ELSEVIER

Blood 142 (2023) 3248–3249

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Phase 1/2 Study of Pacritinib in Combination with Azacitidine in Chronic Myelomonocytic Leukemia

Douglas Tremblay, MD[1], *Alan Shih, MDPhD*[1], *Jonathan Feld, MD*[1], *Erin Moshier*[2], *John Mascarenhas, MD*[1]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY
[2]Department of Population Health Science & Policy, Icahn School of Medicine at Mount Sinai, New York, NY

Introduction and preclinical rationale

Treatment options for chronic myelomonocytic leukemia (CMML) are limited. Hypomethylating agents (HMAs) are the only approved therapies but are associated with unsatisfactory response rates and do not impact disease evolution (Merlevede Nat Comm 2016). JAK inhibition can reduce GM-CSF signaling, which contributes to CMML pathobiology; ruxolitinib has been clinically evaluated in CMML demonstrating promising, but insufficient clinical activity. Pacritinib is a JAK inhibitor that has a unique profile which suggests it may be uniquely well suited for the treatment of CMML, including targeting of CSF1R and IRAK1, both of which are upregulated in CMML and related diseases (Obba Autophagy 2015, Rhyasen Cancer Cell 2013). Additionally, pacritinib was recently shown to be a potent inhibitor of ACVR1 (Oh AJH 2023), potentially allowing for increased iron availability and improvement in anemia.

Pacritinib has been evaluated preclinically in CMML primary samples and mouse models where it demonstrated significant, albeit heterogenous activity (Yoshimi Blood 2017). To enhance the activity of pacritinib in CMML, it was also evaluated in combination with azacitidine in GM-CSF hypersensitive cell lines and primary CMML cells where profound synergy was noted (Ma ASH 2015).

Based on encouraging preclinical data, we hypothesize that the combination of pacritinib with azacitidine will be an effective treatment strategy in CMML patients.

Methods

In this phase 1/2 trial, we will evaluate the safety and efficacy of pacritinib and azacitidine in newly diagnosed or previously treated CMML. Patients must be JAK inhibitor and HMA naïve (≤1 cycle of HMA allowed). Phase 1 will follow a '3+3' dose de-escalation design and will enroll 6-12 patients. The primary objective of this phase is to determine the recommended phase 2 dose (RP2D) of pacritinib in combination with a fixed dose of azacitidine. Pacritinib will be administered at 200mg twice daily (with a lower dose of 100mg twice daily being explored in the case of dose limiting toxicity) in combination with azacitidine 75mg/m ^{2} for 7 days.

Phase 2 will utilize a Simon's two stage design to assess the preliminary efficacy of pacritinib in combination with azacitidine at the RP2D. In the first stage, after treating 6 patients at the RP2D, there will be an interim response assessment as part of the phase 2 portion. If at least 4 among these 6 patients show a response, the trial will proceed to a second stage and enroll an additional 12 patients.

Patients will be treated for 6 cycles of 28 days each with an interim bone marrow biopsy after cycle 3. The primary endpoint of the phase 1 portion is the recommended RP2D through the assessment of dose limiting toxicities and of the phase 2 portion is the overall response rate (ORR) by the end of cycle 6 as defined by a clinical benefit or greater by myelodysplastic syndrome/myeloproliferative neoplasm International Working Group response criteria (Savona 2015). Secondary endpoints include duration of response, disease free survival, overall survival, changes in MPN-SAF total symptom scores, palpable splenomegaly, and adverse events.

Several correlative studies are planned as part of this clinical trial. Modulation of biomarkers of disease activity with treatment including GM-CSF dependent STAT5 phosphorylation, MAPK, and PI3K signaling will be analyzed. We will also evaluate changes in mutational and cytogenetic burden with treatment as well as at baseline to identify predictive biomarkers of response.

Disclosures Tremblay: *Astellas Pharma:* Research Funding; *Cogent Biosciences:* Consultancy; *GSK:* Consultancy; *Sierra Oncology:* Consultancy; *Novartis:* Consultancy; *AbbVie:* Consultancy; *Gilead:* Research Funding; *CTI Biopharma:* Consultancy, Research Funding. **Feld:** *Syros:* Research Funding; *Gilead:* Consultancy. **Mascarenhas:** *Bristol Myers Squibb, Celgene, Con-*

stellation Pharmaceuticals/MorphoSys, CTI BioPharma, Galecto, Geron, GSK, Incyte Corporation, Karyopharm Therapeutics, Novartis, PharmaEssentia, Prelude Therapeutics, Pfizer, Merck, Roche, AbbVie, Kartos: Consultancy, Membership on an entity's Board of Directors or advisory committees; *AbbVie, Bristol Myers Squibb, Celgene, CTI BioPharma, Geron, Incyte Corporation, Novartis, Janssen, Kartos Therapeutics, Merck, PharmaEssentia, Roche:* Research Funding; *Bristol Myers Squibb, Celgene, CTI BioPharma, Geron, Incyte Corporation, Janssen, Kartos Therapeutics, Merck, Novartis, PharmaEssentia, Roche; Participated in consulting or advisory committees - AbbVie, Bristol Myers Squibb, Celgene, Constellation Pharmac:* Research Funding; *Incyte, Novartis, Roche, Geron, GSK, Celgene/BMS, Kartos, AbbVie, Karyopharm, PharmaEssentia, Galecto, Imago, Sierra Oncology, Pfizer, MorphoSys, CTI Bio:* Consultancy; *AbbVie, CTI BioPharma Corp, a Sobi company, Geron, GlaxoSmithKline, Imago, Incyte, Kartos, Kayropharm, MorphoSys, Novartis, Pfizer, PharmaEssentia, Sierra:* Consultancy; *GSK:* Honoraria.

OffLabel Disclosure: Pacritinib

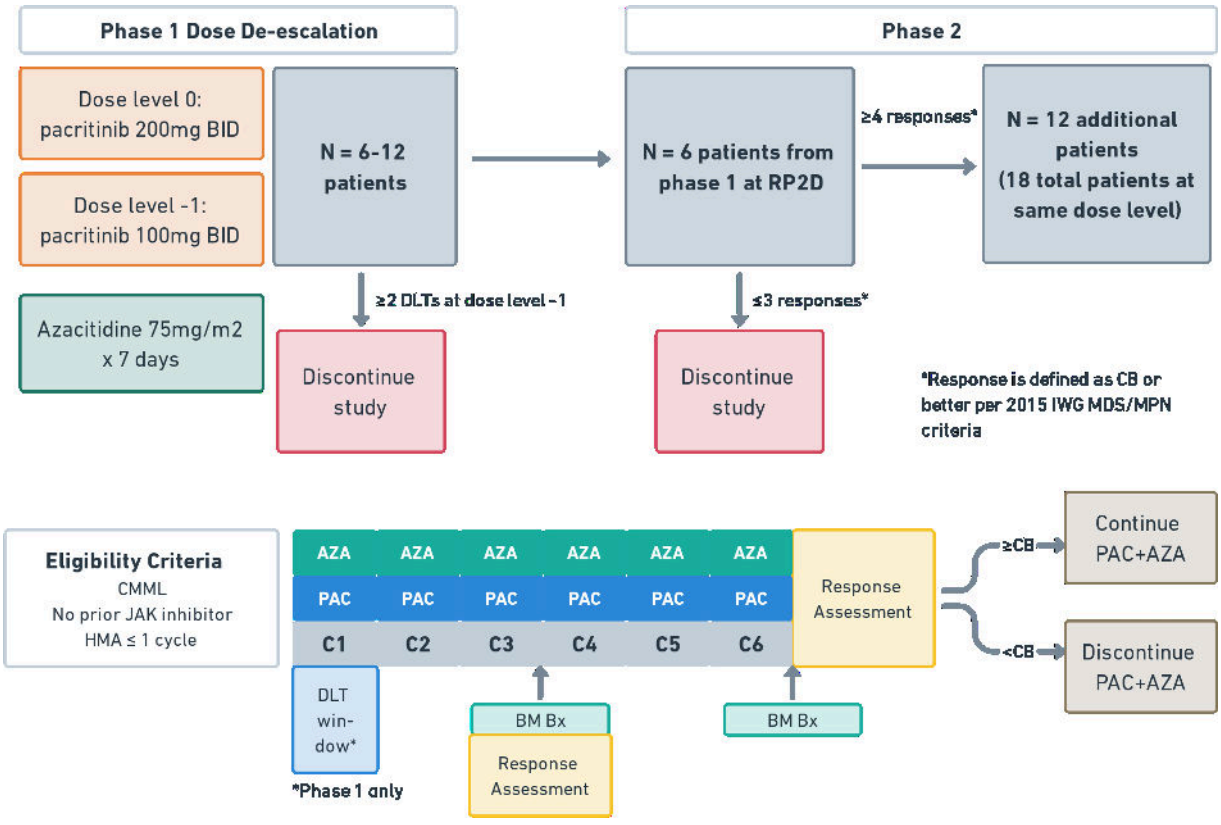

Figure 1

https://doi.org/10.1182/blood-2023-174960