

A phase I study of danusertib (PHA-739358) in adult patients with accelerated or blastic phase chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia resistant or intolerant to imatinib and/or other second generation c-ABL therapy

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PATIENTS AND METHODS (Supplemental File)

Study Objective and Design

The primary objective of the study was to determine the maximum tolerated dose (MTD), and the dose limiting toxicities (DLTs) of danusertib administered as 3-h IV infusion daily for 7 consecutive days (Days 1 to 7) of a 14-day cycle (Schedule A) or daily for 14 consecutive days of a 21-day cycle (Schedule B) in adult patients with advanced CML-AP or CML-BP or Ph+ ALL, resistant or intolerant to imatinib and/or 2nd generation ABL kinase inhibitors. The secondary objectives included the safety and pharmacokinetics of danusertib, the pharmacodynamic modulation of biologic targets and clinical activity in this patient population.

The study was designed to start with assignment of all patients to Schedule A only, until the MTD was determined. Thereafter patients were to be allotted to Schedule B to define MTD with this schedule. A maximum of 6 cycles of treatment were planned in absence of disease progression or unacceptable toxicity. Patients who, in the investigator's judgment, were benefiting from the treatment and who had no Grade ≥ 3 toxicity could receive additional cycles after discussion with the sponsor.

Dose escalation

Cohorts of 3 patients (to be expanded to 6 if 1 patient experienced DLT) were to be sequentially allotted to progressively higher dose levels of danusertib for each schedule of treatment based on a standard "3+3" design. A modified Fibonacci design was followed for the dose escalation scheme. Intra-patient dose escalation was allowed after at least 2 cycles of treatment at the initially assigned dose, i.e. 4 weeks for Schedule A and 6 weeks for Schedule B, by increasing the dose to the next dose level as long as the dose level was deemed safe.

Dose modifications

For any Grade 3 non-hematological toxicity that recovered to Grade ≤ 1 or baseline within ≤ 4 weeks, subsequent cycles could be started without dose reduction while treatment needed to be permanently discontinued if any such toxicity failed to recover by 4 weeks or for any Grade 4 non-hematological toxicity. Cytopenias in the presence of bone marrow blast $\geq 10\%$ or normo/hypercellular marrow, did not require dose reduction/delay while cytopenias (absolute neutrophil count [ANC] $\leq 1 \times 10^9$ /L or platelet [PLT] $\leq 50 \times 10^9$ /L) associated with hypocellular marrow and blasts $< 10\%$ required treatment delay until counts recovered above these levels. The first episode of such cytopenias did not require a dose reduction but a second occurrence mandated dose reduction by one level.

Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 3.0). All patients treated were evaluable for toxicity.

Dose Limiting Toxicity Definitions

DLTs were defined as events occurring in Cycle 1, attributable to test drug including: Grade 4 neutropenia and/or thrombocytopenia for ≥ 6 weeks with bone marrow cellularity $< 10\%$ and in absence

of marrow blasts; Grade ≥ 3 non-hematological toxicity representing a shift of at least 2 grades from baseline; Grade ≥ 3 nausea/vomiting/diarrhea, despite optimal supportive therapy; clinically relevant Grade ≥ 3 electrolyte abnormalities; decrease of the left ventricular ejection fraction (LVEF) to $< 35\%$ by trans thoracic echocardiogram (TTE) or to $< 45\%$ by multi gated acquisition (MUGA) scan; decrease in the LVEF of $\geq 20\%$ compared to the baseline; recurrent or symptomatic hypertension (increases by > 20 mmHg [diastolic] from the baseline or $> 159/99$ mmHg if previously within normal limits) that could not be controlled by optimal antihypertensive treatment; non hematologic toxicity that leads to failure to administer at least 80% of the intended dose of danusertib during Cycle 1; or non-hematological toxicity that led to delay in initiation of the next cycle by more than 2 weeks.

Eligibility

Adults (≥ 18 years) with confirmed diagnosis of CML-AP, CML-BP, or Ph+ALL, resistant or intolerant to imatinib and one 2nd generation Abl-kinase inhibitor therapy were eligible. At sites in France, patients had to be resistant/intolerant to both nilotinib and dasatinib in addition to imatinib. Patients had to be at least 2 weeks away from prior chemotherapy and 5 half-lives from any investigational agent, one week from Abl kinase inhibitors and 6 weeks from stem cell transplantation. Leukapheresis, hydroxyurea, steroids or anagrelide was allowed up to one day prior to starting danusertib. Additional criteria for inclusion were performance status (PS) ≤ 2 , normal blood pressure ($\leq 140/90$ mmHg), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5x$ the upper limit of normal (ULN) or not higher than $5x$ ULN in cases of suspected liver involvement by leukemia, total bilirubin levels $\leq 1.5x$ ULN, creatinine levels $\leq 1.5x$ ULN. Additional important exclusions were active central nervous system (CNS) leukemia, uncontrolled infection, cardiac ejection fraction $< 40\%$ by TTE, uncontrolled cardiac issues e.g. uncontrolled arrhythmias, myocardial infarction or thromboembolic event within 6 months. An amendment added exclusions for QTc >450 msec and risk factors for torsade de pointes including concomitant medications that may prolong QTc.

Intrathecal chemoprophylaxis was allowed during treatment in patients with Ph+ ALL and lymphoid CML-BP. No other approved or investigational anticancer treatment was permitted during the study period.

Response Definition

Conventional cytogenetic, fluorescent in situ hybridization (FISH), real-time polymerase chain reaction (RT-PCR) in peripheral blood and/or bone marrow was done at baseline, on treatment (every 3 months for Schedule A and at end of 2nd and 4th cycle followed by every 3 months for Schedule B) and at the end of treatment. ABL mutation analysis was performed by direct sequencing at baseline and at the end of treatment.

Hematologic response was defined according to Talpaz et al¹ while cytogenetic and molecular responses were according to Baccarani et al². Briefly, complete hematologic response (CHR) required normalization of WBC count in peripheral blood with ANC $\geq 1 \times 10^9/L$ and PLT $\geq 100 \times 10^9/L$, absence of blasts and promyelocytes and no extramedullary involvement. Same criteria were applied for response to be counted as no evidence of leukemia (NEL) but it allowed the PLT to be $\geq 20 \times 10^9/L$ and $\leq 100 \times 10^9/L$ and

ANC $\geq 0.5 \times 10^9/L$ and $\leq 1 \times 10^9/L$. Cytogenetic response (CR) evaluation required assessment of at least 20 metaphases and complete cytogenetic response (CCyR) required absence of Ph+ metaphases while presence of >0 to $\leq 35\%$ Ph+ metaphases defined partial response (PCyR)

Pharmacokinetic and Pharmacodynamic Studies

Plasma samples for evaluation of danusertib PK were collected during Cycle 1 (on Days 1 and 7 or 14 in Schedule A and B, respectively,) at pre-dose, 5 minutes before end infusion (EOI), and 1, 4 and 21 hours after EOI. Plasma concentrations were measured by validated liquid chromatography–tandem mass spectrometry techniques (LC-MS-MS method).

Peripheral blood samples, analyzed for Histone H3 (HH3) and Crkl phosphorylation status (as a surrogate for BCR-ABL kinase inhibition) by western blot, were collected in Cycle 1 Day 1 at pre-dose, 30 minutes before EOI and 21 hours after EOI. Mononuclear cells (PBMC) were separated from blood by using a Ficoll-Hypaque gradient centrifugation procedure and the isolated cells processed as reported by Gontarewicz A. et al (15). Western Blots (WB) were performed and analyzed by densitometric analysis (Bio-Rad GS-700 Imaging Densitometer) using the Quantity One 1-D Analysis software. For each sample the normalization is determined by measuring the level of total histone H3. The following antibodies were used: Phospho-H3-Ser10 (Upstate), Histone-H3 (Abcam) and Phospho-Crkl (Cell Signaling Technology).

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2. Baccarani M, Saglio G, Goldman J, Hochhaus A, Simonsson B, Appelbaum F, *et al.* Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood* 2006; **108**: 1809-1820.