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NCCN Guidelines Panel: Acute Myeloid Leukemia

On behalf of Stemline Therapeutics Inc, I respectfully request the NCCN Acute Myeloid Leukemia (AML) Guideline Panel to review the enclosed data for inclusion of the rare disease, blastic plasmacytoid dendritic cell neoplasm (BPDCN), in the AML guidelines.

Specific Changes: Include a BPDCN algorithm as an AML related neoplasm in the NCCN AML guidelines.

Rationale: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, highly aggressive hematologic malignancy that most commonly involves the bone marrow and skin; lymph nodes and viscera may also be involved.[1] The median overall survival from diagnosis is approximately 8-14 months.[1,2,3] There are currently no drugs approved for BPDCN and no accepted, effective treatment paradigm. A recent review has recommended clinical trials for BPDCN patients in either the first-line or relapsed/refractory settings.[1]

Prior to 2008, this condition had previous names including blastic NK cell leukemia/lymphoma and agranular CD4+/CD56+ hematodermic neoplasm. In 2008, the World Health Organization (WHO) coined the term "BPDCN" for this condition due to the realization that its cell of origin was a precursor of the plasmacytoid dendritic cell (pDC). The 2008 WHO classification formalized the diagnostic criteria for BPDCN to include CD123, CD4, CD56, TCL-1, and other pDC markers. At this time, BPDCN was grouped with AML-related precursor neoplasms in the WHO classification.[4] In 2016, WHO published a revised classification where BPDCN was listed as a separate myeloid neoplasm.[5]

Typical clinical features of BPDCN observe cutaneous involvement in more than 80% of patients at diagnosis, with simultaneous or subsequent bone marrow involvement. Skin lesions can be of various size, shape, and color. They can become scaly over time. They are usually nonpruritic, with solitary or multiple nodules, plaques, or bruise-like infiltrations. Despite the appearance of a somewhat indolent clinical presentation at the outset in patients with skin-only disease, the course of BPDCN is highly aggressive.[1,6] The disease almost always results in a terminal leukemic phase with leading to decreased blood cell counts with resultant infections, bleeding, and invariably death.

The following articles are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

1. Riaz W, Zhang L, Horna P, Sokol L. Blastic plasmacytoid dendritic cell neoplasm: update on molecular biology, diagnosis, and therapy. *Cancer Control.* 2014;21(4):279-289.

2. Pagano L, Valentini CG, Pulsoni A, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. *Haematologica.*2013;98:239-246.

3. Pemmaraju N. Novel pathways and potential therapeutic strategies for blastic plasmacytoid dendritic cell neoplasm (BPDCN): CD123 and beyond [published online ahead of print October 24, 2017]. *Curr Hematol Malig Rep.* doi:10.1007/s11899-017-0425-7.

4. Facchetti F, Jones DM, Petrella T. Blastic plasmacytoid dendritic cell neoplasm. In: WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues, Swerdlow SH, Campo E, Harris NL, et al. (Eds), IARC, Lyon 2008. p.145.

5. 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.

6. Laribi K, et al. Blastic Plasmacytoid Dendritic Cell Neoplasm: From Origin of the Cell to Targeted Therapies. *Biol Blood Marrow Transplant*, 2016; 22:1357–1367.

Sincerely,

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