A PHASE I STUDY INVESTIGATING THE SAFETY & EFFICACY OF DANVATIRSEN AS MONOTHERAPY FOLLOWED BY COMBINATION WITH VENETOCLAX IN PATIENTS WITH RELAPSED/REFRACTORY MDS & AML

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INTRODUCTION

- Only 30% of patients with newly diagnosed acute myeloid leukemia (AML) enjoy long-term survival, while the majority still succumb to their illness.
- STAT3 belongs to the STAT family of seven transcription factors. STAT3 is activated in the cytoplasm when growth factors & cytokines bind to the upstream Janus activating kinase (JAK) and serine kinase receptors. Inappropriate activation of STAT3 dysregulates cellular processes leading to leukemogenesis.
- We have previously demonstrated that STAT3 is overexpressed in Leukemic Stem Cells . A selective antisense oligonucleotide inhibitor of STAT3, Danvatirsen (AZD9150) is a 16-mer generation 2.5 ASO designed by Ionis Pharmaceutical to specifically target human STAT3 mRNA for degradation
- Danvatirsen is rapidly incorporated into MDS/AML hematopoietic stem & progenitor cells (HSPCs) and induces selective apoptosis and down regulation of STAT3 in these cells compared with healthy control HSPCs.
- There is a strong correlation between STAT3 & MCL1 overexpression (Shastri et al, JCI 2018). MCL1 emergence is closely tied to therapy resistance to the BCL2 inhibitor venetoclax.

AIMS

- The current study **(NCT05986240)** is a phase I dose escalation protocol that includes 2 sub-studies to evaluate the safety profile and determine the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of : 1) danvatirsen as monotherapy, 2) danvatirsen in combination with venetoclax, for the treatment of relapsed /refractory Int/high/very-high-risk IPSS-R myelodysplastic syndromes or relapsed/refractory AML.
- The secondary objective of the study is to determine the overall response rate defined as CR + CRi + PR based on the revised IWG response criteria for AML (Cheson B et al, JCO 2003).
- For MDS, the overall response rate (ORR) is defined as CR +CRh + HR the based on the IWG revised criteria for hematologic response in MDS (Platzbecker U et al, Blood 2019).
- The secondary objectives also include evaluating the on-target activity of danvatirsen in hematopoietic stem & progenitor cells (HSPC's), to correlate responses observed to a STAT3 gene expression signature in addition to others as mentioned in Figure 3.

Figure 1. Increased STAT3 expression in prior venetoclax exposed patients is associated with worse overall survival and worse remission duration

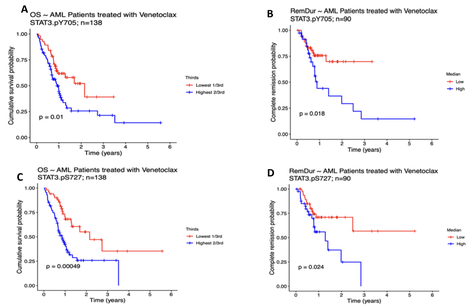


Figure 2. A specific antisense inhibitor of STAT3 Danvatirsen has intracellular uptake and downregulates STAT3 in MDS/AML Hematopoietic Stem & Progenitor Cells

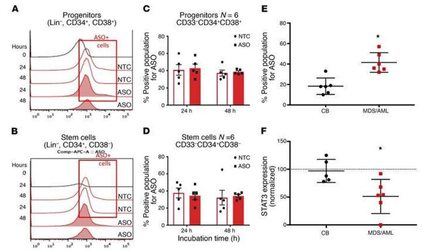


Figure 3. Trial Schema

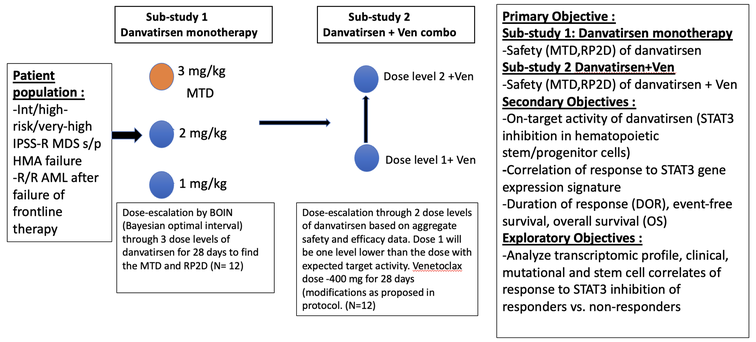
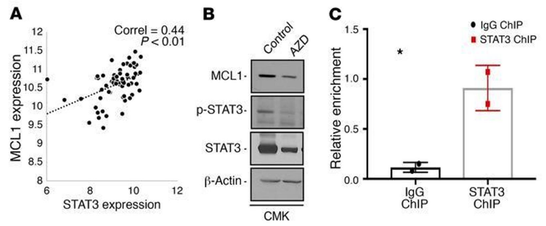


Figure 4. The antiapoptotic protein MCL1 correlates strongly with STAT3 and is downregulated after treatment with Danvatirsen



METHODS

- In each of the sub-studies, we have employed the Bayesian optimal interval (BOIN) design with the 3+3 design run-in, to find the MTD. Sub-study 1 employs a dose escalation through 3 dose levels ranging from 1 mg/kg to 3 mg/kg.
- Cycle 1 consists of 1 week of a loading dose on days 1, 3 and 5 followed by a weekly infusion for 3 weeks. Thereafter, each cycle consists of weekly treatment for 4 weeks. There are no premedications required prior to treatment.
- In sub-study 2, up to 2 dose levels of danvatirsen will be evaluated, while dose for venetoclax is fixed at 400 mg daily equivalent (with azole based dose adjustments per venetoclax label) except where dose modifications are indicated in the protocol.
- The two doses of danvatirsen used will be determined based on aggregate review of data from the single-agent experience. A total of 9-12 DLT evaluable patients will be enrolled into sub-study 1 and sub-study 2 respectively.

CONCLUSIONS

- Recruitment is currently ongoing at the Montefiore Einstein Comprehensive Cancer Center, Bronx, NY and the M.D Anderson Cancer Center, Houston, TX.
- As of November 22 2024, 5 patients have been enrolled onto the study into sub study 1, dose level 1 of 1 mg/kg of danvatirsen and dose level 2 of 2mg/kg of danvatirsen
- At this time sub study 1 dose level 2 is still enrolling.
- Samples for biomarker analysis are collected and being analyzed.

Figure1.A-D. Phospho-proteomic analysis on AML patients treated with Ven shows significant worse OS and worse remission duration with higher expression of p-STAT3(Y705) and p-STAT3(S727), respectively (unpublished data).

Figure 2. MDS/AML–derived stem and progenitor cells were treated with AZD9150/Danvatirsen (ASO) and Non-targeting Control-NTC (ASO) at 2.5 μM, 10 μM and then assessed for uptake of the oligonucleotide after assessment by intracellular flow cytometry with antibody against the oligonucleotide backbone. **(A–D)** Both progenitors and stem cells incorporated AZD9150 & NTC by 24 hours. **(E)** The uptake was greater in MD/AML stem cells compared with cord blood controls. **(F)** STAT3 expression as measured by qPCR was significantly decreased in MDS/AML stem cells (n = 6) compared with cord blood (CB) stem cell controls (n = 6) after treatment with AZD9150. (Two-tailed t test for all, *P < 0.05.)

Figure 4. A. Positive correlation between MCL1 and STAT3 expression is seen in 183 MDS CD34⁺ samples. MCL1 protein downregulation is seen after treatment of leukemia cells with AZD9150. (B) Western blot showing downregulation of MCL1, phospho-STAT3, and total STAT3 in AZD9150-treated CMK cells compared with the control. (C) STAT3 ChIP for MCL1 promoter region in CMK cells shows enrichment when compared with IgG control (P = 0.03, n = 2). *P < 0.05 by two-tailed t test.. (Shastri A et al, JCI 2018)

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- Danvatirsen is provided by Flamingo Therapeutics (Leuven, Belgium)

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