European Journal of Cancer (2015) 51, 1857–1864

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

^{90}Y-clivatuzumab tetraxetan with or without low-dose gemcitabine: A phase Ib study in patients with metastatic pancreatic cancer after two or more prior therapies ☆,☆☆

Vincent J. Picozzi [a], Ramesh K. Ramanathan [b], Maeve A. Lowery [c], Allyson J. Ocean [d], Edith P. Mitchel [e], Bert H. O'Neil [f], Michael J. Guarino [g], Paul R. Conkling [h], Steven J. Cohen [i], Nathan Bahary [j], Richard C. Frank [k], Tomislav Dragovich [l], Benjamin B. Bridges [m], Fadi S. Braiteh [n], Alexander N. Starodub [o], Fa-Chyi Lee [p], Thomas E. Gribbin [q], Donald A. Richards [r], Marie Lee [a], Ronald L. Korn [b], Neeta Pandit-Taskar [c], Stanley J. Goldsmith [d], Charles M. Intenzo [e], Arif Sheikh [f], Timothy C. Manzone [g], Heather Horne [s], Robert M. Sharkey [s], William A. Wegener [s], Eileen M. O'Reilly [c], David M. Goldenberg [s,t,*], Daniel D. Von Hoff [b]

[a] *Virginia Mason Medical Center, Seattle, WA, United States*
[b] *Virginia G. Piper Cancer Center at Scottsdale Healthcare/TGen, Scottsdale, AZ, United States*
[c] *Memorial Sloan-Kettering Cancer Center, New York, NY, United States*
[d] *Weill Cornell Medical College, New York, NY, United States*
[e] *Kimmel Cancer Center of Thomas Jefferson University, Philadelphia, PA, United States*
[f] *UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC, United States*
[g] *Helen F. Graham Cancer Center at Christiana Care Health System, Newark, DE, United States*
[h] *US Oncology Phase II Group, Virginia Oncology Associates, Norfolk, VA, United States*
[i] *Fox Chase Cancer Center, Philadelphia, PA, United States*
[j] *University of Pittsburgh Medical Center, Pittsburgh, PA, United States*
[k] *Whittingham Cancer Center at Norwalk Hospital, Norwalk, CT, United States*
[l] *Banner MD Anderson Cancer Center, Gilbert, AZ, United States*
[m] *St Luke's Mountain States Tumor Institute, Meridian, ID, United States*
[n] *Comprehensive Cancer Centers of Nevada, Las Vegas, NV, United States*
[o] *Indiana University Health Center for Cancer Care, Goshen, IN, United States*
[p] *University of New Mexico Health Science Center, Albuquerque, NM, United States*
[q] *Lacks Cancer Center, Saint Mary's Health Care, Grand Rapids, MI, United States*
[r] *Tyler Cancer Center, US Oncology Research, Tyler, TX, United States*
[s] *Immunomedics, Inc., Morris Plains, NJ, United States*
[t] *Center for Molecular Medicine and Immunology/Garden State Cancer Center, Morris Plains, NJ, United States*

This study was registered with clinicaltrials.gov identifier NCT01510561.

Presented in part at the European Society for Medical Oncology 15th World Congress on Gastrointestinal Cancer, Barcelona, Spain, July 3–6, 2013, and at the American Association for Cancer Research Special Conference on Pancreatic Cancer: Innovations in Research and Treatment, New Orleans, LA, May 19–21, 2014.

* *Corresponding author at:* Center for Molecular Medicine and Immunology/Garden State Cancer Center, 300 American Road, Morris Plains, NJ 07950, United States. Tel.: +1 973 605 8200.

E-mail address: dmg.gscancer@att.net (D.M. Goldenberg).

http://dx.doi.org/10.1016/j.ejca.2015.06.119

Received 21 January 2015; received in revised form 8 May 2015; accepted 7 June 2015
Available online 14 July 2015

KEYWORDS
Pancreatic cancer
Radioimmunotherapy
Clivatuzumab tetraxetan
Gemcitabine
Antibody
Yttrium-90

Abstract ***Background:*** For patients with metastatic pancreatic adenocarcinoma, there are no approved or established treatments beyond the 2nd line. A Phase Ib study of fractionated radioimmunotherapy was undertaken in this setting, administering ^{90}Y-clivatuzumab tetraxetan (yttrium-90-radiolabelled humanised antibody targeting pancreatic adenocarcinoma mucin) with or without low radiosensitising doses of gemcitabine.
Methods: Fifty-eight patients with three (2–7) median prior treatments were treated on Arm A ($N = 29$, ^{90}Y-clivatuzumab tetraxetan, weekly 6.5 mCi/m^2 doses × 3, plus gemcitabine, weekly 200 mg/m^2 doses × 4 starting 1 week earlier) or Arm B ($N = 29$, ^{90}Y-clivatuzumab tetraxetan alone, weekly 6.5 mCi/m^2 doses × 3), repeating cycles after 4-week delays. Safety was the primary endpoint; efficacy was also evaluated.
Results: Cytopaenias (predominantly transient thrombocytopenia) were the only significant toxicities. Fifty-three patients (27 Arm A, 26 Arm B, 91% overall) completed ⩾1 full treatment cycles, with 23 (12 Arm A, 11 Arm B; 40%) receiving multiple cycles, including seven (6 Arm A, 1 Arm B; 12%) given 3–9 cycles. Two patients in Arm A had partial responses by RECIST criteria. Kaplan–Meier overall survival (OS) appeared improved in Arm A versus B (hazard ratio [HR] 0.55, 95% CI: 0.29–0.86; $P = 0.017$, log-rank) and the median OS for Arm A versus Arm B increased to 7.9 versus 3.4 months with multiple cycles (HR 0.32, $P = 0.004$), including three patients in Arm A surviving >1 year.
Conclusions: Clinical studies of ^{90}Y-clivatuzumab tetraxetan combined with low-dose gemcitabine appear feasible in metastatic pancreatic cancer patients beyond 2nd line and a Phase III trial of this combination is now underway in this setting.

1. Introduction

The outlook for patients with advanced pancreatic adenocarcinoma remains poor [1]. In the frontline, median survival was 6.2–6.7 months with gemcitabine alone [2] or with erlotinib [3], 8.5 months combined with albumin-bound paclitaxel (Abraxane) [4] and 11.1 months for those able to tolerate combination chemotherapy (FOLFIRINOX) [5]. Beyond the 1st line, the survival advantage with chemotherapy remains limited [6–8], and after two prior treatments (one usually gemcitabine-based, the other fluoropyrimidine-based), there are no accepted treatments [9–11]. We instead pursued radioimmunotherapy to target and directly irradiate tumour sites without needing to physically overcome transport barriers in pancreatic cancer (high interstitial pressure, dense stromal reaction) or be incorporated into the tumour cells to be effective [12].

PAM4, an anti-MUC5ac monoclonal antibody selectively binding to pancreatic adenocarcinoma mucin [13–16], proved active when radiolabeled in preclinical models of human pancreatic cancer [17,18]. After humanisation and conjugation with DOTA (1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid), the chelate-conjugate (clivatuzumab tetraxetan) was labeled with 90-yttrium (^{90}Y), a beta-emitting radionuclide with a radiation path-length of ~5 mm suitable for bulky tumours. ^{90}Y-clivatuzumab tetraxetan was initially administered as a single dose [19], but fractionated doses should be more effective [20]. Gemcitabine is a known radiosensitiser [21], tolerated clinically at low doses with external radiotherapy [22], and preclinical studies showed enhanced anti-tumour activity combining ^{90}Y-labeled PAM4 with gemcitabine [23–25]. In the frontline, fractionated doses of ^{90}Y-clivatuzumab tetraxetan combined with 200 mg/m^2 doses of gemcitabine achieved 7.7 months median overall survival in patients with Stage III or IV disease, but 11.8 months for those patients given repeated treatment cycles; manageable myelosuppression was the principal side-effect [26].

After receiving two prior treatments, there is an unmet medical need for further therapy. Radioimmunotherapy may be particularly attractive for patients considering continued treatment, but unable or unwilling to tolerate the side effects of further chemotherapy. As such, this Phase Ib study was undertaken to determine if our approach, which had previously been used in the frontline setting, would be safe in such an advanced population. Secondarily, we wanted to further examine the role of low-dose gemcitabine in the treatment regimen before pursuing a large definitive trial.

2. Methods

This was an open-label, multicenter phase Ib study of ^{90}Y-clivatuzumab tetraxetan administered with or without 200 mg/m^2 gemcitabine in patients with metastatic pancreatic adenocarcinoma after ⩾2 prior therapies. Primary study objectives included evaluating treatment safety and tolerability in this setting. Additional objectives were to obtain evidence of efficacy based on survival, CT imaging and CA19-9 serum levels, assess the contribution of gemcitabine to this treatment regimen and evaluate any immunogenicity towards this antibody-based regimen. Institutional review boards at each site approved the study. Written informed consent was obtained from all patients.

2.1. Population

Adults ⩾18 years old with metastatic pancreatic adenocarcinoma must have received ⩾2 prior chemotherapy regimens for their advanced disease and have measureable disease by CT imaging, but no CNS metastases or bulky disease (no single mass ⩾ 10 cm). Other requirements included Karnofsky performance status ⩾ 70%, haemoglobin ⩾ 9 g/dL, neutrophils [ANC] ⩾ 1500/mm^3, platelets ⩾ 100,000/mm^3, creatinine and bilirubin ⩽ 1.5× IULN (institutional upper limit of normal), AST and ALT ⩽ 2.0× IULN, with any prior external radiation therapy <2000 cGy to lungs and kidneys, <3000 cGy to liver, <30% of red marrow, and with ⩽Grade 2 nausea/vomiting, anorexia or signs of intestinal obstruction.

2.2. Treatment and assessments

Immunomedics, Inc., (Morris Plains, NJ) provided clivatuzumab tetraxetan in 10 mg kits to local commercial radiopharmacies for ^{90}Y-radiolabeling. The prior study in treatment of naïve patients found that patients at the 6.5 or 9.0 mCi/m^2 dose levels had adequate platelet and neutrophils levels to initiate a second cycle without the need for dose reduction or delay [26,27]. Since patients in this study likely have decreased bone marrow reserve after two or more prior chemotherapy regimens, the lower dose of 6.5 mCi/m^2 was selected for this population, with ^{90}Y-clivatuzumab tetraxetan administered in the hospital nuclear medicine department by slow injection over 5–10 min without steroids of other premedication. Commercially available gemcitabine prepared by the hospital pharmacy was given intravenously over 30 min.

Patients were alternately assigned to treatment arms by the Sponsor, who was not informed of prior history other than meeting eligibility. In Arm A, patients received 6.5 mCi/m^2 Y-clivatuzumab tetraxetan once-weekly for 3 weeks together with 200 mg/m^2 gemcitabine once-weekly for 4 weeks starting 5 days before beginning ^{90}Y-clivatuzumab tetraxetan and then 2 days after each dose. In Arm B, patients received only 6.5 mCi/m^2 Y-clivatuzumab tetraxetan once-weekly for 3 weeks. For both arms, treatment cycles were repeated after 4 weeks following the last dose until unacceptable toxicity, progressive disease or patient withdrawal. The full ^{90}Y-clivatuzumab tetraxetan dose was administered for ANC ⩾ 1000/mm^3 and platelets ⩾ 100,000/mm^3; otherwise, a 75% dose for ANC ⩾ 750/mm^3 and platelets ⩾ 75,000/mm^3, or a 50% dose for lower values with ANC ⩾ 500/mm^3 and platelets ⩾ 50,000/mm^3, with the dose held if ANC < 500/mm^3 or platelets < 50,000/mm^3 and treatment delayed on a weekly basis until blood levels permitted dosing to continue. Gemcitabine doses were held if ^{90}Y-clivatuzumab tetraxetan doses were held, but were otherwise given without reduction.

Adverse events were graded by NCI-CTCAE v4.0 [28]. Vital signs, physical examination, blood counts, serum chemistries and CA19–9 serum levels were evaluated during treatment cycles, then 4, 8 and 12 weeks after the last cycle. Serum samples were evaluated by enzyme immunoassay for any human anti-hPAM4 antibodies (HAHA). CT scans were obtained at least every 7–8 weeks from treatment initiation until progression and interpreted by local radiologists. Tumour lesion changes were categorised as a complete response (CR), partial response (PR), stable (SD) or progressive disease (PD) by RECIST v1.0 [29], and with disease control defined as achieving PR or CR or else SD for at least 8 weeks from treatment initiation. ^{18}F-FDG-PET or PET/CT imaging was optional. All patients were followed for survival.

2.3. Statistical analysis

The primary endpoint was analysed by frequency of adverse events and toxicities, including cytopaenias. Overall survival (OS) from first dose to death or last contact was analysed by Kaplan–Meier methods, while additional endpoints were summarised by descriptive statistics. An active therapy in this population would be assumed to have a disease control rate of ⩾25% versus 5% for an inactive therapy. Using a SWOG two-stage programme [30] results in a sample size of ⩾25 patients per treatment arm and guards against futility by terminating accrual on an arm at interim assessment if none of the first 15 patients achieve disease control.

3. Results

3.1. Patients and study treatment

Fifty-eight patients with a median of 3 (range, 2–7) prior chemotherapy regimens were treated in Arm A

($N = 29$) or B ($N = 29$) between June 2012 and February 2013. All had received gemcitabine-containing regimens (21% with nab-paclitaxel) while 97% had received fluoropyrimidine-containing regimens (50% with FOLFIRINOX). Table 1 summarises patient demographics and baseline characteristics for each arm.

No drug-related interruptions, discontinuations or adverse reactions occurred with treatment administrations. Five patients rapidly deteriorated before finishing one cycle (stroke, entered hospice, biliary obstruction, pulmonary embolism and severe constipation). Patients terminated further treatment due to disease progression/clinical deterioration or other treatment-unrelated events, with 30/58 (52%) patients (15 per arm) completing only one cycle and 23 (40%) patients (12 Arm A, 11 Arm B) receiving multiple cycles, including 16 (6 Arm A, 10 Arm B) given two cycles and seven (6 Arm A, 1 Arm B) given 3–9 cycles. For cycle 1, 8/58 (14%) patients had $\geqslant 1$ doses of ^{90}Y- clivatuzumab tetraxetan reduced to 75%; but, besides the five patients who rapidly deteriorated, no doses were held. For repeated cycles, 16/23 (70%) patients had $\geqslant 1$ dose reduced to 75% ($N = 7$) or 50% ($N = 9$), including 11 (48%) who also had $\geqslant 1$ dose held.

Table 1
Demographics and baseline characteristics.

	Arm A	Arm B
Patients, *N*	29	29
Sex, M/F	19/10	14/15
Age, median (range)	62 (39–73)	66 (51–80)
Karnofsky performance status, *N*		
90–100	14	10
70–80	15	19
Haematology, median (range)		
Platelets (×1000/μL)	211 (100–577)	224 (113–570)
Neutrophils (×1000/μL)	5.2 (1.9–15.1)	5.4 (3.0–13.4)
Haemoglobin (g/dL)	11.3 (9.2–15.1)	11.6 (9.4–15.8)
Years from diagnosis, median (range)	1.8 (0.3–4.1)	1.5 (0.4–3.7)
Stage IV disease, N (%)	29 (100%)	29 (100%)
Extent of disease, median (range)		
CA19-9 (U/mL)	863 (0.8–UL[a])	2720 (6.5–UL[a])
Sum of index lesions (cm)	9.8 (1.7–19.0)	7.1 (1.2–22.2)
Tumour location, *N* (%)		
Pancreas, including resection bed	11(38%)	15 (52%)
Liver	14 (48%)	17 (59%)
Other abdomen sites	13 (45%)	16 (55%)
Lung	13 (45%)	12 (41%)
Prior therapies		
Pancreatectomy, *N* (%)	15 (52%)	9 (31%)
External radiation, *N* (%)	10 (34%)	8 (28%)
Chemotherapy regimens		
Median (range)	3 (2–7)	3 (2–6)
Most frequent, *N* (%)		
Gemcitabine-containing	29 (100%)	29 (100%)
Gemcitabine/nab-paclitaxel	6 (21%)	6 (21%)
Fluoropyrimidine-containing	28 (97%)	28 (97%)
FOLFIRINOX[b]	17 (59%)	12 (41%)

[a] UL = upper limit of quantitation, nominally >200,000 U/mL.
[b] Irinotecan, oxaliplatin and 5-fluorouracil/leucovorin combination.

3.2. Adverse events

Events considered at least possibly treatment-related were thrombocytopenia, 50% of patients; fatigue, 26%; anaemia, 22%; nausea, 16%; leukopaenia, neutropenia, 12% each; abdominal pain, anorexia, vomiting, diarrhoea, 9% each; bleeding, fever, chills, 7% each; dyspnoea, hyperbilirubinemia, headache, 5% each and others <5%. These included Grade $\geqslant 3$ events of thrombocytopenia, 19%; anaemia, leukopaenia and neutropenia, 7% each ; others $\leqslant 2\%$.

Comparison of events regardless of assumed treatment relationship shows limited differences between treatment arms, and AEs occurring more frequently (>10% difference) in arm A (fatigue, neutropenia, leukopaenia, nausea, diarrhoea, dyspnoea, alkaline phosphatase, headache) or arm B (ascites, asthenia, gastrointestinal pain or tenderness) were primarily limited to Grade 1–2 events (Table 2).

Six patients (three per arm) had serious events considered at least possibly treatment-related. Two patients had cerebrovascular accidents (stroke), one occurring after only one dose and the other one month after cycle 1. One patient developed disseminated intravascular coagulopathy after cycle 2 with Grade 4 thrombocytopenia, acute renal failure and fatal gastrointestinal haemorrhage. Another developed consumptive coagulopathy with Grade 4 thrombocytopenia after cycle 1 recovering within one week and workup revealing lower extremity deep venous thrombosis and sub-acute cerebral infarcts. One patient developed fever after cycle 3 with negative cultures but responded to antibiotics, while another patient with a history of severe infections developed fatal Gram-negative bacteremia during cycle 2; both had undergone recent biliary stent placements and were not neutropenic at time of event.

Overall, 20/58 (34%) patients (10 per arm) developed Grade >3 thrombocytopenia (four given platelets), 14 (11 Arm A, 3 Arm B; 24% overall) developed Grade $\geqslant 3$ neutropenia (four given cytokine support) and 11 (7 Arm A, 4 Arm B; 19% overall) developed Grade >3 anaemia (eight transfused). In patients with follow-up data, only four events (all thrombocytopenia) remained at Grade 4 levels >7 days, while all Grade 3 cytopaenias recovered to Grade 2 levels within 12 weeks. Grade $\geqslant 3$ cytopaenias generally increased with repeated cycles but Grade 4 occurrences generally remaining limited (Table 3).

Infections occurred in 11 (19%) patients, including four serious events [fatal septic entercolitis from pre-study pancreatectomy (Sump syndrome); fatal septic bacteremia from unidentified source; post-interventional Grade 3 acute cholangitis; Grade 3 pneumonia

responding to antibiotics]; and 10 Grade 1–2 events [upper respiratory infection (URI) × 4, urinary tract infection (UTI) × 3, superficial fungal infection × 2, pneumonia, Lyme disease). The fatal bacteremia was considered possibly-related although the patient had a history of severe infections and recent biliary stent placement; other infections were considered unrelated by the investigators. Furthermore, only three patients were neutropenic (700–900 cells/μL) at time of infection (pneumonia, UTI, URI).

Bleeding occurred in nine (16%) patients, including three serious events (fatal GI bleeding from consumptive coagulopathy, Grade 3 melena from concomitant medications, Grade 3 GI bleeding from underlying disease) and seven minor Grade 1 events (bruising × 4, epistaxis, haemorrhoids, conjunctival). Minor bruising was considered at least possibly study drug related, but the other bleeding events were all considered unrelated by the investigators, and only three patients had Grade 3–4 thrombocytopenia at time of event (consumptive coagulopathy, bruising × 2).

3.3. Efficacy

The median overall survival (OS) for all 58 patients was 2.7 months, with all patients now deceased. Kaplan–Meier survival curves (Fig. 1) showed improvement in Arm A versus B beginning at about 3 months, with the relative number of patients remaining alive in Arm A versus B then progressively increasing with time (hazard ratio [HR] 0.55, 95% CI: 0.29–0.86; $P = 0.017$, log-rank test). Median OS for Arm A versus B (Table 4) was only 2.7 versus 2.6 months overall, but increased to 7.9 versus 3.4 months for those patients who received multiple cycles (HR 0.32, $P = 0.004$), including three patients in Arm A surviving >1 year (one for 1.5 years, two for 2.0 years). OS generally increased with better performance status and lower

Table 2
Frequent adverse events regardless of attribution.[a]

Patients with adverse event	Arm A		Arm B	
	All Grades (%)	Grade ⩾3 (%)	All Grades (%)	Grade ⩾3 (%)
Laboratories				
Thrombocytopenia	62	21	52	17
Anaemia	45	14	38	10
Neutropenia	28	10	3	3
Leukopaenia	24	14	3	3
Alkaline phosphatase	24	3	10	0
Hyponatraemia	21	7	14	7
Aspartate aminotransferase	17	0	7	7
Lymphopaenia	14	10	17	10
Hyperbilirubinemia	14	3	21	3
Hyperglycaemia	14	3	14	7
Hypoalbuminaemia	14	0	3	3
Clinical events				
Fatigue	76	3	38	7
Nausea	41	0	24	3
Anorexia	31	0	24	7
Abdominal/gastrointestinal pain or tenderness	31	3	48	10
Constipation	28	0	28	3
Diarrhoea	28	0	10	0
Dyspnoea	28	7	14	0
Infection	24	7	17	7
Vomiting	21	3	28	3
Abdominal distension	17	0	7	0
Bleeding	17	3	14	7
Back pain	17	7	14	0
Cough	17	0	7	0
Dehydration	14	3	17	3
Headache	14	0	0	0
Hypertension	14	7	3	0
Fever	14	0	14	0
Pleural effusion	10	7	17	7
Peripheral oedema	10	0	14	0
Ascites	0	0	14	3
Asthenia	0	0	14	3

[a] Events occurring in >10% of the 29 patients in either treatment arm.

Table 3
Grade 3 and 4 haematological toxicity by treatment cycle.

Cycle	N	Thrombocytopenia		Neutropenia		Anaemia	
		Grade 3 N (%)	Grade 4 N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade 3 N (%)	Grade 4 N (%)
1	58	4 (7)	6 (10)	10 (17)	1 (2)	5 (9)	0 (0)
2	23	7 (30)	2 (9)	3 (13)	0 (0)	4 (17)	0 (0)
3–9	7	3 (43)	2 (29)	1 (14)	1 (14)	3 (43)	0 (0)

CA19-9 serum levels at study entry, and to a lesser degree with fewer prior therapies and smaller tumour burden estimated by summing lengths of index lesions (Table 4).

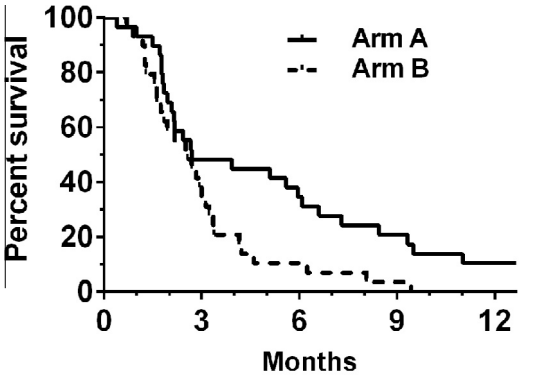
There was >25% disease control (PR + SD) in both treatment arms at interim evaluation, thus meeting the SWOG two-stage criteria to complete enrolment. By RECIST criteria, there were two PRs (both Arm A) and 22 SDs (10 Arm A, 12 Arm B) as best response, with other patients having progressed by first CT evaluation 4 weeks after cycle 1. Median OS for those with PR, SD and PD was 11.5, 5.1 and 1.8 months, respectively. Eleven patients had elevated CA19-9 levels at baseline that decreased with treatment, either 20–50% and considered a minor response ($N = 8$), or >50% and considered an objective response ($N = 3$). Median OS for patients with CA19-9 responses was 3.9 versus 2.5 months for the remaining population.

3.4. Immunogenicity

Five patients (1 arm A, 4 arm B) with baseline serum samples that were HAHA-negative (<50 ng/mL) became HAHA-positive after their first ($N = 3$) or second ($N = 2$) cycle, developing maximum titres of 135–21,611 ng/mL. These were isolated laboratory findings without event and of uncertain clinical significance.

4. Discussion

Patients with metastatic pancreatic cancer who seek additional treatment after two prior treatment regimens represent a select group of all patients with metastatic occurrence of this disease, since only a small minority of such patients currently receives further treatment [31]. Nonetheless, in this trial, 58 patients with metastatic pancreatic cancer and three median (2–7) prior chemotherapies were enrolled within 8 months. The rapidity of accrual reflects both the demand and the unmet need for treatment options beyond the second line as well as demonstrating the feasibility of conducting trials in this setting. The fact that all patients had received gemcitabine-containing regimens (21% with nab-paclitaxel), and 97% had received fluoropyrimidine-containing regimens (50%



Patients Alive at 3, 6, 9, and 12 Months					
	N	3	6	9	12
Arm A	29	14 (48.3%)	10 (34.5%)	6 (20.7%)	3 (10.3%)
Arm B	29	10 (34.5%)	3 (10.3%)	1 (3.4%)	0 (0%)

Fig. 1. Overall survival. Kaplan–Meier curves and time-point analyses over 12 months for all 29 patients in Arm A (^{90}Y-clivatuzumab tetraxetan combined with low-dose gemcitabine) and all 29 patients in Arm B (^{90}Y-clivatuzumab tetraxetan alone).

Table 4
Dependence of overall survival (OS) on treatment and patient factors.

	N	Median (range), months
Treatment		
Arm A, Overall	29	2.7 (0.4–23.9)
Single cycle	17	1.9 (0.4–11.0)
Multiple cycles	12	7.9 (3.9–23.9)
Arm B, Overall	29	2.6 (0.7–9.4)
Single cycle	18	1.7 (0.7–4.1)
Multiple cycles	11	3.4 (1.7–9.4)
Patient factors		
Karnofsky performance status		
90–100	24	4.0 (0.4–23.5)
70–80	34	2.0 (0.7–23.9)
Number of prior systemic treatments		
2	19	2.9 (0.4 –23.9)
3	18	3.1 (0.9–23.5)
>3	21	2.4 (0.7–17.5)
Sum of index lesions (cm)		
1.2–8.1	29	2.9 (0.7–23.5)
8.3–22.2	29	2.6 (0.4–23.9)
Serum CA19-9 (U/mL)		
⩽1257	29	3.9 (0.4–23.9)
>1257	28[a]	2.1 (0.7–8.4)

[a] Baseline CA19–9 unavailable in one patient.

with FOLFIRINOX), further underscores the importance of developing additional treatments for pancreatic cancer.

There were no infusion reactions and, as expected, cytopaenias (predominantly thrombocytopenia) were the only significant toxicities. Even in this population, these were mostly transient and reversible events, with infrequent haematologic support required, and the few infections or major bleeding events that occurred could be attributed to complications of underlying disease. Coagulopathy and thromboembolic events are known risks in advanced pancreatic cancer with 10–20% incidence rates reported in some studies [32], and while treatment-related myelosuppression may have exacerbated the two cases of consumptive coagulopathy that occurred, there is little evidence that treatment was involved in the two cerebrovascular accidents that occurred. Most other AEs were mild-moderate constitutional and gastrointestinal events also expected in advanced pancreatic cancer, and comparison of events between treatment arms showed no substantial differences. Although more limited than previously seen with ^{90}Y-clivatuzumab tetraxetan in less heavily treated patients [18,25], tumour response assessed by CT imaging or CA19-9 levels still showed that our treatment is active in this study, and the improvement of survival with better responses and patient risk factors also supported the consistency of therapeutic results in this advanced population. Thus, this combination approach appears to be an acceptable regimen in this advanced population.

Although median survival was only 2.7 months overall, survival progressively improved with time for patients receiving low-dose gemcitabine (48% versus 35% alive at 3 months, 35% versus 10% at 6 months, 21% versus 3% at 9 months and 10% versus 0% at 1 year). For patients receiving only one cycle, there was little difference between treatment arms, but with multiple cycles median OS increased for the group receiving gemcitabine (3.4 versus 7.9 months), including three patients surviving >1 year. Imbalances of age, KPS, serum CA19.9 levels, prior pancreatectomy and exposure to FOLFIRINOX seen in Table 1 might mean that patients in Arm A were possibly fitter or had better biologic factors that could also contribute to the better results seen for the group treated with gemcitabine. As with any repeated therapy, patients with less aggressive disease would also likely be expected to receive more cycles and do better, and dropouts occurring for other reasons could further complicate treatment interpretation. Since the percent of patients in each arm proceeding to receive multiple cycles was balanced in our study, combining low-dose gemcitabine with radioimmunotherapy appears more likely to be the primary explanation for the increased survival results seen in Arm A. However, this study was powered using prespecified criteria for treatment arm activity, not survival, and patients were alternated to the treatment arm assignment by the Sponsor. The interpretation of survival results is thus limited by the small sample size and imbalances between treatment arms of potential significance, and should be considered encouraging but preliminary.

This trial demonstrated the feasibility of performing clinical studies in metastatic pancreatic cancer patients after $\geqslant$2 prior chemotherapy regimens (3rd line and beyond). This is important, because the benefits of current second-line therapies appear modest, at the cost of drug toxicity [6,8–10], and increased availability of new combination regimens such as FOLFIRINOX and Abraxane/gemcitabine may also influence patient's ability to choose, tolerate or respond to further therapy. Acknowledging the limitations of this study, ^{90}Y-clivatuzumab tetraxetan combined with low-dose gemcitabine may be useful in this difficult-to-treat population, and a Phase III trial of this combination is now underway in this setting. (ClinicalTrials.gov Identifier: NCT01956812.)

Funding

Immmunomedics, Inc. (Sponsor) provided research support to all institutions conducting this study.

Conflict of interest statement

H.H., R.M.S., W.A.W. and D.M.G. are employed by or have financial interests in Immunomedics. The other authors have declared no conflicts of interest.

Acknowledgements

We thank Steven Hamburger, PhD, for a critical review of the manuscript, and all patients, referring physicians and clinical study staff who participated in this study.

References

[1] Hidalgo M. Pancreatic cancer. N Engl J Med 2010;362:1605–17.
[2] Burris 3rd HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15:2403–13.
[3] Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960–6.
[4] Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691–703.

[5] Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817–25.
[6] Rahma OE, Duffy A, Liewehr DJ, Steinberg SM, Greten TF. Second-line treatment in advanced pancreatic cancer: a comprehensive analysis of published clinical trials. Ann Oncol 2013;24:1972–9.
[7] Oettle H, Riess H, Stieler JM, Heil G, Schwaner I, Seraphin J, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. J Clin Oncol 2014;32:2423–9.
[8] Von Hoff D, Li CP, Wang-Gillam A, Bodoky G, Dean A, Jameson G, et al. NAPOLI-1: randomized phase 3 study of MM-398 (NAL-IRI), with or without 5-fluorouracil and leucovorin, versus 5-fluorouracil and leucovorin, in metastatic pancreatic cancer progressed on or following gemcitabine-based therapy. Ann Oncol 2014;25(Suppl 2):ii105–6.
[9] National Comprehensive Cancer Network. NCCN Clinical practice guidelines in oncology. Pancreatic adenocarcinoma, version 2.2014. <www.nccn.org>.
[10] Seufferlein T, Bachet JB, Van Cutsem E, Rougier P. Pancreatic adenocarcinoma: ESMO–ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(suppl 7):vii33–40.
[11] Almhanna K, Kim R. Second-line therapy for gemcitabine-refractory pancreatic cancer: is there a standard? Oncology (Williston Park) 2008;22:1176–83.
[12] Koay EJ, Truty MJ, Cristini V, Thomas RM, Chen R, Chatterjee D, et al. Transport properties of pancreatic cancer describe gemcitabine delivery and response. J Clin Invest 2014;124:1525–36.
[13] Gold DV, Lew K, Maliniak R, Hernandez M, Cardillo T. Characterization of monoclonal antibody PAM4 reactive with a pancreatic cancer mucin. Int J Cancer 1994;57:204–10.
[14] Gold DV, Karanjawala Z, Modrak DE, Goldenberg DM, Hruban RH. PAM4-reactive MUC1 is a biomarker for early pancreatic adenocarcinoma. Clin Cancer Res 2007;13:7380–7.
[15] Gold DV, Goggins M, Modrak DE, Newsome G, Liu M, Shi C, et al. Detection of early-stage pancreatic adenocarcinoma. Cancer Epidemiol Biomarkers Prev 2010;19:2786–94.
[16] Gold DV, Newsome G, Liu D, Goldenberg DM. Mapping PAM4 (clivatuzumab), a monoclonal antibody in clinical trials for early detection and therapy of pancreatic ductal adenocarcinoma, to MUC5AC mucin. Mol Cancer 2013;12:143. http://dx.doi.org/10.1186/1476-4598-12-143.
[17] Cardillo TM, Ying Z, Gold DV. Therapeutic advantage of ^{90}yttrium- versus ^{131}iodine-labeled PAM4 antibody in experimental pancreatic cancer. Clin Cancer Res 2001;7:3186–92.
[18] Gold DV, Cardillo T, Vardi Y, Blumenthal R. Radioimmunotherapy of experimental pancreatic cancer with ^{131}I-labeled monoclonal antibody PAM4. Int J Cancer 1997;71:660–7.
[19] Gulec SA, Cohen SJ, Pennington KL, Zuckier LS, Hauke RJ, Horne H, et al. Treatment of advanced pancreatic carcinoma with ^{90}Y-clivatuzumab tetraxetan: a phase I single-dose escalation trial. Clin Cancer Res 2011;17:4091–100.
[20] DeNardo GL, Schlom J, Buchsbaum DJ, Meredith RF, O'Donoghue JA, Sgouros G, et al. Rationales, evidence, and design considerations for fractionated radioimmunotherapy. Cancer 2002;94:1332–48.
[21] Morgan MA, Parsels LA, Maybaum J, Lawrence TS. Improving gemcitabine-mediated radiosensitization using molecularly targeted therapy: a review. Clin Cancer Res 2008;14:6744–50.
[22] Pauwels B, Korst AE, Lardon F, Vermorken JB. Combined modality therapy of gemcitabine and radiation. Oncologist 2005;10:34–51.
[23] Cardillo TM, Blumenthal R, Ying Z, Gold DV. Combined gemcitabine and radioimmunotherapy for the treatment of pancreatic cancer. Int J Cancer 2002;97:386–92.
[24] Gold DV, Schutsky K, Modrak D, Cardillo TM. Low-dose radioimmunotherapy (^{90}Y-PAM4) combined with gemcitabine for the treatment of experimental pancreatic cancer. Clin Cancer Res 2003;9:3929S–37S.
[25] Gold DV, Modrak DE, Schutsky K, Cardillo TM. Combined ^{90}yttrium-DOTA-labeled PAM4 antibody radioimmunotherapy and gemcitabine radiosensitization for the treatment of a human pancreatic cancer xenograft. Int J Cancer 2004;109:618–26.
[26] Ocean AJ, Pennington KL, Guarino MJ, Sheikh A, Bekaii-Saab T, Serafini AN, et al. Fractionated radioimmunotherapy with ^{90}Y-clivatuzumab tetraxetan and low-dose gemcitabine is active in advanced pancreatic cancer: a phase 1 trial. Cancer 2012;118:5497–505.
[27] Ocean AJ, Guarino MJ, Pennington KL, Springett GM, Gulec SA, Bekaii-Saab TS, et al. Activity of fractionated radioimmunotherapy (RAIT) with ^{90}Y clivatuzumab tetraxetan (^{90}Y-hPAM4) plus gemcitabine (Gem) in advanced pancreatic cancer (APC): Final results from a two-part study. J Clin Oncol 2012;30 [suppl 4; abstr 227].
[28] National Cancer Institute (NCI). Common terminology criteria for adverse events (CTCAE) version 4.0. <http://evs.nci.nih.gov/ftp1/CTCAE>.
[29] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors (RECIST guidelines). J Natl Cancer Inst 2000;92:205–16.
[30] Southwest Oncology Group Statistical Center. Two stage program. <https://www.swogstat.org/stat/public/twostage.htm>.
[31] Smyth EN, Bapat B, Ball DE, André T, Kaye JA. Metastatic pancreatic adenocarcinoma treatment patterns, health care resource use, and outcomes in France and the United Kingdom between 2009 and 2012: A retrospective study. Clin Ther 2015;37(6):1301–16. http://dx.doi.org/10.1016/j.clinthera.2015.03.016.
[32] Lyman GH, Eckert L, Wang Y, Wang H, Cohen A. Venous thromboembolism risk in patients with cancer receiving chemotherapy: a real-world analysis. The Oncologist 2013;18:1321–9.