics for scenarios with 100 participants, 60 events, and a 3-month delayed effect

Scenarios Median PFS in months Arm 1 vs Arm 3 (Hazard ratio)	Probability of Success	Median follow-up period since FPFV (months)†
5.5 vs 5.5 (HR2=1)	0.151	14.1
5.0 vs 5.0 (HR2=1)	0.124	13.3
6.0 vs 6.0 (HR2=1)	0.137	14.8
8.0 vs 6.0 (HR2=0.600)	0.697	16.2
7.5 vs 5.5 (HR2=0.557)	0.735	15.5
6.6 vs 5.0 (HR2=0.557)	0.709	15.5
9.0 vs 6.0 (HR2=0.500)	0.864	16.8
8.5 vs 5.5 (HR2=0.456)	0.914	16.1

HR2: Hazard ratio after the risk change in the two-piece hazard model.
† FPFV of the **Randomized part**.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the Investigator and IRB/IEC

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

site is requested by a regulatory authority, the Investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (see Section 9.2.1) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.) .

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

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

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

14.1 Protocol amendments

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

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

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

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16 Appendices

16.1 Appendix 1: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival, and Overall Survival (based on RECIST 1.1)

16.1.1 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 16.1.2 and the definition of best response in Section 16.1.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.1.3.2 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 16.1.4 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.

16.1.2 Efficacy assessments

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

16.1.2.1 Definitions

16.1.2.1.1 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 16.1.3.2.8

- **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.

16.1.2.1.2 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 16.1.3.2.8.

16.1.2.2 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.

16.1.2.3 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 16.1.2.1.1.
- **Nodal target**: See Section 16.1.2.1.1.

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.

16.1.2.4 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 16-1) and non-target lesions (Table 16-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-3) as well as the presence or absence of new lesions.

16.1.2.4.1 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.

16.1.2.4.2 Determination of target lesion response

Table 16-1 Response criteria for target lesions

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

- SOD for CR may not be zero when nodal lesions are part of target lesions
- Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
- In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 16.1.2.2).

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 16-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of all measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- Nodal lesion decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters

for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.

- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.
- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

16.1.2.4.3 Determination of non-target lesion response

Table 16-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline[2.]

1. The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the investigator or central reviewer does prevail.
2. It is recommended that the investigator and/or central reviewer should use expert judgment to assign a Non-UNK response wherever possible (see notes section for more details)

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.
- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).

Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 16.1.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

16.1.2.4.4 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 16.1.2.5).

- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 16.1.2.2.

16.1.2.5 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 16-3.

Table 16-3 Overall lesion response at each assessment

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

This overall lesion response also applies when there are no non-target lesions identified at baseline.
Once confirmed PR was achieved, all these assessments are considered PR.
As defined in Section 16.1.2.4.

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.

16.1.3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 16.1.3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

16.1.3.1 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 (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

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

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

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

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

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

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

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

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

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

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

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

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

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

16.1.3.2 Time to event variables

16.1.3.2.1 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.

16.1.3.2.2 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.

16.1.3.2.3 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.

16.1.3.2.4 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.

16.1.3.2.5 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.

16.1.3.2.6 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.

16.1.3.2.7 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 16.1.3.2.5. 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.

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

Assessment date

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

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

Start dates

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

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

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

End dates

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

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 16.1.3.2.8).

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.

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

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

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

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

Table 16-4 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 16.1.2.4.

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.

16.1.3.2.10 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 16.1.3.2.7, 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 16-5 Options for event dates used in PFS, TTP, duration of response

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

1.=Definitions can be found in Section 16.1.3.2.7.

2.=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.1.3.2.7.

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 16-5 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.

16.1.4 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).

16.1.4.1 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).

16.1.4.2 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
- Subject/guardian decision
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

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

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

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

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

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

16.1.4.4 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.

16.1.4.5 Programming rules

The following should be used for programming of efficacy results:

16.1.4.5.1 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.

16.1.4.5.2 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 16.1.3.2.7). 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.

16.1.4.5.3 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.

16.1.4.5.4 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)'.

16.1.4.5.5 Study/project specific programming

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

16.1.4.5.6 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 16-4)
- 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 16.1.3.2.7. 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.

16.1.5 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791.

Eisenhauer EA, Therasse P, Bogaerts J, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, Vol.45: 228-47.

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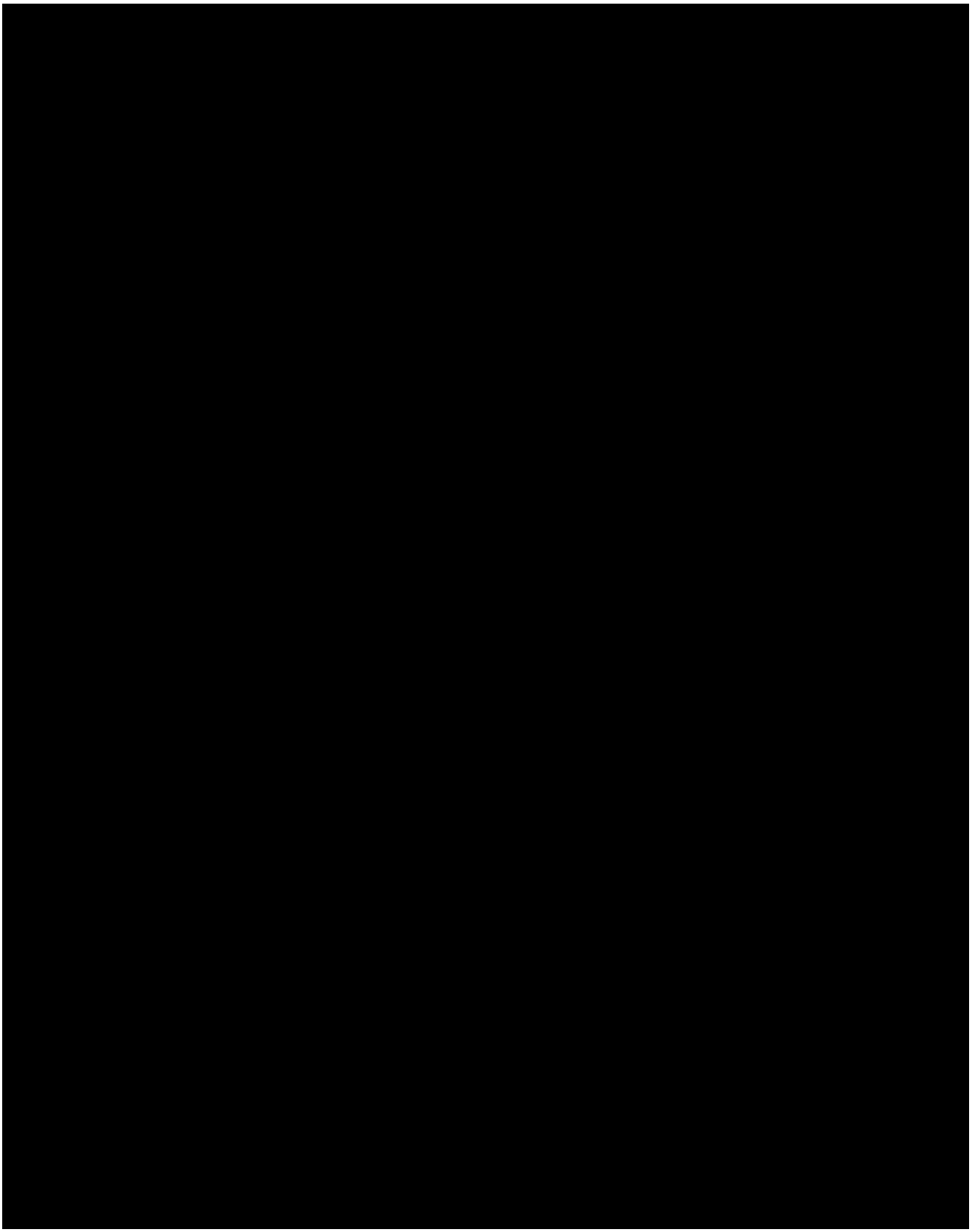
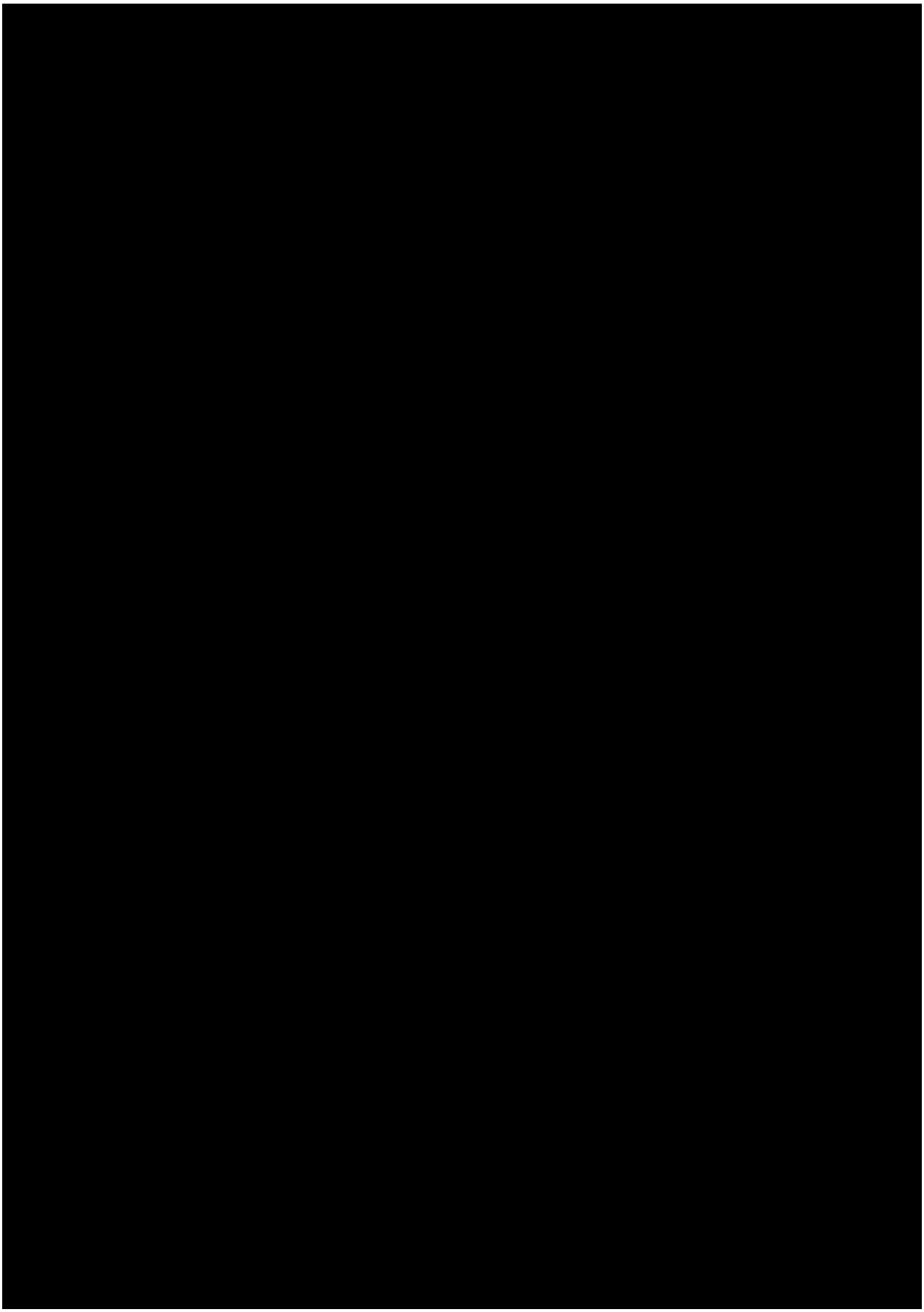
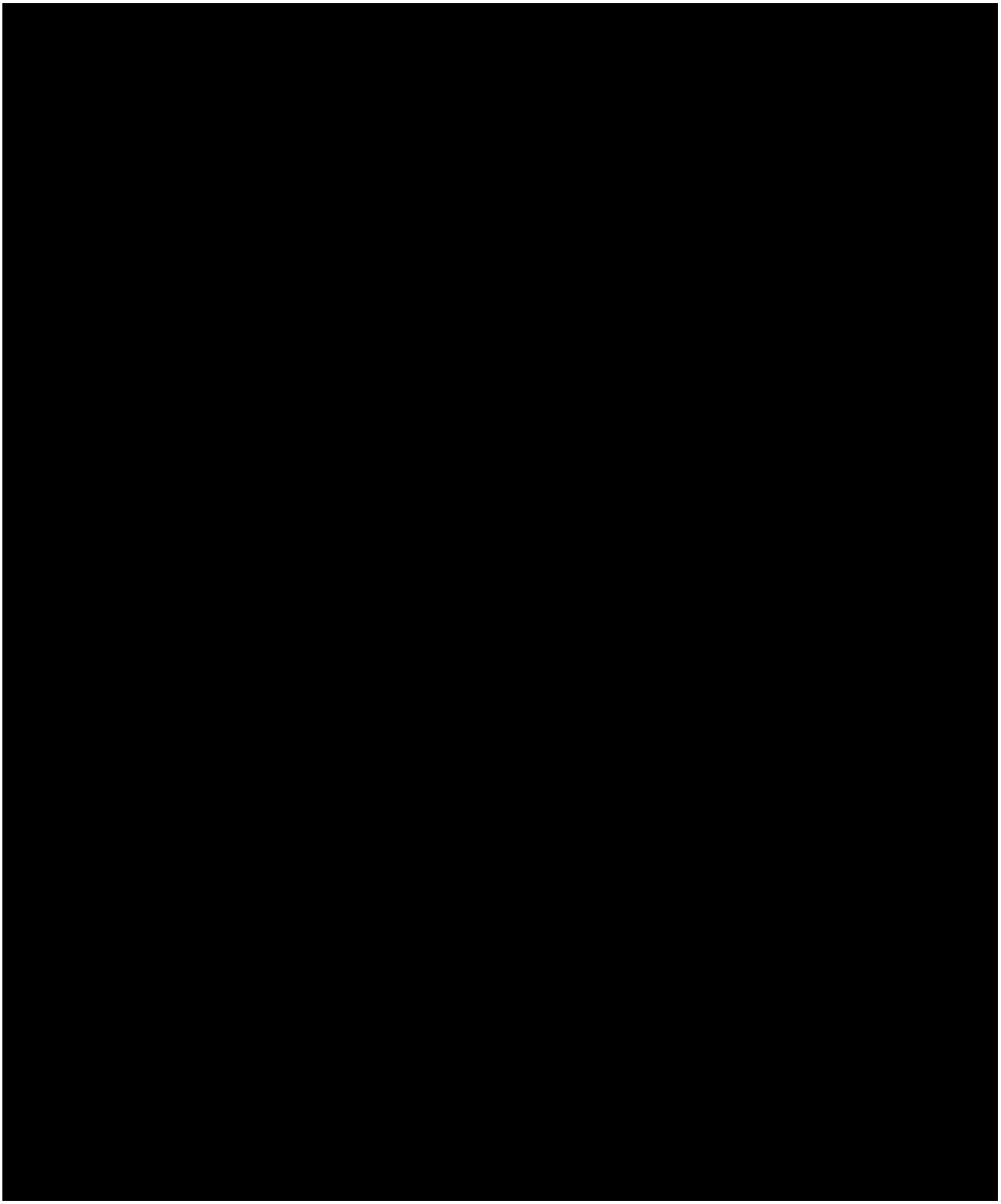
FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005.

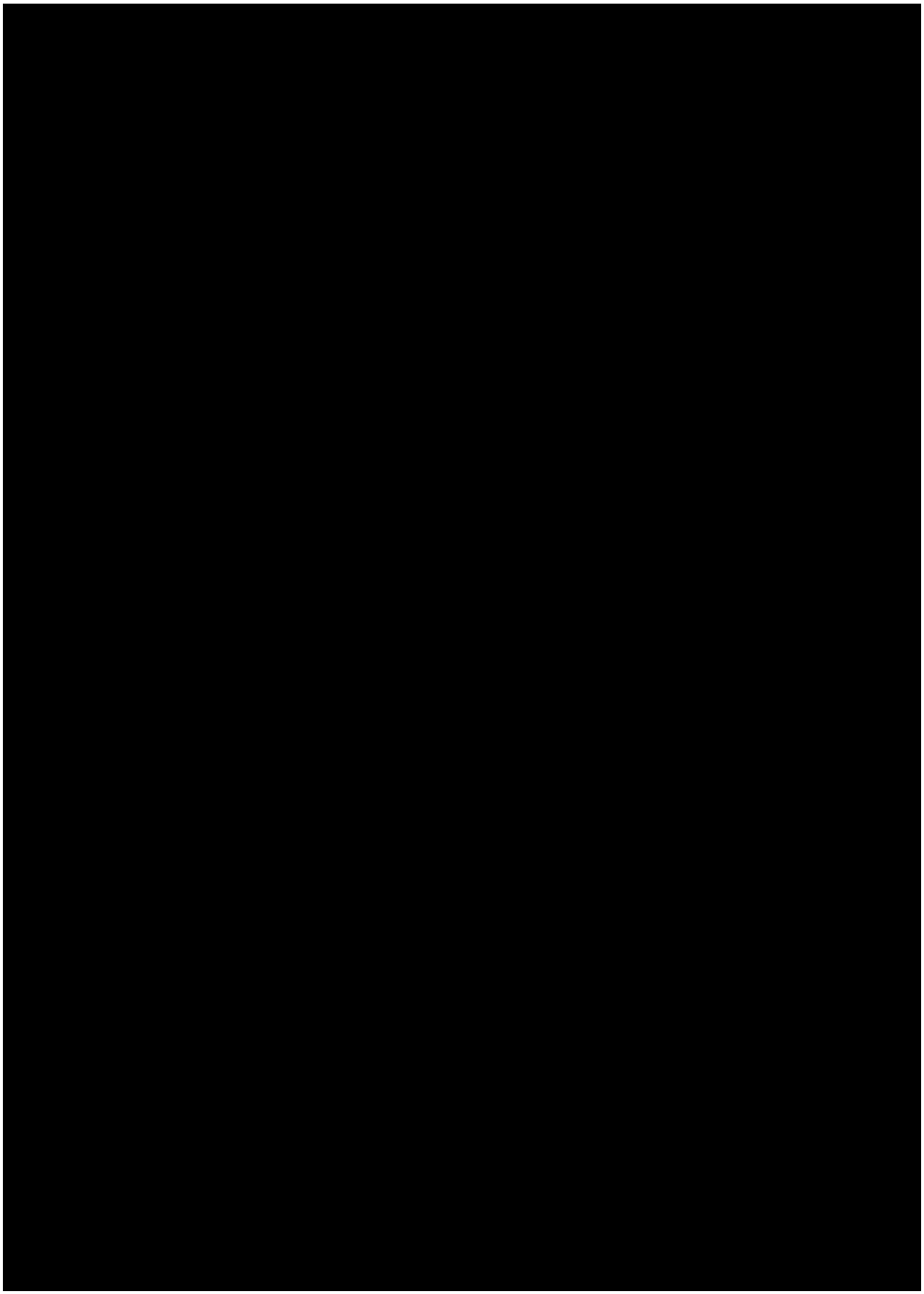
Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9: 11-18.

Therasse P, Arbuck S, Eisenhauer E, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16.









16.3 Appendix 3: List of concomitant medications

In general, the use of any concomitant medication deemed necessary for the care of the participant is permitted in this study, except as specifically prohibited below. Concomitant administration of study treatments could result in DDIs that could potentially lead to reduced activity or enhanced toxicity of the concomitant medications and/or gemcitabine and/or nab-paclitaxel. Please note that all lists in Appendix 3 are not comprehensive. Please refer to regular update online sources and the label of the concomitant drug to decide whether a drug is permitted (with caution) or prohibited based on Section 6.2.2 (prohibited Medications). In case of doubt, please contact the medical monitor with any questions.

16.3.1 Permitted medication to be used with caution

The list of CYP450 substrates and list of CYP450 inhibitors / inducers was compiled from the University of Washington's Drug Interaction Database (updated January 2020) (https://www.druginteractionsolutions.org/). This list is only meant to be used as a guidance.

Table 16-7 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 University of Washington's Drug Interaction Database (updated January 2020)

16.4 Appendix 4: Statistical considerations – Algorithmic based approach for Safety Run-in part

Dose evaluation for NIS793 with spartalizumab and gemcitabine/nab-paclitaxel will follow the algorithm specified in Section 6.5.

In particular, Table 16-8 below specifies the probability of potential confirmation of dose to be tested in **Randomized part**, or switching to a different dose and regimen (if not tested yet), or dropping the study treatment, based on observation of number of DLTs out of six evaluable participants for different true DLT rates.

Table 16-8 Dose evaluation scenarios (NIS793 with spartalizumab and gemcitabine/nab-paclitaxel)

	Probability of observing 0,1 or ≥ 2 DLTs out of 6 participants:	
True probability of DLT	**0 or 1 ***	**≥2****
5%	0.97	0.03
15%	0.78	0.22
25%	0.53	0.47
35%	0.32	0.68
45%	0.17	0.83

*declaration of dose to be tested in **Randomized part** allowed

**dose and regimen not considered safe. Either switch to a different dose and regimen (if not tested yet) or drop the study treatment

16.5 Appendix 5: Bayesian model set-up and prior specifications

16.5.1 Statistical model

For each comparison, the underlying PFS time (in years) will be modeled using a two-piece hazard model. This model allows the specification of different hazard rates before/after the possible delayed effect for NIS793 with spartalizumab and gemcitabine/nab-paclitaxel (**Arm 1**) and for NIS793 with gemcitabine/nab-paclitaxel (**Arm 2**) and constant hazard rate for gemcitabine/nab-paclitaxel (**Arm 3**). Models, below, present the first comparison (**Arm 1** vs **Arm 3**) and the same assumptions apply to the second comparison (**Arm 2** vs **Arm 3**). The hazard function for each arm is given by

$$\lambda_t(t) = \lambda_1 + (\lambda_2 - \lambda_1)\left(\tfrac{1}{2} + \tfrac{1}{2}\tanh\big(s(t-\nu)\big)\right) \text{ and } \begin{cases}\lambda_1 = \mu * \eta \\ \lambda_2 = \mu/\eta\end{cases}$$

$$\lambda_c(t) = -\frac{\log\big(\mathrm{PFS(t)}\big)}{\mathrm{t}},$$

where λ_t and λ_c are the hazard rates for **Arms 1** and **3**, respectively. Parameters λ_1 and λ_2 are the respective hazard rates before/after the delayed effect for **Arm 1**, μ is a type of average hazard and η is the divergence from this average in each period. The study year is depicted by t, $s = 15$ is a fixed slope parameter that dictates the speed with which the hazard changes from period 1 to period 2 and ν is the risk changing timepoint (i.e., the time to the delayed effect). The corresponding HR between **Arm 1** and **Arm 3** after the delayed effect is λ_2/λ_c.

In a clinical trial, the time to progression may lie between the assessment at which the event is observed and day of the previous assessment+1 when participants have an event of progression. It is assumed the time to the event has a uniform distribution within this period.

16.5.2 Prior specifications

Prior for the risk change-point

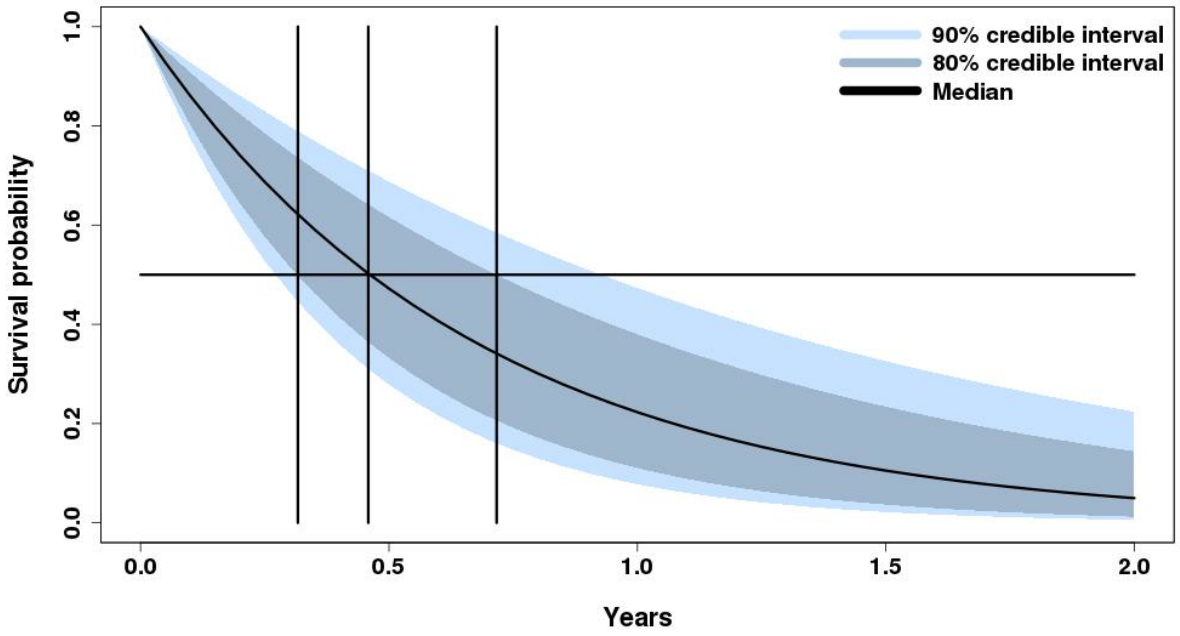
A Gamma prior is used for the time of the risk change-point ν. For **Arms 1** and **2** the prior is selected such that the mode is 0.25 years (i.e. three months) and the variance is 0.015. The resulting priors for ν is Gamma(6, 20).

Prior for Arm 3 PFS

For **Arm 3**, a two component mixture of gamma distributions is used for the prior for λ_c. These components correspond to a median PFS of 0.46 years (i.e. 5.5 months) as reported in the Von Hoff trial and an 80% credible interval of (0.32, 0.72) years (3.8, 8.6 months) (Figure 16-1).

The resulting mixture Gamma distribution is: 0.2*Gamma(2.0, 1.1) + 0.8*Gamma(15.5, 10.0) with median PFS of 0.46 years.

Figure 16-1 Prior distribution for Arm 3 PFS



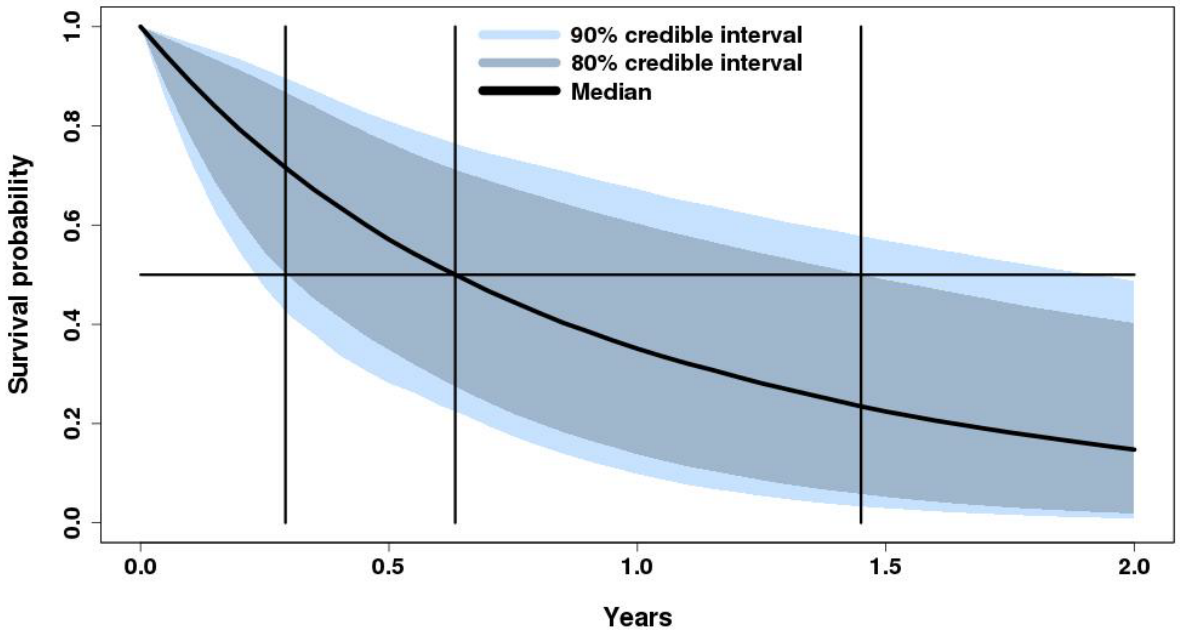
Prior for Arms 1 and 2

The same Gamma priors will be assumed for both **Arms 1** and **2** for the hazard before and after the delayed effect. Gamma priors for μ and η are selected such that the resulted median PFS is at least 2 months higher than the median PFS of **Arm 3** (5.5 months) with a wide credible interval. The resulting priors for μ and η are Gamma(4.6, 4.2) and Gamma(5, 4), respectively.

Full prior

Combining the priors for ν, μ, and η gives the complete specification of the prior of PFS for **Arms 1** and **2** (Figure 16-2). This is a weakly informative prior with median PFS of 0.63 years (i.e. 7.6 months) and a wide 80% credible interval of (0.29, 1.45) years (3.5, 17.4 months).

Figure 16-2 Full prior distribution for Arms 1 and 2 PFS



Operating characteristics

The operating characteristics for the Bayesian analysis described in Section 12.4.2.2 are obtained by performing extensive simulations.

16.5.2.1 Generating hypothetical datasets

Let n_i denote the sample size for each treatment group, and a_j denote the accrual rate in the jth accrual month.

For each treatment group different possible values for the underlying median PFS are specified. For each scenario with one of the specified value for the underlying median PFS, the hypothetical PFS dataset is generated by the following steps:

1. Set accrual waiting time to 0 for the first participant. Generate accrual waiting times for the remaining participants based on equidistance enrollment within each month with the accrual rate being $a_j = 10$ participants/month.
2. Generate a random sample of n_i PFS times in unit of year following the two-piece hazard model with the timepoint of risk change being at 0.25 years.
3. Take a sample of $n_i \times r_e$ participants from the n_i participants without replacement, where r_e is the early dropout rate before the first assessment and is pre-specified as 6.25% in this study. Set the corresponding censoring time as 1 day.

4. Generate a random sample of n_i-$n_i * r_e$ censoring times, based on the assumption of an exponential distribution corresponding to a dropout risk of $r_d = 0.1$ per participant year. Where censoring time is earlier than event time, the participant follow up time is set to the censoring time and the participant is treated as censored in the subsequent analysis.
5. For each participant an assessment schedule is generated, based on tumor assessments occurring every 8 weeks during the first year and every 12 weeks thereafter. A +/- 1 week window is assumed for each assessment, with the timing of the assessment distributed uniformly within this window. For each participant with an event it is assumed the event is observed at the next assessment on or after the day of the event. For censored participants, the day of censoring is the last assessment on or before the day of censoring.
6. Calculate accrual calendar time (i.e., the cumulative sum of the accrual waiting times before the participant enrolled) and scheduled PFS calendar time (i.e., the sum of accrual calendar time and the event/censoring occurred time time). Rank the non-censored scheduled PFS calendar time from the shortest to the longest. Since the primary analysis will be performed after 60 events are observed, the 60th non-censored scheduled PFS calendar time will be considered as the day of analysis.
7. For participants with progression events after the day of analysis, and hence censored in that analysis, the censoring time is set to be the day of last assessment on or before the day of analysis cut-off.

The steps 1-7 above are repeated to generate a total of 1000 hypothetical datasets for each scenario.

16.5.2.2 Posterior analysis

Given the prior distributions and parameter values specified above, the corresponding posterior distributions for each of the 1000 hypothetical datasets are obtained by performing extensive MCMC simulations using Stan with 5000 iterations plus a burn-in length of 3000 for each of four chains. For each pair of posterior values of λ_2 and λ_c the HR after the timepoint of risk change HR2 is calculated as λ_2/λ_c. The calculated HR from the iterations form the posterior distribution for the primary endpoint. The mean, median, standard deviation, and 90%-quantile will be calculated from this posterior distribution. The operating characteristics in terms of probability of success among 1000 hypothetical datasets for the above mentioned Bayesian study design under different true median PFS for each arm are summarized in the following table.

Table 16-9 Probabilities to declare a success under various scenarios, assuming a 3-month delayed effect

Scenarios Median PFS in months Arm 1 vs Arm 3 (Hazard ratio)	Sample size and analysis timing			
	N=100, when 60 events were observed	N=110, when 70 events were observed	N=110, when 75 events were observed	N=120, when 80 events were observed
5.5 vs 5.5 (HR2=1)	0.151	0.117	0.115	0.123
5.0 vs 5.0 (HR2=1)	0.124	0.138	0.124	0.115
6.0 vs 6.0 (HR2=1)	0.137	0.155	0.147	0.131
8.0 vs 6.0 (HR2=0.600)	0.697	0.735	0.751	0.762
7.5 vs 5.5 (HR2=0.557)	0.735	0.801	0.825	0.840
6.6 vs 5.0 (HR2=0.557)	0.709	0.774	0.808	0.821
9.0 vs 6.0 (HR2=0.500)	0.864	0.906	0.920	0.921
8.5 vs 5.5 (HR2=0.456)	0.914	0.919	0.938	0.950

HR2: Hazard ratio after the risk change in the two-piece hazard model.

Note: The success criteria are defined as at least 50% confidence level that HR2≤ 0.7 and at least 90% confidence level that HR2<1.

The sample size of 100 participants with the analysis timing of 60 events is selected. It is the minimum sample size and minimum number of events that ensures approximately 70% probability to declare success if the underlying HR2<0.6, while controlling the probability to declare success at approximately 15% if the underlying HR2=1.

Additional sensitivity analyses for 100 participants and 60 events, while varying the underlying assumption of delayed effect in the NIS793 based arm, are presented in Table 16-10 and Table 16-11. The results imply that the Bayesian model is robust.

Table 16-10 Operating characteristics for scenarios with 100 participants, 60 events, and a 2-month delayed effect

Scenarios Median PFS in months Arm 1 vs Arm 3 (Hazard ratio)	Probability of Success	Median follow-up period since FPFV (months)†
5.5 vs 5.5 (HR2=1)	0.151	14.1
6.0 vs 6.0 (HR2=1)	0.137	14.8
8.0 vs 6.0 (HR2=0.666)	0.607	16.1
7.5 vs 5.5 (HR2=0.636)	0.650	15.5
8.5 vs 5.5 (HR2=0.538)	0.821	14.4
8.0 vs 5.0 (HR2=0.500)	0.866	15.2

HR2: Hazard ratio after the risk change in the two-piece hazard model.
† FPFV of the **Randomized part**.

Table 16-11 Operating characteristics for scenarios with 100 participants, 60 events, and no delayed effect

Scenarios Median PFS in months Arm 1 vs Arm 3 (Hazard ratio)	Probability of Success	Median follow-up period since FPFV (months)†
5.5 vs 5.5 (HR2=1)	0.151	14.1
6.0 vs 6.0 (HR2=1)	0.137	14.8
8.0 vs 6.0 (HR2=0.750)	0.430	16.1
7.5 vs 5.5 (HR2=0.733)	0.448	15.2
8.5 vs 5.5 (HR2=0.647)	0.614	16.0
8.0 vs 5.0 (HR2=0.625)	0.646	15.1

HR2: Hazard ratio after the risk change in the two-piece hazard model.
† FPFV of the **Randomized part**.