Evaluation of Combination Tagraxofusp (SL-401) and Hypomethylating Agent (HMA) Therapy for the Treatment of Chronic Myelomonocytic Leukemia (CMML)

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Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell disorder which often progresses to acute myeloid leukemia (AML). The only known cure for CMML remains allogeneic stem cell transplant. Hypomethylating agents (HMAs) such as Azacitidine (AZA) and Decitabine (DAC) have been utilized to treat CMML patients with variable efficacy, such that complete response only occurs in a minority of patients.

Recent work has identified CD123 (interleukin-3 receptor-α; IL-3R-α) as a potential therapeutic target in myeloid malignancies. CD123 is expressed in a variety of myeloid malignancies, including AML, myelodysplastic syndrome (MDS) and CMML.

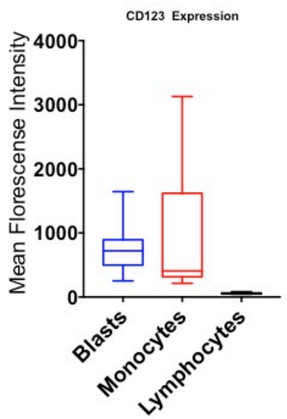
Tagraxofusp (Elzonris™, SL-401) is a targeted therapy directed to CD123, comprised of recombinant IL-3 fused to a truncated diphtheria toxin payload. Clinical studies of tagraxofusp are being carried out in CMML. Data from an ongoing Phase I/II trial of tagraxofusp in relapsed/refractory CMML (n=16 patients) demonstrated spleen size reductions in 100% (8/8) patients with baseline splenomegaly and 2 bone marrow complete responses (BMCRs)

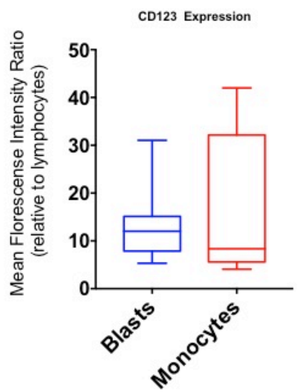
Given this activity, and the known activity of HMAs in CMML, we sought to determine if combination HMA and tagraxofusp may provide added therapeutic utility over HMA therapy alone.

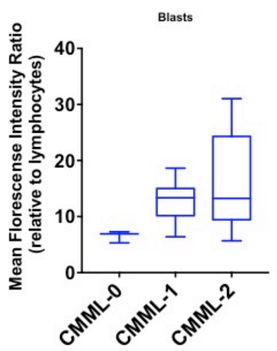
Conclusions

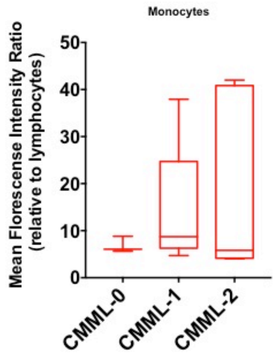
Although HMA therapy has demonstrated efficacy in CMML, the effects are often limited in extent and duration. Our preclinical data, including in primary CMML samples, demonstrates a potential therapeutic role for the combination of an HMA and tagraxofusp in CMML. Further studies are ongoing to characterize this combination strategy.

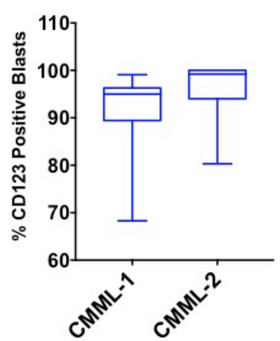
Results



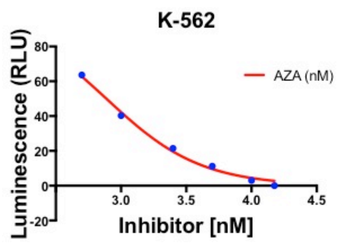


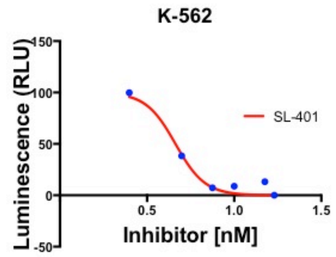


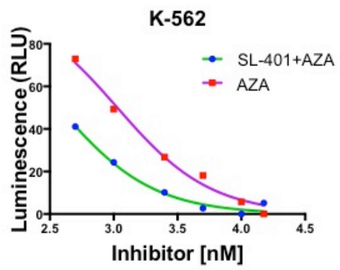




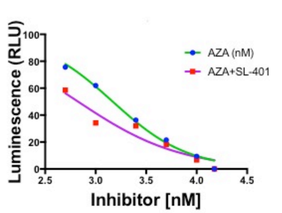
CD123 Expression on monocytes and blasts in CMML patients. CD123 expression was assessed using flow cytometry. Lymphocyte CD123 expression was used as a control. CD123 is highly expressed on blasts and monocytes in CMML patients (N=20 cases)

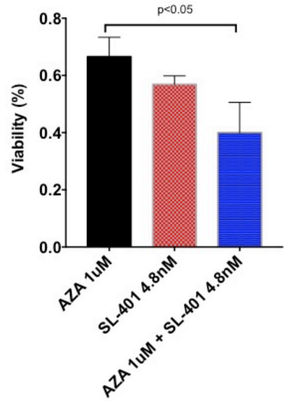




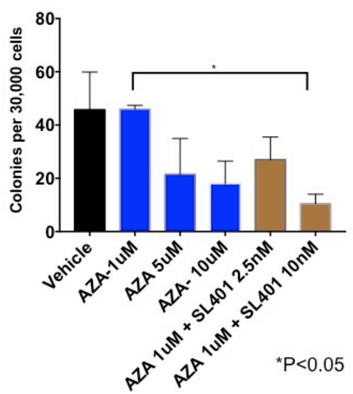


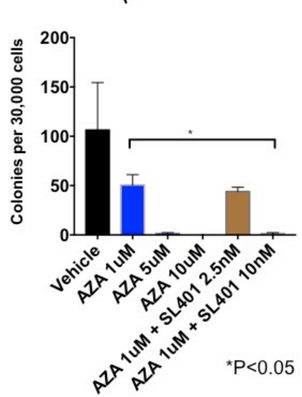
Cell Viability Assays in Leukemia Cell lines: K562 cells have previously been demonstrated to express CD123. Addition of tagraxofusp to AZA decreased cell viability in K562 cell lines both alone and in combination with AZA.

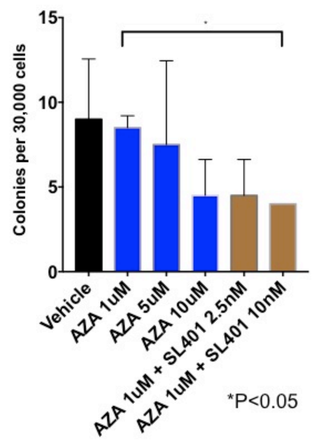




Cell Viability Assays using CMML samples: Mononuclear cells from freshly collected CMML peripheral blood samples were used for cell viability assays. Cells were exposed to AZA, tagraxofusp, or combination of both. AZA and tagraxofusp significantly reduced cell viabilitywhen compared to single agent AZA alone







Colony Forming Assays using CMML samples: Mononuclear cells from freshly collected CMML peripheral blood samples were used for colony forming assays. Cells were exposed to AZA, tagraxofusp, or combination of both. Addition of AZA to increasing concentrations of tagraxofusp demonstrated a significant reduction in colony formation

Disclosures: **Chen:** *Stemline Therapeutics:* Employment, Equity Ownership. **Brooks:** *Stemline Therapeutics:*Employment, Equity Ownership

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