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Multicenter Study of Radiosensitizing Gemcitabine Combined with Fractionated Radioimmunotherapy for Repeated Treatment Cycles in Advanced Pancreatic Cancer

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BACKGROUND

- For pancreatic cancer, survival remains dismal due to lack of early detection and effective treatment.
- Anti-mucin antibody PAM4 is highly sensitive for pancreatic adenocarcinoma & precancerous lesions, but negative for normal pancreas or pancreatitis
- A highly specific/sensitive immunohistochemistry stain and a serum assay are in development for early detection & diagnosis of pancreatic cancer
- In advanced pancreatic cancer, a single dose of ^{90}Y-labeled humanized PAM4 (^{90}Y-hPAM4; ***clivatuzumab tetrexetan***) had several transient reductions of lesions. Bone marrow toxicity limited the maximum dose to 20 mCi/m^2
- Fractionated once-weekly radioimmunotherapy may deliver higher total ^{90}Y doses, based on experience in external radiotherapy & with other antibodies
- Combination therapy with gemcitabine may be more effective, and it is also a radiosensitizer
- ^{90}Y-PAM4 itself was more potent in pre-clinical studies, but combined with gemcitabine, it increased antitumor activity *(Gold et al., Clin Cancer Res 2003;9:3929s-37s, Int J Cancer 2004;109:618-26)*
- A low-dose of 200 mg/m^2 gemcitabine was tolerated with external radiotherapy (*Pauwels et al., Oncologist 2005;10:34-51)*
- This Phase Ib study was undertaken to evaluate repeated treatment cycles of fractionated radioimmunotherapy of clivatuzumab tetraxetan plus low-dose gemcitabine in advanced pancreatic

STUDY POPULATION

- Adults, pancreatic adenocarcinoma, histologically or cytologically confirmed
- Surgically inoperable disease, locally advanced or metastatic (prior incomplete resection allowed)
- Treatment naïve (no prior chemotherapy, radiotherapy or investigational agent)
- KPS ≥ 70 %, expected survival ≥ 3 months
- Hemoglobin > 12 g/dL, ANC > 2K/µl, platelets > 150K/µl, off support
- Creatinine and bilirubin ≤ 1.5 X IULN, AST and ALT ≤ 2.0 X IULN
- No bulky disease (any single mass >10 cm) or CNS involvement
- Prior radiation <3,000 cGy to liver, <2,000 cGy to lungs and kidneys, prior radiation field <30% red marrow.
- Other standard criteria

4-WEEK TREATMENT CYCLE

- Week 1: ^{111}In-hPAM4 dose, followed at least 2 days later by gemcitabine dose
- Weeks 2, 3, 4: ^{90}Y-hPAM4 dose, followed at least 2 days later by gemcitabine dose
- Radiolabeled-hPAM4: slow push over 10 min
- Gemcitabine: IV over 30 min

DOSE LEVELS

Dose Level	Weekly x 3 ^{90}Y Dose	Weekly x 4 Gemcitabine
1	6.5 mCi/m^2	200 mg/m^2
2	9.0 mCi/m^2	200 mg/m^2
3	12.0 mCi/m^2	200 mg/m^2
4	15.0 mCi/m^2	200 mg/m^2

STUDY DESIGN

Dose Level Escalation

- 3 + 3 design
- Heme DLT: Grade 4 Hgb, plts, or ANC >7 days, or not recovered to Grade 1 by 12 weeks (transfusions or growth factors allowed).
- Non-heme DLT: Grade 4 toxicity, any duration, or Grade 3 >5 days

Procedures Per Cycle

- Serial ^{111}In-hPAM4 images for tumor targeting, biodistribution, dosimetry
- Serial ^{111}In serum counts for pharmacokinetics
- CT, PET/CT (if available, with PET continued only for PET avid tumors), CA19.9 levels
- Safety: AEs, routine safety labs

Repeat Treatment Cycle Elgibility

- Acceptable biodistribution and cycle radiation dose estimates of <3,000 cGy (liver), <2,000 (lungs, kidneys), and <300 cGy (red marrow)
- No DLT or disease progression after prior cycle
- Hematologic toxicity recovered to Grade 1 (~ 8 weeks).
- Discontinue in event of clinical symptoms, delayed radiation toxicity, or lab abnormalities

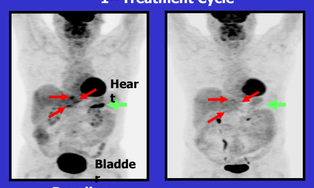
Treatment response assessments

- CT: RECIST criteria
- PET: visual impression and SUVs
- CA19.9: serum levels

DEMOGRAPHICS/BASELINE DATA (N=11)

Sex (male/female)	8/3
Age (yrs), median (range)	60 (47-72)
ECOG: 0, 1	7, 4
Stage III (Locally advanced) IV (Metastatic)	 1 10
Hematology, median (range) Hemoglobin (g/dL) Neutrophils (K/µl) Platelets (K/µl)	 13.2 (9.9-15.7) 3.9 (3.2-8.4) 270 (154-349)
CA-19.9, median (range) Elevated >1000 U/mL	3938 (3.1 – 13,692) 9 7
^{90}Y Dose Level 6.5 mCi/m^2 9.0 mCi/m^2 12.0 mCi/m^2 15.0 mCi/m^2	 4 4 3 Not yet enrolling

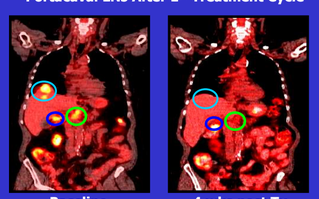
Pt 181-001. PET 3D Images Show Response of Pancreatic Primary and 3 Liver Metastases After 1st Treatment Cycle



Baseline CA19.9 = 1297

4 wks post Tx CA19.9 = 77

Pt 181-002. PET/CT Fusion Images Show Response of Primary, Large Liver Lesion and Portacaval LNs After 1st Treatment Cycle



Baseline

4 wks post Tx

TREATMENT RESPONSES

Patient	Cycles	RECIST	Post-Treatment Outcome
Dose Level 1 (6.5 mCi/m^2 ^{90}Y-hPAM4, 200 mg/m^2 gemcitabine)			
181-001	4	SD	CT lesions decreased 29% , PET turned neg., CA19.9 decreased from 1298 to 78 post 1st cycle. Good performance status for 10 mo, then POD. Expired, 13.5 mo after starting 1st cycle.
181-002	3	PR	CT lesions decreased 46% after 2nd cycle, PET turned neg (CA19.9 near zero at baseline). Good performance status for 9 mo., then POD. Expired, 12.2 mo. after starting 1st cycle.
073-001	1	POD	POD 4 wks p TX. Expired 3.0 mo. after starting 1st cycle.
206-001	1	POD	POD 4 wks p TX. Expired 1.6 mo. after starting 1st cycle.
Dose Level 2 (9.0 mCi/m^2 ^{90}Y-hPAM4, 200 mg/m^2 gemcitabine)			
181-003	1	POD	POD 4 wks p TX. Expired 5.4 mo. after starting 1st cycle.
073-002	2	SD	CT & PET both stable post 1st cycle, CA19.9 decreased slightly from 46 to 36. POD after 2nd cycle. Started cisplatin/gemcitabine.
206-002	1	N/A	Withdrew due to splenic abscess prior to completing 1st cycle. Inevaluable for response assessment.
206-003	1	POD	POD 4 wks after TX. Started gemcitabine.
Dose Level 3 (12.0 mCi/m^2 ^{90}Y-hPAM4, 200 mg/m^2 gemcitabine)			
181-004	1	PR	Lesions 33% decreased 8 wks after TX (Not PET avid, normal CA19.9 at baseline). Response ongoing.
206-004	1	PR	Lesions 37% decreased @ 8 wks. CA19.9 decreased 8450 to 1565. (PET not done). Response ongoing.
076-001	1	TBD	Both CT and PET lesions decreased 4 wks after TX, CA19.9 decreased 11,500 to 450. Response ongoing

HEMATOLOGICAL TOXICITY

Patient	Cycle #	Nadir Grade			Grade 4 >7 days?	Recovered to Grade 1 by 12 wks?	Heme Support
		Hgb	Plts	ANC			
Dose Level 1 (6.5 mCi/m^2 ^{90}Y-hPAM4, 200 mg/m^2 gemcitabine)							
181-001*	1	1	1	1	No	Yes	None
	2	2	2	2	No	Yes	None
	3	2	2	2	No	Yes	None
	4	2	3	2	No	Yes	None
181-002‡	1	2	0	1	No	Yes	2 units RBC
	2	2	2	3	No	Yes	2 units RBC
	3	2	4	2	YES	NO	Multiple RBC/plt transfusions, but Plts remained grade 4 until hospice.
073-001	1	2	0	0	No	Yes	erythropoietin, 2 units RBC
206-001	1	3	3	0	No	N/A	2 units RBC x 4. No f/u on recovery (hospice at wk 4)
Dose Level 2 (9.0 mCi/m^2 ^{90}Y-hPAM4, 200 mg/m^2 gemcitabine)							
181-003	1	2	0	0	No	Yes	erythropoietin
073-002§	1	1	0	2	No	Yes	None
	2	3	4	0	No	Yes	G CSF, 2 units RBC. Gem reduced 75% last dose.
206-002	1	0	2	0	N/A	N/A	None, but pt did not complete TX (splenic abscess)
206-003	1	2	3	0	No	Yes	None
Dose Level 3 (12.0 mCi/m^2 ^{90}Y-hPAM4, 200 mg/m^2 gemcitabine)							
181-004	1	1	1	2	No	Yes	None
206-004	1	1	3	4	No	Yes	None
076-001	1	1	2	2	No	N/A	None. Recovery ongoing.

*Started cycle #2 7 wks after completing cycle #1, cycle #3 14 wks after #2, and cycle #4 10 wks after #3.
‡Started cycle #2 5 wks after completing #1, and cycle #3 21 wks after #2. §Started cycle #2 7 wks after completing #1.

SAFETY

- **Infusion Reactions to Radiolabeled hPAM4:** None
- **Treatment Completion:** All patients completed their 1st cycle, except one pt who withdrew with splenic abscess. Three pts completed 1-3 additional cycles, without ^{90}Y dose reductions, but all had their last gemcitabine dose held or reduced
- **Serious Events:** 5 pts had SAEs (pneumonia, bacteremia, anemia prior to treatment, splenic abscess, mental status changes after anti-anxiety overmedication). Two patients had other non-hematologic grade 3 or 4 events (hypokalemia, biliary obstruction)
- **Infections:** Four pts had infections, including 2 treated with IV antibiotics (pneumonia, bacteremia) and the others with oral medications (herpes zoster, UTI, superficial lesions, oral thrush, unspecified infection)
- **Bleeding or Other Significant Clinical Events:** None

SUMMARY

- Half of the patients (5/10, 50%) showed evidence of disease shrinkage or stabilization, with 3 patients (30%) having partial responses by CT-based RECIST criteria
- Two patients (20%) had good performance status and disease stabilization over course of 3-4 cycles, with both surviving >1 year from start of treatment
- Metabolic imaging (PET) and biomarker (CA19.9) decreases supported evidence of anti-tumor activity
- Therapy was well tolerated. As expected, only hematologic toxicity has been significant:
  - One DLT occurred after the 3rd cycle at the 1st dose level, with development of refractory grade 4 thrombocytopenia
  - Hematological toxicity was otherwise manageable and reversible, even after 4 cycles

CONCLUSIONS

- **There was evidence of therapeutic activity, and possible clinical benefit, in pancreatic cancer with hematological toxicity as the only significant side effect.**
- **Repeated 4-week cycles of fractionated radioimmunotherapy with clivatuzumab tetraxetan plus low-dose gemcitabine appears promising as 1st line therapy for advanced disease, and dose escalation is continuing.**