Poster PS1569

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

Stephen Spurgeon[1] Vasile Musteata[2] Oksana Karnabeda[3] Mengyang Di[4] Nashat Gabrail[5] Laura Calustian[6] Guru Subramanian Guru Murthy[7] Erin Mulvey[8] Vincent Ribrag[9] Michal Taszner[10] Ciprian Tomuleasa[11] Carlo Visco[12] Wu Yin[13] Allison Upalawanna[13] Sen Zhang[13] Vipul Gupta[13] Brian Yoo[13] Frank Basile[13] Margaret Dugan[13] Matthew Ulrickson[14] Adam Olszewski[15]

[1]The Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; [2]Institute of Oncology, ARENSIA Exploratory Medicine, Chisinau, Moldova; [3]ARENSIA Exploratory Medicine LLC, Bogomolets National Medical University, Kyiv, Ukraine; [4]University of Washington Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA, USA; [5]Gabrail Cancer Center, Canton, OH, USA; [6]ARENSIA Institutul Oncologic Bucureşti, Bucureşti, Romania; [7]Medical College of Wisconsin, Milwaukee, WI, USA; [8]Weill Cornell Medicine, New York, NY, USA; [9]Institut Gustave Roussy, Villejuif, France; [10]Department of Hematology and Transplantology, Medical University of Gdańsk, Gdańsk, Poland; [11]ARENSIA Institutul Oncologic Cluj-Napoca, Napoca, Romania; [12]University of Verona, Verona, Italy; [13]Schrödinger, New York, NY, USA, [14]Banner MD Anderson Cancer Center, Phoenix, AZ, USA; [15]Brown University, Providence, RI, USA

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Background

- 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-05544019) as monotherapy in patients with R/R B-cell malignancies, including CLL/SLL.

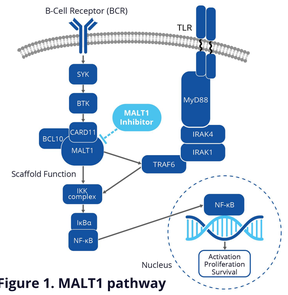

Figure 1. MALT1 pathway

Methods

- SGR-1505-101 is a global study in 8 countries across 37 sites with 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 monotherapy activity.
- Exploratory objective: pharmacodynamics (PD).

Figure 2. Study design

Monotherapy Dose Escalation:
- Arms A & B: ATD transitioning to 3+3 design

Population:
- R/R B-cell neoplasms following ≥ 2 prior lines
- Arms A & B: Indolent forms and aggressive forms of NHL

Schedule:
- Arm A: Once daily dosing (QD), each day of continuous 21-day cycles
- Arm B: Twice daily dosing (Q12H), each day of continuous 21-day cycles

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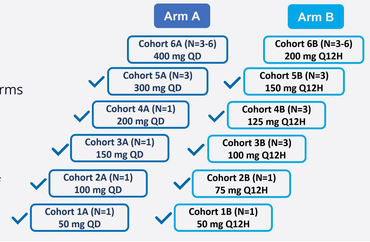

Demographics (N=49)

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's 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

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 (8.2)	4 (8.2)	4 (8.2)

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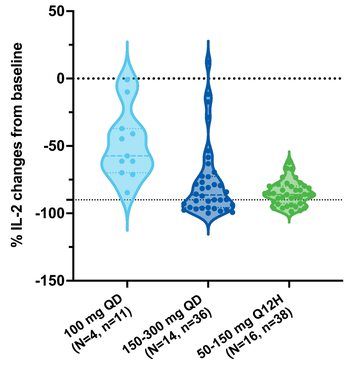
Pharmacodynamics

- 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.

Figure 3. IL-2 inhibition through C2 D1 (steady state) by dose groups †



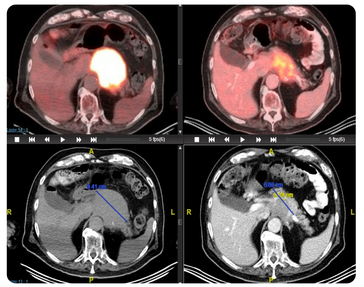
† N = number of participants in the dose groups; n = number of data points in the dose groups

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's 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+).

Preliminary Efficacy (continued)

Figure 4. 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



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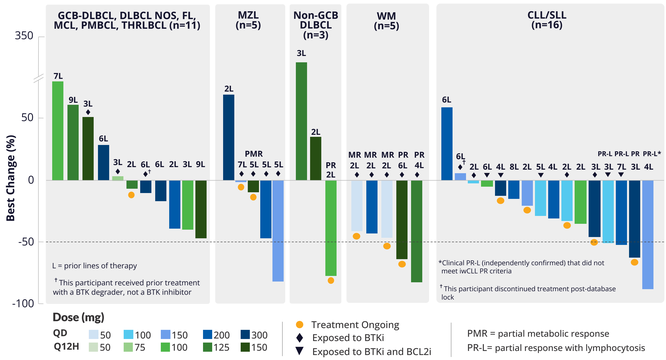
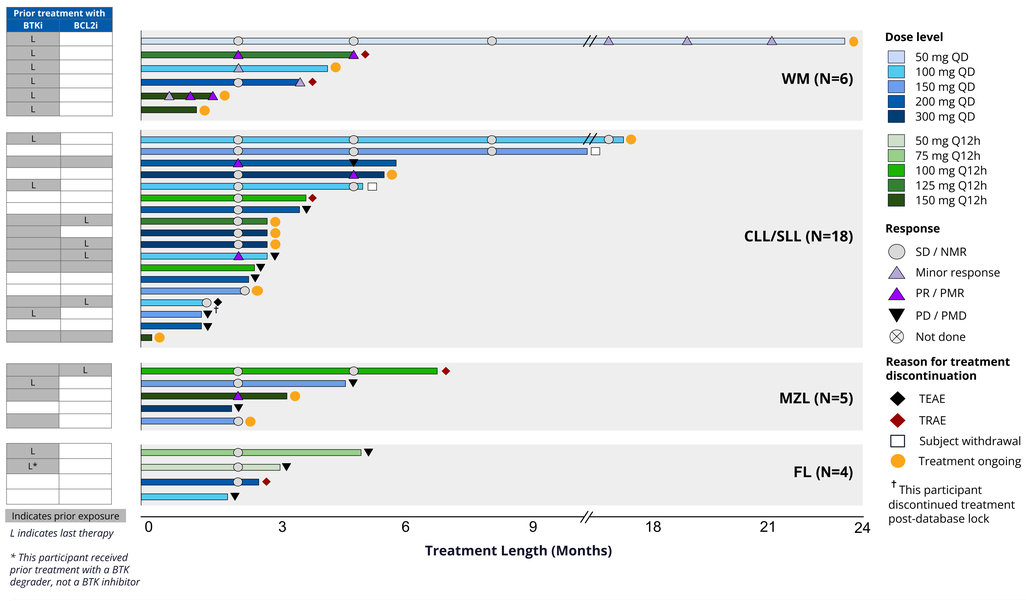


Figure 6. Duration of treatment and overall response per disease assessment classification for indolent NHL participants (N=33)



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.
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Presented at the European Hematology Association (EHA) 2025 Annual Congress, June 12-15, 2025, Milan, Italy

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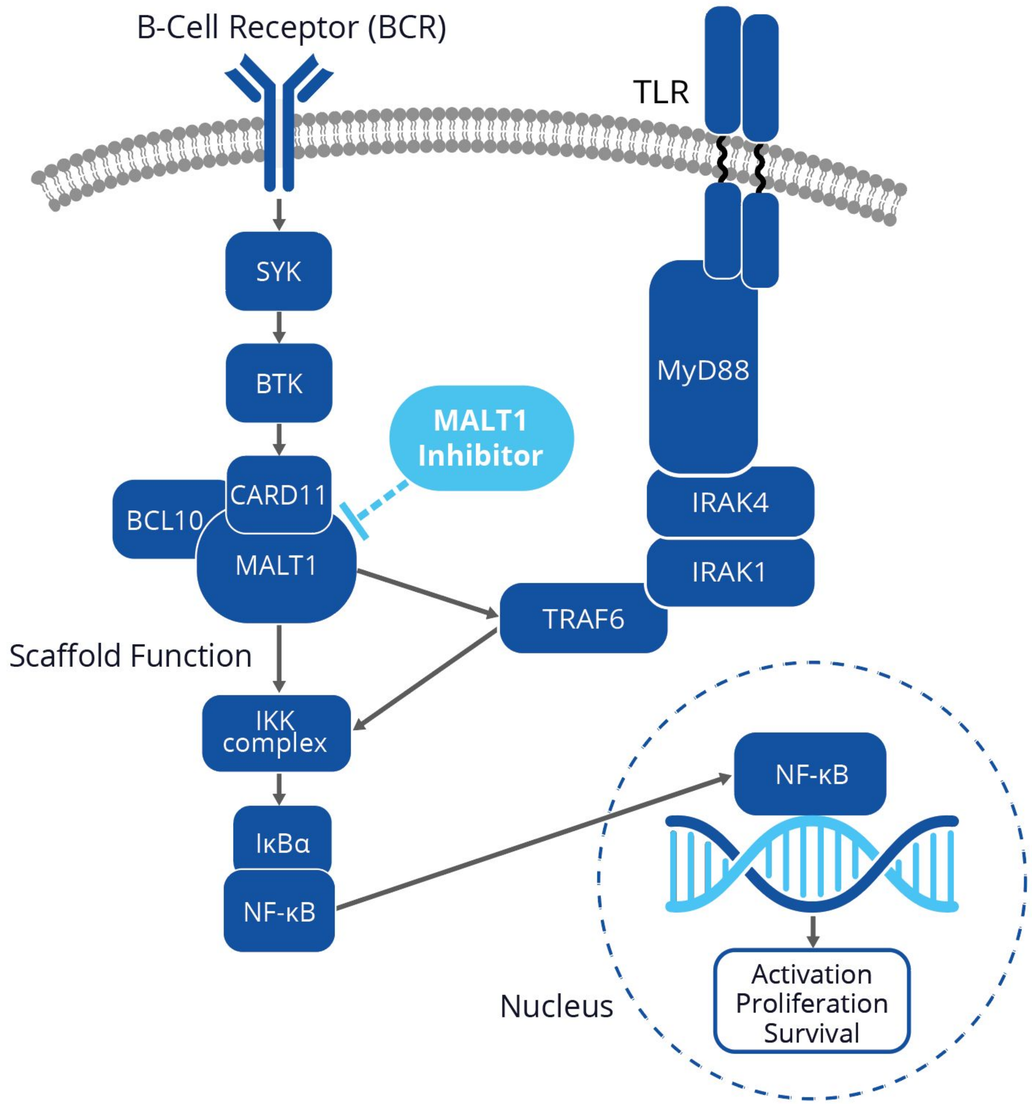

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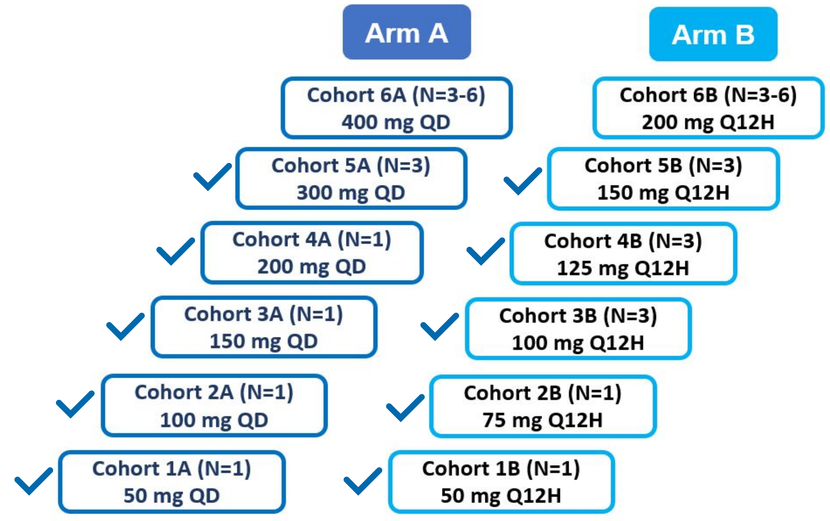

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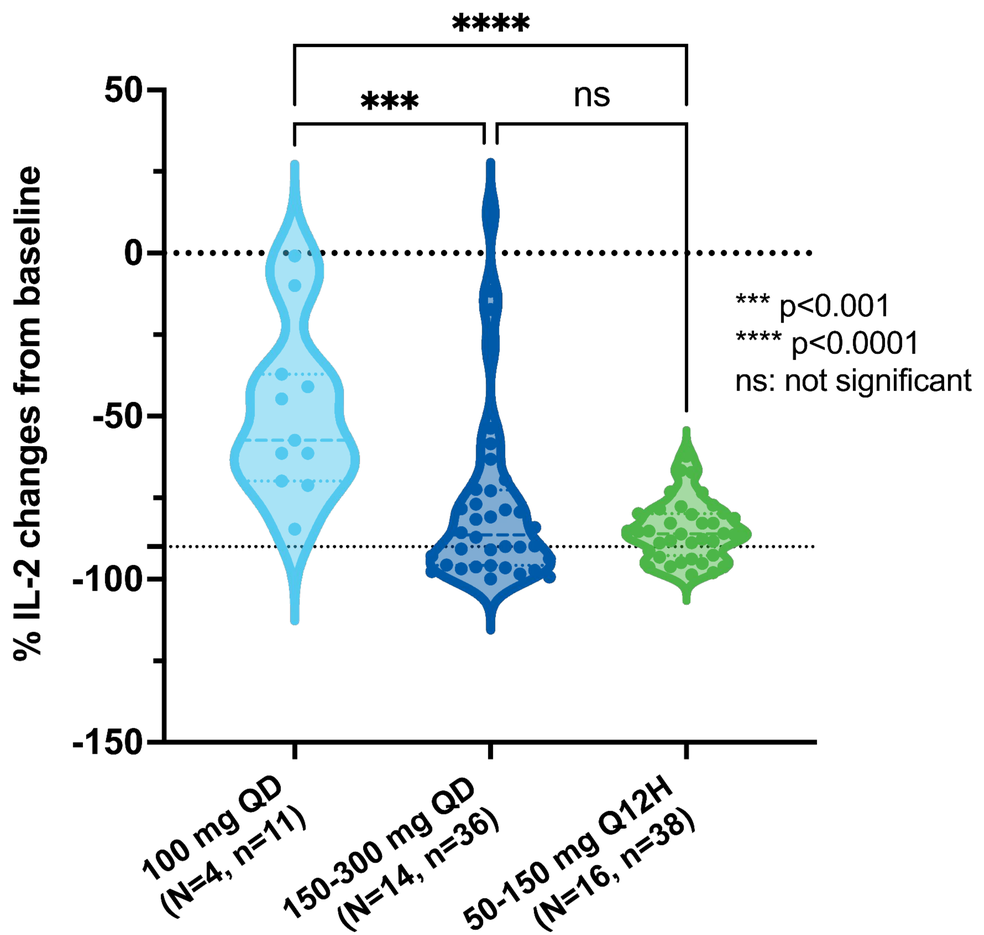

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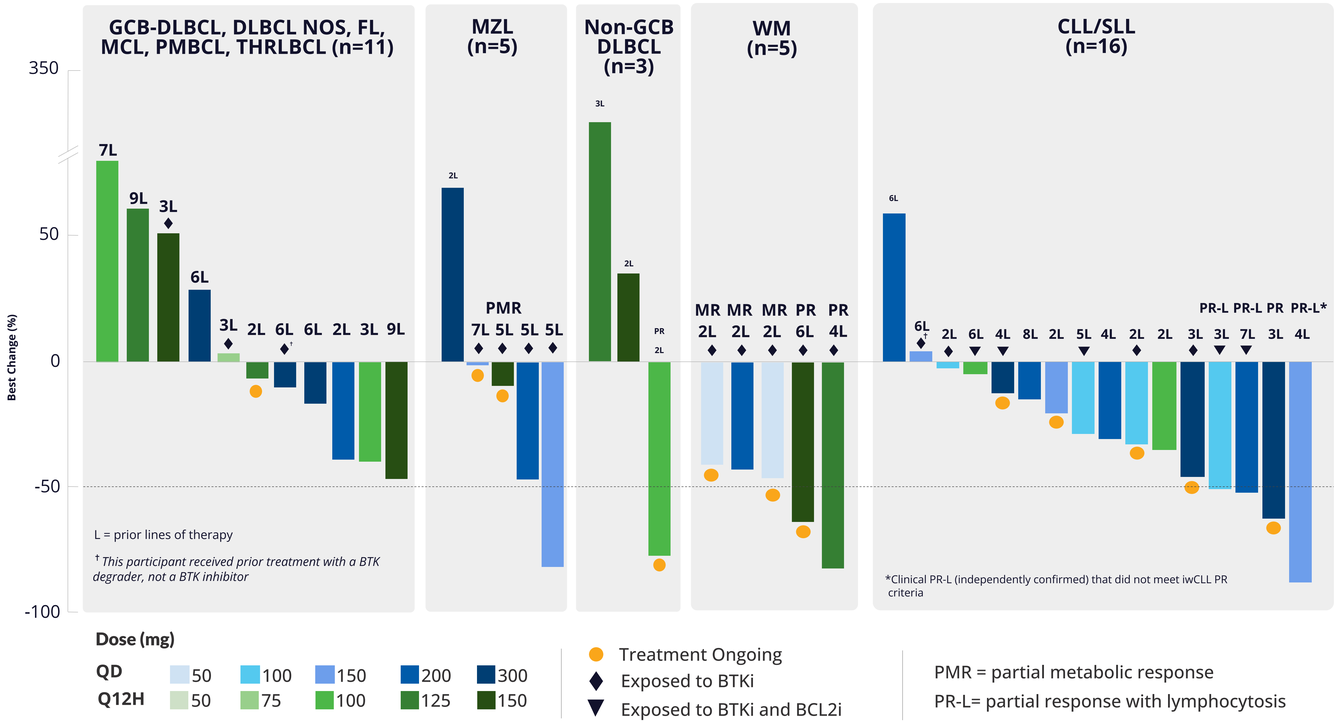

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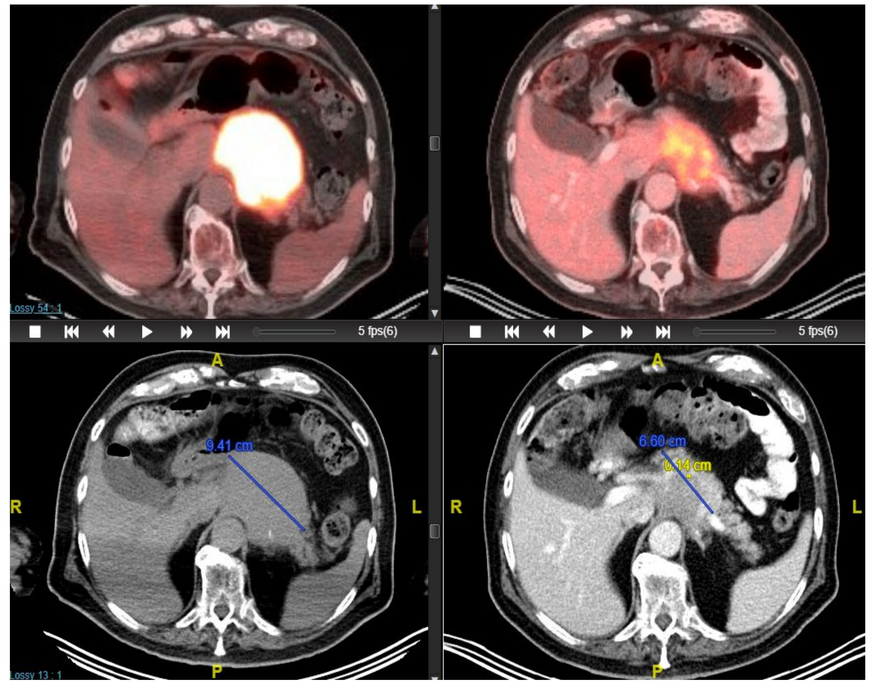

Duration of treatment and overall response per disease assessment classification (N=49)

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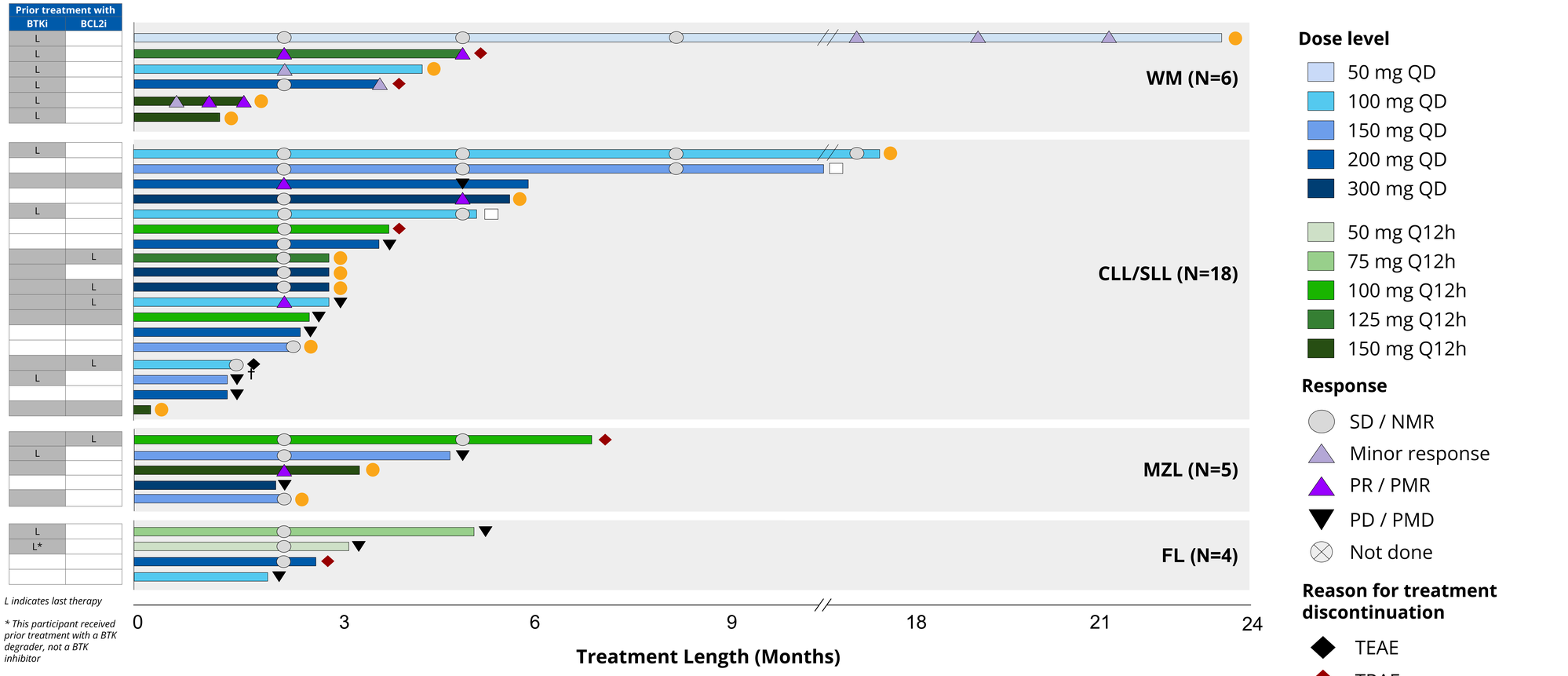

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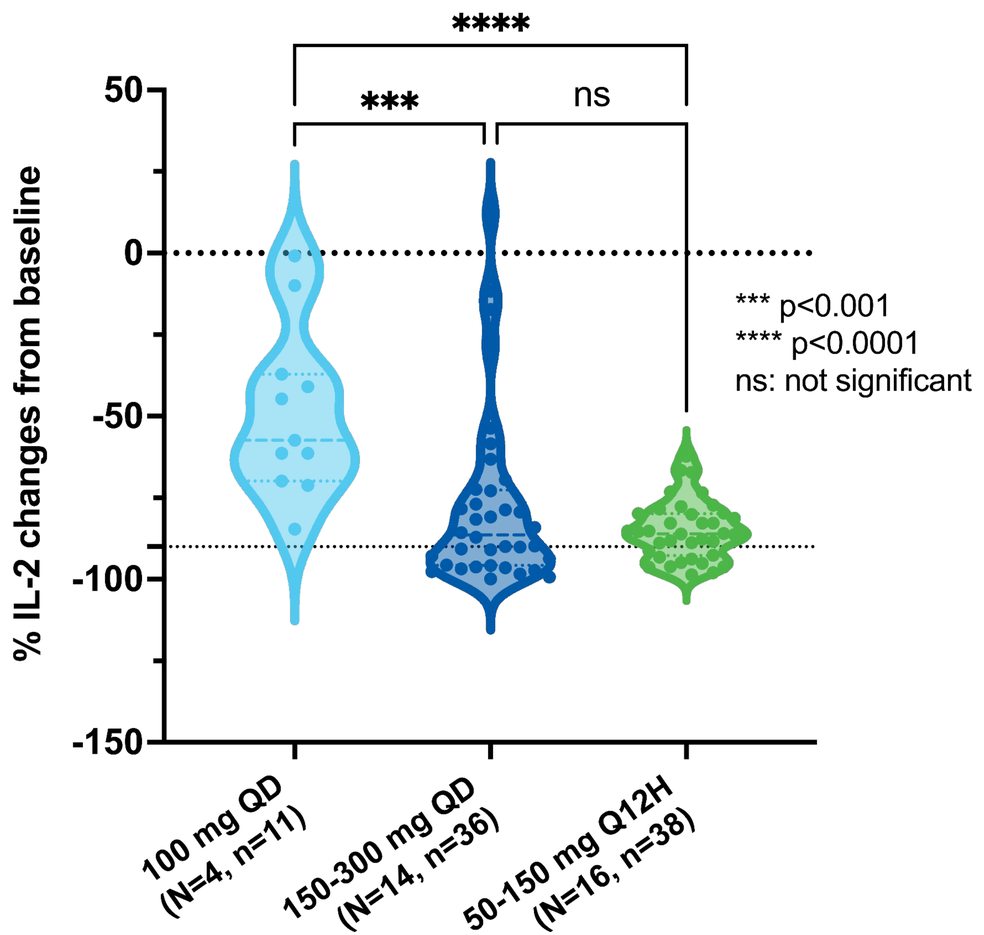

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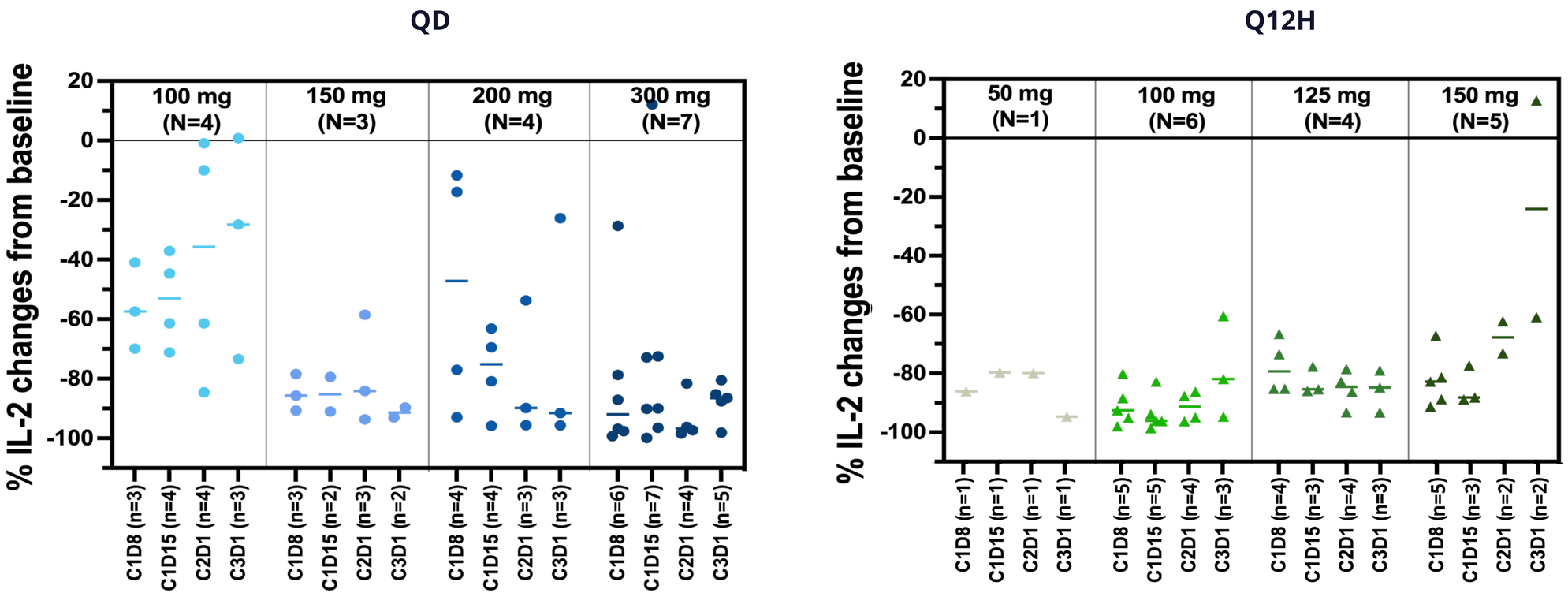
Figure 3. Mean IL-2 inhibition*



*The number of data points at each visit (n) may be different from the number of participants in the cohort (N) as some participants have not yet reached the respective study day or their samples were not able to be evaluated

Duration of treatment and overall response per disease assessment classification (N=49)

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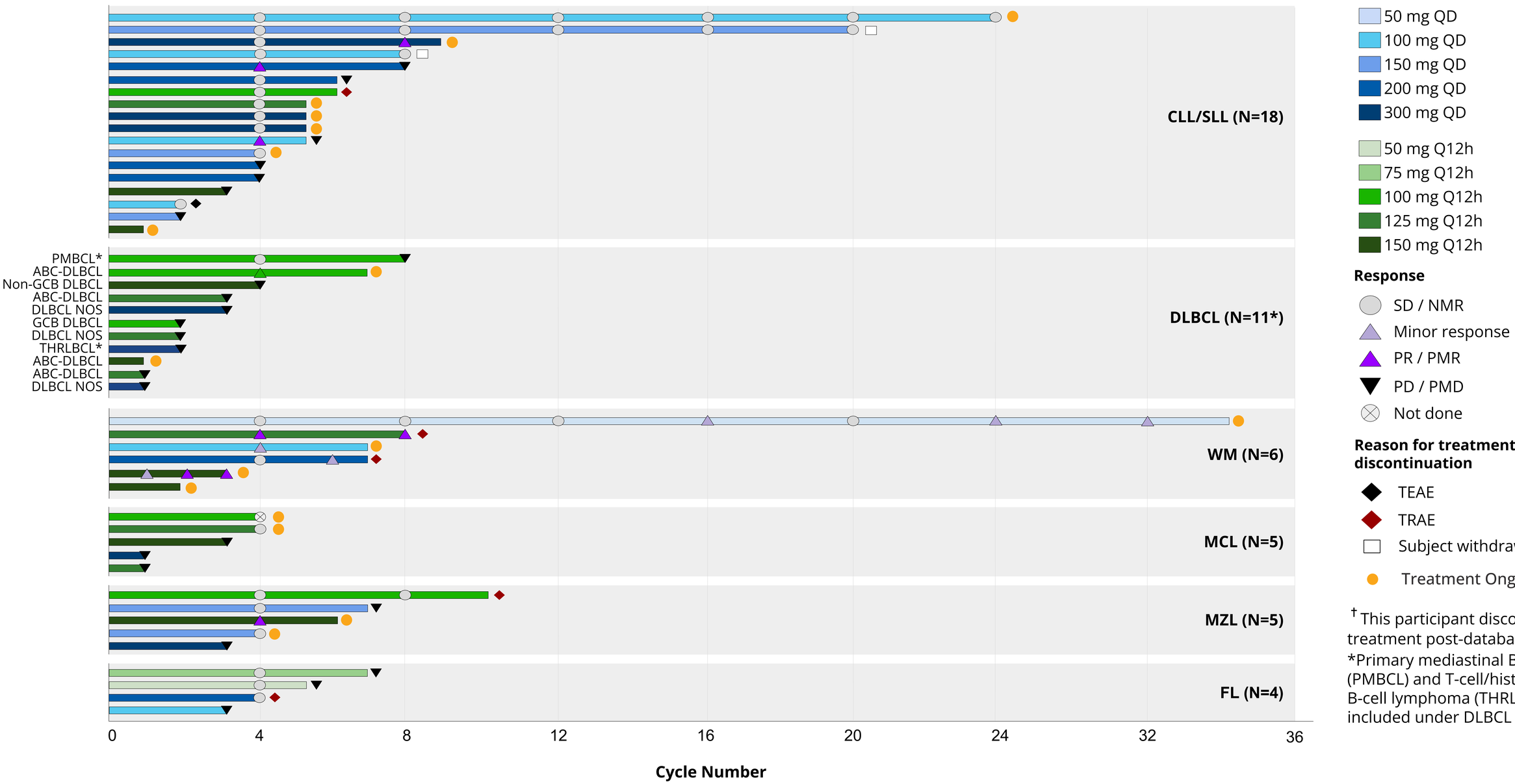

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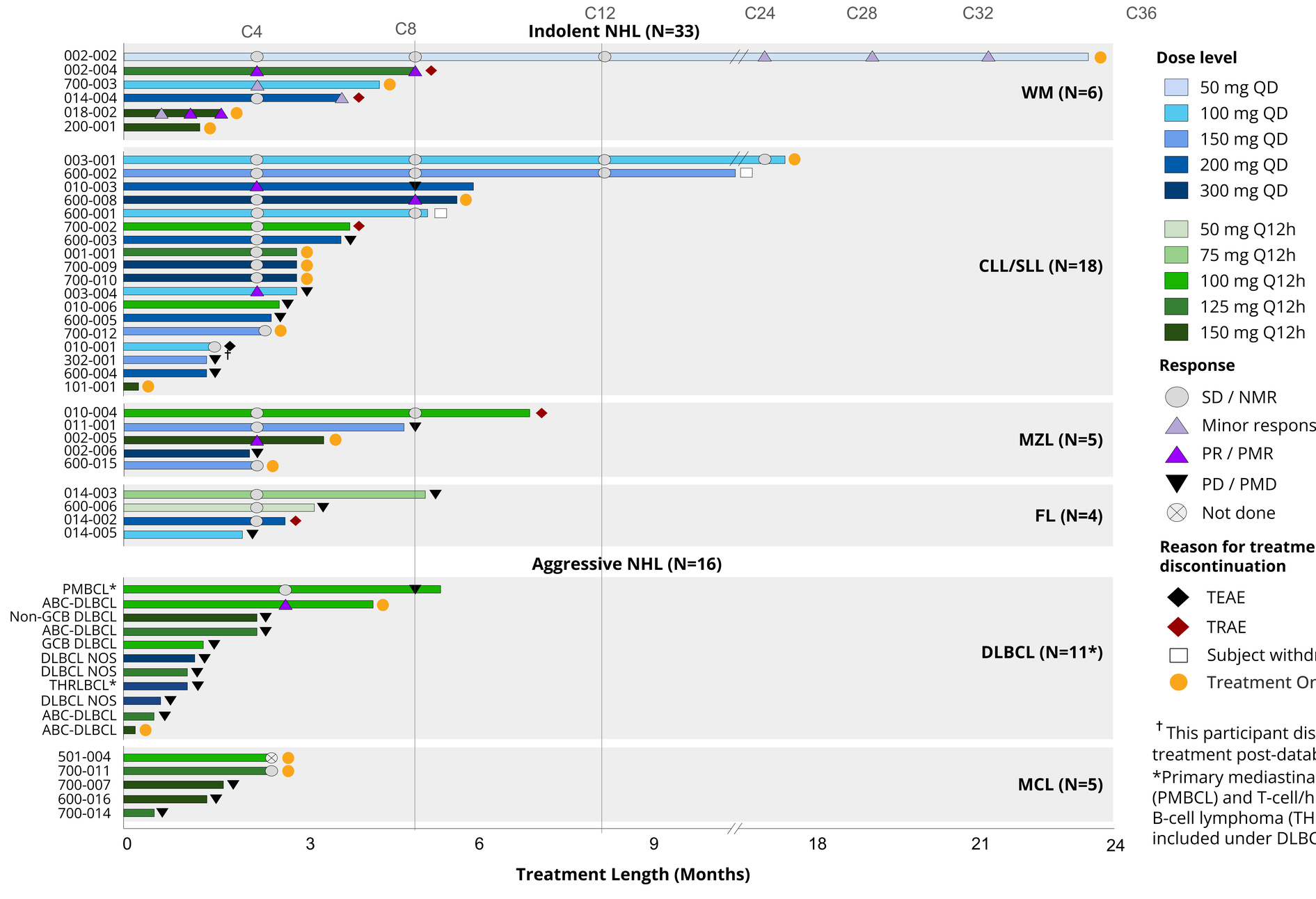

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CLL/SLL (N=18)

†

DLBCL (N=11*)

PMBCL*
ABC-DLBCL
Non-GCB DLBCL
ABC-DLBCL
DLBCL NOS
GCB DLBCL
DLBCL NOS
THRLBCL*
ABC-DLBCL
ABC-DLBCL
DLBCL NOS

WM (N=6)

MCL (N=5)

MZL (N=5)

FL (N=4)

0 4 8 12 16 20 24 32 36

Cycle Number

Dose level

- 50 mg QD
- 100 mg QD
- 150 mg QD
- 200 mg QD
- 300 mg QD
- 50 mg Q12h
- 75 mg Q12h
- 100 mg Q12h
- 125 mg Q12h
- 150 mg Q12h

Response

- SD / NMR
- Minor response
- PR / PMR
- PD / PMD
- Not done

Reason for treatment discontinuation

- TEAE
- TRAE
- Subject withdrawal

- Continuing treatment

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www.schrodinger.com
sdgr-trials-group@schrodinger.com

Background

- 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

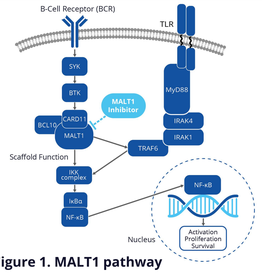


Figure 1. MALT1 pathway

Methods

- SGR-1505-101 is a global study in 8 countries across 37 sites with a total of 49 participants enrolled as of 31-May-2025
- Participants received oral SGR-1505 daily in 21-day cycles in a modified 3+3 dose-escalation design once daily (QD) or twice daily (Q12H)
- Safety evaluations occurred weekly for 2 cycles then every 3 weeks, with reporting using Common Terminology Criteria for Adverse Events (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)

Figure 2. Study design

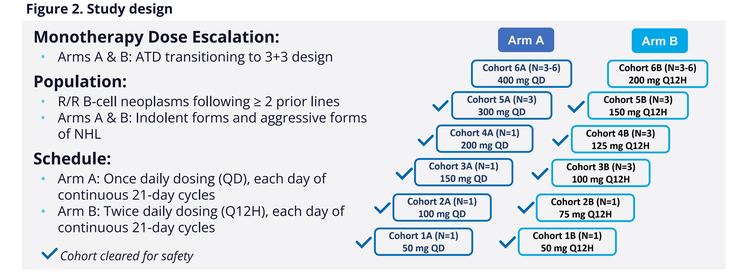


Table 1. Demographics

Demographics (N=49)	
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 (28.1)
Diffuse large B-cell lymphoma	9 (18.4)
Waldenstrom's macroglobulinemia	6 (9.4)
Marginal zone lymphoma	5 (7.8)
Mantle cell lymphoma	5 (7.8)
Other (4 FL, 1 PMBCL, 1 THRLBCL)	6 (12.2)
Select previous treatments, n (%)	
Bruton's tyrosine kinase (BTK) inhibitor	25 (51.0)
BCL-2 inhibitor	9 (18.4)
BTK inhibitor + BCL-2 inhibitor	9 (18.4)
Anti-CD20	46 (93.9)

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 (20.8)	3 (6.1)	3 (6.1)
Fatigue	8 (16.3)	0 (0.0)	6 (12.2)	0 (0.0)
Rash*	7 (14.3)	3 (6.3)	7 (14.3)	3 (6.1)
Blood bilirubin increased	5† (10.2)	4 (8.3)	4 (8.2)	4 (8.2)

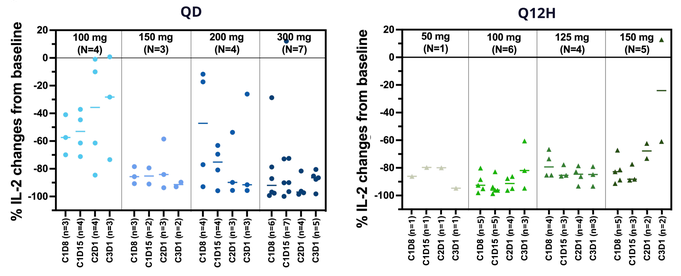
*Rash includes rash, papular rash, and maculo-papular rash

† 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.

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 ~75% subjects treated across 150-300 mg QD and 100-150 mg Q12H
- Q12H dosing provided more sustained IL-2 inhibition compared to QD dosing

Figure 3. Mean IL-2 inhibition*



*The number of data points at each visit (n) may be different from the number of participants in the cohort (N) as some participants have not yet reached the respective study day or their samples were not able to be evaluated

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's 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+)

Preliminary Efficacy (continued)

Figure 4. Scans showing a significant reduction in metabolic activity (above) and size (below) of an para-aortic mass pre- (left) and post- (right) treatment with SGR-1505 in a WM participant

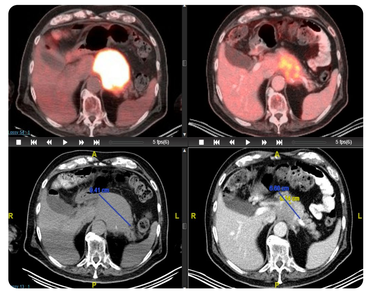


Figure 5. Best change in sum of product diameters or best change in IgM levels

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

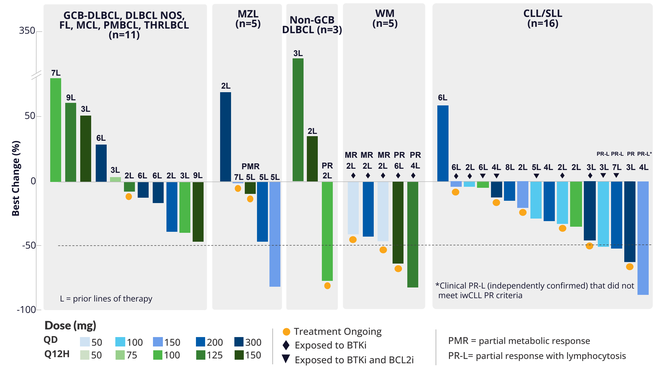
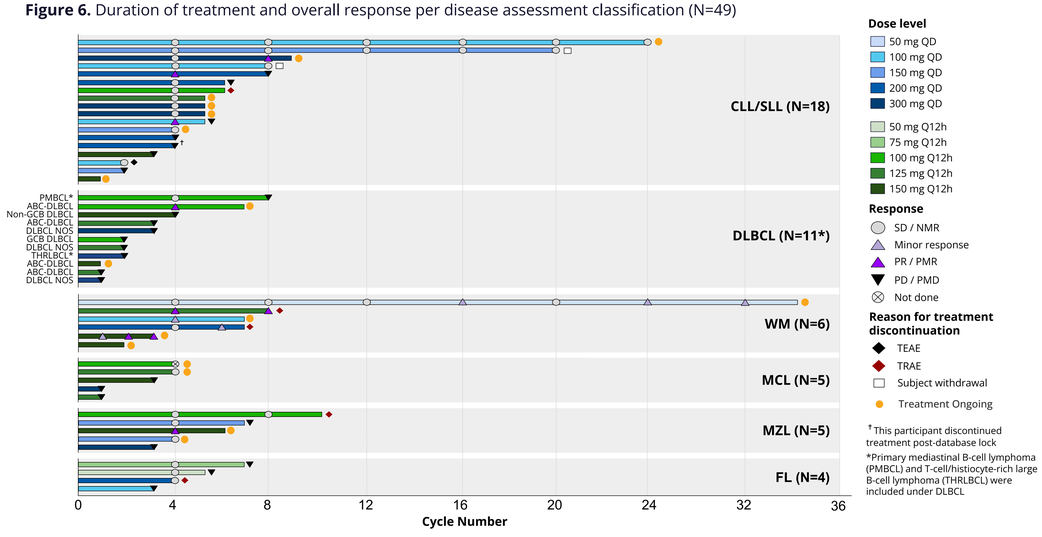


Figure 6. Duration of treatment and overall response per disease assessment classification (N=49)



† This participant discontinued treatment post-database lock

*Primary mediastinal B-cell lymphoma (PMBCL) and T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) were included under DLBCL

Conclusions

- SGR-1505 is safe and well-tolerated
- SGR-1505 demonstrated dose-related increases in exposure from 50-150 mg QD and 50-100 mg Q12H. Dose escalation is complete
- The MAD is 300 mg for QD and 150 mg for Q12H
- Preliminary data indicates that SGR-1505 inhibits T-cell derived IL-2 upon *ex vivo* stimulation achieving the PD target of ~90% inhibition in ~75% subjects treated across 150-300 mg QD and 100-150 mg Q12H
- 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