SESSION 626 | POSTER 4119

ASH ANNUAL MEETING
DECEMBER 9-12
ATLANTA, GA, USA

Phase 1 Clinical Safety, Pharmacokinetics (PK), and Activity of Apilimod Dimesylate (LAM-002A), a First-in-Class Inhibitor of Phosphatidylinositol-3-Phosphate 5-Kinase (PIKfyve), in Patients with Relapsed or Refractory B-Cell Malignancies

ClinicalTrials.gov Identifier: **NCT0259438**

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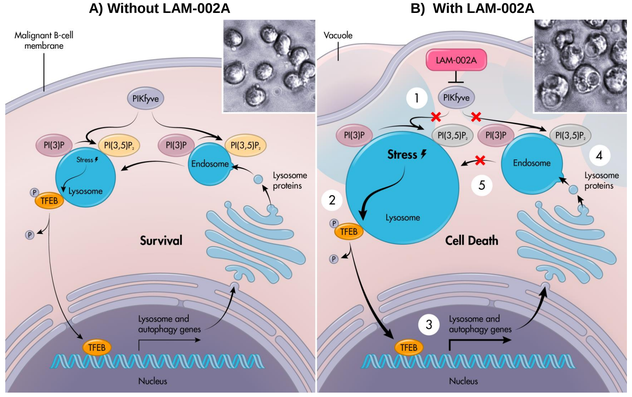
BACKGROUND

- PIKfyve is an endosomal lipid kinase that phosphorylates PI(3)P to phosphatidylinositol 3,5-bisphosphate (PI[3,5]P2), regulating endosomal membrane trafficking.
- PIKfyve has a critical role in autophagy, the removal of damaged proteins by proteases (cathepsins) in autophagolysosomes that promotes cell survival[1, 2] (***Figure 1A***).
- LAM-002A (apilimod dimesylate) is an orally bioavailable, highly potent (81 pM Kd), small molecule (MW 611) with exclusive selectivity for PIKfyve that disrupts lysosomal homeostasis, promoting death of B-cell non-Hodgkin lymphoma (B-NHL) cells[3] (***Figure 1B***).

Figure 1. LAM-002A Inhibition of Autophagy Causes B-NHL Cell Death

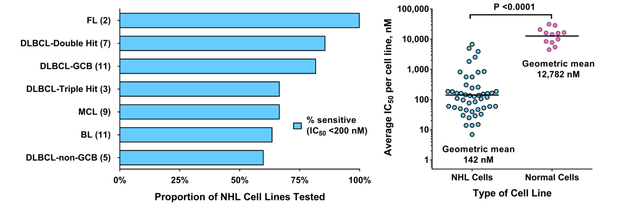


PIKfyve normally synthesizes PI(3,5)P2 on endosomes and lysosomes, supporting ion channel activity and membrane traffic that are critical for normal lysosome function. Low levels of transcription factor EB (TFEB) are sent to the nucleus. TFEB-mediated effects maintain the expression of genes encoding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

1) LAM-002A 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-002A 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.

- *In vitro*, LAM-002A shows selective nanomolar activity in B-cell cancers (***Figure 2***), including diffuse large B-cell lymphoma (DLBCL) harboring c-*MYC* and/or *BCL-2* translocations.[3]

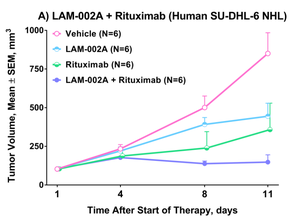
Figure 2. LAM-002A *In Vitro* Activity and Selectivity in Human B-Cell Cancers

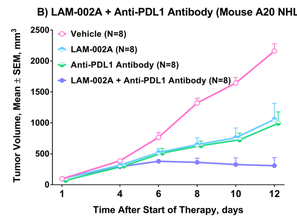


Results from 5-day Cell-Titer Glo viability assays in 48 human B-NHL cell lines and 12 normal cell lines.
Abbreviations: BL, Burkitt lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GCB, germinal center B-cell; IC_{50}, half-maximal inhibitory concentration; MCL, mantle cell lymphoma

- LAM-002A alone and in combination with anti-CD20 and anti-PDL1 antibodies demonstrates significant *in vivo* antitumor activity in B-cell NHL[3] (***Figure 3***).

Figure 3. LAM-002A *In Vivo* Monotherapy/Combination Activity in Mouse Models





A) LAM-002A, 60 mg/kg PO BID × 11 days and rituximab, 7 mg/kg IP every 4 days × 3 injections;
B) LAM-002A, 90 mg/kg PO BID x 3 days → 80 mg/kg PO BID x 9 days and anti-PDL1 antibody, 5 mg/kg IP every 3-4 days x 4 injections.
Abbreviations: BID, 2 times per day; B-NHL, B-cell non-Hodgkin lymphoma; IP, intraperitoneally; PDL1, programmed death ligand 1; PO, orally; SEM, standard error of mean.

References
1. Alinari L. *Blood*. 2017 Mar 30;129(13):1740-1742. PMID: 28360356.
2. Gayle S, et al. *Autophagy*. 2017a Jun 3;13(6):1082-1083. PMID: 28350209.
3. Gayle S, et al. *Blood*. 2017b Mar 30;129(13):1768-1778. PMID: 28104689.

Conflict-of-Interest Disclosures
WAH: LAM Therapeutics (LAM Tx); **CSD**: Genentech (Gen), Bristol Myers Squibb (BMS), Merck, Bayer, LAM Tx, Janssen, Seattle Genetics (S Gen); **NL**: Argule, Merck, Pfizer, Dicerna, Asana, TaiRx, Forty-Seven, Alexion, Formation Biologics. Alexo, Loxo, Beigene, Ascentage, Daiichi Sankyo, Cerulean, Regeneron, LAM Tx, BMS; Novartis; **SCR**: Gen, Juno Therapeutics, LAM Tx; **MTS**: LAM Tx; **SMA**: Merck, BMS, S Gen, Affimed, Celldex; **Sher**: LAM Tx; **DMA**: LAM Tx; **JBC**: Takada, Bioinvent, Infinity, LAM Tx, Janssen, Novartis. BMS; Abbvie, Gen; **DN**: LAM Tx; **SL**: LAM Tx; **KF**: LAM Therapeutics; **LLM**: Presage Biosciences, FLX Bio, EpiThany, Cleveland BioLabs, Oncternal Therapeutics, LAM Tx, eFFECTOR Therapeutics, Zucero, Sunesis; PRONAI Therapeutics, Acerta Pharma, Velos Biopharma; **HL**: LAM Tx; **JSA**: Kite Pharma, Abbvie, LAM Tx, Gilead, Celgene, Gen, S Gen, Novartis.

STUDY DESIGN

Design: Phase 1, dose-ranging study with 3+3 dose escalation.

Objectives: Assessment of maximum-tolerated dose (MTD), dose-limiting toxicities (DLT), recommended dosing regimen (RDR), safety profile, PK, and antitumor activity.

Eligibility: Adults with relapsed or refractory B-cell cancers.

Therapy: Oral administration of LAM-002A BID or 3 times per day (TID) continuously in 28-day cycles until lymphoma progression or unacceptable toxicity.

Assessments: Safety at each at each visit; PK and ex vivo pharmacology over 8 hours postdose on Days 1 and 8; antitumor activity at 6- to 12-week intervals.

RESULTS

Patient Characteristics (***Table 1***)

- The 26 patients ranged in age up to 89 years and 62% had ECOG scores ≥1, indicating symptomatic compromise due to their cancers or comorbidities.
- The most common cancer was DLBCL, with other B-NHL types and CLL also represented.
- Patients were heavily treated, having received a median of >3 prior regimens (up to 10 prior regimens).

Treatment Disposition (***Table 2***)

- Both BID and TID dosing regimens were explored, with LAM-002A doses ranging from 50 mg BID (100 mg/day) to 150 mg BID (300 mg/day).
- The duration of therapy ranged from <1 to ≥12 cycles; with 1 patient with CLL and 1 patient with MZL remaining on therapy for 12 and 12+ cycles, respectively.
- The primary reasons for treatment discontinuation included disease progression or gastrointestinal adverse events (AEs) at higher dose levels.

Table 1: Patient Characteristics (N=26)

Characteristic	N=26
Sex, male/females, n (%)	12 (46)/14 (54)
Age, median (range), years	69 (47-89)
ECOG performance status, n	
0	10 (38)
1	14 (54)
2	2 (8)
Disease type, n	
DLBCL[a]	12
GCB subtype	6
Non-GCB subtype	4
Unknown subtype	2
MCL	4
CLL	4
MZL	3
FL	3
Prior therapies, median (range), n	3 (1-10)

[a] Includes 3 patients (FL [n=2] or MCL [n=1]) with transformed DLBCL

Table 2: Treatment Disposition (N=26)

Disposition	N=26
LAM-002A regimen (total daily dose), n	
50 mg BID (100 mg/day)	3
100 mg BID (200 mg/day)	8
75 mg TID (225 mg/day)	4
125 mg BID (250 mg/day)	6
150 mg BID (300 mg/day)	5
Duration of therapy, range, cycles	<1-12+
Disposition, n	
Discontinued – Reason	22
Progressive disease	13
AE[a]	6
Subject withdrawal[b]	2
Mixed response → CAR T-cells	1
Continuing, n	4

[a] AEs resulting in discontinuation included: neck pain (100 mg BID, n=1); acute renal dysfunction due to TLS (125 mg BID, n=1); dehydration and fatigue (125 mg BID, n=1); nausea, vomiting, and/or diarrhea (75 mg TID, n=2; 150 mg BID, n=1)
[b] Patients who withdrew consent had AEs of nausea, vomiting, and/or diarrhea (150 mg BID, n=2)

Abbreviations: AE, adverse event; BID, 2 times per day; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; GCB, germinal center B cell; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma TID, 3 times per day; TLS, tumor lysis syndrome

Safety – Evaluation of DLTs & Establishment of the RDR (***Table 3***)

- Regimens of 50 mg BID (100 mg/day) and 100 mg BID (200 mg/day) were well tolerated, but 150 mg BID (300 mg/day), and 75 mg/day (225 mg/day) were associated with rapid onset of nausea, vomiting, and/or diarrhea that precluded adequate drug compliance.
- The regimen of 125 mg BID (250 mg/day) was not associated with Cycle 1 DLT; 1 patient with DLBCL-GCB developed Grade 4 TLS shortly after starting LAM-002A at 125 mg BID.
- **125 mg BID was established as the RDR for further evaluation.**

Table 3: Dose and Schedule Evaluation

Dosing Regimen	Total Daily Dose	Total Enrolled N=26	DLT-Evaluable N=23	Outcomes
50 mg BID	100	3	3	Generally well tolerated
↓				
100 mg BID	200	8	6	Generally well tolerated
↓				
150 mg BID	300	5	4	Grade 1-3 nausea, vomiting, and diarrhea resulting in drug discontinuation (n=3) or dose-reduction due to diarrhea-related hyponatremia (n=1)
↓				
75 mg TID	225	4	4	Grade 1-3 nausea and vomiting resulting in drug discontinuation (n=2)
↓				MTD and RDR
125 mg BID	250	6	6	Generally well tolerated except for Grade 4 TLS (n=1)

Abbreviations: BID, 2 times per day; DLT, dose-limiting toxicities; MTD, maximum tolerated dose; RDR, recommended dosing regimen; TID, 3 times per day; TLS, tumor lysis syndrome

RESULTS

Safety – Evaluation of Safety Profile (***Table 4***)

- Gastrointestinal AEs of nausea, vomiting, and diarrhea were commonly observed, showed dose dependency, and were typically attributed to LAM-002A.
- Most AEs were Grade 1 or 2. Notable Grade ≥3 AEs were nausea, diarrhea and 3 recoverable drug-related, serious adverse events (SAEs) in 2 patients (both at 125 mg BID) of Grade 3 renal dysfunction due to Grade 4 TLS and Grade 3 dehydration/fatigue.
- Other AEs were infrequent, not clearly dose dependent, and usually attributed to the underlying cancer or comorbidities.
- Most laboratory abnormalities were low-grade or were attributable to underlying B-NHL, prior therapy, or other conditions. Hyponatremia occurred in some subjects with dehydration. LAM-002A did not show a pattern of drug-related myelosuppression. Low-grade QT prolongation was seen.

Table 4: Treatment-Emergent AEs in ≥4 (15%) Patients and Selected Laboratory Abnormalities (CTCAE Grades 1-4) by Dosing Regimen

Adverse Event (regardless of attribution)	Frequency, n (%) 50 mg BID N=3	100 mg BID N=8	125 mg BID N=6	75 mg TID N=4	150 mg BID N=5	All Regimens
Any AE	3 (100.0)	8 (100.0)	5 (83.3)	4 (100.0)	5 (100.0)	25 (96.2)
Gastrointestinal						
Nausea	0 (0.0)	3 (37.5)	3 (50.0)	3 (75.0)	3 (60.0)	12 (46.2)
Vomiting	0 (0.0)	1 (12.5)	2 (33.3)	3 (75.0)	3 (60.0)	9 (34.6)
Diarrhea	1 (33.3)	1 (12.5)	2 (33.3)	2 (50.0)	2 (40.0)	8 (30.8)
Constipation	0 (0.0)	2 (25.0)	1 (16.7)	2 (50.0)	0 (0.0)	5 (19.2)
Decreased appetite	0 (0.0)	0 (0.0)	3 (50.0)	1 (25.0)	0 (0.0)	4 (15.4)
General disorders						
Fatigue	0 (0.0)	4 (50.0)	2 (33.3)	2 (50.0)	2 (40.0)	10 (38.5)
Peripheral edema	1 (33.3)	1 (12.5)	1 (16.7)	2 (50.0)	0 (0.0)	5 (19.2)
Asthenia	0 (0.0)	1 (12.5)	2 (33.3)	0 (0.0)	1 (20.0)	4 (15.4)
Neurological disorders						
Headache	0 (0.0)	1 (12.5)	0 (0.0)	1 (25.0)	2 (40.0)	4 (15.4)
Psychiatric disorders						
Insomnia	0 (0.0)	1 (12.5)	0 (0.0)	1 (25.0)	2 (40.0)	4 (15.4)
Laboratory abnormalities	3 (100.0)	8 (100.0)	6 (100.0)	4 (100.0)	5 (100.0)	26 (100.0)
ANC decreased	0 (0.0)	2 (25.0)	1 (16.7)	1 (25.0)	0 (0.0)	4 (15.4)
Platelets decreased	1 (33.3)	7 (87.5)	2 (33.3)	3 (75.0)	2 (40.0)	15 (57.7)
Hemoglobin decreased	3 (100.0)	8 (100.0)	6 (100.0)	4 (100.0)	5 (100.0)	26 (100.0)
Bilirubin increased	0 (0.0)	2 (25.0)	1 (16.7)	2 (50.0)	1 (20.0)	6 (23.1)
ALP increased	0 (0.0)	1 (12.5)	2 (33.3)	1 (25.0)	1 (20.0)	5 (19.2)
ALT increased	1 (33.3)	4 (50.0)	3 (50.0)	2 (50.0)	1 (20.0)	11 (42.3)
AST increased	1 (33.3)	6 (75.0)	3 (50.0)	1 (25.0)	3 (60.0)	14 (53.8)
Creatinine increased	2 (66.7)	5 (62.5)	3 (50.0)	2 (50.0)	2 (40.0)	14 (53.8)
Sodium decreased	1 (33.3)	3 (37.5)	2 (33.3)	3 (75.0)	2 (40.0)	11 (42.3)
ECG QT prolonged	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	3 (60.0)	4 (15.4)

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BID, 2 times per day; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; TID, 3 times per day

Pharmacokinetics (***Figure 4*** and ***Table 5***)

- LAM-002 (free base of LAM-002A) was rapidly bioavailable following oral dosing with a mean time of maximum concentration (T_{max}) of 0.9 to 1.7 hours.
- Maximum concentration (C_{max}) and area under the plasma concentration-time curves over 8 hours (AUC_{0-8}) generally increased with increasing dose; the Day 8 AUC_{0-8} showed the closest relationship to dose proportionality.
- As steady-state exposures were achieved, mean Day 8/Day 1 accumulation indices (AI) for C_{max} and AUC_{0-8} across all dose levels were 1.5 and 1.9, respectively.
- Mean terminal elimination half-life ($t_{1/2}$) values ranged from 2.7 to 3.9 hours on Day 1 and from 5.5 to 7.0 hours on Day 8 and did not show dose dependency.

Figure 4. LAM-002 (Free Base of LAM-002A) Exposures by Day and Dose Level

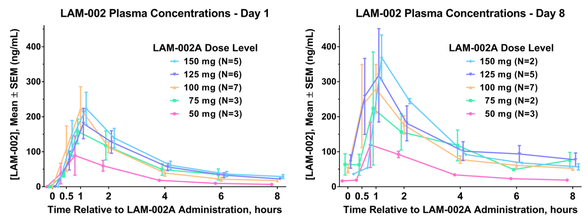


Table 5: Mean Pharmacokinetic Parameters by Dosing Regimen and Day

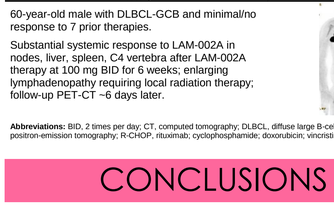
Parameter	Day	Dosing Regimen (N on Day 1/Day 8) 50 mg BID N=3/3	75 mg TID N=3/2	100 mg BID N=7/7	125 mg BID N=6/5	150 mg BID N=5/2
T_{max}, hours	1	1.3	1.0	1.1	1.1	0.9
	8	1.7	1.5	1.1	0.8	1.0
C_{max}, ng/mL	1	117	158	274	207	243
	8	140	245	334	331	369
AUC_{0-8}, h•ng/mL	1	238	454	511	552	669
	8	375	941	931	1125	1057
AI (C_{max})	–	1.2	1.6	1.2	1.6	1.5
AI (AUC_{0-8})	–	1.6	2.1	1.8	2.0	1.6
$t_{1/2}$, hours	1	2.7	2.8	3.9	3.9	3.3
	8	5.6	7.0	5.8	5.5	6.5

Abbreviations: AI, accumulation index (D8/D1); AUC_{0-8}, area under the concentration-time curve through 8 hours; BID, 2 times per day; C_{max}, maximum concentration; $t_{1/2}$, half-life; TID, 3 times per day; T_{max}, time of maximum concentration

Pharmacologic Effects

- Through its inhibition of PIKfyve, LAM-002 decreases lysosomal cathepsin activity in B-NHL cells (***Figure 1***); thus, the effect of LAM-002A-treated patient plasma on cathepsin activity in the B-NHL cell line (WSU-DLCL2) was evaluated relative to Day 8 plasma LAM-002 concentrations.
- Cathepsin activity showed a time-dependent inverse relationship to plasma concentrations (***Figure 5***).

Figure 5: Effect of LAM-002A-Treated Patient Plasma on *Ex Vivo* B-NHL Cathepsin Activity Relative to *In Vivo* Plasma LAM-002 Concentrations



GFP-labeled, LAM-002A-sensitive WSU-DLCL2 B-NHL and unlabeled LAM-002A-resistant WSU-DLCL2 B-NHL (PIKfyve N1939K mutant) cell lines were incubated with patient plasma (from indicated timepoint) for 1 hour and then incubated for 3 hours with a fluorescent cathepsin activity probe. Cathepsin activity was then assayed via flow cytometry. The activity in sensitive cells was normalized to that in resistant cells and plotted as the percentage of the normalized cathepsin signal at the indicated timepoint relative to Cycle 1, Day 1 pre-dose.

Abbreviations: BID, 2 times per day; B-NHL, B-cell non-Hodgkin lymphoma; GFP, green-fluorescent protein; PIKfyve, phosphatidylinositol-3-phosphate 5-kinase; SEM, standard error of mean.

Efficacy

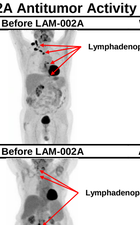
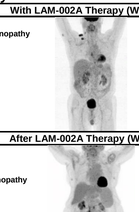
- Positron emission tomography (PET) demonstrated systemic partial metabolic responses in nodal and extranodal lesions in 3 patients with refractory DLBCL-GCB (treated at 125 mg BID, 75 mg TID, and 100 mg BID) (1 of whom also received radiation for bulky axillary adenopathy); concomitant computed tomography (CT) demonstrated anatomic shrinkage of many lesions (***Table 6*** and ***Figure 6***).
- One additional patient with transformed DLBCL-GCB (receiving 125 mg BID) had TLS.
- One patient with MZL and 1 patient with CLL (both receiving 100 mg BID) have had prolonged stable disease through ≥12 cycles.

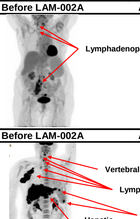
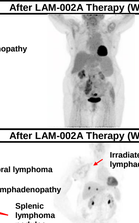
Table 6: LAM-002A Antitumor Activity

Patient ID	Disease	Prior Therapies, n	LAM-002A Regimen	Clinical Activity
8-005	MZL	7	125 mg BID	Metabolic response and 43% decrease in SPD
8-003	DLBCL-GCB	1	75 mg TID	Metabolic response
1-001	DLBCL-GCB	7	100 mg BID	Metabolic/anatomic mixed response with nodes shrinking by >50%
1-002	DLBCL-GCB	3	125 mg BID	TLS
2-005	CLL	3	100 mg BID	SD through Cycle 12; then PD
8-002	MZL	7	100 mg BID	SD ongoing in Cycle 12

Abbreviations: BID, 2 times per day; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B cell; ID, identification number; MZL, marginal zone lymphoma; PD, progressive diseases; SD, stable disease; SPD, sum of the products of the perpendicular diameters; TID, 3 times per day; TLS, tumor lysis syndrome

Figure 6: Radiographic Evidence of LAM-002A Antitumor Activity

History	Before LAM-002A	With LAM-002A Therapy (Week ~8)
60-year-old male with MZL progressing after 7 prior therapies Partial metabolic response (with several nodal regressions) during LAM-002A, 125 mg BID.		

History	Before LAM-002A	After LAM-002A Therapy (Week ~4)
82-year-old female with DLBCL-GCB progressing 8 months after R-CHOP. Partial metabolic response in cervical and retroperitoneal lymph nodes after LAM-002A, 75 mg TID x 1 day→100 mg BID for 4 days.		

History	Before LAM-002A	After LAM-002A Therapy (Week ~8)
60-year-old male with DLBCL-GCB and minimal/no response to 7 prior therapies. Substantial systemic response to LAM-002A in nodes, liver, spleen, C4 vertebra after LAM-002A therapy at 100 mg BID for 6 weeks; enlarging lymphadenopathy requiring local radiation therapy; follow-up PET-CT ~6 days later.		

Abbreviations: BID, 2 times per day; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B cell; MZL, marginal zone lymphoma; PET, positron-emission tomography; R-CHOP, rituximab; cyclophosphamide; doxorubicin; vincristine; prednisone (regimen); TID, 3 times per day

CONCLUSIONS & NEXT STEPS

- LAM-002A (apilimod dimesylate) is the first PIKfyve inhibitor in clinical development for B-cell cancers.
- LAM-002A shows a favorable safety profile at doses of ≤125 mg BID when administered continuously; the only dose-limiting AEs have been gastrointestinal effects.
- PK data demonstrate oral bioavailability and systemic exposure supporting BID dosing.
- LAM-002A shows promising early antitumor activity, including in patients with heavily pretreated and refractory DLBCL and MZL.
- Together with the nonclinical findings, the clinical data support further clinical evaluation of LAM-002A, as continuous monotherapy at the RDR, as intermittent monotherapy with antiemetic/antidiarrheal support, and together with anti-CD20 or anti-PDL1 antibodies.