Clinical Cancer Research

Surufatinib in Advanced Well-Differentiated Neuroendocrine Tumors: A Multicenter, Single-Arm, Open-Label, Phase Ib/II Trial

Jianming Xu[1], Jie Li[2], Chunmei Bai[3], Nong Xu[4], Zhiwei Zhou[5], Zhiping Li[6], Caicun Zhou[7], Ru Jia[1], Ming Lu[2], Yuejuan Cheng[3], Chenyu Mao[4], Wei Wang[5], Ke Cheng[6], Chunxia Su[7], Ye Hua[8], Chuan Qi[8], Jing Li[8], Wei Wang[8,9], Ke Li[8], Qiaoling Sun[8], Yongxin Ren[8], and Weiguo Su[8]

Abstract

Purpose: No antiangiogenic treatment is yet approved for extrapancreatic neuroendocrine tumors (NET). Surufatinib (HMPL-012, previously named sulfatinib) is a small-molecule inhibitor targeting vascular endothelial growth factor receptors, fibroblast growth factor receptor 1 and colony-stimulating factor 1 receptor. We conducted a single-arm phase Ib/II study of surufatinib in advanced NETs.

Patients and Methods: Patients with histologically well-differentiated, low or intermittent grade, inoperable or metastatic NETs were enrolled into a pancreatic or extrapancreatic NET cohort. Patients were treated with surufatinib 300 mg orally, once daily. The primary endpoints were safety and objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (version 1.1).

Results: Of the 81 patients enrolled, 42 had pancreatic NETs and 39 had extrapancreatic NETs. Most patients had radiologic progression within 1 year prior to enrollment (32 patients in each cohort). In the pancreatic and extrapancreatic NET cohorts, ORRs were 19% [95% confidence intervals (CI), 9–34] and 15% (95% CI, 6–31), disease control rates were 91% (95% CI, 77–97) and 92% (95% CI, 79–98), and median progression-free survival was 21.2 months (95% CI, 15.9–24.8) and 13.4 months (95% CI, 7.6–19.3), respectively. The most common grade $\geq$3 treatment-related adverse events were hypertension (33%), proteinuria (12%), hyperuricemia (10%), hypertriglyceridemia, and diarrhea (6% for each), and increased alanine aminotransferase (5%).

Conclusions: Surufatinib showed encouraging antitumor activity and manageable toxicities in patients with advanced NETs. Two ongoing phase III studies, validating the efficacy of surufatinib in patients with NETs, will contribute to the clinical evidence.

Introduction

Neuroendocrine tumors (NET) are rare neoplasms arising from diffusive neuroendocrine cells of various organs. In the past four decades, the age-adjusted incidence rate increased 6.4-fold in the United States, from 1.09 per 100,000 persons in 1973 to 6.98 per 100,000 persons in 2012 (1). In China, a similar trend was identified by a hospital-based, nationwide, retrospective epidemiologic study of gastroenteropancreatic neuroendocrine neoplasms (2). Treatment options for advanced, low, or intermediate grade NETs include somatostatin receptor-targeting therapeutics, peptide receptor radionuclide therapy, systemic chemotherapies, targeted agents including sunitinib in pancreatic NETs, and everolimus in pancreatic, gastrointestinal, and bronchopulmonary NETs, and local-regional treatments (3). Nearly half of all patients with NETs have distant metastasis at initial diagnosis (3). The median survival time for patients with well-differentiated to moderately differentiated distant stage NETs varies by tumor origins, ranging from 103 months for small intestinal origin, to 60 months for pancreatic origin, and 14 months for colonic origin (1).

Although NETs are highly vascularized neoplasms, those originating from diverse organs respond to antiangiogenesis treatment differently (4–6). In a phase III pivotal study, sunitinib significantly prolonged progression-free survival (PFS) in patients with pancreatic NETs compared with placebo [11.4 months vs 5.5 months; HR, 0.42; 95% confidence intervals (CI) 0.26–0.66; $P < 0.001$; ref. 5], but failed to demonstrate efficacy in extrapancreatic NETs (6). Bevacizumab, a potent antivascular endothelial growth factor (VEGF) agent, has been studied in combination with several approved medications for treating NETs. In a phase II randomized study comparing bevacizumab combined with

[1]Department of Gastrointestinal Oncology, The Fifth Medical Center, General Hospital of People's Liberation Army, Beijing, China. [2]Department of Gastrointestinal Oncology, Key laboratory of carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, China. [3]Department of Oncology, Peking Union Medical College Hospital, Beijing, China. [4]Department of Medical Oncology, The First Affiliated Hospital of Zhejiang University, Hangzhou, China. [5]Department of Gastric and Pancreatic Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China. [6]Department of Abdominal Oncology, West China Hospital, Sichuan University, Chengdu, China. [7]Department of Oncology, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China. [8]Hutchison MediPharma Limited, Shanghai, China. [9]School of Mathematical Sciences, Shanghai Jiao Tong University, Shanghai, China.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

J. Xu, J. Li, and C. Bai share primary authorship of this article.

Corresponding Author: Jianming Xu, The Fifth Medical Center, General Hospital of People's Liberation Army Beijing 100071, China. Phone: 86-10-51128358; Fax: 86-10-51128358; E-mail: jmxu2003@yahoo.com

Clin Cancer Res 2019;25:3486–94

doi: 10.1158/1078-0432.CCR-18-2994

Translational Relevance

Patients with neuroendocrine tumors (NET) often have poor prognoses. The median survival time varies by site of origin, which can be as low as 4 months in patients with colonic NETs. As such, there is a need for improvement in treatment strategies, particularly in NETs originating outside of the pancreas. NETs are highly vascularized neoplasms, which presents a potential therapeutic target. Currently, there is no antiangiogenesis therapy approved for the treatment of extrapancreatic NETs. Thus, we tested the efficacy and safety of surufatinib, an inhibitor of angiogenesis, in patients with pancreatic or extrapancreatic NETs. Surufatinib demonstrated promising antitumor activity in both patient cohorts and is the first antiangiogenic drug to display robust antitumor activity in single-drug therapy against extrapancreatic NETs. Surufatinib demonstrated a manageable and expected toxicity profile and has potential as a pharmacologic treatment for patients with pancreatic or extrapancreatic NETs, including those who have previously failed VEGFR inhibitors.

everolimus to everolimus alone in treating pancreatic NETs, a higher response rate of 31% versus 12% ($P = 0.005$) was observed in the bevacizumab arm (7). However, the median PFS was similar between the two arms: 16.7 versus 14 months (HR, 0.80; 95% CI, 0.55–1.17, $P = 0.12$; ref. 7). A similar trend in response rates and PFS was shown in a phase III study comparing the combination of bevacizumab plus octreotide versus interferon alfa-2b plus octreotide [response rate (RR): 12% vs. 4%, $P = 0.008$; PFS: 16.6 vs. 15.4 months; HR 0.93; 95% CI, 0.73–1.18; $P = 0.55$; ref. 8]. However, in spite of all the previous efforts investigating VEGF pathway inhibition, to date, no antiangiogenic treatment is approved for NETs originating outside of the pancreas. Fibroblast growth factor (FGF) 2 was shown to be a potent mediator in antiangiogenesis resistance development, and inhibiting FGF receptor signaling could overcome resistance (9). Preclinical cancer models also showed that macrophages, usually recruited and activated by colony-stimulating factor 1 receptor (CSF-1R), played a proangiogenic role in the tumor microenvironment. Furthermore, eliminating tumor-associated macrophages by inhibiting CSF-1R led to decreased neoangiogenesis (10). Therefore, inhibiting these targets simultaneously could be a promising antiangiogenic strategy.

Surufatinib (HMPL012, previously named as sulfatinib) is a potent, small-molecule tyrosine kinase inhibitor (TKI), selectively targeting VEGF receptors (VEGFR) 1, 2, and 3, FGFR 1, and CSF-1R. In a phase I dose-finding study in patients with advanced solid tumors, surufatinib demonstrated antitumor activity in hepatocellular carcinoma and NETs, both highly vascularized tumors (11). The objectives of this phase Ib/II study were to further evaluate the efficacy, safety, and tolerability of surufatinib in patients with advanced NETs of diverse origins.

Patients and Methods

Study design and eligibility criteria

This was a multicenter, single-arm, open-label, phase Ib/II trial. Patients with pancreatic or extrapancreatic NETs were enrolled in corresponding cohorts in 7 clinical centers across China. The primary objective of this study was to evaluate the efficacy and safety of surufatinib. Pharmacokinetics were evaluated as the secondary objective. Assessing the association between antitumor activities and VEGF/FGF pathway biomarker expression was an exploratory objective.

Eligible patients were ≥18 years, with pathologically confirmed low or intermediate grade (G1 or G2) inoperable or metastatic NETs, had failed prior systemic therapy, or were unable to receive standard treatments. Additional key eligibility criteria included measurable disease at baseline according to Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1 (12) and an Eastern Cooperative Oncology Group performance status of 0 or 1. Adequate bone marrow, liver, renal, and coagulation function were also required.

Key exclusion criteria included any diagnosed thrombosis 12 months prior to the study, significant bleeding 3 months prior, significant cardiovascular disease (e.g., myocardial infarction or unstable angina), gastrointestinal disease affecting medication absorption, untreated or unstable central nervous system metastases, or other malignancy. Patients receiving prior antitumor treatments, including systemic medication, surgery or radical radiotherapy within 4 weeks before surufatinib initiation, or prior palliative radiotherapy within 2 weeks before the first dose of surufatinib, were also excluded.

All patients provided written informed consent, and the study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki, and applicable local laws and regulations. The study was also approved by the institutional review boards of participating centers. This study was registered at ClinicalTrials.gov (NCT02267967).

Treatment and assessments

Patients received surufatinib 300 mg as an initial dose, once daily (QD) and continuously for every 28-day cycle until disease progression, intolerable toxicity, or withdrawal of consent. Treatment beyond progression was allowed at the discretion of investigators for patients who showed radiologic progression only, but who were otherwise experiencing clinical benefit. Tumor response was assessed by investigators, per RECIST v1.1, every 4 weeks for the cycles 1 to 2, then every 8 weeks for the first year, and every 12 weeks thereafter. Patients without disease progression upon surufatinib discontinuation were followed for tumor assessments until initiation of new antitumor treatment, loss to follow-up, withdrawal of consent, or death. Tumor responses were also retrospectively evaluated by a qualified independent radiologist.

Surufatinib treatment could be temporarily interrupted for up to 28 days if there were intolerable toxicities. Surufatinib dose could be reduced to 250 mg and then to 200 mg if grade ≥3 adverse events (AE) occurred. Concomitant antitumor medications were not allowed, except short-term somatostatin analogues for NET-related symptoms.

Clinical and laboratory evaluations were performed every 2 weeks for cycles 1 to 2, then every 4 weeks thereafter. Cardiographs and echocardiograms were conducted every 4 and 12 weeks, respectively. AEs were continually assessed using the Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Pharmacokinetic (PK) sampling was performed for all patients on days 1, 2, 14, and 15 of cycle 1, and on day 1 of cycles 5 and 7. Following consent, blood samples for biomarker analysis were collected at baseline and at each tumor evaluation visit. Plasma

concentrations of VEGF-A (QVE00B, QuantiGlo), sVEGFR-2 (DY357), bFGF (HSFB00D), M-CSF (SMC00B; all R&D Systems), and FGF23 (CY-4000, Kainos) were measured by ELISA.

Efficacy and safety endpoints

The primary endpoints were investigator-assessed safety and objective response rate (ORR). ORR was defined as the proportion of patients whose best tumor response was complete response (CR) or partial response (PR) during study therapy per RECIST v1.1. A confirmatory assessment of response was required $\geq$4 weeks after initial assessment. If a patient's initial CR or PR was not confirmed at the subsequent assessment, stable disease (SD) was assigned as his/her best overall response, provided SD had been demonstrated $\geq$6 weeks since first dosing. Safety was evaluated through AEs according to CTCAE v4.03.

Secondary endpoints included disease control rate (DCR), duration of response (DoR), PFS and PKs. DCR was defined as the proportion of patients who had a CR, PR, or SD as best response. DoR was defined as the time from the first documented evidence of CR or PR until the time of the first documented disease progression or death (any cause), whichever occurred first. PFS was defined as the interval between the first surufatinib dose and the earliest date of disease progression or death (any cause).

Statistical analysis

The recruitment plan was to enroll 80 patients (40 patients in each cohort). For a given AE with a true rate of 10%, 5%, or 1%, the probability of observing $\geq$1 such AE in 80 patients is >99%, 98%, and 55%, respectively. For efficacy evaluation, further investigation was deemed worthy if the observed ORR was 15% in the pancreatic NET cohort and 10% in the extrapancreatic NET cohort, according to the prior literature in this population (5, 13, 14). With a sample size of 40 patients in each cohort, observed ORRs of 15% and 10% would result in exact binomial 95% CI of 5.7%–29.8% and 2.8%–23.7%, respectively.

Patients who received $\geq$1 dose of surufatinib were included in safety and efficacy analyses. Descriptive statistics and graphs were used to summarize demographics, tumor characteristics, toxicity, and tumor response. PFS and DoR were analyzed using the Kaplan–Meier method. PK parameters were calculated by Pharsight Phoenix WinNonlin (Certara) software using a noncompartmental analysis model. A Wilcoxon signed-rank test compared changes in soluble protein levels. Multiple covariate analyses were performed for the association between baseline biomarker levels and PFS. Stepwise selection was carried out at the entry and retaining level of 0.1, the candidate covariates included disease category (i.e., pancreatic NETs and extrapancreatic NETs), all biomarker tested, and interactions between each biomarker with disease category. Statistical analyses of safety, efficacy, and the association between PFS and biomarkers were performed using SAS software (v9.3).

Results

Patient population and baseline characteristics

Between November 6, 2014, and January 8, 2016, 81 patients were enrolled into the trial. Forty-two patients were diagnosed with pancreatic NETs and 39 with extrapancreatic NETs. The median follow-up was 14.7 months (range, 0.6–30.2) as of the cutoff date (August 23, 2017), when the maturity of PFS data was 60% [47 progressive disease (PD) and two death events]. At data cutoff, 16 (20%) patients remained on study treatment (11 in the pancreatic NET cohort, five in the extrapancreatic NET cohort). Reasons for treatment discontinuation included PD (41 patients, 51%), intolerable AEs (18 patients, 22%), withdrawal of consent (5 patients, 6%), and major protocol deviation (1 patient, 1%). All 81 patients received study medication and were included in the safety and efficacy analyses (Supplementary Fig. S1).

Patient demographics and baseline disease characteristics in each cohort are listed in Table 1. Overall, the median age was 49 years (range, 20–71), 44 (54%) patients were men, 65 (80%) had

Table 1. Patient demographics and baseline disease characteristics

Characteristic	Pancreatic NET cohort (n = 42) N (%)	Extrapancreatic NET cohort (n = 39) N (%)
Median age (range), years	46 (20–70)	54 (25–71)
Sex		
Male	25 (60)	19 (49)
Female	17 (40)	20 (51)
ECOG performance status		
0	32 (76)	22 (56)
1	10 (24)	17 (44)
Primary sites of extrapancreatic NETs		
Rectum		14 (36)
Stomach		5 (13)
Lung		4 (10)
Small intestine		3 (8)
Liver		3 (8)
Others/unknown[a]		10 (26)
Pathologic grade		
1	7 (17)	9 (23)
2	35 (83)	30 (77)
Ki-67, %		
Median (range)	5 (1–20)	5 (1–20)
First quartile, third quartile	3, 10	2, 10
Tumor-related syndrome		
Functional tumor	3 (7)	2 (5)
Nonfunctional tumor	39 (93)	37 (95)
Disease stage		
III	1 (2)	1 (3)
IV	41 (98)	38 (97)
Distant metastasis		
Liver	39 (93)	32 (82)
Lymph nodes	20 (48)	17 (44)
Lung	4 (10)	10 (26)
Bone	3 (7)	11 (28)
Others	7 (17)	9 (23)
Time since diagnosis, median (range), months	21 (0–120)	21 (2–108)
Radiologic progression documented before enrollment within		
6 months	30 (71)	31 (80)
12 months	32 (76)	32 (82)
Unknown/not in past 12 months	10 (24)	7 (18)
Prior treatment for advanced disease		
Chemotherapy	8 (19)	15 (38)
Somatostatin analogue	20 (48)	22 (56)
VEGFR inhibitors[b]	13 (31)	5 (13)
Everolimus	5 (12)	7 (18)
Liver-directed therapy[c]	14 (33)	16 (41)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; VEGFR, vascular endothelial growth factor receptor.

[a]Other/unknown primary sites in the extrapancreatic NET cohort include unknown origins [n = 3 (8%)], retroperitoneal lesions and kidney [n = 2 (5%) each], mediastinum, mesenterium, and thymus [n = 1 (3%) each].

[b]VEGFR inhibitors include sunitinib and famitinib.

[c]Liver-directed therapy includes bland embolization, chemoembolization, radiofrequency ablation, or microwave destruction.

Table 2. Tumor response to surufatinib

	Pancreatic NET cohort ($n = 42$) *N* (%)		Extrapancreatic NET cohort ($n = 39$) *N* (%)	
Overall responses (RECIST 1.1)	**Investigators' assessment**	**Independent assessments**	**Investigators' assessment**	**Independent assessments**
CR	0	0	0	0
PR	8 (19)	5 (12)	6 (15)	4 (10)
SD	30 (71)	34 (81)	30 (77)	32 (82)
PD	1 (2)	0	1 (3)	1 (3)
NE	3 (7)	3 (7)	2 (5)	2 (5)
ORR	8 (19; 95% CI, 9–34)	5 (12; 95% CI, 4–26)	6 (15; 95% CI, 6–31)	4 (10; 95% CI, 3–24)
DCR	38 (91; 95% CI, 77–97)	39 (93; 95% CI, 81–99)	36 (92; 95% CI, 79–98)	36 (92; 95% CI, 79–98)

Abbreviations: CR, complete response; DCR, disease control rate; NE, non-evaluable (indicating efficacy non-evaluable patients who had no tumor assessments after baseline or only one tumor assessment as SD within 6 weeks in this study); ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

grade 2 NETs, and 79 (98%) had distant metastases. Fifty-seven (70%) patients had received systemic antitumor drugs prior to enrollment. Most patients had PD, with 64 (79%) patients recording disease progression within 1 year before enrollment; the other 17 (21%) patients experienced clinical deterioration, but without documented radiologic progression because of new diagnosis or irregular follow-up in the prior year.

Treatment

The median treatment duration was 13.7 months (range, 0.1–30.2) for all patients [17.9 months (range, 0.1–29.5) in the pancreatic NET cohort and 9.2 months (range, 0.5–30.2) in the extrapancreatic NET cohort). During treatment, 3 patients concomitantly received octreotide for symptom control: 2 patients used short-acting octreotide for 3 and 4 days, respectively, and one used octreotide acetate microspheres (long-acting release) for 2 cycles.

Efficacy

Tumor evaluations are listed in Table 2. In the pancreatic NET cohort ($n = 42$), 8 patients had confirmed PR and 30 had SD, producing an ORR of 19% (95% CI, 9%–34%) and a DCR of 91% (95% CI, 77%–97%). In the extrapancreatic NET cohort ($n = 39$), 6 patients had confirmed PR and 30 had SD, producing an ORR of 15% (95% CI, 6%–31%) and DCR of 92% (95% CI, 79%–98%). Of the 6 patients who achieved PR in this cohort, the primary tumor origins were stomach, duodenum, jejunum, liver, rectum, and lung, respectively. For patients with PRs, the median DoR was 21.1 months (95% CI, 1.5–21.1) and 12.0 months (95% CI, 6.8–12.9) in the pancreatic NET and extrapancreatic NET cohorts.

Most patients experienced tumor shrinkage from baseline (Fig. 1), with a decrease of target lesions >10% in 25 (61%) and 22 (55%) patients in the pancreatic and extrapancreatic NET cohorts, respectively. Overall, of the 13 patients who progressed on previous antiangiogenesis treatment (i.e., sunitinib or famitinib), 2 had confirmed PR and 11 had SD (including one unconfirmed PR), with an ORR of 15% and DCR of 100%, and the median PFS was 13.8 months (95% CI, 5.6–24.8), all of which were comparable with those reported in the remaining patients.

The median PFS was 21.2 months (95% CI, 15.9–24.8) and 13.4 months (95% CI, 7.6–19.3) in the pancreatic NET and extrapancreatic NET cohorts (Fig. 2A). Among patients with radiologic disease progression within 1 year before treatment ($n = 32$ per cohort), the PFS was 21.2 months (95% CI, 15.9–24.8) and 11.1 months (95% CI, 7.2–16.6) in the pancreatic and extrapancreatic NET cohorts, respectively (Fig. 2B).

Tumor responses assessed retrospectively by the independent reviewer were consistent with investigators' evaluations (Table 2). The ORR was 12% (95% CI, 4%–25%) and 10% (95% CI, 3%–24%) in the pancreatic and extrapancreatic NET cohorts, respectively; median PFS was 19.4 months (95% CI, 14.8–24.8) and 13.6 months (95% CI, 7.6–19.3), respectively.

Safety

All patients had at least one AE of any grade. In all 81 patients, the most common treatment-related AEs were proteinuria (81%), diarrhea (72%), hypertension (60%), elevated blood thyroid-stimulating hormone (52%), asthenia (44%), and elevated aspartate aminotransferase (41%; Table 3). Dermatologic reactions were less common; rash was observed in 3 (4%) patients, hand and foot syndrome in 2 (2%) patients and other dermatologic manifestations were only reported in one (1%) patient separately. The most common treatment-related grade $\geq$3 AEs were hypertension (33%), proteinuria (12%), hyperuricemia (10%), hypertriglyceridemia and diarrhea (6% each), and increased alanine aminotransferase (5%).

Dose interruption and reductions due to AEs occurred in 54 (67%) and 26 (32%) patients, respectively. AEs that resulted in treatment discontinuation were reported in 18 (22%) patients, including proteinuria (5%), abnormal hepatic function (2%), and other AEs (1%). Serious adverse events (SAE) were reported in 22 (27%) patients. SAEs experienced by more than one patient were abnormal hepatic function (5%), intestinal obstruction (4%), anemia, pancreatitis, and upper gastrointestinal hemorrhage (2% each).

Three (4%) patients experienced fatal AEs. One patient with rectal NET discontinued treatment due to PD on day 14 and died from hypovolemic shock, possibly related to surufatinib treatment 4 days after the last dosing. Fatal AEs in the other 2 patients were considered unlikely to be related to surufatinib; a patient with gastric NET died from a biliary tract infection and a patient with pancreatic NET died of multiorgan failure, 28 and 3 days after the last dosing, respectively.

Pharmacokinetics

The PKs of surufatinib were evaluated in 81 patients for day 1 and in 78 patients for day 14 (due to withdrawal of 3 patients; Supplementary Table S1). Following an oral dose of 300 mg on day 1, the geometric mean maximum concentration (C_{max}) of surufatinib was 376 ng/mL, and the median time to maximum concentration (T_{max}) was 2.0 hours. On day 14, the geometric mean C_{max} of surufatinib was 487 ng/mL, and the median T_{max}

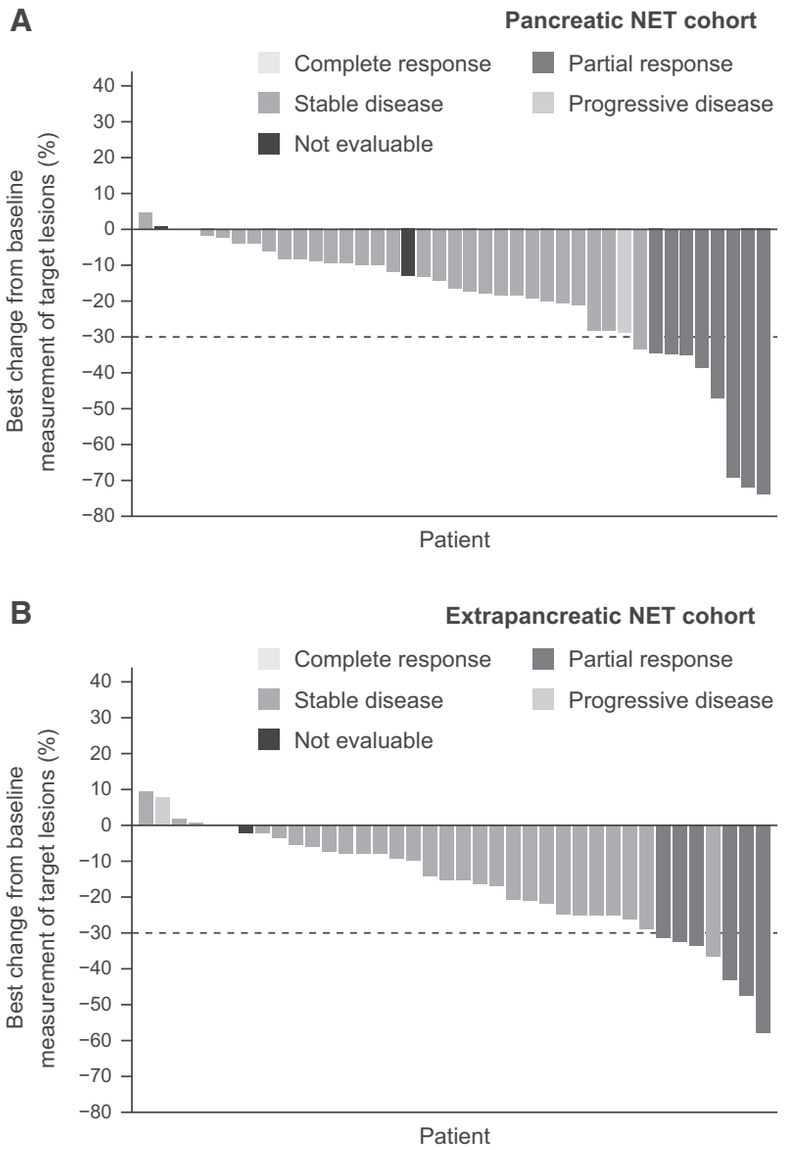

Figure 1.
Waterfall plots of best response in the pancreatic NET cohort (**A**; $n = 41$)* and extrapancreatic NET cohort (**B**; $n = 38$)*. *, One patient from each cohort had no tumor assessment after baseline and were not included in the waterfall plots.

was 2.1 hours. The geometric mean areas under the concentration curve (AUC_{0-24}) were 2,770 and 4,810 hour × ng/mL, for days 1 and 14, respectively. The mean accumulation ratio was 1.91.

Biomarker analysis

Plasma samples were available for 36 patients at baseline and posttreatment (17 patients with pancreatic NETs and 19 patients with extrapancreatic NETs). Surufatinib treatment induced significant increases in plasma VEGF-A, FGF23, and macrophage colony-stimulating factor (M-CSF), and decreases in soluble VEGFR-2 (sVEGFR-2) compared with baseline, indicating a potent blockade of VEGFR, FGFR1, and CSF-1R signaling (Table 4). No significant change in basic FGF (bFGF) levels was determined at the time of best response or PD compared with baseline. Interestingly, higher baseline levels of sVEGFR-2 and lower baseline levels of bFGF were significantly associated with prolonged PFS (Supplementary Table S2), but not in other biomarkers investigated.

Discussion

In this single-arm, phase Ib/II study, surufatinib demonstrated manageable toxicity and promising antitumor activity in patients with NETs of diverse tumor origins. Surufatinib, as a single-drug therapy, is the first antiangiogenic drug to show robust antitumor activity in patients with extrapancreatic NETs. Patients with extrapancreatic NETs obtained a durable response, despite diverse primary tumor origins that correlate with poor prognosis (1, 15). Furthermore, 77% of patients in this cohort had grade 2 NETs and 25% had a Ki 67 >10%. These characteristics suggest that tumors in this study might have more malignant behavior as compared with those from previous clinical trials involving everolimus, octreotide, and other drugs. In those studies, the majority

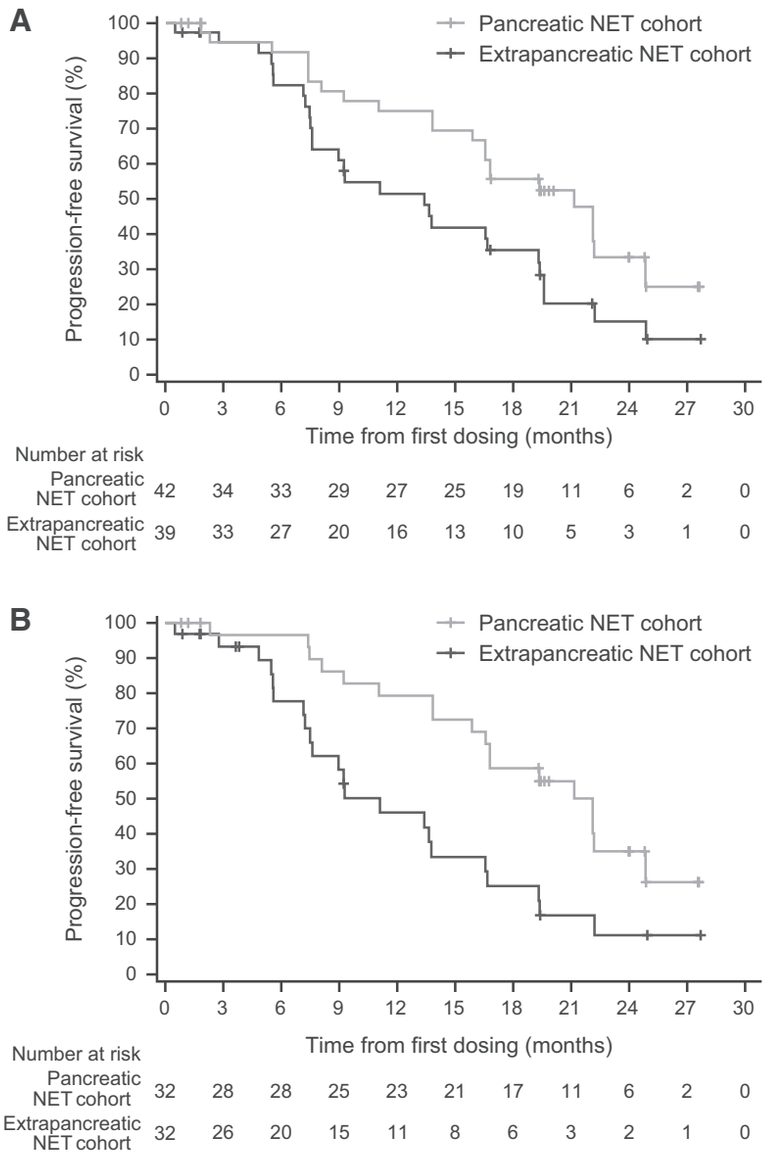

Figure 2.

PFS in all patients (**A**; $n = 81$). PFS in patients who had documented radiologic progression 1 year prior to treatment (**B**; $n = 64$).

of extrapancreatic NETs were grade 1 originating from the small intestine, typically correlating with a better prognosis (1, 4, 13, 14, 16).

Additionally, surufatinib demonstrated potent antitumor activity in pancreatic NETs, including patients who progressed on prior VEGFR inhibitors, possibly owing to its different mechanism of action on the anti-VEGF pathway, anti-FGF pathway, and its ability to regulate the tumor immune microenvironment. The ORR appeared higher and PFS longer in the pancreatic NET cohort than the extrapancreatic NET cohort in this study, which has also been observed in other studies of antiangiogenic treatments (4, 6). To date, investigations characterizing the molecular abnormalities driving the growth of NETs have been limited. In pancreatic NETs, *VHL* alterations lead to increased levels of HIF1α and secondary overexpression of VEGF, indicating the importance of the VEGFR pathway, and mutations in *TSC1/2* and *PTEN* result in activation of the PI3K/mTOR pathway, providing the rationale for mTOR-directed therapies (17). Furthermore, the genes implicated in chromatin remodeling have been found to be frequently mutated in pancreatic NETs, such as *MEN1*, *DAXX*, or *ATRX*, suggesting that DNA methylation and histone modifications may present new potential targets in pancreatic NETs (18, 19). In contrast, most small-intestine NETs are characterized by a loss of tumor suppressor genes on chromosome 18 and no other frequent genetic alterations or putative affected pathways have yet been implicated in the tumorigenesis of small-intestine NETs (18, 20). In general, the varied molecular profiles, biological and clinical behaviors of NETs from diverse tumor origins may provide an explanation for the different treatment responses, but further research is required to elucidate the mechanisms.

Efficacy assessments were mostly similar between investigators and the independent radiologist, although ORRs assessed by the independent radiologist were slightly lower in both cohorts. NETs usually present with multiple liver metastases, making

Table 3. Summary of treatment-related AEs of any grade occurring in ≥10% of patients and treatment-related grade 3 or worse AEs occurring in ≥2% of patients ($N = 81$)

Preferred term	Grade 1–2 *N* (%)	Grade 3 *N* (%)	Grade 4 *N* (%)
Proteinuria	56 (69)	10 (12)	0
Diarrhea	53 (65)	5 (6)	0
Hypertension	22 (27)	27 (33)	0
Blood thyroid-stimulating hormone increased	42 (52)	0	0
Asthenia	34 (42)	2 (2)	0
Aspartate aminotransferase increased	31 (38)	1 (1)	1 (1)
Hypertriglyceridemia	26 (32)	5 (6)	0
Alanine aminotransferase increased	22 (27)	4 (5)	0
Hypoalbuminemia	25 (31)	0	0
Hyperbilirubinemia	23 (28)	2 (2)	0
Blood bilirubin increased	23 (28)	1 (1)	0
Edema peripheral	21 (26)	3 (4)	0
Face edema	21 (26)	2 (2)	0
Hyperuricemia	13 (16)	1 (1)	7 (9)
Anemia	16 (20)	3 (4)	0
Electrocardiogram T wave abnormal	19 (24)	0	0
Neutropenia	16 (20)	3 (4)	0
Decreased appetite	18 (22)	0	0
White blood cell count decreased	16 (20)	1 (1)	0
Blood creatinine increase	16 (20)	0	0
Abdominal pain upper	14 (17)	0	0
Nausea	14 (17)	0	0
Abdominal pain	13 (16)	0	0
Back pain	13 (16)	0	0
Hemoglobin increased	13 (16)	0	0
Hypocalcemia	13 (16)	0	0
Musculoskeletal pain	12 (15)	0	0
Thyroxine-free decrease	12 (15)	0	0
Vomiting	12 (15)	0	0
Abdominal discomfort	11 (14)	0	0
Blood triglycerides increased	8 (10)	2 (2)	0
Occult blood positive	10 (12)	0	0
Sinus bradycardia	10 (12)	0	0
Tri-iodothyronine-free decrease	10 (12)	0	0
Abdominal distention	9 (11)	0	0
Bilirubin conjugated increased	8 (10)	1 (1)	0
Hypothyroidism	9 (11)	0	0
Hypokalemia	5 (6)	2 (2)	0
Thrombocytopenia	4 (5)	1 (1)	1 (1)
Hepatic function abnormal	0	2 (2)	1 (1)

Abbreviation: AE, adverse event.

evaluations challenging (21, 22). In this study, 93% and 82% of patients in both cohorts had liver metastases, most of which were multiple. Different target lesion selection for tumor assessment may have contributed to the discordance between the investigators and the independent radiologist. Despite the difference in ORRs, the antitumor activity of surufatinib was well demonstrated in both assessments. Given that prior studies have reported ORRs between 2% and 9%, DCRs between 69% and 83% and PFS of approximately 11 months (5, 13, 16, 23), surufatinib could present a promising candidate for the treatment of advanced NETs.

The safety profile of surufatinib was similar to other oral antiangiogenesis inhibitors (24), with no unexpected safety signals. Frequently reported grade ≥3 treatment-related AEs were hypertension (33%), proteinuria (12%), and hyperuricemia (10%), all manageable with standard supportive care and/or dose modifications. Treatment discontinuation due to AEs occurred in 22% of patients, due to hypertension and proteinuria in 1% and 5% of patients, respectively. No patient discontinued treatment due to hyperuricemia. It is worth noting that 22.2% of patients had hypertension, 39.5% proteinuria, and 6.2% hyperuricemia recorded as medical history at baseline. The safety and tolerability profiles of surufatinib seem acceptable in patients with advanced NETs, who usually have a long treatment period (median treatment duration of 13.7 months in this study).

Five circulating proteins were evaluated for target inhibition and associations with clinical outcomes. Changes in VEGF-A, sVEGFR-2, FGF23, and M-CSF with surufatinib are in line with previous reports regarding other selective VEGF, FGF, and CSF-1 pathway inhibitors (25–27), supporting the notion that these proteins are putative pharmacodynamic biomarkers of the related targets. Notably, bFGF levels did not significantly change after treatment. This contrasts with observations of significant bFGF elevation at tumor progression following treatment with other antiangiogenesis inhibitors, albeit in different cancer types, suggesting FGF/FGFR activation as a possible mechanism for acquired resistance (28–30). As surufatinib strongly attenuated FGFR1, we speculate that FGF/FGFR signaling might not be the dominant mechanism for resistance to surufatinib. The higher sVEGFR-2 levels and lower bFGF levels at baseline were associated with longer median PFS, which has also been reported in previous studies of other anti-VEGF/VEGFR agents in several cancer types, including metastatic NETs (31–34). Due to the exploratory and

Table 4. Summary of circulating plasma biomarker levels

Soluble protein	Visit	Median, pg/mL (range)	*P* value[a]	The median of the ratio[a]
VEGF-A	Baseline ($n = 36$)	118 (44–2,807)	—	—
	Best response ($n = 36$)	269 (59–1,786)	<0.0001	2.09
	PD ($n = 22$)	188 (48–545)	0.0058	1.90
sVEGFR-2	Baseline ($n = 36$)	5,290 (1,254–9,631)	—	—
	Best response ($n = 36$)	3,368 (1,141–5,911)	<0.0001	0.76
	PD ($n = 22$)	2,485 (936–9,329)	0.0047	0.79
FGF23	Baseline ($n = 36$)	50.7 (22.5–128.1)	—	—
	Best response ($n = 36$)	72.8 (37.0–211.5)	<0.0001	1.41
	PD ($n = 22$)	60.2 (42.0–108.7)	0.1080	1.22
bFGF	Baseline ($n = 36$)	5.52 (0.71–68.9)	—	—
	Best response ($n = 36$)	5.33 (1.67–80.0)	0.4006	1.21
	PD ($n = 22$)	5.86 (0.73–53.88)	0.3849	0.73
M-CSF	Baseline ($n = 36$)	161 (66.4–495)	—	—
	Best response ($n = 36$)	234 (72.8–1,429)	<0.0001	1.42
	PD ($n = 22$)	226 (117–563)	0.0016	1.40

[a]The *P* value and the ratio reflect the difference between plasma protein levels at the visit of best response or PD and the levels detected at baseline.

retrospective nature of the biomarker analysis, validating these results in a larger population is required.

This trial had several limitations. It was a single-arm study without a control group; hence, these findings must be interpreted with caution. Post-study antitumor treatments and survival status data after documented radiologic progression were not collected; consequently, overall survival information for this population is not available. Finally, the small sample size makes it difficult to correlate biomarkers with clinical efficacy for each cohort.

In summary, surufatinib demonstrated promising antitumor activity with an acceptable safety profile in patients with advanced, well-differentiated NETs, regardless of tumor origins. The treatment benefit of surufatinib will be confirmed in two phase III double-blinded, randomized, placebo-controlled trials in patients with pancreatic (NCT02589821) and extrapancreatic NETs (NCT02588170).

Disclosure of Potential Conflicts of Interest

C. Qi, Y. Hua, Y. Ren, and W. Su hold ownership interest (including patents) in Hutchison MediPharma. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: J. Xu, C. Bai, Y. Hua, C. Qi, Y. Ren, W. Su
Development of methodology: J. Xu, C. Bai, C. Qi
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Xu, J. Li, C. Bai, N. Xu, Z. Zhou, Z. Li, C. Zhou, R. Jia, M. Lu, Y. Cheng, C. Mao, W. Wang, C. Su, C. Qi
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Xu, C. Zhou, Y. Hua, C. Qi, J. Li, W. Wang, K. Li, Q. Sun, Y. Ren, W. Su
Writing, review, and/or revision of the manuscript: J. Xu, J. Li, N. Xu, Z. Zhou, C. Zhou, R. Jia, Y. Cheng, W. Wang, C. Su, Y. Hua, J. Li, K. Li, Y. Ren, W. Su
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Z. Zhoui, C. Zhou, R. Jia, Y. Cheng, W. Wang, K. Cheng, C. Su
Study supervision: J. Xu, J. Li, N. Xui, C. Zhou, C. Qi

Acknowledgments

We thank the patients for participating in this trial and all the investigators and site personnel involved in the study. Editorial assistance in manuscript preparation was provided by Nucleus Global, Shanghai, China, funded by Hutchison MediPharma. This study was supported by Hutchison MediPharma (Shanghai) Ltd.

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

Received September 11, 2018; revised January 11, 2019; accepted February 28, 2019; published first March 4, 2019.

References

1. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol 2017;3:1335–42.
2. Fan JH, Zhang YQ, Shi SS, Chen YJ, Yuan XH, Jian LI, et al. A nation-wide retrospective epidemiological study of gastroenteropancreatic neuroendocrine neoplasms in china. Oncotarget 2017;8:71699–708.
3. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology 2016;103:172–85.
4. Phan AT, Halperin DM, Chan JA, Fogelman DR, Hess KR, Malinowski P, et al. Pazopanib and depot octreotide in advanced, well-differentiated neuroendocrine tumours: a multicentre, single-group, phase 2 study. Lancet Oncol 2015;16:695–70.
5. Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011;364:501–13.
6. Kulke MH, Lenz HJ, Meropol NJ, Posey J, Ryan DP, Picus J, et al. Activity of sunitinib in patients with advanced neuroendocrine tumors. J Clin Oncol 2008;26:3403–10.
7. Kulke M, Niedzwiecki D, Foster N, Fruth B, Kunz P, Kennecke H, et al. Randomized phase II study of everolimus (E) versus everolimus plus bevacizumab (E+B) in patients (Pts) with locally advanced or metastatic pancreatic neuroendocrine tumors (pNET), CALGB 80701 (Alliance). J Clin Oncol 2015;33(suppl: abstract 4005).
8. Yao JC, Guthrie KA, Moran C, Strosberg JR, Kulke MH, Chan JA, et al. Phase III prospective randomized comparison trial of depot octreotide plus interferon Alfa-2b versus depot octreotide plus bevacizumab in patients with advanced carcinoid tumors: SWOG S0518. J Clin Oncol 2017;35: 1695–703.
9. Tran TA, Leong HS, Pavia-Jimenez A, Fedyshyn S, Yang J, Kucejova B, et al. Fibroblast growth factor receptor-dependent and -independent paracrine signaling by sunitinib-resistant renal cell carcinoma. Mol Cell Biol 2016; 36:1836–55.
10. Ries CH, Cannarile MA, Hoves S, Benzj Wartha K, Runza V, et al. Targeting tumor-associated macrophages with anti-CSF-1R antibody reveals a strategy for cancer therapy. Cancer Cell 2014;25:846–59.
11. Xu JM, Wang Y, Chen YL, Jia R, Li J, Gong JF, et al. Sulfatinib, a novel kinase inhibitor, in patients with advanced solid tumors: results from a phase I study. Oncotarget 2017;8:4207686.
12. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
13. Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumour growth in patients with metastatic neuroendocrine midgut tumours: a report from the PROMID Study Group. J Clin Oncol 2009;27:4656–63.
14. Caplin ME, Pavel M, Ruszniewski P, Cwikla JB, Phan AT, Raderer M, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med 2014;371:224–33.
15. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after carcinoid: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063–72.
16. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet 2016;387:968–77.
17. Halperin DM, Kulke MH, Yao JC. A tale of two tumors: treating pancreatic and extrapancreatic neuroendocrine tumors. Ann Rev Med 2015;66:1–16.
18. Klöppel G. Neuroendocrine neoplasms: dichotomy, origin and classifications. Visc Med 2017;33:324.
19. Schmitt AM, Marinoni I, Blank A, Perren A. New genetics and genomic data on pancreatic neuroendocrine tumors: implications for diagnosis, treatment, and targeted therapies. Endocr Pathol 2016;27:200–204.
20. Nieser M, Henopp T, Brix J, Stoβ A, Sitek B, et al. Loss of chromosome 18 in neuroendocrine tumors of the small intestine: the enigma remains. Neuroendocrinology 2017;104:302–12.
21. Sahani DV, Bonaffini PA, Fernández-Del Castillo C, Blake MA. Gastroenteropancreatic neuroendocrine tumors: role of imaging in diagnosis and management. Radiology 2013;266:38–61.
22. Bodei L, Sundin A, Kidd M, Prasad V, Modin IM. The status of neuroendocrine tumor imaging: from darkness to light? Neuroendocrinology 2015;101:1–17.

23. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364:514–23.
24. Roodhart JM, Langenberg MH, Witteveen E, Voest EE. The molecular basis of class side effects due to treatment with inhibitors of the VEGF/VEGFR pathway. Curr Clin Pharmacol 2008;3:132–43.
25. Zurita AJ, Khajavi M, Wu HK, Tye L, Huang X, Kuke MH, et al. Circulating cytokines and monocyte subpopulations as biomarkers of outcome and biological activity in sunitinib-treated patients with advanced neuroendocrine tumours. Br J Cancer 2015;112:1199–205.
26. Kim KB, Chesney J, Robinson D, Gardner H, Shi MM, Kirkwood JM. Phase I/II and pharmacodynamic study of dovitinib (TKI258), an inhibitor of fibroblast growth factor receptors and VEGF receptors, in patients with advanced melanoma. Clin Cancer Res 2011;17: 7451–61.
27. Bendell J, Tolcher AW, Jones S, Beeram M, Infante JR, Larsen P, et al. A phase 1 study of ARRY-382, an oral inhibitor of colony-stimulating factor-1 receptor (CSF-1R), in patients with advanced or metastatic cancers. AACR–NCI–EORTC Int Conf Mol Targets Cancer Thera 2013; (abstr A252).
28. Batchelor TT, Sorensen AG, di Tomaso E, Zhang WT, Duda DG, Cohen KS, et al. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. Cancer Cell 2007;11:83–95.
29. Kopetz S, Hoff PM, Morris JS, Wolff RA, Eng C, Glover KY, et al. Phase II trial of infusional fluorouracil, irinotecan, and bevacizumab for metastatic colorectal cancer: efficacy and circulating angiogenic biomarkers associated with therapeutic resistance. J Clin Oncol 2010;28:453–9.
30. Tsimafeyeu I, Demidov L, Ta H, Stepanova E, Wynn N. Fibroblast growth factor pathway in renal cell carcinoma. J Clin Oncol 2010;28: 15 (suppl; abstr 4621).
31. Grande E, Capdevila J, Castellano D, Teule A, Duran I, Fuster J, et al. Pazopanib in pretreated advanced neuroendocrine tumors: a phase II, open-label trial of the Spanish Task Force Group for Neuroendocrine Tumors (GETNE). Ann Oncol 2015;26:1987–93.
32. Cameron D, Brown J, Dent R, Jackisch C, Mackey J, Pivot X, et al. Adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE): primary results of a randomised, phase 3 trial. Lancet Oncol 2013;14:933–42.
33. Moehler M, Gepfner-Tuma I, Maderer A, Thuss-Patience PC, Ruessel J, Hegewisch-Becker S, et al. Sunitinib added to FOLFIRI versus FOLFIRI in patients with chemorefractory advanced adenocarcinoma of the stomach or lower esophagus: a randomized, placebo-controlled phase II AIO trial with serum biomarker program. BMC Cancer 2016;16:699.
34. Keskin M, Ustuner Z, Dincer M, Durmus E, Celik HE, Zafer. Importance of serum VEGF and basic FGF levels in determining response to treatment and survival in patients with metastatic colorectal cancer. J Clin Oncol 2012;30: (suppl; abstr e21050).