

## A Phase I Study of Weekly R1507, A Human Monoclonal Antibody Insulin-like Growth Factor-I Receptor Antagonist, in Patients with Advanced Solid Tumors

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### Abstract

**Purpose:** A phase I study was conducted to evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of R1507—a fully human IgG1 type monoclonal antibody directed against the human insulin-like growth factor-I receptor.

**Experimental design:** Patients with advanced solid tumors were assigned to receive i.v. R1507 weekly (qW), starting with 1 mg/kg. Subsequent cohorts were dosed at 3 and then 9 mg/kg. An additional 12 patients received 9 mg/kg R1507 qW. Patients remained on the study until the development of a dose-limiting toxicity or progressive disease.

**Results:** In total, 37 patients were treated with R1507 qW. No dose-limiting toxicities were identified and the maximum tolerated dose was not reached. The pharmacokinetics of R1507 were characterized by a slow clearance and limited volume of distribution, with an estimated elimination half-life justifying weekly administration. Serum IGF-I ligand levels increased proportionally to dose during the first 72 hours in all cohorts. R1507 was well tolerated. Two patients diagnosed with Ewing's sarcoma had partial responses of 11.5 and >26 months (ongoing at time of submission); 13 patients had stable disease; and 16 had progressive disease as best response by the Response Evaluation Criteria in Solid Tumors.

**Conclusion:** R1507 is well tolerated and shows antitumor activity in patients with solid neoplasms, in particular Ewing's sarcoma. The recommended dose for the weekly schedule is 9 mg/kg qW. *Clin Cancer Res*; 16(8); 2458–65. ©2010 AACR.

The type 1 insulin-like growth factor receptor (IGF-IR) is a constitutively expressed tyrosine kinase receptor that is activated by binding of its ligands—IGF-I and 2. IGF bioavailability is tightly controlled through a range of mechanisms including gene regulation, ligand sequestration, IGF-binding proteins, and IGF-binding proteases

(1–3). Observations that the IGF pathway is involved with the regulation of cellular proliferation and survival (1) have led to interest in its possible role in neoplasia.

Multiple lines of evidence implicate the IGF/IGF-IR axis in tumorigenesis. High plasma concentrations of IGF-I have been linked with increased cancer risk, especially for prostate, breast, and colorectal cancers (4–10). Increased expression of IGF-IR has been documented in many tumor types including cancers of the breast (11), prostate (12), lung (13), colon (14), connective tissue (15), and pancreas (16). Patients with colorectal cancer and lower levels of IGF-binding protein 1 have a higher mortality risk (17).

Alterations in the IGF/IGF-IR axis are common in sarcomas. The EWS-FLI1 fusion protein, frequently expressed in Ewing's sarcoma, seems to affect the transcription of the *IGF-I*, *IGFBP3*, and *IGF-IR* genes (18–20), leading to an autocrine loop that results in constant IGF-IR-mediated signaling and proliferation. The loss of imprinting of the *IGF-2* gene has been documented in Ewing's sarcoma (21) and induction of *IGF-2* transcription occurs in synovial sarcomas, driven by the transforming oncoprotein SYT-SSX1 (22). Furthermore, synovial sarcoma cells express IGF-IR, which has been associated with increased incidence of lung metastases (23).

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### Translational Relevance

This article describes the results of a phase I study evaluating the pharmacokinetics, pharmacodynamics, efficacy, and tolerability of R1507 administered weekly in patients with advanced solid neoplasms. The findings show that R1507 is well tolerated and shows anti-tumor activity in patients with solid neoplasms, in particular Ewing's sarcoma. The findings with R1507 in solid tumors add considerable new information to the understanding and potential application of an insulin-like growth factor-I receptor monoclonal antibody in cancer therapeutics. The publication would be the first full publication of data showing significant single-agent activity of an insulin-like growth factor-I receptor monoclonal antibody in Ewing's sarcoma patients with t(11;22) EWSR1/FLI-1 translocations.

The involvement of the IGF/IGF1-R axis in tumorigenesis makes it an attractive target for anticancer therapeutics. R1507, a fully human IgG1 type monoclonal antibody directed against the human IGF-IR, has been developed to antagonize IGF-IR signaling. R1507 binds the extracellular domain of IGF-IR with high affinity and selectivity, resulting in the displacement of bound IGF-I and loss of the receptor protein on the cell surface due to intracellular internalization and degradation (24). R1507 inhibits tumor proliferation of prostate, lung, breast, pancreas, and sarcoma cell lines at concentrations below 10 nmol/L and delays tumor growth in xenograft models (25).

Here, we present the results of a phase I study evaluating the pharmacokinetics, pharmacodynamics, efficacy, and tolerability of R1507 administered weekly in patients with advanced solid neoplasms.

### Patients and Methods

**Study design.** This was an open-label, multicenter, sequential-group, phase I dose-escalation study. The primary objectives were to describe the pharmacokinetics of R1507, to determine its maximum tolerated dose (MTD), and to assess its effect on tumor expression of IGF-IR in patients with advanced solid neoplasms. Secondary objectives were to assess the tolerability, pharmacodynamics, and efficacy to R1507. Two cohorts of patients participated in the trial: one treated on a weekly basis (qW) and the other treated every 3 weeks (q3W). We present results of the weekly administration here.

R1507 derived from murine SP2/0 cell material was supplied by Hoffmann-La Roche as a sterile solution ready for use. R1507 was initially administered i.v. over 90 min and subsequently, in the absence of any reaction, over 60 min.

Patients were observed for dose-limiting toxicity (DLT) for 3 wk of treatment; if two or more of up to 6 patients

at a dose level developed DLT, the MTD would be exceeded and no further escalation would occur. Adverse events (AE) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). A DLT was defined as any grade 3 or higher toxicity other than inadequately treated nausea, vomiting, or diarrhea requiring i.v. hydration; grade  $\geq 2$  cardiac toxicity; grade 3/4 hematologic toxicity; immediate anaphylactoid-type reaction not ameliorated by lengthening the infusion time despite premedication; or grade 2 true hypersensitivity reaction. No cardiac abnormalities were observed in preclinical toxicology studies with R1507 derived from murine SP2/0 cell material; however, grade  $\geq 2$  cardiac toxicity as a DLT was included as a precautionary measure because of the role of IGF signaling in the growth and physiology of cardiac muscle. Cardiac monitoring consisted of 12-lead electrocardiogram capturing rate, rhythm, interval durations, and axis, performed at baseline and at the final visit. Planned dose levels were 1, 3, and 9 mg/kg. A further 12 patients received 9 mg/kg qW to obtain additional safety, pharmacokinetic, and pharmacodynamic data. After the primary objectives had been completed, patients assigned to doses  $< 9$  mg/kg could be treated according to the 9 mg/kg regimen if they experienced clinical benefit and tolerated R1507. Patients remained on study until the development of DLT or progressive disease.

Patients could be withdrawn at any point of their own volition or if deemed necessary by the investigator. Patients without DLT not completing the first 3 wk of treatment were replaced. The cutoff date for the analysis presented here was March 31, 2008.

**Patients.** Patients were required to have a histologically or cytologically confirmed solid neoplasm or lymphoma that was not amenable to standard therapy. Once accrual was complete for 18 patients and the 9 mg/kg dose was shown not to exceed the MTD, the protocol was amended to accrue an additional 12 evaluable patients with soft tissue or bone sarcoma.

Eligible patients were age  $\geq 17$  y and had an Eastern Cooperative Oncology Group performance status of 0 or 1; adequate baseline organ function; and complete recovery from prior surgery, radiotherapy, or other anti-neoplastic therapy. Exclusion criteria included were as follows: active infection or fever; current use of glucocorticoids; current or previous (within 6 mo) use of immunosuppressants; known hypersensitivity to components of R1507 or other monoclonal antibodies; receiving or recently received investigational therapy; diabetes mellitus, severe uncontrolled systemic disease, congestive heart failure, or any other medical condition deemed likely to interfere with a patient's ability to provide consent, cooperate, and participate in the study, or that would interfere with the interpretation of the results. Concomitant supportive treatments were permitted at the investigator's discretion. Cytotoxic chemotherapy, radiotherapy, chronically administered pharmacologic doses of glucocorticoids, primary prophylactic use of

hematopoietic growth factors, and other systemic anti-neoplastic agents were not allowed.

The study followed the Declaration of Helsinki (1996) and good clinical practice guidelines. Written informed consent was obtained from each participant or from a legally acceptable representative.

**Assessments.** Weekly safety evaluations were done, including physical examination, assessment of vital signs, laboratory tests, and observation/questioning of patients about adverse experiences. Patients were monitored for infusion effects during and for 60 min after infusions. A glucose tolerance test was done using individual investigator/site directives at screening and week 7, and an electrocardiogram was done at the screening and final visits.

Tumor response was evaluated by magnetic resonance imaging or computed tomography scan every 6 wk and was defined according to the Response Evaluation Criteria in Solid Tumors (26). Relevant tumor markers were evaluated at the same time overall tumor assessments were done. Eastern Cooperative Oncology Group performance status was assessed weekly.

**Pharmacokinetic assessments.** Blood samples (5 mL) were drawn before and 15, 60, 90 min and 6, 24, 48, and 72 h following infusions given at week 1 and week 7. Predose samples were also drawn before dosing at weeks 2, 3, 4, 8, and 10. Serum R1507 levels were determined by ELISA. Pharmacokinetic parameters assessed were as follows: maximum plasma concentration, time to maximum plasma concentration, area under the plasma concentration versus time curve (AUC), clearance (Cl), volume of distribution at steady-state ( $V_{ss}$ ), and elimination half-life ( $T_{1/2}$ ).

**Pharmacodynamic and biomarker assessments.** Serum levels of IGF-I signaling family proteins and total IGF-I (The DSL-10-5600 Active IGF-I ELISA kit) were obtained before and 1.5, 6, 24, and 72 h following the infusion at week 1 and before dosing and 6 and 24 h following its completion at week 7.

Archival tumor tissue was analyzed for IGF-IR (IGF1R $\beta$ , Cell Signaling Technology), Akt (anti-Akt; Cell Signaling Technology), phosphorylated Akt [anti-phospho-akt (Ser473; 736E11); Cell Signaling Technology], phosphatase and tensin homologue (PTEN; anti-PTEN; R&D systems), and phosphorylated extracellular signal-regulated kinase [anti-phospho-p44/42 mitogen-activated protein kinase (Thr202/Tyr204) antibody; Cell Signaling Technology]. H-scores were calculated as: intensity 1  $\times$  % of tumor cells stained + intensity 2  $\times$  % of tumor cells stained + intensity 3  $\times$  % of tumor cells stained.

Sera for detection of human-antihuman antibodies (HAHA) were obtained at screening and before dosing at weeks 4 and 10. Sera for HAHA were also obtained at the final visit (30 d after the last dose) and 4 mo after the last dose where possible, to account for any interference of HAHA testing with R1507. The presence of neutralizing antibodies was not investigated.

**Statistical analysis.** Two analysis populations were defined: the all-treated population—any patient who re-

ceived one or more dose of R1507—and the safety population—patients from the all-treated population with one or more postbaseline follow-up. Descriptive statistical analyses were planned and done for safety, efficacy, and pharmacodynamic evaluations. Estimations of pharmacokinetic parameters were done using standard noncompartmental methods. Secondly, pharmacokinetic results were modeled using a population approach, allowing the assessment of interindividual variability.

## Results

**Patient characteristics and duration on therapy.** Thirty-five patients were enrolled into the study at four centers between April 2006 and July 2007. Patients were treated with R1507 weekly: 1 mg/kg ( $n = 6$ ), 3 mg/kg ( $n = 6$ ), and 9 mg/kg ( $n = 23$ ). Four patients—two assigned to the lower doses of R1507 qW and two from the R1507 q3W cohort—were switched to 9 mg/kg qW after they had completed the primary pharmacokinetic objectives. Thus, overall, 37 patients were treated with the weekly schedule. Five patients did not complete 3 weeks of treatment and were replaced. Tumor response after 6 weeks was assessed in 31 of 35 patients (89%). Four patients withdrew before week 6 (death  $n = 2$ ; AEs  $n = 2$ ). Twenty-six patients completed six or more 3-week treatment cycles and nine patients received six or more cycles. The longest exposure to date exceeds 26 months. The median number of infusions per patient was 6 (range, 1-72) and the median interval between infusions was 7 days (range, 7-9 days). Patient demographics and baseline disease characteristics are presented in Table 1.

Twenty-nine of the 37 patients withdrew due to insufficient response. Two patients died of causes unrelated to R1507 (respiratory failure secondary to Ewing's sarcoma and cerebral hemorrhage secondary to anticoagulant treatment). Two patients withdrew due to potentially R1507-related AEs (hyperbilirubinemia and cerebral ischemia) and another two patients withdrew due to causes unrelated to R1507 (brain metastases and breast mass removal). Two patients remain on treatment.

**Pharmacokinetics.** Serum pharmacokinetic noncompartmental parameters following a single i.v. infusion of R1507 are detailed in Table 2. The pharmacokinetics of i.v. R1507 were characterized by a slow Cl and a limited volume of distribution (Fig. 1A). After a single infusion, the mean Cl differed by almost one-half across the dose groups (854 mL/d for 1 mg/kg; 586 mL/d for 9 mg/kg). The  $V_{ss}$  remained in the same range (3.9-4.26 L). The dosing schedule relative to the half-life did not allow for appropriate estimation of the elimination phase; thus,  $T_{1/2}$  was not calculated. However,  $T_{1/2}$  was 8 to 10 days at the 9 mg/kg dose on the q3W schedule (Roche: data on file). Multiple administrations resulted in a steady increase in trough concentration up to day 50 (Fig. 1B). The mean values of Cl and  $V_{ss}$  after multiple administrations remained comparable to those after a single dose.

**Table 1. Patient demographics and baseline disease characteristics (n = 35)**

| Characteristic                        | No. of Patients    | %  |
|---------------------------------------|--------------------|----|
| Gender                                |                    |    |
| Male                                  | 23                 | 66 |
| Female                                | 12                 | 34 |
| Race                                  |                    |    |
| White                                 | 31                 | 89 |
| Other                                 | 4                  | 11 |
| Age (y), mean (range)                 | 48.3 (18-74)       |    |
| Weight (kg), mean (range)             | 76.88 (48.5-126.1) |    |
| Height (cm), mean (range)             | 173.0 (157-194)    |    |
| ECOG performance status, mean (range) | 0.6 (0-1)          |    |
| Days since diagnosis, mean (SD)       | 1,891.1 (2,259.66) |    |
| Diagnosis                             |                    |    |
| Ewing's sarcoma                       | 9                  | 26 |
| Other sarcomas                        | 9                  | 26 |
| Colorectal                            | 3                  | 9  |
| Lung                                  | 2                  | 5  |
| Breast                                | 2                  | 5  |
| Prostate                              | 1                  | 3  |
| Other*                                | 9                  | 26 |
| Primary diagnosis site                |                    |    |
| Local regional                        | 16                 | 46 |
| Metastatic                            | 19                 | 54 |
| Previous cancer-associated treatments |                    |    |
| Surgery                               | 32                 | 91 |
| Radiotherapy                          | 22                 | 63 |
| Hormone therapy                       | 1                  | 3  |
| Biological and/or antibody therapy    | 5                  | 14 |
| Chemotherapy                          |                    |    |
| Relapse-free interval $\leq 2$ y      | 28                 | 80 |
| Relapse-free interval $> 2$ y         | 7                  | 20 |

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

\*Other sites: floor of mouth, gallbladder, pancreas, small bowel, appendix, peritoneum, primary site unknown (one patient each), and skin (two patients).

The model that best fit the data was a two-compartment model with a dual elimination process from the central compartment exhibiting parallel linear and nonlinear (saturable) kinetics.

The Michaelis Menten constant ( $K_m$ ) of the saturable elimination pathway was estimated to be 1.34  $\mu\text{g/mL}$ . Based on this model, trough values of 20  $\mu\text{g/mL}$  were selected as a target concentration required to provide  $>90\%$  saturation of the IGF-I receptor ( $>10\times$  higher than the  $K_m$  value). The trough concentrations at 9 mg/kg qW exceeded the minimum target of 20  $\mu\text{g/mL}$  at all time points.

**Pharmacodynamics.** Serum total IGF-I levels increased during the first 72 hours following a single administration in all dose cohorts; at the 9 mg/kg dose, this was inversely proportional to the serum R1507 concentration (Fig. 2). The maximum increase in serum IGF-I was  $\sim 250\%$  with the 9 mg/kg dose. The mean percentage change from baseline remained within the same range (100-350%) for all dose levels after seven doses. The total IGF-I level reached a plateau once R1507 steady state was achieved and remained fairly stable during the 7-day observation period. IGF-I levels in the 3 and 9 mg/kg cohorts were fairly stable, but levels in the 1 mg/kg cohort showed continued variability.

Of 26 archival tissue samples studied by immunohistochemistry, only 23 showed IGF-IR staining. All 26 samples showed phosphorylated extracellular signal-regulated kinase staining and all but 1 showed PTEN staining. Eleven samples showed phosphorylated Akt staining. Tumor tissue was only available from one of the two patients who had partial response (PR). The sample showed positive cytoplasmic IGF-IR staining (H-score = 40), but no membranous staining. The sample was negative for cytoplasmic pAKT (H-score = 0) and positive for phosphorylated extracellular signal-regulated kinase (H score = 31) and PTEN (H-score = 157). The range of expression of IGF-IR (expressed as H-score) for stable disease patients was 0 to 210 and 5 to 169 for progressive disease patients. Therefore, there was no consistent association between IGF-IR expression and clinical outcome.

**Maximum tolerated dose.** In the first 18 patients, no DLTs were reported in any of the dose levels. Therefore, no MTD was reached and 9 mg/kg qW was well tolerated. Seventeen more patients were included in the trial at this dose level.

**Tolerability.** R1507 was well tolerated, with 35 patients (94.5%) experiencing no grade  $>2$  drug-related AEs. Among the 37 patients, 168 AEs were reported in patients originally assigned to qW treatment and an additional 23 AEs were reported in the 2 q3W patients who switched to 9 mg/kg qW. One of these patients remained on treatment for an additional 40 weeks and accounts for the majority of the 23 AEs reported. Of the total AEs, 27 were considered to be related to R1507 (Table 3). Only two grade  $\geq 3$  drug-related AEs were noted: hyperbilirubinemia grade 3 (in a patient with extensive hepatic metastases) and cerebral ischemia grade 4. The only drug-related AEs reported in more than one patient were fatigue (8%) and anorexia (5%).

One AE of grade 2 diabetes mellitus was reported. This patient had an impaired glucose at baseline, was treated with metformin and repaglinide, and the event was ongoing at the last study visit. Glucose tolerance test was abnormal ( $\geq 110$  mg/dL at time point zero and/or  $\geq 140$  mg/dL at 2 hours postload) in  $\sim 50\%$  of patients throughout the study: 16 of 35 (46%) at baseline, 7 of 14 (50%) at week 7, and 3 of 6 (50%) at final visit.

**Table 2.** Pharmacokinetic parameters following a single i.v. infusion of R1507

| Parameter/dose                | 1 mg/kg (n = 6)  | 3 mg/kg (n = 6)  | 9 mg/kg (n = 23)           |
|-------------------------------|------------------|------------------|----------------------------|
| C <sub>max</sub> (µg/mL)      | 24.3 (17.3)      | 76.4 (22.4)      | 242 (24.1)                 |
| T <sub>max</sub> (h)*         | 1.00 (0.25-1.50) | 0.25 (0.25-6.03) | 1.00 (0.25-5.08)           |
| AUC <sub>0-∞</sub> (µg·h/mL)  | 2,060 (7.1)      | 8,450 (18.5)     | 31,800 (53.3) <sup>†</sup> |
| AUC <sub>0-7d</sub> (µg·h/mL) | 1,600 (13.5)     | 5,570 (24.1)     | 17,900 (22.0) <sup>‡</sup> |
| V <sub>ss</sub> (L)           | 3.90 (28.2)      | 4.88 (21.5)      | 4.26 (22.8) <sup>‡</sup>   |
| Cl (mL/d)                     | 854 (17.5)       | 769 (17.8)       | 586 (33.0) <sup>‡</sup>    |

NOTE: Values presented are mean (SD).

Abbreviations: C<sub>max</sub>, maximum plasma concentration; T<sub>max</sub>, time to maximum plasma concentration.

\*Median values (range) are reported for T<sub>max</sub>.

<sup>†</sup>n = 22.

<sup>‡</sup>n = 19.

Three patients (two treated at 9 mg/kg and one at 1 mg/kg) tested positive for HAHA but none experienced an AE consistent with an immunologic reaction.

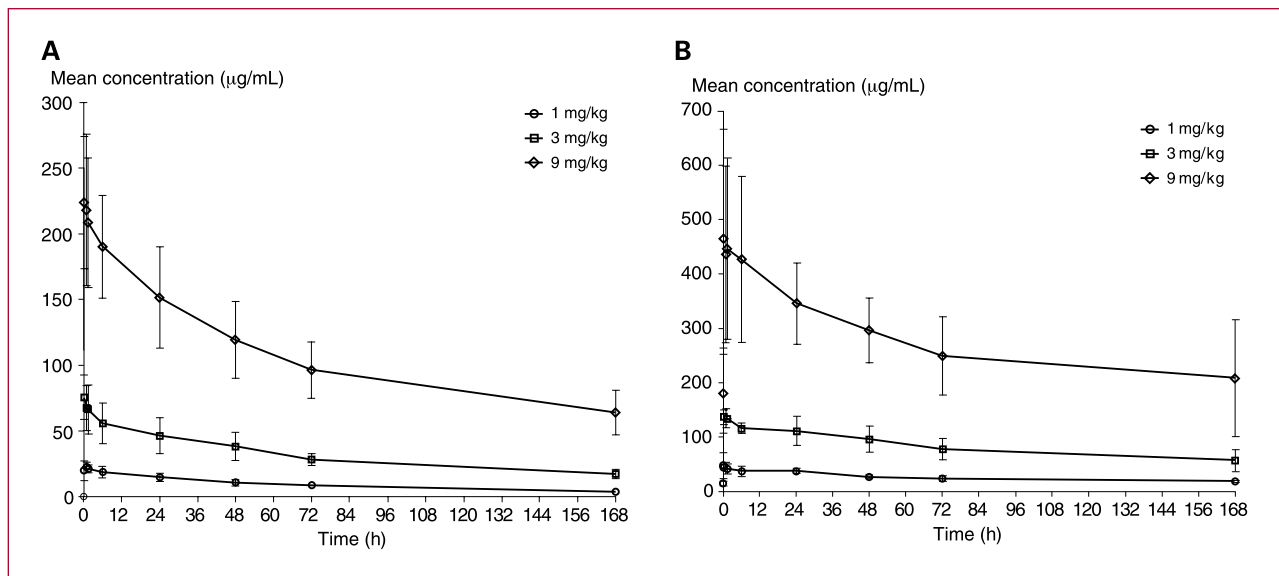
Newly occurring grade 3 or 4 laboratory test results were observed in four patients: aspartate aminotransferase in two patients and alanine aminotransferase and alkaline phosphatase in one patient each. Two patients experienced grade 2 thrombocytopenia. There was no evidence of clinically relevant changes in any of the treatment groups over time for blood pressure or pulse rate during the study. No electrocardiogram changes were noted following treatment with R1507.

**Response.** Two patients with Ewing's sarcoma had confirmed PRs (Fig. 3). The duration of PR was 11.5 months for a patient in the 1 mg/kg qW group (subsequently switched to 9 mg/kg qW) and at least 26 months for a patient

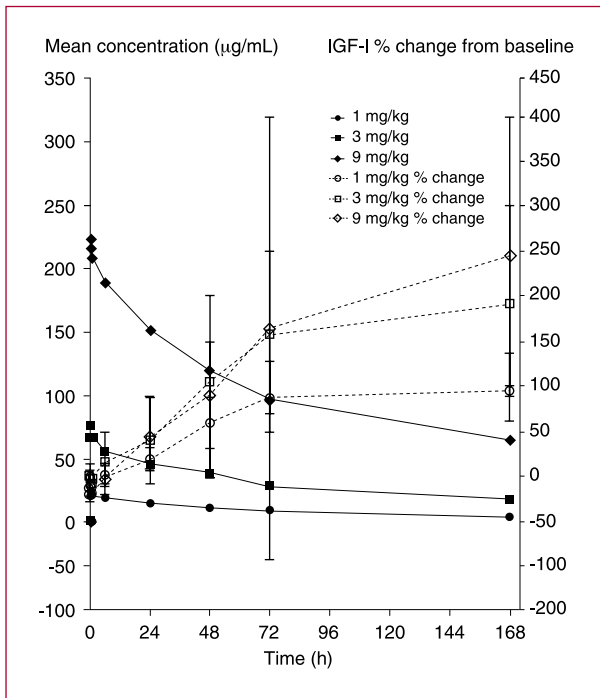
in the 9 mg/kg qW group. Stable disease was reported in 13 patients (including 2 patients with Ewing's sarcoma). In nine patients, stable disease was maintained for ≥3 months; five of these (leiomyosarcoma, Ewing's sarcoma, appendiceal adenocarcinoma, squamous cell carcinoma of the mouth, and prostate adenocarcinoma) maintained their response for ≥6 months. Sixteen patients had progressive disease as best response. Four patients were not evaluable for tumor response.

**Discussion**

Weekly administration of R1507, a fully human IgG1 monoclonal antibody directed against the IGF-IR, was tolerated at the maximal administered dose of 9 mg/kg and MTD was not reached.



**Fig. 1.** Mean (SD) serum concentration versus time profile following (A) single and (B) multiple (week 7; cycle 3) i.v. infusions of R1507.



**Fig. 2.** Mean percentage change from baseline in total IGF-I and the R1507 serum concentration values following a single i.v. administration of R1507 1 mg/kg ( $n = 6$ ), 3 mg/kg ( $n = 6$ ), or 9 mg/kg ( $n = 23$ ). Solid lines, R1507 concentrations; dotted lines, % change in IGF-I level.

R1507 exposure (AUC) increased with dose. The nonlinearity of clearance is explained by dual elimination pathways: a saturable clearance pathway that is mainly involved at low concentrations and is hypothesized to be the result of receptor-mediated endocytosis, and a linear clearance pathway, most likely through the reticuloendothelial system. Such a model has already been proposed for therapeutic monoclonal antibodies (27). Volume of distribution remained in the same range across the dose levels. Mean Cl and  $V_{ss}$  calculated after multiple administrations were comparable with those calculated after a single administration, indicating that the pharmacokinetic characteristics of R1507 remain stable with repeat dosing.  $T_{1/2}$  could not be accurately determined with the qW dosing interval but the value derived from the q3W schedule was 8 to 10 days (28, 29). Based on pharmacokinetic modeling, the mean trough concentration observed for the doses of 3 and 9 mg/kg qW exceeded the target of 20  $\mu\text{g/mL}$ , which was expected to saturate >90% of the receptors.

As expected, total IGF-I levels rose upon treatment with R1507, as downregulation of IGF-IR limited the number of binding sites available to the ligand. The increase was higher in patients exposed to 9 mg/kg qW than in those receiving 1 mg/kg qW.

In general, R1507 was well tolerated, with no significant drug-related toxicities. Patients dosed with 9 mg/kg qW did not show DLTs. Based on IGF-I levels, pharmacokinetic modeling, and preclinical data, it seems unlikely that

higher doses on a qW schedule would generate greater clinical activity.

A low incidence of subclinical hyperglycemia was reported during the study. Hyperglycemia was anticipated as the IGF-IR pathway is known to play a role in glucose metabolism (30, 31). The two patients who developed clinically significant hyperglycemia both had abnormal glucose tolerance at baseline.

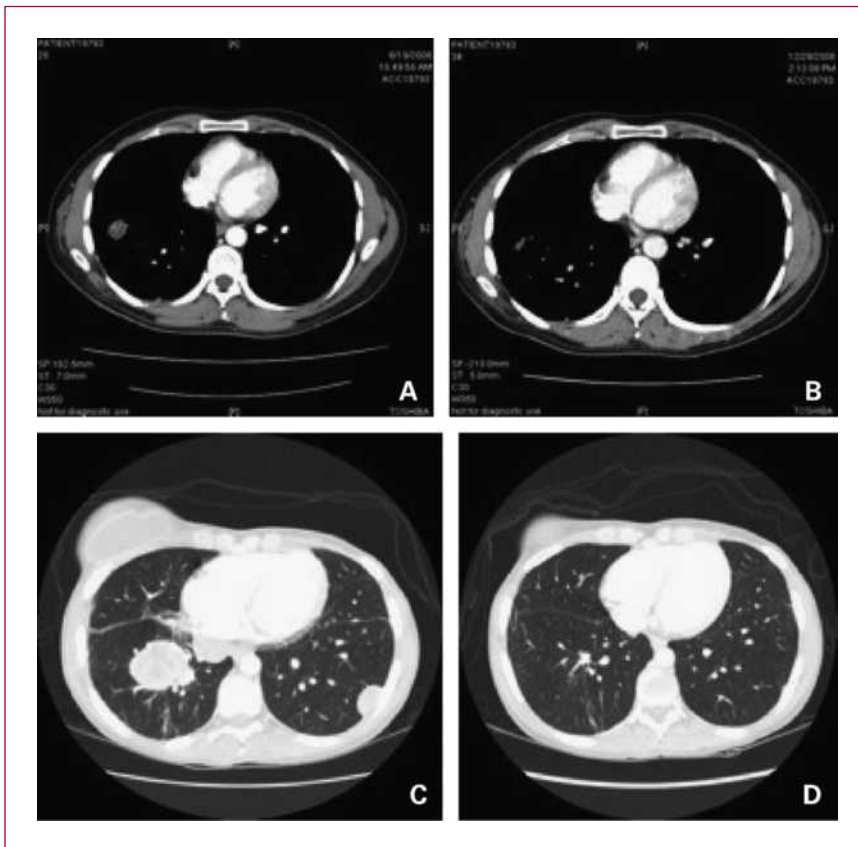
Nine patients with Ewing's sarcoma were treated, of whom two had durable PRs (lasting 11.5 and 26+ months) and two had stable disease (lasting 4.3 and 6 months). Responses in Ewing's sarcoma have been reported with other IGF-IR antagonists, such as AMG479 (an anti-IGFR antibody; refs. 32–34), suggesting that some patients with this tumor may be particularly sensitive to IGF-IR antagonists, and supporting the role of IGF-IR signaling in this malignancy (18–21, 35). The lack of a response in all patients with Ewing's sarcoma may reflect alterations in pathways that are not abrogated by IGF-IR inhibition. In addition to the observed clinical activity in Ewing's sarcoma, stable disease was reported in other sarcomas and solid tumors.

Further investigations are warranted to establish whether IGF-IR blockade with R1507 will improve outcomes in

**Table 3.** AEs considered to be related to i.v. R1507 qW

| AE                       | $n = 37$<br>$n$ (%) |
|--------------------------|---------------------|
| Fatigue                  | 3 (8)               |
| Anorexia                 | 2 (5)               |
| Abdominal pain           | 1 (3)               |
| Anemia                   | 1 (3)               |
| Cerebral ischemia*       | 1 (3)               |
| Deafness                 | 1 (3)               |
| Dehydration              | 1 (3)               |
| Diarrhea                 | 1 (3)               |
| Dizziness                | 1 (3)               |
| Dry mouth                | 1 (3)               |
| Eructation               | 1 (3)               |
| Headache                 | 1 (3)               |
| Hyperbilirubinemia*      | 1 (3)               |
| Hypophosphatemia         | 1 (3)               |
| Muscular weakness        | 1 (3)               |
| Musculoskeletal pain     | 1 (3)               |
| Nausea                   | 1 (3)               |
| Onychoclasia             | 1 (3)               |
| Rash                     | 1 (3)               |
| Rash erythematous        | 1 (3)               |
| Thrombocytopenia         | 1 (3)               |
| Tremor                   | 1 (3)               |
| Type 2 diabetes mellitus | 1 (3)               |
| Weight decreased         | 1 (3)               |

\*Events with grade  $\geq 3$  intensity.



**Fig. 3.** Responses in Ewing's sarcoma. A, 27-y-old male with t(11;22) EWSR1/FLI-1-positive chest wall primary (lung and pleura metastasis), achieved PR (week 23, lasting 11.5 mo) on 1 mg/kg qW before dose increase to 9 mg/kg qW. B, 28-y-old white female t(11;22) EWSR1/FLI-1-positive sacral primary (lung metastasis), achieved PR (week 6, ongoing at 26+ mo) on 9 mg/kg qW.

patients with cancer and whether R1507 used in combination with antineoplastic or with other targeted agents will provide additional benefits. The recommended dose for the weekly schedule is 9 mg/kg qW. International, multicenter phase II studies of R1507 involving administration qW and q3W are ongoing in patients with sarcoma and in lung cancer. The rationale for investigating a q3W regimen is that the administrations would coincide with concomitant backbone chemotherapy, would offer added patient convenience, and is supported by the pharmacokinetic and pharmacodynamic profiles for R1507.

#### Disclosure of Potential Conflicts of Interest

R. Kurzrock: commercial research grant, honoraria, consultant Roche; J. Aisner: blinded review of radiology, Roche; S.G. Eckhardt: commercial research grant, phase I infrastructure funding, consultant, Genentech; S.

Leong: IGF-IR advisory board, Roche. The other authors have no conflicts to declare.

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