Napabucasin + Nab-Paclitaxel With Gemcitabine in Patients (pts) With Metastatic Pancreatic Adenocarcinoma (mPDAC): Results From the Phase 3 CanStem111P Study

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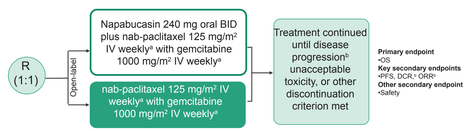
Introduction

- Perturbation of redox balance has been proposed as an anticancer strategy.[1] Increasing reactive oxygen species (ROS) to levels that exceed the antioxidant capabilities of the transformed cell may be cytotoxic
- The antioxidant protein NAD(P)H:quinone oxidoreductase 1 (NQO1) is up-regulated in pancreatic tumor cells[2–5] and correlates negatively with survival[4]
- Napabucasin, an investigational, orally administered ROS generator bioactivated by NQO1, has been shown to increase intracellular levels of ROS. In turn, this may stimulate tumor cell death and may also inhibit the *signal transducer and activator of transcription 3 (STAT3)* pathway[6,7]
- In a dose-finding, phase 1b/2 study of 59 adult pts with mPDAC (20.3% with prior adjuvant treatment), combination treatment with napabucasin plus nab-paclitaxel with gemcitabine was associated with an objective response rate (ORR) of 47.5%, a disease control rate (DCR) of 78.0% (complete response [CR], n=2; partial response [PR], n=26; stable disease [SD], n=18), and median overall survival (OS) of 9.6 months[8]
- The phase 3 CanStem111P study was undertaken to compare napabucasin plus nab-paclitaxel with gemcitabine vs. nab-paclitaxel with gemcitabine alone in adults with previously untreated mPDAC

Methods

- In CanStem111P (NCT02993731), pts aged ≥18 years with previously untreated, cytologically or histologically confirmed mPDAC were randomized (1:1) to receive napabucasin plus nab-paclitaxel with gemcitabine or nab-paclitaxel with gemcitabine alone (**Figure 1**)
  - Randomization was stratified by geographic region, Eastern Cooperative Oncology Group (ECOG) performance status score, and the presence of liver metastases
- Eligible pts had evaluable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; an ECOG performance status score of 0 or 1; and adequate hematologic, liver, and renal function
  - Key exclusion criteria included grade ≥2 neurosensory neuropathy or uncontrolled diarrhea
  - Pts with local disease recurrence following surgical resection of the primary lesion as the only site of disease were also excluded (ie, metastatic disease required)
- Pts received study treatment until disease progression per RECIST version 1.1, unacceptable toxicity, or other discontinuation criterion was met
- The primary endpoint was OS. The key secondary endpoints were progression-free survival (PFS), DCR (proportion of patients with a documented CR, PR, or SD per RECIST version 1.1), and ORR (proportion of patients with a documented CR or PR per RECIST version 1.1)
- In exploratory analyses, the primary and key secondary endpoints were evaluated in the subgroup of patients with pSTAT3-positive tumors (biomarker-positive)
  - Biomarker status was determined via immunohistochemistry using antibody clone D3A7 to detect pSTAT3 in cancer cells and cells of the tumor microenvironment (PharmDx assay, Agilent Technologies, Inc.)

Figure 1. Study Design



[a]Administered on days 1, 8, and 15 of each 28-day cycle.
[b]Per Response Evaluation Criteria in Solid Tumors version 1.1.
BID, twice daily; DCR, disease control rate; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization.

- 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
- It was estimated that 864 events could be observed if 1132 pts, assuming a 5% drop-out rate, were randomized over 24 months and followed for an additional 12 months (36 months in total)
- An interim analysis for futility was scheduled to occur when approximately half (n=432) of all anticipated OS events had been observed

Results

- In total, 1134 pts were randomized, 565 to napabucasin plus nab-paclitaxel with gemcitabine and 569 to nab-paclitaxel with gemcitabine
- Pt demographics and disease characteristics were generally well-balanced between treatment arms **(Table 1)**

Table 1. Baseline demographics and disease characteristics

	Napabucasin + nab-paclitaxel + gemcitabine (n=565)	Nab-paclitaxel + gemcitabine (n=569)
Median age, years (range)	63.0 (31–86)	64.0 (27–86)
<65 years, n (%)	325 (57.5)	295 (51.8)
≥65 years, n (%)	240 (42.5)	274 (48.2)
Male, n (%)	325 (57.5)	306 (53.8)
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)
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)
Location of primary tumor, 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)
Level of CA 19-9, n (%)[b]		
Normal	116 (20.5)	95 (16.7)
<59 x ULN	224 (39.6)	216 (38.0)
≥59 x ULN	222 (39.3)	254 (44.6)
pSTAT3 status, n (%)[c]		
Positive	206 (36.5)	176 (30.9)
Negative	51 (9.0)	67 (11.8)

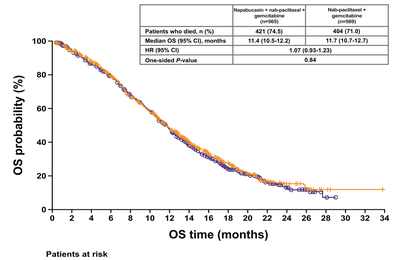
[a]Information on race was not available for one pt randomized to napabucasin plus nab-paclitaxel with gemcitabine and two pts randomized to nab-paclitaxel with gemcitabine alone.
[b]CA 19-9 status was unknown in three pts randomized to napabucasin plus nab-paclitaxel with gemcitabine and four pts randomized to nab-paclitaxel with gemcitabine alone.
[c]pSTAT3 status was unknown in 308 pts randomized to napabucasin plus nab-paclitaxel with gemcitabine and 326 pts randomized to nab-paclitaxel with gemcitabine alone.
CA 19-9, carbohydrate antigen 19-9; ECOG, Eastern Cooperative Oncology Group; pSTAT3, phosphorylated signal transducer and activator of transcription 3; ULN, upper limit of normal.

- The median total number of treatment cycles administered was 6.0 for both the napabucasin plus nab-paclitaxel with gemcitabine and nab-paclitaxel with gemcitabine arms
  - The most common reasons for discontinuing treatment with napabucasin were objective disease progression (55.0% [n=311]) and pt request (14.0% [n=79])
  - Objective disease progression was also the most common reason for discontinuing nab-paclitaxel and gemcitabine in both the napabucasin and control treatment arms
- The primary reason for stopping the study (ie, ending data collection) was lack of OS improvement in the napabucasin plus nab-paclitaxel with gemcitabine arm (ie, meeting the futility criteria)

Efficacy

- Data from the interim analysis of OS were presented to the independent Data Safety and Monitoring Board (DSMB) on June 24, 2019
- Based on the results of the interim analysis and the recommendation of the DSMB, CanStem111P was terminated due to futility on July 2, 2019
- At database lock, 74.5% of pts assigned to napabucasin plus nab-paclitaxel with gemcitabine and 71.0% of those assigned to nab-paclitaxel with gemcitabine had died
- Median (95% confidence interval [CI]) OS in the napabucasin plus nab-paclitaxel with gemcitabine and nab-paclitaxel with gemcitabine arms were 11.4 (10.5–12.2) and 11.7 (10.7–12.7) months, respectively (hazard ratio [HR], 1.07; 95% CI, 0.93–1.23; one-sided *P*=0.84) **(Figure 2)**

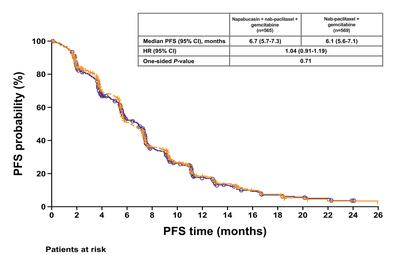
Figure 2. OS in the intent-to-treat population



OS was summarized using the Kaplan–Meier method and compared primarily using a stratified log-rank test adjusted for randomization stratification variables. The HR derived from a Cox proportional hazards model.
CI, confidence interval; HR, hazard ratio; OS, overall survival.

- Median PFS was 6.7 (95% CI, 5.7–7.3) and 6.1 (95% CI, 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) **(Figure 3)**

Figure 3. PFS in the intent-to-treat population



PFS was summarized using the Kaplan–Meier method and compared using a log-rank test stratified by randomization stratification variables. The HR derived from a Cox proportional hazards model.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

- Among those pts with measurable disease per RECIST version 1.1 at randomization, ORR was 43.2% in the napabucasin treatment arm and 42.9% in the control treatment arm **(Table 2)**. The corresponding values for DCR were 74.5% and 76.0%

Table 2. Tumor response in patients with measurable disease per RECIST version 1.1 at randomization

	Napabucasin + nab-paclitaxel + gemcitabine (n=556)	Nab-paclitaxel + gemcitabine (n=559)
ORR, n (%)	240 (43.2)	240 (42.9)
95% CI	39.0–47.4	38.8–47.2
DCR, n (%)	414 (74.5)	425 (76.0)
95% CI	70.6–78.0	72.3–79.5
Best response, n (%)		
CR	4 (0.7)	6 (1.1)
PR	236 (42.4)	234 (41.9)
SD	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; CR, complete response; DCR, disease control rate; ORR, overall response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

- In exploratory analyses performed on the biomarker-positive subgroup, no differences between treatment arms were found for OS, PFS, DCR, or ORR

Safety

- Of the 1134 randomized pts, 1108 (97.7%) received study treatment
  - In total, 0.7% (4/565) of pts randomized to napabucasin plus nab-paclitaxel with gemcitabine compared with 3.9% (22/569) of those randomized to nab-paclitaxel with gemcitabine, did not receive study treatment and were thus excluded from the safety population
  - This may have been due to the open-label nature of the trial (ie, pts may have withdrawn upon randomization to the control arm). However, the impact on study results is likely negligible, as the overall number of randomized pts who were not treated was low (2.3% [26/1134])
- The most common adverse events (AEs) among napabucasin-treated and control-treated pts were diarrhea, nausea, and anemia **(Table 3)**
- Diarrhea was the most common treatment-related AE (TRAE) among pts administered napabucasin plus nab-paclitaxel with gemcitabine (69.2% [n=388])
  - Anemia was the most common TRAE among those administered nab-paclitaxel with gemcitabine alone (49.9% [n=273])
- Similar proportions of napabucasin-treated and control-treated pts had a grade ≥3 AE, most frequently anemia, neutropenia, and neutrophil count decreased **(Table 3)**
- The only serious AEs to occur in ≥5% of pts treated with napabucasin plus nab-paclitaxel with gemcitabine and nab-paclitaxel with gemcitabine treatment alone 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])
- Almost two-fold more pts 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%) **(Table 3)**
  - Following a safety review, it was concluded that this imbalance was not due to a safety signal

Table 3. Safety summary

Patients, n (%)	Napabucasin + nab-paclitaxel + gemcitabine (n=561)	Nab-paclitaxel + gemcitabine (n=547)
Any grade AE*	560 (99.8)	543 (99.3)
Diarrhea	410 (73.1)	213 (38.9)
Nausea	329 (58.6)	252 (46.1)
Anemia	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)
Edema peripheral	179 (31.9)	180 (32.9)
Neutropenia	145 (25.8)	165 (30.2)
Treatment-related AE	543 (96.8)	528 (69.2)
Grade ≥3 AE†	479 (85.4)	459 (83.9)
Anemia	133 (23.7)	108 (19.7)
Neutropenia	104 (18.5)	126 (23.0)
Neutrophil count decreased	100 (17.8)	123 (22.5)
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)

*Preferred terms reported in ≥30% of patients in either treatment arm are presented.
†Preferred terms reported in ≥20% of patients in either treatment arm are presented.
AE, adverse event.

Conclusions

- Adding napabucasin to nab-paclitaxel with gemcitabine did not lead to improvements in survival or response vs. nab-paclitaxel with gemcitabine in pts with previously untreated mPDAC
- The safety profile of napabucasin was consistent with previous reports,[9,10] with diarrhea being the most common AE
- In the general study population, median OS was ~3 months longer than that observed among pts receiving nab-paclitaxel with gemcitabine in the pivotal phase 3 MPACT trial (11.4–11.7 vs. 8.5 months), and ORR was almost two-fold greater (42.9–43.2% vs. 22.9%).[11] Improvements in OS may reflect advances in best supportive care.
- Our data reinforce nab-paclitaxel plus gemcitabine as a backbone for novel therapeutic approaches in mPDAC

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