Disclosures for Andrew D. Zelenetz, MD, PhD

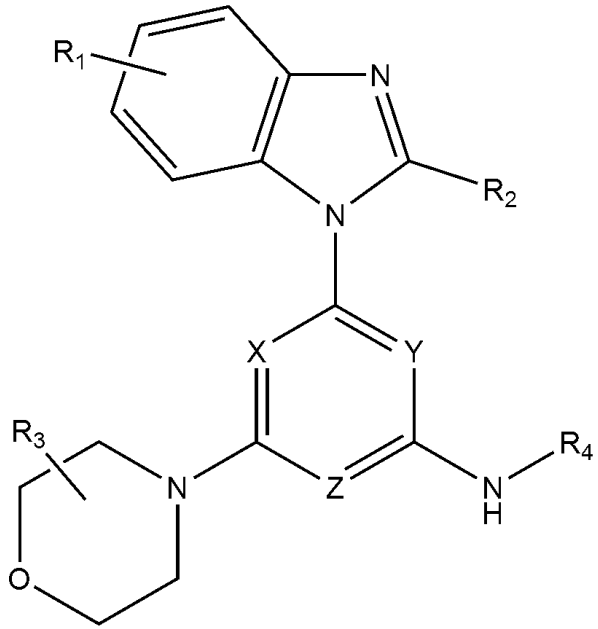
Research Support/P.I.	Genentech/Roche, Gilead, MEI, BeiGene
Employee	None
Consultant	Celegene; Genentech/Roche; Gilead; BeiGene; Amgen; Novartis; Astra-Zeneca; Verastem
Major Stockholder	None
Speakers Bureau	None
Scientific Advisory Board	Lymphoma Research Foundation, Adaptive Biotechnologies
Stockholder	None (not including potential holding of a 401K mutual fund)

ME-401 – A Novel Potent PI3Kδ Inhibitor

- Oral, potent, selective, structurally differentiated PI3Kδ Inhibitor
- Inhibits PI3Kδ at nanomolar concentrations
  - Mean IC50 = 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



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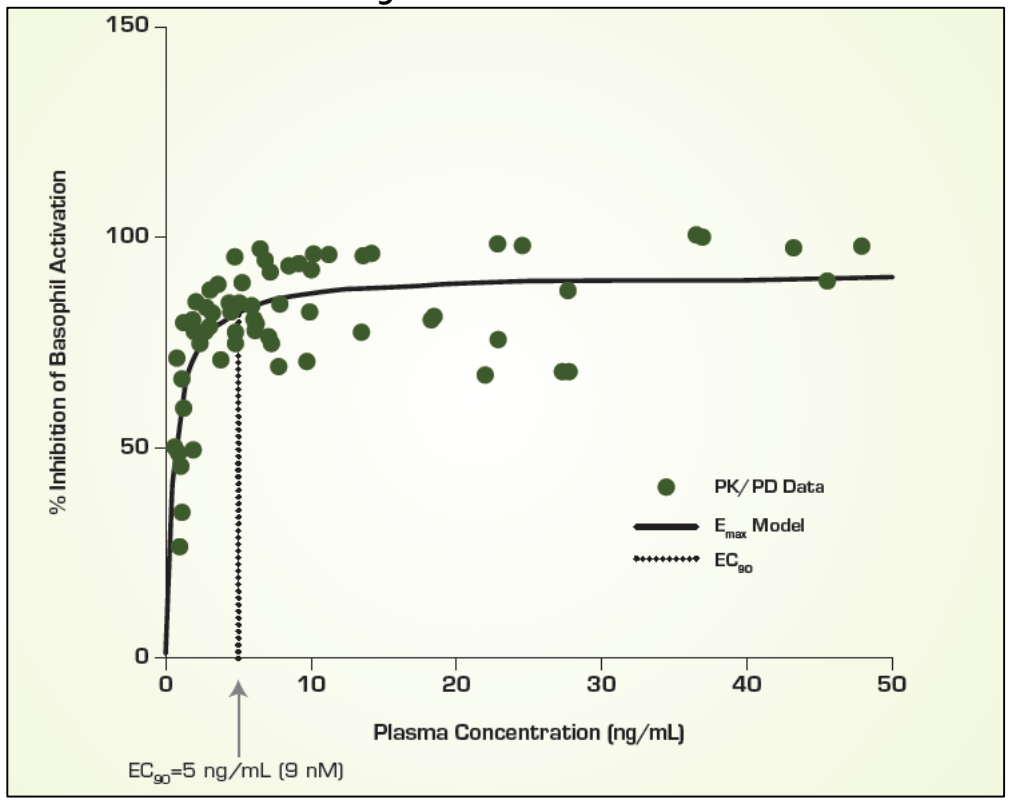
Phase 1 PK/PD Study in Healthy Volunteers

- Single dose of 10, 30, 60, 90 and 150 mg
- Linear PK across doses
- Half-life ~28 hours supports daily dosing
- EC90 ~ 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 EC90
- 60 mg selected as the starting dose level in the present study

EC_{90} in BAT assay



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

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Study Objectives

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

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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 ≥ minimally biologically effective 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 at least 2 cycles to evaluate:
  - A dose schedule for toxicity management in future trials
  - If disease control is maintained 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

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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
  - ME-401 at 60 mg in combination with BTKi planned for Q3

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Patient 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%)

- 50% of FL patients had disease progression within 24 months of initial immunochemotherapy (POD24)
- 50% FL have received ≥ 2 prior therapies
- 5 of 5 patients with CLL/SLL evaluated had unmutated IgVH

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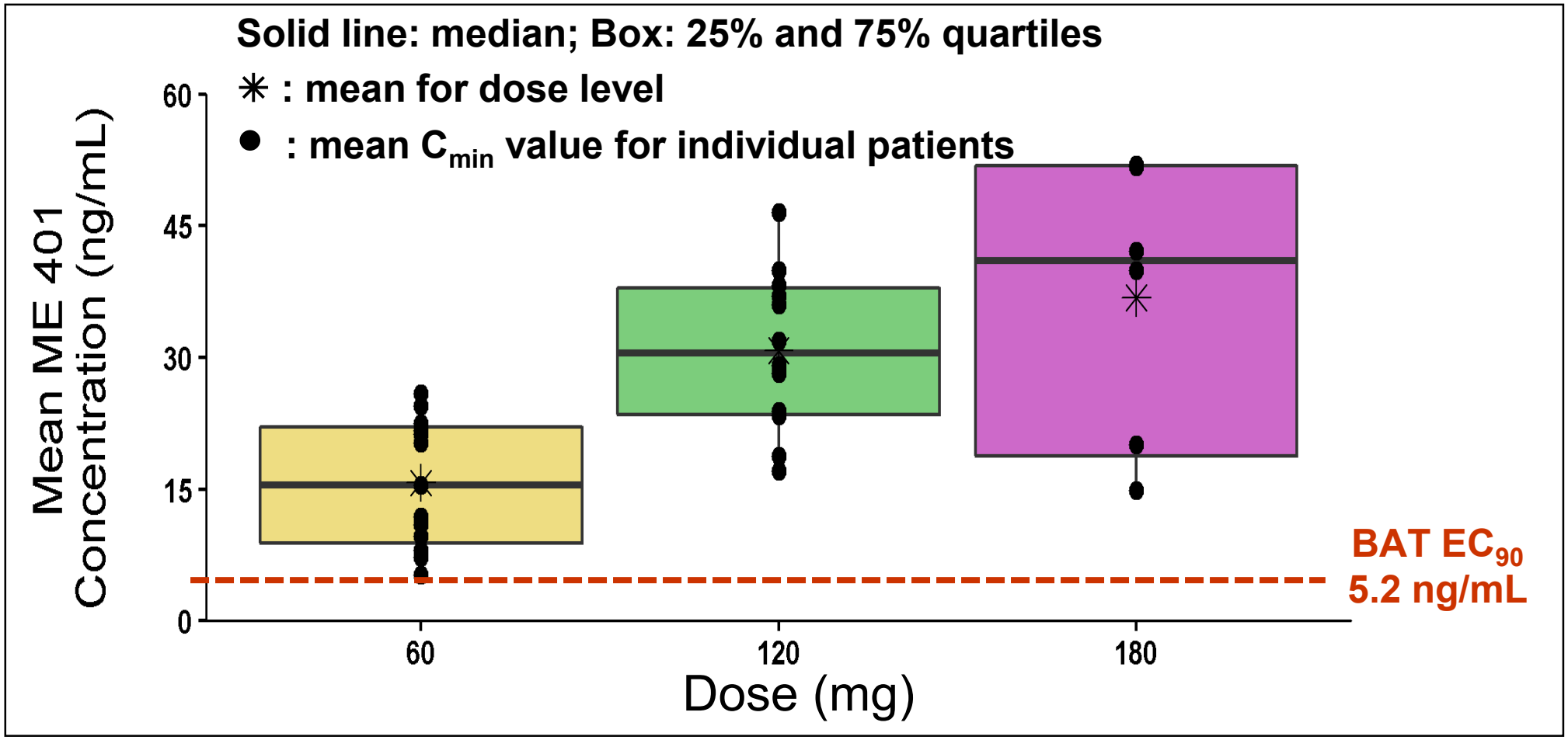
Pharmacokinetics

- Steady state trough plasma concentrations exceed BAT EC90 at all 3 doses



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Overall Response Rates

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

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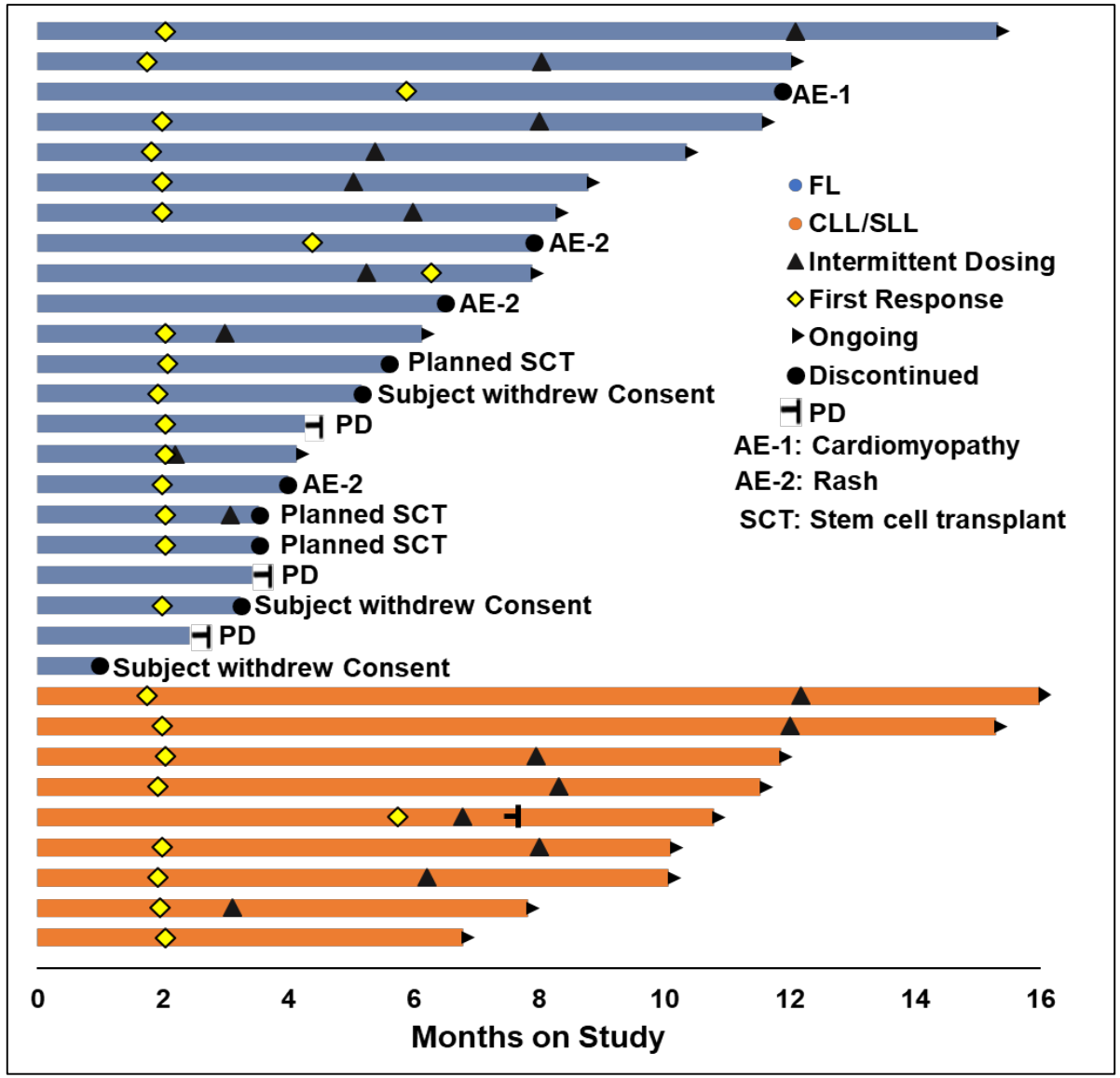
Patient Disposition and Follow-up



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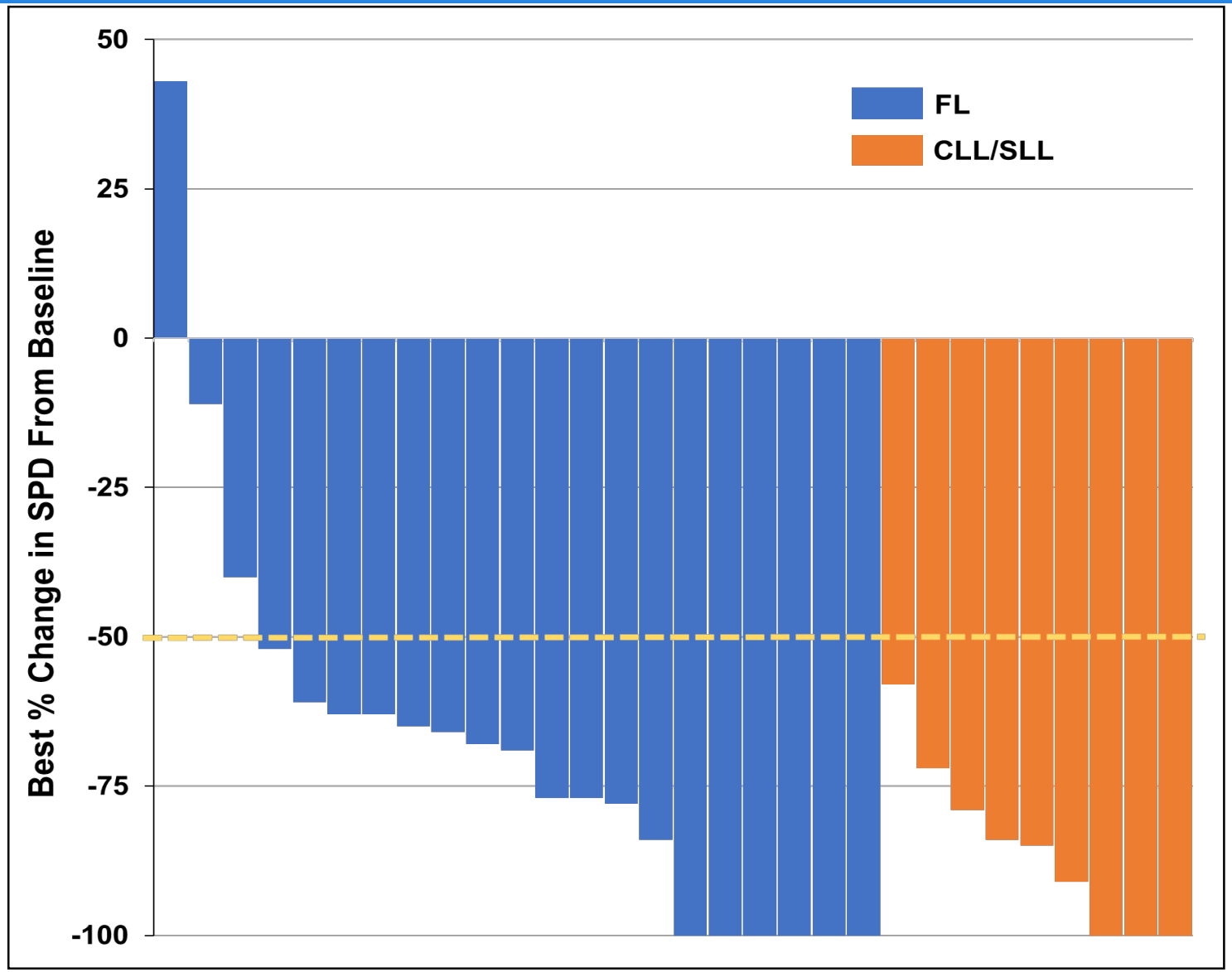
Best overall response



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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 (35%)
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%)

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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**

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Discontinuations

Subject ID	Reason for Discontinuation	Day of Discontinuation
Dose = 60 mg (N = 13)		
0012-001	Adverse event (cardiomyopathy)	333
1012-001	Adverse event (rash)	222
0012-006	Progression of disease	68
0012-003	Subject withdrew consent (personal reason)	28
0012-002	Subject withdrew consent (Gr 3 diarrhea 3 months prior)	145
Dose = 120 mg (N = 12)		
0012-004	Adverse event (rash)	182
0012-005	Adverse event (rash)	112
0200-001	Subject withdrew consent (Gr 3 rash 1 month prior)	91
4005-001	Preplanned stem cell transplant (Gr 3 colitis 2 months prior)	157
4005-004	Preplanned stem cell transplant	99
4005-005	Preplanned stem cell transplant (Gr 3 diarrhea 2 months prior)	99
Dose = 180 mg (n = 6)		
0005-008	Progression of disease	120
0005-011	Progression of disease	96

Drug was discontinued in 13 patients (all FL): AE x4, PD x3, SCT x3, Withdrew consent x3

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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 toxicities 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

Future Directions

- Combinations
  - Rituximab + ME410 Cohort in Phase 1/1B
  - Zanubrutinib + ME410 Cohort in Phase 1/1B

- Dosing
  - Randomized phase 2: ME401 continuous x 2 month then randomization to
    - Continuous dosing
    - 7 days on, 21 days off

Outcome of Grade 3 Adverse Events of Interest (diarrhea/colitis = 8, rash = 4, cardiomyopathy = 1)

Subject	Dose	Dx	Adverse Event	Outcome
12-001	60	FL	Cardiomyopathy Month 9	D/C Month 11
12-002	60	FL	Diarrhea Month 3 – recovered	Withdrew consent Month 5
1012-001	60	FL	Rash Month 4 – Re-challenge at 60 mg – Rash recurred Month 7	D/C Month 7
4005-002	60	FL	Diarrhea – Re-challenge with intermittent dosing	Ongoing 84 days after restart
4005-003	60	FL	Diarrhea – Re-challenge with intermittent	Ongoing 132 days after restart
12-005	120	FL	Rash Month 3	D/C Month 3
12-004	120	FL	Mucositis, AST/ALT Month 4 – Re-challenge at 60 – Rash Month 6	D/C Month 6
18-001	120	SLL	Diarrhea Month 10 on intermittent schedule, recovered restarted ME-401	Ongoing Month 12
200-001	120	FL	Meningoencephalitis then diarrhea at Month 3, recovered	Withdrew consent Month 4
4005-001	120	FL	Colitis, recovered	SCT
4005-005	120	FL	Colitis and rash, recovered	SCT
5-009	180	FL	Diarrhea – re-challenge with intermittent at 180	Ongoing 38 days after restart

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