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A multi-histology trial of fostamatinib in patients with advanced colorectal, non-small cell lung, head and neck, thyroid, and renal cell carcinomas, and pheochromocytomas

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Abstract

Purpose—A multi-cohort phase II study of fostamatinib, an oral multi-kinase inhibitor, was conducted to determine the response rate in patients with advanced colorectal (CRC), thyroid, non-small-cell lung, head and neck, and renal cell carcinomas, and pheochromocytomas.

Methods—Patients received 200 mg fostamatinib BID in 4-week cycles with response assessed every 2 cycles. Blood was collected for pharmacokinetic analysis and measurements of circulating tumor cells (CTCs) and circulating endothelial (progenitor) cells (CE(P)Cs).

Results—A total of 37 patients (22 CRC), median of 4 prior therapies, were enrolled. Due to toxicities in four of the first five patients, the study was amended to incorporate a dose escalation phase for each histology. The maximum-tolerated dose (MTD) was established at 50 mg BID in CRC but was not established for the other cancers. Common grade 3/4 toxicities included transaminitis, hyperbilirubinemia, and hypertension. Pharmacokinetic profile was similar to previous reports. Seventy-three percent of CRC patients had liver involvement and 91% had prior anti-angiogenic therapy. Patients with abnormal liver tests at baseline were more likely to experience grade 2 hepatotoxicity than those with normal tests (44% versus 0%). No responses were observed; disease stabilization rate was 27% in CRC. Reduction in CECs following treatment was associated with a better disease stabilization rate (75% versus 0%) in CRC.

Conclusion—Fostamatinib had limited anti-tumor activity in this first clinical trial in patients with advanced refractory solid tumors; reduction in CECs and CEPs was indicative of anti-angiogenic effects. Abnormal liver testing at baseline appeared to influence drug tolerability.

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Conflict of interest statement

None declared.

Keywords

Fostamatinib; R406; R935788; solid tumors; angiogenesis

Introduction

Protein kinases are integral components of signal transduction pathways that drive and sustain neoplastic transformation. Their activity in malignant cells is often deregulated, allowing tumors to evade apoptotic signals and proliferate. Fostamatinib (R935788; NSC 745942) is a potent, oral prodrug that is rapidly and extensively converted to the active moiety R406 by alkaline phosphatases in the intestinal mucosa [1]. R406 (NSC 742317) is a kinase inhibitor with relative selectivity for spleen tyrosine kinase (Syk) but also inhibits other kinases of particular interest as therapeutic targets in oncology including Flt3, aurora A kinase, and RET [2, 3]. Fostamatinib and R406 have also been shown to decrease vascular endothelial growth factor (VEGF) expression and angiogenesis [4, 5]. R406 showed selective sensitivity in the National Cancer Institute (NCI) 60-cell line screen, with highest sensitivity against the renal carcinoma cell lines with EC₅₀ equivalent to 0.15 μ M, and reduced tumor burden in renal tumor xenografts at doses not associated with appreciable toxicities [6]. R406 also showed activity against some colon and non-small cell lung cancer (NSCLC) lines [6].

Fostamatinib has been studied for the treatment of patients with rheumatoid arthritis (RA), immune thrombocytopenia purpura (ITP), non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) as a Syk kinase inhibitor [7–10]. Syk is an important component of the B-cell receptor signaling pathway, and early results suggest that treatment with fostamatinib results in immunomodulation [2]. Fostamatinib was generally well tolerated and commonly reported adverse events in clinical trials in lymphomas and non-cancer related diseases included diarrhea, neutropenia, hypertension, and transient elevations in liver transaminases [7–10]. The recommended phase II dose of fostamatinib was established at 200 mg PO twice a day (BID), which was the dose selected for our study [7]. This dose had been shown to yield *in vivo* levels that exceed the micromolar levels necessary to produce kinase inhibition *in vitro* [7].

Based on the observed inhibition of multiple kinases known to be important in carcinogenesis, growth inhibitory effects on multiple cell lines in the NCI-60 panel, as well as significant tumor regression in xenograft models of renal cell carcinoma, a multi-histology phase II study of fostamatinib administered BID on a continuous basis was conducted to assess the objective response rate (RR); determine pharmacokinetics (PK); and to assess the effect of fostamatinib on circulating tumor cells (CTCs), circulating endothelial cells (CECs), and circulating endothelial progenitor cells (CEPs). The tumor types for evaluation were selected based on the preclinical data and known literature regarding the importance of the various target kinases in the tumors.

Patients and methods

Eligibility criteria

Patients 18 years of age with histologically confirmed pheochromocytoma; follicular, medullary, or papillary thyroid; colorectal (CRC); non-small-cell lung (excluding squamous cell histology); head and neck (HNC); or renal cell carcinomas (RCC) that were refractory to standard treatments were eligible. Patients with follicular or papillary thyroid cancer were eligible if they had disease which was refractory to I¹³¹ therapy. Other inclusion criteria included: measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST 1.0) [11]; Eastern Cooperative Oncology Group (ECOG) performance status 2; life expectancy 3 months; adequate marrow, hepatic and renal function defined as absolute neutrophil count $1.5 \times 10^9/L$, platelets $100 \times 10^9/L$, total bilirubin $1.5 \times$ upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $2.5 \times$ ULN and creatinine $< 1.5 \times$ ULN or a creatinine clearance $60 \text{ mL/min/1.73 m}^2$ for patients with creatinine levels $1.5 \times$ ULN. Patients with diagnosis of hypertension were required to have adequate blood pressure control prior to enrollment, defined as blood pressure $< 150/90 \text{ mmHg}$.

There were no limits on prior treatments, including prior anti-angiogenic therapy. Prior anticancer therapy must have been completed at least 4 weeks before enrollment. Patients were excluded if they had a second malignancy other than basal or squamous cell skin cancer; uncontrolled intercurrent illness; were pregnant or nursing; had brain metastases within the past 3 months; or were taking medications known to induce or inhibit CYP3A4. Written informed consent was obtained from all patients. This trial was conducted under a NCI-sponsored IND with institutional review board approval. The protocol design and conduct followed all applicable regulations, guidances, and local policies (ClinicalTrials.gov identifier: NCT00923481).

Trial design

Fostamatinib was supplied by the Division of Cancer Treatment and Diagnosis, NCI, under a Collaborative Research and Development Agreement with Rigel Pharmaceuticals, Inc. All patients received fostamatinib orally at 200 mg every 12 hours (BID) on a continuous schedule without regard to meals, in 28-day cycles. Tablets could be dissolved in water or orange juice for patients with G-tubes. Due to toxicities (liver function test abnormalities and hypertension) observed in the first cycle of treatment in four of the first five patients treated that necessitated a dose reduction, the study was amended to lower the starting dose level for all cohorts and incorporate a brief dose escalation phase (Table 1). The 4 patients with significant toxicities had known liver metastases (no evidence of disease progression at the time of observed toxicities) and history of prior anti-angiogenic therapy. Patients likely to have received prior anti-angiogenic therapy as standard of care for their diseases (CRC, NSCLC, RCC) as well as patients with pheochromocytomas (risk of hypertension) were started at the lower dose of 100 mg BID; while patients with HNC and thyroid cancers received 150 mg as the starting dose. One of the possibilities for the observed toxicities in this study compared with prior trials was a difference in PK caused by liver involvement by the cancer. Thus, PK analyses were included in the phase 1 dose escalation part of the study

in a subset of patients from each of the study cohorts to gather data on the relationship between drug exposure and adverse events. The phase 1 part of the study followed the traditional 3+3 design, with the intent to expand at the maximum tolerated dose (MTD).

Adverse events were graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Dose-limiting toxicity (DLT) was defined as an adverse event, that occurred in the first cycle and was felt to be related to the study drug, and fulfilled one of the following criteria: grade 3 non-hematologic toxicity (except for nausea/vomiting and diarrhea without maximal symptomatic/prophylactic treatment and grade 3 electrolyte toxicities corrected within 24–48 hours); grade 4 thrombocytopenia; grade 4 neutropenia; or grade 3 febrile neutropenia. A maximum of 2 dose reductions were permitted before a patient was taken off study.

Safety and efficacy evaluations

Baseline evaluations included history and physical exam, complete blood counts with differential, serum chemistry panel, serum TSH and T4, urinalysis, electrocardiogram, and pregnancy test for women of childbearing potential. Safety assessments included monitoring of adverse events, vital signs, and hematology and blood chemistry profiles throughout the study. Computed tomography scan of chest, abdomen, and pelvis was performed at baseline and every 2 cycles to assess for tumor response according to RECIST 1.0 guidelines [11].

Pharmacokinetics

Whole blood was collected into K₂-EDTA tubes for PK analyses pre-dose and at 1 and 2 hours post dose on days 1 and 7 of cycle 1 and day 1 of cycle 2. Because fostamatinib is a prodrug and very low levels of the parent compound were observed in prior studies, PK parameters were assessed for R406 (the fostamatinib metabolite) using a validated LC/MS/MS assay.

Pharmacodynamics

For the analysis of CECs and CEPs, peripheral blood was drawn into 4 CPT citrate tubes (7.5 mL each) (BD Biosciences, Franklin Lakes, NJ) at baseline and on day 28 of cycle 2. Peripheral blood mononuclear cells (PBMCs) were isolated as previously described [12]; a minimum of 1×10^5 cells were acquired for each analysis. Identification and analysis of CECs and CEPs was performed using a MACSQuant flow cytometer (Miltenyi Biotec, Cologne, Germany) and FlowJo software (Tree Star, Ashland, OR) as previously described [12]. CECs were defined as negative for the hematopoietic marker CD45, positive for the endothelial markers CD31 and CD146, and negative for the progenitor marker CD133. CEPs were defined as the CD45-/CD31+/CD146-/CD133+ population. Viability was defined by the absence of 7-aminoactinomycin D (7-AAD) staining, and analysis was restricted to nucleated cells by gating on Hoechst 33342-positive cells.

For the analysis of CTCs, whole blood (7.5 mL) was collected in a CellSave Preservative Tube (Veridex LLC, Raritan, NJ) from patients at baseline, on cycle 1 week 3, at the beginning of cycle 2, and at the first restaging (8 weeks). The sample was processed on the CellTracks AutoPrep system (Veridex LLC) using the CellSearch CTC Epithelial kit

(Veridex LLC) per the manufacture's protocol, and analyzed by the CellTracks Analyzer II (Veridex LLC).

Statistical Methods

The primary end point for the phase II part of the study was the objective response rate. A two-stage design, either an optimal (NSCLC and CRC) or minimax design (head and neck cancer, pheochromocytoma, thyroid cancer, and RCC) was used to determine the sample size of each of the 6 cohorts in the phase II part of the study [13]. For cohorts of NSCLC and CRC, to rule out a 5% RR ($P_0 = 0.05$) and target a 20% RR ($P_1 = 0.2$) with error probabilities of $\alpha = 0.05$ and $\beta = 0.1$, the first stage in each cohort required that at least 2 of 21 patients have a response before proceeding to the second stage with an additional 20 patients. If objective response was observed in 5 or more of the total of 41 patients, then further evaluation would be warranted. For cohorts of pheochromocytoma, RCC, HNC, and thyroid cancer, assuming $P_0 = 0.05$ and $P_1 = 0.25$ with $\alpha = 0.05$ and $\beta = 0.1$, the first stage required at least 1 of 15 patients to have an objective response before proceeding to the second stage of an additional 10 patients. If 4 or more of the 25 patients were to have a response, further evaluation would be warranted.

Time to progression (TTP) was defined as the time from treatment initiation to the date of disease progression, and analyzed by the Kaplan–Meier method including 95% confidence intervals (CIs). Descriptive statistics were used to summarize patient characteristics, treatment administration, PK parameters, safety, and efficacy. We assessed associations between two categorical variables using Fisher's exact test. Numbers of CTCs were compared using the Wilcoxon rank sum test. *P*-values are two-sided and presented without adjustment for multiple comparisons; for descriptive purposes, $P < 0.05$ will be noted to be statistically significant.

Results

Patient Characteristics

A total of 37 patients (22 with CRC and 15 with varying other eligible histologies) were enrolled between May 2009 and January 2011. Their characteristics at baseline are detailed in Table 2. All patients had evidence of disease progression with prior standard therapy or did not have acceptable standard therapy options. The majority of patients in the CRC cohort were heavily pretreated, having received a median of 4 prior lines of systemic therapy for metastatic disease. Anti-VEGF therapy including bevacizumab, sorafenib, sunitinib, and vandetanib had been previously administered in 91% of CRC patients and 47% of other cancer patients.

Adverse Events

Four grade 3 toxicities were observed in the first five CRC patients enrolled, each dosed at 200 mg PO BID. One patient with liver metastases developed grade 3 alkaline phosphatase (ALP), AST, and bilirubin elevation, with no evidence of biliary dilatation or disease progression on imaging. Another patient also had a grade 3 ALP increase, holding study drug led to resolution of toxicity to grade 1, but recurred upon resuming drug despite two

dose reductions. Two patients developed grade 3 hypertension requiring dose reductions. Due to the unexpected frequency of grade 3 toxicities noted in these patients, the study was amended to incorporate a brief dose escalation phase and to lower the starting dose level for all cohorts. Thus, the subsequent seven patients with CRC initiated treatment at 100 mg PO BID. Among six evaluable patients, two experienced grade 3 adverse events in the first cycle of treatment. One developed bilateral upper extremity deep vein thrombosis (DVT), and the other a grade 3 elevation in bilirubin, which was felt to be related to study drug despite presence of liver metastases. Therefore, the starting dose was further reduced to 50 mg PO BID for the CRC cohort. Ten more patients with CRC were enrolled, and among the eight evaluable patients, one patient with liver metastases experienced a grade 3 elevation in ALP, AST, and ALT. Therefore, the MTD for the CRC cohort was established as 50 mg PO BID.

One of two patients enrolled in the HNC cohort, at 150 mg PO BID, experienced grade 3 hypertension in the first cycle of treatment. No further patients were accrued to this cohort and the MTD was not established. Four patients were enrolled in the NSCLC cohort, at 100 mg PO BID, one of whom experienced grade 3 DVT in the first cycle of treatment; however, as no further patients were enrolled in this cohort, the MTD was not established. Five patients with thyroid cancer were enrolled. The first three at 150 mg PO BID had no significant adverse events, thus permitting dose escalation to 200 mg PO BID for the subsequent two patients. The latter two also tolerated treatment without significant adverse events; however, no further patients were accrued to this cohort and the MTD was not established. Two patients each were enrolled in the pheochromocytoma and RCC cohorts at 100 mg PO BID with no significant adverse events; the MTD was not established.

Table 3 summarizes drug-related adverse events noted during all treatment cycles. All 37 treated patients were assessable for safety. Throughout all dose levels, the most commonly reported adverse events were lymphopenia (51%), AST elevation (43%), ALT elevation (41%), leukopenia (35%), anemia (32%), hypertension (27%), hyperbilirubinemia (24%), and fatigue (22%). The most frequent grade 3 or 4 adverse events were hypertension (8%), ALP increase (8%), hyperbilirubinemia (8%), AST increase (5%), lymphopenia (5%), and thromboembolism (5%). More grade 3 or 4 adverse events were observed at higher doses for all patients taken together, even though tolerability was different across histologies (50 mg dose cohort [10%], 100 mg dose cohort [13%], 150 mg dose cohort [60%], and 200 mg dose cohort [57%]). Of note, patients with baseline elevation of hepatic function tests (ALP, AST, ALT, or bilirubin) experienced significantly higher incidences of grade 2 or more hepatic toxicity (44%; 11/25) than those with normal hepatic function tests at baseline (0%; 0/12; Fisher's exact test, $P = 0.007$). There was no association between prior exposure to anti-angiogenic therapy and adverse events (data not shown).

Treatment Administration

In each dose cohort, median duration of treatment was 2 cycles (range, 1–4 for 50 mg dose cohort, 1–6 for 100 mg dose cohort, 2–4 for 150 mg dose cohort, and 1–6 for 200 mg dose cohort). The dose of fostamatinib was skipped more than 3 times per cycle in five patients (71%) in 200 mg dose cohort, 2 patients (40%) in 150 mg dose cohort, 9 patients (60%) in

100 mg dose cohort, and 4 patients (40%) in 50 mg dose cohort. Reasons for study treatment discontinuation were disease progression (73%), consent withdrawal (11%), adverse events (8%), and intercurrent illness (8%).

Efficacy

No RECIST-defined objective tumor responses were observed. Of the 15 patients with CRC who were evaluable for efficacy, four (27%) had stable disease which lasted more than 12 weeks for three of the patients; one patient received 200 mg for 6 cycles prior to being taken off treatment for disease progression. With a median follow-up of 2.8 months (range, 1.4–6.8 months), the median TTP was 1.9 months (95% CI, 1.8–2.0 months). There were no differences in efficacy between patients who had received prior anti-angiogenic therapy and those who had not; the disease stabilization rate was 23% (3/13) versus 50% (1/2; Fisher's exact test, $P = 0.48$) and median TTP was 1.9 versus 1.8 months (log-rank test, $P = 0.95$).

Among other histologies, two of four evaluable thyroid cancer patients (50%) had stable disease persisting longer than 12 weeks, on 150 mg BID and 200 mg BID, respectively. One of two evaluable HNC patients treated on 150 mg BID, and one patient each with pheochromocytoma and RCC treated on 100 mg BID, had stable disease lasting longer than 12 weeks.

Pharmacokinetics

For the 24 patients in this study who had measurements of plasma concentration at steady-state for doses of 50–200 mg BID, the average C_{max} normalized to a dose of 100 mg BID was 750 ng/mL. This value is similar to the reported value of 762 ng/mL for 12 patients with rheumatoid arthritis receiving 100 mg BID [14]. For patients with lymphoma and chronic lymphocytic leukemia who received 200 mg BID, Friedberg et al. reported a C_{max} of 668 ng/mL for the first dose, with a doubling of concentrations at steady-state [7]. Thus, with correction for the higher dose, steady-state values for this study and the two prior reports are similar.

For the eight patients with CRC and with measurements of fostamatinib at the MTD of 50 mg, the average steady-state C_{max} was 353 ng/mL, supporting the conclusion that increased sensitivity in this subpopulation of patients was not due to higher plasma exposure.

Pharmacodynamics

A total of 16 patients from the various disease cohorts had specimens collected for CECs and CEPs at baseline and at the completion of cycle 2; among them, 15 patients were also evaluable for tumor response. The median change in CECs and CEPs on cycle 2, day 28 compared with baseline was a decrease of 8.6% and 8.9%, respectively (Figures 1A and B). In CRC patients only (nine patients), a decrease of CECs or CEPs was associated with a higher disease stabilization rate (CECs: 75% [3/4] versus 0% [0/5], $P = 0.048$; CEPs: 60% [3/5] versus 0% [0/4], $P = 0.17$) and longer TTP (CECs: median, 3.1 versus 1.9 months, $P = 0.024$; CEPs: median, 2.4 versus 1.9 months, $P = 0.15$; Figure 2A, 2B). Baseline values or changes in the number of CECs and CEPs following administration of fostamatinib did not differ based on previous exposure to anti-angiogenic therapy including bevacizumab,

sorafenib, sunitinib, or vandetanib (data not shown). A decrease in the number of CTCs comparing pre- and post-treatment (cycle 1, day 15) CTC values was associated with a trend to a higher disease stabilization rate (46% [6/13] versus 10% [1/10]; Fisher's exact test, $P = 0.089$; Figure 1C).

Nineteen patients with CRC had paired CTC samples (baseline and cycle 1, day 15), 14 of whom were evaluable for TTP; though not statistically significant, a decrease or no change in CTCs after treatment showed a trend for better TTP (Figure 2C). CTC baseline levels did not predict response to treatment or TTP, although patients with disease stabilization had lower median CTC numbers than those with progressive disease (2 versus 4; Wilcoxon rank sum test, $P = 0.35$).

When counts for CECs/CEPs and CTCs were combined, patients who had decreased values in both CTCs and either CECs or CEPs had a better disease stabilization rate than the others (78% [7/9] versus 0% [0/5]; Fisher's exact test, $P = 0.021$).

Discussion

Fostamatinib has demonstrated clinical benefit in autoimmune disorders such as RA and ITP and B-cell lymphoid malignancies such as NHL and CLL, based presumably on its activity as a Syk inhibitor and its effects on the immune system [7, 8, 10, 15, 16]. Fostamatinib inhibits a number of other kinases, including Flt3, JAK, c-Kit, Lck, and RET, and has demonstrated anti-tumor activity in cancer cell lines and xenograft models [2, 3, 6]. This trial was the first clinical study of fostamatinib in patients with solid tumors. This study was designed to characterize the anti-tumor activity of this novel compound in six parallel patient cohorts: CRC, thyroid cancer, HNC, NSCLC, RCC, and pheochromocytoma.

The initial starting dose of 200 mg BID was the recommended phase II dose from a previous phase I/II study of fostamatinib in patients with NHL/CLL in which neutropenia, thrombocytopenia, and diarrhea were the toxicities [7]; however, 200 mg BID resulted in an unexpectedly high incidence of grade 3 toxicities such as transaminitis and hypertension in four of the first five CRC patients treated on our study. Despite dose reductions in the CRC cohort, fostamatinib was poorly tolerated and the MTD was established at 50 mg BID. This contrasted with the other cohorts in this study in which higher doses of 150 mg and 200 mg were tolerated, even though a true MTD was not established.

The differential tolerance of fostamatinib in patients with the different malignancies may be due to 1) a difference in PK between patients with advanced solid tumors, especially those with liver involvement, as compared to patients with lymphoma and non-neoplastic diseases; 2) increased liver toxicity in patients with liver involvement; 3) prior anti-angiogenic therapy predisposing to increased rates of hypertension. PK sampling had not been prospectively planned as the study drug was already in phase II testing with the PK profile established in humans [7]; however, given the toxicity considerations, PK analysis was performed and no significant differences were observed compared to PK data from prior clinical trials [7]. Presence of metastatic liver involvement may have predisposed to developing hepatic toxicities. Prior anti-angiogenic therapy did not appear to increase the

risk of developing hypertension or other toxicities in this study; however, 91% of patients with CRC on this trial had received prior VEGF/R directed therapy, thus a conclusion could not be drawn regarding the influence of prior anti-angiogenic therapy on the development of toxicities.

A reduction in CECs and CEPs in patients who had disease stabilization following administration of fostamatinib was observed. Growing evidence suggests that CECs and/or bone marrow-derived CEPs play an important role in tumor biology and angiogenesis, and anti-angiogenic drugs suppress the mobilization and levels of CEPs [17–20]. Although there is still controversy about the predictive roles of CECs and CEPs in cancers due to a lack of consensus about the definition of CECs and CEPs, differences in cancer types, treatment, time points for assessment, and a lack of statistical power in previous studies, emerging evidence suggests that baseline levels and/or changes in CEC and/or CEP levels may predict the efficacy of anticancer drug treatment that includes anti-angiogenic agents [21–25]. In particular, the CEC and CEP data could be more powerful than the CTC data because there are greater numbers of cell events in the CEC and CEP counts. Thus, better estimates of statistical significance effect can be done in each patient using the CEC and CEP data with less overlap of uncertainty on the actual numbers of cells present; however, given lack of objective tumor response and the small number of patients in the present study, firm conclusions on whether the kinetics of CECs or CEPs could be surrogate markers for fostamatinib efficacy could not be drawn.

As has been reported with other anti-angiogenic therapies, we observed hypertension, thrombosis, and proteinuria following fostamatinib treatment. The degree of hypertension was related to the dose of study drug, with higher doses of 150 or 200 mg BID resulting in greater incidence (42% versus 20%) and severity (grade 3, 25% versus 0%) of hypertension as compared to the lower doses (50 or 100 mg BID).

Given the lack of objective tumor responses in 37 patients treated on study and the observed toxicities requiring substantial dose reductions, further accrual was stopped. This study highlights the challenges inherent in developing molecularly targeted agents, especially multi-kinase inhibitors, that target multiple growth/survival pathways. Preclinical models that evaluate antitumor effects as well as the vulnerability of normal tissue to chronic inhibition of multiple pathways are urgently needed, addressing considerations surrounding dosing and scheduling to optimize the therapeutic window.

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Fig. 1.

Kinetics of the number of (A) circulating endothelial cells (CECs), (B) circulating endothelial progenitor cells (CEPs), and (C) circulating tumor cells (CTCs) between pre-treatment and post-treatment in the entire patient population. For each patient, objective tumor response is shown as a solid line for stable disease (SD) and a dotted line for progressive disease (PD). PBMC, peripheral blood mononuclear cell

Fig. 2. Kaplan-Meier Curve for time to progression (TTP) according to the change of (A) circulating endothelial cells (CECs), (B) circulating endothelial progenitor cells (CEPs), and (C) circulating tumor cells (CTCs) between pre-treatment and post-treatment (C2D28 for CEC and CEP, and C1D15 for CTC) in the colorectal cancer patient cohort

Table 1

Dose escalation schema

Dose levels	Head and neck/thyroid cancer	Colorectal /pheochromocytoma	Non-small cell lung/renal cell cancer
–2	50 mg q12 hours	–	–
–1	100 mg q12 hours	50 mg q12 hours	50 mg q12 hours
1	150 mg q12 hours	100 mg q12 hours	100 mg q12 hours
2	200 mg q12 hours	150 mg q12 hours	150 mg q12 hours
3	–	–	200 mg q12 hours

Table 2

Baseline patient characteristics

Characteristics	Colorectal cancer (n = 22)	Other cancer (n = 15)
Age, years		
Median (range)	56 (34–75)	62 (43–82)
Gender		
Male	13 (59%)	8 (53%)
Female	9 (41%)	7 (47%)
ECOG performance status		
0	20 (91%)	2 (13%)
1	2 (9%)	12 (80%)
2	0	1 (7%)
Tumor type		
Colorectal cancer	22 (100%)	—
Thyroid cancer (Follicular/papillary)	—	4/1(33%)
Lung cancer	—	4 (27%)
Head and neck cancer	—	2 (13%)
Renal cell cancer	—	2 (13%)
Pheochromocytoma	—	2 (13%)
Sites of metastases		
Lung	20 (91%)	14 (93%)
Liver	16 (73%)	6 (40%)
Lymph node	15 (68%)	10 (67%)
Bone	0 (0%)	6 (40%)
Other	5 (23%)	5 (33%)
No. of lines of prior systemic therapy for metastatic disease		
Median (range)	4 (2–7)	2 (0–10)
<4	8 (36%)	9 (60%)
4	14 (64%)	6 (40%)
Prior anti-VEGF/R therapy		
Bevacizumab	20 (91%)	2 (13%)
Sorafenib	3 (14%)	5 (33%)
Sunitinib	0 (0%)	2 (13%)
Vandetanib	0 (0%)	2 (13%)

ECOG, Eastern Cooperative Oncology Group; VEGF, vascular endothelial growth factor.

Table 3

Treatment-related adverse events reported by 20% of patients or in grade 3 or more severity in each dose level

Fostamatinib Dose ^d :	50 mg (n = 10)		100 mg (n = 15)		150 mg (n = 5)		200 mg (n = 7)	
	All grades	Grade 3	All grades	Grade 3	All grades	Grade 3	All grades	Grade 3
Adverse event, n (%):								
Anemia	4 (40)	0	2 (13)	0	4 (80)	1 (20)	2 (29)	0
Leukopenia	3 (30)	0	2 (13)	0	4 (80)	0	4 (57)	0
Neutropenia	0	0	0	0	1 (20)	0	1 (14)	0
Thrombocytopenia	1 (10)	0	2 (13)	0	0	0	2 (29)	0
Lymphopenia	6 (60)	0	5 (33)	0	3 (60)	1 (20)	5 (71)	1 (14)
Diarrhea	1 (10)	0	0	0	2 (40)	0	1 (14)	0
Nausea	2 (20)	0	4 (27)	0	1 (20)	0	0	0
Fatigue	4 (40)	0	2 (13)	0	1 (20)	0	1 (14)	0
Hair loss	0	0	0	0	1 (20)	0	0	0
Diaphoresis	0	0	0	0	1 (20)	0	0	0
Hypertension	2 (20)	0	3 (20)	0	2 (40)	1 (20)	3 (43)	2 (29)
Thrombosis/embolism ^b	0	0	2 (13)	2 (13)	0	0	0	0
Proteinuria ^b	0	0	1 (7)	0	0	0	0	0
Elevated AST	3 (30)	1 (10)	4 (27)	0	4 (80)	0	5 (71)	1 (14)
Elevated ALT	4 (40)	1 (10)	4 (27)	0	2 (40)	0	5 (71)	0
Elevated ALP	1 (10)	1 (10)	2 (13)	0	1 (20)	0	3 (43)	2 (29)
Hyperbilirubinemia	3 (30)	0	1 (7)	1 (7)	2 (40)	1 (20)	3 (43)	1 (14)
Hypophosphatemia	2 (20)	0	0	0	1 (20)	0	0	0
Hypocalcemia	0	0	0	0	2 (40)	0	0	0
Hypokalemia	0	0	0	0	2 (40)	0	0	0
Hyperkalemia	0	0	0	0	1 (20)	0	0	0
Hypomagnesemia	0	0	0	0	1 (20)	0	0	0
Hypercholesterolemia	0	0	0	0	1 (20)	0	0	0
Elevated CK	0	0	1 (7)	0	1 (20)	0	0	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; CK, creatine kinase.

^aOne dosage of Fostamatinib; i.e., "50" means Fostamatinib twice a day continuously.

Included due to clinical relevance.
b

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