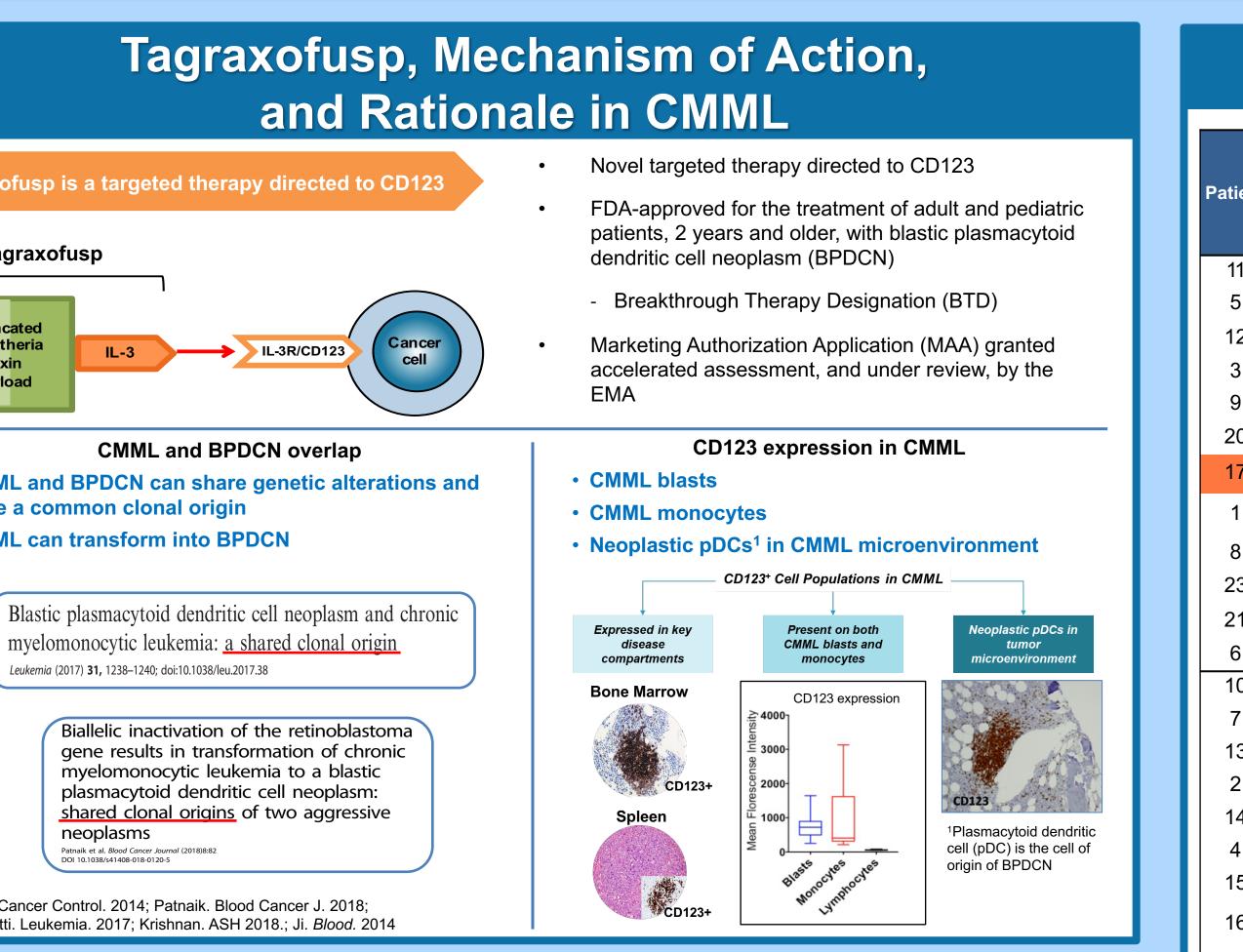
EHA 2019 **PF672**



Introduction and Highlights	
Tagraxofusp	
 Novel targeted therapy directed to CD123 	Tagrax
 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 	T,
 Marketing Authorization Application (MAA) for BPDCN granted accelerated assessment, and under review, by the EMA 	Tru dipl
CD123 target	pa
 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 	• CM
Tagraxofusp and CMML	• СМ
 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 	
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 	Riaz. Brun
 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 10⁹/L 	
○ MP-CMML (myeloproliferative CMML): WBC \geq 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 	¹ B ² P
 Currently: ~50% of CMML now considered a myeloproliferative neoplasm (MPN) 	³ O
 International consortium recommended revising response criteria (historically MDS- focused) to capture MPN elements (Savona, 2015) 	EC
An international consortium proposal of uniform response criteria for myolodycalogical descention of the second se	
myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults BLOOD, 19 MARCH 2015 · VOLUME 125, NUMBER 12	
Table 2. Proposed criteria for measurement of treatment response in adult MDS/MPN CR (presence of all of the following improvements)*	• M
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" (≤grade 1 fibrosis)† Peripheral blood‡ WBC ≤10 × 10 ⁹ cells/L	• Ta 1-
$\begin{split} &Hgb \geq 11 \ g/dL \\ &Platelets \geq 100 \times 10^9/L; \ \leq 450 \times 10^9/L \\ &Neutrophils \geq 1.0 \times 10^9/L \end{split}$	(c
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	• Ko
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*	^a 12 μg
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 of 20 metaphases or FISH§ Partial remission	CMML MTD=
Normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity <i>except</i> in cases of MDS/MPN with ≤5% bone marrow blasts at baseline Marrow response	
Optimal 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, <i>or</i> reduction in grading of reticulin fibrosis from baseline on at least 2 bone marrow evaluations spaced at least 2 mo apart Clinical benefit	
Requires 1 of the following in the absence of progression or CR/partial response and independent of marrow response (cord blood response must be verified at ≥8 wk) to be considered a clinical benefit Erythroid response	
Hgb increase by $\geq 2.0 \text{ g/dL}$ TI for $\geq 8 \text{ wk}$ 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 $\leq 8.5 \text{ g/dL}$ 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 $\leq 20 \times 10^{9}/L$; increase from $< 20 \times 10^{9}/L$ to $> 20 \times 10^{9}/L$ and by at least 100% Pretreatment $> 20 \times 10^{9}/L$ but $\leq 100 \times 10^{9}/L$; absolute increase of $\geq 30 \times 10^{9}/L$	
Neutrophil response Pretreatment $\leq 0.5 \times 10^{9}$ /L at least 100% increase and an absolute increase $\geq 0.5 \times 10^{9}$ /L Pretreatment, $> 0.5 \times 10^{9}$ /L and $\leq 1.0 \times 10^{9}$ /L At least 50% increase and an absolute increase $\geq 0.5 \times 10^{9}$ /L Soleen 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*	Pre
<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	Нур
20-30% 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	Thro
Increase in cytogenetic burden of disease by ≥50% in partial cytogenetic remission via FISH or classic karyotyping New extramedullary disease Worsening splenomegaly	Nau
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	Vom
Extramedullary disease outside of the spleen To include new/worsening hepatomegaly, granulocytic sarcoma, skin lesions, etc. Minor criteria	Fatiç
Transfusion dependence§ Significant loss of maximal 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	Oed
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 ≥50% as per the MPN-SAF TSSII Evidence of clonal evolution (molecular)¶	Weig
	* The

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

Mrinal M. Patnaik¹, Haris Ali², Abdulraheem Yacoub³, Vikas Gupta⁴, Sangmin Lee⁵, Eunice Wang⁶, Gary Schiller⁷, Megan Sardone⁸, Halyna Wysowskyj⁸, Shay Shemesh⁸, Janice Chen⁸, Chris Brooks⁸, Enrique Poradosu⁸, Peter McDonald⁸, Nicole Rupprecht⁸, Animesh Pardanani¹, Ayalew Tefferi¹, Minakshi Taparia⁹, Moshe Talpaz¹⁰, Srdan Verstovsek¹¹, Joseph Khoury¹¹, Naveen Pemmaraju¹¹ ¹Mayo Clinic, Rochester, ²City of Hope, Duarte, ³Kansas University Cancer Center, New York, ⁶Roswell Park Comprehensive Cancer Center, Buffalo, ⁷Ronald Reagan UCLA Medical Center, Los Angeles, ⁸Stemline Therapeutics, New York, ⁹University of Alberta Hospital, Edmonton, AB, Canada,¹⁰University of Alberta Hospital, Edmonton,¹¹The University of Alberta Hospital, Edmonton,¹¹The University of Alberta Hospital, Edmonton,¹¹The University of Alberta Hospital,¹⁰University of Alberta Hospital,¹⁰University of Alberta Hospital,¹⁰University of Alberta Hospital,¹⁰University,¹¹The University,¹¹The Univers



Baseline Demographics and Characteristics

ge, years	n=23
Median [range]	69 [42-80]
ender	
Male	19 (83)
MML Type	
CMML-1	15 (65)
CMML-2	8 (35)
COG	
Median [range]	1 [0-2]
edian Blast Count, %	
Median [range]	6.0 [0-18]
aseline 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)			

involvement defined as blast count ≥5%

atient received prior therapy and SCT One patient did not have these data at the time of cut-off

OG=Eastern Cooperative Oncology Group

Trial Design

Stage 1 Lead-in (Complete)

PN: CMML, MF, SM, and PED

graxofusp (7, 9, or 12 ug/kg) via IV infusion, **days 3** of a 21-day cycle (cycles 1-4), a 28-day cycle ycles 5-7); a 42-day cycle thereafter

ey objectives: To determine optimal dose and gimen 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

/kg/day was highest tested dose (MTD not reached) and selected for Stage 2 -= chronic myelomonocytic leukemia; MF=myelofibrosis, SM=systemic mastocytosis; PED=primary eosinophilic disorders; IV=intravenous; 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)						
formed Torme	All Grade	TRAEs n (%)				
eferred Term	TRAEs	All AEs	G1 & 2	G3	G4	G5
oalbuminaemia	8 (35)	10 (43)	8 (35)			
ombocytopenia	7 (30)	7 (30)		3 (13)	4 (17)	
Isea	6 (26)	7 (30)	5 (22)	1 (4)		
niting	6 (26)	9 (39)	6 (26)			
iemia	5 (22)	8 (35)	1 (4)	4 (17)		
gue	4 (17)	8 (35)	4 (17)			
dema peripheral	4 (17)	10 (43)	4 (17)			
ght increased	4 (17)	7 (30)	4 (17)			
ere were 3 cases of capillary leak syndrome, all grade 2						

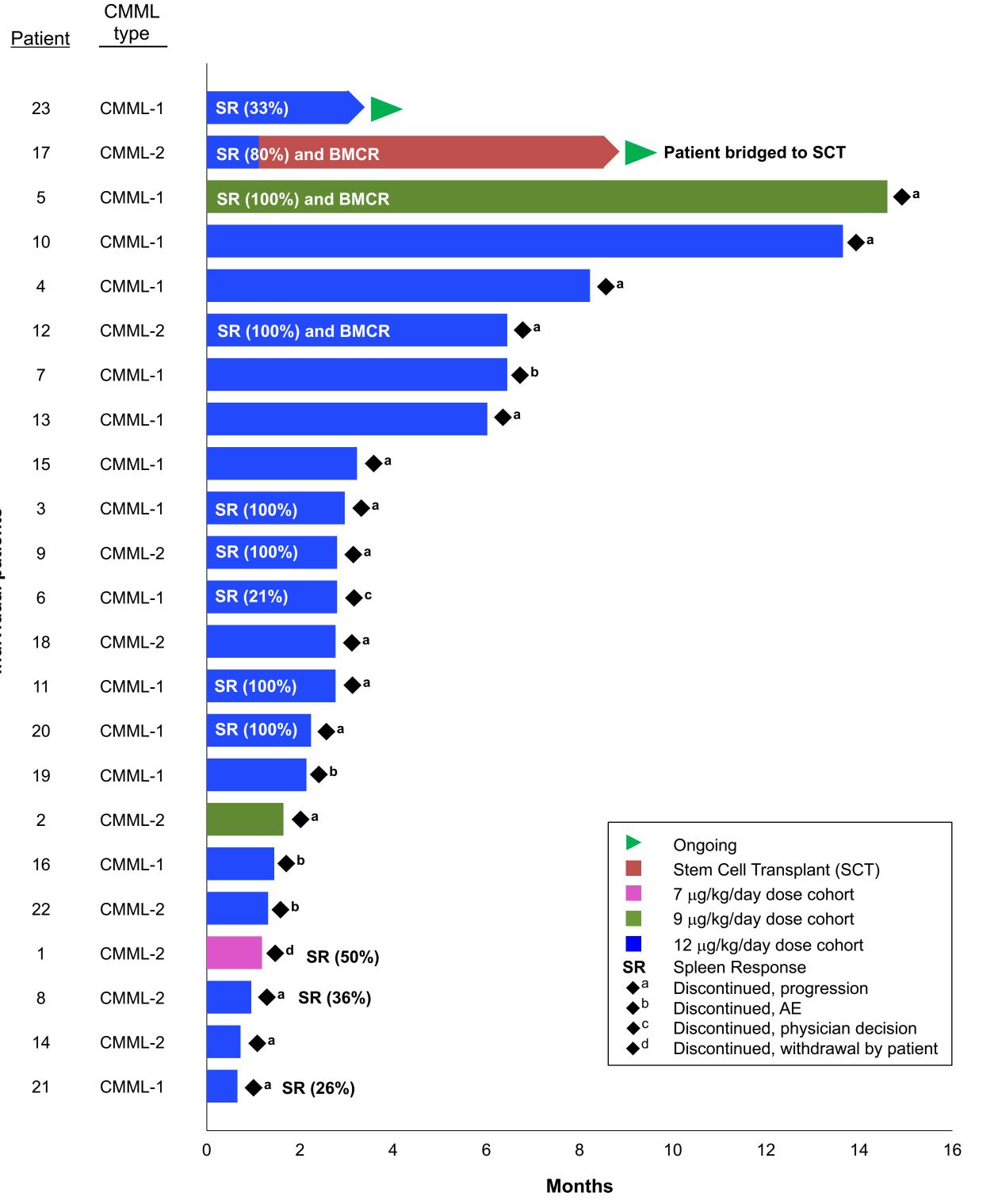
Clinical Activity Overview: CMML

						BONE MARROW				SPLEEN ¹	
ient:	Dose (µg/kg/d)	Line	Prior Therapy	CMML Type	WBC (10 ⁹ /L)	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	<mark>6% → 1%</mark>	5	0	100%
2	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%
7	12	2	PST	CMML-2	8.1	15	2	<mark>15% → 2%</mark>	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%
0	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
3	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
4	12	2	PST	CMML-2	33.8	14	14 SD		No splenomegaly		N/E
4	12	3	HMA; Clo	CMML-1	18.5	0	3	N/E	No splenomegaly		N/E
5	12	1		CMML-1	12.3	6	SD		No splenomegaly		N/E
6	12	2	HMA; SCT	CMML-1	3.3	3	N/A	N/A N/E No splenomeg			N/E
8	12	N/L	N/L	CMML-2	2.3	14	PD	PD No splenomega			N/E
9	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

¹Measured 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			
Γι#	Line	$Pre \to Post$	Pre → Post	% Response		
11	3		$10 \text{ cm} \rightarrow 0 \text{ cm}$	100%		
5	2	6% → 1%	$5 \text{ cm} \rightarrow 0 \text{ cm}$	100%		
12	2	10% → 1%	$4 \text{ cm} \rightarrow 0 \text{ cm}$	100%		
3	2		$2 \text{ cm} \rightarrow 0 \text{ cm}$	100%		
9	2	N/E	$2 \text{ cm} \rightarrow 0 \text{ cm}$	100%		
20	1	N/E	$2 \text{ cm} \rightarrow 0 \text{ cm}$	100%		
17	2	$15\% \rightarrow 2\%$ (bridged to stem cell transplant)	$10 \text{ cm} \rightarrow 2 \text{ cm}$	80%		
1	2		$20 \text{ cm} \rightarrow 10 \text{ cm}$	50%		
8	2		22 cm \rightarrow 14 cm	36%		
23	2	N/E	$6 \text{ cm} \rightarrow 4 \text{ cm}$	33%		
21	2	N/E	$27 \text{ cm} \rightarrow 20 \text{ cm}$	26%		
6	2		14 cm \rightarrow 11 cm	21%		

¹Patients 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 \geq 5cm had reduction by \geq 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