A Phase I Biodistribution and Pharmacokinetic Trial of Humanized Monoclonal Antibody Hu3S193 in Patients with Advanced Epithelial Cancers that Express the Lewis-Y Antigen


Abstract

Purpose: We report a first-in-man trial of a humanized antibody (hu3S193) against the LeY antigen.

Experimental Design: Patients with advanced LeY-positive cancers received four infusions of hu3S193 at weekly intervals, with four dose levels (5, 10, 20, and 40 mg/m²). The first infusion of hu3S193 was trace labeled with Indium-111, and biodistribution, pharmacokinetics, tumor uptake, and immune response were evaluated in all patients.

Results: A total of 15 patients (7 male/8 female; age range, 42-76 years; 6 breast, 8 colorectal cancer, and 1 non–small-cell lung cancer) were entered into the study. Transient grade 1 to 2 nausea and vomiting was observed following infusion of hu3S193 at the 40 mg/m² dose level only. There was one episode of dose-limiting toxicity with self-limiting Common Toxicity Criteria grade 3 elevated alkaline phosphatase observed in one patient with extensive liver metastases. The biodistribution of 111In-hu3S193 showed no evidence of any consistent normal tissue uptake, and 111In-hu3S193 uptake was observed in cutaneous, lymph node, and hepatic metastases. Hu3S193 displayed a long serum half-life (T1/2 = 189.63 ± 62.17 h). Clinical responses consisted of 4 patients with stable disease and 11 patients with progressive disease, although one patient experienced a 89% decrease in lymph node mass, and one patient experienced inflammatory symptoms in cutaneous metastases, suggestive of a biological effect of hu3S193. No immune responses (human anti-human antibody) to hu3S193 were observed.

Conclusion: Hu3S193 is well tolerated and selectively targets tumors, and the long half-life and biological function in vivo of this antibody makes it an attractive potential therapy for patients with LeY-expressing cancers.

The Lewis-y (LeY) antigen is a blood group–related antigen expressed in over 70% of epithelial cancers (including breast, colon, ovary, and lung cancers) and is an attractive target for monoclonal antibody–directed therapy (1–9). A number of phase I clinical trials with mouse or humanized anti-LeY antibodies have been conducted to date. Trials of murine BR55-2 (10, 11), ABL-264 (12), B3 (13), and LMB-1 (murine antibody B3 linked to Pseudomonas exotoxin; ref. 14) have been conducted with some minor responses observed; however, immunogenicity of constructs has restricted the use of these antibodies. Recently, a phase I trial of a humanized anti-LeY antibody IGN311 (based on the murine BR55-2 antibody) was reported to show favorable safety and pharmacokinetic data (15).

A chimeric BR96-doxorubicin construct (16, 17) has also been evaluated in a range of patients with advanced cancers at doses up to 700 mg/m². In clinical trials, upper gastrointestinal toxicity was seen in doses > 200 mg/m², and weak immune responses to BR96-doxorubicin was observed in 37% of patients (18). Phase II trials of BR96-doxorubicin in breast cancer and gastric cancer patients have been performed, with limited clinical activity seen (19, 20). BR96-doxorubicin (SGN-15) has also been evaluated in phase II trials in conjunction with Taxotere in non–small-cell lung carcinoma patients, and an improvement in overall survival compared with Taxotere alone was reported (21). Interestingly, dosing with SGN-15...
prior Taxotere has been shown to have improved the effect assessed by 18F-FDG positron emission tomography scans.

We have developed a CDR-grafted humanized version of murine anti-Le^v monoclonal antibody 3S193 (hu3S193), which has undergone extensive preclinical characterization (22–27). Hu3S193 has potent immune effector function [complement-dependent cytotoxicity (CDC), IC50 1.0 µg/mL and antibody-dependent cellular cytotoxicity (ADCC), IC50 0.5 µg/mL], is rapidly internalized into Le^v expressing cancer cells, and has been shown in preclinical studies alone or in conjunction with isopotes and toxins to cause significant regressions in xenograft models (23–26, 28). We report the results of a first-in-human trial of hu3S193 in patients with Le^v-positive epithelial cancers.

Materials and Methods

Trial design

This first-in-human trial was an open-label, dose escalation phase I study. The primary objectives and end points of the study were to evaluate the safety of hu3S193 in patients with advanced epithelial cancers expressing the Le^v antigen; determine the pharmacokinetics, tissue distribution, and imaging characteristics of i.v. administered 111In-hu3S193; determine the patient’s immune response to hu3S193; and to document observed tumor responses. The protocol was approved by the Human Research and Ethics Committee of the Austin Hospital prior to study commencement. All patients gave written informed consent before study entry. The phase I trial was conducted via a Therapeutic Goods Administration clinical trial notification scheme and under a Food and Drug Administration investigational New Drug Application.

Eligibility criteria included advanced epithelial cancer in patients who had failed at least one line of chemotherapy and/or hormonal therapy but had not received more than three lines of therapy for metastatic disease; measurable or evaluable disease histologically proven to express Le^v antigen; Karnofsky performance status ≥70%; with no serious co-morbidity; expected survival of ≥4 months; adequate marrow, renal, and hepatic function; left ventricular ejection fraction >50%; and no concurrent immunosuppressive therapy. 

Following immunohistochemical assessment of archived tumor samples for Le^v expression, tissue sections were graded as -(negative), + (weak), ++ (moderate), and +++ (strong). Tumors were defined as Le^v positive if >50% of cells were weakly stained, or >30% were moderate to strongly stained.

Hu3S193 was administered weekly × 4 doses at one of four dose levels (5, 10, 20, or 40 mg/m^2) by i.v. infusion over a period of 60 min. The first dose of hu3S193 was trace radiolabeled with Indium-111 (111In; 200-280 MBq, 5-7 mCi) to assess biodistribution and targeting to tumor. Tumor evaluation was done before treatment and 2 weeks after the fourth dose. After one cycle, patients showing evidence of objective tumor response were offered further cycles at the same dose level for up to a further 12 months.

Dose escalation criteria

The first patient at each dose level was observed for 4 weeks before enrollment of any additional patients. If no dose-limiting toxicity (DLT) was observed in any of the first three patients within 4 weeks of the first infusion of hu3S193, three patients were then entered on the next highest dosage tier. If one patient in any cohort of three patients experienced a DLT within 4 weeks from the first dose, an additional three patients (maximum of six) were entered at that dosage level. If no more than one patient out of six in any dose level experienced grade ≥3 toxicity, subsequent patients were entered at the next dosage tier.

DLT was defined as grade 3 nonhematologic toxicity, or grade 4 hematologic toxicity as defined by the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0 (CTCAE v3.0). Maximum tolerated dose was defined as the hu3S193 dose below that where two or more patients out of six experienced DLT.

Radiolabeling of Hu3S193

The antibody hu3S193 was labeled with 111In (MDS Nordion) via the bifunctional metal ion chelate CHX-A^-diethylentriaminepentaacetic acid according to methods described previously (29, 30).

Gamma camera imaging

Whole-body images of 111In-hu3S193 biodistribution were obtained in all patients on day 0 after infusion of 111In-hu3S193 and on at least three further occasions up to day 7 following infusion. Single-photon emission computed tomography images of a region of the body with known tumor were also obtained on at least one occasion during this period. All gamma camera images were acquired on dual-headed gamma cameras (Trixon Research Laboratories or Picker International).

Pharmacokinetics

Blood samples were collected for pharmacokinetics to be analyzed by ELISA for each hu3S193 infusion and by 111In measurement following the first infusion.

Radiolabeled hu3S193. Serum samples were aliquoted in duplicate and counted in a gamma scintillation counter (Packard Instruments), along with appropriate 111In standards. The results of the serum were expressed as % injected dose per liter (% ID/L). Pharmacokinetic calculations were done of serum data using a curve fitting program (WinNonlin, Pharsight Co.). A two-compartment model was fitted to individual labeled infusions for each patient using unweighted nonlinear least squares to calculate pharmacokinetic variables of T1/2z and T1/2β, V1, area under the curve, and clearance. ELISA. Measurement of patient serum hu3S193 protein levels following each infusion was done in triplicate using a validated ELISA assay with a 3.0 ng/mL limit of detection, as previously described (31). A two-compartment model (ADVAN3) was fitted to the pharmacokinetic data from all patients using NONMEM (University of California, San Francisco, CA). Peak and trough serum hu3S193 levels (Cmin, Cmax), clearance, and area under the curve were calculated for each infusion.

Tumor and organ dosimetry of 111In-hu3S193

Regions of interest were defined for suitable tumors at each time point on 111In-hu3S193 image data sets, corrected for background and attenuation, and dosimetry calculation was performed to derive the concentration of 111In-hu3S193 in tumor per gram (32–34). This was converted to milligram hu3S193 per gram tumor tissue based on the injected milligram hu3S193 protein dose. A similar approach was used to calculate uptake in stomach wall at various time points post infusion.

Immune effector function of hu3S193 in vivo

Serum samples were collected from six patients on day 28 (+1 day) following their final infusion of hu3S193 (three patients each at the 20 and 40 mg/m^2 dose levels). The serum samples were heated to 56°C for 30 min to destroy any endogenous complement activity. The samples were then used as a source of hu3S193 antibody in CDC and ADCC assays, with control complement and peripheral blood mononuclear cells used in assays (35, 36). Controls of healthy donor serum added to equivalent levels of hu3S193 and isotype control huA33 (37) were treated and analyzed concurrently with the test samples.

Hu3S193-mediated CDC and ADCC activity in patient serum was measured in triplicate with a 4-h 51Cr release assay based upon previously published methods (35, 36).

Human anti-human antibody

Blood samples for human anti-human antibody (HAHA) assessment were taken before each hu3S193 infusion, then at week 6 and at 30 days
after last hu3S193 infusion, and were analyzed by surface plasmon resonance technology using a BIAcore2000 instrument as previously described (38).

Results

Patients. Fifteen patients with a mean age of 53 years (range, 42-76 years) completed the trial (Table 1). Primary tumor sites, prior therapy history, and sites of disease at study entry are also shown in Table 1. All 15 patients had Leu-positive tumors on screening and fulfilled all inclusion criteria.

Adverse events and HAHA. Adverse events related to hu3S193 are listed in Tables 2 and 3. Overall, hu3S193 was safe and well tolerated at all dose levels, with generally predictable and manageable toxicities being observed. Transient grade 1 to 2 nausea and vomiting was observed following infusion of hu3S193 at the 40 mg/m² dose level only. These symptoms did not occur following all infusions and were self-limiting. The maximum tolerated dose was not reached. One episode of DLT was observed, with asymptomatic grade 3 alkaline phosphatase liver enzyme increase in a patient (patient 05) with extensive liver metastases (baseline grade 2 alkaline phosphatase elevation at study entry). This event was associated with right upper quadrant pain. Elevated alkaline phosphatase resolved to baseline levels following cessation of hu3S193 infusions. No additional DLTs were observed in this expanded cohort nor in higher dose levels. Liver enzyme abnormalities attributable to study drug were not observed in any other patient.

One patient (patient 04, 10 mg/m²) experienced grade 1 chest wall paresthesia and axillary swelling at sites of known disease that was related to the second and fourth hu3S193 infusions.

Grade 1 and 2 asymptomatic elevations in complement levels were also noted in 10 patients. In all but three patients this had resolved at last follow-up. There were no significant changes observed in blood counts, serum electrolytes, or creatinine in any patient. No episodes of delayed toxicity were observed in the follow-up of the 15 patients.

No HAHA was detected in serum. A transient episode of localized urticaria was experienced by one patient (patient 14, 40 mg/m²) with no BIAcore evidence of HAHA. This occurred during the first infusion of hu3S193, resolved spontaneously, and did not recur with subsequent infusions.

Radiolabeling of hu3S193. There were a total of 17 infusions of 111In-hu3S193 administered during the trial. The mean ± SD immunoreactivity of 111In-hu3S193 was measured to be 60.1 ± 8.9%.

Biodistribution of hu3S193. The pattern of 111In-hu3S193 biodistribution in patients at the 5, 10, and 20 mg/m² dose

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
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<td>Patient no.</td>
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<td>15</td>
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Abbreviations: M, male; F, female; KPS, Karnofsky performance status; NSCLC, non–small-cell lung cancer; PD, progressive disease; SD, stable disease; s.c., subcutaneous.
levels was consistent with blood pool activity, which cleared gradually with time. Some minor gut uptake was observed, consistent with gut excretion of free $^{111}$In. At these dose levels, no other normal tissue uptake was observed (Fig. 1). For the two patients receiving infusions of $^{111}$In-hu3S193 in an additional cycle, no change in biodistribution pattern was observed in either patient.

At the 40 mg/m$^2$ dose level, in two patients (patients 13 and 14), some stomach and bowel activity was observed after infusion (day 0 and day 1), which rapidly resolved (Fig. 2). This was associated with infusion related symptoms of nausea and vomiting. Abnormal uptake in stomach or bowel was not seen in patient 15. No other normal tissue uptake was seen at this dose level.

Excellent uptake of $^{111}$In-hu3S193 was observed in tumor sites at all dose levels, with metastatic lesions greater than 2.0 cm visualized in lung, liver, lymph nodes, and bone. Subcutaneous lesions and small metastatic disease in the omentum less than 1.5 cm in size were also visualized (patients 4 and 12).

**Pharmacokinetics.** The results of pharmacokinetic analysis for unlabeled hu3S193 (based on ELISA) was $T_{1/2A} = 10.95 \pm 0.63$ h, $T_{1/2B} = 162.41 \pm 35.88$ h, clearance = $36.84 \pm 12.16$ mL/h, and $V_1 = 3.93 \pm 0.88$. No significant differences or trends were observed between dose level and $T_{1/2A}$, $T_{1/2B}$, volume of distribution, or clearance. As expected, linear relationships were observed for area under the curve, $C_{max}$, and $C_{min}$ with dose level (data not shown).

Following the first infusion, peak serum hu3S193 concentrations ranged from 1.9 $\pm$ 0.55 mg/mL (5 mg/m$^2$ dose level) to 25.07 $\pm$ 2.95 mg/mL (40 mg/m$^2$ dose level; see Supplementary Information).

**Tumor and stomach dosimetry of $^{111}$In-hu3S193.** Tumor dosimetry analysis was completed for 9 of 15 patients. Tumor dosimetry was not done on patients 1, 3, 5, 6, 13, and 14 because tumor was not easily distinguishable on static gamma camera images due to small lesion size. The calculated peak uptake of $^{111}$In-hu3S193 in tumor ranged from 1.2 to 6.3 $\mu$g/g (mean $\pm$ SD $\mu$g/g: 5 mg/m$^2$ dose level) to 25.07 $\pm$ 2.95 mg/mL (40 mg/m$^2$ dose level; see Supplementary Information).

Stomach uptake was maximal at day 0 (immediately after infusion) and increased with dose level (mean $\pm$ SD $\mu$g/g: 5 mg/m$^2$, 0.0062 $\pm$ 0.0054; 10 mg/m$^2$, 0.025 $\pm$ 0.016;
20 mg/m², 0.033 ± 0.021; 40 mg/m², 0.18 ± 0.15). At the 40 mg/m² dose level, activity within the stomach was observed in two patients (Fig. 2), which resulted in a probable overestimate of concentration of hu3S193 in stomach wall in these patients.

Retention of immune effector function of hu3S193 in vivo. The CDC and ADCC results showed retention of hu3S193 immune effector function in patient sera for up to 1 week following administration, with ADCC and CDC levels equivalent to that achieved with fresh hu3S193 added to heat-inactivated healthy donor serum (see Supplementary Information).

Tumor responses. Staging at the completion of cycle 1 showed 11 patients with progressive disease and 4 patients with stable disease (Table 1). Patients 01 and 03 successfully

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Fig. 1. Biodistribution of ¹¹¹In-hu3S193 in patient 10 (20 mg/m² dose level). A, anterior whole-body gamma camera images over 5 d after infusion. Initial blood pool activity (day 0) is seen, with gradual clearance with time. Uptake of ¹¹¹In-hu3S193 in metastatic colon carcinoma in the liver is seen by day 2 (arrows) and increases with time to day 5. B, computed tomography scan of the upper abdomen showing metastatic colon carcinoma.

Fig. 2. Biodistribution of ¹¹¹In-hu3S193 in patient 14 (40 mg/m² dose level). Anterior whole-body gamma camera images over 7 d after infusion. On day 0, blood pool activity is seen, and some activity in the stomach is also evident (arrow). This patient had symptoms of nausea following the infusion and before imaging. By day 1, stomach activity is no longer seen, and activity in the lumen of the large intestine is evident (arrow). This has completely cleared by day 2, and no further gastrointestinal activity is seen at day 5.
completely a second cycle of treatment. At restaging, both had developed progressive disease. Patient 05 (10 mg/m² dose level) did, however, have objective evidence of reduction in size of a clinically palpable left cervical lymph node (14 cm² to 1.5 cm²) after one cycle of hu3S193 and had stable disease at last follow-up.

Discussion

This study represents the first reported demonstration of the biodistribution and targeting of a humanized anti-Le⁰ antibody in patients with epithelial cancers. At doses up to 40 mg/m² given every week, hu3S193 was well tolerated, and maximum tolerated dose was not reached. The biodistribution of hu3S193 in all patients showed gradual clearance of blood pool activity and no consistent normal tissue uptake of ¹¹¹In-hu3S193. Excellent tumor uptake of hu3S193 was also evident, including lung, liver, lymph node, soft tissue and bone metastases, indicating the selectivity of hu3S193 for epithelial tumors known to express the Le⁰ antigen. Importantly, no HAHA response to hu3S193 were observed in any patient entered into the study.

The principal toxicity of hu3S193 was grade 1 to 2 nausea and vomiting at the 40 mg/m² dose level, which was self-limiting. This was associated with (in two patients) some stomach activity on day 0, which cleared by 24 h, and bowel activity subsequently disappeared after 1 to 2 days (Fig. 2). The timing of these symptoms, together with the biodistribution evident on gamma camera images, suggests that the peak concentration of hu3S193 in blood at the 40 mg/m² dose level immediately after infusion (>20 μg/mL) may induce a self-limiting inflammatory process in the gastric mucosa. This observation is consistent with the known expression of Le⁰ antigen in gastric mucosa (1–5). The activity in the stomach (Fig. 2) in the two patients with gastrointestinal symptoms may represent shed ¹¹¹In-hu3S193, or minor blood loss, which traveled within the lumen of the bowel after subsequent days. Calculation of concentration of ¹¹¹In-hu3S193 in stomach wall showed gradual increase with dose, although results were confounded at the 40 mg/m² dose level due to activity within the stomach lumen. In the two patients with symptoms related to the first infusion of hu3S193, no significant drop in blood counts was observed. This observation of gastric symptoms is similar to that reported with IGN311 (15) and with BR96-doxorubicin (SGN-15; refs. 18–21), although this is the first study to identify the temporal relationship of symptoms to the biodistribution of anti-Le⁰ antibody to stomach and gut.

Pharmacokinetic analysis revealed hu3S193 to have a biphasic serum clearance and a long terminal half-life of greater than 1 week. Importantly, no saturable normal tissue compartment was identified, and serum levels increased proportionally with dose. Trough levels of hu3S193 of over 1 μg/mL were seen at dose levels of 10 mg/m² and higher. This concentration achieved >50% killing of tumor cells in in vitro preclinical studies (22) and indicates that biologically significant concentrations could be achieved at the dose levels studied. These results are quite different from humanized antibodies against antigens expressed at high levels in normal tissue (e.g., CD20, epidermal growth factor receptor, ErbB2) where large loading doses are required to achieve saturable pharmacokinetics (39, 40). Quantitative image analysis of tumor uptake at 6 to 7 days after infusion showed concentrations of hu3S193 of >1 μg/g tumor in all patients and increasing accumulation of hu3S193 with dose level. The use of ¹¹¹In to radiolabel hu3S193 enabled accurate quantitative assessment of tumor uptake and retention of hu3S193, whereas radiohalides (e.g., ¹³¹I) would have undergone rapid dehalogenation in the tumor, and subsequent extrusion from the tumor cell (22–24). Hu3S193 also retained potent immune effector function in vivo (both CDC and ADCC). The high concentration of hu3S193 in tumor would allow the continued exposure of tumor cell surface to hu3S193 and immune mediators (complement and effector cells) resulting in optimal conditions for cell killing. These data confirm the ability of hu3S193 to selectively target tumors in patients at concentrations suitable for potent immunologic effect.

Although no objective tumor responses were seen, the schedule of dosing was for only 4 weeks, which may have limited the potential for the effects of hu3S193 to be measured. Interestingly, some biological effect of hu3S193 was observed, including clinical shrinkage of a lymph node in one patient, and another patient experienced left chest wall paresthesia and swelling associated with the second and fourth hu3S193 infusion. The DLT observed (elevated alkaline phosphatase) was also potentially related to the enlargement of lymph nodes near the porta hepatis of the patient, further suggesting a biological effect of hu3S193.

Although other antibodies targeting the Le⁰ antigen have been studied in the clinic, hu3S193 has a number of important properties that make it highly attractive as a therapeutic. First, this trial has clearly showed that hu3S193 selectively targets Le⁰-expressing tumors at high concentrations and with retention of immune effector function in vivo. It is well tolerated, and the lack of immunogenicity is in contrast to SGN-15 (18). The favorable pharmacokinetics of hu3S193 and high tumor

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**Table 4. Pharmacokinetic parameters of ¹¹¹In-CHX-A⁰-DTPA-hu3S193**

<table>
<thead>
<tr>
<th>Dose level (mg/m²)</th>
<th>T¹/₂ α (h), mean (SD)</th>
<th>T¹/₂ β (h), mean (SD)</th>
<th>V₁ (mL), mean (SD)</th>
<th>Clearance (mL/h), mean (SD)</th>
<th>AUC (hμg/mL), mean (SD)</th>
</tr>
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<tr>
<td>5</td>
<td>3.45 (1.08)</td>
<td>166.9 (57.61)</td>
<td>3,657.67 (671.77)</td>
<td>32.01 (14.18)</td>
<td>305.18 (95.09)</td>
</tr>
<tr>
<td>10</td>
<td>5.40 (4.86)</td>
<td>166.67 (54.12)</td>
<td>3,586.42 (388.19)</td>
<td>23.93 (6.86)</td>
<td>803.69 (266.91)</td>
</tr>
<tr>
<td>20</td>
<td>11.98 (7.56)</td>
<td>221.23 (83.07)</td>
<td>2,711.2 (486.27)</td>
<td>15.87 (7.27)</td>
<td>2,220.88 (773.17)</td>
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<tr>
<td>40</td>
<td>6.66 (5.87)</td>
<td>226.67 (50.02)</td>
<td>2,842.51 (746.03)</td>
<td>14.69 (3.54)</td>
<td>4,964.11 (412.56)</td>
</tr>
<tr>
<td>All</td>
<td>6.58 (5.53)</td>
<td>189.63 (62.17)</td>
<td>3,275.85 (642.43)</td>
<td>22.09 (9.87)</td>
<td>4,396.41 (412.56)</td>
</tr>
</tbody>
</table>

Abbreviation: AUC, area under the curve.
concentrations achieved at the dose levels studied in this trial support the use of hu3S193 for immune therapy of solid tumors, alone or in combination with other treatments. Hu3S193 has also been shown to have improved efficacy when radiolabeled and combined with chemotherapy or linked to a drug in preclinical models (25, 26, 28). Collectively, these results, therefore, indicate the potential for hu3S193 treatment of metastatic Le^3-expressing cancers, and further phase I/II trials aimed at optimizing dosage and scheduling of hu3S193 are ongoing.

**Acknowledgments**

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