NOVARTIS

Clinical Development

NIS793

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)

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
30-Sep-2020	Prior to DB lock	Creation of initial version	N/A - First version	NA
26-Oct-2023	Prior to DB lock	Update to keep consistent with protocol amendment 4 and creation of abbreviated CSR	Amendment 1.0	Section 1: Updated wording to keep consistency with the PA04  Section 2.1: Added wording for the purpose of abbreviated CSR. Section 2.3.1: Added “the number (%) of participants treated/untreated” Section 2.3.2: Added BMI for summary and listing Section 2.5.2: The primary analysis criteria of “at least 60 participants” has been updated to “approximately 60 participants” Section 2.5.2.6: The supplementary analyses has been removed due to abbreviated CSR Section 2.5.2.7: The supporting analyses has been removed due to abbreviated CSR Section 2.8.1: The list of AE and SAE summaries has been updated due to abbreviated CSR Section 2.8.1.1: The list of AESIs has been updated

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				Section 2.10.3: Section added for demonstrating analysis for transient and persistent ADA responses. Section 2.12: The analysis for correlation between PD-L1 and CD8 and anti-tumor activity will be explored. The table numbers have been updated inside the text. The table 2-6 has been updated. [redacted] 2.14: The section has been updated as per CSP amendment version 4

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List of abbreviations

ADA	Anti-drug Antibody
AE	Adverse event
AESI	Adverse Event of Special Interest
ALP	Alanine Phosphatase
ALT	Alkaline Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BOR	Best Overall Response
BSA	Body Surface Area
CD8	Cluster of Differentiation 8
C-FAS	Complete Full Analysis Set
CI	Confidence Interval
CR	Complete Response
CSP	Clinical Study Protocol
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DDS	Dose Determining Set
DI	Dose Intensity
DMC	Data Monitoring Committee
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
FAR	First Available Report
FAS	Full Analysis Set
HR	Hazard Ratio
IB	Investigator's Brochure
IG	Immunogenicity
[redacted]	[redacted]
K-M	Kaplan-Meier
LLOQ	Lower Limit of Quantitation
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mPDAC	metastatic Pancreatic Ductal Adenocarcinoma
NMQ	Novartis MedDRA Queries
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamics
PDI	Planned Dose Intensity
PD-L1	Programmed Death-Ligand 1
PDS	Programming Datasets Specifications
PFS	Progression-Free Survival

PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SD	Standard Deviation
SMQ	Standardized MedDRA Queries
SOC	Standard of Care
SOC	System Organ Class
TBL	Total Bilirubin Level
TFLs	Tables, Figures, Listings
TGF-β	Transforming Growth Factor-Beta
TTP	Time-to-Progression
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study CNIS793B12201 that will be presented in the Clinical Study Report (CSR).

The output shells (in-text and post-text) accompanying this document can be found in the Tables, Figures and Listings (TFL) shells document. The specifications for derived variables and datasets can be found in the Programming Datasets Specifications (PDS) document. The content of this SAP is based on protocol amendment version 04 dated 18-April-2022. All decisions regarding analyses, as defined in the SAP document, have been made prior to database lock of the study data.

All changes to the planned analysis described in this document required before or after database lock will be made through an amendment or addendum, respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in the TFL shells document without the need to amend.

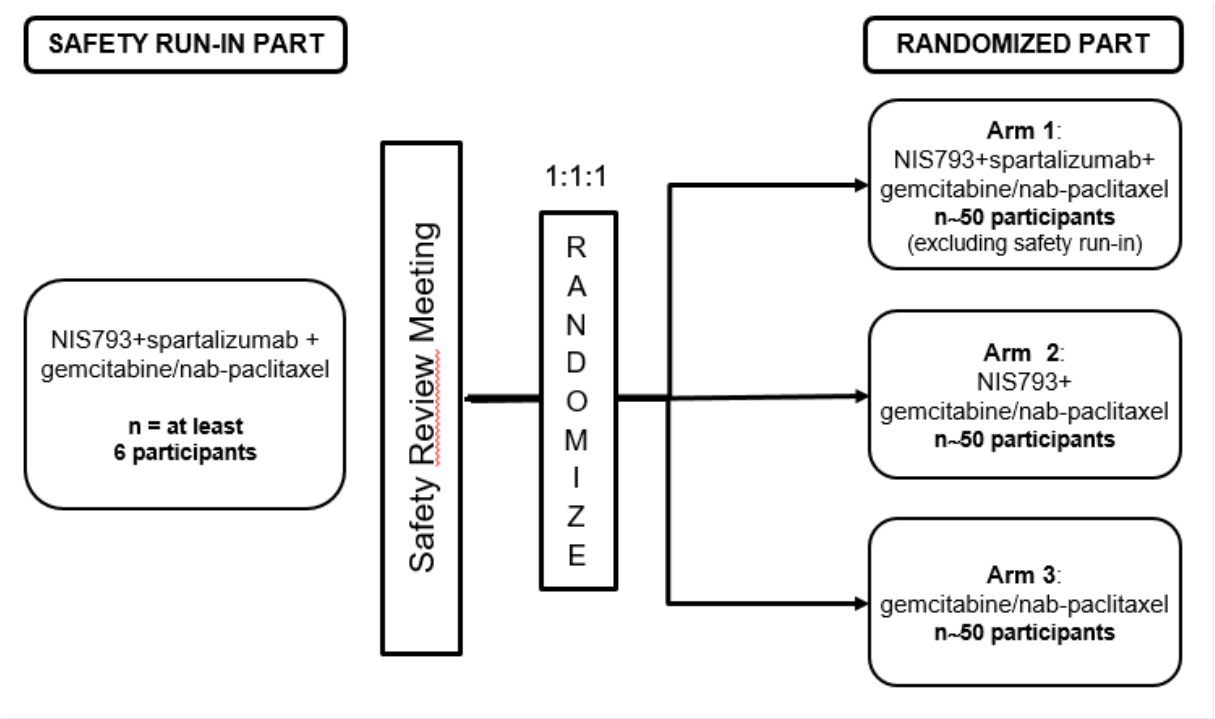
The SAP, TFL shells, and PDS documents may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., IB updates, abstracts, posters, presentations, manuscripts, and management updates. Data used for these analyses will have a status aligned to the database lock guidance.

1.1 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 metastatic pancreatic ductal adenocarcinoma (mPDAC).

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

Figure 1-1 Study design



Safety Run-in part

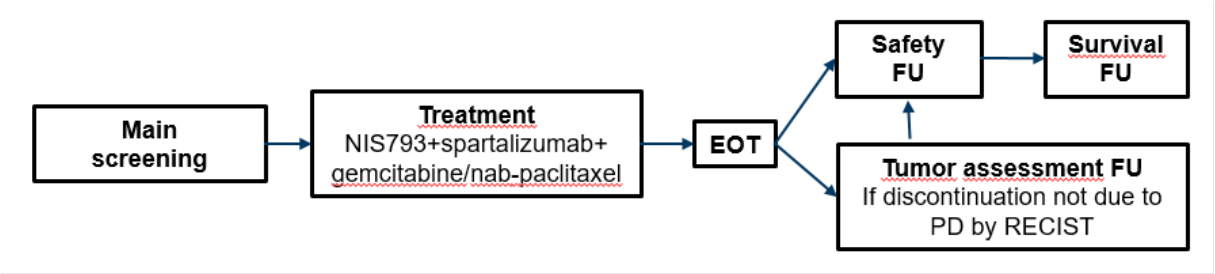
The study will start with a **Safety Run-in part** to assess the safety and tolerability of NIS793 in combination with spartalizumab and standard of care (SOC) gemcitabine/nab-paclitaxel. Doses defined for each study treatment, as part of this quadruplet will be administered in the **Randomized part** in the quadruplet/triplet/doublet-based treatment arms. 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 and 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 CSP Section 6.5.2.1, will take place when six enrolled participants have completed 4 weeks of treatment or discontinued earlier due to dose limiting toxicity (DLT). The dose decision will be guided by an algorithm specified in CSP Section 6.5.2. If a decision to modify the dosing regimen is made at this time, an additional safety review of a new dosing regimen will take place after six additional participants have been enrolled and completed 4 weeks of treatment or have discontinued earlier due to DLT.

Refer to Figure 1-2 for an overview of the **Safety Run-in part** study flow.

Figure 1-2 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

Randomization will not be stratified.

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**.

An independent Data Monitoring Committee (DMC) will monitor safety and efficacy data during the trial. A separate DMC SAP will specify the analyses to be performed for the DMC reviews. No formal interim efficacy analysis is planned in this study.

Progression free survival (PFS) as per local Investigator's review of tumor response based on RECIST 1.1 criteria is the primary endpoint in the **Randomized part** of the study.

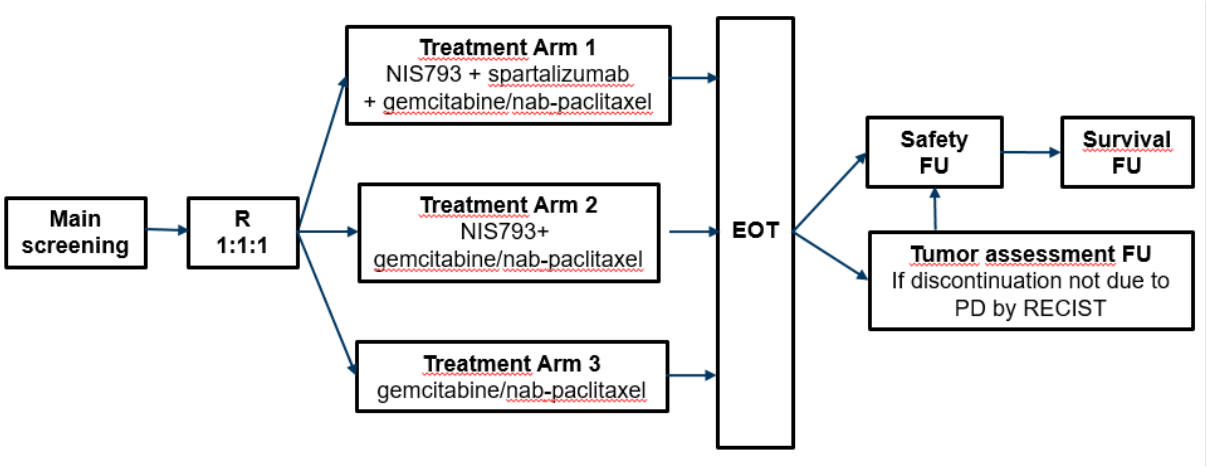
The primary efficacy and primary safety analyses, as well as the overall survival analysis may be performed once both the following criteria are met:

- At least 60 participants have experienced a PFS event (documented progression as per RECIST 1.1 or death due to any cause) in **Arms 1** and **3** and
- at least 60 participants have experienced a PFS event (documented progression as per RECIST 1.1 or death due to any cause) in **Arms 2** and **3**.

The final analysis will be performed after the completion of the study.

Refer to Figure 1-3 for an overview of the study flow in **Randomized part**.

Figure 1-3 Study flow in Randomized part



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

1.2 Study objectives and endpoints

Objectives and related endpoints are described in Table 1-1 below.

Table 1-1 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

Objective(s)	Endpoint(s)
• 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

[redacted]

2 Statistical methods

2.1 Data analysis general information

Novartis will perform the analysis specified in this SAP for the CSR. SAS version 9.4 or later and R version 3.4.3 or later will be used to perform all data analyses and to generate tables, figures, and listings.

At the time of the primary analysis, clinical data obtained from the treatment arms of the randomized part suggested that there was no evidence of clinical benefit when combining NIS793 with spartalizumab and gemcitabine/nab-paclitaxel and, NIS793 with gemcitabine/nab-paclitaxel compared to gemcitabine/nab-paclitaxel alone. In light of these data, the

administration of NIS793 was stopped. Therefore, the reported CSR will be abbreviated. The abbreviated CSR will include at least one output for each primary and secondary endpoint.

The primary efficacy and primary safety analyses, as well as the overall survival analysis may be presented in a First Available Report (FAR) document, if deemed necessary, when at least 60 participants have experienced a PFS event (documented progression as per RECIST 1.1 or death due to any cause) in **Arms 1** and **3** and at least 60 participants have experienced a PFS event in **Arms 2** and **3**. The FAR will include outputs planned within the TFL shells document related to the previously mentioned analyses.

All events with a start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having a documented end date. The cut-off date for the primary analysis will be the date the last of the required events is documented.

All primary and secondary analyses will be reported in the full CSR at the end of the 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 ongoing participants 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 have been reached;
- The study is terminated early. In such case, the end of study will be when all participants have completed the treatment period and the safety follow-up period.

General analysis conventions

Pooling of centers: Unless specified, data from all study centers will be pooled for the analysis. Due to the expected small number of participants enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables overall participants in the **Safety Run-in part** and by treatment arm for participants in the **Randomized part**; a missing category will be included as applicable. Percentages will be calculated using the number of participants in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e., mean, standard deviation, median, minimum, and maximum) overall participants in the **Safety Run-in part** and by treatment arm for participants in the **Randomized part**.

2.1.1 General definitions

Definitions below apply for each part of the study. A participant included in the **Safety Run-in part** will not enter in the **Randomized part**.

2.1.1.1 Investigational drug and investigational treatment

Investigational drug will refer to NIS793 and spartalizumab. Control drug will refer to gemcitabine and nab-paclitaxel.

The terms investigational and control drug may also be referred to as study drug.

Safety Run-in part

Investigational treatment will refer to:

- **Arm 1:** NIS793 + spartalizumab + gemcitabine + nab-paclitaxel.

Randomized part

Investigational treatment will refer to:

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

Control treatment will refer to:

- **Arm 3:** gemcitabine + nab-paclitaxel.

The terms investigational and control treatment may also be referred to as study treatment.

2.1.1.2 Date of first administration of study drug

The date of first administration of study drug is defined as the first date when a non-zero dose of study drug is administered and recorded on the treatment page eCRF. The date of first administration of study drug will also be referred as start of investigational drug.

2.1.1.3 Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug is administered and recorded on the treatment page eCRF. The date of last administration of study drug will also be referred as end of investigational drug.

2.1.1.4 Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a non-zero dose of any component of study treatment was administered as per treatment page eCRF. The date of first administration of study treatment will also be referred as ***start of study treatment***.

For example, if the first dose of NIS793 with spartalizumab and gemcitabine/nab-paclitaxel is taken on 13Oct2020, 25Dec2020, 13Oct2020, and 13Sep2020 respectively, then the date of first administration of study treatment is on 13Sep2020

2.1.1.5 Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a non-zero dose of any component of study treatment was administered as per treatment page eCRF. The date of last administration of study treatment will also be referred as ***end of study treatment***.

For example, if the last dose of NIS793 with spartalizumab and gemcitabine/nab-paclitaxel is taken on 13Oct2020, 25Dec2020, 13Oct2020, and 13Sep2020 respectively, then the date of last administration of study treatment is on 25Dec2020.

2.1.1.6 Study day

The study day describes the day of the event or assessment date, relative to the reference start date. The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

In the **Safety Run-in part**, the reference start date for all assessments is the start of study treatment. In the **Randomized part**, the reference start date for safety assessments (e.g., adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose adjustments, etc.) is the start of study treatment. The reference start date for all other non-safety assessments (i.e., tumor assessment, survival time, disease progression, tumor response, and ECOG performance status) is the date of randomization.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

2.1.1.7 Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

2.1.1.8 Baseline

In the **Safety Run-in part,** the last available assessment on or before the date of start of study treatment is defined as “baseline” assessment for both safety and efficacy.

In the **Randomized part**, for efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as “baseline” value or “baseline” assessment.

In the context of baseline definition, the efficacy evaluations also include [redacted] ECOG performance status. For safety evaluations, the last available assessment on or before the date of start of study treatment is taken as ‘‘baseline” assessment. For safety parameters (e.g., ECGs or vital signs), where study requires multiple replicates per timepoint, the average of these measurements would be calculated for baseline (if not already available in the database).

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If multiple values are from the same laboratory or collected for ECGs or vital signs, then the last value should be considered as baseline.

If participants have no value as defined above, the baseline result will be missing.

2.1.1.9 On-treatment assessment/event and observation periods

For adverse event reporting, the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of participant's informed consent to the day before first administration of study treatment;
2. ***on-treatment period***: from date of first administration of study treatment up to 30 days after date of last actual administration of any study treatment (including start and stop date);
3. ***post-treatment period***: starting at day 30+1 after last administration of study treatment.

Safety summaries (tables, figures) and summaries of on-treatment deaths include only data from the on-treatment period with the exception of baseline data, which will also be summarized where appropriate (e.g., change from baseline summaries). In addition, all deaths which occurred during the study (i.e., during the on-treatment and post-treatment periods) will be summarized.

An ***on-treatment adverse event*** (or ***treatment-emergent*** AEs) is defined as any adverse event reported in the on-treatment period.

An ***on-treatment assessment*** is defined as any assessment performed after the date of first administration of any study drug i.e., assessments performed in the following time interval (including the lower and upper limits): from date of first administration of any study drug +1 up to 30 days after the date of last administration of study treatment.

Data listings will include all assessments/events, flagging those, which are not on-treatment assessment/event (i.e., pre-treatment and post-treatment period).

2.1.1.10 Window for multiple assessments

In order to summarize ECOG performance status collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered. If 2 assessments within a time window are equidistant from the target date, then the earlier of the 2 assessments will be used. If multiple assessments on the same date then the average will be used.

Table 2-1 Time windows for ECOG performance status assessments

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (screening)	Before study Day 1	< Day 1
Cycle 1 Day 1	Study Day 1*	Study Day 1
Cycle 1 Day 8	Study Day 8	Study Day 8-11
Cycle 1 Day 15	Study Day 15	Study Day 15-18
Cycle 2 Day 1	Study Day 29	Study Day 29-32
Cycle 2 Day 8	Study Day 36	Study Day 36-39
Cycle 2 Day 15	Study Day 43	Study Day 43-46
Every cycle thereafter		
Cycle k Day 1	Study Day d = (k - 1) * 28 + 1	Study Day d-(d+3)

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Cycle k Day 8 Cycle k Day 15	Study Day d = (k - 1) * 28 + 8 Study Day d = (k - 1) * 28 + 15	Note: EOT data will be included if obtained within 14 days of last dose of study treatment OR within 14 days of the decision of discontinuation of study treatment
*Study Day 1 = First study treatment		

2.1.1.11 Last contact date

The last contact date will be derived for participants not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-2 Last contact date data sources

Source data	Conditions
Date of Randomization	No condition
Last date participant was known to be alive from Survival Follow-up page	Participant status is reported to be alive, lost to follow-up or unknown
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term
Start/End* dates from treatment page	Non-missing dose. Doses of 0 are allowed
End of treatment date from end of treatment page	No condition
Imaging assessment date	Imaging marked as done
Laboratory/PK collection dates	Sample collection marked as 'done'
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date, unless the participant was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g., the analysis cut-off date programmatically imputed to replace the missing end date of a treatment page) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring, if coming from 'Survival information' eCRF.

The last contact date will be used for censoring of participants in the analysis of time-to-event endpoints.

2.2 Analysis sets

2.2.1 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 study drug of the study treatment (including incomplete infusion)).

2.2.2 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 study 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 study drug of the study treatment (including incomplete infusion)). Participants in the **Randomized part** will be analyzed according to the 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.

2.2.3 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.

2.2.4 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.

2.2.5 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 Safety set 2 with a non-missing baseline anti-drug anti-body (ADA) sample or at least one non-missing post-baseline ADA sample;
- The IG incidence set includes all participants in the IG prevalence set with a non-missing baseline ADA sample and at least one non-missing post-baseline ADA sample.

Participant Classification

Participants may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific participant classification rules defined in Table 2-3. Participants that were randomized by error and did not receive any study drug will not be included in any analysis set.

Table 2-3 Participant classification based on protocol deviations and non-protocol deviation criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written informed consent	Not applicable
C-FAS	No written informed consent	**Safety Run-in part**: No dose of any component of study treatment **Randomized part**: Not applicable
Safety Set 1 and 2	No written informed consent	No dose of any component of study treatment
DDS	No written informed consent	See definition of DDS
NIS-PAS, PDR-PAS, GEM-PAS, dFdU-PAS, and PAC-PAS	No written informed consent	See definitions of NIS-PAS, PDR-PAS, GEM-PAS, dFdU-PAS, and PAC-PAS
Immunogenicity prevalence set	No written informed consent	See definition of IG prevalence set
Immunogenicity incidence set	No written informed consent	See definition of IG incidence set

Withdrawal of inform consent

Any data collected in the clinical database after a participant withdraws informed consent from all further participation in the trial will not be included in the analysis. The date on which a participant withdraws full consent is recorded in the eCRF.

Additional data, for which there is a separate informed consent, collected in the clinical database without having obtained that consent will not be included in the analysis. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.2.6 Subgroup of interest

Not applicable.

2.3 Participant disposition, demographics and other baseline characteristics

Summaries and listings described in this section will be based on the C-FAS, separately for participants in the **Safety Run-in part** and in the **Randomized part**. Summaries will be reported overall participants in the **Safety Run-in part** and by treatment arm for participants in the **Randomized part**.

No inferential statistics will be provided.

2.3.1 Participant disposition

The number (%) of treated (randomized) participants will be presented for the **Safety Run-in part** (**Randomized part**). The number (%) of participants treated/untreated, no. of participants (%) who are still on treatment at the time of cut-off, the no. of participants (%) who discontinued the study phases, and the primary reason for discontinuation, number (%) of patients who discontinued from post treatment follow-up and reasons for discontinuation will be presented. Screen failure and not-treated (not-randomized) participants and the reasons for screening failure and not starting the study treatment will be reported in a listing.

2.3.2 Demographic data

Demographic data including age, sex, race, ethnicity, height, baseline weight, BMI, and ECOG performance status will be listed and summarized. In addition, the following age categories will be summarized: 18- <65 years, 65- < 85 years, and ≥ 85 years.

2.3.3 Medical history

Medical history and current medical conditions, including cancer-related conditions and symptoms entered on eCRF will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT), using the latest Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of reporting. The MedDRA version will be specified in the CSR as a footnote in the applicable tables/listings.

2.3.4 Diagnosis and extent of cancer

The summary and listing of diagnosis and extent of cancer (disease history) will include primary site of cancer, details of tumor histology/cytology, histologic grade, stage at initial diagnosis with time since initial diagnosis, stage at time of study entry, number and type of metastatic sites. Metastatic sites will be based on diagnosis page.

Imputation rules for partially missing dates are provided in Section 5.1.

2.3.5 Protocol deviations

The number (%) of participants in the C-FAS with any protocol deviation, including Covid-19 related protocol deviations, will be tabulated by deviation category. All protocol deviations will be listed.

2.3.6 Analysis sets

The number (%) of participants in each analysis set (defined in Section 2.2) will be summarized and listed.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Cumulative dose, dose intensity (DI), and relative dose intensity (RDI) will be summarized separately for each component of study treatment, overall participants in the **Safety Run-in part** and additionally, by treatment arm for participants in the **Randomized part**. Duration of exposure will be calculated for each component of study treatment. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of participants in each interval. The number (%) of participants who have dose reductions or interruptions, and the reasons, will be summarized by treatment .

Participant level listings of all doses administered on treatment along with dose change reasons will be produced.

Safety sets 1 and 2 will be used for all summaries and listings of study treatment.

2.4.1.1 Duration of exposure to study treatment

The duration of exposure to study treatment is defined considering the duration of exposure of each study drug as:

Duration of exposure to study treatment (days) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1.

Summary of duration of exposure of study treatment will include categorical summaries (<6 weeks, 6-<12 weeks, 12-<18 weeks, 18-<24 weeks, 24-<48 weeks, 48-<72 weeks, +72 weeks) and continuous summaries (i.e., mean, standard deviation etc) using weeks as time units.

2.4.1.2 Duration of exposure to investigational/control drug

Duration of exposure (days) = (last date of exposure to study drug – date of first administration of study drug + 1).

Duration of exposure to NIS793 (days) = (last date of exposure to NIS793 – date of first administration of NIS793 + 13).

Duration of exposure to spartalizumab (days) = (last date of exposure to spartalizumab – date of first administration of spartalizumab + 27).

Duration of exposure to gemcitabine (days) = (last date of exposure to gemcitabine – date of first administration of gemcitabine + 6 or 13).

Duration of exposure to nab-paclitaxel (days) = (last date of exposure to nab-paclitaxel) – (date of first administration of nab-paclitaxel + 6 or 13).

Table 2-4 Definition of last date of exposure to study drug

Scenario	Definition of last date of exposure to study drug	Example
NIS793: Study drug with a Q2W regimen	The planned end date of the last cycle in which the last non-zero dose of the study drug was last administered.	In a 28 day cycle with a Q2W regimen, the last date of exposure is the date of first infusion in the last cycle + 13 days.
Spartalizumab: Study drug with a Q4W regimen	The planned end date of the last cycle in which the last non-zero dose of the study drug was last administered.	In a 28 day cycle with a Q4W regimen, the last date of exposure is the date of first infusion in the last cycle + 27 days.
Gemcitabine / Nab-paclitaxel: Study drug with a Day 1, 8, and 15 regimen	The planned end date of the last cycle in which the last non-zero dose of the study drug was last administered.	In a 28 day cycle with a Day 1, 8, and 15 regimen, the last date of exposure is the date of infusion in the last cycle + • 6 days if infusion is at Day 1 or 8; • 13 days if infusion is at Day 15.
Note: If the participant died or was lost to follow-up before the derived last date, the last date of exposure to study drug is the date of death or the date of last contact, respectively. If the derived last date of exposure goes beyond the data cut-off date, it should be truncated to the date of data cut-off.		

2.4.1.3 Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment components, respectively.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the participant is on the study treatment as documented in the treatment page eCRF.

For participants who did not take any drug, the actual cumulative dose is by definition equal to zero for that drug.

For intermittent dosing, the actual cumulative dose should be defined based on the days when the participant is assumed to have taken a non-zero dose during dosing periods.

NIS793 / Spartalizumab

For NIS793 and spartalizumab the planned cumulative dose is the planned starting dose summed over the number of expected infusions during the treatment period (e.g, a participant treated for 60 days is expected to have two infusions).

Gemcitabine / Nab-paclitaxel

For gemcitabine and nab-paclitaxel the dose in mg/m^2 at cycle N is equal to the dose administered (mg) at cycle N divided by the body surface area (BSA) at the beginning of cycle N using the weight measured before the infusion. For gemcitabine (nab-paclitaxel), the dose in mg/m^2 at cycle N will be the sum of the 3 doses planned to be received at Days 1, 8, and 15 of cycle N. The dose in mg/m^2 will be calculated using the BSA at the beginning of the cycle (i.e., Day 1).

BSA (m^2) at cycle N = $\sqrt{Wt\ (kg) * Ht(cm)/3600}$ (Mosteller formula),

where Wt=weight at the beginning of cycle N (usually this is the weight taken before the infusion of cycle N or last weight available if this is missing) and Ht=Height at the beginning of the study.

2.4.1.4 Dose intensity and relative dose intensity

DI is defined for participants with non-zero duration of exposure. For participants who did not take the drug, the DI is by definition equal to zero.

DI (dosing unit/unit of time) = cumulative dose (dosing unit) / duration of exposure (unit of time)

Planned dose intensity (PDI) is the assigned dose by unit of time planned to be given to participants as per protocol in the same dose unit and unit of time as that of the dose intensity.

DI, PDI, and RDI are defined as:

For NIS793 and spartalizumab:

- DI (mg/cycle) = [cumulative dose (mg) / duration of exposure (days)]*28

- PDI is the planned dose as per protocol in mg (i.e., for NIS793 2100 mg Q2W and for spartalizumab 400 mg Q4W)
- RDI (%) = DI (mg/cycle) / PDI (mg/cycle) * 100

For gemcitabine and nab-paclitaxel

- DI (mg/m^2/cycle) = [cumulative dose (mg/m^2) / duration of exposure (days)]*28
- PDI is the planned dose as per protocol in mg/m^2 (i.e., for gemcitabine 1000 mg/m^2 and for nab-paclitaxel 125 mg/m^2, Days 1, 8, and 15)
- RDI (%) = DI (mg/m^2/cycle) / PDI (mg/m^2/cycle) * 100

The DI and the RDI will be summarized for each study drug component tested within the groups as defined for the cumulative dose above by descriptive statistics. RDI will be summarized in percentage. Summary of RDI includes categorical summaries. The RDI categories are < 50%, ≥ 50% - < 75%, ≥ 75% - < 90%, ≥ 90% - < 110%, and ≥ 110%.

2.4.2 Dose reductions, interruptions, or permanent discontinuations

The number of participants who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized overall participants in the **Safety Run-in part** and by treatment arm for participants in the **Randomized part**, for each of the study drug components. All dosing data will be listed.

'Dose interrupted' and 'Dose permanently discontinued' fields from the treatment page eCRF pages will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields 'Reason for dose change/dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

A dose change is either 'change in prescribed dose level' or 'dosing error' where actual dose administered/total daily dose is different from the prescribed dose.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption are entered on consecutive days with different reasons, they will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Dose reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Therefore, any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the eCRF. Number of reductions will be derived programmatically based on the change and the direction of the change.

NIS793 / Spartalizumab

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**.

Gemcitabine / nab-paclitaxel

Dose reductions are allowed for gemcitabine/nab-paclitaxel and should follow the dose reduction steps described in CSP 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 interruption: Actual dose administered equal to zero, between the first and last non-zero doses, following a non-zero actual dose administered. Number of dose interruptions and corresponding reason will be summarized.

2.4.3 Prior, concomitant and post therapies

Prior anti-neoplastic therapy

Prior anti-neoplastic therapies are not allowed.

Post treatment anti-neoplastic therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed by Anatomical Therapeutic Classification (ATC) and PT.

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a participant coinciding with the study treatment period. Concomitant therapy includes medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing dictionary that employs the WHO-ATC classification system and summarized by lowest ATC class and PT using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and PT. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

All concomitant medications will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing.

2.5 Analysis of the primary objectives

2.5.1 Safety objective

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 the

Randomized part and in future studies of NIS793 with spartalizumab and gemcitabine/nab-paclitaxel.

2.5.1.1 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.

In order to assess tolerability, dose interruptions, reductions, and RDI will be considered.

2.5.1.2 Statistical hypothesis, model, and method of analysis

DLT evaluation will be based on participants included in the DDS and will be guided by an algorithmic-based design. For a dose to be declared safe for the **Randomized part**, DLT rate should be below 33%, as described below.

A cohort of at least six participants will be treated in the higher dose regimen (NIS793 2100 mg Q2W, spartalizumab 400 mg Q4W, gemcitabine 1000 mg/m^2, and nab-paclitaxel 125 mg/m^2). 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. Refer to Section 2.2.3 for more details on evaluable participants.

Dose confirmation will occur if the following conditions are met:

- Six evaluable participants treated at this dose 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, PK, and laboratory 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 a lower dose regimen (NIS793 1400 mg Q2W, spartalizumab 400 mg Q4W, gemcitabine 1000 mg/m^2, and nab-paclitaxel 125 mg/m^2). The same criteria are applied for this new dose regimen. If dose confirmation cannot be declared on this lower dose, the **Randomized part** cannot start and the study will end.

Dose evaluation scenarios based on the algorithmic-based design are given in CSP Appendix 4.

DLTs

DLTs will be listed and their incidence will be summarized by PT and by SOC, PT, and worst grade based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, using the DDS.

Safety and Tolerability

Refer to Section 2.8 for details on safety analysis. For details on tolerability analysis, dose interruptions, reductions, and dose intensity refer to Section 2.4.

2.5.1.3 Handling of missing values/censoring/discontinuations

Participants in the **Safety Run-in part** who are ineligible for the DDS will be excluded from the primary analysis. However, their data will be used for all remaining analyses.

2.5.2 Efficacy objective

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,

in prolonging time to death or radiological progression in first line mPDAC. The primary analysis may be performed once both the following criteria are met:

- Approximately 60 participants have experienced a PFS event (documented progression as per RECIST 1.1 or death due to any cause) in **Arms 1** and **3** and
- Approximately 60 participants have experienced a PFS event (documented progression as per RECIST 1.1 or death due to any cause) in **Arms 2** and **3**.

2.5.2.1 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 two relative effects of the treatment strategies in the presence of a) a potentially new anti-cancer therapy that is not a part of the assigned treatment strategy or/and b) in the presence of treatment discontinuation (due to Covid-19 or any reason not related to new anti-cancer therapy).

The primary population is adult participants with mPDAC who have not received any systemic treatment for metastatic disease. Further details about the population are provided in CSP Section 5.

The primary variable of the study is PFS, defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. For the primary efficacy analysis, PFS will be based on local review of tumor assessments, using RECIST 1.1 criteria

[CSP Appendix 1]. The primary analysis will be based on the FAS and will include all data observed up-to the cut-off date. Discontinuation due to disease progression (collected on the 'End of treatment' and 'End of post-treatment follow up' disposition pages) without supporting objective evidence satisfying progression criteria per RECIST 1.1 will not be considered disease progression for PFS derivation. Clinical deterioration will not be considered as a qualifying event for progression for the primary analysis.

2.5.2.2 Statistical hypothesis, model, and method of analysis

The same Bayesian model will be used to estimate and provide inferential summaries for both PFS hazard ratios (HR) a) **Arm 1** versus **Arm 3** and b) **Arm 2** versus **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** versus **Arm 3**). The same assumptions apply to the second comparison (**Arm 2** versus **Arm 3**).

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

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

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.

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 CSP 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. PFS will be listed by treatment arm, including participants from **Arms 1** and **2** who continue treatment beyond RECIST 1.1 progression according to local investigator assessment based on protocol specified criteria.

[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.

2.5.2.3 Handling of 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** will be handled using the treatment policy strategy**:** 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** will be handled using the treatment policy strategy: 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** will be handled using the treatment policy strategy**:** Tumor assessment data collected after discontinuation of study treatment will be used to derive PFS.

2.5.2.4 Handling of missing values/censoring/discontinuations

In the primary analysis, if a participant has not progressed or died at the analysis cut-off date, PFS will be censored at the date of the last adequate tumor evaluation date before the cut-off date.

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 [CSP Appendix 1].

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of complete response (CR), partial response (PR), or stable disease (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.

2.5.2.5 Sensitivity analysis

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 (**Arm 1** versus **Arm 3** and **Arm 2** versus **Arm 3**) will be summarized by the overall HR with its one-sided 90% confidence interval (CI). Kaplan-Meier (K-M) estimates for PFS as well as medians along with their two-sided 95% CI will be presented for each treatment arm. The corresponding K-M curves will be presented.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary efficacy objectives

Randomized part

The secondary efficacy objectives are to:

- Assess the preliminary anti-tumor activity of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel;

- Assess the Overall Survival (OS) of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel.

2.7.1 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 two relative effects of the treatment strategies in the presence of a) a potentially new anti-cancer therapy that is not a part of the assigned treatment strategy or/and b) in the presence of treatment discontinuation (due to Covid-19 or any reason not related to new anti-cancer therapy).

The same population as for the primary estimand will be considered.

The secondary variables of the study are overall response rate (ORR), duration of response (DOR), time to progression (TTP), and OS.

2.7.2 Statistical hypothesis, model, and method of analysis

All secondary estimands will be analyzed based on the FAS.

Overall response rate

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 [CSP Appendix 1].

ORR and the corresponding 95% CI based on the exact binomial distribution (Clopper and Pearson 1934) will be presented. Overall response will be listed by treatment arm.

Duration of response

DOR only applies to participants whose BOR is CR or PR by Investigator assessment as per RECIST 1.1. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death. Participants continuing without progression or death will be censored at the date of their last adequate tumor assessment. Definition of last adequate tumor assessment is provided in CSP Appendix 1.

DOR will be analyzed for participants with confirmed BOR of CR or PR. If there are at least 8 participants per arm with a confirmed BOR of CR and PR the following analyses will be conducted:

- Unadjusted Cox model for the overall HR and the 95% CI;
- Median DOR, with corresponding 95% CI and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997);
- K-M estimates for DOR proportions at specific timepoints (3, 6, 12, and 18 months), along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002);
- Summary of number (%) of events and censored participants.

Time to progression

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 CSP Appendix 1.

The following analyses will be conducted:

- Unadjusted Cox model for the overall HR and the 95% CI;
- Median TTP, with corresponding 95% CI and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997);
- K-M estimates for TTP rate at specific timepoints (3, 6, 12, and 18 months), along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002);
- Summary of number (%) of events and censored participants.

Overall survival

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

The following analyses will be conducted:

- Unadjusted Cox model for the overall HR and the 95% CI;
- Median OS, with corresponding 95% CI and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997);
- K-M estimates for OS rate at specific timepoints (3, 6, 12, and 18 months), along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002);
- Summary of number (%) of deaths and censored participants.

The corresponding K-M curves will be presented.

2.7.3 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** will be handled using the treatment policy strategy**:** 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** will be handled using the treatment policy strategy: 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** will be handled using the treatment policy strategy**:** Tumor assessment data collected after discontinuation of study treatment will be used to derive the secondary variables.

2.7.4 Handling of missing values/censoring/discontinuations

For handling of missing values, censoring, and discontinuations refer to Section 2.5.2.4.

2.8 Safety analyses

All safety analyses will be based on the Safety sets 1 and 2. Summaries and listings described in this section will be presented, separately, overall participants in the **Safety Run-in part** and by treatment arm for participants in the **Randomized part**.

2.8.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on-treatment period. All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g., AE relationship to study drug, AE outcome etc. AEs will be collected for 30 days from last dose of gemcitabine/nab-paclitaxel, 90 days from last dose of NIS793, and 150 days from last dose of spartalizumab. AEs with start date outside of the on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of participants having at least one AE, having at least one AE in each primary SOC, and for each PT using MedDRA coding. A participant with multiple occurrences of an AE will be counted only once in the respective AE category. A participant with multiple CTCAE grades for the same PT will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary SOC will be presented alphabetically, and the PTs will be sorted within primary SOC in descending frequency. The sort order for the PT will be based on their frequency in the investigational arm.

The following AE summaries will be produced:

- Overview of adverse events (number and % of participants with any AE, any SAE, any fatal SAE, any dose change/interruptions, AE leading to discontinuation, requiring additional therapy) and death;
- AEs suspected to be study drug related by PT and severity;
- AEs suspected to be study drug related leading to discontinuation of study drug
- AEs leading to study drug discontinuation regardless of study drug relationship by PT and severity;

- AEs suspected to be study drug related by primary SOC, PT, and severity;
- AEs leading to study drug discontinuation regardless of study drug relationship by primary SOC, PT, and severity;
- AEs regardless of relationship to study drug by SOC, PT, and severity
- AEs regardless of relationship to study drug by SOC and severity
- AEs regardless of relationship to study drug by PT and severity

In addition, a summary of serious adverse events (SAEs) with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same PT).

The following SAE summaries will be produced:

- SAEs regardless of relationship to study drug by SOC, PT, and severity
- SAEs regardless of relationship to study drug by PT and severity

The following listings will be produced:

- All AEs.

2.8.1.1 Adverse events of special interest / grouping of AEs

An adverse event of special interest (AESI) is a grouping of AEs that are of scientific and medical concern specific to compound NIS793 and/or spartalizumab and/or gemcitabine and/or nab-paclitaxel. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), high level group terms, high level terms, and PTs. Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. An NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of participants with at least one event of the AESI occurring during on-treatment period will be summarized.

A non-exhaustive list of AESI is provided below for each investigational drug.

NIS793 / spartalizumab

- Renal toxicity/serum creatinine ≥ Grade 2
- Neutropenia ≥ Grade 3
- Febrile Neutropenia
- Immunogenicity/Hypersensitivity reactions ≥ Grade 3
- Infusion reactions ≥ Grade 3
- Diarrhea ≥ Grade3
- Hypertension ≥ Grade 3
- Hemorrhage ≥ Grade 3
- Cardiac disorders (valvulopathy, cardiomyopathy)
- Skin reactions ≥ Grade 3
- Eyelid abnormality ≥ Grade 2

A Case Retrieval Sheet (CRS) with the exact composition of the AE groupings is to be used to map reported AEs to the AESI groupings.

The most up-to-date version of NIS793 and spartalizumab specific eCRS will be used. Summaries of these AESI will be provided. A listing of all grouping levels down to the MedDRA PTs used to define each AESI will be generated.

2.8.2 Deaths

Separate summaries for on-treatment deaths by PT and all deaths (including post-treatment deaths) by primary SOC and PT will be produced.

All deaths will be listed and those from post-treatment periods will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened participants.

EudraCT and clinicaltrials.gov requirements for AEs and deaths summaries

For the legal requirements of clinicaltrials.gov and EudraCT, two tables are required.

- All deaths (all-cause mortality) from the pre-, on-, and post-treatment periods by SOC and PT;
- AEs/SAEs regardless of study drug relationship, from on- and post-treatment periods by SOC and PT.

For these tables, respective follow-up periods after the last dose of corresponding study treatments as mentioned in Section 2.8.1 will be considered.

If for the same participant, several consecutive AEs (irrespectively of study treatment causality, seriousness, and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE;
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.3 Laboratory data

Summaries will include all assessments available for the lab parameters collected no later than 30 days after the last study treatment administration date (see Section 2.1.1).

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Shift tables using CTC grades to compare baseline to the worst on-treatment value;
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTC grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST, and alkaline phosphatase (ALP). The number (%) of participants with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- AST and ALT =< ULN at baseline
  - ALT or AST >3x ULN & BILI >2x ULN
  - ALT or AST >3x ULN & BILI >2x ULN & ALP >=2x ULN
  - ALT or AST >3x ULN & BILI >2x ULN & ALP <2x ULN
- AST and ALT > ULN at baseline
  - Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN)
  - Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN) & ALP >=2x ULN
  - Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN) & ALP <2x ULN

* Elevated AST or ALT defined as: >3x ULN if =< ULN at baseline, or (>3x Bsl or 8x ULN) if > ULN at baseline

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

In case the study requires ECG replicates, the average of the ECG parameters should be used. A listing of ECG assessments will be produced and notable values will be flagged. A listing of cardiac imaging data will be produced for participants in the **Randomized part**.

2.8.4.2 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).

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-5

Clinically notable changes in vital signs below.

Table 2-5 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase ≥10% from baseline	decrease ≥10% from baseline
Systolic blood pressure (mmHg)	≥180 with increase from baseline of ≥20	≤90 with decrease from baseline of ≥20
Diastolic blood pressure (mmHg)	≥105 with increase from baseline of ≥15	≤50 with decrease from baseline of ≥15
Pulse rate (bpm)	≥100 with increase from baseline of >25%	≤50 with decrease from baseline of >25%
Body temperature	>= 39.1 °C	-

The number and percentage of participants with notable vital sign values (high/low) in the on-treatment period will be presented.

A listing of all vital sign assessments will be produced and notable values will be flagged. Assessments collected outside the on-treatment period will be flagged.

2.9 Pharmacokinetic endpoints

Randomized part

The PK parameters that will be determined are shown in Table 2-6 PK parameters are derived based on non-compartmental methods using Phoenix WinNonlin® software version 8.0 or higher.

Table 2-6 Non-compartmental PK 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)

Descriptive statistics (n, arithmetic mean, coefficient of variation% (CV%) mean, standard deviation (SD), median, geometric mean, CV% geo-mean, minimum, and maximum) will be presented by study drug and treatment arm for NIS-PAS, PDR-PAS, GEM-PAS, dFdU-PAS, and PAC-PAS for all PK parameters defined in Table 2-6 except Tmax. For Tmax only n, median, minimum, and maximum will be presented.

All individual PK parameters will be listed by study drug and treatment arm using the FAS.

PK concentrations

Descriptive statistics (n, m (number of non-zero concentrations), arithmetic mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum, and maximum) for PK concentration will be presented at each scheduled timepoint by study drug and treatment arm for NIS-PAS, PDR-PAS, GEM-PAS, dFdU-PAS, and PAC-PAS.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ) are set to zero by the bioanalyst and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

At the time of analysis, concentration data from participants may be removed from the estimation of certain PK parameters depending on the number of available blood samples, concomitant medications, vomiting, etc. Specific timepoints might be removed from the analysis set if technical issues with the sample are reported (e.g., sampling issues, missing information). These participants and concentration data points will be identified at the time of analysis.

Missing values for any PK data will not be imputed and will be treated as missing.

2.10 Immunogenicity

Randomized part

Immunogenicity analysis is applicable to **Arms 1** and **2**.

2.10.1 Sample ADA status

Each ADA sample is assessed in a three-tiered ADA testing approach. All ADA samples are analyzed in the initial screening assay (first tier). Samples testing negative in the screening assay are not subject to a confirmatory assay. Samples testing positive in the screening assay are then subjected to the confirmatory assay to demonstrate that ADA are specific for the therapeutic protein product (second tier). The titer of confirmatory positive samples will be subsequently determined in the titration assay (third tier).

Samples can test negative in either the screening or confirmatory assay but for statistical analysis purposes they are not differentiated. The following properties of each sample will be provided in the **source data** (i.e., the third party data output (e.g., WLIMS) processed by PreAdvance):

- Result of assay according to pre-specified confirmatory cut point: 'POSITIVE', 'NEGATIVE', or 'NOT REPORTABLE';
- Titer: numerical representation of the magnitude of ADA response;
- Presence of NAb (for positive samples, if NAb assay results are available): 'POSITIVE' or 'NEGATIVE';
- Threshold for determining treatment-boosted (titer fold change (i.e., x-fold)).

The following definitions apply only to non-missing samples:

- ADA-negative sample: Sample where assay result is 'NEGATIVE'
- ADA-positive sample: Sample where assay result is 'POSITIVE'

The following definitions apply only to post-baseline ADA-positive samples with a corresponding non-missing baseline sample. To be classified as treatment-boosted or treatment-unaffected, both the post-baseline and baseline titer must be non-missing.

- Treatment-induced ADA-positive sample: ADA-positive sample post-baseline with ADA-negative sample at baseline;
- Treatment-boosted ADA-positive sample: ADA-positive sample post-baseline with titer that is at least the titer fold (i.e., x-fold) change greater than the ADA-positive baseline titer;
- Treatment-unaffected ADA-positive sample: ADA-positive sample post-baseline with titer that is less than the titer fold (i.e., x-fold) change greater than the ADA-positive baseline titer.

The following summaries of ADA sample status (n and %) will be provided using the Immunogenicity prevalence set:

- ADA-positive samples (i.e., ADA prevalence), both overall and by time point (including baseline). For summaries by time point, the denominator is the number of participants at that time point with a non-missing sample.

Listings will be provided of ADA sample status together with the corresponding PK concentration.

2.10.2 Participant ADA status

Any ADA sample collected after more than 90 days of the last dose of NIS793 and 150 days of the last dose of PDR001 will not be used for summaries or derivations and will only be included in the listing.

Participant ADA status is defined as follows:

- Treatment-induced ADA-positive participant: participant with ADA-negative sample at baseline and at least one treatment-induced ADA-positive sample;
- Treatment-boosted ADA-positive participant: participant with ADA-positive sample at baseline and at least one treatment-boosted ADA-positive sample;
- Treatment-unaffected ADA-positive participant: participant with ADA-positive sample at baseline, no treatment-boosted ADA-positive samples, and at least one treatment-unaffected ADA-positive sample;
- Treatment-reduced ADA-positive participant: participant with ADA-positive sample at baseline and at least one non-missing post baseline sample, all of which are ADA-negative samples;
- ADA-negative participant: participant with ADA-negative sample at baseline and at least one non-missing post baseline sample, all of which are ADA-negative samples;
- Inconclusive participant: participant who does not qualify for any of the above definitions or a participant for which the baseline sample is missing.

The following summaries of ADA participant status (n and %) will be provided using Immunogenicity incidence set (for % the denominator is the number of participants in the Immunogenicity incidence set unless otherwise specified):

- Participants with ADA-negative sample at baseline;
- Participants with ADA-positive sample at baseline;
- ADA-negative participants;
- Treatment-induced ADA-positive participants; for % the denominator is the number of participants with ADA-negative sample at baseline;
- Treatment-boosted ADA-positive participants; for % the denominator is the number of participants with ADA-positive sample at baseline;
- ADA-positive participants (i.e., ADA incidence): calculated as the number of treatment-boosted ADA-positive and treatment-induced ADA-positive participants;

2.10.3 Transient and persistent ADA responses

Treatment-induced ADA-positive participants will be analyzed for transient and persistent ADA responses

Transient ADA response is defined as follows:

- Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point)

and that sampling time point is 16 weeks or more before an ADA-negative last sample

OR

- Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the participant's last sampling time point is ADA-negative.

Persistent ADA response is defined as follows:

- Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer

OR

- Treatment-induced ADA incidence at the last sampling time point of the treatment or follow-up observation period, or at a sampling time point within less than 16 weeks before an ADA-negative last sample.

2.11 Patient-reported outcomes

Not applicable.

2.12 Biomarkers

Randomized part

As a project standard, Novartis Oncology Biometrics and Data Management will analyze only biomarkers collected in the clinical database. There may be circumstances when a decision is made to stop sample collection, or not perform, or discontinue their analysis due to either practical or strategic reasons. Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

The FAS will be used for all biomarker analyses. Unless otherwise specified, all statistical analyses of biomarker data will be performed on participants with biomarker data.

The expression levels of PD-L1 and CD8 will be listed and summarized by treatment arm, participant and visit/timepoint (Table 2-7). Table with descriptive statistics at baseline, one or several post-baseline timepoints and change from baseline to this/these post-baseline timepoints will be provided.

[redacted]

[redacted]

2.14 Interim analysis

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 **Safety Run-in part**, 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 and PD data. Details of this procedure and the process for communication with Investigators are provided in CSP Section 6.5.

For the **Randomized part**, safety and efficacy data will be monitored on a regular basis by the DMC. Further details will be provided in DMC Charter and DMC SAP. IA of efficacy data of the Randomized part will be conducted to support decision making related to Sponsor's clinical development of NIS793. The IA of the Randomized part data is not planned to support formal design adaptations in the current Phase II study.

3 Sample size calculation

3.1 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. CSP Table 16-8 presents the probability of observing zero, one, or more DLTs out of six participants for different true DLT rates. In case of dose de-escalation to dose level -1 [CSP 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 2.5.2.2.

The evaluation of the success criteria was based on the HR of the PFS (NIS793 with spartalizumab and gemcitabine/nab-paclitaxel versus 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 versus 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 (**Arm 1**: **Arm 2**: **Arm 3**). In this calculation, a 10% risk of drop-out per participant year has been taken into consideration.

Regarding the enrolment plan of the study, we assume that 20 participants will be accrued per month until approximately a total of 156 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 VonHoff study (Hoff et al., 2013). It was, therefore, assumed that the median PFS of gemcitabine/nab-paclitaxel ranged between 5 and 6 months. We expect around 50% reduction in the hazard rate of PFS in **Arms 1** and **2** 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 3-1 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**) and the number of total PFS events to 60 required at the timepoint of the analysis. With this combination, reasonable operating characteristics can be achieved. Description of operating characteristics of alternative sample size can be found in CSP Appendix 5.

Table 3-1 Operating characteristics for scenarios with 100 participants and 60 events

Scenarios (Arm 1 vs. Arm 3) PFS in months (Hazard ratio)	**Probability of Success**
6.2 vs. 5.5 months (HR2=1)	**0.104**
5.9 vs. 5.0 months (HR2=1)	**0.120**

6.5 vs. 6.0 months (HR2=1)	**0.138**
8.4 vs. 5.5 months (HR2=0.600)	**0.684**
8.5 vs. 5.5 months (HR2=0.583)	**0.703**
9.0 vs 6.0 months (HR2=0.583)	**0.711**
8.8 vs 5.0 months (HR2=0.500)	**0.812**
9.4 vs. 5.5 months (HR2=0.500)	**0.846**
HR2: Hazard ratio after the risk change in the two-piece hazard model	

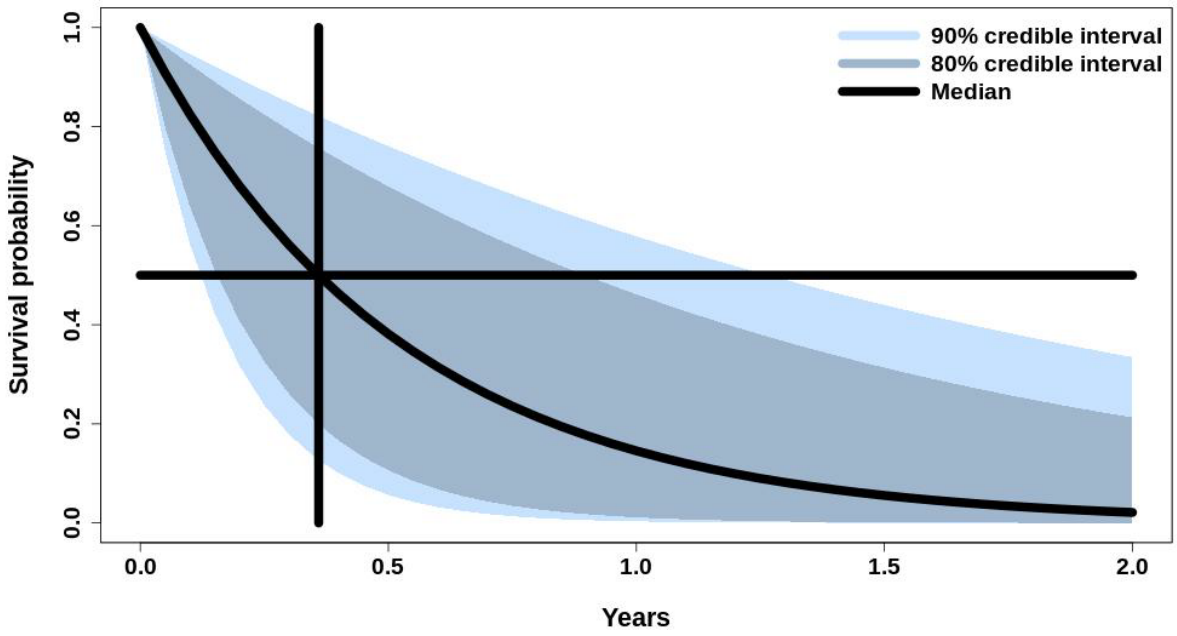
4 Change to protocol specified analyses

- An updated version, compared to the protocol, of the PFS priors is described below.

Gemcitabine/Nab-paclitaxel arm (no delayed effect assumption)

For the gemcitabine/nab-paclitaxel arm 8 historical studies that were investigating the drugs' PFS in first line metastatic pancreatic ductal adenocarcinoma were used to inform the prior (references of the historical studies can be found in Section 6). Using the meta-analytic predictive approach, a 4-component mixture of gamma distributions (including a robustification factor) was derived. The resulting mixture Gamma distribution was: 0.68*Gamma(3.21, 1.69) + 0.11*Gamma(4.71, 0.97) + 0.01*Gamma(1.33, 0.12) + 0.2*Gamma(2.44, 1.00) with median PFS of 0.36 years (i.e., 4.32 months).

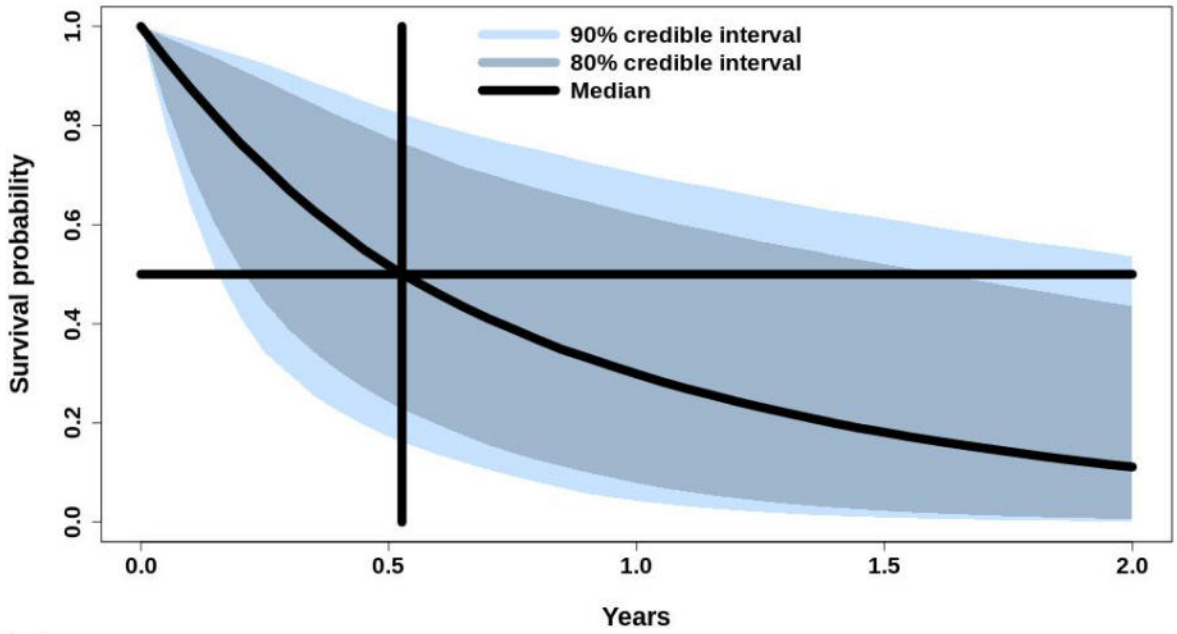
Figure 4-1 Prior distribution for Gemcitabine/Nab-paclitaxel arm



NIS793-based arms (delayed effect assumption)

The same Gamma priors were assumed for both NIS793-based arms 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 the gemcitabine/nab-paclitaxel arm with a wide credible interval. The resulting priors for μ and η are Gamma(3, 2.27) and Gamma(4, 3), respectively.

Figure 4-2 Prior distribution for NIS793-based arms



[redacted]

- Due to abbreviated CSR, the supplementary analyses specified in CSP Section 12.4.2.6 and supportive analyses in CSP Section 12.4.2.7 have been removed from the SAP

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?
- 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.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of the dose end date for a given study treatment component:

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the participant is considered as on-going:

The participant should be treated as on-going, and the cut-off date should be used as the dose end date.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available (prior to any death date or withdrawal of consent date, if available):

Case 1: The dose end date is completely missing and the EOT visit date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Participants with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing, then end-date should not be imputed.

However, if for a participant with a non-zero dose, the information on the participant visit panel is available, the date on this panel will be used to impute the first administration date. Before imputing the date, it will be checked that the date is not after the second administration or after the end date of the first record.

5.1.2 AE date imputation

A missing AE start date will be imputed using the logic matrix described in Table 5-1.

Table 5-1 Imputation rules for a partially missing AE start date

	AEM missing	AEM<TRTM	AEM=TRTM	AEM>TRTM
AEY missing	Not imputation	Not imputation	Not imputation	Not imputation
AEY<TRTY	(D)	(C)	(C)	(C)
AEY=TRTY	(B)	(C)	(B)	(A)
AEY>TRTY	(E)	(A)	(A)	(A)

AEM=Month AE started, AEY=Year AE started
TRTM=Month treatment started, TRTY=Year treatment started

Table 5-2 is the legend to the logic matrix shown in Table 5-1 and details the relationship of AE start date to study treatment start date.

Table 5-2 Imputation legend and AE/treatment start date relationship

AE start date relationship	Imputation
(A) After treatment start or uncertain	MAX(01MMMYYYY, TRTSDT+1)
(B) Uncertain	TRTSDT+1
(C) Before treatment start	15MMMYYYY
(D) Before treatment start	01JULYYYY
(E) After treatment start	01JANYYYY

Before treatment start: Partial date indicates AE start date is prior to treatment start date.
After treatment start: Partial date indicates AE start date is after treatment start date.
Uncertain: Partial date insufficient to determine relationship of AE start date to treatment start date.

No imputation will be performed for missing/incomplete AE end dates.

5.1.3 Concomitant medication date imputation

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 5.1.2). No imputation will be performed for concomitant medication end dates.

5.1.3.1 Prior therapies date imputation

Not applicable.

5.1.3.2 Post therapies date imputation

Start date

Imputed date = max (End of Treatment date + 1, first day of the month), if day is missing.

Imputed date = max (End of Treatment date + 1, 01JAN), if day and month are missing.

Imputed date = End of treatment date +1 if the date is completely missing.

End date

No imputation

5.1.3.3 Other imputations

Diagnosis and extent of cancer

When a date is recorded as a partial date, the missing day is imputed to the 15th of the month (e.g., DEC2007 imputed to 15DEC2007) and if the day and month are both missing then to 1st of January of that year (e.g., 2007 imputed to 01JAN2007). Such imputed data will be flagged in the listings.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g., MRI scan, CT scan) must be completed with day, month, and year. If one or more assessment 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 the latest of all investigation dates (e.g., MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. 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.

5.1.4 Handling missing month/day in date of death/last known participant alive from survival eCRF page

Partial date imputation is allowed for event (death)/censoring if coming from 'Survival information' or death eCRF. Here are the following imputation rules:

- When only the day is missing, the last known participant alive date (from survival page) or date of death will be imputed to the maximum between 1st of the month and year available and any valid date used for last contact derivation + one day;
- When the day and months are missing, the last known participant alive date (from survival page) or date of death will be imputed to the maximum between 1st of January of the year and any valid date used for last contact derivation + one day.

5.2 AEs coding/grading

Adverse events are coded using the MedDRA terminology. AEs will be assessed according to the CTCAE version 5.0.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per National Cancer Institute 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. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 5.0 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE version 5.0, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Table 5-3 CTC grades for laboratory values in Novartis Oncology

CTC Grades (1)								
Lab test (toxicity)	SI unit	Lab test (NCDS)	Normal ranges (Merck manual, July 2015) and *conversion factors*	0	1	2	3	4
Hematology								
WBC ↓ WBC (Leukocytosis)	10^9/L 10^9/L	WBC WBC	3.9 – 10.7 x 10^9/L	≥ LLN	< LLN - 3.0 x 10^9 /L -	< 3.0 – 2.0 x 10^9 /L -	< 2.0 – 1.0 x 10^9 /L > 100 x 10^9 /L	< 1.0 x 10^9 /L -
Hemoglobin (Anemia) Hemoglobin ↑	g/L g/L	HGB HGB	120 - 160 g/L or 7.4 - 9.9 mmol/L (F) 140 - 170 g/L or 8.7 – 10.6 mmol/L (M) *(16.113 x mmol/L = g/L)*	≥ LLN	< LLN - 100 g/L < LLN - 6.2 mmol/L Increase >0-20 g/L above ULN	< 100 - 80 g/L < 6.2 - 4.9 mmol/L Increase >20-40 g/L above ULN	< 80 g/L < 4.9 mmol/L Increase >40 g/L above ULN	- -
Platelets ↓	10^9/L	PLAT	150 - 350 x 10^9/L	≥ LLN	< LLN - 75.0 x 10^9/L	< 75.0 - 50.0 x 10^9 L	< 50.0 - 25.0 x 10^9/L	< 25.0 x 10^9 /L
Neutrophils ↓	10^9/L	NEUT		≥2x10^9 /L	< 2.0 - 1.5 x 10^9 /L	< 1.5 - 1.0 x 10^9 /L	< 1.0 - 0.5 x 10^9 /L	< 0.5 x 10^9 /L
Lymphocytes ↓ Lymphocytes ↑	10^9/L 10^9/L	LYM LYM		≥1.5x10^9 /L	< 1.5 - 0.8 x 10^9 /L -	< 0.8 - 0.5 x 10^9 /L > 4 - 20 x 10^9 /L	< 0.5 - 0.2 x 10^9 /L > 20 x 10^9 /L	< 0.2 x 10^9 /L -
Biochemistry								
AST ↑	U/L	AST	0 - 35 U/L or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT ↑	U/L	ALT	0 - 35 U/L or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN

CTC Grades (1)								
Lab test (toxicity)	SI unit	Lab test (NCDS)	Normal ranges (Merck manual, July 2015) and *conversion factors*	0	1	2	3	4
Total bilirubin ↑	umol/L	BILI	5.1 – 20.5 umol/L or 0.3 – 1.2 mg/dL	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Alk. Phosphatase ↑	U/L	ALP	36 - 92 U/L or 0.5 - 1.5 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine ↑	umol/L	CREAT	61.9 - 115 umol/L or 0.7 – 1.3 mg/dL	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Creatinine kinase↑	U/L	CK	30 - 170 U/L or 0.5 – 2.83 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Albumin (Hypoalbuminemia)	g/L	ALB	35 - 55 g/L or 3.5 to 5.5 g/dL	≥ LLN	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-
Total Cholesterol ↑	mmol/L	CHOL	3.88 – 5.15 mmol/L or 150 - 199 *(38.67 x mg/dL = mmol/L)*	≤ ULN	> ULN - 7.75 mmol/L > ULN - 300 mg/dL	> 7.75 -10.34 mmol/L > 300 – 400 mg/dL	>10.34-12.92 mmol/L > 400 – 500 mg/dL	>12.92 mmol/L > 500 mg/dL
Lipase ↑	U/L	LIPASE	<95 U/L or <1.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Amylase ↑	U/L	AMYLASE	0 - 130 U/L or 0 – 2.17 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Uric acid (Hyperuricemia)	mol/L	URATE	150 - 470 umol/L or 2.5 – 8 mg/dL *(59.48 x mg/dL = umol/L)*	Defined by clinical criteria only in CTCAE V5				
Phosphorus (Hypophosphatemia)	mmol/L	PHOS	0.97 – 1.45 mmol/L or 3.0 - 4.5 mg/dL (0.32 x mg/dL = mmol/L)	Defined by clinical criteria only in CTCAE V5				

CTC Grades (1)								
Lab test (toxicity)	SI unit	Lab test (NCDS)	Normal ranges (Merck manual, July 2015) and *conversion factors*	0	1	2	3	4
Calcium (corrected) (Hypercalcemia) Calcium (corrected) (Hypocalcemia)	mmol/L mmol/L	CACALC CACALC	2.2 - 2.6 mmol/L or 9 - 10.5 mg/dL *(0.2495 x mg/dL = mmol/L)*	≤ ULN ≥ LLN	> ULN - 11.5 mg/dL > ULN - 2.9 mmol/L < LLN - 8.0 mg/dL < LLN - 2.0 mmol/L	> 11.5 - 12.5 mg/dL > 2.9 - 3.1 mmol/L < 8.0 - 7.0 mg/dL < 2.0 - 1.75 mmol/L	> 12.5 - 13.5 mg/dL > 3.1 - 3.4 mmol/L < 7.0 - 6.0 mg/dL < 1.75 - 1.5 mmol/L	> 13.5 mg/dL > 3.4 mmol/L < 6.0 mg/dL < 1.5 mmol/L
Glucose (non-fasting) (Hyperglycemia) Glucose (fasting) (Hyperglycemia)	mmol/L mmol/L	GLUCSN GLUCSF	<7.8 mmol/L or <140 mg/dL (*0.05551* x mg/dL = mmol/L) 3.9 – 5.8 mmol/L or 70 - 105 mg/dL (*0.05551* x mg/dL = mmol/L)	Defined by clinical criteria only in CTCAE V5				
Glucose (Hypoglycemia)	mmol/L	GLUCSN/GLUCSF		≥ LLN	< LLN - 55 mg/dL < LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3.0 - 2.2 mmol/L	<40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Magnesium (Hypermagnesemia) Magnesium (Hypomagnesemia)	mmol/L mmol/L	MG MG	0.62 – 0.99 mmol/L or 1.5 – 2.4 mg/dL *(0.4114 x mg/dL = mmol/L)*	≤ ULN ≥ LLN	> ULN - 3.0 mg/dL > ULN - 1.23 mmol/L < LLN - 1.2 mg/dL < LLN - 0.5 mmol/L	- < 1.2 - 0.9 mg/dL < 0.5 - 0.4 mmol/L	> 3.0 – 8.0 mg/dL > 1.23 – 3.3 mmol/L < 0.9 - 0.7 mg/dL < 0.4 - 0.3 mmol/L	> 8.0 mg/dL > 3.3 mmol/L < 0.7 mg/dL < 0.3 mmol/L

CTC Grades (1)								
Lab test (toxicity)	SI unit	Lab test (NCDS)	Normal ranges (Merck manual, July 2015) and *conversion factors*	0	1	2	3	4
Potassium (Hyperkalemia) Potassium (Hypokalemia)	mmol/L mmol/L	K K	3.5 - 5.0 mmol/L *(0.2558 x mg/dL = mEq/L = mmol/L)*	≤ ULN ≥ LLN	> ULN - 5.5 mmol/L < LLN - 3.0 mmol/L	> 5.5 - 6.0 mmol/L -	> 6.0 - 7.0 mmol/L < 3.0 - 2.5 mmol/L	> 7.0 mmol/L < 2.5 mmol/L
Triglyceride ↑	mmol/L	TRIG	< 2.82 mmol/L or < 250 mg/dL *(0.01129 x mg/dL = umol/L)*	< 150 < 1.71	> 150 - 300 mg/dL > 1.71 – 3.42 mmol/L	> 300 - 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 - 1000 mg/dL > 5.7 – 11.4 mmol/L > 1000 mg/dL > 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L
Sodium (Hypernatremia) Sodium (Hyponatremia)	mmol/L mmol/L	SODIUM SODIUM	136 - 145 mmol/L *(0.435 x mg/dL = mEq/L = mmol/L)*	≤ ULN ≥ LLN	> ULN - 150 mmol/L < LLN - 130 mmol/L	> 150 - 155 mmol/L <129 - 125 mmol/L	> 155 - 160 mmol/L < 124 - 120 mmol/L	> 160 mmol/L < 120 mmol/L
Coagulation								
INR ↑	1	INR	0.8 – 1.2	≤ 1.2	> 1.2- 1.5	> 1.5- 2.5	> 2.5	-
Activated partial thromboplastin time↑	sec	APTT	25 - 35 sec	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Fibrinogen ↓	g/L	FIBRINO	1.5 – 3.5 g/L or 150 – 350 mg/dL (0.01 x mg/dL = g/L)	≥ LLN	< LLN - 0.75 x LLN	< 0.75 - 0.5 x LLN	< 0.5 - 0.25 x LLN	< 0.25 x LLN

CTC Grades (1)								
Lab test (toxicity)	SI unit	Lab test (NCDS)	Normal ranges (Merck manual, July 2015) and *conversion factors*	0	1	2	3	4

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

LAB CTC grades 1, 2, 3, 4 overrule the study specific (central or local) normal range criteria, e.g. if ULN of Sodium is 151 mmol/L and the value is 151 mmol/L, CTC grade 2 is assigned although the value is ≥ ULN.

Clinical criteria such as ‘asymptomatic’ or ‘Life-threatening consequences’ are not considered for determination of LAB CTC grades. Concomitant usage of therapy is also not considered.

Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, ≥ 1.5 x 109 /L (lymphocytes) and ≥ 2 x 109 /L (neutrophils) are considered as LAB CTC grade 0

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e., below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

6 Reference

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