A Phase I Study of Combined Modality $^{90}$Yttrium-CC49 Intraperitoneal Radioimmunotherapy for Ovarian Cancer$^1$


ABSTRACT

Purpose: The purpose of this study was to determine the feasibility and maximum tolerated dose of $^{90}$Yttrium-CC49 ($^{90}$Y-CC49) as the radioimmunotherapy (RIT) component of an i.p. combined modality treatment for recurrent ovarian cancer.

Experimental Design: A Phase I trial of $^{90}$Y-CC49 RIT was conducted in ovarian cancer patients who had persistent or recurrent intra-abdominal disease, had failed one or two prior chemotherapy regimens, and demonstrated TAG-72 expression. Patients were treated with a previously established combined modality treatment protocol of s.c. IFN $\alpha$2b, i.p. paclitaxel, and increasing dosages of i.p. $^{90}$Y-CC49. Patients were monitored for toxicity, generation of human antimouse antibody response, and clinical efficacy.

Results: Twenty eligible patients were treated per study specifications. All patients had been treated with debulking and paclitaxel/carboplatin-based chemotherapy at initial diagnosis. The patients included 11 patients with persistent disease at the time of second look laparotomy and 9 patients with delayed recurrence. Patients were treated with i.p. $^{90}$Y-CC49 given in combination with s.c. IFN $\alpha$2b (dose of $3 \times 10^6$ units for a total of four doses) and i.p. paclitaxel (dose of 100 mg/m$^2$). RIT treatment was associated with primarily hematological toxicity. The maximum tolerated dose of i.p. $^{90}$Y-CC49 was established at 24.2 mCi/m$^2$ in this combined regimen. Of nine patients with measurable disease, two had partial responses lasting 2 and 4 months. Of 11 patients with nonmeasurable disease, median time to progression was 6 months in 7 patients who recurred; 4 of these patients remain no evidence of disease at 9+, 18+, 19+, and 23+ months.

Conclusions: $^{90}$Yttrium-CC49-based RIT in combination with IFN $\alpha$2b and i.p. paclitaxel is feasible and well tolerated at a dose of $\leq24.2$ mCi/m$^2$.

INTRODUCTION

Despite advances in therapy for ovarian cancer, failure to control intra-abdominal disease remains the primary reason for poor overall outcome. We and others have investigated the utility of i.p. administration of radiolabeled monoclonal antibodies as a strategy for achieving long-term disease control in ovarian cancer patients. For our initial Phase I study, the monoclonal antibody CC49, which targets the tumor-associated antigen TAG-72, was conjugated to the novel radioisotope $^{177}$Lu-lutetium ($^{177}$Lu) and administered i.p. to patients with recurrent or persistent ovarian cancer. The results of this Phase I trial demonstrated tumor regression in one patient with gross measurable disease and extended disease-free survival for others with small volume residual disease (1, 2).

We were subsequently able to demonstrate the feasibility of a combined modality strategy of i.p. $^{177}$Lu-CC49 administered with s.c. IFN $\alpha$2b and i.p. paclitaxel with little need for RIT$^3$ dose attenuation (3). IFN $\alpha$2b has been shown to enhance expression of TAG-72 tumor antigen and improve localization of radiolabeled antibody to tumor cells (4, 5). Paclitaxel has activity against ovarian cancer, is a known radiation sensitizer, and has been demonstrated to sensitize ovarian cancer cells to the cytotoxic effects of ionizing radiation (6). This strategy was well tolerated because of nonoverlapping marrow suppression by paclitaxel (14 days) and RIT (6 weeks).

We then sought to determine whether this combined modality strategy was applicable to $^{90}$Yttrium ($^{90}$Y), a pure $\beta$ emitter that has higher $\beta$ energy ($E_{avg} = 935$ KeV) and depth of penetration (range, 1–2 mm) in comparison with $^{177}$Lu ($E_{avg} = 133$ KeV; range, 0.2–0.3 mm). Furthermore, $^{90}$Y has a shorter physical half-life (2.7 days) and does not produce $\gamma$ emissions. The current study was thus designed to identify the MTD, the

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$^3$The abbreviations used are: RIT, radioimmunotherapy; HAMA, human antimouse antibody; MTD, maximum tolerated dose; $E_{avg}$, average energy; CT, computed tomography; UAB, University of Alabama at Birmingham; TTP, time to progression; DOTA, 1,4,7,10-tetra-azacyclododecane $N,N',N''$-tetraacetic acid.
ammonium sulfate precipitation and vialed at 5.1 mg/ml (NSC 647944). The radiolabeling procedure was carried out in the UAB Cancer Center Radiolabeling Shared Facility with appropriate quality controls. The starting dose of 90 Y-CC49 was 14 mCi/m² for the first patient cohort and was escalated by 20% in subsequent patient cohorts until the MTD was reached. Cohorts of three to six patients were treated per dose level. Patients changed position after 90 Y-CC49 administration at least every 15 min for 2 h to facilitate homogeneous distribution. The treatment schema is outlined in Table 1.

Posttreatment Toxicity Evaluation. Patients were admitted to the UAB General Clinical Research Center for administration of paclitaxel and 90 Y-CC49. Vital signs were monitored every 15 min immediately after paclitaxel and 90 Y-CC49 treatment for 4–6 h. Patients were also monitored for acute and late toxicities during hospitalization, on an outpatient basis weekly for 6 weeks after therapy, and then every 12 weeks (if no evidence of disease progression was seen). Hematological toxicity was evaluated weekly after 6 weeks until hematological parameters returned to baseline. Adverse effects were graded using Cooperative Group Trials Common Toxicity Criteria. The MTD was defined as the dose of 90 Y-CC49 that produced at least three of five patients with grade 3 hematological toxicity and no more that two of five patients with grade 4 hematological toxicity. Grade 4 hematological toxicity in more than two of five patients, irreversible grade 3 or 4 hematological toxicity, or any grade 4 nonhematological toxicity established that dose level as exceeding the MTD.

Evaluation of HAMA Response. Serum was collected from all treated patients before treatment and then at various time intervals after treatment to assess HAMA response. HAMA assays were performed with modification as described previously (7).

Clinical Antitumor Monitoring. Although not the primary objective of this study, all patients were evaluated for tumor response. Each patient underwent a pretreatment physical examination and CT scan, which was repeated 6–7 weeks after 90 Y-CC49 infusion. Standard criteria for tumor response were used for those patients with measurable disease. Partial response was defined as a >50% reduction in the product of perpendicular diameter measurements of lesions that can be measured bidimensionally, and progression was defined as a >25% increase in measurable lesions or the appearance of new sites of disease. Patients with nonmeasurable disease were monitored for clinical evidence of recurrence at 3-month intervals, and radiographic studies were used as indicated after the 6 week posttreatment CT scan. TTP was measured from the date of 90 Y-CC49 infusion to the time of clinical progression or to initiation of other cytotoxic chemotherapy in patients with measurable disease or time to clinical detection of recurrence in patients with nonmeasurable disease. CA-125 levels were not considered for criteria of response or progression.

Statistical Methods. This study was designed to determine the MTD and the toxicities associated with the administration of i.p. 90 Y-CC49 when given in combination with s.c. IFN α2b and i.p. paclitaxel in ovarian cancer patients. Another objective of the study was to identify potential clinical efficacy. Using a dose-escalation scheme to determine the MTD, patients

**MATERIALS AND METHODS**

*Eligibility Criteria. A dose-escalating Phase I trial of i.p. administered CC49 antibody radiolabeled with 90Y in combination with IFN α2b and paclitaxel was conducted for patients with persistent/recurrent ovarian cancer. Patients eligible for the study included those with histologically confirmed, TAG-72-reactive ovarian or extraovarian adenocarcinoma; with persistent or recurrent disease after a primary platinum-based chemotherapy program; with disease confined to the peritoneal cavity ± retroperitoneal lymph nodes; and with no tumor nodule >5 cm in diameter. Tumor measurements were made either from CT images or from description of second-look laparotomy findings; CT scans were performed within 3 weeks before therapy, and second-look laparotomy procedures varied from <2 weeks to 10 weeks before therapy. Patients were also required to be ≥18 years old, to have a Karnofsky performance status of ≥60, to have adequate organ function, and to have free flow of fluid in the abdominal cavity by 99m Tc scan within 2 weeks before i.p. therapy. No concurrent nonstudy chemotherapy, radiation, or immunotherapy was allowed. Patients who had a history of other cancers or had received prior i.p. therapies, antibody treatment, or whole abdomen radiation were ineligible for the study. This study was approved by the UAB Institutional Review Board, and all patients signed an informed consent form after receiving a detailed explanation of this study.*

**Study Design and Treatment Plan.** The treatment plan was identical to that in our prior trial investigating 177Lu RIT-based multimodality treatment (3). Specifically, human recombinant IFN α2b (Schering) at a dose of 3 × 10⁶ units was given to all patients s.c. for a total of four doses on alternate days beginning 5 days before administration of 90 Y-CC49. Paclitaxel at a dose of 100 mg/m² was administered i.p. through a previously placed percutaneous peritoneal access catheter in patients 2 days before 90 Y-CC49 administration. Before paclitaxel administration, patients were premedicated with 20 mg of dexamethasone p.o. 14 and 7 h before treatment and with 50 mg of diphenhydramine and 50 mg of ranitidine i.v. 1 h before treatment.

The murine monoclonal antibody CC49, a high affinity murine product that reacts against tumor-associated glycoprotein TAG-72, was produced by continuous proliferation of the hybridoma cell line in liquid flow by the Dow Chemical Company. The CC49-PA-DOTA conjugate was subsequently purified by several sequential passages through ion exchanges after ammonium sulfate precipitation and vialled at 5.1 mg/ml (NSC 620537, BB IND 3496). Radiolabeling of the conjugate with 90Y was performed on the day of each administration using 5 mg of the CC49-PA-DOTA bifunctional conjugate (NSC 647944). The radiolabeling procedure was carried out in the UAB Cancer Center Radiolabeling Shared Facility with appropriate quality controls. The starting dose of 90 Y-CC49 was 14 mCi/m² for the first patient cohort and was escalated by 20% in subsequent patient cohorts until the MTD was reached. Cohorts of three to six patients were treated per dose level. Patients

<table>
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<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>1</th>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>90 Y-CC49</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</table>

Using a dose-escalation scheme to determine the MTD, patients

**Table 1** Treatment schema

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were accrued to four dose cohorts (14, 17, 20.4, and 24.2 mCi/m²). Descriptive statistics (mean, median, and range) on patient characteristics were calculated. Frequencies were tabulated to aid in assessing HAMA response and clinical response. The mean and median TTP were obtained by applying the Kaplan-Meier method (8). This method was done using SAS software (Version 8; SAS Institute, Inc., Cary, NC; Ref. 9).

RESULTS

Study Population. Between October 1999 and August 2000, 20 eligible patients were treated per study specifications (Table 2). The patient characteristics are provided in Table 2. Patient ages ranged from 39 to 77 years (median age, 61 years). All patients were diagnosed with stage II–IV ovarian adenocarcinoma at initial diagnosis. Serous papillary adenocarcinoma was the most frequent pathological diagnosis (55%), and at least 60% of patients had poorly differentiated tumors. All patients had undergone primary tumor reductive surgery, and 55% were optimally debulked. All patients were treated i.v. with at least five cycles of paclitaxel and platinum/carboplatin chemotherapy. Eleven patients (60%) had persistent disease noted at the time of second-look laparotomy, and nine patients were treated at the time of delayed recurrence after primary therapy.

Clinical Toxicity. All patients had adequate i.p. distribution noted on ⁹⁰Y-CC49 radiographic imaging. Bremsstrahlung imaging was also performed in a selected few patients after administration of ⁹⁰Y-CC49 and demonstrated adequate i.p. distribution (Fig. 1). Dose cohorts and toxicities are listed in Table 3. Marrow suppression was the most frequently encountered toxicity. The dose cohort of 24.2 mCi/m² ⁹⁰Y-CC49 fulfilled the definition of MTD with four of five patients having at least grade 3 hematological toxicity and with one of five patients having grade 4 hematological toxicity. Five additional patients were added to this dose cohort. The time to nadir counts were variable with a biphasic decrease in WBC count as described previously (3). Specifically, a nadir occurred 7–14 days after IFN α2b and paclitaxel administration, and a second nadir occurred 4–10 weeks after ⁹⁰Y-CC49 administration. Two patients developed febrile neutropenia, and both responded to antibiotic therapy. Platelet nadirs generally occurred 28–58 days after ⁹⁰Y-CC49 administration at the MTD, and the recov-

Table 2 Patient characteristics

<table>
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<tr>
<th>Patient No.</th>
<th>Age (yrs)</th>
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<th>Histology</th>
<th>Grade</th>
<th>Primary chemotherapy</th>
<th>Timing of accrual</th>
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</tr>
<tr>
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<td>68</td>
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<td>PS</td>
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<td>T/C × 6</td>
<td>REC</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>III Suboptimal</td>
<td>PS</td>
<td>3</td>
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<td>SL</td>
</tr>
<tr>
<td>4</td>
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<td>AD</td>
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<tr>
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<td>PS</td>
<td>3</td>
<td>T/C, PSC 833 × 6</td>
<td>SL</td>
</tr>
<tr>
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<td>III Suboptimal</td>
<td>END</td>
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<td>T/C × 8</td>
<td>SL</td>
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<td>1</td>
<td>T/C × 6</td>
<td>SL</td>
</tr>
<tr>
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<td>60</td>
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<td>PS</td>
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<td>T/C × 6</td>
<td>REC</td>
</tr>
<tr>
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<td>REC</td>
</tr>
<tr>
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<td>PS</td>
<td>3</td>
<td>T/C, unknown no. of courses</td>
<td>REC</td>
</tr>
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<td>END</td>
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<td>T/C × 6</td>
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<td>16</td>
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<td>PS</td>
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<td>T/C × 6</td>
<td>REC</td>
</tr>
</tbody>
</table>

¹ AD, adenocarcinoma; PS, papillary serous adenocarcinoma; END, endometrioid adenocarcinoma; SL, treated for disease noted at second-look laparotomy; REC, treated for delayed recurrence of disease; PSC 833, multidrug resistant protein pump inhibitor; N/A, not available; T/C, paclitaxel and carboplatin; VP16, etoposide.

Fig. 1 Bremsstrahlung image demonstrating dispersion of ⁹⁰Y-CC49 within the peritoneal cavity of a treated patient.
ery to baseline usually required less than 3 weeks in most patients. One patient required both platelet and packed RBC transfusions.

Other toxicities included grade 1 and 2 fevers and myalgia, which occurred in several patients with the first IFN α2b injection. Fewer symptoms were experienced with subsequent IFN α2b injections. Two patients developed a local catheter infection requiring oral antibiotics; another patient had a 1-day hospitalization for i.v. EDTA to reduce bone accumulation of free 89Y. This may reflect the use of the more stable bifunctional chelating agent DOTA. This is the first study to our knowledge investigating the utility of i.p. 89Y-radiolabeled CC49 for this disease. Similar to what has been demonstrated in prior i.p. ovarian cancer studies, myelosuppression was the dose-limiting toxicity. The MTD of 89Y-CC49 in our study, when administered in combination with s.c. IFN α2b and i.p. paclitaxel, was 24.2 mCi/m². This dose is similar to what has been reported in other studies using 89Y-radiolabeled antibodies alone. Specifically, Stewart et al. and Rosenblum et al. reported MTDs of 89Y-HFMG1 (30 mCi) and 89Y-B72 (40 mCi) that were dependent on the concurrent administration of continuous infusion of EDTA to reduce bone accumulation of free 89Y (10–12). Our MTD of 24.2 mCi/m² is similar to or greater than these dose levels and did not require EDTA chelation. This may reflect the use of the more stable bifunctional chelating agent DOTA. This interpretation is supported by a recently completed Phase I trial, which used this same CC49-DOTA conjugate radiolabeled with 89Y and EDTA administered i.v. to patients with advanced non-small cell cancer (13). This study demonstrated no amelioration of marrow suppression at the MTD by continuous infusion of EDTA.

DISCUSSION

The i.p. administration of radiolabeled antibodies for ovarian cancer has been investigated in the context of ovarian cancer for over a decade. This is the first study to our knowledge investigating the utility of i.p. 89Y-radiolabeled CC49 for this disease. Similar to what has been demonstrated in prior i.p. RIT ovarian cancer studies, myelosuppression was the dose-limiting toxicity. The MTD of 89Y-CC49 in our study, when administered in combination with s.c. IFN α2b and i.p. paclitaxel, was 24.2 mCi/m². This dose is similar to what has been reported in other studies using 89Y-radiolabeled antibodies alone. Specifically, Stewart et al. and Rosenblum et al. reported MTDs of 89Y-HFMG1 (30 mCi) and 89Y-B72 (40 mCi) that were dependent on the concurrent administration of continuous infusion of EDTA to reduce bone accumulation of free 89Y (10–12). Our MTD of 24.2 mCi/m² is similar to or greater than these dose levels and did not require EDTA chelation. This may reflect the use of the more stable bifunctional chelating agent DOTA. This interpretation is supported by a recently completed Phase I trial, which used this same CC49-DOTA conjugate radiolabeled with 89Y and EDTA administered i.v. to patients with advanced non-small cell cancer (13). This study demonstrated no amelioration of marrow suppression at the MTD by continuous infusion of EDTA.

We have previously demonstrated that a combined modality strategy of IFN α2b, i.p. paclitaxel, and i.p. 177Lu-CC49 was well tolerated and did not require a reduction in the dose of radiolabeled antibody administered. In this study, we examined a more energetic radioisotope (89Y) antibody conjugate in the same combined modality regimen. Once again, a substantial dose of radiolabeled antibody was well tolerated, and a similar biphasic, nonoverlapping marrow suppression from IFN α2b, paclitaxel, and radiolabeled antibody was observed.

One advantage for using isotopes conjugated to antibodies as an i.p. therapeutic option for patients with ovarian cancer is to ameliorate bowel complications associated with i.p. admin-
administration of unconjugated radioisotopes. Analysis of the results of two large randomized trials in early-stage ovarian cancer demonstrated a 5–10% bowel complication rate associated with i.p. administration of 32P (14). We noted no significant bowel complications in this study, despite the fact that 90Y has a mean β energy (E_{avg} = 935 KeV) and depth of penetration (range, 1–2 mm) that are similar to those of 32P (695 KeV and 1–4 mm, respectively). This diminished rate of bowel complications has been the experience associated with i.p. administration of radiolabeled antibodies both in general and in those trials specifically using 90Y (15).

Although Phase I trials are not designed to estimate response rates or frequency of antitumor efficacy, they do provide evidence for antitumor activity of experimental treatments. Other investigators using i.p. administered 90Y-radiolabeled antibodies for ovarian cancer have also reported antitumor activity. Specifically, Stewart et al. (10) noted laparoscopic evidence of regression of small volume disease in 1 of 14 ovarian cancer patients who were treated with i.p. 90Y-HFMMG1 and palliation of ascites in 3 of 5 affected patients. Rosenblum et al. (12) demonstrated four responses in patients treated with 15–30 mCi of 90Y-B72.3; the duration of response ranged from 1–12 months. Epenetos et al. (16) reported 78% survival at >10 years in a cohort of 21 stage Ic–IV patients who had achieved a clinical complete response after conventional platinum chemotherapy and were treated with i.p. 90Y-HFMMG1.

We have published three sequential Phase I studies (including this trial) with identical patient selection criteria and a variable degree of expansion of the MTD cohort of patients. In our initial trial, 1 of 13 patients (8%) with measurable disease had a partial response. Of the 14 patients with nonmeasurable disease in this prior trial, 3 remained disease free for 21, 27, and 60 months; and 2 remain disease free 72+ and 96+ months after therapy (2). Our second trial used the combined modality of IFN α2b, i.p. paclitaxel, and 177Lu-CC49. Partial response was noted in 4 of 17 patients (24%) with measurable disease. Of the 27 patients with nonmeasurable disease, 8 had disease-free intervals of 16, 16, 16, 17, 22, 34, 34, and 37 months after treatment, and 2 additional patients remain disease free at 31+ and 49+ months after therapy (3). Similarly, partial responses were noted in 2 of 11 patients (18%) with measurable disease treated in the current trial. In addition, the disease-free interval exceeded 12 months in five of nine patients with nonmeasurable disease, and four of these five patients remain cancer free 15+ to 23+ months after treatment. This experience provides evidence that this strategy can be administered safely, is well tolerated, and has antitumor activity. It also provides solid evidence that IFN α2b enhancement of target antigen expression and i.p. administration of substantial dosages of paclitaxel (100 mg/m²) are well tolerated and do not preclude administration of RIT at maximum or near maximum doses in a combined multimodality format.

The supply of this murine CC49-DOTA conjugate has been exhausted, and there are no plans for Phase II trials or production of further conjugate. Rather, we plan to proceed with our i.p. RIT studies using a new genetically engineered construct of CC49 (17, 18). This construct is a humanized (CDR-grafted) CC49 reagent (IgG-1K) with a deletion of the C_{H}2 region (huCC49ΔC_{H}2). This reagent has the ability to bind to an i.p. murine tumor model of TAG-72-positive human tumor cells in a fashion similar to that achieved with the intact antibody while having a much shorter plasma half-life (19). The plasma T_{1/2} of this reagent in humans has recently been determined in patients with metastatic gastrointestinal cancer using i.v. administration of 111In-luCC49ΔC_{H}2.4 The plasma T_{1/2} was 21 h compared with a T_{1/2} of 48–50 h for murine CC49. In i.p. RIT protocols, this reagent should thus have the tumor localization characteristics of murine CC49 and should reduce marrow radiation due to its shorter T_{1/2}. In addition, it should have low immunogenicity and allow repeat cycles of therapy. We plan to explore directly radiolabeled and chelate conjugates of this novel molecule with several different radionuclides in i.p. RIT formats. Our experience with i.p. radiolabeled murine CC49 will aid in our development of this strategy and provide baseline data to compare with our studies with this new reagent.

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REFERENCES


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