Initial Experience Evaluating $^{90}$Ytrium-Radiolabeled Anti-Carcinoembryonic Antigen Chimeric T84.66 in a Phase I Radioimmunotherapy Trial\(^1\)

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Abstract

Chimeric T84.66 ($cT84.66$) is a high-affinity ($5 \times 10^{10} \text{M}^{-1}$) anti-carcinoembryonic antigen (CEA) IgG1. In a recently completed pretherapy imaging trial, 111In-labeled $cT84.66$ demonstrated targeting of CEA-producing metastatic sites and low immunogenicity, with human antichimeric antibody (HACA) response in only 1 of 15 patients after a single administration. The purpose of the present study was to evaluate $cT84.66$-diethyleneetriaminepentaaetic acid labeled with $^{90}$Y in a dose-escalation Phase I trial. Patients with metastatic CEA-producing malignancies received imaging doses of 5 mCi $^{111}$In-labeled $cT84.66$ first, followed 1–2 weeks later by 5 mg $cT84.66$ labeled with the therapeutic dose of $^{90}$Y. Immediately following the therapeutic infusion, diethyleneetriaminepentaaetic acid was administered by continuous i.v. infusion over 3 days at 250 $\mu$g surface area/24 h. Biodistribution, infusion, diethylenetriaminepentaacetic acid was administered by continuous infusion. Localization of the antibody to nonhepatic metastatic sites was observed. Size-exclusion high-performance liquid chromatography demonstrated the formation of CEA:antibody complexes in serum in all three patients. A significant variation among patients in the clearance rate of the antibody and complexes from blood to liver was seen, which resulted in a reciprocal relationship between estimated liver dose and red marrow dose. Patients who demonstrated faster clearance to liver demonstrated greater excretion of a low-molecular-weight metabolite through the urine. Two patients developed HACA responses, which persisted at 4 months after therapy. At this first dose level, no tumor responses were seen and reversible grade 1 thrombocytopenia was observed in 2 patients. $cT84.66$ demonstrated effective localization in CEA-producing tumors. Its low immunogenicity after a single administration makes it attractive for further evaluation as a radioimmunotherapeutic agent. However, further evaluation is needed to determine whether its immunogenicity will remain low after multiple administrations. Additionally, in two of the three patients, we identified rapid clearance of the antibody to the liver. This underscores the need to identify, characterize, and understand further those factors that influence the biodistribution and clearance of anti-CEA antibodies to allow for better selection of patients for therapy and rational planning of radioimmunotherapy.

Introduction

The use of radiolabeled monoclonal antibodies to deliver therapeutic doses of radiation to tumors is undergoing active investigation as a potential form of cancer therapy. Antibodies to a number of tumor-associated antigens have been and continue to be studied in Phase I and Phase II clinical trials (1–8).

Several groups have evaluated antibodies directed against CEA\(^3\) as agents for radioimmunoimaging (9–14) and radioimmunotherapy (15).

CEA provides an attractive tumor antigen target, because it is expressed by a wide variety of tumor types, particularly adenocarcinomas of the gastrointestinal tract, lung, and breast (16–21). Radioimmunoimaging trials have demonstrated effective tumor targeting and imaging of tumors using anti-CEA antibodies radiolabeled with $^{111}$In or $^{111}$In. At this institution, Beatty et al. (22) demonstrated imaging of 69% of primary colorectal carcinomas using an $^{111}$In-labeled, high-affinity, anti-CEA murine monoclonal antibody, mT84.66.

To date, most trials have used murine monoclonal antibodies. Murine antibodies have the disadvantage of being recognized as foreign by the patient's immune system, which can lead to the formation of HAMA in 30–50% of patients (23–26). The formation of HAMA can hasten blood clearance and, therefore, can compromise the imaging or therapeutic efficacy of a subsequently administered antibody (27, 28). Thus, investigators have begun to evaluate chimeric and humanized antibodies, some of which have demonstrated decreased immunogenicity (29–33). Recently, a chimeric version of mT84.66 ($cT84.66$) was developed at the City of Hope National Medical Center and evaluated in a pilot imaging trial. This trial confirmed that $^{111}$In-labeled $cT84.66$ targeted CEA-producing tumors, comparable to other intact anti-CEA antibodies (34). In addition, development of HACA was low (1 of 15 patients) after single administrations (35). Based on these results, a Phase I therapy trial with $^{90}$Y-labeled $cT84.66$ was initiated recently. In the following, we report the results of the first three patients on this therapy trial.

Materials and Methods

Antibody Production and Conjugation. Chimeric T84.66 is an intact IgG1 antibody derived from murine T84.66, an IgG1 monoclonal antibody developed at the City of Hope National Medical Center with high specificity and affinity (approximately 2 $\times 10^{10} \text{M}^{-1}$) for CEA (36, 37). It recognizes the A3 B3 domain of CEA and has little cross-reactivity with normal tissues. As reported by Neumaier et al. (38), genomic clones encoding for the heavy and light chains of T84.66 were isolated from the murine hybridoma. Chimeric genes were constructed by fusing the murine variable regions to the human constant regions, using restriction endonuclease cleavage sites located in the J–C introns. Chimeric light-chain ($\kappa$) and heavy-chain ($\gamma$) genes were inserted into the expression vector pSV2-neo to yield the dual expression vector pSV2J3, containing both the heavy- and light-chain transcription units. Murine myeloma Sp2/0 cells were then transfected with the pSV2J3 plasmid by electroporation. Transfectomas were then subcloned to yield a stable, viral-free, high producer. The affinity constant of the chimeric antibody was comparable (5 $\times 10^{10} \text{M}^{-1}$) to the murine antibody. Large-scale production was accomplished using a hollow-fiber bioreactor. The antibody was purified through a two-step purification process, which included protein A affinity and anion exchange chromatography.

Purified antibody was conjugated to the isothiocyanatobenzyl DTPA chelate of Sumerdon et al. (39). The ratio of chelate:antibody was determined to be 1:4:1 using the method of Meares et al. (40). Characterization of the purified product was assessed by SDS-PAGE (reducing and nonreducing conditions).
and by gel filtration chromatography. The immunoreactivity of cT84.66-DTPA conjugate was >90% by solid-phase CEA RIA. Immunospecificity was evaluated by immunohistochemistry in more than 100 human colorectal cancers and 40 gastric cancers. Ninety-three percent of tumors stained positive with cT84.66, which was similar to its murine antecedent. In addition, the percentage of stained cells, as well as the intensity and location of staining observed, were comparable to murine T84.66, with the majority of tumors demonstrating intense staining of >75% of cells. Seventy-five normal tissues were also evaluated by immunohistochemistry. No staining was seen with normal granulocytes, gabblerd, lung, kidney, spleen, liver, and stomach. There was weak staining at the apex of some of the cells of the intestinal tract.

The final voided lot of purified antibody conjugate used in this study met standards set by Food and Drug Administration guidelines. An Investigational New Drug application for 111In- and 90Y-labeled cT84.66 is currently on file with the Food and Drug Administration.

Radiolabeling of Antibody. Radiolabeling was performed by incubating the cT84.66-DTPA conjugate with 111In (Medi-Physics, Arlington Heights, IL) or 90Y (Nordion International, Kanata, Ontario, Canada) for 30 min at room temperature, with the reaction stopped by the addition of 0.01 M sodium EDTA. Preclinical human serum stability testing demonstrated <4% of 111In activity dissociating from the antibody out to 216 h. Preclinical murine antibody biodistribution studies of 111In-labeled cT84.66-DTPA demonstrated targeting to CEA-producing colon carcinoma xenografts (LS174T) and normal organ biodistributions that were comparable with other intact 111In-labeled anti-CEA antibodies (35). Tumor uptakes in the range of 70% I/D at 48–72 h after infusion were observed. These studies also demonstrated comparable biodistributions between the 111In- and 90Y-labeled cT84.66-DTPA.

Prior to each administration, the sample was purified by size-exclusion HPLC (TSK-G3000 column) and tested for endotoxin by limulus amoebocyte lysate assay (BioWhittaker, Walkersville, MD) and isotope binding by instant TLC before patient administration. For all administered doses, radiolabeling of >90% and endotoxin levels of <1 units/ml was demonstrated. Immunoreactivity by solid-phase CEA RIA was consistently >95%.

Clinical Trial Design. Chimeric T84.66, radiolabeled with 111In or 90Y, was evaluated in a Phase I dose escalation radioimmuno-therapy trial, which is currently ongoing. The primary objective of this trial was to determine the maximum tolerated dose of 90Y-cT84.66 when administered i.v. and to characterize the associated toxicities. Biodistribution, tumor targeting, absorbed radiation dose estimates, and clearance of the antibody were also evaluated through blood samples, 24-h urine collections, and nuclear scans performed at time points out to 7 days after antibody infusion.

Patients were eligible if they were 18 years of age or older and had evidence of metastatic disease that was CEA producing and refractory to conventional therapies. Tumor CEA production was documented by either an elevated CEA concentration and/or metastatic disease that was CEA producing and refractory to conventional therapies. A bowel cathartic was administered to all patients prior to each scan to reduce normal bowel uptake, unless it was thought that the patient could not tolerate such a preparation.

For this trial, a maximum of three therapy cycles at 6-week intervals was planned for each patient. Toxicity was scored using the Southwest Oncology Group toxicity criteria. Informed written consent was obtained for each patient prior to protocol entry. This protocol had full review and approval from the City of Hope Institutional Review Board.

Analysis of HACA Response. The serum HACA response to cT84.66 and cT84.66-DTPA was assayed prior to infusion and at planned time points of 2 weeks and 1, 3, and 6 months after infusion using a double-capture, solid-phase, quantitative RIA, similar to that published by LoBuglio et al. (32). Briefly, patients’ sera were diluted 1:4 or 1:5 in normal saline, and 100 μl each dilution were pipetted into quadruplicate glass tubes. To each tube, 100 μl 111In-labeled cT84.66 (approximately 100,000 cpm) was added. Polystyrene beads coated with cT84.66 or cT84.66-DTPA were then added to the tubes, incubated at room temperature for 90 min, and then washed. The beads were then assayed on a Packard gamma counter (model BS3003) with a window setting of 150–500 keV. Serial dilutions of a goat antihuman Fc preparation of known concentration was used to generate a standard curve from 12.5 to 200 ng/ml. One % BSA in PBS was used as a negative control. A sample was scored positive if it was >12.5 ng/ml, the limit of sensitivity of this particular RIA.

Pharmacokinetic Analysis and Dosimetry Estimates. Whole-body and normal organ absorbed radiation doses were estimated from serial 111In scans of the whole body and local anatomical areas. Opposed images were used to construct the geometric mean uptake as a function of time for those organs seen in both projections. Otherwise, single-view images were acquired. All resultant curves on 111In activity versus time were corrected for background and patient attenuation. Attenuation was estimated using a separate series of experiments involving gamma camera efficiency in counting a 111In phantom source as a function of tissue-equivalent absorber thickness.

Given the geometric mean or single-view uptake values, residence times for 90Y (41) were calculated. Using the ADAPT II software (42), a five-compartment model was used to fit the biodistribution data for the blood, liver, urine, and total body. In the model, blood served as the central (mamillary) compartment, with liver, residual body, urine, and fecal excretion as the other compartments. Modeling of the data was done separately for the imaging and therapeutic 111In infusions. A single rate input into the blood compartment was specified. Residual activity was constrained to be equal to the difference between the total-body activity and the sum of the blood and liver activity.

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Results

Patient Results. To date, three patients have been entered in this trial at the first dose level of 5 mCi/m² ⁹⁹ᵐTc-T84.66. The clinical courses of these patients are summarized in Table 1. All three patients had extensive metastatic colorectal cancer with elevated CEA levels ranging from 97 to 302 ng/ml. CEA immunohistochemistry also was performed on tumor samples from patients 1 and 2 and demonstrated intense and diffuse (>90% cells) tumor staining. All three patients had received two regimens of chemotherapy previously but had not received radiotherapy or monoclonal antibodies previously. Antibody localization to metastatic sites in the abdominal wall, mesentery, and pelvis was seen in patient 1 (Fig. 1). Patients 2 and 3 had only liver metastases, which were imaged as photopenic lesions due to uptake of activity by normal liver, as has been observed with other ¹¹¹In-labeled antibodies (10, 22, 34). Nuclear images were similar after the first and second antibody infusions.

There were no side effects or changes in vital signs associated with the antibody infusion. Two of the three patients developed grade 1 thrombocytopenia, which recovered to baseline. Patient 1 developed headaches and nausea 24 h after initiation of DTPA, which resolved with reduction of the DTPA dose. No other toxicities related to the therapy were observed. At this first dose level, all patients demonstrated tumor progression at 6–10 weeks after therapy, preventing the administration of a second cycle of radiolabeled antibody.

Evaluation of Immunogenicity. Patients 1 and 2 developed HACA responses as early as 2 weeks after the therapeutic infusion.

Fig. 2 shows the time courses and titers of these responses. Both patients developed HACA responses to the antibody, as well as to the conjugated antibody. Titers remained elevated beyond 3 months after infusion and continue to be followed. Patient 3 had a negative HACA response when evaluated at 1 month after the therapeutic infusion. He died prior to the planned 3-month sample.

Pharmacokinetics and Dosimetry Estimates. As observed in the pilot imaging trial (35), significant differences between patients in the rate of antibody clearance from the blood to the liver were observed. Fig. 3 shows antibody uptake and clearance as a function of time for blood, liver, and urine for patients 1 and 3. Patient 1 demonstrated relatively slow blood clearance to the liver, whereas patient 3 demonstrated rapid clearance to the liver. Pharmacokinetics for patient 2 was similar to that of patient 3, with rapid clearance of antibody from the blood to the liver. This interpatient variation in clearance kinetics resulted in variations in projected organ doses and a reciprocal relationship between liver and red marrow doses (Table 2). Size-exclusion HPLC demonstrated the formation of CEA:antibody complexes in serum after antibody infusion (Fig. 4). In patients with high liver accumulation, the CEA complexes disappeared quickly from the serum, whereas in those patients with lower liver accumulation, serum

Fecal activity was constrained to be equal to the difference between the administered activity and the sum of the urine and total-body activity. Blood and urine counts were decay corrected to the time of sampling for either ¹¹¹In or ⁹⁹ᵐTc and expressed as the percentage of injected activity. Therefore, physical decay of the isotope was included explicitly in the system of differential equations used to describe the models. Using the parameter estimates from the compartmental model, Mathematica (43) was used to estimate time-activity curves by calculating the area under the curve for each organ. Dose estimates for ⁹⁹ᵐY cT84.66 were then estimated with the medical internal radiation dose method (41) using the MIRDOS2 program (44).

Bone marrow absorbed doses were estimated using three source organs: cortical bone; marrow; and blood. Relative amounts of activity in cortical bone and marrow in patients 1 and 3 were determined from a single bone marrow biopsy from the iliac crest obtained 5–7 days after the therapeutic infusion. A bone marrow biopsy was not possible in patient 2. Cortical bone and marrow contributions for patient 2, therefore, were estimated using the cortical bone and marrow contributions of patient 3, because both patients demonstrated similar antibody pharmacokinetics. Both cortical bone and marrow uptakes were then normalized to imaging data taken over the sacrum, so that integration of these values over time was possible. Blood contribution was determined using the American Association of Physicsists in Medicine algorithm (45) based on the plasma clearance curves. In this method, the specific activity of the marrow is assumed to be 0.2–0.4 that of the blood. A value of 0.3 was used in our calculations. Blood samples at the various times indicated above permitted evaluation of the plasma clearance and, hence, marrow ¹¹¹In activity versus time curves.

Table 1 Clinical summary of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)/sex</th>
<th>Diagnosis</th>
<th>Pre-infusion CEA (ng/ml)</th>
<th>Previous therapy</th>
<th>Administered ⁹⁹ᵐY activity (mCi)</th>
<th>Tumor response</th>
<th>Toxicities</th>
<th>HACA response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47/female</td>
<td>Colorectal cancer with abdominal wall, mesenteric, and pelvic metastases</td>
<td>97</td>
<td>5-FU/leucovorin, i.p. IUdR⁴</td>
<td>7.5</td>
<td>Progression at 6 wk</td>
<td>Reversible grade 1 thrombocytopenia, headaches and nausea from DTPA</td>
<td>Positive beginning at 2 wk after infusion</td>
</tr>
<tr>
<td>2</td>
<td>57/female</td>
<td>Colorectal cancer with liver metastases</td>
<td>294</td>
<td>5-FU/leucovorin, hydroxyurea</td>
<td>9.5</td>
<td>Progression at 10 wk</td>
<td>None</td>
<td>Positive beginning at 2 wk after infusion</td>
</tr>
<tr>
<td>3</td>
<td>55/male</td>
<td>Colorectal cancer with liver metastases</td>
<td>302</td>
<td>cis-platinum/IUdR/leucovorin, CPT-11</td>
<td>9.9</td>
<td>Progression at 8 wk</td>
<td>Reversible grade 1 thrombocytopenia</td>
<td>Negative at 1 mo after infusion</td>
</tr>
</tbody>
</table>

⁴ 5-FU, 5 Fluouracil; IUdR, iododeoxyuridine; FUdR, fluorodeoxyuridine; CPT-11, irinotecan.
complexes persisted. This observation suggested that some complexes were cleared rapidly to the liver, whereas other complexes were not.

Activity in the urine was primarily in the form of a low-molecular-weight (M, 5000) metabolite seen on HPLC analysis. Variation between patients in the rate of activity cleared through the urine was also observed. Patients 2 and 3, who demonstrated higher and more rapid hepatic uptake, had greater excretion of this low-molecular-weight metabolite, which increased after the therapy infusion, possibly due to the administration of DTPA.

Discussion

Radiolabeled monoclonal antibodies directed against CEA are being explored actively as potential cancer imaging and therapeutic agents (1–8). Earlier trials have evaluated murine monoclonal antibodies, which can result in the formation of HAMA in 30–50% of patients (23–26). The formation of HAMA can hasten the clearance and compromise the imaging or therapeutic efficacy of any subsequently administered antibody (27, 28). Therefore, several groups have evaluated chimeric and humanized antibodies in the clinic, some of which have proven to be less immunogenic (29–33). Recently, our group has evaluated, in a pilot imaging trial, a chimeric version of the high-affinity murine anti-CEA antibody mT84.66 (35). cT84.66 labeled with 111In demonstrated imaging of CEA-producing tumors in 93% (14 of 15) of patients, with an imaging sensitivity of approximately 45%, which was comparable to other intact 111In-labeled murine anti-CEA antibodies (34). No side effects were observed with antibody administration. Immune reactivity was reduced with HAMA response in only 1 of 15 patients after a single administration, with a response developing to the murine portion of the antibody. Average dose estimates of 90Y, assuming a biodistribution for 90Y-cT84.66 similar to that of 111In-cT84.66, were: liver, 40 cGy/mCi; marrow, 5 cGy/mCi; and total body, 2 cGy/mCi. Tumor dose estimates were

Table 2. Estimated total radiation doses to normal organs

<table>
<thead>
<tr>
<th>Patient</th>
<th>Liver (cGy)</th>
<th>Marrow (cGy)</th>
<th>Spleen (cGy)</th>
<th>Total Body (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>234.1</td>
<td>67.0</td>
<td>245.8</td>
<td>14.7</td>
</tr>
<tr>
<td>2</td>
<td>471.2</td>
<td>37.7</td>
<td>258.2</td>
<td>16.6</td>
</tr>
<tr>
<td>3</td>
<td>432.4</td>
<td>42.6</td>
<td>197.1</td>
<td>16.8</td>
</tr>
</tbody>
</table>

* Radiation dose estimates to normal organs from the therapeutic infusions are presented for the three patients. Contributions from both 111In and 90Y were taken into account in estimating doses. Details of the dosimetry methods used are presented in "Materials and Methods."
urine was also observed. Urinary activity was in the form of a
The time course of thrombocytopenia, however, was not typical of
secondary to trapping of platelets in the liver.
Vriesendorp et al. (47) in the beagle dog model, and is thought to be
radioimmunotherapy-induced marrow toxicity at the activities admin-
istered in this trial. The observed thrombocyto
tpenia in patient 3 may
marrow doses. Patient 2 had no observed hematological toxicity.

demonstrated faster serum clearance and higher liver uptake of the
antibody compared with patient 1. The reasons for such interpatient
variability are unclear but may, in part, be related to the degree of
metastatic tumor burden in the liver. Of the 29 patients evaluated with
cT84.66 in this and other imaging protocols at this institution, there have
been 3 patients, including the 2 patients in this trial, with unusually rapid
clearance of the antibody to the liver. All 3 of these patients had significant
metastatic tumor burden in the liver. Patients with smaller liver metasta-
ses did not show rapid clearance to the liver. In addition, at this time, liver
clearance does not seem to be related to total-body tumor burden or to
elevations in liver function studies.

Intervpatient variability in blood clearance resulted in a reciprocal
relationship between radiation dose estimates to the red marrow and
liver, which correlated with the toxicities observed. Patient 1 had
typical clearance kinetics and received the highest radiation-absorbed
dose to the marrow. This resulted in grade 1 thrombocytopenia, with a
count nadir at 4 weeks and recovery to baseline by 8 weeks. The
time course of thrombocytopenia is similar to what has been observed
with other radioimmunotherapeutic agents (1—8). Patients 2 and 3 had
more rapid clearance of antibody to the liver, resulting in lower
marrow doses. Patient 2 had no observed hematological toxicity. Patient 3
had grade 1 thrombocytopenia soon after therapy, with a
nadir at 1 week after infusion and recovery to baseline by 6 weeks.
The time course of thrombocytopenia, however, was not typical of
radioimmunotherapy-induced marrow toxicity at the activities admin-
istered in this trial. The observed thrombocytopenia in patient 3 may
de be due in part to hepatic irradiation, because a rapid drop in platelet
count has been observed after whole-liver irradiation, as reported by
Vriesendorp et al. (47) in the beagle dog model, and is thought to be
secondary to trapping of platelets in the liver.

Intervpatient variation in the rate of activity cleared through the
urine was also observed. Urinary activity was in the form of a
low-molecular-weight metabolite. Patients 2 and 3, with higher and
more rapid uptake of antibody to the liver, demonstrated greater excretion of this low-molecular-weight metabolite, which was en-
hanced after the therapeutic infusion. These observations suggest that
\(^{111}\text{In}-\text{cT84.66}\) undergoes formation of antigen:antibody complexes in
serum, which are cleared to and metabolized by the liver and excreted
out through the urine as a low-molecular-weight metabolite. Patients
2 and 3 demonstrated greater liver uptake, more rapid metabolism,
and, therefore, a greater and more rapid excretion of the low-mole-
cular-weight metabolite through the urine.

In our previous imaging trial, a HACA response after single ad-
ministration of chimeric T84.66 was observed in only 1 of 15 patients.
In the current therapy trial, two of the three patients have developed
HACA. This may indicate that the immunogenicity of the antibody is
increased after more than one administration, because each patient in
the therapy trial received an imaging followed by a therapy infusion of
the antibody. However, more patients need to be evaluated to
characterize fully the frequency and titer of the HACA response after
multiple cT84.66 administrations.

Rapid clearance of radiolabeled antibody to the liver may lessen
marrow toxicity but can compromise tumor uptake and increase the
risk of hepatic toxicity. One possible strategy to improve antibody
biodistribution is to administer unlabeled or "cold" antibody prior to
the radiolabeled antibody. Beatty et al. (48) demonstrated up to a
3-fold reduction in liver uptake without compromising tumor uptake
if up to 0.2 mg unlabeled mT84.66 was administered prior to a 2-µg
dose of \(^{111}\text{In}-\text{labeled mT84.66}\) in nude mice bearing LS174T colon
cancer xenografts. Blood uptake also was increased up to 3-fold by
cold antibody infusion, reflecting the delayed clearance of antibody:
antigen complexes to the liver. The effect seemed to be saturable,
because higher doses of unlabeled mT84.66 (2.0 mg) resulted in no
further decrease in hepatic uptake and began to decrease tumor
uptake. Based on these results, we have initiated an imaging trial in
patients with colorectal cancer in which unlabeled chimeric T84.66 is
given prior to the radiolabeled dose. The unlabeled dose is escalated
in cohorts of five patients. We are currently at a level of 25 mg
unlabeled cT84.66 and have yet to observe significant differences in
liver uptake or clearance kinetics of the radiolabeled antibody. As
predicted from the initial murine experiments, we anticipate that
hundreds of mg monoclonal antibody may be needed to alter human
antibody biodistribution of this construct, particularly in those patients
demonstrating unusually rapid clearance of the antibody to the liver.

cT84.66 is a high-affinity anti-CEA antibody that demonstrates
localization to CEA-producing tumors. Although the incidence of
HACA seems to be low after a single administration, further evalua-
tion is needed to determine whether its immunogenicity will remain
low after multiple administrations. Finally, two of three patients
demonstrated unusually rapid clearance of the antibody to the liver,
leading potentially to unfavorable biodistributions. This underscores
the need to identify, characterize, and understand further those factors
that influence the biodistribution of radiolabeled anti-CEA antibodies,
to allow for better selection of patients for therapy and rational
planning of radioimmunotherapy.

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References


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