original article

Annals of Oncology 21: 376–381, 2010
doi:10.1093/annonc/mdp292
Published online 24 July 2009

Phase I and pharmacokinetic study of lexatumumab (HGS-ETR2) given every 2 weeks in patients with advanced solid tumors

H. A. Wakelee[1]*, A. Patnaik[2†], B. I. Sikic[1], M. Mita[2], N. L. Fox[3], R. Miceli[3], S. J. Ullrich[3], G. A. Fisher[1] & A. W. Tolcher[2†]

[1]Department of Medicine-Oncology, Stanford University, Stanford, CA; [2]Department of Clinical Research, Institute for Drug Development, Cancer Therapy and Research Center, San Antonio, TX and [3]Human Genome Sciences, Rockville, MD, USA

Received 4 February 2009; revised 21 March 2009; accepted 24 April 2009

Background: Lexatumumab (HGS-ETR2) is a fully human agonistic mAb to the tumor necrosis factor-related apoptosis-inducing ligand receptor 2 that activates the extrinsic apoptosis pathway and has potent preclinical antitumor activity.

Materials and methods: This phase 1, dose escalation study assessed the safety, tolerability, pharmacokinetics (PKs) and immunogenicity of lexatumumab administered i.v. every 14 days in patients with advanced solid tumors.

Results: Thirty-one patients received lexatumumab over five dose levels (0.1–10 mg/kg). Most (26 of 31) received four or more cycles of treatment. One patient at 10 mg/kg experienced a possibly related dose-limiting toxicity of grade 3 hyperamylasemia. Nine patients achieved stable disease. One patient with chemotherapy-refractive Hodgkin's disease experienced a mixed response. Lexatumumab PKs were linear up to 10 mg/kg. At the 10 mg/kg dose, the mean (±standard deviation) $t_{1/2b}$ was 13.67 ± 4.07 days, clearance was 4.95 ± 1.93 ml/day/kg, V_1 was 45.55 ml/kg and V_{ss} was 79.08 ml/kg, indicating that lexatumumab distributes outside the plasma compartment. No human antihuman antibodies were detected.

Conclusions: Lexatumumab can be safely administered every 14 days at 10 mg/kg. The PK profile supports this schedule. Further evaluation of lexatumumab at this dose schedule is warranted, including combination trials with other agents.

Key words: apoptosis, HGS-ETR2, lexatumumab, pharmacokinetics, phase I, TRAIL-R2

introduction

Direct targeting of the apoptotic pathway in tumors is an exciting new area of oncology drug development. Activation of the extrinsic apoptosis pathway via the 'death receptors' of the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is one such strategy [1]. These receptors, TRAIL-R1 and TRAIL-R2, are expressed in a wide variety of human tumors [2–7]. *In vitro* studies have shown that apoptosis induction through activation of the TRAIL receptors is fairly selective for cancer cell lines versus normal cell lines [8–12]. The expression of TRAIL-R2 is limited in normal tissue, though it is reported on hepatocytes, glial tissue, bronchial epithelium and myocytes [8]. Receptor expression is necessary for activity of the agent, but levels have not correlated with responsiveness in preclinical studies [10, 13].

Lexatumumab (HGS-ETR2) is an agonistic high-affinity mAb that binds to and activates TRAIL-R2. The compound is a recombinant fully human $IgG_1\lambda$ mAb derived from a mouse myeloma cell line. Preclinical work with human tumor cell lines and in xenograft models showed activity of lexatumumab in renal, hematologic, breast, ovarian and colorectal tumors [6, 7, 14–18]. In the first clinical trial with lexatumumab, it was administered every 21 days and was well tolerated up to 10 mg/kg [19]. However, at 20 mg/kg, three of seven patients developed dose-limiting toxic effects consisting of asymptomatic elevations of amylase, transaminases or bilirubin.

The current study evaluated the safety and tolerability of lexatumumab at escalating doses on a more frequent schedule, every 14 days. Pharmacokinetic (PK) and pharmacodynamic studies and assessment of tumor response were also undertaken.

materials and methods

This was a two-center phase 1, open-label, dose escalation study of lexatumumab in subjects with relapsed or refractory advanced solid malignancies. Patients gave written informed consent for this trial

*Correspondence to: Dr H. A. Wakelee, Stanford Cancer Center, Stanford University, 875 Blake Wilbur Drive, Room 2233, Stanford, CA 94305-5826, USA. Tel: +1-650-736-7221; Fax: +1-650-724-3697; E-mail: hwakelee@stanford.edu

†Present address: Department of Clinical Research, South Texas Accelerated Research Therapeutics, San Antonio, TX, USA.

according to the international guidelines. The protocol was reviewed and treatment monitored by institutional review boards at each participating institution. The primary objective was to evaluate the safety and tolerability of escalating doses of lexatumumab on a 14-day schedule. Secondary objectives included PK evaluation and evaluation of tumor response. All adverse events were graded according to the National Cancer Institutes—Common Terminology Criteria for Adverse Events Version 3.0.

Eligible patients were at least 18 years old, had a life expectancy of at least 6 months and adequate performance status and had relapsed or refractory advanced solid malignancy for which no cure or standard therapy was available. Laboratory values required for study entry were platelets $\geq 100 \times 10^9$/l, hemoglobin ≥10.0 g/dl, absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l, hepatic function studies ≤2.5-fold the upper limit of normal (ULN) except bilirubin level within normal limits, serum creatinine level ≤1.5 fold the ULN and activated partial thromboplastin time ≤1.5 fold the ULN. Exclusion criteria for the study included prior treatment within 4 weeks for most cancer treatments and investigational agents (8 weeks for mAb therapy and 6 weeks for nitrosureas or mitomycin C). Patients were also excluded for known central nervous system metastases, grade 2 or greater neuropathy, previous hematopoietic stem-cell transplant, arterial thrombotic event or heart failure within 6 months, recent infection, known HIV infection or hepatitis A, B or C infection. Contraception was required of all potentially fertile patients during the course of the study and for at least 60 days after last treatment. Pregnant and nursing mothers were excluded.

Dose escalation consisted of five cohorts (dose levels) of lexatumumab, 0.1, 0.3, 1, 3 and 10 mg/kg given i.v. every 14 days (±2 days). The next cohort opened after review of safety data after 28 days of therapy for at least three patients in the prior cohort for the 1, 3 and 10 mg/kg cohorts. Originally, the protocol required observation of at least three subjects for 28 days after the fourth dose of study drug (0.1 and 0.3 mg/kg cohorts), but this was amended after the 0.3 mg/kg cohort. Dose-limiting toxicity (DLT) was defined as adverse events that were at least possibly related to lexatumumab, occurred in the first 28 days and consisted of grade 3 or more adverse event or grade 2 or more allergic or autoimmune reaction. Exceptions were that grade 3 alopecia was not considered a DLT, and nausea/vomiting, diarrhea, rash, arthralgia, myalgia and fatigue were only considered DLTs if they persisted following treatment with an optimal therapeutic regimen. The study was a 3 + 3 phase I design, but with at least four patients in each cohort and 12 at the maximum tolerated dose (MTD). Based on results of a separate phase I trial of the compound given on an every 21-day schedule [19], escalation beyond 10 mg/kg every 14 days was not attempted. Patients were followed for 42 days after the last dose of lexatumumab for safety, PK and immunogenicity assessments.

At baseline, detailed history, physical examination, imaging and laboratory studies, electrocardiogram and tumor biopsy if possible were obtained. On treatment days, patients underwent a focused medical history and examination and laboratory testing. Premedications to reduce the risk of hypersensitivity reactions were left to the discretion of the investigators. For all cycles, patients returned on day 8 (±2) for an abbreviated examination, medical history and laboratory studies. Patients were also examined on days 2 and 5 of cycle 1 and on day 2 of cycle 4 with repeat laboratory testing. After the final cycle, patients returned on days 15, 22, 29 and 43 for medical history, physical examination and laboratory testing.

Disease assessment was carried out at ∼8 weeks following RECIST [20] or per the Prostate-Specific Antigen Working Group Response Guidelines [21]. Those with at least stable disease and no DLTs were allowed to continue on therapy until disease progression or a DLT.

Lexatumumab was supplied by Human Genome Sciences as a sterile, single-use 10-ml vial containing 100 mg of lyophilized product that was reconstituted, then diluted in normal saline and infused i.v. immediately after reconstitution. The 0.1 and 0.3 mg/kg dose levels were infused over 30 min via a syringe pump. The 1, 3 and 10 mg/kg doses were infused at a constant rate over 2 h.

Blood samples for serum lexatumumab levels were collected from patients before dose in cycles 1, 2, 3 and 4; at completion of dosing, 5 min, 8 h and 7 days after dose in cycles 1, 2 and 4 and at 24 h after dose in cycles 1 and 4. Additional samples were collected 2 and 4 days after dose in cycle 1 only, before dose in all additional cycles and 14, 21, 28 and 42 days following a patient's final lexatumumab dose. Serum samples were stored frozen at −70°C until analysis.

Serum samples were analyzed for lexatumumab concentration and anti-lexatumumab immunogenicity by qualified enzyme-linked immunosorbent assays (ELISAs) as previously described [19].

Compartmental PK analysis was carried out with WinNonlin Enterprise (Version 5.0.1; Pharsight Corp., Mountain View, CA). Serum lexatumumab concentration–time profiles for each subject were analyzed individually using actual times after dose, actual dose times relative to the first dose and the actual doses administered. Data were fit using a two-compartment model with first-order elimination from the central compartment. Weighting schemes of 1, $1/p$, $1/p^{0.5}$, and $1/p^2$ (where p is the predicted value for the observation) were assessed. Selection of weighting schemes was based on the precision of the primary model variables, sum of the squared residuals and randomness of the residuals. PK parameters could not be reliably estimated for four subjects because an acceptable fit could not be attained with any model or weighting scheme. Dose proportionality over the evaluated dose ranges was assessed using a one-way analysis of variance (ANOVA).

Paraffin blocks or unstained slides were requested of the original tumor of all patients, with additional tumor biopsies at baseline and on day 8 of cycle 1 as feasible. Staining for TRAIL-R2 was done using a previously published standardized method [19]. Blood samples collected before dosing on all cycles (and on day 8 of cycle 1 and days 15 and 43 after final dose) were assayed for antibodies to lexatumumab using a previously published ELISA technique [19].

Statistical analysis for safety, PK, pharmacodynamic and immunogenicity data was created using WinNonlin Enterprise, Version 5.0.1 (Pharsight Corp.), GraphPad Prism (Version 4.02) software, SoftMaxPro GxP (Version 5) or SAS (Version 9.1).

results

Thirty-one heavily pretreated patients enrolled and received at least one dose of lexatumumab. Baseline characteristics are summarized in Table 1.

The 0.1, 1 and 3 mg/kg cohorts all included four patients who received at least four cycles of drug. The 0.3 mg/kg cohort was expanded to seven patients when three patients were unable to complete four full cycles of therapy (required at the 0.1 and 0.3 mg/kg cohorts); but no DLTs occurred at this dose. The 10 mg/kg cohort was expanded to 12 patients to allow for extensive toxicity and PK analysis. One patient at this dose had grade 3 hyperamylasemia, possibly related to study drug and considered a DLT, though the patient had baseline elevated amylase levels. Based on the previously determined MTD of lexatumumab of 10 mg/kg every 21 days [19], escalation beyond 10 mg/kg was not attempted. The median number of cycles for all 31 patients was 4 (56 days) with a range of 1–41 and a mean of 6.2 (Table 2). Seven patients required dose delays, but only one of these was potentially drug related (hematologic recovery at 10 mg/kg). No patients required dose reduction.

The majority of patients were treated until disease progression. Two died of disease progression while on trial before completing four cycles of therapy. Three patients were discontinued for adverse events, one for hyperamylasemia (10 mg/kg), one for hypercalcemia (0.3 mg/kg) and one for spinal cord compression (0.3 mg/kg). One patient withdrew after four doses.

toxicity

Overall, lexatumumab was very well tolerated. The most common (≥10%) adverse events regardless of causality included fatigue ($n = 15$) and nausea ($n = 11$) and 10 patients each with anemia, anorexia, dyspnea and tachycardia (Table 3). Laboratory toxic effects were generally mild and no treatment-related hepatic toxicity was observed.

Possibly related toxic effects, grade 1 unless indicated, included fatigue ($n = 11$, six grade 2), nausea ($n = 6$), pain ($n = 5$) and anorexia ($n = 4$) (Table 3). Two severe (grade 3) toxic effects, possibly treatment related, were vomiting ($n = 1$ at 3 mg/kg) and hyperamylasemia ($n = 1$ at 10 mg/kg). The hyperamylasemia occurred in a patient with elevated baseline amylase levels who was taking an oral mushroom extract that may have contributed. There were no grade 4 treatment-related toxic effects.

Table 1. Summary of demographics and baseline characteristics

	$N = 31$
Sex, *n* (%)	
Male	21 (67.7)
Female	10 (32.3)
Race, *n* (%)	
White	28 (90.3)[a]
Asian	3 (9.7)
Age (years)	
Mean ± SD	57.7 ± 12.0
Median	61.0
Range	25–77
Primary tumor type, *n* (%)	
Lung (NSCLC)	8 (25.8)
Soft tissue sarcoma	6 (19.4)
Prostate	3 (9.7)
Renal	3 (9.7)
Lymphoma (NHL)	2 (6.5)
Breast, melanoma, osteosarcoma, thymus, thyroid, esophagus, head and neck, neuroendocrine and Hodgkin's lymphoma	1 (3.2) each
Prior therapy, *n* (%)	
Surgery	25 (80.6)
Radiation therapy	20 (64.5)
Systemic therapy	30 (96.8)
Median prior therapies	3 (0–8)

[a]Five were Hispanic or Latin origin.
NSCLC, non-small-cell lung cancer; NHL, non-Hodgkin's lymphoma.

PK results

Serum lexatumumab concentration–time profiles for each dose group are illustrated in Figure 1. PK analyses and one-way ANOVA results are summarized by dose group in Table 4. There were no significant differences in PK parameters, indicating lexatumumab PK were linear across the dose range evaluated. The mean (standard deviation) clearance (CL) was 4.95 (1.93) ml/day/kg and $t_{1/2,\beta}$ was 13.67 (4.07) days, at the MTD of 10 mg/kg.

The mean V_1 values ranged from marginally greater than plasma volume (~42.8 ml/kg) [22] to 38% greater than plasma volume, while V_{ss} are at least 54% greater than V_1 for each cohort. These results indicate that initially lexatumumab may be restricted to the plasma volume, but that it does subsequently distribute to tissues.

The disappearance of lexatumumab from serum is biphasic, with mean $t_{1/2,\alpha}$ of 0.91 to 2.28 days and a mean $t_{1/2,\beta}$ range from 11.02 to 24.22 days. Based on the average $t_{1/2,\beta}$ of 15.18 days, 90% of steady state would be attained 50 days after the first dose. The predicted accumulation factor at steady state is ~2.12.

The mean CL of lexatumumab ranged from 3.37 to 5.94 ml/day/kg. These CL values are much smaller than the glomerular filtration rate (~2571 ml/day/kg) [22], consistent with no renal CL of the antibody.

immunohistochemistry and immunogenicity

Archival tumor specimens were available from 17 of 31 patients, with 15 assessable. Eight of 15 assessable specimens had specific TRAIL-R2 staining on at least 10% of the tumor cells. The staining pattern was heterogeneous within and between tumor specimens for both membrane and cytoplasmic localization.

No confirmed positive human anti-lexatumumab antibodies were found in serum samples collected from all patients at multiple time points.

antitumor activity

Twenty-seven of 31 enrolled patients were assessable for response. No partial responses were seen, but one patient with Hodgkin's disease had a mixed response with regression of tumor in the lung, but growth in other lesions. Eighteen patients were discontinued with disease progression as best response. Stable disease was seen in nine patients (29%) with a variety of tumor types. One patient with a neuroendocrine tumor received 41 doses (20 months) of lexatumumab.

Table 2. Extent of exposure to lexatumumab

Dose level	0.1 mg/kg ($n = 4$)	0.3 mg/kg ($n = 7$)	1 mg/kg ($n = 4$)	3 mg/kg ($n = 4$)	10 mg/kg ($n = 12$)	Total ($N = 31$)
Cycles						
Mean ± SD	4.0 ± 0.0	4.4 ± 2.6	6.3 ± 2.1	7.3 ± 4.3	7.5 ± 10.8	6.2 ± 6.9
Median	4.0	4.0	6.5	6.0	4.0	4.0
Range	4–4	2–9	4–8	4–13	1–41	1–41

Table 3. Number of subjects with treatment-emergent adverse events (≥10% incidence) by MedDRA Preferred Term and severity

Preferred term	Total ($N = 31$), *n* (%)	Related[a], *n* (%)	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Fatigue	15 (48.4)	11 (35.5)	6 (19.4)	8 (25.8)	1 (3.2)	
Nausea	11 (35.5)	6 (19.4)	9 (29.0)	1 (3.2)	1 (3.2)	
Anemia	10 (32.3)	3 (9.7)	1 (3.2)	5 (16.1)	3 (9.7)	1 (3.2)
Anorexia	10 (32.3)	4 (12.9)	6 (19.4)	4 (12.9)		
Dyspnea	10 (32.3)		4 (12.9)	5 (16.1)	1 (3.2)	
Tachycardia	10 (32.3)		10 (32.3)			
Pyrexia	9 (29.0)		5 (16.1)	4 (12.9)		
Cough	8 (25.8)		5 (16.1)	3 (9.7)		
Diarrhea	8 (25.8)	3 (9.7)	3 (9.7)	3 (9.7)	2 (6.5)	
Vomiting	8 (25.8)	3 (9.7)	6 (19.4)		2 (6.5)	
Abdominal pain	7 (22.6)		4 (12.9)	3 (9.7)		
Back pain	7 (22.6)		4 (12.9)	2 (6.5)	1 (3.2)	
Chills	7 (22.6)		5 (16.1)	2 (6.5)		
Constipation	7 (22.6)		3 (9.7)	3 (9.7)	1 (3.2)	
Headache	7 (22.6)		4 (12.9)	2 (6.5)	1 (3.2)	
Hypokalemia	7 (22.6)		5 (16.1)	1 (3.2)	1 (3.2)	
Edema peripheral	7 (22.6)		3 (9.7)	4 (12.9)		
Pain	7 (22.6)	5 (16.1)	6 (19.4)		1 (3.2)	
Hypomagnesemia	6 (19.4)		6 (19.4)			
Musculoskeletal chest pain	6 (19.4)		3 (9.7)	3 (9.7)		
Productive cough	6 (19.4)		5 (16.1)		1 (3.2)	
Abdominal pain upper	5 (16.1)		4 (12.9)	1 (3.2)		
Asthenia	5 (16.1)		2 (6.5)	1 (3.2)	2 (6.5)	
Dysphagia	5 (16.1)		3 (9.7)	2 (6.5)		
Hypotension	5 (16.1)		4 (12.9)	1 (3.2)		
Noncardiac chest pain	5 (16.1)		3 (9.7)	1 (3.2)	1 (3.2)	
Pain in extremity	5 (16.1)		3 (9.7)	1 (3.2)		1 (3.2)
Upper respiratory tract infection	5 (16.1)		5 (16.1)			
Arthralgia	4 (12.9)		4 (12.9)			
Chest pain	4 (12.9)		3 (9.7)	1 (3.2)		
Depression	4 (12.9)		3 (9.7)	1 (3.2)		
Dyspnea, exertional	4 (12.9)		4 (12.9)			
Flank pain	4 (12.9)		2 (6.5)	2 (6.5)		
Hypertension	4 (12.9)		4 (12.9)			
Myalgia	4 (12.9)		4 (12.9)			
Urinary tract infection	4 (12.9)		2 (6.5)	2 (6.5)		

[a]Possibly, probably or definitely related to lexatumumab in at least three patients.

discussion

The development of drugs that specifically target the extrinsic apoptosis pathway, such as lexatumumab, represents a novel approach to the treatment of solid tumors. In this trial, lexatumumab was well tolerated at doses up to 10 mg/kg every 2 weeks with minimal toxicity. The only DLT was in one patient who had grade 3 hyperamylasemia that was considered possibly related to lexatumumab. However, this patient had baseline amylase elevation and was taking a mushroom extract, so it is difficult to determine a definitive causal relationship. Of note, two patients on the every 21-day regimen of lexatumumab also developed hyperamylasemia, both while concurrently taking ciprofloxacin [19]. Monitoring of this toxicity will be necessary in the future development of the compound. Other observed toxic effects of fatigue, nausea and anorexia were mild.

PK assessment in this trial was similar to that previously published with the compound using a 21-day schedule and included dose-proportional and linear increases in concentration and area under the curve (AUC), a volume of distribution that exceeded that of plasma and slow CL with a terminal elimination half-life that averaged 15 days [19]. As expected for administration of lexatumumab with a more frequent dosing schedule of 14 days peak concentrations at steady state, exposure as measured by AUC, and the predicted accumulation factor are higher compared with the 21-day schedule. Preclinically, increased dose frequency improved antitumor activity in xenograft models supporting development of the 14-day schedule.

No human antihuman antibody response to lexatumumab has been identified in this or any other trial with the compound. In the study of the every 21-day schedule,

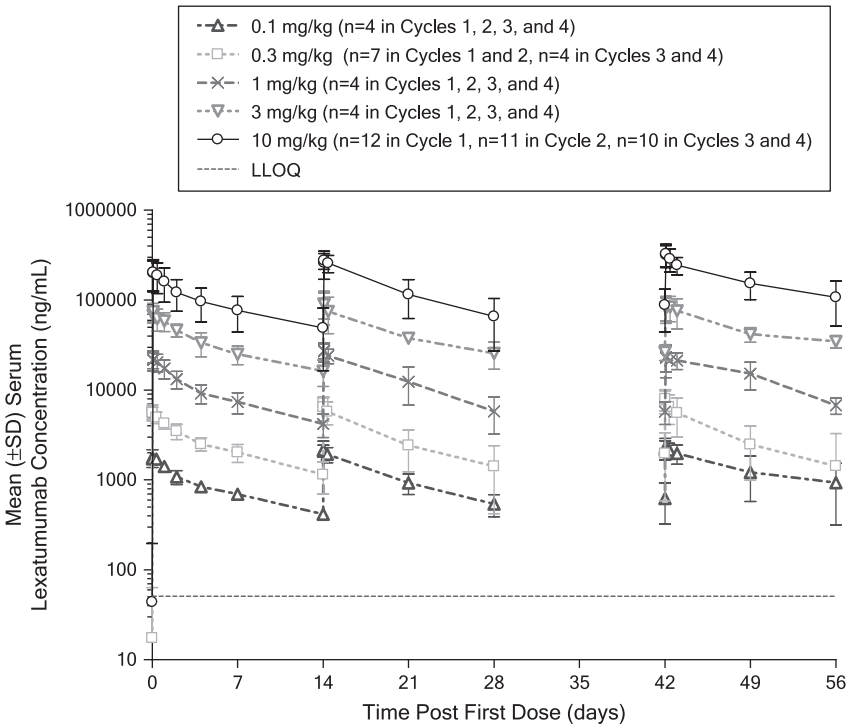

Figure 1. Mean (±standard deviation) serum lexatumumab concentrations following 0.1–10 mg/kg lexatumumab i.v. infusion doses to solid tumor subjects. Lower limit of quantitation (LLOQ) is 51 nanograms lexatumumab/ml of serum.

Table 4. Summary of PK parameters (mean ± standard deviation) following 0.1, 0.3, 1, 3 or 10 mg/kg lexatumumab i.v. infusion doses to solid tumor subjects

Parameter	0.1 mg/kg ($n = 4$)	0.3 mg/kg ($n = 5$)	1 mg/kg ($n = 3$)	3 mg/kg ($n = 4$)	10 mg/kg ($n = 11$)	ANOVA, P value[a]
C_{max} (ng/ml)	1725 ± 311	6130 ± 906	22 103 ± 3053	68357 ± 20 769	223 729 ± 42 836	NA
C_{max}/dose (kg/ml)	0.0172 ± 0.0031	0.0204 ± 0.0030	0.0221 ± 0.0031	0.0228 ± 0.0069	0.0224 ± 0.0043	0.2682
$AUC_{0-\infty}$ (ng·day/ml)	19 175 ± 8869	55 932 ± 13 996	213 035 ± 46 110	893 229 ± 53 380	2 352 527 ± 1 034 868	NA
$AUC_{0-\infty}$/dose (kg·day/ml)	0.1917 ± 0.0887	0.1864 ± 0.0467	0.2130 ± 0.0461	0.2977 ± 0.0178	0.2353 ± 0.1035	0.2390
$t_{1/2,\alpha}$ (day)	1.43 ± 0.80	0.91 ± 0.68	1.95 ± 0.79	2.28 ± 0.89	1.57 ± 0.78	0.1261
$t_{1/2,\beta}$ (day)	13.83 ± 9.56	11.02 ± 3.87	13.14 ± 2.39	24.22 ± 15.74	13.67 ± 4.07	0.1977
MRT (day)	18.41 ± 12.50	14.89 ± 5.16	16.26 ± 4.01	29.89 ± 17.82	17.47 ± 5.65	0.2606
CL (ml/day/kg)	5.94 ± 2.18	5.63 ± 1.39	4.80 ± 1.08	3.37 ± 0.20	4.95 ± 1.93	0.2499
V_1 (ml/kg)	59.10 ± 9.31	49.27 ± 6.02	44.87 ± 6.63	46.80 ± 14.29	45.55 ± 8.69	0.2326
V_{ss} (ml/kg)	90.98 ± 21.71	78.61 ± 15.88	76.63 ± 19.52	98.42 ± 52.28	79.08 ± 22.98	0.8155

PK parameters could not be reliably estimated for four subjects because an acceptable fit could not be attained with any model or weighting scheme.
[a]One-way ANOVA of natural log transformed data.
C_{max}, maximum serum drug concentration for a single dose; $AUC_{0-\infty}$, area under the serum drug concentration–time curve from time 0 to infinite time for a single dose; $t_{1/2,\alpha}$, elimination half-life for the first phase; $t_{1/2,\beta}$, elimination half-life for the second (terminal) phase; MRT, mean residence time; CL, clearance; V_1, volume of distribution for the central compartment; V_{ss}, volume of distribution at steady state; ANOVA, analysis of variance; NA, not applicable.

immunohistochemistry for TRAIL-R2 found specific staining in >10% of tumor cells in the vast majority of patients (16 of 20 assessable specimens) [19]. In our study, 8 of 15 assessable specimens had TRAIL-R2 staining in at least 10% of the tumor cells. There is no clear relationship between expression levels of TRAIL-R2 detected by immunohistochemistry and the activity of lexatumumab [23].

Encouraging preliminary antitumor activity was observed in this trial, including the mixed response in a patient with Hodgkin's disease and several patients with disease stability for over 4 months. The phase I study of the compound every 21 days also documented disease stability in 12 of 37 patients, including three sarcoma patients with stable disease for over 6 months [19].

This study establishes a single-agent dose of lexatumumab at 10 mg/kg every 14 days. The future development of lexatumumab should focus on better identification of patients most likely to benefit from the compound and on combination regimens. Detection of TRAIL-R2 by immunohistochemical analysis has not correlated with response to the agent in preclinical models. Efforts to detect other markers that may more accurately predict response are ongoing. Studies are also ongoing with various chemotherapeutic combinations

(theoretically activating both the intrinsic and extrinsic apoptosis pathways simultaneously). Preclinical studies have demonstrated synergistic or additive activity between lexatumumab and chemotherapeutic agents including cisplatin, doxorubicin and the taxanes [13, 16, 23–25], as well as with radiation [26]. Preliminary results from a phase Ib study of lexatumumab in combination with pemetrexed, liposomal doxorubicin, FOLFIRI (5-fluorouracil, leucovorin and irinotecan) or gemcitabine found the combinations well tolerated [27].

funding

Human Genome Sciences, Inc.; General Clinical Research Center, Stanford University School of Medicine (M01 RR 00070) from the National Institutes of Health.

acknowledgements

These data were previously presented in part at the American Association for Cancer Research (AACR) annual meeting in 2005, the AACR international conference on molecular targets and cancer therapeutics meeting in 2005 and the American Society of Clinical Oncology meeting in 2006.

NLF, SJU and RM are employees of Human Genome Sciences and own stock in the company.

references

1. Bouralexis S, Findlay DM, Evdokiou A. Death to the bad guys: targeting cancer via Apo2L/TRAIL. Apoptosis 2005; 10: 35–51.
2. Daniels RA, Turley H, Kimberley FC et al. Expression of TRAIL and TRAIL receptors in normal and malignant tissues. Cell Res 2005; 15: 430–438.
3. Koornstra JJ, Jalving M, Rijcken FE et al. Expression of tumour necrosis factor-related apoptosis-inducing ligand death receptors in sporadic and hereditary colorectal tumours: potential targets for apoptosis induction. Eur J Cancer 2005; 41: 1195–1202.
4. Spierings DC, de Vries EG, Timens W et al. Expression of TRAIL and TRAIL death receptors in stage III non-small cell lung cancer tumors. Clin Cancer Res 2003; 9: 3397–3405.
5. McCarthy MM, Sznol M, DiVito KA et al. Evaluating the expression and prognostic value of TRAIL-R1 and TRAIL-R2 in breast cancer. Clin Cancer Res 2005; 11: 5188–5194.
6. Shimada O, Wu X, Jin X et al. Human agonistic antibody to tumor necrosis factor-related apoptosis-inducing ligand receptor 2 induces cytotoxicity and apoptosis in prostate cancer and bladder cancer cells. Urology 2007; 69: 395–401.
7. Zhang L, Zhang X, Barrisford GW, Olumi AF. Lexatumumab (TRAIL-receptor 2 mAb) induces expression of DR5 and promotes apoptosis in primary and metastatic renal cell carcinoma in a mouse orthotopic model. Cancer Lett 2007; 251: 146–157.
8. Pitti RM, Marsters SA, Ruppert S et al. Induction of apoptosis by Apo-2 ligand, a new member of the tumor necrosis factor cytokine family. J Biol Chem 1996; 271: 12687–12690.
9. Sheridan JP, Marsters SA, Pitti RM et al. Control of TRAIL-induced apoptosis by a family of signaling and decoy receptors. Science 1997; 277: 818–821.
10. LeBlanc HN, Ashkenazi A. Apo2L/TRAIL and its death and decoy receptors. Cell Death Differ 2003; 10: 66–75.
11. Nagane M, Pan G, Weddle JJ et al. Increased death receptor 5 expression by chemotherapeutic agents in human gliomas causes synergistic cytotoxicity with tumor necrosis factor-related apoptosis-inducing ligand in vitro and in vivo. Cancer Res 2000; 60: 847–853.
12. Ichikawa K, Liu W, Zhao L et al. Tumoricidal activity of a novel anti-human DR5 monoclonal antibody without hepatocyte cytotoxicity. Nat Med 2001; 7: 954–960.
13. Gong J, Yang D, Kohanim S et al. Novel in vivo imaging shows up-regulation of death receptors by paclitaxel and correlates with enhanced antitumor effects of receptor agonist antibodies. Mol Cancer Ther 2006; 5: 2991–3000.
14. Zeng Y, Wu XX, Fiscella M et al. Monoclonal antibody to tumor necrosis factor-related apoptosis-inducing ligand receptor 2 (TRAIL-R2) induces apoptosis in primary renal cell carcinoma cells in vitro and inhibits tumor growth in vivo. Int J Oncol 2006; 28: 421–430.
15. Georgakis GV, Li Y, Humphreys R et al. Activity of selective fully human agonistic antibodies to the TRAIL death receptors TRAIL-R1 and TRAIL-R2 in primary and cultured lymphoma cells: induction of apoptosis and enhancement of doxorubicin- and bortezomib-induced cell death. Br J Haematol 2005; 130: 501–510.
16. Johnson R, Gillotte D, Poortman C et al. Human agonistic anti-TRAIL receptor antibodies, HGS-ETR1 and HGS-ETR2, induce apoptosis in ovarian tumor lines and their activity is enhanced by taxol and carboplatin. Proc Am Assoc Cancer Res 2004; 45: 826 (Abstr 3579).
17. Alderson RF, Birse CE, Connolly K. TRAIL-R2 mAb, a human agonistic monoclonal antibody to tumor necrosis factor-related apoptosis inducing ligand receptor 2, induces apoptosis in human tumor cells. Proc Am Assoc Cancer Res 2003; 44: 193 (Abstr 963).
18. Humphreys R, Alderson RF, Bayever E. TRAIL-R2 mAB, a human agonistic monoclonal antibody to tumor necrosis factor-related apoptosis inducing ligand receptor 2, affects tumor growth and induces apoptosis in human tumor xenograft models in vivo. Proc Am Assoc Cancer Res 2003; 44: 123 (Abstr 642).
19. Plummer R, Attard G, Pacey S et al. Phase 1 and pharmacokinetic study of lexatumumab in patients with advanced cancers. Clin Cancer Res 2007; 13: 6187–6194.
20. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92: 205–216.
21. Scher HI, Eisenberger M, D'Amico AV et al. Eligibility and outcomes reporting guidelines for clinical trials for patients in the state of a rising prostate-specific antigen: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol 2004; 22: 537–556.
22. Davies B, Morris T. Physiological parameters in laboratory animals and humans. Pharm Res 1993; 10: 1093–1095.
23. Belyanskaya LL, Marti TM, Hopkins-Donaldson S et al. Human agonistic TRAIL receptor antibodies Mapatumumab and Lexatumumab induce apoptosis in malignant mesothelioma and act synergistically with cisplatin. Mol Cancer 2007; 6: 66.
24. Wu XX, Jin XH, Zeng Y et al. Low concentrations of doxorubicin sensitizes human solid cancer cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-receptor (R) 2-mediated apoptosis by inducing TRAIL-R2 expression. Cancer Sci 2007; 98: 1969–1976.
25. Humphreys R, Shepard L, Poortman C et al. HGS-ETR2, an agonistic, TRAIL receptor 2 human monoclonal antibody, synergizes with chemotherapeutic agents to increase in vitro cytotoxicity and induce tumor regression in vivo tumor xenografts. Clin Cancer Res 2005; 11 (Suppl): 133.
26. Marini P. Drug evaluation: lexatumumab, an intravenous human agonistic mAb targeting TRAIL receptor 2. Curr Opin Mol Ther 2006; 8: 539–546.
27. Sikic BI, Wakelee HA, von Mehren M et al. A phase Ib study to assess the safety of lexatumumab, a human monoclonal antibody that activates TRAIL-R2, in combination with gemcitabine, pemetrexed, doxorubicin or FOLFIRI. J Clin Oncol 2007; 25: 612s (Abstr 14006).