Subasumstat (TAK-981), a first-in-class SUMO-activating enzyme inhibitor, combined with rituximab in adult patients with CD20-positive relapsed/refractory non-Hodgkin lymphoma: Phase 1 data

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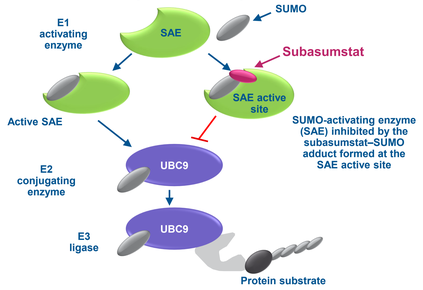
Background

Subasumstat (TAK-981)

- Subasumstat is the first small-molecule inhibitor of SUMOylation to enter clinical trials
  - SUMOylation is a post-translational modification in which small ubiquitin-like modifier (SUMO) proteins are activated and covalently attached to substrate proteins[1]
  - SUMOylation has a central role in constraining type I interferon (IFN-I)-dependent responses[2]
- By blocking SUMOylation (**Figure 1**), subasumstat promotes IFN-I production and increases innate immunity[3]

Figure 1: Inhibition of the SUMOylation cascade by subasumstat[4]

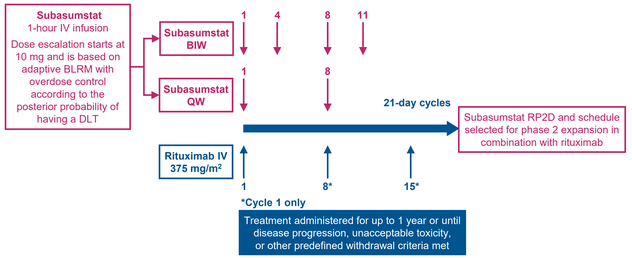


Methods

Rationale for study

- Subasumstat is able to promote activation of macrophages and natural killer cells and thereby increase their cytotoxic/phagocytic activity[5]
  - Therefore, there is a mechanistic rationale for its use in combination with monoclonal antibodies (mAbs) reliant on antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis
- Preclinical studies have shown synergistic antitumor activity between subasumstat and the anti-CD20 mAb rituximab in xenograft models of human B-cell lymphoma[5]
- Based on these data, and preliminary findings from a single-agent subasumstat study (TAK-981-1002; NCT03648372)[6], this phase 1b/2 study is investigating subasumstat plus rituximab in adults with CD20-positive relapsed refractory (R/R) non-Hodgkin lymphoma (NHL) (**Figure 2**)
  - Here, we report data from the phase 1b dose-escalation part of the study

Figure 2: Phase 1b/2, multicenter, open-label, dose-escalation and expansion study (NCT04074330)



BIW, twice weekly; BLRM, Bayesian logistic regression model; DLT, dose-limiting toxicity; IV, intravenous; QW, once weekly; RP2D, recommended phase 2 dose

Phase 1b inclusion criteria

- ≥18 years with CD20-postive R/R aggressive NHL (aNHL) or indolent NHL (iNHL)
  - aNHL included diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), and grade 3b follicular lymphoma (FL)
  - iNHL included grade 1–3a FL and marginal zone lymphoma (MZL)
- aNHL patients had to have received prior rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or equivalent plus 1 additional line of therapy in the R/R setting
- iNHL patients had to be refractory to rituximab or another anti-CD20 mAb, and to have received ≥1 prior therapy for R/R disease
- Ineligible for or refused autologous stem cell transplant

Phase 1b study endpoints

Primary

- Frequency, severity, duration of treatment-emergent adverse events (TEAEs) according to NCI CTCAE v 5.0
  - Cytokine release syndrome (CRS) was graded according to American Society for Transplantation and Cellular Therapy consensus grading for CRS[7]
- Occurrence of DLTs within the first 21-day treatment cycle

Secondary

- Pharmacokinetics (PK)
- Overall response rate (ORR) measured per investigator assessment according to Lugano criteria[8]
- Subasumstat –SUMO adduct formation and SUMOylation pathway inhibition

Question What is the safety and tolerability profile and RP2D of the novel SUMOylation inhibitor subasumstat (TAK-981) in combination with rituximab?

Investigation Patients with CD20-positive R/R aNHL or iNHL (N=27)

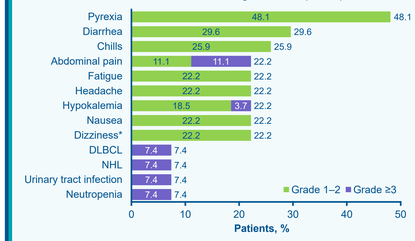
Subasumstat IV QW (D 1, 8) or BIW (D 1, 4, 8, 11) + rituximab IV 375 mg/m² D 1, 8, 15 cycle 1, then D 1 only

Treated in 21-day cycles for up to one year until disease progression, unacceptable toxicity, or other withdrawal criteria met

Results

Preliminary safety

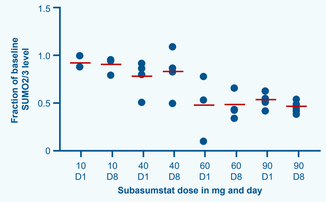
No DLTs have been reported to date and the most common TEAEs have been grade 1–2 (N=27)



*Includes postural dizziness.

Pharmacodynamics

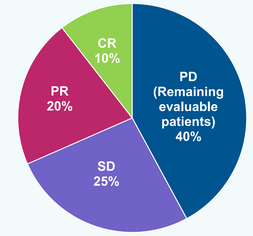
Subasumstat exhibited pharmacodynamic activity in peripheral blood including decreased SUMOylation



Red lines represent mean fold-change at each dose level (1: no change from baseline, <1 decrease compared with baseline, >1 increase compared with baseline). Patients from QW schedule only.

Emerging efficacy

ORR: 30% in 20 response-evaluable patients



CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

Conclusion Subasumstat plus rituximab was well tolerated and resulted in promising clinical activity, supporting continued development of this combination in patients with R/R NHL

Results

Patients

- At data cut-off (October 18, 2021), 27 patients had been enrolled and treated: 21 with subasumstat 10–120 mg QW and 6 with 90 mg BIW
  - 5 patients were ongoing treatment at data cut-off
- Demographics and disease characteristics are shown in **Table 1**

Table 1: Patient characteristics

	All patients (N=27)
Median age, years (range)	65 (29–80)
Male, n (%)	18 (66.7)
Primary disease diagnosis, n (%)	
DLBCL	16 (59.3)
FL*	4 (14.8)
MCL	4 (14.8)
Other†	3 (11.5)
Eastern Cooperative Oncology Group performance status at study entry, n (%)	
0	7 (25.9)
1	17 (63.0)
2	3 (11.1)
Ann Arbor stage III–IV at study entry,‡ n (%)	19 (70.4)
Median lines of prior therapy at study entry, n (range)	3 (1–6)
Prior autologous stem cell transplant	6 (22.2)
Prior chimeric antigen receptor T-cell therapy	3 (11.1)
Prior exposure to 1/ 2/ ≥3 anti-CD20-containing therapies, n (%)	8 (29.6) / 9 (33.3) / 10 (37.0)
Refractory to any prior anti-CD20-containing therapy,# n (%)	20 (74.1)
Refractory to last line of therapy, n (%)	23 (85.2)

*Grade 2–3a (n=2), grade 3b (n=1), or unknown (n=1). †Chronic lymphocytic leukemia/small lymphocytic leukemia (n=1), primary mediastinal (thymic) large B-cell lymphoma (n=1), and T-cell/histiocyte-rich B-cell lymphoma (n=1). ‡1 patient had stage II and 7 had unknown stage. #Defined as failure to respond to, or progression during any previous anti-CD20-containing regimen, or progressive disease within 6 months of last dose anti-CD-20 therapy.

Treatment exposure and safety

- **Table 2** shows the median number of cycles received at each subasumstat dose level
- No DLTs have been reported. **No maximum tolerated dose (MTD) has been identified, and enrollment is ongoing**
  - The RP2D and schedule will be selected based on safety, PK, and pharmacodynamic data
- The safety profile of subasumstat plus rituximab is summarized in **Table 3**, and the most common TEAEs are shown in the **central summary panel**

Table 2: Treatment cycles received at each subasumstat dose level

	10 mg QW (n=3)	40 mg QW (n=4)	60 mg QW (n=3)	90 mg QW (n=7)	120 mg QW (n=4)	90 mg BIW (n=6)	All patients (N=27)
Median number of cycles (range)	17 (4–21)	7 (2–20)*	14 (8–20)*	3 (2–9)	3 (2–3)†	1 (1–3)*	3 (1–21)

*1 patient ongoing. †2 patients ongoing.

- Grade ≥3 TEAEs related to subasumstat were reported in 5 patients: 1 patient in the 40 mg QW cohort had a grade 3 urinary tract infection; 1 and 2 patients in the 40 mg QW and 90 mg BIW cohorts, respectively, had grade 4 neutropenia; and 1 patient in 90 mg BIW cohort had grade 3 white blood cell count decreased
- Common TEAEs were consistent with induction of IFN-I signalling (transient flu-like symptoms: fever, chills, fatigue) and with those observed in the single-agent subasumstat study (data on file); no further subasumstat- or immune-related TEAEs were observed

Table 3: Summary of TEAEs with subasumstat plus rituximab

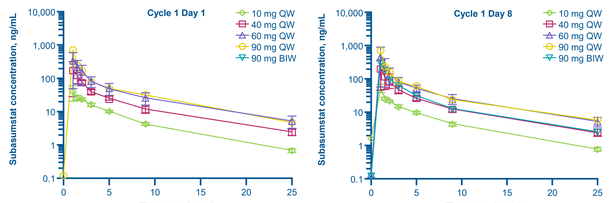
	Subasumstat dose						
n (%)	10 mg QW (n=3)	40 mg QW (n=4)	60 mg QW (n=3)	90 mg QW (n=7)	120 mg QW (n=4)	90 mg BIW (n=6)	All patients (N=27)
Any TEAE	3 (100)	4 (100)	3 (100)	6 (85.7)	4 (100)	6 (100)	26 (96.3)
Related to subasumstat	3 (100)	4 (100)	3 (100)	6 (85.7)	3 (75.0)	6 (100)	25 (92.6)
Any grade ≥3 TEAEs	1 (33.3)	3 (75.0)	1 (33.3)	2 (28.6)	2 (50.0)	4 (66.7)	13 (48.1)
Related to subasumstat	0	2 (50.0)	0	0	0	3 (50.0)	5 (18.5)
Any TEAEs leading to discontinuation	0	3 (75.0)	0	0	1 (25.0)	0	4 (14.8)
Any serious AEs	1 (33.3)	2 (50.0)	0	2 (28.6)	2 (50.0)	4 (66.7)	11 (40.7)
Related to subasumstat	0	1 (25.0)	0	0	1 (25.0)	3 (50.0)	5 (18.5)
On-study deaths*	0	1 (25.0)	0	1 (14.3)	0	2 (33.3)	4 (14.8)

*None related to study drugs.

Pharmacokinetics

- Subasumstat PK were dose-linear and declined in a tri-phasic manner
  - There was minimal accumulation following repeat dosing (**Figure 3**)

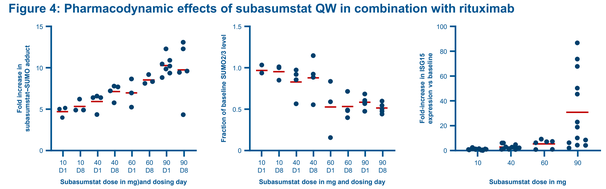
Figure 3: Mean plasma concentration versus time profiles of subasumstat following IV infusions on days 1 and 8 of cycle 1



Pharmacodynamics

- Subasumstat exhibited pharmacodynamic activity in peripheral blood, including on markers of target engagement, decreased SUMOylation, and increased IFN-I-regulated gene expression (**Figure 4 and central summary panel**)

Figure 4: Pharmacodynamic effects of subasumstat QW in combination with rituximab



Target engagement in T cells was detected by flow cytometry with an antibody recognizing the subasumstat–SUMO adduct formed during the inhibition of the SUMO-activating enzyme by subasumstat. Adduct signal increased at 1 hour after the end of infusion on days 1 and 8 of cycle 1 compared to baseline levels observed prior to dosing on day 1 of cycle 1

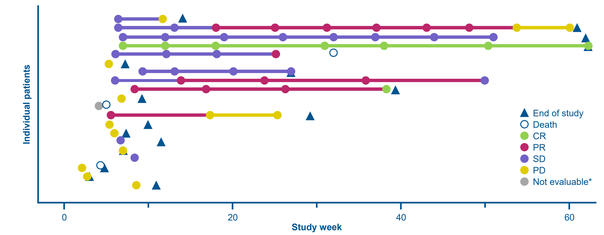
SUMOylation in T cells was detected with an antibody recognizing SUMO2/3 chains. Levels of SUMO2/3 chains at 1 hour after the end of infusion on day 1 or day 8 of cycle 1 were lower vs the baseline level prior to dosing on day 1 of cycle 1, indicating that fewer chains are formed when SAE is inhibited by subasumstat

Expression of ISG15, an IFN-I-regulated gene, in peripheral blood was measured by RNA sequencing at baseline (pre-dose on day 1 of cycle) and at multiple time points post-dose. Maximum fold-increases in expression at 8 or 24 hours post dosing on day 1 and day 8 vs baseline are shown

Treatment response

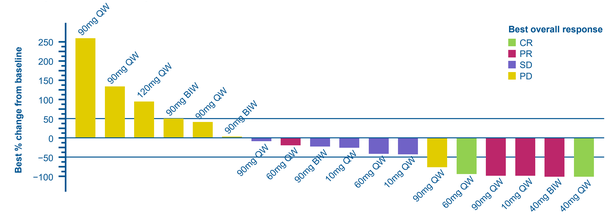
- **ORR:** 30% (6 of 20 response evaluable patients) (**central summary panel, Figure 5**)
  - **2 CRs (1 each 40 and 60 mg QW)**
    - 1 each: R/R MCL after 1 prior therapy; R/R DLBCL after 3 prior therapies
  - **4 PRs (1 each at 10, 40, 60, and 90 mg QW)**
    - 1 each: R/R FL after 4 prior therapies; R/R DLBCL after 2 prior therapies; R/R MCL after 3 prior therapies; R/R PMLBCL after 4 prior therapies including CAR T
  - **5 patients with SD:** including 1 at 10 mg QW with R/R DLBCL after 3 prior therapies with SD lasting ~1 year
- Change in target lesion size from baseline according to best overall response is shown in **Figure 6**
- After a median follow-up of 11.1 months, median duration of response has not been reached

Figure 5: Swimmer plot of responses to subasumstat plus rituximab



*Patient's premature study withdrawal due to disease deterioration was captured as a response assessment

Figure 6: Change in target lesion size from baseline with subasumstat plus rituximab in 18 response-evaluable patients



Conclusions

- The combination of subasumstat and rituximab was well tolerated by patients at each dose level and schedule
  - Common TEAEs consistent with induction of IFN-I signalling (i.e. transient flu-like symptoms)
  - No DLTs reported; MTD not identified
- Subasumstat PK data showed minimal accumulation after repeat dosing
- Pharmacodynamic assays confirmed inhibition of SUMOylation and activation of IFN-I signalling
- Most importantly, the combination of subasumstat and rituximab resulted in promising clinical activity (ORR 30%) in the R/R setting, supporting the continued development of this combination in patients with NHL
  - SUMOylation inhibition may overcome resistance to prior exposure to rituximab
  - Enrollment to phase 1b dose escalation ongoing at 90 mg BIW and 120 mg QW
  - Phase 2 planned at the RP2D and selected schedule

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Off-label disclosure: This presentation contains information about use of subasumstat (TAK-981) as a treatment for relapsed/refractory NHL

Poster presentation at the 63rd Annual Meeting of the American Society of Hematology (ASH), December 11–14, 2021. For questions or comments please contact Sarit E Assouline: sarit.assouline@mcgill.ca