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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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- **Bruyère Mahuzier:** Novartis: Current Employment.
- **Monika Wroclawska:** Novartis: Current Employment.
- **Celine Wilke:** Novartis: Current Employment and Current holder of individual stocks in a privately-held company.
- **Angela Zhang:** Novartis: Current Employment.
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Study rationale

- 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 (RUX) is a first-in-class JAK1/JAK2 inhibitor[3] that 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]
- However, RUX is not curative, cytopenias remain a challenge and some patients lose response or discontinue treatment due to adverse events[6,7]
- The ADORE study (NCT04097821) is a three-part, open-label, multicenter, phase 1/2 platform study assessing the safety and efficacy of RUX in combination with five novel compounds that impact the hematopoietic environment through different mechanisms

1. Cervantes F, et al. *Blood*. 2009;113(13):2895–2901. 2. Harrison CL, et al. *Ann Hematol.* 2017;96(10):1653–1665. 3. JAKAFI (ruxolitinib) Prescribing information (PI). Available from: www.jakafi.com/pdf/prescribing-information.pdf. Accessed October 2021. 4. Harrison C, et al. *N Engl J Med*. 2012;366(9):787–798. 5. Verstovsek S, et al. *N Engl J Med*. 2012;366(9):799–807. 6. Harrison C, et al. *Leukemia*. 2016;30(8):1701–1707. 7. Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):55. 8. Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):156. 9. Vannucchi AM, et al. *Haematologica*. 2015;100(9):2–8. JAK, Janus kinase; MF, myelofibrosis; MPN, myeloproliferative neoplasm; QoL, quality of life; RUX, ruxolitinib.

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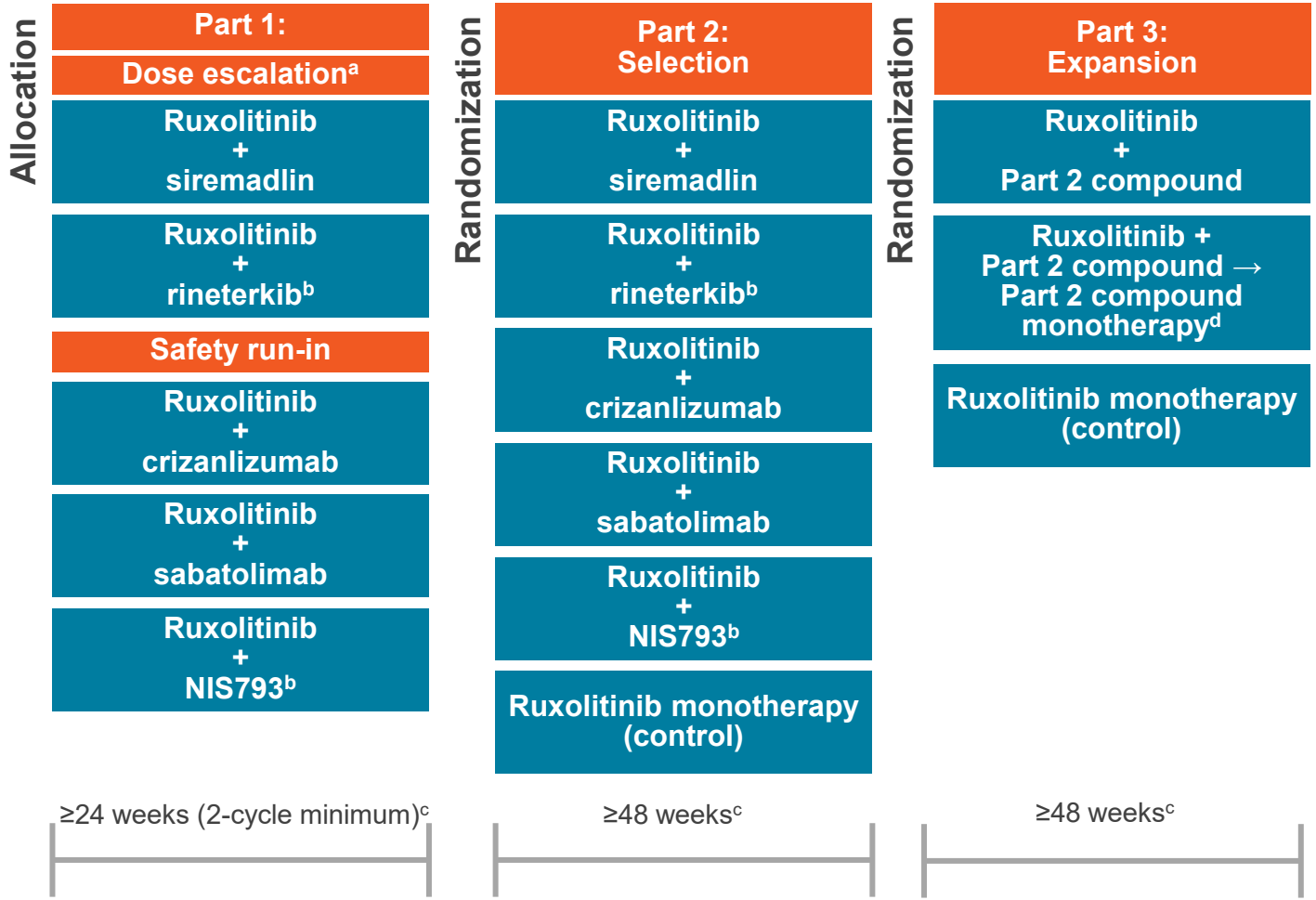
Study design



- **Part 1:** assesses the safety of five RUX combinations; those which are safe and tolerable may be selected for Part 2

  Part 1 primary endpoint: incidence and severity of dose-limiting toxicities within the first 2 cycles

- **Part 2:** patients randomized to one of the selected combinations or RUX monotherapy (control)

- **Part 3:** patients randomized to the combination treatment, RUX cessation[d], or RUX monotherapy

  Parts 2/3 primary endpoint: 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)

[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. RUX, ruxolitinib.

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Key inclusion and exclusion criteria

Inclusion

- 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

Exclusion

- 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*

CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; MF, myelofibrosis; MRI, magnetic resonance imaging; PET-MF, essential thrombocythemia MF; PMF, primary MF; PPV-MF, polycythemia vera MF; RUX, ruxolitinib; TP53, tumor protein 53.

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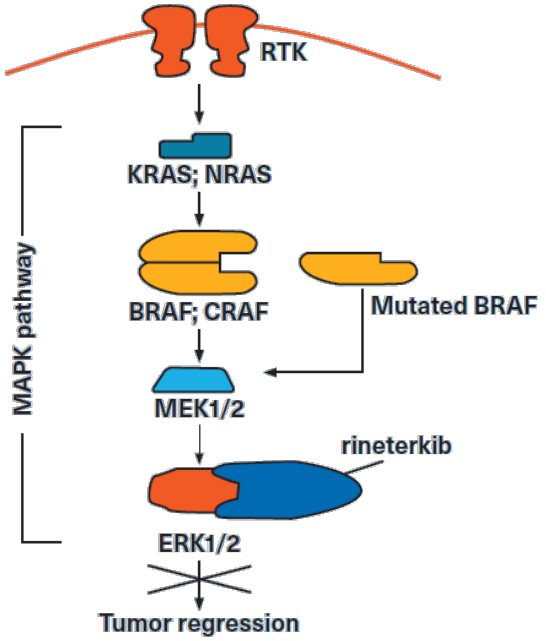
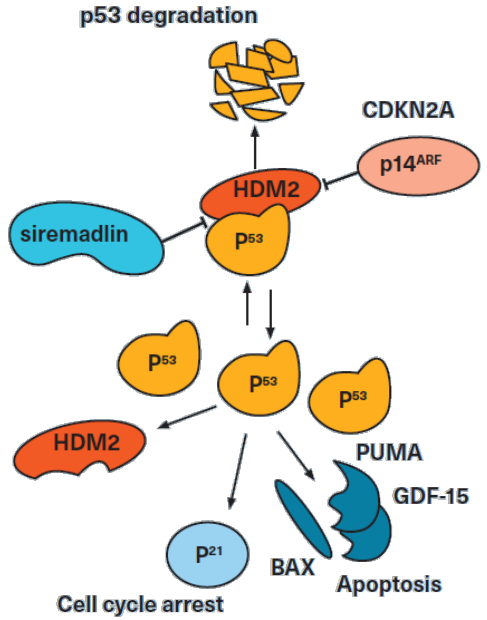
Study compounds

RUX + rineterkib

- Constitutive JAK2 signaling results in activation of MEK/ERK signaling, which may limit the efficacy of JAK2 inhibition[1]
- Rineterkib is a small molecule inhibitor of ERK1/2[2]



RUX + siremadlin



- JAK2 mutations are thought to induce the expression of HDM2, which acts to degrade p53[3,4]
- Siremadlin is a small molecule inhibitor of the p53/HDM2 interaction, protecting p53 from degradation[5]

RUX + crizanlizumab

- In patients with MF, impaired megakaryocytes express high levels of P selectin, which leads to increased TGF-β release and disease progression[6]
- Crizanlizumab is a mAb that binds to and inhibits P-selectin[7]

RUX + sabatolimab

- Sabatolimab is a mAb that blocks the binding of TIM-3 to its ligand PtdSer[8]
- TIM-3 blockade restores activity of exhausted T cells, and may diminish suppressor activity of regulatory T cells[9]

RUX + NIS793

- TGF-β is a pro-inflammatory cytokine that promotes bone marrow fibrosis[10,11]
- NIS793 is a mAb that binds to TGF-β1 and TGF-β2 and displays TGF-β1- and TGF-β2-neutralizing activity[12]

1. Stivala S, et al. *J Clin Invest.* 2019;129(4):1596–1611. 2. Janku F, et al. *Journal of Clinical Oncology*. 38(15_suppl):3640-3640. 3. Saha MN, et al. *J Hematol Oncol.* 2013;6:23. 4. Nakatake M, et al. *Oncogene*. 2012;31:1323–1333. 5. Stachyra-Valat T, et al. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2016 Apr 16-20; New Orleans, LA. Philadelphia (PA): AACR; Cancer Res 2016;76(14 Suppl):Abstract nr 1239. 6. Spangrude GJ, et al. *Stem Cells.* 2016;34:67–82. 7. Ataga KI, et al. *N Engl J Med*. 2017;376:429–439. 8. Sabatos-Peyton CA, et al. Poster presented at the European School of Hematology (ESH), 2021. 9. Sakuishi K, et al. *Trends Immunol*. 2011;32(8):345–349. 10. Zingariello M, et al. *Blood.* 2013;121:3345–3363. 11. Agarwal A, et al. *Stem Cell Investig*. 2016;3:5. 12. Derynck R, et al. *Nat Rev Clin Oncol.* 2021;18(1):9–34.

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Summary

Combining RUX with novel therapies **may deliver clinical benefits in MF**

The ADORE study is **assessing the five novel compounds in combination with RUX** in patients with MF

A total of approximately **240 patients are planned to be enrolled***

As of October 2021, the study is **enrolling the Part 1 siremadlin 30 mg cohort**

*assuming all five combination treatments enter Part 2 and one combination treatment is expanded in Part 3. MF, myelofibrosis; RUX, ruxolitinib.

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