Pharmacokinetically Guided Phase 1 Trial of the IGF-1 Receptor Antagonist RG1507 in Children with Recurrent or Refractory Solid Tumors

R. Bagatell¹, C.E. Herzog⁷, T.M Trippett⁶, J.F. Gripp⁶, G. Cirrincione-Dall⁴, E. Fox¹, M. Macy⁵, J. Bish¹, P. Whitcomb⁶, A. Alkin⁶, G. Wright¹, S. Yurasov⁸, F.M. Balis¹, and L. Gore⁵

Abstract

Purpose: This pediatric phase I study was designed to identify the doses of RG1507, a monoclonal antibody against the Type 1 Insulin-like Growth Factor Receptor (IGF1R), that achieves exposures equivalent to those achieved in adults at recommended doses.

Experimental Design: Children with relapsed or refractory solid tumors were treated using the same doses and administration schedules of RG1507 (3 and 9 mg/kg/wk, and 16 mg/kg every 3 weeks [q3W]) as those studied in adults. Detailed pharmacokinetic (PK) sampling was performed after the first dose; selected peak and trough levels were subsequently obtained. Target exposures were ≥85% of mean areas under concentration x time curves (AUCs) in adults at doses of 9 mg/kg/wk and 16 mg/kg q3W. A maximum tolerated dose could be identified if dose-limiting toxicities (DLT) occurred.

Results: Thirty-one evaluable patients aged 3–17 years were enrolled at 3 mg/kg/wk (n = 18), or 16 mg/kg q3W (n = 10). There were no DLTs. At 9 mg/kg/wk the mean AUC₀–7d (21,000 µg h/mL) exceeded the target (16,000 µg h/mL). At 16 mg/kg q3W, the mean AUC₀–21d (70,000 µg h/mL) exceeded the target (59,400 µg h/mL). Clearance normalized to body weight was age dependent. There were no objective responses. Seven patients had stable disease for >12 weeks, including two patients with osteosarcoma with stable disease for 52+ and 78+ weeks.

Conclusions: The recommended doses of RG1507 in children with solid tumors are 9 mg/kg/wk and 16 mg/kg q3W. This flexible design is well suited for trials of agents associated with limited toxicity. Clin Cancer Res; 17(3); 1–9. © 2010 AACR.

Introduction

RG1507 is a fully human monoclonal antibody directed against the Type 1 Insulin-like Growth Factor Receptor (IGF1R). RG1507 binding results in endosomal degradation of IGF-1R and inhibition of receptor-mediated signaling, which plays an important role in survival, proliferation, and metastasis of neuroblastoma, Ewing family tumors, rhabdomyosarcoma, and Wilms tumor(1–11). Inhibition of IGF-1R signaling reduces tumor growth in preclinical models of childhood cancers (12–14).

RG1507 was well tolerated in adults, and maximum tolerated doses (MTD) were not reached in phase 1 trials. The recommended doses of RG1507 (9 mg/kg weekly [qW] and 16 mg/kg every 3 weeks [q3W]) were based on pharmacokinetic (PK) modeling that demonstrated trough concentrations exceeding concentrations required to saturate RG1507 binding to IGF-1R (15). These concentrations were associated with antitumor activity in preclinical models, and objective responses were observed in adults (15).

These data suggested that using a conventional pediatric phase 1 trial design to define an MTD of RG1507 in children would not be rational. We instead designed a study to identify the RG1507 dose that achieved an area under the serum concentration-time curve (AUC) equivalent to that achieved in adults at recommended doses. This flexible trial design could also define an MTD if unexpected dose-limiting toxicities (DLT) occurred.
Translational Relevance

Signaling via the Type 1 insulin-like growth factor receptor (IGF1R) plays an important role in survival, proliferation, and metastasis of several pediatric tumors. This Phase I study was performed to identify the recommended doses of a monoclonal antibody against the IGF1R, RG1507, in children. A flexible trial design was used and two dosing schedules were studied. Drug-related toxicity was minimal; a maximum tolerated dose was not identified. Detailed pharmacokinetic sampling permitted identification of the doses of this agent that achieved exposures similar to those achieved in adults at recommended doses. Age-dependent clearance and lower drug exposures were observed in the youngest patients when dose was normalized to body weight. Dosing of this antibody based on body surface area may be appropriate in young children. Prolonged stable disease was observed in several patients. RG1507 could potentially be combined with other anticancer agents for the treatment of pediatric solid tumors.

Patients and Methods

Trial design

This open-label, multicenter pediatric phase I trial of RG1507 used the same doses and administration schedules (3 and 9 mg/kg qW, and 16 mg/kg q3W) as those studied in adults. The primary objective was to determine the RG1507 doses that would achieve mean serum drug exposures (AUCs) ≥85% of mean AUCs in adults at doses of 9 mg/kg qW and 16 mg/kg q3W. The MTD could be determined if DLT was observed before the primary PK endpoint was reached. The trial design algorithm is shown (Fig. 1). Toxicity, pharmacokinetics, and response were also evaluated. Intrapatient dose escalation was not permitted. A cycle was 21 days for both schedules. There was no limit on the number of cycles that could be delivered.

The first 3 children received 3 mg/kg of RG1507 qW. The mean AUC0–7d in these patients was compared to the target AUC0–7d of 16,000 μg h/mL (85% of 18,700 μg h/mL in adults). If the mean AUC0–7d documented in the first cohort of 18 adults treated with 9 mg/kg qW,(15) the dose would be escalated to 8 mg/kg qW and 16 mg/kg q3W. The MTD could be determined if DLT was observed before the primary PK endpoint was reached. The trial design algorithm is shown (Fig. 1). Toxicity, pharmacokinetics, and response were also evaluated. Intrapatient dose escalation was not permitted. A cycle was 21 days for both schedules. There was no limit on the number of cycles that could be delivered.

If DLT were observed in 1 of 3 patients at a dose level, up to 3 additional patients would be treated at the same dose. If ≥33% of patients experienced DLT, an MTD rather than a pharmacokinetically determined optimal dose would be identified. The MTD was defined as the highest dose level at which <33% of patients in an expanded cohort experienced DLT. The same design was used to determine the optimal pediatric dose on the q3W schedule. The starting dose was the adult recommended dose of 16 mg/kg/dose. The target AUC0–21d was 59,400 μg h/mL (85% of the mean AUC0–21d in adults receiving 16 mg/kg).

Dose level 3 = \( \frac{18,700 \, \mu g \, h/mL \, AUC_{0–7d} \text{ at } 9 \, mg/kg \cdot 9 \, mg/kg} {} \)

If DLT were observed in 1 of 3 patients at a dose level, up to 3 additional patients would be treated at the same dose. If ≥33% of patients experienced DLT, an MTD rather than a pharmacokinetically determined optimal dose would be identified. The MTD was defined as the highest dose level at which <33% of patients in an expanded cohort experienced DLT. The same design was used to determine the optimal pediatric dose on the q3W schedule. The starting dose was the adult recommended dose of 16 mg/kg/dose. The target AUC0–21d was 59,400 μg h/mL (85% of the mean AUC0–21d in adults receiving 16 mg/kg).

Patient eligibility

Patients ≥2 and <18 years of age with measurable or evaluable, relapsed or refractory solid tumors (including primary brain tumors) were eligible. Participation in PK studies was required as this was a primary study endpoint. Other requirements were recovery from acute toxic effects of prior therapies, Karnofsky or Lansky performance score >60, neutrophils (ANC) ≥1.5×10^9/L, platelets ≥100×10^9/L, age-adjusted normal serum creatinine or clearance ≥60 mL/min/1.73 m², total bilirubin ≤1.5× normal, transaminases ≤2.5× normal, and left ventricular shortening fraction ≥28%. Patients must not have received myelosuppressive therapy within 3 weeks, investigational agents or monoclonal antibodies within 30 days, localized radiotherapy within 2 weeks, radiotherapy to ≥25% of marrow-rich areas within 4 weeks, retinoids within 7 days, or colony stimulating factors within 10 days of study entry. Prior treatment with anti-IGF-1 receptor antibodies was not permitted. Patients were eligible if ≥2 months had elapsed since autologous stem cell transplantation or ≥6 months since allogeneic transplantation, if immunosuppressive therapy had been discontinued ≥30 days prior to study entry and there was no evidence of active graft-versus-host disease. Patients with central nervous system metastases were eligible if lesions were previously resected or radiated, if corticosteroids had not been administered for ≥2 weeks, and if neurological deficits were stable for ≥4 weeks.

Patients with previous hypersensitivity reactions to components of RG1507, prior hypersensitivity reactions to monoclonal antibodies, severe uncontrolled systemic disease, or fever within 3 days of initiation of RG1507 therapy were not eligible. Pregnant or breastfeeding patients, those with known HIV or hepatitis B or C, and those with diabetes mellitus were excluded. This trial was approved by institutional review boards of participating institutions; written informed consent was obtained from patients/legal guardians.

Drug administration

RG1507 derived from murine SP2/0 cell material (F. Hoffmann-La Roche) was diluted with normal saline to a
concentration ≥0.2 mg/mL and administered intravenously over 90 (first dose) or 60 minutes (subsequent doses).

**Toxicities**

Toxicities were graded according to NCI Common Terminology Criteria for Adverse Events version 3.0. DLT was defined as any nonhematologic, drug-related toxicity grade ≥3 occurring in the first cycle of therapy, with the exception of nausea, vomiting, and diarrhea ≤24 hours or hypersensitivity reactions occurring during drug infusion. Other DLT included grade 4 thrombocytopenia or grade 3 thrombocytopenia requiring platelet transfusion, grade 4 neutropenia ≥72 hours duration, grade ≥3 febrile neutropenia, or treatment delay >14 days due to persistent grade ≥2 toxicities other than fatigue. Patients with DLT could be retreated at the next lower dose level. Patients who experienced non–dose limiting toxicity could be re-treated after resolution of toxicity to grade ≤1 or baseline.

**Pretreatment and follow up studies**

At the start of each cycle, histories and physical examinations were done. Complete blood counts, glucose (fasting at screening), electrolytes, phosphorous, calcium, transaminases, lactate dehydrogenase, alkaline phosphatase, albumin, bilirubin, total protein, blood urea nitrogen, and creatinine were obtained at baseline, weekly during the first 2 cycles (qW) or first cycle (q3W), and before subsequent cycles. Pregnancy tests for females of childbearing potential and urinalyses were obtained 7 days prior to the first dose and every 12 weeks. Organ system function requirements were to be met prior to initiation of each cycle of therapy. Triplicate electrocardiograms were performed at least 1 minute apart prior to and immediately following dose 1 and the week 6 (qW) or week 7 (q3W) doses. Sera for detection of Human Anti-Human Antibodies (HAHA) were obtained prior to the first, fourth, and tenth (qW) or first, second, and fourth (q3W) doses and at follow-up. Disease assessments were 14 days before the first dose and every 6 weeks thereafter. Tumor response was assessed using Response Evaluation Criteria in Solid Tumors criteria (16). Expression of IGF-1R, pAKT, pErk, and PTEN in archival tumor tissues was assessed by immunohistochemical staining (results in Supplementary Table S1).

**Serum PK Sampling and RG1507 Assay**

This trial studied the same doses and schedules of RG1507, collected serum samples for pharmacokinetics at the same time points, and measured serum RG1507 concentrations using the same assay method as the adult

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*Figure 1. Dose-escalation scheme for RG1507 on the weekly dosing schedule. If the target AUC0–7d were not achieved with 9 mg/kg, additional dose levels would have been derived using Dose level 3 = (9 mg/kg × 0.85 × adult AUC at 9 mg/kg/dose) / 9 mg/kg.*
trials to allow for meaningful comparisons of data. Blood (2 mL) was collected from a site separate from the drug infusion prior to the first dose, at end of infusion, 6, 24, 48, 72, and 168 hours after the start of the 90-minute infusion for the qW schedule. For the q3W schedule, additional samples were obtained at 336 and 504 hours. Trough blood samples were drawn prior to the fourth, sixth, eighth, and tenth doses on the qW schedule and prior to the third and fourth doses on the q3W schedule. Samples were allowed to clot for 30 minutes; serum was separated by centrifugation and frozen. RG1507 was quantified in serum using an ELISA assay (25 ng/mL lower limit of quantification) (15).

Pharmacokinetic and Pharmacodynamic Analyses

RG1507 serum concentration-time data were analyzed using noncompartmental methods. End of infusion samples estimated the peak concentration (Cmax). Area under the concentration curve to the last measured time point (AUC0-last) was calculated with the linear trapezoidal method and extrapolated to infinity (AUC0-¥) by adding the final measured serum concentration divided by the terminal rate constant, derived from the slope of the natural log-transformed concentrations and times on the terminal elimination phase of the decay curve. The half-life (t1/2) was calculated by dividing 0.693 by the terminal rate constant. Clearance (CL) equaled dose/AUC0-¥ and volume of distribution at a steady state (Vdss) was calculated using noncompartmental methods. End of infusion samples estimated the peak concentration (Cmax). Accumulation (AUC0-¥) was calculated with the linear trapezoidal method and extrapolated to infinity (AUC0-¥). Accumulation of RG1507 was assessed from trough concentrations.

Serum levels of total IGF-1 were analyzed by ELISA (DSL-10–5600 Active® IGF-I ELISA Kit) according to the manufacturer’s instructions. Sera were collected prior to the first dose, at end of infusion, at 6, 24, and 48 hours after the infusion for both schedules. For the qW schedule, samples were also drawn prior to dosing at weeks 2, 6, and 10. For the q3W schedule, additional samples were obtained on days 8 and 15 of cycle 1, and prior to the second, third, and fourth drug doses.

Results

Patient characteristics

Thirty-four patients aged 3–17 years were enrolled at 3 mg/kg qW (n = 3), 9 mg/kg qW (n = 19), or 16 mg/kg q3W (n = 12). Thirty patients completed PK sampling and were evaluable for the primary endpoint; 31 patients were evaluable for toxicity. One patient on each schedule developed disease progression prior to completion of the first cycle of therapy and 1 patient on the q3W schedule did not receive study drug. Patient characteristics are shown in Table 1.

Toxicity

All drug-related toxicities were grade ≤2; there were no DLT and MTD was not defined. Drug-related toxicities reported during cycle 1 are shown in Table 2. There were no treatment interruptions or delays due to toxicity. Toxicities deemed at least possibly related to RG1507 during subsequent cycles included rash, pruritis, nausea, vomiting, anorexia, mucositis, muscle spasms, musculoskeletal pain, fatigue, and neutropenia. Both hyper- and hypoglycemia were observed, but there were no clinical sequelae from altered blood glucose levels and no treatment was required. There was no difference in incidence or severity of toxicities observed on the 2 dosing schedules. There was no relationship between AUC and severity of toxicities in any patient studied.

Pharmacokinetics and pharmacodynamics of RG1507

The serum concentration-time profiles of RG1507 at the 3, 9, and 16 mg/kg dose levels are shown in Figure 2.
PK parameters are summarized by dose level and age group (Table 3). At the starting dose (3 mg/kg qW/wk), the mean AUC$_{0–7d}$ was $5,666$ mg h/mL, well below the target AUC$_{0–7d}$ of $16,000$ mg h/mL. The dose was escalated to 9 mg/kg. At this dose, the mean AUC$_{0–7d}$ ($21,000$ mg h/mL) exceeded the target AUC$_{0–7d}$; 15 of 18 patients had an AUC$_{0–7d} > 16,000$ µg h/mL. Therefore, 9 mg/kg qW is the recommended dose in children. The mean AUC$_{0–21d}$ after 16 mg/kg q3W ($70,000$ µg h/mL) also exceeded the target AUC$_{0–21d}$ of $59,400$ µg h/mL. CL values from the 10 patients enrolled at the 16 mg/kg q3W dose level were equivalent to CL values from the 18 patients treated at the 9 mg/kg dose level, therefore additional patients were not enrolled. The recommended dose in children on the q3W schedule is 16 mg/kg/dose.

Trough serum concentrations after first and subsequent doses are shown in Table 4. At the recommended dose levels, trough concentrations exceeded the $20$ mg/mL levels associated with saturation of 90% of IGF-1 receptors. Based on trough concentrations, RG1507 accumulates 3-fold on the qW schedule and 2-fold on the q3W schedule after 9 weeks of treatment.

Within this pediatric population the CL of RG1507 appeared to be age dependent (Fig. 3). CL in younger children normalized to body weight was higher and AUC$_{0–7d}$ was lower in the youngest age group. Two of the 3 patients who did not achieve the target AUC$_{0–7d}$ at the 9 mg/kg/wk dose level were <6 years of age, and the single patient who did not achieve the target AUC$_{0–21d}$ at the 16 mg/kg dose level was an 8-year old. RG1507 CL was not age dependent when normalized to body surface area (Fig. 3B).

In all patients studied, total IGF-1 levels were increased by 24 hours following dosing, and mean values across all patients remained elevated throughout the dosing interval (Supplementary Table T1). Half of the interpatient variability in total IGF-1 levels was accounted for by patient age (Supplementary Fig. S1).

**Tumor response**

There were no complete or partial responses to RG1507. However, 7 patients had stable disease for >12 weeks. Among the 6 patients with Ewing sarcoma, 2 developed disease progression by week 6, 2 were found to have disease

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### Table 2. RG1507-related toxicity during cycle 1 by dose level and toxicity grade

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</tr>
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*a*Toxicities occurring in the same patient.
progression at week 12, and 2 had stable disease through week 12 but progressed by week 18. One patient with epithelioid sarcoma had stable disease for 36 weeks. Two patients with osteosarcoma continue to receive RG1507; 1 patient has had stable disease for >52 weeks and 1 has had stable disease for >78 weeks.

Immunogenicity assays

One patient had positive HAHA at baseline and week 4, and 1 patient had a positive HAHA at baseline but reverted to negative on study. No hypersensitivity reactions were observed.

Discussion

The clinical development of targeted anticancer agents has highlighted the need for rational dose-finding strategies based on therapeutic endpoints other than toxicity. The MTD of targeted agents may exceed the dose required for therapeutic effect, and dosing at the MTD may unnecessarily expose patients to toxicity. Demonstrating target inhibition in tumor tissue or achieving drug concentrations known to be inhibitory in preclinical studies are potential alternative endpoints for defining an optimal therapeutic dose.

Dose-finding studies in children usually follow and are informed by trials in adults. Dose-escalation trials of cytotoxic agents in children typically start at 80% of the adult MTD and are designed to study fewer dose levels. For agents such as RG1507, for which MTD was not defined in adults, alternative endpoints and trial designs are needed for pediatric dose-finding studies. Serial biopsies of solid tumors for pharmacodynamic analyses are not usually feasible in children, and surrogate tissues such as peripheral blood mononuclear cells are not necessarily predictive of drug effects in tumor. In this trial, we identified the dose of RG1507 required to achieve a drug exposure in children that was equivalent to the exposure achieved at the recommended dose in adults. Recommended doses in children were 9 mg/kg qW and 16 mg/kg q3W. Both schedules result in trough concentrations that have been associated with receptor saturation; the latter schedule may be more convenient for patients.

This study demonstrates the feasibility of conducting a pharmacokinetically guided phase I trial of a molecularly targeted drug in children. Preclinical data and PK modeling, which predicted the concentration of RG1507 required to saturate binding to IGF-1R, were used with clinical data from adult studies to select a target drug exposure for this pediatric trial. The success of this design depends on the low degree of inter-patient variability in pharmacokinetics observed in adults and subsequently in children (C.V. 25% for AUC0–7d at 9 mg/kg dose level).

RG1507 was well tolerated at all doses tested. Although subjects were heavily pretreated, neither DLT nor drug-related grade ≥3 toxicity was observed. Drug-related grade 2 toxicities were easily managed. No cumulative toxicity...
was observed in patients who received up to 52 weeks of RG1507. Mild hyperglycemia has been reported in patients treated with other antibodies directed against the IGF-1R (17, 18); however, no clinically significant, drug-related hyperglycemia was observed during this trial. Thrombocytopenia has also been observed in adults and in a child treated with IGF-1R inhibitors.(17–19) No drug-related thrombocytopenia was observed in this study. Our findings suggest that RG1507 could be combined with other anticancer agents, and could be given safely over an extended time period.

The PK profile of RG1507 in children is similar to that of other monoclonal antibodies and is characterized by a small volume of distribution (mean Vdss, 50 mL/kg) and slow elimination (mean CL, 6.2 mL/d/kg). The drug is measurable in serum throughout the dosing interval on both schedules. Although the lower CL and longer t1/2 with the 16 mg/kg q3W dose compared to 9 mg/kg qW could indicate dose-dependent pharmacokinetics, the nonlinearity observed more likely results from differences in the duration of sampling (21 vs. 7 days). For a direct comparison of exposure and assessment of dose proportionality in children receiving the qW and q3W schedules, the AUC should be calculated to the same last time point. The mean AUC0–7d is 38,000 mg h/mL for the 16 mg/kg dose level and 21,000 mg h/mL for the 9 mg/kg dose. This 1.8-fold increase in dose and AUC0–7d indicates that the RG1507 exposure in children is dose proportional over the dose range studied. The t1/2 from the 16 mg/kg dose (mean, 10 days) is likely more accurate than that derived on the weekly schedule because of the longer sampling interval.

### Table 3. Mean (%CV) pharmacokinetic parameters for RG1507 by dose level and age group

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<tr>
<th>Dose level, mg/kg</th>
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*Every 3 weeks schedule with pharmacokinetic sampling to day 21.

Abbreviations: Cmax, peak serum concentration; Cmin, trough serum concentration prior to the second dose.

### Table 4. Trough (Cmin) RG1507 serum concentrations and serum total IGF levels (expressed as percent change from baseline) following the first and subsequent doses at 9 mg/kg weekly and 16 mg/kg every 3 weeks

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<td>5</td>
</tr>
</tbody>
</table>

aThe accumulation index is the ratio of the trough concentration after the second and subsequent doses divided by the trough concentration after the first dose.
We studied 6 children each in 3 age groups at the 9 mg/kg qW dose level, and observed age-dependent drug CL and lower drug exposures (AUCs) in the youngest patients when the dose was normalized to body weight. Although the mean AUC0–7d in the 6 children aged 2–6 years exceeded the target AUC0–7d, 2 of the 6 had an AUC0–7d below the target. CL normalized to body surface area was not age dependent (Fig. 1B). Therefore, we assessed whether dosing RG1507 based on BSA would provide more uniform drug exposure across the pediatric age group. For each of the 18 patients treated at the 9 mg/kg/wk dose level, we derived dose per m2 by dividing the administered dose by patient BSA and normalized the AUC0–7d to a dose of 300 mg/m2. The mean simulated AUC0–7d for the 2–6, 7–11, and 12–17 year age groups were 23,100, 23,000, and 24,400, respectively. In addition, the AUC0–7d of all 6 2- to 6-year-old patients exceeded the target AUC0–7d with 300 mg/m2. Many antibodies and other proteins are dosed based on body weight, but this analysis suggests that dosing based on body surface area, at least with this compound, may be more appropriate in young children.

The trial design used in this study permits dose-escalation decision making based upon either toxicity or PK data. This design is well suited for trials of agents for which there are robust preclinical pharmacodynamic and PK data and limited toxicity in adults. The design also maintains a focus on patient safety and toxicity monitoring but may facilitate timely dose identification, as it may obviate the need to amend the study protocol if unexpected DLTs are observed. This flexible design may therefore be advantageous for both pediatric and adult phase I trials of new anticancer drugs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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R. Bagatell, C.E. Herzog, T.M Trippett, et al.

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