Results of a completed Phase 1 study of LAM-002 (apilimod dimesylate), a first-in-class phosphatidylinositol-3-phosphate 5 kinase (PIKfyve) inhibitor, administered as monotherapy or with rituximab or atezolizumab to patients with previously treated follicular lymphoma or other B-cell cancers.

**Background:** LAM-002 is a selective inhibitor of PIKfyve that disrupts lysosomal homeostasis, inducing cytotoxicity in B-cell lymphoma models as monotherapy or with anti-CD20 or anti-PD-L1 antibodies (Gayle et al., Blood 2017;129(13):1768).

**Methods:** In this study, patients received LAM-002 orally 2-3 times per day (BID or TID) in a 3+3 escalation. Additional patients received LAM-002 125 mg BID as monotherapy; with rituximab 375 mg/m² intravenously (IV) and or subcutaneously weekly (Q1W) x 4 → Q8W x 4; or atezolizumab 1200 mg IV Q3W until disease progression or unacceptable toxicity. Pharmacokinetics (PK) were assessed for 8 hours postdose on Days 1 and 8. Efficacy was evaluated Q6-12W.

**Results:** The study enrolled 62 patients (M:F n=32/30); median [range] age=69 [46-89] years; with diagnoses (n) of diffuse large B-cell lymphoma (25), follicular lymphoma (19), marginal zone lymphoma (8), mantle cell lymphoma (5), or chronic lymphocytic leukemia (5) to receive LAM-002 alone (n) at 50 mg BID (3), 100 mg BID (8), 150 mg BID (8), 75 mg TID (4), or 125 mg BID (20); LAM-002/rituximab (12); or LAM-002/atezolizumab (7). During LAM-002 dose-ranging (50 mg BID → 100 mg BID → 150 mg BID → 75 mg TID → 125 mg BID) transient, reversible nausea and/or diarrhea occurred at 150 mg BID and 75 mg TID, resulting in a LAM-002 recommended Phase 2 dosing regimen (RP2DR) of 125 mg BID. Among 39 patients receiving LAM-002, 125 mg BID, alone or in combination for up to 22 cycles (1.9 years), adverse events were typically low-grade. LAM-002 PK showed rapid absorption, dose proportionality, minimal accumulation, and no substantive changes with rituximab or atezolizumab coadministration. In patients with follicular lymphoma and median [range] prior therapies=3 [1-9] treated with the RP2DR, objective response rates were 2/7 (29%; 1 complete response [CR], 1 partial response [PR]) with LAM-002, 5/8 (63%; 1 CR, 4 PRs) with LAM-002/rituximab, and 2/2 (100%; 2 PRs) with LAM-002/atezolizumab.

**Conclusions:** LAM-002, the first clinical PIKfyve inhibitor, is safe alone or with full-dose anti-CD20 or anti-PD-L1 inhibition. LAM-002 does not cause the myelosuppressive or immune adverse events associated with lenalidomide or PI3K inhibitors. Promising efficacy supports registration-directed Phase 2/3 testing of LAM-002 monotherapy and combination therapy for patients with previously treated follicular lymphoma.
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