A Single-Arm, Phase II Study of Apatinib in Refractory Metastatic Colorectal Cancer

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TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT03190616
- **Sponsor:** The First Affiliated Hospital with Nanjing Medical University

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- **IRB Approved:** Yes

LESSONS LEARNED

- Patients with metastatic colorectal cancer with good performance status or no liver metastasis could benefit from apatinib.
- Circulating tumor DNA abundance may be a predictor in serial monitoring of tumor load.

ABSTRACT

Background. Apatinib, an oral vascular endothelial growth factor (VEGF) receptor-2 inhibitor, has been approved as third-line treatment for metastatic gastric cancer in China. The aim of this study was to evaluate the efficacy and safety of apatinib, in the treatment of patients with refractory metastatic colorectal cancer after failure of two or more lines of chemotherapy.

Methods. In this open-label, single-arm, phase II study, patients with histological documentation of adenocarcinoma of the colon or rectum were eligible if they had received at least two prior regimens of standard therapies including fluoropyrimidine, oxaliplatin, and irinotecan. These patients were treated with apatinib in a daily dose of 500 mg, p.o., in the third-line or higher setting. Capture sequencing was dynamically performed to identify somatic variants in circulating tumor DNA (ctDNA) with a panel of 1,021 cancer-related genes. The primary endpoint was progression-free survival (PFS) and the tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Interim analysis was applied as predefined.

Results. From June 1, 2016 to December 31, 2017, 26 patients were enrolled. The median PFS of the whole group was 3.9 months (95% confidence interval [CI]: 2.1–5.9). The median overall survival (OS) was 7.9 months (95% CI: 4.6–10.1+).
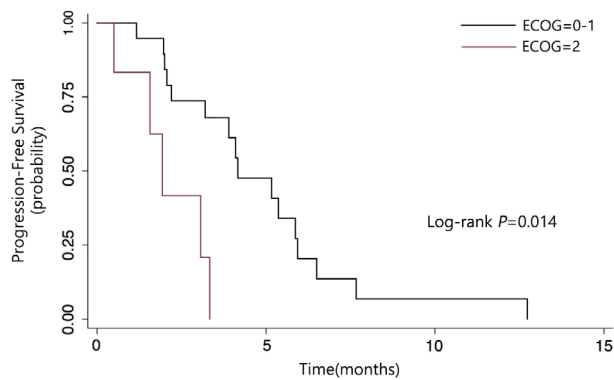
Patients with performance status (PS) 0–1 had longer PFS than those with PS 2 (4.17 months vs. 1.93 months, p = .0014). Patients without liver metastasis also had longer PFS than those who had live metastasis (5.87 months vs. 3.33 months, p = .0274). The common side effects of apatinib were hypertension, hand-foot syndrome, proteinuria, and diarrhea. The incidence of grade 3–4 hypertension, hand-foot syndrome, proteinuria, and diarrhea was 76.92%, 11.54%, 73.08%, and 23.08%, respectively. All of the patients received dose reduction because of adverse effect. Results of capture sequencing showed *APC*, *TP53*, and *KRAS* were most frequently mutant genes. ctDNA abundance increased before the radiographic assessment in ten patients.

Conclusion. Apatinib monotherapy showed promising efficiency for patients with refractory colorectal cancer, especially in patients with PS 0–1 or no liver metastasis. ctDNA abundance may be a predictor in serial monitoring of tumor load. *The Oncologist* 2019;24:883–e407

DISCUSSION

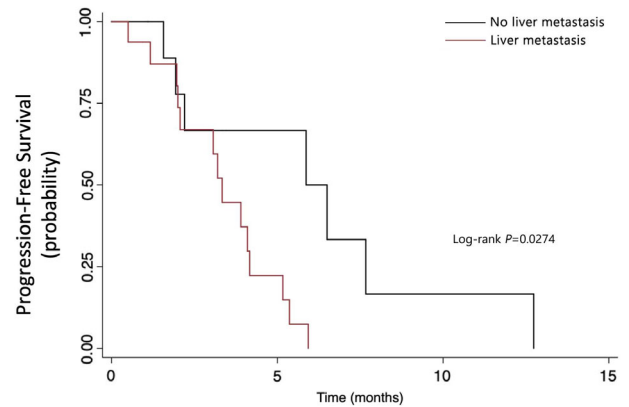Here we report results from an open-label, single-arm, phase II study aiming to evaluate the efficacy and safety of

Figure 1. Subgroup analysis of progression-free survival by ECOG performance status.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Figure 2. Subgroup analysis of progression-free survival by whether patients had liver metastasis.

apatinib as a salvage treatment for refractory metastatic colorectal cancer. To our knowledge, this is the first prospective clinical trial to investigate the safety and efficacy of apatinib in refractory metastatic colorectal cancer.

After two or more lines of prior chemotherapy, efficacy of apatinib in our study seemed to be comparable with other tyrosine kinase inhibitors reported in previous studies. However, compared with other studies, it seems that a higher incidence of adverse events of apatinib occurred. Firstly, patients in our study already have received multiple lines of chemotherapy before apatinib, with cumulative toxicity of previous drugs. Secondly, patients in our trial were required to record their blood pressure and other symptoms every day and were closely followed up by online tools; thus more adverse events could be recorded. In addition, the relatively small sample size of our study might impair the generalization of our conclusions. Patients with PS 0–1 had longer PFS than those with PS 2 in our study. A possible reason might be that patients with good physical status showed better tolerance of apatinib and thus benefited from it.

In metastatic colorectal cancer, ctDNA was reported to be an early marker of chemotherapy. Increasing ctDNA has been found ahead of radiographic detection of progression in 10 of 13 patients who had serial ctDNA detections in our study, suggesting that detection of ctDNA was associated with radiographic tumor burden. A challenge to the application of angiogenesis inhibitors is finding suitable biomarkers to select patients who are most likely to benefit from it. Here we sequenced a panel of 1,021 cancer-related genes in all patients. At least one mutation in ctDNA was detected in the baseline blood sample in 21 of 26 (81%) patients. The most frequently detected mutations were in *APC* (n = 16, 76%), *P53* (n = 12, 57%), *KRAS* (n = 9, 43%), *PIK3CA* (n = 5, 24%), *INHBA* (n = 4, 19%), *ATR* (n = 4, 14%), *BRCA2* (n = 4, 14%), *MTOR* (n = 4, 14%), *BRAF* (n = 2, 10%), and *BRD3* (n = 2, 10%). We performed a survival analysis to determine whether *APC*, *TP53*, or *KRAS* mutation was associated with PFS and OS; however, no statistical difference was found, potentially confounded by the small size of the study.

In conclusion, this study provides supporting evidence that apatinib exhibits efficacy for patients with refractory colorectal cancer, especially in patients with PS 0–1 or no liver metastasis. The common side effects of apatinib were hypertension, hand-foot syndrome, proteinuria, and diarrhea. Given that sample size was small in this study, further investigation in a larger population is required in the future.

TRIAL INFORMATION	
Disease	Colorectal cancer
Disease	Advanced cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	More than two prior regimens
Type of Study – 1	Phase II
Type of Study – 2	Single arm
Primary Endpoint	Progression-free survival
Investigator's Analysis	Active and should be pursued further

DRUG INFORMATION	
Drug 1	
Generic/Working Name	Apatinib
Trade Name	Aitan

Company Name	Jiangsu HengRui Medicine Co., Ltd.
Drug Type	Small molecule
Drug Class	Angiogenesis - VEGF
Dose	500 milligrams (mg) per flat dose
Route	Oral (po)
Schedule of Administration	28-day cycle

Patient Characteristics

Number of Patients, Male	16
Number of Patients, Female	10
Stage	IV
Age	Median (range): 57 (28–75) years
Number of Prior Systemic Therapies	Median (range): 4 (3–6)
Performance Status: ECOG	0 — 2 1 — 18 2 — 6 3 — 0 Unknown — 0
Cancer Types or Histologic Subtypes	Right or transverse colon, 6; left colon, 10; rectum, 10

Primary Assessment Method for Phase II Apatinib

Title	Total patient population
Number of Patients Screened	26
Number of Patients Enrolled	26
Number of Patients Evaluable for Toxicity	26
Number of Patients Evaluated for Efficacy	26
Evaluation Method	RECIST 1.1
Response Assessment CR	$n = 0$ (0%)
Response Assessment PR	$n = 0$ (0%)
Response Assessment SD	$n = 14$ (23%)
Response Assessment PD	$n = 9$ (69%)
Response Assessment OTHER	n = 3 (8%)
(Median) Duration Assessments PFS	3.9 months
(Median) Duration Assessments OS	7.9 months
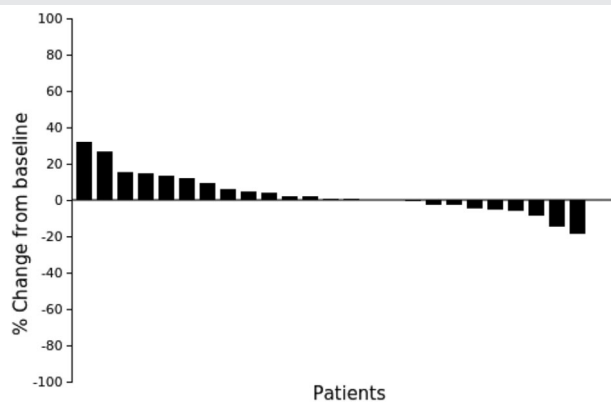
Waterfall plot showing the percentage of tumor diameter change at time of best response. Only 25 cases were recorded because one patient died before the first evaluation.

ADVERSE EVENTS

All Cycles

Name	NC/NA, %	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5, %	All grades, %
Hypertension	0	0	23	77	0	0	100
Palmar-plantar erythrodysesthesia syndrome	0	23	65	12	0	0	100
Proteinuria	4	0	23	73	0	0	96
Diarrhea	23	4	50	23	0	0	77
White blood cell decreased	73	12	15	0	0	0	27
Neutrophil count decreased	73	23	4	0	0	0	27
Platelet count decreased	73	8	15	4	0	0	27
Anemia	73	27	0	0	0	0	27
Alanine aminotransferase increased	54	42	4	0	0	0	46
Blood bilirubin increased	65	31	4	0	0	0	35
Creatinine increased	88	12	0	0	0	0	12
Alkaline phosphatase increased	61	23	8	8	0	0	39
Hypothyroidism	77	15	4	4	0	0	23

Adverse Events Legend
Toxicities occurring in every patient over the entire duration on study.
Abbreviation: NC/NA, no change from baseline/no adverse event.

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion	Study completed
Investigator's Assessment	Active and should be pursued further

Here we reported results from an open-label, single-arm, phase II study aiming to evaluate the efficacy and safety of apatinib as a salvage treatment for refractory metastatic colorectal cancer (mCRC). A total of 54 participants were planned to be enrolled. From June 1, 2016 to December 31, 2017, 26 patients were enrolled. The median PFS was 3.9 months and median OS was 7.9 months. As shown in Figure 1, patients with performance status (PS) 0–1 had longer PFS than those with PS 2 (4.17 months vs. 1.93 months, p = .0014). As shown in Figure 2, patients without liver metastasis also had longer PFS than those who had live metastasis (5.87 months vs. 3.33 months, p = .0274).

Apatinib has demonstrated encouraging anticancer activity across a broad range of malignancies, including epithelial ovarian cancer [1], glioma [2], breast cancer [3, 4], gastric cancer [5, 6], and hepatocellular carcinoma [7]. There are still another 181 undergoing studies registered at ClinicalTrials.gov (https://www.clinicaltrials.gov). Two retrospective results about apatinib in advanced mCRC had been reported. Recently a real-world retrospective study explored the apatinib used in mCRC [8]. Median progression-free survival (PFS) of this study was 3.82 months, and median overall survival (OS) was not reached. Another pilot study also suggested that apatinib was active as a third-line treatment of refractory mCRC with PFS of 4.8 months and OS of 10.1 months [9]. Although there were data from pilot and real-world retrospective studies of apatinib, this is the first prospective clinical trial to investigate the safety and efficacy of apatinib in refractory metastatic colorectal cancer to our knowledge.

After two or more lines of prior chemotherapy, the efficacy of apatinib in our study seemed to be comparable with other tyrosine kinase inhibitors (TKIs) reported in previous studies. The CORRECT [10] and CONCUR [11] trials compared regorafenib with placebo among patients with mCRC who had received at least two prior chemotherapy regimens. In the CORRECT study, median PFS and OS were 1.9 months and 6.4 months for the regorafenib group and 3.2 months and 8.8 months, respectively, in the CONCUR study. The FRESCO study [12] evaluated efficacy of oral fruquintinib as third-line or later therapy among patients with mCRC, in which the median PFS and median OS were 3.71 and 9.30 months. In our study, apatinib conferred a 3.9-month median PFS and 7.9-month median OS, which is comparable to that of regorafenib and fruquintinib. The objective response rate was approximately 1%–4.7% in trials of fruquintinib and regorafenib in mCRC [2–4]. No objective responses were observed in our trial. The relatively small sample size of our study might be the possible reason. Objective response might be observed if more patients were included in our trial.

Regarding to the safety of apatinib, hypertension, hand-foot syndrome, proteinuria, and diarrhea are the most common adverse events in our study. These events are also well-known, common adverse events in most studies of small-molecule vascular endothelial growth factor receptor (VEGFR) TKI [6, 13]. VEGFR TKI could reduce blood flow and vessel patency, which were noted not in only tumor cells, but also in normal vasculature, particularly a loss of endothelial cells fenestrae in renal glomeruli and several endocrine

organs [14]. Besides, anti-VEGF-A/VEGFR therapy also contributed to constriction of the feeder arteries supplying tumors, leading to reduced downstream blood flow and systemic hypertension [14]. These findings provided an explanation for some side effects of VEGFR TKI. Compared with other studies, it seems that a higher incidence of adverse events of apatinib occurred in our study. Firstly, patients in our study already have received multiple lines of chemotherapy before apatinib, with cumulative toxicity of previous drugs. Secondly, patients in our trial were required to record their blood pressure and other symptoms every day and were closely followed-up by online tools; thus more adverse events could be recorded. In addition, the relatively small sample size of our study might impair the generalization of our conclusions. All the patients received dose reduction because of adverse events, indicating that a dose of 500 mg each day is unacceptable in heavily pretreated patients with colorectal cancer, and the toxicity administration is very important. Patients with performance status (PS) 0–1 had longer PFS than those with PS 2 in our study. The possible reason might be that patients with good physical status showed better tolerance of apatinib and thus benefit from it.

Circulating tumor DNA (ctDNA) is tumor-derived fragmented DNA in the bloodstream, acting as a surrogate for tumor biopsy that can be detected in patients with cancer by identifying genomic aberrations. Recent studies showed that quantitative ctDNA dynamics could predict therapeutic efficacy before tumor response was assessed by imaging or clinical symptoms [15–17]. In metastatic colorectal cancer, ctDNA was reported to be an early marker of chemotherapy [18, 19]. In our study, increasing ctDNA has been found ahead of radiographic detection in 10 of 13 patients who had serial ctDNA detected, suggesting that detection of ctDNA was associated with radiographic tumor burden, which is consistent with previous studies.

A challenge to the application of angiogenesis inhibitors is finding suitable biomarkers to select patients who are most likely to benefit from it. Unfortunately, there has been no success in identifying biomarkers for any antiangiogenic drugs. As we know, VEGF signal transduction plays an important role in angiogenesis. It is worth mentioning that therapeutic intervention by blocking VEGF signal transduction occurs not only in tumor-associated blood vessels but also in nonmalignant endothelial cells and tumor microenvironment [20, 21]. Tumor microenvironment was considered as potential source of clinical biomarkers [22]. Circulating endothelial cells have been correlated with prognosis in several tumors and with response to bevacizumab in colorectal cancer [23–25]. Here we analyzed a panel of 1,021 cancer-related gene in all of the patients. The mutations detected in baseline ctDNA were showed in Figure 3A, which is consistant with MSK-IMPACT profiles (Fig. 3B). We assessed whether *APC*, *TP53*, or *KRAS* mutation was associated with PFS and OS. Unfortunately, no positive results were found. On one hand, this study was subject to limitations of small sample size; on the other hand, as we mentioned above, antiangiogenic therapies act at least in part on vascular microenvironment rather than on tumor cells, making it more difficult to identify a biomarker in circulating tumor DNA.

It should be noted that there were still some limitations in our study, including small size, possible information bias, and lack of a control group. Multicenter randomized controlled double-blind clinical trials and further follow-up are expected in the future.

In conclusion, this study provides supporting evidence that apatinib exhibits efficacy for patients with refractory colorectal cancer, especially in patients with PS 0–1 or no liver metastasis. The common side effects of apatinib were hypertension, hand-foot syndrome, proteinuria, and diarrhea. Given that sample size was small in this study, the efficacy and safety of apatinib in mCRC requires further investigation in a larger population.

DISCLOSURES
The authors indicated no financial relationships.

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FIGURE
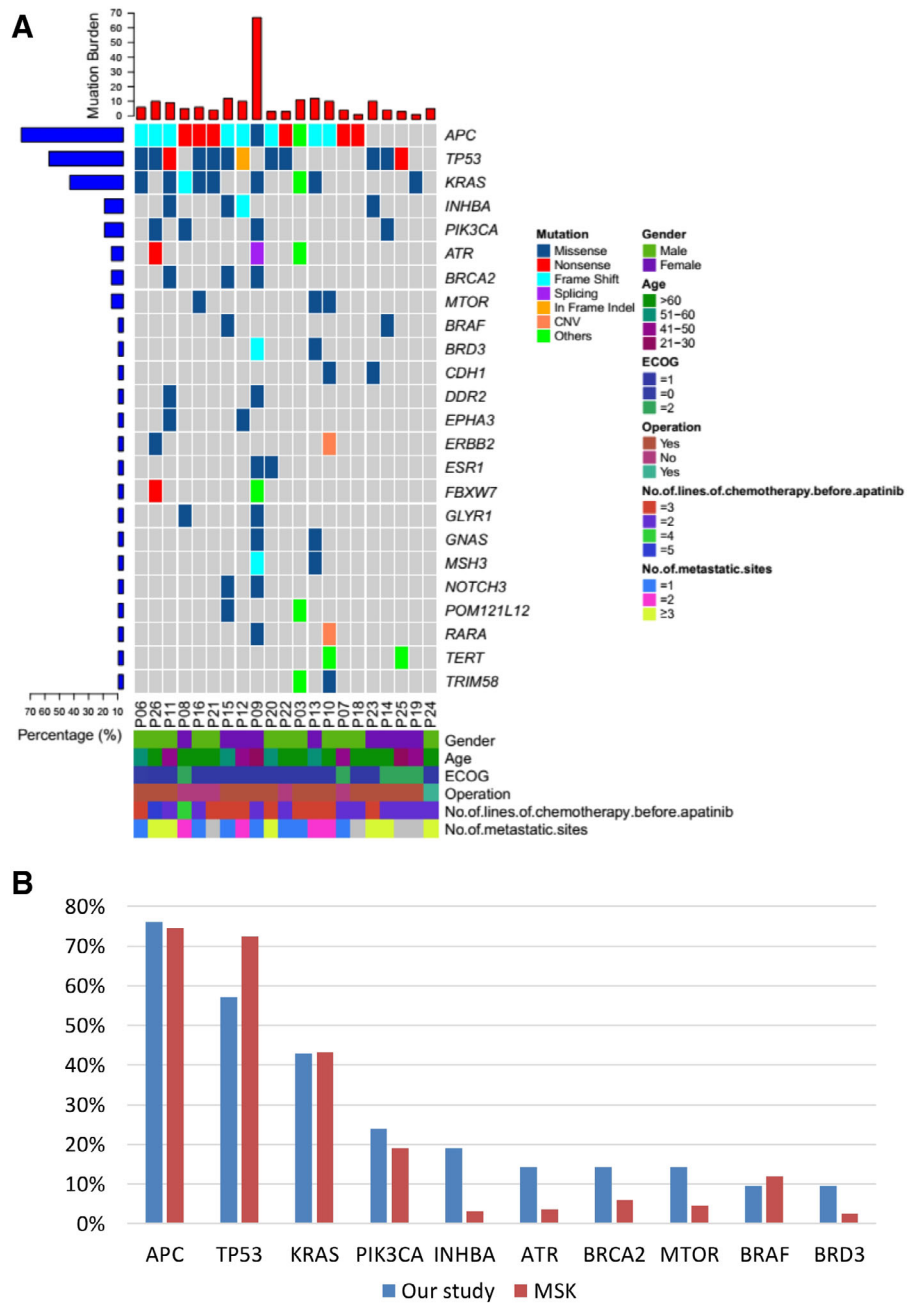
Figure 3. Mutations detected. Mutations detected in baseline **(A)** and mutations of baseline circulating tumor DNA and MSK integrated mutation profiling of actionable cancer targets (IMPACT) profiles **(B)**.
Abbreviations: CNV, copy number variation; ECOG, Eastern Cooperative Oncology Group; MSK, Memorial Sloan Kettering.

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