A Phase 1 study of SGR-1505, an oral, potent MALT1 inhibitor for R/R B-cell malignancies, including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)

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Introduction

- MALT1, a component of the CARMA1-BCL10-MALT1 (CBM) complex, is a key regulator of B and T-cells and NF-κB signaling.
- Constitutive activation of the NF-κB signaling pathway is a molecular hallmark of multiple B-cell malignancies.
- SGR-1505 is a potent MALT1 inhibitor that demonstrated strong preclinical anti-tumor activity and combination potential with standard-of-care agents.
- SGR-1505 is currently being investigated in a first-in-human multicenter open-label phase 1 trial (NCT-0554019) as monotherapy in patients with R/R B-cell malignancies, including CLL/SLL.

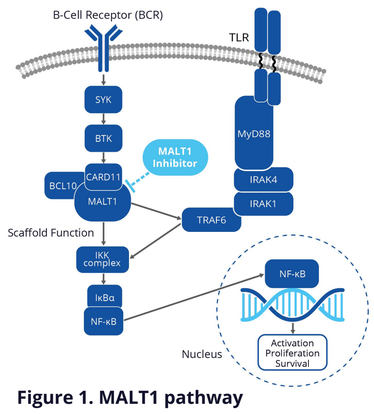


Figure 1. MALT1 pathway

Methods

- SGR-1505-101 is a global study in 8 countries across 37 sites with a total of 49 participants enrolled as of 13-May-2025.
- Oral, daily administration in 21-day cycles in a modified 3+3 dose escalation design once daily (QD) or twice daily (Q12H).
- Aggressive forms of non-Hodgkin lymphoma were excluded at lower doses.
- Safety evaluations occurred weekly for 2 cycles then every 3 weeks using CTCAE v5.0.
- Disease assessments occurred every 12 weeks using disease-specific standard response criteria (Lugano, iwCLL 2018, IWWM6).
- Primary objectives: safety and tolerability, identifying the maximum tolerated dose (MTD) or maximum administered dose (MAD) and/or recommended dose(s) (RD).
- Secondary objectives: pharmacokinetics (PK) and preliminary anti-tumor activity of SGR-1505 as monotherapy.
- Exploratory objective: pharmacodynamics (PD).

Demographics

Table 1. Demographics

Median age, years (range)	64 (31 - 82)
Male, n (%), **female**, n (%)	32 (65.3), 17 (34.7)
ECOG PS, n (%)	
0, 1	25 (51.0), 24 (49.0)
Median prior lines of therapy (range)	4 (2 - 9)
Histologies, n (%)	
Chronic lymphocytic leukemia/small lymphocytic leukemia	18 (36.7)
Diffuse large B-cell lymphoma	9 (18.4)
Waldenstrom macroglobulinemia	6 (12.2)
Marginal zone lymphoma	5 (10.2)
Mantle cell lymphoma	5 (10.2)
Other (4 FL, 1 PMBCL, 1 THRLBCL)	6 (12.2)
Select previous treatments, n (%)	
Bruton's tyrosine kinase (BTK) inhibitor*	27 (55.1)
BCL-2 inhibitor	9 (18.4)
BTK inhibitor + BCL-2 inhibitor	9 (18.4)
Anti-CD20	46 (93.9)

*Two participants were previously treated with only a BTK degrader and not a BTK inhibitor

Results – Safety

- Forty two participants (86%, 42/49) experienced ≥1 treatment-emergent adverse event (TEAE), 23 participants (47%) ≥G3, most common (≥10%) TEAEs were neutrophil count decreased (20%), fatigue (16%), rash (14%), blood bilirubin increased (10%).
- Twenty one participants (43%, 21/49) experienced ≥1 treatment-related adverse event (TRAE), 12 participants (25%) ≥G3, most common TRAEs (≥10%) were rash (14%) and fatigue (12%).
- Ten participants (20%) experienced treatment-emergent SAEs. One SAE was treatment-related: herpes simplex reactivation (G3).
- No DLTs, no cases of Hy's law, and no deaths due to TEAEs.
- Thirty two participants (65%) experienced ≥G1 total bilirubin laboratory elevations, 10% were G3; none were G4. Forty three participants (88%) experienced ≥G1 indirect bilirubin laboratory elevations, 29% were G3, and 2% (1 participant) was G4.
- All total and indirect bilirubin laboratory elevations were asymptomatic and predominantly G1/2.

Table 2. Common (≥10%) TEAE/TRAEs in the safety population (N=49)

Common (≥10%) **TEAE/TRAEs**	TEAE		TRAE	
	Any grade (n, %)	**Grade ≥3 (n, %)**	**Any grade (n, %)**	**Grade ≥3 (n, %)**
Any TEAE	**42 (85.7)**	**23 (46.9)**	**21 (42.9)**	**12 (24.5)**
Neutrophil count decreased	10 (20.4)	10 (20.4)	3 (6.1)	3 (6.1)
Fatigue	8 (16.3)	0 (0.0)	6 (12.2)	0 (0.0)
Rash*	7 (14.3)	3 (6.1)	6 (12.2)	3 (6.1)
Blood bilirubin increased	5 † (10.2)	4 (8.3)	4 (8.2)	4 (8.2)

*Rash includes rash, papular rash, and maculo-papular rash.
† All were asymptomatic, from participants with UGT1A1 polymorphisms, and none were G4. One participant with G2 unrelated hyperbilirubinemia reported a G1 AST elevation 23 days later, when the participant was progressing radiographically.

Results – Pharmacodynamics

- Preliminary data indicate that SGR-1505 inhibits T-cell derived IL-2 upon *ex vivo* stimulation achieving the PD target of ~90% inhibition in the majority of PD-evaluable participants treated at ≥150 mg QD and all Q12H doses at steady state.
- Q12H dosing provided more sustained IL-2 inhibition compared to QD dosing.

Results - Preliminary Efficacy

- Of 49 total participants, 45 have had at least one post-baseline disease assessment or progressed clinically.
- Ten participants demonstrated objective responses for an overall response rate of 22% (10/45) across all dose levels.
- 3/17 evaluable CLL subjects achieved PR, including 2 subjects with both prior BTKi and BCL2 directed therapy (double-exposed).
- 5/5 evaluable Waldenstrom Macroglobulinemia subjects achieved objective responses (2 PR, 3 MR); all had prior BTKi therapy.
- Objective responses (PR) were also observed in 1 ABC-DLBCL and 1 Marginal Zone Lymphoma (MZL).
- Of 49 total participants, 13 have been on treatment for ≥120 days (127+, 127+, 147, 148, 149, 149, 163, 169+, 182, 208, 421, 492+, 752+).

Figure 2. Scans showing a significant reduction in metabolic activity (upper panel) and size (lower panel) of an para-aortic mass pre- (left) and post- (right) treatment with SGR-1505 in a WM participant

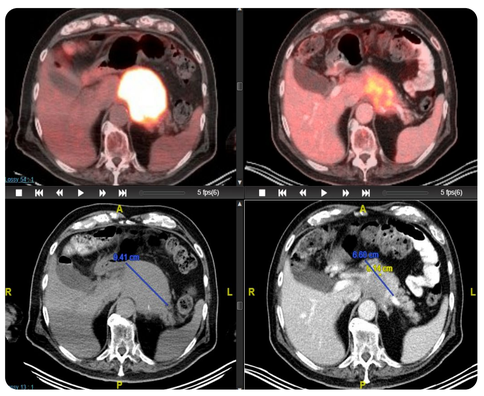


Figure 3. Best change in sum of product diameters or best change in IgM levels

The figure below includes 40 subjects with ≥1 follow-up disease assessment with measurable disease or IgM assessment

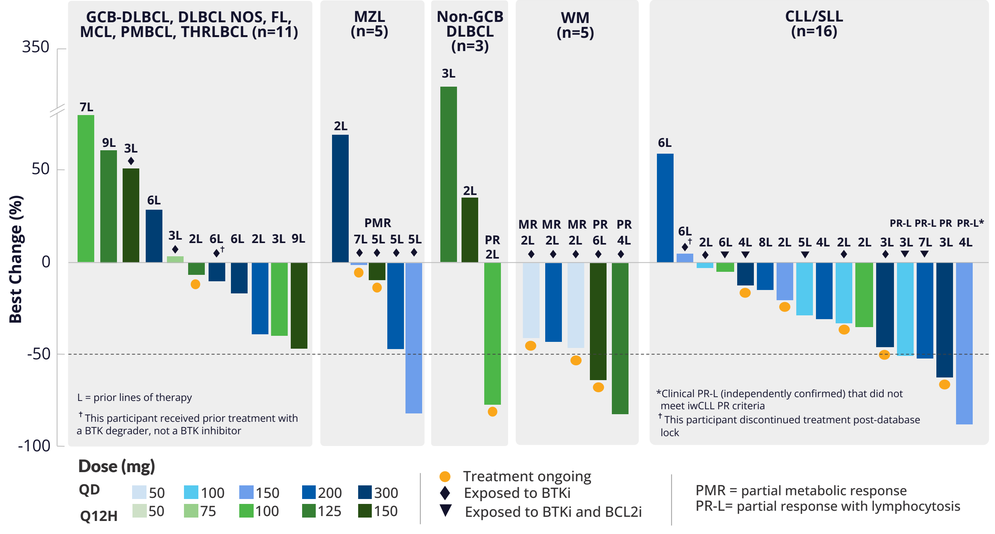
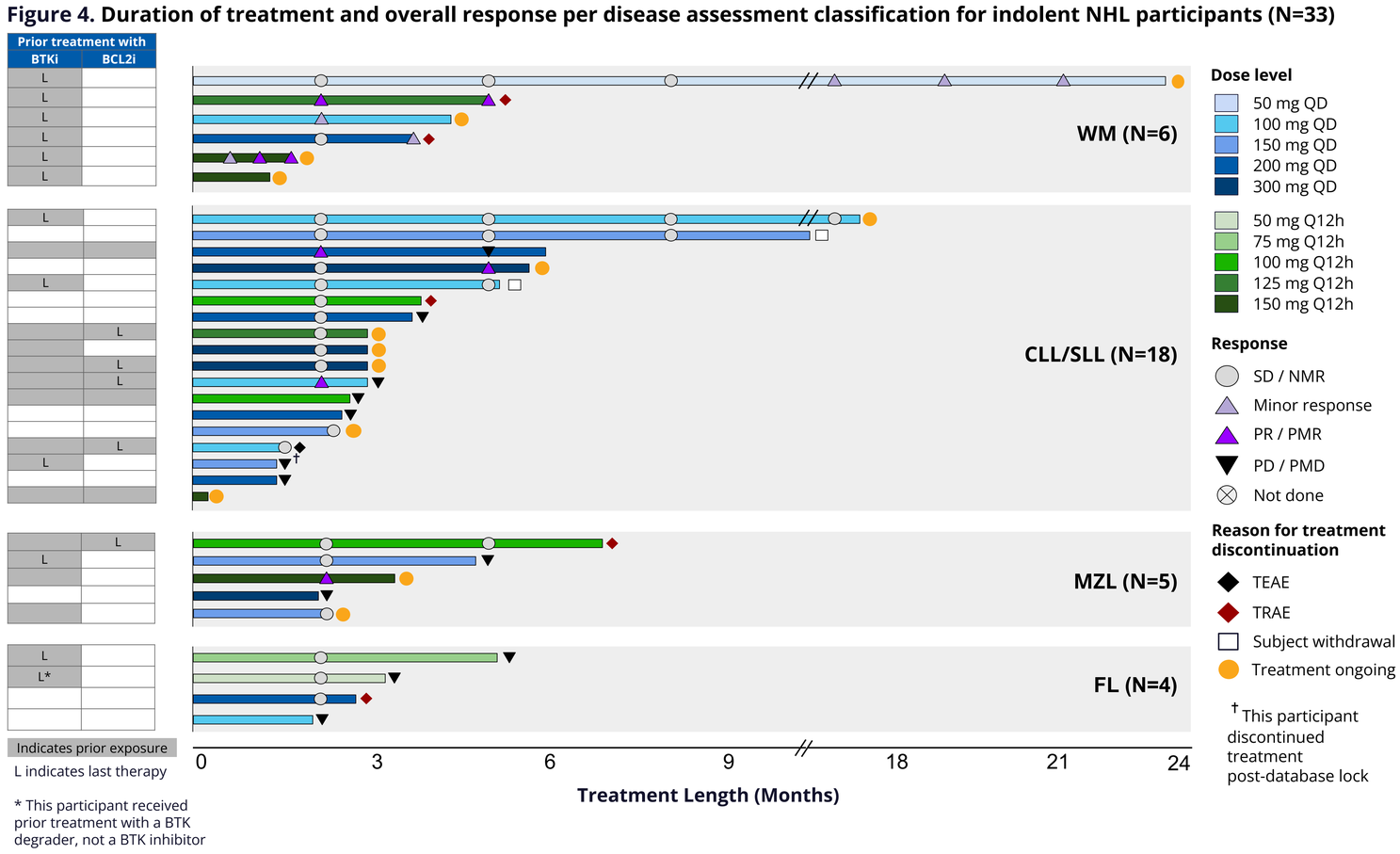


Figure 4. Duration of treatment and overall response per disease assessment classification for indolent NHL participants (N=33)



Conclusions

- SGR-1505 was observed to be safe and well-tolerated.
- Dose-related increases in exposure were observed from 50-150 mg QD and 50-100 mg Q12H.
- The MAD is 300 mg for QD and 150 mg for Q12H. Dose escalation is complete.
- Preliminary data indicates that SGR-1505 inhibits T-cell derived IL-2 upon *ex vivo* stimulation achieving the PD target of ~90% inhibition in the majority of PD-evaluable participants treated at ≥150 mg QD and all Q12H doses at steady state.
- Q12H dosing provided more sustained IL-2 inhibition compared to QD dosing.
- Preliminary efficacy is demonstrated with objective responses across multiple B-cell malignancies, including in double-exposed CLL/SLL and post-BTKi WM.
- The observed safety profile, PD effects, and preliminary efficacy support further investigation of SGR-1505.

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