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Original research

A multicenter, randomized phase 2 study to establish combinations of CBP501, cisplatin and nivolumab for ≥3rd-line treatment of patients with advanced pancreatic adenocarcinoma

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ABSTRACT

Background: There is no standard of care for ≥ 3rd-line treatment of metastatic pancreatic adenocarcinoma (PDAC). CBP501 is a novel calmodulin-binding peptide that has been shown to enhance the influx of platinum agents into tumor cells and tumor immunogenicity. This study aimed to (1) confirm efficacy of CBP501/cisplatin/nivolumab for metastatic PDAC observed in a previous phase 1 study, (2) identify combinations that yield 35% 3-month progression-free survival rate (3MPFS) and (3) define the contribution of CBP501 to the effects of combination therapy.

Methods: CBP501 16 or 25 mg/m^2 (CBP(16) or CBP(25)) was combined with 60 mg/m^2 cisplatin (CDDP) and 240 mg nivolumab (nivo), administered at 3-week intervals. Patients were randomized 1:1:1:1 to (1) CBP(25)/CDDP/nivo, (2) CBP(16)/CDDP/nivo, (3) CBP(25)/CDDP and (4) CDDP/nivo, with randomization stratified by ECOG PS and liver metastases. A Fleming two-stage design was used, yielding a one-sided type I error rate of 2.5% and 80% power when the true 3MPFS is 35%.

Results: Among 36 patients, 3MPFS was 44.4% in arms 1 and 2, 11.1% in arm 3% and 33.3% in arm 4. Two patients achieved a partial response in arm 1 (ORR 22.2%; none in other arms). Median PFS and OS were 2.4, 2.1, 1.5 and 1.5 months and 6.3, 5.3, 3.7 and 4.9 months, respectively. Overall, all treatment combinations were well tolerated. Most treatment-related adverse events were grade 1–2.

Conclusions: The combination CBP(25)/(16)/CDDP/nivo demonstrated promising signs of efficacy and a manageable safety profile for the treatment of advanced PDAC.

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1. Introduction

CBP501 is a unique cell-permeable peptide that binds to calmodulin and has been shown to enhance accretion of platinum agents by tumor cells, leading to increased DNA adduct formation and cytotoxicity [1]. In addition, CBP501 has been shown to induce tumor immunogenic cell death [2], suppress the function of tumor-associated macrophages [3], reduce cancer stem cell populations [3], and reduce migration and invasion by inhibiting the epithelial-to-mesenchymal transition of tumor cells [4]. The induction of immunogenic cell death by the combination of CBP501 and cisplatin [2] and the suppression of M2 macrophages by CBP501 [3] are biological effects expected to render tumors sensitive to immune checkpoint inhibitors. Consistent with these effects, in the CT26 syngeneic tumor model, treatment with CBP501/cisplatin/nivolumab was significantly more effective than CBP501/cisplatin, cisplatin/nivolumab, or any single agent [2].

Phase 1 studies in advanced solid tumors showed that CBP501 is well tolerated alone and in combination with cisplatin [5]. Based on preclinical studies demonstrating the efficacy of CBP501/ cisplatin/nivolumab combination therapy, a phase 1, open-label, multicenter, dose escalation trial with dose confirmation cohorts was conducted to assess the safety of CBP501/cisplatin/nivolumab combination therapy in patients with advanced solid tumors and to assess preliminary evidence of efficacy in advanced PDAC and microsatellite stable colorectal cancer [6]. Of the 14 PDAC patients evaluable for efficacy in the phase 1 study, median OS was 4.9 months [7]. Although the sample size was small, results for CBP501/cisplatin/nivolumab combination therapy in PDAC compared favorably with an expected median OS of 3 months [7].

We report here a multicenter, randomized, phase 2 study in $\geq$ 3rd-line PDAC designed to confirm the treatment effect observed for CBP501/cisplatin/nivolumab in the phase 1 study, as well as to identify the optimal dose level of CBP501 and the contribution of CBP501 to the effects observed with combination immunochemotherapy.

2. Methods

2.1. Study design

This was a phase 2, open-label, multicenter, randomized, parallel-group study designed and sponsored by CanBas Co., Ltd. The study was conducted in accordance with the Declaration of Helsinki and was approved by local or central Institutional Review Boards at each investigational site. All patients provided written informed consent to participate in the study.

2.2. Patient selection

Per protocol, patients with pathologically confirmed stage IV PDAC who had received at least 2 lines of systemic therapy for metastatic disease, life expectancy $\geq$ 3 months, and ECOG performance status 0–1 were enrolled. Protocol exclusion criteria included radiation therapy to $>$ 30% of bone marrow, evidence of grade $\geq$ 2 peripheral neuropathy, active CNS metastases, requirement for systemic steroid therapy or other forms of immunosuppressive medication, known risk factors for bowel perforation, active autoimmune disease, absolute neutrophil count (ANC) $<$ 1500/mm^3, white blood cell count (WBC) $\geq$ 10,000/mm^3, hemoglobin $<$ 9 g/dL, aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $>$ 2.5 x upper limit of normal (ULN), total bilirubin $>$ 1.5 x ULN, and INR $>$ 1.5 x ULN and serum creatinine $>$ ULN or creatinine clearance $<$ 45 mL/min (by Cockroft & Gault formula or alternate calculation by 24hr urine collection).

2.3. Study objectives

The primary objective was to determine the percentage of patients who remained progression-free at 3 months (3MPFS). Secondary objectives included safety and tolerability, progression-free survival (PFS), confirmed and timepoint objective response rates (ORR) by RECIST v1.1 criteria, duration of response (DOR), disease control rate (DCR), and overall survival (OS).

2.4. Treatment plan

Patients were randomized 1:1:1:1 to four treatment groups, with randomization stratified by ECOG performance status (0 vs 1) and liver metastases (present vs absent): (1) CBP501 25 mg/m^2 + cisplatin 60 mg/m^2 + nivolumab 240 mg [CBP(25)/CDDP/nivo], (2) CBP501 16 mg/m^2 + cisplatin 60 mg/m^2 + nivolumab 240 mg [CBP(16)/CDDP/nivo], (3) CBP501 25 mg/m^2 + cisplatin 60 mg/m^2 [CBP(25)/CDDP] and (4) cisplatin 60 mg/m^2 + nivolumab 240 mg [CDDP/nivo]. Cisplatin dose was reduced 50% in all arms for creatinine clearance (CrCl) between 45 to 59 mL/min.

Drugs were administered by intravenous (IV) infusion on Day 1 of each 21-day cycle of treatment. CBP501 and cisplatin were administered concurrently, followed by nivolumab infusion. No more than four cycles of combination therapy were administered but patients who remained progression-free after four cycles could receive up to an additional six cycles of single-agent nivolumab. The limitation to four cycles of cisplatin combination therapy was made based on results from the precedent CBP17–01 study of cisplatin combination therapy which found that 3 of 6 patients who received more than 4 cycles developed increased creatinine, despite protocol-specified prehydration.

Appropriate prophylactic medications for cisplatin-induced kidney injury, CBP501-related infusion reactions, and emesis were given prior to each administration of study drugs. The protocol-specified hydration to mitigate cisplatin-induced kidney injury involved administering 1.0 L of 0.9% Sodium Chloride Injection with 2 g Magnesium Sulfate, run at 500 mL/hour; after completing one hour of hydration, administering 12.5 g of Mannitol Injection by IV bolus injection; after administering the Mannitol Injection, starting the cisplatin infusion while continuing the hydration infusion; and maintaining a urinary output of 250 mL/hour over the duration of hydration, administering additional mannitol (12.5 to 50.0 g via IV bolus injection) as needed. The protocol-specified anaphylactoid reaction prophylaxis included administering loratadine 10 mg PO (or equivalent) the day prior to CBP501 infusion, the day of infusion, and the day after; and diphenhydramine 50 mg IV bolus and famotidine 20 mg IV bolus (or alternative histamine H2-receptor antagonists such as cimetidine) prior to starting the CBP501 infusion. The protocol-specified antiemetic prophylaxis, given prior to CBP501 and cisplatin infusions, included dexamethasone 12 mg IV (or equivalent), palonosetron 0.25 mg IV (or equivalent), and fosaprepitant 150 mg IV (or equivalent), infused over 20–30 min. Patients could receive standard treatment for concomitant conditions, prophylactic low dose anticoagulants, supportive therapy, including treatment for anaphylactic reactions, aggressive treatment for cancer pain and symptoms, hematopoietic growth factors (from cycle 2 forward), and palliative radiation for analgesia if the radiation field did not include target lesions and less than 30% of bone marrow was exposed. CYP450- isozymes 2C8, 2C19 and 2D6 inhibitors were avoided unless there were no alternatives; patients were monitored for potential drug-drug interactions.

2.5. Safety assessments

Regular safety assessments were performed, including physical examination, ECOG performance status, vital signs, and laboratory parameters conducted at screening, prior to each cycle of treatment, and at the End-of-Treatment (EOT) visit. Adverse events (AEs) were assessed at each visit and assigned a grade, as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) and relationship to study treatment (i.e., related or unrelated for each drug in the combination). All patients who received at least one study treatment were included in the safety analyses.

2.6. Efficacy assessments

Tumor assessment by RECIST v1.1 criteria was performed at screening, every 8 weeks starting after Cycle 1 Day 1, at the EOT visit, and every 3 months after the EOT visit until disease progression was observed. ORR, DOR, DCR, 3MPFS and PFS were calculated based on tumor assessments by each site. All patients with on-study tumor assessments were included in analysis of 3MPFS and PFS and all patients randomized were included in analysis of OS.

2.7. Statistical methods

A Fleming two-stage design was used. For each study arm, the null hypothesis that the true 3MPFS is 10% was tested against a one-sided alternative. In the first stage, 9 patients were to be accrued to each study arm. In the first stage, if one or fewer patients were progression-free at 3 months the study arm was to be stopped for futility and if 4 or more patients were progression-free at 3 months the study arm was to be stopped and the null hypothesis rejected. Otherwise, 14 additional patients were to be accrued for a total of 23 and the null hypothesis was to be rejected if 6 or more of 23 patients were progression-free at 3 months. This design yields a one-sided type I error rate of 2.5% and 80% power when the true 3MPFS is 35%.

The intent-to-treat (ITT) population was used to assess 3MPFS.

3. Results

3.1. Patients

Between December 2021 and August 2022, 36 patients were randomized, with 9 allocated to each treatment group (Figure 1). Baseline demographics were similar between treatment arms (Table 1): The median age was 69 years (range: 41–80) with 64% > 65 years of age, slightly over half of patients were males and most patients were Caucasians. The population was heterogeneous in terms of baseline disease characteristics, with differences between groups in the distribution of tumor grades, percentage of patients who had surgery for their primary tumor, number of prior lines of systemic therapy for metastatic disease, and best overall response to prior systemic therapy for metastatic disease (Table 1, Table S1). For treatment of metastatic disease, most patients had received FOLFIRINOX and gemcitabine/nab-paclitaxel. All but five patients had prior exposure to platinum; Table S1 shows percentages of PR and CR on prior platinum-containing treatment.

3.2. Efficacy

The number of cycles administered varied across treatment arms, with a median 3.5 cycles (range: 2–10) of CBP(25)/CDDP/nivo, 3 cycles (range: 2–10) of CBP(16)/CDDP/nivo, 2 cycles (range: 1–3) of CBP(25)/CDDP and 2.5 cycles (range: 2–10) of CDDP/nivo (Table 2). Among the 33 patients who received study treatment, only 14 (42%) received more than 2 cycles. Most patients (73%) discontinued treatment for progressive disease.

Of the 36 patients randomized, 32 patients were evaluable for assessment of 3MPFS. Of the four patients who did not have on-study tumor assessments, three were not treated (one died and one discontinued for rapid disease progression prior to receiving treatment and one was found to be ineligible due to low GFR on the day of scheduled treatment) and one patient withdrew consent following the first study

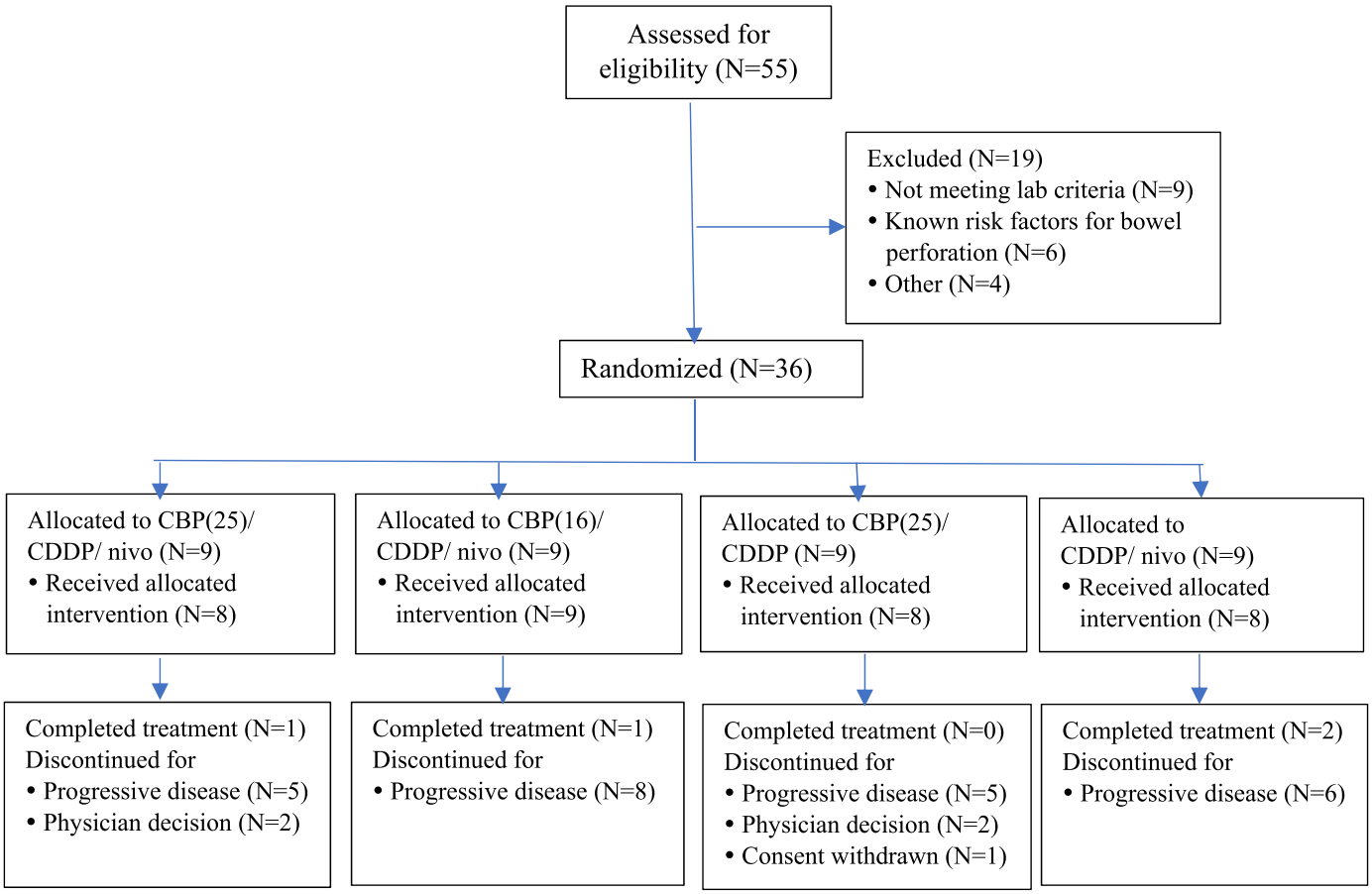

Fig. 1. Patient disposition.

Table 1
Baseline Characteristics.

Characteristic	CBP (25)/ CDDP/ nivo, N = 9	CBP (16)/ CDDP/ nivo, N = 9	CBP (25)/ CDDPN= 9	CDDP/ nivoN= 9
Median age (range), y	67 (41, 78)	68 (49, 77)	74 (50, 81)	71 (49, 82)
Age > 65 y, n (%)	5 (55.6)	6 (66.7)	5 (55.6)	7 (77.8)
Male sex, n (%)	5 (55.6)	4 (44.4)	5 (55.6)	5 (55.6)
White race, n (%)	7 (77.8)	8 (88.9)	9 (100)	8 (88.9)
ECOG performance status, n (%)				
0	3 (33.3)	3 (33.3)	2 (22.2)	3 (33.3)
1	5 (55.6)	6 (66.7)	6 (66.7)	6 (66.7)
missing	1 (11.1)	0	1 (11.1)	0
Tumor grade, n (%)				
Gx (undetermined)	5 (55.6)	4 (44.4)	4 (44.4)	3 (33.3)
G1 (well differentiated)	1 (11.1)	0	0	0
G2 (moderately differentiated)	2 (22.2)	5 (55.6)	2 (22.2)	2 (22.2)
G3 (poorly differentiated)	1 (11.1)	0	2 (22.2)	3 (33.3)
G4 (undifferentiated)	0	0	1 (11.1)	1 (11.1)
Site of metastases, n				
Liver	6 (66.7)	5 (55.6)	6 (66.7)	5 (55.6)
Lung	5 (55.6)	6 (66.7)	4 (44.4)	3 (33.3)
Lymph node	2 (22.2)	3 (33.3)	4 (44.4)	3 (33.3)
Other	3 (33.3)	3 (33.3)	3 (33.3)	0
Prior surgery for primary tumor, n (%)	4 (44.4)	4 (44.4)	2 (22.2)	5 (55.6)
Prior systemic therapy for metastatic disease, n (%)	9 (100)	9 (100)	9 (100)	9 (100)
Median lines (range) of prior systemic therapy for metastatic disease	3 (2-4)	3 (2-4)	2 (2-3)	3 (2-4)
FOLFIRINOX	6 (66.7)	6 (66.7)	5 (55.6)	6 (66.7)
gemcitabine/nab-paclitaxel	9 (100)	8 (88.9)	8 (88.9)	8 (88.9)

Table 2
Treatment Exposure and Response.

	CBP (25)/ CDDP/ nivo, N = 9	CBP (16)/ CDDP/ nivo, N = 9	CBP (25)/ CDDPN= 9	CDDP/ nivoN= 9
Median (range) number of cycles	3.5 (2, 10) (N = 8)	3 (2, 10) (N = 9)	2 (1, 3) (N = 8)	2.5 (2, 10) (N = 8)
Efficacy assessments:				
3MPFS, % (n/N)	44.4 (4/9)	44.4 (4/9)	11.1 (1/9)	33.3 (3/9)
95% CI	10.9, 77.8	3.4, 51.3	3.4, 51.3	15.7, 45.0
Median PFS, months	2.4	2.1	1.5	1.5
95% CI	0.8, 4.0	0.4, 3.7	0.4, 2.6	0.1, 2.9
Median OS, months	6.3	5.3	3.7	4.9
95% CI	3.3, 9.3	3.5, 7.1	1.9, 5.4	2.8, 7.0
ORR, % (n/N)	22.2 (2/9)	0	0	0
95% CI	3.2, 65.1	0, 33.6	0, 45.9	0, 41.0
CR	0	0	0	0
PR	2	0	0	0
SD	1	1	0	3
Median DOR, months	4.1	0	0	0
DCR % (n/N)	33.3 (3/9)	11.1 (1/9)	0	33.3 (3/9)
95% CI	8.5, 75.5	0.3, 48.2	0, 45.9	9.9, 81.6

3MPFS: percentage of patients progression-free at 3 months; CI: confidence interval; CR: complete response; DCR: disease control rate; DOR: duration of response; NA: not applicable; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; SD: stable disease

treatment.

In the first stage of the study, based on the number of patients progression-free at 3 months (the protocol-specified primary endpoint), both triplet therapy arms (CBP 25 and 16/CDDP/nivo) met criteria to reject the null hypothesis and the CBP(25)/CDDP arm met criteria to stop for futility (Table 2). Although the CDDP/nivo arm met criteria to proceed to stage 2, the Safety Monitoring Committee recommended terminating the study arm because the CBP(25)/CDDP/nivo regimen demonstrated longer median PFS (2.4 vs 1.5 months) (Table 2 and Fig. 2A) and median OS (6.3 vs 4.9 months) (Table 2, Fig. 2B, Table S2). Objective responses were only observed on the CBP(25)/CDP/nivo arm, which showed 22% ORR with 4.1 months DOR (Fig. 3). DCR was 33.3% for CBP(25)/CDDP/nivo and CDDP/nivo arms, 11.1% for CBP(16)/CDDP/nivo and 0% for CBP(25)/CDDP.

3.3. Safety and tolerability

Of the 33 treated patients, 88% (29/33) experienced at least one treatment-related adverse event (TRAE) and 12% (4/33) experienced at least one grade 3 TRAE; no grade 4–5 TRAEs were reported. The most common TRAEs, occurring in $\geq$ 10% of patients overall, were gastrointestinal events of nausea (27%) and diarrhea (12%); fatigue (42%); infusion-related reaction (58%); neutrophil count decreased (15%); and decreased appetite (15%) (Table 3). The only common TRAEs that occurred with higher frequency in CBP501-containing arms were infusion-related reaction (76% vs 0%), decreased neutrophil count (20% vs 0%), anemia (12% vs 0%), and hypokalemia (12% vs 0%).

One TRAE, CBP501-related grade 2 infusion-related reaction resulted in study drug discontinuation (arm 3). Grade 1–2 CBP501-associated infusion-related reactions (itching, hives, redness) caused drug infusion interruption for 64% (16/25) of patients who received CBP501; interruptions lasted from 6 to 84 min until symptoms lessened, after which the infusion was resumed. One SAE of acute kidney injury that occurred after one cycle of treatment was assessed to be probably related to CBP501 and definitely related to CDDP (arm 3).

4. Discussion

Safety and efficacy results, based on the 3MPFS primary endpoint, suggested the combination of 25 mg/m^2 CBP501 + 60 mg/m^2 cisplatin + 240 mg nivolumab [CBP(25)/CDDP/nivo] is a regimen that deserves further evaluation in PDAC patients who have progressed following at least 2 lines of treatment in the metastatic setting. Overall toxicities were manageable by limiting CBP501 and cisplatin to a maximum of 4 cycles and by instituting dose interruptions (typically due to CBP501-associated infusion-related reactions) and dose reductions (50% reduction in cisplatin dose for CrCl between 45 to 59 mL/min). In terms of efficacy, the CBP(25)/CDDP/nivo arm met the primary endpoint, with 4 of 9 patients progression-free at 3 months. Moreover, CBP(25)/CDDP/nivo was the only regimen that showed objective treatment responses.

Although CDDP/nivo is not a standard of care treatment in pancreatic cancer, per regulatory guidance it was necessary to include this study arm along with the CDDP/CBP501 arm to assess the contribution of CBP501 to CBP501/CDDP/nivo combination therapy. Immune checkpoint inhibitors such as nivolumab have demonstrated limited clinical benefit in PDAC, possibly owing to the profoundly immunosuppressive tumor microenvironment [8]. However, chemoimmunotherapy has shown evidence of activity in preclinical models of PDAC [9,10] and a recent randomized clinical study showed that the addition of nivolumab to first-line gemcitabine/nab-paclitaxel chemotherapy led to a modest but statistically significant improvement in 1-year survival [11], suggesting the potential for chemoimmunotherapy in PDAC. The 4.9 months median OS for CDDP/nivo was longer than the expected 3.0 months median OS for 3rd-line therapy [7], suggesting some a treatment benefit of the combination therapy.

Comparing results from the CBP501(25)/CDDP/nivo, CBP501(25)/

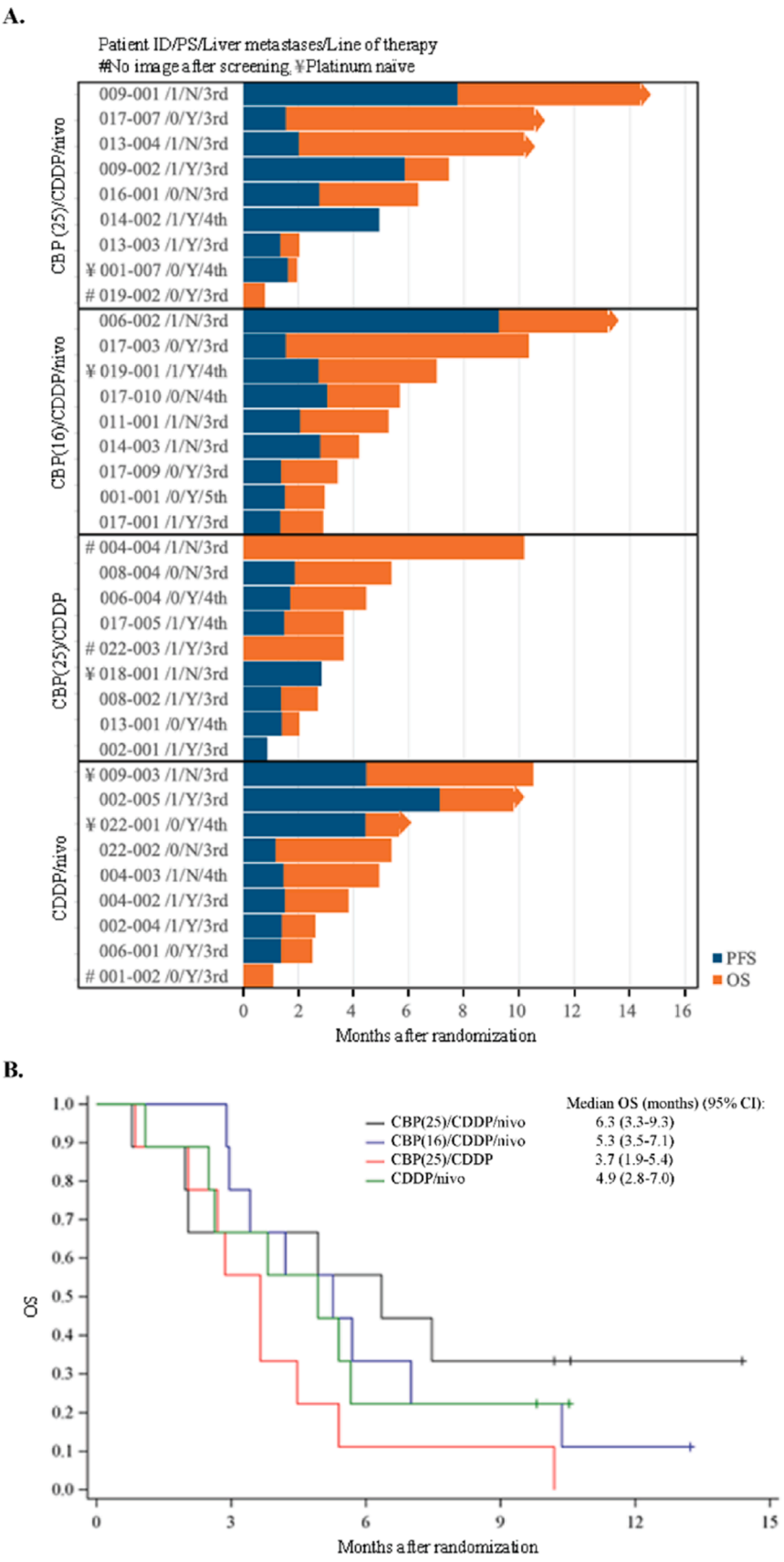

Fig. 2. Swimmer Plot (A) and Kaplan-Meier Plot (B) showing Progression-Free Survival (PFS) (A) and Overall Survival (OS) (A,B).

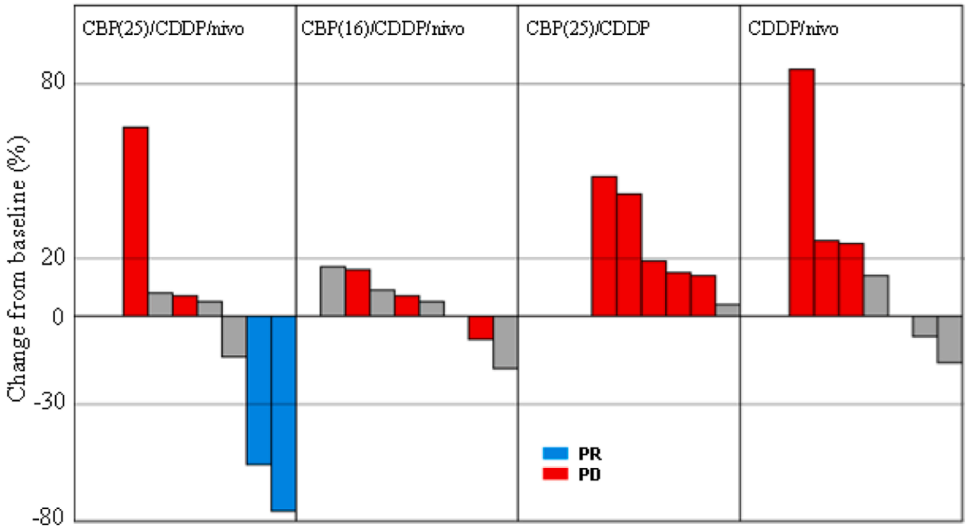

Fig. 3. Waterfall Plot of Tumor Responses.

Table 3
Treatment-Related Treatment-Emergent Adverse Events Occurring in 2 or More Patients or Reaching Grade ≥ 3.

System OrganPreferred Term	CBP (25)/CDDP/nivoN= 8		CBP (16)/CDDP/nivoN= 9		CBP (25)/CDDPN= 8		CDDP/nivoN= 8	
	Total n (%)	Gr ≥ 3	Total	Gr ≥ 3	Total	Gr ≥ 3	Total	Gr ≥ 3
Patients with at least one event	7 (87.5)	2 (25.0)	9 (100)	0	8 (100)	2 (25.0)	5 (62.5)	0
Blood and lymphatic system disorders								
Anemia	2 (25.0)	1 (12.5)	0	0	1 (12.5)	1 (12.5)	0	0
Ear and labyrinth disorders								
Tinnitus	0	0	0	0	1 (12.5)	0	1 (12.5)	0
Gastrointestinal disorders								
Abdominal pain	0	0	1 (11.1)	0	1 (12.5)	0	0	0
Diarrhea	0	0	1 (11.1)	0	1 (12.5)	0	2 (6.1)	0
Dyspepsia	0	0	1 (11.1)	0	0	0	2 (6.1)	0
Nausea	1 (12.5)	0	4 (44.4)	0	1 (12.5)	0	3 (37.5)	0
Vomiting	0	0	2 (22.2)	0	0	0	0	0
General disorders								
Fatigue	2 (25.0)	0	6 (66.7)	0	3 (37.5)	0	3 (37.5)	0
Malaise	0	0	1 (11.1)	0	0	0	1 (12.5)	0
Injury, poisoning and procedural complications								
Infusion related reaction	7 (87.5)	0	6 (66.7)	0	6 (75.0)	0	0	0
Investigations								
CrCl decreased	1 (12.5)	0	1 (11.1)	0	0	0	0	0
Neutrophil count dec	3 (37.5)	0	2 (22.2)	0	0	0	0	0
Platelet count dec.	0	0	1 (11.1)	0	0	0	1 (12.5)	0
TSH increased	1 (12.5)	0	1 (11.1)	0	0	0	0	0
Metabolism disorders								
Decreased appetite	0	0	3 (33.3)	0	1 (12.5)	0	1 (12.5)	0
Dehydration	0	0	1 (11.1)	0	1 (12.5)	0	0	0
Hypokalemia	2 (25.0)	0	0	0	1 (12.5)	0	0	0
Musculoskeletal and connective tissue disorders								
Myalgia	0	0	1 (11.1)	0	0	0	1 (12.5)	0
Renal and urinary disorders								
Acute kidney injury	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Respiratory, thoracic and mediastinal disorders								
Hiccups	0	0	1 (11.1)	0	0	0	1 (12.5)	0
Vascular disorders								
Hypertension	1 (12.5)	1 (12.5)	0	0	0	0	0	0

CDDP and CDDP/nivo arms, results from the first stage of the trial suggest a beneficial contribution of CBP501 to CDDP/nivo combination therapy: CBP(25)/CDDP was not active (per protocol, terminated for futility) and CDDP/nivo had shorter median OS (4.9 vs 6.3 months) and median PFS (1.5 vs 2.0 months) than the recommended regimen of CBP (25)/CDDP/nivo.

Notably, the 6.3 months median OS for ≥ 3rd-line treatment with CBP(25)/CDDP/nivo was comparable to reported results from larger studies of frequently used 2nd-line treatment regimens: Median OS ranged from 3.7 to 11 months in four 2nd-line studies of FOLFOX [12–15], 4 and 5 months in two 2nd-line studies of FOLFIRI [14,16], 4.9 and 5.2 months in two 2nd-line studies of liposomal irinotecan [17,18], 6.2 months in a 2nd-line study of liposomal irinotecan combined with 5-fluorouracil [17] and 5.8 months in a 2nd-line study of nab-paclitaxel combined with gemcitabine [19]. The median OS in the CBP (25)/CDDP/nivo arm was more remarkable considering that 67% of patients had liver metastases, known to be associated with worse OS [17, 20,21].

A Fleming two-stage design, which is commonly used for early screening of cancer drugs based on objective response rate, was selected as an efficient regimen screening design. However, the well-recognized difficulty in achieving objective responses in the 3rd-line setting precluded using objective response rate as a primary endpoint in this study. The 3MPFS endpoint was selected based on a phase 2 study of durvalumab with or without tremelimumab for 2nd-line treatment of metastatic PDAC, which revealed median OS of 3.1 and 3.6 months and a disease control rate at 3 months of 6.1% and 9.4% for the single and doublet arms, respectively [22]. Though the durvalumab study did not meet its threshold for efficacy, since the reported median survival durations in the durvalumab study were similar to the historical median OS of 3 months for 3rd-line treatment of metastatic PDAC [7], it seemed reasonable to use the equivalent of disease control rate at 3 months as the primary endpoint for this regimen-finding study. A 3MPFS target of 35% was selected for this study, as the 9% 3MPFS in the durvalumab study was not associated with improved efficacy.

Sample sizes in this study were determined by the Fleming two-stage statistical design, which specified enrollment of 9 patients per arm in the first phase and then expansion to a total of 23 patients per arm for arms that were not discontinued in the first stage for either futility or success. This design yields a one-sided type I error rate of 2.5% and 80% power when the true 3MPFS is 35%.

We acknowledge study limitations due to the small sample size. Nevertheless, results from our study are encouraging and stimulated further development of CBP501/cisplatin/nivolumab combination therapy for 3rd-line treatment of metastatic PDAC. CanBas has initiated an open-label, randomized, multicenter proof-of-concept study designed to compare the overall survival for CBP501/cisplatin/nivolumab combination therapy and Physician's choice of therapy in patients with PDAC who have received at least two prior lines of systemic therapy for metastatic disease.

Ethics approval and consent to participate

The study protocol was approved by an independent institutional review board (IRB) at each investigational site: Advarra IRB, Mary Crowley Medical Research Center IRB, Ochsner Clinic Foundation IRB, U.S. Oncology IRB, University of Colorado IRB, University of Michigan IRB, and WCG IRB, Inc. The study was conducted according to the principles of the Declaration of Helsinki and was performed in compliance with Good Clinical Practice guidelines. Written informed consent was obtained from each patient.

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CRediT authorship contribution statement

T. Enzler, A. Nguyen, J. Misleh, V.J. Cline, M. Johns, N. Shumway, S. Paulson, R. Siegel, T. Larson, W. Messersmith, D. Richards, J. Chaves, E. Pierce and D. Orr provided study patients and were involved in the acquisition of data and data analysis/interpretation. T. Kawabe was involved in the concept and design of the study, collection and assembly of data, data analysis/interpretation, and provided study materials. S.A. Ruste and A. Haun were medical monitors for the study. All authors participated in the review and approval of the manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: T. K. is an employee, patent holder on CBP501 and shareholder of CanBas Co., Ltd and was involved in the study concept and design, collection and assembly of data, and data analysis/interpretation. A.H. and S.A.R. are employees of Veristat LLC, which received commercial research support from CanBas Co., Ltd. All other authors reported no competing interest with respect to CanBas Co., Ltd. and CBP501.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.113950.

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