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#PS1063

# Results of Pivotal Phase 2 Trial of Tagraxofusp (SL-401) in Patients with Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

Naveen Pemmaraju[1], Andrew A. Lane[2], Kendra L. Sweet[3], Anthony S. Stein[4], Sumithira Vasu[5],, David A. Rizzieri[6], Eunice S. Wang[7], Madeleine Duvic[1], Sharon Spence[8], Shay Shemesh[8], Janice Chen[8], Christopher L. Brooks[8], Ivan Bergstein[8], Peter McDonald[8], J. Mark Sloan[9], Todd Rosenblat[10], Oleg Akilov[11], Jeffrey E. Lancet[2], Hagop M. Kantarjian[1], Marina Konopleva[1]

*[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Dana-Farber Cancer Institute, Boston, MA; [3]H. Lee Moffitt Cancer Center, Tampa, FL; [4]City of Hope National Medical Center, Duarte, CA; [5]The Ohio State University, Columbus, OH; [6]Duke University Medical Center, Durham, NC; [7]Roswell Park Cancer Institute, Buffalo, NY; [8]Stemline Therapeutics, Inc., New York, NY;[9]Boston University School of Medicine, Boston, MA; [10] Columbia University Medical Center, New York, NY; [11] University of Pittsburgh Medical Center, Pittsburgh, PA.*

## Introduction and Highlights

**Tagraxofusp**

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

**CD123**

- CD123 is expressed on multiple malignancies including blastic plasmacytoid dendritic cell neoplasm (BPDCN), acute myeloid leukemia (AML), certain myeloproliferative neoplasms (MPN), multiple myeloma, and a variety of other myeloid and lymphoid cancers

**BPDCN**

- Highly aggressive hematologic malignancy, often with cutaneous and other extramedullary (e.g. lymph node, viscera) manifestations
- Poor prognosis, with a median overall survival (OS) 8-14 months from diagnosis

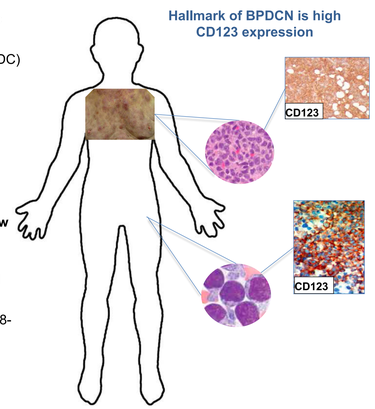
**Tagraxofusp Phase 2 Pivotal Trial in BPDCN**

- Tagraxofusp demonstrated high levels of clinical activity, with a consistent and predictable safety profile, in patients with BPDCN
- Pivotal trial results of tagraxofusp in BPDCN served as the basis for U.S. approval

## BPDCN

- **Highly aggressive hematologic malignancy**
  - plasmacytoid dendritic cell (pDC) origin
- **Diagnostic signature:**
  **CD123 / CD4 / CD56 – *"Think 123456"***
- **Middle aged-elderly; male predominance**
- **Previously considered a lymphoma then a leukemia, now classified as unique entity**
- **Bone marrow and skin involvement, lymph nodes and viscera as well**
- **Poor prognosis -** Median OS of 8-14 months from diagnosis
- **Prior to tagraxofusp approval, BPDCN was an unmet medical need**

**Hallmark of BPDCN is high CD123 expression**

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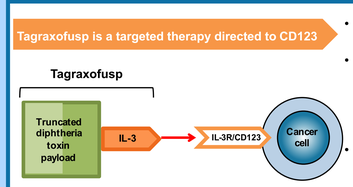
## Tagraxofusp, Mechanism of Action, and Rationale in BPDCN

**Tagraxofusp is a targeted therapy directed to CD123**

**Tagraxofusp**




- Novel targeted therapy directed to CD123
- FDA-approved for the treatment of adult and pediatric patients, 2 years and older, with BPDCN
  - Breakthrough Therapy Designation (BTD)
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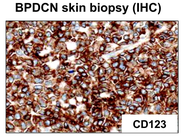
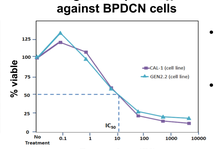
**BPDCN skin biopsy (IHC)**




**Tagraxofusp fM $IC_{50}$ against BPDCN cells**




- CD123 overexpressed on BPDCN and other hematologic cancers
- Tagraxofusp demonstrated potent preclinical activity against BPDCN *in vitro* ($IC_{50}$ *in femtomolar range)* and *in vivo*

## Tagraxofusp: Study Design and Inclusion / Exclusion

| Stage 1 (Lead-in, Dose Escalation) | Stage 2 (Expansion) | Stage 3 (Pivotal, Confirmatory) |
|---|---|---|
| • BPDCN (1L and R/R)<br>• Tagraxofusp (7 and 12 mcg/kg) via IV infusion, days 1-5 of a 21-day cycle<br>• Key objectives: To determine optimal dose and regimen for Stage 2 | • BPDCN (1L and R/R)<br>• Tagraxofusp (12 mcg/kg) via IV infusion, days 1-5 of a 21-day cycle<br>• Key objectives: To further define safety and efficacy | • BPDCN (1L)<br>• Tagraxofusp (12 mcg/kg) via IV infusion, days 1-5 of a 21-day cycle<br>• Key objective: To confirm efficacy for registration |

**Select inclusion criteria**

- **Patient Population:**
  - **Stage 1: BPDCN (1L or R/R)**
  - **Stage 2: BPDCN (1L or R/R)**
  - **Stage 3: BPDCN (1L)**
- **Age ≥18; ECOG PS 0-2**
- **Adequate organ function including: LVEF ≥ lower limit of normal, creatinine ≤1.5 mg/dL, albumin ≥3.2 g/dL, bilirubin ≤1.5 mg/dL, AST/ALT ≤2.5×ULN**

**Select exclusion criteria**

- **Persistent clinically significant toxicities from prior chemotherapy**
- **Received chemotherapy or other investigational therapy within the prior 14 days**
- **Clinically significant cardiopulmonary disease**
- **Receiving immunosuppressive therapy**

## Tagraxofusp: Demographics

| Parameter | Treatment-Naïve BPDCN n=29 | Previously-Treated BPDCN n=15 |
|---|---|---|
| Gender, N (%) | | |
| Male | 23 (79) | 13 (87) |
| Female | 6 (21) | 2 (13) |
| Race, N (%) | | |
| Asian | 0 | 2 (13) |
| White | 28 (97) | 13 (87) |
| Other | 1 (3) | 0 |
| Age (years) | | |
| Median | 67.0 | 72 |
| Minimum, Maximum | 22, 84 | 44, 80 |
| ECOG, N (%) | | |
| 0 | 15 (52) | 5 (33) |
| 1 | 14 (48) | 10 (67) |
| BPDCN at baseline, N (%) | | |
| Skin | 28 (97) | 13 (87) |
| Bone Marrow | 14 (48) | 9 (60) |
| Peripheral Blood | 7 (24) | 1 (7) |
| Lymph Nodes | 13 (45) | 8 (53) |
| Viscera | 4 (14) | 0 |

## Safety Profile in Patients in Pivotal Trial (STML-401-0114)

**Safety: Tagraxofusp (12 mcg/kg/day)**

Safety of tagraxofusp assessed in 94 adults with treatment-naïve or previously-treated malignancies treated with tagraxofusp at the labeled dose and schedule.

- Most common adverse reactions (incidence ≥30%): capillary leak syndrome (CLS), nausea, fatigue, peripheral edema, pyrexia, and weight increase
- Most common laboratory abnormalities (incidence ≥50%): decreases in albumin, platelets, hemoglobin, calcium, sodium, and increases in glucose, alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
- CLS[1] in clinical trials was 55% in patients receiving tagraxofusp, including Grades 1 or 2 in 46% (43/94), Grade 3 in 6% (6/94), Grade 4 in 1% (1/94), and 2 fatal events (2/94, 2%)

In an additional 76 patients treated at 12 µg/kg/day in all schedules, there were 3 Grade 3 (4%), 1 Grade 4 (1%)[2] and 1 Grade 5 (1%) investigator-assessed CLS events

**Adverse Reactions in ≥ 10% of Patients Receiving 12 mcg/kg**

| | N=94 | | | N=94 | |
|---|---|---|---|---|---|
| | All Grades (%) | Grade ≥ 3 (%) | | All Grades (%) | Grade ≥ 3 (%) |
| Capillary leak syndrome | 55 | 9 | Febrile neutropenia | 20 | 18 |
| Nausea | 49 | 0 | Dyspnea | 19 | 2 |
| Fatigue | 45 | 7 | Insomnia | 17 | 0 |
| Peripheral edema | 43 | 1 | Tachycardia | 17 | 0 |
| Pyrexia | 43 | 0 | Anxiety | 15 | 0 |
| Weight increase | 31 | 0 | Hypertension | 15 | 6 |
| Chills | 29 | 1 | Cough | 14 | 0 |
| Headache | 29 | 0 | Epistaxis | 14 | 1 |
| Hypotension | 29 | 9 | Oropharyngeal pain | 12 | 0 |
| Decreased appetite | 24 | 0 | Confusional state | 11 | 0 |
| Constipation | 23 | 0 | Hematuria | 10 | 0 |
| Vomiting | 21 | 0 | Pain in extremity | 10 | 2 |
| Back pain | 20 | 2 | Petechiae | 10 | 0 |
| Diarrhea | 20 | 0 | Pruritus | 10 | 0 |
| Dizziness | 20 | 0 | | | |

[1]Defined as any event reported as CLS during treatment with tagraxofusp or the occurrence of at least 2 of the following CLS manifestations within 7 days of each other: hypoalbuminemia, edema, hypotension.
[2]A myocardial infarction, Grade 5, was reported in this patient.

## Tagraxofusp: Clinical Activity

**Response Rates in BPDCN Patients (12 mcg/kg) (n=44)**

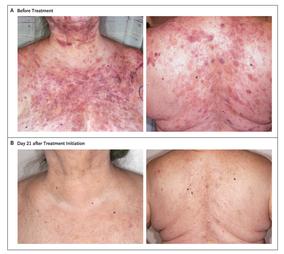
| Efficacy Measures | Treatment-Naïve Patients (N=29) | Previously-Treated Patients (N=15) |
|---|---|---|
| ORR, % (n) | 90% (26) | 67% (10) |
| CR/CRc rate, % (n) | 72% (21) | 13% (2) |
| Median duration of CR/CRc, months (min, max) | Not yet reached (1, 42) | Not yet reached (3.7, 13.9) |
| Bridged to SCT, % (n) | 45% (13) | 7% (1) |

- Stage 3 was designed to serve as the pivotal, confirmatory cohort for the STML-401-0114 study in BPDCN
- Stage 3 met its primary endpoint with a 54% rate (7/13) of CR + CRc [95% CI: 25.1, 80.8]

CR=complete response; CRc=clinical complete response; ORR=overall response rate; SCT=stem cell transplant

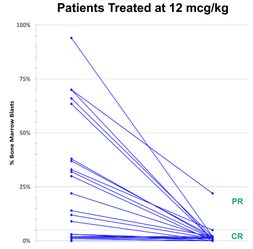
## Tagraxofusp: Clinical Responses

- **71 year old female with BPDCN**
- Treatment-naive patient with extensive skin and bone marrow (BM) involvement
- Received six cycles of tagraxofusp at 12 mcg/kg
- Panel A (baseline): Extensive skin and BM involvement
  - BM blasts – 14%
  - mSWAT – 11.3%
- Panel B (day 21): Skin and BM responses
  - BM blasts – 3%
  - mSWAT – 0%
- **Bridged to stem-cell transplantation after achieving CR and 6 cycles of tagraxofusp**

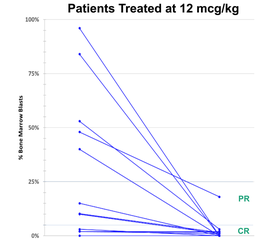



## Tagraxofusp: Bone Marrow Responses

**Bone Marrow Response – Baseline to Best Response Treatment-Naive Patients Treated at 12 mcg/kg**



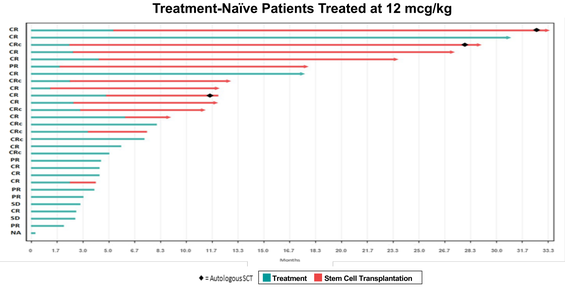

**Bone Marrow Response – Baseline to Best Response Previously-Treated Patients Treated at 12 mcg/kg**




N=38 evaluable patients; four patients treated with 12 mcg/kg did not have follow-up bone marrow results

## Tagraxofusp: Best Response and Treatment Duration

**Swimmer Plot–Best Response & Treatment Duration**
**Treatment-Naïve Patients Treated at 12 mcg/kg**




Each horizontal line represents 1 patient. Color of the bar represents first response and bridge to stem cell transplantation, if applicable. Length of bar represents follow-up through last assessment. Arrow represents patient is in remission.
Abbreviations: CR = Complete Response; CRc = Clinical Complete Response, CRi = Complete Response with incomplete blood count recovery; PR= Partial Response, SD=Stable Disease, PD= Progressive disease, NA =not assessed; outcome not assessed (patient died)

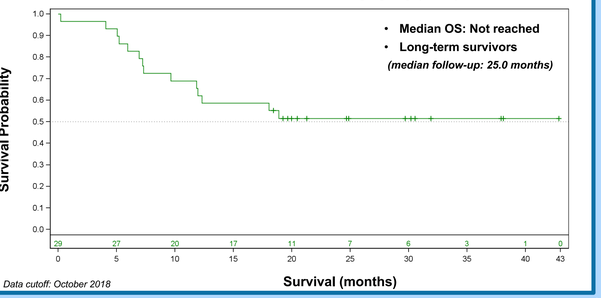
## SCT Treatment Outcomes in Treatment-naïve Patients Treated at 12 mcg/kg

| Patient Number | Age (years) | Best Response | Duration of Response (days) | Survival (days) |
|---|---|---|---|---|
| **Patients Who Were Bridged to Stem Cell Transplantation** | | | | |
| 1 | 65 | CR | 552+ | 608+ |
| 2 | 68 | CRc | 161+ | 223 |
| 3 | 53 | PR | 903+ | 919+ |
| 4 | 57 | CR | 601+ | 623+ |
| 5 | 65 | CR | 1284+ | 1305+ |
| 6 | 45 | CRc | 1112+ | 1154+ |
| 7 | 71 | CR | 297+ | 361 |
| 8 | 28 | CR | 757 | 971+ |
| 9 | 69 | CR | 485+ | 575 |
| 10 | 22 | CRc | 541+ | 561+ |
| 11 | 32 | CRc | 573+ | 586+ |
| 12 | 69 | CR | 910+ | 930+ |
| 13 | 72 | CR | 63+ | 124 |
| **Patients Who Were Not Bridged to Stem Cell Transplantation** | | | | |
| 14 | 79 | CR | 727+ | 751+ |
| 15 | 31 | PR | 27 | 757+ |
| 16 | 73 | CR | 68 | 211 |
| 17 | 68 | CRc | 201 | 549 |
| 18 | 74 | CRc | 221 | 598+ |
| 19 | 63 | CR | 47 | 294 |
| 20 | 72 | CR | 1129+ | 1160+ |
| 21 | 67 | CRc | 112 | 904+ |
| 22 | 84 | CR | 75 | 364 |
| 23 | 84 | PR | 25 | 159 |
| 24 | 76 | PR | 21 | 181 |
| 25 | 61 | CR | 44 | 375 |
| 26 | 70 | PR | 43 | 648+ |

Abbreviations: CR=complete response; CRc (clinical CR) = complete response with residual skin abnormality not indicative of active disease; PR = partial response; SCT=stem cell transplant

## Tagraxofusp: Overall Survival (OS)

**Treatment-naïve BPDCN treated at 12 mcg/kg/day (n=29)**




- **Median OS: Not reached**
- **Long-term survivors**
- ***(median follow-up: 25.0 months)***

*Data cutoff: October 2018*

## Tagraxofusp: Summary and Conclusions

**Pivotal Trial Results**

- Tagraxofusp, a novel targeted therapy directed to CD123, demonstrated high levels of clinical activity in patients with BPDCN
- In previously-untreated patients:
  - 90% overall response rate (ORR)
    - Majority of responses were complete remissions (72% CR/CRc rate)
  - 45% of patients were bridged to stem-cell transplantation, including older patients who might have been excluded from intensive therapy
  - Overall survival rates of 59% at 18 months and 52% at 24 months
- 67% overall response rate in previously-treated patients
- Tagraxofusp demonstrated a predictable and manageable safety profile
  - Most common adverse reactions in patients with treatment-naïve or previously-treated malignancies treated with tagraxofusp at the labeled dose and schedule include: capillary leak syndrome (55%), nausea (49%), fatigue (45%), peripheral edema and pyrexia (each 43%)

**Tagraxofusp approved and commercially available in the U.S. for BPDCN**

- On the basis of these data, tagraxofusp has been FDA-approved for treatment of adult and pediatric patients, 2 years and older, with BPDCN, and is commercially available in the U.S.
- Tagraxofusp is the first and only approved treatment for BPDCN
  - Received Breakthrough Therapy Designation (BTD) designation
- Marketing Authorization Application (MAA) for BPDCN granted accelerated assessment, and under review, by the EMA

**Other tagraxofusp studies**

- Tagraxofusp is being clinically evaluated in additional indications including chronic myelomonocytic leukemia (CMML), myelofibrosis (MF), acute myeloid leukemia (AML), and multiple myeloma (MM)

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