A Phase I Safety and Pharmacokinetic Study of the Death Receptor 5 Agonistic Antibody PRO95780 in Patients with Advanced Malignancies

D. Ross Camidge, Roy S. Herbst, Michael S. Gordon, S. Gail Eckhardt, Razelle Kurzrock, Blythe Durbin, Josephine Ing, Tanyifor M. Tohnya, Jason Sager, Avi Ashkenazi, Gordon Bray, and David Mendelson

Abstract

Purpose: PRO95780 is a fully human IgG1 monoclonal antibody that triggers the extrinsic apoptosis pathway through death receptor 5. This first-in-human study assessed the safety, tolerability, pharmacokinetics, and any early evidence of efficacy of PRO95780 in patients with advanced malignancies.

Experimental Design: Target concentrations were predicted to occur at 10 mg/kg. Patients received up to eight cycles of PRO95780 i.v. using a 3+3 dose escalation design at 1 to 20 mg/kg every 14 days (every 28 days in cycle 1; stage 1), with cohort expansion at either the maximum tolerated dose or 10 mg/kg, whichever was lower (stage 2). Patients were evaluated for response every other cycle.

Results: The maximum tolerated dose was not reached within this study. Four (8%) of 50 patients reported adverse events of greater than grade 2 at least possibly related to PRO95780, including 2 patients with reversible grade 3 transaminase elevation. The mean terminal half-life was 8.8 to 19.3 days, with dose-dependent increases in exposure (peak plasma concentration and area under the concentration) across 1 to 15 mg/kg. Most patients treated with 10 mg/kg or above achieved trough concentration above the target efficacious concentration at day 15 with moderate accumulation after multiple doses. No objective responses occurred, although three minor responses were observed in patients with colorectal and granulosa cell ovarian cancers (each treated with 4 mg/kg) and chondrosarcoma (10 mg/kg).

Conclusions: PRO95780 is safe and well tolerated at doses up to 20 mg/kg. Evidence of activity was noted in several different tumor types at 4 and 10 mg/kg. Pharmacokinetic analysis supports a dosing regimen of 10 to 15 mg/kg every 2 to 3 weeks.

Resistance to apoptosis is a hallmark of virtually all malignancies (1, 2). Apoptosis occurs through two main pathways: the intrinsic pathway, typically mediated by p53-dependent damage recognition and release of mitochondrial cytochrome C into the cytosol, and the extrinsic pathway, mediated by stimulation of cell surface proapoptotic death receptors (DR). Both pathways converge at the level of effector caspases, which proteolytically cleave critical cellular substrates (3–5).

Conventional antitumor therapies (i.e., chemotherapy and radiotherapy) exert their apoptotic effects primarily through activation of the intrinsic pathway. Loss of p53 function occurs in over 50% of human cancers and may be a significant driver of resistance to both chemotherapy and radiotherapy (6–8). In contrast, the extrinsic apoptotic pathway functions independently of p53 status. Novel proapoptotic receptor agonists (PARA) that activate the extrinsic apoptotic pathway may therefore be able to circumvent intrinsic pathway-based resistance to apoptosis (2).

The monoclonal antibody PRO95780 (Genentech) is a PARA that specifically targets DR5 (9, 10). DR5 is expressed in a wide range of solid tumors and hematologic malignancies (4, 11–13). PRO95780 induces apoptosis in a variety of human cancer cell lines and xenograft models both alone and in combination with other antineoplastic agents, but has shown little deleterious effect in nonmalignant cell cultures (3, 10, 14). Preclinical modeling strongly suggested that the minimal efficacious serum concentration of PRO95780 would be 0.9 to 22 μg/mL, depending on the tumor type (14, 15), and that trough concentration (Cmin) at the higher end of this concentration range would be achievable in humans at doses of 10 mg/kg or above administered every 3 weeks. To explore the safety, tolerability, and pharmacokinetics of a regimen potentially compatible with chemotherapy administered every 2 weeks as well as every 3 weeks, following an extended
Translational Relevance

Traditional cancer therapies (i.e., radiotherapy and chemotherapy) can activate apoptosis, but they do so indirectly as a secondary response to DNA damage, and often encounter tumor resistance. Recent efforts to improve cancer therapy have focused on developing more selective mechanism-based approaches that can help to overcome tumor resistance as well as minimize toxic side effects associated with conventional treatments. One potentially promising new class of agents, the proapoptotic receptor agonists, target the extrinsic apoptotic pathway, which may help to circumvent some of the most common antiapoptotic mutations present in cancer cells. Results presented here enable further safety and efficacy testing of one member of this class of agents, PRO95780, in subsequent clinical trials, both as a single-agent and in combination therapy regimens.

cycle 1 to gain a full pharmacokinetic profile of the drug over 28 days. In subsequent cycles, we tested a regimen of PRO95780 given once every 14 days.

The objectives of this phase I study were as follows: (a) to evaluate the safety and tolerability of single and multiple doses of PRO95780, (b) to characterize the pharmacokinetics of PRO95780, (c) to determine its maximal tolerated dose (MTD) across the dose ranges explored, including the dose predicted to confer efficacious serum concentrations in humans based on preclinical modeling, and (c) to perform a preliminary assessment of the antineoplastic activity of PRO95780.

Materials and Methods

Institutional Review Board approval was obtained at each participating clinical trial site before the start of the study. The study was conducted in accordance with the U.S. Food and Drug Administration Good Clinical Practice guidelines, and with the Health Insurance Portability and Accountability Act of 1996. Informed consent was obtained from each patient.

Study design. This was a phase I, open-label, dose escalation study of PRO95780 in patients with locally advanced or metastatic solid tumors, or non–Hodgkin’s lymphoma (NHL), who had failed or refused standard therapies or for whom there was no alternative therapy. The study consisted of two stages. The primary goals of stage 1 were to evaluate the safety, tolerability, pharmacokinetics, and MTD of PRO95780 across the 1 to 20 mg/kg dose range. Using a 3+3 dose escalation cohort design, the MTD was the dose level before the one at which ≥33% of the patients experienced a dose-limiting toxicity (DLT). A DLT was defined as any study drug-related, grade 3 or higher, hematologic or major organ toxicity (16), or a study drug-related elevation in serum creatinine to ≥2.5 mg/dL on two measurements at least 14 d apart, occurring from the start of treatment up to and including cycle 2, day 1. In stage 1, a maximum of 30 patients were planned for enrollment in five different dose cohorts: 1, 4, 10, 15, and 20 mg/kg. Patients received up to eight cycles of PRO95780 i.v. over 60 min every 14 d (every 28 d in cycle 1). Preclinical pharmacokinetic and pharmacodynamic modeling results suggest that efficacious concentrations could be achieved with a dosing regimen of 10 mg/kg administered every 3 wk (see Discussion). We explored a 14-d dose regimen that could be compatible with chemotherapy regimens administered every 2 wk. Doses higher than 10 mg/kg were also studied in case human data did not match the preclinical pharmacokinetic modeling and to evaluate safety and tolerability as loading doses, or for use in regimens with less frequent administration. The first cycle of PRO95780 was 28 d to allow for adequate determination of the terminal elimination phase, followed by 14-d cycles for cycles 2 through 8. Dose escalation proceeded as long as no more than one of three to six patients in each dose group experienced a DLT through cycle 2, day 1. If one DLT occurred in the first three patients, up to three additional patients were added to the cohort to characterize the safety and tolerability of that dose level further. The goals of stage 2 (expansion) were to obtain additional safety, pharmacokinetic, and tumor response information at the dose anticipated to be used in subsequent studies. In stage 2, 21 to 24 additional patients were treated at either the MTD of PRO95780, as determined during stage 1, or 10 mg/kg (assuming preclinical pharmacokinetic predictions were accurate), whichever was lower.

Each stage of the study consisted of two study periods: the Primary Study Period and the Extension Study Period. The Primary Study Period consisted of cycles 1 to 4. Patients who completed the Primary Study Period without DLT and with evidence of clinical benefit were eligible to receive up to four additional cycles of PRO95780, resulting in a maximum of eight cycles of treatment. Additional dosing beyond eight cycles in the absence of tumor progression was considered on a per-patient basis.

Patients. Key inclusion criteria included the following: age of ≥18 y; histologically documented, incurable, locally advanced, or metastatic solid malignancy or NHL; assessable disease; recovery to pretreatment or stabilization of all cancer treatment–related toxicities; Eastern Cooperative Oncology Group performance status of 0 or 1; and adequate hematologic, kidney, and liver function.

Major exclusion criteria included central nervous system disease; chemotherapy, hormonal therapy, radiotherapy, or immunotherapy within 4 wk of study commencement; and history of any chronic liver disease, active hepatic infection, or evidence of hepatic cirrhosis.

Assessments. Safety assessments including clinical adverse events (AE), changes in vital signs, physical findings, and laboratory assessments (complete blood count with platelet count and differential, serum chemistries, International
Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT), thyroid profile, serum amylase and lipase, and urinalysis were collected on days 1, 2, 4, 8, and 15 for cycle 1, and days 1 and 8 for all subsequent cycles. The safety and tolerability of PRO95780 were assessed by the incidence and nature of DLTs, the incidence, nature, and severity of AEs reported; and the incidence of anti-PRO95780 antibodies.

Patients were assessed for response and progression after every other cycle of PRO95780. Objective response was defined as a complete or partial response, per Response Evaluation Criteria in Solid Tumors (17), and confirmed by repeat assessment 24 wk after initial response.

**Pharmacokinetics.** Pharmacokinetic samples were collected on day 1 of cycle 1 preinfusion; 0.5 and 4 h following completion of PRO95780 infusion; and on days 2, 4, 8, and 15. During cycles 2 to 8, samples were collected on day 1 preinfusion; and on days 2, 4, 8, and 15.

PRO95780 serum concentrations were measured by a direct ELISA. The assay uses immobilized DR5 extracellular domain (PeproTech) to capture PRO95780 from human serum samples. Bound PRO95780 is detected with goat anti-human, λ light chain-horseradish peroxidase (ICN), and tetramethyl benzidine (Kirkegaard & Perry Labs) is used as the substrate for color development to quantify serum PRO95780 concentrations against a known standard curve. The assay has a reporting range from 100 to 6,000 ng/mL, and a mean accuracy from 81% to 102%. The percent coefficient variation for the intra-assay and interassay were <5% and 14%, respectively.

PRO95780 concentration × time data were analyzed by noncompartmental pharmacokinetic analysis. The area under the concentration × time curve from time 0 to 28 d post cycle 1 (AUC0–28) was determined using the log-linear trapezoidal rule. The peak plasma concentration (Cmax) was determined by inspection of the concentration × time profile. A power model (exposure = Doseb) was used to assess dose dependence, in which exposure is AUC0–28 or Cmax. a is the y-intercept and b is the slope of the exposure-dose straight line. The terminal phase elimination rate constant (λz) was obtained by log-linear regression analysis. The terminal phase half-life was calculated as ln2/λz. Total body clearance (CL) was determined by the total dose divided by the AUC and the volume of distribution (Vz) was calculated as CL divided by λz.

**Immunogenicity.** Serum samples were assayed for anti-PRO95780 antibodies preinfusion and on day 1 of each cycle using an electrochemiluminescent assay. This assay measures bridges formed by anti-PRO95780 antibodies between the biotinylated capture PRO95780 and the BVTAGed detection PRO95780. Samples were read on a BioVeris M384 analyzer. The relative sensitivity of the assay is 262 ng/mL.

**Statistical analysis.** Demographic and baseline disease characteristics for study patients were summarized using means, medians, SDs and ranges for continuous variables, and proportions for categorical variables. Mean serum PRO95780 concentration × time data were plotted by dose level, and mean (±SD) pharmacokinetic parameter estimates were tabulated.

**Results**

**Study population.** A total of 50 patients were enrolled and received at least one infusion of PRO95780 (28 in the dose escalation stage and 22 in the expansion stage). Demographic characteristics for patients enrolled in both stages are presented in Table 1 by dose group. All 50 patients were evaluable for safety and 41 were evaluable for efficacy (having undergone at least one posttreatment assessment of response).

Baseline disease characteristics and prior treatment history for patients who participated in this study are presented in Table 2.

### Table 1. Patient baseline demographics according to dose cohort

<table>
<thead>
<tr>
<th>n (%)</th>
<th>1.0 mg/kg</th>
<th>4.0 mg/kg</th>
<th>10.0 mg/kg</th>
<th>15.0 mg/kg</th>
<th>20.0 mg/kg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 3)</td>
<td>(n = 3)</td>
<td>(n = 30)</td>
<td>(n = 3)</td>
<td>(n = 11)</td>
<td>(n = 50)</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>61</td>
<td>56</td>
<td>56</td>
<td>72</td>
<td>54</td>
<td>58</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3 (100)</td>
<td>2 (67)</td>
<td>15 (50)</td>
<td>1 (33)</td>
<td>5 (46)</td>
<td>26 (52)</td>
</tr>
<tr>
<td>Male</td>
<td>0 (0)</td>
<td>1 (33)</td>
<td>15 (50)</td>
<td>2 (67)</td>
<td>6 (54)</td>
<td>24 (48)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0 (0)</td>
<td>1 (33)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1 (8)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>White</td>
<td>3 (100)</td>
<td>2 (67)</td>
<td>26 (87)</td>
<td>3 (100)</td>
<td>10 (81)</td>
<td>44 (88)</td>
</tr>
</tbody>
</table>

*The 20 mg/kg cohort was initially expanded from 3 to 6 patients for a DLT (grade 3 elevation of INR) later considered to be unrelated to study drug, and then to 11 patients to replace patients who withdrew for non-DLT-related reasons before cycle 1, day 1, and thus considered inevaluable for MTD assessment (see text).
Study drug exposure. The median number of PRO95780 doses administered was 2 with a range of 1 to 12. There was no obvious relationship between dose level and the median number of doses administered. There were 11 patients enrolled in the 20 mg/kg dose cohort. One of the first three patients experienced a grade 3 elevation of INR, believed at the time of reporting to be dose limiting. This patient was receiving warfarin for maintenance of central venous catheter patency at the time of the event. At baseline and throughout the study, this patient had only minor (i.e., grade 1 or 2) elevations of serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT). This event was subsequently determined to be unrelated to PRO95780 treatment by which time three additional patients were enrolled into the 20 mg/kg dose cohort, per protocol. Four of the initial six patients were replaced as a result of discontinuing the study before completing cycle 2, day 1, for reasons other than DLT (disease progression, withdrawal of consent, or non-DLT toxicity). One additional patient was enrolled erroneously to replace a patient thought to have discontinued the study before cycle 2 for non-DLT-related reasons but who was, in fact, continuing in the trial.

Three patients remained on study for at least eight cycles without progressing. Two of these patients (both treated at 10 mg/kg) received 12 cycles under a protocol waiver before exhibiting progressive disease.

Safety. After 2 cycles of treatment (through cycle 2, day 1) at each dose level in stage 1, the MTD was not reached and, per protocol, the 10 mg/kg cohort was expanded. Forty-nine (98%) of 50 treated patients experienced at least one AE, regardless of attribution. Overall, 22 patients (44%) experienced at least one AE that was judged to be related to study treatment. The most common of these were fatigue (14%), headache (12%), and chills (12%). The majority of AEs were National Cancer Institute Common Tendency Criteria grade 1 or 2 in severity. No relationship between dose level and incidence, nature, or severity of study-drug related AEs was observed (Table 3).

Study drug exposure. The median number of PRO95780 doses administered was 2 with a range of 1 to 12. There was no obvious relationship between dose level and the median number of doses administered. There were 11 patients enrolled in the 20 mg/kg dose cohort. One of the first three patients experienced a grade 3 elevation of INR, believed at the time of reporting to be dose limiting. This patient was receiving warfarin for maintenance of central venous catheter patency at the time of the event. At baseline and throughout the study, this patient had only minor (i.e., grade 1 or 2) elevations of serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT). This event was subsequently determined to be unrelated to PRO95780 treatment by which time three additional patients were enrolled into the 20 mg/kg dose cohort, per protocol. Four of the initial six patients were replaced as a result of discontinuing the study before completing cycle 2, day 1, for reasons other than DLT (disease progression, withdrawal of consent, or non-DLT toxicity). One additional patient was enrolled erroneously to replace a patient thought to have discontinued the study before cycle 2 for non-DLT-related reasons but who was, in fact, continuing in the trial.

Three patients remained on study for at least eight cycles without progressing. Two of these patients (both treated at 10 mg/kg) received 12 cycles under a protocol waiver before exhibiting progressive disease.

Safety. After 2 cycles of treatment (through cycle 2, day 1) at each dose level in stage 1, the MTD was not reached and, per protocol, the 10 mg/kg cohort was expanded. Forty-nine (98%) of 50 treated patients experienced at least one AE, regardless of attribution. Overall, 22 patients (44%) experienced at least one AE that was judged to be related to study treatment. The most common of these were fatigue (14%), headache (12%), and chills (12%). The majority of AEs were National Cancer Institute Common Tendency Criteria grade 1 or 2 in severity. No relationship between dose level and incidence, nature, or severity of study-drug related AEs was observed (Table 3).
Twenty-five (50%) patients experienced at least one grade 3 or 4 AE; however, only 4 (8%) experienced events that were considered drug related. These included one instance of grade 3 AST elevation (4 mg/kg), two instances of grade 3 ALT elevation (one coincident with the aforementioned grade 3 AST elevation, and one in a patient treated at 10 mg/kg), a grade 3 superior sagittal sinus thrombosis 10 days after discontinuation of PRO95780 for disease progression (1 mg/kg) and a grade 4 pulmonary embolus (10 mg/kg; see below). On detailed review of serum chemistry data, two additional patients, one treated at 10 mg/kg and the other at 20 mg/kg, exhibited grade 3 elevations in serum AST while under observation [cycle 2, day 8 and day 29 (study termination), respectively], although these were not reported as AEs at the time.

There were two DLTs observed, both in patients treated at 10 mg/kg (one in the dose escalation stage and one in the expansion stage). The initial DLT was observed in a 54-year-old female with ovarian cancer and multiple liver metastases who, after receiving her first dose of PRO95780, exhibited asymptomatic elevation of hepatic transaminase levels (National Cancer Institute Common Toxicity Criteria grade 3 elevation of serum ALT, as noted above; grade 2 elevation of serum AST) beginning on day 8 of study with resolution off treatment by day 53 (Fig. 1). The second DLT occurred in a 57-year-old male with colorectal carcinoma who developed a grade 4 pulmonary embolus on day 4 of the study. Neither patient was rechallenged with PRO95780. Two patients died while on study, both due to complications of progressive disease.

**Pharmacokinetics.** Pre- and post-cycle 1 samples for pharmacokinetic analysis were available in 31 patients, and sufficient serum samples for calculation of all pharmacokinetic parameter estimates were available in 25 patients. Mean serum concentration × time profiles for PRO95780 from 1 to 20 mg/kg and pharmacokinetic parameter estimates are shown in Fig. 2 and Table 4, respectively. The elimination of PRO95780 was characterized by a biexponential decline, with a mean terminal half-life ranging from 8.8 to 19.3 days. A dose-dependent increase in AUC and $C_{\text{max}}$ was observed for the 1 to 15 mg/kg doses, but with little evidence of an increase in exposure between 15 and 20 mg/kg. The mean clearance (CL) of 5.4 mL/d/kg (range, 3.1-9.1) seemed largely independent of the doses administered. The mean volume of distribution ($V_z$), 82.9 mL/kg (range, 73.5-95.1), was also similar across dose levels and suggests low-level distribution of PRO95780 outside of the serum compartment.

Figure 2 shows mean concentration × time profiles for all dose levels tested. The data revealed that on day 15 of cycle 1, 23 of 28 patients at the 10 mg/kg dose level achieved concentrations >22 μg/mL with a group mean (±SD) of 40 μg/mL (±26 μg/mL). On day 29, the $C_{\text{min}}$
after the first dose were maintained above 22 μg/mL for most patients. Moderate drug accumulation was observed following multiple doses. By day 43, C_{min} for all 10 mg/kg patients were above 22 μg/mL, with a mean (±SD) of 74 μg/mL (±36 μg/mL). Based on limited data in the 15 mg/kg dose cohort (n = 3), mean C_{min} were 44 and 118 μg/mL on days 29 and 43, respectively. Other cycle 1 pharmacokinetic parameters are shown in Table 4.

**Immunogenicity.** One of the 50 patients had a positive titer at cycle 2, day 1; however, this patient also tested positive at baseline and the titer did not increase over time, suggesting that this result was not treatment related.

**Efficacy.** Forty-one patients were evaluable for tumor response. No confirmed complete or partial responses per Response Evaluation Criteria in Solid Tumors were observed. A total of 20 (49%) patients had a best response of stable disease and 21 (51%) had a best response of progressive disease. A waterfall plot showing the best response for each study patient by tumor type is shown in Fig. 3. Three patients showed minor responses. A 57-year-old female with a granulosa cell ovarian tumor associated with peritoneal studding, liver metastases, and a history of multiple prior chemotherapies showed a 23% reduction in measurable disease after eight cycles of PRO95780 (4 mg/kg). According to the investigative site, the patient had undergone multiple surgical resections for treatment of initial and recurrent disease but had received no prior systemic therapy. She had a 20% reduction in measurable disease at the point of maximal response to treatment, receiving a total of 12 cycles of PRO95780 (10 mg/kg) before progressing.

**Discussion**

PRO95780 is a fully human, IgG1, monoclonal antibody that can trigger apoptosis through the extrinsic pathway through selective agonistic interaction with DR5. PRO95780 administered i.v. every 14 days (after a 28-day initial cycle) was generally well tolerated across doses ranging from 1 to 20 mg/kg; a MTD was not observed at the doses and schedule used. The most common study-drug related AEs were fatigue, chills, and headache; all episodes were mild or moderate in severity. There was no apparent relationship between the incidence of study drug-related AEs and study drug dose (Table 3).

Hepatocytes are known to express functional levels of DRs (18). Preclinical and clinical studies of other PARAs suggested that the liver might be a source of potential toxicity for PRO95780 (19). Grade 2/3 elevations in serum AST/ALT that occurred in four patients (including one in whom transaminase elevation was considered dose limiting; see Fig. 1) following treatment with PRO95780 at doses varying from 4 to 20 mg/kg is consistent with this possibility. However, longitudinal evaluation of liver function studies in all patients suggests that this toxicity may be sporadic. The rapid reversibility of serum transaminase elevations in the patient for whom this abnormality was dose limiting suggests that close monitoring of hepatic enzymes could abrogate the risk of clinically significant hepatotoxicity during any routine clinical use. Just as factors that may be predictive of tumor sensitivity for these agents continue to be elucidated (see below), those that predispose patients to toxicity may also become more clear in the future.

### Table 4. Pharmacokinetic parameter estimates based on cycle 1 data

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Patient (n)</th>
<th>AUC_{0-28} (days*μg/mL)</th>
<th>C_{min} (μg/mL)</th>
<th>C_{max} (μg/mL)</th>
<th>CL (mL/d/kg)</th>
<th>V_s (mL/kg)</th>
<th>t_{1/2} (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>220 ± 55.9</td>
<td>3.5 ± 1.4</td>
<td>26.1 ± 6.2</td>
<td>3.6 ± 0.9</td>
<td>73.5 ± 17.1</td>
<td>14.5 ± 2.0</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>980 ± 331</td>
<td>16.8 ± 9.6</td>
<td>99.4 ± 13.7</td>
<td>3.1 ± 1.7</td>
<td>78.8 ± 19.5</td>
<td>19.3 ± 4.9</td>
</tr>
<tr>
<td>10</td>
<td>13</td>
<td>1500 ± 418*</td>
<td>27.7 ± 14.4†</td>
<td>210 ± 47.0§</td>
<td>6.4 ± 2.1</td>
<td>80.1 ± 30.6</td>
<td>9.1 ± 2.8</td>
</tr>
<tr>
<td>15</td>
<td>3</td>
<td>3310 ± 1280</td>
<td>43.9 ± 23.3†</td>
<td>330 ± 37.2</td>
<td>3.4 ± 1.8</td>
<td>74.4 ± 48.7</td>
<td>14.7 ± 8.9</td>
</tr>
<tr>
<td>20</td>
<td>3</td>
<td>2140 ± 605</td>
<td>51.3 ± 32.4</td>
<td>333 ± 49.2</td>
<td>9.1 ± 4.2</td>
<td>95.1 ± 23.4</td>
<td>8.8 ± 5.7</td>
</tr>
</tbody>
</table>

* Pharmacokinetic parameters are derived from samples obtained at cycle 1 only.

† Estimation of AUC_{0-28} is based on data from 12 patients in this dose group.

§ Estimation is based on n = 4 patients.

\^ Estimation is based on n = 19 patients.

E estimation is based on n = 2 patients.
Pharmacokinetic and pharmacodynamic modeling of data from tumor growth inhibition studies using human tumor xenograft models suggested a minimal inhibitory concentration for PRO95780 of 0.9 to 22 μg/mL, depending on the tumor type (14, 15). Based on these data, a mean PRO95780 serum Cmin at a steady state (C_sst-min) of ~60 μg/mL was selected as a pharmacokinetic target, which would allow for expected variability in C_sst-min and ensure that most patients attain the highest minimal inhibitory concentration (22 μg/mL). Using allometric scaling, such exposures were predicted to be achievable in humans with a dosing regimen of 10 mg/kg administered every 3 weeks. Individual patient data from the current study also reveals that a regimen of 10 to 15 mg/kg every 2 to 3 weeks would achieve steady-state drug concentrations above the target of 22 μg/mL and a mean above 60 μg/mL for most patients. On day 15 of cycle 1, 23 of 28 patients at the 10 mg/kg dose level achieved concentrations of >22 μg/mL with a group mean (±SD) of 40 μg/mL (±26 μg/mL; Fig. 2). Moderate drug accumulation was observed following multiple doses and by day 43; Cmin for all 10 mg/kg patients were above 22 μg/mL, with a mean (±SD) of 74 μg/mL (±36 μg/mL).

Although no patients experienced complete or partial responses in the current study, three patients exhibited minor responses at 4 to 10 mg/kg with 20% to 28% reductions in measurable disease coincident with study treatment for 8 to 12 cycles.

Several other DR4 or DR5 agonistic monoclonal antibodies and recombinant human Apo2 ligand/tumor necrosis factor–related apoptosis-inducing ligand (dulanermin), which can signal apoptosis through the engagement of both DR4 and DR5, have been investigated recently in early-phase clinical studies of advanced cancer patients (20–26). Considering these compounds as representatives of the same or similar classes of agents, it is noteworthy that the tumor types with clinical evidence of single-agent activity to these agents partially overlap with those manifesting minor responses to PRO95780, specifically colorectal cancer and certain soft tissue sarcomas. Ovarian cancer responsiveness in the clinic has not previously been reported, but this may be a reflection of limited clinical exploration of proapoptotic DR agonism in this tumor type to date. Apo2 ligand/tumor necrosis factor–related apoptosis-inducing ligand is known to have activity across a range of preclinical models of ovarian cancer (27).

Although several factors that predict sensitivity and resistance to PARAs have been described in vitro, biomarkers that predict sensitivity to these agents in the clinic remain to be determined (28). Receptor presence alone seems insufficient to guarantee a response (21). Recent preclinical data have suggested that the level of certain O-glycosyl transferases, which are implicated in O-linked glycosylation of DR4 and DR5, may broadly correlate with sensitivity to the recombinant human Apo2 ligand/tumor necrosis factor–related apoptosis-inducing ligand in cancer cell lines (29).

Taken together, our data suggest that PRO95780 is safe and well tolerated. Pharmacokinetic analysis supports a dosing regimen of 10 to 15 mg/kg every 2 to 3 weeks, potentially compatible with standard chemotherapy regimens used for the treatment of common solid tumors. At

---

6 Unpublished data, Genentech.
10 mg/kg, the mean target Cmin was achieved in the majority of patients in the first cycle, and in all patients following drug accumulation after multiple doses. Prclini- cally, a range of efficacious concentrations were noted depending on the tumor type, suggesting differences in absolute sensitivity even among tumors sensitive to these agents, and clinical efficacy was noted at dose of 4 mg/kg and above. However, in light of its good safety profile, and the potential to achieve efficacious doses more quickly at 15 mg/kg, we have selected the higher PRO95780 dose as the more appropriate to explore in phase II studies. Additional studies will be required to further define the relationship between PRO95780 therapy and patient outcome, as well as to identify predictive biomarkers of efficacy and toxicity that will aid in patient selection.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

Thanks to Bert L. Lum and Lie Ling for their contributions to the design and clinical conduct of the study, and Yanhe Tong who assisted with the pharmacodynamic and antibody assays. In previous presentations, PRO95780 has been called Apomab. However, Apomab is an internationally registered trademark of Medvet Science Pty Ltd. Genentech’s antibody (PRO95780) is not affiliated, connected, or associated with Medvet Science Pty Ltd.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received 5/19/09; revised 11/6/09; accepted 11/19/09; published OnlineFirst 2/9/10.

References

A Phase I Safety and Pharmacokinetic Study of the Death Receptor 5 Agonistic Antibody PRO95780 in Patients with Advanced Malignancies


Clin Cancer Res 2010;16:1256-1263. Published OnlineFirst February 15, 2010.

Updated version
Access the most recent version of this article at:
doi: 10.1158/1078-0432.CCR-09-1267

Cited articles
This article cites 23 articles, 7 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/16/4/1256.full#ref-list-1

Citing articles
This article has been cited by 19 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/16/4/1256.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.