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A Phase I Study of a Combination of Yttrium-90 labeled Anti-CEA Antibody and Gemcitabine in Patients with CEA Producing Advanced Malignancies

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Abstract

Purpose—To determine the maximum tolerated dose of combined therapy using an yttrium-90 labeled anti-CEA antibody with gemcitabine in patients with advanced CEA producing solid tumors.

Experimental Design—The chimeric human/murine cT84.66 is an anti-CEA intact IgG1, with high affinity and specificity to CEA. This was given at a fixed yttrium-90 labeled dose of 16.6 mCi/m² to subjects who had an elevated CEA in serum or in tumor by immunohistochemistry. Also required was a tumor that imaged with an ¹¹¹In labeled cT84.66 antibody. Patients were treated with escalating doses of gemcitabine given intravenously over 30 minutes on day 1 and 3 after the infusion of the yttrium-90 labeled antibody. Patients were treated in cohorts of 3. The maximum tolerated dose was determined as the highest level at which no more than 1 of 6 patients experienced a dose limiting toxicity.

Results—A total of 36 patients were enrolled, and all but one had prior systemic therapy. The maximum tolerated dose of gemcitabine in this combination was 150mg/m². Dose limiting toxicities at a gemcitabine dose of 165mg/m² included a grade 3 rash and grade 4 neutropenia. One partial response was seen in a patient with colorectal cancer, and 4 patients had a > 50% decrease in baseline CEA levels associated with stable disease. Human antichimeric antibody responses were the primary reason for stopping treatment in 12 patients.

Conclusions—feasibility of combining gemcitabine with an yttrium-90 labeled anti-CEA antibody is demonstrated with preliminary evidence of clinical response.

Keywords

Radioimmunotherapy; gemcitabine; CEA

Introduction

Radiolabeled monoclonal antibodies have been studied as a possible treatment for human malignancies. Monoclonal antibodies have shown potential to act as therapeutic agents and have shown efficacy especially with hematologic malignancies as evidenced by the approval of rituximab and more recently of yttrium-90-labeled ibritumomab tiuxetan for low-grade non-Hodgkin's lymphoma (1-3). Solid tumors have been treated with immune-guided radiotherapy, albeit with lower response rates due to complex factors related to tumor targeting, tumor vasculature, vascular permeability, and therapeutic index (4,5).

Radiosensitization has been a strategy to increase the efficacy of immune-guided radiotherapy. A recent study has demonstrated the feasibility of combining a 120-hour infusion of 5-fluorouracil with the anti-CEA yttrium-labeled IgG1 murine monoclonal antibody designated T84.66 (6). Stable disease and 2 mixed responses were seen. Other studies have also demonstrated the feasibility of this approach (7).

Gemcitabine is currently FDA approved for a variety of tumors including pancreas, breast, ovarian and lung cancer. Laboratory studies have demonstrated strong radiosensitization properties possibly due to inhibition of ribonucleotide reductase, effects on deoxyribonucleotide pool composition, and to incorporation into DNA with subsequent early chain termination. Preclinically radiosensitization was greatest when cells were exposed to gemcitabine between 2 to 24-48 hours before radiation. Radiosensitization was observed for approximately 2 days after exposure (8,9). The maximum radiosensitization correlated with a drop in adenosine diphosphate and occurred at relatively low gemcitabine doses (10). Gemcitabine has also demonstrated significant radioenhancing properties with immune-guided radiotherapy in vivo (11-13).

Clinical studies combining gemcitabine with radiation have confirmed potent radiosensitizing properties. In head and neck patients, doses of gemcitabine needed de-escalation from a starting weekly dose of 300 mg/m² (10). At doses of 30 mg/m², gemcitabine triphosphate levels were in the same range as with the 150 mg/m² dose. The levels of dFdCTP in biopsy specimens were similar to those seen in in vitro radiosensitizing experiments suggesting that significant interactions were occurring at these dose levels. Other studies report tolerance of radiation and gemcitabine in upper gastrointestinal tumors, also with less than full systemic doses (14,15). Studies with lung cancer have also been reported, albeit with increased esophagitis (16).

Based on this information we designed this study to determine the tolerance of a combination of gemcitabine and ⁹⁰Y-T84.66 anti-CEA antibody. Gemcitabine was given in two equal doses 48 hours apart to maximize radiation sensitization with starting doses based on previous phase I data on twice weekly dosing schedules (15,17)

Material and Methods

Antibody Production and Conjugation

Human/murine cT84.66 is an anti-CEA intact IgG1, with high affinity ($K_A = 1.16 \times 10^{11} \text{ M}^{-1}$) and specificity to CEA. Details of its production, characterization, purification, conjugation, and radiolabeling have been reported previously (18). Briefly, for this study, cT84.66 was conjugated to isothiocyanatobenzyl DTPA. Preparation of the radiolabeled dose involved incubation of ¹¹¹In at a ratio of 1 mCi to 1 mg and yttrium (⁹⁰Y) at a ratio of 10 mCi to 1 mg followed by size exclusion HPLC purification. All administered doses demonstrated radiolabeling > 90%, endotoxin levels < 1 unit/ml, and immunoreactivity > 95%. The final vial lot of purified conjugated antibody met standards set by the FDA. Investigational New Drug applications for ¹¹¹In-DTPA-cT84.66 and ⁹⁰Y-DTPA-cT84.66 are currently on file with the FDA.

Clinical Trial Design

The primary objective of this trial was determine the maximum tolerated dose (MTD) and associated toxicities of gemcitabine in combination with ⁹⁰Y-DTPA-cT84.66. Patients were enrolled in cohorts of 3 with escalating doses of gemcitabine (Table 1). Gemcitabine was administered intravenously over 30 minutes beginning on day 1 and on day 3 after infusion of the therapeutic dose of ⁹⁰Y-DTPA-cT84.66 (16.6 mCi/m²). This therapeutic dose was determined in a previous phase I study of ⁹⁰Y-DTPA-cT84.66 as single agent (19).

Gemcitabine dose escalation continued until a dose-limiting toxicity (DLT) was noted defined as any treatment-related grade III non-hematologic toxicity not reversible to grade II or less within 24 hours, or any grade IV toxicity. Up to 3 cycles of therapy were allowed with DLTs determined based on first cycle tolerance. Toxicity was graded using the NCI common toxicity criteria (CTC) version 2.0. Further patients were entered and further dose escalation continued if no further DLTs were noted in a completed cohort of 6 patients. The MTD was defined as the highest level at which ≤ 1 of 6 patients experienced a DLT. Biodistribution, tumor targeting, absorbed radiation dose estimates, and clearance of the antibody were also evaluated through serial blood samples, 24-h urine collection, and nuclear scans performed at time points out to 7 days after antibody infusion.

The following studies were performed before antibody administration: complete blood count and platelet count; complete metabolic panel; creatinine clearance; electrocardiogram; pulmonary function tests; urinalysis; serum HIV testing; serum pregnancy testing if indicated; plasma CEA levels; and serum human anti-chimeric antibody (HACA) response. Additionally, chest X-ray, and CT scans of relevant anatomical locations corresponding to areas of metastatic or suspected metastatic disease were obtained. If clinically indicated, bone scan, magnetic resonance imaging, or positron emission tomography images were also performed to assess disease location and extend. All blood studies were done within 2 weeks and all radiological studies within 6 weeks of antibody infusion.

For the initial cycle of therapy, each patient first received an imaging dose of 5 mCi/5 mg ^{111}In -DTPA-cT84.66, which was used to track antibody activity and evaluate tumor targeting. The therapeutic dose of ^{90}Y -DTPA-cT84.66 was subsequently given within 2 weeks and included 5 mCi of indium-111 labeled ^{90}Y -DTPA-cT84.66. Initially, a test dose of 100 μg of radiolabeled antibody was administered i.v. over 5 min. After 15 min., if there were no side effects, the remainder of the antibody was administered over 30 minutes. Subsequent cycles of therapy were not preceded by a separate imaging infusion. Serial blood samples were taken for pharmacokinetics at 30 min, 1 hr, 4 hr, and at each scan time after antibody infusion. Urine collections (24 h) were done daily for 5 consecutive days after antibody administration for pharmacokinetic analysis. Blood and urine samples were counted for ^{111}In activity on a Packard gamma counter (Model 5530; Packard, Inc., Downers Grove, IL) with a window setting of 150-500 keV and were processed on a size exclusion HPLC Superose 6 column. Planar and whole body imaging studies were performed at 6 h, 24 h, 48 h, and 4-7 days after antibody administration using a Toshiba dual head 7200 camera with SPECT capability. In all cases, 20% energy windows were set over each of the two γ -ray energies of ^{111}In . A medium energy high-resolution collimator was used throughout. Scan speed of 20 cm/min over a distance of 200 cm was used for the whole body imaging. SPECT scans were performed of relevant areas of 48 h and 4-7 days after antibody administration.

Gemcitabine in escalating doses was given intravenously on day 1 over 30 minutes, followed within 5 hours by the therapeutic dose of ^{90}Y -DTPA-cT84.66, which was 16.6 mCi/m² in all patients. A second dose of gemcitabine was given on day 3.

DTPA as a calcium salt was given at a dose of 250 mg/m²/24 hours in divided doses every 12 hours for 3 days after the dose of ^{90}Y -DTPA-cT84.66 in an effort to reduce hematologic toxicity. This approach has been used in previous trials including the trial that established the MTD of ^{90}Y -DTPA-cT84.66 as monotherapy (19). A previous trial using ^{90}Y -DOTA-c84.66 documented an increase in hematologic toxicity with the omission of the Ca-DTPA infusion(20).

Radiological studies, including CT scans, were repeated at 5-6 weeks post-therapy to assess tumor response. Response criteria were defined as follows: complete response, disappearance of all measurable and evaluable disease and no new lesions; partial response, $\geq 50\%$ decrease from baseline in the sum of the products of perpendicular diameters of all measurable lesions, with no progression of evaluable disease or development of new lesions; stable disease, does not qualify for complete response, partial response, or progression; progressive disease, 25% increase in the sum of products of measurable lesions over the smallest sum observed, or reappearance of any lesion that had disappeared, or appearance of any new lesion/site.

HACA Response

Serum HACA responses to cT84.66 and cT84.66-DTPA were assayed before infusion and at 2 weeks, 1, 3, and 6 months post-infusion using a double capture solid-phase quantitative, radioimmunoassay as described previously (18). Serum samples incubated with ^{111}In -DTPA-cT84.66 were also examined by size exclusion HPLC using two tandem Superose 6 columns to detect possible immune responses not found by radioimmunoassay. Patients were felt to have anti-idiotypic response if serum samples were positive by HPLC assay but were negative by radioimmunoassay.

Pharmacokinetic Analysis and Absorbed Dose Estimates

Blood and urine samples were counted for ^{111}In activity on a gamma counter and were processed on a HPLC size-exclusion Superose 6 column. Samples containing both ^{111}In and ^{90}Y were counted sequentially in γ and β well counters. In the latter case, Cerenkov radiation was used with quench correction to determine the amount of ^{90}Y present. Samples were homogenized in aqueous media and bleached before counting. Standards were used to calibrate the absolute accuracy of the counting systems.

For those organs seen in both projections, ^{111}In activity in normal organs was estimated using parallel-opposed nuclear images to construct the geometric mean uptake as a function of time. Otherwise, single view images were acquired. All resultant curves demonstrating ^{111}In activity versus time were corrected for background and patient attenuation. Attenuation was estimated using each patient's CT scans and attenuation coefficients obtained from a separate series of experiments involving gamma camera efficiency in counting a planar ^{111}In phantom source as a function of tissue-equivalent absorber thickness. Given the geometric mean or single view uptake values and measured blood and urine activity, a five-compartment modeling analysis was performed to estimate residence times for ^{111}In and ^{90}Y activity in blood, urine, liver, and whole body. Details of this compartmental model have been published previously (21). ^{90}Y radiation doses to normal organs based on biodistribution of ^{111}In -cT84.66 were estimated with the medical internal radiation dose method (22) using S values obtained from the MIRDDOSE3 program (23). Doses were calculated using male and female phantom organ sizes in these estimates. As previously reported, ^{90}Y -DTPA-cT84.66 and ^{111}In -DTPA-cT84.66 biodistributions were comparable in the mouse model (24). Red marrow radiation dose estimates were performed using the American Association of Physicists in Medicine algorithm (25) based on blood residence times determined from the five compartmental model.

Tumor absorbed radiation doses were estimated using ^{111}In uptake versus time curves determined from serial nuclear imaging data. Regions of interest were drawn around each tumor lesion, and the conjugate view method (26) was used to estimate activity. Trapezoidal interpolation was used to integrate the time activity curve and estimate residence time. CT scans were used to define tumor volume as well as the effective attenuation factor for the conjugate view method. For lesions not clearly defined by CT scans, nuclear medicine

region of interest (length and width) was used to estimate the tumor volume, assuming an ellipse with the third dimension defined by the geometric mean of the length and width. Absorbed fraction was a function of tumor size and determined via separate Monte Carlo simulation. Edge effects were thus taken into account (27). Uniform uptake was assumed within the tumor. This methodology still uses the medical internal radiation dose strategy but requires that we compute the effective β loss caused by the finite range of ^{90}Y β radiation (28) using the formula:

$$\beta \text{ dose} = 2.12 E_{\beta} \text{ AUC}(\text{tumor}) * \text{absorbed fraction} / (\text{tumor mass}),$$

where E_{β} is the mean β energy of ^{90}Y or 0.93 MeV, area under the curve (residence time) is in hours and tumor mass is in grams.

Results

A total of 36 patients were enrolled. The majority of patients were diagnosed with colorectal cancer and other gastrointestinal malignancies and all but one had previous systemic treatment (Table 2). Four patients did not image with ^{111}In -DTPA-cT84.66 and no further treatment was given except in one case. This one patient was initially felt to image at the right adrenal gland, a site of known disease. However, it was subsequently determined that imaging represented a dilated gallbladder and a false positive on target and the patient received no further therapy beyond the first course.

The MTD level was established at a gemcitabine dose of 150 mg/m². Toxicities at one dose level above this (165 mg/m²) included grade 3 rash and grade 4 hematologic. Grade 3 rash was noted in a 53 year old female with metastatic pancreatic cancer who had had prior treatment with ifosfamide and etoposide as well as gemcitabine and capecitabine. The patient developed a pruritic erythematous rash over the chest, back, abdomen and extremities beginning on day 3 after administration of the ^{90}Y -DTPA-cT84.66 and resolved over the next 2 weeks. The patient had stable disease after the first course, but developed a HACA reaction and no further protocol therapy was given. The second patient developed grade 4 neutropenia but recovered uneventfully. This patient was a 76 year old female with stage IV non-small cell lung cancer with no previous radiation, but with previous systemic therapy including carboplatin/paclitaxel, carboplatin/docetaxel, pemetrexed, and gemcitabine.

Three of 36 patients completed the protocol maximum of 3 treatment cycles with four further patients completing 2 cycles. Twelve patients developed a HACA response precluding further therapy, all after the first treatment. Reasons for stopping therapy in 33 treated patients are listed in Table 3 with progressive disease or HACA being the most common.

The most frequent first cycle toxicities were hematologic. There was a trend for more leucopenia with increasing dose of gemcitabine with scattered instances of thrombocytopenia. Rash was also seen at various levels, but reached a grade 3 DLT level with a gemcitabine dose of 150 mg/m². Rash occurred between day 1-5, and in all cases resolved when treatment was stopped. Other toxicities, including nausea, fluid retention, fever or pulmonary toxicity were not seen. See Table 4 for further details.

A 59 year old female patient with colon cancer with pelvic and peri-pancreatic disease had a partial response after the first cycle of treatment and received 2 treatment cycles with a gemcitabine dose level of 45 mg/m². Her CEA level was stable during treatment staying within 15% of baseline. She had been diagnosed with T3N2 colon cancer 4 years earlier and

had received 1 year of adjuvant 5-fluorouracil. Subsequent treatment for recurrent disease included capecitabine, irinotecan, 5-fluorouracil and leucovorin (IFL), capecitabine/gemcitabine, as well as post-surgical radiation to a mass causing left hydronephrosis.

CEA levels were tabulated and correlated with clinical outcome. Progressive disease was noted in 6 of 7 patients with a 50% or greater rise in CEA, and stable disease was seen in all 4 cases with a CEA decrease of more than 50%.

Individual tumor radiation doses were estimated in cases where a clear delineation of a target lesion was possible, and responses for each of these lesions were recorded (Table 5, 6). Lesions where a partial response was noted had a higher average dose (8702 ± 1411 rad), but a reverse trend was seen in comparing stable (2834 ± 5763) and progressive lesions (5872 ± 4216), with large standard deviations in each case. Estimated organ and total body doses are similar to previous reports (Table 7) (19). Tumor size with estimated Y-90 dose is presented in Table 5. When doses are tabulated by tumor volumes, the tumors with the highest dose included those below 10 cc with all tumors receiving a dose greater than 100 rad/mCi in this size range (Fig 1).

Discussion

This study demonstrates the feasibility of combining gemcitabine with the ^{90}Y -DTPA-cT84.66 anti-CEA antibody. The MTD was defined at a gemcitabine dose of 150 mg/m^2 given on day 1 and 3 of radioimmunotherapy. Overall the primary toxicity was hematologic, which was well tolerated with resolution before 6 weeks and with no instances of neutropenic fever.

Rash was noted in several patients at several dose levels. This rash occurred between 1 to 5 days after initiation of treatment and resolved within 1 to 2 weeks. Rash has been noted with single agent gemcitabine in the past and it is possible that its occurrence could be related to gemcitabine alone (29). However interaction with radiation and skin toxicity has been noted with gemcitabine in the context of radiation recall (30) and with increased skin toxicity during radiation (10). It is difficult to determine if the skin toxicity is clearly greater than what might be caused by gemcitabine alone due to the small number of cases, but an interaction is possible. Rash has also been reported with immune-guided radiotherapy alone, possibly due to an immune mediated process (31;32). This remains a possibility in this study as instances of rash appeared sporadic and not clearly associated with higher doses of gemcitabine. A HACA response was associated with the rash in 2 of 3 cases, but not seen in the DLT defining case.

The gemcitabine dose escalation scheme was conservative due to evidence for a strong interaction with radiation, and one of the concerns was that of increased hematologic effects. Results, including the lack of neutropenic fever, do not suggest a prohibitive interaction between RIT and gemcitabine. In addition there were no clinically significant instances of thrombocytopenia and no patient required a platelet transfusion. This is despite the use of doses that have been documented to be radiosensitizing in other studies (10).

It is of interest that the patient with a partial response was treated at a relatively low dose of gemcitabine (45 mg/m^2) and had received and progressed through previous gemcitabine. As noted, in head and neck cancer patients treated with weekly gemcitabine and radiation, dFdCTP levels in tumor biopsies obtained during treatment were similar in patients receiving gemcitabine doses of 50 to 300 mg/m^2 . The fact that more objective responses were not seen at higher levels is likely due to the heavily pretreated nature of the study population. However, 4 patients did have at least a 50% decrease in CEA level that was associated with stable disease in all cases. These cases were spread through out various

gemcitabine dose levels and are a further indication of possible clinical benefit. Although CEA levels are not measurable in terms of response, levels, especially if changed by more than 50% have been associated with clinical response (33;34). Of note, 2 of 4 patients with an initial increase in CEA maintained stable disease during further treatment. This may indicate that in some cases an increased CEA early in treatment may have been due to tumor necrosis and may predict response rather than progression (35;36).

There was a lack of clear correlation with radiation dose and response when individual tumors were evaluated. This may again be because to the heavily pretreated and heterogeneous nature of the patients enrolled on this study. It is of interest that the 2 tumors showing a partial response did receive relatively high radiation doses, and also higher levels of gemcitabine. However, tumors with stable disease when compared progressive lesions, received a lower dose on average across a broad range of gemcitabine doses. There was a tendency for smaller tumors to have a higher Y-90 dose suggesting better antibody penetration possibly based on better perfusion and lower interstitial pressure. However, among the 6 lesions with a dose greater than 100 rad/mCi, there were 1 partial response, 1 stable disease, and 4 instances of progressive disease again suggesting a lack of correlation between dose and response. Tumor doses ranged between 6.3 to 740.0 rad/mCi indicating an overall good therapeutic ratio when compared to red marrow and total body estimates.

In several cases, grade 3 lymphopenia was noted, scattered across treatment levels (Table 3). Radiation therapy has been associated with lymphocyte depletion in the past with differing effects on various lymphocyte subsets (37). There is also evidence that chemotherapy in combination with external beam radiation may increase lymphocytopenia (38). No specific clinical consequence related to increased rates of infection were noted during the course of this study. Among patients with grade 3 lymphopenia, 8 of 11 developed a HACA response.

HACA responses continue to be a problem, and were the primary reason for stopping treatment in 12 patients. It is possible that a number of these cases could have had a more prolonged period of stable disease or experienced a response with continued treatment. The primary strategies to overcome this would include using more humanized antibodies, use of antibody fragments and potentially use of immunosuppressive agents such as cyclosporine (5). These strategies would potentially allow the repetitive dosing that would allow for more effective treatment.

Although the formal definition of DLT was met, further dose escalation might have been possible given the nature of toxicities seen. However several factors contributed to our decision to forgo further dose escalation. First, as noted, the dose of gemcitabine was in the range noted to be radiosensitizing in other studies, and there was evidence for clinical activity, including a partial response, at levels below the ultimate MTD. Second, HACA responses, as noted, were limiting and we were transitioning to a humanized version of the ⁹⁰Y-DTPA-cT84.66 antibody. A clinical trial has since been initiated evaluating the ⁹⁰Y-labeled humanized - T84.66

Responses consisted mainly of stable disease, with one patient showing an objective response. Although this combination appears feasible, activity as a primary therapy in patients with bulky disease appears limited. This may be related to tumor factors including heterogeneity of vasculature and interstitial pressure that impede macromolecule penetration, although the degree of IgG penetration into solid tumors is not yet completely defined. Strategies for the future include studying combination therapy in minimal disease, use of antibody fragments with potentially improved therapeutic ratios, and using RIT in combination with full dose chemotherapy as a chemosensitizer(5;39;40).

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Statement of Translational Relevance

This manuscript describes the feasibility of immune-guided radiotherapy using a monoclonal anti-CEA antibody combined with gemcitabine at radiosensitizing doses. Importantly, evidence of clinical activity was seen in this cohort of heavily pretreated patients. This combination could be applied to less heavily pretreated patients in future trials, which could lead to higher response rates with better demonstration of clinical benefits. This regimen might have even greater utility in low volume tumor states, including in the adjuvant setting in CEA positive gastrointestinal cancer or other sites where penetration of bulky tumors would not be an issue. In these settings immune guided-radiotherapy would represent a systemic agent with a unique mechanism of action that could potentially be integrated into multimodality treatment.

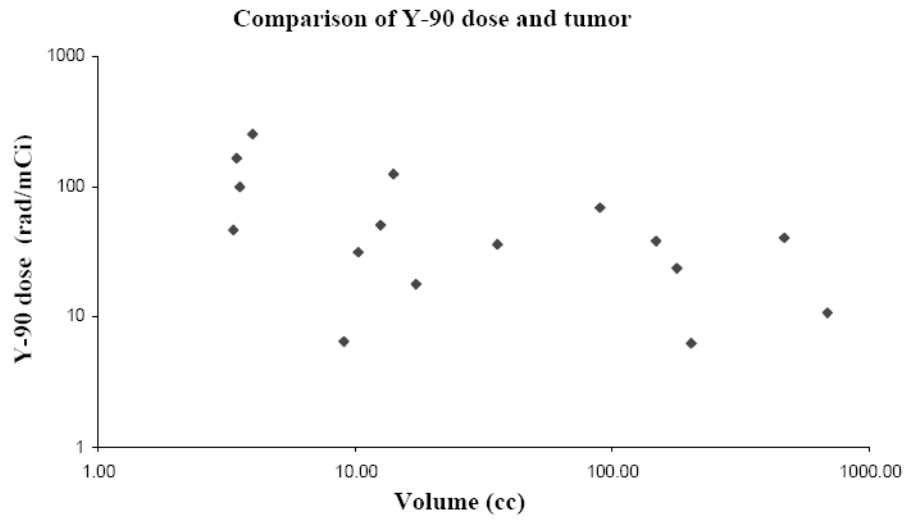


Fig. 1. Y-90 dose (rad/mCi) to individual tumors compared with the volume of the individual tumors.

Table 1

Gemcitabine Dose Escalation Schema

Level	Dose (mg/m ²)
1	30
2	45
3	60
4	75
5	90
6	105
7	120
8	135
9	150
10	165

Table 2

Patient Characteristics

Characteristic	No. of Patients
Gender	
Male	20
Female	16
Median Age	62.7
Race/Ethnicity	
Caucasian	32
Asian	3
African American	1
Diagnoses	
Colorectal	18
Appendix	1
Gastric/esophagus	3
Pancreas	2
Lung	7
Breast	2
Medullary thyroid	2
Testicular	1
Prior Treatment	
Chemotherapy	35
Radiation	10
Surgery	35

Table 3

Reason for Treatment Cessation

HACA	12
Protocol completion*	4 (one with 2 cycles)
Disease progression	13
Toxicity	3

*The protocol had included 2 cycles of treatment but was amended to allow up to 3 cycles.

Table 4

Cycle 1 Toxicities (grade 3/4)

Treatment Level	1	2	3	4	5	6	7	8	9	10
Leukopenia			1		2		2	1	2	2
Lymphopenia	2	3	1				2		2	1
Platelet		1			1					1
Rash						1*			1*	1
Anemia										2

* grade 2

Table 5

Summary of Y-90 Dose to Tumors

Patient (dose ¹)	Diagnosis	Location	Volume ² (cc)	Y-90 AUC (mCi* hr/mCi)	Y-90 Dose (rad/mCi)	Delivered Dose (rad)	Response
1 (45)	colorectal	peri-hilar	10.3	0.162	31.2	989.7	stable
		pancreas	203.7	0.648	6.3	200.1	stable
		periclavicular	9.1*	0.029	6.4	202.0	-
2 (60)	colorectal	left lingular	0.4	0.076	392.9	11079.1	progression
		peri-hilar	0.3	0.054	403.1	11368.7	progression
		right hepatic	149.2	whole liver dose	37.7	1064.1	stable
3 (90)	NSCLC	mediastinum	14.1	0.873	122.5	3392.2	progression
4 (120)	colorectal	subcarinal	36.1	0.649	35.7	3502.4	progression
		right lung	17.2	0.152	17.6	1728.1	stable
		left lung	3.6	0.179	98.9	9700.3	PR
5 (120)	NSCLC	right lower lobe	179.6	2.121	23.4	552.9	stable
6 (135)	colorectal	mesenteric node	4.0	0.517	253.4	7704.2	PR
		subcarinal	3.4	0.079	46.5	1414.8	stable
7 (135)	teratoma	left lung	688.3	3.729	10.8	433.2	stable
8 (150)	colorectal	Peri-hilar	12.7	0.321	50.0	1795.7	progression
9 (150)	colorectal	right hepatic	470.5	whole liver dose	40.4	1005.1	stable
		paratracheal	3.5	0.293	164.4	4093.9	progression
10 (150)	colorectal	lung nodule	0.5	0.192	740.0	191667.0	stable
		right liver	89.5	3.115	69.0	1788.5	stable

¹ gemcitabine dose level – mg/m²² By CT scan except as noted

* By nuclear medicine scan

Table 6

Summary of Y-90 Dose to Tumors

	Volume (cc)	Y-90 Dose (rad/mCi)	Delivered Dose (rad)
Average	99.8	134.2	4272.8
STD	184.4	190.6	5172.5
Maximum	688.3	740.0	19167.0
Median	12.7	46.5	1788.5

Table 7

Organ Y-90 Dose Estimates

Organ (n = 23)	Average (rad/mCi)	Standard Deviation
Marrow	3.00	1.28
Liver	21.78	8.86
Kidney	11.15	3.55
Total body	2.09	0.45