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POSTER ABSTRACTS

631.MYELOPROLIFERATIVE SYNDROMES AND CHRONIC MYELOID LEUKEMIA: BASIC AND TRANSLATIONAL

Zinpentraxin Alfa Reduces Myelofibrosis in a *JAK2*-V617F Mouse Model of Myeloproliferative Neoplasms

Shivam Rai[1], *Hui Hao-Shen*[1], *Stefan Dirnhofer*[2], *Julien Roux*[3], *Rajbharan Yadav*[4], *Anamarija Pfeiffer*[5], *Jakob Vowinckel*[6], *Audrey Arjomandi*[7], *Brian Higgins*[8,9], *Lyrialle Han*[8], *Kerstin Trunzer*[10], *Pontus Lundberg*[10], *Radek C. Skoda, MD*[11,12]

[1] Department of Biomedicine, Experimental Hematology, University Hospital Basel and University of Basel, Basel, Switzerland
[2] Institute of Pathology, University Hospital Basel, Basel, Switzerland
[3] University of Basel and University Hospital Basel, Basel, Switzerland
[4] Preclinical and Translational Pharmacokinetics and Pharmacodynamics, Genentech Inc., South San Francisco, CA
[5] Biognosys AG, Zurich, Switzerland
[6] Biognosys AG, Schlieren, Switzerland
[7] Genentech, Inc., South San Francisco, CA
[8] Genentech Inc., South San Francisco, CA
[9] Roche Innovation Center, New York, NY
[10] F. Hoffmann-La Roche Ltd., Basel, Switzerland
[11] University Hospital Basel, Basel, Switzerland
[12] Experimental Hematology, Department of Biomedicine, University Hospital and University, Basel, Switzerland

Background:
Myeloproliferative neoplasms (MPNs) are clonal disorders of the hematopoietic stem cell (HSC), caused by somatic mutations in *JAK2*, *MPL* or *CALR* . Myelofibrosis, characterized by increased deposition of reticulin and/or collagen fibers, is found in advanced stages of MPN. Pentraxin-2 (PTX2, serum amyloid P component/SAP) belongs to the family of short pentraxins and acts as an inhibitor of fibrocyte differentiation and modulator of macrophage polarization. Zinpentraxin alfa (PRM-151, ZPN), a recombinant form of human PTX2, was reported to reduce myelofibrosis in a retroviral model of MPN driven by *MPL*-W515L (Verstovsek S et al, J Exp Med 2016). ZPN has also been investigated as monotherapy and in combination with ruxolitinib (RUX) in a phase 2 clinical study in patients with myelofibrosis (NCT01981850; Verstovsek S et al, Haematologica 2023). Evidence of clinical activity and tolerable safety as monotherapy and in combination with RUX was shown in that open-label, non-randomized trial. Here, we examined the effects of ZPN alone or in combination with RUX in a mouse model of MPN driven by Cre-inducible expression of human *JAK2*-V617F (Tiedt R et al, Blood 2008).
Methods:
To obtain sufficient numbers of mice for drug testing, bone marrow cells from *JAK2*-V617F mice were transplanted into lethally irradiated C57BL/6 recipients (Kubovcakova L et al., Blood 2013), and groups of 6 mice were sacrificed at 16, 20, and 24 weeks to determine the histological grade of reticulin fibrosis. 24 weeks post transplantation, grade 1-2 fibrosis was confirmed in these satellite mice and treatment was initiated. During treatment, weight and complete blood counts were monitored (n=8 mice per group). At terminal work-up, spleen weight and fibrosis grade were determined, along with flow cytometry of bone marrow and peripheral blood, single cell RNA sequencing of bulk bone marrow, and proteomics analysis by mass spectrometry of bone marrow and plasma. Additionally, we characterized the plasma pharmacokinetics (PK) in these mice following single IP (10 mg/kg) administration of ZPN.
Results:
Systemic exposure after IP administration was confirmed in each animal (T_{max} at 4 h, C_{max} 27.9 ug/mL,AUC_{0-48} 381 h*ug/mL). No weight loss or mortality were observed in ZPN monotherapy cohorts, and the slight weight loss observed in RUX treated animals was not potentiated by the addition of ZPN. A trend towards lower platelet, monocyte and total leukocyte counts was observed for ZPN treatment groups compared to vehicle controls (Figure 1A). RUX alone largely normalized hemoglobin values, while ZPN alone or in combination with RUX had less effect on hemoglobin. Terminal work-up showed grade 1-2 fibrosis in the vehicle group, whereas reticulin fibrosis decreased in the majority of mice with ZPN monotherapy or in combination

with RUX (Figure 1B). ZPN monotherapy did not reduce spleen weight. Single cell RNA sequencing and proteomics analyses are currently being analyzed and data will be shown.

Conclusion:

ZPN treatment in a *JAK2*-V617F mouse model of MPN with myelofibrosis was well tolerated as monotherapy and in combination with RUX. A reduction in the grade of myelofibrosis was observed in all ZPN treatment groups. ZPN showed promising trends in reducing platelet and monocyte counts, while the decrease in hemoglobin by RUX was in part prevented in combination with ZPN.

Disclosures Yadav: *Genentech Inc.:* Current Employment, Current equity holder in publicly-traded company. **Pfeiffer:** *Biognosys AG:* Current Employment. **Vowinckel:** *Biognosys AG:* Current Employment. **Arjomandi:** *Genentech Inc.:* Current Employment, Current equity holder in publicly-traded company. **Higgins:** *Genentech:* Current Employment, Current equity holder in publicly-traded company; *F. Hoffmann-La Roche:* Current Employment, Current equity holder in publicly-traded company. **Han:** *Genentech Inc.:* Current Employment, Current equity holder in publicly-traded company. **Trunzer:** *F. Hoffman-La Roche:* Current Employment, Current equity holder in publicly-traded company. **Lundberg:** *F. Hoffmann-La Roche Ltd, Basel:* Current Employment, Current equity holder in publicly-traded company. **Skoda:** *Ajax Therapeutics:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *F. Hoffmann-La Roche:* Research Funding; *BMS/Celgene,AOP, GSK,Baxalta, Pfizer, and Novartis:* Consultancy, Honoraria, Speakers Bureau.

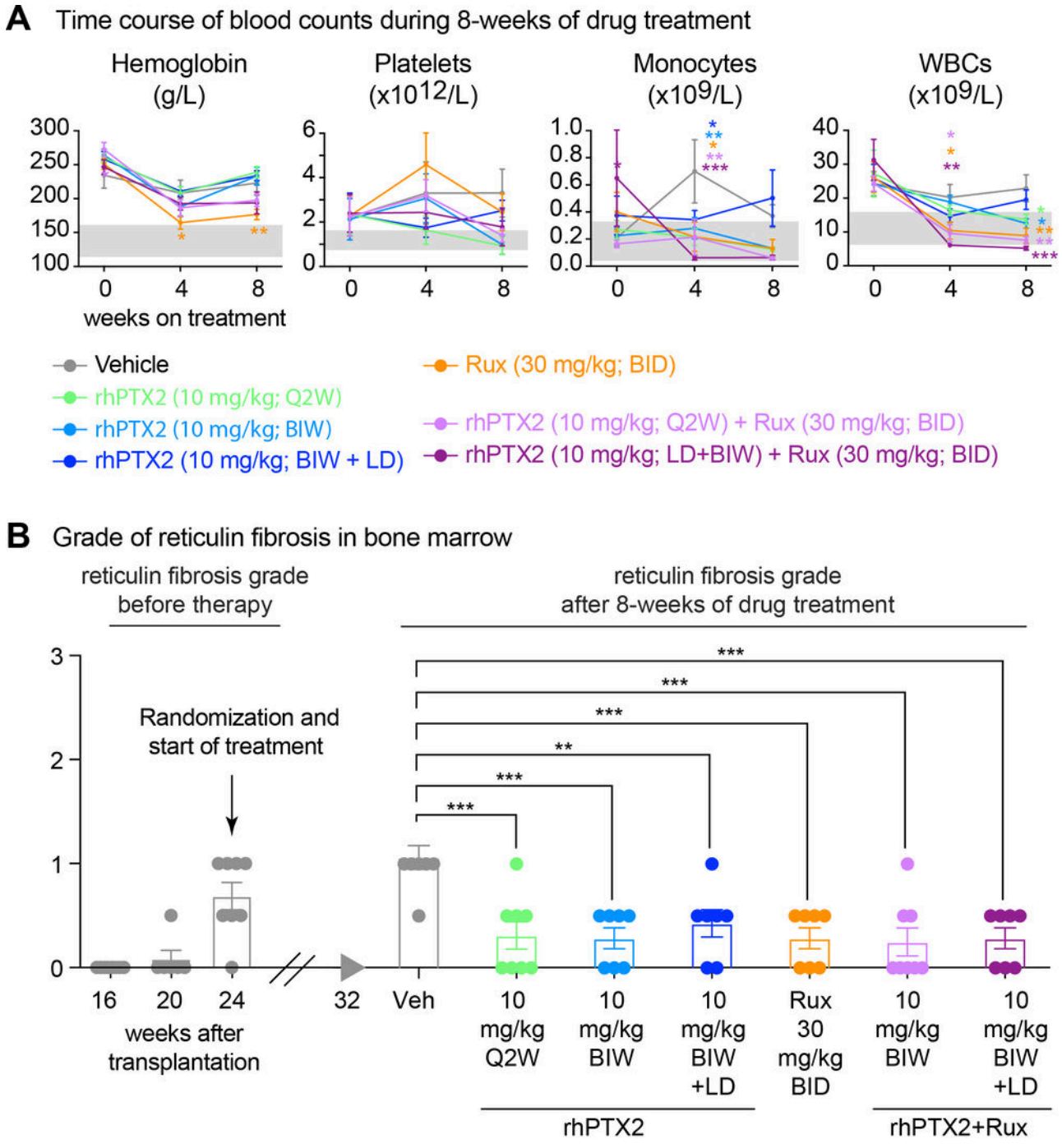

Figure 1

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