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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

NIS793 and spartalizumab (PDR001)

Trial Indication(s)

First-line metastatic pancreatic ductal adenocarcinoma

Protocol Number

CNIS793B12201

Protocol Title

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

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase 3

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Study Start/End Dates

Study Start Date: October 16, 2020 (Actual)

Primary Completion Date: April 26, 2024 (Actual)

Study Completion Date: May 02, 2024 (Actual)

Reason for Termination (If applicable)

The study was early terminated following the NIS793 treatment halt and urgent safety measure (USM) issued in July 2023. Actions were classified as an USM due to the unfavorable benefit-risk ratio observed in the review of the available data by the data monitoring committee (DMC). Furthermore, on 19-Mar-2024, decision was made to terminate the study, as the continued evaluation of SoC alone would not support the original purpose of the study. At the time of early termination decision, two participants were still on treatment, with SoC only.

Study Design/Methodology

It was a randomized, open label, parallel arms, multi-center, Phase II study of NIS793 (with and without spartalizumab) in combination with SoC chemotherapy gemcitabine/nab-paclitaxel, and gemcitabine/nab-paclitaxel alone in participants with first-line metastatic pancreatic ductal adenocarcinoma (mPDAC) with measurable disease as per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1.

The study consisted of two parts: Safety run-in part and Randomized part.

The Safety run-in part assessed the safety and tolerability of NIS793 in combination with spartalizumab and SoC gemcitabine/nab-paclitaxel. Doses defined for each study treatment, as part of this quadruplet were administered in the Randomized part in the quadruplet/triplet/doublet-based treatment arms.

After Safety run-in part completion, the Randomized part opened, and participants were randomized in a 1:1:1 ratio to one of the three treatment arms as arm 1, arm 2 and arm 3 described below.

– Arm 1: NIS793 with spartalizumab and gemcitabine/nab-paclitaxel

- Arm 2: NIS793 with gemcitabine/nab-paclitaxel
- Arm 3: gemcitabine/nab-paclitaxel

Centers

31 centers in 14 countries: Taiwan(2), Switzerland(2), Czech Republic(1), Belgium(1), Finland(1), Singapore(2), Italy(4), Austria(2), Australia(2), France(2), United Kingdom(1), Germany(3), Spain(3), United States(5)

Objectives:

The primary objectives of the trial were:

Safety run-in part:

- To assess the safety and tolerability of NIS793+spartalizumab in combination with gemcitabine/nab-paclitaxel

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

The secondary objectives of the trial were:

Randomized part:

- To evaluate the safety and tolerability of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel
- To assess the preliminary anti-tumor activity of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel

- To assess Overall Survival (OS) of NIS793 with and without spartalizumab in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel
- To assess the CD8 and PD-L1 status of the participants at screening and on treatment versus gemcitabine/nab-paclitaxel
- To characterize the incidence of immunogenicity of NIS793 and spartalizumab in combination with gemcitabine/nab-paclitaxel
- To characterize the pharmacokinetics (PK) of NIS793, spartalizumab, gemcitabine/nab-paclitaxel in combination treatment or alone (gemcitabine/nab-paclitaxel)

Test Product (s), Dose(s), and Mode(s) of Administration

For this study, the investigational drugs were NIS793 and spartalizumab. The study treatment was NIS793 with and without spartalizumab plus SOC treatment of gemcitabine plus nab-paclitaxel.

The treatment period started on Cycle 1 Day 1 wherein each treatment cycle duration was 28 days.

NIS793 was 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/m^2 on Days 1, 8, and 15) and nab-paclitaxel (125 mg/m^2 on Days 1, 8, and 15) were given as per label. All study drugs were administered by intravenous infusion.

Study treatment had to be discontinued under following conditions: participant/guardian decision, any situation resulting in a safety risk to the participant or death.

Statistical Methods

Efficacy Analysis:

The primary variable of the study was the progression free survival (PFS), defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. The primary analysis was based on the Full

Analysis Set (FAS) and included all data observed up-to the cut-off date. Discontinuation due to disease progression without supporting objective evidence satisfying progression criteria per RECIST 1.1 was not considered disease progression for PFS derivation. The FAS included all patients to whom study treatment was assigned by randomization.

Bayesian model was used to estimate and provide inferential summaries for both PFS hazard ratios a) arm 1 versus arm 3 and b) arm 2 versus arm 3. Inferential summaries based on the posterior distribution was presented, including median and one-sided 90% credible interval. The estimated posterior median of the HR after the delayed effect no larger than 0.7 and the upper limit of the one-sided 90% credible interval smaller than 1 was considered as preliminary evidence for efficacy of NIS793 with spartalizumab and gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel.

The secondary endpoints included overall survival (OS), overall response rate (ORR), duration of response (DOR), and time to progression (TTP).

Safety Analysis:

All safety analyses were based on the Safety set 1 (Safety run-in) and Safety set 2 (Randomized part). The Safety set 1 included all patients who received at least one dose of study treatment in the Safety run-in part, and the Safety set 2 included all patients who received at least one dose of study treatment in the Randomized part. Adverse event (AE) summaries included number and percentage of participants having AEs by System Organ Class (SOC) and Preferred Term (PT) using MedDRA coding. Separate summaries for on- and post-treatment deaths, and all deaths (including survival deaths) were produced.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1- Signed informed consent must be obtained prior to participation in the study.

2- Male or female ≥ 18 years of age at the time of informed consent.

3- Participants with histologically or cytologically confirmed treatment-naïve metastatic adenocarcinoma of the pancreas with measurable disease as per RECIST 1.1.

4- Participants must have a site of disease amenable to biopsy, and be candidate for tumor biopsy according to the treating institution's guidelines. Participants must be willing to undergo a tumor biopsy at screening and during therapy on the study. In the event a new biopsy cannot be safely performed at study entry, an archival sample (collected <6 months prior) may be substituted following documented discussion with Novartis.

5- ECOG performance status ≤ 1.

Exclusion Criteria:

1- Previous radiotherapy, surgery (with exception of placement of biliary stent, which is allowed), chemotherapy or any other investigational therapy for the treatment of metastatic pancreatic cancer. Participants having received previous chemotherapy in the adjuvant setting.

2- Participants amenable to potentially curative resection.

3- Participants with a diagnosis of pancreatic neuroendocrine tumors (NETs), acinar, or islet cell tumors.

4- Having out of range laboratory values as pre-defined in the protocol.

5- Participants with MSI-H pancreatic adenocarcinoma.

6- Presence of symptomatic CNS metastases, or CNS metastases that require local CNS directed therapy (such as radiotherapy or surgery), or increasing doses of corticosteroids 2 weeks prior to study entry.

7- History of severe hypersensitivity reactions to any ingredient of study drug(s) and other mAbs and/or their excipients.

8- The participant exhibits any of the events outlined in the contra-indications or special warnings and precautions sections of gemcitabine and nab-paclitaxel as per locally approved labels.

9- Impaired cardiac function or clinically significant cardiac disease.

10- Known history of testing positive HIV infection.

11- Active HBV or HCV infection. Participants whose disease is controlled under antiviral therapy should not be excluded.

12- History of or current interstitial lung disease or pneumonitis grade ≥ 2

13- High risk of clinically significant gastrointestinal tract bleeding or any other condition associated with or history of significant bleeding.

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Participant Flow Table

Safety run-in part

	Run-in: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	Arm 2: NIS793 + gemcitabine/nab-paclitaxel	Arm 3: gemcitabine/nab-paclitaxel	Total
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the safety run-in part	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part	
Started	11	0	0	0	11
Safety set 1	11	0	0	0	11
Completed	0	0	0	0	0
Not Completed	11	0	0	0	11
Adverse Event	4	0	0	0	4
Physician Decision	1	0	0	0	1
Progressive Disease	6	0	0	0	6

Randomized part

	Run-in: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	Arm 2: NIS793 + gemcitabine/nab-paclitaxel	Arm 3: gemcitabine/nab-paclitaxel	Total
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part	

	standard of care chemotherapy in the safety run-in part	standard of care chemotherapy in the randomized part			
Started	0	50	51	52	153
Full Analysis Set (FAS)	0	50	51	52	153
Safety set 2	0	46	49	45	140
Completed	0	0	0	0	0
Not Completed	0	50	51	52	153
Adverse Event	0	11	5	5	21
Death	0	3	4	2	9
Physician Decision	0	2	2	9	13
Progressive Disease	0	24	31	23	78
Study terminated by sponsor	0	1	0	0	1
Participant Decision	0	5	7	6	18
Not treated	0	4	2	7	13

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Baseline Characteristics

	Run-in: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	Arm 2: NIS793 + gemcitabine/nab-paclitaxel	Arm 3: gemcitabine/nab-paclitaxel	Total
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the safety run-in part	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part	
Number of Participants [units: participants]	11	50	51	52	164
Baseline Analysis Population Description					
Age, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)					
18 - <65 years	5	20	23	23	71
65 - <85 years	6	30	28	29	93
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation					
	63.5±8.77	64.3±10.91	64.2±9.90	64.8±8.25	64.4±9.59
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)					
Female	5	21	21	20	67
Male	6	29	30	32	97

Race/Ethnicity, Customized
(units: participants)
Analysis Population Type: Participants
Count of Participants (Not Applicable)

White	9	39	35	33	116
Black or African American	0	1	1	3	5
Asian	2	9	15	15	41
Unknown	0	1	0	1	2

Primary Outcome Result(s)

Safety run-in part: Number of participants with Dose-Limiting Toxicities (DLTs)

Description	A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 where the relationship to study treatment cannot be ruled out and is not clearly related solely to disease, disease progression, inter-current illness or concomitant medications, which occurs within the DLT evaluation period. The DLT evaluation period is the first 28 days of treatment with NIS793 with spartalizumab in combination with gemcitabine/nab-paclitaxel. Other clinically significant toxicities may be considered to be DLTs, even if not CTCAE grade 3 or higher.
Time Frame	First cycle of treatment (28 days)
Analysis Population Description	Dose-Determining Set (DDS) including all participants in the Safety run-in part who met the minimum exposure criterion defined in the protocol and had sufficient safety evaluations after 4 weeks of treatment or experienced a DLT during the first 4 weeks of treatment.

	Run-in: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the safety run-in part
Number of Participants Analyzed [units: participants]	6

Safety run-in part: Number of participants with Dose-Limiting Toxicities (DLTs) (units: participants)	**Count of Participants (Percentage)**
Any DLT	1 (16.67%)
Colitis	1 (16.67%)

Safety run-in part: Number of participants with AEs and SAEs during the on-treatment period

Description	Number of participants with AEs (any adverse events regardless of seriousness) and serious adverse events (SAEs), including changes from baseline in vital signs, electrocardiograms and laboratory results qualifying and reported as AEs. AE grades to characterize the severity of the AEs were based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For CTCAE v5.0, Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = death related to AE. The on-treatment period is defined from the day of first administration of any study treatment up to 30 days after the date of the last actual administration of any study drug.
Time Frame	Up to approximately 0.8 years
Analysis Population Description	Safety set 1

	Run-in: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the safety run-in part
Number of Participants Analyzed [units: participants]	11
Safety run-in part: Number of participants with AEs and SAEs during the on-treatment period (units: participants)	**Count of Participants (Percentage)**
AEs	11 (100%)
Treatment-related AEs	11 (100%)

AEs with grade>=3	11 (100%)
Treatment-related AEs with grade>=3	8 (72.73%)
SAEs	8 (72.73%)
Treatment-related SAEs	3 (27.27%)
Fatal SAEs	1 (9.09%)
Treatment-related fatal SAEs	0 (%)

Safety run-in part: Number of participants with dose reductions and dose interruptions of NIS793, spartalizumab, gemcitabine and nab-paclitaxel

Description	Number of participants with at least one dose reduction and at least one dose interruption of study drugs. Dose adjustments were permitted for patients who did not tolerate the protocol-specified dosing schedule. No dose reductions were allowed for NIS793 and spartalizumab beyond the first 28 days period of Safety run-in part.
Time Frame	Up to approximately 0.7 years
Analysis Population Description	Safety set 1

	Run-in: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the safety run-in part
Number of Participants Analyzed [units: participants]	11

Safety run-in part: Number of participants with dose reductions and dose interruptions of NIS793, spartalizumab, gemcitabine and nab-paclitaxel (units: participants)	**Count of Participants (Percentage)**
NIS793: At least one dose reduction or interruption	5 (45.45%)
NIS793: At least one dose reduction	0 (%)
NIS793: At least one dose interruption	5 (45.45%)
Spartalizumab: At least one dose reduction or interruption	3 (27.27%)
Spartalizumab: At least one dose reduction	0 (%)
Spartalizumab: At least one dose interruption	3 (27.27%)
Gemcitabine: At least one dose reduction or interruption	9 (81.82%)
Gemcitabine: At least one dose reduction	2 (18.18%)
Gemcitabine: At least one dose interruption	9 (81.82%)
Nab-paclitaxel: At least one dose reduction or interruption	9 (81.82%)
Nab-paclitaxel: At least one dose reduction	3 (27.27%)
Nab-paclitaxel: At least one dose interruption	9 (81.82%)

Safety run-in part: Dose intensity of NIS793 and spartalizumab

Description	Dose intensity of NIS973 and spartalizumab was calculated as cumulative actual dose in milligrams divided by duration of exposure in days and multiplied by 28 days. Dose adjustments were permitted for patients who did not tolerate the protocol-specified dosing schedule.
Time Frame	Cycle 1 and Cycle 3. The duration of each cycle was 28 days.

Analysis Population Description	Patients in the Safety set 1 who received NIS793 or spartalizumab at each reported treatment cycle.

	Run-in: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the safety run-in part
Number of Participants Analyzed [units: participants]	11
Safety run-in part: Dose intensity of NIS793 and spartalizumab (units: mg per cycle)	**Mean ± Standard Deviation**
NIS793 - cycle 1 (n=11)	3627.3 ± 980.91
NIS793 - cycle 3 (n=5)	4200.0 ± 0.00
Spartalizumab - cycle 1 (n=11)	400.0 ± 0.00
Spartalizumab - cycle 3 (n=5)	400.0 ± 0.00

Safety run-in part: Dose intensity of gemcitabine and nab-paclitaxel

Description	Dose intensity of gemcitabine and nab-paclitaxel was calculated as cumulative actual dose in milligrams/m^2 divided by duration of exposure in days and multiplied by 28 days.
Time Frame	Cycle 1 and Cycle 3. The duration of each cycle was 28 days.
Analysis Population Description	Patients in the Safety set 1 who received gemcitabine or nab-paclitaxel at each reported treatment cycle.

	Run-in: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel

Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the safety run-in part
Number of Participants Analyzed [units: participants]	11
Safety run-in part: Dose intensity of gemcitabine and nab-paclitaxel (units: mg per m^2 per cycle)	**Mean ± Standard Deviation**
Gemcitabine - cycle 1 (n=11)	2425.4 ± 698.27
Gemcitabine - cycle 3 (n=5)	2619.1 ± 508.19
Nab-paclitaxel - cycle 1 (n=11)	303.3 ± 87.18
Nab-paclitaxel - cycle 3 (n=5)	327.6 ± 63.65

Randomized Part: Progression-Free Survival (PFS) per RECIST v1.1 – Bayesian model

Description	PFS was based on local review of tumor assessments, using Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria. PFS is defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. If a subject had not had an event, PFS was censored at the date of last adequate tumor assessment. PFS was estimated using a Bayesian model. For each comparison (arm 1 versus arm 3 and arm 2 versus arm 3), PFS was modeled using a two-piece hazard model, with specifying hazard rates before and after the possible delayed effect for arms 1 and 2 and constant hazard rate for arm 3. Results in the table as expressed as estimated posterior median hazard rate and one-sided 90% credible interval.
Time Frame	Up to approximately 2 years. Risk changing timepoint=approximately 0.3 years.
Analysis Population Description	Full Analysis Set (FAS)

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	Arm 2: NIS793 + gemcitabine/nab-paclitaxel	Arm 3: gemcitabine/nab-paclitaxel
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part

Number of Participants Analyzed [units: participants]	50	51	52
Randomized Part: Progression-Free Survival (PFS) per RECIST v1.1 – Bayesian model (units: events (progression, death) per year)	**Median (90% Confidence Interval)**	**Median (90% Confidence Interval)**	**Median (90% Confidence Interval)**
Hazard rate before the risk changing timepoint	2.54 (0 to 3.34)	1.23 (0 to 1.79)	2.09 (0 to 2.53)
Hazard rate after the risk changing timepoint	1.46 (0 to 2.06)	2.94 (0 to 3.86)	2.09 (0 to 2.53)

Statistical Analysis

Groups	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel, Arm 3: gemcitabine/nab-paclitaxel	
Type of Statistical Test	Other	
Method	Other Bayesian two-piece hazard model	
Hazard Ratio (HR)	0.70	Estimated posterior median of the HR after the risk changing timepoint and one-sided 90% credible interval are reported.
90 % Confidence Interval 1-Sided	to 1.04	

Statistical Analysis

Groups	Arm 2: NIS793 + gemcitabine/nab-paclitaxel, Arm 3: gemcitabine/nab-paclitaxel	
Type of Statistical Test	Other	
Method	Other Bayesian two-piece hazard model	

Hazard Ratio (HR)	1.41	Estimated posterior median of the HR after the risk changing timepoint and one-sided 90% credible interval are reported.
90 % Confidence Interval 1-Sided	to 1.96	

Randomized Part: Progression-Free Survival (PFS) per RECIST v1.1 – Kaplan-Meier curves and Cox model

Description	PFS was based on local review of tumor assessments, using RECIST 1.1 criteria. PFS is defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. If a subject had not had an event, PFS was censored at the date of last adequate tumor assessment. PFS was analyzed based on the Kaplan-Meier curves and the Cox model.
Time Frame	Up to approximately 2 years
Analysis Population Description	Full Analysis Set (FAS)

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	**Arm 2: NIS793 + gemcitabine/nab-paclitaxel**	**Arm 3: gemcitabine/nab-paclitaxel**
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	50	51	52
Randomized Part: Progression-Free Survival (PFS) per RECIST v1.1 – Kaplan-Meier curves and Cox model (units: months)	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**
	3.91 (3.06 to 6.93)	5.52 (3.94 to 7.29)	4.37 (3.55 to 7.20)

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Statistical Analysis

Groups	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel, Arm 3: gemcitabine/nab-paclitaxel
Type of Statistical Test	Other
P Value	0.46
Method	Regression, Cox
Hazard Ratio (HR)	1.02
90 % Confidence Interval 2-Sided	0 to 1.37

Statistical Analysis

Groups	Arm 2: NIS793 + gemcitabine/nab-paclitaxel, Arm 3: gemcitabine/nab-paclitaxel
Type of Statistical Test	Other
P Value	0.38
Method	Regression, Cox
Hazard Ratio (HR)	1.08
90 % Confidence Interval 2-Sided	0 to 1.44

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Secondary Outcome Result(s)

Randomized Part: Number of participants with AEs and SAEs during the on-treatment period

Description	Number of participants with AEs (any adverse events regardless of seriousness) and serious adverse events (SAEs), including changes from baseline in vital signs, electrocardiograms and laboratory results qualifying and reported as AEs. AE grades to characterize the severity of the AEs were based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For CTCAE v5.0, Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = death related to AE. The on-treatment period is defined from the day of first administration of any study treatment up to 30 days after the date of the last actual administration of any study drug.
Time Frame	Up to approximately 1.8 years
Analysis Population Description	Safety set 2

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	**Arm 2: NIS793 + gemcitabine/nab-paclitaxel**	**Arm 3: gemcitabine/nab-paclitaxel**
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	46	49	45
Randomized Part: Number of participants with AEs and SAEs during the on-treatment period (units: participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
AEs	45 (97.83%)	49 (100%)	43 (95.56%)
Treatment-related AEs	45 (97.83%)	45 (91.84%)	38 (84.44%)
AEs with grade>=3	42 (91.3%)	42 (85.71%)	35 (77.78%)
Treatment-related AEs with grade>=3	34 (73.91%)	37 (75.51%)	24 (53.33%)

SAEs	32 (69.57%)	26 (53.06%)	26 (57.78%)
Treatment-related SAEs	19 (41.3%)	12 (24.49%)	12 (26.67%)
Fatal SAEs	3 (6.52%)	1 (2.04%)	4 (8.89%)
Treatment-related fatal SAEs	1 (2.17%)	0 (%)	0 (%)

Randomized Part: Number of participants with dose reductions and dose interruptions of NIS793, spartalizumab, gemcitabine and nab-paclitaxel

Description	Number of participants with at least one dose reduction and at least one dose interruption of study drugs. Dose adjustments were permitted for patients who did not tolerate the protocol-specified dosing schedule. No dose reductions were allowed for NIS793 and spartalizumab in the Randomized part.
Time Frame	Up to approximately 1.7 years
Analysis Population Description	Safety set 2

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	**Arm 2: NIS793 + gemcitabine/nab-paclitaxel**	**Arm 3: gemcitabine/nab-paclitaxel**
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	46	49	45
Randomized Part: Number of participants with dose reductions and dose interruptions of NIS793, spartalizumab, gemcitabine and nab-paclitaxel (units: participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**

NIS793: At least one dose reduction or interruption (n=46,49,0)	35 (76.09%)	31 (63.27%)	(NaN%)
NIS793: At least one dose reduction (n=46,49,0)	0 (%)	0 (%)	(NaN%)
NIS793: At least one dose interruption (n=46,49,0)	35 (76.09%)	31 (63.27%)	(NaN%)
Spartalizumab: At least one dose reduction or interruption (n=46,0,0)	21 (45.65%)	(NaN%)	(NaN%)
Spartalizumab: At least one dose reduction (n=46,0,0)	0 (%)	(NaN%)	(NaN%)
Spartalizumab: At least one dose interruption (n=46,0,0)	21 (45.65%)	(NaN%)	(NaN%)
Gemcitabine: At least one dose reduction or interruption (n=46,49,45)	38 (82.61%)	41 (83.67%)	32 (71.11%)
Gemcitabine: At least one dose reduction (n=46,49,45)	25 (54.35%)	23 (46.94%)	19 (42.22%)
Gemcitabine: At least one dose interruption (n=46,49,45)	35 (76.09%)	36 (73.47%)	29 (64.44%)
Nab-paclitaxel: At least one dose reduction or interruption (n=46,49,45)	39 (84.78%)	43 (87.76%)	34 (75.56%)
Nab-paclitaxel: At least one dose reduction (n=46,49,45)	26 (56.52%)	27 (55.1%)	19 (42.22%)
Nab-paclitaxel: At least one dose interruption (n=46,49,45)	34 (73.91%)	37 (75.51%)	32 (71.11%)

Randomized Part: Dose intensity of NIS973 and spartalizumab

Description	Dose intensity of NIS973 and spartalizumab was calculated as cumulative actual dose in milligrams divided by duration of exposure in days and multiplied by 28 days. Dose adjustments were permitted for patients who did not tolerate the protocol-specified dosing schedule.
Time Frame	Cycle 1 and Cycle 3. The duration of each cycle was 28 days

Analysis Population Description	Patients in the Safety set 2 who received NIS793 or spartalizumab at each reported treatment cycle.

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	Arm 2: NIS793 + gemcitabine/nab-paclitaxel	Arm 3: gemcitabine/nab-paclitaxel
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	46	49	0
Randomized Part: Dose intensity of NIS973 and spartalizumab (units: mg per cycle)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
NIS793 - cycle 1 (n=46,49,0)	3515.2 ± 995.32	3857.1 ± 784.22	
NIS793 - cycle 3 (n=26,42,0)	3796.2 ± 844.03	3550.0 ± 982.59	
Spartalizumab - cycle 1 (n=46,0,0)	400.0 ± 0.00		
Spartalizumab - cycle 3 (n=24,0,0)	400.0 ± 0.00		

Randomized Part: Dose intensity of gemcitabine and nab-paclitaxel

Description	Dose intensity of gemcitabine and nab-paclitaxel was calculated as cumulative actual dose in milligrams/m^2 divided by duration of exposure in days and multiplied by 28 days.
Time Frame	Cycle 1 and Cycle 3. The duration of each cycle was 28 days
Analysis Population Description	Patients in the Safety set 2 who received gemcitabine or nab-paclitaxel at each reported treatment cycle

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	Arm 2: NIS793 + gemcitabine/nab-paclitaxel	Arm 3: gemcitabine/nab-paclitaxel
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	46	49	45
Randomized Part: Dose intensity of gemcitabine and nab-paclitaxel (units: mg per m^2 per cycle)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Gemcitabine - cycle 1 (n=46,49,45)	2442.3 ± 675.34	2644.8 ± 543.43	2392.1 ± 651.00
Gemcitabine - cycle 3 (n=29,42,29)	2293.9 ± 710.08	2426.5 ± 696.10	2445.3 ± 561.36
Nab-paclitaxel - cycle 1 (n=46,49,45)	305.7 ± 84.91	330.7 ± 67.95	298.8 ± 80.96
Nab-paclitaxel - cycle 3 (n=29,42,29)	286.2 ± 86.45	296.2 ± 88.06	299.1 ± 70.08

Randomized Part: Overall Response Rate (ORR) per RECIST v1.1

Description	ORR is the percentage of patients with a confirmed best overall response of complete response (CR) or partial response (PR), based on local investigator assessment per Response Evaluation Criteria for Solid Tumors (RECIST) v1.1. For RECIST v1.1, CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Time Frame	Up to approximately 1.7 years
Analysis Population Description	Full Analysis Set (FAS)

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	Arm 2: NIS793 + gemcitabine/nab-paclitaxel	Arm 3: gemcitabine/nab-paclitaxel
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of	NIS793 2100 mg every 2 weeks i.v. with standard of care	Standard of care chemotherapy in the randomized part

	care chemotherapy in the randomized part	chemotherapy in the randomized part	
Number of Participants Analyzed [units: participants]	50	51	52
Randomized Part: Overall Response Rate (ORR) per RECIST v1.1 (units: percentage of participants)	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**
	22.0 (11.5 to 36.0)	31.4 (19.1 to 45.9)	15.4 (6.9 to 28.1)

Randomized Part: Duration of Response (DOR) per RECIST v1.1

Description	DOR per RECIST v1.1 is defined as the time from the first documented response of CR or PR to the date of the first documented progression or death. DOR only applies to patients with a best overall response of CR or PR by investigator assessment per RECIST v1.1. Participants continuing without progression or death were censored at the date of their last adequate tumor assessment. DOR was analyzed using the Kaplan-Meier method.
Time Frame	Up to approximately 1.7 years
Analysis Population Description	Participants in the Full Analysis Set (FAS) with CR or PR

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	**Arm 2: NIS793 + gemcitabine/nab-paclitaxel**	**Arm 3: gemcitabine/nab-paclitaxel**
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	11	16	8
Randomized Part: Duration of Response (DOR) per RECIST v1.1 (units: months)	**Mean (95% Confidence Interval)**	**Mean (95% Confidence Interval)**	**Mean (95% Confidence Interval)**

	7.75 (5.09 to NA[1])	4.86 (3.71 to 7.39)	11.70 (3.61 to 16.20)

[1]: Not estimable due to insufficient number of participants with events.

Randomized Part: Time to Progression (TTP) per RECIST v1.1

Description	TTP per RECIST v1.1 is defined as the time from the date of randomization to the date of event defined as the first documented progression per RECIST v1.1 or death due to underlying cancer. If a participant had no progression or death, the participant was censored at the date of last adequate tumor assessment. DOR was analyzed using the Kaplan-Meier method.
Time Frame	Up to approximately 1.7 years
Analysis Population Description	Full Analysis Set (FAS)

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	**Arm 2: NIS793 + gemcitabine/nab-paclitaxel**	**Arm 3: gemcitabine/nab-paclitaxel**
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	50	51	52
Randomized Part: Time to Progression (TTP) per RECIST v1.1 (units: months)	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**
	3.94 (3.55 to 7.03)	5.59 (4.57 to 7.36)	5.36 (3.68 to 8.61)

Randomized Part: Overall Survival (OS)

Description	Overall survival is defined as the time from the date of randomization to the date of death due to any cause. OS was analyzed using the Kaplan-Meier method.

Time Frame	Up to approximately 2 years
Analysis Population Description	Full Analysis Set (FAS)

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	Arm 2: NIS793 + gemcitabine/nab-paclitaxel	Arm 3: gemcitabine/nab-paclitaxel
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	50	51	52
Randomized Part: Overall Survival (OS) (units: months)	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**
	10.7 (7.2 to 12.7)	8.5 (7.7 to 9.9)	10.1 (6.5 to 13.4)

Randomized Part: Change from baseline in PD-L1 expression

Description	The tumor expression of programmed cell death-ligand 1 (PD-L1) was measured by immunohistochemical methods. Results are expressed as absolute change from baseline in PD-L1 expression.
Time Frame	Baseline (Screening), on-treatment (anytime between Cycle 3 Day 2 and Day 4). The duration of each cycle was 28 days.
Analysis Population Description	Participants in the Full Analysis Set (FAS) who had a valid assessment of PD-L1 tumor expression at both baseline and on-treatment.

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	Arm 2: NIS793 + gemcitabine/nab-paclitaxel	Arm 3: gemcitabine/nab-paclitaxel
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg	NIS793 2100 mg every 2 weeks i.v. with standard of care	Standard of care chemotherapy in the randomized part

	every 4 weeks i.v and standard of care chemotherapy in the randomized part	chemotherapy in the randomized part	
Number of Participants Analyzed [units: participants]	4	12	5
Randomized Part: Change from baseline in PD-L1 expression (units: percentage of PD-L1 positive tumor cells)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	7.625 ± 10.4193	7.917 ± 17.0572	4.000 ± 8.9443

Randomized Part: Change from baseline in CD8 expression

Description	The tumor expression of CD8 was measured by immunohistochemical methods. Results are expressed as absolute change from baseline in CD8 expression.
Time Frame	Baseline (Screening), on-treatment (anytime between Cycle 3 Day 2 and Day 4). The duration of each cycle was 28 days.
Analysis Population Description	Participants in the Full Analysis Set (FAS) who had a valid assessment of CD8 tumor expression at both baseline and on-treatment.

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	**Arm 2: NIS793 + gemcitabine/nab-paclitaxel**	**Arm 3: gemcitabine/nab-paclitaxel**
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	3	14	6
Randomized Part: Change from baseline in CD8 expression (units: percentage of CD8 marker area expression)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	10.1 ± 11.01	1.4 ± 2.64	2.1 ± 1.82

NOVARTIS

Randomized Part: Number of participants with anti-NIS793 antibodies

Description	The immunogenicity (IG) against NIS793 was assessed in serum using a validated enhanced electrochemiluminescence immunoassay (ECLIA). Patient anti-drug antibodies (ADA) status was defined as follows: • ADA-negative at baseline: ADA-negative sample at baseline • ADA-positive at baseline: ADA-positive sample at baseline • ADA-negative post-baseline: patient with ADA-negative sample at baseline and at least 1 post baseline sample, all of which are ADA-negative samples • ADA-inconclusive post-baseline = patient who does not qualify as ADA-positive or ADA-negative post-baseline • Treatment-induced ADA-positive = ADA-negative sample at baseline and at least 1 treatment-induced ADA-positive sample
Time Frame	Baseline (before first dose) and post-baseline (assessed throughout the treatment up to approximately 1.7 years)
Analysis Population Description	Participants in the safety set 2 who received NIS793 and had a non-missing baseline ADA sample and at least one non-missing post-baseline ADA sample.

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	**Arm 2: NIS793 + gemcitabine/nab-paclitaxel**
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	41	44
Randomized Part: Number of participants with anti-NIS793 antibodies (units: participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
ADA-negative at baseline	41 (100%)	44 (100%)
ADA-positive at baseline	0 (%)	0 (%)
ADA-negative post-baseline	41 (100%)	44 (100%)
ADA- inconclusive post-baseline	0 (%)	0 (%)

Treatment-induced ADA-positive	0 (%)	0 (%)

Randomized Part: Number of participants with anti-spartalizumab antibodies

Description	The immunogenicity (IG) against spartalizumab was assessed in serum using a validated a validated homogenous enzyme-linked immunosorbent assay (ELISA). Patient anti-drug antibodies (ADA) status was defined as follows: • ADA-negative at baseline: ADA-negative sample at baseline • ADA-inconclusive at baseline: patient who does not qualify as ADA-positive or ADA-negative at baseline • ADA-positive at baseline: ADA-positive sample at baseline • ADA-negative post-baseline: patient with ADA-negative sample at baseline and at least 1 post baseline sample, all of which are ADA-negative samples • ADA-inconclusive post-baseline = patient who does not qualify as ADA-positive or ADA-negative post-baseline • Treatment-induced ADA-positive = ADA-negative sample at baseline and at least 1 treatment-induced ADA-positive sample
Time Frame	Cycle 1 and Cycle 3. The duration of each cycle was 28 days
Analysis Population Description	Participants in the safety set 2 who received spartalizumab and had a non-missing baseline ADA sample and at least one non-missing post-baseline ADA sample.

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	41
Randomized Part: Number of participants with anti-spartalizumab antibodies (units: participants)	**Count of Participants (Percentage)**
ADA-negative at baseline	40 (97.56%)
ADA- inconclusive at baseline	1 (2.44%)

ADA-positive at baseline	0 (%)
ADA-negative post-baseline	35 (85.37%)
ADA- inconclusive post-baseline	2 (4.88%)
Treatment-induced ADA-positive	4 (9.76%)

Randomized Part: Maximum observed serum concentration (Cmax) of NIS793

Description	Pharmacokinetic (PK) parameters were calculated based on NIS793 serum concentrations by using non-compartmental methods. Cmax is defined as the maximum (peak) observed concentration following a dose.
Time Frame	Cycle 1 and Cycle 3: pre-dose, 1, 24, 168 and 336 hours after the end of the infusion on Day 1. The duration of the infusion was 30 minutes. One cycle=28 days
Analysis Population Description	Participants in the pharmacokinetic analysis set (PAS) who received NIS793 and had an available value for the outcome measure. PAS consisted of all patients who received one dose (complete infusion) of the planned treatments and provided at least one valid primary PK parameter.

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	**Arm 2: NIS793 + gemcitabine/nab-paclitaxel**
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	42	39
Randomized Part: Maximum observed serum concentration (Cmax) of NIS793 (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 1 (n=42,39)	603000 ± 181000	622000 ± 192000
Cycle 3 (n=21,31)	821000 ± 235000	784000 ± 286000

Randomized Part: Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of NIS793

Description	PK parameters were calculated based on NIS793 serum concentrations by using non-compartmental methods. The linear trapezoidal method was used for AUClast calculation.
Time Frame	Cycle 1 and Cycle 3: pre-dose, 1, 24, 168 and 336 hours after the end of the infusion on Day 1. The duration of the infusion was 30 minutes. One cycle=28 days
Analysis Population Description	Participants in the pharmacokinetic analysis set (PAS) who received NIS793 and had an available value for the outcome measure. PAS consisted of all patients who received one dose (complete infusion) of the planned treatments and provided at least one valid primary PK parameter.

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	**Arm 2: NIS793 + gemcitabine/nab-paclitaxel**
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	42	39
Randomized Part: Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of NIS793 (units: h*ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 1 (n=42,39)	84700000 ± 29300000	96000000 ± 26100000
Cycle 3 (n=21,31)	153000000 ± 52300000	151000000 ± 55000000

Randomized Part: Trough serum concentration (Ctrough) of NIS793

Description	Ctrough is defined as the concentration reached immediately before the next dose is administered. All drug concentrations below the lower limit of quantification were treated as zero for the calculation of PK parameters.

Time Frame	Cycle 1: pre-dose on Day 1. Cycle 3: pre-dose on Day 1 and Day 15 (combined). One cycle=28 days
Analysis Population Description	Participants in the pharmacokinetic analysis set (PAS) who received NIS793 and had an available value for the outcome measure. PAS consisted of all patients who received one dose (complete infusion) of the planned treatments and provided at least one valid primary PK parameter.

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	**Arm 2: NIS793 + gemcitabine/nab-paclitaxel**
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	26	34
Randomized Part: Trough serum concentration (Ctrough) of NIS793 (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 1 (n=26,34)	137000 ± 51700	156000 ± 50100
Cycle 3 (n=22,34)	289000 ± 121000	291000 ± 126000

Randomized Part: Maximum observed serum concentration (Cmax) of spartalizumab

Description	PK parameters were calculated based on spartalizumab serum concentrations by using non-compartmental methods. Cmax is defined as the maximum (peak) observed concentration following a dose.
Time Frame	Cycle 1 and Cycle 3: pre-dose, 1, 24, 168 and 648 hours after the end of the infusion on Day 1. The duration of the infusion was 30 minutes. One cycle=28 days
Analysis Population Description	Participants in the pharmacokinetic analysis set (PAS) who received spartalizumab and had an available value for the outcome measure. PAS consisted of all patients who received one dose (complete infusion) of the planned treatments and provided at least one valid primary PK parameter.

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel

Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	42
Randomized Part: Maximum observed serum concentration (Cmax) of spartalizumab (units: µg/mL)	**Mean ± Standard Deviation**
Cycle 1 (n=42)	109 ± 22.4
Cycle 3 (n=21)	120 ± 38.0

Randomized Part: Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of spartalizumab

Description	PK parameters were calculated based on spartalizumab serum concentrations by using non-compartmental methods. The linear trapezoidal method was used for AUClast calculation.
Time Frame	Cycle 1 and Cycle 3: pre-dose, 1, 24, 168 and 648 hours after the end of the infusion on Day 1. The duration of the infusion was 30 minutes. One cycle=28 days
Analysis Population Description	Participants in the pharmacokinetic analysis set (PAS) who received spartalizumab and had an available value for the outcome measure. PAS consisted of all patients who received one dose (complete infusion) of the planned treatments and provided at least one valid primary PK parameter.

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	42

Randomized Part: Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of spartalizumab (units: h*µg/mL)	**Mean ± Standard Deviation**
Cycle 1 (n=42)	10800 ± 4900
Cycle 3 (n=21)	3240 ± 1900

Randomized Part: Trough serum concentration (Ctrough) of spartalizumab

Description	Ctrough is defined as the concentration reached immediately before the next dose is administered. All drug concentrations below the lower limit of quantification were treated as zero for the calculation of PK parameters.
Time Frame	Cycle 2, 3 and 4: pre-dose on Day 1. One cycle=28 days
Analysis Population Description	Participants in the pharmacokinetic analysis set (PAS) who received spartalizumab and had an available value for the outcome measure. PAS consisted of all patients who received one dose (complete infusion) of the planned treatments and provided at least one valid primary PK parameter.

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	32
Randomized Part: Trough serum concentration (Ctrough) of spartalizumab (units: µg/mL)	**Mean ± Standard Deviation**
Cycle 2 (n=32)	22.3 ± 8.67
Cycle 3 (n=21)	31.9 ± 11.7
Cycle 4 (n=23)	30.5 ± 14.3

Randomized Part: Maximum observed plasma concentration (Cmax) of gemcitabine

Description	PK parameters were calculated based on gemcitabine plasma concentrations by using non-compartmental methods. Cmax is defined as the maximum (peak) observed concentration following a dose.
Time Frame	Cycle 1 and Cycle 4: pre-dose, end of infusion, and 2, 3, 5 and 24 hours after the start of infusion on Day 1. The duration of the infusion was according to the product labelling and local guidance. One cycle=28 days
Analysis Population Description	Participants in the pharmacokinetic analysis set (PAS) who received gemcitabine and had an available value for the outcome measure. PAS consisted of all patients who received one dose (complete infusion) of the planned treatments and provided at least one valid primary PK parameter.

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	**Arm 2: NIS793 + gemcitabine/nab-paclitaxel**	**Arm 3: gemcitabine/nab-paclitaxel**
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	42	40	44
Randomized Part: Maximum observed plasma concentration (Cmax) of gemcitabine (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 1 (n=42,40,44)	9830 ± 8580	12000 ± 6850	10600 ± 6170
Cycle 4 (n=23,28,24)	7950 ± 5650	8830 ± 6150	7000 ± 4210

Randomized Part: Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of gemcitabine

Description	PK parameters were calculated based on gemcitabine plasma concentrations by using non-compartmental methods. The linear trapezoidal method was used for AUClast calculation.
Time Frame	Cycle 1 and Cycle 4: pre-dose, end of infusion, and 2, 3, 5 and 24 hours after the start of infusion on Day 1. The duration of the infusion was according to the product labelling and local guidance. One cycle=28 days

Analysis Population Description	Participants in the pharmacokinetic analysis set (PAS) who received gemcitabine and had an available value for the outcome measure. PAS consisted of all patients who received one dose (complete infusion) of the planned treatments and provided at least one valid primary PK parameter.

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	Arm 2: NIS793 + gemcitabine/nab-paclitaxel	Arm 3: gemcitabine/nab-paclitaxel
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	42	40	44
Randomized Part: Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of gemcitabine (units: h*ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 1 (n=42,40,44)	7270 ± 6950	9900 ± 6140	8040 ± 4490
Cycle 4 (n=23,28,24)	5270 ± 4730	5980 ± 4410	4920 ± 2830

Randomized Part: Trough serum concentration (Ctrough) of gemcitabine

Description	Ctrough is defined as the concentration reached immediately before the next dose is administered. All drug concentrations below the lower limit of quantification were treated as zero for the calculation of PK parameters.
Time Frame	Cycle 4: pre-dose on Day 1. One cycle=28 days
Analysis Population Description	Participants in the pharmacokinetic analysis set (PAS) who received gemcitabine and had an available value for the outcome measure. PAS consisted of all patients who received one dose (complete infusion) of the planned treatments and provided at least one valid primary PK parameter.

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

Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	24	30	23
Randomized Part: Trough serum concentration (Ctrough) of gemcitabine (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 4	0 ± 0	0 ± 0	0 ± 0

Randomized Part: Maximum observed plasma concentration (Cmax) of nab-paclitaxel

Description	PK parameters were calculated based on nab-paclitaxel plasma concentrations by using non-compartmental methods. Cmax is defined as the maximum (peak) observed concentration following a dose.
Time Frame	Cycle 1 and Cycle 4: pre-dose, end of infusion, and 2, 3, 5 and 24 hours after the start of infusion on Day 1. The duration of the infusion was according to the product labelling and local guidance. One cycle=28 days
Analysis Population Description	Participants in the pharmacokinetic analysis set (PAS) who received nab-paclitaxel and had an available value for the outcome measure. PAS consisted of all patients who received one dose (complete infusion) of the planned treatments and provided at least one valid primary PK parameter.

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	**Arm 2: NIS793 + gemcitabine/nab-paclitaxel**	**Arm 3: gemcitabine/nab-paclitaxel**
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	37	38	43
Randomized Part: Maximum observed plasma concentration (Cmax) of nab-	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**

paclitaxel (units: ng/mL)			
Cycle 1 (n=37,38,43)	9990 ± 37100	4120 ± 3370	3490 ± 1760
Cycle 4 (n=19,28,24)	4570 ± 4910	4050 ± 2410	2900 ± 1370

Randomized Part: Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of nab-paclitaxel

Description	PK parameters were calculated based on nab-paclitaxel plasma concentrations by using non-compartmental methods. The linear trapezoidal method was used for AUClast calculation.
Time Frame	Cycle 1 and Cycle 4: pre-dose, end of infusion, and 2, 3, 5 and 24 hours after the start of infusion on Day 1. The duration of the infusion was according to the product labelling and local guidance. One cycle=28 days
Analysis Population Description	Participants in the pharmacokinetic analysis set (PAS) who received nab-paclitaxel and had an available value for the outcome measure. PAS consisted of all patients who received one dose (complete infusion) of the planned treatments and provided at least one valid primary PK parameter.

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	**Arm 2: NIS793 + gemcitabine/nab-paclitaxel**	**Arm 3: gemcitabine/nab-paclitaxel**
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	37	38	43
Randomized Part: Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of nab-paclitaxel (units: h*ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 1 (n=37,38,43)	15700 ± 52400	5080 ± 2820	4820 ± 2500
Cycle 4 (n=19,28,24)	5960 ± 3650	5020 ± 3050	4250 ± 2550

Randomized Part: Trough serum concentration (Ctrough) of nab-paclitaxel

Description	Ctrough is defined as the concentration reached immediately before the next dose is administered. All drug concentrations below the lower limit of quantification were treated as zero for the calculation of PK parameters.
Time Frame	Cycle 4: pre-dose on Day 1. One cycle=28 days
Analysis Population Description	Participants in the pharmacokinetic analysis set (PAS) who received nab-paclitaxel and had an available value for the outcome measure. PAS consisted of all patients who received one dose (complete infusion) of the planned treatments and provided at least one valid primary PK parameter.

	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	**Arm 2: NIS793 + gemcitabine/nab-paclitaxel**	**Arm 3: gemcitabine/nab-paclitaxel**
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	19	30	23
Randomized Part: Trough serum concentration (Ctrough) of nab-paclitaxel (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 4	455 ± 1320	2.13 ± 10.4	3.25 ± 5.08

Post-Hoc Outcome Result(s)

All-Collected Deaths

Description	On-treatment and post-treatment safety follow-up (FU) deaths were collected from first dose of study treatment to 90 days after last dose of NIS793, 150 days after last dose of spartalizumab and 30 days after last dose of gemcitabine and nab-paclitaxel, whichever was longer. Survival FU deaths were collected from 91 days after last dose of NIS793, 151 days after last dose of spartalizumab and 31 days after last

dose of gemcitabine and nab-paclitaxel, whichever was longer, until end of study. All deaths refer to the sum of pre-treatment deaths, on-treatment and post-treatment safety FU deaths, and survival FU deaths.

Time Frame: On-treatment and post-treatment safety FU deaths: up to approximately 1 year (run-in part) and 1.9 years (randomized part). Survival FU deaths: up to approximately 1.8 years (run-in part) and 2 years (randomized part)

Analysis Population Description: Safety set 1 (safety run-in) and Full Analysis Set (randomized part)

	Run-in: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel	**Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel**	**Arm 2: NIS793 + gemcitabine/nab-paclitaxel**	**Arm 3: gemcitabine/nab-paclitaxel**
Arm/Group Description	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the safety run-in part	NIS793 2100 mg every 2 weeks i.v. with spartalizumab 400 mg every 4 weeks i.v and standard of care chemotherapy in the randomized part	NIS793 2100 mg every 2 weeks i.v. with standard of care chemotherapy in the randomized part	Standard of care chemotherapy in the randomized part
Number of Participants Analyzed [units: participants]	11	50	51	52
All-Collected Deaths (units: Participants)				
On-treatment and post-treatment safety FU deaths (n=11,50,51,52)	5	18	19	4
Survival FU deaths (n=6,28,30,41)	5	15	22	35
All deaths (n=11,50,51,52)	10	33	41	39

Safety Results

Time Frame	On- and post-treatment safety FU: from first dose of study treatment to 90 days after last dose of NIS793, 150 days after last dose of spartalizumab and 30 days after last dose of gemcitabine and nab-paclitaxel, whichever was longer, up to approx. 1 year (run-in part) and 1.9 years (randomized part). Deaths in survival period: after completing safety FU until end of study, up to approx. 1.8 years (run-in part) and 2 years (randomized part).
Additional Description	Deaths in the survival period are not considered Adverse Events (AEs). No AEs were collected in the survival period. Deaths were assessed in the Safety set 1 (run-in part) and Full Analysis Set (randomized part). AEs were assessed in the Safety set 1 (run-in part) and Safety set 2 (randomized part).
Source Vocabulary for Table Default	MedDRA (27.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Run-in: NIS793 + spartalizumab + gemcitabine /nab-paclitaxel_On- and post-treatment N = 11	**Arm 1: NIS793 + spartalizumab + gemcitabine /nab-paclitaxel_On- and post-treatment N = 50**	**Arm 2: NIS793 + gemcitabine /nab-paclitaxel_On- and post-treatment N = 51**	**Arm 3: gemcitabine /nab-paclitaxel_On- and post-treatment N = 52**	**All Participants _On- and post-treatment N = 164**	**Run-in: NIS793 + spartalizumab + gemcitabine/ nab-paclitaxel_Survival period N = 6**	**Arm 1: NIS793 + spartalizumab + gemcitabine/ nab-paclitaxel_Survival period N = 28**	**Arm 2: NIS793 + gemcitabine/ nab-paclitaxel_Survival period N = 30**	**Arm 3: gemcitabine/ nab-paclitaxel_Survival period N = 41**
Arm/Group Description	Safety data up to 90 days after last dose of NIS793, 150 days after last dose of spartalizumab and 30 days after	Safety data up to 90 days after last dose of NIS793, 150 days after last dose of spartalizumab and 30 days after	Safety data up to 90 days after last dose of NIS793 and 30 days after last dose of gemcitabine and nab-paclitaxel,	Safety data up to 30 days after last dose of gemcitabine and nab-paclitaxel	Safety data up to 90 days after last dose of NIS793, 150 days after last dose of spartalizumab and 30 days after	Deaths collected in the survival follow-up period (starting from Day 90 after last dose of NIS793, Day 151 days after	Deaths collected in the survival follow-up period (starting from Day 90 after last dose of NIS793, Day 151 days after	Deaths collected in the survival follow-up period (starting from Day 90 after last dose of NIS793 and Day 31 after	Deaths collected in the survival follow-up period (starting from Day 31 after last dose of gemcitabine and nab-

	last dose of gemcitabine and nab-paclitaxel, whichever was longer	last dose of gemcitabine and nab-paclitaxel, whichever was longer	whichever was longer		last dose of gemcitabine and nab-paclitaxel, whichever was longer	last dose of spartalizumab and Day 31 after last dose of gemcitabine and nab-paclitaxel, whichever was longer). No AEs were collected during this period.	last dose of spartalizumab and Day 31 after last dose of gemcitabine and nab-paclitaxel, whichever was longer). No AEs were collected during this period.	last dose of gemcitabine and nab-paclitaxel, whichever was longer). No AEs were collected during this period.	paclitaxel). No AEs were collected during this period.
Total Number Affected	5	18	19	4	46	5	15	22	35
Total Number At Risk	11	50	51	52	164	6	28	30	41

Serious Adverse Events

Time Frame	On- and post-treatment safety FU: from first dose of study treatment to 90 days after last dose of NIS793, 150 days after last dose of spartalizumab and 30 days after last dose of gemcitabine and nab-paclitaxel, whichever was longer, up to approx. 1 year (run-in part) and 1.9 years (randomized part). Deaths in survival period: after completing safety FU until end of study, up to approx. 1.8 years (run-in part) and 2 years (randomized part).
Additional Description	Deaths in the survival period are not considered Adverse Events (AEs). No AEs were collected in the survival period. Deaths were assessed in the Safety set 1 (run-in part) and Full Analysis Set (randomized part). AEs were assessed in the Safety set 1 (run-in part) and Safety set 2 (randomized part).
Source Vocabulary for Table Default	MedDRA (27.0)

NOVARTIS

Collection Approach for Table Default Systematic Assessment

	Run-in: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel_On- and post-treatment N = 11	Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel_On- and post-treatment N = 46	Arm 2: NIS793 + gemcitabine/nab-paclitaxel_On- and post-treatment N = 49	Arm 3: gemcitabine/nab-paclitaxel_On- and post-treatment N = 45	All Participants_On- and post-treatment N = 151
Arm/Group Description	Safety data up to 90 days after last dose of NIS793, 150 days after last dose of spartalizumab and 30 days after last dose of gemcitabine and nab-paclitaxel, whichever was longer	Safety data up to 90 days after last dose of NIS793, 150 days after last dose of spartalizumab and 30 days after last dose of gemcitabine and nab-paclitaxel, whichever was longer	Safety data up to 90 days after last dose of NIS793 and 30 days after last dose of gemcitabine and nab-paclitaxel, whichever was longer	Safety data up to 30 days after last dose of gemcitabine and nab-paclitaxel	Safety data up to 90 days after last dose of NIS793, 150 days after last dose of spartalizumab and 30 days after last dose of gemcitabine and nab-paclitaxel, whichever was longer
Total # Affected by any Serious Adverse Event	8	34	28	26	96
Total # at Risk by any Serious Adverse Event	11	46	49	45	151
Blood and lymphatic system disorders					
Anaemia	0 (0.00%)	2 (4.35%)	6 (12.24%)	2 (4.44%)	10 (6.62%)
Blood loss anaemia	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Febrile neutropenia	0 (0.00%)	2 (4.35%)	1 (2.04%)	1 (2.22%)	4 (2.65%)
Haemolysis	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)

Haemolytic uraemic syndrome	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Leukopenia	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Neutropenia	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Cardiac disorders					
Pericardial effusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	1 (0.66%)
Supraventricular tachycardia	0 (0.00%)	1 (2.17%)	0 (0.00%)	1 (2.22%)	2 (1.32%)
Endocrine disorders					
Glucocorticoid deficiency	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Hypopituitarism	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Gastrointestinal disorders					
Abdominal pain	1 (9.09%)	2 (4.35%)	0 (0.00%)	3 (6.67%)	6 (3.97%)
Abdominal pain lower	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Abdominal pain upper	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Colitis	1 (9.09%)	2 (4.35%)	1 (2.04%)	1 (2.22%)	5 (3.31%)
Constipation	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Diarrhoea	0 (0.00%)	5 (10.87%)	0 (0.00%)	0 (0.00%)	5 (3.31%)
Diarrhoea haemorrhagic	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Duodenal obstruction	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Duodenal perforation	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Enterocolitis	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Gastric haemorrhage	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Gastritis	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)

Gastritis haemorrhagic	1 (9.09%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	2 (1.32%)
Gastrointestinal haemorrhage	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Gastrointestinal pain	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Gastrointestinal toxicity	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	1 (0.66%)
Haematemesis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	1 (0.66%)
Ileus	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Immune-mediated enterocolitis	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Impaired gastric emptying	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Melaena	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Nausea	0 (0.00%)	0 (0.00%)	1 (2.04%)	1 (2.22%)	2 (1.32%)
Pancreatitis	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Rectal haemorrhage	0 (0.00%)	0 (0.00%)	2 (4.08%)	0 (0.00%)	2 (1.32%)
Small intestinal haemorrhage	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Small intestinal obstruction	0 (0.00%)	1 (2.17%)	0 (0.00%)	1 (2.22%)	2 (1.32%)
Subileus	0 (0.00%)	0 (0.00%)	2 (4.08%)	0 (0.00%)	2 (1.32%)
Upper gastrointestinal haemorrhage	0 (0.00%)	0 (0.00%)	2 (4.08%)	0 (0.00%)	2 (1.32%)
Vomiting	0 (0.00%)	0 (0.00%)	1 (2.04%)	1 (2.22%)	2 (1.32%)
General disorders and administration site conditions					
Asthenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	1 (0.66%)
Chest pain	0 (0.00%)	1 (2.17%)	0 (0.00%)	1 (2.22%)	2 (1.32%)

Chills	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Fatigue	0 (0.00%)	3 (6.52%)	0 (0.00%)	0 (0.00%)	3 (1.99%)
Gait inability	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
General physical health deterioration	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	1 (0.66%)
Pain	1 (9.09%)	1 (2.17%)	1 (2.04%)	1 (2.22%)	4 (2.65%)
Pyrexia	2 (18.18%)	5 (10.87%)	3 (6.12%)	5 (11.11%)	15 (9.93%)
Hepatobiliary disorders					
Biliary obstruction	0 (0.00%)	1 (2.17%)	2 (4.08%)	0 (0.00%)	3 (1.99%)
Cholangitis	0 (0.00%)	2 (4.35%)	2 (4.08%)	0 (0.00%)	4 (2.65%)
Cholecystitis	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Cholecystitis acute	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Gallbladder rupture	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Hepatic failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	1 (0.66%)
Hepatitis	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Hypertransaminasaemia	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Immune-mediated hepatitis	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Infections and infestations					
Abdominal infection	0 (0.00%)	0 (0.00%)	1 (2.04%)	1 (2.22%)	2 (1.32%)
Acarodermatitis	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Anal abscess	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	1 (0.66%)
Bacteraemia	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)

Biliary sepsis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	1 (0.66%)
Biliary tract infection	0 (0.00%)	1 (2.17%)	1 (2.04%)	0 (0.00%)	2 (1.32%)
Campylobacter infection	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
COVID-19	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
COVID-19 pneumonia	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Device related infection	0 (0.00%)	0 (0.00%)	3 (6.12%)	0 (0.00%)	3 (1.99%)
Febrile infection	0 (0.00%)	0 (0.00%)	2 (4.08%)	0 (0.00%)	2 (1.32%)
Infection	0 (0.00%)	3 (6.52%)	1 (2.04%)	0 (0.00%)	4 (2.65%)
Large intestine infection	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Lower respiratory tract infection	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Pneumonia	1 (9.09%)	4 (8.70%)	0 (0.00%)	0 (0.00%)	5 (3.31%)
Pneumonia bacterial	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Pneumonia pseudomonal	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Postoperative wound infection	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Relapsing fever	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Sepsis	0 (0.00%)	4 (8.70%)	3 (6.12%)	3 (6.67%)	10 (6.62%)
Septic shock	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	1 (2.04%)	1 (2.22%)	2 (1.32%)
Injury, poisoning and procedural complications					
Acetabulum fracture	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)

Craniofacial fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	1 (0.66%)
Fall	0 (0.00%)	1 (2.17%)	1 (2.04%)	0 (0.00%)	2 (1.32%)
Femur fracture	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Head injury	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Infusion related reaction	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Scapula fracture	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Spinal fracture	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Investigations					
Alanine aminotransferase increased	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Aspartate aminotransferase increased	1 (9.09%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	2 (1.32%)
Blood bilirubin increased	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Gamma-glutamyltransferase increased	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
General physical condition abnormal	1 (9.09%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	2 (1.32%)
Myocardial necrosis marker increased	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Metabolism and nutrition disorders					
Dehydration	0 (0.00%)	0 (0.00%)	2 (4.08%)	1 (2.22%)	3 (1.99%)
Diabetic ketoacidosis	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Hyperglycaemia	0 (0.00%)	0 (0.00%)	1 (2.04%)	1 (2.22%)	2 (1.32%)

Hypoalbuminaemia	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Hypokalaemia	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Hypomagnesaemia	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Hyponatraemia	0 (0.00%)	1 (2.17%)	0 (0.00%)	1 (2.22%)	2 (1.32%)
Musculoskeletal and connective tissue disorders					
Back pain	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Degenerative bone disease	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Squamous cell carcinoma of skin	0 (0.00%)	1 (2.17%)	1 (2.04%)	0 (0.00%)	2 (1.32%)
Tumour obstruction	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Nervous system disorders					
Demyelinating polyneuropathy	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Hepatic encephalopathy	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Syncope	0 (0.00%)	1 (2.17%)	1 (2.04%)	0 (0.00%)	2 (1.32%)
Renal and urinary disorders					
Acute kidney injury	0 (0.00%)	3 (6.52%)	1 (2.04%)	0 (0.00%)	4 (2.65%)
Bladder tamponade	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Haematuria	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Proteinuria	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)

Renal failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	1 (0.66%)
Reproductive system and breast disorders					
Orchitis noninfective	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Respiratory, thoracic and mediastinal disorders					
Dyspnoea	0 (0.00%)	0 (0.00%)	2 (4.08%)	1 (2.22%)	3 (1.99%)
Interstitial lung disease	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Pleural effusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	1 (0.66%)
Pneumomediastinum	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Pneumonitis	0 (0.00%)	0 (0.00%)	1 (2.04%)	1 (2.22%)	2 (1.32%)
Pneumothorax	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Pulmonary embolism	0 (0.00%)	0 (0.00%)	2 (4.08%)	0 (0.00%)	2 (1.32%)
Pulmonary fibrosis	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Pulmonary oedema	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Respiratory failure	0 (0.00%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (0.66%)
Skin and subcutaneous tissue disorders					
Rash	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	1 (0.66%)
Rash maculo-papular	0 (0.00%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Vascular disorders					
Deep vein thrombosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	1 (0.66%)
Hypotension	0 (0.00%)	0 (0.00%)	2 (4.08%)	0 (0.00%)	2 (1.32%)
Venous thrombosis	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)

Other (Not Including Serious) Adverse Events

Time Frame	On- and post-treatment safety FU: from first dose of study treatment to 90 days after last dose of NIS793, 150 days after last dose of spartalizumab and 30 days after last dose of gemcitabine and nab-paclitaxel, whichever was longer, up to approx. 1 year (run-in part) and 1.9 years (randomized part). Deaths in survival period: after completing safety FU until end of study, up to approx. 1.8 years (run-in part) and 2 years (randomized part).
Additional Description	Deaths in the survival period are not considered Adverse Events (AEs). No AEs were collected in the survival period. Deaths were assessed in the Safety set 1 (run-in part) and Full Analysis Set (randomized part). AEs were assessed in the Safety set 1 (run-in part) and Safety set 2 (randomized part).
Source Vocabulary for Table Default	MedDRA (27.0)
Collection Approach for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 5%

	Run-in: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel_On- and post-treatment N = 11	**Arm 1: NIS793 + spartalizumab + gemcitabine/nab-paclitaxel_On- and post-treatment N = 46**	**Arm 2: NIS793 + gemcitabine/nab-paclitaxel_On- and post-treatment N = 49**	**Arm 3: gemcitabine/nab-paclitaxel_On- and post-treatment N = 45**	**All Participants_On- and post-treatment N = 151**
Arm/Group Description	Safety data up to 90 days after last dose of NIS793, 150 days after last dose of spartalizumab and 30 days after last dose of gemcitabine and nab-	Safety data up to 90 days after last dose of NIS793, 150 days after last dose of spartalizumab and 30 days after last dose of gemcitabine and nab-	Safety data up to 90 days after last dose of NIS793 and 30 days after last dose of gemcitabine and nab-paclitaxel, whichever was longer	Safety data up to 30 days after last dose of gemcitabine and nab-paclitaxel	Safety data up to 90 days after last dose of NIS793, 150 days after last dose of spartalizumab and 30 days after last dose of gemcitabine and nab-

	paclitaxel, whichever was longer	paclitaxel, whichever was longer			paclitaxel, whichever was longer
Total # Affected by any Other Adverse Event	11	45	48	40	144
Total # at Risk by any Other Adverse Event	11	46	49	45	151
Blood and lymphatic system disorders					
Anaemia	5 (45.45%)	29 (63.04%)	33 (67.35%)	20 (44.44%)	87 (57.62%)
Leukocytosis	1 (9.09%)	3 (6.52%)	0 (0.00%)	2 (4.44%)	6 (3.97%)
Leukopenia	1 (9.09%)	4 (8.70%)	2 (4.08%)	3 (6.67%)	10 (6.62%)
Neutropenia	5 (45.45%)	11 (23.91%)	9 (18.37%)	9 (20.00%)	34 (22.52%)
Neutrophilia	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Thrombocytopenia	2 (18.18%)	7 (15.22%)	4 (8.16%)	4 (8.89%)	17 (11.26%)
Gastrointestinal disorders					
Abdominal discomfort	0 (0.00%)	0 (0.00%)	3 (6.12%)	1 (2.22%)	4 (2.65%)
Abdominal pain	1 (9.09%)	4 (8.70%)	9 (18.37%)	4 (8.89%)	18 (11.92%)
Abdominal pain upper	1 (9.09%)	4 (8.70%)	8 (16.33%)	5 (11.11%)	18 (11.92%)
Aphthous ulcer	1 (9.09%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	2 (1.32%)
Constipation	1 (9.09%)	16 (34.78%)	16 (32.65%)	12 (26.67%)	45 (29.80%)
Diarrhoea	5 (45.45%)	26 (56.52%)	19 (38.78%)	18 (40.00%)	68 (45.03%)
Dry mouth	0 (0.00%)	1 (2.17%)	4 (8.16%)	3 (6.67%)	8 (5.30%)
Dyspepsia	2 (18.18%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	3 (1.99%)
Gastrooesophageal reflux disease	0 (0.00%)	1 (2.17%)	5 (10.20%)	4 (8.89%)	10 (6.62%)
Gingival bleeding	2 (18.18%)	1 (2.17%)	6 (12.24%)	0 (0.00%)	9 (5.96%)
Gingival hypertrophy	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)

Gingival swelling	2 (18.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.32%)
Haemorrhoids	1 (9.09%)	1 (2.17%)	3 (6.12%)	0 (0.00%)	5 (3.31%)
Ileal perforation	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Ileus	1 (9.09%)	1 (2.17%)	0 (0.00%)	0 (0.00%)	2 (1.32%)
Nausea	7 (63.64%)	20 (43.48%)	27 (55.10%)	20 (44.44%)	74 (49.01%)
Rectal haemorrhage	1 (9.09%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	2 (1.32%)
Stomatitis	0 (0.00%)	1 (2.17%)	4 (8.16%)	0 (0.00%)	5 (3.31%)
Tongue coated	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Tongue disorder	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Vomiting	3 (27.27%)	10 (21.74%)	18 (36.73%)	12 (26.67%)	43 (28.48%)
General disorders and administration site conditions					
Asthenia	5 (45.45%)	12 (26.09%)	16 (32.65%)	11 (24.44%)	44 (29.14%)
Chills	1 (9.09%)	3 (6.52%)	2 (4.08%)	5 (11.11%)	11 (7.28%)
Fatigue	7 (63.64%)	23 (50.00%)	18 (36.73%)	14 (31.11%)	62 (41.06%)
Mucosal inflammation	1 (9.09%)	5 (10.87%)	4 (8.16%)	1 (2.22%)	11 (7.28%)
Oedema	1 (9.09%)	3 (6.52%)	0 (0.00%)	2 (4.44%)	6 (3.97%)
Oedema peripheral	4 (36.36%)	11 (23.91%)	15 (30.61%)	8 (17.78%)	38 (25.17%)
Pain	1 (9.09%)	2 (4.35%)	1 (2.04%)	1 (2.22%)	5 (3.31%)
Pyrexia	7 (63.64%)	19 (41.30%)	11 (22.45%)	14 (31.11%)	51 (33.77%)
Hepatobiliary disorders					
Hepatobiliary disease	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Immune-mediated hepatitis	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Infections and infestations					

COVID-19	1 (9.09%)	13 (28.26%)	6 (12.24%)	5 (11.11%)	25 (16.56%)
Infection	1 (9.09%)	2 (4.35%)	0 (0.00%)	0 (0.00%)	3 (1.99%)
Pneumonia	0 (0.00%)	0 (0.00%)	2 (4.08%)	3 (6.67%)	5 (3.31%)
Urinary tract infection	0 (0.00%)	7 (15.22%)	6 (12.24%)	1 (2.22%)	14 (9.27%)
Injury, poisoning and procedural complications					
Fall	1 (9.09%)	1 (2.17%)	1 (2.04%)	1 (2.22%)	4 (2.65%)
Infusion related reaction	1 (9.09%)	2 (4.35%)	0 (0.00%)	2 (4.44%)	5 (3.31%)
Wound dehiscence	1 (9.09%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	2 (1.32%)
Investigations					
Alanine aminotransferase increased	4 (36.36%)	14 (30.43%)	10 (20.41%)	10 (22.22%)	38 (25.17%)
Amylase increased	1 (9.09%)	5 (10.87%)	2 (4.08%)	2 (4.44%)	10 (6.62%)
Aspartate aminotransferase increased	4 (36.36%)	13 (28.26%)	9 (18.37%)	7 (15.56%)	33 (21.85%)
Blood alkaline phosphatase increased	2 (18.18%)	4 (8.70%)	2 (4.08%)	3 (6.67%)	11 (7.28%)
Blood bilirubin increased	0 (0.00%)	1 (2.17%)	5 (10.20%)	4 (8.89%)	10 (6.62%)
Blood creatinine increased	0 (0.00%)	3 (6.52%)	1 (2.04%)	0 (0.00%)	4 (2.65%)
Blood lactate dehydrogenase increased	0 (0.00%)	2 (4.35%)	3 (6.12%)	1 (2.22%)	6 (3.97%)
C-reactive protein increased	0 (0.00%)	4 (8.70%)	2 (4.08%)	0 (0.00%)	6 (3.97%)

Gamma-glutamyltransferase increased	4 (36.36%)	1 (2.17%)	1 (2.04%)	2 (4.44%)	8 (5.30%)
Lipase increased	2 (18.18%)	5 (10.87%)	3 (6.12%)	2 (4.44%)	12 (7.95%)
Neutrophil count decreased	2 (18.18%)	7 (15.22%)	8 (16.33%)	9 (20.00%)	26 (17.22%)
Platelet count decreased	1 (9.09%)	8 (17.39%)	10 (20.41%)	9 (20.00%)	28 (18.54%)
Tri-iodothyronine decreased	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Weight decreased	2 (18.18%)	2 (4.35%)	6 (12.24%)	5 (11.11%)	15 (9.93%)
White blood cell count decreased	0 (0.00%)	3 (6.52%)	3 (6.12%)	3 (6.67%)	9 (5.96%)
Metabolism and nutrition disorders					
Decreased appetite	4 (36.36%)	10 (21.74%)	17 (34.69%)	15 (33.33%)	46 (30.46%)
Hyperglycaemia	0 (0.00%)	4 (8.70%)	1 (2.04%)	3 (6.67%)	8 (5.30%)
Hypocalcaemia	2 (18.18%)	1 (2.17%)	1 (2.04%)	1 (2.22%)	5 (3.31%)
Hypochloraemia	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Hypokalaemia	1 (9.09%)	8 (17.39%)	6 (12.24%)	9 (20.00%)	24 (15.89%)
Hypomagnesaemia	1 (9.09%)	4 (8.70%)	2 (4.08%)	3 (6.67%)	10 (6.62%)
Hyponatraemia	1 (9.09%)	1 (2.17%)	2 (4.08%)	2 (4.44%)	6 (3.97%)
Hypophosphataemia	3 (27.27%)	9 (19.57%)	7 (14.29%)	2 (4.44%)	21 (13.91%)
Musculoskeletal and connective tissue disorders					
Arthralgia	1 (9.09%)	4 (8.70%)	5 (10.20%)	8 (17.78%)	18 (11.92%)
Back pain	1 (9.09%)	6 (13.04%)	5 (10.20%)	2 (4.44%)	14 (9.27%)
Myalgia	0 (0.00%)	3 (6.52%)	1 (2.04%)	4 (8.89%)	8 (5.30%)

Neck pain	1 (9.09%)	1 (2.17%)	1 (2.04%)	1 (2.22%)	4 (2.65%)
Pain in extremity	0 (0.00%)	0 (0.00%)	5 (10.20%)	2 (4.44%)	7 (4.64%)
Nervous system disorders					
Dizziness	0 (0.00%)	1 (2.17%)	3 (6.12%)	4 (8.89%)	8 (5.30%)
Dysgeusia	1 (9.09%)	6 (13.04%)	5 (10.20%)	4 (8.89%)	16 (10.60%)
Headache	1 (9.09%)	2 (4.35%)	1 (2.04%)	2 (4.44%)	6 (3.97%)
Hypoaesthesia	0 (0.00%)	3 (6.52%)	3 (6.12%)	3 (6.67%)	9 (5.96%)
Neuropathy peripheral	0 (0.00%)	5 (10.87%)	11 (22.45%)	5 (11.11%)	21 (13.91%)
Neurotoxicity	0 (0.00%)	1 (2.17%)	0 (0.00%)	4 (8.89%)	5 (3.31%)
Paraesthesia	2 (18.18%)	4 (8.70%)	3 (6.12%)	6 (13.33%)	15 (9.93%)
Peripheral sensory neuropathy	0 (0.00%)	4 (8.70%)	2 (4.08%)	4 (8.89%)	10 (6.62%)
Polyneuropathy	1 (9.09%)	5 (10.87%)	5 (10.20%)	1 (2.22%)	12 (7.95%)
Psychiatric disorders					
Anxiety	0 (0.00%)	3 (6.52%)	4 (8.16%)	0 (0.00%)	7 (4.64%)
Insomnia	1 (9.09%)	4 (8.70%)	3 (6.12%)	7 (15.56%)	15 (9.93%)
Renal and urinary disorders					
Haematuria	0 (0.00%)	3 (6.52%)	1 (2.04%)	0 (0.00%)	4 (2.65%)
Reproductive system and breast disorders					
Prostatomegaly	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Respiratory, thoracic and mediastinal disorders					
Cough	1 (9.09%)	3 (6.52%)	11 (22.45%)	12 (26.67%)	27 (17.88%)
Dyspnoea	1 (9.09%)	1 (2.17%)	8 (16.33%)	7 (15.56%)	17 (11.26%)

Epistaxis	2 (18.18%)	11 (23.91%)	14 (28.57%)	1 (2.22%)	28 (18.54%)
Nasal dryness	0 (0.00%)	0 (0.00%)	3 (6.12%)	1 (2.22%)	4 (2.65%)
Pulmonary embolism	1 (9.09%)	4 (8.70%)	3 (6.12%)	1 (2.22%)	9 (5.96%)
Skin and subcutaneous tissue disorders					
Acne	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Alopecia	3 (27.27%)	11 (23.91%)	15 (30.61%)	7 (15.56%)	36 (23.84%)
Dry skin	0 (0.00%)	3 (6.52%)	3 (6.12%)	1 (2.22%)	7 (4.64%)
Erythema	1 (9.09%)	4 (8.70%)	3 (6.12%)	1 (2.22%)	9 (5.96%)
Night sweats	1 (9.09%)	0 (0.00%)	2 (4.08%)	0 (0.00%)	3 (1.99%)
Onycholysis	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Pruritus	2 (18.18%)	14 (30.43%)	8 (16.33%)	1 (2.22%)	25 (16.56%)
Rash	6 (54.55%)	13 (28.26%)	18 (36.73%)	5 (11.11%)	42 (27.81%)
Rash macular	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Rash maculo-papular	2 (18.18%)	10 (21.74%)	1 (2.04%)	0 (0.00%)	13 (8.61%)
Skin toxicity	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Vascular disorders					
Deep vein thrombosis	0 (0.00%)	2 (4.35%)	2 (4.08%)	3 (6.67%)	7 (4.64%)
Hypertension	1 (9.09%)	3 (6.52%)	4 (8.16%)	2 (4.44%)	10 (6.62%)
Hypotension	0 (0.00%)	4 (8.70%)	6 (12.24%)	4 (8.89%)	14 (9.27%)
Jugular vein thrombosis	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)
Vein rupture	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)

Conclusion:

- In the randomized part of the study, the efficacy data did not show any evidence of prolonging PFS in participants with NIS793 with/without spartalizumab and gemcitabine/nab-paclitaxel compared to gemcitabine/nab-paclitaxel (SoC).
- Secondary objectives such as ORR, DoR, TTP or OS also did not show any advantage by adding NIS793 with or without spartalizumab to the SoC. Immunohistochemistry (IHC) measurements for PD-L1 and CD8 showed the expected on-target activity in tumor with increases seen in both of these biomarkers in their respective treatment cohorts.
- In the Safety-run-in period, one participant experienced a DLT of grade 3 colitis, which was suspected to be related to study treatment as per Investigator, showing good tolerability of the treatment combination.
- Safety profile of NIS793 with/without spartalizumab was confirmed in the Randomized part.
- Overall, the addition of NIS793 to SoC (gemcitabine/nab-paclitaxel), alone or in combination with spartalizumab, showed unfavorable benefit-risk ratio in this difficult to treat population of mPDAC.

Date of Clinical Trial Report

17-Dec-2024