Poster 1489

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ADORE: A Randomized, Open-Label, Phase 1/2, Open-Platform Study Evaluating Safety and Efficacy of Novel Ruxolitinib Combinations in Patients with Myelofibrosis

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SUMMARY

- Myelofibrosis (MF) is a progressive, life-threatening disease and although ruxolitinib (RUX) has changed the treatment paradigm, there remains an unmet need to improve outcomes
- Combining RUX with novel therapies may deliver clinical benefits, such as improvement in cytopenia and bone marrow fibrosis, for patients with MF
- The ADORE study is a three-part, open-label, multicenter, phase 1/2 platform study assessing the safety and efficacy of five novel compounds in combination with RUX in patients with MF
- A total of approximately 240 patients are planned to be enrolled, assuming all five combination treatments enter Part 2 and one combination treatment is expanded in Part 3
- As of October 2021, the study has completed enrollment of the Part 1 siremadlin 20 mg, siremadlin 40 mg, rineterkib 200 mg and crizanlizumab cohorts; and is currently enrolling the siremadlin 30 mg cohort

ADORE STUDY CONTACTS

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STUDY RATIONALE

The burden of MF
- MF is a myeloproliferative neoplasm (MPN) that can develop *de novo* (primary MF) or from the progression of antecedent MPNs, in particular polycythemia vera (PPV-MF) or essential thrombocythemia (PET-MF)
- MF is a progressive, severe, and life-threatening MPN characterized by bone marrow fibrosis and splenomegaly, and is associated with debilitating constitutional symptoms as well as reduced survival[1,2]

Ruxolitinib is the standard of care in MF
- RUX is a first-in-class JAK1/JAK2 inhibitor approved for the treatment of MF[3]
- As the standard of care for MF, RUX has shown superiority over placebo (COMFORT-I) and best available therapy (COMFORT-II) in improving splenomegaly, MF-related symptoms, and QoL[4,5], and has demonstrated an overall survival benefit[6–9]

An unmet need remains
- However, RUX is not curative, cytopenias remain a challenge and some patients lose response or discontinue treatment due to adverse events[6,7]
- RUX combined with novel agents may deliver clinical benefits (improvement of PFS, improvement of cytopenia and in particular anemia), as well as improvement in QoL and reduction of bone marrow fibrosis

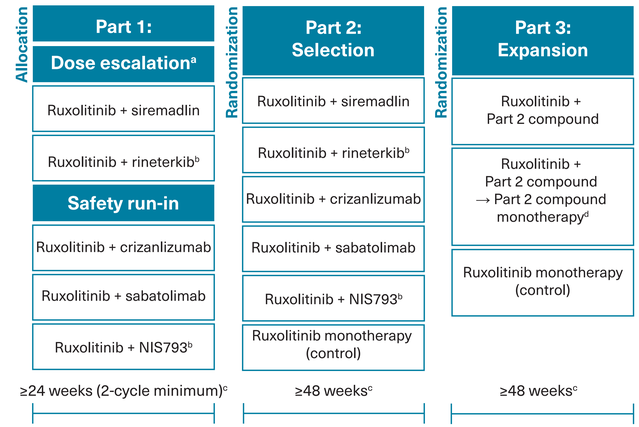
STUDY DESIGN

- The ADORE study (NCT04097821, EUDRACT 2019-000373-23) is a three-part, open-label, multicenter, phase 1/2 platform study (**Figure 1**) assessing the safety and efficacy of RUX in combination with five novel compounds that impact the hematopoietic environment through different mechanisms
- **Part 1** will assess the safety of five RUX combinations; those which are safe and tolerable may be selected for Part 2
- In **Part 2**, patients will be randomized to one of the selected combinations or RUX monotherapy (control); interim analyses of preliminary efficacy and futility after ≥24 weeks of combination treatment will determine if the combination treatment will proceed to Part 3
- In **Part 3**, patients will be randomized to the combination treatment, RUX cessation, or RUX monotherapy; patients in the RUX cessation arm will be treated with combination therapy for 12 weeks, followed by RUX tapering and novel agent monotherapy

Table 1: Study endpoints

Primary	**Part 1:** • Incidence and severity of dose-limiting toxicities within the first 2 cycles	**Parts 2/3:** • Response rate (a composite of anemia improvement [increase in Hb of 1.5 g/dL], no spleen volume progression, and no symptom worsening) at the end of cycle 8 (NIS793 arms) or cycle 6 (other arms) (24 weeks)
Secondary	**All parts:** • PK parameters • Presence and/or concentration of anti-crizanlizumab, anti-sabatolimab or anti-NIS793 antibodies • Frequency, duration and severity of AEs, abnormalities in vital signs, laboratory test values, and ECG data	**Parts 2/3:** • Proportion of subjects achieving improvement of Hb levels of ≥1.5 g/dL and ≥2.0 g/dL from baseline • Change in MFSAF v4.0 and EORTC QLQ C30 from baseline • Change in spleen length (by palpation) and/or volume (by MRI/CT) from baseline • PFS • Proportion of subjects achieving improvement in bone marrow fibrosis of 1 grade from baseline

Figure 1: ADORE study design



[a]Dose escalation required to determine Phase 2 dose for siremadlin and rineterkib arms (already known for other agents). [b]Rineterkib and NIS793 added to study protocol in November 2020. [c]NIS793 has a 21-day cycle; all other arms have 28-day cycles. [d]Patients will be treated with combination therapy for 12 weeks, followed by novel agent monotherapy. Part 1 dosing: ruxolitinib, 5 to 25 mg administered orally twice daily (administered at the same stable dose used prior to study entry); siremadlin, 20 mg starting dose and higher dose levels include 30 mg and 40 mg, orally once daily on days 1 to 5 of a 28-day cycle; rineterkib, 200 mg starting dose and higher dose level of 300 mg, orally once daily in 28-day cycles; crizanlizumab, 5 mg/kg intravenously every 4 weeks; sabatolimab, 800 mg intravenously every 4 weeks; NIS793, 2100 mg intravenously every 3 weeks. Part 2/3: as per Part 1 except siremadlin and rineterkib, which will use recommended Phase 2 dose established in Part 1.

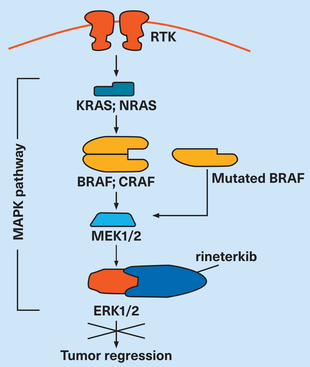
Table 2: Key inclusion and exclusion criteria

Inclusion ✓	Exclusion ✗
• Age ≥ 18 years • ECOG performance status of 0-2 • Diagnosis of PMF, PET-MF or PPV-MF • Palpable spleen of at least 5 cm from the left costal margin or enlarged spleen volume of at least 450 cm^3 per MRI or CT scan • Treated with RUX for at least 12 weeks prior to study treatment • Stable (no dose adjustments) RUX dose (between 5 and 25 mg bid) for ≥ 4 weeks prior to first dose of study treatment • Hb < 11 g/dL (≤ 6.8 mmol/L) • Absolute neutrophil count ≥ 1,000/μL • Part 1: Platelet counts ≥ 75,000/μL • Part 2 and part 3: Platelet counts ≥ 50,000/μL	• Received any investigational agent for the treatment of MF (except RUX) within 30 days of first dose of study treatment • Peripheral blood blasts count of > 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 *TP53* mutation or deletion of *TP53* • Received blood platelet transfusion within 28 days prior to first dose of study treatment

STUDY COMPOUNDS

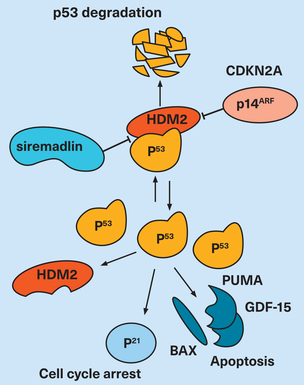
RUX + rineterkib
ERK1/2 inhibitor

- Constitutive *JAK2* signaling results in activation of MEK/ERK signaling, which may limit the efficacy of *JAK2* inhibition[10]
- Rineterkib is a small molecule inhibitor of ERK1/2 that has demonstrated preclinical activity in multiple MAPK activated cancer cells and xenograft models[11]
- Combined *JAK2*/ERK inhibition reduced proliferation of *Jak2*^{V617F} cells and corrected erythrocytosis and splenomegaly of *Jak2*^{V617F} MPN mice[12]



RUX + siremadlin
HDM2 inhibitor

- HDM2 is a key negative regulator of the tumor suppressor p53[13]
- *JAK2* mutations are thought to induce the expression of HDM2, which acts to degrade p53[13,14]
- Siremadlin is a small molecule inhibitor of the p53/HDM2 interaction, protecting p53 from degradation and restoring the p53-mediated apoptotic pathway[15]
- Siremadlin has demonstrated potent, single agent activity in various *in vitro* and *in vivo* tumor models with wild type *TP53*[14,16,17]



RUX + crizanlizumab anti-P-selectin mAb	• In patients with MF, impaired megakaryocytes express high levels of surface P selectin, which triggers a process of neutrophil emperipoiesis and leads to increased TGF-β release and disease progression[18] • Crizanlizumab is a mAb that binds to and inhibits P-selectin on platelet and endothelial cell surfaces[19] • Pharmacologic inhibition of P-selectin in combination with RUX treatment normalized TGF-β signaling in the bone marrow of an MF mouse model, leading to improvement in cellularity and a decrease in fibrosis[20]
RUX + sabatolimab TIM-3-targeting mAb	• TIM-3 is an immune checkpoint molecule expressed on activated and regulatory T cells, NK cells, and multiple subsets of myeloid cells and DCs[21-23] • Sabatolimab is a mAb that blocks the binding of TIM-3 to its ligand PtdSer[23] • TIM-3 blockade restores activity of exhausted T cells, and may diminish suppressor activity of regulatory T cells[24]
RUX + NIS793 TGFβ-targeting mAb	• TGF-β is a pro-inflammatory cytokine that promotes bone marrow fibrosis[25,26] • NIS793 binds to TGF-β1 and TGF-β2 and displays TGF-β1- and TGF-β2-neutralizing activity[27] • In mouse models of MF, lack or inhibition of TGF-β1 led to no or reduced fibrosis and reduced extramedullary hematopoiesis[25,28]

AE, adverse event; AML, acute myeloid leukemia; BAX, bcl-2-like protein 4; bid, twice daily; CDKN2A cyclin dependent kinase inhibitor 2A; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ C30: European organization for research and treatment of cancer quality of life questionnaire; ERK, extracellular signal-regulated kinase; GDF-15, growth/differentiation factor-15; Hb, hemoglobin; HDM2, human double minute 2; JAK, Janus kinase; KRAS, kirsten rat sarcoma virus; mAb, monoclonal antibody; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; MFSAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imaging; MPN, myeloproliferative neoplasm; NRAS, neuroblastoma RAS viral oncogene homolog; PFS, progression-free survival; PK, pharmacokinetics; PMF, primary myelofibrosis; PtdSer, phosphatidylserine; PUMA, p53 upregulated modulator of apoptosis; QoL, quality of life; RTK, receptor tyrosine kinase; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; TIM-3, T-cell immunoglobulin and mucin domain-3; TP53, tumor protein 53.

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