ELSEVIER

Blood 142 (2023) 6440–6442

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

A Phase I Study of Ruxolitinib in Combination with Abemaciclib for Patients with Primary or Post-Polycythemia Vera/Essential Thrombocythemia Myelofibrosis

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Background and Significance: Patients (pts) with primary or secondary myelofibrosis (MF) experience variable degrees of constitutional symptoms, cytopenias and risk of progression to acute myeloid leukemia leading to a reduced life-expectancy compared to age-matched controls. Although several oral Janus Kinase (JAK) inhibitors such as ruxolitinib (RUX) have been approved by the US FDA based on improvements in symptom burden and spleen volume compared to physician's choice of best available therapy, the duration of response to these agents is generally time-limited and treatment with JAK inhibitors is not considered to have disease-modifying potential. Furthermore, the median overall survival after RUX discontinuation is only 11-14 months highlighting the need for novel mechanism-based therapies for pts with disease progression on RUX.
JAK2 V617F mutations promote transition from the G1 to S-phase of the cell cycle via increased expression of CDC25A, which is also upregulated in primary MPN patient samples. Additional cell cycle regulators such as CDK6 and Cyclin D have also been implicated in MF pathogenesis and contribute to myeloproliferation. Finally, we and others have shown synergistic effects of the combination of CDK4/6 inhibitors and RUX in murine models of MF (Rampal et al., CCR 2021) including improvement in bone marrow fibrosis suggesting the potential for disease-modifying activity. Several CDK4/6 inhibitors have been approved by the US FDA for the treatment of hormone receptor-positive metastatic breast cancer establishing a robust record of safety data. These preclinical data and known safety profile of CDK4/6 and RUX as single agents, provide rationale for combining CDK4/6 and JAK inhibition in pts with MF.
Methods: This multicenter, phase I dose-escalation trial (NCT05714072) evaluates the safety of RUX + the CDK4/6 inhibitor abemaciclib in primary or secondary MF pts with intermediate-1/2 or high-risk disease by DIPSS who require treatment and had an inadequate response to RUX. Inadequate response to RUX is defined by (I) palpable splenomegaly ≥5 cm below the left costal margin at study entry AND/OR (II) active MPN symptoms, as defined by the presence of one symptom score ≥5 or two symptom scores ≥3 using the screening MPN-SAF TSS. Pts must have been on a stable dose of 10 mg or 15 mg BID of RUX for at least 4 weeks prior to enrollment with adequate platelet (≥75 x 10^9/L) and neutrophil counts (≥1.5 x 10^9/L). Key exclusion criteria include prior treatment with a CDK4/6 inhibitor, accelerated- or blast-phase MPN, platelet count <50 x 10^9/L in the 4 weeks before screening or platelet transfusion(s) within 8 weeks before screening, and absolute neutrophil count <0.5 x 10^9/L in the 4 weeks before screening. Among the currently FDA-approved CDK4/6 inhibitors, abemaciclib was chosen for combination therapy due to less myelosuppressive effects compared with other CDK4/6 inhibitors.
This trial uses a conventional "3+3" dose-escalation design (**Figure**), pts will be treated with increasing doses of abemaciclib added to a stable dose of RUX (10 mg or 15 mg BID). The pre-study dose of RUX will be maintained to determine the maximum tolerated dose of the combination of RUX and abemaciclib. The primary endpoint is to determine the maximum tolerated dose of RUX + abemaciclib. Secondary endpoints include measures of efficacy such as overall response rate, duration of response and survival endpoints. Exploratory endpoints include changes in allele fraction of driver mutations, gene expression profiling, and clonal architecture to identify biomarkers of response, mechanisms of resistance, and to assess for any disease-modifying effects of the combination therapy. At this time, 2 pts have been enrolled at dose level 0 without any dose-limiting toxicities observed. In line with the known adverse event profile of abemaciclib, grade 1 diarrhea occurred in one patient. One patient developed grade 3 neutropenia which promptly resolved with holding abemaciclib. No unexpected safety signal

was noted and enrollment continues. This trial is open to enrollment at Memorial Sloan Kettering Cancer Center and will commence at MD Anderson Cancer Center later this year.

Disclosures Masarova: *MorphoSys US:* Membership on an entity's Board of Directors or advisory committees. **Pemmaraju:** *Physician Education Resource (PER):* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Patient Power:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Imedex:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Magdalen Medical Publishing:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Intellisphere:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Harborside Press:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Dava Oncology:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Celgene:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; 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*United States Department of Defense (DOD):* Research Funding; *Pacylex:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Neopharm:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *EUSA Pharma:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Curio Science:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Protagonist Therapeutics, Inc.:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Stemline:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Cimeio Therapeutics AG:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *ClearView Healthcare Partners:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *CTI BioPharma:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; 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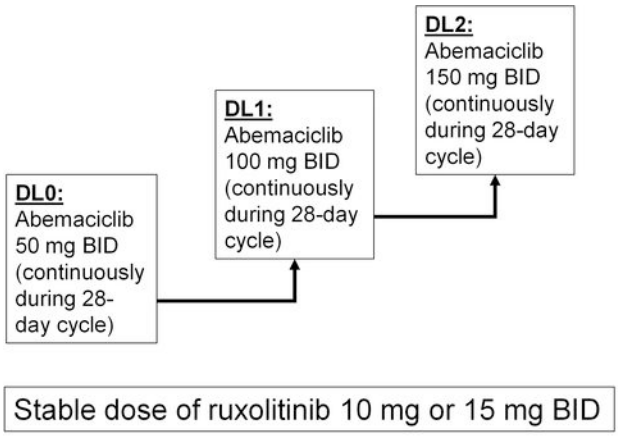
*AbbVie:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *HemOnc Times/Oncology Times:* Other: Uncompensated; *Bristol Myers Squibb Pharmaceuticals:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Stein:** *Eisai:* Research Funding; *PinotBio:* Consultancy; *Novartis:* Consultancy; *Bristol Myers Squib:* Consultancy, Research Funding; *Servier:* Consultancy; *Calithera:* Consultancy; *Daiichi:* Consultancy; *Aptose:* Consultancy; *Foghorn:* Consultancy; *CTI Biopharma:* Consultancy; *Janssen:* Consultancy; *Syros:* Consultancy; *Astellas:* Consultancy; *Blueprint:* Consultancy; *Ono Pharma:* Consultancy; *OnCusp:* Consultancy; *Syndax:* Consultancy; *Neoleukin:* Consultancy; *Gilead:* Consultancy; *Agios:* Consultancy; *Jazz:* Consultancy; *Menarini:* Consultancy; *Genentech:* Consultancy; *Genesis:* Consultancy; *Abbvie:* Consultancy. **Mauro:** *Pfizer:* Consultancy, Honoraria, Other: Travel, accommodation, and expenses, Research Funding; *Takeda:* Consultancy, Honoraria, Other: Travel, accommodation, and expenses, Research Funding; *Bristol Myers Squibb:* Consultancy, Honoraria, Other: Travel, accommodation, and expenses, Research Funding; *Sun Pharma/SPARC:* Research Funding; *Novartis:* Consultancy, Honoraria, Other: Travel, accommodation, and expenses, Research Funding. **Rampal:** *Zentalis:* Consultancy; *Celgene-BMS:* Consultancy; *Incyte:* Research Funding; *Servier:* Consultancy; *Zentalis:* Research Funding; *GSK-Sierra:* Consultancy; *Kartos:* Consultancy; *Morphosys/Constellation:* Consultancy; *Sumitomo:* Consultancy; *Dainippon:* Consultancy; *Karyopharm:* Consultancy; *Constellation:* Research Funding; *Stemline:* Research Funding; *Galecto:* Consultancy; *CTI BioPharma Corp:* Consultancy; *Pharmaessentia:* Consultancy; *Ryvu:* Research Funding; *Incyte:* Consultancy. **Bose:** *Kartos, Telios, Ionis, Disc, Janssen, Geron:* Research Funding; *Incyte, BMS, CTI, Morphosys, Blueprint, Cogent, Sumitomo:* Honoraria, Research Funding; *GSK, Novartis, Karyopharm, AbbVie, Pharma Essentia, Jubilant, Morphic:* Honoraria.



Inclusion	Exclusion
• Adult patients with PMF or post-PV/ET MF • Inadequate response to ruxolitinib: palpable splenomegaly ≥5 cm AND/OR active MPN symptoms[7] • Treated with ruxolitinib for ≥12 weeks with a stable dose (10mg or 15mg BID) for the preceding ≥4 weeks. • Adequate hematologic (ANC ≥1.5 X 10^9/L, Platelets ≥75 x 10^9/L) and organ function	• Prior therapy with CDK4/6 inhibitors • Splenic irradiation within the 4 months preceding study treatment initiation. • Platelet count <50 × 10^9/L in the 4 weeks before screening or platelet transfusion(s) within 8 weeks before screening. • ANC <0.5 × 10^9/L in the 4 weeks before screening. • Concurrent use of strong inhibitors or inducers of CYP3A

Figure. Study design, key inclusion and exclusion criteria and endpoints. This is a multicenter, phase I dose-escalation trial of abemaciclib in combination with ruxolitinib in patients with primary or secondary myelofibrosis. The study will follow a conventional "3+3" dose escalation design with safety as the primary endpoint.

Figure 1

https://doi.org/10.1182/blood-2023-174322