

## **Abstract: PB1792**

### **Title: REPURPOSING OF ANTIBIOTICS INHIBITING MITOCHONDRIAL TRANSLATION IN COMBINATION WITH VENETOCLAX IN ACUTE MYELOID LEUKEMIA: FROM PRECLINICAL MODELS TO CLINICAL PRACTICE**

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#### **Background:**

The introduction of the BCL-2 inhibitor Venetoclax (VEN) in combination with chemotherapy or hypomethylating agents (HMA) represents a major advancement in Acute Myeloid Leukemia (AML) therapy. However, VEN resistance is still an unmet clinical need. In this light, pharmacological disruption of mitochondrial respiratory chain is a promising strategy to circumvent VEN resistance. Tigecycline (Tig) and Linezolid (Lin), two antibiotics largely used in AML patients (pts), inhibit mitochondrial respiration in preclinical models.

#### **Aims:**

Characterization in vitro activity of Tig and Lin in combination with VEN in AML preclinical models and assessment of non-hematologic toxicities and clinical outcomes in pts treated with these combinations in clinical practice.

#### **Methods:**

We assessed viability in cells exposed to Tig, Lin and VEN in two BCL-2 positive AML cell lines, MOLM-13 and MV4-11, using the cell Titer-Glo assay™. We retrospectively reviewed a multicentric cohort of all AML pts treated with VEN between 2018 and 2023 within the Hematology Working Group of Alliance against Cancer (ACC-Hema) Network, focusing on pts receiving VEN and concomitant antibiotic therapy with Lin or Tig for at least 7 days in the context of infective complications during the normal clinical practice.

#### **Results:**

Tig and Lin inhibited cell viability in a time and dose dependent manner at clinically achievable concentrations in AML cell lines. Tig and Lin treatment led to downregulation of COX1, indicative of respiratory chain inhibition. Notably, the antiproliferative effects of these antibiotics were enhanced by cotreatment with VEN, with synergistic interactions assessed with the Chou-Talalay method in AML cell lines. Following these preliminary observations, we analyzed clinical data of 13 AML pts treated with Lin 600 mg bid (n=9) or Tig 50 mg bid (n=4) during VEN-based regimens at 5 ACC-Hema Centers. VEN-based regimens included HMA in 12 cases, cytarabine (AraC) in 1 patient. Median age was 51 y.o. (35-76), median time of exposure to combination treatment was 9 days (7-24). Two heavily pretreated pts died of sepsis shortly after treatment (unrelated to Lin), without response evaluation. Notably, in the remaining pts (n=11) we did not observe any renal, liver toxicity or delayed hematologic recovery. Three pts died of disease progression: 1 treated in first-line, the other 2 in second line. Overall, 11 pts were evaluable for response. Complete remission (CR) was observed in 6 pts: 4 pts treated in first-line achieved CR [3 pts treated with decitabine (DEC)-VEN-Lin and 1 with azacytidine (AZA)-VEN-Tig]. The remaining 2 pts achieving CR were treated for their second AML recurrence with AZA-VEN-Tig and AraC-VEN-Lin. Four of the pts achieving CR had high risk AML, 2 had intermediate risk. Partial remission was achieved in 2 pts treated with AZA-VEN-Tig and DEC-VEN-Lin in the relapse/refractory setting. The overall response rate (ORR) in the whole cohort was 73%, with a CR rate of 54%. The ORR in first-line AML was 80%, all CR.

#### **Summary/Conclusion:**

These data suggest that mitochondrial translation inhibitors such as Lin or Tig could enhance VEN efficacy in preclinical AML models. Our retrospective clinical data collection showed the safety of the combination treatment with promising efficacy signals in a difficult-to-treat patient population. Considering the safety observed we are now enrolling more pts in this retrospective study to better define the role of these associations. These findings

and preliminary clinical data provide rationale for repurposing of this class of drugs in combination with VEN in AML.

**Keywords:** Acute myeloid leukemia, Venetoclax, Drug interaction, Mitochondria