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

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Introduction and Highlights

Tagraxofusp (SL-401)

- Novel targeted therapy directed to CD123
- Breakthrough Therapy Designation (BTD) for blastic plasmacytoid dendritic cell neoplasm (BPDCN), an aggressive malignancy derived from the plasmacytoid dendritic cell (pDC)
- BLA under Priority Review; PDUFA date Feb. 21, 2019

CD123 target

- Expressed by multiple malignancies including myeloid precursors that may give rise to certain myeloproliferative neoplasms (MPN) such as myelofibrosis (MF) and chronic myelomonocytic leukemia (CMML)
  - CD123+ pDCs detected in tumor microenvironment

Tagraxofusp and MF

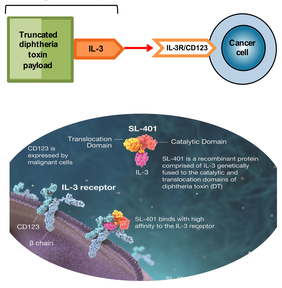
- In this Phase 1/2 trial, tagraxofusp monotherapy demonstrated efficacy **(improvements in splenomegaly)** with a manageable safety profile in patients with relapsed/refractory MF, an area of high unmet medical need
- Based on these encouraging results, next steps for the program are being evaluated including single agent, combination, and registration-directed trials in patients with relapsed/refractory MF, including poor-prognosis MF patients with monocytosis

Background: Myelofibrosis (MF)

- MF is a BCR-ABL1–negative myeloproliferative neoplasm characterized by clonal myeloproliferation, dysregulated kinase signaling, and release of abnormal cytokines
- MF may occur as a sequelae of polycythemia vera (PV), essential thrombocythemia (ET), or may develop in the absence of these associated myeloproliferative conditions (primary MF)
- Prominent clinical manifestations include severe anemia, marked splenomegaly and hepatomegaly, and constitutional symptoms (including 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
- **No approved therapies or standard of care in relapsed/refractory MF, an unmet medical need**
- In patients with MF, development of monocytosis (>1x10^9/L monocytes) is associated with rapid disease progression and short survival, and indicates an accelerated phase of the disease
  - **Innovative therapeutic approaches may be required in this patient subset, in particular**
- Targeting MF via a CD123-directed therapeutic may offer a novel approach for the treatment of these patients

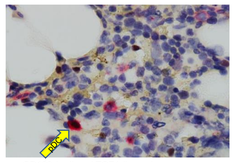
Tagraxofusp, Mechanism of Action, and Rationale

Tagraxofusp is a targeted therapy directed to CD123



MF and CD123: pDCs and monocytes

- **CD123+ pDCs, reported in the bone marrow tumor microenvironment of certain malignancies, may be tumor-promoting and a potential target for therapeutic intervention**



  - CD123 (red) and TCF4 (brown) immunohistochemistry double staining of bone marrow taken at baseline
  - CD123+ TCF4+ pDCs are indicated by arrows
- **In MF, monocytosis (>1x10^9/L monocytes) is associated with an accelerated disease phase and poor prognosis**
- **Monocytes share a common precursor cell with pDCs and express CD123**

Study Design, Response and Inclusion Criteria

Stage 1 Lead-in (Completed)	Stage 2 Expansion (Enrolling)
• MPN: CMML, **MF**, SM, and PED • Tagraxofusp (7, 9, or 12 μg/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	• MPN: CMML or **MF** without evidence of transformation • Tagraxofusp (12 μg/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

MF response criteria

- Revised IWG-MRT and ELN Response Criteria
- Efficacy assessments**:** First assessment performed at the end of cycle 4

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 ≥0.5×10^9/L

[a]12 μg/kg/day was highest tested dose (MTD not reached) and selected for Stage 2

Abbreviations: CMML = chronic myelomonocytic leukemia; MF = myelofibrosis, SM = systemic mastocytosis; PED = primary eosinophilic disorders; IV = intravenous; MTD = maximum tolerated dose; ECOG = Eastern Cooperative Oncology Group; LVEF = left ventricular ejection fraction; AST/ALT = aspartate/alanine aminotransferase; ULN = upper limit of normal; ANC = absolute neutrophil count

Demographics

Age, years	n = 23
Median [range]	69 [55 – 81]
Gender	
Female	13 (61)
ECOG	
Median [range]	1 [0-2]
Median Blast Count, %	
Median [range]	3 [0-16]
Baseline sites of disease [n, (%)]	
Bone marrow (BM)[1]	10 (44)
Spleen	20 (87)
Liver	5 (22)

Prior systemic therapy for MF [n, (%)][2]	
JAK inhibitor (JAKi)	15 (65)
Stem cell transplant (SCT)	4 (17)
Hypomethylating agent (HMA)	2 (9)
Median [range]	3 (1-3)
Myelofibrosis type[3]	
Primary MF	13 (57)
Post-Polycythemia MF	4 (17)
Post-Essential Thrombocythemia MF	2 (9)
DIPSS-plus score[4]	
High	5 (22)
Intermediate-2	12 (52)
Intermediate-1	3 (13)
Myelofibrosis karyotype[5]	
No known abnormal karyotype	14 (61)
Abnormal karyotype	4 (17)

Abbreviations: ECOG = Eastern Cooperative Oncology Group
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

- **Generally well-tolerated and manageable safety profile**
- **Low rates of thrombocytopenia and not dose-limiting**
- **No apparent cumulative AEs, including in the bone marrow, over multiple cycles**

MF (all doses); Stages 1 and 2 (n=23)

Most Common Adverse Events (≥ 15% of treatment related adverse effects, TRAEs)						
Preferred Term	**All Grades n (%)**		**TRAEs n (%)**			
	TRAEs	**All AEs**	**G1 & 2**	**G3**	**G4**	**G5**
Headache	5 (22)	6 (26)	5 (22)	--	--	--
Hypoalbuminaemia	5 (22)	7 (30)	5 (22)	--	--	--
Alanine aminotransferase increased	4 (17)	5 (22)	4 (17)	--	--	--
Thrombocytopenia	4 (17)	7 (30)	2 (8)	1 (4)	1 (4)	--

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

Efficacy

Patient	Dose (ug/kg/d)	Line	Prior Therapy	Monocytes (10^9/L), baseline	Platelet count (10^9/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	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; Invest. agent	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; Invest. Agent	0.27	23	17	16	6%
9	12	2	JAKi	4.90	23	19	18	5%
10	12	3	JAKi; Invest. agent (2)	0.00	136	13	13	-
11	7	3	JAKi; Prep for SCT	0	52	21	23	-
12	12	3	JAKi	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; Invest. Agent	0.00	385	13	Pending	N/E
18	12	N/A	--	0.73	66	Palpable, N/A	N/A	N/E
19	12	N/A	--	7.36	35	Palpable, N/A	N/A	N/E
20	12	2	PST	0.53	8	Palpable, N/A	N/A	N/E
21	12	3	JAKi; HMA; Hydrea	0.26	35	No splenomegaly		N/E
22	12	2	PST	4.07	56	No splenomegaly		N/E
23	12	N/A	--	0.42	46	No splenomegaly		N/E

Monocyte count ≥1 x10^9/L Platelet count ≤50 x10^9/L Platelet count ≤100 x10^9/L

JAKi = JAK inhibitor; HMA = hypomethylating agent; Benda = bendamustine; 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)

Responders

All Patients
- **56% (9/16) spleen responses**
- **44% (7/16) reductions in ≥29% spleen size**
- **25% (4/16) reductions in >45% spleen size**

Patients with monocytosis
- **100% (5/5) spleen responses**
- **80% (4/5) reductions in ≥29% spleen size**
- **40% (2/5) reductions in >45% spleen size**

Patient	Dose (ug/kg/d)	Line	Prior Therapy	Monocytes (10^9/L), baseline	Platelet count (10^9/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%
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6	12	3	JAKi; Lenalidomide	0.07	56	17	12	29%
7	12	2	JAKi	2.22	59	14	10	29%
9	12	2	JAKi	4.90	23	19	18	5%
8	12	3	JAKi; Invest. Agent	0.27	23	17	16	6%

Monocyte count ≥1 x10^9/L Platelet count ≤50 x10^9/L Platelet count ≤100 x10^9/L

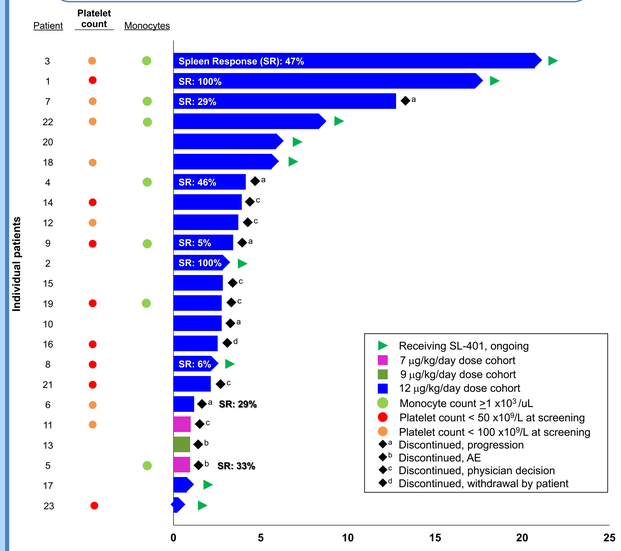
JAKi = JAK inhibitor; HMA = hypomethylating agent; Benda = bendamustine; PST = prior systemic therapy; N/A = not applicable / no measurement currently available; N/E = not evaluable
[1]Measured by physical exam (cm below costal margin)

		All patients: Response rate (All)	All patients: Response rate (≥5cm BCM)	Patients with monocytosis (≥1 x10^9/L): Response rate (All)	Patients with monocytosis (≥1 x10^9/L): Response rate (≥5cm BCM)
Spleen responses[1]	All size reductions	56% (9/16)	57% (8/14)	100% (5/5)	100% (5/5)
	≥29% size reduction	44% (7/16)	43% (6/14)	80% (4/5)	80% (4/5)
	>45% size reduction	25% (4/16)	21% (3/14)	40% (2/5)	40% (2/5)

[1]Patients with palpable spleen at baseline
BCM = below costal margin (by physical exam)

Treatment Duration

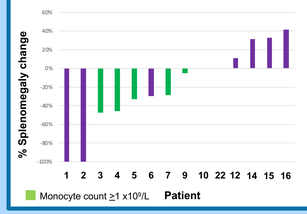
- **6 patients with treatment duration of 6+ months; 5 patients ongoing**
- **5 patients with baseline thrombocytopenia (platelets <100K) with treatment durations 6+ months; 4 patients ongoing**
  - **Includes 1 patient with platelets <50K**
- **3 patients with baseline monocytosis with treatment duration 8+ months; 2 patients ongoing**



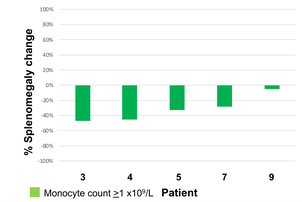
MF Patients with Monocytosis: Unmet Medical Need

- **In patients with MF, monocytosis (>1x10^9/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 pDCs and express CD123**
- **As such, innovative therapeutic approaches, including CD123-targeted strategies, may be required, in particular, 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
3	12	3	5	0	100%
1	12	3	1	0	100%
22	12	1	1	0	100%
14	12	1	3	0	100%
15	12	1	3	1	66%
8	12	4	5	2	60%
4	12	2	9	5	44%
16	12	3	5	3	40%
10	12	3	5	3	40%
9	12	2	6	4	33%
21	12	4	7	5	29%
6	12	4	4	3	25%
13	9	2	1	1	
12	12	4	4	5	
11	7	3	3	6	
5	7	3	2	N/A	N/E
7	12	2	N/A	2	N/E
2	12	5	N/A	6	Pending
17	12	3	N/A	5	N/E
18	12	N/A	N/A	N/A	Pending
19	12	N/A	0	N/A	N/E
20	12	N/A	N/A	N/A	Pending
23	12	N/A	N/A	N/A	Pending

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

- 80% (12/15) of evaluable patients had improvement in Overall Quality of Life (QOL) Score
  - 100% (7/7) 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 efficacy (improvements in splenomegaly), with a manageable safety profile, in patients with relapsed/refractory MF, an area of unmet medical need; Patient enrollment and follow up continues
- 57% of evaluable patients, with baseline spleen size ≥5cm, had reduction in baseline splenomegaly
  - 43% had reduction by ≥29%; 21% 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%
- 6 patients with spleen response had treatment duration of 6+ months; 5 patients ongoing
  - 5 patients with baseline thrombocytopenia (platelet count <100K) had treatment duration of 6+ months; 4 ongoing
  - 3 patients with baseline monocytosis (>1x10^9/L) had treatment duration of 8+ months; 2 patients ongoing
- Initial quality of life (QOL) assessments appear promising; full symptom score analyses are ongoing

Safety

- Most common TRAEs include headache and hypoalbuminemia (each 22%), and alanine aminotransferase increased and thrombocytopenia (each 17%). The most common TRAE, grade 3+, was thrombocytopenia (8%)

Next steps

- Presence of monocytosis in MF patients, historically, is associated with rapid disease progression and short survival, suggesting an accelerated phase of the disease, and innovative therapeutic approaches may be required
- Tagraxofusp 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, including poor-prognosis MF patients with monocytosis, an area of unmet medical need

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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