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Date of request: September 25, 2018
NCCN Guidelines Panel: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

On behalf of Verastem, Inc. (Verastem), I respectfully request the NCCN CLL/SLL Guideline Panel to consider the enclosed data for duvelisib for the treatment of patients with relapsed/refractory CLL/SLL (R/R CLL/SLL).

Specific Changes: Please consider the following:

- **CSLL-D 2 of 5: CLL/SLL without del(17p)/TP53 mutation**
  - Add duvelisib as a preferred regimen under “Relapsed/Refractory Therapy, Frail patient with significant comorbidity or age ≥65 y and younger patients with significant comorbidities” and “Age <65 y without significant comorbidities”

- **CSLL-D 3 of 5: CLL/SLL with del(17p)/TP53 mutation**
  - Add duvelisib as a preferred regimen under “Relapsed/Refractory”

FDA Clearance: On September 24, 2018, the FDA approved duvelisib for the treatment of adult patients with:

- Relapsed or refractory CLL or SLL after at least two prior therapies
- Relapsed or refractory follicular lymphoma after at least two prior systemic therapies

Rationale:

Duvelisib, an oral dual inhibitor of PI3K-δ (delta) and PI3K-γ (gamma), demonstrates efficacy as a monotherapy in patients with R/R CLL/SLL with or without del(17p)/TP53 mutations who had received at least one previous therapy, as demonstrated by significant median progression-free survival (mPFS) and overall response rate (ORR) improvement.

Supporting Literature: Flinn et al. reported results of the Phase 3, global, multicenter, randomized, open-label DUO™ study of duvelisib in patients with R/R CLL/SLL, including del(17p)/TP53 mutations (1, 2). The primary endpoint of the study was PFS. Secondary endpoints included ORR, and overall survival (OS). Patients that had progressed after at least one previous CLL/SLL therapy were randomized 1:1 to take either duvelisib (n=160) or ofatumumab (n=159) between January 21, 2014 and December 9, 2015. With a median follow-up of 22.4 months, median PFS per blinded Independent Review Committee (IRC) was significantly longer in patients taking duvelisib (13.3 months) versus ofatumumab (9.9 months) (HR 0.52; p=0.0001). Median PFS in patients with del(17p) per IRC was 12.7 months in patients taking duvelisib compared to 9.0 months in the ofatumumab arm (HR 0.40; p=0.0002). ORR per IRC was also significantly higher at 73.8% in the duvelisib arm compared to 45.3% for those taking ofatumumab
Lymph node response rate per IRC was significantly greater in duvelisib-treated patients (85.0%) compared to ofatumumab-treated patients (15.7%; p<0.0001). OS was not reached in both duvelisib and ofatumumab arms. Adverse events were considered manageable. Most common ≥ Grade 3 adverse events in the duvelisib arm were neutropenia (30%), diarrhea (15%), pneumonia (14%), anemia (13%), and colitis (12%).

In patients who received at least 2 prior lines of therapy, per IRC, the ORR was 78% vs 39% in patients receiving duvelisib and ofatumumab, respectively. In this heavily pretreated subgroup, the mPFS by IRC was 16.4 months in patients receiving duvelisib, compared to 9.1 months in patients receiving ofatumumab (HR=0.4).

Patients with radiographically confirmed progressive disease from the Phase III DUO™ study were allowed to crossover and receive opposite therapy in a crossover extension study (3, 4). Patients that progressed on ofatumumab and rolled over to receive duvelisib (n=89) demonstrated an ORR of 73% (5% CRi [Complete Response/Remission with incomplete marrow recovery]; 68% PR [Partial Response/Remission]) and a median PFS of 15 months. The safety profile of duvelisib was considered manageable and consistent with what was observed in the phase 3 DUO™ study described above.

In summary, duvelisib demonstrated a favorable risk/benefit profile, with a manageable adverse event profile and significant clinical activity in a difficult to treat R/R CLL/SLL patient population, including in patients with del(17p)/TP53 mutations.

The following key study publications are submitted, including the FDA prescribing information.

1. Flinn et al. Results from the Phase 3 DUO™ Trial: A Randomized Comparison of Duvelisib Vs Ofatumumab in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. American Society of Hematology Annual Meeting and Exposition; Oral Presentation, December 2017; Blood 2017; 130:493.
2. Flinn et al. The phase 3 DUO trial: duvelisib versus ofatumumab in relapsed and refractory CLL/SLL. Blood, October 2018; final draft accepted.
4. Hillman et al. The Efficacy of Duvelisib Monotherapy Following Disease Progression on Ofatumumab Monotherapy in Patients with Relapsed/Refractory CLL or SLL in a Phase 3 Crossover Extension Study. 23rd Congress of the European Hematology Association (EHA); June 2018, Abstract PF354.

Sincerely,

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