EHA2021 VIRTUAL

S164

# RVU120/SEL120 CDK8/19 INHIBITOR - A DRUG CANDIDATE FOR THE TREATMENT OF MDS CAN INDUCE ERYTHROID DIFFERENTIATION IN TRANSFORMED CD34+ HEMATOPOIETIC PROGENITOR CELLS

Topic: 09. Myelodysplastic syndromes - Biology & Translational Research

Keywords: Anemia MDS

Tomasz Rzymski[1], Urszula Pakulska[1], Kristina Goller[1], Elzbieta Adamczyk[1], Katarzyna Dziedzic[1], Katarzyna Wiklik[1], Michal Combik[1], Michal Mikula[2], Marta Obacz[1], Milena Mazan[1], Kinga Keska[1], Magdalena Masiejczyk[1], Przemyslaw Juszczynski[3], Johan Flygare[4], Krzysztof Brzozka[1]

[1] Ryvu Therapeutics, Cracow, Poland
[2] The Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw, Warsaw, Poland
[3] Institute of Hematology and Transfusion Medicine, Warsaw, Poland
[4] Lund University, Lund, Sweden

**Background:**

Myelodysplastic syndrome (MDS) is a disorder of hematopoietic cells that as a result of genetic and epigenetic changes do not give rise to mature blood cells. Production and accumulation of dysplastic cells leads to cytopenias and can often evolve to acute myeloid leukemia (AML). Primary clinical goals in MDS are to achieve remissions, alleviate symptoms associated with cytopenias and to minimize the transfusion burden. While supportive red blood cell transfusions and erythropoiesis-stimulating agents may lead to clinical improvement, frequent transfusions may lead to iron overload and decreased quality of life. Several additional therapeutics are now available for the treatment of symptomatic anemia, however there is a need for novel agents as majority of patients eventually develop resistance. RVU120 (formerly known as SEL120) is a specific, selective inhibitor of CDK8 and its paralog CDK19. A first- in- human phase Ib clinical trial with RVU120 in patients with AML or HR-MDS is currently ongoing. Preclinical studies indicated strong antileukemic potential of RVU120 that was often associated with multilineage commitment of CD34+ AML cells. Moreover, RVU120 could improve proliferation and induce erythroid differentiation of CD34+ cells derived from Diamond-Blackfan anemia patients.

**Aims:** Primary aim was to evaluate erythroid differentiation potential of RVU120 in transformed lineage depleted (Lin-) CD34+ blood cells characterized with the early block in erythroid differentiation.

**Methods:**

Primary cellular model was based on cord blood cells transduced with TLS-ERG - a fusion gene generated from t(16;21)(p11;q22) translocation associated with primary AML and secondary AML associated MDS. Transformed cells displayed increased capacity for self-renewal, proliferation and altered erythroid differentiation. Cells were treated with RVU120 and global transcriptional changes and chromatin status were analyzed by RNAseq, ATACseq and ChIPseq. Cell cycle, proliferation and lineage specific markers were studied by flow cytometry in liquid and semi-solid methylcellulose-based media.

**Results:** RVU120 treatment leads to transcriptional reprogramming of transformed (Lin-) CD34+ cells. The most profound changes included decreased CDK8 occupancy and increased RNA Pol II loading. RVU120 could repress many genes associated with stem cells and importantly induce the expression of genes involved in erythroid commitment, including regulators of erythroid/megakaryocytic fate, such as RGS18, KLF1, FLI1, INHBA, GATA1/2 and hemoglobin genes. Detailed analysis by flow cytometry at early and late time points reflected sequential changes in the expression of lineage-specific surface markers, leading to differentiation and the presence of GlyA+/CD71+ erythroblasts. Observed effects on differentiation towards erythroid cells were independent of erythropoietin.

**Summary/Conclusion:**

Presented results indicate strong erythroid differentiation potential of RVU120 in (Lin-) CD34+, that acquired

genetic abnormalities resulting in arrested erythroid commitment, characteristics of many MDS and AML subtypes. Observed differentiation phenotype strikingly resembles effects of RVU120 in DBA cells caused by disruption of genes encoding ribosomal proteins. Detailed transcriptomic profiling strongly associated differentiation with enrichment of genes representing regulators of erythroid commitment and hemoglobin metabolism. Further studies are warranted to investigate efficacy of RVU120 in anemias associated with bone marrow failures in AML and MDS patients.

---



**Abstract Book Citations:** Authors, Title, HemaSphere, 2021;5:(S2):pages. Abstract Book, DOI:
http://dx.doi.org/10.1097/HS9.0000000000000566