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A phase I, dose-escalation study of pomalidomide (CC-4047) in combination with gemcitabine in metastatic pancreas cancer ☆

Jeffrey R. Infante [a,b,*], *Suzanne F. Jones* [a], *Johanna C. Bendell* [a,b], *David R. Spigel* [a,b], *Denise A. Yardley* [a,b], *Colin D. Weekes* [c], *Wells A. Messersmith* [c], *John D. Hainsworth* [a,b], *Howard A. Burris III* [a,b]

[a] *Sarah Cannon Research Institute, Nashville, TN, USA*
[b] *Tennessee Oncology, PLLC, Nashville, TN, USA*
[c] *University of Colorado, Aurora, CO, USA*

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ABSTRACT

Introduction: Pomalidomide is an investigational immunomodulating drug (IMiD®) that also inhibits angiogenesis and has direct anti-tumour effects. This phase I study was performed to identify the optimal dose of pomalidomide to be used in combination with gemcitabine in the treatment of patients with metastatic pancreatic cancer.

Methods: Eligible patients had histologically documented metastatic adenocarcinoma of the pancreas. No prior gemcitabine for metastatic disease or for primary treatment of locally advanced disease was allowed although prior radiation therapy with 5-flourouracil (5-FU) or gemcitabine as a radiosensitizer was allowed. All patients received gemcitabine 1000 mg/m^2 IV on days 1, 8 and 15 of a 28 day cycle. Pomalidomide was administered orally on days 1–21 at doses escalated from 2 to 10 mg daily. Patients were re-evaluated every 8 weeks; treatment continued until disease progression or intolerable toxicity occurred.

Results: Twenty-three patients were enrolled with a median age of 62 and Eastern Cooperative Oncology Group (ECOG) performance status 0 (87%) and 1 (13%). The maximum tolerated dose (MTD) was 10 mg/day on days 1–21. Neutropaenia was the most common grade 3/4 toxicity (38%); other grade 3/4 toxicity included deep vein thrombosis (DVT) (22%) and anaemia (9%). While efficacy was not a primary end-point of this study, 3 of 20 evaluable patients (15%) had partial responses and 10 patients (50%) had >50% decrease in CA 19-9 levels.

Conclusions: The combination of pomalidomide and gemcitabine was feasible and safe in most patients receiving first-line chemotherapy for metastatic pancreatic cancer. Neutropaenia, the dose-limiting toxicity, was brief and reversible. Intermittent dosing of pomalidomide allowed substantially higher doses than were previously reported with a continuous schedule. This combination merits further evaluation in the treatment of metastatic pancreatic cancer.

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* *Corresponding author*: Address: Sarah Cannon Research Institute, 250 25th Avenue North, Ste 110 Nashville, TN 37203, USA.
E-mail addresses: jinfante@tnonc.com, david.hainesiii@scresearch.net (J.R. Infante).

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1. Background

Carcinoma of the pancreas remains among the most lethal of the human cancers. As with most tumours without effective early detection strategies, the majority of patients, approximately 85%, present with advanced unresectable disease.[1] Even with surgical resection offering the only possibility of cure, the recurrence rate is extremely high, and the 5-year overall survival rate following a pancreaticoduodenectomy is 8–20%.[2–5]

For those patients with advanced or recurrent disease, gemcitabine is considered as a standard treatment. As compared to 5-flourouracil (5-FU), gemcitabine improved clinical benefit and reported a modest improvement in overall survival (mOS 5.65 vs. 4.41 months, $P = 0.0025$).[6] Unfortunately, gemcitabine combinations with other cytotoxic agents have failed to improve upon the median overall survival of approximately 6 months.[7] A meta-analysis of the gemcitabine trials in combination with capecitabine suggested a mild improvement in overall survival[8], despite the fact that all three individual trials comparing the combination to gemcitabine alone failed to meet their respective primary overall survival end-points.[9,10] Multiple agents that target important molecular pathways such as *kRas*, epidermal growth factor receptor (EGFR), and angiogenesis have also been studied in combination with gemcitabine.[7] To date, erlotinib, the EGFR tyrosine kinase inhibitor, is the only agent to modestly improve survival in combination with gemcitabine.[11]

Further improvement of treatment for patients with pancreatic cancer is urgently needed. Pomalidomide (CC-4047) is a next generation immunomodulating drug (IMiD®). Similar to thalidomide, pomalidomide possesses strong anti-angiogenesis properties.[12] Pancreatic cancers are known to overexpress vascular endothelial growth factor (VEGF) and show strong tumour neoangiogenesis.[13] In addition to the anti-angiogenic and direct anti-tumour properties, pomalidomide is immunomodulatory with anti-inflammatory monocyte/macrophage activation and T-cell co-stimulatory properties both *in vitro* and *in vivo*.[12] This study was designed to determine the appropriate dose of pomalidomide to give in combination with gemcitabine in patients with treatment-naïve advanced pancreatic cancer.

2. Patients and methods

This open-label phase 1 study (clinicaltrials.gov #NCT00540579) was conducted at the Sarah Cannon Research Institute and the University of Colorado between 12/2007 and 01/2009. The protocol was approved by the institutional review board for each institution and all patients provided informed written consent prior to enrolment.

2.1. Patient eligibility

Eligible patients had histologically documented metastatic adenocarcinoma of the pancreas. No prior chemotherapy for metastatic disease or for primary treatment of locally advanced disease was allowed. Participants may have been previously treated with adjuvant radiation therapy; concurrent 5-fluorouracil or gemcitabine may have been used as a radiosensitizer in this setting. Following radiation therapy, no further adjuvant treatment with gemcitabine or 5-fluorouracil was allowed. All patients had measurable disease per Response Evaluation Criteria in Solid tumours (RECIST 1.0).[14] Patients also had to be able to take daily aspirin (81 or 325 mg) as a prophylactic anticoagulation agent (patients intolerant of aspirin were able to use low dose warfarin or low molecular weight heparin). Patients with a history of, or active, venous thromboembolic events (VTE) were eligible as long as they were therapeutically managed on a stable dose of an appropriate anticoagulant.

Other eligibility criteria included: age $\geqslant$18 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; negative serum pregnancy test; ability to swallow intact capsules of pomalidomide; adequate organ function [defined as absolute neutrophil count (ANC) $\geqslant 1.5 \times 10^9$/L, platelet count $\geqslant 100 \times 10^9$/L, serum bilirubin $\leqslant$ 2.0 mg/dL (34 μmol/L), serum SGOT/AST or SGPT/ALT 3× the upper limit of normal (ULN) or 5× ULN in the case of liver metastases and serum creatinine $\leqslant$2.5 mg/dL (221 μmol/L)]. The study excluded: patients with known brain or leptomeningeal metastases; clinically significant cardiovascular disease; or a history of another malignancy (except basal cell or squamous cell carcinoma or carcinoma *in situ* of the cervix or breast, localised prostate cancer with PSA < 1.0 mg/dL) unless free of disease for $\gg$3 years, or pregnant or lactating females.

2.2. Study design and treatments

The primary objective of this phase 1 dose-escalation study was to determine the maximum tolerated dose (MTD) and safety of the pomalidomide/gemcitabine combination. The secondary objective was to explore the anti-tumour activity of this combination in patients with metastatic pancreatic carcinoma.

Pomalidomide was administered orally on days 1–21 followed by 7 d without treatment (28-day cycle). Gemcitabine was administered at a fixed dose of 1000 mg/m^2 IV on days 1, 8, and 15 every 28 d (Fig. 1). Per dose-escalation scheme shown in Table 1, the dose of pomalidomide was escalated in sequential cohorts of three patients each. A cohort was expanded to six patients if 1 of the first 3 patients had a dose-limiting toxicity (DLT) during cycle 1. Dose-escalation continued if 0–1 of 6 patients experienced a DLT. The MTD was surpassed if $\geqslant$2 patients in a cohort experienced a DLT. Adverse events (AEs) were defined by CTCAE version 3.0. DLT's were protocol-defined as follows: inability to complete cycle 1 of therapy due to a drug-related toxicity; grade 3 or 4 non-haematologic toxicities (excluding alopecia) despite optimal supportive care; febrile neutropaenia; grade 4 neutropaenia that occurred prior to day 21 (grade 4 neutropaenia that occurred after day 21 but resolved within 7 d was not considered a DLT); grade 4 thrombocytopenia; and the inability to initiate cycle 2 within 7 d of scheduled start date.

Dose modifications were not permitted during cycle 1 of any cohort unless the subject experienced a DLT. The protocol defined specific modifications and interruptions for subsequent cycles. Intra-cycle gemcitabine dose modifications/interruptions for haematologic toxicities on days 8 and 15 of the

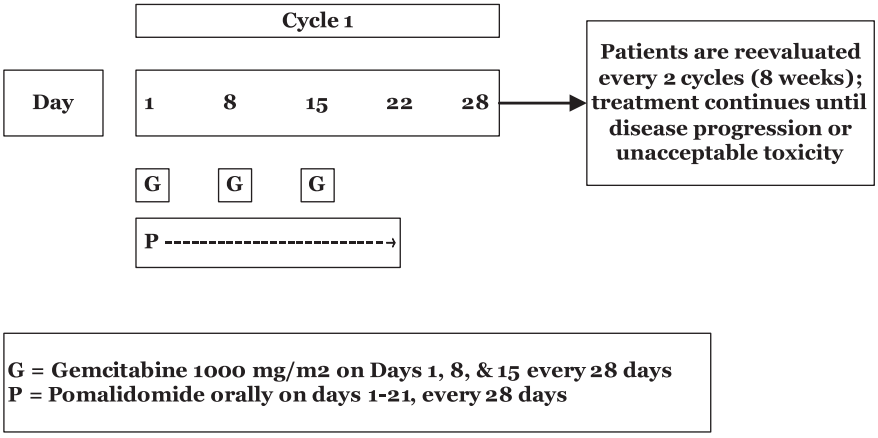

Fig. 1 – Pomalidomide and gemcitabine administration schema.

Table 1 – Dose-escalation schedule and summary of dose-limiting toxicities (DLTs).

Dose level	Pomalidomide dose (mg/day)	Gemcitabine dose (mg/m^2)	Patients at each dose level	Number with DLT	DLT description
−1	1	750			
1[a]	2	1000	5[b]	0	
2	3	1000	4	0	
3	5	1000	3	0	
4	7	1000	3	0	
5	10	1000	8[c]	1	Febrile neutropaenia

[a] Initial dose level.
[b] One pt Withdrew consent and 1 pt with concurrent subdural haematoma unevaluable for DLT.
[c] One pt Withdrew consent, unevaluable for DLT.

cycle were similar to the product label. The ANC had to be $\geqslant$1000/μL and the platelet count $\geqslant$75,000/μL to begin a new cycle of therapy. The specific dose of pomalidomide and gemcitabine implemented in the new cycle was based on the toxicity and dose reduction encountered in the previous cycle.

2.3. *Study assessments*

Prior to treatment, patients were evaluated by history, physical exam and laboratory testing (including a serum CA 19-9 level). Baseline tumour staging was performed using computed tomography (CT) and/or magnetic resonance imaging (MRI) of the chest, abdomen and pelvis. Evaluations were repeated after every two cycles using RECIST guidelines.[14] Patients who tolerated therapy were allowed to remain on study until evidence of disease progression. Intra-patient dose-escalation was not allowed.

2.4. *Statistical methods*

The study population for all analyses included patients who received at least one dose of study medication. Descriptive statistics summarised baseline values, safety, and efficacy data.

3. Results

3.1. *Patient demographics and clinical characteristics*

Baseline characteristics of the 23 patients are detailed in Table 2. Three (13%) of the patients had recurrence of disease after prior pancreaticoduodenectomy. One of these patients had also received prior adjuvant radiation in combination with radiosensitizing doses of 5-flourouracil.

3.2. *Safety and tolerability for all cohorts*

The median number of cycles received for all 23 patients on study was 3 (range: 1–14). Table 1 summarises all DLTs by cohort. Two of the five patients enrolled in the first dose level were inevaluable for DLT. One patient on warfarin for atrial fibrillation suffered a subdural haematoma on day 2 after an accidental fall. Another patient withdrew consent after 1 week of dosing to pursue alternative therapies. One patient in dose level 5 also withdrew consent due to feasibility of travel to and from the clinic. The first and only DLT was febrile neutropaenia occurring at dose level 5. The MTD was not formally defined and dose-escalation was stopped at 10 mg of pomalidomide in combination with gemcitabine 1000 mg/m^2. This was the highest planned dose level per protocol and was defined as the highest studied dose (HSD).

Table 2 – Patient characteristics (*N* = 23).

Median age (range)	62 (47–78)
Gender	
Male	16 (70%)
Female	7 (30%)
ECOG PS	
0	20 (87%)
1	3 (13%)
Prior therapy	
Pancreaticoduodenectomy	3 (13%)
Adjuvant XRT	1 (4%)

As summarised in Table 3, neutropaenia (all grades) occurred in 52% of patients and was the most frequent haematologic adverse event. Grade ⩾3 neutropaenia occurred in 39% of patients, but only two patients experienced grade 4 neutropaenia. Neither of these patients had received prior adjuvant radiation. Febrile neutropaenia occurred in only one patient. At doses of pomalidomide >5 mg, 4 of 11 pts (36%) had grade 3/4 neutropaenia, one of which was febrile neutropaenia. Grade 3/4 thrombocytopenia and anaemia were uncommon (0% and 9%, respectively).

Treatment-related non-haematologic adverse events are outlined in Table 4. Fatigue (57%), rash (48%), constipation (43%), oedema (43%), and diarrhoea (39%) were the most frequent, but always grade 1–2. One patient had grade 3 nausea and vomiting that occurred during a hospitalisation for intestinal obstruction. Grade 3 weakness was associated with a serious adverse event of intestinal perforation occurring at the end of cycle 2 in a patient with a history of prior adjuvant radiation. At the first restaging assessment, this patient had a decrease in the CA 19-9 and a minor reduction in tumour volume of CT scans. The perforation occurred at the site of the anastomosis within the radiation field. The patient recovered and eventually received further gemcitabine off study. One patient had a known history of VTE prior to going on study.

Table 3 – Treatment emergent haematologic adverse events (AEs) and venous thromboembolic events (VTE) by pomalidomide dose level.

Dose level	1	2	3	4	5	Total
Pomalidomide	2 mg	3 mg	5 mg	7 mg	10 mg	
N	5	4	3	3	8	23
Neutropaenia						
Grade 1–2	0	0	0	0	3	3 (13%)
Grade 3–4	1	1	3	3	1	9 (39%)
Thrombocytopenia						
Grade 1–2	1	1	2	3	2	9 (39%)
Grade 3–4	0	0	0	0	0	0
Anaemia						
Grade 1–2	2	0	3	2	3	10 (43%)
Grade 3–4	0	1	0	0	1	2 (9%)
VTE (n = 22)[a]						
Grade 3	0	2	1	1	1	5 (23%)

[a] *n* = 22 Due to prior history of VTE in a patient that was on full dose anticoagulation prior to study entry.

Table 4 – Treatment-related non-haematologic toxicity (*N* = 23).

	Number of patients (%) Grade			
	1	2	3	4
Non-haematologic				
Fatigue	9 (39%)	4 (17%)	0	0
Rash	10 (43%)	1 (4%)	0	0
Constipation	9 (39%)	1 (4%)	0	0
Oedema – peripheral	9 (39%)	1 (4%)	0	0
Diarrhoea	2 (9%)	7 (30%)	0	0
Nausea	7 (30%)	1 (4%)	1 (4%)[a]	0
Vomiting	6 (26%)	1 (4%)	1 (4%)[a]	0
Anorexia	7 (30%)	0	0	0
Deep vein thrombosis (DVT)	0	0	5 (22%)	0
Dizziness	5 (22%)	0	0	0
Weakness	3 (13%)	1 (4%)	1 (4%)[b]	0

[a] Patient admitted with intestinal obstruction due to disease.
[b] Associated with grade 4 intestinal perforation.

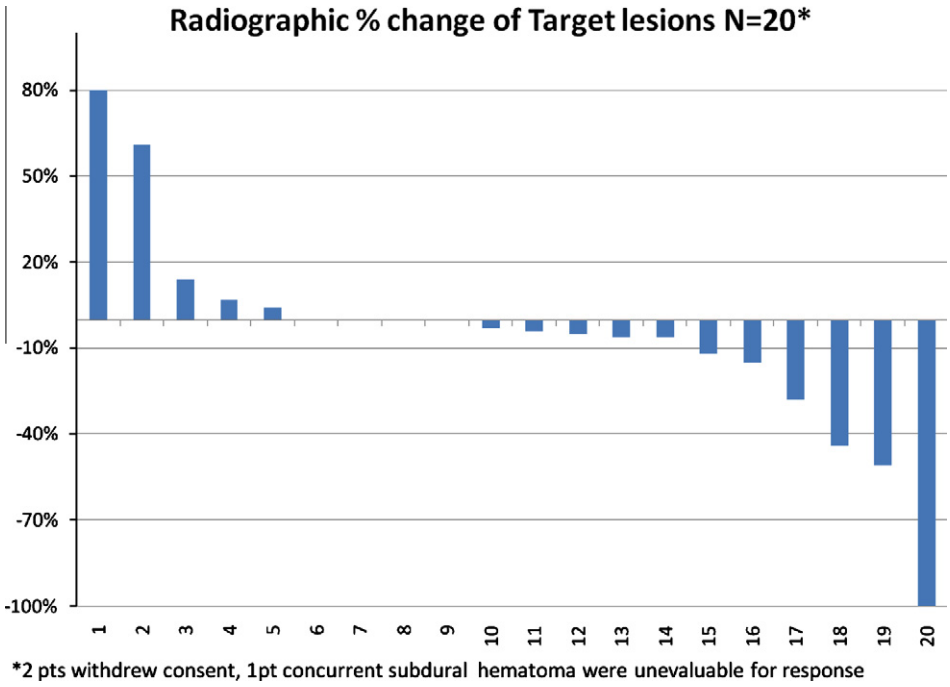

Fig. 2 – Radiographic response of target lesions by patient.

Despite prophylaxis with aspirin, 5 of the other 22 (23%) patients developed a VTE while on study. These events did not correlate to a specific dose level or a specific time on study (Table 3). VTE events occurred at 4 of 5 dose levels with two occurring in cycle 1, one in cycle 2, and two in cycle 4.

Dose delays or modifications were relatively uncommon. Five patients required dose reductions, all due to neutropaenia-related events. One pt in dose level 2 was reduced in cycle 6 for grade 3 ANC, 2 pts in dose level 3 were reduced for ANC $\geqslant$ grade 3 during cycles 3 and 4, 1 pt in dose level 3 was held for grade 4 ANC which recovered and did not require dose reduction. Two patients in dose level 5 had dose reductions: one patient was reduced for grade 3 ANC during cycle 3 and another patient was reduced for febrile neutropaenia. There were three episodes of dose delays due to rash, diarrhoea, and pneumonitis.

3.3. *Efficacy*

Twenty patients received at least one cycle of therapy and nine patients received $\geqslant$6 months of treatment. Eight of the nine patients were in cohorts receiving doses of pomalidomide $\geqslant$ 5 mg. Three patients did not complete cycle 1 as outlined previously (subdural haematoma [1] and withdrawal of consent [2]).

Partial responses were observed in three patients (15%). Four patients had early progression prior to cycle 3 and the rest had stable disease after two cycles. CA 19-9 levels decreased by >50% in 43% of patients (Fig. 2).

4. Discussion

This phase 1, dose-escalation trial demonstrates that pomalidomide can be administered safely in combination with gemcitabine. The HSD was 10 mg of pomalidomide on days 1–21 in combination with gemcitabine 1000 mg/m^2 intravenous on days 1, 8, and 15 of a 28 day cycle.

Based on previous single agent studies with pomalidomide, myelosuppression was expected to be the DLT with this combination. In a phase 1 study in advanced multiple myeloma, the MTD of pomalidomide was 2 mg daily.[15] Dose-limiting neutropaenia occurred in six of the 24 patients. Thrombocytopaenia was usually mild with only three grade 3 events and no grade 4 events. In an ongoing phase I study in patients with solid tumours, pomalidomide produced dose-limiting neutropaenia at a daily dose of 5 mg; a 4 mg daily dose is currently being evaluated.[16]

In our study, we were able to give 10 mg daily of pomalidomide for 21 of 28 d in combination with full dose gemcitabine on days 1, 8, and 15 of a 28 day cycle. The ability to give 10 mg of pomalidomide was likely due to the intermittent schedule and the relatively chemotherapy-naïve patient population. Although neutropaenia was very common (52% all grades), it was usually brief and accounted for only one DLT. However, neutropaenia was the reason for all five dose modifications occurring after patients were on study for multiple cycles. Thrombocytopaenia was mild with no grade 3 or 4 events and similar to that produced by single agent gemcitabine.[8,17,18]

As seen in the multiple myeloma patient population[15], treatment emergent non-haematologic adverse events associated with pomalidomide were usually grade 1 or 2. Similar to thalidomide, fatigue, rash and constipation remained common but manageable without dose modifications. In contrast, peripheral neuropathy and somnolence were very rare. One patient experienced grade 3 weakness in association with a grade 4 intestinal perforation event. Although the perforation occurred in the radiation bed at the site of an anastomosis

from a prior pancreaticoduodenectomy, the known risk of gastrointestinal perforation with other angiogenesis inhibitors mandates close attention to this issue in future studies.

The occurrence of VTE is increased in patients with pancreatic cancer.[19] In the prospective CONKO 004 trial, VTE occurred in 22 (14%) of the 152 patients undergoing chemotherapy for advanced pancreatic cancer without prophylactic low molecular weight heparin.[20] VTE has also been associated with thalidomide treatment[7], so this toxicity was of special concern in this study. Of the 22 patients without a prior history of VTE, 5 (23%) developed a VTE while on study. There were no deaths associated with the VTE events and patients were allowed to remain on study with therapeutic anticoagulation. These VTE events occurred despite prophylactic anticoagulation with aspirin. Whether pomalidomide carries the same risk of VTE as thalidomide and whether aspirin is adequate for prophylaxis in this patient population remains unknown.

Although this phase I study was not designed to assess the efficacy of this combination, the activity against pancreatic cancer is encouraging. Three patients (15%) had partial responses, while CA 19-9 levels decreased by at least 50% in 10 patients. Nine patients received treatment for more than 6 months.

At present, there is no therapeutic role for agents that only target angiogenesis in the treatment of advanced pancreatic cancer. An initial phase II study of bevacizumab in combination with gemcitabine found 21% of patients with advanced pancreatic cancer to have confirmed partial responses and a median progression-free survival of 5.4 months.[21] Unfortunately, the preliminary analysis from the CALGB 80303 double-blinded randomized phase III trial failed to confirm an improvement in survival with gemcitabine/bevacizumab when compared to gemcitabine alone.[22] A second randomized study in which bevacizumab was added to the combination of gemcitabine/erlotinib also failed to improve overall survival.[18] Finally, the addition of axitinib, an oral VEGF receptor tyrosine kinase inhibitor, to gemcitabine did not meet its primary survival end-point as compared to gemcitabine alone.[23]

Although the IMiDs have anti-angiogenic properties[12], they may also have other mechanisms of action. IMiDs may also induce tumour cell death directly and may co-stimulate T-cells to enhance anti-tumour immunity. Schey et al demonstrated these immunomodulatory properties *in vivo* in multiple myeloma patients.[15] In addition to increasing serum levels of cytokine IL-12, pomalidomide induced CD4+ and CD8+ T-cell activation suggesting a switch to a Th1 immune response. The contribution of these various mechanisms to the anti-tumour activity of pomalidomide is unknown.

In summary, the combination of pomalidomide with gemcitabine can be given safely to patients with treatment-naïve metastatic pancreatic cancer. The toxicity profile is manageable with brief and reversible neutropaenia as the most common reason for the occasional dose modification. The ability to give pomalidomide at a dose of 10 mg daily for 21 of 28 d in combination with standard dosing of gemcitabine is encouraging. This dose is 2–4 times higher than the MTD when pomalidomide is administered on a continuous schedule.[15,16] These results support the further development of pomalidomide in combination with gemcitabine as a first-line treatment for patients with advanced pancreatic cancer.

Conflict of interest statement

None declared.

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