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NCCN Clinical Practice Guidelines in Oncology
(NCCN Guidelines®)

Acute Myeloid Leukemia

Overall management of Acute Myeloid Leukemia is described in the full NCCN Guidelines® for Acute Myeloid Leukemia. Visit NCCN.org to view the complete library of NCCN Guidelines.

NCCN National Comprehensive Cancer Network®

INTRODUCTION

Decisions about diagnosis and management for BPDCN should involve multidisciplinary consultation at a high-volume center with use of appropriate interventions. Consider referral to an academic institution.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Blastic Plasmacytoid Dendritic Cell Neoplasm (Age ≥18 years)

EVALUATION/WORKUP FOR BPDCN[a,b]

- H&P
- CBC, platelets, differential, comprehensive metabolic panel
- Analysis of skin lesions (collaboration with dermatology is recommended),[c] peripheral blasts, BM aspirate/biopsy, and lymph node biopsy including:
  - Dendritic cell morphology assessment
  - Immunohistochemistry
  - Flow cytometry
  - Cytogenetic analysis (karyotype and/or FISH)
  - Molecular analysis (most common abberations include: *ASXL1*, *IDH1–2*, *IKZF1–3*, *NPM1*, *NRAS*, *TET1–2*, *TP53*, *U2AF1*, *ZEB2*)[d]
- PET/CT scan for other sites, if clinical suspicion for extramedullary disease and/or lymphadenopathy
- LP to rule out CNS disease; follow with IT prophylaxis[e] if clinically indicated

→

DIAGNOSIS[d]

BPDCN diagnosis requires at least 4 of 6 BPDCN antigens:
- CD123
- CD4
- CD56
- TCL-1
- CD2AP
- CD303/BDCA-2

without myeloid,[f] T or B lineage expression markers

→ BPDCN confirmed → See Treatment Induction (BPDCN-2)

[a] See Principles of BPDCN (BPDCN-A).
[b] Facchetti F, Petrella T, Pileri SA. Blastic plasmacytoid dendritic cell neoplasm. In: Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. IARC Press: Lyon 2017:173-177.
[c] Pemmaraju N, et al. N Engl J Med 2019;380:1628-1637. Close collaboration with dermatology is recommended. For guidance on classification and measurement of skin lesions, see page MFSS-3 in the NCCN Guidelines for Primary Cutaneous Lymphomas.
[d] Menezes J, et al. Leukemia 2014;28:823-829.
[e] Sullivan JM, Rizzieri DA. Hematology Am Soc Hematol Educ Program 2016;2016:16-23.
[f] Myeloid markers include MPO, lysozyme, CD14, CD34, CD116, and CD163.

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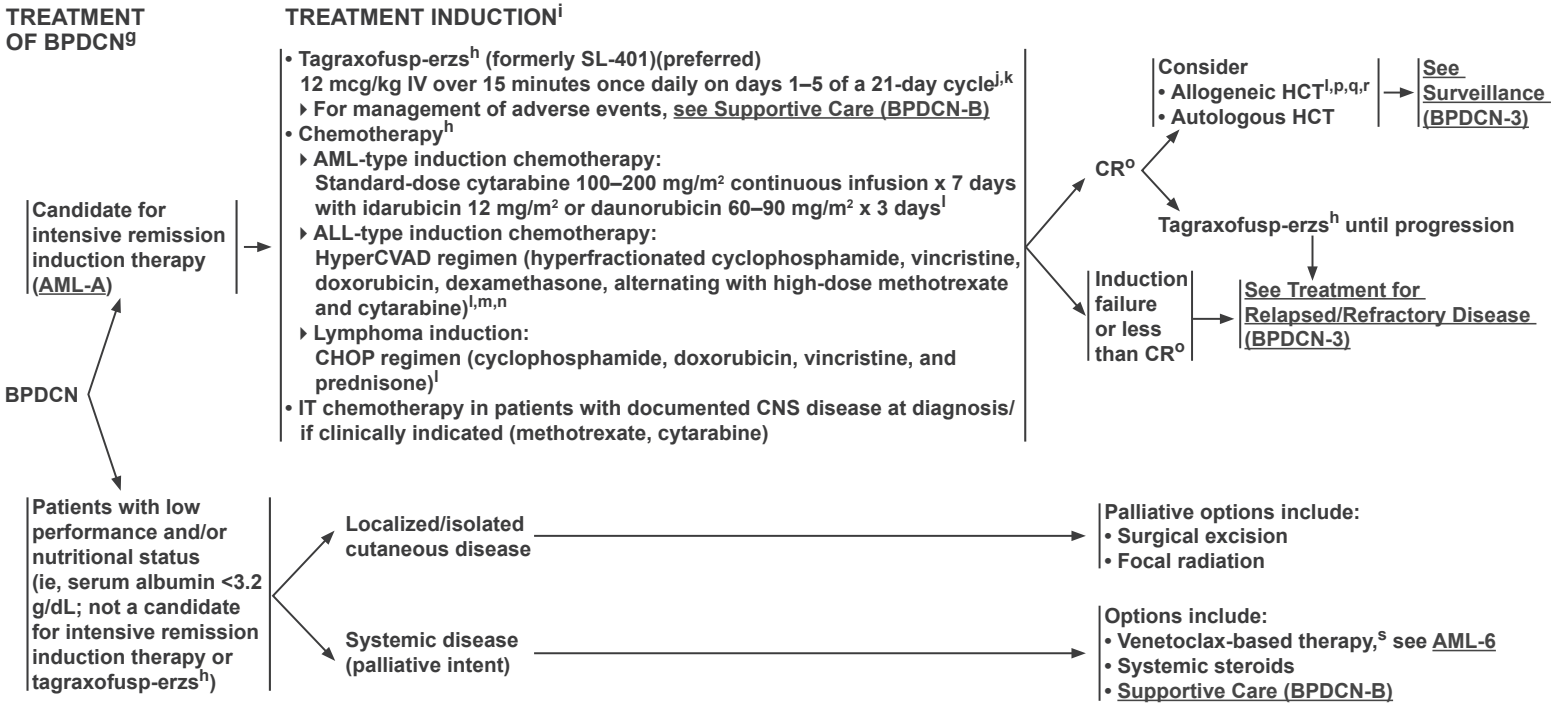
Blastic Plasmacytoid Dendritic Cell Neoplasm (Age ≥18 years)



[g] See Principles of Supportive Care for BPDCN (BPDCN-B).
[h] Consider CNS prophylaxis for patients with overt systemic disease.
[i] Pemmaraju N, et al. Blood 2019;134(Supplement_1):2723.
[j] Frankel AE, et al. Blood 2014;124:385-392.
[k] Pemmaraju N, et al. N Engl J Med 2019;380:1628-1637.
[l] Pagano L, et al. Haematologica 2013;98:239-246.
[m] Reimer P, et al. Bone Marrow Transplant 2003;32:637-646.
[n] Deotare U, et al. Am J Hematol 2016;91:283-286.

[o] CR in BPDCN has the same hematologic criteria as AML (See AML-E), but it is also important to document resolution of any extramedullary sites including CNS and skin lesions. If the skin still shows microscopic disease (CRc), consider continuing additional cycles (at least 4) of therapy before managing as relapsed/refractory disease. For appropriate studies to assess CR, see Pemmaraju N, et al. N Engl J Med 2019;380:1628-1637.
[p] Kharfan-Dabaja MA, et al. Br J Haematol 2017;179:781-789.
[q] Roos-Weil D, et al. Blood 2013;121:440-446.
[r] Aoki T, et al. Blood 2015;125:3559-3562.
[s] DiNardo CD, et al. Am J Hematol 2018;93:401-407.

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Blastic Plasmacytoid Dendritic Cell Neoplasm (Age ≥18 years)

SURVEILLANCE

- CBC, platelets every 1–3 mo for 2 y, then every 3–6 mo up to 5 y
- BM aspirate and biopsy only if peripheral smear is abnormal or cytopenias develop
- Repeat PET/CT scan for patients with prior evidence of extramedullary disease
- Consider re-biopsy for any suspicious skin or extramedullary lesions

→ Relapsed/ refractory BPDCN →

TREATMENT FOR RELAPSED/REFRACTORY DISEASE

- Evaluate CNS for disease/prophylaxis[t]
- Consider
  - Clinical trial (preferred)
  - Tagraxofusp-erzs[h,k] (preferred, if not already used)
    For management of adverse events, see Supportive Care (BPDCN-B)
  - Chemotherapy (if not already used), see Treatment Induction (BPDCN-2)
  - Local radiation to isolated lesions/areas
  - Systemic steroids
  - Venetoclax-based therapy,[s,u,v] see AML-6
- Donor search should be initiated at first relapse in appropriate patients concomitant with institution of other therapy if no sibling donor has been identified

[h] Consider CNS prophylaxis for patients with overt systemic disease.
[k] Pemmaraju N, et al. N Engl J Med 2019;380:1628-1637.
[s] DiNardo CD, et al. Am J Hematol 2018;93:401-407.
[t] Martin-Martin L, et al. Oncotarget 2016;7:10174-10181.
[u] Montero J, et al. Cancer Discovery 2017;7:156-164.
[v] Rausch CR, et al. Blood 2017;130:1356.

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Blastic Plasmacytoid Dendritic Cell Neoplasm (Age ≥18 years)

PRINCIPLES OF BPDCN

General Principles:

- **BPDCN is a disorder of immature dendritic cells that regulate effector T-cell function.**
- **It constitutes only 0.44% of hematologic malignancies and <1% of acute leukemia presentations.[1]**
- **It occurs in all races and geographic areas.**
- **It is more common in adults (median age, 65–67 years) with an approximate male-to-female ratio of 3:1.**
- **It most commonly presents as asymptomatic skin lesions,[2] cytopenias, circulating peripheral blasts (leukemic phase), lymphadenopathy, and CNS manifestations.**
- **Prognosis for BPDCN is poor and the median overall survival (OS) is approximately 8–12 months when patients are treated with chemotherapy.[3,4]**
- **Studies suggest that being in first remission (CR1) during receipt of allogeneic HCT significantly enhances the median OS.[4-6] Reduced-intensity conditioning may be considered in patients who achieve CR but cannot tolerate myeloablative transplantation.[7]**
- **For fit patients, current treatment options for BPDCN include tagraxofusp-erzs and chemotherapy, whereas those with low albumin and/or comorbidities should receive localized therapy or supportive care as shown in the algorithm (see BPDCN-2).**
  - **Hypoalbuminemia and capillary leak syndrome are known, potentially serious adverse events associated with tagraxofusp-erzs treatment,[8] and must be monitored closely during therapy (see Principles of Supportive Care for BPDCN [BPDCN-B]).**

[1] Bueno C, Almeida J, Lucio P, et al. Incidence and characteristics of CD4(+)/HLA DRhi dendritic cell malignancies. Haematologica 2004;89:58-69.
[2] Pemmaraju N, Lane AA, Sweet KL, et al. Tagraxofusp in blastic plasmacytoid dendritic-cell neoplasm. N Engl J Med 2019;380:1628-1637. Close collaboration with dermatology is recommended. For guidance on classification and measurement of skin lesions, see page MFSS-3 in the NCCN Guidelines for Primary Cutaneous Lymphomas.
[3] Dalle S, Beylot-Barry M, Bagot M, et al. Blastic plasmacytoid dendritic cell neoplasm: is transplantation the treatment of choice? Br J Dermatol 2010;162:74-79.
[4] Pagano L, Valentini CG, Pulsoni A, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. Haematologica 2013;98:239-246.
[5] Deotare U, Yee KW, Le LW, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: 10-Color flow cytometry diagnosis and HyperCVAD therapy. Am J Hematol 2016;91:283-286.
[6] 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;121:440-446.
[7] Pagano L, Valentini CG, Grammatico S, Pulsoni A. Blastic plasmacytoid dendritic cell neoplasm: diagnostic criteria and therapeutical approaches. Br J Haematol 2016;174:188-202.
[8] 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;124:385-392.

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Blastic Plasmacytoid Dendritic Cell Neoplasm (Age ≥18 years)

PRINCIPLES OF SUPPORTIVE CARE FOR BPDCN

Administration/Management of Toxicities Associated with Tagraxofusp-erzs[1]

- Patients must have a baseline serum albumin of 3.2 g/dL or higher to be able to start tagraxofusp-erzs.
  - Replace serum albumin if <3.5 g/dL or if there is a reduction of ≥0.5 from baseline.
- Capillary leak syndrome (life-threatening/fatal) can occur in patients receiving this drug.
- The first cycle of this drug should be administered in the inpatient setting. Closely monitor toxicity during and after drug administration. It is recommended that patients remain in the hospital for at least 24 hours after completion of the first cycle.
  - Premedicate with an H1-histamine antagonist, acetaminophen, corticosteroid, and H2-histamine antagonist prior to each infusion.
  - Administer tagraxofusp-erzs at 12 mcg/kg IV over 15 minutes once daily on days 1–5 of a 21-day cycle. Alternately, 5 doses can be administered over a 10-day period, if needed for dose delays.
- Prior to each dose of drug: Check vital signs, albumin, transaminases, and creatinine.
- Collaboration with a dermatologist for supportive care is essential.

Hold Tagraxofusp-erzs Dosing for the Following Reasons:

- Serum albumin <3.5 g/dL or a reduction from baseline of ≥0.5
- Body weight ≥1.5 kg over prior day
- Edema, fluid overload, and/or hypotension
- Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increase >5 times the upper limit of normal
- Serum creatinine >1.8 or creatinine clearance (CrCl) ≤ 60 mL/min
- Systolic blood pressure (SBP) ≥160 or ≤80 mmHg
- Heart rate (HR) ≥130 bpm or ≤40 bpm
- Temperature ≥38°C
- Mild to severe hypersensitivity reaction

[1] For full details on administration and toxicity management, see: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761116s000lbl.pdf

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

INDICATION

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

IMPORTANT SAFETY INFORMATION

Boxed WARNING: CAPILLARY LEAK SYNDROME

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

WARNINGS AND PRECAUTIONS

Capillary Leak Syndrome

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

Hypersensitivity Reactions

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

Hepatotoxicity

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

ADVERSE REACTIONS:

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

Please see accompanying full Prescribing Information, including Boxed WARNING.

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

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