Initial Results of a Dose Escalation Study of ME-401, a Selective and Structurally Differentiated PI3Kδ Inhibitor, in Relapsed/Refractory (R/R) Follicular Lymphoma (FL) and Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

Abstract #7519

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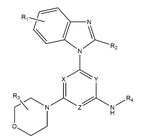
ME-401 – A Novel Potent PI3Kδ Inhibitor

- Oral, potent, selective, structurally differentiated PI3Kδ Inhibitor
- Inhibits PI3Kδ at nanomolar concentrations; mean IC_{50} = 0.6 nM
- Highly selective to the δ isoform

PI3K isoform	α	β	γ
IC_{50} fold increase	22,867	30	713



- Volume of distribution ~100x blood volume
  - Extensive distribution to tissues
- Readily permeates into cells
- Residence time on PI3Kδ protein ~5.5 hours
  - Prolonged target signal inhibition

Phase 1 PK/PD Study in Healthy Volunteers

- Single dose of 10, 30, 60, 90 and 150 mg
- Linear PK across doses
- Half-life ~28 hours supports daily dosing
- EC_{90} ~5.2 ng/mL in the basophil activation test (BAT) assay (Figure 1)
- Daily dosing at 60 mg projected to achieve trough plasma concentrations greater than BAT EC_{90}
- 60 mg selected as the starting dose level in the present study

O. Moreno, et al. Cancer Res 2016; 76 (14): CT157

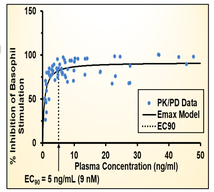


Figure 1. EC_{90} in BAT assay

Study Design

- Patients with R/R FL or CLL/SLL after > 1 prior systemic therapy
- No prior PI3K inhibitor therapy
- Dose escalation using a modified continuous reassessment model
  - 6 patients per dose level
  - Option to enroll 6 additional patients at any dose ≥ mBED to further assess disease response
- Once daily oral dosing in 28-day cycles
- Planned dose levels: 60, 120, 180, and up to 780 mg
- Intermittent schedule (Days 1-7/cycle) implemented since January 2018 in all patients who completed ≥ 2 cycles of therapy to evaluate:
  - A dose schedule for toxicity management in future trials
  - Disease control in the 3-week treatment-free interval
- PJP prophylaxis for all patients
- Responses assessed after Cycles 2 and 6, and then every 6 cycles
- Efficacy assessed using the Lugano and IW-CLL criteria

Study Objectives

- Safety
- Dose Limiting Toxicity (DLT) evaluated on Days 0-56 (2 cycles)
- Maximum Tolerated Dose (MTD)
- Overall response rate (ORR) and complete response (CR) rate
- Minimal Biologic Effective Dose (mBED): ORR ≥ 30% and DLT rate ≤ 25%
- Recommended Phase 2 Dose (RP2D)
- Pharmacokinetics (PK)

Study Status

- Dose escalation phase completed
- Median follow-up of 8 months (range 2.4-16.5 months)
- No DLTs observed at the first 3 dose levels
- Doses >180 mg not evaluated due to high ORR and similar safety profiles at the initial 3 dose levels
- MTD not identified
- RP2D defined as 60 mg
- Ongoing additional cohorts
  - Expansion cohort of ME-401 at 60 mg in FL and CLL/SLL
  - ME-401 at 60 mg in combination with rituximab in B-cell malignancies

Patient Characteristics

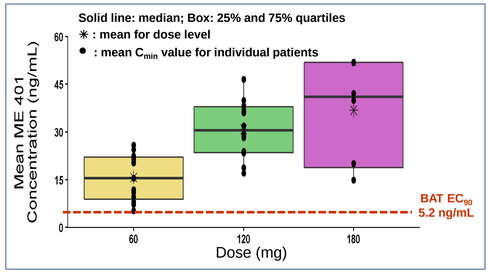
- 31 patients dosed with ME-401 (Table 1)
  - 1 subject at 60 mg dose replaced due to early withdrawal
- 50% of FL patients had disease progression within 24 months of initial immunochemotherapy (POD24)
- 50% FL have received ≥ 2 prior therapies
- 5 of 5 CLL/SLL patients evaluated had unmutated IgVH

Table 1. Demographics and Disease Characteristics

	FL N = 22	CLL/SLL N = 9	Total N = 31
Age in years, median (range)	65 (47-76)	60 (50-79)	65 (47-79)
Men, N (%)	14 (64%)	7 (78%)	21 (68%)
Number of prior therapies, median (range)	2 (1-5)	1 (1-2)	1 (1-5)
Subjects with prior anti-CD20 therapy, N (%)	22 (100%)	7 (78%)	29 (94%)
Subjects with prior alkylating therapy, N (%)	19 (86%)	8 (89%)	27 (87%)
Subjects with lymph nodes ≥ 5 cm, N (%)	11 (50%)	5 (56%)	16 (52%)

Pharmacokinetics

Steady state trough plasma concentrations exceed BAT EC_{90} at all 3 doses



Efficacy

Table 2. Overall Response Rates

	60 mg N = 12	120 mg N = 12	180 mg N = 6	Total N = 30
FL (N = 21)	*n = 6*	*n = 10*	*n = 5*	*n = 21*
ORR	5 (83%)	9 (90%)	4 (80%)	18 (86%)
Nodal/metabolic CR	2 (33%)	4 (40%)	0	6 (21%)
CLL/SLL (N = 9)	*n = 6*	*n = 2*	*n = 1*	*n = 9*
ORR	6 (100%)	2 (100%)	1 (100%)	9 (100%)
Nodal/metabolic CR	3 (50%)	0	0	3 (33%)
All evaluable patients	*n = 12*	*n = 12*	*n = 6*	*n = 30*
ORR	11 (92%)	11 (92%)	5 (83%)	27 (90%)
Nodal/metabolic CR	5 (42%)	4 (33%)	0	9 (30%)

- Objective responses in 27/30 (90%) patients (Table 2 and Figure 3)
- Nodal and/or metabolic complete response in 9/30 (30%) patients
- Objective responses in 10/10 (100%) POD24 patients
- Objective responses in 9/11 (82%) FL patients treated in ≥ 3rd line therapy
- 85% of responses (23/27) occurred at the 1st disease assessment at end of Cycle 2 (Figure 2)
- 1 responder had disease progression at Week 18
- Duration of response ranging from 1.5 to 15+ months, with 13 of 18 active patients having a response duration greater than 6+ months

Figure 2. Patient Disposition and Follow-up

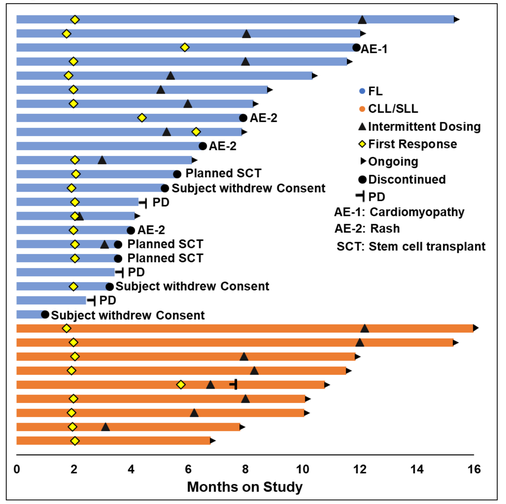
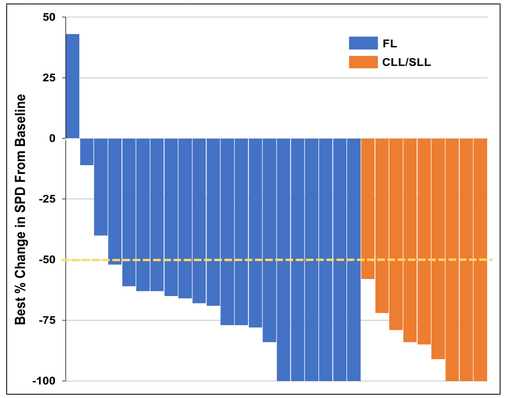


Figure 3. Best Overall Response



Safety

Table 3. Most Common Adverse Events

	Grade 1	Grade 2	Grade 3	All Grades
Diarrhea	5 (16%)	3 (10%)	6 (19%)	14 (45%)
Rash	5 (16%)	4 (13%)	4 (13%)	13 (42%)
Cough	11 (36%)	0	0	11 (36%)
Fatigue	5 (16%)	6 (19%)	0	11 (36%)
Nasal congestion	9 (29%)	0	0	9 (29%)
Stomatitis	2 (6%)	3 (10%)	1 (3%)	6 (19%)
GERD	3 (10%)	3 (10%)	0	6 (19%)
Nausea	5 (16%)	1 (3%)	0	6 (19%)
Appetite decreased	3 (10%)	2 (6%)	0	5 (16%)
Abdominal pain	4 (13%)	1 (3%)	0	5 (16%)
Edema peripheral	3 (10%)	2 (6%)	0	5 (16%)
Dry mouth	5 (16%)	0	0	5 (16%)
Colitis	0	0	2 (6%)	2 (6%)

Table 4. Laboratory Abnormalities

	All Grades	Grade 3	Grade 4
Neutropenia	14 (45%)	3 (10%)	1 (3%)*
Thrombocytopenia	7 (22%)	0	0
Anemia	4 (13%)	0	0
AST increased	8 (25%)	2 (6%)	0
ALT increased	12 (39%)	2 (6%)	0

* Patient with CLL had Grade 3 neutropenia at enrollment

- Adverse events in > 15% of patients are shown in Table 3
- No Grade 4-5 adverse events
- 4 patients (13%) discontinued due to an adverse event (Figure 2)
- All Grade 3 diarrhea/colitis (N = 8) and rash (N = 4) reported in Cycle 3 or later, and resolved with drug interruption and corticosteroids
- No early transaminitis; Grade 3 AST/ALT elevation reported in only 2 patients who also had diarrhea and/or rash (Table 4)
- Neutropenia infrequent and not associated with infections (Table 4)
- No drug-related hypertension or hyperglycemia reported

Conclusions

- ME-401 achieves a high objective response rate in patients with relapsed/refractory FL (86%) and CLL/SLL (100%)
- Nodal and/or metabolic complete responses in 30% of patients
- High response rates in FL patients treated in ≥ 3rd line therapy (82%) and in POD24 (100%)
- Responses appear durable, with 13/18 active patients having a response duration greater than 6+ months
- Intermittent dosing resulted in tumor regrowth in only 1 patient with CLL; disease responded upon return to daily dosing
- Comparable rates of adverse events across the dose range studied
- Diarrhea/colitis and rash are expected with PI3Kδ inhibition and manageable with ME-401 interruption and corticosteroids
- Neutropenia infrequent and has not been associated with infections
- Grade 3 transaminitis infrequent and observed only in patients with late diarrhea and/or rash
- No opportunistic infections or non-infectious pneumonitis reported
- Global clinical study in follicular lymphoma planned late 2018

Disclosures / Inquiries

- Study sponsored and funded by MEI Pharma, Inc.
- J. Soumerai is supported by a research grant from the Lymphoma Research Foundation
- We would like to thank the investigators, site staff, and especially the patients for participating in this study

- For inquiries, contact: inquiries@meipharma.com
- Clinicaltrials.gov identifier: NCT02914938