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NCCN Guidelines Panel: Acute Myeloid Leukemia (AML)

Dear NCCN Acute Myeloid Leukemia Guidelines Panel:

On behalf of Stemline Therapeutics, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Acute Myeloid Leukemia (AML) panel to review the enclosed data relating to the treatment of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) with ELZONRIS™ (tagraxofusp) for your consideration.

Specific Changes: Request for NCCN Guidelines Panel to review data for a specific indication.

- Request inclusion of ELZONRIS (tagraxofusp) for the treatment of patients with first-line and relapsed/refractory blastic plasmacytoid dendritic cell neoplasm (BPDCN).

FDA Clearance:

- Tagraxofusp, a novel biologic targeted therapy directed to the interleukin-3 receptor (IL-3R/CD123), was granted Priority Review status, and has a PDUFA action date of February 21, 2019. If approved, tagraxofusp would be marketed under the brand name ELZONRIS and indicated for the treatment of patients with BPDCN.

Rationale:

1. BPDCN is a highly aggressive hematologic malignancy with cutaneous manifestations, derived from the plasmacytoid dendritic cell (pDC), which expresses high levels (>95%) of CD123. Patients with BPDCN have diverse clinical features with similarity to other hematologic malignancies which has contributed to misdiagnosis. BPDCN carries a poor prognosis with a median survival of approximately 8 to 14 months from diagnosis. There is currently no standard of care established or effective treatment regimen for BPDCN in either first-line or relapsed/refractory settings; thus, BPDCN represents an area of unmet medical need.[1]

2. The FDA is currently evaluating the results from Study 401-0114 (NCT02113982; Study 0114) as the basis for approval of ELZONRIS. If approved, ELZONRIS would represent the first approved treatment for patients with BPDCN.

Background:

- ELZONRIS is a CD123-directed therapeutic comprised of a recombinant human interleukin-3 (IL-3) and truncated diphtheria toxin (DT) fusion protein that inhibits protein synthesis and induces apoptosis (cell death) in cells expressing the interleukin-3 receptor (IL-3R/CD123).[2]

Study Details and Safety Information:

- The efficacy and safety of ELZONRIS was evaluated in a nonrandomized, open-label, single-arm, multicenter study of seven centers across the US.[1] The trial consisted of 3 stages: Stage 1 (lead-in, dose escalation), Stage 2 (expansion), and Stage 3 (pivotal, confirmatory). A total of 29 treatment-naïve patients and 13 previously-treated patients with BPDCN were treated in

Study 401-0114. This is the largest prospectively designed study in patients with BPDCN.[1]

- The recommended dose of ELZONRIS is 12 µg/kg administered as a daily 15-minute intravenous infusion for five consecutive days of a 21-day cycle. The first cycle of ELZONRIS was administered in an inpatient setting with subsequent cycles administered in an inpatient or an appropriate outpatient setting.[1]

- The primary evidence of efficacy was determined by the rate of complete response (CR) plus clinical complete response (CRc), with CRc defined as complete response with minimal residual skin abnormality not indicative of active disease.[1]

- Among 29 treatment-naive patients treated with 12 µg/kg/day across all stages, the CR + CRc rate was 72% (95% CI: 52.8, 87.3). The overall response rate was 90%. Thirteen [13/29 (45%)] of these patients [median age 65 years (range 28-72)] were successfully bridged to stem cell transplantation after achieving remission with ELZRONRIS. At the data cut-off date, the median overall survival from study entry has not yet been reached among treatment-naive patients with median follow-up 23.0 (range 0.2-41+ months).[1]

- Among 13 patients with previously-treated disease the overall response rate was 69% (9/13) (95% CI: 38.0, 91.0). One previously-treated patient was bridged to allogeneic stem cell transplantation.[1]

- The most common treatment-related adverse events (>15% by preferred term) across clinical trials at 12 µg/kg/day (n=148) included increased alanine aminotransferase levels (44%), increased aspartate aminotransferase levels (44%), and hypoalbuminemia (44%). Capillary leak syndrome had an all grade incidence of 17%; Grade 1-2 for 16 patients (11%), Grade 3 for 5 patients (3%), Grade 4 for 3 patient (2%) and Grade 5 for 1 patient (0.7%). Safety measures have been implemented that may identify symptoms early and reduce adverse outcomes.[1]

A copy of the approved ELZONRIS prescribing information including the complete safety information and references will be submitted in support of this proposed change. The data were recently presented by Dr. Naveen Pemmaraju at the 60th American Society of Hematology (ASH) 2018 Annual Meeting. The data have also been submitted for publication. The manuscript is currently under review and will be submitted to NCCN upon publication.

We appreciate the opportunity to provide this information for consideration by the NCCN AML Panel. If you have any questions or need additional information, please do not hesitate to contact me at 1-646-502-1389 or via e-mail at dsieminski@stemline.com.

Thank you for your time and consideration.

Sincerely,

Debra Sieminski, MS, PA-C
Medical Affairs

Reference(s):

1. Pemmaraju N. Results of Pivotal Phase 2 Trial of Tagraxofusp (SL-401) in Patients with Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN). 60th American Society of Hematology (ASH) Annual Congress; December 1-4, 2018; San Diego, CA. Oral Presentation, S765.
2. Frankel, A. E., et al. (2014). Activity of SL-401, a targeted therapy directed to interleukin-3 receptor, in blastic plasmacytoid dendritic cell neoplasm patients. Blood 124(3): 385-392.
3. Sun, W. First pediatric experience of SL-401, a CD123-targeted therapy, in patients with blastic plasmacytoid dendritic cell neoplasm: report of three cases. J Hematol Oncol. 2018 May 2;11(1):61. doi: 10.1186/s13045-018-0604-6