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# Pacritinib to inhibit JAK/STAT signaling in refractory metastatic colon and rectal cancer

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**Contributions:** (I) Conception and design: AC Lockhart, T Regenbogen; (II) Administrative support: AC Lockhart, A Brown, E Ratchford; (III) Provision of study materials or patients: A Wang-Gillam, BR Tan, M Amin, KS Pederson, H Park, R Suresh, KH Lim, AC Lockhart; (IV) Collection and assembly of data: T Regenbogen; (V) Data analysis and interpretation: T Regenbogen, L Chen, K Trinkhaus; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Background:** Treatment options for patients with refractory colorectal cancer are limited and typically provide a chance of only modest benefit. The goal of this study was to evaluate the benefit of inhibiting the JAK/STAT inflammatory pathway with single agent pacritinib in patients with metastatic refractory colorectal adenocarcinoma.

**Methods:** A single arm institutional trial was initiated and enrolled patients with metastatic colorectal cancer refractory to at least two standard lines of treatment. Pacritinib 400 mg daily was administered orally continuously in 28 day cycles.

**Results:** The trial was discontinued prior to reaching the planned accrual due to an FDA hold on pacritinib and a lack of treatment benefit. Eleven patients were enrolled and seven were evaluated for response. Median baseline C-reactive protein level was 12.1 (2.1–147) mg/L. One patient had stable disease at eight weeks by RECIST criteria and six progressed. There were no grade 4 or 5 adverse events while patients were on study. The grade 2 and lower AE events experienced were consistent with prior pacritinib trials.

**Conclusions:** In seven evaluable patients there were no objective responses. The trial was discontinued prior to completing planned accrual based on a low likelihood that the progression free survival goal of 4 months would be met.

**Keywords:** Pacritinib; refractory; colorectal cancer

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## Introduction

Treatment options for patients with metastatic colon and rectal cancer (CRC) that have progressed following standard first and second lines of treatment are limited. The approvals of regorafenib and TAS-102 filled a void; however, results are disappointing for most patients (1,2). Patients with microsatellite unstable tumors may benefit from immunotherapy, however this represents a minority

of cases (3). Novel approaches are needed for patients with refractory CRC (4).

Pre-clinical studies have demonstrated that cytokine mediated inflammation plays a role in carcinogenesis and prognosis in CRC (5). Interleukin-6 (IL-6) is an inflammatory cytokine that binds to receptors that mediate signaling by the JAK/STAT pathway. Phosphorylated STAT3 is a transcription promoter of genes associated with

cell survival, proliferation, angiogenesis, metastasis, cell adhesion, and inflammation (6). Inhibiting this pathway in both CRC cell lines and mouse CRC xenograft models resulted in apoptosis and tumor responses (7).

Pacritinib is an orally administered multi-kinase inhibitor with potent JAK and FLT3 inhibition. It has been extensively evaluated in early phase trials in hematologic malignancies including myelofibrosis, AML, and myeloproliferative neoplasms and shown to have a favorable safety profile (8).

This phase II single arm, single institutional trial sought to examine the effect of JAK/STAT inhibition with pacritinib in patients with refractory colorectal cancers.

## Methods

### *Eligibility criteria*

Eligible patients had metastatic CRC refractory or intolerant to at least two lines of chemotherapy and evaluable or measurable disease by RECIST version 1.1, and Eastern Cooperative Oncology Group performance status of 0 or 1. Patients also had to be  $\geq 18$  years old with adequate bone marrow, hepatic and renal function as well as life expectancy of at least 3 months. Key exclusion criteria included prior therapy with JAK or FLT3 inhibitors, chemotherapy or targeted agent within 2 weeks of initiating study drug, known brain metastasis, or uncontrolled intercurrent illness. The protocol (ClinicalTrials.gov identifier: NCT02277093) was approved by the institutional review board of Washington University (IRB00009237) and written informed consent was obtained for all patients before performing study-related procedures.

### *Drug administration and study design*

Pacritinib was administered orally continuously on a 28-day cycle at a dose of 200 mg twice daily. This dose was determined based on published phase one studies of pacritinib in patients with myeloid malignancies and myeloproliferative neoplasms (9). Patients underwent a baseline history and physical examination, ECG including QTc measurement, CT chest/abdomen/pelvis within 4 weeks, and CBC, CMP, and magnesium measurement. While on treatment patients were monitored with weekly blood work and every other week office visits and ECG with QTc measurement. Response assessment was by CT scans every two cycles or sooner if deemed necessary by the

treating physician.

### *Correlative studies*

Planned correlative studies included measurement of erythrocyte sedimentation rate and C-reactive protein. Serum IL-6 and interleukin-8 (IL-8) levels were also measured at baseline and monthly on treatment.

### *Statistical considerations*

We proposed a meaningful primary outcome favoring continued development of pacritinib in refractory CRC was a median PFS of 4 months. The planned sample size of 38 patients would have given the study  $\geq 0.90$  power to identify an increase in median PFS from 1.7 to 4.0 months.

## Results

### *Patient population*

Eleven patients with refractory metastatic colon or rectal cancer were enrolled between September 2015 and February 2016. Patient characteristics are presented in *Table 1*. Median age was 63 years. All patients had been treated with FOLFOX and FOLFIRI. The three RAS wildtype patients had received panitumumab and nine patients had received bevacizumab. Five patients had participated in other clinical trials. The baseline median CRP level was 12.1 mg/L with a range of 2.1 to 147 mg/L.

### *Adverse events*

All patients experienced at least grade 1 or 2 adverse events. The most common being nausea (5 patients, 50%) followed by abdominal cramping and constipation. Five patients experienced a total of 14 unique grade 3 adverse events. There were no grade 4 or 5 events on study (*Table 2*).

### *Correlative studies*

CRP and interleukin concentrations at baseline and after the first cycle were available for 7 and 9 patients respectively. Interleukin 6 and 8 plasma levels were measured by Luminex high sensitivity multiplex assay. The patient with stable disease by RECIST at 2 months had the lowest baseline CRP of 2.1 mg/L. The patient with the highest CRP on study, 147 mg/L had a large burden of

**Table 1** Characteristics of the eleven patients

Characteristic	Value
Age, year	
Median [range]	63 [43–80]
Female, no. [%]	7 [64]
Primary site, no. [%]	
Right colon	7 [64]
Left colon	2 [18]
Rectum	2 [18]
RAS mutation, no. [%]	8 [73]
Baseline CRP, mg/L	
Median [range]	12.1 [2.1–147]
Received adjuvant therapy, no. [%]	3 [27]
Prior lines of therapy for metastatic disease, no.	
Median [range]	4 [2–6]
Prior treatment, no. [%]	
FOLFOX/XELOX	11 [100]
FOLRIRI	11 [100]
Bevacizumab	9 [82]
Regorafenib	6 [55]
TAS-102	5 [45]
Clinical trial	5 [45]
Panitumumab	3 [27]
Xeloda	2 [18]

liver metastasis and an elevated total bilirubin not related to pacritinib. IL-6 and IL-8 levels increased in all patients after 1 month of treatment (*Figure 1*).

### *Antitumor efficacy*

Seven patients were evaluable for response while four patients discontinued due to an FDA hold on pacritinib prior to first radiographic imaging. Of the 7 evaluable patients, 6 had disease progression while 1 had stable disease by RECIST criteria. No patient continued pacritinib for longer than 8 weeks.

## Discussion

This study sought to demonstrate that inhibition of the

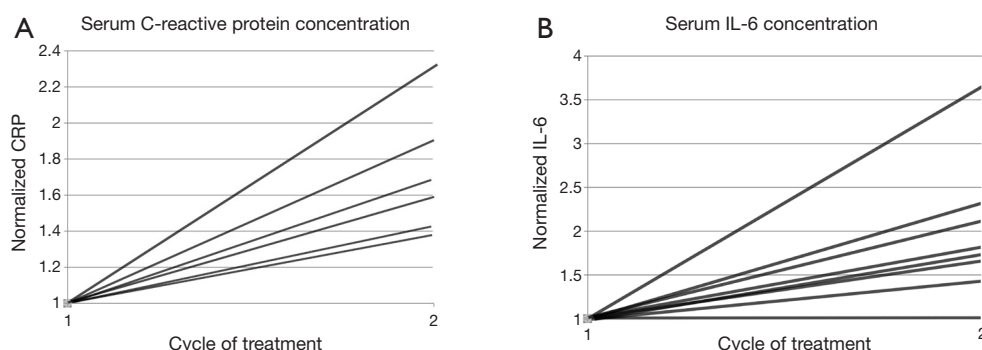
**Table 2** Adverse events in 10 evaluable patients

Event	No. of events [%]	
	Grade 1/2	Grade 3
Any adverse event	45 [100]	14 [50]
Nausea	5 [50]	1 [10]
Abdominal discomfort	4 [40]	0
Constipation	3 [30]	0
Fatigue	3 [30]	0
Mucositis	2 [20]	0
Peripheral edema	2 [20]	0
Diarrhea	1 [10]	0
Vomiting	1 [10]	0
Rash	1 [10]	0
Thrombocytopenia	0	1 [10]
Alkaline phosphatase increase	0	1 [10]
Serum bilirubin increase	0	1 [10]
Pleural effusion	0	1 [10]
Anemia	0	1 [10]

There were no grade 4/5 events reported. One patient was not included due to short duration on treatment.

JAK/STAT cytokine signaling pathway would lead to clinically meaningful responses in patients with refractory CRC. After eleven patients accrued and were initiated on treatment the Food and Drug Administration of the United States issued an order holding administration of pacritinib and halting clinical trial enrollment. This was based on emerging adverse safety data from the PERSIST-1 trial in patients with myelofibrosis treated with pacritinib. During the clinical hold we determined that re-opening the study with additional safety parameters was not in the best interest of our patients given the lack of observed response to the investigational agent and uncertainty as to the safety of pacritinib.

While we cannot evaluate the effect of pacritinib on our primary and secondary endpoints, several observations were made. The drug was only discontinued in one patient due to intolerance. There were no grade 4/5 events and no cardiovascular events were observed. The safety evaluation is limited by the short duration of treatment. Correlative analysis of inflammatory markers demonstrated an increase over the course of one month on treatment. Our opinion is



**Figure 1** Study participant serum concentrations for CRP and IL-6. Normalized serum concentrations of (A) CRP and (B) IL-6 at baseline and after one cycle of treatment with pacritinib. Each line represents an individual patient who had both the blood test at baseline and at the beginning of cycle 2. CRP, C-reactive protein.

that this finding is most likely related to progressive disease but the possibility of an interaction with pacritinib should be explored further. We were unable to find published reports of CRP, IL-6 or IL-8 measurement in patients treated with pacritinib or other JAK inhibitors.

The hypothesis that patients with high CRP levels would be more likely to respond to pacritinib was not supported by our observations. However, since no patient had an objective response to treatment this hypothesis cannot be evaluated.

The phase III CORRECT trial of regorafenib versus placebo found a small survival benefit in favor of regorafenib. Despite the modest difference, it supported a role for small-molecule multikinase inhibitors in the treatment of refractory colorectal cancer. Our median PFS expectation for pacritinib was deliberately set based on these results and pacritinib did not meet this endpoint. Further study of pacritinib as a single agent is not warranted based on our study, however; novel combinations with drugs targeting other molecular pathways could be explored.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest

to declare.

*Ethical Statement:* The protocol (ClinicalTrials.gov identifier: NCT02277093) was approved by the institutional review board of Washington University (IRB00009237) and written informed consent was obtained for all patients before performing study-related procedures.

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