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^{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*

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* *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).

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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.