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Preliminary Safety and Efficacy 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 1b study, with comparable response rates and safety profile at the 3 doses evaluated (*Soumerai, et al, ASCO 2018:#7519*).

Rationale for Intermittent Dosing

- The most common delayed (i.e., after 2 cycles) grade 3 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 (irAEs) 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 repopulation/reactivation (*Mahnke et al, Int J Cancer 2007;120:2723*)
  - 7 daily doses achieving plasma concentrations needed to inhibit PI3Kδ
  - 7 days (~ 5 half-lives) without treatment for plasma drug clearance
  - 14 days without treatment for Tregs recovery
- Intermittent dosing introduced in cycle 3 may preserve objective responses to ME-401 typically observed in the first 2 cycles of therapy and decrease late occurring irAEs

Study Design, Treatment Groups, Patients

- Key eligibility criteria
  - Failure of ≥1 prior systemic therapy
  - ECOG performance status 0-2
  - No prior PI3K 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
  - Beginning in December 2017, 18 ongoing patients were switched to IS after various durations of exposure to CS
- Group 2: ME-401 in combination with rituximab (enrollment ongoing)
  - Patients with FL, CLL/SLL, marginal zone lymphoma (MZL) and diffuse large B-cell lymphoma (DLBCL)
  - ME-401 at 60 mg once daily for the first 2 cycles then IS
  - Rituximab 375 mg/m^2 weekly x4 then 1 dose/cycle in Cycles 3-6
- Group 3: ME-401 monotherapy expansion cohort (enrollment ongoing)
  - Patients with FL and CLL/SLL
  - ME-401 at 60 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

Table 1. Demographics and Disease Characteristics

	Group 1 (n = 31)	Group 2 (n = 16)	Group 3 (n = 13)
Age, median (range) in years	65 (47-79)	65 (38-81)	68 (48-80)
Male / Female	68%/32%	63%/37%	92%/8%
Diagnosis			
FL	22 (71%)	9 (56%)	11 (85%)
CLL/SLL	9 (29%)	1 (6%)	2 (15%)
MZL	0	1 (6%)	0
DLBCL	0	5 (32%)	0
Prior anti-lymphoma therapy			
Median (range) number of prior therapies	2 (1-5)	2 (1-10)	2 (1-6)
Patients with ≥3 prior lines of therapy	13 (42%)	13 (82%)	7 (54%)
Prior anti-CD20 antibody therapy	30 (97%)	16 (100%)	12 (92%)
Median (range) months since last therapy	13 (1-74)	3.4 (1-13)	16 (1-152)
Patients with last treatment in ≤12 months	15 (48%)	14 (88%)	5 (39%)

Efficacy – High Objective Response Rate in Indolent NHL and CLL/SLL with Durable Responses Observed

Table 2. Overall Response By Histology and Regimen

	Groups 1+3 ME-401 Alone (N = 39)	Group 2 ME-401+Rituximab (N = 16)	Total Efficacy Evaluable (N = 55)
FL	22/29 (76%)	7/9 (78%)	29/38 (76%)
CLL/SLL	10/10(100%)	1/1 (100%)	11/11 (100%)
MZL	N/A	1/1 (100%)	1/1 (100%)
DLBCL	N/A	1/5 (20%)	1/5 (20%)

Figure 1. Best Nodal Response

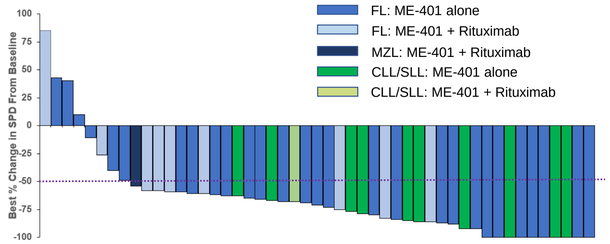


Figure 2. Duration of Response

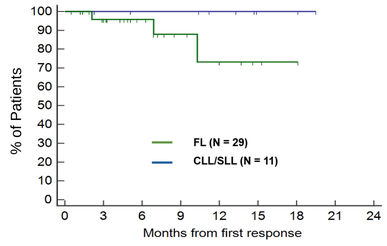
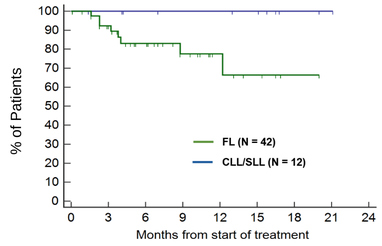


Figure 3. Failure-Free Survival



- Response assessed by the Lugano criteria for FL, MZL and DLBCL, and iw-CLL criteria for CLL and SLL
- Response assessed by CT scan or PET/CT scan obtained after 2 and 6 cycles, and then every 6 cycles or as clinically indicated
- 55 patients had ≥ 1 disease assessment while on therapy and are 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
- Duration of response (Figure 2) and failure-free survival (Figure 3) in patients with FL and CLL/SLL
- 6 patients (3 FL, 3 CLL/SLL) switched from the IS to the CS after PD and who continue on therapy are shown as having an ongoing response in the KM plots
- Median duration of response not reached; median follow-up of 9.3 months (range, 2.1+ to 19.5+)
- Median failure-free survival not reached; median follow-up of 6.9 months (range, 0.4+ to 21.1+)

Safety and Disease Control with the Intermittent Dosing Schedule

Fewer delayed grade 3 irAEs observed in patients on IS

- 47/60 patients (78%) have completed more than 2 cycles of therapy and are informative for delayed irAEs
  - 2 patients have not yet completed 2 cycles, 2 have not yet switched to IS, 1 withdrew consent, 1 discontinued due to AE, and 7 discontinued due to PD (4 DLBCL, 3 FL)
- The incidence of irAEs was lower in patients treated with the IS compared to the CS (Table 3)
- The 4 cases of irAEs on the IS occurred 14-58 days after the switch to intermittent dosing and may reflect residual immune dysregulation initiated on daily dosing

Table 3. Delayed Grade 3 irAEs on IS *vs* CS

Group	No. of Patients With ≥ 3 Cycles	No. of Patients with irAEs	Days from Start of IS to irAEs
Group 1 on CS	29	10 (34%)	N/A
Group 1 switched late to IS*	17	2 (12%)	18, 58
Group 1-3 switched to IS in cycle 3	19	2 (11%)	14, 15

* Median from start of therapy to switch to IS = 6 months (range, 3-11)

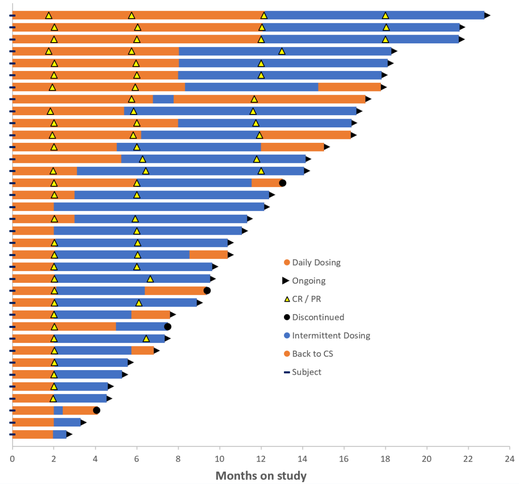
Successful retreatment on IS in patients with irAEs

- 7/7 patients retreated with the IS after symptoms resolution remain on therapy without recurrence of the AE
  - Median of 8 months (range: 4+ to 11+ months) after restarting the IS
- 7 patients developed irAEs on the CS and were discontinued; this occurred before the IS was implemented in the study
  - 2 patients retreated on the CS at reduced dose after resolution of AE had recurrence of AE symptoms within 4-6 weeks of retreatment
  - 5 patients were not retreated with ME-401 after resolution of the irAE

Objective responses maintained by the majority of patients on the IS

- 36 patients were administered the IS
  - 23 FL, 11 CLL/SLL, 1 MZL, 1 DLBCL
- 32/36 patients (89%) remain on therapy, and 16 have been on therapy for more than 1 year (Figure 4)
- 26/36 of patients (72%) have no evidence of disease progression on IS
  - Median therapy on IS of 7.9 months (range, 0.8+ to 10.5+)
  - 1 patient withdrew for AE on IS
- 10/36 of patients (28%) had PD and were switched back to daily dosing
  - 7 patients (3 FL, 3 CLL/SLL, 1 MZL) are ongoing for a median of 1.9 months after switch to daily dosing (range, 1.1+ to 8.6+ months)
  - 3 patients (3 FL) did not respond and were discontinued

Figure 4. Patient Outcome After Switch to IS



Conclusions

- ME-401 achieves a high response rate in patients with relapsed/refractory FL and CLL/SLL
  - 76% in FL and 100% in CLL/SLL
- Encouraging duration of response and failure-free survival
- Lower incidence of grade 3 irAEs observed on the intermittent dosing schedule
- Intermittent dosing can be used successfully to retreat patients with grade 3 irAEs
- Disease control maintained in most patients treated on the intermittent dosing schedule
  - 72% of patients have not experienced disease progression
  - Recapture of disease response in 70% of patients retreated with daily dosing after evidence of disease progression on intermittent dosing
- Launching a global, randomized, double-blind, 2-arm study in patients with relapsed or refractory FL after failure of ≥ 2 prior systemic therapies
  - One arm will evaluate a higher dose intensity approach using a continuous daily dosing, with mitigation of immune-related toxicity by switching to an intermittent dosing in the presence of grade ≥ 2 immune-related adverse events
  - One arm will evaluate a lower dose intensity approach using an intermittent schedule after the initial 2 cycles of daily dosing, with a switch to daily dosing if tumor regrowth
  - This randomized experiment will determine which approach results in longer duration of exposure to ME-401, maximizes disease control, and is better tolerated

Disclosures and Inquiries

- Study sponsored and funded by MEI Pharma, Inc.
- Author disclosures
  - ADZ: Consulting/advisory boards: MEI Pharma, Amgen, Astra-Zeneca, Bayer, Beigene, Celgene, DAVA Oncology, Genentech/Roche, Gilead, Janssen, Karyopharm. Morphosys, Novartis, Pharmacyclics/AbbVie, Pfizer, Verastem
  - JDS: Research support: Roche/Genentech, BeiGene, TG Therapeutics. Consulting: Versatem. Research grant from the Lymphoma Research Foundation
  - NMR: Research grant: AbbVie, BMS, Adaptive Biotechnologies, Gilead, Genentech
  - AS: Travel grants: Abbvie, Pharmamar. Clinical trials grants: Amgen, Bayer, Novartis, Pfizer, Roche, MEI Pharma
  - KP: Consultancy: AstraZeneca, Celgene, Genentech, Juno Pharmaceuticals, Sunesis Pharmaceuticals, Speakers Bureau: AstraZeneca, Genentech. Pharmacyclics. Research finding: AstraZeneca, Celgene, Curis, MEI Pharma, Millenium/Takeda, Sunesis Pharmaceuticals
  - RGG: employee of MEI Pharma
  - JMP: Consulting: Pharmacyclics, Gilead, and Astra Zeneca
  - "There are no relationship to disclose" for DJ, ASA, HSS, VPK, HJ, AI
- We would like to thank the patients for participating in this study
- Clinicaltrials.gov identifier: NCT02914938