TITLE: A PHASE I/II TRIAL OF RADIOIMMUNOTHERAPY (Y-90 cT84.66), GEMCITABINE AND HEPATIC ARTERIAL INFUSION OF FUDR FOR METASTATIC COLORECTAL CARCINOMA TO THE LIVER

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Site: Colorectal/Hepatic Metastases
Stage: IV
Modality: RIT, gemcitabine, fluorodeoxyuridine
Type: Phase I/II

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SCHEMA:

THERAPY CONSISTS OF TWO PARTS:

Part I – Protocol Therapy (RIT/Gemcitabine/FUdR)

^{90}Y-cT84.66 (16.6 mCi/m^2):	Day 9
Gemcitabine (105 mg/m^2) infused over 30 mins. i.v.	Days 9 and 11
Continuous hepatic arterial infusion FUdR x 14 days:	Days 1 – 14
(starting dose level 0.10 mg/kg/day to contain Decadron 1 mg/day)	
Ca-DTPA (250 mg/m2/day): infused over 60 minutes i.v.	Day 9 – 11

A maximum of 3 cycles every 6 weeks is planned.

This will be followed by:

Part II – Best Systemic Therapy (see section 7.8 for details):

Additional hepatic arterial infusion of FUdR permitted for a maximum of 4 cycles (including cycles delivered during Part I of protocol therapy with RIT/gemcitabine). Systemic therapy may be given in combination with hepatic arterial infusion FUdR at the discretion of the treating physician. Systemic therapy may be continued after completion of hepatic arterial infusion at the discretion of the treating physician.Amended 07/20/05

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	Day 1 FUdR/Decadron (starting dose level 0.10 mg/kg)	**Day 2** FUdR/Decadron	**Day 3** FUdR/Decadron	**Day 4** FUdR/Decadron	**Day 5** FUdR/Decadron	**Day 6** FUdR/Decadron
Day 7 FUdR/Decadron	**Day 8** FUdR/Decadron	**Day 9** FUdR/Decadron Gemcitabine (105 mg/m^2) RIT (16.6 mCi/m^2) Ca-DTPA	**Day 10** FUdR/Decadron Ca-CTPA	**Day 11** FUdR/Decadron Gemcitabine (105 mg/m^2) Ca-DTPA	**Day 12** FudR/Decadron	**Day 13** FudR/Decadron
Day 14 FUdR/Decadron	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**
Day 21	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**
Day 28	**Day 29**					

1.0 OBJECTIVES

1.1   To determine the maximum tolerated dose (MTD) and associated toxicities of concurrent hepatic arterial infusion (HAI) fluorodeoxypyrimidine (FUdR)/Decadron and intravenous gemcitabine combined with intravenous yttrium-90 (^{90}Y) chimeric T84.66 (cT84.66) in colorectal cancer patients after hepatic resection or maximum surgical debulking (to < 3 cm) of liver metastases. This is the primary objective.

1.2   To study the feasibility and toxicities of such adjuvant therapy following resection and/or ablation of liver metastases

1.3   To evaluate the biodistribution, clearance and metabolism of ^{90}Y and ^{111}In (indium-111) chimeric T84.66 administered intravenously.

1.4   To estimate radiation doses to whole body, normal organs, and tumor through serial nuclear imaging.

1.5   To correlate proteomic profiles pre and post-therapy with toxicities and anti-tumor effects.

2.0 BACKGROUND

Hepatic Arterial Infusion Chemotherapy: Surgical resection of liver metastases from colorectal carcinoma can produce a 20% 5 year survival. However, subsequent recurrences in the liver as well as in extrahepatic sites are the rule. A prospective randomized trial at the City of Hope using resection and intra-arterial FUdR [1] demonstrated the value of adjuvant therapy following complete resection of hepatic metastases in preventing disease recurrence. Further randomized studies of intra-arterial FUdR have demonstrated evidence of benefit [2,3]. In one study 156 colorectal patients with resected liver metastasis were randomized to 6 cycles of HAI with FUdR plus systemic 5-fluorouracil, or to systemic 5-fluorouracil alone. After 2 year the actuarial rate of survival was better in the HAI group (86 vs 72%, P = 0.03). Hepatic recurrences were also reduced in the HAI group (90 vs 60%, P < 0.001). There were more hepatic side effects in the HAI group with 18% of patients developing serum bilirubin levels greater than 3.0 mg/dl. Biliary stents were required in 4 patients with subsequent normalization in 2 of these. Hepatic toxicity was managed by dose reductions and the use of intrahepatic dexamethasone. Nevertheless, only 26%of patients received more than 50% of the planned dose.

In another study, 109 colorectal patients with 1 –3 resected hepatic metastatses were randomized to no further therapy or to HAI with FUdR combined with systemic infusional 5-fluorouracil. The HAI group had a 4-year recurrence free rate of 46% vs 25% for the controls (p = 0.04). The 4-year liver recurrence free rate was also improved (67 vs 43%, P = 0.03). The HAI group consisting of protocol eligible patients had a longer median survival (63.7 vs 49, P = 0.60). Increases in liver tranaminases were seen in 8/30 patients, and 2 required biliary stenting with all patients eventually recovering. Two thirds of patients received all 4 planned chemotherapy cycles.

A German study [4] randomized 226 colorectal patients with resected liver metastases to HAI with 5-flourouracil for 5 days plus systemic 5-fluorouracil vs observation alone. No benefit in terms of survival or time to progression was noted. Grade 4/4 toxicities including stomatitis, and nausea occurred in 62.9% of treated patients. Based on this, the study was stopped at an interim analysis. The length of hepatic arterial infusion of 5 days vs 14 days in other studies, as well as the use of 5-fluorouracil as opposed to FUdR may have affected the result. Various grade 1 – 4 liver function abnormalities were seen in between 12.2 and 17.6% of the treatment courses given.

Attempts have been made to incorporate potentially more effective systemic therapies in conjuction with HAI to potentially reduce the rate on non-hepatic recurrences. A recent study demonstrated the feasibility of combining irinotecan with HAI [5]. In this study colorectal patients with resectable hepatic metastases were treated with 6 cycles of HAI FUdR. Inrinotecan at a dose of 200mg/m^2 was found to be feasible in combination with a 14-day infusion of FUdR 0.12mg/kg/day.

In another study, colorectal patients with resected, or ablated liver metastases were treated adjuvantly with HAI FUdR at a dose of 0.2mg/m^2/day combined with dexamethasone 1 mg/day for 14 days [6]. Oxaliplatin on day 1 at a dose of 130mg/m^2 with capecitabine 1000mg/m^2 twice daily for 14 days were given during weeks 4-5. Cycles were repeated every 6 weeks for a total of 4 treatments. An increase in grade 3 diarrhea but not hepatic toxicity was noted.

A study combining oxaliplatin based treatments with HAI has also been reported [7]. In this study, colorectal patients with unresected liver metastases were treated with HAI 0.12mg/kg/day for 14

days. Systemic therapy was given every other week and consisted of oxaliplatin combined with either 5-fluorouracil and leucovorin or with irinotecan. The MTD of oxaliplatin/5FU was 100mg/m^2 and 1400mg/m2 by continuous infusion over 48 hours respectively with diarrhea and hepatotoxity limiting therapy. With oxaliplatin and CPT-11, the MTD was 100mg/m^2 and 150mg/m^2 respectively. Hepatotoxicity, hematologic toxicity, and diarrhea were seen at the DLT level.

Gemcitabine: Many clinical trials demonstrate a measurable advantage to a combination of chemotherapy and radiation over treatment with radiation alone. Trials with esophageal cancer using combined chemoradiation demonstrate response rates of 15-30% with 5FU/CDDP or 5FU/mitomycin C regimens with complete responses at radiation doses as low as 3000 cGy. [8]. Clinical evidence of improvement with chemoradiation have been documented in other cancers including rectal cancer[9], pancreatic cancer [10], anal cancer [11] and head and neck cancer [12] . Cell cultures studies have demonstrated experimental radiosensitization with a variety of drugs including 5-fluororuracil, other antimetabolites, cisplatin [13] , topoisomerase I inhibitors [14] , as well as taxanes[15] . The exact mechanism of radiosensitization remains under study, but likely involves multiple bilateral interactions between radiation and various chemotherapy drugs involving functions such as DNA repair and apoptosis [16].

A drug with good preclinical radiosensitization properties is gemcitabine. This has been approved by the Food and Drug Administration for the treatment of advanced pancreatic cancer based on results of superior clinical benefit and activity in a phase III trial [17]. It is given as a 30-minute infusion on a weekly basis. It has been shown to improve the quality of life as well as improve survival in pancreatic cancer patients in comparison to 5-fluorouracil treatment. The primary toxicity is hematologic, although other toxicities such as fluid retention, pulmonary toxicity, and cardiac toxicity may be significant [18,19].

Laboratory studies have demonstrated strong radiosensitization properties when gemcitabine is tested in cell culture [20]. The exact method of radiosensitization is under investigation but likely relates to inhibition of ribonucleotide reductase with subsequent effects on deoxyribonucleotided pools, and to gemcitabine incorporation into DNA with subsequent chain termination. Radiosensitization was greatest in one study when cells were exposed to gemcitabine for 2- hours 24 - 48 hours before radiation exposure. Radiosensitization was observed for approximately 2 days after exposure [21]. The maximal sensitization has correlated with a drop in adenosine diphosphospate in response to gemcitabine (which is an inhibitor of ribonucleotide reductase). Interestingly, radiosensitization appears to occur at relatively low, minimally cytotoxic gemcitabine levels. In another study, radiosensitization is again seen when gemcitabine is given before radiation [22]. S-phase Chinese hamster fibroblasts (V79) and a human colon cancer cell line (Widr) were again exposed to gemcitabine for 2 hours followed by radiation. The maximum interaction in this study appeared 2 hours after the 2-hour treatment. In summary, it appears that radiosensitization occurs after gemcitabine exposure although the time course of this sensitization may vary depending on the conditions.

Clinical studies combining gemcitabine with radiation have confirmed that gemcitabine is a potent radiation sensitizer. In studies with head and neck patients [23], doses of gemcitabine required progressive reduction from a starting dose of 300mg/m^2 due to severe toxicity. Doses below 100mg/m^2 were planned in an attempt to determine a tolerable dose. Interestingly, at a dose of 150 mg/m^2, levels of gemcitabine triphosphate (dFdCTP) remained in the same range as those seen at the 300 mg/m^2 dose level. The levels of dFdCTP were similar to those seen in *in vitro*

radiosensitization experiments suggesting that even at low doses, significant interactions were occurring.

Other studies have reported tolerance of gemcitabine and external beam radiation in upper gastrointestinal tumors [24,25]. Studies with lung cancer have also been reported, noting increased esophagitis with the combination [26].

Radioimmunotherapy with Y-90 cT84.66: The rapidly growing field of molecular medicine offers exciting new strategies for targeted delivery of cancer therapy. Through molecular and genetic engineering, agents can now be custom designed against specific tumor targets with properties optimized for therapy. Monoclonal antibodies (Mab) against tumor antigens were some of the first of these agents to be evaluated. Conjugated to radionuclides, Mab guided radiation therapy or radioimmunotherapy (RIT), demonstrated significant promise in laboratory models. This promise has been realized in the clinic for the more radiosensitive hematologic malignancies, particularly B-cell lymphomas and myeloid leukemias, which have reported response rates ranging from 30-85% [27-35], with complete responses rates as high as 80% with myeloablative, bone marrow transplant supported doses in patients with relapsed disease [27].

For the more radioresistant solid tumors, results have been less successful, but remain encouraging. At non-myeloablative doses in patients with chemotherapy refractory, metastatic disease, current RIT regimens have reported primarily stable disease and mixed, and minor responses in patients with colorectal, breast, medullary thyroid, and ovarian cancer [36-45]. More encouraging are trials evaluating RIT at higher, myeloablative doses. For example, 50% partial responses of short duration have been reported in an ongoing trial with myeloablative, stem cell supported doses of ^{90}Y-DTPA-BrE3 in patients with advanced, metastatic breast cancer [46].

Current non-stem cell supported RIT regimens only achieve the biologic equivalent of 2000 cGy to tumor and therefore do not achieve high enough tumor doses to be used as single modality therapy, particularly for gross disease. This is not surprising given the experience with external beam radiotherapy, where 2000 cGy (at 200 cGy per day) rarely results in shrinkage of carcinomas, particularly for chemo- and radiation refractory recurrences. Comparable radiation doses to tumor are delivered by RIT and comparable results are seen in Phase I trials entering heavily pre-treated patients. Therefore, future therapy trial development should focus on increasing the tumoricidal efficacy of RIT through concomitant delivery with chemotherapy agents known to enhance radiation effects. The same RIT radiation dose of 2000 rads combined with other systemic chemotherapy agents, especially those with demonstrated radiation enhancing properties (e.g., 5-FU and halogenated pyrimidines), has a likelihood of increasing tumor responses compared to each modality alone, resulting in major responses. Successful examples of using partial doses of external beam radiotherapy with appropriate chemotherapy agents are found throughout the literature. For example, the early trials with esophageal cancer demonstrated pathologic complete response rates of 15-30% with 5-FU/cis-platinum or 5-FU/mitomycin-C regimens combined with conventionally fractionated external beam radiation doses as low as 3000 rads. The results were improved over that of chemotherapy alone or with what would be expected after 3000 rads alone [47]. Similar examples exist for other disease sites [48-50].

Carcinoembryonic antigen (CEA) is a well-studied tumor surface antigen that has proven to be a useful target for RIT. CEA is expressed in many common tumor types such as colon, breast, non-small cell lung, gastric, pancreatic, biliary, cervix, uterine and ovarian cancer [51-54]. Radiolabeled anti-CEA antibodies have been successfully used in the clinic to treat and image CEA-producing

malignancies [55,56]. Radiolabeled anti-CEA antibodies have been the most extensively studied in colorectal cancer, since 90-95% of tumors produce CEA. Animal studies demonstrate significant tumor growth delay after therapy with ^{131}I or ^{90}Y labeled anti-CEA Mabs [57]. Tumor responses further improved (resulting in long term tumor control in some studies) in animal models which explored myeloablative RIT doses with BMT [58], RIT with small micrometastases [59], and RIT combined with 5-FU chemotherapy [60].

Murine T84.66 is an IgG$_1$ monoclonal antibody developed at the City of Hope with high specificity and affinity (approximately 1.16×10^{11} M^{-1}) for CEA [61,62]. It recognizes the A3 domain of the CEA molecule and has little cross reactivity with normal tissues. Using ^{111}In murine T84.66 Beatty et al. [56] demonstrated successful targeting and imaging of colon cancer with this antibody. Further refinements of T84.66 have been made by investigators at the City of Hope in preparation for using this antibody in RIT trials. A human-mouse chimeric T84.66 has been developed (IgG$_1$ isotype) by Dr. Michael Neumaeir in the Department of Immunology. By humanizing the non-antigen binding portions of the molecule, the chances for development of anti-antibodies against T84.66 is potentially decreased, allowing for multiple administrations of the radiolabeled antibody for therapy.

Chimeric T84.66 (cT84.66) was radiolabeled with ^{111}In and evaluated in imaging/biodistribution trials in patients with CEA-producing malignancies (IRB protocols 91064 and 91169/BB-IND 4040). These two trials demonstrated the following: 1) ^{111}In intact cT84.66 targeted CEA-producing tumors with imaging result comparable to other ^{111}In labeled intact anti-CEA antibodies.; 2) immunogenicity was less after single administration of up to 105 mg of antibody protein compared to intact murine monoclonal antibodies.; 3) the antibody was well tolerated,; and 4) dosimetry estimates showed that high and potentially therapeutic radiation doses can be delivered to some tumors, regional metastatic lymph nodes, and small hepatic metastases.

Based on these encouraging findings a Phase I therapy trial (IRB 94001) was initiated to define the maximum tolerated dose of intravenously administered ^{90}Y-cT84.66 [63]. On this trial, twenty-two patients received at least one cycle of therapy, with one individual receiving 2 cycles and two receiving 3 cycles of therapy. All were heavily pre-treated and had progressive disease prior to entry on this trial. Reversible leukopenia and thrombocytopenia were the primary dose-limiting toxicities observed. Maximum tolerated dose (MTD) was reached at 22 mCi/m^2. Thirteen patients developed an immune response to the antibody. HACA was more frequent on this trial possibly due to the fact that each patient received an imaging dose of the antibody followed by the therapy dose a week later. Dose estimates to tumor ranged from 66 to 1670 cGy (8.7 to 52.2 cGy/mCi ^{90}Y) for each cycle of therapy delivered. Although no major responses were observed, 3 patients demonstrated stable disease of 12 to 28 weeks duration and 2 demonstrated a mixed response. In addition, a 41 to 100% reduction in tumor size was observed with 5 tumor lesions.

As a result a successor Phase I trial (IRB 96063) was developed evaluating the combination of Y-90-cT84.66 given in combination with continuous infusion 5-FU. Considerable interest has been generated recently for continuous infusion 5-FU as an alternative dose schedule to bolus administration for several reasons. At least six phase III randomized trials have compared continuous infusion 5-FU for $\geq$ 5 days versus bolus administration and have reported comparable or improved response rates to varying degrees [64-68]. Furthermore, phase II trials of continuous infusion 5-FU have reported response rates in the 30-40% range in advanced metastatic colorectal cancer. Second, myelotoxicity in all studies is significantly reduced making it a more attractive alternative in combination with other myelotoxic agents, such as RIT. Continuous infusion 5-FU

may provide an improved approach toward 5-FU sensitization of radiation tumoricidal activity [69] [70]. Finally, Remmenga et al. demonstrated a significant decrease in tumor growth when combining continuous infusion 5-FU with ^{90}Y-CC49 in an LS174T nude mouse model [60].

IRB 96063 has been completed and results recently published [71]. Dose escalation to the highest planned dose level of 5-FU has been achieved (1000 mg/m2/day x 5 days). Twenty-one heavily pretreated patients (almost all having failed previous 5-FU) have been treated. Dose-limiting toxicity was defined as grade 4 hematologic and/or grade 3 non-hematologic toxicity on this trial. As in previous RIT studies, dose-limiting toxicities were hematologic, primarily thrombocytopenia and leukopenia. All 21 patients demonstrated hematologic toxicity. Other toxicities observed were similar to those observed with 5-FU. These include: grade 1 GI (nausea/vomiting or loose stool) toxicity in 16 patients and grade 2 GI toxicity in 2 patients; grade 1 fatigue in 14 patients; grade 1 erythema or skin rash in 8 patients; grade 1 mucositis in 9 patients, grade 3 mucosits in 1 patient and grade 4 mucositis in 1 patient. In addition 2 patients had transient grade 1 flu-like symptoms. No hepatotoxicty was observed. Three patients had grade 1 elevations in transaminases felt secondary to disease progression. 5-FU did not appear to alter antibody pharmacokinetics, but did appear to decrease the HACA response possibly due to its effects on the immune system, with only 3 of 17 demonstrating HACA. Of 18 evaluable patients, 9 demonstrated stable disease of 3-8 months duration. One patient demonstrated a mixed response. A decrease in size of 53-100% was seen in 3 lesions. This trial demonstrated the feasibility of combining chemotherapy with radioimmunotherapy.

This first concomitant RIT/chemotherapy trial at COH was followed by IRB 00148, a Phase I trial evaluating ^{90}Y-cT84.66 RIT at 16.6 mCi/m^2 given on day 1 with concomitant IV gemcitabine given on Days 1 and 3. The gemcitabine dose level cohorts studied thus far have been 30, 45, 60, 75,90 and 105 mg/m^2. This trial was initiated based on pre-clinical studies document an additive to supra-additive increase in anti-tumor effect with the combination [72-74]. To date 17 patients have been treated on this study, with 1 partial response and 10 patients with stable disease observed. In addition, one patient had stable disease of multiple lung metastases after one cycle but developed a new brain metastasis. Toxicity has been primarily hematologic, and dose-limiting toxicity has not yet been reached.

The proposed Phase I trial is a successor trial to IRB 00148 and IRB 96063 and integrates the experience of HAI FUdR. Patients post attempted hepatic resection or ablation for liver metastases with all hepatic and extra-hepatic disease debulked to <3.0 cm will receive FUdR by HAI in combination with systemic gemcitabine and Y-90-cT84.66. This trial therefore incorporates three important concepts felt to be critical for successful application of RIT. First, it evaluates RIT in combination with radiation-enhancing chemotherapy. The feasibility of combining RIT with systemic gemcitabine was established in the earlier trial. The proposed trial builds on this experience and evaluates the feasibility of adding HAI FUdR to systemic gemcitabine and Y-90 cT84.66 RIT as adjuvant therapy.

Second, this trial will evaluate hepatic regional combined modality therapy. Patients post hepatic metastases resection, who are therefore at high risk of liver progression or recurrences present the ideal patient population for study. Potential subclinical tumor deposits are irradiated by specific tumor targeting of antibody to tumor as well as non-specific Y-90-cT84.66 activity that localizes in surrounding liver. Radiation is deposited concomitantly with regional delivery of FUdR.

Finally, patients on this study will have smaller volume or subclinical disease. Studies predict that RIT will have its greatest impact on subclinical disease. In small tumors, factors such as tumor vascularity and tumor interstitial pressure are more favorable for antibody delivery [75], allowing for greater antibody penetration, higher antibody uptake, more uniform distribution and, hence, more effective radiation doses to tumor [8,76]. For example, Behr et al. [77] in a colon cancer liver metastases mouse model, improved survival and prevention of liver metastases in mice receiving I-131 radiolabeled anti-CEA. Results were superior to that observed with 5-FU or irinotecan. These encouraging results led to a clinical trial by the same group evaluating I-131-hMN14 anti-CEA in patients with hepatic metastases from colon cancer after hepatic resection [78]. Of 9 patients receiving adjuvant RIT, 8 remain disease free at 24+ months which compares favorably to other therapies delivered post-hepatic resection. Of 19 evaluable patients with measurable disease, 3 demonstrated a PR of 3-15 months duration and 8 demonstrated a minor response of 3-14 months duration. Promising results have been reported by Hird et al. [79] who reported on 15 patients with FIGO stage IIb-IV ovarian cancer who had negative second look laparotomies after surgery and chemotherapy. Median survival after single dose intraperitoneal therapy with ^{90}Y-DOTA-HMFG1 or ^{90}Y-DTPA-HMFG1 was 11 months (range 2-31 months), which was superior to historical controls from the same institution. Based on these encouraging results, a randomized Phase III trial was initiated to compare standard chemotherapy versus standard chemotherapy and Y-90-HMFG1. The proposed study will enter patients who have potentially resectable liver metastases and potentially resectable limited extra-hepatic disease. Those with resection/maximum debulking (to less than or equal to 3.0 cm) will receive protocol therapy consisting of RIT/Gemzar and intrahepatic pump infusion of FUdR.

Proteomic Studies: Proteomics involves the analysis of biological samples for their protein content usually in a differential analysis to determine which proteins change during the course of treatment or other changes to the biological system [80-83]. Although the ultimate goal is to develop protein chips analogous to other microarray technologies, the field is still at the discovery stage and often uses mass spectrometry as a high throughput sensitive method that can rapidly identify proteins in complex biological samples. Although many mass spectrometric approaches have been applied to proteomics, MALDI-TOF-MS (matrix assisted laser desorption time of flight mass spectrometry) remains a method of choice because it can rapidly analyze peptides and proteins ranging from low to high mass without interference from salts and low molecular compounds usually present in biological samples. This approach requires only microliter amounts of sample and can be spotted on 100 well format plates with an analysis time of seconds for each sample. In the context of this study, we are interested in analyzing serum samples from patients undergoing a combination of RIT and chemotherapy to determine if any protein signatures correlate to their course of treatment. Since the number of patients is small, we do not expect to reach statistical significance. Instead we propose to determine if the patients undergoing this therapy exhibit a common protein signature that can lead to the identification of markers to be more thoroughly screened in larger patient number studies.

3.0 DRUG INFORMATION

3.1   5-Fluoro-2'-deoxyuridine (FUdR)

      3.1.1   Mechanism of Action: FUdR is an antimetabolite which is rapidly converted into 5-FU. The actions and toxicity of FUdR are similar to 5-FU, the primary cytotoxic effect being a block of thymidylate synthesis with resulting interference with DNA synthesis. Also, the drug blocks the incorporation of uracil and orotic acid into

RNA, thereby depressing RNA synthesis. When given via the hepatic artery, 95% of FUdR is extracted by the liver with only 5% having systemic circulation or effect.

3.1.2 Toxicity: anorexia, nausea, vomiting, stomatitis, diarrhea, hepatitis, gastritis, leukopenia, thrombocytopenia, anemia, alopecia, dermatitis, skin hyperpigmentation, and cerebellar ataxia. In patients receiving continuous hepatic artery infusions biliary sclerosis can also occur.

3.1.3 Formulation and Storage: FUdR is supplied in vials containing 500 mg of crystalline drug which can be reconstituted in 30 cc of normal saline for parenteral (intra-arterial) use.

3.2 Gemcitabine

3.2.1 Chemistry/ Mechanism of action: Gemcitabine is a nucleoside analogue in which 2' position of the carbohydrate moiety has been changed to form 2'-deoxy –2',2' difluorocytidine. Gemcitabine is metabolized by tumor cells to the di- and triphosphate nucleotide. Ribonucleotide reductase activity is inhibited by the active metabolite dfdCDP. DNA polymerase is also inhibited by dFdCTP and dFdCMP incorporated into DNA.

3.2.2 Human toxicities: Gemcitabine therapy is associated with nausea, vomiting, diarrhea, stomatitis, myelosuppression, and renal insufficiency. Long-term animal studies to evaluate the carcinogenic potential of gemcitabine have not been conducted. Gemcitabine induced forward mutations *in vitro* in a mouse lymphoma assay. Gemcitabine is embryotoxic causing fetal malformation and should not be used in pregnant women.

3.2.3 Formulation: Gemcitabine is available in 200 mg or 1 gram vials as a sterile powder with NaOH added to achieve pH adjustment upon the addition of sterile water.

3.2.4 Administration: Gemcitabine will be diluted in 5% dextrose (or half-normal saline in patients with diabetes) IV solution.

3.3 Y-90-DTPA-cT84.66

3.3.1. Chemistry/Mechanism of Action: cT84.66 is a chimeric human/murine IgG1 monoclonal antibody developed at the City of Hope National Medical Center. It recognizes the A3 domain of the CEA molecule and has little cross reactivity with other molecules. It binds CEA with a high affinity (approximately 2×10^{10} /M) and is able to bring a bound radioisotope into close proximity. It is labeled with indium -111 or yttrium- 90 to form the imaging and therapeutic agent.

3.3.2 Human toxicities: In phase I trials, the primary toxicity has been hematologic. A possible complication of treatment is also the development of human anti-chimeric antibodies (HACA).

3.3.3. Formulation: Yttrium-90 and indium-111 cT84.66 anti-CEA antibody is produced and labeled at the City of Hope by the Divisions of Immunology and Radioimmunotherapy.

3.3.4. Supplier: cT84.66 anti-CEA antibody is an investigational agent produced and labeled at the City of Hope by the Divisions of Immunology and Radioimmunotherapy.

3.4 DTPA (Diethyltriaminepenatacetic acid)

3.4.1. Drug Formulation and Procurement
DTPA will be purchased from Heyl Pharmaceuticals, Berlin, Germany. It is supplied as a 1 gram ampule in 5 mls.

3.4.2 Drug toxicity
DTPA has been known to cause headaches, fever, chills, flu-like symptoms, nasal stuffiness, nausea, vomiting, abdominal cramping, and diarrhea. Other side effects that are less common include pain at the injection site, dehydration, decreased blood pressure, irregularities of heart rhythm, decreased blood counts, increased calcium, numbness and tingling, sneezing, excessive tearing, kidney damage, and zinc deficiency (which can result in a facial and perianal rash and tongue and mouth sores). In addition, there is always a risk of a very uncommon or previously unknown side effect occurring. Stopping the infusion or reducing the dose of DTPA normally reverses the side effects. Headaches and tingling have been observed at the City of Hope but were reversible.

3.4.3. Drug Storage, Reconstitution and Stability
The DTPA solution will be diluted with 100 mls normal saline and administered IV over 1 hour. DTPA has a long aqueous stability but should be used within 48 hours of being drawn up by the pharmacy. DTPA will be administered intravenously at a dose of 125 mg/m^2 every 12 hours for a total of six administrations.

3.5 Decadron

3.5.1 Chemistry/Mechanism of Action
Decadron is a corticosteroid with anti-inflammatory action. Multiple glucocorticoid and mineralocorticoid effects occur. The agent is metabolized in the liver and excreted out through the urinary system.

3.5.2 Human Toxicities
Reported reactions, particularly with long-term use of Decadron, include peptic ulcer disease, osteoporosis, adrenal insufficiency, weight gain, immunosuppression, nausea, dyspepsia, increased appetite, edema, headache, dizziness, mood swings, insomnia, anxiety, exacerbation of hypertension, hyperglycemia, cushingoid features, Cushing's syndrome, menstrual irregularities, ecchymoses, acne, skin atrophy, impaired wound healing with long-term use.

3.5.3 Formulation and Administration

Decadron will be administered along with hepatic arterial infusion of FUdR at a dose of 1 mg per day x 14 days per cycle of treatment.

4.0 ELIGIBILITY CRITERIA

4.1   **Pre-operative eligibility criteria:**

4.1.1   Patients must have a physiological age of $\geq$ 18 years and $\leq$ 70 years.

4.1.2   Patients must have a Karnofsky performance status of $\geq$ 60%. This must be met pre-surgery and pre-study therapy.

4.1.3   Patients must have histological confirmation of colorectal carcinoma and present with potentially resectable or ablatable metachronous or synchronous hepatic metastases.

4.1.4   Patients must have colorectal tumors that produce CEA as documented by either immunohistochemistry or by an elevated serum CEA.

4.1.5   Prior radiotherapy, immunotherapy, or chemotherapy must have been completed at least four weeks prior to start of FUdR/RIT therapy on this study (6 weeks if mitomycin-C or nitrosoureas were part of last therapy) and patients must have recovered from all expected side effects of the prior therapy.

4.1.6   Adequate bone marrow function as evidenced by hemoglobin > 10 gm %, WBC >4000/ul, an absolute granulocyte count of > 1,500/mm3, and platelets > 150,000/ul. Patients may be transfused to reach a hemoglobin >10 gm %. These must be met pre-surgery and pre-study therapy.

4.1.7   Patients may have history of prior malignancy for which the patient has been disease-free for five years with the exception of basal or squamous cell skin cancers or carcinoma in situ of the cervix.

4.1.8   Patients must have no prior history of radiation therapy to the liver.

4.1.9   Patients must have a total bilirubin < 1.5 (unless reversibly obstructed due to the metastatic tumor) and a serum creatinine of < 2.0. This must be met pre-surgery and pre-study therapy.

4.1.10   Patients must have evidence of intrahepatic metastases involving < 60% of the functioning liver.

4.1.11   Patients cannot have evidence of extrahepatic disease with the following exceptions:

4.1.11.1   Patients known to have a resectable "anastomotic" or local recurrence of their tumor.

<table>
<tr><td></td><td>4.1.11.2</td><td>Patients who undergoing their initial surgery for resection of their primary colorectal carcinoma can have potentially resectable porta hepatis and/or mesenteric lymph node involvement in addition to liver metastases.</td></tr>
</table>

        4.1.11.3   Patients who have disease extension from the liver metastasis that can be resected <u>en bloc</u> (eg., diaphragm, kidney, and abdominal wall).

        4.1.11.4   Patients who have minimal, potentially resectable to less than 3 cm extrahepatic disease.

4.1.12   The pre-operative eligibility checklist must be completed.

4.1.13   If a patient has previously received murine or chimeric antibody, then serum anti-antibody testing must be negative. This must be met pre-surgery if possible.

4.1.14   Serum HIV testing and hepatitis B surface antigen and C antibody testing must be negative.

4.1.15   Women of childbearing potential must have a negative serum pregnancy test prior to entry and while on study must be practicing an effective form of contraception. This must be met pre-surgery and pre-study therapy.

4.2   **Intra-operative and post-operative eligibility**

4.2.1   Patients must have resectable or ablatable liver metastases as determined by the attending surgeon.

4.2.2   Colorectal carcinoma must be confined to the liver except as noted in 4.1.11 above.

4.2.3   Patients with limited extrahepatic disease as defined in 4.1.11 (primary, lymph node, or anastomotic recurrence) must have disease resected or debulked to less than 3 cm in greatest dimension.

4.2.4   To receive study therapy, patients must be at least 3 weeks post-surgery but no more than 16 weeks post surgery and without evidence of post-operative complications, such as infection or poor wound healing.

4.2.5   Patients must have <40% liver resected at the close of completion of the hepatic resection.

4.3   **Ineligibility Criteria**:

4.3.1   Patients that have received radiation therapy to greater than 50% of their bone marrow (see Appendix II).

4.3.2   Patients with any nonmalignant intercurrent illness (example cardiovascular, pulmonary, or central nervous system disease) which is either poorly controlled with currently available treatment or which is of such severity that the investigators deem it unwise to enter the patient on protocol shall be ineligible.

4.3.3   Biopsy-proven chronic active hepatitis.

4.4   Note: for patients who have had surgery prior to signing the consent form, the pre-operative and intra-operative eligibility criteria may be verified retrospectively, prior to study therapy.

5.0 STAGING CRITERIA

Staging will be by the TNM system of the AJCC.

6.0 DESCRIPTIVE FACTORS/STRATIFICATION/RANDOMIZATION SCHEME

This is a Phase I study. Patients shall be entered according to the treatment plan in section 7.0. There shall be no randomization nor stratification. Descriptive factors shall include patient age, previous treatment, primary malignancy, location and extent of metastases.

7.0 TREATMENT PLAN

Patients fulfilling all pre-operative and intra-operative requirements (as noted in section 4.0 above) will have attempt at complete resection or ablation of hepatic metastases and implantation of infusion pump with the catheter in the hepatic artery.

Post-hepatic resection therapy on this trial consists of two parts:

Amended 7/20/05

Part I – Protocol Therapy: ^{90}Y-MxDTPA-cT84.66/Gemcitabine/hepatic arterial FUdR/Decadron for a maximum of 3 cycles every 6-10 weeks between cycles. There can be up to 10 weeks between cycles if more time is needed for recovery from toxicities. If more than 10 weeks are required, then the patient will be off-study.

Amended 7/20/05

Part II – Additional courses of hepatic arterial infusion FUdR/Decadron with best systemic therapy.
Additional hepatic arterial infusion of FUdR permitted for a maximum of 4 cycles (including cycles delivered during Part I of protocol therapy with RIT/gemcitabine). Systemic therapy may be given in combination with hepatic arterial infusion FUdR at the discretion of the treating physician. Systemic therapy may be continued after completion of hepatic arterial infusion at the discretion of the treating physician.

7.1   General Principles of Protocol Therapy (Part I)

Amended 7/20/05

7.1.1   All patients will receive combined modality therapy consisting of chemotherapy and concomitant radioimmunotherapy (Y-90-DTPA-cT84.66). A therapy cycle will consist of systemic gemcitabine, systemic Y-90-DTPA-cT84.66 and the HAI administration of FUdR/Decadron. Each

treatment cycle will be 6 weeks for a maximum of 3 cycles in Part I (protocol therapy).

7.1.2 Patients will begin treatment on day 1 with HAI FUdR/Decadron for 14 days. On day 9, Y-90-cT84.66 will be given as a single IV bolus infusion. On days 9 and 11, gemcitabine will be administered as a single IV bolus infusion.

7.1.3 Any patient who has an actual body weight or surface area that is > 10% in excess of ideal body weight or surface area will have chemotherapy doses calculated by averaging the ideal and actual values.

7.1.4 Protocol therapy can be initiated as early as 3 weeks post-surgery but no later than 16 weeks post-surgery.

7.2 Administration of FUdR/Decadron (Day 1-14 of each cycle) (Part I)

7.2.1 Patients will receive a dose of FUdR/Decadron administered for 14 consecutive days. Solutions used to fill the intrahepatic infusion pump should contain 1000 units of heparin/ml. Decadron will be given at a dose of 1mg/day x14 days mixed with the FUdR in the infusion pump.

7.2.2 During times when the patient is not receiving chemotherapy with the intrahepatic infusion pump a solution of normal saline with 1000 units/ml of heparin or alternatively a glycerol water solution will be used to maintain the patency of the pump catheter.

7.2.3 The starting dose level (dose level 1) on this Phase I trial will be 0.10 mg/kg/day. Per phase I protocol design using a modified Fibonacci scheme the dose will be escalated in cohorts of 3-6 patients, until an MTD is defined and dose-limiting toxicities are reached. (Table 1)

7.2.4 A maximum of three dose levels are anticipated to be required to reach the MTD. Following a standard phase I dose escalation design (see Table 1), three to six patients will be entered per dose level. The maximum dose level will be 0.2 mg/kg/day.

TABLE I
DOSE ESCALATION SCHEME

	Dose Level 1	Dose Level 2	Dose Level 3
FUdR dose	0.10 mg/kg/day	0.15 mg/kg/day	0.20 mg/kg/day

7.2.5 Each cycle of treatment for a given patient will be at the same dose, unless there is toxicity requiring a dose modification (see Section 8.2). A patient will be removed from protocol treatment if there is unacceptable toxicity,

progressive disease, or development of an anti-antibody response (see Section 7.5)

7.3   Administration of gemcitabine (Day 9 and 11 of each cycle) (Part I)

7.3.1   Patients will receive gemcitabine at a dose of 105 mg/m^2/day by bolus intravenous infusion over 30 minutes.

7.3.2   Each cycle of treatment for a given patient will be at the same dose, unless there is toxicity requiring a dose modification (see Section 8.2). A patient will be removed from protocol treatment if there is unacceptable toxicity, progressive disease, or development of an anti-antibody response (see Section 6.6).

7.4   Intravenous infusion of radiolabeled anti-CEA antibody (chimeric T84.66) (Part I)

7.4.1   The infusion will contain 5 mCi of Indium-111 (^{111}In) labeled cT84.66 and the therapeutic dose of Yttrium-90 (^{90}Y) labeled cT84.66. The ^{111}In labeled cT84.66 will be used to track antibody activity and to estimate absorbed radiation dose to tumor and normal organs. The total amount of antibody protein infused will be kept constant at 5 mg. Intravenous infusion will involve first a test infusion of 100 ug of antibody. If there is no adverse reaction the rest of the antibody will be infused over approximately 25 minutes. The ^{90}Y cT84.66 infusion will be on Day 9 approximately 4 hours after gemcitabine infusion.

7.4.2. The dose level on this trial will be 16.6 mCi/m^2 Y-90-cT84.66.

7.4.3. Each cycle of treatment for a given patient will be at the same dose, unless there is toxicity requiring a dose modification (see Section 8.2). A patient will be removed from protocol treatment if there is unacceptable toxicity, progressive disease, or development of an anti-antibody response (see Section 7.5).

7.4.4   <u>DTPA infusion.</u>   Although the Mx-DTPA chelate binds Y-90 tightly, it is not possible to have an off-rate of zero. Since any free Y-90 can target to bone, resulting in increased bone marrow toxicity, patients will receive a DTPA infusion for 3 days after Y-90 chimeric T84.66 infusion. The dose of DTPA will be 250 mg/m^2/24 hours for 3 days (given in equally divided doses every 12 hours for a total of 6 doses). Each infusion is only 60 mins. i.v. DTPA will be administered as a calcium salt. This dose and schedule has been used by other investigators administering Y-90 labeled antibodies and has resulted in increased urinary excretion of free Y-90 and less hematologic toxicity.

7.4.5   <u>Serial nuclear scans</u>. Radionuclide total body planar imaging will be done at approximately 1-3 hours post start of infusion, and at 1 day, 2 days, 3-5 days, and at a late time point between 6-7 days post infusion. A SPECT nuclear scan will also be performed at 2 days and a time point between 3-5 days post infusion. These studies will be used to estimate absorbed

radiation doses to tumor, normal organs (liver, lung, kidney, bone marrow), and whole body.

    7.4.6 <u>Serial blood and urine collections.</u> Serial blood (5 cc) samples will be collected at pre-main infusion (post test dose), approximately 1 hour and 3-4 hours post start of infusion, and at scan times of 1 day, 2 days, 3-5 days and 6-7 days post antibody infusion. Urine collections will be done daily for 5 consecutive days. Blood and urine samples will be analyzed for total activity and by radiometric HPLC. These studies will acquire data on antibody metabolism and pharmacokinetics.

7.5 (Part I) Subsequent cycles (up to three total) will be given six weeks apart. A subsequent cycle can be delayed up to a total of 10 weeks between cycles if more time is needed for recovery from toxicity (expected to be primarily hematologic). If more than 10 weeks is required the patient is off protocol treatment. The subsequent courses will consist of the same dose of In-111 chimeric T84.66 and Y-90 chimeric T84.66, gemcitabine and FUdR (i.e., no dose escalation within a patient). However, if toxicity occurs, a dose reduction with the next cycle for a given patient is warranted (see Section 8.2). A patient will receive no further protocol therapy (but still evaluable) if he/she develops unacceptable toxicity, disease progression, or an anti-antibody response.

7.6 <u>Proteomic analysis of blood samples</u>. (Part I) Before the first cycle of protocol therapy, and after each subsequent cycle, a blood sample will be obtained for proteomic analysis to evaluate any correlations to toxicities and anti-tumor effects. <u>Protocol:</u> plasma or serum samples are diluted 3-5 fold with water or PBS usually containing 20% acetonitrile. High molecular weight proteins components are precipitated using either acetone or trichloroacetic acid and separated by centrifugation. The supernatant containing the low molecular weight peptide and protein fraction is concentrated in a vacuum centrifuge and then bound to a C18 reverse phase support. After washing with water to remove salts, the bound components are eluted with an aqueous solvent containing 50-80% acetonitrile. An aliquot of the sample solution is spotted onto a matrix assisted laser desorption ionization (MALDI) sample plate along with a solution of the MALDI matrix, typically sinapinic acid or a-cyano-4-hydroxycinnamic acid. Protein profiles are acquired on a MALDI time-of-flight (TOF) mass spectrometer. Components of interest in the protein profile are identified by comparisons to samples taken from the same patient at different time points, and/or comparisons to other patient or control samples. Those components are further characterized by fractionation of the low molecular weight fraction by liquid chromatography, enzyme digestion, tandem MS analysis and database matching to identify the proteins. Since the number of patients sampled is limited, the objective is not to perform a statistical analysis, but instead, to identify potential markers of therapy or toxicity for future studies.

7.7 Once the MTD has been established, an additional 10 patient expanded cohort will be accrued for proteomic correlative studies.

7.8 **Part II – Conventional Therapy:**

After treatment with ^{90}Y-MxDTPA-cT84.66/gemcitabine/HAI FUdR, patients will proceed to further systemic therapy. Systemic therapy, at the discretion of the treating physician, will be combined with additional cycles of HAI FUdR. Additional hepatic arterial infusion of FUdR permitted for a maximum of 4 cycles (including cycles delivered during Part I of protocol therapy with RIT/gemcitabine). Systemic therapy may be given in combination with hepatic arterial infusion FUdR at the discretion of the treating physician. Systemic therapy may be continued after completion of hepatic arterial infusion at the discretion of the treating physician.

7.9 The following tests and procedures will be performed prior to each cycle of therapy and for the study:

Study Parameters

	Baseline (pre-surgery)	Weekly between RIT cycles (starting 1 week post Y-90 dose)	Before ea cy of RIT & Off Part I of study	Every other week during FUdR therapy*	Off Part II of study
History & Physical	X[%]	X	X	X	X
Vital Signs	X[%]	X	X	X	X
Weight	X[%]	X	X	X	X
KPS	X[%]	X	X	X	X
CT/MRI Tumor	X[%]		X		X
Tumor Measurement[#]	X[%,@]		X		X
CBC, ANC, PLT	X[%]	X	X	X	X
CMP + Mg	X[%]	X	X	X	X
HIV	X				
Serum CEA	X[%]		X[$]		
CXR	X				
EKG	X				
Anti-Antibody Assay	X		X[$]		
Proteomic Analysis of blood sample	X		X		
Creatinine clearance	X[%]		X		
Hep B Surf Ag & Hep C Ab	X				

*or at the discretion of the treating physician

[#] If a complete or partial response is noted, this must be confirmed by measurements at least 4 weeks apart. During part II of therapy, tumor measurements should be obtained after every 2 cycles of therapy. If there is evidence of tumor response and patient goes off study, we will perform tumor measurements and CEA measurements at 3 mo and 6 mo off-study or as indicated by ongoing treatment.

[$] Anti-Ab assay and CEA should also be performed at 3 mo and 6 mo post last antibody infusion.

[%] For pts who signed the ICF prior to surgery, these tests must be repeated prior to study therapy.

[@] Tumor measurements are not required on the pre-surgery CT scan.

7.9   Criteria for Removal from Protocol Treatment

7.9.1 Patients with progressive disease: 25% increase in the sum of products of measurable lesions over smallest sum observed, OR reappearance of any lesion which had disappeared, OR clear worsening of any evaluable disease (see 9.1 and 9.2), OR appearance of any new lesion/site. For scan only bone disease, increased uptake does not constitute clear worsening. Worsening of existing non-evaluable disease does not constitute progression.

7.9.2 Patients developing unacceptable toxicity after any cycle (see Section 8.0).

7.9.3 Patients developing anti-antibody response after any course.

7.9.4 Patient refusal of further therapy.

7.9.5 Investigator's decision to remove the patient. The reason must be clearly documented on the case report forms.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1   Both hematologic and non-hematologic toxicity will be monitored. Hepatic, renal, pulmonary, cardiac, and hematologic toxicity will be monitored through studies outlined in Section 7.6. Dose-limiting toxicity is expected to be hematologic, GI, or hepatic. Lymphopenia is not a dose limiting toxicity. Toxicity will be scored by Common Toxicity Criteria outlined in Appendix IV.

8.2   Dose modification of subsequent cycles of Part I PROTOCOL therapy (RIT/GEMCITABINE/FUdR)for a given patient.

Patients with $\geq$ grade 3 non-hematologic or grade 4 hematologic toxicity will be taken off study. In all other patients, the therapy is to be repeated only after toxicity has reversed to at least grade 1 within 10 weeks from the last RIT therapy infusion. Dose modification for the next cycle should be made in a given patient experiencing adverse effects as follows:

	Grade 3 or 4 non-hematologic or Grade 4 hematologic toxicity	Grade 2 non-hematologic or Grade 3 hematologic	Grade 0, 1, or Grade 2 hematologic
FUdR	No further protocol treatment	Decrease one level	No Change
Gemcitabine	No further protocol treatment	Decrease one level 90 mg/m^2	No Change
^{90}Y cT84.66	No further protocol treatment	Decrease one level 12 mCi/m^2	No Change

If grade 3 or 4 non-hematologic, or grade 4 hematologic toxicity is observed at any dose level, that patient will be taken off protocol therapy. Two occurrences of grade 3 non-

hematologic toxicity, two occurrences of grade 4 hematologic or one occurrence of grade 4 non-hematologic toxicity at the starting dosage level one will necessitate revision of starting dosages.

The next cycle of treatment can be delayed for up to 4 weeks to allow for recovery from toxicity. After more than 10 weeks between treatments, the patient is off protocol treatment.

A patient will receive no further protocol therapy if:
a) any grade 4 toxicity occurs,
b) any grade 3 non-hematologic toxicity occurs
c) a second grade 3 hematologic toxicity occurs after dose modification, or
d) toxicity not reversible to grade 1 or less occurs.

9.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

9.1   The response endpoints will be: a) Progression-free survival, defined as first documented evidence of treatment failure. Recurrence should be diagnosed by biopsy if at all possible (see below); b) Overall Survival; c) Sites of recurrence.

9.2   Diagnosis of Treatment Failure

Every effort to biopsy recurrence of malignant disease should be made whenever possible.

Suspicious findings do not constitute treatment failure and patients should not be taken off study on this basis.

Below are listed examples of acceptable and unacceptable evidence for treatment failure at various sites.

9.2.1   Abdominal and/or Pelvic

(1)   Anastomotic

(a)   Acceptable -- positive cytology or biopsy

(b)   Suspicious -- abnormal barium enema, change in bowel habit, palpable mass, abnormal PET scan.

(2)   Abdominal, pelvic and retroperitoneal nodes

(a)   Acceptable -- positive cytology or biopsy, progressively enlarging node (> 2 cm) as evidenced by 2 CT scans separated by at least a 4 week interval, ureteral obstruction in the presence of a mass as documented on CT scan

(b)   Suspicious -- abnormal sonogram PET scan or CT scan or ureteral obstruction without mass

(3)   Peritoneum (including visceral and parietal peritoneum, omentum)

(a)   Acceptable -- positive cytology or biopsy, progressively enlarging intraperitoneal <u>solid</u> mass as evidenced by 2 CT scans separated by at least a 4 week interval

(b)   Suspicious -- abnormal sonogram or CT scan without solid mass

(4)   Ascites

(a)   Acceptable - Positive cytology or biopsy

(b)   Suspicious -- ascites without proof of tumor cells present

(5)   Liver

(a)   Acceptable - Positive cytology or biopsy

(b)   Suspicious: Any <u>3</u> of the following which are not associated with benign disease:

      a.   Recent or progressive hepatomegaly, abnormal liver contour

      b.   Positive radionuclide liver scan, PET scan, MRI scan, sonogram or CT scan

      c.   Abnormal liver function studies defined as > 3 times the upper limit of normal

      d.   Elevated CEA: A persistent rise in CEA titer confirmed on 2 determinations separated by a 4 week interval. The determination should be performed by the same laboratory using the same method.

      NOTE: An <u>elevated CEA</u> level will, as of itself, <u>not</u> be considered acceptable evidence of treatment failure. Non-protocol therapy will not be instituted on the basis of an abnormal CEA level.

(6)   Pelvic mass

(a)   Acceptable -- positive cytology or biopsy, progressively enlarging intrapelvic <u>solid</u> mass (> 2 cm) as evidenced by 2 CT scans separated by at least a 4 week interval

(b)   Suspicious -- abnormal sonogram PET scan or CT scan without solid mass

(7)   Abdominal wall, perineum and scar

(a)   Acceptable -- positive cytology or biopsy

9.2.2   Non-abdominal and non-pelvic sites

(1)   Skeletal

(a)   Acceptable -- (i) x-ray evidence of lytic, blastic, or mixed lytic/blastic lesions on skeletal films with or without bone scan confirmation, (ii) biopsy proof of bone metastasis, (iii) bone scan consistent with bone metastases in a patient with bone pain, or (iv) progressive bone scan changes over at least a 4 week period are necessary in asymptomatic patients with only bone scan abnormalities (v) progressive changes on MRI scan.

NOTE: In the absence of progressive disease by scan, a biopsy is strongly recommended. Any positive bone scan in the joints or in a recent area of trauma (surgical or otherwise) cannot be used as an indication of treatment failure.

(2)   Lung

(a)   Acceptable -- (i) positive cytology or biopsy or (ii) the presence of multiple pulmonary nodules which are felt to be consistent with pulmonary metastases

NOTE: If a solitary lung lesions is found and no other lesions are present on CT scan, further investigations such as biopsy, needle aspiration or resection should be performed. Proof of neoplastic pleural effusion should be established by cytology or pleural biopsy.

(3)   Bone marrow

(a)   Acceptable -- positive cytology, aspiration or biopsy

(b)   Suspicious -- unexplained depression of peripheral counts and/or erythroblastic blood picture

(4)   Central nervous system

(a)   Acceptable -- (i) positive MRI or CT scan, usually in a patient with neurological symptoms or (ii) biopsy or cytology (for a diagnosis of meningeal involvement)

9.2.3   Post-mortem examination

Autopsies should be done whenever possible and reports sent to Biostatistics.

10.0   DATA AND SAFETY MONITORING PLAN & DATA SUBMISSION SCHEDULE

A.   Definition of Risk Level

This is a Risk Level 4 study, as defined in the Guidance, Policy and Procedures for Data and Safety Monitoring for In-House Trials at City of Hope", http//www.infosci.coh.org/gcrc/doc/dsmp.doc, involving hepatic arterial infusion of chemotherapy (Fluorodeoxypyrimidine (FUdR)) and radiation therapy (Yttrium-90-labeled chimeric T84.66 anti CEA antibody).

B.   Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA/protocol nurse, and statistician are responsible for monitoring the data and safety of this study, including implementation of the stopping rules for the safety and efficacy.

Monitoring by the PMT will be done using the Phase I tracking log (see attached Appendix VI of protocol) to monitor data and safety for dose escalation. Data and safety will be reported to the COH DSMB after each dose level. Reporting of data and safety to the DSMB will occur at each dose level using the PMT report.

C.   Adverse Events

Reporting: Adverse events must be reported to the COH DSMB, IRB**,** and GCRC according to definitions and guidelines at http://www.infosci.coh.org/gcrc/doc/dsmp.doc and http://resadmin.coh.org/doc/irb3810.doc, which are defined below. AEs will be monitored by the PMT. Less than serious adverse events will be reported only at the time of protocol continuation reports. Grade 4 lymphopenia is not a reportable event.

All IND reports that are submitted to the FDA on this protocol will also be submitted to the DSMB for review.

A record of any interventional radiologic complications related to antibody infusion will be recorded on the Case Report Form.

Adverse Event - An adverse event (AE) is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention. All AEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be recorded on the City of Hope National Medical Center Adverse Events (COH AER) form (http://resadmin.coh.org/doc/irb3820.doc) form**.**

Serious Adverse Event - A serious adverse event (SAE) is defined as *any expected or unexpected adverse event* (AE, generally equivalent to CTCAE grades 3, 4 or 5) that is *related or unrelated* to the intervention that results in any of the following outcomes**:**

- Death
- A life-threatening event
- In-patient hospitalization (not required as part of the treatment) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Causes cancer
- Is an overdose

Certain medical events that may not result in death, be life-threatening, or require hospitalization, may also be considered a serious adverse event when appropriate medical or surgical intervention is necessary to prevent one of the outcomes listed above.

Unexpected Adverse Event – Any event in which the severity or specificity is not consistent with the risk information described in the protocol, and the event is not anticipated from the subject's disease history or status.

Expected Adverse Event - Any event in which the severity or specificity is consistent with the risk information described in the protocol or is anticipated based on the subject's medical history.

Attribution - For reporting purposes, attribution is the assessment of the likelihood that an AE is caused by the research agent or protocol intervention. The attribution is assigned by the Principal Investigator after considering the clinical information, the medical history of the subject, and past experience with the research agent/intervention. This is recorded using the Adverse Event Report (COH AER) form (http://resadmin.coh.org/doc/irb3820.doc) in one of 5 categories scored as the following: 5=related, 4=probably related, 3=possibly related, 2=unlikely related and 1=unrelated. The attribution is subject to change as follow-up information becomes available, and it can be changed by the DSMB or by the IRB in the process of review.

All primary data will be maintained by the assigned Data Manager from the Department of Biostatistics. Data will be submitted to the Data Manager at the time of each patient evaluation. These will include flow sheets, pathology reports, as well as off-study information. Records will be stored in a secure location within the Department of Biostatistics.

11.0 STATISTICAL CONSIDERATIONS

This is a Phase I/II trial. The primary objective of this trial is to determine the maximum tolerated dose and associated toxicities of intravenously administered gemcitabine and Y-90 cT84.66 delivered in combination with hepatic arterial infusion FUdR. Secondary objectives of the trial include the evaluation of the biodistribution, clearance and metabolism of Y-90 and In-111-cT84.66 and the estimation of radiation doses to whole body, normal organs, and tumor through serial nuclear imaging.

The maximum tolerated dose (MTD) and level at which dose-limiting toxicity (DLT) is experienced will be determined as follows:

Three patients will be enrolled at each dose level. If none of the three patients has Grade 3 non-hematologic toxicity or Grade 4 hematologic toxicity after the first cycle, then three patients may be enrolled at the next dose level.

At each dose level, if in two of three patients, Grade 4 hematologic toxicity or Grade 3 non-hematologic toxicity related to therapy occurs after the first cycle, then the level at which DLT occurs is established.

If Grade 3 non-hematologic toxicity or Grade 4 hematologic toxicity occurs in one of three patients, then three additional patients are entered at the same dose level. Then if Grade 3 non-hematologic toxicity or Grade 4 hematologic toxicity occurs after the first cycle in:

1. 1 of 6 patients, proceed to the next dose level
2. 2 of 6 patients, that dose is the dose level at which DLT occurs.

If Grade 4 non-hematologic toxicity related to therapy occurs after the first cycle at a dose level, no further patients will be treated at that dose level and the DLT will be established.

Once the dose level at which DLT is established, three additional patients will be enrolled at the preceding dose level to a total of six patients. The study will be closed after six patients have been accrued at a preceding level with the occurrence of no Grade 4 non-hematologic toxicity, and at most one Grade 3 non-hematologic toxicity or Grade 4 hematologic toxicity. The level at which DLT occurs will be defined as the minimum intolerable dose (MID). The preceding dose level at which no more than 1 of 6 patients experience Grade 3 non-hematologic toxicity and Grade 4 hematologic toxicity and no patients experience reversible Grade 4 non-hematologic toxicity, will be defined as the maximum tolerated dose (MTD).

MTD and MID will based on toxicities observed with the first cycle of therapy.
The two major endpoints will be 2 year progression-free survival and sites of recurrence (liver or distant sites). Since our City of Hope feasibility study (IRB 89188) suggested that only fewer than 40% of the entered patients will actually undergo surgical resection and adjuvant therapy, twice as many patients will be entered on study as will receive treatment.

The duration of progression-free and overall survival will be estimated using the product-limit method of Kaplan-Meier, and 95% confidence limits calculated for these estimates. The historical control data will then be compared to the Kaplan-Meier estimates of the 2-year progression-free survival rates.

Proteomic parameters will be compared with clinical response and toxicities in an exploratory manner. However, the heterogeneity of the population and the small number of patients treated make formal statistical analysis of these correlative studies unlikely.

12.0 PATHOLOGY REVIEW

All patients will have advanced malignancy confirmed by review of their biopsy specimens by the Division of Pathology of the City of Hope National Medical Center.

13.0 REGISTRATION GUIDELINES

Once a signed, written informed consent has been obtained and all pretreatment evaluations have been performed, patients will be entered on study, after review of patient eligibility criteria by the assigned Data Manager from the City of Hope Department of Biostatistics. Patients may be screened for registration by calling the Department of Biostatistics, ext. 2468.

14.0 SPECIAL INSTRUCTIONS

None.

15.0 ETHICAL AND REGULATORY CONSIDERATIONS

This study is to be approved by the Institutional Review Board according to City of Hope ethical and regulatory guidelines. All patients will have signed an informed consent for participation in research activities, and will have been given a copy of the Experimental Subject's Bill of Rights.

When results of this study are reported in medical journals or at meetings, identification of those taking part will be withheld. Medical records of patients will be maintained in strictest confidence, according to current legal requirements. However, they will be made available for review, as required by the Food and Drug Administration (FDA) or other authorized users such as the National Cancer Institute (NCI), under the guidelines established by the Federal Privacy Act.

16.0 REFERENCES

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APPENDIX I

ADMINISTRATION OF INTRAVENOUS RADIOLABELED ANTIBODY:

First, 100 ug of the antibody will administered intravenously over 2-3 minutes as a test dose. If there is no acute reaction after 15 minutes, the remainder of the dose will be administered intravenously over approximately 25 minutes. Although uncommon, possible adverse reactions that may occur include: 1) chills and fever, 2) itching, rash, or erythema, 3) pain in chest, flank or back (signs of anaphylaxis), 4) bronchospasm (may be sign of anaphylaxis), 5) hypotension (rare, may be sign of anaphylaxis), and 6) anaphylaxis. Infusion will be terminated for any of the following reasons: 1) fall in blood pressure > 25 mm Hg systolic, 2) respiratory distress, 3) pulse greater than 130/min, 4) temperature > 102°F, 5) clinician's judgment, or 6) patient's request. Nursing and physician personnel will be present at all times during the administration and post administration period. Vital signs will be monitored prior to administration, every 5-15 minutes during administration and in the immediate post administration period. After administration, the IV will be flushed with IV fluid and then discontinued. IV tubing, and any bottles or syringes used for administration of radiolabeled antibody will be counted post administration to ensure no excessive remaining activity in the tubing. A special 1" Plexiglass and lead holder for a 60 cc syringe has been constructed for shielding of the syringe which will contain the administered ^{90}Y antibody.

Percent Red Marrow in Irradiated Bone

Anatomic Site	Percent Total Red Marrow
Head	**13.1**
Cranium	12
Mandible	1.1
Upper Limbs	**8.3**
2 Humerus	2.0
2 Scapulae	4.8
2 Clavicles	1.5
Sternum	**2.3**
Ribs	**7.9**
Vertebrae	**42.3**
Cervical	3.4
Thoracic	14.1
Lumbar	10.9
Sacral	13.9
Lower Limb Girdle	**26.1**
2 Os Coxae	22
2 Femoral Head and neck	4

APPENDIX III

KARNOFSKY PERFORMANCE SCALE

100 Normal; no complaints; no evidence of disease

90 Able to carry on normal activity; minor signs or symptoms of disease

80 Normal activity with effort; some sign or symptoms of disease

70 Cares for self, unable to carry on normal activity or do active work

60 Requires occasional assistance, but is able to care for most personal needs

50 Requires considerable assistance and frequent medical care

40 Disabled; requires special care and assistance

30 Severely disabled; hospitalization is indicated, although death is not imminent

20 Very sick; hospitalization necessary; active support treatment is necessary

10 Moribund; fatal processes progressing rapidly

0 Dead

APPENDIX IV.

COMMON TOXICITY GRADING

USE CTC VERSION 3.0

http://ctep.cancer.gov/forms/CTCAEv3.pdf

PHASE I TRACKING LOG FOR IRB #: _____

Pt#	Med Rec #c	Name	Dose* Level (Arm)	Eval-uable for DLT?	> = Grade 3?	If Yes: Highest Grade (3,4) Toxicities Per Organ System During Cycles used for MTD Evaluation		Decision Re: Next Pt's Dose Level	Reason for Decision (Complete for each patient)
						DLT	**Non-DLT**		
						Grd Organ Sys	Grd Organ Sys		
___	_____-__	L _____	___	___Yes	___Yes	___ _____	___ _____	___ Same Dose	_____
		F _____		___ No	___ No	___ _____	___ _____	___ Escalate	_____
	Date					___ _____	___ _____	___ De-escalate	_____
	on-Study:	___/___/_____				___ _____	___ _____	___ MD Initials	_____
						Grd Organ Sys	Grd Organ Sys		
___	_____-__	L _____	___	___Yes	___Yes	___ _____	___ _____	___ Same Dose	_____
		F _____		___ No	___ No	___ _____	___ _____	___ Escalate	_____
	Date					___ _____	___ _____	___ De-escalate	_____
	on-Study:	___/___/_____				___ _____	___ _____	___ MD Initials	_____
						Grd Organ Sys	Grd Organ Sys		
___	_____-__	L _____	___	___Yes	___Yes	___ _____	___ _____	___ Same Dose	_____
		F _____		___ No	___ No	___ _____	___ _____	___ Escalate	_____
	Date					___ _____	___ _____	___ De-escalate	_____
	on-Study:	___/___/_____				___ _____	___ _____	___ MD Initials	_____
						Grd Organ Sys	Grd Organ Sys		
___	_____-__	L _____	___	___Yes	___Yes	___ _____	___ _____	___ Same Dose	_____
		F _____		___ No	___ No	___ _____	___ _____	___ Escalate	_____
	Date					___ _____	___ _____	___ De-escalate	_____
	on-Study:	___/___/_____				___ _____	___ _____	___ MD Initials	_____

1.1.1   **What is the waiting period for evaluating toxicities prior to entering the next patient?** _____

* Dose Levels: 1. _____   2. _____   3. _____   4. _____   5. _____   6. _____

7. _____   8. _____   9. _____   10. _____   11. _____   12. _____