



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 |
|-----------------|---|

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) 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) 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) 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 (\pm 161000) | 663000 (\pm 999) | | |
| NIS793: Cycle 3 Day 1 | 967000 (\pm 285000) | 1130000 (\pm 999) | | |
| tislelizumab: Cycle 1 Day 1 | 999 (\pm 999) | 71800 (\pm 10300) | | |
| tislelizumab: Cycle 3 Day 1 | 999 (\pm 999) | 90300 (\pm 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 (\pm 59800) | 173000 (\pm 18700) | | |
| NIS793: Cycle 3 Day 1 | 406000 (\pm 178000) | 284000 (\pm 136000) | | |
| NIS793: Cycle 3 Day 15 | 439000 (\pm 165000) | 273000 (\pm 12700) | | |
| NIS793: Cycle 6 Day 1 | 699000 (\pm 324000) | 999 (\pm 999) | | |
| tislelizumab: Cycle 1 Day 15 | 999 (\pm 999) | 28600 (\pm 40300) | | |
| tislelizumab: Cycle 3 Day 1 | 999 (\pm 999) | 21500 (\pm 8710) | | |
| tislelizumab: Cycle 3 Day 15 | 999 (\pm 999) | 23600 (\pm 3700) | | |
| tislelizumab: Cycle 6 Day 1 | 999 (\pm 999) | 48800 (\pm 30300) | | |

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/mFOL FOX6) | Safety Run-In Arm 2: NIS793 + TISLE + SoC (FOLFIRI/mFOL FOX6) | | |
|---|---|---|--|--|
| 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: (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/mFOL FOX6) | Safety Run-In Arm 2: NIS793 + TISLE + SoC (FOLFIRI/mFOL FOX6) | | |
|--|---|---|--|--|
| 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: (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) 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) 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) 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 (Ctough) of NIS793 and tislelizumab

| | |
|-----------------|---|
| End point title | (Expansion part) Trough Concentration (Ctough) of NIS793 and tislelizumab ^[19] |
|-----------------|---|

End point description:

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

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

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 26 (0.00%) 0 | 0 / 52 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 26 (3.85%) 1 | 3 / 52 (5.77%) 3 |
| Metabolism and nutrition disorders Hypomagnesaemia subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 26 (0.00%) 0 | 0 / 52 (0.00%) 0 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 26 (0.00%) 0 | 0 / 52 (0.00%) 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 occurrences (all) | 1 / 18 (5.56%) 1 | 0 / 79 (0.00%) 0 | |
| Haemorrhage subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 0 / 79 (0.00%) 0 | |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) | 3 / 18 (16.67%) 3 | 0 / 79 (0.00%) 0 | |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 3 / 79 (3.80%) 3 | |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 4 / 79 (5.06%) 5 | |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 2 / 79 (2.53%) 2 | |

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

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

