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Results from Ongoing Phase 1/2 Clinical Trial of Tagraxofusp (SL-401) in Patients with Relapsed/Refractory Chronic Myelomonocytic Leukemia (CMML)

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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 certain myeloproliferative neoplasms (MPN) such as chronic myelomonocytic leukemia (CMML) and myelofibrosis (MF)
  - CD123+ CMML progenitors
  - CD123+ CMML blasts
  - CD123+ pDCs, part of malignant clone, in tumor microenvironment

Tagraxofusp and CMML

- In this Phase 1/2 trial, tagraxofusp has demonstrated efficacy (spleen and bone marrow responses), with a manageable safety profile, in patients with relapsed/refractory CMML
  - Patient enrollment and follow up continues

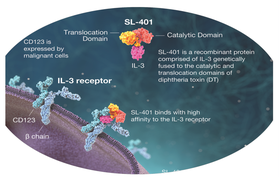
➢ ***Based on encouraging results observed in this trial to date, a registrational trial, or pivotal cohort, is being designed***

Background: Chronic Myelomonocytic Leukemia (CMML)

- **Aggressive myeloid malignancy, characterized by monocytosis**
- **Presents with myelodysplastic or myeloproliferative features**
  - Originally classified as an myelodysplastic syndrome (MDS)
  - Since re-classified as an MDS/MPN (myelodysplastic/myeloproliferative) neoplasm:
    - MD-CMML (myelodysplastic CMML): WBC <13 x 10^9/L
    - MP-CMML (myeloproliferative CMML): WBC ≥13 x 10^9/L; characterized by advanced disease, RAS pathway alterations, splenomegaly, poor prognosis
  - International consortium recommended revising response criteria to capture proliferative elements (Savona, 2015)
- **Splenomegaly has historically been associated with advanced disease, morbidity, and poor prognosis**
  - ~30%- 50% of CMML patients present with splenomegaly
  - Predominant clinical manifestation of MP-CMML
  - Poor quality of life / serious sequelae: abdominal pain, early satiety, risks associated with splenic rupture, splenectomy, as well as poor transplant outcomes
- **Targeting the proliferative component of CMML, namely alleviation of splenomegaly**, could result in meaningful clinical benefit and and address a key unmet medical need

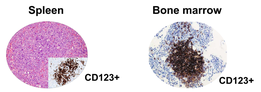
Tagraxofusp, Mechanism of Action, and Rationale

Tagraxofusp is a targeted therapy directed to CD123

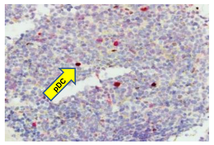


CMML and CD123

- **CD123 is expressed in key CMML disease compartments**



- **CD123+ pDCs in the tumor microenvironment; 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

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

CMML response criteria

- Response as defined in the International Working Group (IWG) consensus report
- 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 = 20
Median [range]	69.5 [43 – 80]
Gender	
Male	16 (80)
CMML Type	
CMML-1	12 (60)
CMML-2	8 (40)
ECOG	
Median [range]	1 [0-2]
Median Blast Count, %	
Median [range]	6.8 [0-18]
Baseline sites of disease [n, (%)]	
Bone marrow (BM)[1]	16 (80)
Spleen	10 (50)
Liver	4 (20)

Prior systemic therapy for CMML [n, (%)][1]	
Hypomethylating agent (HMA)	10 (50)
Stem cell transplant (SCT)	2 (10)
No prior systemic therapy for CMML	2 (10)
Cytogenetic risk category[2]	
High risk	6 (30)
Intermediate risk	8 (40)
Low risk	4 (20)
Other mutations	1 (5)

Abbreviations: ECOG = Eastern Cooperative Oncology Group
1. BM involvement defined as Blast Count ≥ 5%
2. One patient did not have these data at the time of cut-off

Safety and Tolerability

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

CMML (all doses); Stages 1 and 2 (n=20)

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
Hypoalbuminaemia	7 (35)	9 (45)	7 (35)	--	--	--
Thrombocytopenia	7 (35)	7 (35)	--	2 (10)	5 (25)	--
Nausea	6 (30)	7 (35)	5 (25)	1 (5)	--	--
Vomiting	6 (30)	9 (45)	6 (30)	--	--	--
Fatigue	4 (20)	7 (35)	4 (20)	--	--	--
Oedema peripheral	4 (20)	9 (45)	4 (20)	--	--	--
Alanine aminotransferase increased	3 (15)	5 (25)	3 (15)	--	--	--
Back pain	3 (15)	7 (35)	3 (15)	--	--	--
Capillary leak syndrome	3 (15)	3 (15)	3 (15)	--	--	--
Pyrexia	3 (15)	7 (35)	3 (15)	--	--	--
Weight increased	3 (15)	7 (35)	3 (15)	--	--	--

Efficacy

						Spleen[1]			Bone Marrow		
Pt #	Dose (μg/kg/d)	Line	Prior Therapy	CMML type	WBC (10^9/L)	Baseline (cm)	Best response (cm)	% spleen size reduction	Baseline (BM blast %)	Best response (BM blast %)	BMCR
11	12	3	HMA	CMML-1	5.3	10	0	100%	5	22	
5	9	2	HMA	CMML-1	44.7	5	0	100%	6	1	6% → 1%
12	12	2	PST	CMML-2	9.3	4	0	100%	10	1	10% → 1%
3	12	2	HMA	CMML-1	99.2	2	0	100%	7.6	14.6	
9	12	2	HMA	CMML-2	66.1	2	0	100%	18	N/A	N/E
20	12	1	--	CMML-1	16.3	2	0	100%	4	Pending	N/E
17	12	2	PST	CMML-2	8.1	10	2	80%	15	2	15% → 2%
1	7	2	PST; SCT	CMML-2	33.8	20	10	50%	15	15	
8	12	2	HMA	CMML-2	64.2	22	14	36%	6	63.5	
6	12	2	PST	CMML-1	27.2	14	11	21%	8	N/A	N/E
10	12	2	HMA	CMML-1	2.7	No splenomegaly		N/E	11	9	
7	12	2	HMA	CMML-1	15.0	No splenomegaly		N/E	9	7	
13	12	2	PST	CMML-1	26.1	No splenomegaly		N/E	6	4.9	
2	9	2	PST	CMML-2	21.9	No splenomegaly		N/E	5	25	
14	12	2	PST	CMML-2	33.8	No splenomegaly		N/E	14	18.5	
4	12	3	HMA; Clo	CMML-1	18.5	No splenomegaly		N/E	0	3	N/E
15	12	1	--	CMML-1	12.3	No splenomegaly		N/E	6	11	
16	12	2	HMA; SCT	CMML-1	3.3	No splenomegaly		N/E	3	N/A	N/E
18	12	N/L	N/L	CMML-2	2.3	No splenomegaly		N/E	14	29	
19	12	2	HMA	CMML-1	8.8	No splenomegaly		N/E	3	Pending	N/E

= Patient bridged to SCT in remission on tagraxofusp

HMA = hypomethylating agent; PST = prior systemic therapy; Clo = clofarabine; N/E = not evaluable; N/L = not listed; N/A = not available
[1]Measured by physical exam (cm below costal margin [BCM])

Responders

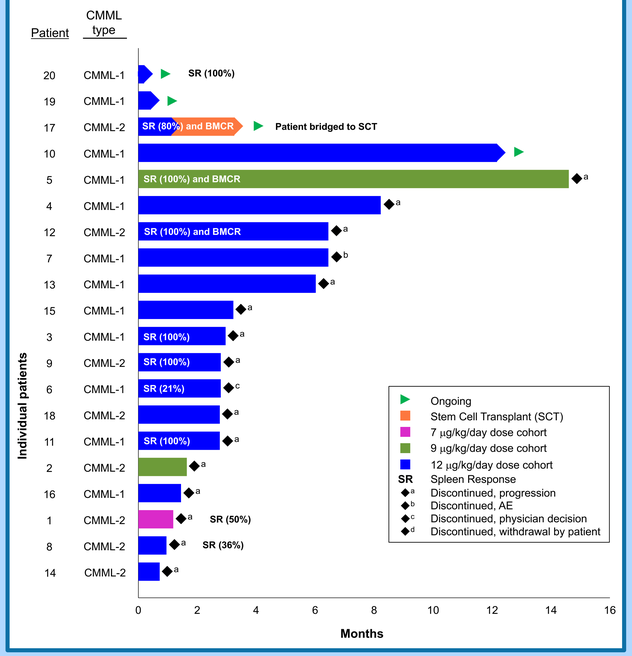
- **100% (10/10) spleen responses**
  - **80% (8/10) had reduction of ≥50%**
  - **67% (4/6) with baseline ≥5cm had reduction ≥50%**
- **3 bone marrow complete responses (BMCRs)**
- **1 patient bridged to stem cell transplant in remission on tagraxofusp**

		Spleen responders[1]		Bone Marrow CR
Pt #	Line	Pre → Post	% response	Pre → Post
11	3	10 cm → 0 cm	100%	
5	2	5 cm → 0 cm	100%	6% → 1%
12	2	4 cm → 0 cm	100%	10% → 1%
3	2	2 cm → 0 cm	100%	
9	2	2 cm → 0 cm	100%	N/E
20	1	2 cm → 0 cm	100%	N/E
17	2	10 cm → 2 cm	80%	15% → 2% (bridged to stem cell transplant)
1	2	20 cm → 10 cm	50%	
8	2	22 cm → 14 cm	36%	
6	2	14 cm → 11 cm	21%	N/E

		Response rate	Responders	Evaluable[1]
Spleen responses	All size reductions	100%	10	10
	≥50% size reduction	80%	8	10
	≥50% size reduction, baseline ≥5cm BCM	67%	4	6

[1]Patients with palpable spleen at baseline
BCM = below costal margin (by physical exam); N/E = not evaluable

Duration of Treatment



Conclusions and Next Steps

- Tagraxofusp demonstrated efficacy (**spleen and bone marrow responses**), with a manageable safety profile, in patients with relapsed/refractory CMML, an area of unmet medical need
  - Patient enrollment and follow up continues
- 100% of evaluable patients had reduction in baseline splenomegaly
  - 80% had reduction by ≥50%
  - 67% with baseline spleen size ≥5cm had reduction by ≥50%
- 3 bone marrow complete responses (BMCRs)
- 1 patient bridged to stem cell transplant in remission on tagraxofusp
- Most common TRAEs include hypoalbuminemia (35%), thrombocytopenia (35%), nausea (30%) and vomiting (30%). Most common TRAEs, grade 3+, include thrombocytopenia (35%) and nausea (5%)
- Splenomegaly has historically been associated with serious sequelae including early satiety and intractable pain, as well as poor transplant outcomes and a higher propensity for AML transformation
- Targeting the proliferative component of CMML, namely alleviation of splenomegaly, could result in meaningful clinical benefit and address a key unmet medical need
- **Based on the encouraging results seen in this trial, a registrational trial design, or pivotal cohort, is being designed**

References

- 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
- Aldinucci et al. Leuk Lymphoma 2005; 46:303-11
- Tehranchi et al. NEJM 2010; 363:1025-37
- Loghavi et al. Blood Adv. 2018;2:1807
- Orazi et al. Leukemia 2008; 22:1308
- Pophali et al. Am. J. Hematol. 2018; 93:1347
- Patnaik et al. Am. J. Hematol. 2016; 91:631
- Christie et al. ASH 2015; Abstract #3797
- Black et al. Leukemia 2003; 17:155-9
- Diefenbach et al. Blood 2011; 118:3737
- Brooks et al. Blood 2013; 122:4104
- Pemmaraju et al. ASH 2017; Abstract #1298
- Chauhan et al. Leukemia 2017; 135
- Solary et al. Blood 2017; 130:126-136
- Alfonso et al. Amer J Hematol 2017; 92:599-606
- Savona et al. Blood 2015; 125:1857

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