**ADORE: A Randomized, Open-label, Phase 1b, Open-Platform Study Evaluating Safety and Efficacy of Novel Ruxolitinib Combinations in Patients with Myelofibrosis**

**STUDY DESIGN**

- **The ADORE study (NCT04957621, EU4A1ACT 2019-003775-25) is a three-part, open-label, multicenter, open-platform study (Figure 1) that assesses the safety and efficacy of RUX in combination with two novel compounds that impact the hematopoietic environment through distinct mechanisms.**

- **Part 1** will assess the safety of five RUX combinations; those which are safe and tolerable may proceed to Part 2.

- **In Part 2, patients will be randomized to one of the selected combinations or RUX monotherapy.** Initial analyses of safety, efficacy, and tolerability of each combination arm will occur in Part 3.

- **Part 2a** will include safety, efficacy, and endpoints for the primary outcomes of the RUX + siremadlin arm, progressing to Part 2b for additional endpoints and endpoints for other arms.

- **Part 2b** will include safety, efficacy, and endpoints for the primary outcomes of the RUX + rineterkib b arm, progressing to Part 2c for additional endpoints and endpoints for other arms.

- **Part 2c** will include safety, efficacy, and endpoints for the primary outcomes of the RUX + DORE28 arm, progressing to Part 2d for additional endpoints and endpoints for other arms.

- **In Part 3,** the 4 arms will be expanded to 1:1:1:1 dose ratios, with the combination arms moving to a 3:1 dose ratio, and the RUX monotherapy arm to 0.5:1 ratio.

**Study Population**

- **Eligible patients must be ≥18 years old, have a confirmed diagnosis of MF based on bone marrow biopsy, and have documented MFSAF v4.0 ≥4.0.**

- **Patients must have received RUX as monotherapy or in combination with another compound at least once, and have been on RUX therapy for at least 3 months.**

- **Patients must have a baseline Hb < 11 g/dL (≤6.8 mmol/L) and a stable RUX dose of at least 25 mg BID (20 mg BID for dose-escalation studies).**

- **Patients must have a bone marrow biopsy with MF features, and have a baseline MFSAF v4.0 ≥4.0.**

**Inclusion Criteria**

- **Age ≥ 18 years**

- **Diagnosis of PMF, PMF-PV or PMF-PP**

- **Palliative spleen of at least 2 cm from the left costal margin or enlarged splenic volume of at least 450 cm³ per MRI or CT scan**

- **Treated with RUX for at least 12 weeks prior to study treatment**

- **Stable (no dose adjustments) RUX dose for at least 4 weeks prior to first dose of study treatment**

- **Hb ≥ 11 g/dL (≥6.8 mmol/L)**

- **Absolute neutrophil count ≥ 1,000/µL**

- **Platelet counts ≥ 75,000**

- **Part 2 and part 3: Platelet counts ≥ 50,000**

**Exclusion Criteria**

- **Receives any investigational agent for the treatment of MF (RUX monotherapy or combination) within 30 days of first dose of study treatment**

- **Peripheral blood blasts count >10%**

- **Inadequate liver function and/or severely impaired renal function**

- **Active infection that requires therapy**

- **History of a second primary malignancy in the past 3 years in need of systemic treatment**

- **History or current diagnosis of uncontrolled or significant cardiac disease**

- **Significant immune deficiency (including use of immunosuppressive drugs)**

- **Subjects with known IFU mutation or deletion of TP53**

- **Receives blood platelet transfusion within 28 days prior to first dose of study treatment**

**STUDY RATIONALE**

- **Myelofibrosis (MF) is a progressive, life-threatening disease and although ruxolitinib (RUX) changed the treatment paradigm, there remains an unmet need to improve outcomes**

- **Combining RUX with novel therapies may deliver clinical benefit, such as improvement in cytopenia associated marrow fibrosis, for patients with MF.**

- **The ADORE study is a three-part, open-label, multicenter, phase 3/4 platform study designed to assess the safety and efficacy of novel RUX combinations in combination with RUX in patients with MF.**

- **A total of approximately 240 patients are planned to be enrolled, and the study is designed to assess the safety and efficacy of RUX combinations in combination with RUX in patients with MF.**

**CRITERIA OF STUDY**

- **RUX is a first-in-class JAK1/2 inhibitor approved for the treatment of MF.**

- **Avani Mohapatra, Associate Clinical Development Medical Director, Novartis:**

- **FRCP, FRCPath, Jean-Jacques Kiladjian, MD, PhD:**

- **Alessandro Ross, MD, PhD:**

**REFERENCES**


