Evaluation of Tagraxofusp (SL-401) Alone and in Combination with Ruxolitinib for the Treatment of Myeloproliferative Neoplasms

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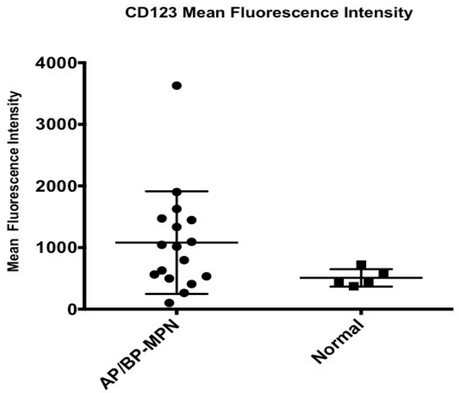
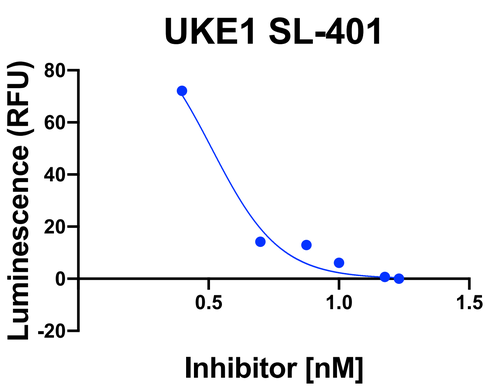
Introduction

The introduction of the JAK1/2 inhibitor Ruxolitinib has resulted in significant benefits for patients with MPNs, including reduction of splenomegaly and improvement in symptom burden. However, patients often lose response to Ruxolitinib or suffer disease progression despite therapy with Ruxolitinib. CD123 (interleukin-3 receptor-α; IL-3R-α) has been identified as a therapeutic target in myeloid malignancies. CD123 is expressed in a variety of myeloid malignancies, including AML, myelodysplastic syndrome (MDS) and CMML. Further, Tagraxofusp (Elzonris™, SL-401) a targeted therapy directed to CD123, comprised of recombinant IL-3 fused to a truncated diphtheria toxin payload, was recently FDA approved for the treatment of Blastic Plasmacytoid Dendritic cell Neoplasm (BPDCN). In an ongoing Phase 1/2 trial, Tagraxofusp has demonstrated single agent clinical activity, in patients with relapsed/refractory Myelofibrosis (MF). Thus, Tagraxofusp appears to have activity in MF. However, the utility of Tagraxofusp in more advanced forms of MPN (such as accelerated phase MPN), as well as the utility of combination Ruxolitinib and Tagraxofusp, have not been evaluated to date.

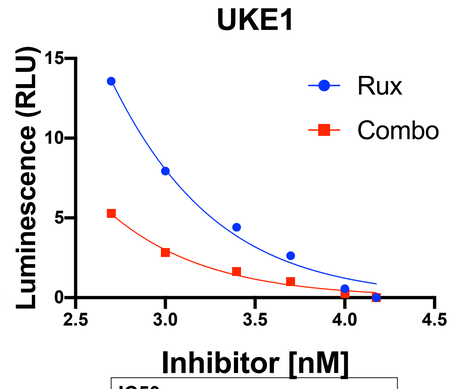
Results



CD123 Expression on mononuclear cells in MPN patients. CD123 expression was assessed using flow cytometry in the peripheral blood of MPN patients with Accelerated or Blast-phase disease. Lymphocyte CD123 expression was used as a control.



IC50
SL-401: 2.959 –3.574nM

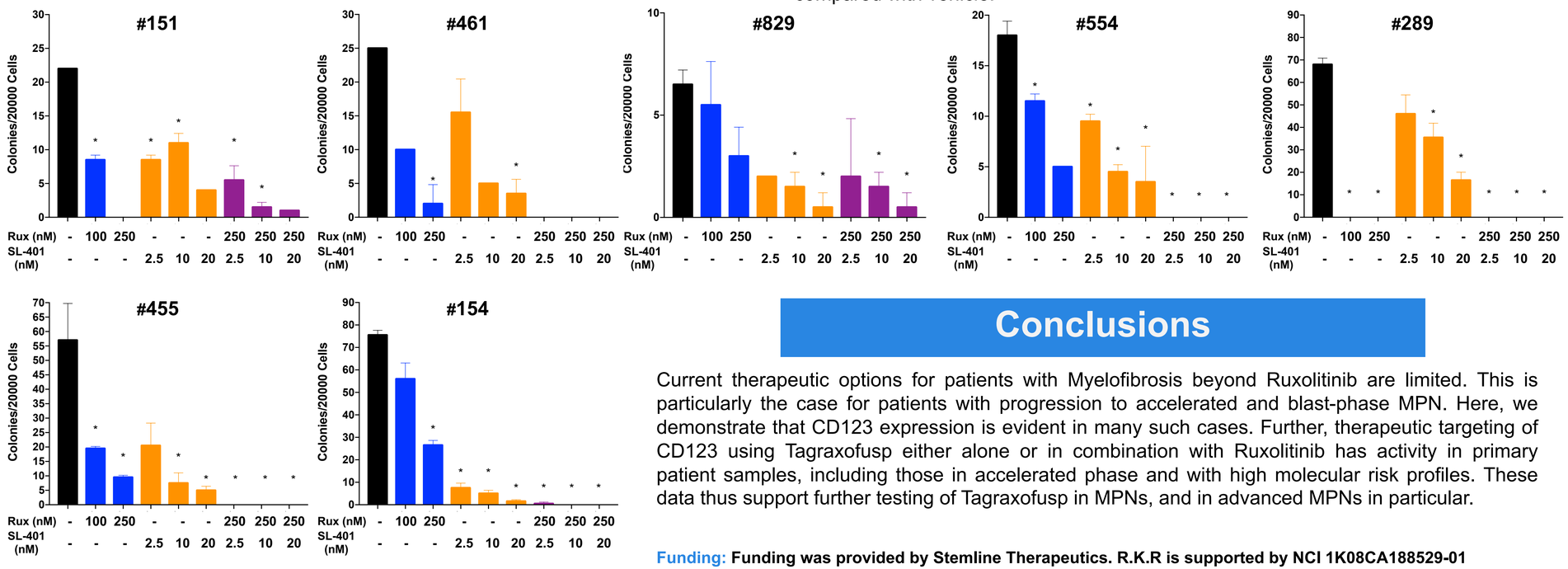


IC50
Rux: 44.42 – 70.93nM
RUX+SL-401: 11.72 – 21.6nM

Cell Viability Assays in Leukemia Cell lines: Tagraxofusp, both alone and in combination with Ruxolitinib, decreased cell viability in the *JAK2*V617F mutant UKE1 cell line in a dose-dependent manner.

Sample ID	Diagnosis	Mutations	Absolute PB monocytes (Normal, increased)	Blast CD123 expression	Blast %
151	MPN/MDS Overlap	CALR, TP53, CHEK2	Normal	+	15%
461	MF	DNMT3A	Normal	N/A	<5%
829	MF	MPL, ASXL1, CBL, KDM5C, U2AF1	Normal	+	<5%
554	MF	CALR	Normal	+	<5%
289	MF	JAK2, ASXL1, GNAS	Increased	+	3%
455	MF	CALR	Normal	+	10%
154	MF	MPL, TET2, SRSF2	Increased	N/A	<5%

Colony Forming Assays using MPN Patient Samples: Mononuclear cells from viably frozen MPN peripheral blood samples were used for cell viability assays. Patient characteristics are displayed in table above. Cells were exposed to vehicle, ruxolitinib, tagraxofusp, or combination of ruxolitinib and tagraxofusp. * P<0.05 when compared with vehicle.



Conclusions

Current therapeutic options for patients with Myelofibrosis beyond Ruxolitinib are limited. This is particularly the case for patients with progression to accelerated and blast-phase MPN. Here, we demonstrate that CD123 expression is evident in many such cases. Further, therapeutic targeting of CD123 using Tagraxofusp either alone or in combination with Ruxolitinib has activity in primary patient samples, including those in accelerated phase and with high molecular risk profiles. These data thus support further testing of Tagraxofusp in MPNs, and in advanced MPNs in particular.

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