A phase I study of axitinib (AG-013736) in combination with bevacizumab plus chemotherapy or chemotherapy alone in patients with metastatic colorectal cancer and other solid tumors


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Background: Axitinib and bevacizumab are targeted therapies against the vascular endothelial growth factor pathway.

Methods: Patients with previously treated solid tumors received axitinib (starting dose 5 mg twice daily) combined with FOLFOX plus bevacizumab (1, 2, or 5 mg/kg, cohorts 1–3, respectively), FOLFIRI (cohort 4), or FOLFOX (cohort 5). Safety and pharmacokinetics were assessed.

Results: Thirty patients were enrolled (n = 16, 8, and 6 for cohorts 1–3, 4, and 5, respectively). Plasma concentrations and pharmacokinetic (PK) parameters were similar when drugs were administered alone and in various combinations. Most treatment-emergent adverse events (AEs) were mild to moderate and clinically manageable (most common: nausea, fatigue, diarrhea, anorexia, hypertension). Two of the four patients receiving axitinib with FOLFOX plus 5 mg/kg bevacizumab experienced dose-limiting toxicity (DLT) of inability to resume treatment for 14 days following treatment interruption (associated AE: hypertension); the maximum tolerated dose of bevacizumab in this combination was 2 mg/kg. No DLTs occurred with axitinib plus FOLFIRI or FOLFOX. Ten patients had RECIST-confirmed partial tumor responses (objective response rate: 33.3%).

Conclusion: Axitinib is well tolerated in combination with FOLFOX, FOLFIRI, or FOLFOX plus 2 mg/kg bevacizumab. PK interactions appear to be absent.

Key words: axitinib, bevacizumab, colorectal cancer, FOLFIRI, FOLFOX

Introduction

Chemotherapy is a mainstay of treatment of advanced colorectal cancer (CRC) and has been shown to prolong survival, control symptoms, and improve quality of life [1]. Molecularly targeted therapies play an important role in combination with chemotherapeutic regimens in treatment of metastatic colorectal cancer (mCRC) [2]. Agents targeting vascular endothelial growth factor (VEGF) pathway, a key regulator of tumor angiogenesis [3], hold promise for effective treatment of advanced CRC.

Axitinib (AG-013736; Pfizer, New York, NY) is an oral, potent, and selective inhibitor of VEGF receptors 1, 2, and 3 and has direct antiangiogenic effects [4]. It has been shown to possess a broad spectrum of activity against various tumors in phase II studies, including advanced thyroid cancer [5], advanced non-small-cell lung cancer [6], cytokine- and sorafenib-refractory metastatic renal cell carcinoma (mRCC) [7, 8], metastatic breast cancer in combination with docetaxel [9], and pancreatic cancer in combination with gemcitabine [10].

In patients with mCRC, the combination of bevacizumab (Avastin®; Genentech, San Francisco, CA), a recombinant humanized mAb that binds to VEGF, with 5-fluorouracil (5-FU)-based regimens has significantly improved survival compared with chemotherapy alone [11]. As bevacizumab targets the VEGF ligand and axitinib targets the VEGF receptor (and all its known isoforms), the current trial investigated axitinib in combination with chemotherapy and bevacizumab. In addition, preclinical studies have shown that axitinib can inhibit the growth of human CRC xenografts that are
unresponsive to bevacizumab [12], indicating a possible role for this combination in mCRC.

This open-label, randomized, three-arm, multicenter, phase II study with lead-in phase I portion was designed to evaluate the efficacy and safety and maximum tolerated dose (MTD) of axitinib plus FOLFIRI, axitinib plus FOLFOX and bevacizumab (at different dose levels), and axitinib plus FOLFIRI in patients with previously untreated advanced CRC and other solid tumors. Results from the randomized phase II portion of the study are pending; here, we report the phase I portion.

methods

patient population

Patients, aged ≥18 years, had locally advanced or metastatic solid tumors measurable by RECIST; Eastern Cooperative Oncology Group performance status of zero or one; and no evidence of preexisting uncontrolled hypertension. Patients who had previously received adjuvant chemotherapy (with radiation therapy) >12 months before enrollment were eligible, as were patients who had previously received no or one prior chemotherapy for ≤3 months. Patients were excluded if they had received prior antiangiogenic agents; radiation therapy, major surgery, or treatment with an investigational agent within 4 weeks before study entry; a history of significant bleeding episodes; active seizure disorder or brain/central nervous system metastases; or clinically significant gastrointestinal abnormalities. All patients gave written informed consent.

study treatment

Patients were sequentially assigned to one of the five treatment groups using a centralized registration system. All patients received a 5-mg twice daily (b.i.d.) starting dose of axitinib. This dose was chosen because it is considered to be clinically relevant [13], having demonstrated RECIST-defined tumor shrinkage, responses, and survival benefit in phase II trials in several tumor types [5–7]. Furthermore, 5 mg b.i.d. has demonstrated a mean area under the plasma concentration–time curve (AUC) that is well within the range of exposure necessary to achieve pharmacodynamic activity as determined by dynamic contrast-enhanced magnetic resonance imaging [14] and clinical exposures associated with VEGF receptor inhibition [4]. As such, patients received axitinib at a starting dose of 5 mg b.i.d. and cohort dose escalations and/or de-escalations were not planned. Provision was made, however, for prompt intrapatient dose adjustments (after cycle 2) in response to observed tolerability/toxicity, a strategy made possible by the relatively short half-life of axitinib (terminal plasma half-life between 2 and 5 h) [13, 14] and oral b.i.d. administration. Available doses of axitinib comprised 2, 3, 5 (starting dose), 7, and 10 mg b.i.d. As the toxic effects of axitinib do not largely overlap with those of the chemotherapeutic agents, the initial cohorts enrolled at full doses of both axitinib and FOLFOX or FOLFIRI [13, 15, 16]. There are, however, potentially overlapping toxic effects between axitinib and bevacizumab, notably hypertension and proteinuria [2, 13]. The initial triple-combination cohort therefore received bevacizumab at a dose of 1 mg/kg every 2 weeks, escalating to 5 mg/kg in subsequent cohorts. The rationale for the use of this starting dose of bevacizumab was that the lowest efficacious dose of bevacizumab has yet to be defined, and doses of rhuMAb VEGF as low as 0.3 mg/kg have been reported to bind all free VEGF in serum [17]. Treatment cohorts in the phase I portion of the study are presented in Table 1. For cohorts 1–3, bevacizumab and chemotherapy were given in 2-week cycles and axitinib 5 mg was administered orally b.i.d. with food, starting on day 3, cycle 1, and then continuously (before chemotherapy on day 1 of cycle 2 and subsequent cycles). Patients in cohorts 4 and 5 received FOLFIRI and FOLFOX, respectively, in 2-week cycles and continuous daily dosing with axitinib was started on day 3 of cycle 1.

The study was carried out in accordance with International Conference on Harmonization Good Clinical Practice guidelines with protocol approval by appropriate institutional review boards or independent ethics committees.

adverse events, dose-limiting toxic effects, MTD, and dose reductions

Adverse events (AEs) were graded according to the National Cancer Institute—Common Terminology Criteria for Adverse Events, version 3.0. Dose-limiting toxicity (DLT) during the first two cycles was defined as afebrile grade 4 neutropenia 28 days or grade 4 febrile neutropenia; grade 4 thrombocytopenia for 28 days; proteinuria of ≥2 g/24 h; inability to resume axitinib dosing within 14 days of stopping because of treatment-related toxicity; inability to resume bevacizumab or chemotherapy dosing within 14 days of scheduled administration because of treatment-related toxicity; or any grade 3 or more non-hematological toxicity for ≥14 days. The MTD was defined as the dose at which zero or one patient in any cohort experienced a DLT. Patients experiencing DLT had treatment suspended until toxicity returned to grade ≤1. Doses of axitinib and/or bevacizumab could be delayed or reduced for AEs including hypertension, proteinuria, hemoptysis, diarrhea, and stomatitis. Doses of chemotherapeutic agents could be adjusted for AEs including neutropenia, thrombocytopenia, skin toxicity, neurotoxicity, and gastrointestinal toxicity.

pharmacokinetic assessments and analyses

Blood sampling was carried out before dose and at intervals after dose on day 1/cycle 1 and day 1/cycle 2 for oxaliplatin or irinotecan, 5-FU, and bevacizumab where applicable and on day 8/cycle 1 and on day 1/cycle 2 for axitinib. Pharmacokinetic (PK) parameters for bevacizumab, irinotecan, oxaliplatin, 5-FU, and axitinib were estimated from plasma concentration–time data using standard noncompartmental methods. Due to the long half-life of bevacizumab (~21 days), cycle 2 concentrations were corrected (for contributions from the cycle 1 bevacizumab dose) by extrapolating cycle 1 concentrations from the last collection time point. All analyses were carried out using WinNonlin, Professional Version 4.1 (Pharsight Corp., Mountain View, CA).

results

patient characteristics

Enrolled patients (n = 30) are detailed in Table 1. Although in the interests of rapid patient recruitment patients with advanced solid tumors were eligible for study participation, the majority of the enrolled population had CRC.

treatment

Patients who discontinued the study (28 of 30; 93%) did so due to AEs related to study drug (6 of 30; 20%), disease progression (8 of 30; 27%), withdrawal of consent (9 of 30; 30%), investigator discretion (3 of 30; 10%), or death (2 of 30; 7%). Patients discontinued due to bradycardia, thrombocytopenia, palmar–plantar erythrodysesthesia syndrome, anorexia, uncontrolled hypertension, and uncontrolled diarrhea (all n = 1). Exposure to treatments and patient dose reductions are summarized in Table 2. In patients with axitinib dose reductions, doses ranged from 2 to 8 mg/day, and axitinib dose reductions due to hypertension (generally to 3 or 2 mg b.i.d.)
were more common in cohorts 1–3 than in cohorts 4 and 5 (12 of 16; 75% compared with 2 of 14; 14%). Most patients in cohorts 1–3 received at least four cycles of bevacizumab and at least four cycles of chemotherapy, and only one patient receiving bevacizumab had a dose reduction (in cohort 1; reduced from 1 to 0.8 mg/kg every 2 weeks).

safety and tolerability

All patients were assessable for toxicity. The majority of AEs were mild to moderate and clinically manageable; the most common treatment-emergent AEs were nausea, fatigue, diarrhea, anorexia, and hypertension (Table 3). Hypertension (any grade) was seen in 13 of 16 (81%) patients receiving axitinib combined with bevacizumab and 4 of 14 (27%) patients receiving axitinib without bevacizumab. Hematological AEs (Table 3) of grade 3/4 occurred in 12 patients overall (40%), including one patient (3%) with grade 4 neutropenia in cohort 1. There were no incidences of grade 5 toxicity.

dose-limiting toxic effects

As shown in Table 2, one patient in cohort 1 experienced a DLT of inability to resume bevacizumab dosing within 14 days of treatment interruption. The AE resulting in this DLT was hypertension. Bevacizumab (1 mg/kg) treatment was restarted at the lower dose of 0.8 mg/kg and the axitinib dose was reduced to 3 mg b.i.d. During the 14-day interval before DLT, the patient received lisinopril (9 days, 5 days at 10 mg then 4 days at 20 mg), lisinopril plus metoprolol (3 days, 40 mg lisinopril), and lisinopril plus metoprolol plus amlodipine (2 days, 40 mg lisinopril) to control blood pressure. There were no DLTs in cohort 2 (bevacizumab 2 mg/kg). Two of the four patients in cohort 3 (bevacizumab 5 mg/kg) experienced DLTs of inability to resume bevacizumab therapy within 14 days of treatment interruption. As for the patient in cohort 1, hypertension was the AE resulting in treatment interruption in the cohort 3 patients. During the 14-day interval before DLT, one of these patients was treated with olmesartan (13 days) and olmesartan plus hydrochlorothiazide (1 day). The second patient was treated with valsartan during the 14-day interval before DLT. Thus, the MTD for bevacizumab in combination with axitinib and FOLFOX was 2 mg/kg. There were no DLTs for axitinib with FOLFIRI or FOLFOX in cohorts 4 and 5.

efficacy

Objective responses were seen in all the treatment arms using RECIST criteria (Table 4). Ten of the 30 patients had partial responses (33.3%). The best overall responses in all cohort arms were an overall response rate of 33.3% (10 of 30). The median duration of response was 5.5 (95% CI: 2.1–15.1) months for the 10 responders. The median time to progression was 4.8 (95% CI: 3.2–7.5) months, and the median overall survival was 17.7 (95% CI: 12.5–25.8) months. The safety and tolerability profile of the combination of axitinib and bevacizumab were consistent with what is expected clinically, with a manageable safety profile and no unexpected toxic effects. The combination was well tolerated, and the MTD was determined.
and presence of axitinib (Figure 1C and Table 5). Mean (%CV) dose-normalized exposure [area under the plasma concentration–time curve from zero to time of the last quantifiable concentration (AUC_{last})] was 3482 (17) μg·h/ml and 4048 (23) μg·h/ml in the absence and presence of axitinib, respectively.

**Pharmacokinetics**

Plasma profiles and PK data for axitinib and the coadministered agents are shown in Figure 1 and summarized below. Generally, PK parameters (maximum plasma concentration, AUC, clearance, apparent volume of distribution of the drug during the elimination phase, and plasma terminal elimination half-life) for the coadministered agents were similar in the absence and presence of axitinib (Table 5). In addition, PK parameters for axitinib were similar in the absence and presence of the coadministered agents.

**Oxaliplatin.** Plasma profiles and PK parameters of platinum in plasma ultrafiltrate (PUF) for oxaliplatin (n = 21) were similar in the absence and presence of axitinib, regardless of the dose of bevacizumab (Figure 1A and Table 5). Mean [% coefficient of variation (%CV)] PUF exposure [area under the plasma concentration–time curve from zero to infinity (AUC_{inf})] was 5797 (54) ng·h/ml and 6287 (28) ng·h/ml in the absence and presence of axitinib, respectively.

**5-Fluorouracil.** Plasma profiles and PK parameters of 5-FU (in FOLFOX and FOLFIRI) (n = 19) were similar in the absence and presence of axitinib, regardless of the dose of bevacizumab (Figure 1B and Table 5). Mean (%CV) plasma exposure [area under the plasma concentration–time curve from 0 to 24 h (AUC_{0–24})] was 18 752 (29) ng·h/ml and 22 560 (31) ng·h/ml in the absence and presence of axitinib, respectively.

**Bevacizumab.** Plasma profiles and dose-normalized PK parameters of bevacizumab (n = 9) were similar in the absence and presence of axitinib (Figure 1C and Table 5). Mean (%CV) bevacizumab exposure [area under the plasma concentration–time curve from zero to infinity (AUC_{inf})] and plasma ultrafiltrate (PUF) for oxaliplatin (n = 1) were similar in the absence and presence of bevacizumab (Figure 1F and Table 5). Mean (%CV) irinotecan exposure (AUC_{inf}) was 3482 (17) μg·h/ml and 4048 (23) μg·h/ml in the absence and presence of axitinib, respectively.

**Discussion**

Our study found that axitinib appears to be well tolerated at a starting dose of 5 mg b.i.d. in combination with FOLFOX and bevacizumab 1 or 2 mg/kg. Dose reductions of axitinib due to hypertension, typically to 3 or 2 mg b.i.d., were common in patients receiving bevacizumab 5 mg/kg. The MTD of bevacizumab in combination with axitinib and chemotherapy
was 2 mg/kg, and toxic effects were manageable. The cohort receiving 5 mg/kg bevacizumab in combination with 5 mg b.i.d. axitinib (cohort 3) enrolled only four patients because two patients had hypertension that prevented reinitiation of study medication within 14 days of interruption, thereby formally incurring DLT. In our study, maximal antihypertensive therapy was defined on an individual patient basis, according to the judgment of the investigator, and could include up to four antihypertensive medications given for 2 weeks. It is notable that in cohort 3, one of the patients with hypertension-associated DLT subsequently achieved blood pressure control, resumed therapy, and achieved a partial response. Indeed, in this cohort, three of four patients achieved a partial response and two of four incurred the same DLT. It is also apparent that the patients with DLT-associated hypertension did not receive maximal antihypertensive therapy within the 2 weeks allowed before DLT was incurred. This indicates that the study definition of a DLT as the inability to resume therapy within

Table 3. Grade 1/2 treatment-emergent, non-hematological adverse events that occurred in ≥24 patients in any cohort or at grade 3/4 intensity in any patient and all hematological adverse events.

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Hematological

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<tr>
<td>Leukopenia</td>
<td>1 (17) 1 (17) 0 3 (50) 2 (33) 0 3 (100) 0 0 3 (43) 2 (29) 0 3 (75) 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>2 (33) 0 0 3 (60)b 0 0 1 (33) 0 0 3 (43) 1 (14) 0 0 1 (25) 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (17) 0 1 (17) 3 (50) 1 (17) 0 2 (67) 0 0 0 3 (43) 0 2 (50) 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (83) 0 0 5 (83) 0 0 1 (33) 0 0 2 (25) 0 0 2 (50) 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Grade 3/4, non-hematological adverse events reported in only one patient overall are listed above.

a No grade 5 events were reported.

b n = 5.

c n = 8.

Grade 3/4, non-hematological adverse events reported in only one patient overall—cohort 1: grade 3 bradycardia, device migration, hypoxia, and left ventricular dysfunction; grade 4 respiratory failure and sepsis; cohort 2: grade 3 pulmonary embolism; cohort 3: grade 3 diverticular perforation and intestinal abscess; cohort 4: grade 3 infection; cohort 5: grade 3 catheter site infection, cholangitis, gastrointestinal hemorrhage and hyperglycemia; grade 4 intestinal obstruction and wound dehiscence.
14 days of interruption resulted in potentially manageable hypertension being designated a DLT and may have limited the dose escalation of a potentially effective therapy.

We also investigated axitinib combined with FOLFOX or FOLFIRI as these regimens may potentially have clinical utility. Axitinib, given at a starting dose of 5 mg b.i.d., was well tolerated in combination with FOLFOX or FOLFIRI, with no DLTs observed.

The most common treatment-emergent AEs were nausea, fatigue, diarrhea, anorexia, and hypertension, a finding consistent with those of previous axitinib studies [5, 6, 8–10]. The most common grade 3 or more AE, neutropenia (seen in the absence and presence of bevacizumab), was consistent with the known side-effects of the chemotherapy regimens used.

Hypertension (any grade) was more common in patients receiving axitinib with bevacizumab (13 of 16; 81.3%), compared with those receiving axitinib without bevacizumab (4 of 14; 26.6%). As hypertension is an AE individually associated with both axitinib and bevacizumab and is normally manageable with medication [2, 13], this was an anticipated concern. Thus, in this study, antihypertensive medications could be started or increased to manage hypertension, including early introduction for grade 1/2 hypertension. Grade 3 hypertension was seen only in patients receiving both agents, and, as noted above, hypertension was the only DLT reported.

Table 4. Best response to treatment (by RECIST)

<table>
<thead>
<tr>
<th>Best response, n (%)</th>
<th>Cohort 1 (n = 6)</th>
<th>Cohort 2 (n = 6)</th>
<th>Cohort 3 (n = 4)</th>
<th>Cohort 4 (n = 8)</th>
<th>Cohort 5 (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>2 (33)</td>
<td>1 (17)</td>
<td>3 (75)</td>
<td>2 (25)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (67)</td>
<td>1 (17)</td>
<td>0</td>
<td>2 (25)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>0</td>
<td>1 (17)</td>
<td>0</td>
<td>1 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>0</td>
<td>3 (50)</td>
<td>1 (25)</td>
<td>3 (38)</td>
<td>3 (50)</td>
</tr>
</tbody>
</table>

Stable disease, less than a 50% reduction and less than a 25% increase in the sum of the products of two perpendicular diameters of all measured lesions and the appearance of no new lesions.

Figure 1. Plasma pharmacokinetics of oxalaplatin, 5-FU, bevacizumab, axitinib, irinotecan, and SN-38. (A) Oxalaplatin in the absence (n = 19) and presence (n = 19) of axitinib (pooled data from patients who received 0, 1, 2, or 5 mg/kg of bevacizumab). One patient excluded due to missing pharmacokinetic samples on cycle 2/day 1; two patients excluded due to dose reduction in cycle 2. (B) 5-FU (in FOLFOX or FOLFIRI) in the absence (n = 19) and presence (n = 19) of axitinib (pooled data from patients who received 0, 1, 2, or 5 mg/kg of bevacizumab). Data analysis excludes five patients due to missing cycle 2/day 1 pharmacokinetic samples, one patient due to nonestimable half-life and three patients due to collection discrepancies. (C) Bevacizumab (+FOLFOX) in the absence (n = 9) and presence (n = 9) of axitinib (pooled data from patients who received axitinib and bevacizumab). Three patients excluded due to nonestimable half-life and three patients due to collection discrepancies. (D) Bevacizumab (+FOLFOX) in the absence (n = 9) and presence (n = 9) of axitinib (pooled data from patients who received axitinib and bevacizumab). Three patients excluded due to nonestimable half-life in cycle 1. (D) Irinotecan in the absence (n = 7) and presence (n = 7) of axitinib. (E) SN-38 in the absence (n = 7) and presence (n = 7) of axitinib. (F) Axitinib in the absence (n = 18) and presence (n = 18) of FOLFOX (with or without bevacizumab) or FOLFIRI (pooled data from patients who received FOLFOX with or without bevacizumab, respectively, and patients who received FOLFIRI). Three patients excluded due to missing cycle 2 day 1 pharmacokinetic samples. 5-FU, 5-fluourouracil; PUF, plasma ultrafiltrate; C, cycle; D, day.
in these patients. This indicates that hypertension should be managed aggressively in patients more than one agent targeting the VEGF receptor. In the absence of bevacizumab, axitinib plus FOLFOX led to hypertension-associated dose reductions in only a minority of patients (one patient each in cohorts 4 and 5), indicating that both of these combination regimens are feasible in trials designed to optimize patient outcome.

In our study, bevacizumab 2 mg/day when given with axitinib 5 mg b.i.d. was well tolerated, leading to no reductions in axitinib doses for hypertension in four of six patients in cohort 2. This dose of bevacizumab is lower than the 5 or 10 mg/kg dose recommended for use in patients with mCRC [18]. However, lower doses of bevacizumab may be active as a study of axitinib monotherapy in which there were indications for bevacizumab, oxaliplatin, and 5-FU. Axitinib is primarily metabolized via oxidation by the cytochrome P450 3A4 and to a lesser extent via glucuronidation by uridine diphosphate-glucuronosyltransferase 1A1 (UGT 1A1), while bevacizumab is eliminated via the reticuloendothelial system and other mechanisms [24]. Oxlupatin undergoes nonenzymatic biotransformation and is cleared through the kidneys [25], while 5-FU rapidly undergoes reductive catabolism via dihydropyrimidinidehydrogenase [26]. Our results are consistent with previous reports, and our analysis indicates that there is no PK interaction between axitinib and irinotecan, despite the UGT 1A1 route of metabolism that they are known to share [27, 28]. Observed plasma concentrations of axitinib in combination with either FOLFOX or FOLFIRI or FOLFOX plus bevacizumab were consistent with those reported in a phase I study of axitinib monotherapy in which there were indications of antitumor activity [13] and were above the threshold associated with pharmacodynamic modulation of tumor vasculature [4, 14].

In summary, axitinib is well tolerated at a starting dose of 5 mg b.i.d. in combination with bevacizumab 2 mg/kg every 2 weeks and FOLFOX; pharmacokinetics appeared to be similar.

### Table 5. Plasma PK parameters [mean estimates with coefficient of variation (%)] of oxaliplatin (pooled from cohorts 1–3 and 5)\(^a\), bevacizumab (pooled from cohorts 1–3)\(^b\), irinotecan/SN-38 (cohort 4), and axitinib (pooled from all cohorts)\(^c\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>C(_{\text{max}}) (ng/ml)</th>
<th>AUC(_{\text{inf}}) (ng h/ml)</th>
<th>CL (l/h)</th>
<th>Vz (l)</th>
<th>t(_{1/2}) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin (in FOLFOX) alone, (n = 21)(^d)</td>
<td>278 (89)</td>
<td>5797 (54)</td>
<td>27.6 (34)</td>
<td>696 (26)</td>
<td>18 (25)</td>
</tr>
<tr>
<td>Oxaliplatin (in FOLFOX) + axitinib, (n = 21)(^d)</td>
<td>331 (153)</td>
<td>6287 (28)</td>
<td>25.8 (33)</td>
<td>693 (33)</td>
<td>19 (18)</td>
</tr>
<tr>
<td>5-FU (in FOLFOX or FOLFIRI) alone, (n = 19)(^e)</td>
<td>28 758 (59)</td>
<td>18 752 (29)</td>
<td>176 (58)</td>
<td>103 (82)</td>
<td>0.41 (52)</td>
</tr>
<tr>
<td>5-FU (in FOLFOX or FOLFIRI) + axitinib, (n = 19)(^e)</td>
<td>31 654 (65)</td>
<td>22 560 (31)</td>
<td>164 (53)</td>
<td>107 (80)</td>
<td>0.45 (49)</td>
</tr>
<tr>
<td>Bevacizumab (+FOLFOX) alone, (n = 9)(^f)</td>
<td>20.7 (47)</td>
<td>3482 (17)</td>
<td>13.0 (44)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bevacizumab (+FOLFOX) + axitinib, (n = 9)(^g)</td>
<td>24.2 (62)</td>
<td>4048 (23)</td>
<td>12.0 (69)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Irinotecan (in FOLFIRI) alone, (n = 7)</td>
<td>1971 (12)</td>
<td>15 019 (39)</td>
<td>26.0 (37)</td>
<td>229 (30)</td>
<td>6.0 (21)</td>
</tr>
<tr>
<td>Irinotecan (in FOLFIRI) + axitinib, (n = 7)</td>
<td>1800 (29)</td>
<td>12 351 (32)</td>
<td>30.0 (53)</td>
<td>249 (36)</td>
<td>7.0 (19)</td>
</tr>
<tr>
<td>SN-38 metabolite of irinotecan (in FOLFIRI) alone, (n = 7)</td>
<td>26.0 (34)</td>
<td>399 (49)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>SN-38 metabolite of irinotecan (in FOLFIRI) + axitinib, (n = 7)</td>
<td>23.0 (81)</td>
<td>315 (50)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Axitinib alone, (n = 18)(^h)</td>
<td>42.0 (78)</td>
<td>398 (75)</td>
<td>67.8 (42)</td>
<td>252 (187)</td>
<td>3.5 (88)</td>
</tr>
<tr>
<td>Axitinib + bevacizumab/FOLFOX or FOLFIRI, (n = 18)(^h)</td>
<td>33.9 (68)</td>
<td>336 (54)</td>
<td>68.3 (158)</td>
<td>368 (198)</td>
<td>5.0 (141)</td>
</tr>
</tbody>
</table>

\(^a\)Patients received 5-mg dose of axitinib and 0, 1, 2, or 5 mg/kg doses of bevacizumab.
\(^b\)Data are dose normalized to the 1 mg/kg bevacizumab dose.
\(^c\)Data excludes one patient due to missing PK samples on day 1/cycle 2.
\(^d\)Data excludes eight patients due to missing samples or collection discrepancies.
\(^e\)C\(_{\text{max}}\) given in ng/ml and AUC\(_{\text{inf}}\) in ng h/ml.
\(^f\)Accumulation was accounted for by correcting cycle 2 concentrations by extrapolating cycle 1 concentrations from the last collection time point.
\(^g\)Data excludes eight patients due to missing samples.
\(^h\)PK, pharmacokinetic; 5-FU, 5-fluorouracil; C\(_{\text{max}}\), maximal plasma concentration; AUC\(_{\text{inf}}\), area under the plasma concentration–time curve from zero to infinity; AUC\(_{0–24}\), area under the plasma concentration–time curve from 0 to 24 h; CL, clearance; Vz, apparent volume of distribution of the drug during the elimination phase; t\(_{1/2}\), plasma terminal elimination half-life; NA, not available.
when administered in combination and the combinations showed evidence of clinical activity. The MTD of bevacizumab was 2 mg/kg in combination with axitinib, and inability to resume therapy for 14 days following interruption due to hypertension was the DLT. Trials using 5 mg b.i.d. axitinib with or without bevacizumab 2 mg/kg combined with FOLFIRI are feasible, as are trials using 5 mg b.i.d. axitinib plus FOLFOX. The ongoing, three-arm, phase II part of this trial will further explore the safety and efficacy of 5 mg b.i.d. axitinib plus FOLFIRI (arm 3), 5 mg/kg bevacizumab plus FOLFOX (arm 2), and 5 mg b.i.d. axitinib plus 2 mg/kg bevacizumab plus FOLFOX (arm 3) in 123 patients with locally advanced or metastatic CRC (ClinicalTrials.gov; NCT00460603; A0061020).

**funding**

Pfizer Inc. to S.S. and R.L.R.; Genentech to R.L.R.

**acknowledgements**

Editorial assistance was provided by ACUMED (Tytherington, UK), supported by funding from Pfizer Inc.

**disclosure**

SS has received honoraria from Pfizer. JT, SK, MT, and YC are all employees of Pfizer and own stock in Pfizer. VA, REB, JJ, and RCT have nothing to disclose.

**references**