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NCCN Guidelines Panel: T-cell Lymphomas

On behalf of Verastem Oncology, Inc., I respectfully request the NCCN T-cell Lymphomas Guideline Panel to consider the enclosed data for duvelisib for the treatment of patients with relapsed/refractory (R/R) Peripheral T-cell Lymphomas (PTCL).

Specific Changes: Please consider the following:

- **TCEL-B 2 of 5: PTCL-NOS, EATL; MEITL; Nodal PTCL, TFH; FTCL**
  - **Add duvelisib as a preferred regimen, single agents under "Second-line Therapy (with intention to proceed to transplant) and Subsequent Therapy" and under "Second-line Therapy (no intention to transplant) and Subsequent Therapy"**
- **TCEL-B 3 of 5: AITL**
  - **Add duvelisib as a preferred regimen, single agents under "Second-line Therapy (with intention to proceed to transplant) and Subsequent Therapy" and under "Second-line Therapy (no intention to transplant) and Subsequent Therapy"**
- **TCEL-B 4 of 5: ALCL**
  - **Add duvelisib as a preferred regimen, single agents under "Second-line Therapy (with intention to proceed to transplant) and Subsequent Therapy" and under "Second-line Therapy (no intention to transplant) and Subsequent Therapy"**

FDA Clearance: On September 24, 2018, the FDA approved duvelisib for the treatment of adult patients with R/R CLL or SLL and R/R follicular lymphoma after at least two prior therapies.

- Duvelisib is not FDA approved for T-cell lymphomas (TCL)

Rationale:

Duvelisib, an oral inhibitor of PI3K-δ (delta) and PI3K-γ (gamma), demonstrated encouraging clinical activity in R/R PTCL as demonstrated by median progression-free survival (mPFS), overall response rate (ORR), and complete response (CR).

Supporting Literature: Horwitz et al. reported results of the activity of the dual PI3K-δ and PI3K-γ inhibitor duvelisib in a subset of R/R TCL patients (n=35)[1] from a Phase 1 trial (N=210) in patients with advanced hematologic malignancies[1]. The phase 1 trial from which this report of a subset of TCL patients is derived included 139 patients who were extensively pretreated for R/R leukemia or lymphoma and previously untreated CLL. The overall Phase 1 study employed a dose-escalation phase (DEP) to determine the maximum tolerated dose (MTD) with disease specific expansion cohorts at and below the maximum tolerated dose (MTD) of 75mg twice daily (BID). Patients with TCL (n=35) were enrolled between June 2012 and January 2014, and 27 (77%) were treated at the MTD. The other 8

patients received 25 mg (n = 1), 50 mg (n = 1), 60 mg (n = 4), or 100 mg (n = 2) twice daily. Sixteen patients had peripheral T-cell lymphoma (PTCL) and 19 patients had cutaneous T cell lymphoma (CTCL). The median duration of duvelisib treatment in the PTCL population was 11.3 weeks (range: 1.9 to 95.6 weeks), with 50% receiving ≥ 4 cycles and 38% receiving ≥ 6 cycles. One patient with PTCL remains on therapy at > 50 months. The ORR was 50.0% (3 CRs, 5 partial responses [PRs]) in the PTCL patients (95% confidence interval 24.7, 75.3). The ORR among patients with PTCL who received the MTD of 75mg BID was 54% (7/13; 2 CRs). All CRs occurred in < 2 months and all PRs in < 4 months. Responses were seen across a variety of PTCL subtypes with CRs in patients with EATL, AITL, and PTCL-NOS, and PRs in those with SPTCL (n = 2), ALCL, AITL, and PTCL-NOS. The duration of response in the PTCL population ranged from 1.8 to 17.3 months with median PFS of 8.3 months and median OS of 8.4 months. Two patients who achieved CR and PR completed > 12 months on treatment at the time of data analysis.

The safety profile of duvelisib in patients with TCL was considered reasonable and consistent with the Phase 1 overall patient population. Grade 3/4 treatment-emergent AEs (TEAEs) that occurred in ≥ 15% of PTCL or CTCL patients were elevated transaminases (40%), neutropenia (18%), pneumonia(17%) and maculopapular rash (17%).

Also, Horwitz et al. reported results of the Phase 1 combination study with expansion cohorts, multicenter, open label, parallel study of duvelisib plus romidepsin and duvelisib plus bortezomib in patients with R/R T-cell Lymphomas which included PTCL and Cutaneous T-cell Lymphomas (CTCL)[2]. Two expansion cohort arms included giving duvelisib as a single agent lead-in for one month prior to combining with either romidepsin or bortezomib. At the duvelisib MTD of 75mg BID for the combination with romidepsin, when duvelisib was given as a single agent for one month, the ORR was 50% (7/14 patients), 29% were CRs (4/14 patients). At the duvelisib MTD of 25mg BID for the combination with bortezomib, when duvelisib was given as a single agent for one month, the ORR was 41% (5/12 patients), 25% were CRs (3/12 patients).

In summary, duvelisib demonstrated a favorable benefit/risk profile with encouraging clinical activity and an acceptable adverse event profile in a difficult to treat R/R PTCL patient population.

The following key study publications are submitted. 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. Horwitz et al. Activity of the PI3K-δ,γ inhibitor duvelisib in a phase 1 trial and preclinical models of T-cell lymphoma. American Society of Hematology Annual Meeting and Exposition. Blood. 2018; 131:888-898.
2. Horwitz et al. The Combination of Duvelisib, a PI3Kδ,γ Inhibitor, and Romidepsin Is Highly Active in Relapsed/Refractory Peripheral T-cell Lymphoma with Low Rates of Transaminitis: Results of Parallel Multicenter, Phase 1 Combination Studies with Expansion Cohorts. American Society of Hematology Annual Meeting and Exposition; Oral Presentation, December 2018; Blood 2018; 132:683. http://www.bloodjournal.org/content/132/Suppl_1/683
3. COPIKTRA™ (duvelisib) [package insert]. Needham, MA: Verastem, Inc. 2018

Sincerely,

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