A Phase 1/2 Study of Single-Agent Tagraxofusp, a First-in-Class CD123-Targeted Therapy, in Patients with Relapsed/Refractory Myelofibrosis

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Disclosures

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Background

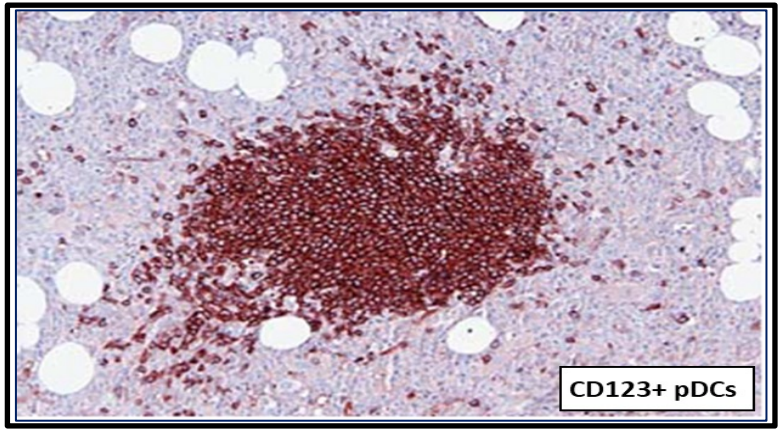
- Myelofibrosis (MF) is an aggressive form of myeloproliferative neoplasm (MPN) with an annual rate of transformation to acute myeloid leukemia (AML) of about 20%

- The type I JAK 1/2 inhibitors (JAKi), ruxolitinib and fedratinib, are the only currently FDA approved therapies. Neither significantly impacts the natural history or biology of the disease and novel therapies are required

Novel targets: Pre-clinical rationale

- CD123 (IL-3Rα) is normally expressed on maturing myeloid cells and plasmacytoid dendritic cells (pDCs)

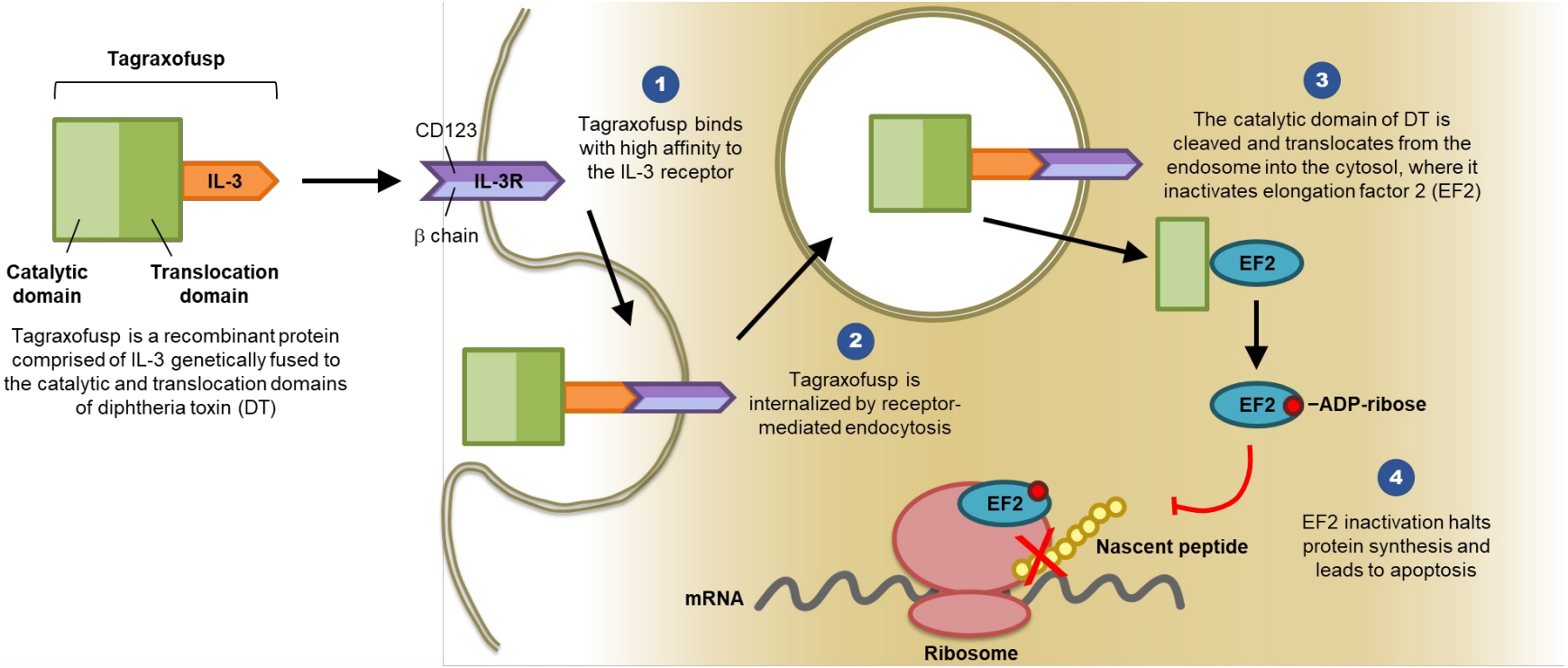
- Therapeutic targeting of CD123 using tagraxofusp (TAG) either alone or in combination with ruxolitinib has activity in primary patient samples, including those in the accelerated-phase and with high molecular risk profiles[1]. These data support clinical studies testing TAG in patients with MF.



1. Krishnan et al, *Blood*. 2019 Nov; 134(Supp_1): 2967. 2. Facchetti et al. *Mod Pathol*. 2016 Feb;29(2):98-11 (image)

Targeting CD123

- Tagraxofusp* structure and mechanism of action



O'Brien J, et al. *Drugs Future.* 2018;43:873-880.
*TAG is FDA and EMA approved for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN)

Study Design

Stage 1: Single-arm Lead in, n=4

- Tagraxofusp dosing schedule:
  - 7, 9, or 12 mcg/kg via IV infusion, days 1-3 of a 21-day cycle (C1-4); 28-day cycle (C5-7); and 42-day cycle thereafter
- Key objectives: Determine the optimal dose and regimen for Stage 2

Stage 2: Single-arm Expansion, n=35

- Tagraxofusp dosing schedule:
  - 12 mcg/kg via IV infusion, days 1-3 of a 21-day cycle (C1-4); 28-day cycle (C5 and beyond)
- Key objectives: Further define safety and efficacy

Select Inclusion Criteria

- Prior therapy/relapsed/refractory (R/R) MF
- Intermediate-1 or higher risk-classification
- Evidence of acceleration
- Age ≥18; ECOG PS 0-2

Stage 2 MF Study Endpoints[1]

- Safety:
  - Treatment-emergent Adverse Events (TEAE)
- Efficacy:
  - Spleen Size Reduction (Exam, Imaging (CT/MRI)
  - Total Symptom Score (TSS) Reduction*

1. Tefferi A., et al. *Am J Hematol* 2013A; 88:142-150.

*Responses were based on the revised IWG-MRT-ELN 2013 Response Criteria

Clinicaltrials.gov: NCT02268253

Baseline Patient Demographics

Characteristic	N=39
Median age, years [range]	70 [54, 87]
Female, n (%)	18 (46)
ECOG PS, n (%) 0 1 2	 4 (10) 24 (62) 11 (28)
Splenomegaly, n (%)	29 (74)
Hepatomegaly, n (%)	5 (13)
Platelets (10^9/L), median [range] >100, n (%) >50-100, n (%) ≥20-50, n (%) <20, n (%)	67 [5, 651] 16 (41) 7 (18) 12 (31) 4 (10)
Hemoglobin (g/dL), median [range]	8.3 [5.7-14.1]
WBC (x10^9/L), median [range]	12 [1-74]

Characteristic	N=39
Prior Systemic Therapy, n (%) JAKi Hypomethylating Agents Stem Cell Transplant	 36 (92) 4 (10) 4 (10)
Median # of prior treatments, median [range]	2 [1, 8]
Myelofibrosis subtype, n (%) Primary MF Post-PV Post-ET	 26 (67) 8 (21) 5 (13)
DIPSS-plus risk score[1], n (%) High Intermediate-2 Intermediate-1	 11 (28) 18 (46) 10 (26)

1. Tefferi A., *Am J Hematol* 2021;96:145-162.

Baseline Cytogenetic and Molecular Characteristics

Cytogenetics, n (%)	N=39
Abnormal Karyotype	**19 (49)**
20q-	4 (10)
-7/7q-	3 (8)
-5/5q-	2 (5)
12p-	2 (5)
I(17q)	1 (3)
13q-	1 (3)
Other	6 (15)

Molecular mutations, n (%)	N=39
Driver Mutations	
JAK2 V617F	24 (62)
CALR	3 (8)
MPL	2 (5)
Triple Negative	10 (26)
Prognostic Mutations*	
ASXL1	9 (23)
SF3B1/U2AF1	7 (18)

*As reported by local site investigator

Safety Analysis

Treatment-emergent adverse events (TEAEs) occurring in ≥15% of patients

	Any Grade, n (%)	*Grade ≥3, n (%)*
Hypoalbuminemia	15 (39)	1 (3)
Pyrexia	12 (31)	3 (8)
Headache	11 (28)	0
Thrombocytopenia	10 (26)	6 (15)
Chills	9 (23)	0
Increased alanine aminotransferase	7 (18)	0

	Any Grade, n (%)	*Grade 3, n (%)*	*Grade 4, n (%)*	*Grade 5, n (%)*
Capillary Leak Syndrome (CLS)	3 (8)	1 (3)	1 (3)	0

- Of the patients who experienced CLS (n=3), the median duration to any-grade CLS was 5 days (range: 2-8 days); no cases of CLS after cycle 1
- No Grade 5 CLS was reported

Spleen Responses* (N=24)

- 24/39 patients (62%) had baseline splenomegaly (≥5 cm palpable BCM)

	n (%)	Baseline Thrombocytopenia		Baseline Monocytosis
		Platelets <100× 10^9/L	Platelets <50× 10^9/L	Monocytes ≥1 %
Any reduction	13 (54%)	5 (21%)	5 (21%)	3 (13%)
≥50% reduction	7 (29%)	2 (12%)	2 (12%)	0

- 3/24 (13%) with concomitant monocytosis
- 10/24 (42%) with concomitant thrombocytopenia

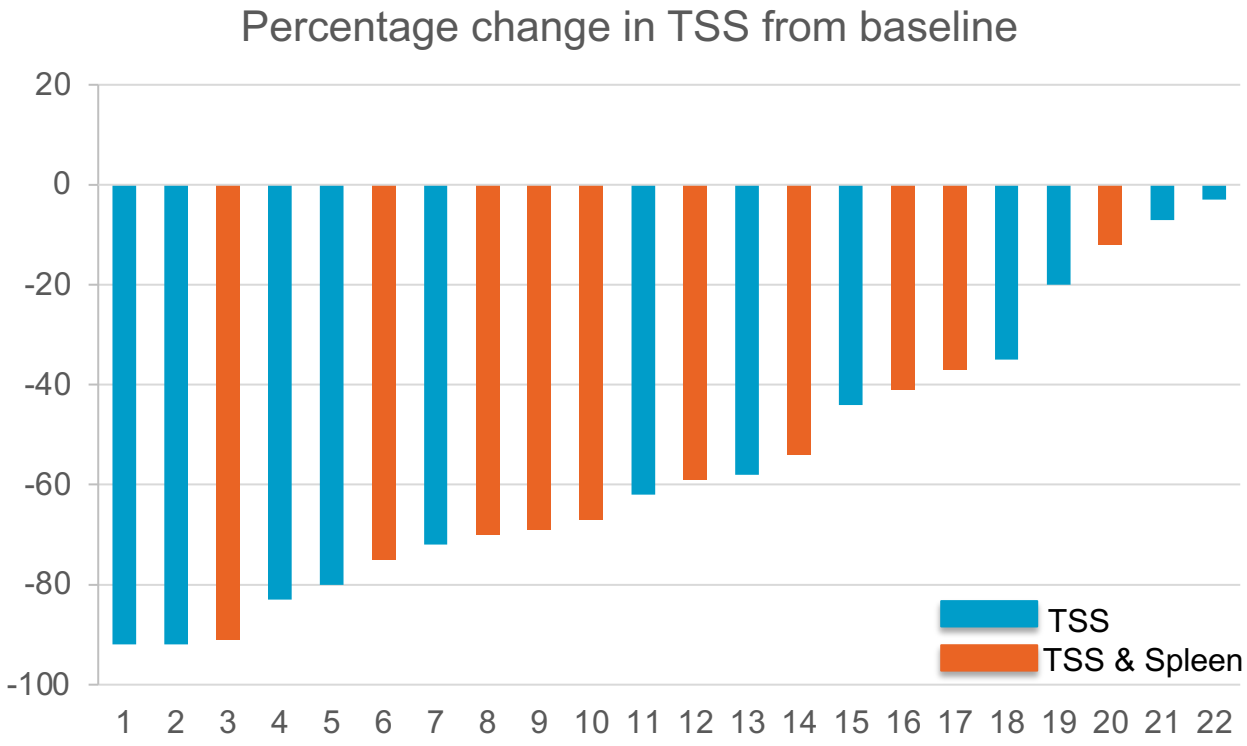
* Patients with palpable spleen at baseline
BCM, below costal margin

Spleen Volume Reduction (SVR)

Patient	Spleen Volume Reduction (SVR)		
#	Baseline	Best response	Reduction, %
1	3150	1528	**52**
2	1169	754	**36**
3	4006	3252	**19**
4	2471	2143	**13**
5	1154	999	**13**
6	2404	2128	**11**
7	2265	2039	**10**
8	3580	3291	8
9	1616	1511	6
10	2091	2043	2
11	1676	1676	0
12	2711	2711	0
13	3519	3519	0
14	3142	3142	0
15	417	417	0

- Spleen responses were assessed objectively by imaging (CT, MRI) in 15 patients with baseline splenomegaly
- 7/15 patients (47%) achieved ≥10% reduction in size
- 4/15 (27%) also had monocytosis
- 7/15 (47%) also had thrombocytopenia
  - 3/15 (20%) with platelets <100
  - 4/15 (27%) with platelets <50

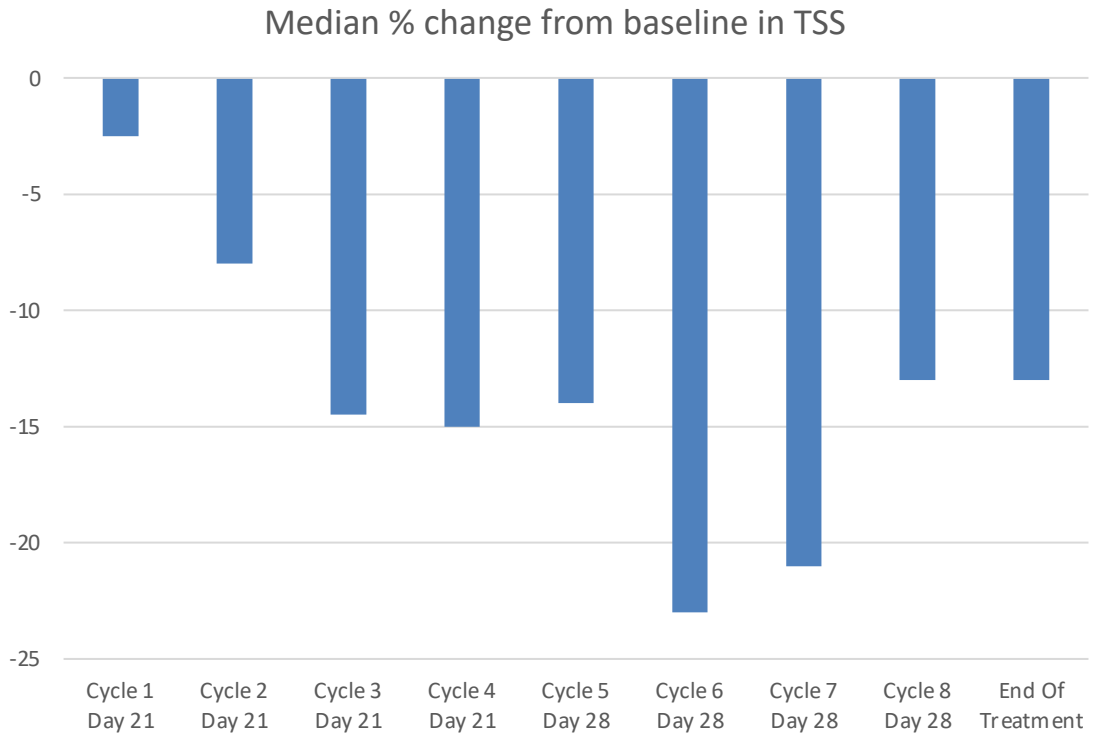
TSS & Spleen Responses



- Total Symptom Score (TSS)[1] was reduced in 22/39 patients (56%)
- 14/39 patients had a ≥50% improvement in clinical symptom score
- 10/39 (26%) had reductions from baseline in both TSS and spleen size

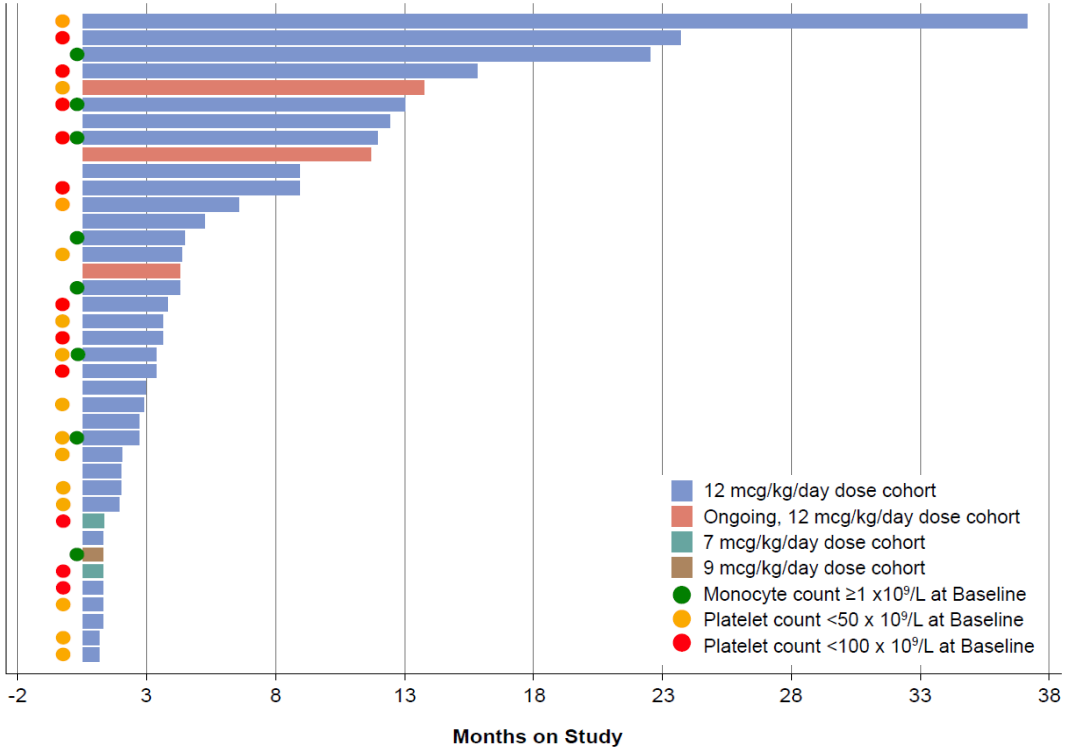
1. Mesa et al., *Cancer* 2011: 117(21); 4869-4877

TSS Responses Over Time



Treatment Duration

- Median duration of follow-up was 26.1 months (95% CI 16.0, 46.6)

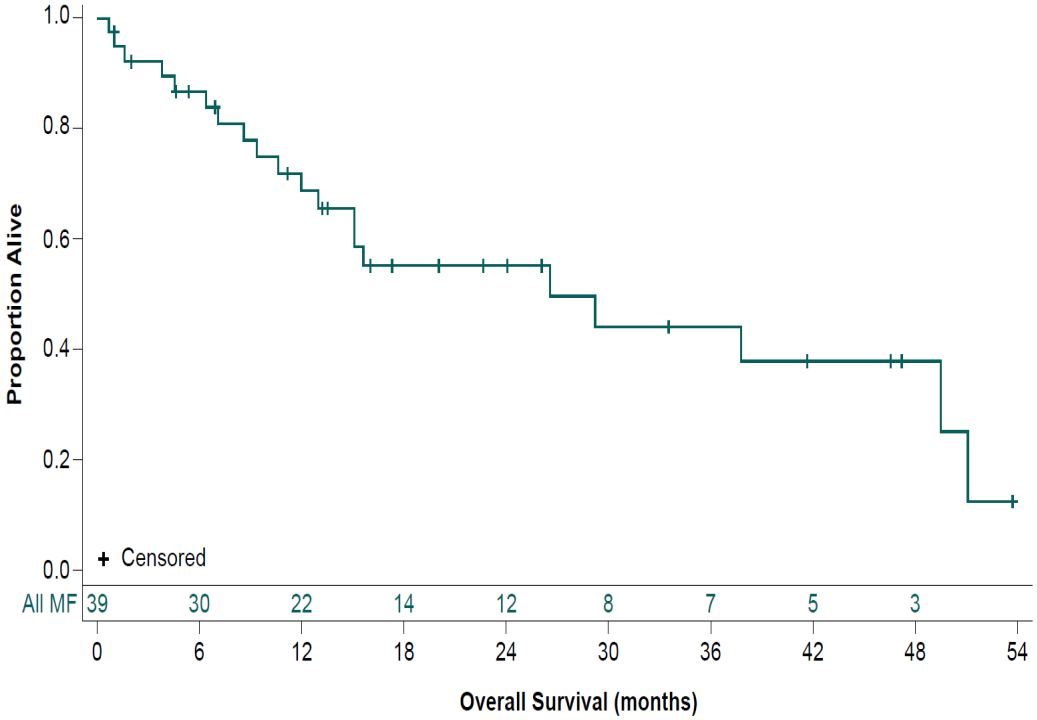


Patient Disposition

- 36/39 patients (92%) have discontinued treatment

Reason, n (%)	
Disease progression	10 (26)
Adverse Event	9 (23)
Other	6 (15)
Physician Decision	5 (13)
Patient withdrawal of consent	3 (8)
Death from any cause	2 (5)
Patient received allogenic stem cell transplant	1 (3)

Overall Survival



- 19/39 patients (49%) remain alive at data cutoff date of September 30, 2021
- Median overall survival:
  - 26.6 months (95%: CI 12.9, 51.1)
  - Range, months [0.66, 53.72]

Conclusions

- The results of this phase 1/2 study of tagraxofusp monotherapy in previously treated MF patients with high-risk clinical features demonstrated clinical efficacy and a predictable and manageable safety profile

- Modest splenic responses were observed. Clinical benefit in terms of total symptom scores were also noted

    - This includes in patients who were refractory to JAKi therapy and those with associated monocytosis and thrombocytopenia

- Overall survival was 26.6 months in this cohort suggesting disease modifying properties of tagraxofusp

- Based on the clinical findings of this study, as well as promising pre-clinical evidence of anti-tumor activity on primary patient samples, a combination of TAG with a JAKi in high-risk patients with MF will now be assessed

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