Leukemia Research 60 (2017) 11–17

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

A phase 2 study of momelotinib, a potent JAK1 and JAK2 inhibitor, in patients with polycythemia vera or essential thrombocythemia

Srdan Verstovsek[a,*], Stephane Courby[b], Martin Griesshammer[c], Ruben A. Mesa[d], Carrie Baker Brachmann[e], Jun Kawashima[e], Julia D. Maltzman[e], Lixin Shao[e], Yan Xin[e], Daniel Huang[f], Ashish Bajel[g]

[a] The University of Texas, MD Anderson Cancer Center, Houston, TX, USA
[b] Centre Hospitalier Universitaire de Grenoble, Grenoble, France
[c] Johannes Wesling Klinikum Minden, University of Bochum, Germany
[d] Mayo Clinic, Scottsdale, AZ, USA
[e] Gilead Sciences, Inc., Foster City, CA, USA
[f] The Oncology Institute of Hope and Innovation, Santa Ana, CA, USA
[g] Department of Clinical Haematology and Bone Marrow Transplantation, Royal Melbourne Hospital, Victoria, Australia

ARTICLE INFO

Keywords:
Momelotinib
Polycythemia vera
Essential thrombocythemia
Phase 2 study

ABSTRACT

Momelotinib is a potent inhibitor of JAK1 and JAK2 that demonstrated efficacy in patients with primary and secondary myelofibrosis. This phase 2, open-label, randomized study evaluated the efficacy and safety of oral once-daily momelotinib (100 mg and 200 mg) for the treatment of polycythemia vera (PV) and essential thrombocythemia (ET). The primary endpoint for PV was overall response rate (ORR), defined as the proportion of patients with hematocrit < 45%, white blood cell count $< 10 \times 10^9$/L, platelet count $\leq 400 \times 10^9$/L, and resolution of palpable splenomegaly, each lasting ≥4 weeks. The definition of ORR for ET excluded the hematocrit component. A total of 39 patients (28 PV, 11 ET) were enrolled, with 28 patients receiving ≥12 weeks of treatment. The study was terminated due to limited efficacy. Two patients (ORR 5.1%) met the primary efficacy endpoint (both PV 200 mg). Predose plasma levels of momelotinib were stable over time. A total of 31 (79.5%) patients experienced momelotinib-related adverse events (AEs), the most frequent being headache (23.1%), dizziness (18.0%), somnolence (15.4%), nausea (15.4%), and fatigue (15.4%). Three patients experienced serious AEs (7.7%), with 1 considered related to momelotinib (dyspnea). Peripheral neuropathy occurred in 7 (17.9%) patients (4 PV, 3 ET).

1. Introduction

Polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (MF) belong to a group of *BCR-ABL1*-negative myeloproliferative neoplasms (MPNs) [1], characterized by excessive clonal myeloproliferation, resulting, characteristically, in erythrocytosis in PV and thrombocytosis in ET [1,2]. Other disease characteristics may include leukocytosis, splenomegaly, thrombosis, bleeding, microcirculatory symptoms, and several constitutional symptoms (headache, fatigue, dizziness, pruritus, and sweating) [2,3]. Standard therapies for PV and ET are ineffective or intolerable in some patients [4,5]. Therefore, there is a need for improved, biologically targeted therapies.

A single acquired substitution of valine for phenylalanine in codon 617 in the Janus kinase (JAK) 2 gene ($JAK2^{V617F}$) is frequently present in patients with PV (about 97%) or ET (about 57%) [6–9]. This mutation renders JAK2 kinase constitutively active, disrupts Signal Transducer and Activator of Transcription (STAT) signaling, and leads to cell transformation [7,9,10]. Higher burden of $JAK2^{V617F}$ is associated with pruritus and an increased risk of fibrotic transformation in PV [11] and arterial and venous thrombosis in ET [12]. Less common MPN-associated mutations include *JAK2* exon 12 mutation (seen in PV), and calreticulin or myeloproliferative leukemia virus oncogene mutations (seen in ET) [2,13]. All of these mutations activate the JAK-STAT pathway in hematopoietic cells. A hyperactive JAK-STAT pathway, therefore, is a unifying biological abnormality in MPNs and is a target for new drug development (ie, JAK inhibitors).

Several small-molecule compounds developed to inhibit activity of JAK2 have demonstrated efficacy in patients with MF, PV, and ET [14–20], but many had further development stalled due to their toxicity

* Corresponding author at: The University of Texas, MD Anderson Cancer Center, 1515 Holcombe Blvd, Dept. of Leukemia, Unit 428, Houston, TX 77030, USA.
E-mail addresses: kjnewber@mdanderson.org, sverstov@mdanderson.org (S. Verstovsek).

http://dx.doi.org/10.1016/j.leukres.2017.05.002
Received 19 January 2017; Accepted 4 May 2017
Available online 30 May 2017

(eg, neurological side effects) and/or limited efficacy [21]. One of the newer compounds, momelotinib (formerly CYT387), is an aminopyrimidine derivative that inhibits activity of JAK1 and JAK2 [22,23], and demonstrates activity in a mouse model of *JAK2*^{V617F}-driven PV-like MPN [24] and in patients with primary and secondary MF [25,26].

This paper presents results of an open-label phase 2 study of momelotinib in patients with PV and ET. The study was terminated early due to limited efficacy. This paper discusses possible explanations for why momelotinib is efficacious in MF, but did not benefit patients with PV or ET.

2. Methods

2.1. Patients

Male or nonpregnant, nonlactating females, ≥18 years old diagnosed with either PV or ET, as defined by the 2008 WHO Diagnostic Criteria, requiring treatment, were eligible for this study [1]. Patients were required to have direct bilirubin ≤2x upper limit of normal (ULN); liver transaminases ≤3x ULN; calculated creatinine clearance of ≥45 mL/min; an Eastern Cooperative Oncology Group performance status of 0, 1, or 2; and a life expectancy > 24 weeks. Key exclusion criteria included prior splenectomy, major surgery within 28 days of first dose of study drug, myeloproliferative neoplasm-directed therapy (other than aspirin, hydroxyurea, anagrelide, and/or phlebotomy) within 21 days of first dose of study drug, use of strong cytochrome P450 3A4 inhibitors or inducers within 1 week of the first dose of study drug, prior use of a JAK1 or JAK2 inhibitor, hepatitis B or C infection, human immunodeficiency virus-positive, unresolved (grade > 1) nonhematologic toxicities from prior therapies, or the presence of peripheral neuropathy grade ≥2. All patients provided signed informed consent.

2.2. Study design

This was an open-label, randomized phase 2 study (ClinicalTrials.gov # NCT01998828). Patients with PV or ET were randomized via interactive voice/web response system 1:1 to receive either 100 or 200 mg of oral momelotinib once daily. Momelotinib 200 mg tablets were chosen for their equivalence to 300-mg capsules (data not shown), which demonstrated effectiveness in MF patients [25,26]. The 100-mg tablet of momelotinib achieved approximately 50% exposure compared with the 200-mg capsule, and was expected to be efficacious based on preliminary dose-response analyses (data not shown). The 100-mg dose was administered in this study to determine whether a lower dose would be sufficient to treat PV or ET compared with the dose needed to treat MF.

All patients were observed for 4 h after the first dose of momelotinib due to possible first-dose hypotension, which was reported within hours after first dose and returned to baseline within 24 h in a previous study on momelotinib in MF patients [26]. In the event of a grade 3 or 4 toxicity considered related to momelotinib, the treatment was interrupted for a maximum of 28 days and was restarted following resolution with dose reduced by 50 mg. If a recurrent grade 3 or 4 toxicity related to momelotinib occurred in patients already taking the 100-mg dose, the treatment was discontinued permanently. The treatment was administered for 24 weeks or until study discontinuation. Following completion of 24 weeks of treatment or study discontinuation, patients were followed for safety and disease status for 30 days. Patients had the option of continuing with maintenance treatment beyond 24 weeks at the clinically beneficial and/or tolerated dose, at investigators' discretion (separate rollover study). This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice.

2.3. Study endpoints and assessments

The primary efficacy endpoint was the overall response rate (ORR), defined for the PV cohort as the proportion of patients with hematocrit < 45% in the absence of phlebotomy, white blood cell (WBC) count < 10×10^9/L, platelet count ≤400×10^9/L, and resolution of palpable splenomegaly; each lasting for at least 4 weeks. For the ET cohort, ORR was defined as WBC count < 10×10^9/L, platelet count ≤400×10^9/L, and resolution of palpable splenomegaly; each criterion met for at least 4 weeks. For patients to be considered responders, all criteria had to be met at some point during the treatment period (not necessarily for the same 4 weeks).

A key secondary endpoint was confirmed ORR for PV or ET, defined as the proportion of responders who maintained the overall response for 12 weeks (all criteria not necessarily met for the same 12 weeks). Other secondary endpoints included proportion of patients with hematocrit < 45% in the absence of phlebotomy, WBC < 10×10^9/L, platelet count ≤400×10^9/L, and resolution of palpable splenomegaly, all lasting for at least 4 weeks; and proportion of patients with ≥10-point decrease from baseline in the modified Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) lasting for at least 12 weeks.

Following screening, patients received an electronic diary to complete the modified MPN-SAF TSS daily through the week 24 or study drug discontinuation visit. Clinical laboratory and disease assessments were performed at the scheduled visits every other week during the first 8 weeks of treatment, and every 4 weeks thereafter.

To monitor the pharmacokinetics of momelotinib and its metabolites, plasma samples were collected prior to dosing at 2, 4, 8, 12, 16, 20, and 24 weeks. Safety was evaluated by characterization of laboratory abnormalities and adverse events (AEs), which were graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

JAK2^{V617F} allele burden was determined in whole blood by allele-specific quantitative real-time polymerase chain reaction (Cancer Genetics Inc., Rutherford, NJ). Relevant plasma markers were analyzed by immunoassay (Myriad MAPv2.0, Austin, TX).

2.4. Statistical analyses

Efficacy was assessed in the intent-to-treat analysis set, which included all randomized patients. The pharmacokinetic analysis set included all patients who received ≥1 dose of momelotinib and had ≥1 momelotinib plasma concentration measurement. Safety analyses included all patients who received ≥1 dose of momelotinib, with study treatment assignment designated according to the actual treatment received.

For each treatment group, ORR and corresponding 90% exact confidence intervals, confirmed ORR, and proportions of patients meeting the criteria of secondary endpoints were calculated using the binomial distribution. Resolution of splenomegaly was defined as 100% reduction in spleen size postbaseline, with baseline spleen size defined as the last spleen size measurement by palpation from the baseline period prior to randomization. Patients who met hematocrit (PV only), WBC, and platelet criteria could be counted as responders if their postbaseline spleen size (0– < 5) remained unchanged.

Baseline and postbaseline MPN-SAF TSS was defined as the average of daily total symptom score (TSS) from the 7-day period. Daily TSS was defined as the sum of 7 individual symptom scores (each on a 0–10 point scale) collected on the same day. The steady state trough plasma concentrations (at 22–26 h postdose) of momelotinib and its metabolites were summarized by dose and nominal sampling time using descriptive statistics.