EHA 2019
PF668

Results from Ongoing Phase 1/2 Clinical Trial of Tagraxofusp (SL-401) in Patients with Intermediate or High Risk Relapsed/Refractory Myelofibrosis

Naveen Pemmaraju[1], Vikas Gupta[2], Haris Ali[3], Abdulraheem Yacoub[4], Eunice Wang[5], Sangmin Lee[6], Gary Schiller[7], Megan Sardone[8], Halyna Wysowskyj[8], Shay Shemesh[8], Janice Chen[8], Chris Brooks[8], Enrique Poradosu[8], Peter McDonald[8], Nicole Rupprecht[8], Animesh Pardanani[9], Ayalew Tefferi[9], Moshe Talpaz[10], Minakshi Taparia[11], Srdan Verstovsek[1], Joseph Khoury[1], Mrinal M. Patnaik[9]

[1]The University of Texas MD Anderson Cancer Center, Houston, [2]Princess Margaret Cancer Centre, Toronto, Canada, [3]City of Hope, Duarte, [4]Kansas University Cancer Center, Westwood, [5]Roswell Park Cancer Institute, Buffalo, [6]Weill Cornell Medical Center, New York, [7]Ronald Reagan UCLA Medical Center, Los Angeles, [8]Stemline Therapeutics, New York, [9]Mayo Clinic, Rochester, [10]University of Michigan Health System, Ann Arbor, [11]University of Alberta Hospital, Edmonton

Introduction and Highlights

Tagraxofusp
- Novel targeted therapy directed to CD123
- FDA-approved for the treatment of adult and pediatric patients, 2 years and older, with blastic plasmacytoid dendritic cell neoplasm (BPDCN)
  - Breakthrough Therapy Designation (BTD) designation
- Marketing Authorization Application (MAA) for BPDCN granted accelerated assessment, and under review, by the EMA

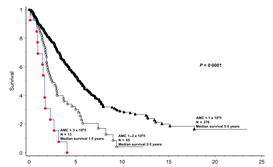
CD123 target
- Expressed by multiple malignancies, including certain myeloproliferative neoplasms (MPN) such as chronic myelomonocytic leukemia (CMML) and myelofibrosis (MF), certain acute myeloid leukemia (AML) patient subsets, BPDCN and others

Tagraxofusp and MF
- In this Phase 1/2 trial (NCT02268253), tagraxofusp monotherapy demonstrated clinical activity, with a predictable and manageable safety profile, in patients with relapsed/refractory MF, including poor-prognosis MF patients with monocytosis, areas of unmet medical need
- Patient enrollment is ongoing
- Based on these encouraging results, next steps for the program are being evaluated including single agent, combination, and registration-directed trials in patients with relapsed/refractory MF

Background: Myelofibrosis (MF)

- MF is a BCR-ABL1–negative myeloproliferative neoplasm characterized by clonal myeloproliferation, dysregulated kinase signaling, and release of abnormal cytokines
- Prominent clinical manifestations include severe anemia, marked splenomegaly and hepatomegaly, and constitutional symptoms (fatigue, fever, and night sweats)
- Ruxolitinib is approved in the US and EU for intermediate/high risk MF in the frontline setting; approval was based on improvement in splenomegaly and constitutional symptoms
- Patients with myelofibrosis (MF) who fail or are intolerant to JAK inhibitors (JAKi) have no standard treatment options, and is an area of unmet medical need
- In patients with MF, development of monocytosis (>1x10⁹/L monocytes) is associated with rapid disease progression and short survival, and indicates an accelerated phase of the disease
- Targeting MF via a CD123-directed therapeutic may offer a novel approach for treatment of these patients

Monocytosis is a Powerful and Independent Predictor of Inferior Survival in Primary Myelofibrosis

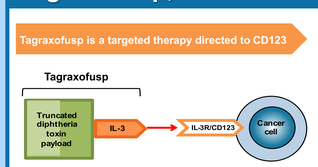


Survival data in 454 patients with primary myelofibrosis, stratified by absolute monocyte count.

Tefferi. Br J Haematol. 2018.

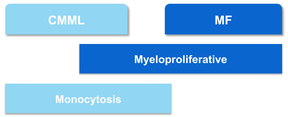
Tagraxofusp, Mechanism of Action, and Rationale

Tagraxofusp is a targeted therapy directed to CD123



- Novel targeted therapy directed to CD123
- FDA-approved for the treatment of adult and pediatric patients, 2 years and older, with blastic plasmacytoid dendritic cell neoplasm (BPDCN)
  - Breakthrough Therapy Designation (BTD)
- Marketing Authorization Application (MAA) for BPDCN granted accelerated assessment, and under review, by the EMA

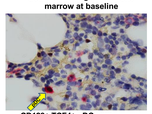
CMML and MF overlap
- **~50% of CMML presents with myeloproliferative features (MP-CMML), e.g. splenomegaly, etc. (similar to MF); associated with poor prognosis**
- **~10-20% of MF presents with monocytosis (similar to CMML); associated with poor prognosis**
  - ***Monocytes share a common progenitor with CD123+ plasmacytoid dendritic cells (pDCs)***



Padron. Blood Cancer J, 2015; Tefferi. Br J Haematol. 2018; Facchetti. Mod Pathol. 2016

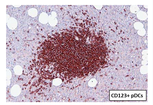
CD123 Expression in MF
- **CD123+ pDCs in MF tumor microenvironment**

CD123 (red) and TCF4 (brown) immunohistochemistry double staining of MF bone marrow at baseline



CD123+ TCF4+ pDCs are indicated by arrows

CD123+ staining in MF bone marrow



- **In MF, monocytosis (>1x10⁹/L monocytes) is associated with an accelerated disease phase and independent predictor of poor prognosis**
- **Monocytes share a common precursor cell with CD123+ pDCs**

Pemmaraju N, et al. ASH 2018. Abstract 1773; Facchetti F, et al. Mod Pathol. 2016;29:98-111

Trial Design

Stage 1 Lead-in (Complete)
- MPN: CMML, MF, SM, and PED
- Tagraxofusp (7, 9, or 12 ug/kg) via IV infusion, **days 1-3** of a 21-day cycle (cycles 1-4), a 28-day cycle (cycles 5-7); a 42-day cycle thereafter
- Key objectives: To determine optimal dose and regimen for Stage 2

Stage 2 Expansion (Enrolling)
- MPN: CMML or MF without evidence of transformation
- Tagraxofusp (12 ug/kg)[a] via IV infusion, **days 1-3** of a 21-day cycle (cycles 1-4), a 28-day cycle (cycles 5-7); a 42-day cycle thereafter
- Key objectives: To further define safety and efficacy

Select Inclusion Criteria:
- Patient population
  - Stage 1 - Advanced, high-risk MPN, including CMML, MF, SM, and PED
  - Stage 2 - CMML or MF without evidence of transformation
- Age ≥18; ECOG PS 0-2
- Adequate baseline organ function, including: LVEF ≥ LLN, creatinine ≤1.5 mg/dL, albumin ≥3.2 g/dL, bilirubin ≤1.5 mg/dL, AST/ALT ≤2.5 times ULN, creatine phosphokinase (CPK) ≤2.5 times ULN, ANC ≥0.5×10⁹/L

[a]12 µg/kg/day was highest tested dose (MTD not reached) and selected for Stage 2
CMML=chronic myelomonocytic leukemia; MF=myelofibrosis, SM=systemic mastocytosis; PED=primary eosinophilic disorders; MTD=maximum tolerated dose

Demographics

Age, years	n = 27
Median [range]	69 [54-81]
Gender	
Female	14 (52)
ECOG	
Median [range]	1 [0-2]
Median Blast Count, %	
Median [range]	3 [0-16]
Baseline sites of disease [n, (%)]	
Bone marrow (BM)[1]	5 (19)
Spleen	22 (81)
Liver	5 (19)
Baseline Platelets	
Median [range]	59 [13-579]
≤100×10⁹/L, [n, (%)]	18 (67)
≤50×10⁹/L, [n, (%)]	10 (37)

Prior systemic therapy for MF [n, (%)][2]	
JAK inhibitor (JAKi)	19 (70)
Stem cell transplant (SCT)	2 (7)
Hypomethylating agent (HMA)	3 (11)
Median [range]	3 (1-3)
Myelofibrosis type[3]	
Primary MF	17 (63)
Post-Polycythemia MF	7 (26)
Post-Essential Thrombocythemia MF	3 (11)
DIPSS-plus score[4]	
High	9 (33)
Intermediate-2	16 (59)
Intermediate-1	1 (4)
Myelofibrosis karyotype5	
No known abnormal karyotype	19 (70)
Abnormal karyotype	8 (30)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; DIPSS = Dynamic International Prognostic Scoring System
1. BM involvement defined as Blast Count ≥ 5%. 2. Three patients did not have these data available at the time of cut-off. 3. Four patients did not have these data available at the time of cut-off. 4. Three patients did not have these data available at the time of cut-off.
5. Five patients did not have these data available at the time of cut-off

Safety and Tolerability

- **Predictable and manageable safety profile**
- **No apparent cumulative AEs, including in the bone marrow, over multiple cycles**

MF (all doses); Stages 1 and 2 (n=27)

Most Common (≥15%) Treatment-Related Adverse Events (TRAEs)

Preferred Term	All Grades, n (%)		TRAEs, n (%)			
	TRAEs	All AEs	G1 & 2	G3	G4	G5
Alanine aminotransferase increased	5 (19)	6 (22)	5 (19)	--	--	--
Headache	5 (19)	6 (22)	5 (19)	--	--	--
Hypoalbuminaemia	5 (19)	9 (33)	5 (19)	--	--	--
Anaemia	4 (15)	9 (33)	0 (0)	4 (15)	--	--
Thrombocytopenia	4 (15)	7 (26)	2 (8)	1 (4)	1 (4)	--

There was one case of capillary leak syndrome, which was Grade 3

Clinical Activity Overview

Patient	Dose (ug/kg/d)	Line	Prior Therapy	Monocytes (K/uL), baseline	Platelet count (10⁹/L), baseline	Spleen[1] Baseline (cm)	Spleen[1] Best Response (cm)	Spleen[1] Spleen size reduction
1	12	3	JAKi	0.4	19	5	0	100%
2	12	3	JAKi; HMA; Hydrea	0.00	7	3	0	100%
3	12	3	JAKi	1.10	72	19	10	47%
4	12	2	JAKi	4.50	181	35	19	46%
5	7	3	Benda; IA	2.23	77	30	20	33%
6	12	3	JAKi; Lenalidomide	0.07	56	17	12	29%
7	12	2	JAKi	2.22	59	14	10	29%
8	12	3	JAKi; IA	0.27	23	17	16	6%
9	12	2	JAKi	4.90	23	19	18	5%
10	12	3	JAKi; IA (2)	0.00	136	13	13	-
11	7	3	JAKi; Prep for SCT	0.00	52	21	23	-
12	12	3	JAKi; SCT	0.23	78	9	10	-
13	9	2	JAKi	0.73	191	11	13	-
14	12	2	PST	0.00	29	16	21	-
15	12	2	PST	0.94	232	3	4	-
16	12	3	JAKi	0.93	21	12	17	-
17	12	3	JAKi; IA	0.00	385	13	13	-
18	12	3	JAKi; Hydrea	0.88	17	22	Pending	N/E
19	12	3	JAKi; HMA; Hydrea	0.73	66	Palpable, N/A		N/E
20	12	2	JAKi	7.36	35	Palpable, N/A		N/E
21	12	2	PST	0.53	8	Palpable, N/A		N/E
22	12	3	JAKi; HMA; Hydrea	0.26	35	No splenomegaly		N/E
23	12	2	PST	4.07	56	No splenomegaly		N/E
24	12	2	JAKi	0.42	46	No splenomegaly		N/E
25	12	N/A	Pending	0.00	138	Palpable, N/A		N/E
26	12	N/A	Pending	0.00	13	No splenomegaly		N/E
27	12	N/A	Pending	0.70	222	No splenomegaly		N/E

Monocyte count ≥1 x10⁹/L; Platelet count ≤50 x10⁹/L; Platelet count ≤100 x10⁹/L

JAKi = JAK inhibitor; HMA = hypomethylating agent; Benda = bendamustine; IA = Investigational agent; PST = prior systemic therapy; N/A = not applicable / no measurement currently available; N/E = not evaluable
[1]Measured by physical exam (cm below costal margin)

Spleen Responses in Patients with MF, including with Monocytosis

Patient	Line	Prior Therapy	Monocytes (10⁹/L), baseline	Platelet count (10⁹/L), baseline	SPLEEN[1] Baseline (cm)	SPLEEN[1] Best Response (cm)	SPLEEN[1] Spleen size reduction
1	3	JAKi	0.4	19	5	0	100%
2	3	JAKi, HMA, Hydrea	0	7	3	0	100%
3	3	JAKi	1.10	72	19	10	47%
4	2	JAKi	4.50	181	35	19	46%
5	3	Benda, IA	2.23	77	30	20	33%
6	3	JAKi, Lenalidomide	0.07	56	17	12	29%
7	2	JAKi	2.22	59	14	10	29%
8	3	JAKi, IA	0.27	23	17	16	6%
9	2	JAKi	4.90	23	19	18	5%

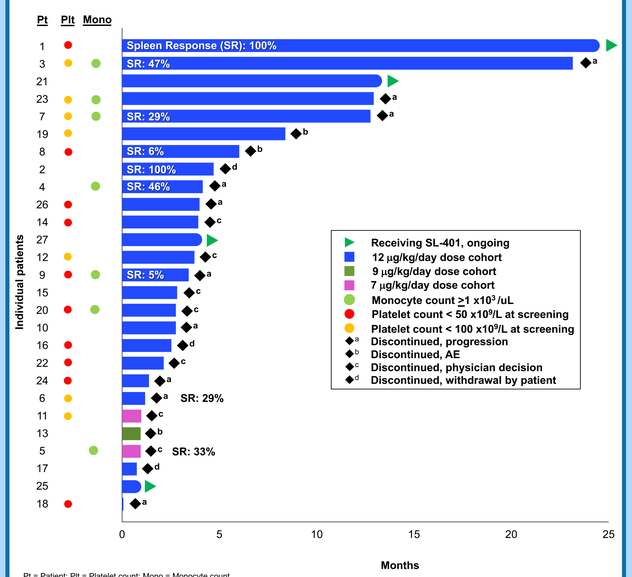
Spleen responses[1]	ALL PATIENTS Response rate (All)	ALL PATIENTS Response rate (≥5cm BCM)	PATIENTS WITH MONOCYTOSIS (≥1 x10⁹/L) Response rate (All)	PATIENTS WITH MONOCYTOSIS (≥1 x10⁹/L) Response rate (≥5cm BCM)
All size reductions	53% (9/17)	53% (8/15)	100% (5/5)	100% (5/5)
≥29% size reduction	41% (7/17)	40% (6/15)	80% (4/5)	80% (4/5)
>45% size reduction	24% (4/17)	20% (3/15)	40% (2/5)	40% (2/5)

[1]Measured by physical exam (cm below costal margin)
JAKi = JAK inhibitor; HMA = hypomethylating agent; Benda = bendamustine; IA = Investigational agent; PST = prior systemic therapy; N/A = not applicable / no measurement currently available; N/E = not evaluable

Monocyte count ≥1 x10⁹/L; Platelet count ≤50 x10⁹/L; Platelet count ≤100 x10⁹/L

Treatment Duration and Outcomes

- **5 patients with treatment duration of 12+ months; 2 patients ongoing (13+, 24+ months)**
- **3 patients with baseline monocytosis with treatment duration 12+ months**
- **6 patients with baseline thrombocytopenia (platelets <100K) with treatment durations 6+ months; 1 patient ongoing**
  - **Includes 1 patient with platelets <50K**

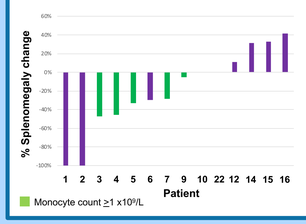


Pt = Patient; Plt = Platelet count; Mono = Monocyte count

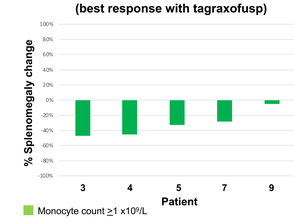
MF Patients with Monocytosis - Unmet Medical Need

- In patients with MF, monocytosis (>1x10⁹/L) is associated with rapid disease progression and short survival, and indicates an accelerated phase of the disease. Monocytosis in primary MF is similar to that seen in CMML, but does not lead to disease reclassification
- In some cases, morphological and/or molecular (e.g., ASXL1, TET2, SRSF2 mutations) characteristics overlapping MF and chronic myelomonocytic leukemia (CMML) are observed. These mutations are also common in BPDCN, the lead indication for tagraxofusp
- Such cases likely represent primary MF with monocytosis, dysplasia, and secondary (non-driver) mutations at presentation. Alternatively, they may represent a true 'gray zone' of neoplasms that display aggressive clinical behavior
- Monocytes share a common precursor cell with CD123+ pDCs
- Innovative therapeutic approaches, including CD123-targeted strategies, may be required, in this poor-prognosis patient subset

All patients with splenomegaly (best response with tagraxofusp)



All patients with monocytosis at baseline and splenomegaly (best response with tagraxofusp)



Quality of Life Assessment

Patient	Dose (µg/kg/day)	Line	Overall QOL Baseline	Best Response	Decrease
1	12	3	1	0	100%
3	12	3	5	0	100%
14	12	1	3	0	100%
23	12	1	1	0	100%
26	12		5	1	80%
27	12		4	1	75%
15	12	1	3	1	66%
8	12	4	5	2	60%
4	12	2	9	5	44%
10	12	3	5	3	40%
16	12	3	5	3	40%
9	12	2	6	4	33%
22	12	4	7	5	29%
6	12	4	4	3	25%
24	12	N/A	6	6	
2	12	5	5	5	
11	7	3	3	6	
12	12	4	4	5	
13	9	2	1	1	
19	12	N/A	N/A	N/A	Pending
21	12	N/A	N/A	N/A	Pending
18	12		7	N/A	Pending
25	12		2	N/A	Pending
5	7	3	2	N/A	N/E
7	12	2	N/A	2	N/E
17	12	3	N/A	5	N/E
20	12	N/A	0	N/A	N/E

N/A = not available; N/E = not evaluable

- 69% (9/13) of evaluable patients had improvement in Overall Quality of Life (QOL) Score
  - 100% (4/4) of patients with baseline score of ≥5 had improvement
  - 4 patients achieved a best response of 0
- Symptom scores measured using Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)
- TSS is patient assessed and includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers
- Each symptom is scored from 0 (absent/as good as can be) to 10 (worst imaginable/as bad as it can be)
- A full TSS analysis is ongoing and will be reported separately

Conclusions and Next Steps

Efficacy
- Tagraxofusp monotherapy demonstrated clinical activity, with a predictable and manageable safety profile, in patients with relapsed/refractory MF, an unmet medical need
- 53% of evaluable patients, with baseline spleen size ≥5cm, had reduction in baseline splenomegaly
  - 40% had reduction by ≥29%; 20% had reduction by ≥45%
- 100% of evaluable patients with monocytosis and baseline spleen size ≥5cm had reduction in baseline splenomegaly
  - 80% had reduction by ≥29%; 40% had reduction by ≥45%
- 5 patients had treatment duration of 12+ months; 2 ongoing (13+, 24+ months)
  - 3 patients with baseline monocytosis (>1x10⁹/L) had treatment duration of 12+ months
  - 6 patients with baseline thrombocytopenia (platelet count <100K) had treatment duration of 6+ months; 1 ongoing
- Initial quality of life (QOL) assessments appear promising; full symptom score analyses are ongoing

Safety
- Most common TRAEs include alanine aminotransferase increased, headache and hypoalbuminemia (each 19%), and anaemia and thrombocytopenia (each 15%). The most common TRAE, grade 3+, was thrombocytopenia (8%)

Next steps
- Patient enrollment is ongoing
- Tagraxofusp, FDA approved for BPDCN, may offer MF patients, and MF patients with monocytosis in particular, a novel treatment option
- Based on these encouraging results, next steps are being evaluated including single agent, combination, and registration-directed trials in patients with relapsed/refractory MF, an unmet medical need

References

- ELZONRIS™ [prescribing information]. New York, NY: Stemline Therapeutics Inc; 2018
- Frankel et al. Blood 2014; 124:385-92
- Jordan et al. Leukemia 2000; 14:1177-84
- Pardanani et al. Leukemia 2015; 29:1605-8
- Chauhan et al. Cancer Cell 2009; 16:309-23
- Frovola et al. Br J Haematol. 2014; 166:862-74
- Coustan-Smith et al. Blood 2011; 117:6267-6276
- Munoz et al. Haematologica 2001; 86:1261-9
- Tehranchi et al. NEJM 2010; 363:1025-37
- Boiochi et al. Mod Pathol 2018; 31:429-441
- Christie et al. ASH 2015; Abstract#3797
- Black et al. Leukemia 2003; 17:155-9
- Diefenbach et al. Blood 2011; 118:3737
- Aldinucci et al. Leuk Lymphoma 2005; 46:303-11
- Harrison et al. N Engl J Med 2012; 366:787
- Brooks et al. Blood 2013; 122:4104
- Pemmaraju et al. N Engl J Med; 2019; 380(17):1628-1637
- Chauhan et al. Leukemia 2017; 135
- Tefferi et al. Am J Hematol 2013; 88:142
- Tefferi et al. Blood, 2018;132:492

Disclosures: *Sardone*: Stemline - employment, equity ownership; *Wysowskyj*: Stemline - employment, equity ownership; *Shemesh*: Stemline - employment, equity ownership; *Chen*: Stemline - employment, equity ownership; *Brooks*: Stemline - employment, equity ownership; *Poradosu*: Stemline - employment, equity ownership; *McDonald*: Stemline - employment, equity ownership; *Rupprecht*: Stemline - employment, equity ownership; *Khoury*: Stemline - research funding; *Pemmaraju*: Stemline - research funding; *Schiller*: Stemline - research funding; *Patnaik*: Stemline - research funding