Phase I Study of P-cadherin-targeted Radioimmunotherapy with ⁹⁰Y-FF-21101 Monoclonal Antibody in Solid Tumors

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ABSTRACT

Purpose: ⁹⁰Y-FF-21101 is a Yttrium-90-conjugated, chimeric mAb that is highly specific for binding to human placental (P)-cadherin, a cell-to-cell adhesion molecule overexpressed and associated with cancer invasion and metastatic dissemination in many cancer types. We report the clinical activity of ⁹⁰Y-FF-21101 in a first-in-human phase 1 study in patients with advanced solid tumors.

Patients and Methods: The safety and efficacy of ⁹⁰Y-FF-21101 were evaluated in a phase 1 3+3 dose-escalation study in patients with advanced solid tumors (n = 15) over a dose range of 5–25 mCi/m². Dosimetry using ¹¹¹In-FF-21101 was performed 1 week prior to assess radiation doses to critical organs. Patients who demonstrated clinical benefit received repeated ⁹⁰Y-FF-21101 administration every 4 months.

Results: ¹¹¹In-FF-21101 uptake was observed primarily in the spleen, kidneys, testes, lungs, and liver, with tumor uptake observed in the majority of patients. Organ dose estimates for all patients were below applicable limits. P-cadherin expression H-scores ranged from 0 to 242 with 40% of samples exhibiting scores ≥100. FF-21101 protein pharmacokinetics were linear with increasing antibody dose, and the mean half-life was 69.7 (±12.1) hours. Radioactivity clearance paralleled antibody clearance. A complete clinical response was observed in a patient with clear cell ovarian carcinoma, correlating with a high tumor P-cadherin expression. Stable disease was observed in a variety of other tumor types, without dose-limiting toxicity.

Conclusions: The favorable safety profile and initial antitumor activity observed for ⁹⁰Y-FF-21101 warrant further evaluation of this radioimmunotherapeutic (RIT) approach and provide initial clinical data supporting P-cadherin as a potential target for cancer treatment.

Introduction

Cadherins are cell-surface glycoproteins that mediate calcium-dependent cell–cell adhesion required for the formation of solid tissue (1). The so-called classic cadherins, epithelial (E), neural (N), and placental (P)-cadherin, were among the earliest studied and are known to be associated with adherens junctions of cells. Their structures are notable for having repeated 110 amino acid sequences, forming extracellular cadherin (EC) domains. These EC domains provide the means for cadherins to bind to and interact with other cells and extracellular matrix proteins. Five EC domains have been identified, EC1–EC5, with EC1 playing a critical role in mediated cell–cell adhesion.

Because cadherins have been shown to be overexpressed in a variety of tumors, they are believed to play a role in effecting malignant cell behavior (2) and, accordingly, may be an attractive target for tumor-specific therapies. Results from numerous preclinical models have now shown that targeting or disrupting cadherins results in antitumor activity (2–5). P-cadherin, encoded by the gene CDH3, represents a particularly attractive target because it is overexpressed in a variety of tumors, with minimal expression in normal tissues of adult humans (Supplementary Fig. S1; refs. 2, 4, 6–9). Park and colleagues and Zhang and colleagues previously characterized an unmodified, humanized mAb, PF-03732010, directed against P-cadherin (5, 10), which showed promising antitumor activity in preclinical models. However, although PF-03732010 was well tolerated in initial human trials, it did not demonstrate clinical efficacy (9, 11), suggesting that the unmodified anti-P-cadherin antibody may not be suitable for the treatment of solid tumors.

More recently, targeted antibodies or peptides have been conjugated with radionuclides to enhance their antitumor activity. This approach has been used successfully to treat well-differentiated neuroendocrine tumors of the pancreas (12, 13), prostate cancer (14), and lymphomas (15). In this paper, we describe the initial Phase 1 study results for a chimeric human/mouse immunoglobulin G (IgG1) monoclonal...
Translational Relevance

Cadherins are cell-surface glycoproteins that mediate calcium-dependent cell–cell adhesion required for the formation of solid tissue. Several cadherins, including placental (P)-cadherin, are overexpressed in many tumor types, correlating with increased tumor cell motility and invasiveness. P-cadherin is of particular interest clinically because, while highly expressed in many tumor types, it is minimally expressed in normal tissue, making it a selective antitumor target. Promising activity has been demonstrated in preclinical models using monoclonal antibodies targeting P-cadherin. Here, we report the clinical activity of 90Y-FF-21101, an anti-P-cadherin antibody conjugated to a radionuclide to enhance its antitumor activity. In this first-in-human phase I study, 90Y-FF-21101 was well tolerated and demonstrated signs of antitumor activity in patients with advanced solid tumors, including a complete response in a patient with ovarian cancer. These results provide initial clinical data supporting the potential for P-cadherin as a target for cancer treatment using a radioimmunotherapeutic approach.

Patients and Methods

Trial design and patient eligibility

The phase I, first-in-human, open-label, dose-escalation study was conducted at the University of Texas MD Anderson Cancer Center (MDACC, Houston, TX), in accordance with the Declarations of Helsinki. The primary objective was to determine the safety and tolerability in patients who receive 90Y-FF-21101 for the treatment of advanced solid tumors refractory to or relapsed from prior therapy (ClinicalTrials.gov Identifier: NCT02454010). Secondary endpoints included determination of overall response rate (ORR), duration of response, progression-free survival (PFS), overall survival (OS), and evaluation of serum antibody protein pharmacokinetics (PK) and presence of human anti-DH3 human/mouse chimeric antibody (HACA). Baseline tumor P-cadherin expression was evaluated in all patients with a biopsy-accessible tumor to characterize and correlate response to potential markers of activity. To allow patients to proceed to treatment with 90Y-FF-21101, estimation of the radiation absorbed 90Y-FF-21101 dose to marrow and major organs was evaluated by measurement of Indium-111 (111In)–FF-21101 biodistribution, and, as a secondary objective, selective uptake of 111In-FF-21101 in tumor tissue was also assessed.

The protocol was approved by the institutional review board at MDACC, and all patients provided written informed consent prior to all study-related procedures. Adult patients must have been ≥18 years of age with histologically or cytologically confirmed advanced solid tumor malignancy and refractory or relapsed from prior therapy with no available therapy likely to provide clinical benefit or for whom no alternative therapy is available. Patients had to be at least 3 weeks beyond the last chemotherapy (or ≥5 half-lives, whichever was shorter), radiotherapy, major surgery, or experimental treatment and recovered from all acute toxicities (≥ grade 1). Adequate performance status (Eastern Cooperative Oncology Group (ECOG) ≤ 2), hematologic parameters, renal and hepatic function, and at least one measurable disease site that meets target lesion requirements by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, were required.

Dose escalation proceeded in a standard 3+3 design with observation for dose-limiting toxicity (DLT) for 6 weeks post the initial treatment. A minimum of 6 weeks elapsed between the last subject dosed in a cohort and the first subject in a new cohort. The highest 90Y-FF-21101 level below the level eliciting DLT would be declared the maximum tolerated radioactivity. The dose-escalation phase was followed by an expansion phase, which is currently ongoing.

Radioiodinated antibody preparation

Radiolabeling of FF-21101 with 111InCl3 for dosimetry or with 90YCl3 for treatment was carried out by the clinical site radio-pharmacy. The mAb conjugated to DOTA (FF-21101) was provided as a 5 mg/mL solution in 250 mmol/L sodium acetate, pH 5.5, by FUJIFILM Diosynth Biotechnologies U.S.A., Inc. A clinical formulation buffer [25 mmol/L sodium acetate, 2 mg/mL ascorbic acid, 0.3 mg/mL diethylenetriaminepentaacetic acid (DTPA), and 0.72% sodium chloride; pH 5.5] was provided for dilution. 111In chloride sterile solution (Mallinckrodt, Inc.) and 90Y chloride sterile solution (Eckert & Ziegler Radiopharma, GmbH) were used for radioiodination. Solutions were prepared to maintain a specific radioactivity of 1 mCi/mg (±10%) 111In-FF-21101 for dosimetry and 8 mCi/mg (±10%) for 90Y-FF-21101 at the time of injection. Validation procedures were performed at each site prior to patient dose preparation. Three consecutive batches of 40 mCi 90Y-FF-21101 were prepared and tested against acceptance criteria for appearance, radioactivity, radiochemical purity, pH, bacterial endotoxin, sterility, and stability. Quality control testing of each patient dose was also performed prior to administration including visual inspection (clear, colorless to pale yellow, free of visible particulate matter) and radiochemical purity by thin-layer chromatography (±5%). Other quality attributes of prepared drug doses (purity by SEC, immunoreactivity by ELISA) were optionally tested and documented in site-specific compounding validation records.

111In-FF-21101 dosimetry

111In radioactivity in serum and urine was evaluated, and axial SPECT, CT, and fused (SPECT/CT) and whole-body anterior/ posterior planar 111In scintigraphy was performed in all patients approximately 1 week prior to administration of the therapeutic dose to assess the acceptability of radiation dose estimates to critical organs and red marrow. The prepared 111In-FF-21101 dose was administered intravenously through a 0.22-μm in-line filter by slow injection at a rate not to exceed 1 mL/minute (approximately 10 minutes). Anterior and posterior whole-body planar scintigrams were acquired using a dual-head gamma camera (Symbia S, Siemens Medical Solutions USA, Inc.) at 0.25, 4, 24, 72, and 144 hours after 111In-FF-21101 administration; SPECT images were acquired 24 hours postadministration, followed by a CT scan (750HD, GE Healthcare) for SPECT attenuation correction and organ volume contouring. The images were used to...
generate organ region of interest time–activity curves (TAC), which were fitted to exponential functions using Prism 6 (GraphPad) to obtain 111In-FF-21101 and, by converting from 111In to 90Y radioactive decay, estimated 90Y-FF-21101 organ residence times. Blood samples were obtained at 0.5, 1, 2, 4, 24, 72, and 144 hours after 111In-FF-21101 administration to compute 111In-FF-21101 and 90Y-FF-21101 red marrow TACs and residence times using the Sgouros formula (19). Residence times and CT-based lung, liver, kidney, and spleen organ mass estimates were entered into OLINDA/EXM 1.1 (Vanderbilt University, Nashville, TN) to generate estimated 111In-FF-21101 and 90Y-FF-21101 organ doses (20). Serum and urine 111In radioactivity concentrations (% ID/L) were measured using a precalibrated gamma scintillation counter.

90Y-FF-21101 treatment

The administered radioactivity in the first cohort was 5 mCi/m2 (185 MBq/m2, ±10%) 90Y-FF-21101, which was then escalated in 5 mCi/m2 increments to 10, 15, 20, and 25 mCi/m2 (370, 555, 740, and 925 MBq/m2; ±10%) in subsequent cohorts. 90Y-FF-21101 was administered intravenously through a 0.22-μm in-line filter on day 1 by slow injection at a rate not to exceed 1 mL/minute (approximately 10 minutes). Patients were monitored for 4 hours after each dose of 90Y-FF-21101 for infusion reactions. At the highest dose level to be explored (25 mCi/m2), the maximum radioactivity allowed per infusion was limited to 60 mCi (2,220 MBq) as a safety precaution based on dosimetry performed in animals and estimated radiation absorbed dose to the lungs that would exceed the maximum allowable limit defined for external beam radiotherapy (21, 22). The delivered activity estimates were required to be below standard limits for external beam radiotherapy typically used for nonmyeloablative radioimmunotherapy (RTI; <3 Gy for red marrow, <30 Gy for liver, and <20 Gy for kidney and lung). If an estimate exceeded the limit, option for treatment at a lower radioactivity was allowed if within allowable limits.

For purposes of scheduling study procedures, cycles were defined as each 28-day period following the initial 90Y-FF-21101 administration. On the basis of estimates of organ radiation dose being well below the standard limits for external beam radiation, the lack of observed toxicities, coupled with response observed including an objective response observed at Cohort 3, the protocol was amended to allow repeated administration at a frequency of every 4 months in responding patients or patients who demonstrated clinical benefit if the following criteria were fulfilled: hemoglobin ≥10 g/dL, absolute neutrophil count ≥1.5 × 10^9 cells/L, platelets >100,000 × 10^9 cells/L, creatinine ≤1.5 × upper limit of normal (ULN), or creatinine clearance ≥60 mL/minute × 1.73 m2/BSA, bilirubin <1.5 × ULN, ALT and AST ≤2.5 × ULN (≤5 × ULN if liver metastases), and ECOG Performance status ≤2. Additional therapeutic doses of 90Y-FF-21101 were allowed until disease progression (PD), observation of unacceptable adverse events (AE), intercurrent illness, or changes in the patient’s condition that prevented further study participation.

Efficacy assessment

Disease assessments based on CT or MRI were obtained at week 8 and every 8 weeks thereafter until documented PD and classified according to RECIST v1.1 (23). The primary efficacy endpoint was the proportion of subjects with objective response [complete response (CR) + partial response (PR)] achieved by week 8 (ORR). The best overall response was defined as the best response recorded across all time points. Clinical benefit was defined as confirmed CR, PR, or stable disease (SD). When SD was believed to be the best response, it must also have met the protocol-specified minimum duration from baseline (8 weeks), including for assessment of clinical benefit. Progression-free survival was calculated from the date of first dose of 90Y-FF-21101 to the date of first objective evidence of disease progression or death, whichever was earlier. Overall survival was calculated from the date of first dose of 90Y-FF-21101 to the date of death due to any cause.

Safety assessments

Safety and tolerability based on AEs and laboratory parameters were assessed from the day of 111In-FF-21101 administration through the end of study (28 days after the last treatment). Adverse events were classified according to the Medical Dictionary for Regulatory Affairs (MedDRA) and graded using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Patients were monitored during the conduct of the physical examination throughout the study for signs of potential pulmonary toxicity (e.g., cough, wheezing, dyspnea with or without fever, radiation pneumonitis, etc.). Radiologic assessment could be used as necessary to confirm findings, and symptoms treated with corticosteroids as required. Eye examinations consisted of visual acuity and field tests, slit lamp examination fundoscopy, and optical coherence tomography performed at cycle 1 and every 30 days thereafter. Dose modification or delay was allowed on the basis of protocol-defined criteria.

DLT was defined as grade 4 hematologic toxicity lasting ≥7 days; grade 4 neutropenia with a fever (single temperature >38.3°C or sustained temperature of ≥38°C for more than 1 hour); ≥grade 3 thrombocytopenia with clinically significant bleeding; failure of platelets, ANC, or hemoglobin to recover to ≤grade 1 within 12 weeks of dosing with 90Y-FF-21101, despite allowance of supportive measures to aid recovery (e.g., RBC, platelet transfusions, growth factors); grade 4 nonhematologic toxicity of any duration; grade 3 nonhematologic toxicity lasting ≥3 days, despite the use of supportive care measures (e.g., antiemetics, antiarrheals); or any protocol defined ophthalmologic toxicity. A minimum of 6 weeks would elapse between the last subject dosed in a cohort and the first subject in a new cohort for safety assessment. The highest 90Y-FF-21101 dose level below the dose level eliciting DLT, or the highest dose tested in the absence of DLT, was declared the maximum tolerated activity.

Patients remained on study until they chose to discontinue participation or developed PD, unacceptable AEs, or an intercurrent illness or change in medical status that prevented further study participation. Long-term follow-up involved a clinic visit or telephone call every 3 months for up to 12 months.

Pharmacokinetic assessment

Serum FF-21101 antibody concentrations were assessed during cycle 1 by electrochemiluminescence (ECL) analysis using a validated method with a dynamic range of 5–1,000 ng/mL. Data were collected using a MSD Sector Imager 6000 and pharmacokinetic parameters estimated using a noncompartmental approach (Phoenix pharmacokinetic software, Certara). Pharmacokinetic parameters (trough levels, t_{1/2}, t_{max}, C_{max}, AUC, CL) were assessed on the basis of individual and mean concentrations of FF-21101 on days 1, 8, and 15. Analysis of anti-drug antibodies (ADA) was performed in samples obtained on days 1 (pretreatment), 8, 15, and 22 of all cycles using a bivalent ECL immunooassay fully validated in human serum that binds anti-FF-21101 to both biotin- and ruthenium-labeled FF-21101. Qualitative ECL immunooassay was used to initially screen for the presence of antibodies to FF-21101. Test samples that confirmed positive for the presence of anti-FF-21101 antibodies were titrated to report the sample titer.
Analysis of P-cadherin expression

P-cadherin expression by IHC in formalin-fixed paraffin-embedded archived or fresh tumor biopsy was correlated with clinical outcome as an exploratory endpoint. IHC staining of paraffin-embedded 4-μm patient tumor tissue sections was performed using a Benchmark Ultra automated immunostaining device (Ventana Medical Systems) with heat-induced antigen retrieval and Optview DAB detection. Murine monoclonal anti–P-cadherin antibody was purchased from BD Biosciences (material number 610227/8) and applied at 2 μg/mL. Polymer-negative control serum (BioCare Medical) was used as a negative control. Samples were processed at a single CLIA reference laboratory (Covance). P-cadherin expression was scored on the basis of staining intensity and the percentage of positive tumor cells with membrane staining. Staining intensity was rated as 0; absent; 1; weak; 2, moderate; or 3, strong. The approximate percentage of tumor cells with membrane staining at each intensity was reported from 0% to 100%. An H-score for each tissue specimen was calculated as follows, based on the percentage of cells at each intensity: H-score = 3 × (% of cells at 3+ intensity) + 2 × (% of cells at 2+ intensity) + 1 × (% of cells at 1+ intensity). The maximum H-score was 300, representing 100% of tumor cells positive for P-cadherin with a staining intensity of 3.

Statistical analyses

Response rates were summarized using the number and percentage of patients with best overall response of CR, PR, or SD. For PFS and OS, the Kaplan–Meier product-limit method was used to estimate the median survival. Patients who did not experience disease progression or death were censored at the date of the last evaluable disease assessment. For patients who have not died, OS was censored at the date the patient was last known to be alive or the date of last contact, whichever was later. Descriptive statistics were used to summarize demographic data, baseline disease characteristics, and safety outcomes in the dose-escalation phase. All analyses were performed using SAS for Windows version 9.3 or higher (SAS Institute, Cary, NC).

Results

Patient characteristics

From January 21, 2016 to July 1, 2019, 15 patients (6 males, 9 females) with advanced primary tumors (stage IV) were treated in five cohorts of the 3+3 dose-escalation phase study (Table 1). Patients with a variety of tumor types were enrolled including sarcomas [leiomyosarcoma, liposarcoma, clear cell sarcoma (n = 2), desmoplastic small cell tumor], gynecologic cancers [vaginal, ovarian (n = 2)], gastrointestinal cancers (colon, appendix, cholangiocarcinoma), and neuroendocrine tumors (lung, pancreatic). All patients were heavily pretreated and had received prior surgery, radiation, and/or chemotherapy with a median number of prior treatment regimens of 6.5 (range 3–10).

Dosimetry

Images from whole-body scintigraphy and single-photon emission CT/X-ray CT (SPECT/CT) demonstrated $^{111}$In-FF-21101 uptake primarily in the spleen, kidneys, testes, lungs, and liver (Table 2). Total $^{90}$Y Gy organ radiation dose estimates are shown by increasing administered activity over cohorts 1–5. For all patients, estimates for the $^{90}$Y-FF-21101 administered activity were below the applicable limits for external beam radiotherapy to red marrow (<3 Gy), liver (<30 Gy), kidneys, and lungs (<20 Gy; ref. 22). The spleen had the highest amount of uptake in all patients except one who had prior splenectomy.

Although only limited assessment of tumor localization could be performed, radiotracer activity was appreciable at the location of the primary tumor and in known sites of metastatic disease in the majority of patients evaluated. Figure 1A (i–iii) shows axial SPECT, CT, and fused (SPECT/CT) images of the pelvis obtained 24 hours after the administration of 5 mCi/m² (5.54 mCi) $^{111}$In-FF-21101 in a patient with squamous cell carcinoma of the anus enrolled in the first cohort, providing early radiographic evidence of P-cadherin targeted antibody uptake in tumor. Increased radiotracer uptake was shown corresponding to a 6.5 × 3.0 × 4.4 cm soft tissue metastasis in the right pelvis in this patient, with serial whole-body planar images demonstrating the temporal accumulation of radiotracer in the pelvic lesion and in metastases to the right hepatic lobe and anterior abdominal wall and rectal regions, with maximal tumor uptake observed by 72 hours postadministration [Fig. 1A (iv)]. Image (iv) also reveals gradually increasing splenic uptake. Although appreciable tumor uptake was observed, the patient unfortunately was withdrawn following dosimetry due to rapidly progressing disease. Overall, evidence of radiotracer activity in tumor was observed in all but two patients evaluated, one with ovarian cancer who achieved a CR as further described below, and another with cholangiocarcinoma for which uptake in the periporal region was indeterminate. The latter patient had received three treatments approximately 4 months apart, with stable disease maintained through cycle 12 (48 weeks) before progressing.

$^{90}$Y-FF-21101 treatment and P-cadherin staining

Subsequent $^{90}$Y-FF-21101 treatment was initiated at an administered radioactivity of 5 mCi/m² (185 MBq/m²; ±10%), similar to that used in previous clinical trials for $^{90}$Y-drug conjugates (24–28), at a specific activity of 8 mCi/mg antibody. Dose was escalated to
Table 2. Normalized $^{90}$Y-FF-21101 organ radiation-absorbed dose estimates based on $^{111}$In-FF-21101 dosimetric imaging.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Mean (mGy/mCi)</th>
<th>StdDev</th>
<th>CV (%)</th>
<th>Cohort 1 5 mCi/m²</th>
<th>Cohort 2 10 mCi/m²</th>
<th>Cohort 3 15 mCi/m²</th>
<th>Cohort 4 20 mCi/m²</th>
<th>Cohort 5 25 mCi/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen</td>
<td>1.031.5</td>
<td>399.9</td>
<td>38.8</td>
<td>12.62</td>
<td>18.99</td>
<td>20.38</td>
<td>43.95</td>
<td>37.42</td>
</tr>
<tr>
<td>Testes</td>
<td>339.5</td>
<td>122.6</td>
<td>36.1</td>
<td>3.22</td>
<td>11.01</td>
<td>N/A</td>
<td>15.62</td>
<td>14.06</td>
</tr>
<tr>
<td>Kidneys</td>
<td>19.7</td>
<td>75.8</td>
<td>34.5</td>
<td>2.70</td>
<td>3.20</td>
<td>6.62</td>
<td>8.92</td>
<td>8.15</td>
</tr>
<tr>
<td>Lungs</td>
<td>169.8</td>
<td>56.9</td>
<td>33.7</td>
<td>1.88</td>
<td>2.88</td>
<td>4.51</td>
<td>6.65</td>
<td>8.05</td>
</tr>
<tr>
<td>Liver</td>
<td>160.6</td>
<td>58.5</td>
<td>36.4</td>
<td>1.85</td>
<td>2.73</td>
<td>4.08</td>
<td>6.39</td>
<td>7.32</td>
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<tr>
<td>Heart wall</td>
<td>89.7</td>
<td>18.1</td>
<td>20.1</td>
<td>0.67</td>
<td>1.99</td>
<td>2.45</td>
<td>3.84</td>
<td>5.08</td>
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<tr>
<td>Osteogenic cells</td>
<td>34.7</td>
<td>13.2</td>
<td>38.2</td>
<td>0.30</td>
<td>0.71</td>
<td>0.98</td>
<td>1.24</td>
<td>2.30</td>
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<tr>
<td>Red marrow</td>
<td>29.6</td>
<td>11.0</td>
<td>37.1</td>
<td>0.30</td>
<td>0.56</td>
<td>0.78</td>
<td>1.02</td>
<td>1.87</td>
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<tr>
<td>Total body</td>
<td>25.7</td>
<td>2.6</td>
<td>10.1</td>
<td>0.20</td>
<td>0.55</td>
<td>0.69</td>
<td>0.99</td>
<td>1.38</td>
</tr>
<tr>
<td>Ovaries</td>
<td>14.6</td>
<td>4.3</td>
<td>29.6</td>
<td>0.11</td>
<td>0.26</td>
<td>0.36</td>
<td>0.61</td>
<td>0.93</td>
</tr>
<tr>
<td>Uterus</td>
<td>14.6</td>
<td>4.3</td>
<td>29.6</td>
<td>0.11</td>
<td>0.26</td>
<td>0.36</td>
<td>0.61</td>
<td>0.93</td>
</tr>
<tr>
<td>All other organs</td>
<td>12.5</td>
<td>5.1</td>
<td>40.6</td>
<td>0.09</td>
<td>0.29</td>
<td>0.36</td>
<td>0.50</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Note: All 16 (7 male, 9 female) patients were evaluated (1 male patient did not proceed to therapy). Total dose estimates for each patient were their individual normalized dose estimates multiplied by their administered $^{90}$Y radioactivity, and are shown by increasing administered activity over cohorts 1–5 (tests N/A for Cohort 3, as all were female). $^{111}$In-FF-21101 uptake was observed primarily in the spleen, testes, kidneys, lungs, and liver. For all patients, estimates for $^{90}$Y-FF-21101 administered activity were below the applicable limits for external beam radiotherapy (<3 Gy to red marrow, <50 Gy to the liver, and <20 Gy to the kidneys and lungs).

Pharmacokinetics and ADA titers

Over the dose range administered of 0.625 to 3.2 mg/m² $^{211}$FF-21101 protein, $^{211}$FF-21101 antibody pharmacokinetics in serum demonstrated generally dose proportional increases in exposure with increasing dose, as measured by maximum concentration ($C_{max}$) and area-under-the-concentration-time curve from zero to infinity ($AUC_{0→∞}$) with a mean (±StdDev) half-life for the circulating antibody in serum of 69.7 (±12.1) hours [Fig. 1B (ii)]. With a physical half-life for $^{90}$Y of 64.1 hours, the effective half-life for $^{90}$Y-FF-21101 was calculated as 33.4 hours. Mean clearance and steady-state volume of distribution (Vss) for the $^{211}$FF-21101 antibody ranged from 10.2 to 43.7 mL/hour/kg and from 1,390 and 3,940 mL, respectively. On the basis of a limited number of patients per cohort, there was high variability in exposure within each cohort. However, the serum pharmacokinetics of the $^{211}$FF-21101 protein appears to be linear and not dose dependent in humans. Mean radioactivity clearance in serum ($^{111}$In-FF-21101 percent injected dose per liter, %ID/L) paralleled antibody clearance from 0 to 144 hours [Fig. 1B (iii)], with an initial %ID/L of 20% at 0.5 hours (CV, 33%) that was more rapidly eliminated to <1% measurable at 144 hours postadministration. Evidence of the formation of circulating antibodies against the FF-21101 antibody was observed in only 2 patients within 4 weeks following the initial treatment.

In both patients enrolled at Cohort 4 (20 mCi/m²), ADA titers ranged from low-intermediate to high and remained stable throughout the course of treatment. It is unknown at this time if the ADA is neutralizing. However, these patients went on to receive subsequent doses of $^{90}$Y-FF-21101 and maintained stable disease, one for 4 months and one for 12 months.

Clinical activity

One patient achieved a CR; no other patients achieved a PR, so the ORR was 6.7% (1/15). Median PFS was 24 weeks, and the median OS was 90 weeks. The clinical benefit rate defined as confirmed CR, PR, or SD for a minimum of 8 weeks was 73% (11/15 patients). The CR was observed in a 60-year-old woman with metastatic clear cell ovarian carcinoma (Fig. 3). The patient was a nulligravida female who presented with a persistent cough for several months. A diagnostic work-up at the local emergency room for worsening abdominal pain, nausea, and vomiting confirmed a 10-cm left pelvic mass and a 6-mm splenic lesion suspected to be metastatic disease. Her CA-125 was elevated at 83 U/mL. She underwent exploratory laparotomy, total abdominal hysterectomy with bilateral salpingo-oophorectomy, radical debulking, left pelvic and para-aortic lymph node sampling, and partial omentectomy. Final pathology showed a stage IIC clear cell carcinoma of the ovary. According to the operative report, the spleen was unremarkable and she was optimally debulked. Comprehensive next-generation DNA sequencing of the resected tumor (Foundation Medicine) showed PIK3CA E545K and N1044S mutations. Surgery was followed by six cycles of carboplatin/paclitaxel. Evidence of progressive nodal disease was seen on CT scan approximately 1 year later. Pelvic and para-aortic lymphadenectomy showed 10 of 13 positive lymph nodes and was followed by radiotherapy (36 Gy in 27 fractions to high-risk areas) and hepatic resection of metastasis approximately 7 months before study entry. Further analysis of the patients’ tumor confirmed the previous PIK3CA mutation [Oncology Hotspot Panel (50 genes), semi4], and the following profile: cMET, PD-1, PTEN, TOP2A, and TUBB3-positive, PD-L1–negative (Caris Life Sciences). A follow-up restaging scan showed recurrence in the left axilla, and biopsy of the left axillary lymph node at the time of

25 mCi/m² over five cohorts, with 5 patients who received more than one treatment (Fig. 2A). The median (range) time on study following the first $^{90}$Y-FF-21101 administration was 24 (4–90) weeks. Tumor samples from 13 of 15 subjects were available for IHC analysis. P-cadherin staining was predominantly localized in the tumor cell membrane, with some nontumor staining of occasional fibroblasts and endothelial cells (Fig. 2B, a–d). P-cadherin expression H-scores ranged from 0 to 242 with 40% of samples exhibiting scores ≥100. One subject with metastatic clear cell ovarian carcinoma had the most marked P-cadherin staining (H-score of 242, Fig. 2B, a–d) and achieved a clinical CR by RECIST, as further described below. Strong P-cadherin staining was also observed in patients with pancreatic neuroendocrine tumor, intrahepatic cholangiocarcinoma, and sarcoma, specifically in clear cell, smooth muscle tissue.

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Figure 1. Dosimetry and pharmacokinetics in a phase I study of 90Y-FF-21101. A, Dosimetric imaging in a 33-year-old male with metastatic squamous cell carcinoma of the anus. Axial SPECT (i), CT (ii), and fused (SPECT/CT) images (iii) of the pelvis obtained 24 hours after the administration of 5.54 mCi of 111In-FF-21101 demonstrate increased radiotracer uptake corresponding to a 6.5 × 5.0 × 4.4 cm soft tissue metastasis in the right pelvis (white arrows). Serial whole-body planar images in the anterior view demonstrate the time course of 111In-FF-21101 uptake in this patient (iv). The patient had metastases to the right anterior abdominal wall, right pelvis, and rectal region, with maximal tumor uptake observed by 72 hours postadministration (green arrow heads). Red arrows depict sequential radiotracer uptake in the right pelvic metastasis shown on the axial images. In addition, there was heterogeneous radiotracer activity at the site of multifocal metastases in the right hepatic lobe, the largest with central necrosis (circled in whole body planar (iv) and SPECT/CT (v) images). Gradually increasing uptake was also noted in the spleen. B, Mean (±StDev) serum FF-21101 antibody protein concentration versus time following a single dose of 90Y-FF-21101 (n = 3/cohort except Cohort 1 where n = 1). Following the administration of 5 to 25 mCi/m2 90Y-FF-21101 over Cohorts 1-5 (equal to 0.625 to 3.2 mg/m2 FF-21101 protein), antibody protein was measurable in serum up to 300 hours postadministration. High variability in exposure was observed within each cohort; however, the serum pharmacokinetics of the FF-21101 protein appeared to be linear and not dose dependent in humans. The mean (±StDev) biologic half-life for the circulating antibody in serum was 69.7 (±12.1) hours, with an effective half-life for 90Y-labeled FF-21101 of 33.4 hours. Radioactivity clearance in serum (%ID/L) is shown for all patients in the dosimetry phase (n = 16) following administration of 5 mCi (±10%) 111In-FF-21101, containing 5 mg FF-21101, percent injected dose per liter, %ID/L) is shown for all patients in the dosimetry phase (n = 16) following administration of 5 mCi (±10%) 111In-FF-21101, containing 5 mg FF-21101, approximately 1 week prior to 90Y-FF-21101 dosing (ii). Radioactivity clearance paralleled antibody clearance from 0 to 144 hours. The mean initial %ID/L was 20% at 0.5 hours (CV, 33%; see inset) and <1% at 144 hours post 111In-FF-21101 administration.
evaluation for study entry was positive for metastatic clear cell carcinoma. In addition, mildly enlarged abdominal adenopathy was observed in the para-aortic region in addition to numerous enlarged nodes in the retroperitoneum surrounding the abdominal aorta and a prominent gastro-hepatic node. The patient was then referred for study enrollment in the third dose-escalation cohort to receive treatment with 90Y-FF-21101 at a dose of 15 mCi/m² (24.2 mCi). Visible tumor uptake in the target axillary nodes was not clearly appreciable in serial whole-body planar scintigrams nor the SPECT image acquired at 24 hours following 111In-FF-21101 administration. However, following a single 90Y-FF-21101 treatment, a PR in target lesions was observed at the initial restaging at cycle 2 (week 8), which was confirmed at week 16 (59.9% decrease in sum of diameters of target lesions). Given the excellent response, the protocol was amended to allow administration...
of additional doses in responding patients and her treatment was continued every 4 months for three additional doses with continued disease response (Fig. 3B), followed by an additional fifth dose approximately 7 months later (cycle 20). Restaging at cycle 24 subsequently showed achievement of a CR of her target lesion (axillary lymph node), and no evidence of metastatic abdominopelvic disease. The patient was thereafter followed by her local physician every other cycle beginning with cycle 25 and has maintained a CR with no further treatment. CA-125 values decreased from 30 to 15 U/mL over the course of 90Y-FF-21101 treatment and, as noted above, tumor response in this patient correlated with a high P-cadherin expression H-score > 200 (242), the highest documented on study (Fig. 2A–C).

An additional patient with metastatic low-grade serous ovarian carcinoma had stable disease following a single 90Y-FF-21101 treatment at a dose of 10 mCi/m² (21.9 mCi). This patient had disease involving the rectum and abdominal wall and was progressing prior to study entry in the 2nd cohort, with a P-cadherin expression H-score of 180. Although disease was stable following 90Y-FF-21101 treatment, the patient subsequently came off study after 16 weeks due to personal logistical (nonmedical) reasons. Stable disease responses were maintained for approximately 50 weeks on study in an additional 4 patients, one with a pancreatic neuroendocrine tumor (NET) treated with a single dose at the lowest dose level of 5 mCi/m² (9.8 mCi), one with metastatic intrahepatic cholangiocarcinoma treated in the third cohort with 15 mCi/m² (25.4 mCi) for 3 doses, one with a lung NET treated with 2 doses of 20 mCi/m² (36.3 mCi) administered 4 months apart, and one with a clear cell sarcoma who received a total of 4 doses administered 4 months apart at the highest dose level of 25 mCi/m² (49.5 mCi; Fig. 2A). P-cadherin expression H-scores were ≥ 100 in two of these patients (clear cell sarcoma and pancreatic NET), but...
notably absent in the patient with lung NET (H-score of 3). Patients with an H-score ≥ 100 remained on study for a median (range) of 54 (47–64) weeks compared with 8 (4–46) weeks in patients with an H-score < 100.

Safety and treatment-related adverse events

DLT was not observed in any patient on study and dose reductions were not required over the course of the dose escalation. Patients did not exceed the allowed per treatment amount of calculated radiation exposure (Table 2). Treatment-emergent AEs (all events related and unrelated) were typical of a phase I solid tumor trial, with the most common being lymphopenia (75%), increased AST (56%), fatigue (56%), anemia (44%), diarrhea (44%), dysgeusia (38%), leukopenia (38%), increased ALT (25%), anorexia (25%), constipation (25%), dizziness (25%), dyspnea (25%), and hyperkalemia (25%).

Similar to other 90Y-conjugated therapeutic antibodies, there were reversible myeloid effects (28, 29). The most common drug-related AE was lymphopenia, which occurred in 11 (68.8%) of 16 patients [grade 3 (n = 3) or 4 (n = 1)] severity in four patients, 25%; Table 3]. In cohort 4, one subject experienced grade 4 lymphopenia within 1 week of the therapeutic dose but had normal overall white blood cell counts; this event did not meet DLT criteria. Transient grade 3 lymphopenia and leukopenia was observed in one additional patient at cohort 4. There were no SAEs reported at Cohort 4, and no grade 3 or 4 lymphopenia observed in cohort 5 (25 mCi/m²). Drug-related leukopenia and thrombocytopenia occurred in 31.3% and 25.0% of patients, respectively, and were of grade 3 or 4 severity in only one patient each. Grade 1 or 2 dysgeusia, increased AST, and rash were other common drug-related AEs observed in more than 10% of patients. All AEs were reversible. No evidence of pulmonary function impairment or ocular effects was observed. There were no grade 3 or 4 AEs observed at the highest dose level (25 mCi/m²), and no drug-related serious AEs, discontinuations, or deaths were observed on study. A maximum tolerated administered activity was therefore not reached in dose escalation based on the lack of DLT in patients receiving up to 60 mCi/dose and cumulative doses up to 100 mCi administered on an every 4-month schedule.

Discussion

Antigens that are unique or virtually unique to tumors offer the promise of targets that will yield drugs with both increased efficacy and decreased toxicity. RIT offers some advantages over other target-directed therapeutic modalities such as potent toxins or direct target binding, and has recently undergone a surge of interest as more sophisticated drugs and targeted therapies have found success (30). There have been successes with RIT such as 90Y ibritumomab tiuxetan (Zevalin; Acrotech Biopharma, LLC), as well as radiolabeled peptide therapies such as lutetium177 Lu dotatate (Lutathera; Advanced Accelerator Applications USA, Inc.; ref. 31). However, it is a challenging development path; there are also failures, such as RIT directed against CEA and MUC1, where early promising results have not yielded effective therapies (28, 29, 32). Success requires the right target, delivery vehicle, and therapeutic effector.

Caderhins represent a very attractive target due to their frequent overexpression in a wide variety of tumors. Overexpression of P-cadherin has been measured by both IHC and mRNA-based methods in many tumor types, but because the literature on this subject describes varying definitions and assay techniques, cross-study comparisons of P-cadherin expression are difficult to perform and require cautious interpretation. Although the precise quantification of P-cadherin in tumor tissues may not have universal agreement, P-cadherin clearly appears to be expressed in greater amounts than in normal tissue, particularly in epithelial tumors. It should be appreciated that nonepithelial tumors also overexpress cadherins, including P-cadherin (9).

Strengthening the idea that P-cadherin is an important target, it is notable that the majority of P-cadherin–directed therapies seem to have good activity in preclinical models. Furthermore, because cadherins interact with and make up part of the tumor microenvironment (TME), P-cadherin–directed therapy may complement other therapies that require TME alteration for greater effect. The elegant preclinical work reported by Zhang and colleagues also supports the role of the TME in tumor viability and progression (10). Despite these potential advantages, it should be noted that downregulation of P-cadherin may stimulate some malignant cell properties in certain settings (33). Therefore, although P-cadherin is an attractive target, as previously mentioned, RIT therapy against the similarly attractive CEA and MUC1 led to disappointing results.

Here, we report the dose-escalation results of a first-in-human clinical trial of an RIT targeting P-cadherin. These data represent the first reported clinical trial results of a P-cadherin–directed therapy. Descriptions of several antibody therapies directed against a cadherin target have been previously published (9), but there have been no definitive results reported on their activity or safety in humans. Phase I studies have been conducted with PF-06671008, a bispecific antibody against both P-cadherin and CD3 (NCT02659631), as well as with two additional cadherin-directed antibody–drug conjugates, PCA-062...
(NCT02375958) and HKT288 (NCT02947152; ref. 34), directed against P-cadherin and Cadherin 6, respectively. Yoshioka and colleagues reported preclinical data obtained from administration of a radioimmune-coupled mAb directed against P-cadherin, Mab-6 (35). Their preclinical data are strikingly similar to those reported for 90Y-FF-21101; however, no further information has been made available on the progression of the compound to human trials.

Coupled to a highly energetic (0.934 MeV mean and 2.28 MeV maximum energies) beta emitter, 99Y-FF-21101 may offer advantages for targeting and affecting multiple tumor cells simultaneously. With a mean emission penetration of only 4 mm, it requires only modest external radiation precautions. Preclinical data have also previously demonstrated that the FF-21101 anti-P-cadherin antibody appears to be preferentially taken up by tumors, without evidence of off-target toxicity or the formation of anti-drug antibodies (refs. 17, 18; Supplementary Figs S1–S3). In this clinical study, 99mTc-FF-21101 doses up to 25 mCi/m² were found to be very well tolerated in a heavily pretreated population of patients with advanced solid tumors. Because P-cadherin is expressed in the retina, one safety concern was ophtalmologic effects; however, repeated ophthalmology evaluations revealed no ocular findings in any patient on study.

Dosimetric imaging revealed the organ with the highest radiotracer uptake was the spleen. As P-cadherin is a myo-epithelial antigen, this may not have been anticipated. However, analysis of P-cadherin expression in tumors and normal tissues demonstrates a moderate amount of P-cadherin expression in normal splenic tissue (mean ± StdDev CDH3 mRNA transcripts per million, 15.8 ± 10.2; Supplementary Fig. S1). Nonspecific binding as well as macrophage uptake, as previously observed with some mAbs (36, 37), may also play a role in the observed accumulation in the spleen, in addition to potential aggregation/complexation. Variable accumulation of radioactivity in the spleen as a consequence of variable aggregation could possibly explain the non-dose-related lymphopenia observed. Although the analytic methodology used in this study was not capable of measuring aggregation, this, and complexation with ADA, remain potential contributing factors. Our clinical data to date demonstrates posttreatment ADA titers in only 2 patients, with one showing a relatively high titer. Lack of measurable serum ADA could also be a function of complexation of the circulating antibody with low titer ADA, therefore additional evaluation is needed to further define this aspect of antibody fate. On the basis of the serum protein pharmacokinetics, mean clearance and volume of distribution for the FF-21101 antibody were consistent with largely intravascular distribution, although some evidence of extravascular distribution is demonstrated by the range of individual distributional volumes. The Vss in our study was determined using noncompartmental analysis. While reasonable for estimating a pharmacokinetic parameter, this type of model assumes all drug elimination occurs from the central compartment, which for antibodies that bind and internalize within cells in tissues sites, tends to also overestimate the Vss.

Further analysis of the antibody pharmacokinetics showed the measured t1/2 for the FF-21101 protein was 2.9 days, which is somewhat less than some approved therapeutic chimeric monoclonal IgG antibodies, but is similar to the t1/2 for agents such as trastuzumab (2.7 days) and cetuximab (4.1 days). The half-life of IgG is 23 days, and its slow degradation is dependent on protection by FcRn binding to the Fc portion of the antibody. FF-21101 may be cleared faster than other therapeutic antibodies due to reduced affinity for the FcRn receptor. Other factors which may contribute to the increased elimination of FF-21101 compared with other IgG-derived therapeutics include the relative immunogenicity, the degree of glycosylation, and susceptibility to proteolysis.

Localization of 111In-FF-21101 in tumor tissue in this study showed uptake in lesions in the majority of patients evaluated; however, by design, there were limitations for detailed evaluation of tumor targeting. While the whole-body anterior/posterior planar 111In scintigraphy was conducted on multiple days up to 144 hours post 111In-FF-21101 administration, the SPECT/CT scan covering the lung, liver, and kidney regions was acquired only at one time point on day 2 (approximately 24 hours postinfusion), primarily to correct organ time-activity curves for attenuation and scatter, and mass-correct organ radiation-absorbed doses. As illustrated by the lack of appreciable uptake observed in target axillary nodes in the ovarian cancer patient who achieved a complete clinical response, assessment of tumor targeting can be challenging and complex, requiring three-dimensional imaging at multiple late time points for adequate contrast to assess smaller lesions, which was not performed in this study. In addition, the inherent sensitivity of gamma camera imaging for detection of radioactivity in very small lesions and micrometastases, which are not uncommon, is low. And while further assessment will be warranted throughout the course of development, evidence of tumor targeting may not always be used as a future prerequisite for treatment to proceed. As an example, the FDA eventually approved removal of pretreatment assessment of tumor uptake during the course of development of Zevalin, due to its benefit in patients who were known to have disease but lacked visual evidence of uptake in 111In-radioimmunoconjugate imaging.

In this initial phase I study enrolling multiple types of solid tumors, a dose response was not observed. However, as a first-in-human dose-escalation phase trial with a novel radioimmunoconjugate, this study is considered a signal-seeking study in patients with advanced and refractory tumors, where lack of response may have been a consequence of multiple prior treatments and the refractoriness of advanced cancers. The response to therapy in our patient with clear cell ovarian cancer despite reactivity was intriguing, and the high tumor P-cadherin expression in this tumor (H-score = 242), one not commonly associated with P-cadherin overexpression (38, 39), underscores the importance of further evaluation of target expression as a potential correlate for activity. Although some patients with low expression maintained stable disease, the majority of patients with longer term disease control had relatively high expression (H-score > 100).

Because of the need for more definitive assessment of antitumor activity, the trial is now amended to evaluate defined tumor types for a more quantitative measure. Two expansion phase cohorts are being evaluated, one for ovarian carcinoma and another for solid tumors inclusive of triple-negative breast cancer, head and neck squamous cell carcinoma, cholangiocarcinoma, pancreatic carcinoma, and colorectal cancer, at the recommended phase II administered activity of 25 mCi/m² (not exceeding 60 mCi/dose) every 3 months, with potential for more frequent administration to be explored. All types of ovarian carcinomas are eligible. These expansion cohorts will allow better characterization of safety, as well as provide more robust indications for a definitive trial of efficacy. Analysis of P-cadherin expression continues to be performed for all patients in this expansion phase of development.

In summary, data from the dose escalation of 90Y-FF-21101 are promising, but preliminary. As noted, patients received a variety of doses, a different number of doses, and had varying results. At this early stage, it is not possible to discern a definitive pattern of response based on P-cadherin expression score, tumor type, dose, or other...
variables in this small number of patients. Much remains to be explored, including, as noted above, the current schedule of treatment every 3–4 months, which is largely empirical. In the dose-escalation study, patients who received multiple (2–5) doses every 4 months tolerated that schedule well, with cumulative activities that ranged from 40 to 100 mCi. More frequent dosing may be beneficial and appears to be promising for other radiopharmaceuticals such as those being evaluated for treatment of prostate cancer (30). Investigation of higher dose levels may also be of value. A cautious limitation for dose escalation up to a maximum activity of 25 mCi/m² was predefined in this study based on estimates to remain below standard organ radiation dose limits typically used for external beam radiation therapy. However, DLTs that have been observed at lower doses with other agents of this type, such as myelosuppression (24–28), were not observed with 90Y-FF-21101 even at highest activity level. This improved safety margin may reflect a more limited distribution of the target antigen in normal tissue, supporting the prospect for further escalation beyond the initial recommended phase II activity level administered every 3 months. In addition, based on observations thus far that demonstrate 90Y-FF-21101 is nonmyeloablative, there is potential for combination with other therapies including immunotherapy, targeted therapy, or even chemotherapy. The favorable safety profile shown in this initial clinical dose-escalation study, along with some early signs of antitumor activity, warrant further evaluation of this RIT approach.

Disclosure of Potential Conflicts of Interest

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