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Phase 1b study of Wnt inhibitor ipafricept (IPA) with nab-paclitaxel (Nab-P) and gemcitabine (G) in patients with previously untreated stage IV pancreatic cancer (mPDAC)

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Abstract

Background: The recombinant fusion protein ipafricept (IPA) blocks Wnt signaling, and in combination with gemcitabine (G) and nab-paclitaxel (Nab-P) caused tumor regression in xenografts. This phase 1b study evaluated the combination of IPA with Nab-P+G in untreated metastatic PDAC (mPDAC) patients.

Methods: Dose escalation started with standard dose Nab-P+G and IPA (3.5 mg/kg days 1, 15). Due to fragility fractures seen with different anti-Wnt agents, following cohorts had ≥6 patients treated with IPA 3 - 5 mg/kg on day 1, and included bone marker monitoring and prophylactic bisphosphonates as indicated. Based on pre-clinical data sequential dosing was evaluated in cohort 4 (IPA day 1 followed Nab-P+G day 3). Objectives included safety, MTD, RP2D, pharmacokinetics, immunogenicity, pharmacodynamics, and efficacy.

Results: 26 patients were enrolled, 5 in the cohort 1 and 7 each in cohorts 2-4. IPA-related AEs of any grade included fatigue, nausea, vomiting, anorexia and pyrexia. IPA-related AEs grade ≥3 included 2 events of AST elevation, and 1 each of nausea, rash, vomiting and leucopenia. No DLTs or fragility fractures were observed. Nine patients (34.6%) had PR, 12 (46.2%) SD as best response, with clinical benefit rate of 81%. Median PFS was 5.9m (95%CI 3.4-18.4), median OS

1. ASCO-GI meeting in January 2019: Dotan E, et al. Phase 1b Study of WNT Inhibitor Ipafricept (IPA) with nab-paclitaxel (Nab-P) and gemcitabine (G) in patients (pts) with previously untreated stage IV pancreatic Cancer (mPC). J Clin Oncol 2019, 37; Supple 4: abstr 369.

2. ESMO meeting 2016: Weekes C, et al. Phase 1b study of WNT inhibitor ipafricept (IPA, decoy receptor for WNT ligands) with nab-paclitaxel (Nab-P) and gemcitabine (G) in patients (pts) with previously untreated stage IV pancreatic cancer (PC). ESMO meeting October 2016, Abstract 3410 (poster discussion).

was 9.7m (95%CI: 7.0-14). The study was terminated by the sponsor due to bone-related toxicity within this therapeutic program and concerns for commercial viability. One patient remains on therapy under compassionate use.

Conclusions: IPA can be administered with Nab-P+G with reasonable tolerance. Wnt pathway remains a therapeutic target of interest in mPDAC.

Keywords

Pancreatic Cancer; Ipafricept; Wnt inhibitors

Introduction:

Metastatic pancreatic cancer (mPDAC) is a lethal disease with a poor prognosis and relatively limited treatment options. In the United States, it is the third leading cause of cancer-related death among both men and women [1]. Two chemotherapy combinations are approved for treatment of patients in this setting which include the 3-drug combination of FOLFIRINOX (5-flourouracil, oxaliplatin and irinotecan) and the 2-drug regimen of Gemcitabine (G) and nab-Paclitaxel (Nab-P) (MPACT trial) [2, 3]. The combination of 5FU and liposomal irinotecan (nal-IRI) has been approved for use in the second line setting [4]. These treatments produce initial reduction in tumor burden which is short-lived possibly due to the continued presence of cancer stem cells (CSC) that are treatment resistant [5, 6]. Targeting surface proteins that are part of the Wnt pathway is an attractive approach to inhibit CSCs. A specific subset of Frizzled (FZD) receptors have been defined, FZD4, FZD5 and FZD8, that appear to be central to canonical Wnt signaling, although key contributions by other FZD receptors have also been demonstrated [7, 8]. Wnt-FZD signaling through β-catenin is known as the “canonical” pathway and is the key pathway de-regulated in cancer. The Wnt pathway has been linked and studied in cancer, with evidence of increased Wnt signaling being linked to the development and progression of PDAC [9, 10]. In particular, β-catenin signaling of the canonical Wnt pathway plays a central role in the regulation of CSCs.

Ipafricept (IPA; OMP-54F28) is a recombinant fusion protein (immunoadhesin) consisting of a combination of the extracellular ligand binding domain of human FZD8 receptor and the human IgG1 Fc fragment [8, 11]. IPA inhibits Wnt signaling by acting as a decoy receptor while binding and sequestering Wnt ligands. IPA binds to all Wnt proteins; therefore, it functions as a broad spectrum Wnt antagonist. Pre-clinical studies combining IPA with G plus Nab-P conducted with patient-derived xenograft models of pancreatic cancers revealed the potent synergistic interactions resulting in tumor regression with this combination [12, 13]. In the first-in-human Phase 1 study of IPA in patients with refractory solid tumors, maximum tolerated dose (MTD) was not determined with the highest dose level of 20 mg/kg every 3 weeks and the recommended phase 2 dose of 15mg/kg every 3 weeks [11]. Based on these results the current open-label phase 1b dose escalation study of IPA in combination with G and Nab-P in patients with untreated mPDAC was launched. Safety, tolerability by dose limiting toxicity, recommended phase 2 dose, as well as preliminary efficacy were evaluated.

Materials and methods:

Patients:

This was an open-label phase 1b dose escalation study with IPA in combination with G and Nab-P for the treatment of patients with previously untreated mPDAC. Patients over the age of 18 years with histologically documented adenocarcinoma of the pancreas, ECOG performance status 0-1, evaluable disease by RECIST and adequate hematologic and end-organ function were enrolled. Due to previously established on-target toxicity of WNT antagonists demonstrating evidence of bone fragility fractures, patients required a normal calcium, vitamin D, and TSH level at time of enrollment [14]. Patients with history of osteoporosis, or evidence of bone metastases with pathologic fractures were excluded. All patients provided signed written informed consent and the protocol was approved by the Institutional Review Boards (IRB) at participating institutions. The study was conducted according to US and international standards of Good Clinical Practice (GCP) and in compliance with the scientific principles outlined in the Declaration of Helsinki.

Treatment schedule:

Patients were treated in 4 dose escalation cohorts outlined in Figure 1. In each cohort patients received a chemotherapy backbone of Nab-P 125 mg/m^2 and G 1000mg/m^2 given on days 1,8, and 15 of a 28-day cycle. Patients in cohort 1 were treated with IPA 3.5 mg/kg (n=3) administered intravenously (IV) on days 1 and 15 of a 28-cycle. Following enrollment of 3 patients in cohort 1, fragility bone fractures were seen in other ongoing phase 1 studies evaluating different WNT pathway inhibitors [15, 16]; therefore, each of the subsequent cohorts enrolled a minimum of six patients who were observed under a strict bone safety monitoring plan. In addition, the IPA treatment schedule was revised to a single dose on day 1 of 28-day cycles (cohort 2: IPA 3 mg/m^2; cohorts 3 and 4: IPA 5 mg/m^2) (Figure 1). Based on pre-clinical data suggesting improved efficacy with sequential dosing of IPA prior to chemotherapy, patients in cohort 4 received IPA on day 1 followed by G and Nab-P chemotherapy given on days 3, 10 and 17 of each 28-day cycle.

The adverse events (AE) were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 with weekly toxicity evaluations. Dose-limiting toxicities (DLT) were assessed during the DLT assessment window of 28 days following the first administration of IPA (cohorts 1-3). For cohort 4, which used a sequential dosing schedule, the DLT assessment window was extended to day 31 of cycle 1. In addition, a bone safety window following administration of the study drug was set for 56 days for cohorts 2 and 3, and extended to 59 days for cohort 4. DLTs were defined as prolonged grade ≥3 non-hematologic toxicity that did not respond to standard supportive care measures, grade 4 thrombocytopenia or neutropenia lasting more than 7 days, grade ≥3 febrile neutropenia and grade ≥3 total bilirubin or hepatic transaminases elevation.

Patients remained on study until disease progression by RECIST v1.1, or excessive toxicity. Tumor response was evaluated using RECIST v1.1. Progression-free survival (PFS), was defined as the number of days from study treatment initiation to death or disease progression

as defined by RECIST v1.1. Overall Survival (OS) was defined as the number of days from study treatment initiation until death. Blood samples were collected for determination of anti-drug (IPA) antibodies (ADA) and evaluation of serum concentrations and PK parameters of IPA.

Bone Safety Monitoring:

Given the known risk for bone toxicity associated with Wnt inhibition and following the reports of fragility fractures with this class of drugs, a bone safety plan was implemented to prevent fractures by close monitoring, early intervention with zoledronic acid and withholding or discontinuing IPA as needed [17]. This included evaluation of the risk for fracture at the time of screening (as measured by fracture risk assessment [FRAX] tool score) [18], regular monitoring for potential bone toxicity using dual-energy X-ray absorptiometry (DEXA) scans, beta C-terminal telopeptide (β-CTX), a serum marker for bone resorption and 3 markers for bone formation (osteocalcin, bone-specific alkaline phosphatase [BSAP], procollagen type 1 amino-terminal propeptide [P1NP]). All patients received prophylactic Vitamin D (1000 IU QD) and calcium (500-600mg BID). In case of high FRAX score, history of fractures, decline of T-Score to <−2.5, or doubling of β-CTX during the treatment period, zoledronic acid was administered. Fragility fractures were defined as a new fracture occurring without history of trauma or fall. Any such fracture occurring during the bone safety window was considered related to IPA.

Due to identification of fragility fractures in IPA-treated patients of a phase 1a study and phase 1b ovarian cancer study, and among patients treated with a different Wnt inhibitor agent, vantictumab, the study was amended for cohorts 2-4 to include a more stringent bone toxicity monitoring plan and every 4 week dosing [19]. In addition, preventative administration of zoledronic acid was made mandatory for postmenopausal females, bone safety monitoring window was extended to first 2 cycles with increased frequency of bone turnover markers monitoring, and lowered threshold criteria for initiation of zoledronic acid were added.

Biomarker analysis:

To evaluate the potential pharmacodynamic (PD) effects of the IPA combination with G and Nab-P, hair follicles and tumor biopsies were planned for collection as per the protocol at baseline, and an optional tumor biopsy following IPA administration (day 36). Unfortunately, only very few patients provided post dosing tumor biopsies, and only one paired pre and post biopsies were evaluable, limiting this part of the analysis. Hair follicles were stored frozen in PicoPure extraction buffer until RNA extraction (PicoPure RNA Isolation kit from Life Technologies). Samples from healthy volunteers were used for control. Tumor samples were collected from archival tissue or as formalin-fixed fresh biopsy. RNA was isolated from FFPE tissue using RNeasy Fibrous Tissue Mini Kit (Qiagen, Valencia, CA). Affymetrix human gene chip U133 Plus 2.0 arrays were used for profiling gene expression levels in hair follicle and in tumor RNA samples. GCRMA software was used to normalize the arrays and summarize the signals. Empirical Bayes analysis was used to identify the genes differentially expressed in the samples between pre-treatment and post-treatment time points and between different dosing groups [20]. Paired-sample

bootstrapping was used to assess the significance of fold changes. The fold-change represents the gene expression ratio comparing post-treatment to pre-treatment (day 1) samples. Gene Set Enrichment Analysis was performed to obtain the biological processes affected by IPA in hair follicles [21]. A 6-gene signature (PYGO1, PLCB1, ACVR2B, SRC, PLAU, TGFB1) previously identified in preclinical human xenograft models, was analyzed on FFPE tumor tissue for correlation with PFS and OS using a cutoff of 50th percentile. The same 6-gene signature was tested on a pancreatic ductal adenocarcinoma RNA Sequence dataset from The Cancer Genome Atlas (TCGA) [22].

Statistical analysis:

In this phase 1b dose escalation study of IPA, cohort 1 was conducted using a modified 3+3 design with a minimum of 3 patients and up to 6 patients. The MTD was defined as the highest dose level at which < 2 of 6 patients experienced a DLT. For cohorts 2-4, a minimum of 6 patients each was enrolled in each cohort. In addition, rules for a bone safety review were included and MTD based on bone safety was defined as highest dose level at which < 2 of 6 patients experienced grade ≥ 1 fragility fracture. The general analytical approach for evaluating all endpoints was descriptive in nature. For categorical variables, descriptive statistics included counts and percentages per category. Statistics describing time-to-event variables utilized the Kaplan-Meier method. The Intent-to-Treat (ITT) population comprised all patients who received at least 1 partial or complete dose of IPA. The Safety population comprised all patients who received at least 1 partial or complete dose of IPA and who had at least 1 postdosing safety evaluation.

For the microarray gene expression analysis, genes were considered significant at a 95% confidence interval and a gene expression change of greater than 1.5-fold. Paired sample bootstrapping was used to generate the CI (SAS, R). The 95% CI (bias-corrected and accelerated, BCa) was calculated according to standard methods, applying a nonparametric bootstrap procedure [23, 24]. Post-dose sample data were compared with pretreatment sample data from the same patient in a paired-sample analysis. For statistical significance, the limits of the CIs cannot cross zero. Thus, for the upregulated genes, the lower confidence boundary (lb) had to be greater than þ1.1; for the downregulated genes, the upper confidence boundary (ub) had to be less than þ1.1. The untreated control subjects were analyzed using the same methods. For the 6-gene signature analysis, the Cox proportional hazard model was used to interrogate the association of the gene signature with OS and PFS by both p value and hazard ratio. All analyses and tabulations were performed using SAS® version 9.2 or higher

Results:

Patients characteristics:

Twenty six patients were enrolled between January 2014 and May 2017. Patients' median age was 61.7, with over 70% males and 100% caucasians (Table 1). All patients received the combination of IPA, G and Nab-P. Most patients discontinued therapy due to disease progression (n=15, 58%), four patients (15.3%) due to investigator decision based on the patient's best interest, two (7.6%) due to consent withdrawl, and five (19%) due to early

termination of the study by the sponsor. The dose intensity of IPA was high for all patients with mean of 97% (Table 1).

Safety Evaluation, Dose-Limiting Toxicities and Maximum Tolerated Dose:

All 26 patients were analyzed for safety, and all reported at least 1 treatment related adverse event. Whereas 21 patients (80.8%) reported at least one IPA related AE, none of these resulted in discontinuation of IPA. During the evaluation period, one patient discontinued Nab-P and one G due to toxicity. No toxicity-related death occurred on the study.

Most commonly reported AEs related to any of the agents of any grade included fatigue (77%), peripheral neuropathy (69%), nausea (54%), alopecia (50%), pyrexia (42%) vomiting (42%), decreased appetite (38%), diarrhea (38%), and neutropenia (31%) (Table 2). Most common treatment-related AEs of any grade that were considered possibly related to IPA were fatigue (58%), nausea (31%), decreased appetite and vomiting (27% each), pyrexia (23%), diarrhea and dysgeusia (19% each), and alopecia (15%) (Table 2).

Eighteen patients (69%) reported treatment-related AEs ≥ grade 3 which included mainly neutropenia and peripheral neuropathy (Table 2). One patient reported grade 3 elevation of alkaline phosphatase and bilirubin along with dehydration, rash, hyponatremia and lymphedema who was thought to have a hemolytic uremic syndrome (confirmed by biopsy). Six patients reported IPA-related AEs of ≥ grade 3 which included grade 3 aspartate aminotransferase and bilirubin increase, nausea, rash, vomiting and white blood cell decrease (Table 2).

One DLT of grade 3 AST elevation was reported for cohort 1. This dose was considered unsafe due to fragility fractures and the study was amended for a once every 4 weeks dosing schedule in the subsequent cohorts in which no DLTs or skeletal events were reported. The MTD was not determined during this study, as additional doses beyond 5 mg/kg once every 4 weeks were not evaluated due to sponsor decision to terminate the program.

Fifteen (57.6%) patients received zoledronic acid or denosumab during the study: one for bone metastases, one for a low DEXA score, 6 for post menopausal status, and 7 for a change in their bone marker level. One patient in cohort 1 experienced a pathologic fracture in the setting of rapidly progressive disease with new bone metastases. No fragility fractures were seen among patients who took part in this study.

Pharmacokinetics and Immunogenicity:

IPA serum concentrations were within the expected drug exposure levels at the doses and frequencies studied and correlated with the prior phase 1 trial [11]. Three patients developed anti-drug antibodies (ADA) during the study, thus the overall immunogenicity incidence was 11.6%. There was no evidence of an impact of ADA on drug exposure.

Efficacy Evaluation:

Efficacy data were available for 24 patients and is summarized in Table 2 and Figure 2. Nine (35%) patients had an unconfirmed partial response and 12 (46%) patients had stable disease resulting in a clinical benefit rate of 81%. The median PFS for the ITT was 5.9 months (95%

CI: 3.4-18.4 months). Six-months OS rate for all study patients was 72% and 1-year OS rate was 35.7%. The median OS for the ITT population was 9.7 months (95% CI: 7.0-14.0 months) (Figure 2B). Following termination of the study by the sponsor two patients remained on treatment under compassionate use. One patient was treated for 665 days before discontinuation due to progression. The second patient remains on treatment for 59 months with no evidence of disease.

Biomarker analysis:

Due to early termination of the study, a full biomarker analysis was not completed. Microarray analysis of RNA extracted from available baseline and post treatment biopsies from one patient demonstrated down regulation of Wnt-regulated genes *AXIN2* and *MYC*, 1.34 and 1.96-fold respectively, following IPA treatment. While it is not possible to draw firm conclusions from one patient, it suggests inhibition of the Wnt pathway at the tumoral level. Similar analysis of hair follicles derived from 20 patients demonstrated down-regulation of Wnt pathway gene expression (e.g., *FZD10, LEF1, AXIN2*) across all patients following IPA treatment, demonstrating on-target effects. Specifically, down regulation of *AXIN2* was observed in patients from all dosing cohorts. In contrast, *DDK3*, a gene associated with cellular differentiation was up-regulated following IPA treatement (Figure 3).

Fourteen FFPE baseline tumor samples were available and evaluable for RNA isolation and analysis of the 6-gene signature (PYGO1, PLCB1, ACVR2B, SRC, PLAU, TGFB1) showed an association with PFS (HR 0.104; p=0.004) and OS (HR=0.186, p=0.023), with high signature expression associated with worse outcome (Figure 4). Analysis of the same 6-gene signature expression in a pancreatic ductal adenocarcinoma RNA Sequencing dataset from The Cancer Genome Atlas (TCGA) revealed a worse prognosis for patients with high signature expression (p=0.009), suggesting the signature may be a negative prognostic biomarker for mPDAC.

Discussion:

Wnt pathway inhibitors, such as IPA, a recombinant fusion protein which acts as a decoy receptor for the Wnt ligand, have shown pre-clinical activity in multiple tumor models. Pre-clinical studies showed reduction in CSC when IPA is used alone and in combination with chemotherapy [25, 26]. This phase 1b dose escalation study evaluated the safety and tolerability, DLT and MTD of the combination of G plus Nab-P with IPA in patients with newly diagnosed untreated mPDAC. The study was terminated early by the sponsor due to bone-related toxicity within this therapeutic program and concerns for commercial viability. Thus, all evaluated doses of IPA in this trial were lower than the previously recommended phase II dose, and the MTD was not reached. This report outlines the observed tolerability and outcomes in 26 patients who took part in this study.

Although there is significant interest in the therapeutic potential of targeting the Wnt pathway, this has proven challenging due to the essential role of this pathway in stem cell maintenance and tissue homeostasis which raises concerns for significant toxicity [14]. In our study, the addition of IPA to G plus Nab-P did not significantly increase toxicity, and no

overlapping toxicities or new safety concerns were noted. No DLTs were documented in the study following the amendment for bone safety which was instituted in cohort 2. Furthermore, treatment with IPA was not discontinued due to AEs during the study. These data demonstrates the overall reasonable tolerability of this agent in combination with G plus Nab-P.

Wnt signaling is known to play an important role in bone homeostasis [17]. Other studies with IPA and a different Wnt inhibitor, vantictumab, demonstrated increased risk for fragility fractures among treated patients [16]. In this study no fragility fractures were recorded. The reasons for the absence of fragility fractures in this study are unknown. It may be related to the patient population suffering from an aggressive tumor, with few co-morbidities otherwise, and no exposure to prior anti-cancer therapies. Furthermore, the low number of patients in this study does not allow definitive conclusions regarding the true risks of IPA in this patient population.

The investigator-assessed unconfirmed overall response rate was 35% and the clinical benefit rate was 81%. Of note only 3 patients had progressive disease as their best response, all other patients had some degree of decreased tumor burden associated with treatment on study. Furthermore, two patients had prolonged responses to this treatment, one who remains on treatment with single-agent IPA under compassionate use. The ORR in this study falls in the same range as the reported ORR in the MPACT study (independent read confirmed ORR of 29%). However, the clinical benefit observed in this study is higher than that reported for the MPACT study (~50%) which raises the hypothesis that the addition on Wnt inhibition may enhance the activity of cytotoxic chemotherapy [3]. Albeit, the limited number of patients treated in the current study and the difference in the response assessment methodology (ie, Investigator assessed unconfirmed response versus Independent central-read confirmed response in MPACT) may hinder the ability to draw definitive conclusions.

Biomarker analysis of Wnt-pathway associated genes was conducted on hair follicles among patients and healthy controls demonstrating down regulation of these genes in response to IPA therapy. This observation supports on-target effect of IPA therapy. Furthermore, Gene Set Enrichment Analysis (GSEA) of tumor specimens identified a 6-gene panel that was associated with improved PFS and OS demonstrating its capacity to potentially serve as a predictive biomarker to identify PDAC patients likely to respond to IPA. The same 6-gene set may also serve as a negative prognostic marker for patients with stage IV PDAC as was demonstrated in the same analysis in untreated samples. In summary, the biomarker analysis holds promise for application to future studies evaluating Wnt inhibition in PDAC.

A variety of compounds have been reported to inhibit the Wnt pathway. Natural compounds, such as vitamin A and D, polyphenols (i.e. curcumin and resveratrol), and non-steroidal anti-inflammatory drugs (NSAIDS) have been shown to inhibit the Wnt pathway, yet lacked significant therapeutic activity as single agents [27]. Similarly, pyrvinium and niclosamide used for the treatment of pinworm and tapeworm infections, respectively, have been shown to inhibit the Wnt pathway and have demonstrated activity in colon cancer, ovarian cancer and other tumors [8, 28, 29]. Several small molecules have been found to affect the interaction of various components within the Wnt pathway including beta-catenin with pre-

clinical activity seen in multiple tumors [30, 31]. Ongoing clinical trials are aiming to target the Wnt pathway through its ligands or cross talk with other cell signaling pathways [32]. For example, the Porcupine inhibitor LGK974, which results in decreased secretion of Wnt ligands, is currently being tested in a phase I clinical trial alone and in combination with immunotherapy in multiple tumors (NCT01351103) [33]. Additional agents inhibiting the cross talk between Wnt/beta-catenin, Wnt/Notch and Wnt/hedgehog, Wnt co-activator antagonists as well as Wnt5a mimetics are all under evaluation in clinical trials [32]. However, the concern for toxicities related to the effect of Wnt inhibition on normal Wnt-dependant stem cells and the regulation of bone formation continues to hinder clinical development of these agents.

In summary, our study outlines the feasibility and tolerability of the combination of IPA and G+Nab-P chemotherapy. Although development of this agent has been halted, investigation of Wnt pathway inhibition as a therapeutic target in PDAC remains of interest. This would require better biologic understanding of this pathway, and more precise agents that would have limited effect on normal Wnt-dependant tissue and bone formation, and thus less toxicities.

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Statement of Translational Relevance:

The recombinant fusion protein ipafricept (IPA) blocks Wnt signaling, and in combination with gemcitabine (G) and nab-paclitaxel (Nab-P) induced tumor regression in xenografts. This phase 1b study evaluated the combination of IPA with Nab-P+G in untreated metastatic PDAC patients. The results of this trial demonstrate the feasibility and tolerance of this regimen without any bone related adverse events which are typical for this family of agents. Biomarker analysis demonstrates on-target effect of IPA therapy. This data provides support for further investigation of Wnt pathway inhibition as therapeutic target in PDAC.

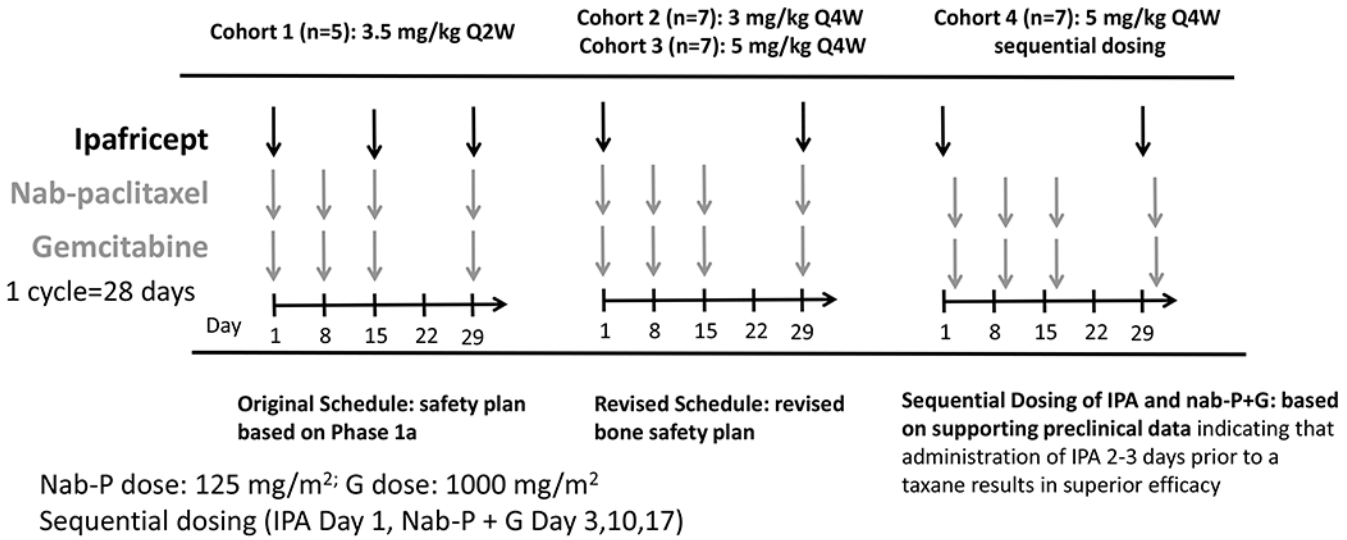

Figure 1:
Study schema outlining the cohorts of this study.

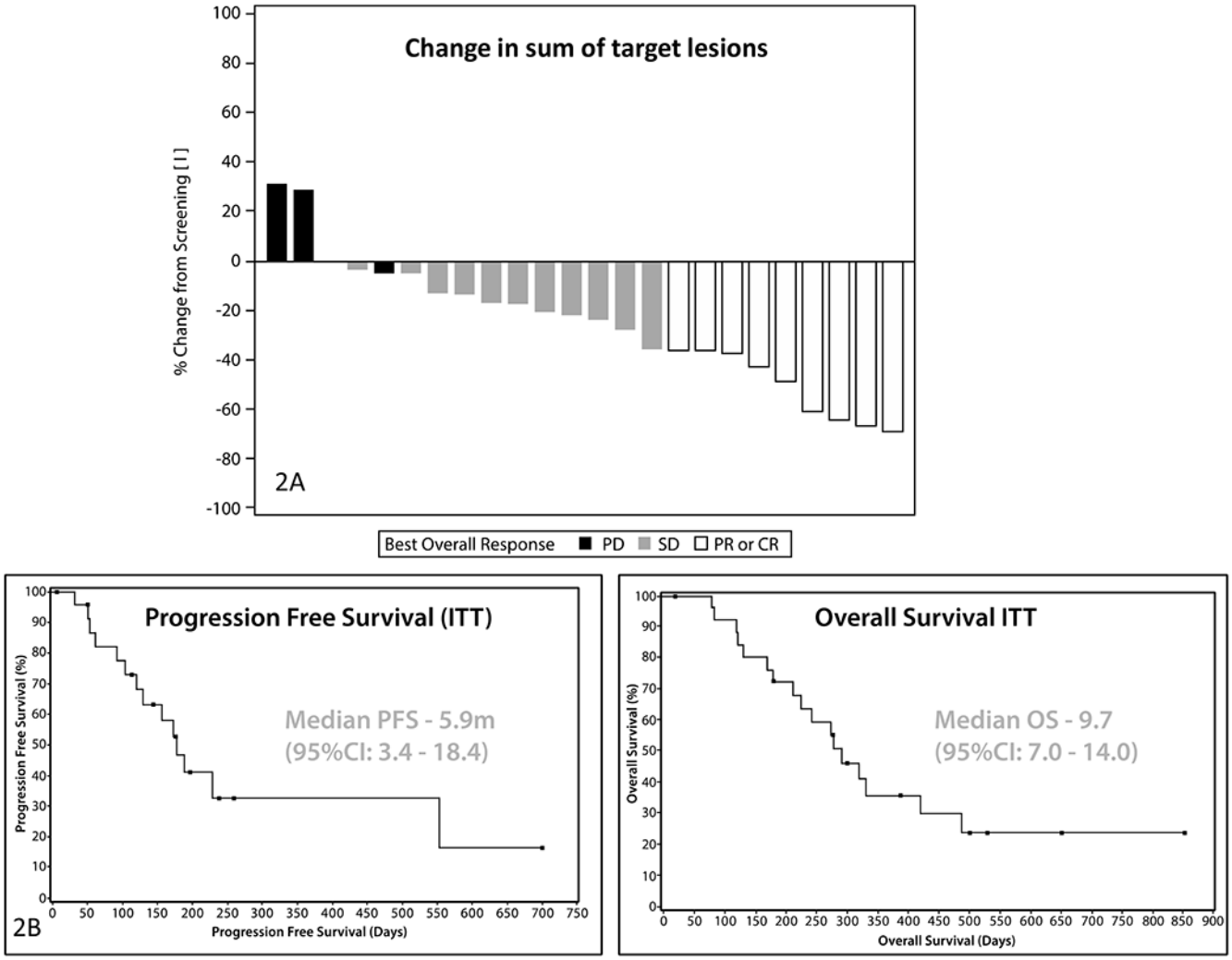

Figure 2:

A: Waterfall plot depicting the maximum change in sum of target lesions in diameter among all patients treated with IPA, G and Nab-P. Nine patients (35%) had partial responses and 12 patients had stable disease as their best response with an unconfirmed overall response rate of 35%, and clinical benefit rate of 81%. PD = Progressive Disease; SD = stable disease; PR = partial response; CR = complete response. **B:** Kaplan Meyer curves demonstrating progression free survival (PFS) and overall survival (OS) among the intent to treat (ITT) population with median PFS of 5.9 months (95% CI: 3.4-18.4) and median OS of 9.7 months (95% CI: 7.0-14.0). 2 patients remained on treatment following termination of the study under compassionate use. One patient was treated for 665 days before progression. The second patient remains on treatment for 59 months with ongoing response.

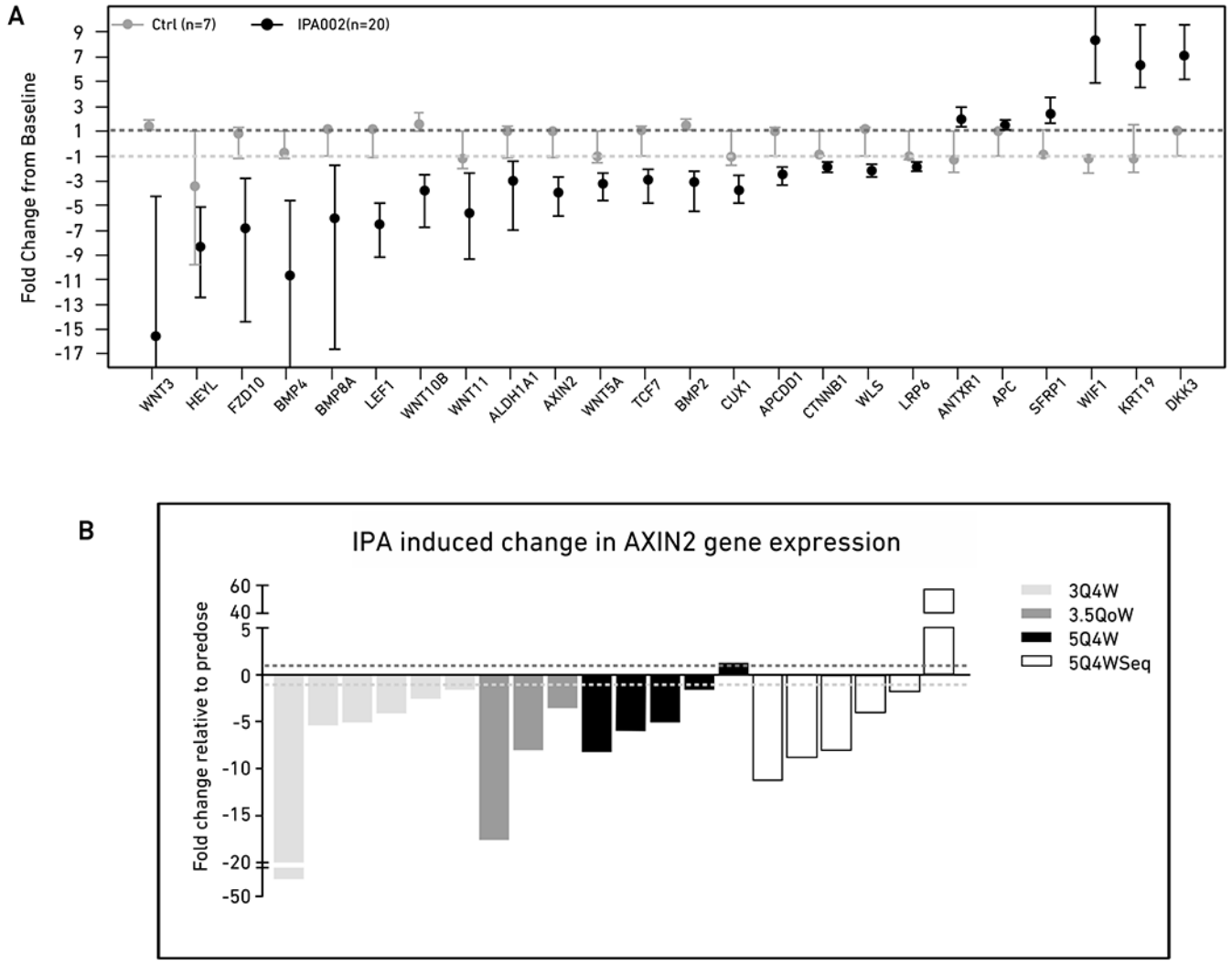

Figure 3:

(A). Representation of down regulation of Wnt-pathway genes expression in hair follicles among patients (in red) and controls (in gray). (B) Fold change in expression of Wnt-pathway gene AXIN2 expression fold change induced by IPA treatment in hair follicles of 20 patients represented by the different cohorts.

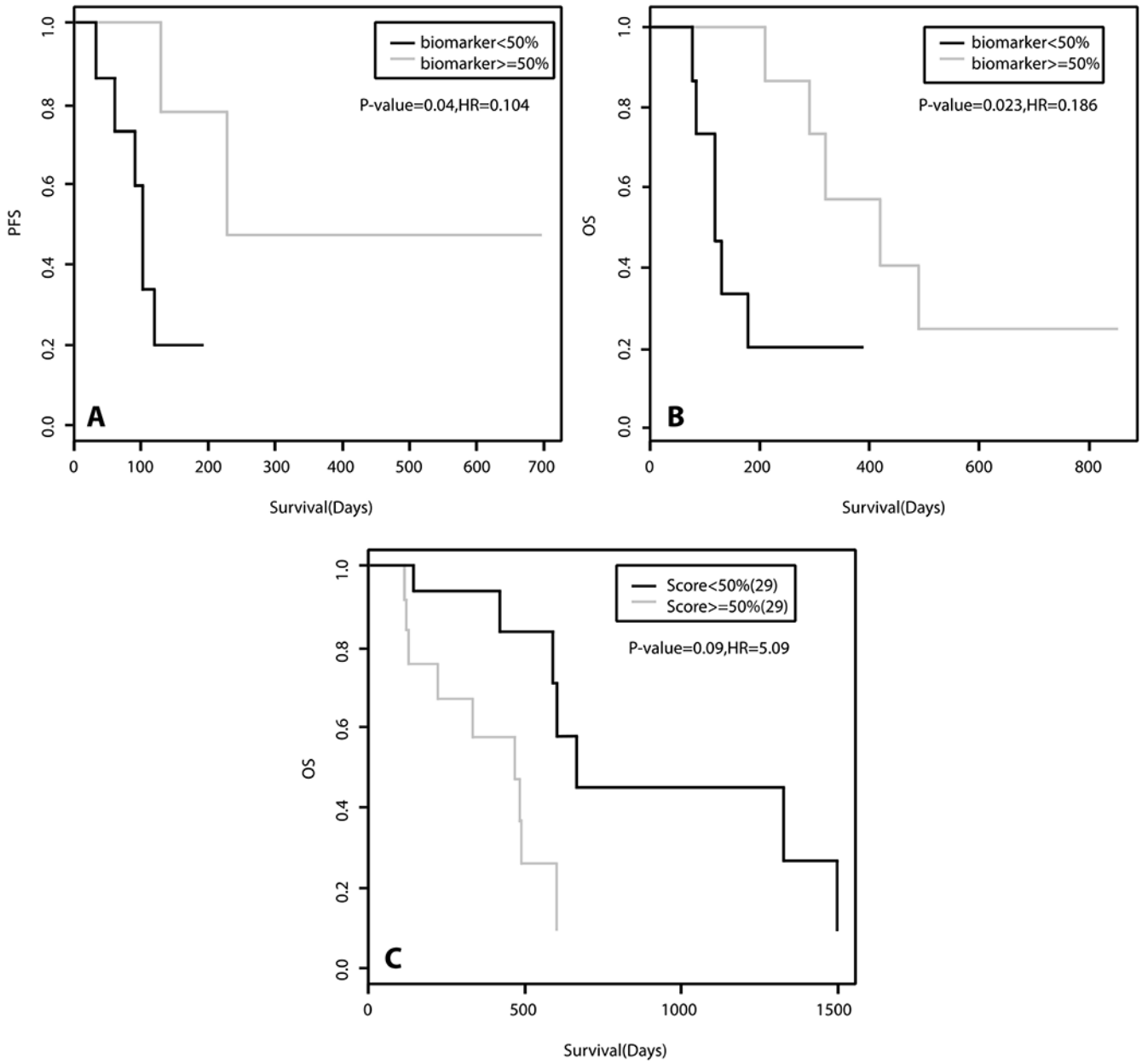

Figure 4:

Evaluation of 6-gene signature on RNA isolated from FFPE PDAC tumor samples of 14 patients using a cutoff at the 50th percentile. (A) Association of 6-gene signature with PFS; (B) Association of 6-gene signature with OS; (C) Assocation of 6-gene signature with OS on pancreatic ductal carcinoma RNA Seq dataset from The Cancer Genome Atlas (TCGA). High signature levels ≥ 50^{th} percentile (green line) compared to low signature levels < 50^{th} percentile (red line).OS-Overall Survival.

Table 1:

Patients' and treatment characteristics

	Cohort 1 3.5mg/kg q2wk (n=5)	Cohort 2 3mg/kg q4wk (n=7)	Cohort 3 5mg/kg q4wk (n=7)	Cohort 4 5mg/kg q4wk sequential dosing (n=7)	Overall n=26
Median Age (range) (years)	64 (59-71)	63 (49-69)	65 (53-72)	57 (41-78)	62.5 (41-78)
Gender: Male (%) Female(%)	 4(80) 1 (20)	7 (100)	 4 (57) 3 (43)	 4 (57) 3 (43)	 19 (73.1) 7 (26.9)
ECOG PS n(%) 0 1	 1 (20) 4 (80)	 3 (43) 4 (57)	 3 (43) 4 (57)	 1 (14) 6 (86)	 8 (31) 18 (69)
Stage at Dx n(%) II III IV Unknown	 0 0 4 (80) 1 (20)	 0 1 (14) 5 (72) 1 (14)	 0 0 7 (100) 0	 1 (14) 0 6 (86) 0	 1 (4) 1 (4) 22 (85) 2 (7)
Prior surgery n(%) Yes No	 0 5 (100)	 1 (14) 6 (86)	 0 7 (100)	 1 (14) 6 (86)	 2 (8) 24 (92)
Prior chemotherapy n(%) Yes No	 0 5	 1 (14) 6 (86)	 0 7 (100)	 1 (14) 6 (86)	 2 (8) 24 (92)
Prior Radiotherapy n(%) Yes No	 0 5 (100)	 1 (14) 6 (86)	 0 7 (100)	 1 (14) 6 (86)	 2 (8) 24 (92)
Treatment characteristics					
IPA dose intensity Mean (SD)	0.94 (0.15)	0.98 (0.06)	0.97 (0.08)	0.98 (0.03)	0.97 (0.08)
Nab-P dose intensity Mean (SD)	0.71 (0.17)	0.72 (0.22)	0.74 (0.18)	0.76 (0.10)	0.73 (0.16)
G dose intensity Mean (SD)	0.77 (0.15)	0.76 (0.16)	0.78 (0.15)	0.81 (0.12)	0.78 (0.14)
Discontinuation reason n(%) Withdrawl consent Disease progression* Patient's best interest Study terminated	 0 3 (60) 2 (40) 0	 1 (14) 5 (72) 0 1 (14)	 0 5 (72) 1 (14) 1 (14)	 1 (14) 2 (29) 1 (14) 3 (43)	 2 (8) 15 (58) 4 (15) 5 (19)

q2wk = every 2 weeks; q4wk = every 4 weeks

IPA = Ipafricept; Nab-P = Nab-Paclitaxel; G = Gemcitabine;

*Disease progression included radiographic and clinical.

Table 2:

Toxicity and efficacy summary

	Dose Escalation			Sequential Dosing	Overall (N=26) n (%)
	Cohort 1 3.5 mg/kg q2wk (n=5) n (%)	Cohort 2 3.0 mg/kg q4wk (n=7) n (%)	Cohort 3 5.0 mg/kg q4wk (n=7) n (%)	Cohort 4 5.0 mg/kg q4wk (n=7) n (%)	
G/Nab-P/IPA-related AEs any grade occurring in ≥10%	**5 (100)**	**7(100)**	**7(100)**	**7(100)**	**26(100)**
Fatigue	3 (60)	6 (86)	6 (86)	5 (71)	20 (77)
Peripheral neuropathy *	2 (40)	5 (71)	6 (86)	5 (71)	18 (69)
Nausea	4 (80)	3 (43)	3 (43)	4 (57)	14 (54)
Alopecia	0	6 (86)	5 (71)	2 (29)	13 (50)
Pyrexia	5 (100)	3 (43)	0	3 (43)	11 (42)
Vomiting	3 (60)	3 (43)	3 (43)	2 (29)	11 (42)
Rash	1 (20)	3 (43)	4 (57)	3 (43)	11 (42)
Decreased appetite	2 (40)	4 (57)	3 (43)	1 (14)	10 (38)
Diarrhea	0	5 (71)	1 (14)	4 (57)	10 (38)
Neutropenia	2 (40)	1 (14)	3 (43)	2 (29)	8 (31)
IPA-related AE any grade occurring in ≥10%	**4 (80)**	**5 (71)**	**6 (86)**	**4 (57)**	**20 (77)**
Fatigue	0	6 (86)	6 (86)	3 (43)	15 (58)
Nausea	2 (40)	3 (43)	1 (14)	2 (29)	8 (31)
Decreased appetite	1 (20)	3 (43)	2 (29)	1 (14)	7 (27)
Vomiting	2 (40)	2 (29)	2 (29)	1 (14)	7 (27)
Pyrexia	3 (60)	1 (14)	0	2 (29)	6 (23)
Diarrhea	0	3 (43)	0	2 (29)	5 (19)
Dysgeusia	2 (40)	1 (14)	2 (29)	0	5 (19)
Alopecia	0	2 (29)	1 (14)	1 (14)	4 (15)
ALT increased	1 (20)	1 (14)	1 (14)	0	3 (11)
AST increased	1 (20)	1 (14)	1 (14)	0	3 (11)
Chills	1 (20)	1 (14)	1 (14)	0	3 (11)
Rash	1 (20)	0	1 (14)	1 (14)	3 (11)
Weight decreased	1 (20)	0	1 (14)	1 (14)	3 (11)
Overall (G/Nab-P/IPA)-related AE ≥Grade 3	**4 (80)**	**5 (71)**	**5 (71)**	**4 (57)**	**18 (69)**
Neutropenia	2 (40.0)	2 (29)	1 (14)	3 (43)	8 (31)
Peripheral Neuropathy *	0	3 (43)	2 (29)	0	5 (19)
WBC decreased	0	2 (29)	0	1 (14)	3 (11)
Rash	0	0	2 (29)	1 (14)	3 (11)
ALT/AST increased	1 (20)	1 (14)	0	0	2 (8)
Anemia	0	2 (29)	0	0	2 (8)

	Dose Escalation			Sequential Dosing	Overall (N=26) n (%)
	Cohort 1 3.5 mg/kg q2wk (n=5) n (%)	Cohort 2 3.0 mg/kg q4wk (n=7) n (%)	Cohort 3 5.0 mg/kg q4wk (n=7) n (%)	Cohort 4 5.0 mg/kg q4wk (n=7) n (%)	
Diarrhea	0	1 (14)	0	1 (14)	2 (8)
Fatigue	0	1 (14)	1 (14)	0	2 (8)
Vomiting	1 (20)	1 (14)	0	0	2 (8)
Nausea	1 (20)	0	0	0	1 (4)
Alk Phos increase	0	0	0	1 (14)	1 (4)
Bilirubin increased	0	0	1 (14)	0	1 (4)
Dehydration	0	0	1 (14)	0	1 (4)
HUS	0	1 (14)	0	0	1 (4)
Hyponatremia	0	0	0	1 (14)	1 (4)
Nausea	1 (20)	0	0	0	1 (4)
IPA-related AE ≥Grade 3	**1 (20)**	**2 (29)**	**2 (29)**	**1 (14)**	**6 (23)**
AST increased	1 (20)	1 (14)	0	0	2 (8)
Rash	0	0	1 (14)	1 (14)	2 (8)
Bilirubin increased	0	0	1 (14)	0	1 (4)
Nausea	1 (20)	0	0	0	1 (4)
Vomiting	1 (20)	0	0	0	1 (4)
WBC decreased	0	1 (14)	0	0	1 (4)
Efficacy results by RECIST v1.1	**Cohort 1 3.5 mg/kg q2wk (n=5) n (%)**	**Cohort 2 3.0 mg/kg q4wk (n=7)n (%)**	**Cohort 3 5.0 mg/kg q4wk (n=7)n (%)**	**Cohort 4 5.0 mg/kg q4wk (n=7) n (%)**	**Overall (n=26) n (%)**
Complete Response (CR)	0	0	0	0	0
Partial Response (PR)	2 (40)	3 (43)	2 (29)	2 (29)	9 (35)
Stable Disease (SD)	0	3 (43)	5 (71)	4 (57)	12 (46)
Progressive Disease	2 (40)	1 (14)	0	0	3 (11)
Not Evaluable	1 (20)	0	0	1 (14)	2 (8)
Overall Response Rate % (CR or PR)	2 (40)	3 (43)	2 (29)	2 (29)	9 (35)
Clinical Benefit Rate % (CR, PR or SD)	2 (40)	6 (86)	7 (100)	6 (86)	21 (81)
6 months OS rate %	60.0	71.4	85.7	66.7	72.0
12 months OS rate %	20.0	42.9	28.6	66.7	35.7

q2wk = every 2 weeks; q4wk = every 4 weeks; G = Gemcitabine; Nab-P = Nab-Paclitaxel; IPA = Ipafricept; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; Alk Phos = Alkaline Phosphatase; WBC = White Blood Cell; HUS = Hemolytic Uremic Syndrome; RECIST = Response Evaluation Criteria in Solid Tumors; OS = Overall survival;

* includes sensory and motor neuropathy