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ARTICLE

Safety, pharmacokinetics, pharmacodynamics, and antitumor activity of SAR439459, a TGFβ inhibitor, as monotherapy and in combination with cemiplimab in patients with advanced solid tumors: Findings from a phase 1/1b study

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Abstract

SAR439459 (SAR'459), a "second-generation" human anti-transforming growth factor beta (TGFβ) monoclonal antibody, enhances the activity of immune checkpoint inhibitors. In this phase I/Ib study, we evaluated the safety, pharmacokinetics (PK), pharmacodynamics, and antitumor activity of SAR'459 ± cemiplimab (intravenous) in patients with advanced solid tumors. Increasing doses of SAR'459 were administered every 2 or 3 weeks (Q2W, Q3W) alone (Part 1A) or with 3 mg/kg cemiplimab Q2W or 350 mg Q3W (Part 1B). In Part 2A (dose expansion), melanoma patients were randomly (1:1) administered 22.5 or 7.5 mg/kg SAR'459. In Part 2B (dose expansion), 22.5 mg/kg SAR'459 and 350 mg cemiplimab Q3W were administered. The primary end points were maximum tolerated dose (MTD) or maximum administered dose (MAD; Part 1), preliminary antitumor activity (Part 2B), and optimal monotherapy dose (Part 2A). Twenty-eight and 24 patients were treated in Parts 1A and 1B, respectively; MTD was not reached, MAD was 15 (Q2W) and 22.5 mg/kg (Q3W) alone and in combination, respectively. Fourteen and 95 patients, including 14 hepatocellular carcinoma (HCC) patients, were treated in Parts 2A and 2B, respectively. The population PK model yielded satisfactory

Affiliation at the time of the study.

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goodness-of-fit plots and adequately described the observed data by a two-compartment PK model with linear elimination. Objective responses were not observed in Parts 1 and 2A. In Part 2B, objective response rate was 8.4% and 7.1% across tumor types and the HCC cohort, respectively. The most frequent treatment-emergent adverse effects were hemorrhagic events (43.5%), keratoacanthoma (6.8%), and skin neoplasms (6.2%). Fatal bleeding occurred in 21.4% HCC patients despite the implementation of mitigation measures. SAR'459 monotherapy and combination with cemiplimab appeared relatively safe and tolerable in limited number of patients in dose escalation. However, the study was discontinued due to the unclear efficacy of SAR'459 and bleeding risk, particularly in HCC patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

TGFβ is a multifunctional cytokine that has an important role in the regulation of tumor growth. High TGFβ expression is observed in patients with anti-programmed cell death-1 (PD-1) therapy-resistant/refractory tumors and is correlated to poor survival outcomes. Novel therapies that target the TGFβ-PD-1/PD-L1 nexus are needed to enhance the immune response against tumor.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study assessed the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of SAR'459 alone and in combination with the PD-1 inhibitor cemiplimab in patients with advanced solid tumors.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

SAR'459 in monotherapy and combination with cemiplimab appeared relatively safe and tolerable in limited number of patients in the dose-escalation cohort. However, due to lack of sufficient antitumor response and the observed bleeding risk particularly in HCC cohort, the study was terminated during dose expansion.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study revealed bleeding risk as an important risk of TGFβ inhibition, and that the incidence and severity of the risk may vary according to the population treated. Despite evidence for pathway modulation in the blood and the tumor, TGFβ inhibition did not lead to promising antitumor activity when combined with an anti-PD1 inhibitor. Further research may be needed to determine biomarkers predicting the responses.

INTRODUCTION

Transforming growth factor beta (TGFβ)—a multifunctional cytokine—plays a key role in the regulation of tumor growth.[1] Previous studies have correlated increased TGFβ signaling with poor response to anti-programmed death-ligand-1 (PD-[L]1) therapies in various types of cancer, including immune-excluded metastatic urothelial cancer (UC), hepatocellular carcinoma (HCC), and colon cancer.[2–4]

SAR439459 (SAR'459), a "second-generation" human anti-TGFβ immunoglobulin G4 (IgG4) monoclonal antibody, can neutralize all isoforms of TGFβ.[2] In preclinical models, SAR'459 decreased tumoral TGFβ level, counteracted the immunosuppressive tumor microenvironment, and enhanced the activity of checkpoint modulators, such as anti-PD-1.[5,6] It was hypothesized that the combination of SAR'459 and the anti-PD-1 agent, cemiplimab, might benefit patients with cancer resistant to anti-PD-1 or anti-PD-L1 monotherapy.[7]

In this phase I/1b first-in-human study (NCT03192345), we evaluated the safety, pharmacokinetics (PK), pharmacodynamics, and antitumor activity of SAR'459 alone and in combination with the PD-1 inhibitor cemiplimab in patients with advanced solid tumors.

METHODS

Study design and patient population

This first-in-human, open-label study of SAR'459 alone or in combination with cemiplimab (NCT03192345) included patients with advanced solid tumors (melanoma, non-small cell lung carcinoma [NSCLC], HCC, UC, and colorectal cancer [CRC]); it involved two phases, namely, dose escalation (Part 1) and dose expansion (Part 2) (Figure S1).

Study treatment

Parts A (1A and 2A) and B (1B and 2B) involved SAR'459 monotherapy and administration of SAR'459, followed by cemiplimab, respectively. Treatment period was two cycles every 2 weeks (Q2W) or one cycle every 3 weeks (Q3W) (Part 1A: Q2W; Part 1B: Q2W or Q3W; Parts 2A and 2B: Q3W). End-of-treatment visit was ≥30 days after the last day of administration of the study drug or until the patient received another anticancer therapy, whichever was earlier.

In Part 1A (dose-escalation phase, monotherapy), increasing doses (0.05, 0.25, 1, 3, 10, and 15 mg/kg) of SAR'459 were administered intravenously (IV) Q2W. Dose escalation was based on an adaptive Bayesian design in cohorts of at least three patients, with an overdose control preceded by accelerated escalation for the first two dose levels (DLs) in one patient per DL.

In Part 1B (dose-escalation phase, combination), SAR'459 (IV) doses (0.25, 1, 3, 10, 15 mg/kg Q2W, and 22.5 mg/kg Q3W) selected from Part 1A (Q2W) were investigated in combination with cemiplimab (IV; 3 mg/kg Q2W or 350 mg Q3W), using a 3 + 3 design. The 22.5 mg/kg Q3W dose was selected based on a preliminary population PK model due to its equivalency to 15 mg/kg Q2W regimen, given the linearity of SAR'459 PK.

In Part 2A (dose-expansion phase, monotherapy), patients with advanced melanoma refractory to anti-PD-1/PD-(L)1 treatment randomly (1:1) received SAR'459 (IV) Q3W at the preliminary recommended phase II dose (pRP2D), that is, 22.5 mg/kg, or a lower dose of 7.5 mg/kg (based on the preliminary population PK model).[6]

In Part 2B (dose-expansion phase, combination), patients with selected advanced solid tumors (post-anti-PD-(L)1 melanoma, NSCLC, and HCC; anti-PD-(L)1-naïve UC; and mesenchymal CRC, irrespective of previous anti-PD-(L)1 therapy) received 22.5 mg/kg SAR'459 and 350 mg cemiplimab IV Q3W. During the trial, the protocol was amended, and SAR'459 dose was reduced from 22.5 mg/kg Q3W to 15 mg/kg Q3W as a mitigation measure for bleeding risk. Histamine-H1 antagonist was administered 1 h before SAR'459 administration, which was given first in combination.

Patient population

Patients with histologically confirmed, advanced unresectable, or metastatic solid tumors, without a suitable alternative therapy, were included in the dose-escalation (monotherapy: Part 1A; combination: Part 1B) and monotherapy dose-expansion (Part 2A; patients with melanoma only) phases. Furthermore, patients in Parts 2A and 2B were required to have a suitable biopsy site and measurable disease as per the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). For Part 2B, the selected tumor types were mesenchymal CRC, HCC, melanoma, NSCLC, and UC; except for patients with CRC and UC, other patients were required to have failed or progressed after an anti-PD-1/PD-(L)1 therapy (Table S1).

Study end points

The primary end point of dose-limiting toxicities (DLTs) in Parts 1A and 1B was assessed during Cycle 1 (C1) and C1 and C2 for Q3W and Q2W dosing schedules, respectively. The primary end point of Part 2A was treatment-emergent adverse events meeting DLT criteria in adult patients with advanced melanoma who were refractive to previously administered anti-PD-1 or anti-PD-(L)1 therapy; their inclusion was based on the available data, including safety and tolerability profile at all cycles, PK, pharmacodynamics, ORR, other efficacy end points, and immunogenicity. The primary end point of Part 2B was ORR (RECIST 1.1).

Pharmacokinetics and population pharmacokinetics

SAR'459 concentrations were determined in serum samples from the patients using a validated enzyme-linked immunosorbent assay with a lower limit of quantitation of 0.0078 μg/mL. Rich PK samplings were performed in C1 in Parts 1A, 2A, and 1B, followed by sparse samplings in other cycles. Sparse samplings were collected in Part

2B (see details in Table S2). Part 1A and 1B concentration data were used to develop a population PK model. The population PK analysis was performed using the Stochastic Approximation Expectation–Maximization (SAEM) algorithm for nonlinear mixed–effect models implemented in MONOLIX software (R1 2019). Several structural PK models were tested with linear and/or nonlinear elimination. This model quantified interindividual PK variability within the evaluated population, assessed the impact of baseline covariates on SAR'459 PK, and provided individual PK exposure parameter estimates for patients enrolled in Parts 1A, 1B, 2A, and 2B (Figure S2).

Preliminary recommended phase II dose assessment

The pRPIID for the dose-expansion cohorts was determined by the study committee based on safety, efficacy, and PK data as well as PK thresholds determined in the preclinical PK/pharmacodynamic model. This model was developed using MC38 tumor model mice to determine the PK concentration threshold that could inhibit tumoral active TGFβ (Tables S2, S3 and Figures S3–S5). Population PK simulations were performed to determine the best clinical dosing schedule to optimize drug exposure.

Statistical analysis

Descriptive analyses were separately performed on the treated population. Continuous data were summarized using the number of available datapoints, that is, mean, standard deviation, median, minimum, and maximum, for each DL (Supplemental material, Appendix S1). Categorical and ordinal data were summarized using the number and percentage of patients in each DL.

Preliminary efficacy was descriptively presented based on the all-treated population (RECIST 1.1) and was summarized using two-sided 95% confidence interval, if appropriate. Dose-expansion efficacy data were analyzed by tumor type.

Safety data, including DLTs, were descriptively summarized by DLs for each part of the escalation and expansion phases and overall, as appropriate. The type, frequency, seriousness, severity, and relatedness of TEAEs were analyzed as per the Medical Dictionary for Regulatory Activities. Laboratory abnormalities were analyzed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Pharmacodynamics biomarkers were assessed by comparing their values during the treatment period with those at the baseline, using descriptive statistics at each DL.

RESULTS

Patient disposition

The study was conducted between June 1, 2017, and January 17, 2022, at 43 centers across Australia, Belgium, Germany, Spain, Estonia, France, United Kingdom, Italy, Netherlands, Republic of Korea, Taiwan, United States, and Canada. 161 patients, with 52 and 109 patients in Parts 1 and 2 were enrolled, respectively (Figure 1). All patients enrolled in Part 1 were evaluated for safety and PK; only 24 and 21 patients were evaluable for DLT in Parts 1A and 1B, respectively. In Part 2A, all patients were evaluable for safety and PK; in Part 2B, all patients were assessed for safety, with 85 and 75 patients evaluable for PK and antitumor response of SAR'459, respectively.

All patients discontinued the study, with the most common reason being progressive disease (PD; 73.7%–100%).

Baseline characteristics

In Parts 1A and 1B, the median age was 60.5 and 63.0 years; 26/28 (92.9%) and 24/24 (100%) patients had metastatic disease at baseline; and 10/10 (100%) and 8/9 (88.9%) patients had previously received ≥1 line of immunotherapy, respectively. In Parts 2A and 2B, the median age was 62.5 and 63.0 years; 13 (92.9%) and 82 (98.8%) patients had metastatic disease at baseline; and 5 and 3 patients had previously received ≥3 lines of immunotherapy, respectively (Table 1).

Treatment exposure

In Part 1A, 4, 3, 3, 10, 4, and 4 patients were assigned to 0.05, 0.25, 1, 3, 10, and 15 mg/kg SAR'459 groups, respectively. Similarly, in Part 1B, 3, 3, 3, 3, 4, and 8 patients were assigned to 0.25, 1, 3, 10, 15, and 22.5 mg/kg SAR'459 groups, respectively, along with 3 mg/kg cemiplimab once Q2W or 350 mg flat dose Q3W.

In Part 2A, 8 and 6 patients were enrolled in 7.5 and 22.5 mg/kg groups, respectively. In Part 2B, 25, 24, 15, 17, and 14 were enrolled in melanoma, CRC, UC, NSCLC, and HCC groups, respectively. Nine patients in the HCC cohort were initially treated at the highest dose, that is, 22.5 mg/kg Q3W, followed by dose reduction to 15 mg/kg Q3W SAR'459 in five additional patients as a bleeding risk mitigation measure (refer to Safety section). Treatment exposures are described in Table S4.

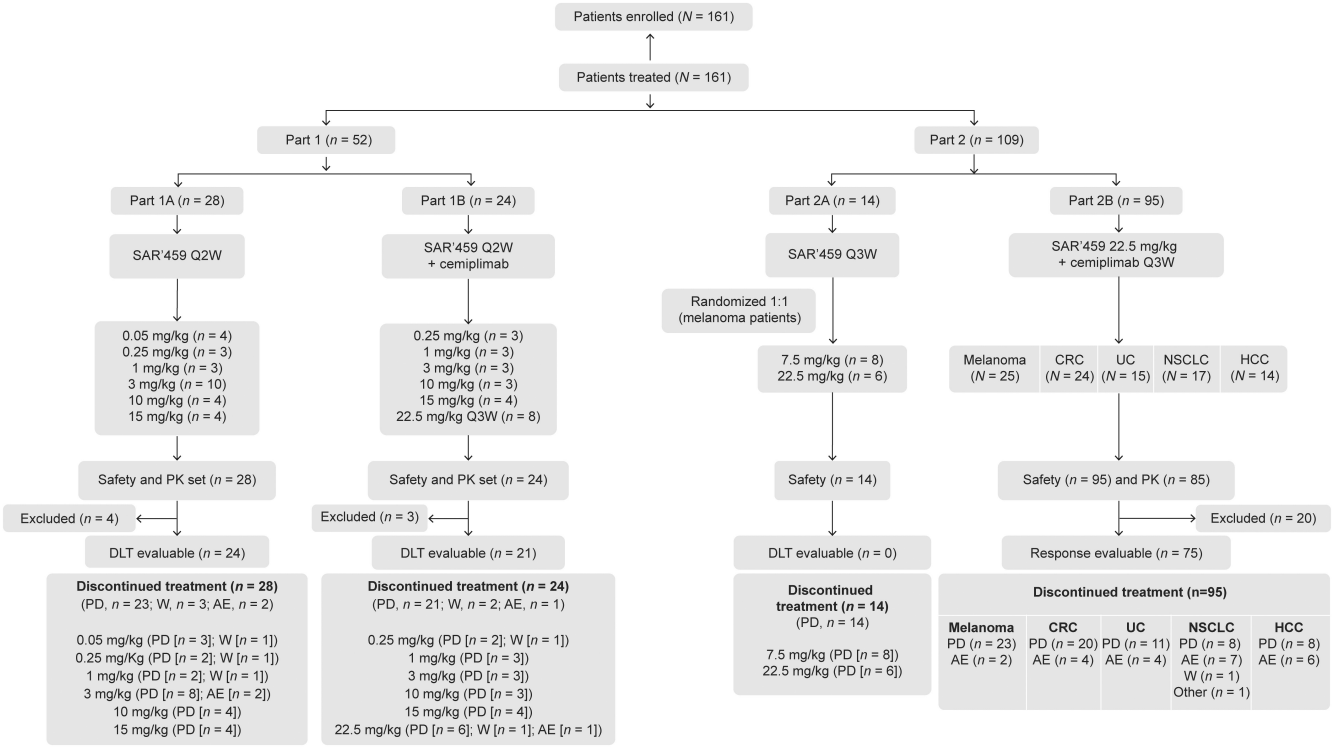

FIGURE 1 CONSORT diagram. AE, adverse event; CONSORT, Consolidated Standards of Reporting Trials; CRC, colorectal cancer; DLT, dose-limiting toxicity; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; PD, progressive disease; QW, weekly; Q2W, every 2 weeks; Q3W, every 3 weeks; UC, urothelial cancer; W, withdrawal by subject.

Findings from Part 1: Dose-escalation phase

Safety

Dose-limiting toxicities and maximum tolerated dose

In Part 1A, 24 patients were DLT evaluable. Two DLTs were reported in 2/8 evaluable patients at 3 mg/kg Q2W SAR'459 dose: grade 5 brainstem hemorrhage (C2) because of concomitant use of therapeutic enoxaparin and grade 3 myocardial infarction (C1). DLTs did not occur at higher doses of SAR'459 in Part 1A.

In Part 1B, 21 patients were DLT evaluable; in 1/6 evaluable patients at 22.5 mg/kg Q3W, one grade 3 alanine and aspartate aminotransferase level increase was observed (Supplemental Material; Appendix S2).

Treatment-emergent adverse events

In Part 1A, TEAEs were reported in 25 (89.3%) patients (Table 2), with SAR'459-related TEAEs, grade ≥3 SAR'459-related TEAEs, and definitive treatment discontinuation due to TEAEs in 13 (46.4%), 4 (14.3%), and 2 (7.1%) patients, respectively. In Part 1B, 22 (91.7%) patients reported TEAEs, with SAR'459-related TEAEs and grade ≥3 SAR'459-related TEAEs in 14 (58.3%) and 5 (20.8%) patients, respectively. None of the patients discontinued the treatment due to TEAEs. Overall, in Parts 1A and 1B, TEAEs leading to death were reported in 5 (17.9%) and 1 (4.2%) patients, respectively. Four deaths were related to disease progression, and one death in Part 1A was due to brainstem hemorrhage, a DLT (Supplemental material, Appendix S2).

Efficacy

In Parts 1A and 1B, six and two patients, respectively had stable disease (SD). Moreover, complete or partial response (PR) was not noted (Table 3).

Population pharmacokinetics and determination of preliminary recommended phase II dose

The final PK dataset included 52 patients treated with 0.05–15 mg/kg Q2W and 22.5 mg/kg Q3W. The best PK model for SAR'459 was a two-compartment model with linear elimination. Two significant covariates were included in the final population PK model: patient body weight and sex. These covariates had limited effect on SAR'459 exposure with <30% change of exposure in PK

TABLE 1 Patient baseline characteristics.

	Part 1A: SAR'459 (DL)							Part 1B: SAR'459 (DL) + CEMI						
mg/kg Q2W	**0.05 (*N*=4)**	**0.25 (*N*=3)**	**1 (*N*=3)**	**3 (*N*=10)**	**10 (*N*=4)**	**15 (*N*=4)**	**All (*N*=28)**	**0.25 (*N*=3)**	**1 (*N*=3)**	**3 (*N*=3)**	**10 (*N*=3)**	**15 (*N*=4)**	**22.5[c] (*N*=8)**	**All (*N*=24)**
Median age, years (range)	58.00 (38.0–72.0)	51.00 (34.0–75.0)	65.00 (63.0–91.0)	61.50 (25.0–78.0)	52.50 (43.0–80.0)	57.00 (50.0–69.0)	60.50 (25.0–91.0)	73.00 (64.0–81.0)	63.00 (54.0–68.0)	64.00 (58.0–67.0)	63.00 (59.0–78.0)	64.00 (58.0–75.0)	56.00 (43.0–73.0)	63.00 (43.0–81.0)
Age group (years), n (%)														
<65	3 (75.0)	2 (66.7)	1 (33.3)	6 (60.0)	3 (75.0)	3 (75.0)	18 (64.3)	1 (33.3)	2 (66.7)	2 (66.7)	2 (66.7)	2 (50.0)	6 (75.0)	15 (62.5)
65–75	1 (25.0)	0	1 (33.3)	3 (30.0)	0	1 (25.0)	6 (21.4)	1 (33.3)	1 (33.3)	1 (33.3)	0	1 (25.0)	2 (25.0)	6 (25.0)
≥75	0	1 (33.3)	1 (33.3)	1 (10.0)	1 (25.0)	0	4 (14.3)	1 (33.3)	0	0	1 (33.3)	1 (25.0)	0	3 (12.5)
Male, n (%)	3 (75.0)	0	1 (33.3)	6 (60.0)	2 (50.0)	1 (25.0)	13 (46.4)	2 (66.7)	2 (66.7)	1 (33.3)	3 (100)	3 (75.0)	3 (37.5)	14 (58.3)
Race, n (%)														
White	3 (75.0)	3 (100)	3 (100)	10 (100)	2 (50.0)	4 (100)	25 (89.3)	1 (33.3)	3 (100)	2 (66.7)	3 (100)	4 (100)	7 (87.5)	20 (83.3)
Black/African American	0	0	0	0	1 (25.0)	0	1 (3.6)	1 (33.3)	0	1 (33.3)	0	0	1 (12.5)	3 (12.5)
Asian	1 (25.0)	0	0	0	1 (25.0)	0	2 (7.1)	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	1 (4.2)
Ethnicity, n (%)														
Hispanic/Latino	0	0	0	0	1 (25.0)	0	1 (3.6)	0	0	0	0	0	0	0
Non-Hispanic/Latino	4 (100)	2 (66.7)	3 (100)	10 (100)	3 (75.0)	4 (100)	26 (92.9)	3 (100)	3 (100)	3 (100)	3 (100)	4 (100)	8 (100)	24 (100)
Unknown	0	1 (33.3)	0	0	0	0	1 (3.6)	0	0	0	0	0	0	0
ECOG performance, n (%)														
0	2 (50.0)	2 (66.7)	2 (66.7)	4 (40.0)	1 (25.0)	3 (75.0)	14 (50.0)	1 (33.3)	0	1 (33.3)	1 (33.3)	3 (75.0)	3 (37.5)	9 (37.5)
1	2 (50.0)	1 (33.3)	1 (33.3)	6 (60.0)	3 (75.0)	1 (25.0)	14 (50.0)	2 (66.7)	3 (100)	2 (66.7)	2 (66.7)	1 (25.0)	5 (62.5)	15 (62.5)
Metastasis, n (%)	4 (100)	2 (66.7)	3 (100)	10 (100)	4 (100)	3 (75.0)	26 (92.9)	3 (100)	3 (100)	3 (100)	3 (100)	4 (100)	8 (100)	24 (100)
Time from initial diagnosis to date of start of the first infusion (years)[a]														
Median (range)	3.26 (0.7–4.3)	5.04 (3.0–5.4)	3.70 (3.5–6.3)	3.28 (0.8–5.2)	1.61 (0.8–15.4)	2.12 (1.1–4.6)	3.28 (0.7–15.4)	1.96 (1.8–23.2)	2.87 (2.0–5.2)	3.47 (1.3–10.5)	3.53 (3.1–5.5)	7.69 (0.6–12.7)	3.96 (0.6–16.2)	3.50 (0.6–23.2)
Number of previous anticancer therapies, n (%)														
1	1 (25.0)	0	1 (33.3)	0	1 (25.0)	0	3 (10.7)	0	1 (33.3)	0	0	1 (25.0)	1 (12.5)	3 (12.5)
2	1 (25.0)	0	2 (66.7)	1 (10.0)	2 (50.0)	3 (75.0)	9 (32.1)	1 (33.3)	1 (33.3)	2 (66.7)	0	1 (25.0)	3 (37.5)	8 (33.3)
≥3	2 (50.0)	3 (100.0)	0	9 (90.0)	1 (25.0)	1 (25.0)	16 (57.1)	2 (66.7)	1 (33.3)	1 (33.3)	3 (100)	2 (50.0)	4 (50.0)	13 (54.2)
Number of previous immunotherapies, n														
1	0	0	1 (100)	3 (100)	2 (100)	4 (100)	10 (100)	2 (100)	0	1 (100)	2 (66.7)	0	3 (100)	8 (88.9)
2	0	0	0	0	0	0		0	0	0	1 (33.3)	0	0	1 (11.1)

TABLE 1 (Continued)

	Part 2A			Part 2B					
mg/kg Q3W	**7.5 (*n* = 8)**	**22.5 (*n* = 6)**	**All patients (*N* = 14)**	**Melanoma (*n* = 25)**	**CRC (*n* = 24)**	**UC (*n* = 15)**	**NSCLC (*n* = 17)**	**HCC (*n* = 14)**	**All patients (*N* = 95)**
Median age, years (range)	61.00 (36.0–75.0)	64.00 (41.0–73.0)	62.50 (36.0–75.0)	56.00 (37.0–90.0)	61.50 (32.0–75.0)	70.00 (47.0–85.0)	66.00 (39.0–73.0)	63.50 (35.0–82.0)	63.00 (32.0–90.0)
Age group (years), n (%)									
<65	4 (50.0)	3 (50.0)	7 (50.0)	16 (64.0)	15 (62.5)	6 (40.0)	7 (41.2)	7 (50.0)	51 (53.7)
65–75	2 (25.0)	3 (50.0)	5 (35.7)	6 (24.0)	8 (33.3)	5 (33.3)	10 (58.8)	5 (35.7)	34 (35.8)
≥75	2 (25.0)	0	2 (14.3)	3 (12.0)	1 (4.2)	4 (26.7)	0	2 (14.3)	10 (10.5)
Male, n (%)	3 (37.5)	3 (50.0)	6 (42.9)	11 (44.0)	11 (45.8)	13 (86.7)	10 (58.8)	10 (71.4)	55 (57.9)
Race, n (%)									
White	5 (62.5)	2 (33.3)	7 (50.0)	22 (88.0)	22 (91.7)	11 (73.3)	14 (82.4)	9 (64.3)	78 (82.1)
Black/African American	0	0	0	0	1 (4.2)	0	0	3 (21.4)	4 (4.2)
Asian	0	0	0	0	0	2 (13.3)	2 (11.8)	0	4 (4.2)
Native Hawaiian/Pacific Islander	0	0	0	1 (4.0)	0	0	0	0	1 (1.1)
Not reported	3 (37.5)	4 (66.7)	7 (50.0)	1 (4.0)	1 (4.2)	1 (6.7)	1 (5.9)	2 (14.3)	6 (6.3)
Unknown	0	0	0	1 (4.0)	0	1 (6.7)	0	0	2 (2.1)
Ethnicity									
Hispanic/Latino	0	0	0	0	2 (8.3)	0	0	0	2 (2.1)
Non-Hispanic/Latino	4 (50.0)	1 (16.7)	5 (35.7)	23 (92.0)	17 (70.8)	9 (60.0)	14 (82.4)	10 (71.4)	73 (76.8)
Not reported	4 (50.0)	5 (83.3)	9 (64.3)	2 (8.0)	5 (20.8)	5 (33.3)	2 (11.8)	4 (28.6)	18 (18.9)
Unknown	0	0	0	0	0	1 (6.7)	1 (5.9)	0	2 (2.1)
ECOG performance, n (%)									
0	2 (25.0)	2 (33.3)	4 (28.6)	13 (52.0)	9 (37.5)	6 (40.0)	12 (70.6)	11 (78.6)	51 (53.7)
1	6 (75.0)	4 (66.7)	10 (71.4)	12 (48.0)	15 (62.5)	9 (60.0)	5 (29.4)	3 (21.4)	44 (46.3)
Metastasis	7 (87.5)	6 (100)	13 (92.9)	25 (100)	24 (100)	15 (100)	16 (94.1)	2 (100)	82 (98.8)
Time from initial diagnosis to date of start of the first infusion (years)[b]									
Median (range)	2.19 (0.9–3.8)	4.65 (2.8–11.8)	2.76 (0.9–11.8)	3.34 (0.5–29.8)	3.37 (1.5–11.8)	1.67 (0.3–14.8)	1.78 (0.4–7.5)	0.91 (0.4–3.1)	2.07 (0.3–29.8)
Number of previous anticancer therapies, n (%)									
1	3 (37.5)	0	3 (21.4)	12 (48.0)	2 (8.3)	14 (93.3)	7 (41.2)	8 (57.1)	43 (45.3)
2	3 (37.5)	1 (16.7)	4 (28.6)	8 (32.0)	5 (20.8)	1 (6.7)	9 (52.9)	6 (42.9)	29 (30.5)
≥3	2 (25.0)	5 (83.3)	7 (50.0)	5 (20.0)	17 (70.9)	0	1 (5.9)	0	23 (24.2)

(Continues)

TABLE 1 (Continued)

	Part 2A			Part 2B					
mg/kg Q3W	7.5 (*n* = 8)	22.5 (*n* = 6)	All patients (*N* = 14)	Melanoma (*n* = 25)	CRC (*n* = 24)	UC (*n* = 15)	NSCLC (*n* = 17)	HCC (*n* = 14)	All patients (*N* = 95)
Number of previous immunotherapies, n									
1	3 (37.5)	0	3 (21.4)	14 (56.0)	3 (100)	0	17 (100)	14 (100)	48 (81.4)
2	4 (50.0)	2 (33.3)	6 (42.9)	8 (32.0)	0	0	0	0	8 (13.6)
≥3	1 (12.5)	4 (66.7)	5 (35.7)	3 (12.0)	0	0	0	0	3 (5.1)

Note: Number corresponds to the count of patients with non-missing data used for the calculation of the percentage.

Abbreviations: CEMI, cemiplimab; CRC, colorectal cancer; DL, dose level; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; Q2/3W, every 2/3 weeks; UC, urothelial cancer.

[a] If the date of last progression was missing, the difference in the number of months between the last progression date and the date of first infusion was used.

[b] If the day of initial date of diagnosis is missing, it is considered as the first day of the month.

[c] Q3W.

parameters for extreme covariate values compared with median value. Cemiplimab had no effect on SAR'459 PK exposure. Final population PK model yielded satisfactory goodness-of-fit plots and adequately described the observed data (Tables S2 and S3; Figures S2 and S3).

Population PK simulations revealed that 22.5 mg/kg Q3W dose would provide $C_{trough} \geq 200\,\mu g/mL$, which is close to the SAR'459 concentration required for maximal inhibition of tumoral TGFβ in the MC38 PK/pharmacodynamic model, and 7.5 mg/kg Q3W dose would provide $C_{trough} \geq 30\,\mu g/mL$, which is close to the concentration required for 50% inhibition of tumoral TGFβ in the MC38 PK/pharmacodynamics model. These two doses (Q3W) were considered as pRP2D for Part 2 (Figure 2). This model was further used to derive exposure parameters for 99 patients from the expansion cohorts.

Recommended Phase II dose confirmation

In Part 2A, an early safety review was performed after 12 patients had completed C1. Six patients each were treated at 7.5 mg/kg Q3W and 22.5 mg/kg Q3W. No TEAEs meeting DLT criteria were observed in any patients in the first cycle. In Part 2B, upon completion of C1 in 10 patients, the overall safety profile was comparable to the Part 1A, Part 1B, and Part 2A. Thus, it was recommended to continue enrollment at the DL of 22.5 mg/kg in combination with cemiplimab 350 mg Q3W.

Findings from Part 2: dose-expansion phase

Efficacy

In Part 2A, of the 14 evaluable patients, 2/8 (25.0%) and 6/8 (75.0%) patients had SD and PD, respectively, at 7.5 mg/kg; whereas at 22.5 mg/kg dose 6/6 (100%) had PD. None of the patients presented an objective response. In Part 2B, objective responses were observed in 8 (8.4%) of the 95 evaluable patients; 4 of the 8 responses were observed in post-PD-(L)1 setting, and responses of three additional patients were unconfirmed (NSCLC $n = 1$, melanoma $n = 1$, and HCC $n = 1$, at 22.5 mg/kg DL). As best response, 25 (26.3%) and 55 (57.9%) patients had SD and PD, respectively (Table 3).

The UC cohort was discontinued because of evolving treatment landscape and slow accrual. All other cohorts either met the prespecified futility threshold or were discontinued because of low likelihood of meeting the threshold at informal interim analysis.

Due to the observed bleeding risk and efficacy signal (one confirmed PR and one unconfirmed PR) observed

TABLE 2 TEAEs in ≥10% of patients.

	Part 1A (*N* = 28)		Part 1B (*N* = 24)		Part 2A 7.5 mg/kg Q3W (*N* = 8)		Part 2A 22.5 mg/kg Q3W (*N* = 6)		Part 2B All (*N* = 95)	
Preferred term *n* (%)	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Any TEAE	25 (89.3)	15 (53.6)	22 (91.7)	14 (58.3)	8 (100)	4 (50.0)	6 (100)	3 (50.0)	95 (100)	66 (69.5)
Any hemorrhagic event	7 (25.0)	3 (10.7)	12 (50.0)	5 (20.8)	3 (37.5)	0	3 (50.0)	1 (16.7)	45 (47.4)	7 (7.4)
Epistaxis	1 (3.6)	0	2 (8.3)	0	0	0	2 (33.3)	0	18 (18.9)	1 (1.1)
Gingival bleeding	1 (3.6)	0	3 (12.5)	0	2 (25.0)	0	2 (33.3)	0	13 (13.7)	0
Other hemorrhagic events[a]	5 (17.8)	3 (10.7)	7 (29.2)	5 (100)	1 (12.5)	0	3 (50.0)	1 (16.7)	14 (14.8)	6 (6.3)
Fatigue	10 (35.7)	4 (14.3)	9 (37.5)	0	3 (37.5)	1 (12.5)	0	0	24 (25.3)	1 (1.1)
Decreased appetite	7 (25.0)	0	9 (37.5)	0	2 (25.0)	0	2 (33.3)	0	20 (21.1)	1 (1.1)
Nausea	9 (32.1)	0	7 (29.2)	0	0	0	3 (50.0)	0	20 (21.1)	1 (1.1)
Pruritus	0	0	5 (20.8)	0	1 (12.5)	0	1 (16.7)	0	18 (18.9)	3 (3.2)
Skin neoplasms	0	0	0	0	4 (50.0)	3 (37.5)	1 (16.7)	0	15 (15.8)	7 (7.4)
KA	0	0	0	0	1 (12.5)	0	1 (16.7)	0	8 (8.4)	3 (3.2)
CSCC	0	0	0	0	3 (37.5)	3 (37.5)	0	0	7 (7.4)	4 (4.2)
Disease progression	3 (10.7)	3 (10.7)	0	0	0	0	1 (16.7)	1 (16.7)	15 (15.8)	14 (14.7)
Constipation	5 (17.9)	0	6 (25.0)	0	1 (12.5)	0	1 (16.7)	0	13 (13.7)	0
Diarrhea	3 (10.7)	0	4 (16.7)	0	0	0	0	0	12 (12.6)	2 (2.1)
Anemia	0	0	4 (16.7)	4 (16.7)	0	0	1 (16.7)	0	10 (10.5)	7 (7.4)
Rash	0	0	0	0	0	0	1 (16.7)	0	10 (10.5)	2 (2.1)
Rash maculo-papular	0	0	3 (12.5)	0	2 (25.0)	0	0	0	10 (10.5)	2 (2.1)
Pyrexia	0	0	0	0	1 (12.5)	0	1 (16.7)	0	10 (10.5)	0
Asthenia	0	0	0	0	0	0	3 (50.0)	1 (16.7)	8 (8.4)	2 (2.1)
Back pain	5 (17.9)	1 (3.6)	3 (12.5)	0	1 (12.5)	0	2 (33.3)	0	7 (7.4)	1 (1.1)
Headache	0	0	0	0	1 (12.5)	0	1 (16.7)	0	7 (7.4)	0
Dysgeusia	0	0	0	0	0	0	3 (50.0)	0	3 (3.2)	0
Dry mouth	0	0	0	0	1 (12.5)	0	2 (33.3)	0	2 (2.1)	0
Chills	0	0	0	0	0	0	3 (50.0)	0	1 (1.1)	0
Tumor-associated fever	0	0	0	0	0	0	2 (33.3)	0	0	0
Insomnia	3 (10.7)	0	0	0	0	0	0	0	0	0
Dyspnea	4 (14.3)	1 (3.6)	5 (20.8)	0	0	0	0	0	0	0
Cough	3 (10.7)	0	0	0	0	0	0	0	0	0

(Continues)

TABLE 2 (Continued)

Preferred term *n* (%)	Part 1A (*N* = 28)		Part 1B (*N* = 24)		Part 2A 7.5 mg/kg Q3W (*N* = 8)		Part 2A 22.5 mg/kg Q3W (*N* = 6)		Part 2B All (*N* = 95)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Abdominal pain	6 (21.4)	2 (7.1)	4 (16.7)	0	0	0	0	0	0	0
Vomiting	4 (14.3)	0	4 (16.7)	0	0	0	0	0	0	0
Abdominal distension	3 (10.7)	1 (3.6)	0	0	0	0	0	0	0	0
Upper abdominal pain	3 (10.7)	0	0	0	0	0	0	0	0	0
Arthralgia	3 (10.7)	0	6 (25.0)	0	0	0	0	0	0	0
Decreased weight	3 (10.7)	0	3 (12.5)	0	0	0	0	0	0	0
Hemoptysis	0	0	3 (12.5)	0	0	0	0	0	0	0

Note: Sorted by AEs with descending frequency in the 2B-ALL column.

Abbreviations: AE, adverse event; CSCC, squamous cell carcinoma of skin; GI, gastrointestinal; KA, keratoacanthoma; Q3W, every 3 weeks; TEAE, treatment-emergent adverse event.

[a]Other hemorrhagic events included: Tumor hemorrhage ($n = 2$), GI hemorrhage ($n = 7$), hematuria ($n = 10$), hemoptysis ($n = 9$), rectal hemorrhage, post-procedure ($n = 3$, each), vaginal/intermenstrual bleeding ($n = 3$), hemorrhoidal, tumor and pulmonary hemorrhage ($n = 2$), laryngeal, mouth, hepatic, conjunctival, small intestine, brain stem, hemangioma rupture, intra-abdominal, shock, and adrenal hemorrhage ($n = 1$, each).

in nine patients treated at full dose, that is, 22.5 mg/kg, the HCC cohort received lower dose of 15 mg/kg Q3W. Of the 5 patients treated at lower dose, 1 (20.0%) had SD, 3 (60.0%) had PD, and 1 (20.0%) was unevaluable. Further enrollment was discontinued due to increased bleeding risk and the absence of any further objective response at the lower dose.

Pharmacodynamics

SAR'459 alone or in combination with cemiplimab reduced plasma TGFβ1 levels by ≥90% at all DLs. A decreasing trend in active TGFβ levels was also observed in paired biopsy specimens in Part 2 expansion studies at 7.5 or 22.5 mg/kg DLs (Figure 2).

Safety

Treatment-emergent adverse events

All patients (100%) in Part 2 experienced at least one TEAE; 67% and 34% TEAEs were grades ≥3 and SAR'459-related, respectively. Frequently reported TEAEs occurred in ≥10% patients is presented in Table 2.

In Part 2A, 11/14 (78.6%) and 5/14 (35.7%) patients had SAR'459-related and grade ≥3 SAR'459-related TEAEs, respectively. None of the patients experienced TEAE(s) leading to definitive treatment discontinuation. In Part 2B, 70/95 patients (73.7%) experienced treatment-related TEAEs and 32/95 (33.7%) patients had grade ≥3 SAR'459-related TEAEs; 20/95 (21.1%) patients reported TEAEs leading to definitive treatment discontinuation, with dose being reduced in 2 (2.1%) patients. Overall, 1/14 (7.1%) patients in Part 2A and 19/95 (20.0%) patients in Part 2B reported TEAEs leading to death. Of the 19 deaths in Part 2B, 11 were due to disease progression. Most common treatment-emergent adverse event (TEAE) leading to death by system organ classification was disease progression, which was observed in 11/95 (11.6%) patients in Part 2B. Five patients (5.3%) in Part 2B reported hemorrhagic events that led to death.

Adverse events of special interest from Parts 1 and 2

Bleeding events

Of 161 patients treated with SAR'459 alone or in combination with cemiplimab, 70 patients (43%) experienced hemorrhagic TEAEs of different grades. Most frequently reported hemorrhagic TEAEs were gingival bleeding (21

TABLE 3 Best overall response.

	Part 1A SAR'459 (DL)							Part 1B SAR'459 (DL) + CEMI						
	0.05 mg/kg Q2W (*n* = 4)	0.25 mg/kg Q2W (*n* = 3)	1 mg/kg Q2W (*n* = 3)	3 mg/kg Q2W (*n* = 10)	10 mg/kg Q2W (*n* = 4)	15 mg/kg Q2W (*n* = 4)	All (*N* = 28)	0.25 mg/kg Q2W (*n* = 3)	1 mg/kg Q2W (*n* = 3)	3 mg/kg Q2W (*n* = 3)	10 mg/kg Q2W (*n* = 3)	15 mg/kg Q2W (*n* = 4)	22.5 mg/kg Q3W (*n* = 8)	All (*N* = 24)
Best overall response, n (%)														
SD	2 (50.0)	–	3 (100)	–	1 (25.0)	–	6 (21.4)	–	–	–	1 (33.3)	–	1 (12.5)	2 (8.3)
PD	2 (50.0)	2 (66.7)	–	9 (90.0)	3 (75.0)	4 (100)	20 (71.4)	3 (100)	2 (66.7)	2 (66.7)	1 (33.3)	3 (75.0)	6 (75.0)	17 (70.8)
Non–CR/non–PD	–	–	–	–	–	–	–	–	–	1 (33.3)	–	1 (25.0)	–	2 (8.3)
NE	–	1 (33.3)	–	1 (10.0)	–	–	2 (7.1)	–	1 (33.3)	–	1 (33.3)	–	1 (12.5)	3 (12.5)

	Part 2A SAR'459 (DL)			Part 2B SAR'459 (DL) + CEMI						
n (%)	7.5 mg/kg Q3W (*n* = 8)	22.5 mg/kg Q3W (*n* = 6)	All mg/kg Q3W (*N* = 14)	Melanoma 22.5 mg/kg (*n* = 25)	CRC 22.5 mg/kg (*n* = 24)	UC 22.5 mg/kg (*n* = 15)	NSCLC 22.5 mg/kg (*n* = 17)	HCC 22.5 mg/kg (*n* = 9)	HCC 15 mg/kg (*n* = 5)	All (*N* = 95)
ORR	–	–	–	2 (8.0)	1 (4.2)	3 (20.0)	1 (5.9)	1 (11.1)	–	8 (8.4)
PR	–	–	–	2 (8.0)	1 (4.2)	3 (20.0)	1 (5.9)	1 (11.1)	–	8 (8.4)
SD	2 (25.0)	–	2 (14.3)	6 (24.0)	5 (20.8)	3 (20.0)	7 (41.2)	3 (33.3)	1 (20.0)	25 (26.3)
PD	6 (75.0)	6 (100)	12 (85.7)	16 (64.0)	16 (66.7)	9 (60.0)	8 (47.1)	3 (33.3)	3 (60.0)	55 (57.9)
NE	–	–	–	1 (4.0)	2 (8.3)	–	1 (5.9)	2 (22.2)	1 (20.0)	7 (7.4)

Abbreviations: CEMI, cemiplimab; CR, complete response; DL, dose level; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; SD, stable disease.

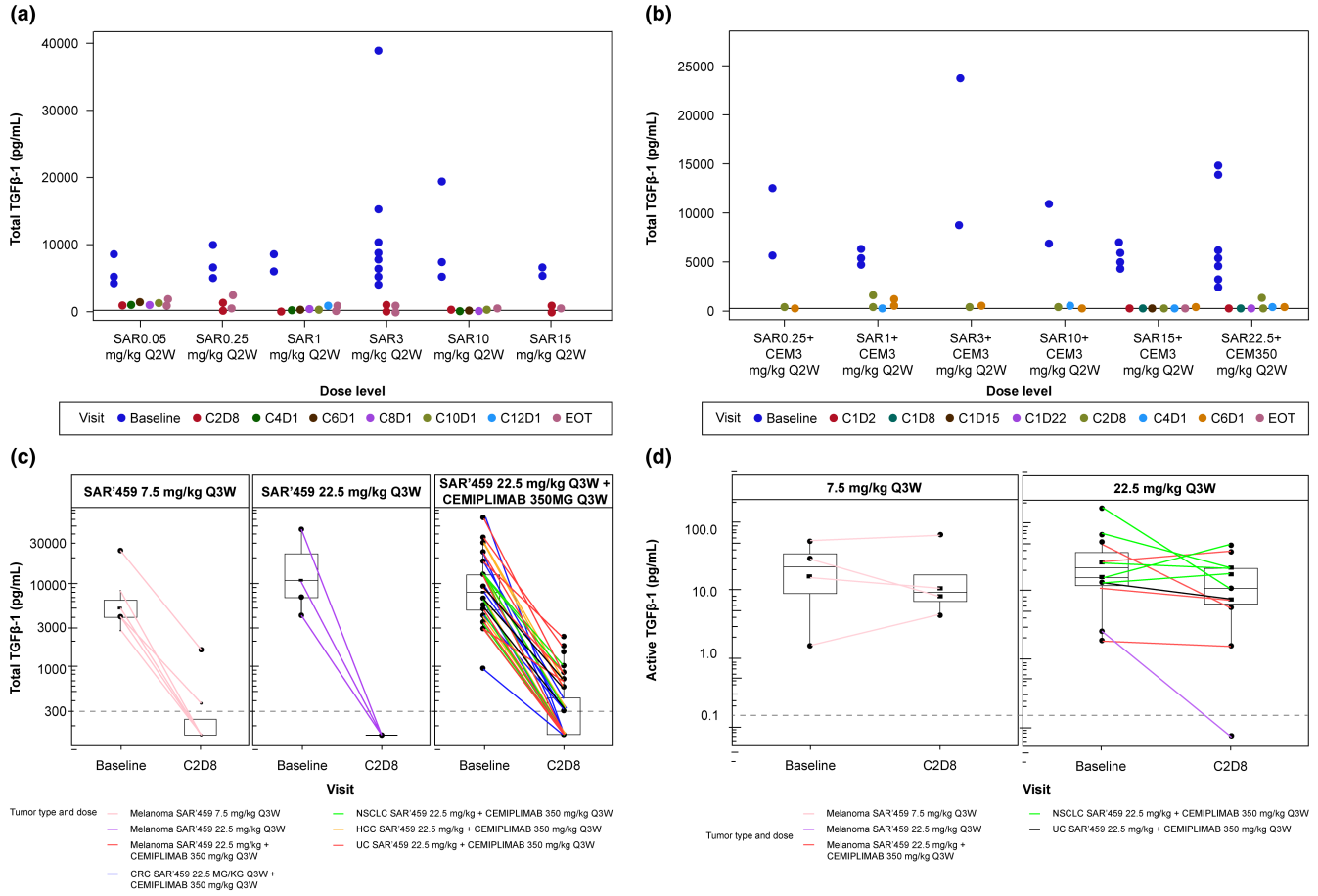

FIGURE 2 Modulation of total TGFβ-1 level by (a) SAR'459 monotherapy in plasma (Part 1) and (b) SAR'459 in combination with cemiplimab in plasma (Part 1); (c) low and high doses of SAR'459 monotherapy or in combination with cemiplimab in plasma (Part 2); (d) regulation of active TGFβ-1 in tumor by SAR'459, alone and in combination with cemiplimab, in paired tumor biopsy samples (Part 2). C, cycle; CEM, cemiplimab; CRC, colorectal cancer; D, dose; EOT, end of treatment; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; TGFβ, transforming growth factor beta, UC, urothelial cancer.

[13%]) and epistaxis (23 [14%]). Sixteen (9.9%) patients experienced grade ≥3 hemorrhagic TEAEs, which resulted in the death of 6 (3.7%) patients due to brain stem hemorrhage (3 mg/kg Q2W; $n=1$), intra-abdominal hemorrhage and intracranial tumor hemorrhage ($n=1$; each), and hepatic hemorrhages ($n=3$) (Supplemental Material; Appendix S3).

Two of these fatal cases were reported from the nine HCC patients treated with SAR'459 22.5 mg/kg + cemiplimab: one occurred at the liver biopsy puncture site and one due to hepatic bleeding in the context of progression. One fatality due to hepatic hemorrhage after SAR'459 15 mg/kg + cemiplimab treatment was also observed (Supplemental Material; Appendix S3). An exposure-bleeding event analysis suggested dose dependency of the bleeding events related to SAR'459.

Following treatment with SAR'459 22.5 mg/kg ($n=9$), the dose was reduced to 15 mg/kg Q3W ($n=5$). The protocol was amended to introduce additional risk mitigation measures, requiring brain imaging at baseline and prohibiting on-treatment biopsy. However, another fatal hepatic hemorrhage was reported in a patient with bulky HCC treated with a reduced dose of SAR'459; this was consistent with HCC rupture occurring within the first cycle because of rapid volumetric progression. All three HCC patients with fatal hemorrhagic events had extensive HCC burden. Hemorrhagic events of grade ≥3 were more likely to occur early: 56% and 88% cases occurred within the first 3 and 9 weeks, respectively. Of six overall fatal hemorrhagic events, 4 (66%) occurred within the first 3 weeks.

Skin events

Of 161 patients treated in this study, 11 events of keratoacanthoma (KA) and 12 of cutaneous squamous cell carcinoma (CSCC) were observed in 21 (13%) patients; 2 patients had both KA and CSCC. Sixteen of 21 (76%) patients were aged >60 years.

Nine (43%) patients had melanoma. Nineteen (90%) patients developed lesions within the first 4 months. Six (28%) patients had a single lesion, whereas multiple lesions were observed in other patients; the sun-exposed areas of the patients were typically affected, that is, face, neck, chest, extremities, or shoulder. Of the 12 cases with CSCC, 5 were reported as "well-differentiated" or "KA-type" CSCC, whereas pathological details were not available for others. Eight (67%) of 12 cases of CSCC were resolved: 5 cases were resolved after drug withdrawal, and 3 cases were resolved by surgical excision.

New primary malignancy

One case of secondary malignancy other than CSCC was observed (Supplemental Material; Appendix S4).

Cardiac valvular disorders

Doppler echocardiography did not reveal progressive pattern of valve thickening or regurgitation in any patient.

DICUSSION

In this study, safety, PK, pharmacodynamics, and efficacy of SAR'459 alone and in combination with cemiplimab were evaluated in patients with advanced malignancy. SAR'459 monotherapy and combination with cemiplimab appeared relatively safe and tolerable in limited number of patients in dose escalation. The study was discontinued due to lack of clear efficacy across several solid tumor cohorts and bleeding risk that led to fatal outcomes, especially, in the HCC cohort and slow accrual in an evolving treatment landscape.

The MTD for SAR'459 was not reached. pRP2D for dose-expansion phase was determined to be 22.5 mg/kg Q3W in combination with cemiplimab, based on safety, tolerability, and population PK modeling analyses. Optimal dose could not be determined for Part 2A.

Pharmacodynamic assessment revealed peripheral target engagement by SAR'459 with robust reduction in plasma TGFβ levels, tumor target engagement, and with a trend of down-regulation of the TGFβ pathway activation genes which was in accordance with the studies on SAR'459.[5,7] This suggests that the co-inhibition of TGFβ and PD-1 increases T-cell activity and tumor regression.[5,8,9]

In Part 1 of the study, peripheral target engagement was documented from the first DL. Upon treatment of more patients in various indications in Part 2B, TEAEs leading to dose reduction occurred in 2.1% patients, and TEAEs leading to treatment discontinuation occurred in 21% patients. The safety profile differed according to the tumor type, with higher occurrence of bleeding events and serious bleeding events in patients with HCC. Although several DLs were tested in Part 2A, the results were inconclusive due to limited sample size and early discontinuations. However, a lower dose was investigated for the HCC cohort, which led to the final decision to terminate the study. Notably, a severe event, when occurring at a low rate, may not be detected in small cohorts of patients in the dose-escalation phase.

A response rate of 8.4% (melanoma: 8%; CRC: 4.2%; UC: 20%; NSCLC: 5.9%; HCC: 11.1%) was reported in the dose-expansion phase with combination therapy (Part 2B), including patients previously treated with anti-PD-(L)1. Previously, similar modest response (ORR: 4.8%) was reported in patients with NSCLC with primary refractory or acquired resistance to immune checkpoint inhibitors treated with bintrafusp alfa, an anti-TGFβ-PD-(L)1 inhibitor.[10] Furthermore, limited response rate is likely not linked to anti-drug antibody occurrence because the dose-escalation analysis revealed that no samples were confirmed as positive for SAR'479 ADA.

Key potential risks of TGFβ pathway inhibition include bleeding, cutaneous proliferative manifestations, secondary malignancies, and cardiac valvular disorders. In this study, the key risks were SAR'459-related valvular heart disease, grade ≥3 immune-related adverse events (AEs), KA, and CSCC; grade ≥3 bleeding events were considered potential important risks. Notably, skin and hemorrhagic events have been observed with other TGFβ inhibitors, which are consistent with those observed for SAR'459; however, the frequencies varied.[11–14]

The occurrence of hemorrhagic events was higher in patients with HCC treated with 22.5 mg/kg SAR'459. Overall, >40% patients had hemorrhagic TEAEs, of which approximately 33.5% were grade 1 or 2 and included five deaths. Exploratory PK/hemorrhagic AE analysis elucidated a trend toward higher frequency of any grade SAR'459-related and fatal hemorrhagic AE in patients with higher exposure (Figure S3). Despite the decrease in dose to 15 mg/kg SAR'459 Q3W in the HCC cohort, fatal hemorrhagic events were observed. Although the fatal events were confounded by previously administered anticancer therapies, concomitant medications, or underlying diseases, relatedness to SAR'459 could not be excluded. Extensive analyses were performed to identify patient characteristics or disease patterns associated with an increased risk for bleeding for the implementation of additional mitigation measures; however, no clear relationship with bleeding risk was observed. Nevertheless, several mitigation measures were implemented including the discontinuation of on-treatment biopsy unless medically

imperative; for the HCC cohort, baseline biopsy was allowed only from normal parenchyma samples at least 14 days prior to the first treatment.

A previous study on bintrafusp alfa in patients with recurrent glioblastoma also reported higher rate of bleeding events (64.4%; 15.3% grade 3).[15] Another study on bintrafusp alfa elucidated that dose reduction without permanent treatment discontinuation (restarting the dose at RP2D or at 50% dose) could be preferable in hemorrhagic event management.[16] Hemorrhagic events in solid tumors have also been reported for GC1008 or fresolimumab, with low-grade hemorrhage in a small proportion of patients; however, its relationship with fresolimumab was not established.[12] The underlying mechanism for bleeding due to TGFβ inhibition is unclear; moreover, bleeding could be multifactorial. Given the pro-angiogenic role of TGFβ, Glanzmann thrombasthenia-like bleeding phenomenon is possible.[17] Since TGFβ promotes the healing process and angiogenesis and maintains hemostasis, its inhibition may impair the healing process and contribute to bleeding risk. A study on a pan-TGFβ inhibitor reported the detachment of abdominal wall and dose-dependent reduction of scarring fibrosis in a monkey model.[18] However, Sanofi's internal studies did not report wound healing impairment upon treatment with 1D11, a surrogate antibody of fresolimumab.

Other AEs of special interest observed in the study were KA and CSCC. KA has been observed post-treatment with multikinase, B-RAF, or TGFβ inhibitors in various studies.[11,12,19–21] Treatment with fresolimumab at high doses or for an extended period is related to KA development; however, it resolves with time.[11] Overall, previous studies on TGFβ inhibition reported 5%–9% occurrence of KA, whereas ~9% was observed in the present study.[10,22,23]

TGFβ inhibits keratinocyte proliferation and enhances differentiation.[24] TGFβ inhibition could be one of the mechanisms responsible for the development of KA/CSCC. Moreover, unlike patients with other tumor types, patients with melanoma who develop KA or CSCC are predisposed due to high cumulative exposure to sun; the underlying mechanism behind the occurrence of KA or CSCC during SAR'459 treatment is unlikely to be solely based on the oncogenic effect of TGFβ inhibition, which could explain the occurrence of CSCC in the present study. Patients with melanoma are more likely to have a history of sun-damaged skin and common predisposing factors contributing to a higher risk of KA/CSCC. However, it is unclear whether SAR'459 is associated with the development of secondary malignancy.

In the present study, dose escalation was performed using an adaptive Bayesian design, with overdose control preceded by an accelerated escalation for the first 2 DLs. Thus, the advantage of continuous assessment of efficacy and benefit/risk ratio led to the quick decision of ensuring safety and continuing patient accrual. Interim data analyses were conducted to enable quick study-related decisions, after exposing, on average, four patients per cohort. Rapid transition from dose escalation to multiple, homogeneous, small efficacy cohorts minimized the number of patients and time necessary to cease the development of this inactive combination.

This study had few limitations. First, the small sample size limited the statistical power, preventing a robust evaluation of biomarker associations with clinical response. Consequently, no specific efficacy biomarker could be identified. Second, the presence of low intra-tumoral TGFβ levels in many tumor biopsies posed challenges in establishing a cutoff point for patient selection. Third, anticipating low rates of severe bleeding events in the initial dose-escalation phase was also difficult due to the small patient group. Lastly, the testing of these combinations in patients with same indication showed comparable safety and efficacy across varying dosage levels.

SAR'459 alone and in combination with cemiplimab yielded a noteworthy safety profile, and MTD could not be reached during the dose-escalation phase. However, due to the lack of sufficient antitumor response and the observed bleeding risk, especially in the HCC cohort, the study was terminated during the expansion phase, and the antitumor activity of SAR'459 was not further investigated.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript, designed the research, performed the research, and analyzed the data.

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CONFLICT OF INTEREST STATEMENT

TJB: *Grant*: Sanofi, Pfizer, Astellas, Xencor, Impact Therapeutics, Synermore Biologics, Changchun Intellicrown Pharm, Exelixis, Tolero, SQZ, Nektar, Takeda; *Consulting*: Sanofi; *Stock ownership*: Fortyseven, Moderna, Zymeworks, Aprea, Merus, Hylapharm. **DR, BD, MB:** Declare no conflict of interest. **RS**: *Grants*: Merck; *Consulting*: AstraZeneca, BMS, Iovance, Merck, Novartis, Oncosec, Pfizer, Replimune; *Advisory Board*: AstraZeneca, BMS, Iovance, Merck, Novartis, Oncosec, Pfizer, Replimune, Duke University, Yale University. **AS**: *Consulting*: Sanofi; *Honoraria*: Takeda, BMS, Roche, Abb-Vie, Amgen, Celgene, Servier, Gilead, AstraZeneca, Pfizer, Arqule, Lilly, Sandoz, Eisai, Novartis, Bayer, MSD; *Advisory Board*: BMS, MSD, Servier, Gilead, Pfizer, Eisai, Bayer. **JJG**: *Consulting or Advisory Board*: BMS, MSD Oncology, Roche/ Genentech, Novartis, Amgen, Pierre Fabre, Merck KGaA, Sun Pharma, Sanofi, Roche, Philogen, U'tmovacs; *Speakers' Bureau*: Novartis; *Travel, Accommodations, Expenses*: BMS, USD Oncology, Novartis, Pierre Fabre. **OB:** *Advisory board*: Sanofi. **MV:** *Personal fees*: Roche, EMD Serono, TFS. **MJdM:** *Honoraria*: Roche, MSD, Janssen. **DS:** *Grants*: Roche, Bristol-Myers Squibb, Merck, Sharp & Dohme, Novartis, Amgen, Pfizer; *Others*: Roche, Bristol-Myers Squibb, Merck, Sharp & Dohme, Novartis, Pierre Fabre, Nektar, Regeneron, Sanofi, Replimune, Philogen, Neracre, Sun Pharma; *Personal fees*: Bristol-Myers Squibb, Merck, Sharp & Dohme, Novartis, Pierre Fabre, Nektar, Regeneron, Sanofi, Replimune, Pfizer, Philogen, Neracre, Sun Pharma, Daiichi Sankyo, Immatics, Ultimovacs; *Non-financial support*: Merck, Sharp & Dohme, Novartis, Pierre Fabre, Nektar, Regeneron, Sanofi, Replimune. **MJ:** *Grant*: Abbvie, Acerta, Adaptimmune, Amgen, Apexigen, Arcus Biosciences, Array BioPharma, Artios Pharma, AstraZeneca, Atreca, BeiGene, BerGenBio, BioAtla, Black Diamond, Boehringer Ingelheim, Bristol-Myers Squibb, Calithera Biosciences, Carisma Therapeutics, Checkpoint Therapeutics, City of Hope Nation Medical Center, Corvus Pharmaceuticals, Curis, CytomX, Daiichi Sankyo, Dracen Pharmaceuticals, Dynavax, Eli Lilly, Elicio Therapeutics, EMD Serono, EQRx, Erasca, Exelixis, Fate Therapeutics, Genentech/Roche, Genmab, Genocea Biosciences, GlaxoSmithKline, Gritstone Oncology, Guardant Health, Harpoon, Helsinn Healthcare SA, Hengrui Therapeutics, Hutchinson MediPharma, IDEAYA Biosciences, IGM Biosciences, Immunitas Therapeutics, Immunocore, Incyte, Janssen, Jounce Therapeutics, Kadmon Pharmaceuticals, Kartos Therapeutics, Loxo Oncology, Lycera, Memorial Sloan-Kettering, Merck, Merus, Mirati Therapeutics, Mythic Therapeutics, NeoImmune Tech, Neovia Oncology, Novartis, Numab Therapeutics, Nuvalent, OncoMed Pharmaceuticals, Palleon Pharmaceuticals, Pfizer, PMV Pharmaceuticals, Rain Therapeutics, RasCal Therapeutics, Regeneron Pharmaceuticals, Relay Therapeutics, Revolution Medicines, Ribon Therapeutics, Rubius Therapeutics, Sanofi, Seven and Eight Biopharmaceuticals/Birdie Biopharmaceuticals, Shattuck Labs, Silicon Therapeutics, Stem CentRx, Syndax Pharmaceuticals, Takeda Pharmaceuticals, Tarveda, TCR2 Therapeutics, Tempest Therapeutics, Tizona Therapeutics, TMUNITY Therapeutics, Turning Point Therapeutics, University of Michigan, Vyriad, WindMIL Therapeutics, Y-mAbs Therapeutics; *Consulting*: Abbvie, Amgen, Arcus Biosciences, Arrivent, Astellas, AstraZeneca, Axelia Oncology, Black Diamond, Calithera Biosciences, Daiichi Sankyo, EcoR1, Genentech/Roche, Genmab, Genocea Biosciences, GlaxoSmithKline, Gritstone Oncology, IDEAYA Biosciences, Immunocore, iTeos, Janssen, Jazz Pharmaceuticals, Merck, Mirati Therapeutics, Molecular Axiom, Novartis, Oncorus, Pyramid Biosciences, Regeneron Pharmaceuticals, Revolution Medicines, Sanofi-Aventis, SeaGen, Synthekine, Takeda Pharmaceuticals, Turning Point Therapeutics, VBL Therapeutics. **AA**: Currently employed by Ipsen. **FSH**: *Grants*: Sanofi, Bristol-Myers Squibb, Novartis, Merck, Genentech, Glaxo Smith Kline, Merus, CTEP; *Royalties*: Novartis; *Consulting fees*: Bristol-Myers Squibb, Merck, Novartis, Surface, Compass Therapeutics, Apricity, Bicara, Checkpoint Therapeutics, Genentech, Bioentre, Gossamer, Iovance, Rheos, Catalym, Immunocore, Kairos, Zumutor, Corner Therapeutics, Curis, Astra Zeneca; *Travel*: Parker Institute for Cancer Therapy; *Patents*: Methods for Treating MICA-Related Disorders (#20100111973); Tumor Antigens and Uses Thereof (#7250291), Angiopoiten-2 Biomarkers Predictive of Anti-immune Checkpoint Response (#20170248603); Compositions and Methods for Identification, Assessment, Prevention, and Treatment of Melanoma

Using PD-(L)1 Isoforms (#20160340407). Therapeutic Peptides (#20160046716); Methods of Using Pembrolizumab and Trebananib; Vaccine Compositions and Methods for Restoring NKG2D Pathway Function Against Cancers (#10279021); Antibodies that Bind to MHC Class I Polypeptide-related Sequence A (#10106611); NTI-Galectin Antibody Biomarkers Predictive of Anti-immune Checkpoint and Anti-angiogenesis Responses (#20170343552); *Others*: Apricity, Bicara; *Stock/Stock options*: Apricity, Bicara. **AA, BD, GA, RW, RP, HW, and JSL** are/were Sanofi employees and may hold stocks or stock options.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient-level data and related documents (e.g., the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications). Patient-level data will be anonymized, and the study documents will be redacted to protect the privacy of the participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://vivli.org/.

ETHICAL APPROVAL

The study was conducted in compliance with the Declaration of Helsinki, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Guidelines for Good Clinical Practice, and other applicable laws, rules, and regulations. Written informed consent was obtained from all study participants prior to enrollment. The patients were not directly involved in the design, conduct, and reporting of this research.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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