Poster P-5

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Phase II study (daNIS-1) of the anti-TGF-β monoclonal antibody (mAb) NIS793 with and without the PD-1 inhibitor spartalizumab in combination with nab-paclitaxel/gemcitabine (NG) versus NG alone in patients (pts) with first-line metastatic pancreatic ductal adenocarcinoma (mPDAC)

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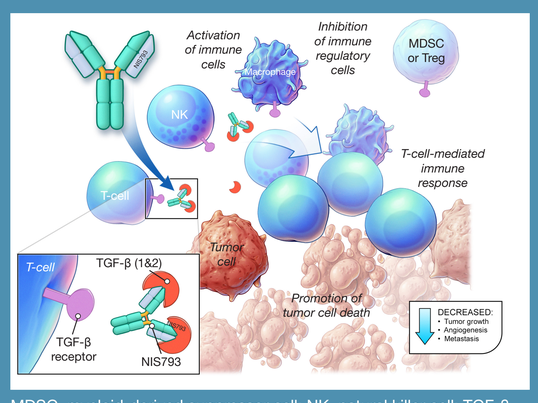
This study is sponsored by Novartis Pharmaceuticals Corporation.
Poster presented at the ESMO 2022 World Congress on Gastrointestinal Cancer, Barcelona, Spain, 29 June–2 July 2022

INTRODUCTION

- Pancreatic ductal adenocarcinoma (PDAC) is an aggressive, systemic disease with increasing incidence and dismal prognosis, despite approved therapies.[1]
- PDAC is predicted to become the second most frequent cause of cancer-related death by 2030 if treatment options do not improve.[2]
- FOLFIRINOX and combined treatment with nab-paclitaxel/gemcitabine (NG) in metastatic PDAC (mPDAC) have shown improved overall survival (OS) in comparison with gemcitabine monotherapy.[3,4] Despite these approved chemotherapies, the 5-year OS rate is still below 10%.[5]

Figure 1. Proposed mechanism of action of NIS793



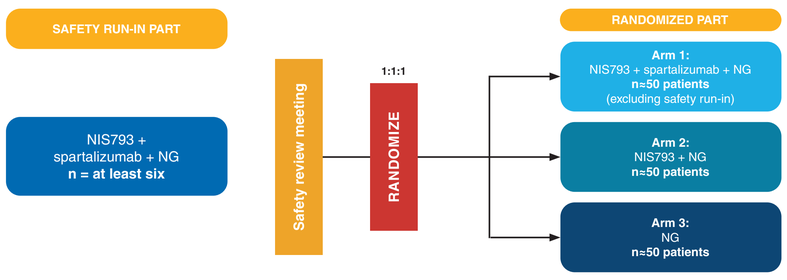
MDSC, myeloid-derived suppressor cell; NK, natural killer cell; TGF-β, transforming growth factor-beta; Treg, Regulatory T cells

- PDAC is characterized by an abundance of intratumoral fibrosis, which may contribute to the lack of treatment efficacy and act as a mechanical barrier to effective penetration of therapeutics.
- Emerging evidence points to roles of transforming growth factor-beta (TGF-β) as a key activator of cancer-associated fibroblasts, which lead to the development of fibrotic networks and immune exclusion, and in maintaining an immunosuppressive tumor microenvironment (TME).
- In preclinical models, TGF-β blockade altered the TME to restore immunocompetence and reduce stromal fibrosis, which may improve immune infiltration and treatment delivery, thus providing rationale for evaluating TGF-β–neutralizing agents in combination therapies/regimens.[6]
- NIS793 is a human, anti–TGF-β, immunoglobulin G2 monoclonal antibody that binds to TGF-β1 and TGF-β2 with high affinity (**Figure 1**). Preclinical data showed TGF-β blockade by NIS793 to target the development of intratumoral fibrosis[5] and augment the response to programmed cell death-1 (PD-1) blockade.
- First-in-human clinical data showed an acceptable safety profile of NIS793 in combination with spartalizumab in pts with advanced solid tumors.[7]
- Here, we present the design of an ongoing study investigating NIS793, with and without spartalizumab, combined with NG for the treatment of chemo-naive mPDAC.

STUDY DESIGN

- This is a parallel-arm, open-label, randomized, multicenter, Phase II study evaluating the safety and efficacy of NIS793, with and without spartalizumab, combined with NG in first-line mPDAC (NCT04390763).
  - The study is designed to have a safety run-in period (≥6 pts) followed by randomization (~150 pts in a 1:1:1 ratio) (**Figure 2**).
  - A safety review meeting will occur when ≥6 enrolled pts have completed 4 weeks of treatment or discontinued earlier due to dose-limiting toxicities.
  - If after the safety review meeting a decision is made to modify the regimen, another cohort of ≥6 pts will be enrolled in the safety run-in.
- Details of the drug dosages and administration schedules are shown in **Figure 3**.
- Crossover between treatment arms is not permitted at any time during the study.
- Pts will have safety evaluations for 150 days (safety run-in and Arm 1), 90 days (Arm 2), and 30 days (Arm 3) after the last dose of NIS793, spartalizumab, and NG, respectively, whichever is longer.
- Study objectives and endpoints are listed in **Table 1**, and key eligibility criteria are listed in **Table 2**.

Figure 2. Study design[a,b]



[a]Treatment will continue until unacceptable toxicity, disease progression, discontinuation by investigator's or patient's choice, or withdrawal of consent; [b]The dose regimen for the randomized part of the study will be determined following the safety review.
NG, nab-paclitaxel/gemcitabine.

Table 1. Objectives and endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
Safety run-in part: • Assess the safety and tolerability of NIS793 + spartalizumab in combination with NG	• Incidence of any DLTs that may occur during the first 4 weeks of treatment • Safety: Incidence and severity of treatment-emergent AEs and SAEs, changes between baseline and post-baseline laboratory parameters, vital signs, and ECG parameters • Tolerability: Dose interruptions, dose reductions, and dose intensity
Randomized part: • Evaluate the PFS associated with NIS793 + spartalizumab in combination with NG versus NG alone • Evaluate the PFS associated with NIS793 + NG versus NG alone	• PFS based on RECIST v1.1 as per local investigator's review
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
Randomized part: • Safety and tolerability in each treatment arm	• Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs, and ECGs; dose interruptions, dose reductions, and dose intensity
• Antitumor activity and OS in each treatment arm	• ORR, DOR, and TTP per RECIST v1.1 as per local investigator's review, and OS
• PK, pharmacodynamics, and immunogenicity	• PK parameters and concentration–time profiles; changes from baseline in CD8 and PD-L1 IHC-related markers; ADA prevalence at baseline and on treatment (anti-NIS793 and anti-spartalizumab)

ADA, anti drug antibody; AE, adverse event; CD8, cluster of differentiation 8; ECG, electrocardiogram; DOR, duration of response; IHC, immunohistochemistry; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PK, pharmacokinetics; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious AE; TTP, time to progression.

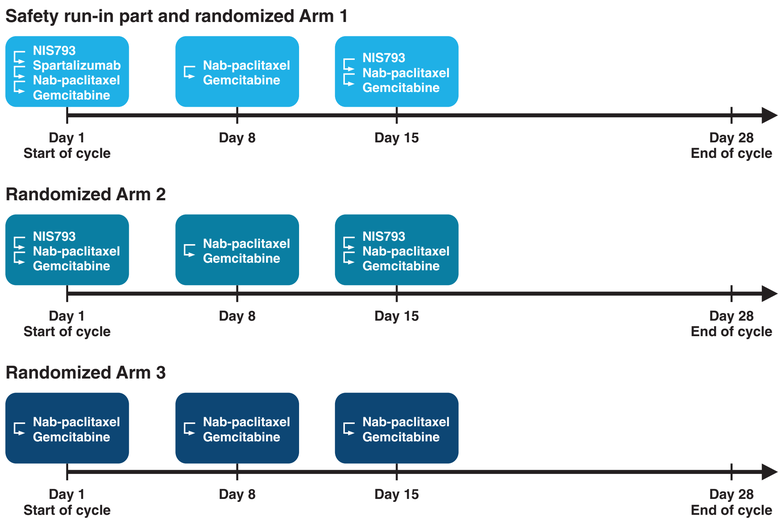
Table 2. Key eligibility criteria

Key inclusion criteria
Aged >18 years (pts from Japan aged <20 years require written consent from the patient and their legal representative)
Histologically/cytologically confirmed, treatment-naive metastatic adenocarcinoma of the pancreas with measurable disease as per RECIST v1.1
Have a site of disease amenable to biopsy and should be a candidate for tumor biopsy according to the treating institution's guidelines
Willingness to undergo a tumor biopsy at screening and during therapy
ECOG performance status ≤1
Key exclusion criteria
Previous radiotherapy, surgery (with exception of placement of biliary stent), chemotherapy, or any other investigational therapy for the treatment of metastatic pancreatic cancer; chemotherapy in the adjuvant setting
Pts amenable to potentially curative resection
Pts with MSI-H pancreatic adenocarcinoma or diagnosis of a PNET, acinar, or islet cell tumor
Pts with out-of-range laboratory values as pre defined in the protocol, or history of severe hypersensitivity reactions to any ingredients of study drug(s) or other mAbs and/or their excipients
Presence of symptomatic CNS metastases, or CNS metastases that require local CNS-directed therapy, or increasing doses of corticosteroids 2 weeks prior to study entry
Impaired cardiac function, HIV infection, active HBV or HCV infection (unless controlled by antiviral therapy), or interstitial lung disease or pneumonitis Grade ≥2

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; mAb, monoclonal antibody; MSI-H, microsatellite instability-high; PNET, pancreatic neuroendocrine tumor; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

Dosage and administration

Figure 3. Dosages and administration



- In the safety run-in, pts will receive intravenous administration of: NIS793 (2100 mg) once every 2 weeks, with spartalizumab (400 mg) once every 4 weeks with gemcitabine (1000 mg/m^2) on Days 1, 8, and 15, and nab-paclitaxel (125 mg/m^2) on Days 1, 8, and 15 (**Figure 3**). One cycle is 28 days.

Assessments

- All assessments are done locally, except biomarker, and pharmacokinetic (PK), pharmacodynamic (PD) and immunogenicity (IG) analyses, which are done at central laboratories.

Efficacy

- Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) and Response Evaluation Criteria In Solid Tumors For Immunotherapy Trials (iRECIST) (for exploratory endpoints).

Safety

- Safety assessments include monitoring adverse events, physical examinations, vital signs, Eastern Cooperative Oncology Group performance status, laboratory analyses, electrocardiograms, cardiac imaging, and troponin and N-terminal pro B-type natriuretic peptide analyses.

Other assessments

- Additional tests include carbohydrate antigen 19-9. PK/PD/IG samples must be drawn before biochemistry and other blood sampling are performed. PK is assessed for NIS793, spartalizumab, and NG; IG is assessed for NIS793 and spartalizumab and PD is assessed for NIS793.

Trial status

- This trial is a multicenter, international study recruiting pts with first-line mPDAC.
- The first patient was treated on October 22, 2020. Enrollment for the randomized part of the study started on August 9, 2021.
- This study is ongoing and will enroll pts from 31 sites across 14 countries **Supplementary Figure S1**.[8]

Click for supplementary material

SUMMARY

- This study is a randomized, parallel-arm, open-label, multicenter, Phase II study investigating the safety and efficacy of the combination of NIS793, with and without spartalizumab, and NG in pts with first-line mPDAC.
- The primary objective of the safety run-in is to evaluate the safety and tolerability of NIS793 in combination with spartalizumab and NG. The primary objective of the randomized part is to evaluate progression-free survival per investigator assessment associated with NIS793, with and without spartalizumab, in combination with NG versus NG alone.
- Secondary objectives include assessing the safety, tolerability, preliminary antitumor activity, OS, and PK of the NIS793-based treatment arms compared with NG alone. Other secondary objectives include cluster of differentiation 8 (CD8) and Programmed death-ligand 1 (PD-L1) status at screening and on treatment versus NG.

Acknowledgments

- The authors would like to thank the patients taking part in the trial and their families, and the staff at each site involved with the study.
- The authors would like to thank the study principal investigators: Emiliano Calvo Aller, Thomas Aparicio, Nathan Bahary, Li-Yuan Bai, Bruno Bockorny, Joelle Collignon, Maria Diab, Thomas Ettrich, Ralph Fritsch, Richard Greil, Rosine Guimbaud, Daniel Horber, Masafumi Ikeda, Daniel Laheru, Teresa Macarulla Mercade, Michael Michael, Gerald Prager, Michele Reni, Jens Siveke, Christoph Springfeld, Wai Meng David Tai, Colin Weekes, and Mark Ka Wong.
- This study is sponsored by Novartis Pharmaceuticals Corporation.
- Editorial writing assistance was provided by Sivanjaa Manoj, PhD, of Articulate Science Ltd., and was funded by Novartis Pharmaceuticals Corporation.

Disclosures

- Shivan Sivakumar reports reseach funding from Bristol Myers Squibb and Celgene.
- Theresa Macarulla receives consulting or advisory fees and travel accommodation expenses from Sanofi, Celgene, Servier, prIME Oncology and Incyte; consulting or advisory fees only from Merck and H3 Biomedicine and travel accommodation expenses only from Roche, QED Therapeutics, Baxter, Lilly, Ispen, AstraZeneca, MSD, Eisai, Genzyme, Lab. Menarini, Ability Pharmaceuticals SL, Advance Medical HCMS, BioLineRX, Zymeworks, Aptitude Health, (SOBI) Swedish Orpahn Biovitrum AB, Basilea Pharma, Medscape, Novocure, Parexel, PPD Development, Ellipses, Got It Consulting (ANGEM), Hirslanden/GITZ, Imedex, Janssen, Marketing Farmaceutico & Investigacion Clinica, Polaris Consulting, Scilink Comunicacion Cientifica SC and Surface Oncology. Teresa Macarulla's institute receives research funding only from Celgene, AGIOS Pharmaceuticals Inc, ASLAN Pharmaceutical PTE LTD, Bayer, Roche, Genetech, AstraZeneca, Immunomedics, Lilly S.A., Merrimack, Millennium, Novocure GMBH, Pfizer, S.L.U and Pharmacyclics, AbbVie, Ability pharmaceuticals, AMC Medical Research, Amgen, Armo Biosciences, Basilea Pharmaceutica International, BeiGene, Biokeralty Research Institute, Bioline Rx, Blueprint Medicines, Boston Biomedical, Bristol Myers Squibb, Cantargia AB, Eisai, Erytech Pharma, F. Hoffmann-La Roche, Fibrogen, Halozyme, Incyte, Ipsen, Loxo Oncology, Medimmune, Merck Sharp & Dohme, Nelum, Novartis, Oncomed Pharmaceuticals,VCN Biosciences, and Zymeworks.
- Peter Grell reports consulting or advisory fees and travel expenses from Servier and consulting or advisory fees from Roche.
- Cheng Ean Chee receives honoraria from Roche/Genetech and AstraZeneca and consulting or advisory fees from Guardant Health AMEA and travel, accommodation expenses from Tahio Pharmaceutical.
- Anuradha Krishnamurthy has nothing to disclose.
- Mark Wong receives consulting or advisory fees and speaker's bureau from MSD Oncology and speaker's bureau only fromSirtex Medica.
- Michael Michael consulting or advisory fees and research funding from Ipsen and consulting or advisory fees only from Merck and Isotopen Technologien and travel accommodation expenses from Novartis Australia.
- Michele Milella reports honoraria and research funding from Roche and honoraria fees only from AstraZeneca, MSD, Pfizer, EUSA Pharma, Boehringer Ingelheim and Ispen and consulting or advisory fees from Novartis.
- Gerald Prager receives consulting or advisory fees from Bayer, Servier, MSD, BMS, Lilly, Sanofi, Roche, Merck, Incyte, and Pierre Fabre.
- Christoph Springfeld receives consulting or advisory fees and travel expenses from Servier and consulting or advisory fees only from Eisai, Roche, MSD, and Bayer.
- Joelle Collignon's institution receives consulting or advisory fees and travel and accommodation expenses from Roche; consulting or advisory fees only from Celgene, Ipsen, Sevier, Baer, Lilly, Sanofi, Novartis, and Merck and travel accommodation expenses only from Pfizer, and Amgen.
- Jens Siveke report stock ownership in Pharma 15 and consulting or advisory fees only from Celgene, AstraZeneca, Immunocore, Bayer, and Roche. Jens Siveke's institution receives consulting or advisory fees from AstraZeneca and research funding from Bristol Myers Squibb, Celgene, and Roche.
- Armando Santoro reports consulting or advisory fees and speakers' bureau fees from, Servier, Gilead Sciences, Pfizer, Eisai, Bayer, MSD, and ArQule; consulting or advisory fees only from Bristol Myers Squibb, Incyte, and Sanofi and speakers' bureau fees only from Takeda, Roche, AbbVie, Amgen, Celgene, AstraZeneca, Lilly, BMS, Sandoz, and Novartis.
- Chia-Chi Lin reports consulting or advisory fees, travel expenses, and honoraria fees from Novartis and Daiichi Sankyo; travel expenses and honoraria fees from Lilly; consulting or advisory fees only from Boehringer Ingelheim, and Blueprint Medicines, AbbVie, and PharmaEngine; travel expenses only from BeiGene and honoraria fees only from Roche.
- Katriina Peltola reports an immediate family member employed by Terveystalo; stock ownership of Faron Pharmaceuticals; consulting or advisory fees and travel expenses from Bristol Myers Squibb and Roche and consulting or advisory fees only from MSD Oncology, Lilly, Pfizer, Novartis, and Ipsen.
- Geraldine Bostel and an immediate family member are both Novartis employees, and both report stock ownership of Novartis.
- Dragana Jankovic and Claire Fabre are Novartis employees, and report stock ownership of Novartis.
- Maria-Athina Altzerinakou is a Novartis employee.
- Li-Yuan Bai receives honoraria from Syncore, Pfizer, Eli Lilly, Cstone Pharmaceuticals, Ono Pharmaceutical and Ipsen; consulting or advisory fees from Bristol-Myers Squibb and Zai Lab and research funding from Eisai.

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