Pharmacokinetics and Biomarker Analysis From a Phase 1/2 Open-label Study of The Anti-GPC3 T-cell Engager SAR444200, in Patients With Advanced Solid Tumors

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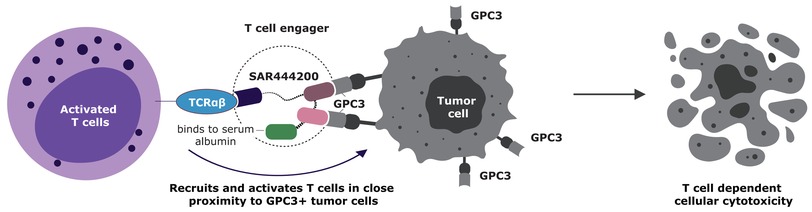
BACKGROUND

- SAR444200, a novel NANOBODY® T cell engager, simultaneously binds with T cell receptor (TCR)αβ and glypican-3 (GPC3) to co-engage T cells with GPC3-expressing tumor cells (**Figure 1**), resulting in T cell dependent cellular cytotoxicity[1–3]
- GPC3 is a cell-surface glycoprotein that plays a crucial role in cellular signaling, such as cell growth and differentiation[4]. GPC3 has limited expression on normal tissues; however, high expression in some tumor types has been reported, thus making it an attractive target for an immune cell engager anti-cancer therapy[5,6]
- In preclinical studies, SAR444200 has demonstrated potent anti-tumor activity[7]
- Here, we present the safety, pharmacokinetics (PK), and biomarker data from 6 dose levels (DLs) of SAR444200 in patients with advanced solid tumors in dose escalation cohort (Part 1A) from the first-in-human Phase 1/2 study (EudraCT 2021-006623-17/ NCT05450562)

Figure 1: Mechanism of action

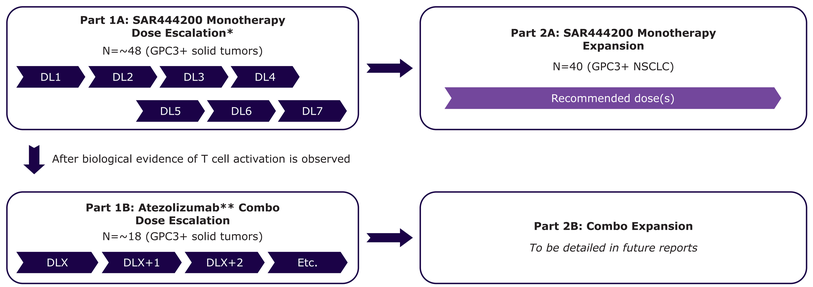


GPC3, glypican-3; mAbs, monoclonal antibodies; TCRαβ, T cell receptor alpha beta.

METHODS

- This ongoing Phase 1/2 trial evaluated open label, intravenously (IV) administered SAR444200 (every week [QW] with lead-in doses) at DL1 (3 mg), DL1A (1 mg), DL2A (2.5 mg), DL3A (4.5 mg), DL4A (18 mg), and DL5A (36 mg) in adult patients with GPC3+ solid tumors (**Figure 2**)
- On-study imaging was performed every 9 weeks after the date of first infusion of SAR444200
- Whole blood samples were collected to assess the plasma concentrations of SAR444200, and for biomarker analysis
- PK analysis was performed with an electrochemiluminescence-based total PK assay using Meso Scale Discovery platform

Figure 2: Study design



*Bayesian logistic regression model (BLRM) design with at least 3 participants per DL.
**Atezolizumab will be provided by Roche.
SAR444200 IV or in combination will be administered over a 21-day cycle.
DL, dose level; GPC3, glypican-3; IV, intravenous; NSCLC, non-small cell lung cancer.

Primary endpoints:

Part 1A and 1B

- Dose-limiting toxicity (DLT), adverse events (AEs), and serious AEs

Part 2A

- Objective response rate (ORR)

Secondary endpoints:

Part 1A and 1B

- ORR

Part 1A, 2A and 1B

- Duration of response (DoR), PK, and incidence of antidrug antibodies

Part 2A

- Progression-free survival (PFS), AEs, and serious AEs (SAE)

Table 1: Key inclusion and exclusion criteria[8]

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • Positive GPC3 expression on tumor tissue • **For Part 1A and 1B** – Metastatic and/or unresectable HCC diagnosed by histology and/or cytology, or diagnosed clinically by the AASLD criteria (patients without liver cirrhosis must be diagnosed histologically). Or other histologically/ cytologically proven advanced and/or metastatic non-HCC solid tumors – Not amenable to available standard of care	• ECOG performance status of ≥2 • Predicted life expectancy ≤3 months • For participants with HCC: Child Pugh Class B or C liver score within 14 days of initiation of IMP. Participants with Child Pugh Class B-7 score are allowed for Part 1A • Known uncontrolled HIV, hepatitis B infection, or known untreated current hepatitis C infection • Platelets <100 × 10^3 µ/L (after ≥3 days without platelet transfusion) for participants with non-HCC solid tumor, or <75 × 10^3 µ/L (after ≥3 days without platelet transfusion) for participants with HCC • Aspartate aminotransferase and/or alanine aminotransferase >3 × ULN (or >5 × ULN for participants with HCC or liver metastases)

AASLD, American Association for the Study of Liver Diseases; ECOG, Eastern Cooperative Oncology Group; GPC3, glypican-3; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; IMP, investigational medicinal product; ULN, upper limit of normal.

RESULTS

- As of January 19, 2024, a total of 24 patients (DL1: n=4, DL1A: n=4, DL2A: n=4, DL3A: n=4, DL4A: n=4, DL5A: n=4) with GPC3+ tumors received SAR444200 in Part 1A dose escalation (**Table 2**)
- Patients were heavily pre-treated; median number of prior lines of therapy ranged between 4 (2.0–7.0)
- Most of the patients (n=17, 70.8%) had hepatocellular carcinoma

Table 2: Patient baseline characteristics

Patient baseline characteristics	Part 1A						All (N=24)
	DL1 3 mg (n=4)	DL1A 1 mg (n=4)	DL2A 2.5 mg (n=4)	DL3A 4.5 mg (n=4)	DL4A 18 mg (n=4)	DL5A 36 mg (n=4)	
Age, median (range), years	56.0 (29.0–76.0)	55.0 (51.0–69.0)	56.5 (47.0–72.0)	53.5 (30.0–61.0)	61.5 (40.0–66.0)	65.5 (55.0–76.0)	59 (29.0–76.0)
Male, n (%)	3 (75.0)	3 (75.0)	3 (75.0)	3 (75.0)	2 (50.0)	4 (100)	18 (75.0)
Race, n (%)							
White	1 (25.0)	1 (25.0)	2 (50.0)	2 (50.00)	1 (25.0)	1 (25.0)	8 (33.3)
Asian	3 (75.0)	3 (75.0)	2 (50.0)	2 (50.0)	3 (75.0)	3 (75.0)	16 (66.7)
GPC3 expression membranous H-score, median (range)	16 (7–70)	14 (3–20)	102 (2–300)	95 (0–190)	30 (5-280)	155 (40-160)	22 (0-300)
Number of prior regimens, median (range)	4.5 (2.0–6.0)	3.5 (2.0–6.0)	4.5 (3.0–5.0)	4 (4.0–5.0)	3.5 (2.0–7.0)	3 (3.0-4.0)	4 (2.0–7.0)
Disease location at diagnosis, n (%)*	DL1 3 mg (n=4)	DL1A 1 mg (n=4)	DL2A 2.5 mg (n=4)	DL3A 4.5 mg (n=4)	DL4A 18 mg (n=4)	DL5A 36 mg (n=4)	All (N=24)
Liver	3 (75.00)	4 (100)	2 (50.00)	1 (25.00)	4 (100)	3 (75.00)	17 (70.83)
Cecum	0	0	0	1 (25.00)	0	0	1 (4.17)
Colon	0	0	1 (25.00)	0	0	0	1 (4.17)
Esophagus	0	0	0	1 (25.00)	0	0	1 (4.17)
Gall bladder	1 (25.00)	0	0	0	0	0	1 (4.17)
Gastrointestinal tract	0	0	0	1 (25.00)	0	0	1 (4.17)
Lung	0	0	0	0	0	1 (25.00)	1 (4.17)
Stomach	0	0	1 (25.00)	0	0	0	1 (4.17)

*Cut-off date for the disease location data was April 2024
DL, dose level; GPC3, glypican-3; n/N, number of patients.

Safety

- No DLTs were observed in the 24 DLT evaluable patients; no treatment-emergent adverse event (TEAE) led to SAR444200 discontinuation
- All TEAEs for cytokine release syndrome (CRS) (19 [79%]) and infusion-related reactions (7 [29%]) were Grade 1 or 2
- Grade ≥3 TEAEs were dyspnoea and insomnia experienced by 1 (4.2%) patient each
- Twenty-two patients (92%) reported treatment-related adverse events (TRAEs) of any grade, including 3 patients with a serious TRAE (2 events with hospitalization prolongation for a Grade 1 and 2 (CRS) that recovered completely without and with tocilizumab, respectively, 1 event with pneumonitis Grade 3 was also observed) (**Table 3**)

Table 3: Any grade TRAEs with incidence in ≥2 patients

Type of TRAE, n (%)	Part 1A						Total (N=24)
	DL1 3 mg (n=4)	DL1A 1 mg (n=4)	DL2A 2.5 mg (n=4)	DL3A 4.5 mg (n=4)	DL4A 18 mg (n=4)	DL5A 36 mg (n=4)	
CRS	4 (100)	1 (25.0)	3 (75.0)	4 (100)	3 (75.0)	5 (83.3)	20 (76.9)
Nausea	2 (50.0)	1 (25.0)	2 (50.0)	2 (50.0)	1 (25.0)	1 (16.7)	9 (34.6)
Infusion related reaction	1 (25.0)	0	1 (25.0)	1 (25.0)	2 (50.0)	3 (50.0)	8 (30.8)
Myalgia	1 (25.0)	0	2 (50.0)	1 (25.0)	0	3 (50.0)	7 (26.9)
Pyrexia	0	0	2 (50.0)	1 (25.0)	1 (25.0)	2 (33.3)	6 (23.1)
Fatigue	0	0	1 (25.0)	3 (75.0)	1 (25.0)	0	5 (19.2)
Vomiting	1 (25.0)	1 (25.0)	0	0	1 (25.0)	1 (16.7)	4 (15.4)
Dyspnoea	1 (25.0)	0	0	1 (25.0)	0	1 (16.7)	3 (11.5)
Diarrhoea	0	0	1 (25.0)	0	1 (25.0)	1 (16.7)	3 (11.5)
Decreased appetite	1 (25.0)	0	0	0	1 (25.0)	0	2 (7.7)
Headache	1 (25.0)	0	0	1 (25.0)	0	0	2 (7.7)
Cough	0	0	0	1 (25.0)	1 (25.0)	0	2 (7.7)
Abdominal distension	0	0	0	1 (25.0)	1 (25.0)	0	2 (7.7)
Dyspepsia	1 (25.0)	0	1 (25.0)	0	0	0	2 (7.7)
Hyperhidrosis	1 (25.0)	0	1 (25.0)	0	0	0	2 (7.7)
Chills	0	0	0	1 (25.0)	1 (25.0)	0	2 (7.7)

CRS, cytokine release syndrome; DL, dose level; TRAE, treatment-related adverse event.

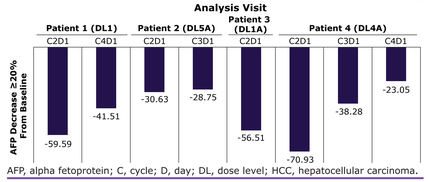
Efficacy

- Of the 24 exposed patients, 8 had a best overall response (BOR) of stable disease (SD), 14 had a BOR of progressive disease (PD), and 2 were not evaluable
- Fourteen patients with hepatocellular carcinoma had baseline alpha fetoprotein (AFP) >20 ng/mL, of which 4 (29%) had ≥20% AFP decrease on treatment (**Figure 3**)
- Two patients (both with HCC) have been on study drug treatment for >6 months

Pharmacokinetics (PK)

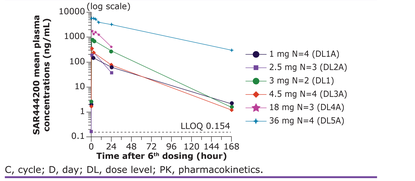
- The maximum observed concentration (C_{max}) of SAR444200 was observed at the end or shortly after the end of infusion then concentrations appeared to decline with mean half-life value (CV%) close to 26 hours (83%) at DL5A (**Figure 4**)

Figure 3: HCC patients with AFP decrease ≥20% from baseline



AFP, alpha fetoprotein; C, cycle; D, day; DL, dose level; HCC, hepatocellular carcinoma.

Figure 4: Mean PK Profiles of SAR444200 at C2D1

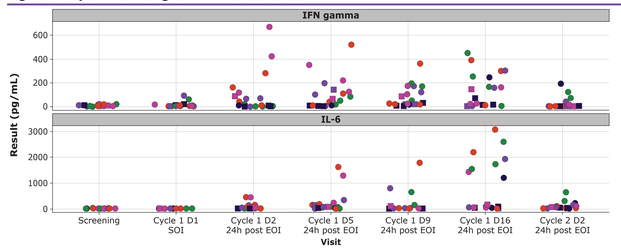


C, cycle; D, day; DL, dose level; PK, pharmacokinetics.

Biomarker analysis

- Biomarker analysis showed an increase of interleukin-6 (IL-6) and interferon gamma (IFNG/ IFNγ) during lead-in doses, supporting CRS (**Figure 5**)
- Cytokines declined after Cycle 1

Figure 5: Cytokine changes in five dose levels



C, cycle; CRS, cytokine release syndrome; D, day; DL, dose level; EOI, end of infusion; h, hour; IFN, interferon; IL-6, interleukin-6; N, no; SOI, start of infusion; Y, yes.

CONCLUSIONS

- Results suggest that SAR444200 was tolerated at the tested dose levels in patients with GPC3+ advanced solid tumors
- AFP decreases and disease stability in a subset of patients are suggestive of preliminary anti-tumor efficacy
- Dose escalation continues at this time

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- **MCP:** Served on advisory Board for BMS and Eisai. Personal fees from BMS, Eisai, Merck, and Incyte

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