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NCCN Guidelines Panel: T-cell Lymphomas

On behalf of Verastem Oncology, Inc. (Verastem), I respectfully request the NCCN T-cell Lymphomas Guideline Panel to consider the enclosed data for duvelisib in combination with romidepsin 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 plus romidepsin as a preferred regimen, combination regimen under "Second-line Therapy (with intention to proceed to transplant and no intention to transplant) and Subsequent Therapy"**
- **TCEL-B 3 of 5: AITL**
  - **Add duvelisib plus romidepsin as a preferred regimen, combination regimen under "Second-line Therapy (with intention to proceed to transplant and no intention to transplant) and Subsequent Therapy"**
- **TCEL-B 4 of 5: ALCL**
  - **Add duvelisib plus romidepsin as a preferred regimen, combination regimen under "Second-line Therapy (with intention to proceed to transplant and 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 combination with romidepsin in patients with R/R PTCL as evidence of disease response by median progression-free survival (mPFS), overall response rate (ORR), and complete response rate (CR).

Supporting Literature: Horwitz et al. reported results of the Phase 1, multicenter, open label, parallel combination study with expansion cohorts of duvelisib plus romidepsin or bortezomib in patients with R/R T-cell Lymphomas which included PTCL and Cutaneous T-cell Lymphomas (CTCL)[2,3]. The primary endpoint of the study was to define the maximum tolerated dose (MTD) of the combinations of duvelisib plus romidepsin or bortezomib. Key secondary endpoints included characterizing safety and toxicity with extended treatment of the combinations, ORR, CR, and PFS. Patients that had progressed after at least one prior systemic therapy were enrolled into the study[4]

For the cohort of patients that received duvelisib plus romidepsin, the MTD was determined to be duvelisib 75mg orally twice daily plus romidepsin 10 mg/m^2 intravenously dosed Day 1, Day 8 and Day 15 of 28 day cycles.[3]

Of the 38 patients evaluable for efficacy across all dose levels in the duvelisib plus romidepsin arm, (PTCL, n=27; CTCL, n=11), 21 responded (9 CRs and 12 PRs) for an ORR of 55%. Sixteen of the 27 patients with PTCL responded (9 CRs and 7 PRs) for an ORR of 59%. Five of the 11 patients with CTCL responded (all PRs) for an ORR of 45%. Median PFS for patients with PTCL was 6.72 months, confounded by 6 patients (22%) who were able to proceed to allogeneic stem cell transplant. Median PFS was 5.41 months for patients with CTCL.

The safety profile of duvelisib plus romidepsin was considered reasonable. Thirty-one patients were treated at the MTD. The most common Grade 3-4 adverse events (greater than or equal to 10% of patients) included neutropenia (32%), transaminase elevation (23%), diarrhea (19%), hyponatremia (13%), and thrombocytopenia (10%).

In summary, duvelisib in combination with romidepsin demonstrated a favorable benefit:risk profile with encouraging clinical activity and an acceptable adverse event profile with 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. COPIKTRA™ (duvelisib) [package insert]. Needham, MA: Verastem, Inc. 2018.
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. Horwitz SM, Moskowitz AJ, Jacobsen ED, 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. Presented at the 11th Annual T-Cell Lymphoma Forum, January 10-12, 2019, La Jolla, CA.
4. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29. Identifier NCT02783625, a trial of duvelisib in combination with either romidepsin or bortezomib in relapsed/refractory T-cell lymphoma [cited 2019 Apr 04]. Available from: https://clinicaltrials.gov/ct2/show/NCT02783625.

Sincerely,

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