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Results of the PI3Kδ Inhibitor ME-401 Alone or with Rituximab in Relapsed/Refractory (R/R) Follicular Lymphoma (FL)

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ME-401: A PI3Kδ Inhibitor with Optimal Pharmaceutical Properties

- Orally bioavailable
- Half-life of ~28 hours supports once daily dosing
- Extensive distribution to extravascular tissues, including lymph nodes
- Selective to the δ isoform with no off-target effects
- Inhibits PI3Kδ at low nanomolar concentrations with IC_{50} = 0.6 nM
- Prolonged noncovalent binding to PI3Kδ protein >5.5 hours

Study Design, Treatment Groups, Patients

- Main eligibility criteria
  - Age ≥18
  - ECOG performance status 0-2
  - Failure of ≥1 prior therapy, or ≥2 prior therapies for DLBCL and high-grade lymphoma
  - No prior PI3K therapy
- Initial group was a dose-escalation study in FL and CLL/SLL[1]
  - ME-401 at 60, 120, 180 mg once daily continuously in a 28-day cycle
- Dose-escalation group closed due to high and comparable response rate at the 3 doses, similar safety profile, and no dose-limiting toxicities
- 2 additional groups evaluated ME-401 at 60 mg daily x2 cycles, then on an intermittent schedule (IS)
  - As monotherapy in FL and CLL/SLL
  - In combination with rituximab in B-cell malignancies, with rituximab at 375 mg/m^2 weekly x4 and then on Day 1 of Cycles 3-6
- Cohort evaluating ME-401 plus zanubrutinib recently opened to enrollment
- PJP prophylaxis in all patients

Rationale for Intermittent Schedule

- The continuous schedule (CS) demonstrated delayed (>Cycle 2) grade 3 adverse events (AEs), primarily diarrhea/colitis and skin rash, in approximately 1/3 of patients
- We hypothesized that these AEs were a consequence of on-target inhibition of regulatory T cells (Tregs) and that an intermittent schedule might allow for Tregs repopulation and ameliorate the development of these delayed AEs
- IS of 60 mg days 1-7, repeated every 28 days
  - 1 week of full inhibition, 1 week (~5 half-lives) washout, 2 weeks for Treg recovery[2]
- IS begins at Cycle 3, after 2 cycles of daily dosing
  - Most responses are observed at the end of Cycle 2
  - Delayed AEs typically occur in Cycles 3-6
- Patients can be reverted to CS if stable disease or progression of disease (PD) on IS

Patient Population with Follicular Lymphoma

Table 1. Demographics and Disease Characteristics of Patients with FL

	ME-401 Monotherapy (N = 40)	ME-401 + Rituximab (N = 14)	IS Group (N = 23)	CS Group (N = 31)	Total Patients (N = 54)
Age, in years Median (range) ≥65 years	66 (47-82) 22 (55%)	61 (38-81) 4 (29%)	61 (38-82) 9 (39%)	65 (47-81) 17 (55%)	63.5 (42-82) 26 (48%)
Sex: Male / Female, %	67.5 / 32.5	78.6 / 21.4	69.6 / 30.4	71 / 29	70 / 30
Prior lymphoma therapy • Median number of prior therapies (range) • Patients with ≥2 prior lines of therapy • Prior anti-CD20 antibody	2 (1-6) 25 (62.5%) 38 (95%)	3 (1-10) 10 (72%) 14 (100%)	2 (1-6) 18 (78%) 22 (95%)	2 (1-10) 17 (55%) 30 (97%)	2 (1-10) 35 (65%) 52 (96%)

Efficacy – High Objective Response Rate (ORR) and Durable Responses Observed

Figure 1. Best Change from Baseline of Measurable Lesions (N = 49*)

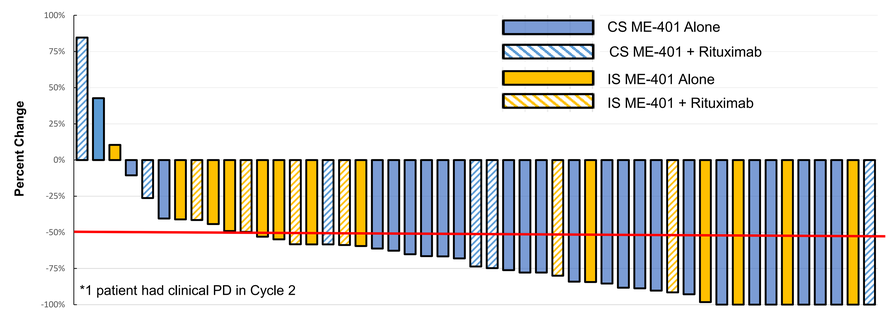
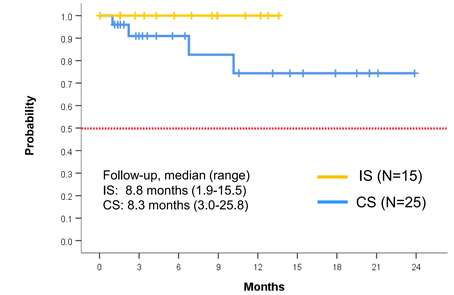


Table 2. Disease Response

Evaluable Patients	Overall Response
All groups (N = 50) Complete response (CR)	40 (80%) 10 (20%)
By treatment arm ME-401 monotherapy (N = 38) ME-401 + rituximab (N = 12)	30 (79%) 10 (83%)
By schedule IS Group (N = 20) CS Group (N = 30)	15 (75%) 25 (83%)

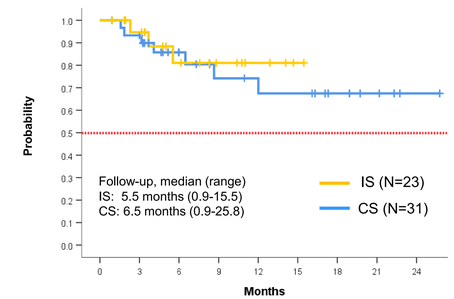
- Disease assessment at end of Cycles 2 and 6, and then every 6 months using the Lugano criteria
- ORR 80% with 20% CR (Table 2 and Figure 1)
  - 35/40 (88%) of responders had an objective response by end of Cycle 2; median 1.8 months
  - 24/26 responses (92%) in POD24 patients receiving ME-401 as 2nd or later line of therapy
- Duration of response (DOR) (Figure 2) and progression-free survival (PFS) (Figure 3)
- Patients enrolled in the CS cohort who never switched to IS or switched to IS upon various exposure to CS analyzed as CS. Patients enrolled in the IS cohort and reverted to CS analyzed as IS

Figure 2. Duration of Response (DOR)



- DOR: from 1st documentation of response to the occurrence of PD for patients on CS who never switched to IS *or* to the occurrence of a PD on CS in patients who switched from IS to CS
- Censoring: patients who discontinued without PD or are still on therapy at the time of analysis
- 6 patients (4 IS, 2 CS) who are still on therapy after reverting from IS to CS due to PD are not counted as having an event

Figure 3. Progression-Free Survival (PFS)



- PFS: from Day 1 to occurrence of an event (PD or death) for patients on CS who never switched to IS *or* to an event while on CS for patients who switched from IS to CS
- Censoring: discontinued without an event or still on therapy at the time of analysis
- 6 patients who are still on therapy after reverting from IS to CS due to PD are not counted as having an event

Patient Disposition, Safety, and Tolerability

Table 3. Patient Disposition

	CS Group (N = 31)	IS Group (N = 23)
Continuing on therapy	14 (45%)	18 (78%)
Discontinued therapy Progressive disease Adverse event Stem cell transplant Other	 7 (23%) 4 (13%) 3 (10%) 3 (10%)	 2 (9%) 0 1 (4%) 2 (9%)
Follow-up Median (range), months	6.5 (0.9-25.8)	5.5 (0.9-15.5)

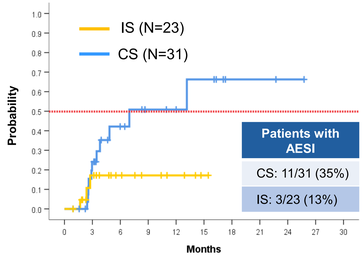
Table 4. AEs in ≥15% of Patients (N = 54)

	Number (%) of Patients	
	All Grades	Grade 3
Diarrhea/colitis	20 (40.7%)	9 (17.0%)
Fatigue	19 (35.2%)	0
Cough	18 (33.3%)	0
Rash, all types	13 (24.1%)	5 (9.3%)
ALT increased	13 (24.1%)	3 (5.6%)
Nausea	13 (24.1%)	0
AST increased	12 (22.2%)	2 (3.7%)
Decreased appetite	9 (16.7%)	0

Table 5. Patients with Drug-Related AESI (AE of Special Interest)

	All Grades		Grade 3	
	CS Group (N = 31)	IS Group (N = 23)	CS Group (N = 31)	IS Group (N = 23)
Diarrhea/colitis	11 (35.5%)	9 (39.1%)	5 (16.1%)	2 (8.7%)
Rash, all types	11 (35.5%)	2 (8.7%)	4 (12.9%)	0
ALT increased	7 (22.6%)	6 (26.1%)	2 (6.5%)	1 (4.3%)
AST increased	7 (22.6%)	5 (21.7%)	2 (6.5%)	0
Pneumonia	2 (6.5%)	0	2 (6.5%)	0
Mucositis	6 (19.4%)	1 (4.3%)	1 (1.9%)	0

Figure 4. Time to Grade 3 AESI



Patient Disposition
- 32 patients (59%) remain on therapy
- Reasons for discontinuation (Table 3)

Safety Summary
- No grade 4-5 clinical AEs (Table 4)
- Grade 3 AST/ALT elevations reported concurrently with Grade 3 diarrhea or rash in 3 patients; no occurrence of isolated Grade 3 AST/ALT elevations
- AESI defined as drug-related diarrhea/colitis, rash, mucositis, AST/ALT elevation, and pneumonia/pneumonitis (Table 5)
- Time to Grade 3 AESI shows a plateau in Cycle 3 for IS group (Figure 4)

Conclusions

- **ME-401 achieves a high ORR of 80% in patients with relapsed/refractory FL**
  - **The majority of responses (88%) occur early**
  - **Responses are durable, with median not reached**
- **The tolerability of ME-401, as assessed by the development of delayed, Grade 3 AEs, is improved with IS**
- **The DOR, PFS, and time to Grade 3 AESI analyses, using our modified definitions, suggest that IS may provide superior overall clinical benefit (risk-to-benefit)**
- **These results are being further evaluated in an ongoing, global Phase 2 study, formally randomizing patients between IS and CS (NCT03768505)**

References:
1. Soumerai JD, et al. *J Clin Oncol*. 2018;36(suppl 15):7519.
2. Mahnke MK, et al. *Int J Cancer*. 2007;120:2723-2733.

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