First-in-Human Phase 1 Study of SAR442257 in Patients with Relapsed/Refractory Multiple Myeloma and Non-Hodgkin Lymphoma

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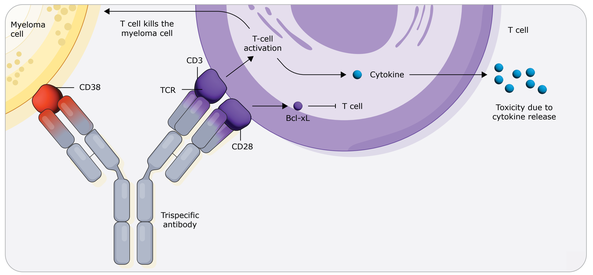
INTRODUCTION

- SAR442257 is a trispecific antibody targeting CD38 on tumor cells, as well as CD3 and CD28 on T cells, with a human Immunoglobulin G4 Fc domain lacking effector functions (**Figure 1**)[1]
- SAR'257 direct T cells to tumor cells, causing their death through degranulation and release of cytotoxic molecules such as granzyme and perforin
- SAR'257's ability to target CD28 on multiple myeloma (MM) and lymphoma cells[2,3] may be important when CD38 binding sites are downregulated or occupied by prior anti-CD38 therapies[4]
- SAR'257 suppressed myeloma growth, stimulated memory/effector T cell proliferation, and reduced regulatory T cells in pre-clinical studies[4,5]
- This first-in-human study reports the safety, tolerability, pharmacokinetics (PK), and preliminary efficacy of SAR'257 in patients with relapsed/refractory (rr) MM and rr non-Hodgkin lymphoma (NHL)

Figure 1: The mechanism of action of SAR'257[6]

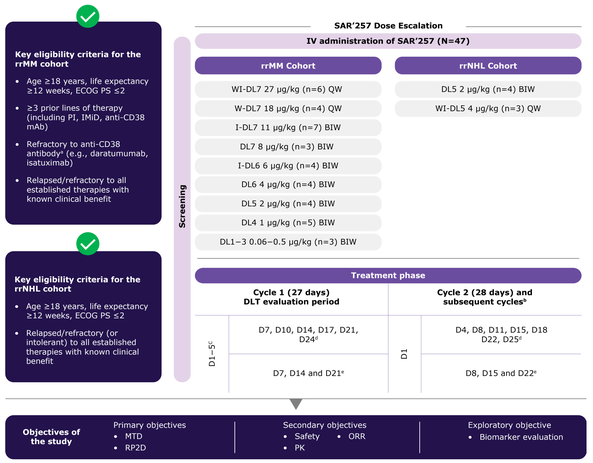


Bcl-xL, B cell lymphoma-extra large; CD, cluster of differentiation; TCR, T cell receptor.

METHODS

- This is an open-label, Phase 1, single-agent, dose-escalation study of SAR'257 in patients with rrMM and rrNHL (NCT04401020)
- SAR'257 was administered intravenously with lead-in doses (Days 1–5) in the first week, followed by twice-weekly (BIW) or once-weekly (QW) dosing
  - The rrMM cohort had 9 target dose levels (DLs) (7 DLs: 0.06–11 µg/kg BIW and 2 DLs: 18–27 µg/kg QW), while the rrNHL cohort had 2 DLs (2 µg/kg BIW and 4 µg/kg QW) (**Figure 2**)

Figure 2: Study design and objectives



[a]Previous amendments required a prior dose of anti-CD38 within 12 months. [b]As determined by totality of data collected, including PK/PD, safety and preliminary efficacy. [c]Lead-in dose, daily for 5 days. [d]SAR'257 dosing at DL1 to 3 DL7 in rrMM cohort and at DL5 in rrNHL cohort. [e]SAR'257 dosing at W-DL7 and WI-DL7 in rrMM cohort and WI-DL5 in rrNHL cohort.
ADA, anti-drug antibodies; BIW, twice a week; CT, computed tomography; ECOG PS, eastern cooperative oncology group performance status; I, intermediate; IMiD, immunomodulatory imide drug; mAb, monoclonal antibody; MTD, maximum tolerated dose; ORR, overall response rate; PD, pharmacodynamic; PI, proteasome inhibitor; PK, pharmacokinetics; QW, every week; RP2D, recommended Phase 2 dose; rrMM, relapsed/refractory multiple myeloma; rrNHL, relapsed/refractory non-Hodgkin lymphoma; W, weekly.

RESULTS

Baseline demographics

- The median number of prior therapy lines was 5 in both cohorts (**Table 1**)
- In the rrMM cohort, all patients had a prior exposure to anti-CD38 monoclonal antibodies, with 52.5% refractory at the last line before study entry, and 40% achieving a best overall response (BOR) of minimal response, stable disease, or progressive disease
- The median time from the last anti-CD38 dose in the rrMM cohort was 2.7 months (range: 1–65 months)
- The rrNHL cohort consisted of patients naïve to anti-CD38 therapy, with 71.4% being refractory to anti-CD20 therapy.

Table 1: Patient demographics and baseline characteristics

Characteristics	rrMM cohort (N=40)	rrNHL cohort (N=7)*
Age in years [Median (Min–Max)]	64 (40–84)	70 (18–75)
Gender, male [n (%)]	30 (75.0)	6 (85.7)
Race [n (%)]		
White	34 (85.0)	6 (85.7)
Black or African American	0	1 (14.3)
Asian	4 (10.0)	0
Not reported	1 (2.5)	0
Unknown	1 (2.5)	0
Number of prior lines by participant [Median (Min–Max)]	5 (3–12)	5 (2–7)
Refractory to immunomodulatory imide drug [n (%)]	37 (92.5)	-
Refractory to proteasome inhibitor [n (%)]	37 (92.5)	-
Refractory to anti-CD38 agents [n (%)]	40 (100)	-
Refractory to anti-CD20 monoclonal [n (%)]	-	5 (71.4)

*1 tFL, 2 CTCL, 2 MCL, 1 DLBCL GCB subtype, 1 T cell and histiocyte rich LBCL.
CD, cluster of differentiation; CTCL, cutaneous T cell lymphomas; DLBCL, diffuse large B cell lymphoma; LBCL, large B cell lymphoma; MCL, mantle cell lymphomas; rrMM, relapsed/refractory multiple myeloma; rrNHL, relapsed/refractory non-Hodgkin lymphoma; tFL, transformed follicular lymphoma.

Safety

- Overall, 70.2% (n=33) of patients experienced treatment-emergent adverse events (TEAEs) of special interest, with cytokine release syndrome (CRS) being the most common, occurring in 55% (n=22) of patients in the rrMM cohort and 57.1% (n=4) in the rrNHL cohort (**Table 2**)
- Higher DLs led to more frequent CRS episodes
- Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infections/reactivations were observed in both patient cohorts, along with infusion-related reactions (IRRs), though most were non-severe
- Four dose-limiting toxicities (DLTs) were observed in rrMM and three in rrNHL cohorts (**Table 2**)

Table 2: TEAEs of special interest[a] by grade and preferred term

PRIMARY SYSTEM ORGAN CLASS Preferred Term n (%)	DLs for rrMM cohort									DLs for rrNHL cohort		All (N=47)
	DL1–DL3 (n=3)	DL4 (n=5)	DL5 (n=4)	DL6 (n=4)	I-DL6 (n=4)	DL7 (n=3)	I-DL7 (n=7)	W-DL7 (n=4)	WI-DL7 (n=6)	DL5 (n=4)	WI-DL5 (n=3)	
Any class (All Grade) [n (%)]	0	2 (40.0)	2 (50.0)	4 (100)	3 (75.0)	2 (66.7)	5 (71.4)	3 (75.0)	6 (100)	3 (75.0)	3 (100)	33 (70.2)
Grade ≥3	0	1 (20.0)	1 (25.0)	1 (25.0)	0	0	1 (14.3)	1 (25.0)	2 (33.3)	2 (50.0)	1 (33.3)	10 (21.3)
INFECTIONS AND INFESTATIONS [n (%)]												
Cytomegalovirus infection reactivation (All Grade)	0	0	0	0	0	0	2 (28.6)	1 (25.0)	3 (50.0)	1 (25.0)	0	7 (14.9)
Grade ≥3	0	0	0	0	0	0	1 (14.3)[b]	0	1 (16.7)[c]	0	0	2 (4.3)
Epstein-Barr virus infection reactivation (All Grade)	0	0	0	0	0	0	1 (14.3)	1 (25.0)	2 (33.3)	1 (25.0)	0	5 (10.6)
Grade ≥3	0	0	0	0	0	0	1 (14.3)[b]	1 (25.0)[c]	1 (16.7)[c]	0	0	3 (6.4)
IMMUNE SYSTEM DISORDERS [n (%)]												
Cytokine release syndrome (All Grade)	0	1 (20.0)	0	4 (100)	3 (75.0)	2 (66.7)	4 (57.1)	3 (75.0)	5 (83.3)	2 (50.0)	2 (66.7)	26 (55.3)
Grade ≥3	0	0	0	0	0	0	1 (14.3)[d]	0	0	0	0	1 (2.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS [n (%)]												
Infusion related reactions (All Grade)	0	0	1 (25.0)	1 (25.0)	1 (25.0)	0	0	0	4 (66.7)	2 (50.0)	0	9 (19.1)
Grade ≥3	0	0	0	0	0	0	0	0	0	1 (25.0)	0	1 (2.1)
DLTs (Grade ≥3) [Events]	0	0	0	1[e]	0	0	1[f]	0	2[g]	2[h]	1[i]	7

SAR'257 was administered BIW at DL1 to I-DL7 in the rrMM cohort and at DL5 in the rrNHL cohort, and QW at W-DL7 to WI-DL7 in the rrMM cohort and at WI-DL5 in the rrNHL cohort.
[a]The following are AESIs: IRRs Grade ≥2, CRS any grade, CNS toxicity Grade ≥2, EBV/CMV reactivation: Grade ≥2, DLTs and AEs meeting DLT criteria beyond Cycle 1, pregnancy, symptomatic overdose, and secondary primary malignancies. [b]Grade 4, [c]Grade 3, [d]Grade 5, [e]Grade 3, hepatotoxicity, Grade 5, CRS–EBV reactivation. [f]Grade 3, CMV infection reactivation and Grade 3, febrile neutropenia in same patient. [g]Grade 4, neutropenia and Grade 4, thrombocytopenia in same patient. [h]Grade 4, immune effector cell-associated neurotoxicity syndrome. [i]Grade 4, immune effector cell-associated neurotoxicity syndrome.
rrMM, relapsed/refractory multiple myeloma; rrNHL, relapsed/refractory non-Hodgkin lymphoma.

Pharmacokinetics

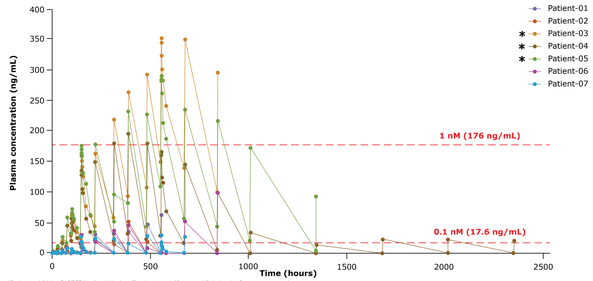
- In the rrMM cohort, 2 out of 3 patients from the DL7 (8 µg/kg BIW) and 3 out of 7 patients from the I-DL7 (11 µg/kg BIW) reached SAR'257 levels within the efficacious range (0.1 to 1 nM) during the first treatment cycle (**Table 3 and Figure 3**)
- After switching to the QW dosing regimen, 1 out of 6 subjects treated at WI-DL7 (27 µg/kg) reached C_{trough} levels within the efficacious range, while none of the subjects treated at W-DL7 (18 µg/kg) reached this range in the first cycle
- While the PK data showed drug exposure consistent with a theoretically efficacious range (based on *ex vivo* models), limited clinical response was observed

Table 3: SAR'257 PK parameters at steady state[a] in rrMM and rrNHL cohorts[b]

Parameters	DLs in rrMM cohort									DLs for rrNHL cohort	
	DL1 (n=1)	DL2 (n=1)	DL3 (n=1)	DL4 (n=4)	DL5 (n=3)	DL6 (n=3)	I-DL6 (n=4)	DL7 (n=3)	I-DL7 (n=7)	W-DL7 (n=4)	WI-DL7 (n=6)	DL5 (n=3)	WI-DL5 (n=2)
T_{max} (hour) [Median (Min–Max)]	6.1 (6.1–6.1)	4.37 (4.37–4.37)	5.97 (5.97–5.97)	4.17 (4.05–6.38)	4.28 (4.08–6)	4.28 (4.02–4.78)	4 (4–4.18)	4.08 (4.08–4.47)	4 (0–70.83)	3.87 (3.58–4.08)	4.18 (0–5.43)	3.97 (3.85–4)	4.14 (3.92–4.35)
C_{max} (ng/mL) [Geo mean (CV%)]	2.73 (NC)	0.683 (NC)	19.8 (NC)	3.27 (157)	9.99 (116)	8.28 (24)	15.6 (159)	86.8 (84)	29 (112)	38.3 (38)	91.6 (183)	6.04 (44)	3.85 (7)
AUC_{last} [Geo mean (CV%)]	58.4 (NC)	4.15 (NC)	426 (NC)	28.8 (175)	136 (127)	49.3 (51)	127 (173)	1160 (94)	427 (132)	390 (72)	1070 (222)	30.9 (28)	36.9 (72)
T_{last} (hour) [Median [Min–Max)]	29.13 (29.13–29.13)	12.37 (12.37–12.37)	28.23 (28.23–28.23)	28.18 (5–28.53)	28 (12.25–28.08)	28.22 (11.75–29.08)	28 (7.9–28)	28 (27.43–28.08)	27.67 (4–70.83)	51.58 (11.87–76)	75.55 (12.25–76.2)	28 (7.92–28.1)	20.29 (12.4–28.17)

[a]Steady state at Cycle 1, Day 24 for BIW dosing and Cycle 1, Day 21 for QW dosing. [b]SAR'257 was administered BIW at DL1 to I-DL7 in the rrMM cohort and at DL5 in the rrNHL cohort, and QW at W-DL7 to WI-DL7 in the rrMM cohort and at WI-DL5 in the rrNHL cohort.
AUC_{last} area under the concentration-time curve to the last measurable concentration; BIW, Twice weekly; C_{max}, maximum plasma concentration; CV, coefficient of variation; Geo mean, geometric mean; NC, not calculated; QW, Once weekly; rrMM, relapsed/refractory multiple myeloma; rrNHL, relapsed/refractory non-Hodgkin lymphoma; TDLs, target dose levels; Tlast, time of the last measurable (quantifiable) concentration; T_{max}, Time to maximum plasma concentration.

Figure 3: Mean SAR'257 PK profiles for subjects in I-DL7 (11 µg/kg) BIW



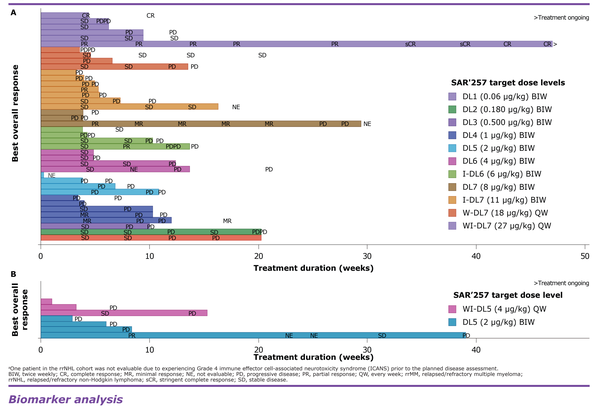
*Patients exhibiting SAR'257 levels within the efficacious range (0.1 to 1 nM) during the first treatment cycle.
BIW, twice weekly; DL, dose level; I, intermediate; PK, pharmacokinetics.

Efficacy

- In the rrMM cohort, the overall response rate (ORR; defined as partial response [PR] or better) was 5% (n=2), with one stringent complete response[a] and one complete response[c] at the WI-DL7 (27 µg/kg) QW (**Figure 4**)
- In the rrNHL cohort, the ORR was 14.3%, with one PR[c] at the DL5 (2 µg/kg) BIW
- The disease control rate (DCR), defined as stable disease or better for >8 weeks, was 60% (n=24) in the rrMM cohort and 28.6% (n=2) in the rrNHL cohort

[a]Duration of response (DOR)=9.9 months, on-going. [b]DOR= 1.4 months, stopped SAR'257 due to Grade 3 EBV infection/reactivation. [c]DOR=7.1 months.

Figure 4: Best overall response in patients with (A) rrMM and (B) rrNHL[a]

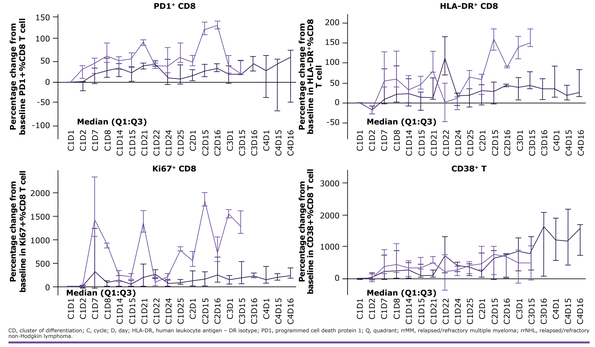


[a]One patient in the rrNHL cohort was not evaluable due to experiencing Grade 4 immune effector cell-associated neurotoxicity syndrome (ICANS) prior to the planned disease assessment.
BIW, twice weekly; CR, complete response; MR, minimal response; NE, not evaluable; PD, progressive disease; PR, partial response; QW, every week; rrMM, relapsed/refractory multiple myeloma; rrNHL, relapsed/refractory non-Hodgkin lymphoma; sCR, stringent complete response; SD, stable disease.

Biomarker analysis

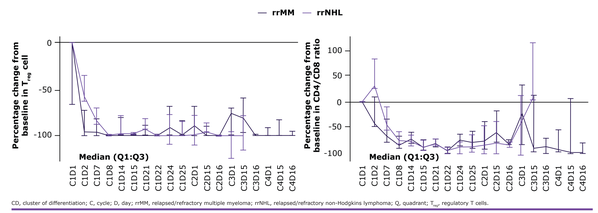
- SAR'245 treatment increased the percent $PD1^+$, $HLA\text{-}DR^+$, $Ki67^+$, and $CD38^+$, $CD8^+$ T cells in both the rrMM and rrNHL cohorts (**Figure 5**)
- Regulatory T (T_{reg}) cells and CD4/CD8 ratio in blood decreased with SAR'257 treatment (**Figure 6**)
- CD38 expression on plasma cells positively correlates with the time since the last anti-CD38 dose (**Figure 7**)
- Cytokine levels, including Interleukin(IL)-6, IL-8, IL-10, and C-reactive protein (CRP), peak value in the first cycle is significantly higher in patients who experienced CRS events compared to those who did not (**Figure 8**)

Figure 5: Peripheral blood T cells activation when treated with SAR'257



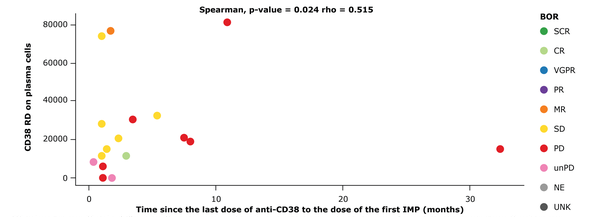
CD, cluster of differentiation; C, cycle; D, day; HLA-DR, human leukocyte antigen – DR isotype; PD1, programmed cell death protein 1; Q, quadrant; rrMM, relapsed/refractory multiple myeloma; rrNHL, relapsed/refractory non-Hodgkin lymphoma.

Figure 6: T_{reg} cells and CD4/CD8 ratio in blood when treated with SAR'257



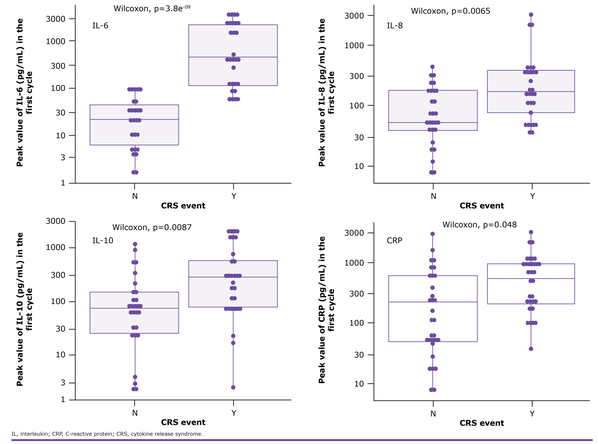
CD, cluster of differentiation; C, cycle; D, day; rrMM, relapsed/refractory multiple myeloma; rrNHL, relapsed/refractory non-Hodgkin lymphoma; Q, quadrant; T_{reg}, regulatory T cells.

Figure 7: Correlation between CD38 receptor density (RD) on plasma cells and time since last anti-CD38 dose



BOR, best overall response; CD, cluster of differentiation; CR, complete response; IMP, investigational medicinal product; MR, minimal response; NE, not evaluable; PD, progressive disease; PR, partial response; RD, receptor density; sCR, stringent complete response; SD, stable disease; UNK, unknown; unPD, unconfirmed progressive disease; VGPR, very good partial response.

Figure 8: Cytokines peak value in the first cycle in patients with and without CRS event



IL, interleukin; CRP, C-reactive protein; CRS, cytokine release syndrome.

CONCLUSIONS

- The Phase 1 study of SAR'257 demonstrated an anti-tumor response in a limited number of patients from the rrMM and rrNHL cohorts
- The biomarker analysis indicated that SAR'257 induces T cell activation in both rrMM and rrNHL cohorts, supporting its mechanism of action
- The study encountered significant safety issues, particularly high rates of EBV and CMV reactivation, along with recurrent episodes of CRS at higher dose levels
- Due to these safety concerns, the study was terminated during the dose escalation phase

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