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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

- 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 CMML

- Tagraxofusp has demonstrated clinical activity, with a predictable and manageable safety profile, in this Phase 1/2 trial (NCT02268253) of patients with relapsed/refractory CMML
- Patient enrollment is ongoing
- ➢ **Given the encouraging data from this trial and the unmet medical need in patients with CMML, a pivotal program is being constructed**

Background: CMML

- **Aggressive myeloid malignancy, characterized by monocytosis**
- **Median age: 72-76 years**
- **Poor prognosis**
- **Presents with myelodysplastic (MDS) or myeloproliferative (MPN) features**
  - Originally classified as an myelodysplastic syndrome (MDS)
  - Has since been re-classified as an MDS/MPN
    - MD-CMML (myelodysplastic CMML): WBC <13 x 10^9/L
    - MP-CMML (myeloproliferative CMML): WBC ≥13 x 10^9/L; characterized by advanced disease, splenomegaly, RAS pathway mutations, poor prognosis
- **Historically:** Hypomethylating agents (HMAs) were approved for myelodysplastic syndrome (MDS) at a time when CMML was considered an MDS
  - First-line CMML, historically:
    - In MDS pivotal trials, ORR 11%-27%
    - Subsequent to approvals, additional clinical trials demonstrated ORR centered at ~30%-40% (range ~25%-75%) upon initial exposure to HMAs, but responses generally not sustained, with CR rates ~15%
    - Median overall survival (OS): 24-36 months
  - Relapsed/refractory CMML, historically:
    - Outcomes have been described as dismal, irrespective of management
    - Median OS: 6-7 months
- **Currently:** ~50% of CMML now considered a myeloproliferative neoplasm (MPN)
  - International consortium recommended revising response criteria (historically MDS-focused) to capture MPN elements (Savona, 2015)

An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults

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Table 2. Proposed criteria for measurement of treatment response in adult MDS/MPN

CR (presence of all of the following improvements)*
Bone marrow: <5% myeloblasts (including monocytic blast equivalent in case of CMML) with normal maturation of all cell lines and return to normal cellularity*
Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (cgrade 1 fibrosis)‡
Peripheral blood‖
WBC >10 × 10^9 cells/L
High >11 g/dL
Platelets ≥100 × 10^9/L; <400 × 10^9/L
Neutrophils >1.0 × 10^9/L
Blasts 0%
Neutrophil precursors reduced to ≤ 2%
Monocytes <1 × 10^9/L
Extramedullary disease: Complete resolution of extramedullary disease present before therapy (eg, cutaneous disease, disease-related serous effusions), including palpable hepatosplenomegaly
Provisional category of CR with resolution of symptoms‖ CR as described above, and complete resolution of disease-related symptoms as noted by the MPN-SAF TSS
Persistent low-level dysplasia is permitted given subjectivity of assignment of dysplasia*
Complete cytogenetic remission
Resolution of previously present chromosomal abnormality (known to be associated with myelodysplastic, syndrome myeloproliferative neoplasms, or MDS/MPN), as seen on classic karyotyping with minimal at 20 metaphases or FISH‖
Partial remission
Normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity, except in cases of MDS/MPN with >5% bone marrow blasts at baseline
Marrow response
Optional marrow response: Presence of all marrow criteria necessary for CR without normalization of peripheral blood indices as presented above.
Partial marrow response: Bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity, or reduction in grading of reticulin fibrosis from grade 3 to grade 2 at least if bone marrow evaluations spaced at least if mo apart
Clinical benefit
Requires 1 of the following in the absence of progression or CR/partial response and independent of marrow response (and blood response must be verified at ≥8 wk) to be considered a clinical benefit
Erythroid response
High increase by ≥2.0 g/dL
Tr for ≥ 8 wk for patients requiring at least 4 packed red blood cell transfusions in the previous 8 wk
Only red blood cell transfusions given based on physician's judgment for a pretreatment Hgb of ≤8.0 g/dL will count in the red blood cell TI response evaluation‖
Platelet response
Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 wk
Pretreatment <20 × 10^9/L increase from <20 × 10^9/L to >20 × 10^9/L and by at least 100%
Pretreatment >20 × 10^9/L but ≤ 100 × 10^9/L absolute increase of >30 × 10^9/LII
Neutrophil response
Pretreatment <0.5 × 10^9/L at least 100% increase and an absolute increase >0.5 × 10^9/L
Pretreatment, >0.5 × 10^9/L and <1.0 × 10^9/L At least 50% increase and an absolute increase >0.5 × 10^9/LII
Splenic response
Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable
Symptom response
Improvement in symptoms as noted by decrease of ≥50% as per the MPN-SAF TSS scoring ‖20 were not considered eligible for measuring clinical benefit.¶

Table 3. Proposed criteria for measurement of disease progression in adult MDS/MPN

Combination of 2 major criteria, 1 major and 2 minor criteria, or 3 minor criteria from list
Major criteria
Increase in blast count*
≤5% blasts: ≥50% increase and to >5% blasts
5-10% blasts: ≥50% increase and to >10% blasts
10-20% blasts: ≥50% increase and to >20% blasts
20-30% blasts: ≥50% increase and to >30% blasts‡
Evidence of cytogenetic evolution‖
Appearance of a previously present or new cytogenetic abnormality in complete cytogenetic remission via FISH or classic karyotyping
Increase in cytogenetic burden of disease by ≥50% in partial cytogenetic remission via FISH or classic karyotyping
New extramedullary disease
Worsening splenomegaly
Progressive splenomegaly that is defined by IWG-MRT: the appearance of a previously absent splenomegaly that is palpable at ~5 cm below the left-costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of >10 cm
Extramedullary disease outside of the spleen
To include new/worsening hepatomegaly, granulocytic sarcoma, skin lesions, etc.
Minor criteria
Transfusion dependency‖
Significant loss of maternal response on cytopenias ≥50% decrement from maximum remission/response in granulocytes or platelets
Reduction in Hgb by ≥1.5g/dL from best response or from baseline as noted on complete blood count
Increasing symptoms as noted by increase in ≥30% as per the MPN-SAF TSS‖
Evidence of clonal evolution (molecular)¶

Tagraxofusp, Mechanism of Action, and Rationale in CMML

Tagraxofusp is a targeted therapy directed to CD123

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CMML and BPDCN overlap

- **CMML and BPDCN can share genetic alterations and have a common clonal origin**
- **CMML can transform into BPDCN**

Blastic plasmacytoid dendritic cell neoplasm and chronic myelomonocytic leukemia: a shared clonal origin
Leukemia (2017) **31,** 1238–1240; doi:10.1038/leu.2017.38

Biallelic inactivation of the retinoblastoma gene results in transformation of chronic myelomonocytic leukemia to a blastic plasmacytoid dendritic cell neoplasm: shared clonal origins of two aggressive neoplasms
Haferlach et al. *Blood Cancer Journal* (2018)8:82
DOI 10.1038/s41408-018-0120-5

CD123 expression in CMML

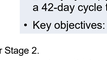
- **CMML blasts**
- **CMML monocytes**
- **Neoplastic pDCs[1] in CMML microenvironment**

CD123+ Cell Populations in CMML

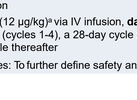
Expressed in key disease compartments

Bone Marrow

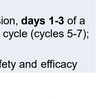
Spleen



Present on both CMML blasts and monocytes



Neoplastic pDCs in tumor microenvironment



[1]Plasmacytoid dendritic cell (pDC) is the cell of origin of BPDCN

Riaz. Cancer Control. 2014; Patnaik. Blood Cancer J. 2018; Brunetti. Leukemia. 2017; Krishnan. ASH 2018.; JI. *Blood.* 2014

Baseline Demographics and Characteristics

Age, years	n=23
Median [range]	69 [42-80]
Gender	
Male	19 (83)
CMML Type	
CMML-1	15 (65)
CMML-2	8 (35)
ECOG	
Median [range]	1 [0-2]
Median Blast Count, %	
Median [range]	6.0 [0-18]
Baseline Sites of Disease, n (%)	
Bone marrow (BM)[1]	17 (74)
Spleen	12 (52)
Liver	4 (17)

Prior Therapy for CMML, n (%)	
Hypomethylating agent (HMA)	11 (48)
Prior Systemic Therapy (PST)	9 (39)
Stem cell transplant (SCT)[2]	3 (13)
No prior systemic therapy for CMML	2 (9)
Cytogenetic Risk Category[3]	
High risk	8 (35)
Intermediate risk	8 (35)
Low risk	4 (17)
Other mutations	2 (9)

[1] BM involvement defined as blast count ≥5%
[2] Patient received prior therapy and SCT
[3] One patient did not have these data at the time of cut-off
ECOG=Eastern Cooperative Oncology Group

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 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

[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; IV=intravenous; MTD=maximum tolerated dose

Safety and Tolerability

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

CMML (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
Hypoalbuminaemia	8 (35)	10 (43)	8 (35)	--	--	--
Thrombocytopenia	7 (30)	7 (30)	--	3 (13)	4 (17)	--
Nausea	6 (26)	7 (30)	5 (22)	1 (4)	--	--
Vomiting	6 (26)	9 (39)	6 (26)	--	--	--
Anaemia	5 (22)	8 (35)	1 (4)	4 (17)	--	--
Fatigue	4 (17)	8 (35)	4 (17)	--	--	--
Oedema peripheral	4 (17)	10 (43)	4 (17)	--	--	--
Weight increased	4 (17)	7 (30)	4 (17)	--	--	--

* There were 3 cases of capillary leak syndrome, all grade 2

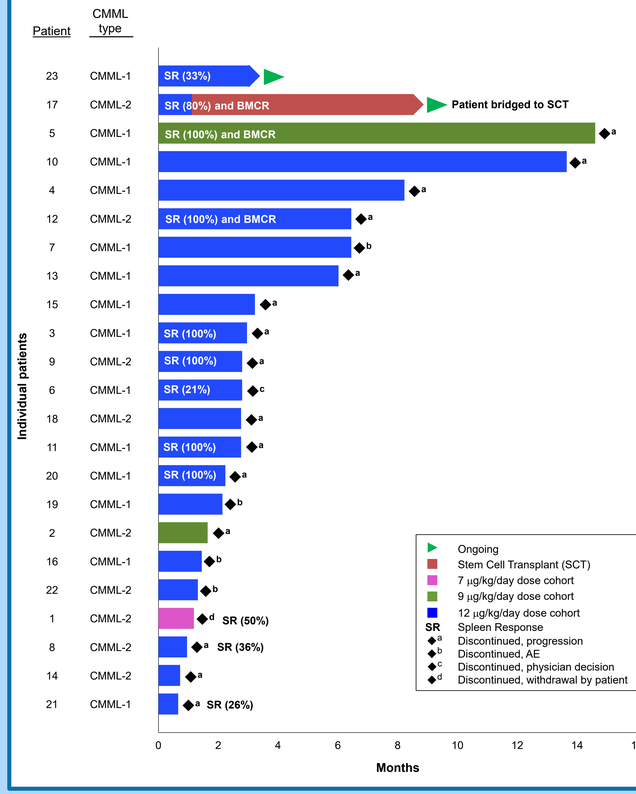
Clinical Activity Overview: CMML

Patient	Dose (µg/kg/d)	Line	Prior Therapy	CMML Type	WBC (10^9/L)	BONE MARROW			SPLEEN[1]		
						Baseline (BM blast %)	Best Response (BM blast %)	BMCR	Baseline (cm)	Best Response (cm)	Spleen Size Reduction
11	12	3	HMA	CMML-1	5.3	5	PD		10	0	100%
5	9	2	HMA	CMML-1	44.7	6	1	6% → 1%	5	0	100%
12	12	2	PST	CMML-2	9.3	10	1	10% → 1%	4	0	100%
3	12	2	HMA	CMML-1	99.2	7.6	SD		2	0	100%
9	12	2	HMA	CMML-2	66.1	18	N/A	N/E	2	0	100%
20	12	1	--	CMML-1	16.3	4	SD	N/E	2	0	100%
17	12	2	PST	CMML-2	8.1	15	2	15% → 2%	10	2	80%
1	7	2	PST; SCT	CMML-2	33.8	15	SD		20	10	50%
8	12	2	HMA	CMML-1	64.2	6	PD		22	14	36%
23	12	2	PST	CMML-1	31.8	2	Pending	N/E	6	4	33%
21	12	2	PST	CMML-1	25.6	2	N/A	N/E	27	20	26%
6	12	2	PST	CMML-1	27.2	8	N/A		14	11	21%
10	12	2	HMA	CMML-1	2.7	11	7		No splenomegaly		N/E
7	12	2	HMA	CMML-1	15.0	9	7		No splenomegaly		N/E
13	12	2	PST	CMML-1	26.1	6	4.9		No splenomegaly		N/E
2	9	2	PST	CMML-2	21.9	5	PD		No splenomegaly		N/E
14	12	2	PST	CMML-2	33.8	14	SD		No splenomegaly		N/E
4	12	3	HMA; Clo	CMML-1	18.5	0	3	N/E	No splenomegaly		N/E
15	12	1	--	CMML-1	12.3	6	SD		No splenomegaly		N/E
16	12	2	HMA; SCT	CMML-1	3.3	3	N/A	N/E	No splenomegaly		N/E
18	12	N/L	N/L	CMML-2	2.3	14	PD		No splenomegaly		N/E
19	12	2	HMA	CMML-1	8.8	3	PD	N/E	No splenomegaly		N/E
22	12	3	HMA; SCT	CMML-2	4.3	6	N/A	N/E	No Splenomegaly		N/E

= Patient bridged to SCT in remission on tagraxofusp

[1]Measured by physical exam (cm below costal margin [BCM])
HMA=hypomethylating agent; PST=prior systemic therapy; SCT = stem cell transplant; Clo=clofarabine; N/E=not evaluable; N/L=not listed; N/A=not available; SD=stable disease; PD=progressive disease

Duration of Treatment



Bone Marrow and Spleen Responses

- **3 bone marrow complete responses (BMCRs)**
- **1 patient bridged to stem cell transplant in remission on tagraxofusp**
- **100% (12/12) spleen responses**
  - **67% (8/12) had reduction of ≥50%**
  - **50% (4/8) with baseline ≥5 cm had reduction ≥50%**

Pt #	Line	Bone Marrow CR	Spleen Responses[1]	
		Pre → Post	Pre → Post	% Response
11	3		10 cm → 0 cm	100%
5	2	6% → 1%	5 cm → 0 cm	100%
12	2	10% → 1%	4 cm → 0 cm	100%
3	2		2 cm → 0 cm	100%
9	2	N/E	2 cm → 0 cm	100%
20	1	N/E	2 cm → 0 cm	100%
17	2	15% → 2% (bridged to stem cell transplant)	10 cm → 2 cm	80%
1	2		20 cm → 10 cm	50%
8	2		22 cm → 14 cm	36%
23	2	N/E	6 cm → 4 cm	33%
21	2	N/E	27 cm → 20 cm	26%
6	2		14 cm → 11 cm	21%

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

Summary of Tagraxofusp Trial Results

- In this Phase 1/2 trial, tagraxofusp was clinically active, with a predictable and manageable safety profile in patients with relapsed/refractory CMML – in particular, in patients with baseline splenomegaly (historically associated with advanced disease, morbidity, and poor prognosis)
  - 3 bone marrow CRs
  - 1 patient bridged to stem cell transplant (SCT)
  - 100% (12/12) of evaluable patients had a reduction in baseline splenomegaly
    - 67% (8/12) had reduction by ≥50%
    - 50% (4/8) with baseline spleen size ≥5cm had reduction by ≥50%
- Most common TRAEs include hypoalbuminemia (35%), thrombocytopenia (30%), nausea (26%) and vomiting (26%). Most common TRAEs, grade 3+, include thrombocytopenia (30%) and nausea (4%)
- Next steps include a pivotal program in patients with CMML

Next Steps for Tagraxofusp in Patients with CMML

- **Given the encouraging data from this trial and the unmet medical need in patients with CMML, a pivotal program is being constructed**
- **The protocol is currently being designed to incorporate these elements**
  - Eligibility
    - Patients with CMML who failed first-line cytoreductive therapy
  - Endpoints and criteria
    - ORR (CR + PR), supported by duration, transfusion independence, safety
    - Additional endpoints and criteria to be assessed for potential clinical benefit include
      - BM response with partial hematopoietic recovery; correlation to transfusion-independence and decreased risk of infections
      - Spleen size
      - CD123 expression level
  - Trial design
    - Single-arm, non-randomized
    - Open new cohort (Stage 3) to current study 0314
      - Stage 3a: assess potential clinical benefit of additional efficacy endpoints and criteria
      - Stage 3b: ORR +/- additional elements assessed in Stage 3a
    - *An additional arm of patients with first-line CMML unlikely to benefit from available therapies is also under consideration*

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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; *Schiller*: Stemline - research funding; *Patnaik*: Stemline - research funding