Efficacy and Safety Results With an Intermittent Dosing Schedule of the PI3Kδ Inhibitor ME-401 Alone or in Combination with Rituximab for B-cell Malignancies


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**Background**

- **ME-401**, a potent and selective oral PI3Kδ inhibitor, achieved high response rates in patients with follicular lymphoma (FL), chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) when administered once daily in 28-day cycles in a dose escalation Phase 1 study, with comparable response rates and safety profiles at the 3 doses evaluated (Soumerai, et al. ASCO 2018 #4719).

**Rationale for Intermittent Dosing**

- The most common delayed (i.e., after 2 cycles) grade adverse events (AEs) on the continuous daily dosing (CS) were diarrhea and rash. These AEs were reversible with drug interruption and/or corticosteroid therapy and likely immune-related (ir)AEs due to on-target inhibition of regulatory T-cells (Tregs).

- We postulated an intermittent dosing schedule (IS) of 7 days on/21 days off therapy would enable sufficient Treg recovery to prevent irAEs.

- This schedule was based on ME-401 half-life and the known kinetics of Treg depletion and recovery (M. Narula in Cancer 2017;32:2372).

- 7 cycles achieving plasma concentrations needed to inhibit PI3Kδ after 6-8 cycles and then every 8 cycles or as clinically indicated.

- 56 patients had 2 disease assessments while on therapy and were evaluable for response, with best response shown in Table 2.

- 23 FL, 11 CLL/SLL, 1 MZL, 1 DLBCL

- Intermittent dosing introduced in cycle 3 may preserve objective response rates in ME-401 typically observed in the first 2 cycles of therapy.

- Duration of response (Figure 2) and failure-free survival (Figure 3) in patients with FL and CLL/SLL.

**Study Design, Treatment Groups, Patients**

- **Key eligibility criteria**:
  - Failure of ≥2 prior systemic therapy
  - ECOG performance status (PS) ≤ 2
  - No prior PI3Kδ therapy or disease progression (PD) on a BTK inhibitor

- **Group 1**: ME-401 dose escalation (enrollment completed)
  - Patients with FL, CLL/SLL
  - ME-401 at 60, 120, 180 mg once daily by CS in a 28-day cycle

- **Group 2**: Beginning in December 2018, patients were switched to IS after various durations of exposure to CS
  - Group 2: ME-401 in a rituximab arm (enrollment ongoing)
  - Patients with FL, CLL/SLL, marginal zone lymphoma (MZL), and diffuse large B-cell lymphoma (DLBCL)

- **Group 3**: ME-401 at 60 mg once daily for the first 2 cycles then IS
  - Rituximab 375 mg/m² weekly x 4 then 1 dose/cycle in Cycles 3-6

- **Group 3**: ME-401 monotherapy expansion cohort (enrollment ongoing)
  - Patients with FL, CLL/SLL
  - ME-401 at 80 mg once daily for the first 2 cycles then IS

- Patients on IS allowed to switch back to daily dosing if they experience disease progression while on the IS

**Safety and Disease Control with the Intermittent Dosing Schedule**

- **Fever delayed grade 3 irAEs observed in patients on IS**
  - 47/60 patients (78%) had at least 7 days off therapy and ≥ 2 cycles of therapy and are evaluable for delayed irAEs
  - 2 patients had not yet completed 2 cycles, 2 patients had not yet switched to IS, 1 withdrew consent, 1 discontinued due to AE, and 7 discontinued due to PD (4 DLBCL, 3 FL)

- **Response assessed by the Lugano criteria for FL, MZL, and CLL/SLL and are informative for delayed irAEs**

- 56 patients had 2 disease assessments while on therapy and were evaluable for response, with best response shown in Table 2.

- **Best nodal response (change in SPD) in patients with FL (n = 37), MZL (n = 1), and CLL/SLL (n = 11) shown in Figure 1**

- **Lower incidence of grade 3 irAEs observed on the intermittent dosing schedule**

- **Interruption dosing can be used successfully to retreat patients with grade 3 irAEs**

- **Objective responses maintained by the majority of patients on the IS**

- **Conclusion**

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