A First-in-Man Phase I and Pharmacokinetic Study on CHR-2797 (Tosedostat), an Inhibitor of M1 Aminopeptidases, in Patients with Advanced Solid Tumors

Alison H.M. Reid, Andrew Protheroe, Gerhardt Attard, Nikki Hayward, Laura Vidal, James Spicer, Heather M. Shaw, Elizabeth A. Bone, Joanne Carter, Leon Hooftman, Adrian Harris, and Johann S. De Bono

Abstract

Purpose: To determine the maximum tolerated dose, dose-limiting toxicity, pharmacokinetics, and preliminary therapeutic activity profile of CHR-2797 (tosedostat), a novel, orally bioavailable inhibitor of the M1 family of aminopeptidases with antiproliferative and antiangiogenic activity in vitro.

Experimental Design: A phase I study of accelerated titration design that escalated through nine doses (10–320 mg) in patients (Eastern Cooperative Oncology Group performance status, ≤2) with advanced solid tumors. CHR-2797 was administered once daily.

Results: Forty patients (median age, 60 years; range, 24–80 years; male, 27; female, 13) were treated in 12 cohorts with once daily doses (10–320 mg). Dose-limiting toxicities were thrombocytopenia, dizziness, and visual abnormalities in one patient, and anemia, blurred vision, and vomiting in a second patient at 320 mg, resulting in an inability to complete 28 days of study drug. The most commonly observed toxicities were fatigue, diarrhea, peripheral edema, nausea, dizziness, and constipation. One patient had a partial response (renal cell carcinoma) and four patients had stable disease for >6 months. CHR-2797 and its active metabolite, CHR-79888, show dose-proportional increases in plasma AUC and C<sub>max</sub>. The terminal half-life for CHR-2797 is ~1 to 3.5 hours and between 6 and 11 hours for CHR-79888. Intracellular (packed blood cells) exposure to CHR-79888 is consistent with intracellular levels that proved to be efficacious in xenograft models.

Conclusion: CHR-2797 is well tolerated and can be safely administered at doses that result in intracellular levels of CHR-79888 that are associated with activity in preclinical models. The recommended dose for single agent therapy in solid tumors is 240 mg/d.

CHR-2797 (tosedostat) is a metalloenzyme inhibitor with pleiotropic activity against a range of human cancer cells in vitro and in vivo. Exposure of cells to the ester, CHR-2797, causes intracellular accumulation of its acid metabolite, CHR-79888, which exerts a powerful inhibitory effect on intracellular aminopeptidases, resulting in antiproliferative, proapoptotic, and antiangiogenic effects. Although the most important intracellular metalloenzyme targets for CHR-2797 have not been fully elucidated, there is a substantial body of evidence indicating that they are likely to be members of the M1 family of aminopeptidases, for example, puromycin-sensitive aminopeptidase, leukotriene A<sub>4</sub> hydrolase, or the M17 family member, leucine aminopeptidase (IC<sub>50</sub> values of CHR-2797 and CHR-79888 for these aminopeptidases are detailed in Fig. 1A, all of which are often overexpressed in human cancers; refs. 1–5). The antiproliferative effects of CHR-2797 likely depend on the simultaneous inhibition of more than one intracellular aminopeptidase. The M1 class of aminopeptidases plays a critical role in the final steps of protein recycling downstream of proteasomal degradation (6), and inhibition of aminopeptidases by CHR-2797 and/or CHR-79888 may, like proteasome inhibition, disrupt the turnover of cell cycle intermediates, affecting cancer cell survival or proliferation (Fig. 1B).

In addition, inhibition of aminopeptidases by CHR-2797 and its metabolite in transformed cells of the hematopoietic lineage seems to lead to an accumulation of small peptides and results in a deficiency of free amino acids for new protein synthesis (1).
Translational Relevance

CHR-2797 (tosedostat) is a metalloenzyme inhibitor with pleiotropic activity against a range of human cancer cells in vitro and in vivo. It has shown an inhibitory effect on intracellular aminopeptidases, resulting in antiproliferative, proapoptotic, and antiangiogenic effects. We describe here the first-in-man phase I dose-escalation study of CHR-2797 to define the safety, tolerability, and maximum tolerated dose when administered orally daily to patients with advanced solid tumors. Secondary objectives were to assess pharmacokinetic variables of CHR-2797 and make a preliminary assessment of antitumor activity. This study will inform the future administration and development of this agent in solid tumors. CHR-2797 is currently showing encouraging activity in phase II trials for patients with hematologic malignancies.

This conclusion is inferred from the induction of a cellular stress response known as the amino acid deprivation response (7). One of the consequences of the amino acid deprivation response is the up-regulation of proapoptotic proteasome proteins such as CHOP and Noxa (1, 8), which serve to prime the cell for apoptosis. It is not currently entirely clear why transformed cells are more sensitive to amino acid deprivation than normal cells, but this disparity in sensitivity is also noted with other types of cell stress (9). Indeed, it has been known for some time that tumor cells are critically dependent on specific amino acids, for example, arginine, for their survival. Depletion of intracellular arginine has more profound effects on transformed than normal cells, which correlates well with the effects of CHR-2797 (10, 11). Aminopeptidase inhibition also reduces phosphorylation of mTOR substrates and rates of protein synthesis, both indicative of amino acid depletion (1). Natural product inhibitors of aminopeptidases, particularly bestatin, exhibit similar, albeit weaker, pharmacologic actions to CHR-2797, including its proapoptotic, antiproliferative, and antiangiogenic effects, and its ability to induce amino acid deprivation response–related gene expression changes (1). Bestatin has an IC50 against puromycin-sensitive aminopeptidase of 400 nmol/L but, as a charged molecule, is relatively weak in cell-based systems such as proliferation assays. Bestatin is approved in Japan as a maintenance therapy in patients with nonlymphocytic leukemia and has been shown to improve overall survival in a phase III double blind placebo-controlled neo-adjuvant trial in stage I to II squamous cell lung carcinoma (12). CHR-2797 is considerably more potent than bestatin in preclinical studies, showing 300 to 1000 times greater inhibitory effect of cell proliferation as measured by [3H]thymidine incorporation in a selection of cell lines (1).

We therefore conducted a phase I dose-escalation study to define the safety, tolerability, and maximum tolerated dose of CHR-2797 when administered orally daily to patients with advanced solid tumors. Secondary objectives were to assess the pharmacokinetic variables of CHR-2797 and make a preliminary assessment of antitumor activity.

Patients and Methods

Patient eligibility. Patients with the age of ≥18 y with histologically or cytologically confirmed advanced solid malignancies refractory to conventional treatment were enrolled. Eligibility criteria included life expectancy of ≥12 wk, Eastern Cooperative Oncology Group performance status of ≤2, no previous antitumor therapy within 4 wk of study entry (6 wk for mitomycin and nitrosoureas), and adequate hematopoietic (absolute neutrophil count ≥1.5 × 10⁹/L; platelets ≥100 × 10⁹/L), hepatic (bilirubin ≤1.5 × upper normal limit; aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤2.5 × upper normal limit or ≤5 × upper normal limit in the presence of liver metastases), and renal function (creatinine, ≤1.5 × upper normal limit). Patients with known brain tumors or brain metastases and patients who had not recovered from acute adverse effects of previous therapies were excluded. The local research ethics committees at both participating centers approved the study protocol, and written informed consent was obtained from all patients before any study-related procedures.

Study design and dose-escalation schedule. This was an open-label, nonrandomized, phase I dose-escalation study of accelerated titration design (13). CHR-2797 capsules (5, 10, 20, and 40 mg) were taken orally daily after food at the same time each day. The study involved three distinct phases for evaluation of dose: (a) a fixed dose with increasing duration, (b) dose escalation over a fixed duration, and (c) an expansion of the recommended dose level to a maximum of 12 patients. The starting dose for cohort one was 10 mg, administered as a single dose for seven consecutive days, followed by a 21-d rest period. Assuming that patients in cohort 1 tolerated 7 d of dosing, patients in cohorts 2, 3, and 4 would also be treated with 10 mg once daily but for 14, 21, and 28 d, respectively. If no NCI-Common Termina l Criteria for Adverse Events (CTCAE) version 3 grade 2 toxicity was seen in the first phase and safety of 28-d continuous dosing was shown, the study would continue into the second phase, in which doses were increased according to an accelerated titration design. Cohorts consisted of one patient each, and permitted dose increments were of 100% until grade 2 toxicity was observed. Patients received 28 d of therapy before a new patient could start study drug at an increased dose level. Once drug-related grade 2 toxicity was documented, the design required a minimum of three patients to receive at least 28 d of treatment in subsequent cohorts, and dose increments of 25% to 40% were used. When cohorts included three or more subjects, 14 d of treatment had to be completed before the next two subjects were enrolled. No intrapatient dose escalation was permitted.

Definition of maximum tolerated dose and dose-limiting toxicity. The maximum tolerated dose was defined as the dose level below which more than one of three or two of six patients developed grade 3 to 4 toxicity or dose-limiting toxicity. Dose-limiting toxicity was defined as any of the following events that was determined to be possibly or probably related to CHR-2797 and occurred during the first course (28 d) of treatment: absolute neutrophil count <0.5 × 10⁹/L (lasting for >5 d or with sepsis), platelet count <25 × 10⁹/L, grade 2 or above neurotoxicity/cardioxicity, any drug-related, nonhematologic grade 3 to 4 toxicity, and the inability to tolerate 28 d of daily oral therapy due to toxicity.

Dose modification due to toxicity. Any patient in whom a dose-limiting toxicity occurred during the course of treatment was to have treatment withheld until toxicity resolved to baseline or grade 1 or better. Upon resolution, therapy could be re instituted at the next lower dose level. The granulocyte count and platelet count had to be >1.5 × 10⁹/L and >100 × 10⁹/L, respectively, for further dosing. Drug-induced nonhematologic toxicities had to have improved to grade ≤1 before re-treatment. Treatment could be delayed for up to 2 wk to allow sufficient recovery from toxicity. If the hematologic or nonhematologic toxicities had not resolved within 2 wk, the patient was considered to have a dose-limiting toxicity and was discontinued from the study.

Patient evaluation and follow-up. Toxicity assessment, hematology, and clinical biochemistry were done at baseline and weekly during
the study. Full physical and Eastern Cooperative Oncology Group performance status were recorded at each month of therapy. The initial study period was 28 d. If, in the opinion of the investigator, treatment for longer than this time might be beneficial, it could be extended at the same daily dose until progressive disease or unacceptable toxicity. Response was evaluated according to the Response Evaluation Criteria in Solid Tumors 1 (14) at 28 d and subsequently every 1 or 2 mo. Radiologic responses were confirmed by repeat imaging done after an interval of at least 28 d. Patients were taken off study upon disease progression, unacceptable toxicity, investigator discretion, serious violation of protocol, or at their own request. Following a serious adverse event of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, subsequent patients underwent serial ADAMTS-13 functionality testing before and throughout their time on study drug until a drug effect was ruled out. Samples were analyzed at the Haemostasis Unit, University College, London.

**Pharmacokinetic assessments.** Pharmacokinetic analyses included measurements of CHR-2797 and CHR-79888 concentrations in plasma and, intracellularly, in packed blood cells (i.e., combined red and white cells) on all patients. Blood samples (2 × 3 mL) were taken at baseline and at 30 and 60 min and 2, 4, 6, 8, 24, and 48 h post first dose. Pharmacokinetic samples were taken up to 24 h after the last dose in cycle 1 [i.e., D7 (cohort 1), D14 (cohort 2), D21 (cohort 3), and D28 (all subsequent cohorts)]. All patients had pharmacokinetic blood samples taken at the end of each monthly cycle up to the end of the third month. Pharmacokinetic parameters were calculated using the WinNonlin Professional software (version 4.1; Pharsight Corporation). No pharmacodynamic assay for aminopeptidase inhibition or downstream effect was available for this first clinical dose finding trial of CHR-2797, and therefore, no correlations could be established between the cytoreductive effect of the agent and the degree of amino-acid depletion in cells. Once the daily dose had escalated to ≥40 mg, patients whose tumors were accessible...

![Figure 1](link)

**A.** Chemical structure and aminopeptidase inhibition. From left to right, the chemical structures of the ester CHR-2797, its active metabolite CHR-79888, and the aminopeptidase inhibitor bestatin. IC_{50} values (nanomoles per liter) are listed for each compound for several aminopeptidases.

<table>
<thead>
<tr>
<th>Aminopeptidase</th>
<th>CHR-2797</th>
<th>CHR-79888</th>
<th>Bestatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>PuSA</td>
<td>150</td>
<td>850</td>
<td>350</td>
</tr>
<tr>
<td>LTA4 hydrolase</td>
<td>&gt;10000</td>
<td>8</td>
<td>200</td>
</tr>
<tr>
<td>LAP</td>
<td>100</td>
<td>30</td>
<td>4</td>
</tr>
</tbody>
</table>

**B.** Mechanism of action of CHR-2797. CHR-2797 inhibits aminopeptidase activity and, as a result, seems to deplete cellular amino acid pools selectively in tumor cells. The class of aminopeptidases inhibited by CHR-2797 plays a critical role in the final steps of protein recycling downstream of proteasomal degradation. Therefore, inhibition of aminopeptidases by CHR-2797 may, like proteasome inhibition (as with bortezomib here), disrupt the turnover of cell cycle intermediates in such a way that it affects cancer cell survival or proliferation.
by biopsy were offered to consent to baseline and on therapy biopsies.

**Results**

**General trial conduct.** Between October 2004 and February 2007, 40 patients received 107 cycles of CHR-2797 in 12 cohorts across nine dose levels. Patient demographics are detailed in Table 1 and study design in Table 2. Patients were treated in cohorts of one patient until the 40-mg cohort (second phase), which was expanded to three patients as the first patient developed reversible grade 2 ALT elevation. Overall, minimal toxicity was observed at the first five dose levels (10-90 mg; Table 3). The maximum tolerated dose was declared at 240 mg as two patients experienced dose-limiting toxicity at the 320-mg dose.

**Dose-limiting toxicities.** Dose-limiting toxicities were reported in two of four patients at 320 mg because of a combination of thrombocytopenia, dizziness, and visual abnormalities in one patient, and anemia, blurred vision, and vomiting in a second patient, leading to the patients being unable to complete 28 days of daily oral therapy. The first dose-limiting toxicity patient was a 74-year-old female with pseudomyxoma peritonei, who presented with grade 2 dizziness on day 10 of cycle 1. Hematology revealed a grade 2 drop in hemoglobin and platelets. She had also experienced grade 1 visual disturbance. The drug was stopped, and all symptoms and hematologic abnormalities recovered. Neurologic examination was normal throughout, and a magnetic resonance imaging (MRI) scan of the brain showed no abnormality. The second patient, a 69-year-old female with a solitary fibrous lung carcinoma with pleural metastases, had an episode of vasovagal syncope on day 5 of cycle 1. Hematology revealed a grade 3 drop in hemoglobin. The patient was transfused, study drug was discontinued, and her hemoglobin levels remained stable thereafter. This patient also complained of grade 2 hearing loss and difficulty focusing. An MRI scan of the brain was normal.

**Maximum tolerated dose.** Following these two dose-limiting toxicities at 320 mg, the maximum tolerated dose based on 28 days of dosing was determined to be 240 mg/d continuous dosing, and in accordance with the protocol, nine additional patients were treated at 240 mg for at least 28 days in the third phase of the study to further evaluate the antitumor activity and tolerability of the 240-mg dose of CHR-2797. In this expansion phase, one patient experienced grade 3 toxicity presenting with right upper quadrant abdominal pain and grade 3 ALT and AST elevations on cycle 1 day 7. This patient suffered from a congenital metabolic form of liver cirrhosis complicated by hepatocellular carcinoma and entered the study with a grade 1 elevation of liver transaminases. CHR-2797 was discontinued, and ALT/AST returned subsequently to within the reference range by cycle 1 day 28. Drug was restarted at this point with close monitoring of the LFTs; ALT and AST following this event never exceeded grade 1 derangement. This patient continued daily treatment on the same dose for another 11 months without interruption. CHR-2797 240 mg was chosen as the recommended dose for further studies.

**Overall safety and tolerability.** In general, CHR-2797 was well tolerated. Non–dose limiting toxicities that occurred in ≥15% of patients and all grade ≥3 adverse events that occurred in two or more patients at any time on study, regardless of relationship to drug, are listed in Table 3. The most common nonhematologic toxicities were fatigue, diarrhea, peripheral edema, nausea, dizziness, and constipation. Diarrhea and nausea were usually self-limiting and easily managed with anti-diarrheal/antiemetic agents as required. Grade 2 dizziness was a feature of one of the dose-limiting toxicities at 320 mg, which resolved on discontinuation of the study drug. A further 12 patients complained of grade 1 dizziness, which was self-limiting and did not necessitate study drug discontinuation. In addition to the patient on 240 mg CHR-2797 described earlier, two

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**Table 2. Dose escalation schedule and dose-limiting toxicities**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Dose</th>
<th>No. of patients</th>
<th>No. of DLTs (in first 28 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First phase</td>
<td>10 mg (for 7, 14, 21, 28 d)</td>
<td>1 each</td>
<td>0</td>
</tr>
<tr>
<td>Second phase</td>
<td>20 mg</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>40 mg</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>60 mg</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>90 mg</td>
<td>3</td>
<td>0</td>
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<tr>
<td></td>
<td>130 mg</td>
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<td>0</td>
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<tr>
<td></td>
<td>180 mg</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>240 mg</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>320 mg</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Third phase</td>
<td>240 mg</td>
<td>10*</td>
<td>1†</td>
</tr>
</tbody>
</table>

**Table 1. Patient characteristics [n = 40; median age, 60 (24-80) y]**

<table>
<thead>
<tr>
<th>Gender</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>27</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
</tr>
<tr>
<td>Eastern Cooperative Oncology Group performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>No. of previous chemotherapies, median (range)</td>
<td>2 (1-6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor types</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cell</td>
<td>11</td>
</tr>
<tr>
<td>Colorectal</td>
<td>6</td>
</tr>
<tr>
<td>Lung</td>
<td>5</td>
</tr>
<tr>
<td>Prostate</td>
<td>3</td>
</tr>
<tr>
<td>Breast</td>
<td>2</td>
</tr>
<tr>
<td>Adenocarcinoma (unknown primary)</td>
<td>1</td>
</tr>
<tr>
<td>Bladder/transitional cell carcinoma (paraganglioma)</td>
<td>2</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Liver/lower esophageal/melanoma/pancreas/ovarian/ pseudomyxoma/unknown</td>
<td>1 each</td>
</tr>
</tbody>
</table>

**Abbreviation: DLTs, dose-limiting toxicities.**

*Two patients reduced to 180 mg at 7 and 12 weeks due to toxicity (grade 3 diarrhea and grade 3 facial flushing, respectively).

†This patient was in the cohort expansion and therefore is not a true dose-limiting toxicity.
Further patients (on 40 and 240 mg) experienced a grade 2 and 3 elevation of transaminases, respectively, both in the first week of treatment. Dechallenge and rechallenge of study drug revealed a probable drug relationship in the patient with the grade 3 increase, but LFTs never exceeded grade 1 on rechallenge. There was no recurrence of transaminase derangement in the patient with grade 2 increase on drug rechallenge. Other liver indices were not seen to increase in the first 28 days.

Less commonly, hematologic toxicity was considered possibly related to study drug, with some patients experiencing anemia and thrombocytopenia. Anemia was predominantly grade 1 to 2, except for one patient who suffered grade 3 (a dose-limiting toxicity). There seemed to be a dose-dependent reduction in platelets, which was first observed between days 7 and 21. This rarely led to thrombocytopenia (five patients had grade 1-2 thrombocytopenia and one patient (discussed below) had grade 4).

One patient with advanced nonalveolar fibrosarcoma with extensive lung involvement, who had been treated with 90 mg CHR-2797 for >2 months without incident, developed thrombotic thrombocytopenic purpura/hemolytic uremic syndrome and died 3 weeks later. The underlying cause of the thrombotic thrombocytopenic purpura was never elucidated, and ADAMTS-13 testing to examine the functionality of the von Willebrand factor-cleaving protease was within normal limits. This event was ultimately felt unlikely to be related to study drug. However, for safety reasons, ongoing and new patients treated with CHR-2797 subsequent to this event underwent serial ADAMTS-13 testing before and throughout their time on study drug. No association between drug treatment and reduced ADAMTS-13 functionality was reported.

There did not seem to be any discernible influence of this agent on the metalloenzyme ADAMTS13, and blood films of patients were normal.

**Pharmacokinetics.** The pharmacokinetics of CHR-2797 and the active metabolite, CHR-79888, in plasma and packed blood cells were measured on days 1 and 28, and selected variables are shown in Fig. 2. For doses up to 240-mg exposure to CHR-2797 and CHR-79888 on day 1 increased in an approximately dose-proportional manner in plasma and packed blood cells. On day 28, exposure to CHR-2797 was dose proportional, as was CHR-79888 in plasma, but intracellular exposure to CHR-79888 was sub–dose proportional. Exposure to CHR-2797 and CHR-79888 was generally higher in the plasma than in the packed blood cells across the entire dose range on days 1 and 28, with the exception of CHR-79888 at doses 10 to 40 mg on day 28. Overall, exposure to CHR-79888 was higher than that for CHR-2797 on days 1 and 28 in plasma and packed blood cells. The pharmacokinetic results indicate that there is no accumulation of CHR-2797 in plasma or packed cells following repeat dosing for 28 days. Exposure to CHR-79888 in packed blood cells on day 28 is higher than on day 1, across the entire dose range, and in plasma samples up to 40 mg dose. The terminal elimination half-life for plasma CHR-2797 was relatively short, ~1 to 3.5 hours, whereas the half-life for CHR-79888 was considerably longer at ~6 to 11 hours (day 28 values). There was no correlation between AUC0–t/dose versus weight or body surface area (Fig. 2), which supported fixed drug dosing. In animal model studies in which significant inhibition of tumor growth was observed, the levels of CHR-79888 in tumors (250-750 ng/mL) 24 hours after the last dose of CHR-2797 were comparable with the steady state levels of CHR-79888 (250 ng/mL) in...
packed cells from patients dosed at ≥130 mg and to the intratumoral levels of CHR-79888 measured in resected metastatic skin lesions (500 ng/mL) of a renal cell carcinoma patient on 130 mg of CHR-2797, who achieved a partial response.

**Antitumor activity.** A patient with metastatic renal cell carcinoma achieved a confirmed partial response at 84 days, which was maintained for a further 112 days (Fig. 3A and B). Of the 16 patients with reported stable disease on day 28, seven met Response Evaluation Criteria in Solid Tumors criteria for stable disease 3 months later, with doses of CHR-2797 ranging from 40 to 240 mg. The four patients who continued to have stable disease for >6 months had the following tumor types: hepatocellular cancer (240 mg; 9 months), metastatic breast cancer (180 mg; 7.5 months), ovarian cancer (40 mg; 7 months), non–small cell lung carcinoma (90 mg; 6 months). The median duration on study for each patient is depicted in Fig. 3C.

**Discussion**

We describe here the results of a first-in-man phase I study of CHR-2797, an orally bioavailable aminopeptidase inhibitor with antiproliferative activity ~300 times more potent in vitro than the natural product aminopeptidase inhibitor, bestatin. Krige et al. (1) recently published an extensive preclinical investigation into the proposed mechanism of action of CHR-2797, showing marked antiproliferative activity of CHR-2797 against a wide range of tumor cell lines. We now show that CHR-2797
is safe and well tolerated up to an maximum tolerated dose of 240 mg, with preliminary evidence of antitumor activity in solid tumors. The results of this phase I study and preclinical data in leukemic cells have led to the exploration of CHR-2797 in a phase I/II study in patients with refractory/relapsed acute myeloid leukemia/myelodysplastic syndrome and multiple myeloma, wherein encouraging preliminary clinical activity has been reported (15, 16).

The principal aim of this study in solid tumor patients was to establish safety, maximum tolerated dose, and dose-limiting toxicity. Dose-limiting toxicities included a combination of thrombocytopenia, dizziness, and visual abnormalities in one patient, and anemia, blurred vision, and vomiting in a second patient, precluding continuation with study drug at the 320-mg dose. The maximum tolerated dose was therefore declared at 240 mg/d. The most common adverse events, largely grade 1 or 2, were fatigue, diarrhea, peripheral edema, nausea, dizziness, and constipation. Three patients had transient transaminases, which returned to normal on stopping the drug. On drug rechallenge, one patient had no recurrence, the other two patients’ transaminases did not increase above grade 1, and all three patients continued study drug.

Fig. 3. Preliminary antitumor activity and duration of CHR-2797 treatment. A patient with metastatic renal cell carcinoma showed a partial response by Response Evaluation Criteria in Solid Tumors after 84 d on study drug. This response was confirmed with a repeat computed tomography scan 4 wk later. The patient remained on study for 7 mo. A, a perigastric node at baseline circled in blue and following 5.5 mo on study drug (B). The duration of CHR-2797 treatment is indicated in (C) for each patient by an individual black column. Red arrow, 6-mo time point.
One patient experienced thrombotic thrombocytopenic purpura, and we investigated whether, as a metalloenzyme inhibitor, CHR-2797 might directly affect ADAMTS-13 function. Thrombotic thrombocytopenic purpura is associated with a severe deficiency of von Willebrand factor–cleaving protease (17–20), now known as ADAMTS-13 metalloprotease (21). ADAMTS-13 levels were within normal limits in this patient, and the incorporation of blood tests to check ADAMTS-13 functionality in all new and ongoing patients showed no drug-related effect of CHR-2797/CHR-79888 on ADAMTS-13 activity. In vitro work examining the direct effect of CHR-2797 and CHR-79888 on ADAMTS-13 activity also concluded that there did not seem to be a direct inhibitory effect of this agent on ADAMTS-13 function. No mechanistic basis for this case of thrombotic thrombocytopenic purpura could be established. There are many possible alternative causes of acquired thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, particularly in the presence of a disseminated malignancy. Overall, to date >122 patients have now been treated in multiple trials with CHR-2797, either alone or in combination with paclitaxel, with no further cases of thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (15, 16).

The pharmacokinetic profile confirmed that daily oral administration of CHR-2797 resulted in intracellular (packed blood cell) levels of CHR-79888 consistent with intratumoral levels at which anticancer activity was reported in preclinical models. Clinically meaningful antitumor activity was seen in a patient with renal cell carcinoma with a partial response (Fig. 3), who remained on study for 7 months. Four other patients had confirmed stable disease by Response Evaluation Criteria in Solid Tumors in excess of 6 months: hepatocellular carcinoma (9 months; 240 mg), breast cancer (7.5 months; 180 mg), ovarian cancer (7 months; 40 mg), and NSCLC (6 months; 90 mg).

Preclinical studies have shown CHR-2797 to have synergy with various anticancer drugs in inducing antiproliferative effects in vitro (1). A focus for future development of CHR-2797 will be to test the drug in combination with a range of conventional cytotoxics and specific molecular targeting agents, particularly antiangiogenics. A Phase I study on CHR-2797 with paclitaxel has recently closed accrual. In conclusion, CHR-2797 (tosedostat) has shown an acceptable safety profile for patients with advanced solid tumors at doses up to 240 mg/d. Evidence of antitumor activity was seen in patients with a range of tumor types and Phase II studies in elderly and/or treatment-refractory acute myelogenous leukemia patients have shown encouraging preliminary results.

Disclosure of Potential Conflicts of Interest

E. Bone, J. Carter, and L. Hoofman are employed by Chroma Therapeutics. J.S. De Bono has served as a consultant for Chroma Therapeutics. Chroma Therapeutics is a spin-off company from the Institute of Cancer Research. A. Reid, L. Vidal, J. Spicer, H. Shaw, and J.S. De Bono are employed by the Institute of Cancer Research. The Institute of Cancer Research has a commercial interest in Chroma Therapeutics.

Acknowledgments

The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research thank the NHS funding to the NIHR Biomedical Research Centre.

References

Correction: A First-in-Man Phase I and Pharmacokinetic Study on CHR-2797 (Tosedostat), an Inhibitor of M1 Aminopeptidases, in Patients with Advanced Solid Tumors

In this article (Clin Cancer Res 2009;15:4978–85), which was published in the August 1, 2009 issue of Clinical Cancer Research (1), the Acknowledgment section was incomplete. The correct statement is, as follows: The Royal Marsden NHS Foundation Trust, the Institute of Cancer Research, and the Oxford Radcliffe NHS Trust thank the NHS Biomedical Research Centre programme and Experimental Cancer Medicine Centre.

Reference
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