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Phase II trial of Lestaurtinib, a JAK2 inhibitor, in patients with myelofibrosis

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Myelofibrosis (MF) is a myeloproliferative neoplasm (MPN) characterized by bone marrow fibrosis and clonal myeloid proliferation which can eventually evolve into acute myeloid leukemia (AML). Dysregulated Janus associated kinase (JAK) and signal transducer and activator of transcription (STAT) signaling is the unifying pathophysiologic process resulting in an increase in production of pro-inflammatory cytokines as well as cell proliferation [1]. The current treatment landscape is limited with only one Food and Drug Administration (FDA) approved therapy, ruxolitinib (Jakafi, Incyte), a selective JAK1/2 inhibitor. Pivotal phase III studies have shown that when compared to placebo or best available therapy, ruxolitinib significantly improves symptom burden and splenomegaly [2,3]. However, ruxolitinib treatment does not result in bone marrow histopathologic responses, or molecular remission, or prevent evolution to MPN-blast phase [4].

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Declaration of interest statement

In accordance with Taylor & Francis policy and my ethical obligation as a researcher, I am reporting that I, John Mascarenhas, am on the clinical trial steering committee for Incyte, Roche, and CTI Biopharma. In addition, clinical trial funding paid to my institution includes Incyte, Roche, Novartis, Merck, CTI Biopharma, Janssen, Celgene, and Promedior. I have disclosed those interests fully to Taylor & Francis, and I have in place an approved plan for managing any potential conflicts arising.

Lestaurtinib (CEP-701, Teva) is an oral multi-kinase inhibitor that potently inhibits JAK2 (IC_{50} 1 nM) and attenuates growth of primary MPN cells *in vitro* [5]. A single-center phase II trial of lestaurtinib at a dose of 80mg twice daily in MF demonstrated limited clinical activity [6]. In addition, a multicenter phase II study of lestaurtinib 80mg twice daily in patients with polycythemia vera (PV) and essential thrombocythemia (ET) resulted in only minimal reduction in *JAK2V617F* allele burden [6]. Given these results, a phase I study was performed and determined a maximum tolerated dose (MTD) of 140mg twice daily, with gastrointestinal toxicity the most common treatment-related adverse event [7].

The Myeloproliferative Disorders Research Consortium (MPD-RC) 104 trial was a National Cancer Institute (NCI)-sponsored multicenter, open-label, phase II study designed to evaluate the safety and efficacy of lestaurtinib 140 mg twice daily in patients with *JAK2V617F*-positive MF (NCT00668421). This single-arm study enrolled patients with primary MF (PMF), ET-related MF, or PV-related MF who were either newly diagnosed with intermediate or high-risk Lille score, relapsed, or had symptomatic splenomegaly. Patients received lestaurtinib at the MTD of 140 mg twice daily. The planned accrual was 40 patients. The primary efficacy endpoint was 15% or greater reduction in the *JAK2V617F* variant allele burden as quantitated in peripheral blood granulocytes after 24 weeks of treatment. Secondary endpoints were disease response by European Myelofibrosis Network (EUMNET) criteria at month 3 and 6 [8] and symptom improvement as measured by the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ). Adverse events (AEs) were classified and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAEv4.0).

From May 2010 to February 2013, 26 patients were enrolled on study. The trial was stopped early for administrative reasons in consultation with the Data Safety and Monitoring Board (DSMB) due to a combination of poor tolerability and changing treatment landscape. The median age was 74 years (range 53–87) and 57.7% of patients were male; 14 patients (53.8%) were high risk by Dynamic International Prognostic Scoring System (DIPSS) and 8 (30.8%) were intermediate-2. The median number of prior therapies was 1 (Table 1). The median time on treatment (actively receiving therapy) was 16.7 weeks (range 2–245) and the median time on study (includes period after study drug discontinuation and prior to study participation termination) was 18.1 weeks (range 2–249). Reasons for treatment discontinuation were AEs (n=13; 50.0%), patient refusal of further drug treatment (n=7; 26.9%), disease relapse (n=3; 11.5%), treatment completion per protocol (n=1; 3.8%), poor compliance (n=1; 3.8%), and medication no longer available (n=1; 3.8%).

Eight patients (30.8%) completed 12 weeks of treatment and 4 patients (15.4%) completed 24 weeks of treatment. By EUMNET criteria, no patient had a complete response at 12 or 24 weeks. Four of 8 patients (50%) had a major response at week 12, and 1 of the 4 evaluable patients at 24 weeks achieved a major response. A complete spleen response was observed in 6 of 8 evaluable patients (75%) at 12 weeks and 1 of 4 evaluable patients (25%) at 24 weeks. Quantitation of the *JAK2V617F* variant allele burden was available in 5/8 patients at 12 weeks and 3/4 patients at 12 weeks. A 15% or greater reduction in the *JAK2V617F*

variant allele burden was achieved in 2 out of 5 (40%) evaluable patients at 12 weeks and 1 out of 3 (33.3%) evaluable patients at 24 weeks. The median percent change at 12 weeks was −4% (−33.8% to 3.6%) and at 24 weeks was 0.4% (−41.5% to 9.3%).

The median MPN-TSS at baseline was 31.1 (4.4–68.9). At 12 weeks, the change in MPN-TSS in patients still on study was 0.0 (range −42.2–16.7). No individual components of the MPN-TSS significantly improved at 12 weeks. The only component of the EORTC QLQ that changed was role functioning (an assessment of ability to perform daily tasks), which worsened by a median of 16.7 points (p=0.02). No other changes in EORTC QLQ domains were observed at 12 weeks (Supplemental Table 1).

The most commonly reported (≥10%) non-hematologic AEs with lestaurtinib are listed in Supplemental Table 2 and were primarily grade 1 or 2 in severity. Diarrhea was the most common AE observed (18 patients [69.2%] grade 1/2, 2 patients [7.7%] grade 3/4) followed by nausea (15 patients [57.7%] grade 1/2, 0 patients grade 3/4]) and vomiting (6 patients [23.1%] grade 1/2, 0 patients grade 3/4). The most common hematologic adverse event was thrombocytopenia (2 patients [7.7%] grade 1/2, 6 patients [23.1%] grade 3/4), followed by anemia (2 patients [7.7%] grade 1/2, 4 patients [15.4%] grade 3/4) and leukopenia (1 patient [3.8%] grade 1/2, 1 patient [3.8%] grade 3/4) (Supplemental Table 2).

This is the first phase 2 clinical trial of lestaurtinib at a previously determined MTD of 140 mg twice daily. These preliminary results suggest that lestaurtinib may provide a spleen response in some patients at 12 weeks. However, toxicity, particularly gastrointestinal AEs, limited utility as AEs (50%) were the primary reason for study discontinuation. Unfortunately, this limited interpretation of both primary and secondary outcomes, with only 4 patients remaining on study at week 24.

As demonstrated in the phase I study of lestaurtinib, phospho-STAT5 inhibition by plasma from treated patients suggested that at doses lower than 140 mg was incomplete. Additionally, lestaurtinib is bound primarily to alpha-1-acid glycoprotein, an acute phase reactant, leading to variable amounts of free drug available for inhibition [7]. Given dose-limiting gastrointestinal AEs, the narrow therapeutic index of lestaurtinib precludes most patients from deriving clinical benefit. Thus, this agent should not be developed further for the treatment of MF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1.

Baseline Characteristics	**N=26**
Median age, years (range)	74 (53–87)
Median disease duration, months (range)	18.1 (1.4–221.4)
Disease subtype	
PMF	17 (65.4%)
PPV-MF	8 (30.8%)
PET-MF	1 (3.8%)
Lille Score	
0	11 (42.3%)
1	11 (42.3%)
2	4 (15.4%)
DIPSS	
Intermediate-1 risk	4 (15.4%)
Intermediate-2 risk	8 (30.8%)
High risk	14 (53.8%)
Karyotype	
Favorable	14 (53.8%)
Unfavorable	7 (26.9%)
Not available	5 (19.2%)
Median spleen size, cm	
0	3 (11.5%)
1–10	3(11.5%)
11–20	13(50.0%)
>20	7(26.9%)
Median number of prior MF treatments	
0	3(11.5%)
1	12(46.2%)
2	7(26.9%)
3	2(7.7%)
4	1(3.8%)
5	1(3.8%)
Prior JAK2 inhibitors	2 (7.7%)
*JAK2V617F*allele burden(%)	
Missing	11
<50%	2(11.87%)
>=50%	15(88.2%)