Tagraxofusp (SL-401) therapy for blastic plasmacytoid dendritic cell neoplasm (BPDCN) patients post-autologous or post-allogeneic hematopoietic cell transplantation

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Table of Contents

Protocol Body

1.0 Objectives

Primary Objective

To evaluate the safety of tagraxofusp in patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) after autologous (auto) or allogeneic (allo) hematopoietic cell transplantation (HCT).

Secondary Objectives

1. To estimate progression-free survival (PFS) in patients with BPDCN receiving maintenance therapy with tagraxofusp after auto-HCT or allo-HCT.
2. To estimate the overall survival (OS) in patients with BPDCN receiving maintenance therapy with tagraxofusp after auto-HCT or allo-HCT.

2.0 Background and Rationale

BPDCN is a rare hematologic malignancy. The exact incidence is unknown because of changing nomenclature over time and a variety of clinical presentations. Nevertheless, it is estimated that BPDCN accounts for approximately 0.44% of all hematologic malignancies and approximately 0.7% of cutaneous lymphomas as misdiagnosed cases. When coupled with accurately diagnosed cases, the incidence is estimated at about 500 new cases, or more, in the U.S. per year.[1] Males are more commonly affected by BPDCN with a male/female ratio of 3.5/1 and the median age at diagnosis is 66 years.[2]

Pathogenesis: BPDCN arises from precursors of myeloid origin, the plasmacytoid dendritic cells (pDC; type 2 dendritic cells)3. There is no single genetic abnormality that has been identified as the hallmark of BPDCN, however, a wide array of chromosomal aberrations has been described including a complex karyotype with deletions on chromosomes 5q21 or 5q34 (72%), 12p13 (64%), 13q13-q21 (64%), 6q23-qter (50%), 15q (43%) and 9 (28%) and sporadic genetic alterations affecting RB1, LATS2, CDKN1B, CDKN2A, and TP53 gene.[3] In addition, TET24 and FLT3-ITD1 mutations have also been described in the literature.

Clinical presentation: The clinical behavior of BPDCN is usually aggressive. Skin lesions are frequently the initial manifestation of the disease, prompting medical advice[5], with the face or scalp commonly affected.[6] Without further therapy, the disease can rapidly progress and result in cytopenias due to bone marrow involvement, lymphadenopathy, and splenomegaly.[5] Some patients present with disseminated disease at the outset, with multi-organ involvement. In a large analysis of patients with BPDCN with leukemic presentation, 23% did not have any skin lesions.[1] The blasts can be frequently identified in the blood but hyperleukocytosis is not common.[5] Other reported sites of involvement include central nervous system (CNS), eyes, paranasal cavities, tonsils, lungs, and soft tissues.[5] The neuromeningeal involvement ranges between 4-9% at diagnosis and 17-33% at relapse.[5]

Immunophenotype: BPDCN tumor cells express CD4 and CD56 (WHO classification, 2017). In addition, the expression of at least one pDC-associated marker, BDCA-2 (blood dendritic cell antigen-2, also termed CD303, CLEC4E), CD123 (also termed interleukin-3 alpha-chain, IL3RA), TCL1 (also termed TCL1A)], or SPIB is needed5. Tumor cells lack marker expression for B cells, T cells, myeloid or monocytic cells, and NK cells5. CD5, CD7, CD33, and cytoplasmic CD3 may be positive in some cases.[5]

Diagnosis: The diagnosis of BPDCN can be challenging due to lack of specific chromosomal abnormalities. Several immunophenotypic variations have been described[5]. A large series of more than 300 published cases suggested that CD123, CD4, CD56, and TCL1 are the most reliable markers to establish the diagnosis of BPDCN.[7]

Differential diagnosis: BPDCN needs to be differentiated from extranodal (nasal-type) CD56+ NK/T-cell lymphoma (often associated with EBV), cutaneous T-cell lymphoma (usually do not express CD56, CD123, and BDCA2), CD33+AML CD4+/CD56+, undifferentiated AML, AML with myelomonocytic/monocytic differentiation, or ambiguous lineage leukemia (most AML cases are usually positive for MPO and express myeloid antigens such as CD13, CD15, and CD117).[5]

2.1 Treatment of BPDCN

2.1.1 Tagraxofusp

Tagraxofusp (SL-401), a targeted therapy directed to CD123 (the a subunit of the IL3 receptor). Tagraxofusp is comprised of recombinant human interleukin-3 (IL-3) fused to a truncated diphtheria toxin payload. It is composed of IL3 fused via a Met-His linker to the catalytic and translocation domains of a truncated diphtheria toxin (DT).[14-19] The IL3 domain of tagraxofusp binds to its natural receptor, IL3 receptor which is then internalized, leading to translocation of the DT A fragment to the cytosol, followed by ADP ribosylation of elongation factor 2, inactivation of protein synthesis, and cell death.[14] Tagraxofusp inhibits protein synthesis and DT-GMCSF fusion proteins have been shown to active and subsequently kill leukemic cells in the resting G0 phase.[20] BPDCN blasts overexpress CD123, and tagraxofusp demonstrated impressive preclinical and, subsequently, clinical results.

Delettre et al. assessed the cytotoxicity of tagraxofusp in BPDCN patient-derived cell lines (CAL-1 and GEN2.2) and primary BPDCN cells isolated directly from patients (n = 12).[21] Cells were treated for 18 or 48 hours with tagraxofusp single agent and were then compared cells treated with other cytotoxic agents. Cells rerated with tagraxofusp at concentrations substantially lower than peak concentrations achieved in patients, induced a 92% decrease in viability of BPDCN cell lines and 80% in primary BPDCN cells, more effective than most chemotherapeutic agents. Furthermore, NOD-SCID mice were treated with 2Gy radiation followed by injection of GEN 2.2 cells. Mice were then treated with tagraxofusp at clinically relevant doses. The median OS was significantly longer in mice receiving therapy with tagraxofusp vs. untreated controls (53 days vs. 15 days, respectively).

The first clinical experience of tagraxofusp in patients with BPDCN was in a Phase 1/2 study, in which 11 patients with BPDCN received a single course of 12.5 mcg/kg IV over 15 minutes daily for up to 5 doses (Frankel et al).[14] Seven of 9 evaluable first-line or relapsed/refractory BPDCN patients (78%) had major response (5 CR and 2 PR) with a single course of tagraxofusp. The

Reference Location, N	Diagnostic criteria	Treatment	CR rate	Response duration	Proportion bridged to SCT	Survival from diagnosis
		treatment x 2	(37%) 17/41 (41%)d			
Poret (2015) France N=86	-	AML-like x 19 ALL-like x 17 CHOP-like x 16 NK/T-like x 16 Other x 12	34/80 (43%)	Median DOR 8-14 months across the different treatments	34/80 (43%)	Median = 8 months
Feuillard (2002) France N=23	CD4+/CD56+ DC2 cells	Polychemothera py N=2 untreated	18/23 (78%)	Median DOR = 9 months	2/20 (10%) adults	Median = 12 months
Petrella (2005) France/ Netherlands	CD4+/CD56+ (CD123 PDCs)	Polychemo therapy N=2 untreated	21/28 [e] (78%)	Median DOR = 11 months	-	Median for those treated = 13 months
N=30						

a = Aggressively treated patients.
b = All treated patients (including palliative cases).
c = After induction therapy.
d = After consolidation therapy.
e = 21/28 patients showed a “good response”. The term “CR” was not used.

2.2.3 Autologous HCT

The data regarding auto-HCT in BPDCN is limited to small case series. There is no consensus on optimal conditioning regimens. In a report, Reimer et al.16 treated 4 patients with Cyclophosphamide-Total body irradiation (TBI) +/- Etoposide. Three patients died, all from disease relapse. One patient was alive and in CR. In another series of 6 patients by Suzuki et al.17, median survival was 13.5 months with auto-HCT, however, the conditioning regimen was no specified. In a recent analysis by Kharfan-Dabaja et al.15, outcomes of 8 patients with BPDCN who underwent auto-HCT were reported. Five of the 8 patients were in CR at the time of auto-HCT. Median age was 67 (45-72) years. One-year PFS and OS were 11%. The median PFS and OS was 12 months for both endpoints.

2.2.4 Allogeneic HCT

The outcomes of BPDCN are more favorable in patients receiving allo-HCT, with long-term remissions more likely in patients who receive SCTin CR. [18] In an Italian study by Pagano et al., [1]

43 patients were retrospectively analyzed. In the 6 patients that received allo-HCT the OS was 22.7 months (range 12-32.9) compared to the non-transplanted patients in whom the OS was 7.1 months (p=0.03). In a registry report from the European Group for Blood and Marrow Transplantation (EBMT), 34 patients with BPDCN who received allo-HCT [myeloablative conditioning (MAC) in 74%; 56% in CR1) had a 3-year cumulative incidence of relapse, disease-free survival (DFS), and OS of 32%, 33%, and 41%, respectively. [1] Three-year non-relapse mortality (NRM) was 30%. Patients who underwent allo-HCT in CR1 trended toward better 3-year DFS (36%) and OS (52%) compared with patients who underwent allo-HCT during more advanced disease (DFS, 26%; OS, 29%). All patients who received reduced intensity conditioning (RIC) experienced early relapse or early death and no patient achieved long-term disease control. In a more recent report, outcomes of 37 patients with BPDCN undergoing allo-HCT at different centers in the US were analyzed. [1] The median age was 50 (range: 14-74) years. One-year and 3-year OS was 68% and 58%, respectively. Three-year OS in patients receiving allo-HCT in CR1 was 74% vs 0% in patients transplanted beyond CR1 ($p < 0.0001$).

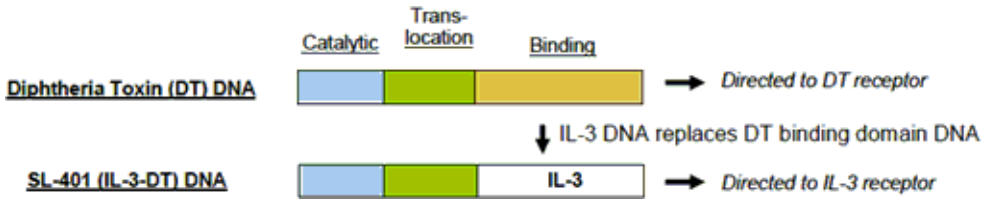
In summary, the available data suggest that long-term remission can be expected in approximately 50% of patients undergoing allo-HCT. The outcomes are significantly superior if patients are transplanted in CR1. However, the relapse rate remains a major concern and strategies are needed to minimize this risk.

2.3 Rationale for tagraxofusp use in this study

As evident from the above data, BPDCN is an aggressive disease with limited therapeutic options. Patients undergoing allo-HCT can have long-term remissions, however, despite allo-HCT the relapse rate remains high. BPDCN blasts overexpress CD123 and tagraxofusp, which targets the IL-3 receptor has shown impressive clinical activity with unprecedented response rates. This study intends to assess the safety and clinical activity of tagraxofusp in patients with BPDCN post-HCT, in attempt to reduce the rate of post-HCT relapse and improve OS.

2.3.1 Background drug information (Tagraxofusp)

Tagraxofusp is a 524- amino acid recombinant fusion protein expressed in Escherichia coli from a hybrid gene comprised of a DNA sequence of human IL-3 recombinantly fused to a truncated DT payload engineered such that IL-3 replaces the native DT receptor-binding domain. In this way, the IL-3 domain of tagraxofusp directs the cytotoxic truncated DT payload to cells that express CD123. After binding to the CD123, tagraxofusp is internalized by receptor-mediated endocytosis and localized to early endosomes. The translocation domain of DT changes conformation in the acidic environment of the endosome, and the RXRR motif (residues 191-194) located between the catalytic and translocation domains of DT is cleaved by endosomal furin. The translocation domain of DT then inserts into the endosomal membrane. As the TAT-like domain of DT (residues 201-230) interacts with cytosolic heat shock protein 90 (Hsp90) and thioreduxin reductase, the catalytic domain (A fragment) unfolds, is reduced, and translocates to the cytosol. Upon release into the cytosol, the A fragment refolds and catalytically inactivates cellular protein synthesis by adenosine diphosphate (ADP)-ribosylating the diphthamide residue in domain IV of elongation factor 2 (EF-2), leading to apoptosis (Investigator Brochure).



2.3.2 Safety data

The most common individual treatment emergent adverse events (TEAEs) reported to date with tagraxofusp, regardless of dose, were ALT increased (69 patients, 55%) and AST increased (68 patients; 54%); hypoalbuminemia (66 patients; 53%); fatigue (61 patients, 49%); nausea (58 patients; 46%); peripheral edema (55 patients; 44%); pyrexia (54 patients; 43%); thrombocytopenia (44 patients; 35%), and headache and hyperglycemia (each 38 patients; 30%). A summary of the most common (i.e.; incidence ·10%) TEAEs reported among tagraxofusp -treated patients, regardless of dose, is presented in Table 2. See Version 4.0 of the SL-401 Investigators Brochure for additional safety information.

Table 2. Most Common ([3] 10%) Treatment-Emergent Adverse Events, Overall and by Indication/Study, by MedDRA Preferred Term (Safety Population)

		Stemline-Sponsored Study			
	Study 0114 (BPDCN)	Study 0114 (AML)	Study 0214	Study 0314	Total
MedDRA Preferred Term	(N=47) n (%)	(N=49) n (%)	(N=14) n (%)	(N=15) n (%)	(N=125) n (%)
At least 1 TEAE	47 (100.0)	49 (100.0)	14 (100.0)	15 (100.0)	125 (100.0)
Alanine aminotransferase increased	30 (63.8)	30 (61.2)		6 (42.9)	3 (20.0)69 (55.2)
Aspartate aminotransferase increased	28 (59.6)	33 (67.3)		5 (35.7)	2 (13.3)68 (54.4)
Hypoalbuminemia	26 (55.3)	30 (61.2)		7 (50.0)	3 (20.0)66 (52.8)
Fatigue	21 (44.7)	27 (55.1)		6 (42.9)	7 (46.7)61 (48.8)
Nausea	21 (44.7)	26 (53.1)		6 (42.9)	5 (33.3)58 (46.4)
Oedema peripheral	24 (51.1)	19 (38.8)		3 (21.4)	9 (60.0)55 (44.0)

		Stemline-Sponsored Study		
	Study 0114 (BPDCN)	**Study 0114 (AML)** **Study 0214**	**Study 0314**	**Total**
Pyrexia	21 (44.7)	22 (44.9)	5 (35.7)	6 (40.0)54 (43.2)
Thrombocytopenia	23 (48.9)	11 (22.4)	6 (42.9)	4 (26.7)44 (35.2)
Headache	12 (25.5)	16 (32.7)	4 (28.6)	6 (40.0)38 (30.4)
Hyperglyc1emia	17 (36.2)	17 (34.7)	3 (21.4)	1 (6.7)38 (30.4)
Chills	16 (34.0)	12 (24.5)	5 (35.7)	3 (20.0)36 (28.8)
Dyspnea	6 (12.8)	18 (36.7)	3 (21.4)	9 (60.0)36 (28.8)
Anemia	11 (23.4)	13 (26.5)	3 (21.4)	7 (46.7)34 (27.2)
Hypotension	13 (27.7)	16 (32.7)	2 (14.3)	3 (20.0)34 (27.2)
Decreased appetite	12 (25.5)	15 (30.6)	2 (14.3)	4 (26.7)33 (26.4)
Weight increased	18 (38.3)	11 (22.4)	3 (21.4)	1 (6.7)33 (26.4)
Vomiting	8 (17.0)	14 (28.6)	3 (21.4)	5 (33.3)30 (24.0)
Diarrhea	7 (14.9)	13 (26.5)	3 (21.4)	6 (40.0)29 (23.2)
Dizziness	8 (17.0)	12 (24.5)	3 (21.4)	6 (40.0)29 (23.2)
Back pain	12 (25.5)	10 (20.4)	2 (14.3)	4 (26.7)28 (22.4)
Constipation	11 (23.4)	10 (20.4)	2 (14.3)	4 (26.7)27 (21.6)

		Stemline-Sponsored Study		
	Study 0114 (BPDCN)	**Study 0114 (AML)** **Study 0214**	**Study 0314**	**Total**
Capillary leak syndrome	9 (19.1)	10 (20.4)	2 (14.3)	4 (26.7)25 (20.0)
Hypokalemia	10 (21.3)	11 (22.4)	1 (7.1)	3 (20.0)25 (20.0)
Febrile neutropenia	5 (10.6)	17 (34.7)	1 (7.1)	023 (18.4)
Insomnia	7 (14.9)	8 (16.3)	2 (14.3)	6 (40.0)23 (18.4)
Cough	3 (6.4)	13 (26.5)	2 (14.3)	4 (26.7)22 (17.6)
Hypocalcemia	11 (23.4)	8 (16.3)	1 (7.1)	2 (13.3)22 (17.6)
Tachycardia	7 (14.9)	10 (20.4)	2 (14.3)	2 (13.3)21 (16.8)
Pain in extremity	5 (10.6)	8 (16.3)	1 (7.1)	5 (33.3)19 (15.2)
Hyponatremia	9 (19.1)	7 (14.3)	1 (7.1)	1 (6.7)18 (14.4)
Neutropenia	8 (17.0)	7 (14.3)	2 (14.3)	1 (6.7)18 (14.4)
Anxiety	9 (19.1)	4 (8.2)	0	4 (26.7)17 (13.6)

Hypertension	10 (21.3)	5 (10.2)	0	2 (13.3)17 (13.6)
Epistaxis	3 (6.4)	11 (22.4)	1 (7.1)	1 (6.7)16 (12.8)
Blood alkaline phosphatase increased	5 (10.6)	9 (18.4)	1 (7.1)	015 (12.0)
Blood lactate dehydrogenase increased	5 (10.6)	8 (16.3)	2 (14.3)	015 (12.0)
Abdominal pain	4 (8.5)	5 (10.2)	2 (14.3)	3 (20.0)14 (11.2)
Blood creatinine increased	6 (12.8)	6 (12.2)	2 (14.3)	014 (11.2)
Hypoxia	3 (6.4)	6 (12.2)	1 (7.1)	3 (20.0)13 (10.4)
Myalgia	1 (2.1)	8 (16.3)	2 (14.3)	2 (13.3)13 (10.4)

In response to the initial case of Grade 5 CLS, which occurred in a patient with BPDCN treated at the 7 mcg/kg dose level early in the clinical program in Study SL-401-0114, all tagraxofusp protocols were amended to exclude patients with left ventricular ejection fraction (LVEF) below the institutional lower limit of normal, and specify that tagraxofusp infusions should be withheld for patients who have an increase in body weight during the dosing period or other potential early evidence of CLS. After the occurrence of Grade 4 CLS, additional precautions were implemented in all tagraxofusp protocols, including instructions that tagraxofusp dosing cease within a given cycle in the setting of substantial albumin reductions or · Grade 3 transaminase elevations. The second Grade 5 case of CLS occurred in a patient with AML treated with tagraxofusp at the 16 mcg/kg dose level, in Study STML-401-0114, a dose level above the MTD determined in that study of 12 m/kg/day.

2.3.3 Carcinogenesis, Mutagenesis, and Impairment of Fertility

At present, reproductive and developmental toxicology studies have not been performed for tagraxofusp; consequently, it is recommended that females of childbearing potential and sexually active males use adequate birth control during study participation and for 2 months after the last dose of tagraxofusp.

3.0 Patient Eligibility

3.1 Inclusion criteria

1. Eligible patients will be aged >/= 18 years. Pediatric patients age 2 years and older will be considered on a case by case basis.
2. Diagnosis of Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) according to WHO classification or confirmed by hematopathology.[24,25]
3. The patients must be in partial response or better (see Appendix A.).
4. > 30 days post-transplant without active or chronic infections.
5. Karnofsky performance status >/= 60%; Lansky >/= 60 (see Appendices B. and C.).

6. LVEF >/= institutional lower limit of normal by MUGA scan or echocardiogram within 30 days of first protocol treatment.
7. Pulmonary function: DLCO, FEV1, FVC > 40% of predicted value (corrected for hemoglobin) within 3 months of registration.
8. Adequate organ function:
    a. Serum creatinine </= 1.5 mg/dL (133 mmol/L).
    b. Serum albumin >/= 3.2 g/dL (or >/= 32 g/L) without IV albumin within the previous 72 hours.
    c. Bilirubin </= 1.5 x the upper limit of normal ([ULN] except patients with Gilbert syndrome in whom bilirubin level of > 1.5x ULN will be allowed).
    d. AST and ALT </= 2.5 times ULN.
    e. Hemoglobin >/= 8 g/dL with or without transfusion in the last 7 days.
    f. Absolute neutrophil count (ANC) >/= 1000 without GCSF or GMCSF in the last 2 weeks prior to screening.
    g. Platelets >/= 50,000/mL.
9. For allo-HCT, no >/= grade 2 visceral (gut or liver) acute GVHD and no >/= grade 3 or any other acute GVHD (Patients with chronic GVHD will be allowed at the discretion of the investigator).
10. Patient agrees to use acceptable contraceptive methods for the duration of time in the study, and to continue to use acceptable contraceptive methods for 2 months after the last tagraxofusp infusion.
11. Woman of child bearing potential (WOCBP) with a negative serum or urine pregnancy test within 14 days of tagraxofusp treatment.
12. Patient or patient's legal representative, parent(s) or guardian able to sign informed consent.
13. The patient can adhere to the study visit schedule and other protocol requirements, including follow-up for survival assessment.

3.2 Exclusion criteria

1. The patient has persistent clinically significant non-hematologic toxicities >/= Grade 2 (excluding alopecia, nausea, and fatigue).
2. Evidence of CNS involvement.
3. Uncontrolled and active pulmonary disease.
4. Requirement for oxygen treatment.
5. Receiving chemotherapy, radiotherapy or other anti-cancer therapy within 14 days of first dose of study drug. There must be at least a 6-week interval from the last immunotherapy therapy.
6. Uncontrolled infection.
7. HIV/Hepatitis B and/or C.
8. Any history of invasive malignancy in the last 2 years excluding any malignancy such as cervical cancer or skin cancer (excluding melanoma) that is considered cured at the time of screening.
9. Pregnant or breast-feeding woman.
10. Patient has uncontrolled intercurrent illness or medical/psychiatric condition that would limit compliance with study requirements or that would in the Investigator's opinion place the patient at an unacceptably high risk for toxicities.
11. Clinical significant cardiopulmonary disease including uncontrolled or NYHA class 3 or 4 congestive heart failure, uncontrolled angina, uncontrolled hypertension, uncontrolled arrhythmia, myocardial infarction or stroke within 6 months of first protocol treatment or QTc > 480 ms.

4.0 Treatment Plan

4.1 Treatment initiation

Between Day + 45 and Day +180 post HCT if the patient meets the eligibility criteria.

4.2 Treatment duration

- Patients in CRi or PR post-transplant will be treated until disease progression or unacceptable toxicity.
- Patients in CR or CRc post-transplant will be treated for 24 cycles, then:
  - Patients who are MRD-positive or have different characteristics that, in the opinion of the investigator, put them at a high-risk o relapse, may continue to receive treatment as long as they continue to derive benefit and remain in remission.
  - Patients who are MRD-negative and don't have other characteristics indicative of high-risk of relapse will stop treatment after 24 cycles, unless the Investigator has a reason to continue treatment (for example, conversion from MRD-positive to MRD-negative only shortly before the 24th cycle).

4.3 Pre-medication

Approximately 60 minutes prior to receiving tagraxofusp.
- Acetaminophen 650 mg PO
- Diphenhydramine 50 mg IV
- Methylprednisolone 50 mg IV (or equivalent dosage of another corticosteroid)
- Ranitidine 50 mg IV (or equivalent dosage of another H2-histamine antagonist)
- Ondansetron 16 mg IV

4.4 Dose and schedule

First three patients:
- Cycles 1-4: Tagraxofusp 9 mcg/kg IV on Days 1, 2, and 3.
- Cycles 5 and beyond: Tagraxofusp 12 mcg/kg IV on Days 1 and 2 (if no unacceptable toxicities at the 9 ug/kg/day IV dose, as defined in the statistical section).

Patient number 4 and beyond:
- Cycles 1-4: Tagraxofusp 12 ug/kg/day IV on Days 1, 2, and 3.
- Cycles 5 and beyond: Tagraxofusp 12 ug/kg/day IV on Days 1 and 2.

Cycle Length: 28 days

During a 28-day cycle, if the patient experiences related non-hematological toxicity with resolution to Grade ≤1 or baseline by day 28, the tagraxofusp dose may be continued during the next cycle at the same dose.

Otherwise tagraxofusp-related non-hematological toxicity not resolved to Grade ≤ 1 or baseline by day 28, the start of the next cycle will be delayed until resolution to Grade ≤ 1 or baseline up to a maximum of additional 28 (56 total) days.

After this treatment delay dosing may be continued during the next cycle at same dose.

4.5 Route and Administration

Tagraxofusp is administered by IV infusion via syringe pump over 15 minutes. Prior to infusion, venous access should be established and maintained with sterile 0.9% Sodium Chloride Injection, USP. The total infusion time will be controlled using a syringe pump to deliver the entire dose over 15 minutes.

Attach the tagraxofusp syringe containing the patient's dose to one port and the saline flush syringe to the other port of a Smith's Medical Y connector or equivalent. Clamp off the ports until needed. Attach the opposite end of the Y connector to the microbore tubing. Attach an in- line filter to the opposite end of the microbore tubing. Prime the saline port of the Y connector up to the intersection and clamp shut until the saline flush is required. Next, prime the entire administration set up with the diluted tagraxofusp dose so that it is ready to attach inline. When the tagraxofusp syringe is empty, remove it from the pump and place the saline flush syringe in the syringe pump. Open the clamp on the saline flush side of the Y connector and resume infusion via the syringe pump at the pre-specified flow. Note that the flush syringe will not be emptied entirely at the end of the 15-minute infusion, since it is just intended to push remaining tagraxofusp out of the infusion line to complete drug delivery.
The dose of tagraxofusp will be dependent upon the patient's body weight in kg. The dose for subsequent cycles is to be recalculated only if there is a 10% change in body weight from baseline. The aliquot is calculated from the mg/kg dose x patient weight in kg (all patient doses are calculated in mg/kg body weight). Dose changes should only occur once a cycle has been completed. Intra-cycle dose modifications are not permitted.

Inpatient admission for cycle 1 only (day 1 or one day before day 1). After cycle 1, Tagraxofusp can be administered in the inpatient setting or in a suitable outpatient ambulatory care setting that is equipped for intensive monitoring of patients with hematopoietic malignancies undergoing treatment, per the discretion of the investigator and institutional guidelines and capabilities.

Observation post-dosing should continue until it is clear that the patient does not have evidence/symptoms of capillary leak syndrome (e.g., no weight gain, edema, hypotension, or decrease in albumin) or hypersensitivity reaction. Participants will be monitored as described in Section 5.0, Evaluations During Study.

Supportive care is permitted according to standard institutional/department of MD Anderson Stem Cell Transplantation and Cellular Therapy protocols.

4.6 Dose modifications for tagraxofusp related hematological toxicity

It is often very challenging to differentiate disease-related from treatment-related hematological toxicities in patients with BPDCN. Patients with neutropenia, anemia, or thrombocytopenia as a consequence of their disease do not require treatment interruptions for myelosuppression. Dose-interruptions in these patients should be considered on a case-by-case basis and discussed with the PI.

4.7 Discontinuation of treatment

Treatment will continue until maximal duration of maintenance therapy is reached (as specified in Section 4.0, Treatment Duration), or the occurrence of any of the following events:

- Disease progression
- Adverse event(s) that, in the judgment of the Investigator/Medical Monitor, may cause severe or permanent harm or which rule out continuation of maintenance study drug.
- Graft failure
- Development of grade III-IV acute GVHD
- Development of severe chronic GVHD
- Suspected pregnancy
- Inability to start planned cycle of tagraxofusp within 56 days of intended start date of each cycle.
- Major violation of the study protocol (to include subject noncompliance with study medications or protocol-specified procedures) at the discretion of the PI

4.8 Procedures During Dosing Period

Monitor vital signs and check albumin, transaminases, and creatinine prior to preparing each dose of tagraxofusp. During each cycle, testing and procedures that may result in withholding of a scheduled tagraxofusp infusion, largely based on unresolved manifestations of fluid retention and/or other relevant acute toxicities during daily dosing, are described below. Details are presented in Table 3.

Table 3: Recommended Dose Modifications

Parameter	Severity Criteria	Dose Modification
Serum albumin	Serum albumin < 3.5 g/dL or reduced ≥ 0.5 g/dL from value measured prior to initiation of the current cycle	See CLS Management Guidelines (Appendix D.)
Body weight	Body weight increase ≥1.5 kg over pretreatment weight on prior treatment day	See CLS Management Guidelines (Appendix D.)
Aspartate aminotransferase (AST) or alanine aminotransferase ALT)	ALT or AST increase > 5 times the upper limit of normal	Withhold tagraxofusp until transaminase elevations are ≤ 2.5 times the upper limit of normal.
Serum creatinine	Serum creatinine > 1.8 mg/dL (159 micromol/L) or creatinine clearance < 60 mL/minute	Withhold tagraxofusp until serum creatinine resolves to ≤ 1.8 mg/dL (159 micromol/L) or creatinine clearance ≥ 60 mL/minute.
Systolic blood pressure	Systolic blood pressure ≥ 160 mmHg or ≤ 80 mmHg	Withhold tagraxofusp until systolic blood pressure is < 160 mmHg or > 80 mmHg.
Heart rate	Heart rate ≥ 130 bpm or ≤ 40 bpm	Withhold tagraxofusp until heart rate is < 130 bpm or > 40 bpm.
Body temperature	Body temperature ≥ 38°C	Withhold tagraxofusp until body temperature is < 38°C.

Parameter	Severity Criteria	Dose Modification
Hypersensitivity reactions	Mild or moderate	Withhold tagraxofusp until resolution of any mild or moderate hypersensitivity reaction. Resume tagraxofusp at the same infusion rate.
	Severe or life-threatening	Discontinue tagraxofusp permanently.

Except in conditions specified above, tagraxofusp may be re-administered subsequently in the same cycle, pending normalization of the abnormalities and pending evidence of stabilization of the underlying clinical conditions resulting in these abnormalities. Postponed doses may be administered within a 10-day period following the initial day of treatment within a cycle.

In the setting of findings possibly consistent with infection, tagraxofusp may be administered pending resolution, provided that an appropriate evaluation for infectious etiologies has been undertaken, and provided that the investigator determines that there is minimal likelihood of uncontrolled systemic infection including sepsis; this may occur on the same day as the temperature elevation, or on subsequent days.

4.9 Management of Specific Toxicities Capillary leak syndrome (CLS)

Capillary leak syndrome (CLS) is associated with vascular endothelial injury related to tagraxofusp administration and often occurs 3-8 days after initiation of treatment.

See Appendix D. for management of CLS and associated symptoms (hypoalbuminemia, edema, weight gain and hypotension).

In the setting of delays secondary to findings consistent with CLS (i.e., in the setting of resolved hypotension, tachycardia, increased weight, or albumin reductions of a magnitude lower than those warranting withholding of tagraxofusp for the duration of a given cycle), subsequent tagraxofusp is to be administered on days subsequent to the identification of the abnormality (not the same day), pending determination by the investigator that there is no/minimal evidence of ongoing CLS and pending discussion with the PI.

5.0 Evaluation During Study

Every effort will be made to adhere to the schedule of events and all protocol requirements. Variations in schedule of events and other protocol requirements that do not affect the rights and safety of the patient will not be considered as deviations. Such variations may include laboratory assessments completed outside of schedule and occasional missed required research samples. Missed samples for correlative studies will not constitute protocol deviations.

Table of Evaluations

	Pre-treatment[2]	Pre-Infusion	Cycles 1-6[1]					Cycles 7-12			Cycles 13+	
			Day 1	Day 2	Day 3	Day 7	Day 15[5]	Day 1	Day 2	Day 15[5]	Day 1	Day 2
Physical exam	X[3]		X[4]			X	X	X[4]			X[4]	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X
Lab tests	X[6]	X[7]	X	X	X	X	X	X		X	X	X
Pregnancy test	X[8]											
12-lead EKG	X	X[9]	X									
ECHO, PFTs	X											
Bone Marrow aspiration/ biopsy	X[10]											
CT (chest, abdomen, pelvis)	X											
Lumbar puncture	X[11]											
AE, SAE Monitoring		X	X	X	X	X	X	X	X	X	X	X

1 Cycle 1: Administered as inpatient. While in the hospital, the observation post-dosing should continue, as clinically indicated, until it is clear that the patient doesn't have evidence/symptoms of capillary leak syndrome (e.g., no weight gain, edema, hypotension, or decrease in albumin) or hypersensitivity reaction. At discharge after Cycle 1: At least once/week for 2 weeks: Physical exam, vital signs, weight, AE and SAE monitoring, clinical lab tests: CBC w/diff; serum electrolytes and chemistry (including albumin), and coagulation parameters.

2 Pre-treatment evaluations: Within 30 days of enrollment unless otherwise specified.

3 Physical exam, pre-treatment: Include detailed skin examination (+/- skin biopsy, as clinically indicated).

4 Physical exam, Cycles 1-6,Cycles 7-12 and Cycle 13+ Day 1: Within 48 hours of tagraxofuspinfusion.

5 Day 15: (+/-3 days).

6 Pre-treatment labs: CBC with differential, serum chemistries including electrolytes, renal function tests, coagulation parameters, albumin, and liver function tests, lactate dehydrogenase (LDH), uric acid HIV/Hepatitis B and/or C.

7 Pre-infusion labs: CBC with differential, serum electrolytes and chemistry (including albumin), renal function tests, and liver function tests, lactate dehydrogenase (LDH), uric acid and coagulation parameters.

8 Serum or urine pregnancy test for women of child bearing potential (WOCBP), within 14 days of starting treatment.

9 12-lead EKG: Before infusion, Cycle 1 only.

10 Bone marrow aspiration and biopsy for pathologic review, immunophenotyping/flowcytometry, cytogenetic, molecular, and FISH analysis

11 Lumbar puncture for CSF analysis with routine CSF studies, cytology, and flow cytometry (optional, if not done previously and has history of CNS involvement).

5.1 Disease specific monitoring

Disease specific monitoring will be performed per Stem Cell Transplantation and Cellular Therapy guidelines.

5.2 Evaluations during follow up

All patients who do not discontinue study drug for toxicity will need to be followed for 30 days post-discontinuation to address any late developing toxicities which may occur. This follow up will cease when patients start a new therapy if prior to the 30-day follow up interval.

5.3 Duration of follow up

Participants will be followed for one year after removal from protocol therapy with either clinic visit or a phone call, or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.4 Outside Physician Participation During Treatment

Starting Cycle 2, post tagraxofusp infusion: Laboratory tests and follow up visit can be performed locally and results sent to MDACC.

5.4.1 MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record.

5.4.2 A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix E.).

5.4.3 Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.

5.4.4 Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.

5.4.5 A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician

5.4.6 Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.

5.4.7 The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.

5.4.8 Patients will return to MDACC for each 28-day tagraxofusp infusion cycle.

6.0 Adverse Events and Reporting Requirements

An adverse event (AE) is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

For the purpose of this study, the investigational component of the treatment plan is tagraxofusp (SL-401). Therefore, serious and unexpected adverse events occurring from the time of infusion of tagraxofusp up to 30 days of the last infusion of tagraxofusp, as defined below, will be reported according to MDACC policy and procedures below. The end of active treatment is the completion of the last infusion of tagraxofusp. Serious adverse events must be followed until clinical recovery and laboratory test have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

AEs will graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. A copy of CTCAE version 5.0 can be downloaded from the CTEP website https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Grade – Severity of the adverse event. Grades were developed using the following guidelines:

Grade 0 – No adverse event or within normal limits
1 – Mild adverse event
2 – Moderate adverse event
3 – Severe adverse event
4 – Life-threatening or disabling adverse event
5 – Fatal adverse event

Abnormal laboratory values not included in the CTCAE guidelines will be defined per protocol.

Time for AE Collection

Adverse events will be collected from the start of the study drug until 30 days after the last infusion of tagraxofusp.

Adverse Event Reporting

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events, and assigning attribution for each event on all subjects enrolled on this study.

Data collection

Collection of adverse events will reflect the onset and resolution date and maximum grade. Intermittent events should be labeled as such and followed until resolution. If a patient is taken off study while an event still ongoing, this will be followed until resolution unless another therapy is initiated. Pre-existing medical conditions will be recorded only if an exacerbation occurs during the active treatment period.

Patients will be registered in MD Anderson's Clinical Trial Management System, OnCore.

Adverse events and all protocol specific data will be entered into the electronic case report form (REDCap).

Events not to be considered adverse events in this study are those related to original disease or expected in the post-allogeneic transplant period.

Isolated changes in laboratory parameters such as electrolyte, magnesium and metabolic imbalances, uric acid changes, elevations of LDH and alkaline phosphatase will not be monitored.

Concomitant medications

Patients treated on this protocol will require supportive care treatment (concomitant medications). These medications are considered standard of care and have no scientific contribution to the protocol; therefore no data will be captured on various medications needed or their side effects. All antiviral therapy will be captured in the medical record.

6.1 Serious Adverse Event (SAE) Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office. -
- OnCore, will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32. A copy of this form will be submitted to Stemline Therapeutics at the same time it is submitted to the IND Office.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

7.0 Criteria for Removal from the Study

Participants will be removed from the study when any of the following criteria apply:

1. Patient withdrawal of the informed consent.
2. Patient's inability or unwillingness to have follow-up visits and/or laboratory tests required by this protocol.
3. General or specific circumstances, which render the participant unacceptable for further treatment in the judgment of the treating investigator.
4. An unexpected toxicity that is deemed unacceptable by the study chairman.
5. Disease progression.
6. After one year of treatment completion.
7. Death.
8. Lost to follow up

8.0 Statistical Considerations

Type of study: Open label, single-arm, single center, Phase 2 clinical trial

Number of patients planned: 20

Expected accrual rate: 5-10 patients/year

Toxicity monitoring

Continuous monitoring of toxicity will be performed in all 20 patients. The first 3 patients will be treated with 9 mcg/kg in first 4 cycles. From cycle 5 and beyond in the first 3 patients, the dose will be 12 ug/kg/day. All subsequent patients will be treated with 12 ug/kg/day. Unacceptable toxicities are defined as tagraxofusp-related toxicities which prevent initiation of Cycle 2 of therapy (Any adverse event ³ grade 3 that is both a) considered related to tagraxofusp, and b) does not resolve to ≤ grade 2 after a maximum delay of 56-days). Assuming a prior beta distribution of (0.4, 1.6), corresponding to an unacceptable toxicity rate of 30%, treatment will terminate if the Pr (dt > 0.20 |data) > 0.95, where dt is the toxicity rate attributable to the tagraxofusp treatment. The decision rule for terminating for toxicity is presented in Table 4 and the software used for this Bayesian toxicity monitoring rule is Multc Lean version 2.1.0. The operating characteristics for this rule are presented in Table 5. The method used to produce the decision rule and operating characteristics was designed by Thall, Simon, and Estey [26, 27] and extended by Thall and Sung.[28]

Table 4 Stopping criteria

Total Patients Enrolled	Stopping Condition (# of patients experiencing unacceptable toxicities)
3-4	3-4
5-8	4-8
9-11	5-11
12-14	6-14
15-18	7-18
19	8-19
20	Patient enrollment ends

Table 5 Operating characteristics

True % of DLTs	Pr (stopping early)	Average # of patients treated
0.05	0.00	20
0.10	0.01	20
0.20	0.11	19
0.30	0.38	16
0.40	0.70	12
0.50	0.91	9

Analysis

Demographic and baseline characteristics will be summarized. Categorical measures will be summarized using frequencies and percentages while continuous variables will be summarized using mean, standard deviation, median, minimum, and maximum.

The primary endpoint of the study is the tolerability of tagraxofusp post-SCT, where tolerability is defined as receipt of at least 75% of planned tagraxofusp doses in at least 4 cycles of therapy. The following table shows the exact 95% confidence intervals for different percentages of patients, out of 20 patients, experiencing tolerability:

Patients experiencing tolerability		**95% Exact**
Number	**Percentage**	**Confidence Interval**
2	10%	1.2% - 31.7%
5	25%	8.7% - 49.1%
10	50%	27.2% - 72.8%
15	75%	50.9% - 91.3%

The percentage of patients considered ‘tolerating’ by this definition will be presented along with the associated 95% exact confidence interval.

PFS is defined as the duration from treatment start date to date of disease progression or death. Patients who are still alive at the end of the study with no evidence of disease will be censored. OS is defined as the time from treatment start date to death. Patients who are still alive at the end of the study will be censored. PFS and OS will be estimated using the Kaplan-Meier method. Median PFS and OS as well as rates with corresponding 95% confidence intervals will be presented.

Summary Reports

The Investigator is responsible for completing a toxicity/tolerability summary report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval. This should be submitted after the first 3 evaluable patients, complete 1 cycle of study treatment, and every 2-3 evaluable patients, thereafter, following Table 4 stopping criteria guidelines.
For tolerability, an updated summary report should be submitted every 2-5 patients complete 4 cycles of study therapy, in accordance to the table located in the “Analysis” section of the protocol.

A copy of the toxicity summary should be placed in the Investigator’s Regulatory Binder under “sponsor correspondence”.

9.0 References

1. Pagano L, Valentini CG, Pulsoni A, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. *Haematologica* 2013; **98**(2): 239-46.

2. Facchetti F, Ungari M, Marocolo D, Lonardi S, Vermi W. Blastic plasmacytoid dendritic cell neoplasm *Hematology Meeting Reports* 2009; **3**(3): 1-3.

3. Sapienza MR, Fuligni F, Agostinelli C, et al. Molecular profiling of blastic plasmacytoid dendritic cell neoplasm reveals a unique pattern and suggests selective sensitivity to NF-kB pathway inhibition. *Leukemia* 2014; **28**(8): 1606-16.

4. Jardin F, Ruminy P, Parmentier F, et al. TET2 and TP53 mutations are frequently observed in blastic plasmacytoid dendritic cell neoplasm. *British journal of haematology* 2011; **153**(3): 413-6.

5. Pagano L, Valentini CG, Grammatico S, Pulsoni A. Blastic plasmacytoid dendritic cell neoplasm: diagnostic criteria and therapeutical approaches. *British journal of haematology* 2016; **174**(2): 188-202.

6. Julia F, Petrella T, Beylot-Barry M, et al. Blastic plasmacytoid dendritic cell neoplasm: clinical features in 90 patients. *The British journal of dermatology* 2013; **169**(3): 579-86.

7. Facchetti F. Plasmacytoid Dendritic Cell Neoplasms. *Knowles Neoplastic Hematopathology In 3rd Edition (eds by Orazi, A, Weiss, LM, Foucar, KA & Knowles, DM) Lippincott Williams & Wilkins, Philadelphia* 2013.

8. Dalle S, Beylot-Barry M, Bagot M, et al. Blastic plasmacytoid dendritic cell neoplasm: is transplantation the treatment of choice? *The British journal of dermatology* 2010; **162**(1): 74-9.

9. Hashikawa K, Niino D, Yasumoto S, et al. Clinicopathological features and prognostic significance of CXCL12 in blastic plasmacytoid dendritic cell neoplasm. *Journal of the American Academy of Dermatology* 2012; **66**(2): 278-91.

10. Naveen Pemmaraju DAT, Hagop Kantarjian, Susan Mary O'Brien, Naval Guastad Daver, Aziz Nazha, Sherry Pierce, Guillermo Garcia-Manero, Jorge E. Cortes, Stefan Faderl Analysis of outcomes of patients (pts) with blastic plasmacytoid dendritic cell neoplasm (BPDCN). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2012; **30, no. 15_suppl** 6578-.

11. Tsagarakis NJ, Kentrou NA, Papadimitriou KA, et al. Acute lymphoplasmacytoid dendritic cell (DC2) leukemia: results from the Hellenic Dendritic Cell Leukemia Study Group. *Leukemia research* 2010; **34**(4): 438-46.

12. Lucioni M, Novara F, Fiandrino G, et al. Twenty-one cases of blastic plasmacytoid dendritic cell neoplasm: focus on biallelic locus 9p21.3 deletion. *Blood* 2011; **118**(17): 4591-4.

13. Roos-Weil D, Dietrich S, Boumendil A, et al. Stem cell transplantation can provide durable disease control in blastic plasmacytoid dendritic cell neoplasm: a retrospective study from the European Group for Blood and Marrow Transplantation. *Blood* 2013; **121**(3):440-6.
14. Frankel AE, Woo JH, Ahn C, et al. Activity of SL-401, a targeted therapy directed to interleukin-3 receptor, in blastic plasmacytoid dendritic cell neoplasm patients. *Blood* 2014; **124**(3): 385-92.
15. Kharfan-Dabaja MA, Al Malki MM, Deotare U, et al. Haematopoietic cell transplantation for blastic plasmacytoid dendritic cell neoplasm: a North American multicentre collaborative study. *British journal of haematology* 2017; **179**(5): 781-9.
16. Reimer P, Rudiger T, Kraemer D, et al. What is CD4+CD56+ malignancy and how should it be treated? *Bone marrow transplantation* 2003; **32**(7): 637-46.
17. Suzuki R, Suzumiya J, Nakamura S, et al. Hematopoietic stem cell transplantation for natural killer-cell lineage neoplasms. *Bone marrow transplantation* 2006; **37**(4):425-31.
18. Kharfan-Dabaja MA, Lazarus HM, Nishihori T, Mahfouz RA, Hamadani M. Diagnostic and therapeutic advances in blastic plasmacytoid dendritic cell neoplasm: a focus on hematopoietic cell transplantation. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation* 2013; **19**(7): 1006-12.
19. FitzGerald DJ. Targeted diphtheria toxin to treat BPDCN. *Blood* 2014; **124**(3): 310-2.
20. Jedema I, Barge RM, Frankel AE, Willemze R, Falkenburg JH. Acute myeloid leukemia cells in G0 phase of the cell cycle that are unresponsive to conventional chemotherapy are sensitive to treatment with granulocyte-macrophage colony-stimulating factor/diphtheria toxin fusion proteins. *Experimental hematology* 2004; **32**(2): 188-94.
21. Delettre Fanny AEF, Estelle Seilles, Sabeha Biichle, Bsc, Eric Deconninck, Francis Bonnefoy, Baptiste Lamarthee, Christopher L. Brooks, Eric Rowinsky, Philippe Saas and Francine Garnache Ottou. Preclinical Studies Of SL-401, a Targeted Therapy Directed To The Interleukin-3 Receptor (IL3-R), In Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN): Potent Activity In BPDCN Cell Lines, Primary Tumor, and In An In Vivo Model. *Blood* 2014; **122:3942**.
22. Naveen Pemmaraju KS, Andrew Lane et al. RESULTS OF PIVOTAL PHASE 2 TRIALOF SL-401 IN PATIENTS WITH BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM. *European Hematology Association annual meeting abstracts* June 15, 2018; **S116**.
23. Naveen Pemmaraju AAL, Kendra Lynn Sweet, Anthony Selwyn Stein, Sumithira Vasu, William G. Blum. Results from phase 2 registration trial of SL-401 in patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN): Lead-in completed, expansion stage ongoing. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2016; **34, no. 15_supp**: 7006-.
24. Facchetti F, Jones DM, Petrella T. Blastic plasmacytoid dendritic cell neoplasm. In: WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues, Swerdlow SH, Campo E, Harris NL, et al. (Eds), IARC, Lyon 2008. p.145.

25. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition, Swerdlow SH, Campo E, Harris NL, et al. (Eds), International Agency for Research on Cancer (IARC), Lyon 2017.

26. Thall PF, Simon RM, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. *Statistics in medicine* 1995; **14**(4): 357-79.

27. Thall PF, Simon RM, Estey EH. New statistical strategy for monitoring safety and efficacy in single-arm clinical trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1996; **14**(1): 296-303.

28. Thall PF, Sung HG. Some extensions and applications of a Bayesian strategy for monitoring multiple outcomes in clinical trials. *Statistics in medicine* 1998; **17**(14): 1563-80.