ORIGINAL ARTICLE

Tagraxofusp in Blastic Plasmacytoid Dendritic-Cell Neoplasm

Naveen Pemmaraju, M.D., Andrew A. Lane, M.D., Ph.D., Kendra L. Sweet, M.D., Anthony S. Stein, M.D., Sumithira Vasu, M.D., William Blum, M.D., David A. Rizzieri, M.D., Eunice S. Wang, M.D., Madeleine Duvic, M.D., J. Mark Sloan, M.D., Sharon Spence, M.S., Shay Shemesh, M.S., Christopher L. Brooks, Ph.D., John Balser, Ph.D., Ivan Bergstein, M.D., Jeffrey E. Lancet, M.D., Hagop M. Kantarjian, M.D., and Marina Konopleva, M.D., Ph.D.

From the University of Texas M.D. Anderson Cancer Center, Houston (N.P., M.D., H.M.K., M.K.); Dana–Farber Cancer Institute (A.A.L.) and Boston University School of Medicine (J.M.S.), Boston, and Veristat, Southborough (J.B.) — all in Massachusetts; H. Lee Moffitt Cancer Center, Tampa, FL (K.L.S., J.E.L.); City of Hope National Medical Center, Duarte, CA (A.S.S.); Ohio State University, Columbus (S.V.); Winship Cancer Institute of Emory University, Atlanta (W.B.); Duke University Medical Center, Durham, NC (D.A.R.); and Roswell Park Comprehensive Cancer Center, Buffalo (E.S.W.), and Stemline Therapeutics, New York (S. Spence, S. Shemesh, C.L.B., I.B.) — both in New York. Address reprint requests to Dr. Pemmaraju at the Department of Leukemia, University of Texas M.D. Anderson Cancer Center, 1400 Holcombe Blvd., Unit 428, Houston, TX 77030, or at npemmaraju@mdanderson.org.

Drs. Pemmaraju and Lane contributed equally to this article.

N Engl J Med 2019;380:1628-37.
DOI: 10.1056/NEJMoa1815105

ABSTRACT

BACKGROUND

Blastic plasmacytoid dendritic-cell neoplasm (BPDCN) is an aggressive hematologic cancer that is caused by transformed plasmacytoid dendritic cells that overexpress interleukin-3 receptor subunit alpha (IL3RA or CD123). Tagraxofusp (SL-401) is a CD123-directed cytotoxin consisting of human interleukin-3 fused to truncated diphtheria toxin.

METHODS

In this open-label, multicohort study, we assigned 47 patients with untreated or relapsed BPDCN to receive an intravenous infusion of tagraxofusp at a dose of 7 μg or 12 μg per kilogram of body weight on days 1 to 5 of each 21-day cycle. Treatment continued until disease progression or unacceptable toxic effects. The primary outcome was the combined rate of complete response and clinical complete response among patients who had not received previous treatment for BPDCN. A secondary outcome was the duration of response.

RESULTS

Of the 47 patients, 32 were receiving tagraxofusp as first-line treatment and 15 had received previous treatment. The median age of the patients was 70 years (range, 22 to 84). Among the 29 previously untreated patients who received tagraxofusp at a dose of 12 μg per kilogram, the primary outcome occurred in 21 (72%), and the overall response rate was 90%; of these patients, 45% went on to undergo stem-cell transplantation. Survival rates at 18 and 24 months were 59% and 52%, respectively. Among the 15 previously treated patients, the response rate was 67%, and the median overall survival was 8.5 months. The most common adverse events were increased levels of alanine aminotransferase (64%) and aspartate aminotransferase (60%), hypoalbuminemia (55%), peripheral edema (51%), and thrombocytopenia (49%). Capillary leak syndrome was reported in 19% of the patients and was associated with one death in each of the dose subgroups.

CONCLUSIONS

In adult patients with untreated or relapsed BPDCN, the use of tagraxofusp led to clinical responses. Serious adverse events included capillary leak syndrome; hepatic dysfunction and thrombocytopenia were common. (Funded by Stemline Therapeutics and the Leukemia and Lymphoma Society Therapy Acceleration Program; ClinicalTrials.gov number, NCT02113982.)

Blastic plasmacytoid dendritic-cell neoplasm (BPDCN) is an aggressive hematologic cancer that confers a predisposition to leukemic transformation and poor outcomes.[1] The exact incidence of BPDCN is unknown but may represent 0.5% of all hematologic cancers.[2] The median age at presentation is approximately 70 years, and most patients are men. Patients with BPDCN have diverse clinical features, with cutaneous tumors in nearly all cases; the high incidence of such tumors distinguishes this disease from other myeloid cancers.[3,4] Other sites of involvement include bone marrow, peripheral blood, lymph nodes, spleen, and other extramedullary organs. Outcomes with conventional treatments that are modeled after therapies for acute leukemia and lymphoma have been disappointing. Patients who undergo allogeneic or autologous stem-cell transplantation during first remission often do well, but traditional chemotherapy has been associated with rates of early death of 17 to 26% and high relapse rates.[2,5-7]

The overexpression of interleukin-3 receptor subunit alpha (IL3RA or CD123) occurs in virtually all cases of BPDCN.[8-10] Tagraxofusp (formerly SL-401) is a CD123-directed cytotoxin consisting of recombinant human interleukin-3 fused to a truncated diphtheria toxin.[11] Tagraxofusp has shown potent antitumor activity against BPDCN cells in both in vitro and in vivo models, with cytotoxicity at femtomolar concentrations.[12] On this basis, a pilot investigator-sponsored clinical study involving 11 patients with BPDCN was conducted.[13] After reviewing the positive results from that study, we designed this evaluation to characterize the safety of tagraxofusp and prospectively assess and confirm its efficacy in patients with BPDCN.

Methods

Patients

From 2014 through 2017, we enrolled adults (≥18 years of age) in whom BPDCN had been diagnosed, according to the 2008 World Health Organization classification.[14] Full eligibility criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. Inclusion criteria included a performance-status score of no more than 2 on the Eastern Cooperative Oncology Group scale (with scores ranging from 0 to 5, with higher scores indicating greater disability) and adequate organ function, which included a cardiac left-ventricular ejection fraction equal to or above the lower limit of the normal range, a creatinine level of 1.5 mg per deciliter (133 μmol per liter) or less, an albumin level of at least 3.2 g per deciliter, a total bilirubin level of 1.5 mg per deciliter (26 μmol per liter) or less, and alanine aminotransferase and aspartate aminotransferase levels of 2.5 times the upper limit of the normal range or less. Patients were excluded from the study if they had received chemotherapy or other investigational therapy in the previous 14 days, had clinically significant active cardiopulmonary disease, or were receiving immunosuppressive therapy at the time of enrollment.

Study Design

This study was designed as a nonrandomized, multistage, open-label, multicenter evaluation of tagraxofusp as monotherapy in patients with BPDCN, regardless of whether they had received previous treatment. Each stage represented a separate phase of the development program, including a pivotal phase that included elements required for a confirmatory study (Fig. 1). Stage 1 followed a standard 3-plus-3 design in which escalating doses of tagraxofusp were administered to identify the dose for the phase 2 portion of the study. After completion of stage 1 and the selection of a recommended dose, stage 2 was initiated to evaluate efficacy and further characterize the safety profile of tagraxofusp in a larger population of patients at the selected dose (12 μg per kilogram of body weight). The results from stages 1 and 2 provided the basis for the design of stage 3 for confirmation of efficacy, a pivotal cohort involving patients who had not received previous treatment for BPDCN, according to a prespecified statistical analysis plan. Stage 4 was added to provide patients with ongoing access to tagraxofusp in a clinical study.

In all study stages, tagraxofusp was administered as a daily intravenous infusion on days 1 through 5 of each 21-day cycle. The study design allowed for a 10-day treatment window in which patients could receive the total of five drug infusions, to allow for dose interruptions, if needed. (Details are provided in the Supplementary Appendix.) Adverse events were evaluated in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

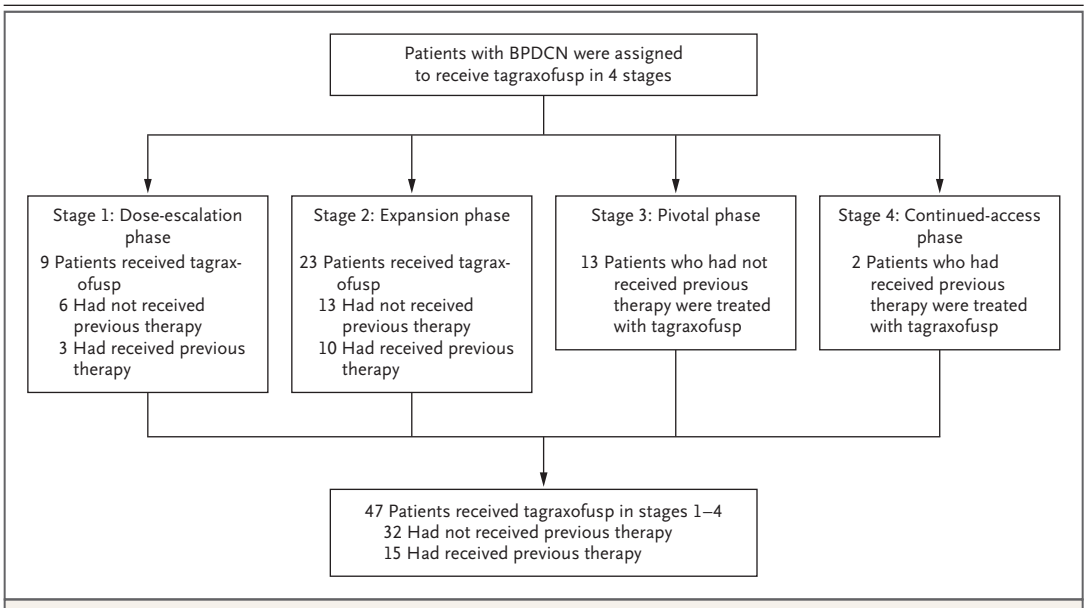

Figure 1. Study Phases and Subgroups.

A total of 47 patients received tagraxofusp for the treatment of blastic plasmacytoid dendritic-cell neoplasm (BPDCN) as part of a four-stage, dose-escalation study. Of these patients, 32 had not received previous treatment for BPDCN and 15 had been treated. In stage 1, among the 6 previously untreated patients, 3 received tagraxofusp at a dose of 7 μg per kilogram of body weight; all the other patients throughout the study received a dose of 12 μg per kilogram. The primary outcome was the combined rate of complete response and clinical complete response among the patients who received first-line treatment with tagraxofusp.

STUDY MONITORING

The study was approved by the institutional review board at each participating site and was conducted in accordance with the principles of the Declaration of Helsinki, with adherence to all clinical practice guidelines. The principal investigators and the sponsor (Stemline Therapeutics) collaboratively designed the study. The sponsor collected the data, and the investigators performed the statistical analysis in collaboration with the study statistician. The study was monitored by the sponsor, with the medical monitor and principal investigators providing medical expertise to inform decisions pertaining to the study conduct. All the authors vouch for the integrity and completeness of the reported data and adherence to the protocol, which is available at NEJM.org. No one who is not an author contributed to the writing of the manuscript.

RESPONSE CRITERIA

Before the conduct of this study, no consensus guidelines for measuring a response to therapy had been developed for patients with BPDCN, and the published literature lacked well-defined response criteria, especially of cutaneous and extramedullary sites of disease. Therefore, we developed a comprehensive set of response criteria that included the evaluation of the most commonly involved disease compartments (skin, bone marrow, peripheral blood, lymph nodes, and viscera) in patients with BPDCN. We used the following measurements to assess each patient: cutaneous measurement by means of skin biopsy and the Modified Severity Weighted Assessment Tool,[15] assessment of bone marrow and peripheral blood by means of standard criteria for acute myeloid leukemia,[16] and evaluation of lymph nodes and viscera by means of standard criteria based on computed tomography.[17] (Details are provided in Response Criteria for BPDCN in the Supplementary Appendix.) A complete response was defined as the disappearance of disease in each site of initial disease. We also identified a need to document patients who had a complete response in all nonskin disease

sites and had marked clearance of all skin lesions from baseline but had residual skin abnormalities not indicative of active BPDCN (e.g., hyperpigmentation or only microscopic abnormality). For this scenario, we established a novel outcome of clinical complete response, which was validated as a measure of clinical benefit.

STATISTICAL ANALYSIS

We assessed the preliminary evidence of efficacy from a descriptive analysis of the overall response rates among all the patients with BPDCN who were enrolled in stages 1 and 2 of the study, regardless of treatment history. The primary evidence of efficacy was derived from an analysis of the rates of complete response and clinical complete response in patients who had not received previous treatment for BPDCN and who were enrolled in stage 3 of the study; a secondary outcome was the durability of response.

In the primary efficacy analysis, we compared the lower boundary of the 95% confidence interval (calculated by the Clopper–Pearson method) for the observed rates of complete response and clinical complete response, with statistical significance determined by a value of more than 10%. The sample size in this cohort ensured a power of at least 90% for the primary efficacy assessment. The null hypothesis was informed by an evaluation of pertinent information, mainly the lack of approved therapies or standard of care, expected effect size, and historical experience with empirical approaches. Before defining the primary efficacy outcome, we validated the outcome of clinical complete response by showing that response durations for patients who had a clinical complete response came from the same probability distribution as response durations in patients who had a complete response.

RESULTS

PATIENTS

Of the 47 patients with BPDCN who were enrolled, 32 had not received previous treatment for the disorder and 15 had received treatment. Of the 32 previously untreated patients, 29 (90%) received tagraxofusp at a dose of 12 μg per kilogram, and 3 patients received a dose of 7 μg per kilogram; the latter patients were not included in the efficacy analysis. All 15 patients who had received previous treatment received the higher dose of 12 μg per kilogram (Fig. 1).

The patients' characteristics at baseline were consistent with historical experience and similar regardless of whether they had received previous treatment (Table 1). Among the 32 previously untreated patients, the median age was 68 years (range, 22 to 84), and 81% were men. Among the 15 previously treated patients, the median age was 72 years (range, 44 to 80), and 87% were men; in this group, 9 patients (60%) had received one line of therapy, 4 patients (27%) had received two or three lines, and 2 patients (13%) had received four or more lines. The patients' disease presentation at baseline was similar regardless of the treatment history, with 94% of the 47 patients having disease manifestations in skin disorders, 51% in bone marrow, 45% in lymph nodes, 17% in peripheral blood, and 17% in visceral sites.

CLINICAL ACTIVITY

The combined rate of complete response and clinical complete response (the primary outcome) was assessed in 13 patients who were enrolled in stage 3. In these patients, the combined rate of complete response and clinical complete response was 54% (95% confidence interval [CI], 25 to 81). In addition, this outcome was assessed in 29 patients (median age, 67 years [range, 22 to 84]) who had not been previously treated and had who received the higher dose of tagraxofusp (12 μg per kilogram). In these patients, the rate of complete response plus clinical complete response was 72% (95% CI, 53 to 87). The median time until response was 43 days (range, 14 to 131), and the overall response rate (partial response or better) was 90%.

The median duration of the primary outcome was not reached at the time of this analysis, with a median duration of follow-up of 19 months (range, 1 to 42). Notably, 13 of the 29 previously untreated patients (45%) were successfully bridged to stem-cell transplantation while they were in remission after treatment with tagraxofusp. Of the 13 patients, 10 underwent allogeneic stem-cell transplantation and 3 underwent autologous stem-cell transplantation. In addition, at the time of the analysis (median follow-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	No Previous Treatment (N=32)	Previous Treatment (N=15)	All Patients (N=47)
Median age (range) — yr	68 (22–84)	72 (44–80)	70 (22–84)
Male sex — no. (%)	26 (81)	13 (87)	39 (83)
White race — no. (%)†	30 (94)	13 (87)	43 (91)
ECOG performance-status score — no. (%)‡			
0	17 (53)	5 (33)	22 (47)
1	15 (47)	10 (67)	25 (53)
BPDCN manifestation — no. (%)			
Bone marrow	15 (47)	9 (60)	24 (51)
Peripheral blood	7 (22)	1 (7)	8 (17)
Skin	31 (97)	13 (87)	44 (94)
Lymph nodes	13 (41)	8 (53)	21 (45)
Previous lines of therapy — no. (%)			
1	NA	9 (60)	NA
2–4	NA	4 (27)	NA
>4	NA	2 (13)	NA

* BPDCN denotes blastic plasmacytoid dendritic-cell neoplasm, and NA not applicable.
† Race was reported by the patients.
‡ Performance-status scores on the Eastern Cooperative Oncology Group (ECOG) scale range from 0 to 5, with 0 indicating no symptoms and higher scores indicating an increasing severity of symptoms.

up, 25 months), survival probabilities in this group were 59% at 18 months and 52% at 24 months (Fig. 2). A summary of treatment outcomes according to status regarding stem-cell transplantation is provided in the Supplementary Appendix. A representative response in patients with skin manifestations is shown in Figure 3.

Among the 15 patients with previously treated disease, the overall response rate was 67% (95% CI, 38 to 88). In this group, the median time until response was 24 days (range, 17 to 48), with a median duration of response of 2.8 months (range, 0.7 to 14.0). One previously treated patient who had disease remission while receiving tagraxofusp underwent allogeneic stem-cell transplantation. The median duration of overall survival in previously treated patients was 8.5 months. (Details regarding the response to treatment and survival among patients in this subgroup are provided in the Supplementary Appendix.)

SAFETY ANALYSIS

Among the 32 previously untreated patients, the median duration of tagraxofusp exposure was 96 days (range, 2 to 927). The patients in this subgroup underwent a median of 5 treatment cycles (range, 1 to 43). Among the 15 previously treated patients, the median duration of exposure was 48 days (range, 6 to 138), and the median number of cycles was 3 (range, 1 to 7). In all the patients, the most common adverse events were increased alanine aminotransferase and aspartate aminotransferase levels, hypoalbuminemia, peripheral edema, and thrombocytopenia (Table 2). Adverse events of grade 3 or higher occurred in 25 of the 32 previously untreated patients (78%) and in 13 of 15 previously treated patients (87%). (Details regarding adverse events are provided in the Supplementary Appendix.)

An important toxic effect in this study was capillary leak syndrome. Among the 44 patients who received the higher dose of tagraxofusp (12 μg per kilogram), capillary leak syndrome was reported in 8 (18%); of these patients, 6 (14%) had a grade 2 event, 1 (2%) had a grade 4 event, and 1 (2%) had a grade 5 event (death). One additional death occurred in a patient who had received tagraxofusp at a dose of 7 μg per kilogram before the implementation of additional

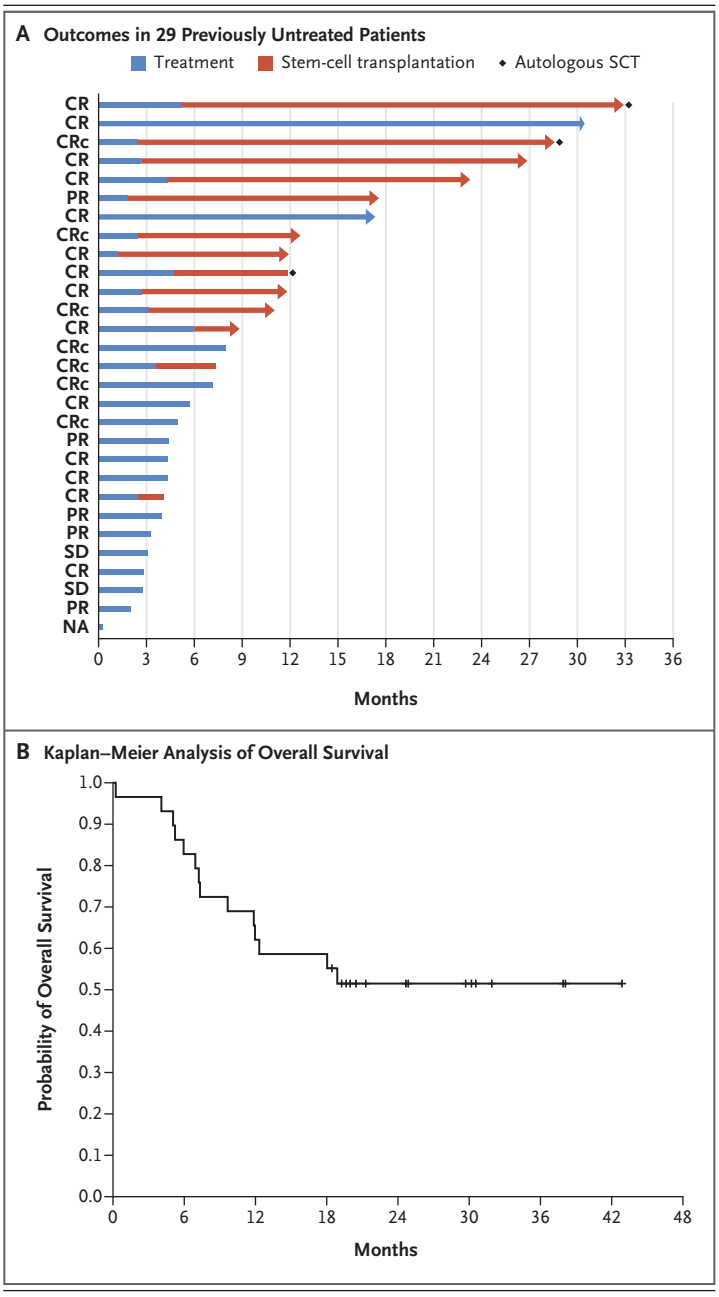

Figure 2. Outcomes in 29 Previously Untreated Patients and Overall Survival.

Panel A shows a swimmer plot of the outcomes of 29 patients with BPDCN who received first-line treatment with tagraxofusp at a dose of 12 μg per kilogram of body weight. The outcomes are complete response (CR), clinical complete response (CRc), partial response (PR), and stable disease (SD); NA indicates that the outcome was not assessed because the patient died. For each patient, the color of the bar represents the first response to treatment, followed by possible conditioning therapy for stem-cell transplantation (SCT), if applicable. The length of the bar represents follow-up through the last assessment in the study, and the arrow indicates that the patient was in remission at the last follow-up. Of the 13 patients who underwent stem-cell transplantation, allogeneic procedures were performed in 10 and autologous procedures in 3 (indicated by a black diamond). Panel B shows the probability of overall survival as measured from treatment initiation to the date of death from any cause. The tick marks indicate censoring of data for patients without an event at the time of last contact. As of October 2018, the median duration of overall survival had not been reached, with a median follow-up of 25 months. At that time, the rate of survival was 62% at 12 months, 59% at 18 months, and 52% at 24 months.

safety measures. After this death during stage 1, the protocol was amended to provide mitigation strategies, including a requirement of normal cardiac function to participate in the study and thresholds for early signs of capillary leak syndrome within a treatment cycle. After the implementation of this amendment, when 34 of the patients in the study had been enrolled, one death occurred in a patient who was receiving 12 μg per kilogram of tagraxofusp. The median time until the onset of capillary leak syndrome was 5 days (range, 4 to 51), and the median duration was 4 days (range, 3 to 19). Of the eight cases of capillary leak syndrome, all but one occurred during the first cycle of tagraxofusp administration. A decrease in albumin during the initial treatment days appeared to be the most consistent predictor of capillary leak syndrome. Management included delaying or withholding additional tagraxofusp doses, administering intravenous albumin on the basis of protocol-specified measures (see the Supplementary Appendix), the use of glucocorticoids, and close management of volume status (diuresis if the patient had fluid-volume overload and intravenous fluids if the patient had hypotension or volume depletion). With vigilant monitoring and early interventions, capillary leak syndrome was manageable and did not preclude restarting tagraxofusp after resolution.

DISCUSSION

In this clinical study involving 47 patients with BPDCN, we observed a 90% overall response rate among previously untreated patients who received tagraxofusp at a dose of 12 μg per kilogram,

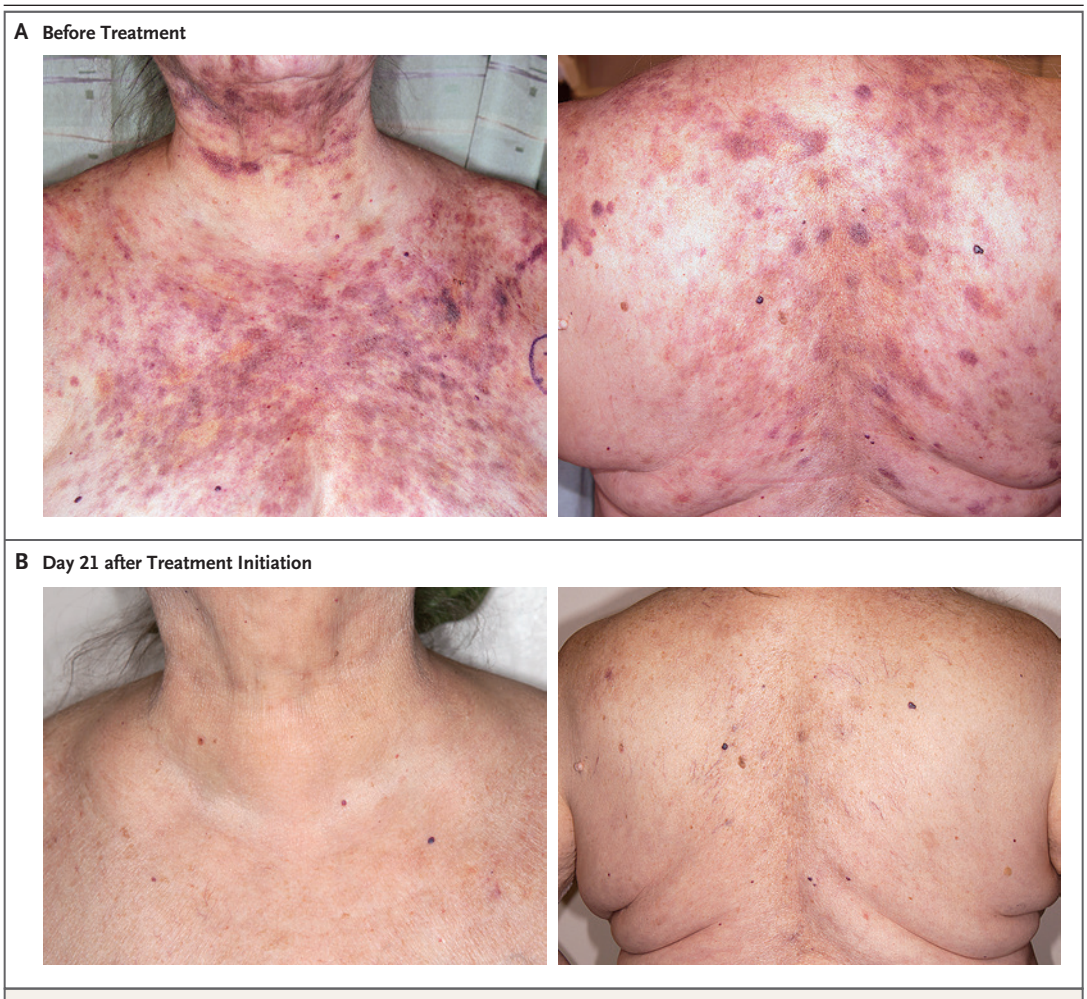

Figure 3. Dermatologic Responses to Tagraxofusp in a 71-Year-Old Patient.
Shown are photographs of the chest and back of a female patient with extensive BPDCN involving skin and bone marrow at baseline (Panel A) and on day 21 during the first cycle of treatment with tagraxofusp (Panel B). The patient was enrolled for first-line treatment that included six cycles of tagraxofusp at a dose of 12 μg per kilogram. She discontinued treatment while in remission to undergo autologous stem-cell transplantation.

with the majority of responses being complete remission. In addition, 45% of the patients were bridged to stem-cell transplantation, including older patients who earlier might have been excluded from this intensive therapy. Among the 29 previously untreated patients, the survival rates of 59% at 18 months and 52% at 24 months — rates that were influenced by the number of patients who went into remission after tagraxofusp therapy and could thus undergo hematopoietic stem-cell transplantation — represent an improvement over rates in historically published data. We also observed a 67% overall response rate among previously treated patients. Notably, we report a meaningful survival with tagraxofusp among patients with relapsed or refractory disease (median overall survival, 8.5 months).

Tagraxofusp was associated with a variety of toxic effects, with the most common being hypoalbuminemia, increased liver-enzyme levels, and thrombocytopenia, most of which were restricted to the first cycle of therapy. The most serious side effect was capillary leak syndrome, with two deaths attributed to this toxicity. Although we instituted safety measures that may identify symptoms early and reduce adverse outcomes, severe adverse events may still occur.

BPDCN has historically been a difficult dis-

Table 2. Adverse Events.

Adverse Event	No Previous Treatment (N=32)	Previous Treatment (N=15)	All Patients (N=47)
	number of patients (percent)		
Serious adverse event	13 (41)	10 (67)	23 (49)
Death from any cause	2 (6)	1 (7)	3 (6)
Any adverse event*	32 (100)	15 (100)	47 (100)
Alanine aminotransferase increased	22 (69)	8 (53)	30 (64)
Aspartate aminotransferase increased	21 (66)	7 (47)	28 (60)
Hypoalbuminemia	14 (44)	12 (80)	26 (55)
Peripheral edema	13 (41)	11 (73)	24 (51)
Thrombocytopenia	16 (50)	7 (47)	23 (49)
Fatigue	13 (41)	8 (53)	21 (45)
Nausea	15 (47)	6 (40)	21 (45)
Pyrexia	11 (34)	10 (67)	21 (45)
Weight increased	13 (41)	5 (33)	18 (38)
Hyperglycemia	11 (34)	6 (40)	17 (36)
Chills	9 (28)	7 (47)	16 (34)
Hypotension	7 (22)	6 (40)	13 (28)
Back pain	7 (22)	5 (33)	12 (26)
Appetite decreased	7 (22)	5 (33)	12 (26)
Headache	11 (34)	1 (7)	12 (26)
Anemia	8 (25)	3 (20)	11 (23)
Constipation	10 (31)	1 (7)	11 (23)
Hypocalcemia	7 (22)	4 (27)	11 (23)
Hypertension	6 (19)	4 (27)	10 (21)
Hypokalemia	6 (19)	4 (27)	10 (21)
Anxiety	6 (19)	3 (20)	9 (19)
Capillary leak syndrome	5 (16)	4 (27)	9 (19)
Hyponatremia	5 (16)	4 (27)	9 (19)
Dizziness	6 (19)	2 (13)	8 (17)
Hypomagnesemia	5 (16)	3 (20)	8 (17)
Neutropenia	3 (9)	5 (33)	8 (17)
Vomiting	6 (19)	2 (13)	8 (17)

* The listed adverse events are those of any grade that occurred in at least 15% of the patients. Events include preferred terms defined with the use of the *Medical Dictionary of Regulatory Activities*, version 19.0.

ease to diagnose and to treat. In the absence of approved therapies and no consensus approach to treating patients, regimens that have been used in patients with acute lymphoblastic leukemia, acute myeloid leukemia, and lymphoma have had very limited success. In most large retrospective series (involving ≥30 patients) that have been performed since the establishment of the World Health Organization diagnostic criteria for BPDCN, complete remission rates ranged from 41 to 55% with various chemotherapy-based approaches. Such remissions have typically had a short duration and did not translate into long-term survival benefit, with consistent

reports of a median survival of 8 to 14 months.[2,5,18] Stem-cell transplantation with myeloablative conditioning for younger patients, or with reduced-intensity conditioning for a select group of older patients, has been associated with improved survival, particularly if the procedure is performed during the first complete remission.[6,7] The major clinical problem in BPDCN is that the median age in most adults is 68 to 72 years, an age at which many patients are unable to undergo intensive chemotherapy used in acute leukemia and thus do not proceed to stem-cell transplantation. Since BPDCN cells were shown to be dependent on BCL2 (B-cell lymphoma 2), clinical case reports have shown a response to treatment with the BCL2 inhibitor venetoclax in patients with this disorder.[19,20] The results of a prospective clinical study of venetoclax in patients with BPDCN (ClinicalTrials.gov number, NCT03485547) have not yet been reported, but the study raises the possibility of future combinations to test with tagraxofusp.

The incidence of occult central nervous system (CNS) involvement in BPDCN may be 10% or higher, and many chemotherapy regimens that have been used in BPDCN have included prophylactic intrathecal chemotherapy.[21] Therefore, it may be notable that there were no cases of overt CNS relapse of disease in this study. However, we did not perform routine lumbar punctures to assess for occult CNS disease, and patients with known CNS disease were excluded from the study. Thus, definitive evidence of tagraxofusp activity against CNS manifestations would require further study, including dedicated CNS assessments.

In conclusion, in adult patients with untreated or relapsed BPDCN, the use of tagraxofusp led to clinical responses. Serious adverse events included capillary leak syndrome, and hepatic dysfunction and thrombocytopenia were common. On the basis of this study, tagraxofusp was recently approved by the Food and Drug Administration for this indication in adults and in children 2 years of age or older.

Presented in part at the 59th American Society of Hematology Annual Meeting, Atlanta, December 9–12, 2017, at the 23rd Congress of the European Hematology Association, Stockholm, June 14–17, 2018, and at the 60th American Society of Hematology Annual Meeting, San Diego, December 1–4, 2018.

Supported by Stemline Therapeutics and the Leukemia and Lymphoma Society Therapy Acceleration Program.

Dr. Pemmaraju reports receiving consulting fees and honoraria from Celgene, Incyte, Roche Diagnostics, and LFB, grant support, consulting fees, and honoraria from MustangBio and Novartis, and grant support from Samus Therapeutics, Cellectis, Plexxikon, Daiichi Sankyo, Affymetrix, and Patient Power; Dr. Lane, receiving grant support from AbbVie and consulting fees from N-of-One, and holding a pending patent (62/579,583) on methods for determining and treating cellular resistance to ADP-ribosylating toxin; Dr. Sweet, receiving advisory board fees, travel support, and writing assistance from Ariad Pharmaceuticals, honoraria, lectures fees, consulting fees, advisory fees, and travel support from Novartis Pharmaceuticals, lecture fees, consulting fees, advisory fees, travel support, and writing assistance from Pfizer, consulting fees, advisory fees, and travel support from Otsuka Pharmaceutical, nonfinancial support from Seattle Genetics, lecture fees, travel support, and writing assistance from Jazz Pharmaceuticals, lecture fees and travel support from Celgene, honoraria, advisory board fees, and travel support from Bristol-Myers Squibb, consulting fees, advisory board fees, and travel support from Agios, advisory board fees, writing assistance, and research funding from Astellas, grant support (paid to her institution) from Incyte, and grant support and travel support from Karyopharm; Dr. Stein, receiving lecture fees from Amgen, Celgene, and Stemline; Dr. Vasu, receiving grant support from Alexion Pharmaceuticals, Boehringer Ingelheim, and Pfizer and consulting fees from Omeros; Dr. Blum, receiving grant support and consulting fees from Boehringer Ingelheim, lecture fees from Pfizer, consulting fees and travel support from Gilead and Novartis, grant support from AbbVie, Celgene, Xencor, and Forma, and consulting fees from Astellas, Tolero, and AmerisourceBergen; Dr. Rizzieri, receiving lecture fees and advisory board fees from Celgene, advisory board fees from Teva, consulting fees from Amgen and Celltrion/Teva, consulting fees and advisory fees from Kite, Arog Pharamaceuticals, Pharmacyclics, Pfizer, Novartis, Sanofi-Aventis, Jazz, and AbbVie, and consulting fees, advisory fees, and lecture fees from Seattle Genetics, Incyte, and Gilead; Dr. Wang, receiving lecture fees from Novartis and Jazz Pharmaceuticals, grant support and lecture fees from Astellas, grant support, advisory board fees, and lecture fees from Pfizer, grant support, advisory board fees, and consulting fees from Amgen, grant support and advisory board fees from Agios, advisory board fees from Celyad, and grant support from Stemline Therapeutics, Eisai/H3 Biomedicine, Incyte, Forma Therapeutics, Tolero, Arog Pharmaceuticals, Immunogen, Trovagene, Daiichi Sankyo, Oscotec, and Ono Pharmaceuticals; Dr. Duvic, receiving grant support and consulting fees from Stemline Therapeutics; Dr. Sloan, receiving fees for serving on an end-point review committee from AbbVie and EMD Serono (Merck), fees for serving on a data and safety monitoring board from Molecular Templates, fees for serving as a safety monitor from OncoQuest, lecture fees and travel support from Alexion, grant support from Gilead, grant support from Seattle Genetics, and provision of drugs from Bristol-Myers Squibb and Genzyme; Mr. Shemesh and Drs. Brooks and Bergstein, being employed by Stemline Therapeutics; Dr. Lancet, receiving consulting fees from Pfizer, Jazz Pharmaceuticals, AbbVie, Daiichi Sankyo, and Agios; Dr. Kantarjian, receiving grant support and honoraria from AbbVie, Agios, Amgen, Immunogen, and Pfizer, grant support from Ariad, Astex, BMS, Cyclacel, Daiichi Sankyo, Jazz Pharmaceuticals, and Novartis, advisory board fees from Actinium, and honoraria from Orsinex and Takeda; and Dr. Konopleva, receiving grant support and consulting fees from Stemline Therapeutics. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

REFERENCES

1. 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;118:4591-4.
2. Pagano L, Valentini CG, Pulsoni A, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. Haematologica 2013;98:239-46.
3. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391-405.
4. Facchetti F, Petrella T, Pileri SA. Blastic plasmacytoid dendritic cell neoplasm. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC Press, 2017:353-67.
5. Martín-Martín L, López A, Vidriales B, et al. Classification and clinical behavior of blastic plasmacytoid dendritic cell neoplasms according to their maturation-associated immunophenotypic profile. Oncotarget 2015;6:19204-16.
6. Aoki T, Suzuki R, Kuwatsuka Y, et al. Long-term survival following autologous and allogeneic stem cell transplantation for blastic plasmacytoid dendritic cell neoplasm. Blood 2015;125:3559-62.
7. Dietrich S, Andrulis M, Hegenbart U, et al. Blastic plasmacytoid dendritic cell neoplasia (BPDC) in elderly patients: results of a treatment algorithm employing allogeneic stem cell transplantation with moderately reduced conditioning intensity. Biol Blood Marrow Transplant 2011;17:1250-4.
8. Jordan CT, Upchurch D, Szilvassy SJ, et al. The interleukin-3 receptor alpha chain is a unique marker for human acute myelogenous leukemia stem cells. Leukemia 2000;14:1777-84.
9. Han L, Qiu P, Zeng Z, et al. Single-cell mass cytometry reveals intracellular survival/proliferative signaling in FLT3-ITD-mutated AML stem/progenitor cells. Cytometry A 2015;87:346-56.
10. Testa U, Pelosi E, Frankel A. CD 123 is a membrane biomarker and a therapeutic target in hematologic malignancies. Biomark Res 2014;2:4.
11. Frankel A, Liu JS, Rizzieri D, Hogge D. Phase I clinical study of diphtheria toxin-interleukin 3 fusion protein in patients with acute myeloid leukemia and myelodysplasia. Leuk Lymphoma 2008;49:543-53.
12. Fanny D, Frankel AE, Seilles E, et al. 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 2013;122:3942. abstract.
13. 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;124:385-92.
14. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 2009;114:937-51.
15. Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol 2011;29:2598-607.
16. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003;21:4642-9.
17. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-68.
18. Dalle S, Beylot-Barry M, Bagot M, et al. Blastic plasmacytoid dendritic cell neoplasm: is transplantation the treatment of choice? Br J Dermatol 2010;162:74-9.
19. Montero J, Stephansky J, Cai T, et al. Blastic plasmacytoid dendritic cell neoplasm is dependent on BCL2 and sensitive to venetoclax. Cancer Discov 2017;7:156-64.
20. Agha ME, Monaghan SA, Swerdlow SH. Venetoclax in a patient with a blastic plasmacytoid dendritic-cell neoplasm. N Engl J Med 2018;379:1479-81.
21. Martín-Martín L, Almeida J, Pomares H, et al. Blastic plasmacytoid dendritic cell neoplasm frequently shows occult central nervous system involvement at diagnosis and benefits from intrathecal therapy. Oncotarget 2016;7:10174-81.