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Date of request: June 11, 2020
National Comprehensive Cancer Network (NCCN®) Guidelines Panel: T-cell Lymphomas
Re: Duvelisib for Relapsed/Refractory (R/R) Peripheral T-cell Lymphomas (PTCL)

Rationale: R/R PTCL is an aggressive lymphoma with a dismal median overall survival (OS) of 6 months.[1] Available therapies induce response in ~25% of patients with R/R PTCL, suggesting there is a critical unmet need in this population[2]. Duvelisib demonstrated clinically significant activity in R/R PTCL in the ongoing phase 2 PRIMO study[3] and a phase 1 study[4]. This indication has Fast Track status by the FDA. These data are also under review by FDA for assessment of suitability for submission of an application for Breakthrough Therapy designation.

Reason for submission: As duvelisib represents an effective option to fill the urgent need for an aggressive disease with suboptimal treatment, inclusion in the NCCN Guidelines would increase patient access to duvelisib. To date, there have been 16 academic centers, including 11 NCCN institutions, who have requested the use of duvelisib in PTCL.

Specific Changes: We respectfully request the NCCN Panel to consider the following:

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

FDA Clearance: Duvelisib is approved for the treatment of adult patients with R/R CLL or SLL and R/R follicular lymphoma after at least two prior therapies. The follicular lymphoma indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.[5]

Supporting Literature:

Phase 2 PRIMO Dose Optimization Phase: PRIMO is an open-label, multi-center phase 2 study evaluating duvelisib in patients with R/R PTCL.[3] Enrolled patients have received ≥2 cycles of a prior regimen. In the dose optimization phase, 33 patients received duvelisib at 75 mg or 25 mg twice daily. Table 1 summarizes the results of objective response rate (ORR) and duration of response (DOR). An overall objective response rate per Independent Review Committee (IRC) assessment of 62% and 40% were observed, respectively, including complete response (CR) rates of 31% and 25%. Rates of ORR per investigator assessment were 54% and 35% in the 75 mg and 25 mg cohorts, respectively. Serious treatment-emergent adverse events (TEAE) occurred in 69% (9/13) of patients in the 75 mg cohort and in 75% (15/20) of patients in the 25 mg cohort. Serious TEAEs in ≥ 2 patients were colitis, diarrhea, abdominal pain, pyrexia, PD, sepsis, pneumonia, hyponatremia, rash maculopapular, dyspnea, and respiratory failure There were 5 fatal AEs in the 25 mg cohort and 1 in the 75 mg cohort.

Discontinuations due to AEs occurred in 30% (6/20) of the 25 mg cohort and 8% (1/13) of the 75 mg cohort.[3] The safety profile observed in PRIMO is consistent with the current safety profile of duvelisib.[3]

The following updated information on PRIMO was submitted to FDA on June 10, 2020 to request assessment of the suitability of the data for submission of a Breakthrough Therapy Designation application; these data are not available in the public domain and are included here for panel discussion only. Please refrain from disclosing this information in public until notification that the embargo is lifted.

Phase 2 PRIMO Update (23 Mar 2020 data cutoff):

Dose Optimization Phase Efficacy Update: As of the data cutoff, 2 patients (1 each cohort) remain on treatment. Median follow-up among all 33 patients was 5.6 months. One patient in each cohort achieved CR and proceeded to undergo stem cell transplant or consolidated radiation therapy with curative intent.

Dose Expansion Phase Initial Summary: In the expansion phase, a total of 100 patients are targeted to be enrolled and will receive 75 mg twice daily for two cycles followed by 25 mg twice daily for all subsequent cycles. As of the data cutoff of 23 March 2020, a total of 25 patients have been dosed, 20 of whom were expected to undergo at least one disease assessment (Table 1).

Table 1. PRIMO Update (23 Mar 2020): A summary of ORR and DOR for Both Phases

	Dose Optimization Phase				**Expansion Phase (75 mg/25 mg BID) N=20**
	Cohort 1 (25 mg BID) (N=20)		**Cohort 2 (75 mg BID) (N=13)**		
	INV	**IRC**	**INV**	**IRC**	**INV**
ORR, n (%)	7 (35)	8 (40)	7 (54)	8 (62)	8 (40)
CR, n (%)	5 (25)	0	4 (31)	0	6 (30)
DOR in months (Median, 95% CI)	2.99 (1.64, NE)	1.87 (0.95, NE)	12.2 (1.77, 12.2)	12.2 (1.38, 12.2)	NE (NE, NE)

Abbreviations: BID = twice daily; CI = confidence interval; CR = complete response; DOR= duration of response; INV = investigator assessment; IRC = independent review committee; NE = not evaluable; ORR = objective response rate.

Kaplan-Meier estimates for DOR for each cohort of the dose optimization phase are presented in Figure 1 below.

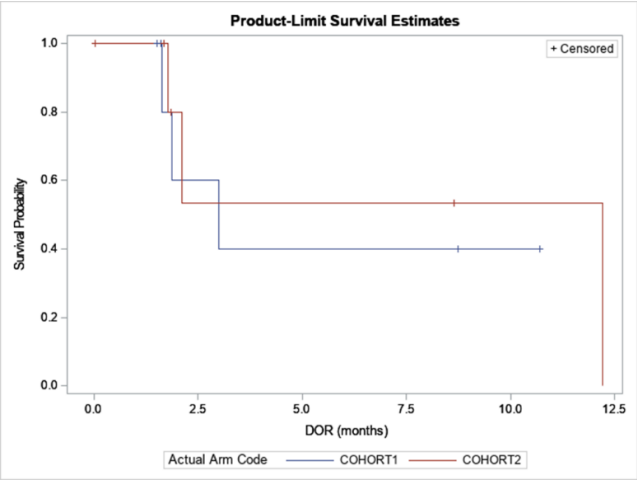

Figure 1: Kaplan-Meier estimate of DOR – Dose Optimization Phase

Phase 1:

The above results were consistent with a subset of R/R T-cell lymphoma (TCL) patients (N=35) from an earlier phase 1 monotherapy trial (N=210) in patients with advanced hematologic malignancies.[4] In the TCL cohort (16 PTCL; Table 2), 77% (27/35) of patients were treated at 75mg twice daily, the other 8 patients received 25 mg (n = 1), 50 mg (n = 1), 60 mg (n = 4), or 100 mg (n = 2). Responses were seen across a variety of PTCL subtypes.

No new toxicity was identified during phase 2 of the PRIMO study. The AEs observed in phase 2 of the study were consistent with what was observed in phase 1 of the PRIMO study.[4]

Table 2. Phase 1 TCL: A summary of R/R PTCL Efficacy Results

	Duvelisib R/R PTCL (n=16)
ORR, n (%)	8 (50)
CR, n (%)	3 (19)
DOR, range (months)	1.8 - 17.3
PFS, median (months)	8.3
OS, median (months)	8.4

Abbreviations: CR = complete response; DOR= duration of response; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PTCL = peripheral T-cell lymphoma; R/R = relapsed/refractory.

In summary, the duvelisib data observed to date show a favorable benefit/risk profile with clinically significant activity and a manageable safety profile in a difficult-to-treat R/R PTCL patient population.

Sincerely,

Emile Youssef

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References:

1. Campo E, et al. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood.* 2011. May 12;117(19):5019-5032.
2. Horwitz SM, Moskowitz A, Jacobsen E, et al. The Combination of Duvelisib, a PI3K-δ,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. *Blood.* 2018. 132 (Supplement 1): 683.
3. Horwitz SM, Mehta-Shah N, Pro B, et al. Dose optimization of duvelisib in patients with relapsed or refractory PTCL from the phase 2 PRIMO trial: selection of regimen for the dose-expansion phase. *Blood*. 2019;134 (Supplement_1):1567.
4. Horwitz SM, Koch R, Porcu P, et al. Activity of the PI3K-δ,γ inhibitor duvelisib in a phase 1 trial and preclinical models of T-cell lymphoma. *Blood*. 2018. Feb 22;131(8):888-898.
5. COPIKTRA® (duvelisib) [package insert]. Needham, MA: Verastem Oncology, 2019.