Napabucasin plus nab-paclitaxel with gemcitabine versus nab-paclitaxel with gemcitabine in previously untreated metastatic pancreatic adenocarcinoma: an adaptive multicentre, randomised, open-label, phase 3, superiority trial

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Summary

Background Compared with normal cells, tumour cells contain elevated levels of reactive oxygen species (ROS). Increased levels of the antioxidant protein NAD(P)H:quinone oxidoreductase 1 (NQO1) and phosphorylated signal transducer and activator of transcription 3 (pSTAT3) correlate negatively with the survival of patients with pancreatic cancer. Napabucasin is an investigational, orally administered ROS generator bioactivated by NQO1.

Methods In the open-label, phase 3 CanStem111P study (NCT02993731), adults with previously untreated metastatic pancreatic adenocarcinoma (mPDAC) were randomised (1:1) to napabucasin plus nab-paclitaxel with gemcitabine or nab-paclitaxel with gemcitabine alone. The primary endpoint was overall survival (OS). In exploratory analyses, OS was evaluated in the subgroup of patients with tumours positive for pSTAT3 (biomarker-positive).

Findings Between 30 January 2017 and 20 February 2019, a total of 1779 patients were screened across 165 study sites in Austria, Australia, Belgium, Canada, China, Czech Republic, France, Germany, Italy, Japan, Korea, Netherlands, Poland, Portugal, Russia, Singapore, Spain, Taiwan, Ukraine, and the US. Of the 565 and 569 patients randomised to the napabucasin and control treatment arms, respectively, 206 and 176 were biomarker-positive. Median (95% confidence interval [CI]) OS in the napabucasin and control treatment arms was 11.4 (10.5–12.2) and 11.7 (10.7–12.7) months, respectively (hazard ratio, 1.07; 95% CI, 0.93–1.23). Due to the lack of OS improvement in the napabucasin arm, CanStem111P was terminated due to futility. In the biomarker-positive subgroup, no

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difference between treatment arms was found for OS. Grade ≥3 adverse events were reported in 85.4% and 83.9% of napabucasin-treated and control-treated patients, respectively. The incidence of gastrointestinal-related grade ≥3 events was higher with napabucasin (diarrhoea: 11.6% vs 4.9%; abdominal pain: 10.0% vs 4.8%).

Interpretation Our findings suggested that although the addition of napabucasin to nab-paclitaxel with gemcitabine did not improve efficacy in patients with previously untreated mPDAC, the safety profile of napabucasin was consistent with previous reports. CanStem111P represents the largest cohort of patients with mPDAC administered nab-paclitaxel with gemcitabine in the clinical trial setting. Our data reinforce the value of nab-paclitaxel plus gemcitabine as a platform for novel therapeutics approaches in mPDAC.

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Keywords: Napabucasin; Pancreatic cancer; Adenocarcinoma; Metastatic pancreatic adenocarcinoma; Phosphorylated signal transducer and activator of transcription 3

Research in context

Evidence before this study

We searched PubMed on September 6, 2022 using: (pancreatic cancer [Title/Abstract]) AND (metastatic [Title/Abstract]) OR (pancreatic adenocarcinoma [Title/Abstract]) AND (metastatic [Title/Abstract]), filtered for randomized controlled trials in the last 5 years. The resulting 63 studies were then manually limited to those adding one or more agents to nab-paclitaxel plus gemcitabine for patients who had not received prior systemic treatment. A total of 8 studies evaluating 9 different drugs were identified (1 study added 2 drugs to nab-paclitaxel plus gemcitabine). None of the regimens demonstrated a survival advantage compared to nab-paclitaxel plus gemcitabine alone.

Added value of this study

This trial, as with others, failed to demonstrate an improvement in overall survival (OS) compared to nab-paclitaxel plus gemcitabine alone. However, it is a large trial providing a contemporary benchmark for OS using nab-paclitaxel plus gemcitabine as a first line regimen.

Implications of all the available evidence

Nab-paclitaxel plus gemcitabine has been in use for almost 10 years following the MPACT trial published in 2013. In CanStem111P, the median OS (mOS) of nab-paclitaxel plus gemcitabine was 11.7 months, over 3 months longer than the mOS of 8.5 months observed in MPACT. The longer mOS must be considered when planning future trials where a drug is added to nab-paclitaxel plus gemcitabine.

Introduction

In 2020, pancreatic cancer was diagnosed in approximately 496,000 people worldwide and was the seventh leading cause of cancer-specific mortality, with 466,000 deaths.[1] Pancreatic cancer has the poorest prognosis of any malignancy,[2,3] with a 5-year survival rate of ≤10%,[3–7] and is projected to become the second leading cause of cancer death by 2040.[8] Adenocarcinoma accounts for 80–90% of all pancreatic cancers.[6,9,10]

Surgery is the only potentially curative treatment option, but most patients (60–95%) are diagnosed at the locally advanced or metastatic disease stage.[3,6,10] In the first-line setting, standard-of-care treatments for patients with metastatic pancreatic adenocarcinoma and good Eastern Cooperative Oncology Group (ECOG) performance status include leucovorin plus 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) and nab-paclitaxel plus gemcitabine.[6,7,9] As these regimens are associated with a median OS (mOS) duration of only 11.1 and 8.5 months, respectively,[11,12] patients with metastatic pancreatic adenocarcinoma remain in need of improved first-line treatment options.

Compared with normal cells, malignant cells contain elevated levels of ROS, highly reactive oxygen-containing molecules that can damage DNA, proteins, and lipids; stimulate the proliferation and metastasis of tumour cells; and mediate cell death.[13,14] To compensate for the greater amount of ROS, transformed cells also exhibit increased antioxidant capacity. As the balance between ROS and antioxidant proteins in tumour cells is precarious, perturbation of redox balance has been proposed as an anticancer strategy.[14] It is believed that further increasing ROS to levels that exceed the antioxidant capabilities of the transformed cell may be cytotoxic. The antioxidant protein NQO1 is up-regulated in pancreatic tumour cells[15,16] and has been shown to correlate negatively with survival.[15]

Napabucasin is an investigational, orally administered ROS generator bioactivated by NQO1.[17,18] In the preclinical setting, napabucasin was demonstrated to

increase intracellular levels of ROS, which may stimulate tumour cell death and inhibit the signal transducer and activator of transcription 3 (STAT3) pathway.[17,18] *STAT3* is an oncogene, with an established role in the development, invasiveness, and metastatic potential of pancreatic tumour cells.[19–21] Increased levels of pSTAT3 have been shown to associate negatively with survival in patients with pancreatic cancer.[22,23] pSTAT3 expression, associated with in vitro sensitivity to napabucasin,[17] has been explored as a potential predictive and/or prognostic biomarker of napabucasin in the clinical trial setting.[24] Additionally, in a xenograft model of pancreatic cancer, napabucasin was found to inhibit the spherogenesis of cancer stem cells, which are typically resistant to chemotherapy, and prevent disease relapse.[25]

In a dose-finding, phase 1b/2 study of 59 adults with metastatic pancreatic adenocarcinoma (20.3% with prior adjuvant treatment), combination treatment with napabucasin plus nab-paclitaxel with gemcitabine conferred a disease control rate (DCR) of 78.0%, with a complete response (CR) in two patients, partial response (PR) in 26, and stable disease (SD) in 18, and a median OS duration of 9.6 months.[26] Based on these early-stage clinical trial results, the phase 3 CanStem111P study was undertaken to compare the efficacy and safety of napabucasin plus nab-paclitaxel with gemcitabine vs nab-paclitaxel with gemcitabine alone in patients with previously untreated metastatic pancreatic adenocarcinoma.

Methods

Study design and patients

CanStem111P was an international, adaptive multicentre, open-label, randomised, phase 3 study (NCT02993731) of adults (≥18 years) with treatment-naive, cytologically or histologically confirmed metastatic pancreatic adenocarcinoma. Eligible patients had evaluable disease per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1[27]; an ECOG performance status score of 0 or 1; and adequate haematologic (haemoglobin ≥9.0 g/dL, platelet count $>100 \times 10^9$/L, absolute neutrophil count $\geq 1.5 \times 10^9$/L), hepatic (aspartate and alanine aminotransferase ≤2.5 × the upper limit of normal [ULN] or ≤5 × ULN in the presence of liver metastases, total bilirubin ≤1.5 × ULN), and renal (serum creatinine within normal limits or calculated clearance >60 mL/min/1.73 m^2) function. Key exclusion criteria included prior chemotherapy or biologic therapy for pancreatic adenocarcinoma, major surgery in the 4 weeks prior to randomisation, known brain or leptomeningeal metastases (even if treated), uncontrolled intercurrent illness, and grade ≥2 neurosensory neuropathy or uncontrolled diarrhoea. Patients with local disease recurrence following surgical resection of the primary lesion were also excluded (ie, metastatic disease required).

Randomisation and masking

Eligible patients were randomised (1:1) using a permuted block randomisation procedure to receive napabucasin plus nab-paclitaxel with gemcitabine or nab-paclitaxel with gemcitabine alone. Randomisation was stratified by geographic region (North America/Western Europe/Australia vs Japan/Korea vs rest of world), ECOG performance status score (0 vs 1), and the presence of liver metastases (yes vs no). Crossover was not allowed (ie, patients could not switch study arms).

Sample size calculation

Assuming a one-sided alpha of 2.5%, a total of 864 events would have 90% power to detect a 20% reduction in the risk of death when napabucasin is added to nab-paclitaxel with gemcitabine vs nab-paclitaxel with gemcitabine alone (hazard ratio [HR] of 0.80, corresponding to a targeted effect of median OS from 8.5 to 10.6 months, which is deemed clinically meaningful). It was estimated that 864 events could be observed if 1132 patients, assuming a 5% drop-out rate, were randomised over 24 months and followed for an additional 12 months (36 months in total). An interim analysis was performed when half (n = 432) of all anticipated deaths had been observed. The interim analysis was for futility only, with the futility boundary set at a HR ≥ 1. If the trial was not stopped due to futility at the first interim analysis, a second interim analysis was scheduled to occur when 80% (n = 691) of all anticipated OS events had been observed. The second interim analysis was for efficacy only with the null hypothesis rejected if the one-sided p-value was <0.0122. A stratified log-rank test was to be used for each interim analysis with nominal p-values based on the Lan-DeMets error spending function using an O'Brien-Fleming stopping boundary to preserve the overall one-sided alpha level at 0.025.

Study drug administration

Napabucasin 240 mg was administered orally twice daily (total daily dose of 480 mg). Nab-paclitaxel 125 mg/m^2 was intravenously infused over 30 min at least 2 h following the first daily dose of napabucasin. Upon completion of nab-paclitaxel, gemcitabine 1000 mg/m^2 was intravenously infused over 30–60 min. Both nab-paclitaxel and gemcitabine were administered on Days 1, 8, and 15 of each 28-day cycle. To manage adverse events (AEs), dose modification of napabucasin, nab-paclitaxel, and/or gemcitabine was permitted (Supplemental Table S1). Patients continued study treatment until disease progression per RECIST version 1.1, unacceptable toxicity, or other discontinuation criterion was met. If nab-paclitaxel and/or gemcitabine was discontinued due to toxicity, napabucasin monotherapy was continued until another discontinuation criterion was met. If napabucasin was discontinued due to toxicity, nab-paclitaxel with gemcitabine was continued until another discontinuation criterion was met.

Ethics

CanStem111P was conducted in accordance with the principles originating from the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and applicable national and local regulatory requirements. The study protocol was approved by the Independent Ethics Committee or Institutional Review Board at each participating site. All patients provided written informed consent prior to participation.

Endpoints

The primary endpoint was OS, defined as the time from randomisation until death from any cause. The key secondary endpoints were progression-free survival (PFS; time from randomisation to first objective documentation of disease progression or death due to any cause, whichever occurred first), DCR (proportion of patients with a documented CR, PR, or SD per RECIST version 1.1), and overall response rate (ORR; proportion of patients with a documented CR or PR per RECIST version 1.1). Tumour responses were assessed every 8 weeks by study investigators. Safety was evaluated throughout the study by central review. Safety evaluations occurred at pre-defined intervals and included physical examinations; haematologic, biochemical, urine, and cardiac assessments; and pregnancy testing. AE evaluations continued for at least 28 days after the last dose of study treatment. Serious AEs (i.e., life-threatening AEs or those resulting in death, hospitalisation, disability incapacity, birth defects, or other important medical events) were reported within 24 h. AEs (type, frequency, and severity) were coded to the Medical Dictionary for Regulatory Activities version 19.0 and graded per Common Terminology Criteria for Adverse Events version 4.0. In exploratory analyses, the primary and key secondary endpoints were evaluated in the subgroup of patients with pSTAT3-positive tumours (hereafter referred to as biomarker-positive). Biomarker status was determined via immunohistochemistry using antibody clone D3A7 to detect pSTAT3 in cancer cells and in cells of the tumour microenvironment (PharmDx assay, Agilent Technologies, Inc.).

Statistical analysis

The primary analysis was performed on the intent-to-treat population, comprising all randomised patients who were analysed according to the treatment to which they were randomised. SAS software was used to conduct the analyses. OS was summarised using the Kaplan–Meier method and compared primarily using a stratified log-rank test adjusted for randomisation stratification variables. The HR for the treatment effect was estimated based on a Cox proportional hazards model. To prevent sponsor bias, an unblinded reporting team was assembled and tasked with reporting the results of the interim analyses and providing regular safety updates to the Data Safety and Monitoring Board (DSMB). Aggregated data by treatment arm were not reviewed or analysed by the blinded study team until trial termination.

Regarding the key secondary endpoints, PFS was analysed using a log-rank test stratified by randomisation stratification variables. Patients with measurable disease per RECIST version 1.1 at randomisation were analysed for DCR and ORR, compared between treatment arms using a one-sided Cochran–Mantel–Haenszel test adjusted for randomisation stratification factors. The 95% CIs were estimated using the Miettinen and Nurminen method adjusted for randomisation stratification factors. For safety, all patients who received $\geq$1 dose of study drug were analysed according to the treatment received. AEs were summarised using descriptive statistics.

The study was terminated due to futility based on (1) the results of the first interim analysis, which was performed by the contract research organization (CRO), and (2) the recommendation of the DSMB. Therefore, no multiplicity adjustment was conducted in the final analysis. The clinical cut-off date for the final statistical analysis, which was performed by the CRO, was 19 November 2020.

All analyses and descriptive summaries were based on observed data. No imputation was undertaken for missing data, except in select situations: (1) When a death date was missing, the date was imputed as the day after the last date the patient was known to be alive (or the first of the month if only the day was missing or the first of January if the month was also missing). (2) When the date of the last dose of study treatment was unknown, the data cut-off date was used if no death was recorded. If a death date or end-of-treatment date was recorded, this date was imputed. If the day was missing the last day of the month was used; if both the day and month were missing, and arbitrary imputation of the 31st of December was used. (3) When dates regarding AEs or concomitant therapies/medications were missing, the missing day was imputed as he day of the first dose of study treatment or the first of the month in which the event occurred; if both the day and month were missing, the 31st of December of the year of the occurrence (or death date if in the same year) was used. If a date was completely missing, then no imputation was done, and the event was considered treatment emergent (for AEs) or concomitant (for medications), unless the end date ruled out this possibility. (4) When dates of prior therapies were missing, the earlier of either the 15th of the month or date of informed consent was used. If the month was missing, the first of July of the year or date of informed consent was used, whichever occurred first. (5) No missing values were imputed for the primary and secondary efficacy analyses. For time-to-event endpoints, non-event observations were censored. For ORR and DCR, patients were

counted as non-responders if there was no baseline tumour evaluation and/or post-baseline tumour evaluation. (6) Missing data on age were computed from the birth date to the date of informed consent. If the birth date was missing the day, the date was imputed as the 15th of the month; if both the day and month were missing, the birth date was set to the first of July of the birth year.

Role of the funding source

The sponsor, in collaboration with the clinical trial investigators, designed the study protocol. The sponsor also assisted in data analysis and interpretation and reviewed the manuscript for clinical accuracy. The authors had full access to all the data in the study and accept responsibility to submit for publication.

Results

Patients

Between 30 January 2017 and 20 February 2019, a total of 1779 patients were screened across 165 study sites in Austria, Australia, Belgium, Canada, China, Czech Republic, France, Germany, Italy, Japan, Korea, Netherlands, Poland, Portugal, Russia, Singapore, Spain, Taiwan, Ukraine, and the US. A total of 565 patients were randomised to napabucasin plus nab-paclitaxel with gemcitabine and 569 randomised to nab-paclitaxel with gemcitabine alone (Fig. 1). The median (interquartile range [IQR]) age of the study population was 63.0 (57–69) years, with the majority of patients being white (62.1%) and having more than one metastatic site (98.6%) (Table 1). Approximately half (55.6%) of all randomised patients were male, and 33.7% were positive for pSTAT3 (ie, biomarker-positive). Patient demographic and disease characteristics were generally well-balanced between treatment arms.

The most common reasons for discontinuing treatment with napabucasin were objective disease progression (n = 311 [55.0%]) and patient request (n = 79 [14.0%]). Objective disease progression was also the most common reason for discontinuation of nab-paclitaxel and gemcitabine in both the napabucasin and control treatment arms. The most common reason an individual patient stopped participation in the study (ie, ended survival follow-up data collection) was death (napabucasin plus nab-paclitaxel with gemcitabine, n = 420; nab-paclitaxel with gemcitabine, n = 404). A total of 89 patients withdrew consent to survival follow-up (39 in the napabucasin arm, 50 in the control arm), and only 15 patients were lost to follow-up (5 in the napabucasin arm, 10 in the control arm).

Treatment

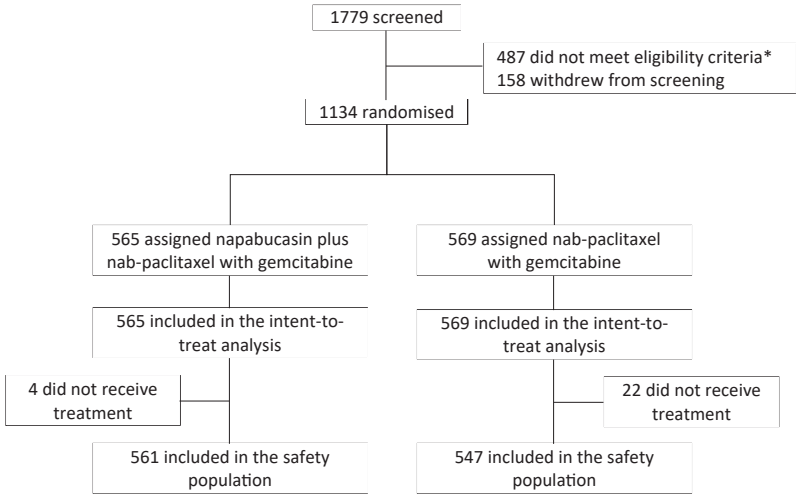
The median total number of treatment cycles was 6.0 for both the napabucasin plus nab-paclitaxel with gemcitabine and nab-paclitaxel with gemcitabine arms. The median (IQR) duration of exposure to napabucasin was 173.0 (73–263) days, with a median (IQR) relative dose intensity of 85.9% (44.1–97.6%) (Supplemental Table S2). The median (IQR) duration of exposure to nab-paclitaxel among patients randomised to the napabucasin and control treatment arms was 24.3 (12.0–38.3) and 21.3 (12.0–32.9) weeks, respectively; the corresponding values for gemcitabine exposure were 24.3 (12.0–39.7) and 24.0 (12.0–37.0) weeks. The median relative dose intensities of nab-paclitaxel (55.0–59.1%) and gemcitabine (59.4–61.1%) were comparable in both treatment arms.

Efficacy

Data from the interim analysis of OS were presented to the independent DSMB on 24 June 2019. Due to the lack of OS improvement in the napabucasin plus nab-paclitaxel with gemcitabine arm, the stopping criteria were met (HR 1.06) and the DSMB recommended that the CanStem111P be terminated due to futility. However, patients continued to be followed (provided they did not withdraw) and could continue to receive study treatment, if deemed by the investigator and consenting patient to be in the patient's best interest.

At database lock, 74.5% of patients assigned to napabucasin plus nab-paclitaxel with gemcitabine and 71.0% of those assigned to nab-paclitaxel with gemcitabine had died. Median (95% CI) OS in the two treatment arms were 11.4 (10.5–12.2) and 11.7 (10.7–12.7) months, respectively (HR, 1.07; 95% CI, 0.93–1.23; one-sided p = 0.84) (Fig. 2A). The OS rate at 12 months was similar for napabucasin plus nab-paclitaxel with gemcitabine (46.6%) and nab-paclitaxel with gemcitabine alone (47.8%). No statistically significant differences in OS were seen between treatment arms in subgroups defined by geographic region (Supplemental Fig. S1). Following the end of study treatment, the proportion of patients who received subsequent anti-cancer therapy was similar for napabucasin plus nab-paclitaxel with gemcitabine (57.2%) and nab-paclitaxel and gemcitabine alone (56.8%). The most common subsequent anti-cancer treatment was chemotherapy, received by 55.0% of patients in the napabucasin treatment arm and 54.7% of those in the control treatment arm.

Median (95% CI) PFS was 6.7 (5.7–7.3) and 6.1 (5.6–7.1) months for napabucasin plus nab-paclitaxel with gemcitabine and nab-paclitaxel with gemcitabine alone, respectively (HR, 1.04; 95% CI, 0.91–1.19; one-sided p = 0.71) (Fig. 2B). Of the 565 and 569 patients randomised to the napabucasin and control treatment arms, respectively, 556 (98.4%) and 559 (98.2%) had measurable disease per RECIST version 1.1 at randomisation and were analysed for DCR and ORR. DCR among napabucasin-treated and control-treated patients was 74.5% and 76.0%, respectively, and ORR was 43.2% and 42.9%, respectively (Table 2).



*Reason Not Eligible	N
Objective laboratory criteria not met	156
Uncontrolled comorbid conditions	91
Minimum weight or BMI requirement not met	63
Nab-paclitaxel + gemcitabine not appropriate per investigator	59
ECOG performance status ≥2	35
Co-occurrence of other malignancies	21
Pancreatic cancer was not metastatic	20
Did not have pancreatic cancer	16
Received prior systemic therapy	14
Not able to adhere to treatment and/or follow-up schedule	7
Central nervous system disease present	2
Pregnant or breastfeeding	2
Taking part in another trial	1

Fig. 1: **Trial profile.**

A total of 36.5% (206/565) and 30.9% (176/569) of patients randomised to napabucasin plus nab-paclitaxel with gemcitabine and nab-paclitaxel with gemcitabine alone, respectively, had tumours positive for pSTAT3. Only 9.0% (n = 51) and 11.8% (n = 67) of patients, respectively, had tumours negative for this biomarker. pSTAT3 status was unknown in the remainder (napabucasin plus nab-paclitaxel with gemcitabine, 54.5% [n = 308]; nab-paclitaxel with gemcitabine, 57.3% [n = 326]), as the study protocol did not require patients to provide tumour samples. In exploratory analyses performed on the biomarker-positive subgroup, no differences between treatment arms were found for OS, PFS, DCR, or ORR (Supplemental Table S3). There was also no statistically significant prognostic impact of pSTAT3 when OS was evaluated in biomarker-positive vs biomarker-negative patients in the control arm, with median OS (95% CI) of 10.78 (9.40–12.55) and 11.50 (9.46–14.95) months, respectively (HR, 1.08; 95% CI, 0.77–1.50).

Safety

Of the 1134 patients randomised to CanStem111P, 1108 (97.7%) received study treatment. In total, 0.7% (4/565) of patients assigned to napabucasin plus nab-paclitaxel with gemcitabine compared with 3.9% (22/569) of those assigned to nab-paclitaxel with gemcitabine alone did not receive study treatment and were thus excluded from the safety population. The higher rate of withdrawal among patients randomised to the control arm may have been due to the open-label nature of the study. However, the impact on study results is likely negligible, as the overall number of randomised patients who were not treated was low (2.3% [26/1134]).

All but one patient who received napabucasin plus nab-paclitaxel with gemcitabine and four treated with nab-paclitaxel with gemcitabine alone experienced an AE (99.8% vs 99.3%, respectively) (Table 3). The most common AEs among napabucasin-treated and control-treated patients were diarrhoea (73.1% vs 38.9%),

	Napabucasin + nab-paclitaxel + gemcitabine (n = 565)	Nab-paclitaxel + gemcitabine (n = 569)
Median age, years (IQR)	63.0 (57–69)	64.0 (57–70)
<65 years, n (%)	325 (57.5)	295 (51.8)
≥65 years, n (%)	240 (42.5)	274 (48.2)
Gender		
Male, n (%)	325 (57.5)	306 (53.8)
Female, n (%)	240 (42.5)	263 (46.2)
Race, n (%)[a]		
White	350 (61.9)	354 (62.2)
Black	10 (1.8)	18 (3.2)
Asian	194 (34.3)	188 (33.0)
Other	10 (1.8)	7 (1.2)
Region, n (%)		
Asia	187 (33.1)	181 (31.8)
North America	163 (28.8)	159 (27.9)
Western Europe	126 (22.3)	133 (23.4)
Eastern Europe	66 (11.7)	72 (12.7)
Australia	23 (4.1)	24 (4.2)
ECOG performance status, n (%)		
0	255 (45.1)	255 (44.8)
1	310 (54.9)	314 (55.2)
Number of metastatic sites, n (%)		
1	3 (0.5)	11 (1.9)
≥2	562 (99.5)	556 (97.7)
Liver metastases present, n (%)	445 (78.8)	446 (78.4)
Presence of measurable disease per RECIST version 1.1, n (%)	556 (98.4)	559 (98.2)
Location of primary tumour, n (%)		
Head of pancreas	213 (37.7)	216 (38.0)
Tail of pancreas	181 (32.0)	173 (30.4)
Body of pancreas	171 (30.3)	178 (31.3)
Median (Q1 to Q3) sum of target lesion, cm	8.6 (5.5–11.6)	8.0 (5.5–11.5)
Level of CA 19-9, n (%)		
Normal	116 (20.5)	95 (16.7)
<59 × ULN	224 (39.6)	216 (38.0)
≥59 × ULN	222 (39.3)	254 (44.6)
Median (Q1 to Q3) neutrophil-to-lymphocyte ratio	3.21 (2.33–4.75)	3.29 (2.44–4.61)
Median (Q1 to Q3) albumin, g/L	40.0 (37.0–43.0)	40.0 (37.0–43.0) (37.0–43.0)
pSTAT3 status, n (%)		
Positive	206 (36.5)	176 (30.9)
Negative	51 (9.0)	67 (11.8)
Unknown	308 (54.5)	326 (57.3)

CA 19-9, carbohydrate antigen 19-9; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; pSTAT3, phosphorylated signal transducer and activator of transcription 3; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal. [a]Information on race was not available for one patient randomised to napabucasin plus nab-paclitaxel with gemcitabine and two patients randomised to nab-paclitaxel with gemcitabine alone.

Table 1: **Baseline patient and disease characteristics – intent-to-treat population.**

nausea (58.6% vs 46.1%), and anaemia (54.5% vs 58.1%). Treatment-related AEs due to any study drug (ie, napabucasin and/or nab-paclitaxel and/or gemcitabine) were reported in 96.8% of patients administered napabucasin plus nab-paclitaxel with gemcitabine, most commonly diarrhoea (n = 388 [69.2%]), and 96.5% of those administered nab-paclitaxel with gemcitabine alone, most commonly anaemia (n = 273 [49.9%]). Similar proportions of napabucasin-treated and control-treated patients had a grade ≥3 AE (85.4% vs 83.9%), the most frequent of which were anaemia (23.7% vs 19.7%), neutropenia (18.5% vs 23.0%), and neutrophil count decreased (17.8% vs 22.5%). However, the incidence of gastrointestinal-related grade ≥3 events was higher with napabucasin (diarrhoea: 11.6% vs 4.9%; abdominal pain: 10.0% vs 4.8%).

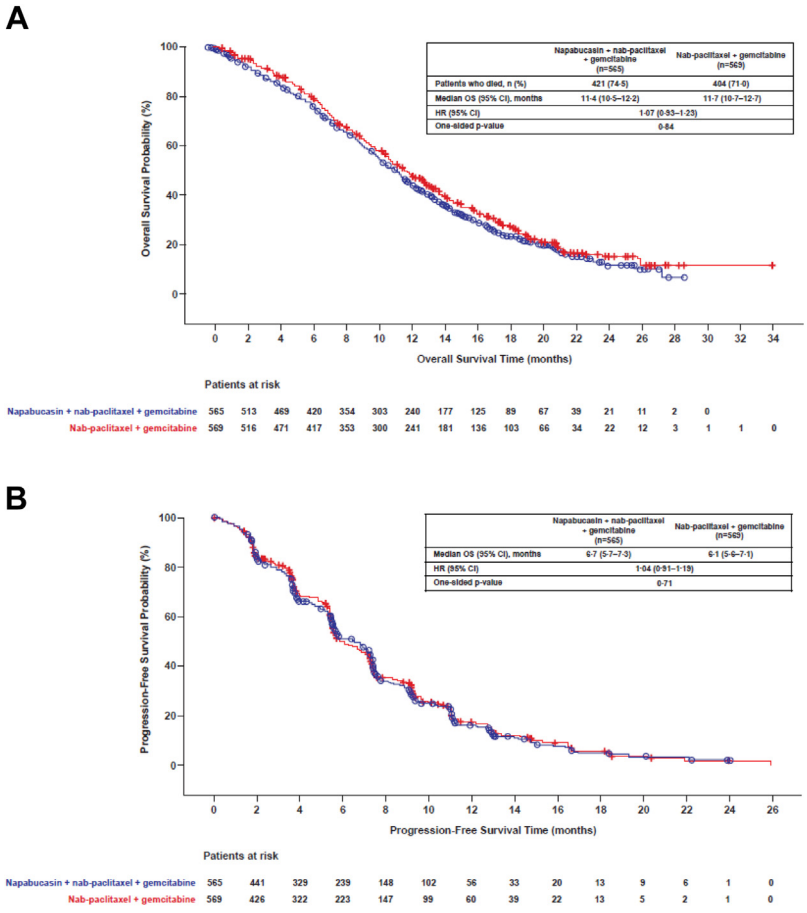


Fig. 2: **Survival in the intent-to-treat population (A) OS and (B) PFS.** CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

	Napabucasin + nab-paclitaxel + gemcitabine (n = 556)	Nab-paclitaxel + gemcitabine (n = 559)
Disease control rate, n (%)	414 (74.5)	425 (76.0)
95% CI	70.6–78.0	72.3–79.5
Difference in DCR (95% CI) [5]	0.02 (−0.03, 0.07)	
One-sided P-value [6]	0.7238	
Overall response rate, n (%)	240 (43.2)	240 (42.9)
95% CI	39.0–47.4	38.8–47.2
Difference in ORR (95% CI) [5]	−0.00 (−0.06, 0.05)	
One-sided P-value [6]	0.4472	
Best response, n (%)		
Complete response	4 (0.7)	6 (1.1)
Partial response	236 (42.4)	234 (41.9)
Stable disease	174 (31.3)	185 (33.1)
Progressive disease	66 (11.9)	62 (11.1)
Not evaluable	76 (13.7)	72 (12.9)

CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumours.

Table 2: **Tumour response in patients with measurable disease per RECIST version 1.1 at randomisation – intent-to-treat population.**

Serious AEs were reported in 58.8% of patients treated with napabucasin plus nab-paclitaxel with gemcitabine and 49.9% of those administered nab-paclitaxel with gemcitabine alone. The only serious AEs to occur in ≥5% of patients in either treatment arm were progressive disease (8.0% [n = 45] vs 4.0% [n = 22]), abdominal pain (5.3% [n = 30] vs 3.8% [n = 21]), and pyrexia (6.1% [n = 34] vs 5.3% [n = 29]). In total, 27.5% (n = 154) and 21.9% (n = 120) of patients in the napabucasin and control treatment arms, respectively, experienced a serious AE considered related to any study drug, most commonly from MedDRA System Organ Class gastrointestinal disorders (10.3% [n = 58] vs 6.8% [n = 37]). In the napabucasin and control treatment arms, 91.1% and 84.5% of patients, respectively, required dose modification of any study drug. In total, 11.1% of napabucasin-treated and 6.2% of control-treated patients died due to an AE. The most common TEAE leading to death in both treatment arms was disease progression (6.6% [n = 37] and 2.7% [n = 15], respectively). Of the TEAEs leading to death, eight

Patients, n (%)	Napabucasin + nab-paclitaxel + gemcitabine (n = 561)	Nab-paclitaxel + gemcitabine (n = 547)
Any grade AE[a]	560 (99.8)	543 (99.3)
Diarrhoea	410 (73.1)	213 (38.9)
Nausea	329 (58.6)	252 (46.1)
Anaemia	306 (54.5)	318 (58.1)
Vomiting	250 (44.6)	162 (29.6)
Decreased appetite	233 (41.5)	177 (32.4)
Abdominal pain	215 (38.3)	124 (22.7)
Alopecia	212 (37.8)	210 (38.4)
Pyrexia	211 (37.6)	203 (37.1)
Fatigue	205 (36.5)	189 (34.6)
Constipation	194 (34.6)	209 (38.2)
Oedema peripheral	179 (31.9)	180 (32.9)
Neutropenia	145 (25.8)	165 (30.2)
Asthenia	143 (25.5)	137 (25.0)
Neutrophil count decreased	138 (24.6)	155 (28.3)
Neuropathy peripheral	125 (22.3)	133 (24.3)
White blood cell count decreased	120 (21.4)	137 (25.0)
Platelet count decreased	111 (19.8)	143 (26.1)
Thrombocytopenia	105 (18.7)	126 (23.0)
Treatment-related AE	543 (96.8)	528 (69.2)
Grade ≥3 AE[b]	479 (85.4)	459 (83.9)
Anaemia	133 (23.7)	108 (19.7)
Neutropenia	104 (18.5)	126 (23.0)
Neutrophil count decreased	100 (17.8)	123 (22.5)
White blood cell count decreased	70 (12.5)	70 (12.8)
Diarrhoea	65 (11.6)	27 (4.9)
Abdominal pain	56 (10.0)	26 (4.8)
Serious AE	330 (58.8)	273 (49.9)
AE leading to modification of any study drug	511 (91.1)	462 (84.5)
AE leading to a dose delay of any study drug	421 (75.0)	372 (68.0)
AE leading to a dose reduction of any study drug	290 (51.7)	261 (47.7)
AE leading to discontinuation of any study drug	184 (32.8)	136 (24.9)
AE leading to death	62 (11.1)	34 (6.2)

AE, adverse event. [a]Preferred terms reported in ≥20% of patients in either treatment arm are presented. [b]Preferred terms reported in ≥10% of patients in either treatment arm are presented.

***Table 3*: Safety summary – safety population.**

(1.4%) in the napabucasin treatment arm and six (1.1%) in the control treatment arm were considered related to any study drug.

Discussion

The primary endpoint of the phase 3 CanStem111P trial was not met. In patients with previously untreated metastatic pancreatic adenocarcinoma, the addition of napabucasin to nab-paclitaxel with gemcitabine did not lead to improvements in OS relative to treatment with nab-paclitaxel and gemcitabine alone. Although median OS was similar for napabucasin-treated and control-treated patients in the present study (11.4 and 11.7 months, respectively), the survival duration was approximately 3 months longer than that observed among patients receiving nab-paclitaxel with gemcitabine in the pivotal phase 3 MPACT trial (median OS: 8.5 months).[12] The 12-month OS rate among patients treated with nab-paclitaxel plus gemcitabine in CanStem111P and MPACT was 48% and 35%, respectively. The improvements in OS seen in CanStem111P may reflect the availability of additional effective therapies or advances in best supportive care since the MPACT trial was undertaken. Over 55% of patients in CanStem111P received subsequent chemotherapy, while the proportion of patients in MPACT to receive subsequent therapy was only approximately 40%.

The study populations in CanStem111P and MPACT had similar median ages and proportions of male/female participants. However, in CanStem111P, there were proportionally fewer patients reporting as white

(62.1% vs 88%) and proportionally more reporting as Asian (33.7% vs 2%). CanStem111P included patients from Japan and South Korea, and these patients had the longest OS in both the napabucasin and control treatment arms.

As with OS, outcomes on the key secondary endpoints of PFS (6.1–6.7 months), DCR (74.5–76.0%), and ORR (42.9–43.2%) were comparable between treatments arms in CanStem111P. Of note, ORR in the control arm of CanStem111P was almost two-fold greater than that observed among nab-paclitaxel-plus-gemcitabine–treated patients in MPACT (42.9% vs 22.9%).[12] Higher response rates relative to MPACT were also observed in the control arms of the contemporary RESOLVE (42%) and HALO 109-301 (36%) trials.[28,29] One potential reason for this difference may be that fewer patients in the CanStem111P control arm had prior radiotherapy (n = 3, 0.5%) or prior systemic therapy (n = 0, 0.0%) compared to MPACT (n = 11, 3% prior radiotherapy and n = 12, 3% prior chemotherapy). Similarly, in CanStem111P, 44 (3.9%) patients had previously undergone pancreaticoduodenectomy (ie, Whipple procedure) versus 62 (7%) patients in MPACT.

In the phase 3 CO.23 study, patients with refractory advanced colorectal cancer were randomised to receive best supportive care in combination with either napabucasin or placebo.[24] No statistically significant difference in the primary endpoint of median OS was seen between treatment arms in CO.23, but an exploratory analysis suggested that survival was statistically significantly longer for napabucasin vs placebo in the subgroup of patients whose tumours were positive for pSTAT3. Based on this finding, pre-specified, exploratory analyses of efficacy were undertaken in the subgroup of patients in CanStem111P with pSTAT3-positive tumours. There were no statistically significant differences in OS, PFS, DCR, or ORR between the napabucasin and control treatment arms; thus, pSTAT3-positivity was not predictive of a treatment effect from napabucasin. Additionally, pSTAT3-positivity had little prognostic impact, as median OS was similar in pSTAT3-positive and pSTAT3-negative patients randomised to the control arm. Of note, the exploratory analyses in this study used the pSTAT3 scoring algorithm developed for patients with colorectal cancer. However, given the lack of data suggesting a beneficial clinical effect from napabucasin in either the overall or biomarker patient populations, development of a scoring algorithm specific to pancreatic cancer was not pursued.

Combination treatment with napabucasin plus nab-paclitaxel with gemcitabine was generally tolerable, as the percentages of patients discontinuing any study drug due to an AE was similar for the napabucasin and control treatment arms (32.8% vs 24.9%). In addition, napabucasin did not appear to adversely affect chemotherapy administration, as the median dose intensities of nab-paclitaxel and gemcitabine were similar in both treatment arms. As in prior clinical studies,[24,30] the most common AE associated with napabucasin was diarrhoea, and no new safety signals were detected when napabucasin was combined with nab-paclitaxel and gemcitabine. Similar percentages of patients in both treatment arms experienced a grade ≥3 AE (83.9–85.4%), and other than diarrhoea (11.6% vs 4.9%) and abdominal pain (10.0% vs 4.8%), which were more common among napabucasin-treated patients, the frequencies of individual grade ≥3 AEs were comparable. Serious AEs were proportionally more common among patients administered napabucasin plus nab-paclitaxel with gemcitabine (58.8%) vs nab-paclitaxel with gemcitabine alone (49.9%), mostly due to a two-fold increase in the proportion of patients with disease progression reported as a serious AE (8.0% vs 4.0%, respectively). Additionally, similar proportions of patients in the napabucasin and control treatment arms had a serious AE considered by investigators to be related to any study drug (27.5% and 21.9%, respectively). It should be noted that almost two-fold more patients treated with napabucasin plus nab-paclitaxel with gemcitabine vs nab-paclitaxel with gemcitabine alone experienced an AE resulting in death (11.1% vs 6.2%), most commonly disease progression (6.6% vs 2.7%). Following a safety review, it was concluded that this imbalance was not due to a safety signal, as similar percentages of patients experienced a treatment-related AE leading to death (napabucasin plus nab-paclitaxel with gemcitabine, 1.4%; nab-paclitaxel with gemcitabine, 1.1%).

In conclusion, although the addition of napabucasin to nab-paclitaxel with gemcitabine did not improve efficacy in patients with previously untreated metastatic pancreatic adenocarcinoma, the safety profile of napabucasin was consistent with previous reports. In addition, CanStem111P represents the largest cohort of patients with metastatic pancreatic adenocarcinoma administered nab-paclitaxel with gemcitabine in the clinical trial setting. Given that median OS was longer and ORR was greater with nab-paclitaxel plus gemcitabine in CanStem111P than previously reported, our data reinforce the value of this doublet regimen as a backbone for novel therapeutic approaches in metastatic pancreatic adenocarcinoma.

Contributors

Emma Foos and Cindy Oh were involved in the conceptualization and design of the study; and Tanios Bekaii-Saab, Takuji Okusaka, David Goldstein, Michele Reni, Chung-Pin Li, Josep Tabernero, and Eric Van Cutsem were members of the CanStem111P Steering Committee and were involved in the development of the original protocol. Tanios Bekaii-Saab, Takuji Okusaka, David Goldstein, Do-Youn Oh, Makoto Ueno, Tatsuya Ioka, Weijia Fang, Eric C. Anderson, Marcus S. Noel, Michele Reni, Hye Jin Choi, Jonathan S. Goldberg, Sang Cheul Oh, Chung-Pin Li, Josep Tabernero and Eric Van Cutsem enrolled and treated patients, and gathered data. Jian Li, Emma Foos, and Cindy Oh analysed and interpreted the data. Tanios Bekaii-Saab, Jian Li, Emma Foos, and Cindy Oh verified the underlying data. All authors had full access to all the data

in the study, contributed to writing the article, reviewing and revising for intellectual content, and approved the final draft for submission.

Data sharing statement

Data relating to this publication will be disclosed only when disclosure might be required in accordance with pharmacovigilance duties of the parties involved. Individual trial participant data, after deidentification, may be made available in accordance with applicable law to qualified researchers who provide a written request following authorization from the sponsor organization and subject to appropriate data transfer agreements. Data sharing requests should be directed to our corporate website, www.sdponcology.com/about/contact/.

Declaration of interests

Tanios Bekaii-Saab has received research funding (paid to institution) from Agios, Arys, Arcus, Atreca, Boston Biomedical, Bayer, Amgen, Merck, Celgene, Lilly, Ipsen, Clovis, Seattle Genetics, Genentech, Novartis, Mirati, Merus, Abgenomics, Incyte, Pfizer, and Bristol Myers Squibb; served as a consultant (paid to institution) to Ipsen, Array, Pfizer, Seattle Genetics, Bayer, Genentech, Incyte, and Merck; served as a consultant (paid to self) to AbbVie, Boehringer Ingelheim, Janssen, Eisai, Daichii Sankyo, Natera, TreosBio, Celularity, Exact Science, Sobi, Beigene, Xilis, AstraZeneca, and Foundation Medicine; served on independent data monitoring committees/data and safety monitoring boards (paid to self) for AstraZeneca, Exelixis, Lilly, PanCan, and 1Globe; participated in advisory boards for Imugene, Immuneering, and Sun Biopharma; and holds the following inventions/patents: WO/2018/183488 and WO/2019/055687. Takuji Okusaka has received research grants (paid to self and institution) from Eisai, Eli Lilly, Sumitomo Dainippon Pharma Oncology, AstraZeneca, Chugai, Bristol Myers Squibb, Merck Sharp & Dohme, Baxter, and Taiho; participates in advisory boards for Sumitomo Pharma Oncology, Bristol Myers Squibb, and Nihon Servier; and has been a member of speakers' bureaus at Eisai, Novartis, Eli Lilly, Sumitomo Pharma Oncology, AstraZeneca, Chugai, Bristol Myers Squibb, Merck Sharp & Dohme, Taiho, Nihon Servier, Ono, Yakult Honsha, Daiichi Sankyo, Nippon Shinyaku, Pfizer, and Mundipharma. Do-Youn Oh participates in advisory boards (paid to self) for AstraZeneca, Novartis, Genentech/Roche, 13 Merck Serono, Bayer, Taiho, ASLAN, Halozyme, Zymeworks, Bristol Myers Squibb/Celgene, BeiGene, Basilea, Turning Point, Yuhan, Arcus Biosciences and IQVIA and has received research grants (paid to institution) from AstraZeneca, Novartis, Array, Eli Lilly, 15 Servier, BeiGene, Merck Sharp & Dohme, and Handok. Makoto Ueno has been an invited speaker (paid to self) for Taiho, Yakult Honsha, AstraZeneca, Merck, Eisai, Merck Sharp & Dohme, Servier, and Chugai and has received research grants (paid to institution) from Astellas, Taiho, Eisai, AstraZeneca, Ono, Merck Sharp & Dohme, Merck, Incyte, and Chugai. Tatsuya Ioka is a member of speakers' bureaus at and serves as an advisor to Taiho (paid to self), is on the advisory board (paid to self) at Incyte, and has received research grants (paid to institution) from AstraZeneca, Incyte, Eisai, and Astellas. Michele Reni has participated in advisory boards (paid to self) for Eli Lilly, Celgene, AstraZeneca, Shire, Baxter, Servier, SOTIO, Viatris, and Merck Sharp & Dohme.

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Jian Li is a salaried employee of Sumitomo Pharma Oncology. Emma Foos was a salaried employee of Sumitomo Pharma Oncology at the time that these analyses were undertaken. Cindy Oh was a salaried employee of Sumitomo Pharma Oncology at the time that these analyses were undertaken. Eric Van Cutsem has participated in advisory boards Abbvie, ALX, Amgen, Array, Astellas, Astrazeneca, Bayer, Beigene, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi, GSK, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Mirati, Novartis, Nordic, Pierre Fabre, Pfizer, Roche, Seattle Genetics, Servier, Takeda, Terumo, Taiho, Zymeworks. His institution has also received research grants from Amgen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier. Weijia Fang, Eric C. Anderson, Jonathan S. Goldberg, Sang Cheul Oh, David Goldstein, Marcus Noel, and Chung-Pin Li have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101897.

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