Clinical trial results:
An open-label, multi-center, phase II platform study evaluating the efficacy and safety of NIS793 and other new investigational drug combinations with SOC anti-cancer therapy for the 2L treatment of metastatic colorectal cancer (mCRC)

Summary

EudraCT number	2021-000553-40
Trial protocol	CZ DE HU ES BE IT FR
Global end of trial date	20 January 2025

Results information

Result version number	v1 (current)
This version publication date	05 February 2026
First version publication date	05 February 2026

Trial information

Trial identification

Sponsor protocol code	CNIS793E12201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04952753
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Lichtstrasse 35, Basel, Switzerland, 4056
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 January 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 January 2025
Global end of trial reached?	Yes
Global end of trial date	20 January 2025
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the preliminary efficacy and safety of NIS793 and other novel investigational combinations with standard of care (SOC) anti-cancer therapy versus SOC anti-cancer therapy for the second-line treatment of mCRC.

This study aimed to explore whether different mechanisms of action could reverse resistance and improve responsiveness to the then-considered SOC anti-cancer therapy in the second-line metastatic colorectal cancer (mCRC) setting.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 November 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Czechia: 15
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Japan: 22
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Spain: 33
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	United Kingdom: 11

Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	202
EEA total number of subjects	114

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	149
From 65 to 84 years	53
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study spanned 17 countries with multiple centers: Australia (3), Belgium (3), Canada (4), Switzerland (1), Czech Republic (3), Germany (8), Spain (5), France (3), UK (3), Hong Kong (2), Israel (2), Italy (3), Japan (5), Korea (1), Singapore (1), Taiwan (2), USA (7).

Pre-assignment

Screening details:

Not Completed = Discontinued from treatment phase

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Safety Run-In Arm 1: NIS793 + SoC (FOLFIRI)

Arm description:

Safety Run-In (Investigational Arm 1): NIS793 in combination with Standard of Care (bevacizumab and FOLFIRI)

Arm type	Experimental
Investigational medicinal product name	NIS793
Investigational medicinal product code	
Other name	NIS793
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Investigational drug NIS793 was administered intravenously (IV) at the dose and schedule determined in the safety run-in part

Investigational medicinal product name	FOLFIRI
Investigational medicinal product code	
Other name	5FU+Leucovorin+Irinotecan
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-fluorouracil [administered as a continuous infusion], leucovorin [administered IV] (or levoleucovorin [administered IV]), and irinotecan [administered IV]

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Bevacizumab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered intravenously (IV)

Arm title	Safety Run-In Arm 1: NIS793 + SoC (mFOLFOX6)

Arm description:

Safety Run-In (Investigational Arm 1): NIS793 in combination with Standard of Care (bevacizumab and modified FOLFOX6 (mFOLFOX6))

Arm type	Experimental

Investigational medicinal product name	NIS793
Investigational medicinal product code	
Other name	NIS793
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Investigational drug NIS793 was administered intravenously (IV) at the dose and schedule determined in the safety run-in part

Investigational medicinal product name	Modified FOLFOX6
Investigational medicinal product code	
Other name	5FU+Leucovorin+Oxaliplatin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-fluorouracil [administered as a continuous infusion], leucovorin [administered IV] (or levoleucovorin [administered IV]), and oxaliplatin [administered IV]

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Bevacizumab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered intravenously (IV)

Arm title	Safety Run-In Arm 2: NIS793 + TISLE + SoC (FOLFIRI)

Arm description:

Safety Run-In (Investigational Arm 2): NIS793 and Tislelizumab in combination with Standard of Care (bevacizumab and FOLFIRI)

Arm type	Experimental
Investigational medicinal product name	NIS793
Investigational medicinal product code	
Other name	NIS793
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Investigational drug NIS793 was administered intravenously (IV) at the dose and schedule determined in the safety run-in part

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Bevacizumab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered intravenously (IV)

Investigational medicinal product name	FOLFIRI
Investigational medicinal product code	
Other name	5FU+Leucovorin+Irinotecan
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-fluorouracil [administered as a continuous infusion], leucovorin [administered IV] (or levoleucovorin [administered IV]), and irinotecan [administered IV]

Investigational medicinal product name	Tislelizumab
Investigational medicinal product code	
Other name	VDT482
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Investigational drug tislelizumab was administered intravenously (IV)

Arm title	Safety Run-In Arm 2: NIS793 + TISLE + SoC (mFOLFOX6)

Arm description:

Safety Run-In (Investigational Arm 2): NIS793 and Tislelizumab in combination with Standard of Care (bevacizumab and modified FOLFOX6 (mFOLFOX6))

Arm type	Experimental
Investigational medicinal product name	NIS793
Investigational medicinal product code	
Other name	NIS793
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Investigational drug NIS793 was administered intravenously (IV) at the dose and schedule determined in the safety run-in part

Investigational medicinal product name	Modified FOLFOX6
Investigational medicinal product code	
Other name	5FU+Leucovorin+Oxaliplatin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-fluorouracil [administered as a continuous infusion], leucovorin [administered IV] (or levoleucovorin [administered IV]), and oxaliplatin [administered IV]

Investigational medicinal product name	Tislelizumab
Investigational medicinal product code	
Other name	VDT482
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Investigational drug tislelizumab was administered intravenously (IV)

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Bevacizumab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered intravenously (IV)

Arm title	Expansion Arm 1: NIS793 + SoC (FOLFIRI)

Arm description:

Expansion (Investigational Arm 1): NIS793 in combination with Standard of Care (bevacizumab and FOLFIRI)

Arm type	Experimental
Investigational medicinal product name	NIS793
Investigational medicinal product code	
Other name	NIS793
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Investigational drug NIS793 was administered intravenously (IV) at the dose and schedule determined in the safety run-in part

Investigational medicinal product name	FOLFIRI
Investigational medicinal product code	
Other name	5FU+Leucovorin+Irinotecan
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-fluorouracil [administered as a continuous infusion], leucovorin [administered IV] (or levoleucovorin [administered IV]), and irinotecan [administered IV]

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Bevacizumab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered intravenously (IV)

Arm title	Expansion Arm 2: NIS793 + TISLE + SoC (FOLFIRI)

Arm description:

Expansion (Investigational Arm 2): NIS793 and Tislelizumab in combination with Standard of Care (bevacizumab and FOLFIRI)

Arm type	Experimental
Investigational medicinal product name	NIS793
Investigational medicinal product code	
Other name	NIS793
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Investigational drug NIS793 was administered intravenously (IV) at the dose and schedule determined in the safety run-in part

Investigational medicinal product name	Tislelizumab
Investigational medicinal product code	
Other name	VDT482
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Investigational drug tislelizumab was administered intravenously (IV)

Investigational medicinal product name	FOLFIRI
Investigational medicinal product code	
Other name	5FU+Leucovorin+Irinotecan
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-fluorouracil [administered as a continuous infusion], leucovorin [administered IV] (or levoleucovorin [administered IV]), and irinotecan [administered IV]

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Bevacizumab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered intravenously (IV)

Arm title	Expansion Control Arm: SoC (FOLFIRI)

Arm description:

Expansion (Control Arm): Standard of Care (bevacizumab and FOLFIRI)

Arm type	Active comparator
Investigational medicinal product name	FOLFIRI
Investigational medicinal product code	
Other name	5FU+Leucovorin+Irinotecan
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-fluorouracil [administered as a continuous infusion], leucovorin [administered IV] (or levoleucovorin [administered IV]), and irinotecan [administered IV]

Arm title	Expansion Arm 1: NIS793 + SoC (mFOLFOX6)

Arm description:

Expansion (Investigational Arm 1): NIS793 in combination with Standard of Care (bevacizumab and modified FOLFOX6 (mFOLFOX6))

Arm type	Experimental
Investigational medicinal product name	NIS793
Investigational medicinal product code	
Other name	NIS793
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Investigational drug NIS793 was administered intravenously (IV) at the dose and schedule determined in the safety run-in part

Investigational medicinal product name	Modified FOLFOX6
Investigational medicinal product code	
Other name	5FU+Leucovorin+Oxaliplatin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-fluorouracil [administered as a continuous infusion], leucovorin [administered IV] (or levoleucovorin [administered IV]), and oxaliplatin [administered IV]

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Bevacizumab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered intravenously (IV)

Arm title	Expansion Control Arm: SoC (mFOLFOX6)

Arm description:

Expansion (Control Arm): Standard of Care (bevacizumab and modified FOLFOX6 (mFOLFOX6))

Arm type	Active comparator
Investigational medicinal product name	Modified FOLFOX6
Investigational medicinal product code	
Other name	5FU+Leucovorin+Oxaliplatin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-fluorouracil [administered as a continuous infusion], leucovorin [administered IV] (or levoleucovorin [administered IV]), and oxaliplatin [administered IV]

Number of subjects in period 1	Safety Run-In Arm 1: NIS793 + SoC (FOLFIRI)	Safety Run-In Arm 1: NIS793 + SoC (mFOLFOX6)	Safety Run-In Arm 2: NIS793 + TISLE + SoC (FOLFIRI)
Started	13	9	10
Completed	0	0	0
Not completed	13	9	10
Adverse event, serious fatal	-	-	-
Physician decision	2	-	-
Consent withdrawn by subject	-	2	-
Adverse event, non-fatal	1	1	1
Study terminated by sponsor	-	-	-
Progressive disease	10	6	9
Lost to follow-up	-	-	-

Number of subjects in period 1	Safety Run-In Arm 2: NIS793 + TISLE + SoC (mFOLFOX6)	Expansion Arm 1: NIS793 + SoC (FOLFIRI)	Expansion Arm 2: NIS793 + TISLE + SoC (FOLFIRI)
Started	8	67	29
Completed	0	0	0
Not completed	8	67	29
Adverse event, serious fatal	-	1	-
Physician decision	1	9	3
Consent withdrawn by subject	1	4	4
Adverse event, non-fatal	1	4	1
Study terminated by sponsor	-	3	6
Progressive disease	5	46	15
Lost to follow-up	-	-	-

Number of subjects in period 1	Expansion Control Arm: SoC (FOLFIRI)	Expansion Arm 1: NIS793 + SoC (mFOLFOX6)	Expansion Control Arm: SoC (mFOLFOX6)
Started	46	13	7
Completed	0	0	0
Not completed	46	13	7
Adverse event, serious fatal	1	-	-
Physician decision	4	1	-
Consent withdrawn by subject	7	2	2
Adverse event, non-fatal	-	-	-
Study terminated by sponsor	7	-	-
Progressive disease	26	10	5
Lost to follow-up	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Safety Run-In Arm 1: NIS793 + SoC (FOLFIRI)
Reporting group description:	
Safety Run-In (Investigational Arm 1): NIS793 in combination with Standard of Care (bevacizumab and FOLFIRI)	
Reporting group title	Safety Run-In Arm 1: NIS793 + SoC (mFOLFOX6)
Reporting group description:	
Safety Run-In (Investigational Arm 1): NIS793 in combination with Standard of Care (bevacizumab and modified FOLFOX6 (mFOLFOX6))	
Reporting group title	Safety Run-In Arm 2: NIS793 + TISLE + SoC (FOLFIRI)
Reporting group description:	
Safety Run-In (Investigational Arm 2): NIS793 and Tislelizumab in combination with Standard of Care (bevacizumab and FOLFIRI)	
Reporting group title	Safety Run-In Arm 2: NIS793 + TISLE + SoC (mFOLFOX6)
Reporting group description:	
Safety Run-In (Investigational Arm 2): NIS793 and Tislelizumab in combination with Standard of Care (bevacizumab and modified FOLFOX6 (mFOLFOX6))	
Reporting group title	Expansion Arm 1: NIS793 + SoC (FOLFIRI)
Reporting group description:	
Expansion (Investigational Arm 1): NIS793 in combination with Standard of Care (bevacizumab and FOLFIRI)	
Reporting group title	Expansion Arm 2: NIS793 + TISLE + SoC (FOLFIRI)
Reporting group description:	
Expansion (Investigational Arm 2): NIS793 and Tislelizumab in combination with Standard of Care (bevacizumab and FOLFIRI)	
Reporting group title	Expansion Control Arm: SoC (FOLFIRI)
Reporting group description:	
Expansion (Control Arm): Standard of Care (bevacizumab and FOLFIRI)	
Reporting group title	Expansion Arm 1: NIS793 + SoC (mFOLFOX6)
Reporting group description:	
Expansion (Investigational Arm 1): NIS793 in combination with Standard of Care (bevacizumab and modified FOLFOX6 (mFOLFOX6))	
Reporting group title	Expansion Control Arm: SoC (mFOLFOX6)
Reporting group description:	
Expansion (Control Arm): Standard of Care (bevacizumab and modified FOLFOX6 (mFOLFOX6))	

Reporting group values	Safety Run-In Arm 1: NIS793 + SoC (FOLFIRI)	Safety Run-In Arm 1: NIS793 + SoC (mFOLFOX6)	Safety Run-In Arm 2: NIS793 + TISLE + SoC (FOLFIRI)
Number of subjects	13	9	10
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	11	6	6
>=65 years	2	3	4
Sex: Female, Male Units: Participants			
Female	11	3	2
Male	2	6	8

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	2	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	0
White	10	7	9
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	Safety Run-In Arm 2: NIS793 + TISLE + SoC (mFOLFOX6)	Expansion Arm 1: NIS793 + SoC (FOLFIRI)	Expansion Arm 2: NIS793 + TISLE + SoC (FOLFIRI)
Number of subjects	8	67	29
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	5	46	24
>=65 years	3	21	5
Sex: Female, Male Units: Participants			
Female	2	29	11
Male	6	38	18
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	15	5
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	2
White	7	50	20
More than one race	0	0	1
Unknown or Not Reported	0	1	1

Reporting group values	Expansion Control Arm: SoC (FOLFIRI)	Expansion Arm 1: NIS793 + SoC (mFOLFOX6)	Expansion Control Arm: SoC (mFOLFOX6)
Number of subjects	46	13	7
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	36	11	4
>=65 years	10	2	3
Sex: Female, Male Units: Participants			
Female	18	8	2
Male	28	5	5
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	10	4	0
Native Hawaiian or Other Pacific Islander	0	0	0

Black or African American	1	0	0
White	34	9	7
More than one race	0	0	0
Unknown or Not Reported	1	0	0

Reporting group values	Total		
Number of subjects	202		
Age Categorical Units: Participants			
<=18 years	0		
Between 18 and 65 years	149		
>=65 years	53		
Sex: Female, Male Units: Participants			
Female	86		
Male	116		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	40		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	5		
White	153		
More than one race	1		
Unknown or Not Reported	3		

End points

End points reporting groups

Reporting group title	Safety Run-In Arm 1: NIS793 + SoC (FOLFIRI)
Reporting group description:	
Safety Run-In (Investigational Arm 1): NIS793 in combination with Standard of Care (bevacizumab and FOLFIRI)	
Reporting group title	Safety Run-In Arm 1: NIS793 + SoC (mFOLFOX6)
Reporting group description:	
Safety Run-In (Investigational Arm 1): NIS793 in combination with Standard of Care (bevacizumab and modified FOLFOX6 (mFOLFOX6))	
Reporting group title	Safety Run-In Arm 2: NIS793 + TISLE + SoC (FOLFIRI)
Reporting group description:	
Safety Run-In (Investigational Arm 2): NIS793 and Tislelizumab in combination with Standard of Care (bevacizumab and FOLFIRI)	
Reporting group title	Safety Run-In Arm 2: NIS793 + TISLE + SoC (mFOLFOX6)
Reporting group description:	
Safety Run-In (Investigational Arm 2): NIS793 and Tislelizumab in combination with Standard of Care (bevacizumab and modified FOLFOX6 (mFOLFOX6))	
Reporting group title	Expansion Arm 1: NIS793 + SoC (FOLFIRI)
Reporting group description:	
Expansion (Investigational Arm 1): NIS793 in combination with Standard of Care (bevacizumab and FOLFIRI)	
Reporting group title	Expansion Arm 2: NIS793 + TISLE + SoC (FOLFIRI)
Reporting group description:	
Expansion (Investigational Arm 2): NIS793 and Tislelizumab in combination with Standard of Care (bevacizumab and FOLFIRI)	
Reporting group title	Expansion Control Arm: SoC (FOLFIRI)
Reporting group description:	
Expansion (Control Arm): Standard of Care (bevacizumab and FOLFIRI)	
Reporting group title	Expansion Arm 1: NIS793 + SoC (mFOLFOX6)
Reporting group description:	
Expansion (Investigational Arm 1): NIS793 in combination with Standard of Care (bevacizumab and modified FOLFOX6 (mFOLFOX6))	
Reporting group title	Expansion Control Arm: SoC (mFOLFOX6)
Reporting group description:	
Expansion (Control Arm): Standard of Care (bevacizumab and modified FOLFOX6 (mFOLFOX6))	
Subject analysis set title	Expansion Arm 1: NIS793 + Standard of Care
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Expansion (Investigational arm 1): NIS793 in combination with Standard of Care (bevacizumab and either FOLFIRI or modified FOLFOX6 (mFOLFOX6))	
Subject analysis set title	Expansion Arm 2: NIS793 + TISLE + Standard of Care
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Expansion (Investigational arm 2): NIS793 and Tislelizumab in combination with Standard of Care (bevacizumab and FOLFIRI)	
Subject analysis set title	Expansion Control Arm: Standard of Care
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Expansion (control arm): Standard of Care (bevacizumab and either FOLFIRI or modified FOLFOX6 (mFOLFOX6))	
Subject analysis set title	Safety Run-In Arm 1: NIS793 + Standard of Care
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Safety Run-In (Investigational arm 1): NIS793 in combination with Standard of Care (bevacizumab and either FOLFIRI or modified FOLFOX6 (mFOLFOX6))

Subject analysis set title	Safety Run-In Arm 2: NIS793 + TISLE + Standard of Care
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Safety Run-In (Investigational arm 2): NIS793 and Tislelizumab in combination with Standard of Care (bevacizumab and either FOLFIRI or modified FOLFOX6 (mFOLFOX6))

Subject analysis set title	Safety Run-In Arm 1: NIS793 + Standard of Care
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Safety Run-In (Investigational arm 1): NIS793 in combination with Standard of Care (bevacizumab and either FOLFIRI or modified FOLFOX6 (mFOLFOX6)

Subject analysis set title	Safety Run-In Arm 1: NIS793 + Standard of Care
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Safety Run-In (Investigational arm 1): NIS793 in combination with Standard of Care (bevacizumab and either FOLFIRI or modified FOLFOX6 (mFOLFOX6))

Subject analysis set title	Safety Run-In Arm 2: NIS793 + TISLE + Standard of Care
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Safety Run-In (Investigational arm 2): NIS793 and Tislelizumab in combination with Standard of Care (bevacizumab and either FOLFIRI or modified FOLFOX6 (mFOLFOX6))

Subject analysis set title	Safety Run-In Arm 1: NIS793 + Standard of Care
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Safety Run-In (Investigational arm 1): NIS793 in combination with Standard of Care (bevacizumab and either FOLFIRI or modified FOLFOX6 (mFOLFOX6))

Subject analysis set title	Safety Run-In Arm 2: NIS793 + TISLE + Standard of Care
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Safety Run-In (Investigational arm 2): NIS793 and Tislelizumab in combination with Standard of Care (bevacizumab and either FOLFIRI or modified FOLFOX6 (mFOLFOX6))

Subject analysis set title	Safety Run-In Arm 1: NIS793 + SoC (FOLFIRI/mFOLFOX6)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Safety Run-In (Investigational Arm 1): NIS793 in combination with Standard of Care (FOLFIRI and modified FOLFOX6 (mFOLFOX6))

Subject analysis set title	Safety Run-In Arm 2: NIS793 + TISLE + SoC (FOLFIRI/mFOLFOX6)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Safety Run-In (Investigational Arm 2): NIS793 and Tislelizumab in combination with Standard of Care (FOLFIRI and modified FOLFOX6 (mFOLFOX6))

Subject analysis set title	Safety Run-In Arm 1: NIS793 + SoC (FOLFIRI/mFOLFOX6)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Safety Run-In (Investigational Arm 1): NIS793 in combination with Standard of Care (FOLFIRI and modified FOLFOX6 (mFOLFOX6))

Subject analysis set title	Safety Run-In Arm 2: NIS793 + TISLE + SoC (FOLFIRI/mFOLFOX6)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Safety Run-In (Investigational Arm 2): NIS793 and Tislelizumab in combination with Standard of Care (FOLFIRI and modified FOLFOX6 (mFOLFOX6))

Primary: (Safety run-in part) Number of participants with dose limiting toxicities (DLTs) during the first cycle (4 weeks) of treatment.

End point title	(Safety run-in part) Number of participants with dose limiting toxicities (DLTs) during the first cycle (4 weeks) of treatment.[1][2]

End point description:

The primary endpoint for the Safety Run-In part was the incidence of dose-limiting toxicities (DLT) during the first 28 days of treatment with investigational drug(s) (NIS793 with or without tislelizumab) and standard of care anti-cancer therapy. Dose tolerability decisions were based on all safety data and a Bayesian Logistic Regression Model (BLRM) using Escalation with Overdose Control (EWOC) criteria. Dose confirmation required at least six evaluable participants, fulfillment of EWOC criteria, and recommendation by Novartis and investigators after reviewing clinical, pharmacokinetic, and laboratory data.

End point type	Primary

End point timeframe:

Up to 4 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Endpoint applicable to Safety run-in part only

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint applicable to Safety run-in part only

End point values	Safety Run-In Arm 1: NIS793 + SoC (FOLFIRI)	Safety Run-In Arm 1: NIS793 + SoC (mFOLFOX6)	Safety Run-In Arm 2: NIS793 + TISLE + SoC (FOLFIRI)	Safety Run-In Arm 2: NIS793 + TISLE + SoC (mFOLFOX6)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	9	9	0[3]
Units: Participants	1	1	1	

Notes:

[3] - Study ended before RP2D was set for NIS793 + TISLE + SoC (mFOLFOX6)

Statistical analyses

No statistical analyses for this end point

Primary: (Expansion part) Progression-free survival (PFS) by investigator assessment per RECIST 1.1

End point title	(Expansion part) Progression-free survival (PFS) by investigator assessment per RECIST 1.1[4]

End point description:

PFS was defined as the time from the date of enrollment (run-in part) or randomization (randomized part) to the date of the first documented progression based on investigator assessment and according to RECIST 1.1 or death due to any cause

End point type	Primary

End point timeframe:

From randomization up to disease progression or death, assessed up to approximately 11 months

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Endpoint applicable to Expansion part only

End point values	Expansion Arm 1: NIS793 + Standard of Care	Expansion Arm 2: NIS793 + TISLE + Standard of Care	Expansion Control Arm: Standard of Care	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	80	29	53	
Units: Months				
median (confidence interval 95%)	5.1 (3.6 to 5.7)	3.7 (2.2 to 5.6)	7.4 (5.5 to 9.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety run-in part) Percentage of participants with Adverse Events (AEs)

End point title	(Safety run-in part) Percentage of participants with Adverse Events (AEs)[5]

End point description:

Percentage of participants who experienced AEs and SAEs, including changes in laboratory parameters, vital signs, body weight, and cardiac assessments

End point type	Secondary

End point timeframe:

Through Safety Run-in completion, an average of 6 months

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint applicable to Safety run-in part only

End point values	Safety Run-In Arm 1: NIS793 + SoC (FOLFIRI)	Safety Run-In Arm 1: NIS793 + SoC (mFOLFOX6)	Safety Run-In Arm 2: NIS793 + TISLE + SoC (FOLFIRI)	Safety Run-In Arm 2: NIS793 + TISLE + SoC (mFOLFOX6)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	9	10	8
Units: Participants				
Adverse Events (AEs)	13	9	10	8
Serious Adverse Events (SAEs)	6	6	6	5
Fatal SAEs	0	0	0	0
AEs leading to discontinuation	5	3	1	2
AEs leading to dose adjustment/interruption	12	7	9	7
AEs requiring additional therapy	13	9	10	8

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Run-In) Percentage of participants with dose interruptions and dose reductions of investigational drug

End point title	(Safety Run-In) Percentage of participants with dose interruptions and dose reductions of investigational drug[6]

End point description:

Tolerability was measured by the percentage of subjects who had dose adjustments (interruptions or reductions) of investigational drug (NIS793, NIS793 + tislelizumab)

End point type	Secondary

End point timeframe:

Up to approximately 7 months

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint applicable to Safety run-in part only

End point values	Safety Run-In Arm 1: NIS793 + SoC (FOLFIRI)	Safety Run-In Arm 1: NIS793 + SoC (mFOLFOX6)	Safety Run-In Arm 2: NIS793 + TISLE + SoC (FOLFIRI)	Safety Run-In Arm 2: NIS793 + TISLE + SoC (mFOLFOX6)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	9	10	8
Units: Participants				
NIS793: Participants with dose reduction	1	0	0	0
NIS793: Participants with dose interruption	8	6	9	5
Tislelizumab: Participants with dose reduction	999	999	0	0
Tislelizumab: Participants with dose interruption	999	999	5	2

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Run-In) Dose intensity of investigational drug

End point title	(Safety Run-In) Dose intensity of investigational drug[7]

End point description:

Tolerability was measured by the dose intensity of the investigational drug (e.g., NIS793, NIS793 + tislelizumab). Dose intensity was computed as the ratio of the actual cumulative dose received to the actual duration of exposure.

End point type	Secondary

End point timeframe:

Up to approximately 7 months

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint applicable to Safety run-in part only

End point values	Safety Run-In Arm 1: NIS793 + SoC (FOLFIRI)	Safety Run-In Arm 1: NIS793 + SoC (mFOLFOX6)	Safety Run-In Arm 2: NIS793 + TISLE + SoC (FOLFIRI)	Safety Run-In Arm 2: NIS793 + TISLE + SoC (mFOLFOX6)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	9	10	8
Units: mg/cycle				

arithmetic mean (standard deviation)				
NIS793	4171.2 (± 664.81)	3792.7 (± 426.97)	3550.5 (± 387.83)	3703.4 (± 627.94)
Tislelizumab	999 (± 999)	999 (± 999)	273.1 (± 28.72)	277.9 (± 45.58)

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety run-in part) PFS by investigator assessment per RECIST 1.1

End point title	(Safety run-in part) PFS by investigator assessment per RECIST 1.1

End point description:

PFS was defined as the time from the date of enrollment to the date of the first documented progression based on investigator assessment and according to RECIST 1.1 or death due to any cause

End point type	Secondary

End point timeframe:

From enrollment up to disease progression or death, assessed up to approximately 7 months

End point values	Safety Run-In Arm 1: NIS793 + Standard of Care	Safety Run-In Arm 2: NIS793 + TISLE + Standard of Care		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	18		
Units: Months				
median (confidence interval 95%)	3.6 (1.9 to 7.3)	2.1 (1.8 to 4.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety run-in part) Disease control rate (DCR) by investigator assessment per RECIST 1.1

End point title	(Safety run-in part) Disease control rate (DCR) by investigator assessment per RECIST 1.1

End point description:

DCR was defined as the proportion of participants with a best overall response (BOR) of complete response (CR), partial response (PR), or stable disease (SD), as per investigator assessment and according to RECIST 1.1

End point type	Secondary

End point timeframe:

Up to approximately 7 months

End point values	Safety Run-In Arm 1: NIS793 + Standard of Care	Safety Run-In Arm 2: NIS793 + TISLE + Standard of Care		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	18		
Units: Percentage of Responders				
number (confidence interval 95%)	63.6 (40.7 to 82.8)	44.4 (21.5 to 69.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety run-in part) Overall response rate (ORR) by investigator assessment per RECIST 1.1

End point title	(Safety run-in part) Overall response rate (ORR) by investigator assessment per RECIST 1.1

End point description:

ORR was defined as the proportion of participants with a best overall response (BOR) of complete response (CR) or partial response (PR), as per investigator assessment and according to RECIST 1.1

End point type	Secondary

End point timeframe:

Up to approximately 7 months

End point values	Safety Run-In Arm 1: NIS793 + Standard of Care	Safety Run-In Arm 2: NIS793 + TISLE + Standard of Care		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	18		
Units: Percentage of Responders				
number (confidence interval 95%)	4.5 (0.1 to 22.8)	0 (0 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety run-in part) Duration of response (DOR) by investigator assessment per RECIST 1.1

End point title	(Safety run-in part) Duration of response (DOR) by investigator

	assessment per RECIST 1.1

End point description:

DOR was defined as the duration of time between the date of the first documented response (CR or PR) and the date of first documented progression or death due to any cause

End point type	Secondary

End point timeframe:

From first documented response up to disease progression or death, assessed up to approximately 7 months

End point values	Safety Run-In Arm 1: NIS793 + Standard of Care	Safety Run-In Arm 2: NIS793 + TISLE + Standard of Care		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	18		
Units: Months				
median (confidence interval 95%)	9.4 (0 to 999)	999 (999 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety run-in part) Time to response (TTR) by investigator assessment per RECIST 1.1

End point title	(Safety run-in part) Time to response (TTR) by investigator assessment per RECIST 1.1

End point description:

TTR was defined as the duration of time between the date of enrollment and the date of the first documented response of either CR or PR

End point type	Secondary

End point timeframe:

From enrollment up to first documented response, assessed up to approximately 7 months

End point values	Safety Run-In Arm 1: NIS793 + Standard of Care	Safety Run-In Arm 2: NIS793 + TISLE + Standard of Care		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	18		
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety run-in part) Overall Survival (OS)

End point title	(Safety run-in part) Overall Survival (OS)

End point description:

OS was defined as the time from the date of enrollment to the date of death due to any cause

End point type	Secondary

End point timeframe:

From enrollment up to death, assessed up to approximately 7 months

End point values	Safety Run-In Arm 1: NIS793 + Standard of Care	Safety Run-In Arm 2: NIS793 + TISLE + Standard of Care		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	18		
Units: Months				
median (confidence interval 95%)	10.2 (5.8 to 20.8)	11.0 (6.2 to 15.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety run-in part) Maximum concentration (Cmax) of NIS793 and tislelizumab

End point title	(Safety run-in part) Maximum concentration (Cmax) of NIS793 and tislelizumab

End point description:

Blood samples were collected at indicated time-points for analysis of Cmax of NIS793 and tislelizumab.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, Cycle 3 Day 1 (1 cycle = 28 days).

End point values	Safety Run-In Arm 1: NIS793 + Standard of Care	Safety Run-In Arm 2: NIS793 + TISLE + Standard of Care		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	5		
Units: ng/mL				
arithmetic mean (standard deviation)				
NIS793: Cycle 1 Day 1	556000 (± 161000)	663000 (± 999)		
NIS793: Cycle 3 Day 1	967000 (± 285000)	1130000 (± 999)		
tislelizumab: Cycle 1 Day 1	999 (± 999)	71800 (± 10300)		
tislelizumab: Cycle 3 Day 1	999 (± 999)	90300 (± 11100)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety run-in part) Trough Concentration (Ctrough) of NIS793 and tislelizumab

End point title	(Safety run-in part) Trough Concentration (Ctrough) of NIS793 and tislelizumab

End point description:

Blood samples were collected at indicated time-points for analysis of Ctrough of NIS793 and tislelizumab

End point type	Secondary

End point timeframe:

Cycle 1 Day 15, Cycle 3 Day 1, Cycle 3 Day 15, Cycle 6 Day 1 (1 cycle = 28 days)

End point values	Safety Run-In Arm 1: NIS793 + Standard of Care	Safety Run-In Arm 2: NIS793 + TISLE + Standard of Care		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	10		
Units: ng/mL				
arithmetic mean (standard deviation)				
NIS793: Cycle 1 Day 15	164000 (± 59800)	173000 (± 18700)		
NIS793: Cycle 3 Day 1	406000 (± 178000)	284000 (± 136000)		
NIS793: Cycle 3 Day 15	439000 (± 165000)	273000 (± 12700)		
NIS793: Cycle 6 Day 1	699000 (± 324000)	999 (± 999)		
tislelizumab: Cycle 1 Day 15	999 (± 999)	28600 (± 40300)		

tislelizumab: Cycle 3 Day 1	999 (± 999)	21500 (± 8710)		
tislelizumab: Cycle 3 Day 15	999 (± 999)	23600 (± 3700)		
tislelizumab: Cycle 6 Day 1	999 (± 999)	48800 (± 30300)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety run-in part) NIS793 and Tislelizumab Antidrug antibodies (ADA) incidence on treatment

End point title	(Safety run-in part) NIS793 and Tislelizumab Antidrug antibodies (ADA) incidence on treatment

End point description:

Incidence of NIS793 and Tislelizumab Antidrug antibodies (ADA) on treatment was defined as the proportion of participants who were treatment-induced ADA positive (post-baseline ADA positive with an ADA-negative sample at baseline) and treatment-boosted ADA positive (post-baseline ADA positive with a titer that was at least the fold titer change greater than the ADA-positive baseline titer)

End point type	Secondary

End point timeframe:

From the date of first study drug intake up to approximately 7 months

End point values	Safety Run-In Arm 1: NIS793 + SoC (FOLFIRI/mFOLFOX6)	Safety Run-In Arm 2: NIS793 + TISLE + SoC (FOLFIRI/mFOLFOX6)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	10		
Units: Participants				
NIS793: Treatment-induced ADA-positive	0	0		
NIS793: Treatment-boosted ADA-positive	0	0		
Tislelizumab: Treatment-induced ADA-positive	999	2		
Tislelizumab: Treatment-boosted ADA-positive	999	0		

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety run-in part) NIS793 and Tislelizumab Antidrug antibodies (ADA) at baseline

End point title	(Safety run-in part) NIS793 and Tislelizumab Antidrug antibodies (ADA) at baseline

End point description:

Prevalence of NIS793 and Tislelizumab Antidrug antibodies (ADA) at baseline was defined as the proportion of participants who had an ADA positive result at baseline

End point type	Secondary

End point timeframe:

Baseline

End point values	Safety Run-In Arm 1: NIS793 + SoC (FOLFIRI/mFOLFOX6)	Safety Run-In Arm 2: NIS793 + TISLE + SoC (FOLFIRI/mFOLFOX6)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	18		
Units: Participants				
NIS793: ADA-positive (i.e. ADA prevalence)	0	0		
Tislelizumab: ADA-positive (i.e. ADA prevalence)	999	2		

Statistical analyses

No statistical analyses for this end point

Secondary: (Expansion part) Percentage of participants with Adverse Events (AEs)

End point title	(Expansion part) Percentage of participants with Adverse Events (AEs)[8]

End point description:

The percentage of participants who experienced AEs and SAEs, including changes in laboratory parameters, vital signs, body weight, and cardiac assessments

End point type	Secondary

End point timeframe:

Through Expansion completion, an average of 8 months

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint applicable to Expansion part only

End point values	Expansion Arm 1: NIS793 + SoC (FOLFIRI)	Expansion Arm 2: NIS793 + TISLE + SoC (FOLFIRI)	Expansion Control Arm: SoC (FOLFIRI)	Expansion Arm 1: NIS793 + SoC (mFOLFOX6)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67[9]	29	46	13
Units: Participants				
Adverse Events (AEs)	65	26	45	14
Serious Adverse Events (SAEs)	32	9	14	6
Fatal SAEs	0	0	0	0
AEs leading to discontinuation	19	5	9	5
AEs leading to dose adjustment/interruption	47	17	34	9

AEs requiring additional therapy	60	26	39	14

Notes:

[9] - Two participants were mis-randomized to the NIS793+SoC (FOLFIRI) while actually received NIS793+SoC

End point values	Expansion Control Arm: SoC (mFOLFOX6)			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Participants				
Adverse Events (AEs)	7			
Serious Adverse Events (SAEs)	3			
Fatal SAEs	0			
AEs leading to discontinuation	3			
AEs leading to dose adjustment/interruption	5			
AEs requiring additional therapy	6			

Statistical analyses

No statistical analyses for this end point

Secondary: (Expansion part) Percentage of participants with dose interruptions and dose reductions of investigational drug

End point title	(Expansion part) Percentage of participants with dose interruptions and dose reductions of investigational drug[10]

End point description:

Tolerability was measured by the percentage of subjects who had dose adjustments (interruptions) of the investigational drug (e.g., NIS793, NIS793 + tislelizumab)

End point type	Secondary

End point timeframe:

Up to approximately 11 months

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint applicable to Expansion part only

End point values	Expansion Arm 1: NIS793 + SoC (FOLFIRI)	Expansion Arm 2: NIS793 + TISLE + SoC (FOLFIRI)	Expansion Arm 1: NIS793 + SoC (mFOLFOX6)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67[11]	29	13	
Units: Participants				
NIS793: Participants with dose reduction	1	0	0	
NIS793: Participants with dose interruption	40	10	8	
Tislelizumab: Participants with dose reduction	0	0	0	

Tislelizumab: Participants with dose interruption	0	6	0	

Notes:

[11] - Two participants were mis-randomized to the NIS793+SoC (FOLFIRI) while actually received NIS793+SoC

Statistical analyses

No statistical analyses for this end point

Secondary: (Expansion part) Dose intensity of investigational drug

End point title	(Expansion part) Dose intensity of investigational drug[12]

End point description:

Tolerability was measured by the dose intensity of the investigational drug (e.g., NIS793, NIS793 + Tislelizumab). Dose intensity was computed as the ratio of the actual cumulative dose received to the actual duration of exposure.

End point type	Secondary

End point timeframe:

Up to approximately 11 months

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint applicable to Expansion part only

End point values	Expansion Arm 1: NIS793 + SoC (FOLFIRI)	Expansion Arm 2: NIS793 + TISLE + SoC (FOLFIRI)	Expansion Arm 1: NIS793 + SoC (mFOLFOX6)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67[13]	29	13	
Units: mg/cycle				
arithmetic mean (standard deviation)				
NIS793	3865.2 (± 591.35)	3982.1 (± 393.43)	3786.2 (± 437.93)	
Tislelizumab	999 (± 999)	290.8 (± 19.39)	999 (± 999)	

Notes:

[13] - Two participants were mis-randomized to the NIS793+SoC (FOLFIRI) while actually received NIS793+SoC

Statistical analyses

No statistical analyses for this end point

Secondary: (Expansion part) Overall response rate (ORR) by investigator assessment per RECIST 1.1

End point title	(Expansion part) Overall response rate (ORR) by investigator assessment per RECIST 1.1

End point description:

ORR was defined as the proportion of participants with a best overall response (BOR) of complete response (CR) or partial response (PR), as per investigator assessment and according to RECIST 1.1

End point type	Secondary

End point timeframe:

Up to approximately 11 months

End point values	Expansion Arm 1: NIS793 + Standard of Care	Expansion Arm 2: NIS793 + TISLE + Standard of Care	Expansion Control Arm: Standard of Care	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	80	29	53	
Units: Percentage of Responders				
number (confidence interval 95%)	8.8 (3.6 to 17.2)	13.8 (3.9 to 31.7)	15.1 (6.7 to 27.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Expansion part) Disease control rate (DCR) by investigator assessment per RECIST 1.1

End point title	(Expansion part) Disease control rate (DCR) by investigator assessment per RECIST 1.1

End point description:

DCR was defined as the proportion of participants with a best overall response (BOR) of complete response (CR), partial response (PR), or stable disease (SD), as per investigator assessment and according to RECIST 1.1

End point type	Secondary

End point timeframe:

Up to approximately 11 months

End point values	Expansion Arm 1: NIS793 + Standard of Care	Expansion Arm 2: NIS793 + TISLE + Standard of Care	Expansion Control Arm: Standard of Care	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	80	29	53	
Units: Percentage of Responders				
number (confidence interval 95%)	66.3 (54.8 to 76.4)	65.5 (45.7 to 82.1)	79.2 (65.9 to 89.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Expansion part) Time to response (TTR) by investigator assessment per RECIST 1.1

End point title	(Expansion part) Time to response (TTR) by investigator assessment per RECIST 1.1[14]

End point description:

TTR was defined as the duration of time between the date of enrollment and the date of first documented response of either CR or PR

End point type	Secondary

End point timeframe:

From enrollment up to first documented response, assessed up to approximately 11 months

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint applicable to Expansion part only

End point values	Expansion Control Arm: SoC (FOLFIRI)	Expansion Arm 1: NIS793 + Standard of Care	Expansion Arm 2: NIS793 + TISLE + Standard of Care	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[15]	0[16]	0[17]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[15] - Median and 95% CI not estimable due to too few participants with events

[16] - Median and 95% CI not estimable due to too few participants with events

[17] - Median and 95% CI not estimable due to too few participants with events

Statistical analyses

No statistical analyses for this end point

Secondary: (Expansion part) Duration of response (DOR) by investigator assessment per RECIST 1.1

End point title	(Expansion part) Duration of response (DOR) by investigator assessment per RECIST 1.1

End point description:

DOR was defined as the duration of time between the date of the first documented response (CR or PR) and the date of first documented progression or death due to any cause

End point type	Secondary

End point timeframe:

From first documented response up to disease progression or death, assessed up to approximately 11 months

End point values	Expansion Arm 1: NIS793 + Standard of Care	Expansion Arm 2: NIS793 + TISLE + Standard of Care	Expansion Control Arm: Standard of Care	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	80	29	53	
Units: Months				
median (confidence interval 95%)	9.5 (4.0 to 999)	999 (999 to 999)	11.1 (3.8 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Expansion part) Overall Survival (OS)

End point title	(Expansion part) Overall Survival (OS)

End point description:

OS was defined as the time from the date of enrollment to the date of death due to any cause

End point type	Secondary

End point timeframe:

From randomization up to death, assessed up to approximately 11 months

End point values	Expansion Arm 1: NIS793 + Standard of Care	Expansion Arm 2: NIS793 + TISLE + Standard of Care	Expansion Control Arm: Standard of Care	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	80	29	53	
Units: Months				
median (confidence interval 95%)	12.8 (8.0 to 14.2)	10.9 (6.1 to 999)	999 (11.6 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Expansion part) Maximum concentration (Cmax) of NIS793 and tislelizumab

End point title	(Expansion part) Maximum concentration (Cmax) of NIS793 and tislelizumab[18]

End point description:

Blood samples were collected at indicated time-points for analysis of Cmax of NIS793 and tislelizumab

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, Cycle 3 Day 1 (NIS793 only) (1 cycle = 28 days)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Endpoint applicable to Expansion part only

End point values	Expansion Arm 1: NIS793 + SoC (FOLFIRI)	Expansion Arm 2: NIS793 + TISLE + SoC (FOLFIRI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	5		
Units: ng/mL				
arithmetic mean (standard deviation)				
NIS793: Cycle 1 Day 1	598000 (± 178000)	694000 (± 478000)		
NIS793: Cycle 3 Day 1	904000 (± 301000)	871000 (± 315000)		
tislelizumab: Cycle 1 Day 1	999 (± 999)	93400 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Expansion part) Trough Concentration (Ctrough) of NIS793 and tislelizumab

End point title	(Expansion part) Trough Concentration (Ctrough) of NIS793 and tislelizumab[19]

End point description:

Blood samples were collected at indicated time-points for analysis of Ctrough of NIS793 and tislelizumab

End point type	Secondary

End point timeframe:

Cycle 1 Day 15 (NIS793 only), Cycle 2 Day (tislelizumab only), Cycle 3 Day 1, Cycle 3 Day 15 (NIS793 only), Cycle 4 Day (tislelizumab only), Cycle 6 Day 1 (NIS793 only) (1 cycle = 28 days)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint applicable to Expansion part only

End point values	Expansion Arm 1: NIS793 + SoC (FOLFIRI)	Expansion Arm 2: NIS793 + TISLE + SoC (FOLFIRI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	18		
Units: ng/mL				
arithmetic mean (standard deviation)				
NIS793: Cycle 1 Day 15	189000 (± 56200)	181000 (± 50000)		
NIS793: Cycle 3 Day 1	371000 (± 1116000)	391000 (± 100000)		
NIS793: Cycle 3 Day 15	394000 (± 121000)	342000 (± 186000)		
NIS793: Cycle 6 Day 1	365000 (± 180000)	999 (± 999)		
tislelizumab: Cycle 2 Day 1	999 (± 999)	25400 (± 19600)		
tislelizumab: Cycle 3 Day 1	999 (± 999)	29400 (± 12700)		

tislelizumab: Cycle 4 Day 1	999 (± 999)	39400 (± 17100)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Expansion part) NIS793 and Tislelizumab Antidrug antibodies (ADA) incidence on treatment

End point title	(Expansion part) NIS793 and Tislelizumab Antidrug antibodies (ADA) incidence on treatment[20]

End point description:

Incidence of NIS793 and Tislelizumab Antidrug antibodies (ADA) on treatment was defined as the proportion of participants who were treatment-induced ADA positive (post-baseline ADA positive with an ADA-negative sample at baseline) and treatment-boosted ADA positive (post-baseline ADA positive with a titer that was at least the fold titer change greater than the ADA-positive baseline titer)

End point type	Secondary

End point timeframe:

From the date of first study drug intake up to approximately 11 months

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint applicable to Expansion part only

End point values	Expansion Arm 1: NIS793 + SoC (FOLFIRI)	Expansion Arm 2: NIS793 + TISLE + SoC (FOLFIRI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	20		
Units: Participants				
NIS793: Treatment-induced ADA-positive	0	0		
NIS793: Treatment-boosted ADA-positive	0	0		
Tislelizumab: Treatment-induced ADA-positive	999	0		
Tislelizumab: Treatment-boosted ADA-positive	999	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were recorded from first dose of study medication to 30 days after the last dose of Standard of Care, assessed up to approximately 38 months. Safety Run-in lasted about 162.5 days (5.4 months), and Expansion lasted about 221.3 days (7.4 months).

Adverse event reporting additional description:

For both the Safety run-in and Expansion phases, the Safety population comprised all participants who received at least one dose of any study drug, including incomplete infusions, with data pooled by treatment arm. In the Expansion phase, two participants were mis-randomized to NIS793 + SoC (FOLFIRI) but actually received NIS793 + SoC (mFOLFOX6).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	NIS793+SoC(S)
Reporting group description: NIS793+SoC(S)	
Reporting group title	NIS793+TISLE+SoC(E)
Reporting group description: NIS793+TISLE+SoC(E)	
Reporting group title	SoC(E)
Reporting group description: SoC(E)	
Reporting group title	NIS793+TISLE+SoC(S)
Reporting group description: NIS793+TISLE+SoC(S)	
Reporting group title	NIS793+SoC(E)
Reporting group description: NIS793+SoC(E)	

Serious adverse events	NIS793+SoC(S)	NIS793+TISLE+SoC(E)	SoC(E)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	0 / 52 (0.00%)
number of deaths (all causes)	22	26	52
number of deaths resulting from adverse events	0	0	0

Serious adverse events	NIS793+TISLE+SoC(S)	NIS793+SoC(E)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	0 / 79 (0.00%)	
number of deaths (all causes)	18	79	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	NIS793+SoC(S)	NIS793+TISLE+SoC (E)	SoC(E)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 22 (77.27%)	13 / 26 (50.00%)	32 / 52 (61.54%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	6 / 52 (11.54%)
occurrences (all)	0	0	8
Fatigue			
subjects affected / exposed	1 / 22 (4.55%)	2 / 26 (7.69%)	4 / 52 (7.69%)
occurrences (all)	1	2	4
Mucosal inflammation			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	1 / 52 (1.92%)
occurrences (all)	1	1	1
Pyrexia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 26 (7.69%)	2 / 52 (3.85%)
occurrences (all)	0	2	2
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Epistaxis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Pleural effusion			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood thrombin abnormal			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	0 / 52 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	6 / 52 (11.54%)
occurrences (all)	2	1	10
Injury, poisoning and procedural complications			
Stoma site haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	1 / 52 (1.92%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	3 / 22 (13.64%)	0 / 26 (0.00%)	2 / 52 (3.85%)
occurrences (all)	5	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 22 (9.09%)	4 / 26 (15.38%)	0 / 52 (0.00%)
occurrences (all)	2	5	0
Neutropenia			
subjects affected / exposed	5 / 22 (22.73%)	3 / 26 (11.54%)	14 / 52 (26.92%)
occurrences (all)	8	10	20
Eye disorders			
Keratitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Proctalgia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	4 / 52 (7.69%)
occurrences (all)	1	0	5
Diarrhoea			
subjects affected / exposed	2 / 22 (9.09%)	2 / 26 (7.69%)	6 / 52 (11.54%)
occurrences (all)	3	2	8
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 22 (4.55%)	1 / 26 (3.85%)	1 / 52 (1.92%)
occurrences (all)	1	1	1
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	0 / 22 (0.00%)	2 / 26 (7.69%)	1 / 52 (1.92%)
occurrences (all)	0	2	1
Infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	1 / 52 (1.92%)
occurrences (all)	1	0	1
Rectal abscess			

subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	3 / 52 (5.77%)
occurrences (all)	0	1	3
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	NIS793+TISLE+SoC (S)	NIS793+SoC(E)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 18 (72.22%)	37 / 79 (46.84%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
Haemorrhage			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 18 (16.67%)	0 / 79 (0.00%)	
occurrences (all)	3	0	
Fatigue			
subjects affected / exposed	0 / 18 (0.00%)	3 / 79 (3.80%)	
occurrences (all)	0	3	
Mucosal inflammation			
subjects affected / exposed	0 / 18 (0.00%)	4 / 79 (5.06%)	
occurrences (all)	0	5	
Pyrexia			
subjects affected / exposed	1 / 18 (5.56%)	2 / 79 (2.53%)	
occurrences (all)	1	2	

Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 18 (11.11%)	1 / 79 (1.27%)	
occurrences (all)	2	2	
Pleural effusion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood thrombin abnormal			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	1 / 18 (5.56%)	10 / 79 (12.66%)	
occurrences (all)	1	14	
Injury, poisoning and procedural complications			
Stoma site haemorrhage			
subjects affected / exposed	1 / 18 (5.56%)	2 / 79 (2.53%)	
occurrences (all)	1	2	
Infusion related reaction			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 18 (5.56%)	9 / 79 (11.39%)	
occurrences (all)	2	13	
Neutropenia			
subjects affected / exposed	3 / 18 (16.67%)	10 / 79 (12.66%)	
occurrences (all)	4	18	
Eye disorders			

Keratitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Proctalgia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 18 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	2 / 18 (11.11%)	3 / 79 (3.80%)	
occurrences (all)	3	3	
Constipation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 18 (5.56%)	1 / 79 (1.27%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 18 (11.11%)	0 / 79 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
COVID-19			
subjects affected / exposed	1 / 18 (5.56%)	1 / 79 (1.27%)	
occurrences (all)	1	1	
Infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	

Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
Rectal abscess			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 18 (5.56%)	3 / 79 (3.80%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
Hypocalcaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 79 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 November 2021	Amendment 1: The key purpose of this amendment was to add additional treatment arm(s) with new investigational drug(s) in combination with SoC anti-cancer therapy for the second-line treatment of mCRC.
20 September 2022	Amendment 2: The main purpose of this amendment was to clarify independent determination of RP2D for each of the tested regimens, as RP2D for each investigational arm were different for the combination with FOLFIRI and mFOLFOX6, depending on the tolerability of each regimen.
30 May 2023	Amendment 3 (withdrawn on 01-Sep-2023): The key purpose of this amendment was to update the relevant protocol sections to reflect the latest changes made in the Investigator's Brochure Edition 8. Amendment 3 was released on 30-May-2023. On 31 Jul 2023 a communication instructing all participants to discontinue treatment with NIS793 and hold tislelizumab was issued. On 01-Sep-2023, an investigator notification was issued requesting withdrawal of amendment 3 and the corresponding Informed Consent Form (ICFs) in cases where the documents were already submitted to HAs and/or ECs/IRBs, because the newly introduced changes were no longer applicable. Amendment 3 was not implemented in any countries/sites. All countries/sites continued to operate under amendment 2. However, approvals were granted by the Health Authority of Germany and an EC of a single site in Hong Kong and Australia and could not be withdrawn. Accordingly, in these sites, amendment 3 was replaced by amendment 4.
11 March 2024	Amendment 4: As of 20-Feb-2024, 205 participants had been enrolled in the study and 20 were still receiving SoC therapy. Specifically, 39 participants enrolled in the SRI Part (22 in Arm 1, 16 in Arm 2, 1 discontinued at C1D1) and 166 participants enrolled in the Expansion Part (81 in Arm 1, 31 in Arm 2, 53 in Control arm, 1 discontinued at C1D1). No participants were receiving NIS793 nor tislelizumab in the study. Following the daNIS-2 study (CNIS793B12301) DMC's recommendation to stop administration of NIS793 to participants with PDAC, Novartis also decided to halt daNIS-3 study screening and enrollment of new participants, a communication for this was released on 12-Jul-2023. On 31-Jul-2023 the daNIS-3 DMC recommended to stop NIS793 and tislelizumab treatment due to an unfavorable benefit-risk profile observed in the investigational treatment arms in participants with mCRC. Based on the available data, NIS793 showed a deleterious PFS signal and a trend in reduced OS compared to SoC in participants with mCRC. The participant could continue to receive SoC therapy, as per Investigator's assessment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please go to https://www.novctrd.com/#/ for complete trial results