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PHASE I STUDIES

Phase 1 trial of enzalutamide in combination with gemcitabine and nab-paclitaxel for the treatment of advanced pancreatic cancer

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Summary

Background Androgens were shown to play a key role in the growth and progression of pancreatic cancer. We evaluated the safety and tolerability of the combination of enzalutamide, a novel androgen receptor (AR) antagonist with gemcitabine and nab-paclitaxel as a first-line treatment in advanced pancreatic cancer. *Methods* We used the standard 3 + 3 dose escalation design with cohort expansion to evaluate 2 dose levels of enzalutamide: 80 mg and 160 mg/day orally (phase 1a) in combination with gemcitabine and nab-paclitaxel in metastatic pancreatic cancer patients. In the expansion phase (phase 1b), AR+ was a pre-requisite criterion. We also evaluated the full pharmacokinetic (PK) profile for nab-paclitaxel and enzalutamide. *Results* We enrolled 24 patients, 12 patients in phase 1a and 12 patients in phase 1b. The median age was 68 (range, 32–84) years. No DLTs were observed. Grade 3/4 treatment related adverse events included neutropenia (44%), anemia (40%), leukopenia (24%), nausea and vomiting (20%), diarrhea (16%), infections (12%), thrombocytopenia (8%), thromboembolic event (8%), hypertension (8%), hypokalemia (8%), hyponatremia (8%), and ALT elevation (8%). Median overall survival and progression-free survival was 9.73 [95%CI:9.73–13.5] and 7.53 (95%CI:6.05–12.8) months, respectively. PK analysis suggests that the combination therapy does not impact the kinetics of either drug evaluated. Enzalutamide reached steady-state levels between day 22 and 29 and the mean half-life of nab-paclitaxel was 19.6 ± 4.7 h. *Conclusions* Enzalutamide 160 mg daily in combination with gemcitabine and nab-paclitaxel can be safely administered with no unexpected toxicities. We also noticed preliminary signals of efficacy with this combination.

Keywords Enzalutamide · Pancreatic cancer · Nab-paclitaxel · Gemcitabine

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Introduction

Pancreatic adenocarcinoma is the third most common cause of cancer death in the United States with 55, 540 incident cases and 44, 330 deaths estimated in 2018 [1]. Despite the recent advances in therapeutic interventions, the 5-year relative survival rate remains approximately 6%. The current management of patients with metastatic pancreatic adenocarcinoma includes FOLFIRINOX (combination regimen of 5-Flourouracil, oxaliplatin and irinotecan), gemcitabine-nab-paclitaxel or single-agent gemcitabine alone (in patients with Eastern Cooperative Oncology Group performance status 2). Gemcitabine remained the mainstay of the treatment for metastatic pancreatic cancer for over a decade until the combination of nab-paclitaxel and gemcitabine as well as FOLFIRINOX regimen showed promising results in improvement in overall survival (OS) as compared to GEM alone [2]. A randomized phase III trial that evaluated the FOLFIRINOX demonstrated improved OS in advanced pancreatic cancer

patients compared to single agent gemcitabine [3]. However, secondary to high rate of grade 3 or 4 toxicities associated with this regimen only highly selective patient population are suitable candidate for FOLFIRINOX regimen. Another combination therapy with gemcitabine and nab-paclitaxel was FDA approved for patients with metastatic pancreatic cancer in 2013, based on the encouraging results in the phase III MPACT trial [4]. The regimen was well tolerated with a better overall response rate (22 vs 7%) and OS (8.7 vs 6.6 months, $p < 0.001$) compared to gemcitabine alone therapy. Despite the availability of these systemic chemotherapy agents, there has been a limited progress in the OS benefit of metastatic pancreatic cancer. This represents an unmet clinical need for newer therapies that can improve responses in this patient population. We hypothesized that co-targeting the androgen receptors (AR) along with currently available systemic chemotherapy may be a more effective strategy to improve responses in metastatic pancreatic cancer.

The discovery of AR on pancreatic cancer cells suggested that sex steroids (testosterone and dihydrotestosterone) may influence the growth and progression of pancreatic adenocarcinoma [5, 6]. One study demonstrated AR protein overexpression in seven out of eight human pancreatic cancer cell lines tested, and the level predominantly fell into an intermediate range [7]. These findings were seen in other pancreatic tissue and cell line studies as well [5]. Moreover, aromatase and 5-alpha-reductase, which use testosterone as a substrate, are present in pancreatic malignant tissues at higher level than in normal pancreatic tissue [5, 6]. The role of sex steroid hormones in the growth of pancreatic cancer was further elucidated by the dose dependent growth stimulation of AR+ pancreatic cell lines and pancreatic xenograft tumor by testosterone and dihydrotestosterone [7, 8]. Flutamide, a nonsteroidal androgen blocking agent, was demonstrated to have dose dependent growth inhibition on pancreatic cell lines. The growth of pancreatic xenograft tumor was also shown to be inhibited by flutamide [7]. In a phase 2 trial involving 49 pancreatic cancer patients, Greenway et al. reported a significant median survival benefit in the flutamide group as compared to that of placebo (7.5 vs 4 months, $p = 0.01$) [8]. In addition, for the 20 patients in the flutamide group who received at least 6 weeks of therapy, the median survival was 11.7 months. After adjusting for confounding variables, similar encouraging results were seen with flutamide in another phase 2 trial [9]. In-vivo studies with analogues of luteinizing hormone releasing hormone, which reduce serum testosterone concentrations, have shown promising effects in inhibiting pancreatic tumor growth as well [10]. These trials suggest that androgen blocking agents have activity in the treatment of pancreatic cancer.

Enzalutamide (also known as MDV3100) is a novel AR antagonist that acts by inhibiting the nuclear translocation of the AR, DNA binding, and coactivator recruitment. As compared to other androgen blocking agents, enzalutamide has a higher affinity for AR and has pure antagonist activity with no detectable agonist effects [11]. With no partial agonist activity, enzalutamide is a more potent agent in blocking androgen receptor signaling and inducing tumor shrinkage in androgen dependent malignancy [11, 12].

Based on promising pre-clinical activity of androgen receptor blocking agents, this phase 1a/1b study is designed to evaluate the safety and tolerability of enzalutamide in combination with gemcitabine and nab-paclitaxel in patients with metastatic pancreatic cancer.

Patients and methods

Patient eligibility

This phase 1a/1b study included patients ⩾18 years of age with histologically or cytologically confirmed metastatic or unresectable pancreatic cancer who have not received gemcitabine within 6 months of starting the study treatment and 5-Flourouracil or radiation treatment within the last 4 weeks prior to receiving the study drug. Other inclusion criteria included a life expectancy of at 3 months with eastern cooperative oncology group (ECOG) performance status <2 (Karnofsky >60%) and normal organ/bone marrow function (Detailed normal organ and bone marrow function criteria are provided in supplemental data). In dose expansion phase, we restricted the cohort to tumors expressing AR ($\geq$ 1% of tumor cells analyzed) by immunohistochemistry.

Patients were excluded from the study if they had other active malignancy requiring treatment, symptomatic brain metastases, current significant or recent prior history of cardiac disease (unstable angina, arrhythmias, heart failure). A detailed inclusion and exclusion criteria are summarized in Table 1.

Study design

Standard 3 + 3 dose escalation design was used to evaluate 2 dose levels of enzalutamide: 80 mg and 160 mg daily. The doses of chemotherapy were as follows: gemcitabine 1000 mg/m2 IV on days 1, 8 and 15 in combination with nab-paclitaxel 125 mg/m2 IV on days 1, 8 and 15. Duration of each cycle was 4 weeks. Once the recommended phase dose for expansion was determined an additional cohort of 12 patients with pancreatic tumors expressing AR was accrued to better define the safety and tolerability of the combination regimen.

The primary objective of the study was to evaluate the safety and tolerability and determine the maximally tolerated dose (MTD) of enzalutamide in combination with gemcitabine and nab-paclitaxel in advanced pancreatic cancer.

Table 1 Inclusion and Exclusion criteria to be included in the phase 1 trial

Inclusion criteria:

- Histologically or cytologically confirmed metastatic or unresectable pancreatic cancer not on gemcitabine within 6 months of starting the study treatment and 5-Flourouracil or radiation treatment within the last 4 weeks prior to receiving the study drug.
- Life expectancy of atleast 3 months
- Eastern cooperative oncology group (ECOG) performance status <2 (Karnofsky >60%)
- Normal organ/bone marrow function.
- In dose expansion phase➔ tumors expressing AR (> 1% of tumor cells analyzed) by immunohistochemistry.

Exclusion criteria:

- Active malignancy requiring treatment
- Symptomatic brain metastases
- Current significant or recent prior history of cardiac disease (unstable angina, arrhythmias, heart failure)
- Uncontrolled intercurrent illness
- Myocardial infarction in the last 6 months
- Major surgery within 4 weeks prior to starting the study treatment,
- Chronic treatment with immunosuppressant drugs
- Human immunodeficiency virus (HIV) infection or active hepatitis B or hepatitis C
- Active infection not controlled with antibiotics
- History of seizure, on concomitant medications that lower seizure threshold
- History of loss of consciousness or transient ischemic attack within 12 months of starting the study drug
- Reproductive age group not willing to be on birth control pills
- Pregnant and breast-feeding women

Secondary objectives included exploring the efficacy, safety and tolerability of the combination at the MTD established. The local institutional review board approved the protocol per guidelines. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice Guidelines (NCT02138383).

Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0. Dose-limiting toxicities (DLTs) were defined as adverse events (AEs) that occurred in the first 28 days (cycle 1) of study participation that were considered at least possibly related to treatment. DLTs included: grade ≥ 3 nausea, vomiting or diarrhea lasting more than 3 days despite optimal supportive medications; any other grade 3 non-hematological AE (except for electrolytes abnormalities that are reversible or hair loss which is not dose-limiting) that results in greater than 7 days interruption of therapy; and any grade 4 AE; seizures regardless of grade or severity and hepatic toxicity that met Hy's law criteria. Although hematologic toxicity is generally not expected from enzalutamide, for the purposes of the study, any grade 3/4 hematologic event resulting in infection lasting more than 3 days or spontaneous clinically significant bleeding was considered a DLT. Further, whenever participants missed 2 or more doses of gemcitabine or nab-paclitaxel during cycle 1 due to study drug related toxicity, it was considered a DLT. Management and dose modifications associated with the adverse events are outlined in Table 2. No dose modification was allowed during cycle 1 in the dose escalation phase. The dose was interrupted if the treatment criteria were not met based on the DLT. Any patient that required dose interruption for more than 3 weeks was taken off the study. Once the dose was reduced, patients were not dose escalated to previous level.

The treatment was continued until one or more of the following criteria are met: disease progression, intercurrent illness that prevents further administration of treatment, unacceptable adverse events, patient deciding to withdraw from the study, general or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator. The patients who were removed from the study were followed for 30 days for adverse events or until death, whichever occurs first. Patients with significant or unacceptable adverse events at the time of removal from the study therapy were followed until the toxicities resolved or were deemed irreversible.

The dose level reduction for gemcitabine, nab-paclitaxel and enzalutamide based on the DLT are summarized in supplementary data (Supplemental Table 2a-f).

Patient evaluation and assessments

Responses were assessed using Response evaluation criteria in solid tumors (RECIST) version 1.1 for patients with advanced solid tumors. [13] Baseline disease assessments were performed within 4 weeks before initiating treatment. Tumor measurements were conducted every 8 weeks (two cycles). Best overall response was recorded between the start and end of treatment.

Pharmacokinetic analysis

Blood samples for nab-paclitaxel and enzalutamide plasma levels were collected in the study at the pre-determined times as detailed in Fig. 1. The reason for protracted sampling for enzalutamide is that it may take up to 4 weeks for enzalutamide to reach steady state. This pharmacokinetic sampling was performed on all patients in dose escalation cohort and first 10 patients in dose expansion cohort. At the specified time points, 6.0 mL of blood was collected in tubes containing sodium heparin for nab-paclitaxel and enzalutamide concentration determination. Vacutainers were kept on crushed ice after blood collection. Within 30 min, the tubes were centrifuged for 5 min at 1100 x g at 4 °C to separate the plasma. After centrifugation, plasma was transferred into 2 mL polypropylene screw-cap tubes, labeled appropriately for the respective analysis. The plasma samples were stored at temperature of −80 °C until analysis.

Table 2 Dose escalation decision rule based on the number of patients who experienced dose limiting toxicity (DLT)

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

Pharmacokinetic analyses were performed individually for each drug and conducted using non-compartmental methods with Phoenix™ WinNonlin® ver6.3 (www.Pharsight.com).

Circulating tumor cells (CTCs)

As analyzing the CTCs provides the opportunity to do "real time" molecular analysis of tumors, before, during, and after treatment, a total of 10 subjects who had positive AR staining on their tumor samples were selected for CTC AR assay that was performed on day 1 of cycle 1 (baseline) and cycle 3 (2-month follow up). Seven and half ml of peripheral blood was processed for CTC assay though the epic science platform involving Aqua™ slide preparation. We used CTC Odyssey™ assay to stain the slides for cytokeratin (CK), CD45, DAPI and AR. Slides were digitally scanned with the

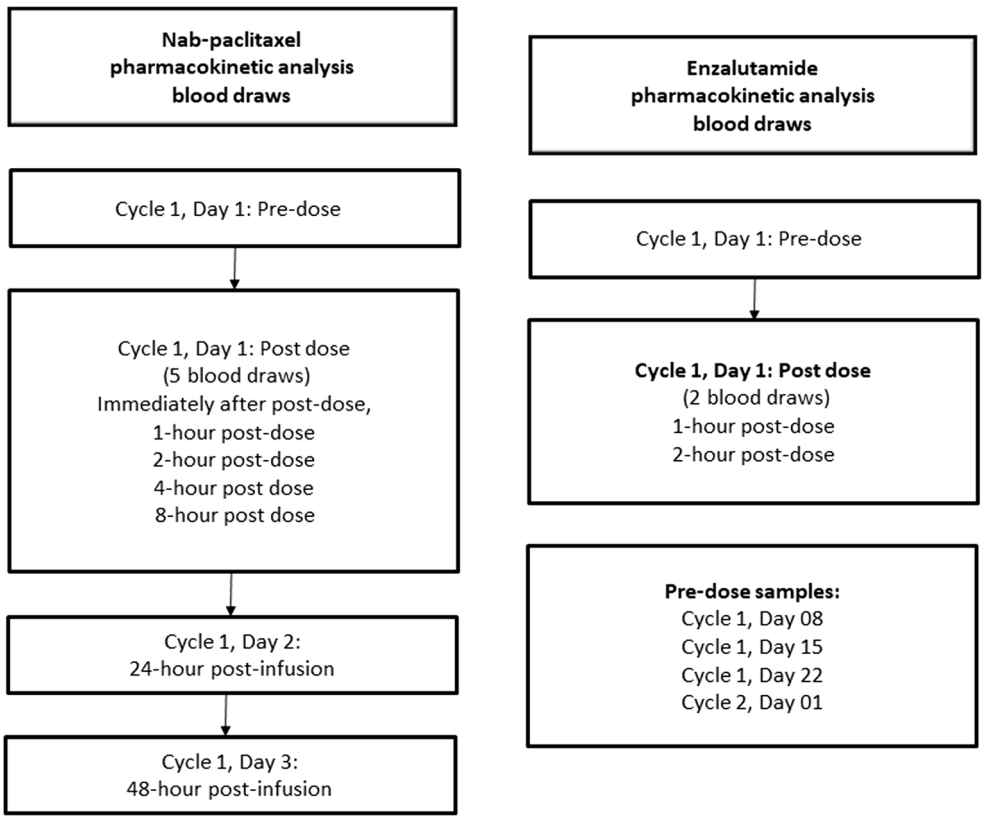

Fig. 1 Flowsheet illustrating the times of blood draws for nab-paclitaxel and enzalutamide pharmacokinetic analysis

Pyxis™ platform and we analyzed the data with the Atlas™ software. The total number of CK+/CD45- cells with intact DAPI nuclei and pathologically determined morphology were counted as the total number of CTC for that sample. The identified CTCs were classified into 5 categories: strong AR nuclear staining with weak or no AR cytoplasmic staining, strong AR nuclear and cytoplasmic staining, weak AR nuclear staining with weak or no AR cytoplasmic staining, weak AR nuclear and cytoplasmic staining, weak AR nuclear staining with strong AR cytoplasmic staining. The number and percentage of CTC in each category were recorded and compared to the number and percentages in the subsequent assays on the same patient.

Statistical analyses

For patients without a DLT in cycle 1, ≥ 85% of the intended cumulative dose of the first 21-day cycle period was required to be evaluable for DLTs. Safety analyses included all patients with one or more doses of study treatment. Efficacy analyses included all patients who had undergone baseline assessment and one on-study tumor assessment or who discontinued early as a result of disease progression. Quantitative variables are summarized using descriptive statistics. The Kaplan-Meier method and the Cox proportional were used for time-to-event variable. The response rate and best overall response along with 95% confidence interval will be reported. The logistic regression model was used to explore the association of response with other potential predictors. A two-side p value of <0.05 was considered statistically significant.

Results

Patient characteristics

Twenty-four patients were enrolled in this trial. Baseline demographics and disease characteristics are summarized in Table 3. Phase 1 consisted of 12 patients with advanced pancreatic cancer. The rest 12 patients who had AR positive disease were enrolled onto phase 1b.

Table 3 Baseline characteristics

Total number of patients with metastasis	24
Median age (years)	68 (range, 32–84)
Sex	
Males	16 (64%)
Females	4 (36%)
Race	
White	21 (84%)
Black	3 (12%)
Asian	1 (4%)
CA 19–9 levels (median, range)	1878 (range, 1.4–308,519)
Current status (at the time of analysis)	
Off study	8 (36%)
Expired	16 (64%)

Safety

Overall, the study drug was investigated in two doses-80 mg and 160 mg along in combination with gemcitabine and nab-paclitaxel. No DLTs were observed. In dose escalation phase (phase Ia), most common grade 1 and 2 AEs included elevated alkaline phosphatase (75%), anemia (67%), thrombocytopenia (67%), fatigue (58%) and elevated alanine aminotransferase (50%). The most frequently reported grade 3 and 4 adverse events included neutropenia (42%), anemia (25%), infections (25%) and decreased white cell count (25%). In dose expansion phase (phase 1b), most common grade 1 and 2 AEs include nausea (75%), peripheral sensory neuropathy (75%), fatigue (65%), hypoalbuminemia (60%), thrombocytopenia (50%) and arthralgia (50%). The most frequently reported grade 3 and 4 adverse events included anemia (58%), neutropenia (50%) and decreased white cell count (33%). None of the patients enrolled in phase Ia and Ib cohorts had grade 5 AEs. Table 4 summarizes all the drug-related AEs reported in >10% of the patients in both the phases.

Pharmacokinetics

Pharmacokinetic analysis suggested that the combination therapy did not impact the kinetics of either drug evaluated. Enzalutamide reached steady state levels between day 22 and 29 and the mean half-life of nab-paclitaxel was 19.6 ± 4.7 h. The pharmacokinetics of enzalutamide and paclitaxel are detailed in Figs. 2 and 3**, respectively**.

Efficacy and survival

Among the patients who were enrolled to dose escalation phase, 33% (4/12) patients had a partial response, and 42% (5/12) achieved stable disease. Best response was not evaluable in three patients. In cohort expansion phase, 90% (9/10) achieved stable disease, 10% (1/10) had partial disease and best response was not available in 2 patients. Median OS and progression-free survival was 9.73 [95%CI: 9.73–13.5] and 7.53 (95%CI: 6.05–12.8) months, respectively (Fig. 4).

Table 4 Drug related adverse events by NCI-CTCAE Grade v4.0^

Adverse event (%)	PHASE I A			PHASE IB			All patients		
	G1–2	G 3–4	All G	G 1–2	G 3–4	All G	G1–2	G 3–4	All G
Investigations									
Alkaline phosphatase increase	75	8.33	83.33	41.67	8.33	50	58.34	8.33	66.67
Platelet decrease	66.67	8.33	75	50	16.67	66.67	58.34	12.50	70.84
ALT increase	50	16.67	66.67	41.67	8.33	50	45.84	12.50	58.34
WBC decrease	33.33	25	58.33	41.67	33.33	75	37.50	29.17	66.67
AST increase	41.67	8.33	50	50	-	50	45.84	4.17	50.01
Neutrophil decrease	8.33	41.67	50	16.67	50	66.67	12.50	45.84	58.34
Lymphocyte decrease	8.33	8.33	16.67	41.67	16.67	58.33	25	12.50	37.50
Bilirubin increase	-	8.33	8.33	25	-	25	12.50	4.17	16.67
Constitutional									
Fatigue	58.33	-	58.33	66.67	-	66.67	62.50	-	62.50
Fever	50	-	50	33.33	-	33.33	41.67	-	41.67
Edema limbs	16.67	-	16.67	33.33	-	33.33	25	-	25
Death	-	-	16.67	-	-	-	-	-	-
Blood and lymphatic-Anemia	66.67	25	91.67	33.33	58.33	91.67	50	41.67	91.67
Gastrointestinal									
Nausea	41.67	16.67	58.33	75	8.33	83.33	58.34	12.50	70.84
Diarrhea	41.67	16.67	58.33	50	16.67	66.67	45.84	16.67	62.51
Vomiting	41.67	-	41.67	41.67	16.67	58.33	41.67	8.33	50
Abdominal pain	33.33	8.33	41.67	25	16.67	41.67	29.17	12.50	41.67
Mucositis	33.33	-	33.33	16.67	-	-	25	-	25
Constipation	33.33	-	33.33	33.33	-	33.33	33.33	-	33.33
Metabolism and nutritional									
Hyponatremia	25	16.67	41.67	41.67	-	41.67	33.34	8.33	41.67
Hypokalemia	16.67	16.67	33.33	8.33	-	8.33	12.50	8.33	20.83
Hypoalbuminemia	25	-	25	58.33	8.33	66.67	41.67	4.17	45.84
Hyperkalemia	8.33	-	8.33	50	-	50	29.17	-	29.17
Dehydration	-	-	-	16.67	8.33	25	8.33	4.17	12.50
Nervous									
Peripheral sensory neuropathy	25	-	25	75	8.33	83.33	50	4.17	54.17
Headache	25	-	25	16.67	-	16.67	20.84	-	20.84
Dizziness	-	-	-	25	-	25	12.50	-	12.50
Musculoskeletal and CT									
Arthralgia	25	-	25	50	-	50	37.50	-	37.50
Myalgia	8.33	-	8.33	25	-	25	16.67	-	16.67
Generalized muscle weakness	16.67	-	16.67	25	-	25	20.84	-	20.84
Respiratory, thoracic and mediastinal									
Dyspnea	25	-	25	33.33	16.67	50	29.17	8.33	37.50
Epistaxis	16.67	-	16.67	16.67	-	-	16.67	-	16.67
Cough	-	-	-	25	-	-	12.50	-	12.50
Skin and subcutaneous									
Alopecia	25	-	-	16.67	-	16.67	20.84	-	20.84
Maculopapular rash	16.67	-	-	33.33	-	33.33	25	-	25
Infections and infestations									
Lung infection	-	16.67	16.67	8.33	-	8.33	4.17	8.33	12.50
Wound infection	16.67	-	16.67	-	-	-	8.33	-	8.33
UTI	-	-	-	25	-	25	12.50	-	12.50
Vascular disorders									
Thromboembolic event	8.33	8.33	16.67	16.67	8.33	25	12.50	8.33	20.83
Hypertension	8.33	-	8.33	8.33	16.67	25	8.33	8.33	16.66
Injury, poisoning and procedural complications									
Fall	–	–	–	25	–	25	12.50	–	12.50

^National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0. G: Grades, CT: connective tissue, UTI: Urinary tract infection, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

Carbohydrate antigen 19–9 (CA 19–9) levels and response to therapy

CA 19–9 follow-up values were available for 21 of 24 patients (87.5%). Among the 21 patients, 76% ($n = 16$) had a notable decrease in CA 19–9 levels. All these 16 participants had at least 20% decrease in CA 19–9 levels from that of baseline values and 33% ($n = 7$) had a decrease of at least 90%. The median percentage decrease in CA 19–9 level of the entire cohort was 87.5% (range, 31–100%). The median time to

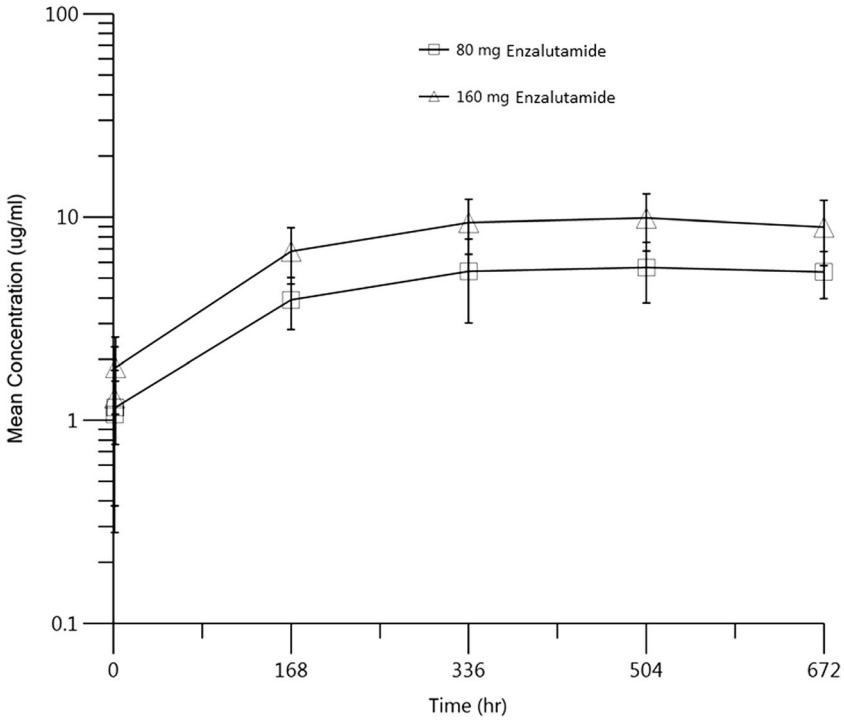

Fig. 2 Enzalutamide Mean Steady-State Plasma Concentrations vs. Time. Mean Steady-State Plasma Concentration vs. Time for Enzalutamide measured weekly for 4 weeks after daily administration of 80 mg or 160 mg (n = 23)

CA 19–9 nadir was 3.5 months (range, 1–6 months). On subgroup analysis, median percentage decrease in CA 19–9 level was much higher in phase 1b [median: 92.5 (range, 56–99) %] as compared to that of phase 1a [median: 79 (31–100) %].

CTCs

CTCs were present in 6 patients at baseline out of 10 patients evaluated in the dose expansion phase. Post treatment, no CTCs were observed in 5 patients and could not be evaluated in 1 patient. Patients who were negative for CTCs at baseline remained negative at subsequent evaluation.

Discussion

The recognition that pancreatic tumor cells harbor ARs led to the exploration of AR inhibitors for the management of advanced/metastatic pancreatic cancer. Here, we report that the selective AR inhibitor enzalutamide at dose of 160 mg/day, when used in combination with gemcitabine and nab-paclitaxel has acceptable toxicity and safety profile in patients with metastatic pancreatic cancer with preliminary evidence of antitumor activity. Enzalutamide at 160 mg dose consistently yielded concentrations in plasma above those shown to inhibit tumor growth and CTCs.

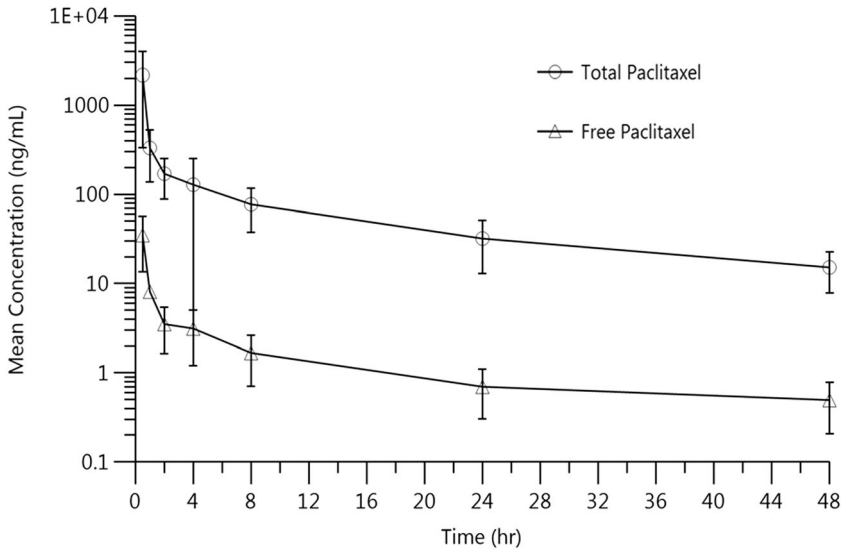

Fig. 3 Nab-paclitaxel Mean Steady State Plasma Concentrations vs. Time. Nab-Paclitaxel infused on day 1 and drug levels measured on day 1 through day 3. (125 mg/m2) (n = 23)

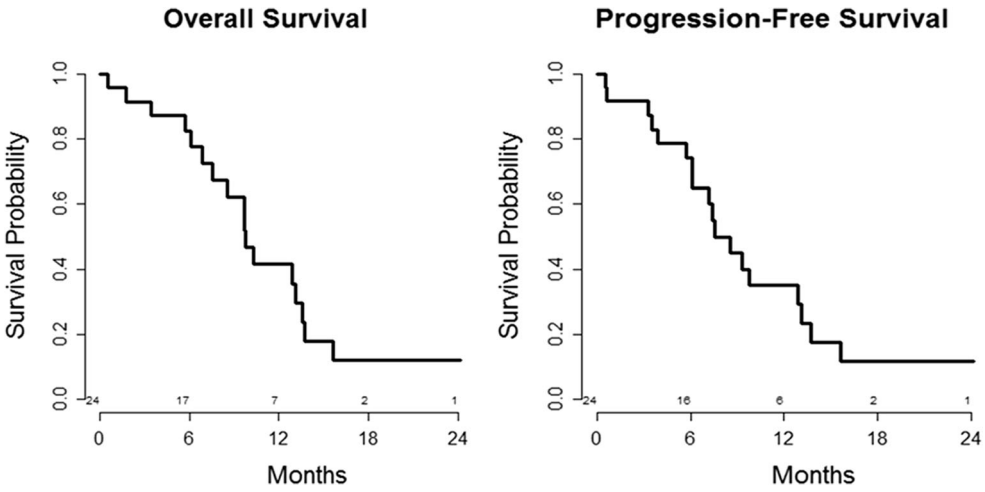

Fig. 4 The independently assessed **a**) median overall survival and **b**) progression-free survival of advanced pancreatic cancer patients on the combination therapy with enzalutamide, nab-paclitaxel and gemcitabine

In this trial, enzalutamide was evaluated in combination with gemcitabine and nab-paclitaxel at maximum total daily dose of 160 mg. As no increased anti-tumor activity was noted with enzalutamide 240 mg and higher doses in the studies with prostate cancer and the rate of grade 3 and 4 adverse events were much higher from the doses 240 mg and higher, we limited the maximum tolerated dose to 160 mg in our trial [14]. At this dose, PK data indicated rapid absorption and sustained bioavailability of enzalutamide with dose-dependent, linear increases in Cmax and area under curve. Paclitaxel also achieved sustained bioavailable concentrations, indicating that all the patients in the study received enzalutamide 160 mg dose achieved target inhibition.

The toxicity profile of the combination regimen was generally acceptable and is consistent with expectations based on the clinical trial data for combination of gemcitabine and nab-paclitaxel [4, 15]. The most commonly reported toxicities observed in the present study were hematologic (decreased peripheral blood cell counts), gastrointestinal (vomiting, nausea, anorexia) and constitutional (fatigue, arthralgia) AEs. Supportive treatment with aggressive use of antiemetics increased tolerability of the combination therapy. In our study, no DLTs were noted. Dose interruptions and dose reductions occurred most commonly because of expected hematologic AEs with the combination, and neuropathy related to nab-paclitaxel. Based on the DLT and AE data, enzalutamide at 160 mg daily dose seems to be well tolerated in combination with gemcitabine and nab-paclitaxel, and has the potential for further evaluation in clinical trials.

In this study, treatment with the combination therapy resulted in stable disease in 75% (9 out of 12 patients) in participants with AR positive cancer cells. It is interesting that five patients in phase 1b cohort remained on the combination regimen for more than 1 year, suggesting that long-term treatment may be feasible. The suitability of the combination therapy was also confirmed by the observations that none of the patients needed dose reduction of enzalutamide. As expected, a greater number of patients (75%) in the phase 1b cohort (AR positivity) achieved stable disease. Moreover, the median OS with the combination therapy (9.73 [95%CI: 9.73–13.5]) was comparable to that of MPACT trial (8.5 [95% CI: 7.89 to 9.53]). Similar trend was seen in progression-free survival again demonstrating the promising nature of the combination especially in the AR positive cells. In addition, the combination regimen resulted in consistent reductions in CA 19–9 levels. Several clinical trials have utilized the CA 19–9 as a surrogate marker of therapeutic efficacy and a decline in the basal CA 19–9 level by ≥20% or by ≥50% has been considered a biochemical response [16–21]. In the present study, we noticed a robust reduction in CA 19–9 levels by a median of 87.5% suggesting a biochemical response with the combination regimen. We noticed that at least 33% of the patients had 90% reduction in CA-19-9 levels as compared to that of baseline value. Our results are comparable to that of phase 3 MPACT trial in which the combination of gemcitabine and nab-paclitaxel showed a 90% reduction in CA 19–9 level reduction in 31% of participants with CA 19–9 data [4].

In conclusion, enzalutamide has an acceptable safety profile with preliminary evidence of clinical benefit in advanced metastatic pancreatic cancer. Given its promising safety and efficacy profile, enzalutamide provides a rationale for its further evaluation in setting of a larger trial for patients with metastatic pancreatic cancer.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest Dr. Richard Kim received honorarium from Lilly, BMS and Bayer. The other authors report no conflicts of interest for this work

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Siegel RL, Miller KD, Jemal A (2018) Cancer statistics, 2018. CA Cancer J Clin 68(1):7–30. https://doi.org/10.3322/caac.21442
2. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol: Off J Am Soc Clin Oncol 15(6):2403–2413. https://doi.org/10.1200/jco.1997.15.6.2403
3. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardiere C, Bennouna J, Bachet JB, Khemissa-Akouz F, Pere-Verge D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364 (19):1817–1825. doi:https://doi.org/10.1056/NEJMoa1011923
4. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF (2013) Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 369 (18):1691–1703. doi:https://doi.org/10.1056/NEJMoa1304369
5. Corbishley TP, Iqbal MJ, Wilkinson ML, Williams R(1986) Androgen receptor in human normal and malignant pancreatic tissue and cell lines. Cancer 57 (10):1992–1995. https://doi.org/10.1002/1097-0142(19860515)57:10<1992::AID-CNCR2820571019>3.0.CO;2-0
6. Iqbal MJ, Greenway B, Wilkinson ML, Johnson PJ, Williams R (1983) Sex-steroid enzymes, aromatase and 5 alpha-reductase in the pancreas: a comparison of normal adult, foetal and malignant tissue. Clin Sci (London, England : 1979) 65(1):71–75
7. Konduri S, Schwarz MA, Cafasso D, Schwarz RE (2007) Androgen receptor blockade in experimental combination therapy of pancreatic cancer. J Surg Res 142(2):378–386. https://doi.org/10.1016/j.jss.2006.09.034
8. Greenway BA (1998) Effect of flutamide on survival in patients with pancreatic cancer: results of a prospective, randomised, double blind, placebo controlled trial. BMJ : Brit Med J 316(7149):1935–1938
9. Negi SS, Agarwal A, Chaudhary A (2006) Flutamide in unresectable pancreatic adenocarcinoma: a randomized, double-blind, placebo-controlled trial. Investig New Drugs 24(3):189–194. https://doi.org/10.1007/s10637-005-3536-2
10. Redding TW, Schally AV (1984) Inhibition of growth of pancreatic carcinomas in animal models by analogs of hypothalamic hormones. Proc Natl Acad Sci U S A 81(1):248–252
11. Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, Wongvipat J, Smith-Jones PM, Yoo D, Kwon A, Wasielewska T, Welsbie D, Chen C, Higano CS, Beer TM, Hung DT, Scher HI, Jung M, Sawyers CL (2009) Development of a second-generation antiandrogen for treatment of advanced prostate Cancer. Science (New York) 324(5928):787–790. https://doi.org/10.1126/science.1168175
12. Jung ME, Ouk S, Yoo D, Sawyers CL, Chen C, Tran C, Wongvipat J (2010) Structure-activity relationship for thiohydantoin androgen receptor antagonists for castration-resistant prostate cancer (CRPC). J Med Chem 53(7):2779–2796. https://doi.org/10.1021/jm901488g
13. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer (Oxford, England : 1990) 45(2):228–247. https://doi.org/10.1016/j.ejca.2008.10.026
14. Golshayan AR, Antonarakis ES (2013) Enzalutamide: an evidence-based review of its use in the treatment of prostate cancer. Core Evidence 8:27–35. https://doi.org/10.2147/CE.S34747
15. Von Hoff DD, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE, Korn RL, Desai N, Trieu V, Iglesias JL, Zhang H, Soon-Shiong P, Shi T, Rajeshkumar NV, Maitra A, Hidalgo M (2011) Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic Cancer: a phase I/II trial. J Clin Oncol 29(34):4548–4554. https://doi.org/10.1200/JCO.2011.36.5742
16. Michele R, Stefano C, Gianpaolo B, Paolo P, Alessia R, Clara F, Elena M, Alessandro Z, Valerio DC, Eugenio V (2009) Carbohydrate antigen 19-9 change during chemotherapy for advanced pancreatic adenocarcinoma. Cancer 115(12):2630–2639. https://doi.org/10.1002/cncr.24302
17. Halm U, Schumann T, Schiefke I, Witzigmann H, Mossner J, Keim V (2000) Decrease of CA 19-9 during chemotherapy with gemcitabine predicts survival time in patients with advanced pancreatic cancer. Br J Cancer 82(5):1013–1016. https://doi.org/10.1054/bjoc.1999.1035
18. Maisey NR, Norman AR, Hill A, Massey A, Oates J, Cunningham D (2005) CA19-9 as a prognostic factor in inoperable pancreatic cancer: the implication for clinical trials. Br J Cancer 93(7):740–743. https://doi.org/10.1038/sj.bjc.6602760
19. Ziske C, Schlie C, Gorschluter M, Glasmacher A, Mey U, Strehl J, Sauerbruch T, Schmidt-Wolf IG (2003) Prognostic value of CA 19-9 levels in patients with inoperable adenocarcinoma of the pancreas treated with gemcitabine. Br J Cancer 89(8):1413–1417. https://doi.org/10.1038/sj.bjc.6601263
20. Poruk KE, Gay DZ, Brown K, Mulvihill JD, Boucher KM, Scaife CL, Firpo MA, Mulvihill SJ (2013) The clinical utility of CA 19-9 in pancreatic adenocarcinoma: diagnostic and prognostic updates. Curr Mol Med 13(3):340–351
21. Ishii H, Okada S, Sato T, Wakasugi H, Saisho H, Furuse J, Ishikawa O, Matsuno S, Yokoyama S (1997) CA 19-9 in evaluating the response to chemotherapy in advanced pancreatic cancer. Hepato-Gastroenterology 44(13):279–283