Phase I Trial of Weekly Tigatuzumab, an Agonistic Humanized Monoclonal Antibody Targeting Death Receptor 5 (DR5)

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Abstract

Background: TRA-8 is a murine agonist monoclonal antibody to death receptor 5 (DR5), which is able to trigger apoptosis in DR5 positive human tumor cells without the aid of crosslinking. It has demonstrated cytotoxicity *in vitro* and *in vivo* antitumor efficacy to a wide range of solid tumors in murine xenograft models. Tigatuzumab is a humanized IgG1 monoclonal antibody derived from TRA-8.

Methods: A phase I trial of tigatuzumab in patients with relapsed/refractory carcinomas ($n = 16$) or lymphoma ($n = 1$) was designed to determine the maximal tolerated dose (MTD), pharmacokinetics, immunogenicity, and safety. Three to six (3–6) patients were enrolled in successive escalating cohorts at doses ranging from 1 to 8 mg/kg weekly.

Results: Seventeen (17) patients enrolled, 9 in the 1-, 2-, and 4-mg/kg dose cohorts (3 in each cohort) and 8 in the 8-mg/kg dose cohort. Tigatuzumab was well tolerated with no DLTs observed, and the MTD was not reached. There were no study-drug-related grade 3 or 4, renal, hepatic, or hematologic toxicities. Plasma half-life was 6–10 days, and no anti-tigatuzumab responses were detected. Seven (7) patients had stable disease, with the duration of response ranging from 81 to 798 days.

Conclusions: Tigatuzumab is well tolerated, and the MTD was not reached. The high number of patients with stable disease suggests antitumor activity.

Key words: antibody, apoptosis, cancer, immunotherapy, targeted therapy

Introduction

The tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), a member of the TNF superfamily of cytokines, is a type 2 membrane protein that is expressed in the majority of normal tissues and can undergo protease cleavage, resulting in a soluble form able to bind to TRAIL receptors.^{1,2} TRAIL has strong apoptosis-inducing activity against cancer cells *in vitro* and potent antitumor activity against tumor xenografts of various cancers *in vivo*.^{3–5} Unlike other death-inducing ligands of the TNF superfamily, TRAIL has been of particular interest in the development of cancer therapies, as it preferentially induces apoptosis of

tumor cells, having little or no effect on normal cells.⁶ Five receptors for TRAIL have been identified, two of which, death receptor (DR)4 (TRAIL-R1) and DR5 (TRAIL-R2), have a cytoplasmic death domain and are able to trigger apoptosis in tumor cells via downstream caspase activation^{7,8}; the other three receptors lack a cytoplasmic death domain and do not mediate apoptosis.^{4,5} Expression of either DR4 or DR5 is frequently detected in human cancers, including colon, gastric, pancreatic, ovarian, breast, and non-small-cell lung cancer with low or no expression in normal tissues.^{9,10} Agonistic monoclonal antibodies that specifically bind to DR4 and DR5 have been produced and represent a new generation of cancer therapy, as they are able to directly induce apoptosis of

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targeted tumor cells.^{3,10} The use of an agonistic monoclonal antibody against the death receptors instead of TRAIL could be advantageous; TRAIL targets multiple receptors, including both death receptors and decoy receptors. In addition, TRAIL has a much shorter circulating half-life, compared with monoclonal antibodies, and this can impact dose and schedule parameters. The very short half-life of TRAIL requires large and frequent dosing, compared with monoclonal antibodies. Further, there is considerable experience in the clinical use of monoclonal antibodies, therefore providing guidance in the development of single-agent and combination regimens.

The murine anti-DR5 monoclonal antibody, TRA-8 (mTRA-8), was selected from a series of anti-DR5 monoclonal antibodies based on its specificity, ability to trigger apoptosis *in vitro* without the use of crosslinking reagents, and lack of toxicity to human hepatocytes.¹¹ It was shown to have potent *in vitro* cytotoxicity to a variety of human tumor cell lines and *in vivo* antitumor efficacy in murine xenograft models of human cancers.¹² Its *in vitro* cytotoxicity and *in vivo* antitumor efficacy can be substantially enhanced in combination with a variety of chemotherapeutic agents and/or radiation.^{12,13} Tigatuzumab (CS-1008) is a humanized monoclonal antibody composed of the CDR regions of mTRA-8, as well as the variable region framework and constant regions of human immunoglobulin IgG-1 mAb58'CL. Tigatuzumab mediates a very similar pattern of *in vitro* cytotoxicity and *in vivo* antitumor efficacy as mTRA-8 and was well tolerated in preclinical toxicology studies in monkeys (unpublished results).

Here, we detail the first phase I dose-escalation trial of tigatuzumab in order to characterize its safety and tolerability as a single agent in patients with relapsed or refractory solid tumors and to determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), pharmacokinetics, and immunogenicity in a weekly schedule of administration.

Patients and Methods

Trial design and objectives

This single-institution trial was designed to determine the MTD and to document the safety profile for tigatuzumab in patients with relapsed or refractory solid tumors or lymphomas (with no leukemic component). In addition, the trial characterized the pharmacokinetics, immunogenicity, and preliminary antitumor effects of tigatuzumab in patients.

Patient eligibility

Patients were eligible if they were ≥ 18 years in age and had histologic proof of metastatic solid tumors or lymphomas (with no leukemic component); expression of DR5 in the tumor cells was not required. Patients were required to be refractory to, or have relapsed after, standard systemic therapy. The number of previous systemic therapies was not limited. Patients recently treated with chemotherapy, immunotherapy, radiation therapy, or experimental drugs were eligible only after 4 weeks had elapsed since the most recent therapy and there was resolution of any toxicity associated with that previous therapy. All patients were required to have a life expectancy of at least 12 weeks and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2. The following laboratory values, completed ≤ 7

days before treatment, were required: a total absolute neutrophil count $\geq 1.5 \times 10^9/L$ ($1500/\mu L$); a platelet count $\geq 100 \times 10^9/L$ ($100,000/\mu L$); a hemoglobin level $\geq 9 g/dL$; a total bilirubin count $\leq 1.5 \times$ upper limit of normal (ULN); a serum creatinine level $< 1.5 mg/dL$ (or creatinine clearance $> 60 mL/min$); and an aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) level $< 2.5 \times$ ULN (in patients with liver metastasis $< 4.5 \times$ ULN). Investigators were required to conduct this trial according to good clinical practice guidelines and the Declaration of Helsinki.

Patients were excluded from protocol accrual for the following conditions: brain metastasis; an uncontrolled seizure disorder; spinal cord compression; carcinomatous meningitis; myocardial infarction; severe or unstable angina pectoris; coronary or peripheral artery bypass graft; New York Heart Association class III or IV congestive heart failure; cerebrovascular accident; transient ischemic attack; pulmonary embolism; deep vein thrombosis; clinically significant pulmonary disease; active infection; HIV-positive patients; chronic diarrhea; inflammatory bowel disease; partial bowel obstruction; a medical or psychiatric condition that might interfere with achieving the trial objectives; and pregnancy or lactation.

Given the institutional (University of Alabama at Birmingham) conflict of interest (i.e., intellectual property), institutional review board (IRB) review and approval were provided by the University of Pennsylvania IRB (Philadelphia, PA). All patients gave written informed consent to participate in the trial.

Trial design

This trial was an open-label, phase I, dose-escalation study with 3–6 patients at each dose level. Cohorts of patients received tigatuzumab at escalating dose levels of 1, 2, 4, and 8 mg/kg administered weekly by intravenous (i.v.) infusion. A treatment cycle was defined as 3 weekly infusions. Dose escalation to the next cohort did not occur until the first 3 patients in the previous cohort had completed 1 cycle of treatment without drug-related DLTs; dose escalation was continued until the MTD was identified or the dose of 8 mg/kg was reached. If a DLT was observed in the first 3 patients enrolled at a dose level, the cohort was expanded to 6 patients; the trial allowed dose escalation if no DLTs were seen in these additional 3 patients. DLTs were defined as follows: grade 3 or 4 nonhematologic toxicities (except alopecia, fatigue, anorexia, nausea, or fever without neutropenia); failure to recover to baseline toxicity after delaying the next dose by more than 2 weeks; grade 3 or 4 neutropenia complicated by fever $\geq 38.5^\circ C$, infection, or grade 4 neutropenia of at least 7 days in duration; and grade 4 thrombocytopenia, or grade 3 thrombocytopenia complicated by hemorrhage. The MTD was defined as the highest dose at which 0 of 3 or 1 of 6 patients experienced DLTs during the first cycle of therapy. The trial allowed enrollment of additional patients (up to 10) at the highest dose level (8 mg/kg) if the MTD was not reached, or at the MTD to further elucidate study-drug safety and pharmacokinetics.

Drug formulation and administration

Tigatuzumab was supplied to the study site by Daiichi Sankyo Pharma (Edison, NJ) as single-use vials containing

5 mg of sterile, preservative-free, monoclonal antibody. The lyophilized material of the vials was reconstituted with 1.2 mL of 0.9% sodium chloride USP. Tigatuzumab was diluted in a 0.9% sodium chloride injection and was administered as a continuous i.v. infusion, using a rate-regulating device. The initial dose was delivered over 90 minutes; if there were no infusion-associated adverse events with the first infusion, subsequent infusions were delivered over 30–60 minutes. The doses administered in this trial were calculated based on the protein content measured by the Lowry method.

Assessments

Baseline assessments included: signed informed consent; medical history and physical examination; serum chemistries (i.e., total bilirubin, serum creatinine, AST, ALT, ALP, lactate dehydrogenase, glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, total protein, uric acid, and creatinine kinase); serum immunoglobulins; urine; hematology analyses [i.e., complete blood counts (CBCs) with differential and platelet counts]; a 12-lead electrocardiogram (ECG); human antitigatuzumab antibodies; and radiographic scans, including a fluorescein deoxy glucose (FDG-PET) scan.

Safety

Patients were monitored throughout the trial by physical examination, laboratory analyses, and assessment of adverse events. Adverse events were graded according to the National Cancer Institute–Common Toxicity Criteria (NCI-CTC), version 3. Complete physical examination, CBC with differential and platelet counts, and serum chemistries (as a baseline assessment) were conducted weekly for as long as the patient was receiving tigatuzumab. Physical examinations, CBC with differential and platelet counts, and serum chemistries (as a baseline assessment) were repeated at the end-of-study visit (30–45 days after the last dose of tigatuzumab), when feasible.

Efficacy

Antitumor responses were measured by using Response Evaluation Criteria In Solid Tumors,¹⁴ the Cotswold criteria for Hodgkin's lymphoma,¹⁵ and the International Workshop Standardized Response Criteria for patients with non-Hodgkin's lymphoma (NHL).¹⁶ Radiologic assessments, such as computed tomography (CT) and/or magnetic resonance imaging (MRI), were performed at baseline and on week 7 (before infusion of the seventh dose of tigatuzumab); patients who continued in the trial (with stable disease, partial response, or complete response) had radiologic assessments every 6 weeks until disease progression.

Tigatuzumab pharmacokinetics

Blood samples for pharmacokinetics were obtained pretherapy and 1, 3, 6, 12, 24, 48, 96, and 168 hours after the first infusion, and prior to study-drug infusion for subsequent cycles to determine study-drug accumulation. After the collection of samples, sera were separated and stored at -80°C until assay at a central laboratory. A validated sandwich-enzyme-linked immunosorbent assay (ELISA) method was

used to measure tigatuzumab concentrations in sera. In brief, microtiter plates precoated with histidine-labeled soluble DR5 were incubated at 37°C for 1 hour with diluted serum samples (1:100) in triplicate. Bound tigatuzumab was detected by using a secondary horseradish peroxidase (HRP)-conjugated goat-antihuman Fc antibody incubated at 37°C for 1 hour, which was then incubated with TMB-soluble reagent at an ambient temperature for 20 minutes. The absorbance was measured with a SPECTRAmax (Molecular Devices, Sunnyvale, CA) 340PC spectrophotometer at 450 nm. Standard and control samples of tigatuzumab in normal human sera were included in each analytic run. The intra- and interassay precision and accuracy of the quality control samples in all the analytic runs were within $\pm 10\%$.

Noncompartmental pharmacokinetic parameters, including maximum plasma or serum concentration (C_{max}), concentration at the end of infusion (C_{eoi}), area under the curve to the last collection point ($\text{AUC}_{0-\text{last}}$), area under the curve for dosing interval ($\text{AUC}_{0-\tau}$), area under the curve extrapolated to infinity ($\text{AUC}_{0-\infty}$), time of maximum concentration (T_{max}), elimination-rate constant (k_{el}), terminal half-life ($t_{1/2}$), total clearance (CL), and volume of distribution at steady state (V_{ss}), were calculated by using the WinNonlin version 4.0 program (Pharsight Corp., Mountain View, CA). Compartmental and population pharmacokinetic analysis were also conducted by using different models, such as the one- or two-compartmental model, with zero- or first-order input.

Human anti-tigatuzumab response

Blood samples were collected prior to dosing with tigatuzumab on days 1, 21, and 49, and then, every 6 weeks during treatment. An additional sample was collected 3 months after the cessation of tigatuzumab, when possible. Human anti-tigatuzumab antibodies were measured by a validated ELISA assay. Briefly, serum samples were added to a tigatuzumab-coated plate and incubated at 37°C for 1 hour, followed by incubation with biotinylated-tigatuzumab at 37°C for 1 hour. Plates were then incubated with streptavidin-HRP conjugate at 37°C for 1 hour, followed by incubation with TMB-soluble reagent at an ambient temperature for 20 minutes. The absorbance was measured with a SPECTRAmax 340PC spectrophotometer at 450 nm. Antibody titers were assessed for positive samples, based on dilutions with signals, above a cut-off point determined from negative control values.

Statistics

Descriptive statistics (i.e., mean, standard deviation, coefficient of variation, standard error of the mean, sample size, number missing, median, geometric mean, geometric coefficient of variation, minimum, and maximum) were used in the analysis of observations from this trial.

Results

Patient characteristics

As seen in Table 1, 17 patients (7 male and 10 female) were enrolled in the trial. Patient age ranged from 31 to 88 years (median, 57), and the majority of patients were white (12 whites and 5 blacks). The patients had a variety of cancer types, with colon cancer ($n = 4$) and cancer of the head and neck ($n = 3$) being the most common. Most patients had been

TABLE 1. PATIENT CHARACTERISTICS

Patient	Dose mg/kg (week)	Number of doses	Age	Gender	Diagnosis	PS	Prior regimens	Response	Duration (days)
1	1	99	57	M	Hepatocellular carcinoma	0	3	SD	798
2	1	6	62	F	Follicular lymphoma	0	2	PD	—
3	1	30	58	M	Carcinoma of head and neck	0	1	SD	232
4	2	5	43	F	Carcinoma of unknown primary	0	3	PD	—
5	2	6	61	M	Esophageal carcinoma	2	3	PD	—
6	2	12	43	F	Colon carcinoma	0	2	SD	84
7	4	23	64	F	Colon carcinoma	1	3	SD	169
8	4	4	31	F	Cervical carcinoma	1	2	PD	—
9	4	12	52	F	Cholangiocarcinoma	0	2	SD	82
10	8	12	44	M	Colon carcinoma	1	2	SD	81
11	8	5	48	F	Carcinoma of unknown primary	0	2	PD	—
12	8	4	72	F	Colon carcinoma	1	3	PD	—
13	8	3	60	M	Carcinoma of head and neck	1	2	PD	—
14	8	2	88	F	Pancreatic carcinoma	1	2	PD	—
15	8	6	69	M	Carcinoma of head and neck	1	1	PD	—
16	8	16	52	M	Hepatocellular carcinoma	1	2	SD	126
17	8	6	50	F	Breast carcinoma	0	3	PD	—

M, male; F, female; SD, stable disease; PD, progressive disease; PS, performance status.

heavily pretreated, with the mean number of prior treatment regimens at 2.2 (range, 1–3). The ECOG PS was 0 in 8 patients; 1 in 8 patients, and 2 in 1 patient.

Phase I dose escalation

Three (3) patients per cohort were enrolled in the first three cohorts (1, 2, and 4 mg/kg), and 8 patients were enrolled in

the highest dose cohort (8 mg/kg). No DLTs associated with tigatuzumab were seen, and the MTD was not reached. Of the 17 patients enrolled, 11 received at least 2 cycles of tigatuzumab (6 weekly doses of study drug). All patients received full doses at their assigned dosing level and schedule. As of December 2008, the total exposure to tigatuzumab ranged from 1000 mg (patient 4 in the 2-mg/kg dose cohort) to 11,400 mg (patient 1 in the 1-mg/kg dose cohort).

TABLE 2. ADVERSE EVENTS OBSERVED IN AT LEAST 2 PATIENTS RECEIVING TIGATUZUMAB

Adverse event	Number of events (NCI-CTC grade) cohorts				Overall
	1 mg/kg (n = 3)	2 mg/kg (n = 3)	4 mg/kg (n = 3)	8 mg/kg (n = 8)	
Nausea	2 (1, 1)	—	3 (1, 1, 1)	3 (2, 2, 3)	8
Fatigue	1 (1)	1 (1)	2 (1, 2)	3 (1, 2, 2)	7
Cough	3 (1, 1, 1)	2 (1, 2)	2 (1, 1)	1 (1)	8
Anemia	1 (2)	1 (2)	1 (2)	2 (2, 2)	5
Pyrexia	1 (1)	—	1 (1)	3 (1, 1, 1)	5
Vomiting	—	—	1 (1)	3 (1, 2, 3)	4
Dyspnea	1 (1)	—	1 (2)	2 (2, 3)	4
Diarrhea	1 (1)	—	—	2 (1, 1)	3
Asthenia	1 (2)	—	1 (1)	1 (3)	3
Arthralgia	1 (1)	—	2 (1, 2)	—	3
Back pain	—	1 (1)	2 (2, 2)	—	3
Rash	—	—	1 (1)	2 (1, 1)	3
Constipation	2 (1, 1)	—	1 (1)	—	3
Edema peripheral	1 (2)	—	—	1 (1)	2
Decreased appetite	—	—	1 (1)	1 (1)	2
Fluid retention	—	1 (1)	—	1 (1)	2
Pleural effusion	—	—	1 (3)	1 (3)	2
Pulmonary embolism	—	—	1 (3)	1 (3)	2
Sinus congestion	1 (1)	1 (1)	—	—	2
Paresthesia	—	1 (1)	1 (1)	—	2
Depression	1 (1)	—	1 (2)	—	2
Bone pain	1 (1)	—	—	1 (1)	2
Abdominal pain: lower	—	—	1 (2)	1 (2)	2
Abdominal pain: upper	—	—	1 (2)	1 (3)	2

NCI-CTC, National Cancer Institute–Common Toxicity Criteria.

FIG. 1. Mean plasma tigatuzumab levels following initial infusion (week 1) for patients in four dose cohorts.

Toxicity

Tigatuzumab was very well tolerated at the doses and schedule used in the trial. There were no infusion reactions. Table 2 details the adverse events that occurred in 2 or more patients. None of these adverse events were classified as related to the study drug, and in general, they were attributed to signs and symptoms of progressive disease. For example, the grade 3 nausea and vomiting was a result of worsening abdominal ascites. One (1) patient with pancreatic cancer in the 8-mg/kg dose group discontinued treatment due to adverse events (weakness/asthenia); however, this was due to disease progression. There were no laboratory abnormalities of grade 3 or 4 severity. There was 1 death during the trial, which occurred 20 days after the last dose of tigatuzumab; this was as a result of radiologically proven disease progression. Thus, no drug-related DLTs were noted, and the MTD was not reached.

Antitumor effects

There were no objective responses in this trial. As seen in Table 1, 7 patients had stable disease lasting longer than 81

days. Patient 1 is notable in that he had stable disease for 26 months. This 57-year-old male entered the trial with progressive metastatic hepatocellular carcinoma, having previously failed treatment with doxorubicin (as a single agent), paclitaxel and carboplatin (given in combination), and docetaxel (as a single agent). He had histologically proven lesions in the liver and the right humerus, with severe pain in the right humerus and right-upper quadrant of the abdomen. The patient became pain free within 6 weeks of initiation of treatment with tigatuzumab and was asymptomatic with stable disease for 26 months.

Tigatuzumab pharmacokinetics

Pharmacokinetic results are shown in Figure 1 and Table 3. Dose-proportional pharmacokinetics were seen with the administration of tigatuzumab. Peak and trough plasma levels of tigatuzumab showed a dose-dependent increase (Table 3) and were maintained for at least 150 hours. The data demonstrated a half-life of 6–10 days for tigatuzumab, with approximately a 3-fold accumulation of the antibody at steady state when given on a weekly schedule, as compared

TABLE 3. PHARMACOKINETIC PARAMETERS^a WEEK 1 OF TIGATUZUMAB INFUSION

CS-1008 (mg/kg)	C_{max} ($\mu\text{g/mL}$)	C_{min} —168 hours ($\mu\text{g/mL}$)	AUC_{0-168} ($\mu\text{g/mL hr}$)	T_{max} (Hours)	$T_{1/2}$ (Hours)	Cl (mL/hours)	V_D (mL)
1	29.6 $\pm$ 2.7	14.0 $\pm$ 3.6	3140.5 $\pm$ 182.9	2.4 $\pm$ 1.6	227.8 $\pm$ 5.4	11.7 $\pm$ 1.0	3875.3 $\pm$ 1105.9
2	56.7 $\pm$ 10.2	30.2 $\pm$ 9.1	6220.9 $\pm$ 1072.1	6.4 $\pm$ 6.0	163.5 $\pm$ 46.2	18.5 $\pm$ 5.8	4256.9 $\pm$ 1521.8
4	110.2 $\pm$ 16.4	48.8 $\pm$ 11.5	10753.8 $\pm$ 876.9	2.2 $\pm$ 0.7	154.9 $\pm$ 25.7	14.4 $\pm$ 1.2	3177.4 $\pm$ 3177.4
8	167.0 $\pm$ 41.4	58.6 $\pm$ 23.9	16,081.0 $\pm$ 4244.9	1.8 $\pm$ 0.4	149.4 $\pm$ 38.6	20.1 $\pm$ 4.7	4174.9 $\pm$ 741.5

^aPharmacokinetic parameters were calculated by the noncompartmental method, using the WinNonlin version 4.0 program (Pharsight Corp., Mountain View, CA).

C_{max} , maximum plasma-serum concentration; C_{min} , minimum plasma-serum concentration; AUC, area under the concentration versus time curve; $T_{1/2}$, serum half-life; Cl, clearance; V_D , volume of distribution.

TABLE 4. HUMAN ANTI-TIGATUZUMAB RESPONSE

Patient	Last day in the trial	HAHA ^a / samples tested
1	798	Negative/22
2	37	Negative/3
3	232	Negative/10
4	33	Negative/2
5	43	Negative/4
6	84	Negative/4
7	169	Negative/5
8	33	Negative/3
9	82	Negative/4
10	81	Negative/4
11	42	Negative/3
12	42	Negative/2
13	16	Negative/2
14	14	Negative/1
15	43	Negative/3
16	126	Negative/5
17	44	Negative/4

^aSerum samples were collected prior to the first dose of tigatuzumab and 1, 21, and 49 days after the first dose. Then, serum samples were collected every 6 weeks until patients were taken off the study.

HAHA, Human anti-human antibodies.

with plasma concentrations observed during the first week of treatment. The plasma-clearance rate was similar to other humanized monoclonal antibodies, and the volume of distribution approximated the normal plasma volume.

Human anti-tigatuzumab immune response

No detectable human anti-tigatuzumab antibody response was detected on any of the analyzed samples (Table 4).

Discussion

TRA-8, the parent murine antibody for tigatuzumab, has been studied extensively and been shown to demonstrate potent *in vitro* cytotoxicity and *in vivo* antitumor efficacy, which can be amplified by combination therapy with chemotherapeutic agents and/or radiation. These preclinical studies used human tumor cell lines and murine xenograft animal models for cancers of the breast,¹² colon,¹⁷ pancreas,^{18,19} ovary,²⁰ cervix,²¹ and brain.^{22,23} In addition, this antibody has considerable cytotoxicity to fresh human ovarian cancer tissue slices without the addition of crosslinking reagents or effector cells.²⁰ Antitumor efficacy was demonstrated in subcutaneous¹² and orthotopic xenograft models.^{18,19} The enhancement of TRA-8-mediated cytotoxicity was observed with a wide range of FDA-approved chemotherapy agents.

Conclusions

These observations support the hypothesis that tigatuzumab, particularly in combination with chemotherapy, may have antitumor efficacy in a variety of human cancers. This phase I trial shows that tigatuzumab, at doses as high as 8 mg/kg/week, is very well tolerated and did not induce DLTs, but did result in long-term disease stabilization (longer than 81 days) in 41% of patients with aggressive, treat-

ment-resistant solid tumors. No adverse events or serious adverse events were related to tigatuzumab. Interest in this strategy of anti-DR5 in the treatment of human cancer is evidenced by an array of additional anti-DR5 reagents in various stages of preclinical and clinical development. These include lexatumumab,²⁴ apomab,²⁵ LBy135,²⁶ WD-1,²⁷ and AMG655.^{28,29} A consistent finding from all these studies is the considerable variability in the sensitivity of various tumor cell lines to anti-DR5-mediated cytotoxicity. Each tumor type appears to have some cell lines that trigger caspase-dependent apoptosis on exposure to small doses of agonistic antibody (5–200 ng of antibody) and other cell lines that do not trigger apoptosis at doses >1000 ng. The combination of antibody and chemotherapy usually enhances the degree of apoptosis and can partially reverse resistance in some cell lines.^{12,13,17–19,23,26,28,29} There is considerable ongoing effort to determine a possible biomarker in tumor specimens that might predict those patients most likely to benefit from such therapy. Based on the safety profile of tigatuzumab in the phase I trial and the results of preclinical studies that have shown additive or synergistic antitumor activity when added to standard chemotherapy agents, clinical trials of tigatuzumab, in combination with chemotherapy, for the treatment of DR5-positive epithelial tumors have been initiated.

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Disclosure Statement

No competing financial interests exist.

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