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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

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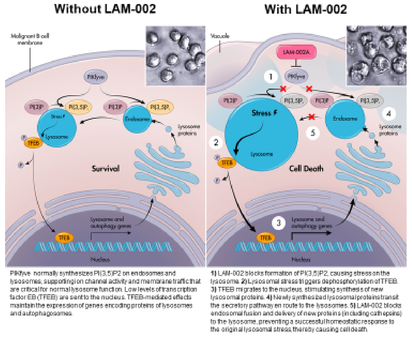
LAM-002 Is a Novel, Selective Inhibitor of PIKfyve that Causes Tumor Cell Death By Modulation of Lysosomal Homeostasis



PIKfyve normally synthesizes PI(3,5)P2 on endosomes and lysosomes, supporting ion channel activity and membrane trafficking that are critical for normal lysosome function. Low levels of transcription factor EB (TFEB) are sent to the nucleus. TFEB-mediated effects maintain the expression of genes encoding proteins of lysosomes and autophagosomes.

1) LAM-002 blocks formation of PI(3,5)P2, causing stress on the lysosome. 2) Lysosomal stress triggers dephosphorylation of TFEB. 3) TFEB migrates to the nucleus, stimulating synthesis of new lysosomal proteins. 4) Newly synthesized lysosomal proteins transit the secretory pathway en route to the lysosomes. 5) LAM-002 blocks endosomal fusion and delivery of new proteins (including cathepsins) to the lysosome, preventing a successful homeostatic response to the original lysosomal stress, thereby causing cell death.

- PIKfyve
  - Lipid kinase that regulates endosomal membrane trafficking[1,2] (left figure panel)
- LAM-002 (apilimod dimesylate)
  - Orally bioavailable, small molecule with exclusive selectivity for PIKfyve inhibition
  - Disrupts lysosomal homeostasis, promoting death of non-Hodgkin lymphoma (NHL) cells (right figure panel)[3]
  - DOES NOT inhibit PI3Kα, β, γ, or δ (ie, distinct from drugs like idelalisib, copanlisib, duvelisib, or umbralisib)

Patient Characteristics Were Typical for Those with NHL; Long Durations of Therapy and Excellent Compliance Were Achieved

Patient Characteristics (Stages 1 and 2)

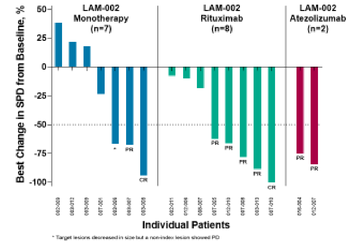
Parameter	N=62
Age	
Median (range), years	69 (46-89)
≥65 years, n (%)	24 (38.7)
<65 years, n (%)	38 (61.3)
Sex, n (%)	
Male	32 (51.2)
Female	30 (48.4)
ECOG performance status, n (%)	
0	18 (29.0)
1	39 (62.9)
2	4 (6.5)
3	1 (1.6)
Disease type, n (%)	
DLBCL	25 (40.3)
FL	19 (30.7)
MZL	8 (12.9)
MCL	5 (8.1)
CLL	5 (8.1)

Treatment Administration/Compliance (Stage 2)

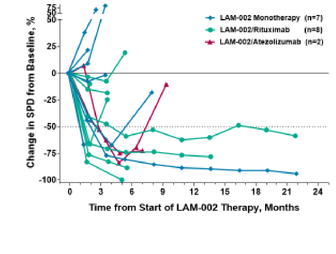
Regimen	LAM-002 Duration median (range), days	LAM-002 Compliance median (range), %
LAM-002 monotherapy (n=20)	39 (5-729+)	86 (14-100)
LAM-002/rituximab (n=11)	156 (15-639+)	94 (3-100)
LAM-002/atezolizumab (n=6)	17 (7-261)	85 (8-99)

- When administered alone or in combination at the LAM-002 RDR, durations of LAM-002 therapy were dictated primarily by response to therapy, with long durations among those with responsive cancers
- Median diary-assessed LAM-002 compliance was >85% whether LAM-002 was given alone or in combination
- LAM-002 dose was modified from 125 → 100 mg BID for drug-related nausea or diarrhea in 3/39 (7.7%) of patients treated at the RDR (LAM-002 alone [n=2]; LAM-002/rituximab [n=1])

Durable LAM-002 Antitumor Activity Was Observed in Patients with Previously Treated Follicular Lymphoma

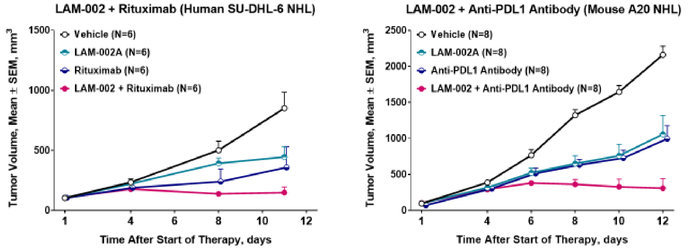


* Target lesions decreased in size but a non-index lesion showed PD



- ORR included: Overall=9/17 (53%); LAM-002 monotherapy=2/7 (29%); LAM-002/rituximab=5/8 (63%); LAM-002/atezolizumab=2/2 (100%)
- Responding patients had 1, 1, 2, 3, 3, 4, 4, 4, 9 prior regimens (including prior ASCT in 3 patients)
- Overall median PFS (n=17) was 7.0 months and median DOR (n=8) was 6.6 months; 4 patients remain on therapy
- In addition, 1 patient with MZL (3 prior therapies) received LAM-002/rituximab and had a PR (-87.9% ↓ in SPD) with DOR of 9.2 months

In Animal Models, LAM-002 Demonstrated Antitumor Activity Alone or in Combination with Anti-CD20 or Anti-PDL1 Antibodies[3]



LAM-002, 60 mg/kg PO BID × 11 days and rituximab, 7 mg/kg IP every 4 days × 3 injections;
LAM-002, 90 mg/kg PO BID × 3 days → 60 mg/kg PO BID × 9 days and anti-PDL1 antibody, 5 mg/kg IP every 3-4 days × 4 injections.

Transient, Reversible Gastrointestinal Events Were the Primary Toxicities, Usually at Doses Exceeding the RDR

Adverse Events in ≥20% of Patients by LAM-002 Monotherapy Regimen

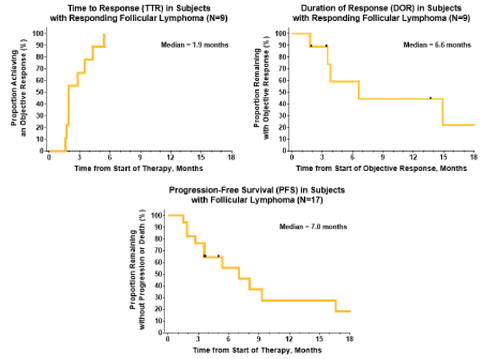
MedDRA Preferred Term	Continuous 50 mg BID N=3	Continuous 100 mg BID N=8	Continuous 150 mg BID N=5	Intermittent 75 mg TID N=4	Intermittent 125 mg BID (RDR) N=20	Intermittent 150 mg BID N=3	All Regimens N=43
	n (%)						
Fatigue	0	4 (50.0)	2 (40.0)	2 (50.0)	9 (45.0)	1 (33.3)	18 (41.9)
Nausea	0	3 (37.5)	3 (60.0)	3 (75.0)	8 (40.0)	0	17 (39.5)
Diarrhea	1 (33.3)	0	2 (40.0)	2 (50.0)	5 (25.0)	2 (66.7)	12 (27.9)
Vomiting	0	1 (12.5)	3 (60.0)	3 (75.0)	4 (20.0)	0	11 (25.6)
Decreased appetite	0	1 (12.5)	0	1 (25.0)	7 (35.0)	0	9 (20.9)
Anemia	0	3 (37.5)	0	2 (50.0)	5 (25.0)	0	10 (23.3)

Adverse Events in ≥20% of Patients by LAM-002 Monotherapy/Combination Regimens

MedDRA Preferred Term	LAM-002 Monotherapy N=20	LAM-002/ Rituximab N=12	LAM-002/ Atezolizumab N=7	All Regimens N=39
	n (%)			
Fatigue	9 (45.0)	5 (41.7)	1 (14.3)	15 (38.5)
Nausea	8 (40.0)	2 (16.7)	4 (57.1)	14 (35.9)
Diarrhea	5 (25.0)	4 (33.3)	1 (14.3)	10 (25.6)
Vomiting	4 (20.0)	2 (16.7)	4 (57.1)	10 (25.6)
Decreased appetite	7 (35.0)	1 (8.3)	1 (14.3)	9 (23.1)
Anemia	5 (25.0)	0	2 (28.6)	7 (17.9)

- Gastrointestinal adverse events showed dose dependency and were typically attributed to LAM-002
- Fatigue and anemia were not clearly dose dependent and may have been related to the underlying cancer
- Neutropenia and thrombocytopenia occurred in <20% of patients and were likely related to disease
- Grade ≥3 TLS was observed in 3 subjects (monotherapy for DLBCL [n=2]; LAM-002/rituximab for MZL [n=1]) with bulky tumors
- A Grade 3 immune colitis following a post-therapy *C. difficile* infection was seen in 1 patient treated with LAM-002/atezolizumab
- At the MTD and RDR (125 mg BID) adverse events were typically low grade; there were no overlapping toxicities with rituximab or atezolizumab

Time-to-Event Data Confirmed the Potential for Rapid and Durable Treatment Benefit



- All responses occurred by the time of the first or second post-baseline scan (~8 or ~16 weeks)
- Median DOR and PFS values were similar
- Protracted disease control was possible with LAM-002-based therapy

The LAM-002 Study Evaluated LAM-002 as Monotherapy and in Combination with Anti-CD20 and Anti-PDL1 Antibodies

Stage 1: 3+3 Dose-Ranging to MTD

Objectives (Stage 1)
- Define MTD and RDR
- Characterize safety
- Evaluate pharmacokinetics
- Determine antitumor activity

Patient Population (Stages 1 & 2)
- Relapsed/refractory NHL
- Adults with ECOG PS ≤2
- Adequate organ function
- Measurable disease

LAM-002, 50 mg BID PO Continuous to PD (n=3)
LAM-002, 100 mg BID PO Continuous to PD (n=8)
LAM-002, 150 mg BID PO Continuous to PD (n=5)
LAM-002, 75 mg TID PO Continuous to PD (n=4)
LAM-002, 125 mg BID PO Continuous to PD (n=6)
LAM-002, 150 mg TID PO 3 Days on/4 Days Off (n=3)

Dose Escalation
- 50 mg BID, 100 mg BID regimens were well tolerated
- 150 mg BID and 75 mg TID regimens caused rapid onset nausea, vomiting, and/or diarrhea precluding adequate compliance
- 125 mg BID was RDR

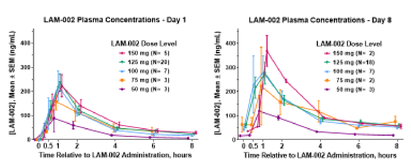
Stage 2: Expansion/Combinations

Objectives (Stage 2)
- Assess monotherapy safety/efficacy
- Assess safety/efficacy with anti-CD20 antibody
- Assess safety/efficacy with anti-PDL1 antibody

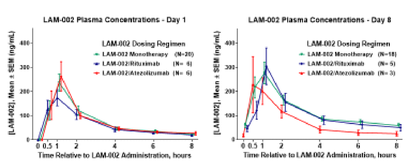
LAM-002, 125 mg BID PO, Continuous to PD Monotherapy (n=20; including 6 patients from Stage 1)
LAM-002, 125 mg BID PO, Continuous to PD Rituximab, 375 mg/m² IV or SC Q1W × 4 → Q8W × 4 (n=12)
LAM-002, 125 mg BID PO, Continuous to PD Atezolizumab, 1200 mg IV Q3W to PD (n=7)

LAM-002 Was Orally Bioavailable and Showed Modest Accumulation at Steady State; Combination Therapy Did Not Alter LAM-002 Exposures

Stage 1: LAM-002 Monotherapy Dose-Ranging



Stage 2: LAM-002 Monotherapy and Combinations



- LAM-002 was rapidly orally bioavailable with a T_{max} of ~1 hour
- The LAM-002 C_{max} and AUC_{0-8} generally increased with increasing dose
- Mean Day 8/Day 1 LAM-002 exposure ratios for C_{max} and AUC_{0-8} were 1.3 and 1.7, respectively
- Mean LAM-002 $t_{1/2}$ values did not change with dose but appeared to increase at steady state (Day 1: 2.7-3.9 hours; Day 8: 5.4-7.0 hours)
- Considering data variability, coadministration with rituximab or atezolizumab did not substantially alter LAM-002 exposures

LAM-002 Conclusions and Next Steps

- LAM-002, the first clinical PIKfyve inhibitor (distinct from PI3K inhibitors), was studied as a novel oral therapy in 62 patients with B-cell NHL
- During dose escalation, regimens of 150 mg BID or 75 mg TID caused gastrointestinal symptoms precluding effective compliance; no other DLTs were observed
- With the recommended dosing regimen (RDR) of 125 mg BID, LAM-002 has been well tolerated for periods to >2 years when given as monotherapy or with rituximab or atezolizumab
  - Median dosing compliance was >95%
  - Only 10% of patients requested dose modification to 100 mg BID (for gastrointestinal symptoms)
- LAM-002 therapy was not associated with drug-induced myelosuppression or immune adverse events (as with lenalidomide or PI3K inhibitors)
- ORR of 9/17 (53%), with durable PRs and CRs, supports Phase 2 and 3 studies of LAM-002 monotherapy and LAM-002/rituximab combination therapy for patients with previously treated follicular lymphoma

References
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2. Gayle S, et al. *Autophagy*. 2017a Jun 3;13(6):1083-1083. PMID: 28350209.
3. Gayle S, et al. *Blood*. 2017b Mar 30;129(13):1768-1778. PMID: 28104689.

Abbreviations
ASCT=autologous stem cell transplantation, AUC_{0-8}=area under the concentration-time curve to 8 hours postdose, BID=2 times per day, CLL=chronic lymphocytic leukemia, C_{max}=maximum concentration, CR=complete response, DLBCL=diffuse large B-cell lymphoma, DOR=duration of response, ECOG=Eastern Cooperative Oncology Group, FL=follicular lymphoma, IP=intraperitoneally, IV=intravenously, MCL=mantle cell lymphoma, MedDRA=Medical Dictionary for Regulatory Activities, MZL=marginal zone lymphoma, MTD=maximum tolerated dose, NHL=non-Hodgkin lymphoma, ORR=objective response rate, PD=progressive disease, PDL1=programmed death ligand 1, PI3K=phosphoinositide 3-kinase, PO=orally, PFS=progression-free survival, PR=partial response, Q1W=weekly, Q3W=every 3 weeks, Q8W=every 8 weeks, RDR=recommended dosing regimen, SPD=sum of the products of the perpendicular diameters, SEM=standard error or the mean, TID=3 times per day, TLS=tumor lysis syndrome, T_{max}=time of maximum concentration, TTR=time to response

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