Care Optimization for Patients With Blastic Plasmacytoid Dendritic Cell Neoplasm Receiving Tagraxofusp

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Abstract

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive, orphan hematologic malignancy that expresses CD123 and frequently presents in skin, bone marrow, blood, and viscera. Tagraxofusp is a first-in-class CD123-targeted therapy and the only US-approved drug to treat BPDCN. Approval was based on a pivotal, multicenter, phase II study (NCT02113982), the largest prospective BPDCN trial to date, in which tagraxofusp monotherapy demonstrated durable clinical responses across treatment-naive and relapsed/refractory BPDCN, and often resulted in patients proceeding to stem cell transplant following tagraxofusp-induced remissions. Advanced practitioners (APs) are critical in providing comprehensive and consistent monitoring, supportive care management for adverse events, and patient education. A core specialized interdisciplinary team coupled with AP-led management optimizes tagraxofusp treatment. This paper reviews best practices for the clinical management of patients with BPDCN receiving tagraxofusp in the context of the US package insert and APs' real-world management approaches.

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive orphan hematologic malignancy that expresses CD123, and frequently presents in skin, bone marrow, and blood; other extramedullary sites, including viscera (lymph nodes, liver, and spleen) and the central nervous system (CNS), may also be affected (Pagano et al., 2013; Pemmaraju et al., 2021, 2023). Blastic plasmacytoid dendritic cell neoplasm is associated with a poor prognosis, and incidence is higher among males and patients aged ≥ 60 years (Pagano et al., 2013). The aim of therapy is to achieve a lasting remission without extended toxicity, including prolonged myelotoxicity.

Upon successful induction of remission, the next goal is stem cell transplantation (SCT) for eligible patients (Pemmaraju et al., 2024a, 2024b). For patients who are not candidates for SCT, the focus shifts to continued management, which may include ongoing maintenance therapy.

Tagraxofusp (Elzonris) is a first-in-class CD123-targeted therapy, and the only drug approved in the United States (US) to treat BPDCN. Tagraxofusp is a recombinant fusion protein consisting of human interleukin-3 conjugated to a truncated diphtheria toxin payload, which inhibits protein synthesis and causes cell death in CD123-expressing cells (Stemline Therapeutics, Inc., 2023; Jen et al., 2020). In the US, tagraxofusp is indicated for the treatment of BPDCN in adults and in pediatric patients ≥ 2 years old (Stemline Therapeutics, Inc., 2023).

The approval of tagraxofusp was based on a multicenter, phase II study (NCT02113982), which remains the largest prospective BPDCN trial to date. This study incorporated prespecified and multisystem response criteria and endpoints (Pemmaraju et al., 2019, 2022). In this pivotal study, 65 treatment-naive and 19 relapsed/refractory (n = 84) patients with BPDCN received tagraxofusp 12 µg/kg intravenously once daily on days 1 through 5 of a 21-day cycle and were efficacy evaluable. At a median follow-up of 34 months, the overall response rate (ORR) was 75% in treatment-naive patients; with 57% achieving complete response (CR) + clinical CR (CRc: CR with residual skin abnormality not indicative of active disease; Pemmaraju et al., 2022). Nineteen CR + CRc patients (51%) were bridged to SCT after receiving a median of 4 cycles of treatment with a median CR + CRc duration of 22.2 months and a median overall survival (OS) of 38.4 months (Pemmaraju et al., 2022).

In addition to its efficacy, tagraxofusp has demonstrated a distinct, well-characterized, and manageable safety profile. The majority of adverse events (AEs) were transient and occurred primarily during cycle 1, with no evidence of cumulative hematologic or non-hematologic toxicity. Capillary leak syndrome (CLS) was reported in 21% of patients and predominantly occurred during the first treatment cycle. Most cases were grade 1 to 2 and were manageable with appropriate monitoring and supportive care (Pemmaraju et al., 2022). Overall, tagraxofusp monotherapy demonstrated clinical responses across both treatment-naive and relapsed/refractory BPDCN, which often resulted in complete responders proceeding to SCT.

As with many oncology treatments (Bruinooge et al., 2018), advanced practitioners (APs)—nurse practitioners, physician assistants, and clinical pharmacists—play a critical role in providing comprehensive and consistent monitoring and supportive care for patients with BPDCN undergoing tagraxofusp treatment. Proper preparation, administration, logistical coordination, monitoring, and supportive care are required for successful tagraxofusp therapy, highlighting the importance of an interdisciplinary team approach. Herein, we review best practices for the clinical management of BPDCN patients receiving tagraxofusp in the context of the US package insert (USPI; Stemline Therapeutics, Inc., 2023) coupled with APs' real-world management approaches.

BEST PRACTICES FOR CLINICAL MANAGEMENT OF TAGRAXOFUSP

As a first-in-class CD123-targeted agent approved for BPDCN, tagraxofusp comes with a set of logistical considerations unique to its class. A core interdisciplinary team approach with strong communication between specialized providers is essential to facilitate tagraxofusp administration. Team members who must interact to ensure comprehensive care and coordination include the lead physician, nurse practitioner (NP)/physician assistant (PA), pharmacist, social worker, nurse, and/or care coordinator. A dermatologist may be involved for ongoing skin assessment as needed. Figure 1 outlines the basic algorithm used by APs to guide the treatment of patients with BPDCN through tagraxofusp treatment. The algorithm was developed based on the USPI, clinical data, and best practices contributed by the AP authors. A checklist is provided as a quick reference guide for APs during tagraxofusp treatment (Appendix A).

PATIENT IDENTIFICATION AND ASSESSMENT

Patient Eligibility

Once an appropriate tagraxofusp candidate is identified, the interdisciplinary team collaborates with the lead physician to review the patient eligibility criteria listed in Table 1. The patient's medical history and concomitant medications

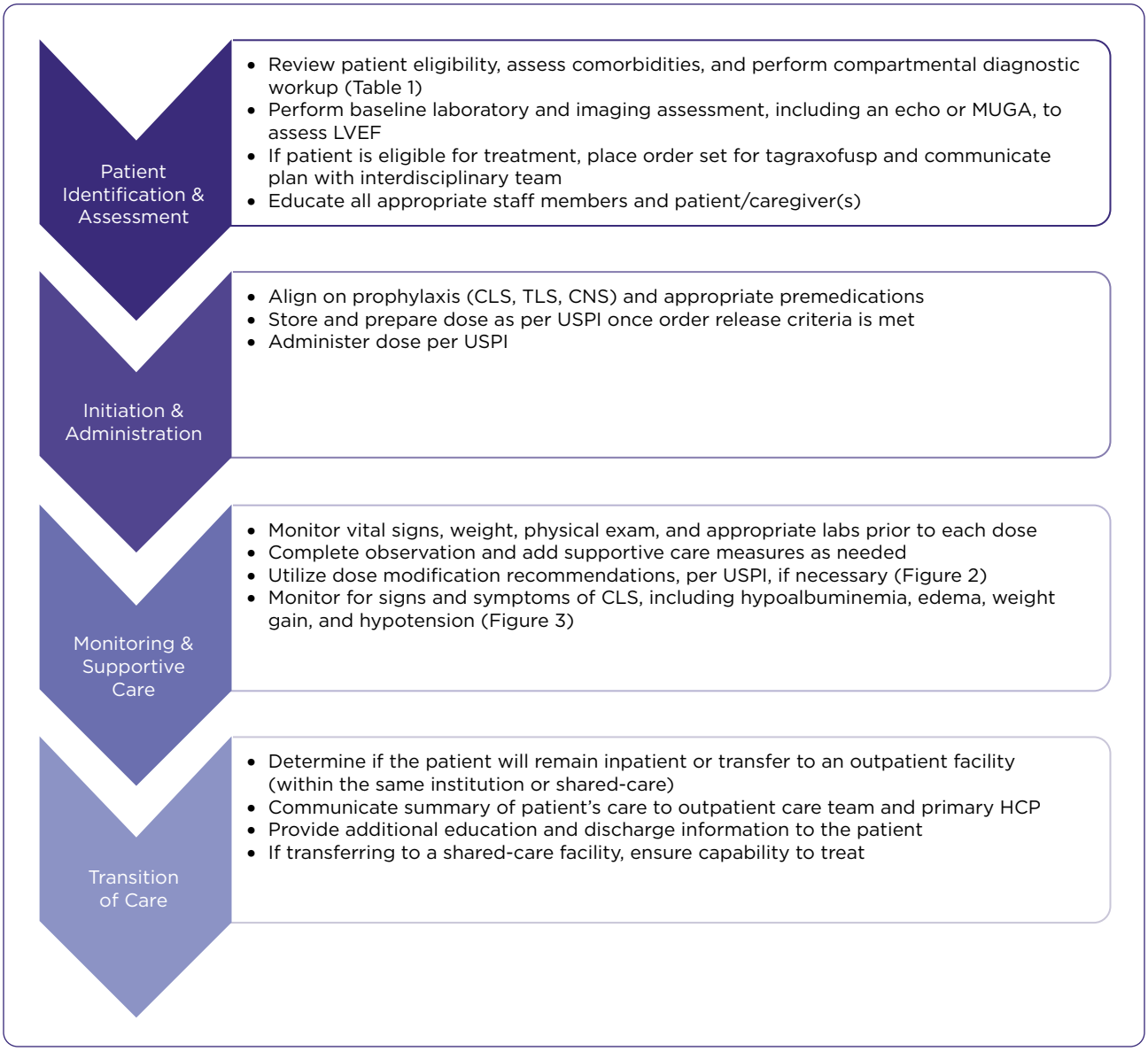

Figure 1. Algorithm of AP best practices for tagraxofusp management in BPDCN. AP = advanced practitioner; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CLS = capillary leak syndrome; CNS = central nervous system; echo = echocardiogram; HCP = health-care provider; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition scan; TLS = tumor lysis syndrome; USPI = United States package insert.

are thoroughly reviewed, and a social worker conducts a psychosocial evaluation. A thorough assessment of baseline comorbidities and organ function should be performed to determine any unmodifiable patient characteristics that would affect eligibility. The USPI baseline laboratory and organ function requirements for tagraxofusp treatment include serum albumin levels ≥3.2 g/dL and a normal echocardiogram (Stemline Therapeutics, Inc., 2023), defined as an ejection fraction greater than the lower limit of institutional normal and a normal electrocardiogram. Furthermore, AP best practices include additional baseline criteria assessments, including evaluation of baseline Eastern Cooperative Oncology Group (ECOG) performance status. For patients with a serum albumin level < 3.2 g/dL, APs may consider supplemental albumin prior to cycle 1

Table 1. Criteria for Tagraxofusp Patient Eligibility Consideration: USPI and AP Best Practices

	USPI	AP Best Practices
Testing/Pathology		• Interdisciplinary case review with lead physician; hematopathologist/dermatologist to determine diagnosis and to ensure all appropriate compartmental assessments (e.g., CNS, lymph nodes/viscera) are completed
Fitness/Evaluation	Adults and pediatric patients ≥ 2 years old	• Social worker to screen and complete psychosocial evaluation • Utilize ECOG PS (e.g., ECOG PS ≤ 2) and KPS requirements to evaluate patient fitness • Thorough assessment of baseline comorbidities and organ function • For cycle 2 and beyond, assess inpatient/outpatient feasibility per patient (e.g., distance from facilities, reliable transportation, tolerability of prior dose, cardiac function/reserve, etc.)
Cardiac function	Adequate cardiac function	• Normal ejection fraction as determined by echo or MUGA, and baseline ECG • Consider chest X-ray, if applicable
Labs	Albumin levels ≥ 3.2 g/dL	• If albumin < 3.2 g/dL, consider albumin prior to C1D1 to optimize serum levels and allow eligibility

Note. AP = advanced practitioner; BPDCN = blastic plasmacytoid dendritic cell neoplasm; C1D1 = cycle 1 day 1; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance score; echo = echocardiogram; ECG = electrocardiogram; KPS = Karnofsky Performance Scale; USPI = United States package insert.

day 1 (C1D1) to optimize albumin levels, potentially allowing for eligibility.

Initial Steps and Communication

Tagraxofusp order sets should be prepopulated to include all potential premedications, supportive care and prophylactic measures, and administration parameters. It is important that the interdisciplinary care team aligns on supportive care medications and prophylaxis for CLS and tumor lysis syndrome (TLS), particularly with respect to fluid management. Central line access is not required for tagraxofusp administration but can be requested if preferred by the patient or care team.

Once the physician and APs agree on the treatment approach, the AP should notify the schedule coordinator to schedule cycle 1 inpatient care if the patient is not already admitted. The designated AP then informs the interdisciplinary care team members to ensure continuity of care and safe administration.

Education

It is important that health-care providers are educated on tagraxofusp through interdisciplinary training sessions, which can be led by APs. Relevant education topics include a review of tagraxofusp mechanism of action, administration components including use of a syringe pump, monitoring, potential side effects, and recognition and management of CLS and other possible side effects. Continued education and reeducation is appropriate for staff and health-care team members involved in direct care prior to each tagraxofusp dose and administration cycle. Advanced practitioners typically utilize the tagraxofusp USPI, institution-specific tagraxofusp protocols, and CLS management protocols during these education sessions. Education is also important for the patient and caregiver(s), especially regarding common AEs, including signs and symptoms related to CLS. Inclusion of printed plain-language patient education also helps to reiterate the information provided.

Patient Assessment

Table 2 summarizes the baseline patient assessment, which includes physical examination, cardiac evaluation, and laboratory considerations. Vital signs, weight, signs and symptoms of CLS (such as weight gain, edema, hypotension, hypoalbuminemia), normal cardiac function, and blood work

Table 2. Recommended Tagraxofusp Patient Assessment Criteria

Physical exam considerations	Labs/Tests[a]
• Vital signs (HR, BP, temperature parameters) • Weight increase (≥ 1.5 kg from previous day's predose weight; best to use the same scale for each weight capture) • CLS signs and symptoms (SOB, rapid weight gain, edema, severe hypotension, dizziness)	• CMP (albumin, creatinine, liver function tests, phosphorus, potassium, calcium, and uric acid) • CBC with differential • Ensure albumin levels are ≥ 3.2 g/dL prior to C1D1, and for C1D2 and beyond albumin levels are ≥ 3.5 g/dL and not reduced by ≥ 0.5 g/dL from the value measured prior to initiation of the current cycle

Note. BP = blood pressure; C1D1 = cycle 1 day 1; C1D2 = cycle 1 day 2; CBC = complete blood count; CLS = capillary leak syndrome; CMP = complete metabolic panel; dL = deciliter; echo = echocardiogram; ECG = electrocardiogram; g = grams; HR = heart rate; kg = kilograms; SOB = shortness of breath; TLS = tumor lysis syndrome.
[a]TLS laboratory cadence varies based on institutional practice and patient risk level (e.g., burden of disease, renal dysfunction)

—including albumin, creatinine and liver function tests—are all critical baseline assessments. These evaluations help the team recognize early signs of AEs and side effects, which may require dose modifications, treatment holds, or supportive care strategies for tagraxofusp.

INITIATION AND ADMINISTRATION

Capillary Leak Syndrome Prophylaxis

In the pivotal study, the safety population for tagraxofusp at 12 µg/kg included 86 treatment-naive and relapsed/refractory BPDCN patients, of whom 18 (21%) experienced CLS events (Pemmaraju et al., 2022). The majority of these 18 events were grade 1 to 2, but 2% each were grade 3, 4, and 5. The median time to onset of CLS was 6 days (range, 3–51), and the median time to resolution was 6 days (range, 3–69; Pemmaraju et al., 2022). In subsequent real-world experience that incorporated CLS training and management, no grade 4 or 5 events occurred in treatment-naive patients, and four grade 3 and one grade 4 events occurred in patients with relapsed/refractory BPDCN (Angelucci et al., 2023; Herling et al., 2024). As in the pivotal study, the majority of CLS events occurred during cycle 1 in the real-world studies, further substantiating the rationale and manageability of outpatient tagraxofusp administration in following cycles. Given the incidence of CLS with tagraxofusp, prophylactic measures may be considered including the use of albumin. The dosing and frequency of albumin in the prophylactic setting are determined by the patient's condition and institutional protocols (Stemline Therapeutics, Inc., 2023).

Tumor Lysis Syndrome Prophylaxis

In a study involving 47 first-line or relapsed/refractory BPDCN patients who received tagraxofusp at doses of 7 µg/kg or 12 µg/kg IV, TLS occurred in 11% of patients (Pemmaraju et al., 2019). Tumor lysis syndrome prophylaxis typically includes IV fluids, oral allopurinol 300 mg daily (with dosing variations), rasburicase (in select cases), and phosphorous binders (e.g., calcium-containing medications, such as calcium acetate and calcium carbonate, or non-calcium phosphate binders, such as sevelamer and lanthanum; Mirrakhimov et al., 2015), depending on disease burden and patient risk factors. Caution should be exercised with IV fluids due to the concurrent risk of CLS.

Central Nervous System Prophylaxis

Recent findings indicate that up to 30% of patients with either treatment-naive BPDCN or relapsed/refractory disease have CNS involvement. This suggests that concomitant administration of prophylactic intrathecal (IT) chemotherapy should be considered alongside tagraxofusp treatment (Pemmaraju et al., 2023; Luskin et al., 2024). Central nervous system assessments should be completed on all patients diagnosed with BPDCN to establish the presence of baseline disease involvement. At this time, it is unknown whether tagraxofusp crosses the blood-brain barrier, which emphasizes the importance of considering IT chemoprophylaxis in these patients (Luskin et al., 2024).

In a single-center retrospective analysis of patients with BPDCN treated with tagraxofusp, data

from five patients with or without CNS disease involvement received IT chemotherapy as primary-intention treatment (n = 3) or as prophylaxis (n = 2; Rivoli et al., 2022). All three patients receiving IT therapy as primary-intention treatment achieved a CR within the CNS. There were no AEs associated with IT chemotherapy. Although the USPI does not provide information pertaining to IT chemoprophylaxis, AP best practices and available order sets indicate IT chemotherapy, typically methotrexate 12 mg or cytarabine 100 mg, may be given intrathecally during a cycle 1 diagnostic lumbar puncture. In addition, IT chemotherapy may be administered once or twice per cycle throughout tagraxofusp treatment or to a specified number of IT doses. Alternatively, some centers elect to adopt primary CNS chemoprophylaxis strategies similar to those used in the treatment of acute lymphoblastic leukemia, which involve alternating administration of IT cytarabine and IT methotrexate twice per cycle, up to a total of 8 to 12 doses. However, this practice has not yet been widely standardized. If a CNS evaluation for BPDCN is positive, IT treatment strategies will increase in intensity in an effort to quickly eradicate the CNS disease.

Premedications

Hypersensitivity reactions can occur during tagraxofusp treatment and most commonly manifest as rash, pruritus, and stomatitis (Stemline Therapeutics, Inc., 2023). Clinical trials reported hypersensitivity reactions in 43% of patients, with 36% experiencing grade 1 to 2 reactions, and 7% experienced at least one grade 3 reaction (Stemline Therapeutics, Inc., 2023). To reduce the risk of hypersensitivity reactions, the USPI recommends administering premedications approximately 60 minutes prior to the tagraxofusp infusion, including an H1-histamine antagonist (e.g., diphenhydramine hydrochloride 50 mg IV or equivalent), H2-histamine antagonist (e.g., famotidine 20 mg IV or equivalent), corticosteroid (e.g., methylprednisolone 50 mg IV or equivalent), and acetaminophen 650 mg by mouth (or paracetamol IV).

Dose Release

Prior to tagraxofusp dose preparation, interdisciplinary team collaboration is needed. The designated AP reviews vital signs, weight, and necessary labs and assesses for signs or symptoms of CLS. The AP communicates with the team to obtain full alignment prior to order release on each day of dosing to ensure all administration parameters have been met. Dose preparation awareness is also provided to any potentially necessary consultants (e.g., nephrology, intensive care unit) due to the risk of CLS. Once the order has been released, after ensuring that the patient meets all criteria for receiving tagraxofusp, the pharmacy may begin preparing the medication for administration per USPI standards (Stemline Therapeutics, Inc., 2023).

Administration

Tagraxofusp is administered inpatient during cycle 1 at a dose of 12 µg/kg IV once daily on days 1 through 5 of a 21-day cycle (Stemline Therapeutics, Inc., 2023). A syringe pump is utilized to deliver the medication over 15 minutes. The dosing period of tagraxofusp can be extended up to day 10 of the cycle to accommodate any potential dose delays, as detailed in the dose modifications section below. Tagraxofusp is administered until the patient is bridged to SCT (if eligible), experiences disease progression, or experiences unacceptable toxicity.

MONITORING AND SUPPORTIVE CARE

Evaluation and Supportive Care

While a patient is receiving tagraxofusp, vital signs and labs must be consistently reviewed and evaluated. The physician or appropriate AP should enter lab orders based on the frequency decided upon by the full interdisciplinary team. Because most CLS events occur in cycle 1, twice-daily labs, consisting of complete blood count (CBC) with differential, complete metabolic panel (CMP), and TLS labs (potassium, calcium, uric acid, and phosphorus), can be considered during the dosing period. For cycle 2 and beyond dosing periods, once-daily labs should be ordered, and include a CBC with differential and a CMP, with TLS monitoring performed only if clinically indicated. Although the risk of CLS is also reduced after cycle 1, CLS laboratory and clinical monitoring should continue during every cycle. Advanced practitioners must carefully monitor labs for any indication that tagraxofusp dose modifications or dose holds are

Parameter	Severity criteria	Action	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	⏸	Hold tagraxofusp and administer 25 g IV albumin (q12h or more frequently as practical).
		▶	Resume when serum albumin is ≥ 3.5 g/dL AND not more than 0.5 g/dL lower than the value measured prior to dosing initiation of the current cycle.
Body weight	Body weight increase ≥ 1.5 kg over pretreatment weight on prior treatment day	⏸	Hold tagraxofusp and administer 25 g IV albumin (q12h or more frequently as practical), and manage fluid status as indicated clinically.
		▶	Resume when body weight increase has resolved (i.e., the increase is no longer ≥ 1.5 kg greater than the previous day's predose weight).
AST or ALT	ALT or AST increase > 5 times the upper limit of normal	⏸	Hold tagraxofusp if ALT or AST increase > 5 times the upper limit of normal.
		▶	Resume tagraxofusp when transaminase elevations are ≤ 2.5 times the upper limit of normal.
Serum creatinine	Serum creatinine > 1.8 mg/dL (159 µmol/L) or creatinine clearance < 60 mL/minute	⏸	Hold tagraxofusp if serum creatinine > 1.8 mg/dL (159 µmol/L) or creatinine clearance < 60 mL/minute.
		▶	Resume tagraxofusp when serum creatinine resolves to ≤ 1.8 mg/dL (159 µmol/L) or creatinine clearance ≥ 60 mL/minute.
Systolic blood pressure	Systolic blood pressure ≥ 160 mmHg or ≤ 80 mmHg	⏸	Hold tagraxofusp if systolic blood pressure ≥ 160 mmHg or ≤ 80 mmHg.
		▶	Resume tagraxofusp when systolic blood pressure is < 160 mmHg or > 80 mmHg.
Heart rate	Heart rate ≥ 130 bpm or ≤ 40 bpm	⏸	Hold tagraxofusp if heart rate ≥ 130 bpm or ≤ 40 bpm.
		▶	Resume tagraxofusp when heart rate is < 130 bpm or > 40 bpm.
Body temperature	Body temperature ≥ 38°C	⏸	Hold tagraxofusp if body temperature ≥ 38°C.
		▶	Resume tagraxofusp when body temperature is < 38°C.
Hypersensitivity reactions	Mild or moderate	⏸	Hold tagraxofusp if patient has a mild or moderate hypersensitivity reaction.
		▶	Resume tagraxofusp at the same infusion rate after resolution of any mild or moderate hypersensitivity reaction.
	Severe or life-threatening	⏹	Discontinue tagraxofusp permanently.

Figure 2. USPI recommendations for tagraxofusp dose modifications during treatment.
AST = aspartate aminotransferase; ALT = alanine aminotransferase; bpm = beats per minute; CLS = capillary leak syndrome; dL = deciliters; g = grams; IV = intravenous; kg = kilogram; µmol = micromoles; mL = milliliters; mmHg = millimeters of mercury; q12h = every 12 hours; USPI = United States package insert.

needed and for signs of CLS, as outlined in Figures 2 and 3, respectively. Labs should be reviewed by the interdisciplinary team, reducing the potential to miss dose holds, modifications, or opportunities for supportive care.

While the labs summarized above are the standard across many institutions, additional labs may be ordered based on patient-specific needs. If a patient begins to exhibit signs or symptoms of CLS, the frequency of lab orders and vital sign monitoring should be increased to closely track serum albumin levels and the patient's overall status (Figure 3).

Observation

The interdisciplinary team should observe patients for signs or symptoms of CLS as well as hypersensitivity reactions. Per the USPI, cycle 1 administration of tagraxofusp includes an observation period of at least 24 hours after the last dose, to allow for close monitoring and management of CLS (Stemline Therapeutics, Inc., 2023). For cycles 2 and beyond, the patient should be observed for a minimum of 4 hours following each infusion (Stemline Therapeutics, Inc., 2023), although some institutions have shortened (e.g., 2 hours) or omit in later cycles for patients tolerating tagraxofusp, at the discretion of the treating physician given tagraxofusp's noncumulative toxicity profile.

Capillary Leak Syndrome Management

Patients must be closely monitored for signs and symptoms of CLS, including hypoalbuminemia, edema, weight gain, shortness of breath (SOB), dizziness, severe hypotension and/or hemodynamic instability. Figure 3 outlines the USPI-supported CLS management algorithm (Stemline Therapeutics, Inc., 2023). Given the potential of weight gain and edema from CLS, some APs recommend strict fluid restriction to 1.5 L/day.

To initiate cycle 1 day 1 (C1D1) treatment with tagraxofusp, the patient must have a serum albumin level ≥ 3.2 g/dL. Following C1D1, if a patient has a serum albumin level < 3.5 g/dL or the albumin level has decreased ≥ 0.5 g/dL from the value measured at the beginning of the current cycle, tagraxofusp should be held, and albumin 25 g IV should be administered every 12 hours. The dose and frequency of albumin may vary based on patient factors and the clinical situation.

If a patient's predose body weight increases by ≥ 1.5 kg compared to the previous day's predose weight, 25 g of albumin should be administered IV every 12 hours along with fluid status management. This may include the use of IV fluids or vasopressors if the patient is hypotensive or diuretics if the patient is normotensive or hypertensive, until body weight increase has resolved. Selection of diuretic and dosing are patient and institution dependent.

If a patient is experiencing edema, hypotension and/or fluid overload, albumin 25 g IV should be administered every 12 hours, or more frequently as practical, until serum albumin is ≥ 3.5 g/dL. Methylprednisolone (or an equivalent) 1 mg/kg/day should be administered along with aggressive fluid status management until resolution of CLS signs/symptoms or as clinically indicated. Fluid management consists of IV fluids and/or vasopressors if the patient is hypotensive, and diuretics if the patient is normotensive or hypertensive, until resolution of CLS.

Tagraxofusp administration may resume in the same cycle if all CLS signs/symptoms have resolved within a 10-day window and IV fluids or vasopressors were not required to treat hemodynamic instability. Tagraxofusp administration may only resume in the next cycle if all CLS signs/symptoms have resolved, and the patient is hemodynamically stable.

Dose Modifications

In the registrational study of 89 first-line and relapsed/refractory BPDCN patients, tagraxofusp was administered at a dose of 12 µg/kg once daily (except three patients who received 7 µg/kg once daily), and dose interruptions were common, occurring in 69% of patients (Pemmaraju et al., 2022). The most common reasons for dose interruptions included weight gain (27%), increased aspartate aminotransferase (19%), increased alanine transaminase (17%), and hypoalbuminemia (16%). Only 7% required dose discontinuation due to adverse events. The median number of doses received during cycle 1 was four (range 1–5). In a post-hoc analysis of the 65 efficacy-evaluable first-line patients who received tagraxofusp 12 µg/kg daily, ORR and CR + CRc were similar for ≤ 3 doses (74%/47%), 4 doses (75%/69%), or 5 doses (77%/57%), respectively, highlighting the

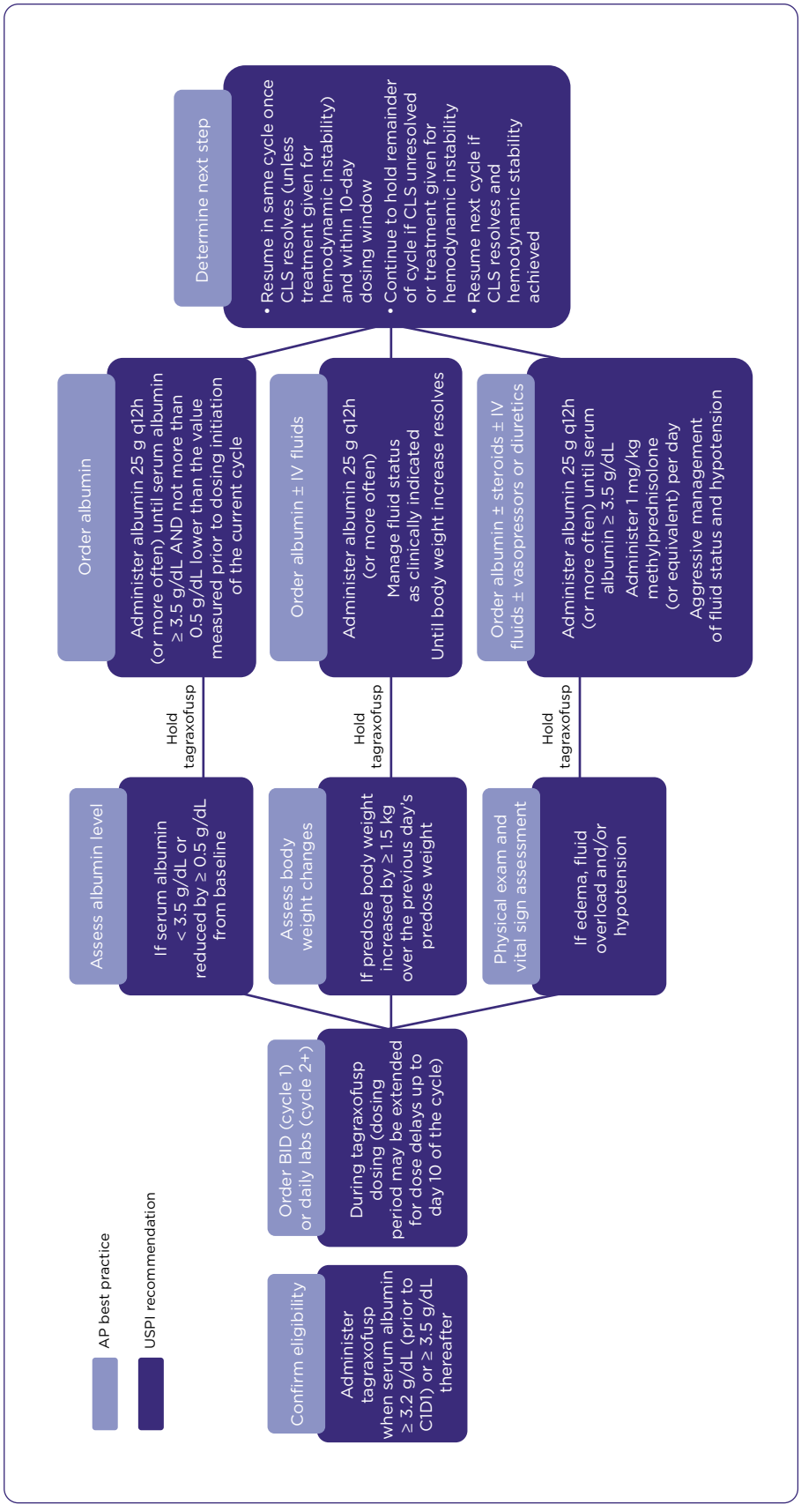

Figure 3. Tagraxofusp-induced CLS management: USPI and AP best practices. AP = advanced practitioners; BID = twice daily; C1D1 = cycle 1 day 1; CLS = capillary leak syndrome; dL = deciliter; g = grams; h = hours; IV = intravenous; kg = kilogram; mg = milligram; q12h = every 12 hours; USPI = United States package insert.

benefit of tagraxofusp despite dose interruptions (Pemmaraju et al., 2022).

Criteria for tagraxofusp dose modifications and holds are outlined in the USPI and include parameters for CLS, liver function, kidney function, vital signs, and hypersensitivity reactions (Stemline Therapeutics, Inc., 2023). No drug-drug interaction studies have been conducted, and no interactions have been observed to date in clinical studies to warrant tagraxofusp dose modifications. Of note, tagraxofusp should be held until AE resolution rather than dose adjustment. Figure 2 defines the USPI dose modification recommendations.

TRANSITION OF CARE

Per the USPI, cycle 2 and subsequent cycles of tagraxofusp can be administered at a suitable outpatient ambulatory care setting equipped with appropriate monitoring for patients with hematologic malignancies undergoing treatment (Figure 4). If the patient experiences complications in cycle 1, and the interdisciplinary team determines the patient is not a good candidate for outpatient administration, the patient can remain under inpatient care until they are deemed appropriate for transition to outpatient care.

Transition to Outpatient Facility

To ensure continuity of care during patient transitions from inpatient to outpatient treatment, AP best practices include treatment plan dissemination to the outpatient care team. The treatment plans are often developed by the internal pharmacy team and contain specific details regarding supportive care, prophylaxis, dosing, and administration. A detailed summary of the patient's care and tolerability of the cycle(s) given inpatient should be relayed to the outpatient facility's care team utilizing transition-of-care notes in the EMR or discharge summary. The summary should also include communication of any AEs or side effects experienced as well as supportive care administered for resolution.

Patients and caregivers should understand all aspects of tagraxofusp treatment, including signs and symptoms of CLS, and be provided written instructions along with contact numbers, upcoming appointments, and steps to take if a side effect occurs. Scheduling orders should block a 6-hour timeframe to account for the USPI recommended observation period of 4 hours. The appointment length can be altered if the total observation time is shortened based on clinical judgement.

Transition to Shared-Care Facility

Additional processes following a shared-care approach should be considered for patients who transfer to an outside outpatient facility. This approach may be relevant for patients receiving treatment at an institution distant from their local hematologist/oncologist or for those transitioning between institutions that are not part of the same care network. In these situations, APs should evaluate the opportunity to transition care to a local setting, given that AEs most commonly occur in cycle 1, typically do not recur, and are not cumulative.

In a shared-care model, the inpatient physician or AP overseeing cycle 1 should contact the physician or AP at the receiving institution to assess the feasibility of administering tagraxofusp at their facility. Feasibility items to consider include accessibility of appropriate administration equipment (i.e., syringe pump, Y-connector, microbore tubing, 0.2 micron polyethersulfone in-line filter), capability to administer albumin, feasibility of obtaining daily labs during infusions with a quick turnaround time, ability to order, ability to store (–25°C to –15°C) and prepare tagraxofusp, ability to build tagraxofusp into the EMR, availability of a treatment plan, and availability of resources to educate staff and patients on administration. Once feasibility is confirmed, communication can proceed as previously outlined in the transition of care to an outpatient facility model. This model may be particularly effective for patients who are not transplant eligible and will remain on tagraxofusp until progression or toxicity.

DISCUSSION

The therapeutic goal for patients with BPDCN is to achieve a deep and durable response, after which eligible patients can proceed to SCT. Intensive multiagent chemotherapy (IC) geared toward acute myeloid leukemia, acute lymphoblastic leukemia, and non-Hodgkin lymphoma are historically difficult to administer due to associated toxicities and early death; remissions are short-lived, as most patients relapse within one year. Moreover,

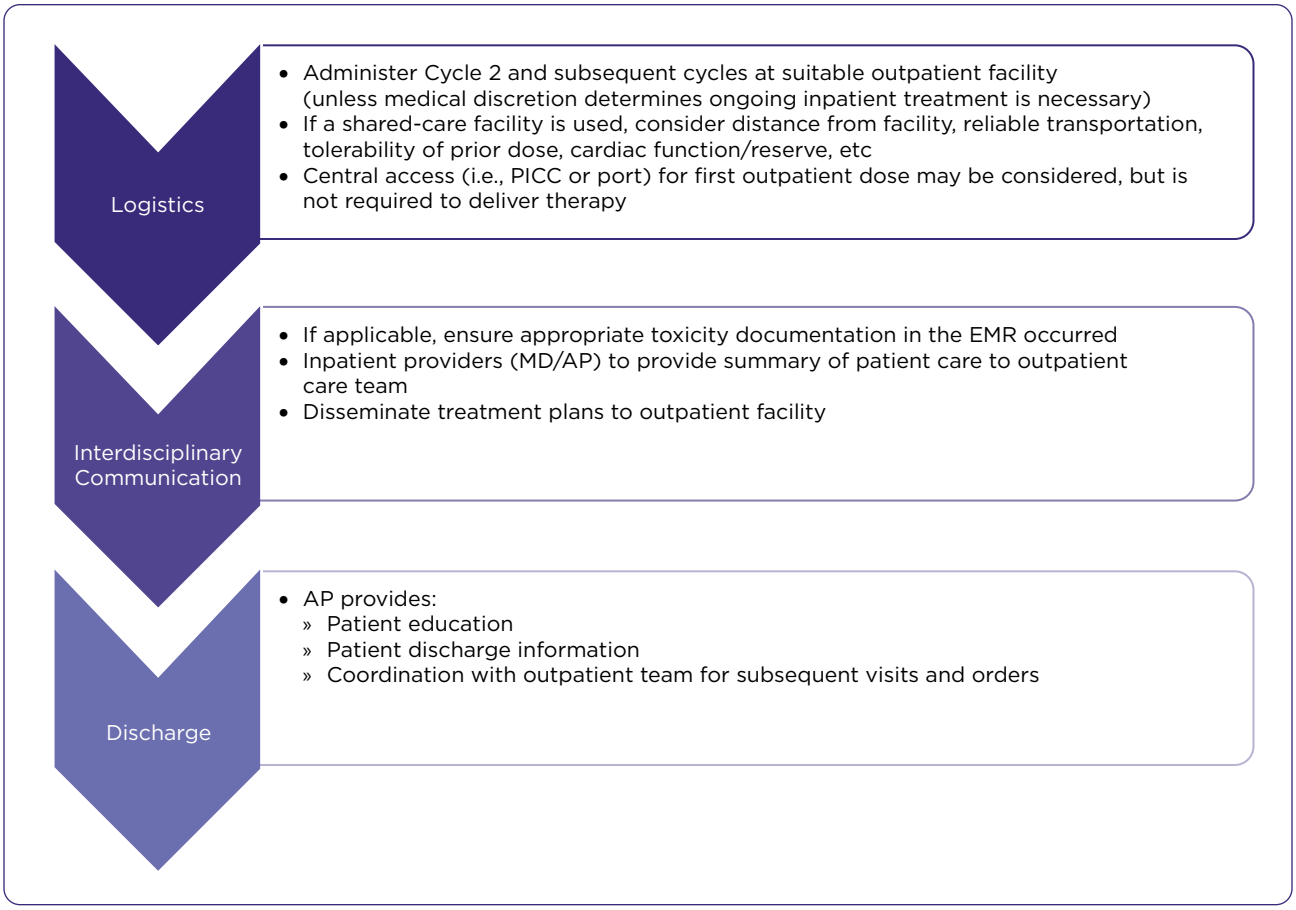

Figure 4. AP best practices for tagraxofusp patient transition of care. AP = advanced practitioner; EMR = electronic medical records; MD = physician; PICC = peripherally inserted central catheter.

IC studies were retrospective without prespecified or multisystem response criteria/endpoints (Pemmaraju et al., 2024a, 2024b). Tagraxofusp offers an opportunity for patients to attain a rapid and durable response, without prolonged myelotoxicity associated with IC, to enable bridging to SCT in eligible patients. In the pivotal trial, 51% of complete responders (19 CR + CRc patients) were bridged to SCT after receiving a median of four cycles of tagraxofusp (Pemmaraju et al., 2022).

The prospective pivotal clinical study confirmed that patients can achieve fast and durable responses, including the opportunity for eligible patients to bridge to SCT following tagraxofusp. Subsequently, results of a retrospective review of patients participating in a European (EU) named patient program of tagraxofusp for BPDCN demonstrated that first-line treatment with tagraxofusp was associated with fast and durable responses and improved OS (Angelucci et al., 2023). The reported ORR was 89% (including a CR of 67%), with a median duration of response (DOR) of 8.9 months (Angelucci et al., 2023). The median OS of 20 months surpassed historical data of 8 to 14 months OS with chemotherapy regimens in BPDCN (Pagano et al., 2013; Martín-Martín et al., 2015). Responses were also seen in the relapsed/refractory population receiving tagraxofusp, including prolonged survival in a population with a generally poor prognosis and limited efficacy with historical standard treatment regimens (Herling et al., 2024). The ORR was 67% (including a CR of 40%), with a median DOR and OS of 5.0 months and 8.6 months, respectively (Herling et al., 2024). Of fifteen patients, 40% bridged to SCT, which further yields support for using tagraxofusp in relapsed/refractory BPDCN (Herling et al., 2024). It is important to emphasize that myelosuppression

and nonhematologic toxicities with tagraxofusp in both populations were not cumulative.

The approval of tagraxofusp in BPDCN patients 2 years and older has changed the treatment landscape within this aggressive, orphan hematologic malignancy. Ongoing clinical research continues to explore newer/novel agents for BPDCN, including venetoclax (NCT03485547), anti-CD123 CAR-NK (NCT06690827), IMGN632 (NCT03386513), and SAR443579 (NCT05086315). In addition, ongoing trials are evaluating tagraxofusp in combination regimens, including with azacitidine/venetoclax (NCT03113643) and with venetoclax and chemotherapy (NCT04216524).

At this time, with tagraxofusp as the only approved agent, effectively administering tagraxofusp and adapting AP best practices will allow for the best overall outcomes for these patients. High importance is placed on interdisciplinary patient-focused care led by APs in care coordination and execution. Interdisciplinary care is particularly important in cycle 1, when treatment is administered inpatient and the majority of adverse events occur, in order to provide patients the best chance for safe and effective administration of tagraxofusp. It is critical that the entire interdisciplinary team undergo training on CLS identification and appropriate management before initiating tagraxofusp treatment. Institutions should utilize tagraxofusp orders with clear CLS management protocols to streamline treatment strategies. With proper selection, monitoring, and directed intervention, CLS is manageable, often limited to the first cycle, and does not recur (Angelucci et al., 2023; Herling et al., 2024). Patient and caregiver education is also critically important and should be written in plain language. Generating or accessing education pamphlets or tools help maintain consistency in education delivery. Defining order release criteria is essential in creating a process to confirm all predose assessments have been completed, and that the patient is able to receive treatment that day.

As clinical teams become more familiar with and comfortable with tagraxofusp administration, APs are anticipated to gain more experience with a shared-care model of transitioning patients to outpatient facilities outside of their institution's network. The shared-care model allows patients to receive tagraxofusp at a local institution during cycle 2 and beyond when the risk of AEs becomes much lower. This model has the potential to allow for improved compliance and maintenance of the tagraxofusp dosing schedule.

Advanced practitioners play a pivotal role in ensuring safe and effective administration of tagraxofusp to patients with BPDCN, including comprehensive education, administration, monitoring, and AE management. A core, specialized interdisciplinary team coupled with AP-led management optimizes tagraxofusp treatment and continuity of care. We propose APs utilize a USPI-based management algorithm coupled with institutional best practices to support and optimize patients being treated with tagraxofusp for BPDCN. Care optimization and best practices should continuously be refined based on emerging data and clinical experience.

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Appendix A. Tagraxofusp Treatment Checklist for Advanced Providers

Infusion days 1–5: required patient observation (check applicable cycle)

☐ Cycle 1: From C1D1 until 24 hours after the completion of C1D5

☐ Cycles 2 and beyond: 4 hours after each dose

Labs (days 1–5 prior to infusion)

☐ CBC with differential

☐ CMP (serum creatinine, creatinine clearance, albumin, liver function)

Premedications (administer approximately 60 minutes prior to tagraxofusp infusion; check all medications ordered)

☐ Acetaminophen 650 mg by mouth (or paracetamol IV)

☐ H1-histamine antagonist (e.g. diphenhydramine 50 mg IV or equivalent)

☐ H2-histamine antagonist (e.g. famotidine 20 mg IV or equivalent)

☐ Corticosteroid (e.g. methylprednisolone 50 mg IV or equivalent)

Monitoring parameters for potential dose modifications

If yes is checked for any item below, stop and refer to USPI table 1 and table 2 for guidance; if no, proceed

No	Yes	
☐	☐	HR ≥ 130 bpm or ≤ 40 bpm
☐	☐	SBP ≥ 160 mmHg or ≤ 80 mmHg
☐	☐	Albumin < 3.5 g/dL or reduced by ≥ 0.5 g/dL from day 1 of current cycle
☐	☐	Weight increased by ≥ 1.5 kg over previous day's pre-dose weight
☐	☐	Temperature ≥ 38°C
☐	☐	ALT or AST increase > 5 times the upper limit of normal
☐	☐	Serum creatinine > 1.8 mg/dL or creatinine clearance ≤60 mL/minute

Physical/Laboratory Exam

Capillary leak syndrome (these symptoms can quickly become life-threatening)

If yes is checked for any item below, stop and refer to USPI table 2 for guidance; if no, proceed

No	Yes	
☐	☐	Hypoalbuminemia
☐	☐	Severe hypotension, dizziness, headaches, fatigue
☐	☐	Shortness of breath, dyspnea, cough
☐	☐	Rapid weight gain, edema (face, arms, hands, legs, or feet)

Orders/Follow-Up

☐ Enter treatment orders and develop plan for next cycle

☐ Labs and clearance visit in clinic prior to next cycle

Note. bpm = beats per minute; C = cycle; CLS = capillary leak syndrome; D = day, dL = deciliter; g = gram, IV = intravenous; kg = kilogram; mg = milligram; mL = milliliter; mmHg = millimeters of mercury; q12h = every 12 hours; USPI = United State package insert.