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POSTER ABSTRACTS

604.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: MYELOID NEOPLASMS

Preclinical and Clinical Evidence for Erythroid-Stimulating Activity of RVU120 CDK8/19 Inhibitor in AML and MDS

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Introduction:
RVU120 is an orally bioavailable small molecule inhibitor targeting mediator complex kinases CDK8 and its paralog CDK19. Preclinical results indicated that treatment with RVU120 could reduce the viability of AML cells, in particular those positive for NPM1 and DNMT3A mutations. Further studies also indicated that RVU120 induces erythroid differentiation of malignant stem cells isolated from AML and MDS patients, likely by the induction of STAT5-GATA1-dependent transcription. The first signs of clinical efficacy have been observed in the ongoing Phase 1 dose escalation study of RVU120 in AML and HR-MDS patients. The presented work provides the preclinical rationale and growing clinical evidence that in addition to previously reported blast reduction, RVU120 has also strong erythropoiesis stimulating activity that may be useful as a potential therapeutic strategy for MDS.
Methods:
RVU120-induced erythroid differentiation was studied in primary malignant stem cells from MDS patients and in a stem cell model derived from cord blood cells transformed by TLS-ERG fusion. Erythroid differentiation was tracked by flow cytometry, chromatin status, and transcriptomic changes using RNAseq, ATACseq and ChIPseq. CLI120-001 study (NCT04021368) is a phase 1 dose escalation study of RVU120 in patients with relapsed/refractory AML and HR-MDS which is currently ongoing. Flow cytometry for erythroid differentiation markers, NGS myeloid panel and bulk RNAseq were performed in all patients enrolled after September 2021.
Results:
At the time of the abstract submission, within 24 evaluable patients' erythroid improvement was reported in 1 patient with HR-MDS, 3 patients with AML MRC, and 1 patient with AML secondary to MF. Interestingly, in these cases, erythroid improvement was observed independently of significant blast reduction, at doses from 25 mg to 135 mg every other day in 3 weeks cycles. Transient induction of erythroid differentiation markers CD71 and/or CD235a was confirmed in 3 additional transfusion-dependent patients treated with RVU120. Bulk RNA-seq confirmed broad transcriptomic changes in BM of selected patients after treatment compared to the pre-dose baseline levels. Robust induction of genes involved in erythroblast differentiation and hemoglobin metabolism genes was confirmed in 2 AML-MRC and 2 AML patients. These changes correlated with the repression of major pro-inflammatory pathways, including hallmark interferon gamma and TNF/NFKB response genes and repression of TGFβ pathway genes. Molecular and flow cytometry changes observed in patients were consistent with the erythroid commitment and sequential induction of erythroid differentiation markers in cultured CD34+ malignant stem cells isolated from MDS and AML-MRC patients treated with RVU120 and other chemically non-related CDK8 inhibitors.
Conclusions:
The presented results provide clinical and preclinical evidence for RVU120 as a candidate for a novel erythroid stimulating agent. Treatment with RVU120 could be a promising addition to the current treatment options for patients with lower-risk MDS who are transfusion-dependent and failing first-line therapies.

Disclosures Angelosanto: *Ryvu Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Zaucha:** *Abbvie:* Honoraria; *Novartis:* Honoraria; *Pfizer:* Honoraria; *Gilead:* Honoraria; *MSD:* Research Funding; *Medical University of Gdańsk:* Current Employment; *Roche:* Honoraria; *AstraZeneca:* Honoraria; *Amgen:* Honoraria; *Takeda:* Honoraria; *Pierre Fabre:* Honoraria; *BMS:* Honoraria, Research Funding. **Sroka-Porada:** *Ryvu Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Ogrodzińska:** *Ryvu Therapeutics:* Current Employment. **Kozakowska:** *Ryvu Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Głowniak-Kwitek:** *Ryvu Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Bukowska-Strakova:** *Ryvu Therapeutics:* Consultancy. **Rzymski:** *Ryvu Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Mazan:** *Ryvu Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Pakulska:** *Ryvu Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Göller:** *Ryvu Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Nogai:** *Bayer Consumer Care:* Current equity holder in publicly-traded company, Ended employment in the past 24 months; *Ryvu Therapeutics:* Current Employment, Current equity holder in publicly-traded company.

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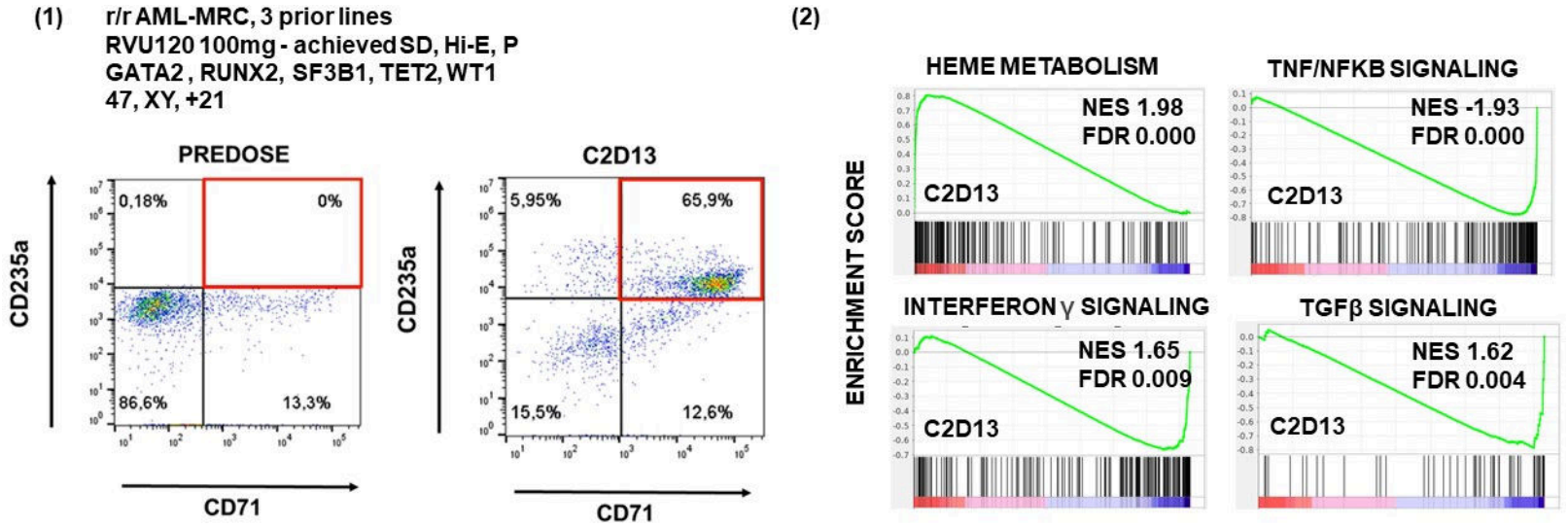

Figure (1): Induction of erythroid maturation markers in AML-MRC patient treated with 100mg RVU120 measured by flow cytometry
Figure (2): Gene expression changes in the BM cells of the same patient measured by bulk RNAseq (GSEA)

Figure 1