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Background: ME-401, a potent and selective oral PI3kδ inhibitor, is being evaluated in a Phase 1b study in patients (pts) with R/R B-cell malignancies (NCT02914938). 70 pts were treated as of January 2019 and we report here results in pts with FL and CLL/SLL.

Methods: Adult pts with ECOG performance status ≤2, no prior PI3K therapy, and progression of disease (POD) after ≥1 prior therapy were initially enrolled in a dose escalation phase (60-180 mg) then in 60 mg expansion cohorts as monotherapy or in combination with rituximab (375 mg/m² x 8 doses in 6 months). ME-401 was given initially on a daily continuous schedule (CS) until POD or unacceptable toxicity. Patients on CS were switched to an intermittent schedule (IS) on days 1-7 of a 28-day cycle in Cycle 3 (n = 20) or in Cycles ≥4 (n = 18) of CS. Toxicity on CS was managed by switch to IS and POD on IS was managed by switch to CS.

Results: 61 pts, 48 with FL and 13 with CLL/SLL received ME-401 alone (n = 48) or with rituximab (n = 13). Median age 65 yrs. (range: 38-81), median prior therapies 2 (range: 1-10), 33 pts had ≥2 prior therapies, and 25 FL pts were POD24. In CLL/SLL pts, IgVH was unmutated in 7, mutated in 2, and not evaluated in 4. 39 pts (64%) remain on therapy with a median follow-up of 12.3 months (range: 1.6-25.1) and 22 pts discontinued: 9 POD, 5 adverse events (AEs), 5 withdrew consent, and 3 were referred to stem cell transplant in CR. Delayed (i.e., Cycle >2) grade 3 immune related AEs (irAEs), primarily diarrhea/colitis and rash, were reported in 13/41 pts (31.7%) on CS and 2/20 pts (10%) who had switched to IS in Cycle 3, with irAEs noted 15 and 18 days after switch to IS. 6 pts with grade 3 irAEs had a drug holiday and corticosteroid therapy then resumed ME-401 on IS without recurrence of the irAE. Objective responses were achieved in 33/43 evaluable FL pts (77%) and 11/11 evaluable CLL/SLL pts (100%). In FL, response rate was 77% with ME-401 alone (including 29% CR by Lugano criteria), 78% with ME-401 plus rituximab, 91% in POD24, and 75% in pts who had ≥2 prior therapies. Of 38 pts switched to IS, 33 (87%) remain on therapy (median: 14.5 months), 26 on IS and 7 who switched back to CS due to POD on IS, 3 pts discontinued due to persistent POD after switch to CS, and 2 pts withdrew.

Conclusions: ME-401 achieves a high rate of durable responses in R/R FL and CLL/SLL. IS appears to reduce the incidence of irAEs and maintain responses. POD on IS can be successfully retreated by reverting to CS. A global study is enrolling pts with R/R FL randomized to ME-401 by IS or CS after 2 cycles of CS, with switch to IS for irAEs and switch to CS if POD on IS (NCT03768505).

Keywords: chronic lymphocytic leukemia (CLL); follicular lymphoma (FL); PI3K/AKT/mTOR.

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TABLE 1

Dosing Schedule	No. of Pts	No. (%) of irAEs	No. Efficacy Evaluable Pts	No. (%) CR+PR
CS or CS → IS in Cycles ≥4	41	13 (31.7%)	34	28 (82%)
CS → IS in Cycle 3	20	2 (10%)	20	16 (80%)

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INVESTIGATING SAFETY AND PRELIMINARY EFFICACY OF AFM13 PLUS PEMBROLIZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA AFTER BRENTUXIMAB VEDOTIN FAILURE

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Background: AFM13 is a bispecific, tetravalent NK cell-engaging antibody construct binding to CD30 on Hodgkin Lymphoma (HL) cells and CD16A on NK cells [1]. Pembrolizumab is a PD-1 blocking antibody that induces high response rates in patients (pts) with relapsed or refractory HL (RRHL) [2]. AFM13 has shown clinical activity in pts with RRHL in a Phase 1 study [3]. Preclinical data of the combination of AFM13 with PD-1 inhibition suggest synergism [4].

Methods: This Phase 1b dose escalation/extension study is evaluating the safety, tolerability and preliminary efficacy of the combination of AFM13 with pembrolizumab as salvage therapy after failure of standard therapies including brentuximab vedotin (BV) in pts with HL (NCT02665650). Pts receive escalating doses of AFM13 in combination with pembrolizumab following the classical 3+3 design. Response assessment is performed every 12 weeks by PET/CT according to the Lugano Classification [5]. Data as of February 12, 2019 are presented.

Results: All thirty pts have been enrolled. The median age is 34 years (18-73), with a median of 4 (3-7) prior lines of therapy. All pts have failed standard treatments including BV and 43% had BV as their latest therapy. Thirty seven percent have undergone prior autologous stem cell transplantation. Twelve pts were enrolled into the dose escalation cohorts and 18 into the Extension Cohort. All 30 pts completed the dose limiting toxicity (DLT) observation period. No DLTs occurred in Cohorts 1/2, one DLT occurred in Cohort 3 (missed ≥25% of AFM13 during the DLT period) and one DLT occurred in the Extension Cohort (Grade (G)4 infusion-related reaction (IRR)). Adverse Events were mainly G1/G2 and included IRRs (87%), rash (30%), nausea (23%), pyrexia (23%), and diarrhea (20%). G3/4 AEs included IRRs (13%), elevated aspartate aminotransferase (3%), gastritis (3%), hypotension (3%), nausea (3%), neutropenia (3%), and vomiting (3%). Included in the efficacy analysis were the best response from all 30 patients. The best overall response rate (ORR) and complete response (CR) rate for pts treated at the dose and schedule chosen for expansion (n=24; Cohort 3 and Extension Cohort) were 88% and 46% by independent assessment. Investigator assessment resulted in an ORR of 88% and CR rate of 42% for these pts. Estimated 6-month PFS rate at the highest treated dose level was 77%. Longer term follow up results will be presented at the meeting.

Conclusions: The combination of AFM13 and pembrolizumab is well-tolerated with most AEs mild to moderate in nature. The ORR of 88% compares favorably to the historical data of pembrolizumab in a similar RRHL population, with the CR rates of 42% and 46% by local and independent assessment, respectively, approximately doubling that of pembrolizumab (CR rates 22-25%) [2].

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TARGETING THE PERIPHERAL T-CELL LYMPHOMA (PTCL) EPIGENOME WITH ORAL 5-AZACYTIDINE AND ROMIDEPSIN: RESULTS AND CLINICAL-MOLECULAR CORRELATIONS FROM A PHASE 2 STUDY

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Introduction: PTCL exhibit pervasive dysfunction of epigenetic operations. This may be a targetable vulnerability, as demonstrated by the single-agent activity of histone deacetylase inhibitors (HDACi) and hypomethylating agents (HMA). We previously showed marked synergism between HDACi and HMA in T-cell lymphoma lines, accompanied by the modulation of >900 unique genes with the combination, but not the single agents. In a recently completed phase-1 study we observed encouraging activity of combined oral 5-azacytidine (AZA)