ELZONRIS™ (tagraxofusp-erzs) for the treatment of Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

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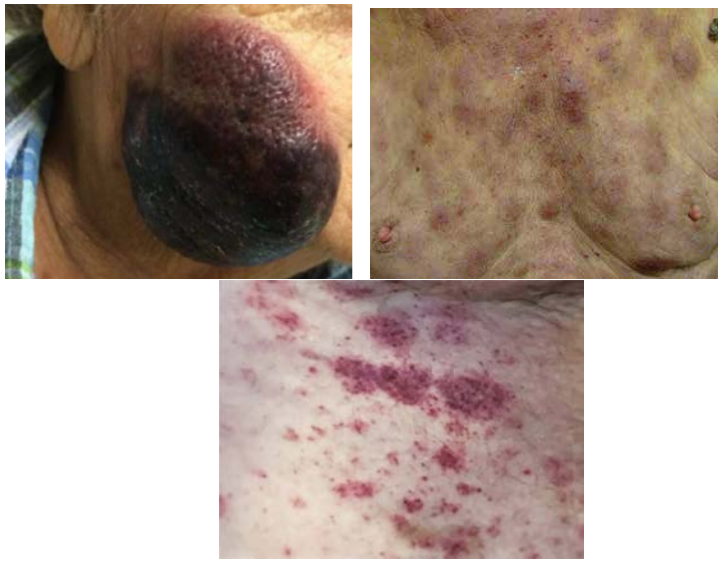
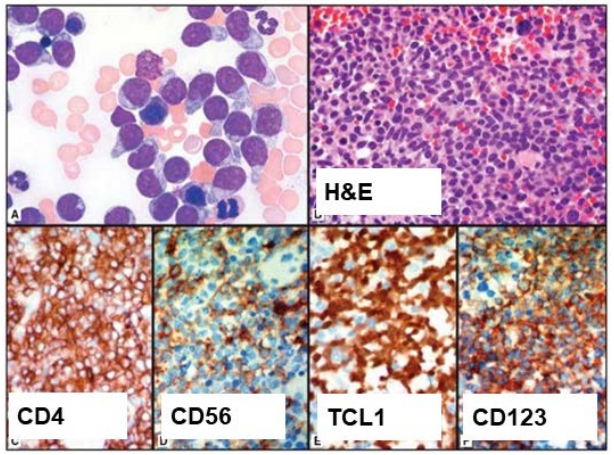
What Is Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)?

Background	• Rare, highly aggressive hematologic malignancy • Middle aged-elderly; median age range at diagnosis: 60-70 years[1] • Male predominance (75%)
Nomenclature	• Named "BPDCN" by WHO in 2008 - Derived from plasmacytoid dendritic cell (pDC) • Previous names (prior to 2008) included: - Blastic NK cell leukemia/lymphoma - Agranular CD4+/56+ hematodermic neoplasm
Diagnostic Signature	• CD123 / CD4 / CD56 and other markers (TCL-1, CD303)
Presentation	• Primary sites: bone marrow and skin; secondary sites: lymph nodes, viscera • May occur as a secondary malignancy; approximately 10%-20% of patients have a history of hematologic malignancies, including MDS, CML, CMML, and AML[2,4]
Unmet Medical Need	• Prior to 2018, there were no approved therapies or standard of care

BPDCN Skin Lesions



BPDCN Bone Marrow



1. Pagano L, et al. *Br J Haematol*. 2016;174(2):188-202.2. Pagano L, et al. *Haematologica*. 2013;98(2):239-246. 3. Taylor J, et al. *Blood*. 2013;122(21 suppl). Abstract 741.4. Julia F, et al. *Br J Dermatol*. 2013;169(3):579-586. 5. **Shapiro R, et al. *J Cell Sci Ther*. S8:008. 6. Riaz W, et al. *Cancer Control*. 2014;21(4):279-289.7. Sullivan JM, Rizzieri DA. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):16-23.**

AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome

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Outcomes for BPDCN Are Poor

BPDCN rapidly progresses *to an aggressive leukemic phase*[1,2]

Median overall survival for BPDCN is approximately **8 to 14 months after diagnosis**[2,3]

- Historically, several empirical chemotherapy regimens were attempted with very little success, and therefore no standard therapy was established for patients with BPDCN; participation in a clinical trial was advised[1]
  - Although initial responses to chemotherapy may be achieved, they are often not durable and result in relapse soon thereafter and progress rapidly[1,2]
  - High risk of treatment-related deaths due to polychemotherapy[2,4]
  - Most patients with BPDCN are older, have multiple comorbidities, or are often unfit for hematopoietic stem cell transplantation (HSCT)[2]

1. Riaz W, et al. *Cancer Control*. 2014;21(4):279-289. 2. Pagano L, et al. *Haematologica*. 2013;98(2):239-246. 3. Pemmaraju N. *Curr Hematol Malig Rep*. 2017;12(6):510-512. 4. Martín-Martín L et al. *Oncotarget* 2015; 6(22): 19204-19216.

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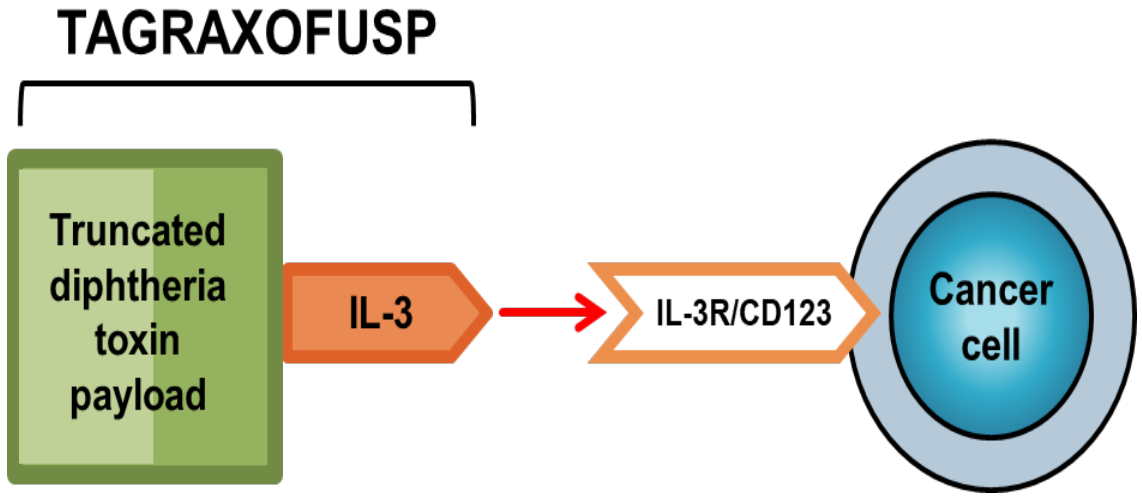
ELZONRIS is a Targeted Therapy Directed to CD123



CD123 is an ideal target due to its high expression on BPDCN cells (~95%)[1-4]

- Negligibly expressed on healthy cells[1-4]
- Can act as a therapeutic target in BPDCN[1,2,5]
- CD123 overexpressed by BPDCN

Tagraxofusp is targeted therapy directed to CD123 (IL-3Rα)[6,7]

- Recombinant fusion protein consisting of human interleukin-3 (IL-3) conjugated to a truncated diphtheria toxin
- Targets CD123 (alpha chain of the IL-3 receptor)
- Binds to CD123-expressing cells and is internalized, irreversibly inhibiting protein synthesis and inducing apoptosis

1. Laribi K, et al. *Biol Blood Marrow Transplant*. 2016;22(8):1357-1367. 2. Facchetti F, et al. *Mod Pathol*. 2016;29(2):98-111. 3. Frankel AE, et al. *Blood*. 2014;124(3):385-392. 4. Pagano L, et al. *Haematologica*. 2013;98(2):239-246. 5. Pemmaraju N. *Curr Hematol Malig Rep*. 2017;12(6):510-512. 6. ELZONRIS [prescribing information]. New York, NY, US: Stemline Therapeutics, Inc.; December 2018. 7. Data on file. Stemline Therapeutics, Inc.

ELZONRIS: Efficacy and Safety Established in a Pivotal Phase 2 BPDCN Trial (STML-401-0114)

- *Largest prospectively designed study in patients with BPDCN*
  - *Enrolled 29 treatment-naïve and 15 previously-treated patients*
- *Primary endpoint[1]: CR + CRc rate*
  Clinical Complete Response (CRc) - complete response with minimal residual skin abnormalities not indicative of active disease
- *Secondary endpoints: ORR, OS, PFS*

Earlier Phases

- BPDCN (1L and R/R)
- Tagraxofusp [7 µg/kg (n=3) or 12 µg/kg (n=29)] via IV infusion, days 1-5 of a 21-day cycle

Confirmatory Phase

- BPDCN (1L)
- Tagraxofusp (12 µg/kg) via IV infusion, days 1-5 of a 21-day cycle

1. ELZONRIS [prescribing information]. New York, NY, US: Stemline Therapeutics, Inc.; December 2018.

CR, complete response; CRc, complete response with minimal residual skin abnormalities; IV, intravenous; ORR, overall response rate; OS, overall survival, PFS, progression free survival; R/R, relapsed/refractory; 1L, first line
Adapted from Pemmaraju N, et al. Results of Pivotal Phase 2 Trial of SL-401 in Patients with Blastic Plasmacytoid Dendritic Cell Neoplasm – ASH December 2018.

Baseline Characteristics in Pivotal Phase 2 BPDCN Trial – Treatment-Naïve Patients

Baseline Patient Characteristics1,2*

Characteristics	Pivotal Cohort (N=13)	Other Cohorts (N=16)	All Cohorts (N=29)
Male, % (n)	84.6% (11)	75.0% (12)	79.3% (23)
Female, % (n)	15.4% (2)	25.0% (4)	20.7% (6)
Median age, years (min, max)	65.0 (22, 84)	67.5 (28, 84)	67.0 (22, 84)
ECOG PS	**% (n)**	**% (n)**	**% (n)**
0	61.5% (8)	43.8% (7)	51.7% (15)
1	38.5% (5)	56.3% (9)	48.3% (14)
BPDCN, % (n)	**% (n)**	**% (n)**	**% (n)**
Skin	100.0% (13)	93.8% (15)	96.6% (28)
Bone marrow	53.8% (7)	43.8% (7)	48.3% (14)
Peripheral blood	23.1% (3)	25.0% (4)	24.1% (7)
Lymph nodes	46.2% (6)	43.8% (7)	44.8% (13)
Viscera	15.4% (2)	12.5% (2)	13.8% (4)

ECOG PS = Eastern Cooperative Oncology Group performance status; measures disease progression from grades 0 (fully active) to 5 (death).

*All-cohorts population (N=29) includes patients from the pivotal cohort (N=13).

1. ELZONRIS [prescribing information]. New York, NY, US: Stemline Therapeutics, Inc.; December 2018.
2. Data on file. Stemline Therapeutics, Inc.

ELZONRIS: Clinical Outcomes in Treatment Naïve Patients with BPDCN

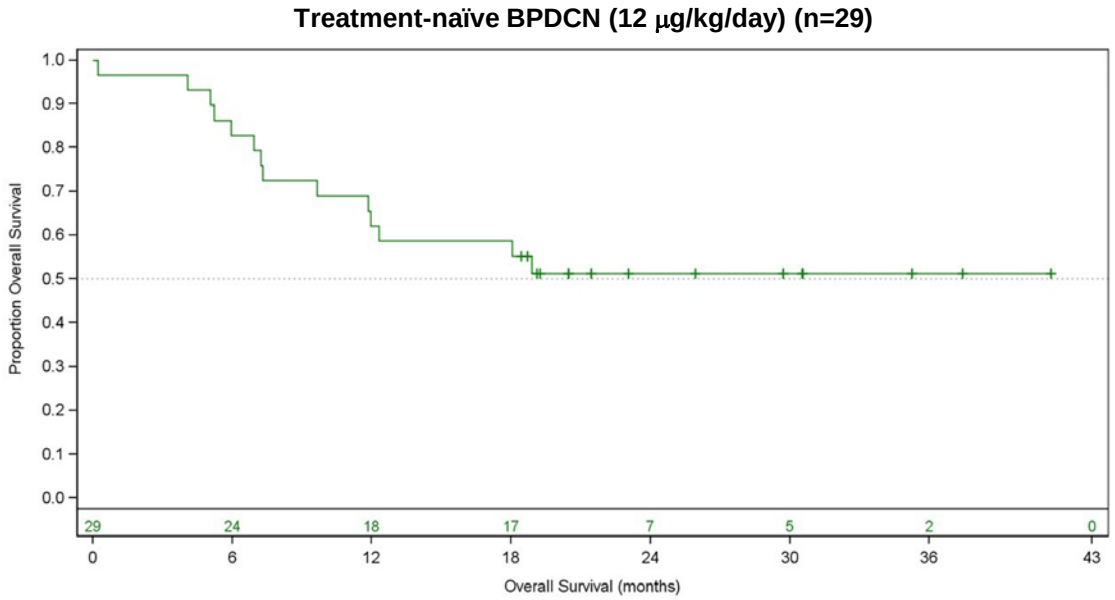
Response Rates

Efficacy: ELZONRIS (12 mcg/kg) - Treatment-naïve BPDCN

Efficacy Measures	Stage 3 (N=13)	Other Stages (N=16)	All Stages (N=29)
CR/CRc rate, % (n)	54% (7)	88% (14)	72% (21)
Median duration of CR/CRc, months (min, max)	Not yet reached (3.9, 12.2)	Not yet reached (1.3, 32.2)	Not yet reached (1.3, 32.2)
ORR, % (n)	77% (10)	100% (16)	90% (26)
Bridged to stem cell transplantation, % (n)	46% (6)	44% (7)	45% (13)

Overall Survival (OS)

- **In treatment-naïve patients at 12 mcg/kg**
  - Median OS, not reached
  - Long- term survivors
  - Median follow up: 23.0 months (0.2-41+ months)



CR, complete response; CRc (clinical CR), complete response with minimal residual skin abnormalities; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory; SCT, stem cell transplant

Adapted from Pemmaraju, N. et al. Results of Pivotal Phase 2 Trial of SL-401 in Patients with Blastic Plasmacytoid Dendritic Cell Neoplasm – ASH December 2018
Data on file. Stemline Therapeutics, Inc. New York, NY.

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ELZONRIS: Clinical Outcomes in Previously-Treated Patients with BPDCN

Baseline Characteristics1,2

Characteristics	Previously-Treated Patients (N=15)
Male, % (n)	86.7% (13)
Female, % (n)	13.3% (2)
Median age, years (min, max)	72 (44, 80)
ECOG PS	**% (n)**
0	33.3% (5)
1	66.7% (10)
BPDCN	**% (n)**
Skin	86.7% (13)
Bone marrow	60.0% (9)
Peripheral blood	6.7% (1)
Lymph nodes	53.3% (8)
Viscera	26.7% (4)
Prior treatments	**% (n)**
Radiation therapy	33% (5)
Stem cell transplantation	27% (4)

1. ELZONRIS [prescribing information]. New York, NY, US: Stemline Therapeutics, Inc.; December 2018. 2. Data on file. Stemline Therapeutics, Inc.

Efficacy Measures For Previously-Treated Patients (12 mcg/kg)1,2

Efficacy Measures	Previously-Treated Patients (N=15)
CR/CRc rate,* % (n)	13% (2)
Median duration of CR/CRc, months Min, max	Not yet reached 3.7, 13.9
ORR, % (n)	67% (10)
Bridged to stem cell transplantation, % (n)	7% (1)

*CRc = clinical complete response; defined as complete response with residual skin abnormality not indicative of active disease.[1]

Previous Lines of Therapy[2]

Number of Lines	Patients, % (n)
1	53% (8)
2-3	27% (4)
≥ 4	13% (2)

Information regarding prior lines of therapy was not captured for 1 patient in this population.

- 80% of patients were refractory to their mostrecent line of therapy (n=12)[2]

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ELZONRIS: Safety Profile in Patients in the Pivotal Phase 2 BPDCN Trial (STML-401-0114)

Safety was assessed in:

- 94 adult patients with newly diagnosed or relapsed/refractory myeloid malignancies*
  - — 58 patients had BPDCN
  - — All patients received 12 mcg/kg

- The overall median number of cycles administered for patients evaluated for safety was 2 (range, 1-43 cycles; N=94)*
  - — The median number of cycles administered for patients with BPDCN was 4 (range, 1-43 cycles; N=58)

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

Reactions	N=94 All Grades (%)	N=94 Grade ≥ 3 (%)
Capillary leak syndrome[a]	55	9
Nausea	49	0
Fatigue	45	7
Peripheral edema	43	1
Pyrexia	43	0
Weight increase	31	0
Chills	29	1
Headache	29	0
Hypotension	29	9
Decreased appetite	24	0
Constipation	23	0
Vomiting	21	0
Back pain	20	2
Diarrhea	20	0
Dizziness	20	0

Reactions	All Grades (%)	Grade ≥ 3 (%)
Febrile neutropenia	20	18
Dyspnea	19	2
Insomnia	17	0
Tachycardia	17	0
Anxiety	15	0
Hypertension	15	6
Cough	14	0
Epistaxis	14	1
Oropharyngeal pain	12	0
Confusional state	11	0
Hematuria	10	0
Pain in extremity	10	2
Petechiae	10	0
Pruritus	10	0

[a]Capillary leak syndrome (CLS) defined as any event reported as CLS during treatment with ELZONRIS or the occurrence of at least 2 of the following CLS manifestations within 7 days of each other: hypoalbuminemia (including albumin value less than 3.0 g/dL), edema (including weight increase of 5 kg or more), hypotension (including systolic blood pressure less than 90 mmHg).

*This population included patients with AML.

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ELZONRIS: Selected Laboratory Abnormalities

Selected Laboratory Abnormalities in Patients Receiving 12 mcg/kg
N=94

Abnormalities	Treatment-Emergent Laboratory Abnormalities All Grades %	Treatment-Emergent Laboratory Abnormalities Grade ≥ 3 %
Hematology		
Platelets decrease	67	53
Hemoglobin decrease	60	35
Neutrophils decrease	37	31
Chemistry		
Glucose increase	87	20
ALT increase	82	30
AST increase	79	37
Albumin decrease	77	0
Calcium decrease	57	2
Sodium decrease	50	10
Potassium decrease	39	4
Phosphate decrease	30	11
Creatinine increase	27	0
Alkaline phosphatase increase	26	1
Potassium increase	21	2
Magnesium decrease	20	0
Magnesium increase	14	3
Bilirubin increase	14	0
Glucose decrease	11	0
Sodium increase	10	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

ELZONRIS [prescribing information]. New York, NY, US: Stemline Therapeutics, Inc.; December 2018.

ELZONRIS™ (tagraxofusp-erzs): Now Approved

Indications and Usage

ELZONRIS is a CD123-directed cytotoxin for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and in pediatric patients 2 years and older.

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ELZONRIS: Dosing and Administration

- Administer ELZONRIS intravenously at 12 mcg/kg over 15 minutes once daily on days 1-5 of a 21 day cycle.
  - The dosing period may be extended for dose delays up to day 10 of the cycle
- Premedicate with an H1-histamine antagonist, acetaminophen, a corticosteroid, and an H2-histamine antagonist prior to each dose of ELZONRIS[1]

Cycle 1

- Cycle 1 administered in the inpatient setting[1]
- Patient observation should occur for at least 24 hours after the last infusion of the first cycle

Subsequent cycles

- Subsequent cycles may be administered in an inpatient setting or an appropriate outpatient setting[1]
- Patients should be observed for a minimum of 4 hours following each infusion

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ELZONRIS Important Safety Information

IMPORTANT SAFETY INFORMATION

Boxed WARNING: CAPILLARY LEAK SYNDROME

- **Capillary Leak Syndrome (CLS), which may be life-threatening or fatal, can occur in patients receiving ELZONRIS. Monitor for signs and symptoms of CLS and take actions as recommended**

WARNINGS AND PRECAUTIONS

Capillary Leak Syndrome

- ELZONRIS can cause capillary leak syndrome (CLS), which may be life-threatening or fatal if not properly managed. The overall incidence of CLS in clinical trials was 55% in patients receiving ELZONRIS, including 46% in Grades 1 or 2, 6% in Grade 3, 1% in Grade 4, and 2 fatal events. Common signs and symptoms (incidence ≥ 20%) associated with CLS that were reported during treatment with ELZONRIS include hypoalbuminemia, edema, weight gain, and hypotension
- Before initiating therapy with ELZONRIS, ensure that the patient has adequate cardiac function and serum albumin is ≥ 3.2 g/dL
- During treatment with ELZONRIS, ensure that serum albumin levels are ≥ 3.5 g/dL and have not been reduced by ≥ 0.5 g/dL from the albumin value measured prior to dosing initiation of the current cycle. Monitor serum albumin levels prior to the initiation of each dose or more often as indicated clinically thereafter. Additionally, assess patients for other signs or symptoms of CLS, including weight gain, new onset or worsening edema including pulmonary edema, hypotension, or hemodynamic instability
- Counsel patients to seek immediate medical attention should signs or symptoms of CLS occur at any time

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ELZONRIS Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Hypersensitivity Reactions

- ELZONRIS can cause severe hypersensitivity reactions. Grade 3 or higher events were reported in 10% of patients in clinical trials. Monitor patients for hypersensitivity reactions during treatment with ELZONRIS. Interrupt ELZONRIS infusion and provide supportive care as needed if a hypersensitivity reaction should occur. If the reaction is severe, discontinue ELZONRIS permanently

Hepatotoxicity

- Elevations in liver enzymes can occur with ELZONRIS. Grade 3 or higher elevations in liver enzymes occurred in approximately 40% of patients in clinical trials
- Monitor alanine aminotransferase (ALT) and aspartate aminotransferase (AST) prior to each infusion with ELZONRIS. Temporarily withhold ELZONRIS if the transaminases rise to greater than 5 times the upper limit of normal (ULN) and resume treatment upon normalization or when resolved

ADVERSE REACTIONS:

The most common adverse reactions in the clinical trials (incidence ≥ 30%) are capillary leak syndrome, nausea, fatigue, peripheral edema, pyrexia, and weight increase. The most common laboratory abnormalities (incidence ≥ 50%) are decreases in albumin, platelets, hemoglobin, calcium, sodium, and increases in glucose, ALT, and AST.

To report SUSPECTED ADVERSE REACTIONS, contact Stemline Therapeutics, Inc. at 1-877-332-7961 or contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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In Summary

- BPDCN is an aggressive and deadly hematologic cancer. Prior to 2018, there were no current treatments approved or standard of care.

- ELZONRIS™ (tagraxofusp-erzs), a targeted therapy directed to CD123, is the first and only approved treatment for BPDCN
  - FDA approved : December 21st, 2018

- In clinical trials, treatment with ELZONRIS at 12 mcg/kg demonstrated:
  - In treatment-naive patients with BPDCN (N=29)
    - 72% CR/CRc rate
    - 90% Overall Response Rate
    - 45% bridged to stem cell transplantation
    - In the pivotal cohort (N=13), patients achieved a 54% CR/CRc rate, 77% ORR, and 46% bridged to stem cell transplantation
  - 67% overall response rate in previously-treated patients
  - The most common adverse reactions (incidence ≥30%) were capillary leak syndrome (CLS), nausea, fatigue, peripheral edema, pyrexia, and weight increase. The most common laboratory abnormalities (incidence ≥50%) were decreases in albumin, platelets, hemoglobin, calcium, sodium, and increases in glucose, alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

- In order to track claims in the inpatient setting, Stemline Therapeutics is respectfully requesting that CMS establish a new ICD procedural code for ELZONRIS

Adapted from Pemmaraju, N. et al. Results of Pivotal Phase 2 Trial of SL-401 in Patients with Blastic Plasmacytoid Dendritic Cell Neoplasm – ASH December 2018

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