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CLINICAL TRIAL REPORT

Phase 1b Multicenter Study of SG001, a Humanized Anti-PD-1 Antibody, in Patients with Advanced Solid Tumors

Jian Fang[1], Ou Jiang[2], Wei Li[3], Jie Lin[4], Meiyu Fang[5], Qun Li[6], Weihong Zhao[7], Ke Wang[8], Huaqiu Shi[9], Zhendong Chen[10], Junyan Yu[11], Xiaojing Xing[12], Mingxuan Zhao[13], Anwen Liu[14], Wei Wang[15], Zhengquan Han[16], Silong Xiang[17], Xiao Zhang[17], Jin Li[6]*, Caicun Zhou[3]*

[1]Department of Thoracic Oncology, Peking University Cancer Hospital, Beijing, People's Republic of China; [2]Department of Cancer Center, Second People's Hospital of Neijiang, Neijiang, People's Republic of China; [3]Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University Medical School Cancer Institute, Tongji University School of Medicine, Shanghai, People's Republic of China; [4]Department of Medical Oncology, The Second Affiliated Hospital of Kunming Medical University, Kunming, People's Republic of China; [5]Department of Chemotherapy, Chinese Academy of Sciences University Cancer Hospital (Zhejiang Cancer Hospital), Hangzhou, People's Republic of China; [6]Department of Oncology, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, People's Republic of China; [7]Department of Medical Oncology, Chinese People's Liberation Army General Hospital, Beijing, People's Republic of China; [8]Department of Gynaecological Oncology, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center of Cancer, Tianjin, People's Republic of China; [9]Department of Oncology, The First Affiliated Hospital of Gannan Medical University, Ganzhou, People's Republic of China; [10]Department of Oncology, The Second Affiliated Hospital of Anhui Medical University, Hefei, People's Republic of China; [11]Department of Oncology, Heping Hospital of Changzhi Medical College, Changzhi, People's Republic of China; [12]Department of Medical Oncology, Liaoning Cancer Hospital and Institute, Shenyang, People's Republic of China; [13]Research center for early clinical trials of Drugs (Vaccines), Anning First People's Hospital Affiliated to Kunming University of Science and Technology, Anning, People's Republic of China; [14]Department of Oncology, Second Affiliated Hospital of Nanchang University, Nanchang, People's Republic of China; [15]Department of Medical Oncology, Hunan Cancer Hospital, Changsha, People's Republic of China; [16]Department of Medical Oncology, The First Affiliated Hospital of Bengbu Medical College, Bengbu, People's Republic of China; [17]CSPC Zhongqi Pharmaceutical Technology Co., Ltd, Shijiazhuang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jin Li, Department of Oncology, Shanghai East Hospital, School of Medicine, Tongji University, No. 1800, Yuntai Road, Shanghai, People's Republic of China, Email lijin@csco.org.cn; Caicun Zhou, Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University Medical School Cancer Institute, Tongji University School of Medicine, Shanghai, People's Republic of China, Email caicunzhoudr@163.com

Background: SG001 is a humanized, IgG4 monoclonal antibody against human PD-1. This phase 1b study aimed to evaluate efficacy and safety of SG001 in advanced solid tumors.

Methods: Patients with previously treated solid tumors that are PD-L1-positive, and/or dMMR/MSI-H, and/or Epstein–Barr virus positive were enrolled in Cohort A, while patients with PD-L1-unselected malignant mesothelioma and PD-L1-unselected non-small cell lung cancer (NSCLC) were enrolled in Cohorts C and E, respectively. All patients in Cohorts A, C, and E received SG001 at a dose of 240mg every two weeks for 2 years or until disease progression, intolerable toxicities, or withdrawal of consent. The primary endpoint was the investigator-assessed overall response rate (ORR).

Results: A total of 87 patients were enrolled: 33 in Cohort A, 24 in Cohort C, and 30 in Cohort E. Investigator-assessed ORR was 39.4% in Cohort A, 12.5% in Cohort C, and 16.7% in Cohort E; corresponding median PFS values were 9.6, 4.1, and 4.0 months. The most common treatment-related adverse events (TRAEs) were increased alanine aminotransferase (13.8%), proteinuria (12.6%), rash (12.6%), and increased aspartate aminotransferase (10.3%). No TRAEs leading to death were reported.

Conclusion: SG001 demonstrated promising activity in patients with pretreated advanced solid tumors, especially those with PD-L1-positive NSCLC. The safety profile was well tolerated.

Clinical Trial Registration: ClinicalTrials.gov identifier: NCT03852823.

Plain Language Summary: SG001 had an anti-tumor activity for pretreated advanced solid tumors.

SG001 demonstrated promising efficacy in PD-L1-positive NSCLC.

SG001 had well tolerated safety profiles.

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Keywords: checkpoint inhibitor, programmed death-1 inhibitor, solid tumors, non-small cell lung cancer, mesothelioma

Introduction

Blocking programmed cell death protein 1 (PD-1), and its ligand, programmed death ligand-1 (PD-L1), represents a validated therapeutic strategy to increase tumor-specific T-cell activation and antitumor activity across various cancers.[1–6] Immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 have been developed and employed as monotherapies or in combination with chemotherapy for treatment of multiple tumor types.[7–9] However, clinical benefits from currently approved PD-1/PD-L1 monotherapies are limited to a subset of patients.[10–12] For instance, accumulating clinical studies have demonstrated that the efficacy of PD-1/PD-L1 inhibitors is significantly diminished in patients with low or negative PD-L1 expression, as compared to their counterparts with high PD-L1 expression.[13] Even in certain tumors, such as esophageal squamous cell carcinoma, the clinical benefits conferred by PD-1/PD-L1 inhibitors in the PD-L1 low/negative subgroup remain comparable to those achieved with conventional chemotherapy.[14] Therefore, PD-1/PD-L1 inhibitors still leave significant room for improvement in the therapeutic management of solid tumors.

SG001 is a recombinant, humanized immunoglobulin G4 monoclonal antibody (mAb) with high affinity and specificity for binding to PD-1. Preclinical characterization has demonstrated that SG001 effectively activates T cells, promotes interleukin-2 and interferon-γ release in vitro, and induces significant antitumor activity in mouse models (unpublished). Additionally, full receptor occupancy (RO) was achieved in cynomolgus monkeys (unpublished), further supporting its potential efficacy in clinical settings. Moreover, favorable clinical trial results supported the approval of SG001 (Enlonstobart) by the National Medical Products Administration in June 2024 for the treatment of recurrent/metastatic (r/m) cervical cancer with PD-L1-positive expression following failure of at least first-line platinum-based chemotherapy.[15,16]

An open-label, multi-center dose-escalation and cohort-expansion, phase I study of SG001 in subjects with advanced tumors was conducted (NCT03852823). During the dose-escalation stage, the 3 mg/kg dose group demonstrated a comparable efficacy and safety profile to the 10 mg/kg dose group, with a sustained RO rate of over 80% for up to 3 weeks. Therefore, the fixed dose of 240 mg, corresponding to 3mg/kg based on bodyweight, was selected as the expansion dose due to its significant advantages over body weight-based dosing, including convenience, cost-effectiveness, and lower risk of dosing errors.[17] Here, we present the efficacy and safety data of SG001 in patients with advanced solid tumors from three of five cohorts in dose-expansion stage. The results for Cohort B have been published previously,[15] while Cohort D was prematurely terminated due to adjustments in development strategy.

Materials and Methods

Study Design and Patients

This open-label, multi-center, Phase 1b, dose-expansion study was conducted from September 28, 2020, to May 31, 2022, across 22 sites in China. The safety and efficacy of SG001 at recommended dose of 240mg every two weeks (Q2W) were evaluated in A, C, and E cohorts: Cohort A included patients with locally advanced, recurrent or metastatic (r/m) solid tumors confirmed histologically or cytologically as PD-L1 positive, and/or deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H), and/or Epstein–Barr virus (EBV) positive; Cohort C included patients with histologically confirmed malignant mesothelioma; and Cohort E, patients with histologically or cytologically confirmed non-small cell lung cancer (NSCLC) without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations (Supplementary Figure 1).

Eligible patients were required to be aged ≥18 years, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a life expectancy of ≥3 months, adequate organ function and laboratory parameters, and at least one measurable lesion according to the modified Response Evaluation Criteria in Solid Tumors (m-RECIST) for malignant mesothelioma or RECIST version 1.1 for other solid tumors. Key exclusion criteria included a history of hypersensitivity reactions to mAbs, prior treatment with any targeted T-cell co-regulated protein (immune checkpoint protein) antibodies/medicines (including PD-1, PD-L1, and cytotoxic T lymphocyte-associated protein 4), primary immunodeficiency, and severe cardiovascular diseases. Detailed inclusion and exclusion criteria were presented in the Supplementary Methods.

The study was approved by independent ethics committees or institutional review boards at each site (See "List of ethics committees" in Supplementary Material), and adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Intervention

SG001 was administered as a 240 mg intravenous infusion over 60 minutes Q2W. Patients received treatment for up to 2 years or until disease progression, intolerable toxicity, or withdrawal. No dose modification was permitted for SG001, but treatment interruption up to two months was allowed to enable toxicity recovery. Treatment was to be permanent discontinued once the interruption exceeded two months or occurred two or more times.

Outcomes

The primary endpoints were the investigator-assessed overall response rate (ORR) per m-RECIST/RECIST v1.1 and the safety of SG001. Secondary endpoints included duration of response (DOR), disease control rate (DCR), time to response (TTR), progress-free survival (PFS), overall survival (OS), pharmacokinetics (PK) profile, T-cell RO rate, and immunogenicity.

Procedure

Tumor evaluation was performed at baseline, every 6 weeks during the treatment period and every 12 weeks following treatment completion or discontinuation until disease progression, initiation of other antitumor therapies, or death, whichever occurred first, using radiographic imaging (computed tomography or magnetic resonance imaging) according to m-RECIST for pleural mesothelioma or RECIST v1.1 for other solid tumors.

Safety/tolerability was assessed from signing informed consent form (ICF) to 90 days after the last SG001 dose or the initiation of other antitumor therapies, whichever came first. Adverse events (AEs) were coded according to Regulatory Activity Medical Dictionary (MedDRA) version 25.0 and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0).

A minimum of 6 patients in every cohort underwent PK sampling. Blood samples for PK analysis were collected at specific time points: pre-dose (within 30min before infusion) and post-dose (0, 2h, 8h, 24h, 48h, 96h, 168h) for doses 1 and 6; pre-dose (within 30min before infusion) and post-dose (0) for doses 2, 3, 4, 5, 7, 10, and 13.

To assess target engagement, RO assessment was also profiled. The occupancy rates of CD3+, CD4+, and CD8+ receptors in peripheral blood were determined by flow cytometry. The pre-defined blood sample collection timepoints were detailed in the Supplementary Material.

Blood samples for immunogenicity analysis were collected pre-dose for doses 1, 2, 4, 7, 10, and 13, and 168h after dose 1, as well as at the end of every 6 cycles through electrochemiluminescence. A positive anti-drug antibody (ADA) response was defined as an ADA-negative sample converting to ADA-positive after baseline, or a 4-fold increase in ADA titer from baseline in baseline-positive samples. Neutralizing antibody (NAb) assessments were performed in patients with a positive ADA response.

Statistical Methods

Cohorts A, C, and E were each limited to a maximum enrollment of 30 patients, which was not determined by hypothesis test.

Continuous data were summarized as mean ± standard deviation or median (range), while categorical data were presented as n (%). Efficacy analyses of ORR, DCR, PFS, and OS were based on the full analysis set (FAS), which included all enrolled patients who received at least one dose of SG001. The ORR and DCR were estimated along with 95% confidence intervals (CIs) using the Clopper–Pearson method. The Kaplan–Meier method was used to calculated median TTR, PFS, DOR, and OS, and their 95% CIs were derived using the Brookmeyer–Crowley method. Safety analysis was based on the safety analysis set (SS), which consisted of all enrolled patients who received at least one dose of SG001 treatment and underwent at least one safety assessment following the first dose. The PK profile was established from the PK concentration analysis set (PKCS), which included patients who received at least one dose of SG001 and

provided at least one post-dose plasma concentration, and PK parameter analysis set (PKPS), comprising patients who received at least one dose of SG001 and provided at least one evaluable PK parameter. T-cell RO rate and immunogenicity analyses were based on the RO analysis set (patients who received at least one dose of SG001 and had a post-dose T-cell RO measurement) and immunogenicity analysis set (patients who received at least one dose of SG001 and provided at least one post-baseline immunogenicity data), respectively.

PK parameters were derived using Phoenix WinNonlin version 8.3.4., and all statistical analyses were performed using SAS version 9.4.

Results

Patient Characteristics

A total of 87 patients from Cohort A (n=33), C (n=24), and E (n=30) were included in our study (Figure 1). The median (range) age was 58.0 (23–83) years, with 67.8% were male. Patients in Cohort A presented with a range of tumor types, the most common being NSCLC (51.5%) (Supplementary Table 1). Fifty-seven patients (65.5%) had an ECOG performance status of 1, 69 patients (79.3%) had stage IV disease, and 73 patients (83.9%) suffered from metastatic cancer. Forty-seven (54.0%) had undergone surgery, and twenty-one (24.1%) patients had received radiotherapy. All patients had received prior chemotherapy and/or targeted therapy. Of the 58 individuals tested for PD-L1, 82.8% (48/58) demonstrated positive expression (Table 1).

As of May 31st, 2022, the median treatment duration of SG001 was 4.10 (range 0.5–20.0) months. At the date cut-off, 73 patients (83.9%) had discontinued SG001 treatment, including 26 in Cohort A, 19 in Cohort C, and 28 in Cohort E. Reasons for discontinuation included disease progression (47/87), intolerable AEs (7/87), death (3/87), and other factors (16/87) (Figure 1). The median follow-up duration was 12.5 months (95% CI 10.6–15.3), 8.4 months (95% CI 3.0–15.3), and 17.7 months (95% CI 11.7–18.5) in Cohorts A, C, and E, respectively.

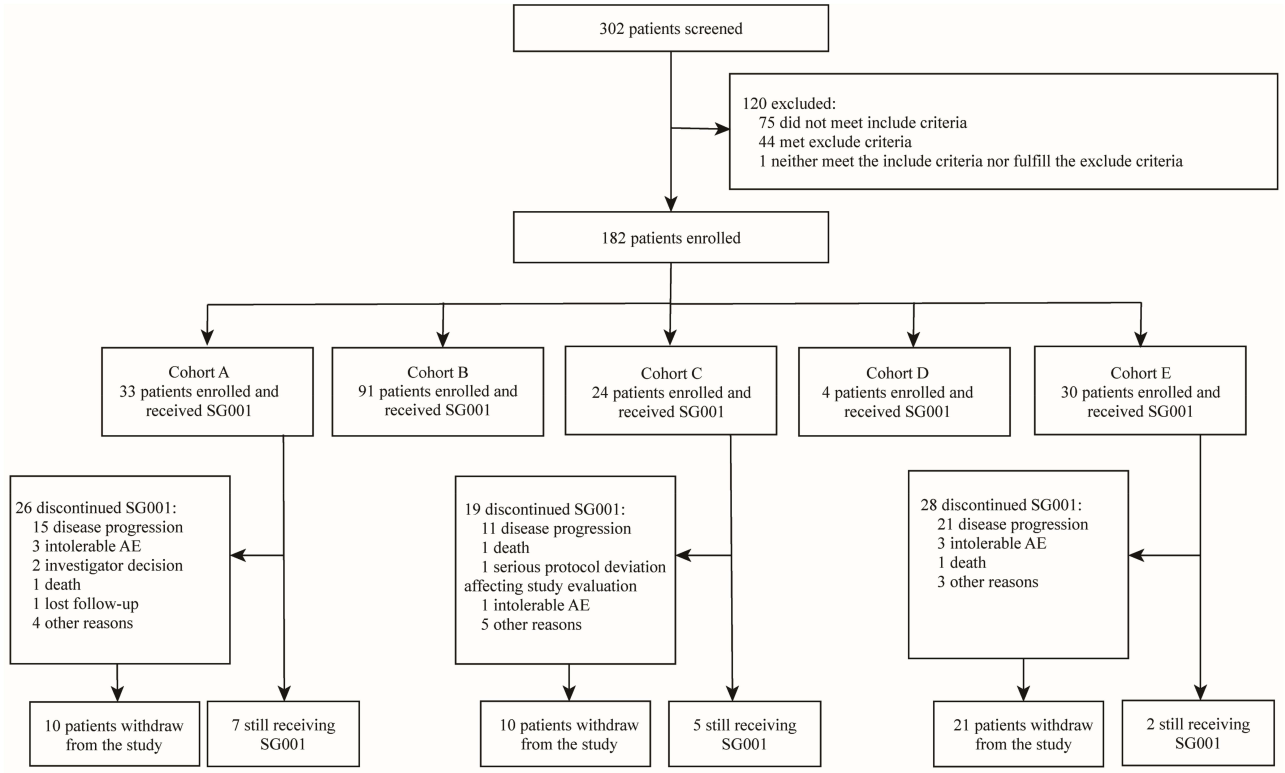

Figure 1 Patients disposition.

Table 1 Baseline Demographic and Clinical Characteristics

	Cohort A n=33	Cohort C n=24	Cohort E n=30	Total N=87
Sex, n (%)				
Male	25 (75.8)	14 (58.3)	20 (66.7)	59 (67.8)
Female	8 (24.2)	10 (41.7)	10 (33.3)	28 (32.2)
Median Age, years (range)	61.0 (41–83)	53.0 (23–74)	63.0 (39–76)	58.0 (23–83)
ECOG, n (%)				
0	13 (39.4)	4 (16.7)	13 (43.3)	30 (34.5)
1	20 (60.6)	20 (83.3)	17 (56.7)	57 (65.5)
PD-L1 expression				
Positive	31 (93.9)	4 (16.7)	1 (3.3)	36 (41.4)
Negative	0	15 (62.5)	7 (23.3)	22 (25.3)
Unknown	2 (6.1) [#]	5 (20.8)	22 (73.3)	29 (33.3)
Tumor type, n (%)				
NSCLC	16 (48.5)	0 (0)	30 (100.0)	46 (52.9)
MPM	0 (0)	12 (87.5)	0 (0)	12 (13.8)
CRC	3 (9.1)	0 (0)	0 (0)	3 (3.4)
EC	3 (9.1)	0 (0)	0 (0)	3 (3.4)
GC	2 (6.1)	0 (0)	0 (0)	2 (2.3)
PeM	0 (0)	3 (12.5)	0 (0)	3 (3.4)
Other*	9(27.3)	0(0)	0(0)	9 (10.3)
Cancer stage at screening				
≤ Stage II	1(3.0)	1 (4.2)	0 (0)	2 (2.3)
Stage III	4 (12.1)	6 (25.0)	6 (20.0)	16 (18.4)
Stage IV	28 (84.8)	17 (70.8)	24 (80.0)	69 (79.3)
Metastasis, n (%)				
Yes	29 (87.9)	18 (75.0)	26 (86.7)	73 (83.9)
No	4 (12.1)	6 (25.0)	4 (13.3)	14 (16.1)
Prior surgery, n (%)	23 (69.7)	14 (58.3)	10 (33.3)	47 (54.0)
Prior radiotherapy, n (%)	13 (39.4)	2 (8.3)	6 (20.0)	21 (24.1)
Prior systemic therapy, n (%)				
Chemotherapy and/or targeted therapy	33 (100.0)	24 (100.0)	30 (100.0)	87 (100.0)
Immunotherapy	0 (0)	0 (0)	0 (0)	0 (0)

Notes: *Including secondary malignant tumors of bone, oral squamous cell carcinoma, pleural squamous cell carcinoma, poorly differentiated squamous cell carcinoma of nasopharynx, cholangiocarcinoma, ovarian cancer, rhinitis cancer, and renal clear cell carcinoma. [#]Two patients in Cohort A who did not undergo PD-L1 testing were diagnosed with dMMR/MSI-H colorectal cancer.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; MPM, malignant pleural mesothelioma; CRC, colorectal cancer; EC, esophageal cancer; GC, gastric cancer; PeM, peritoneal mesothelioma.

Efficacy

A total of 33 patients from Cohort A were included in FAS. The investigator-assessed confirmed ORR in Cohort A was 39.4% (95% CI, 22.9–57.9), entirely driven by patients who achieved partial response (PR;13/33). The DCR was 66.7% (95% CI 48.2–82.0), composing patients who achieved either PR or stable disease (SD; 9/33). The median TTR and median DOR were 2.8 months (95% CI 1.3–4.0) and 12.4 months (95% CI 3.3~ not available [NA]), respectively. Twenty patients exhibited a reduction in target lesion size from baseline, with a median change of −20.40% (95% CI −36.61~-5.08) among 33 patients (Figure 2A). The median PFS was 9.6 months (95% CI 4.0–15.0), with a 12-month PFS rate of 39.8% (95% CI 20.6–58.4), as assessed by the investigator. The median OS had not yet been reached, with a 20-month OS rate of 74.5% (95% CI 55.4–86.4). Among 16 patients with PD-L1-positive NSCLC, the investigator-assessed confirmed ORR was 43.8% (95% CI 19.8–70.1), with DCR of 75% (95% CI 47.6–92.7), including 7 patients who achieved PR and 5 who achieved SD. The median TTR was 2.8 months (95% CI 1.2–4.0), and the 12-month DOR was 64.3% (95% CI 15.1–90.2). The median PFS and OS for these 16 patients were 9.6 months (95% CI 4.0~NA) and NA, respectively (Table 2 and Figure 2B).

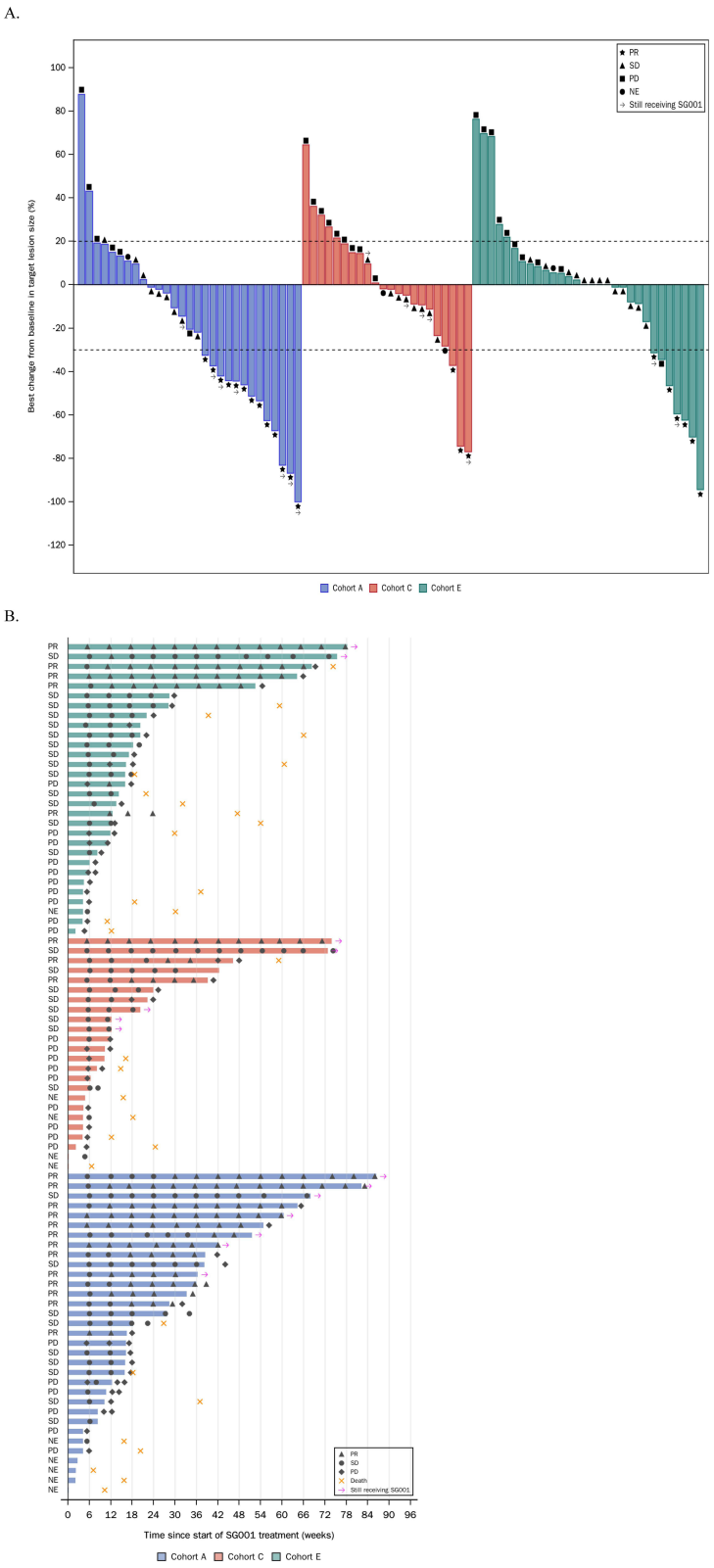

Figure 2 Change in target lesion size and duration of treatment in patients with solid tumors receiving SG001. (**A**) Waterfall plots represent best percentage change from baseline in target lesion size for individual patients receiving SG001 240 mg Q2W. (**B**) Swim lane plots represent duration of treatment and best objective responses for individual patients receiving SG001 240 mg Q2W.

Table 2 Confirmed Tumor Response and Survival Data in Full-Analysis Set

	Cohort A		Cohort C n=24	Cohort E n=30	NSCLC (Cohort A+E) n=46
	NSCLC n=16	Overall n=33			
ORR, n (%)	7 (43.8)	13 (39.4)	3 (12.5)	5 (16.7)	12 (26.1)
95% CI	19.8~70.1	22.9 ~ 57.9	2.7 ~ 32.4	5.6~34.7	14.3~41.1
BOR					
CR, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PR, n (%)	7 (43.8)	13 (39.4)	3 (12.5)	5 (16.7)	12 (26.1)
SD, n (%)	5 (31.3)	9 (27.3)	8 (33.3)	14 (46.7)	19 (41.3)
PD, n (%)	2 (12.5)	6 (18.2)	9 (37.5)	10 (33.3)	12 (2.6)
Not evaluated, n (%)	2 (12.5)	1 (3.0)	2 (8.3)	1 (3.3)	3 (6.5)
DCR, n (%)	12 (75.0)	22 (66.7)	11 (45.8)	19 (63.3)	31 (67.4)
95% CI	47.6~92.7	48.2 ~ 82.0	25.6 ~ 67.2	43.9~80.1	52.0~80.5
DOR, month					
Median (95% CI)	NA (3.3~NA)	12.4 (3.3~NA)	5.3 (3.3~NA)	13.6 (9.7~NA)	13.4 (5.7~NA)
Range (25th and 75th percentile)	5.7~NA	5.7~NA	3.3~NA	11.6~NA	9.7~NA
TTR, month					
Median (95% CI)	2.8 (1.2~4.0)	2.8 (1.3~4.0)	4.1 (1.2~NA)	2.6 (1.2~NA)	2.7 (1.2~4.0)
Range (25th and 75th percentile)	1.3~4.0	1.4~4.0	1.2~6.4	1.3~2.7	1.3~3.4
PFS, month					
Median (95% CI)	9.6 (4.0~NA)	9.6 (4.0~15.0)	4.1 (1.3~9.4)	4.0 (1.4~5.5)	5.0 (3.0~7.4)
Range (25th and 75th percentile)	4.1~NA	2.9~NA	1.3~9.7	1.4~6.8	1.4~15.1
OS, month					
Median (95% CI)	NA (NA~NA)	NA (NA~NA)	13.6 (3.7~NA)	13.9 (8.5~NA)	17.1 (12.4~NA)
Range (25th and 75th percentile)	NA~NA	8.5~NA	3.7~NA	7.4~NA	8.5~NA

Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response.

Twenty-four patients in Cohort C were included in FAS. The confirmed ORR and DCR based on investigator assessment were 12.5% (95% CI 2.7 ~ 32.4) and 45.8% (95% CI 25.6 ~ 67.2), respectively, with 3 patients achieving PR and 8 patients achieved SD. The median DOR was 5.3 months (95% CI 3.3~NA) and the TTR was 4.1 months (95% CI 1.2~NA). Overall, 8/24 patients had a PFS event, and the median PFS was 4.1 (95% CI 1.3–9.4) months; the median OS was 13.6 months (95% CI CI:3.7~NA), with an 18-month OS rate of 46.3% (95% CI 18.3–70.5) (Table 2 and Figure 2B).

In Cohort E, among the 30 patients in FAS, 5 had a confirmed PR and 14 patients had a confirmed SD. The ORR and DCR based on investigator review were 16.7% (95% CI 5.6–34.7) and 63.3% (95% CI, 43.9–80.1), respectively. The median DOR was 13.6 months (95% CI 9.7~NA) and the median TTR was 2.6 months (95% CI 1.2~NA). The overall median PFS was 4.0 months (95% CI 1.4–5.5). The median OS was 13.9 months (95% CI, 8.5~NA), with a Kaplan–Meier estimation, indicating a 59.2% survival rate at 12 months after treatment initiation. The pooled analysis of patients with NSCLC from Cohorts A and E (n=46) revealed an ORR of 26.1% (95% CI 14.3–41.1), a DCR of 67.4% (95% CI 52.0–80.5), a median PFS of 5.0 months (95% CI 3.0–7.4), and a median OS of 17.1 months (95% CI 12.4~NA) (Table 2 and Figure 2B).

Safety

A total of 87 subjects were included in the SS. In this study, 95.4% (83/87) of patients experienced at least one treatment-emergent adverse event (TEAE) of any grade, with grade ≥3 TEAEs reported in 41.4% (36/87) of patients. The most commonly reported TEAEs included anemia (24, 27.6%), increased alanine aminotransferase (ALT) (15, 17.2%), decreased weight (14, 16.1%), hypokalemia (14, 16.1%), proteinuria (14, 16.1%), and increased aspartate transaminase (AST) (12, 13.7%). Grade≥ 3 TEAEs that occurred in two or more patients included malignant tumor progression (8, 9.2%), hypokalemia (6, 6.9%), anemia (3, 3.4%), and increased ALT (2, 3.3%). (Supplementary Table 2) In total, 29 patients (33.3%) experienced treatment-emergent serious adverse events (SAEs), with the most common being malignant tumor progression

(8, 9.2%), immune-mediated pulmonary disease (4, 4.6%), death (3, 3.4%), and hypokalemia (3, 3.4%) (Supplementary Table 3).

Treatment-related adverse events (TRAEs) occurred in 78.1% (68/87) patients. The most frequently observed TRAEs were increased ALT (12, 13.8%), proteinuria (11, 12.6%), rash (11, 12.6%), increased AST (9, 10.3%), pyrexia (8, 9.2%), and increased amylase (7, 8.0%). TRAEs of grade 3 or higher were reported in 12 out of 87 patients (13.8%), with anemia (in 2 patients [2.2%]), immune-mediated pulmonary disease (in 2 patients [2.2%]), and abnormal hepatic function (in 2 patients [2.2%]) occurring in more than one patient (Table 3).

Table 3 Summary of Adverse Events

Preferred Term	Cohort A n=33		Cohort C n=24		Cohort E n=30		Total N=87	
	Any grade	Grade≥ 3	Any grade	Grade≥ 3	Any grade	Grade≥ 3	Any grade	Grade≥ 3
TEAE	30 (90.9)	15 (45.5)	24 (100.0)	10 (41.7)	29 (96.7)	11 (36.7)	83(95.4)	36 (41.4)
SAE	11 (33.3)	10 (30.3)	9 (37.5)	9 (37.5)	9 (30.0)	9 (30.0)	29 (33.3)	28 (32.2)
TRAE	27 (81.8)	5 (15.2)	19 (79.2)	3 (12.5)	22 (73.3)	4 (13.3)	68 (78.1)	12 (13.8)
TEAE leading to SG001 discontinuation	3 (9.1)	0 (0)	1 (4.2)	1 (4.2)	4 (13.3)	3 (10.0)	8 (9.2)	4 (4.6)
TEAE leading to SG001 interruption	6 (18.2)	3 (9.1)	6 (25.0)	3 (12.5)	7 (23.3)	5 (16.7)	19 (21.8)	11 (12.6)
TEAE leading to death	4 (12.1)	/	6 (25.0)	/	4 (13.3)	/	14 (16.1)	/
irAE	8 (24.2)	3 (9.1)	10 (41.7)	2 (8.3)	8 (26.7)	3 (10.0)	26 (29.9)	8 (9.2)
TRAE occurring in at least 3% of patients								
ALT increased	2 (6.1)	0	4 (16.7)	0	6 (20.0)	1 (3.3)	12 (13.8)	1 (1.1)
Proteinuria	9 (27.3)	1 (3.0)	0	0	2 (6.7)	0	11 (12.6)	1 (1.1)
Rash	5 (15.2)	0	3 (12.5)	0	3 (10.0)	0	11 (12.6)	0
AST increased	4 (12.1)	0	2 (8.3)	0	3 (10.0)	0	9 (10.3)	0
Pyrexia	2 (6.1)	0	3 (12.5)	0	3 (10.0)	0	8 (9.2)	0
Amylase increased	4 (12.1)	1 (3.0)	0	0	3 (10.0)	0	7 (8.0)	1 (1.1)
Platelet count decreased	3 (9.1)	0	1 (4.2)	0	2 (6.7)	1 (3.3)	6 (6.9)	1 (1.1)
Maculopapule	1 (3.0)	0	3 (12.5)	0	2 (6.7)	0	6 (6.9)	0
Hyperthyroidism	1 (3.0)	0	4 (16.7)	0	1 (3.3)	0	6 (6.9)	0
Weight decreased	2 (6.1)	0	2 (8.3)	0	1 (3.3)	0	5 (5.7)	0
Hyperglycemia	2 (6.1)	0	1 (4.2)	0	2 (6.7)	0	5 (5.7)	0
Creatinine increased	4 (12.1)	0	1 (4.2)	0	0	0	5 (5.7)	0
Blood bilirubin increased	2 (6.1)	0	0	0	3 (10.0)	0	5 (5.7)	0
CPK increased	3 (9.1)	0	0	0	2 (6.7)	0	5 (5.7)	0
Hyponatremia	2 (6.1)	0	2 (8.3)	0	0	0	4 (4.6)	0
LDH increased	2 (6.1)	0	1 (4.2)	0	1 (3.3)	0	4 (4.6)	0
Vomiting	1 (3.0)	0	1 (4.2)	0	2 (6.7)	1 (3.3)	4 (4.6)	1 (1.1)
Pruritus	3 (9.1)	0	0	0	1 (3.3)	0	4 (4.6)	0
Hypothyroidism	2 (6.1)	1 (3.0)	1 (4.2)	0	1 (3.3)	0	4 (4.6)	1 (1.1)
Lipase increased	2 (6.1)	0	0	0	2 (6.7)	1 (3.3)	4 (4.6)	1 (1.1)
Immune-mediated pulmonary disease	2 (6.1)	0	1 (4.2)	1 (4.2)	1 (3.3)	1 (3.3)	4 (4.6)	2 (2.2)
Hypertriglyceridemia	2 (6.1)	0	0	0	1 (3.3)	0	3 (3.4)	1 (1.1)
γ-GGT increased	1 (3.0)	0	1 (4.2)	0	1 (3.3)	1 (3.3)	3 (3.4)	1 (1.1)
Blood urea increased	2 (6.1)	0	1 (4.2)	0	0	0	3 (3.4)	0
Bilirubin conjugated increased	1 (3.0)	0	0	0	2 (6.7)	1 (3.3)	3 (3.4)	1 (1.1)
TSH increased	1 (3.0)	0	0	0	2 (6.7)	0	3 (3.4)	0
Free thyroxine increased	1 (3.0)	0	1 (4.2)	0	1 (3.3)	0	3 (3.4)	0
Electrocardiogram QT interval prolonged	2 (6.1)	0	0	0	1 (3.3)	0	3 (3.4)	0
Asthenia	2 (6.1)	0	1 (4.2)	0	0	0	3 (3.4)	0
Nausea	2 (6.1)	0	1 (4.2)	0	0	0	3 (3.4)	0
Abnormal hepatic function	1 (3.0)	1 (3.0)	2 (8.3)	1 (4.2)	0	0	3 (3.4)	2 (2.2)

Note: Data are n (%).

Abbreviations: TEAE, Treatment-emergency adverse event; SAE, Serious adverse event; TRAE, Treatment-related adverse event; irAE, Immune-related adverse event; ALT, Alanine transaminase; AST, Aspartate Aminotransferase; CPK, Creatine phosphokinase; LDH, Lactate dehydrogenase; GGT, glutamyl transpeptidase; TSH, Thyroid-stimulating hormone.

Seven (8.0%) patients discontinued treatment because of TRAEs, including immune-mediated pulmonary disease (2/87), abnormal laboratory findings (2/87), abnormal hepatic function (1/87), drug-induced liver injury (1/87), pain (1/87), proteinuria (1/87), and anemia (1/87). Additionally, one patient discontinued treatment due to a TEAE (headache) that was assessed as not related to the SG001. TEAEs leading to dose interruptions occurred in 21.8% (19/87) of patients, most commonly (≥2%) due to pulmonary inflammation (2/87), infectious pneumonia (2/87), and arthritis (2/87). TEAEs leading to death occurred in 14 patients (14/87, 16.1%), none of which were assessed as related to SG001 by the investigators (Supplementary Tables 4–6).

Immune-related AEs (irAEs) were reported in 26 (29.9%) patients receiving SG001 at a dosage of 240 mg Q2W during the on-treatment period. The most common irAEs included hypothyroidism (6, 6.9%), abnormal thyroid function test results (defined as abnormal laboratory values, yet not clinically diagnosed as hypothyroidism or hyperthyroidism) (5, 5.7%), hyperthyroidism (4, 4.6%), and immune-mediated pulmonary disease (4, 4.6%). Most events were grade 1 or 2 in severity, with no irAEs leading to death were observed. Eight patients (9.2%) experienced at least one irAEs of ≥ grade 3. Furthermore, the only irAE of grade ≥3 that occurred in two or more patients was immune-mediated pulmonary disease (2, 2.3%) (Supplementary Table 7).

Pharmacokinetics

The PK profiles of SG001 following both first and multiple doses were characterized from 32 patients. The C_{max} of 71.90 ±21.71 ug/L (mean±SD) was achieved at1.46 (range 1–25.07) hours after the first infusion, with a mean first-dose $t_{1/2}$ of 5.89 (range 2.54–11.21) days. Apparent trough serum concentration at steady state was observed at or before dose 6. The mean (SD) accumulation ratio of 1.27 (0.30) and steady-state trough concentration (C_{trough}) value of 16.35 (8.88) ug/L were observed in our study (Figure 3 and Supplementary Table 8).

T-Cell Receptor Occupancy Rate

Preliminary data from 87 patients in ROS demonstrated a rapid increase in PD-1 RO rate following a single infusion of SG001. The average RO rate exceeded 90% by the end of infusion and maintained for approximately 2 weeks. Furthermore, with 13 infusions of SG001 at 240mg Q2W, the RO rate was sustained above 85% (Supplementary Figure 2).

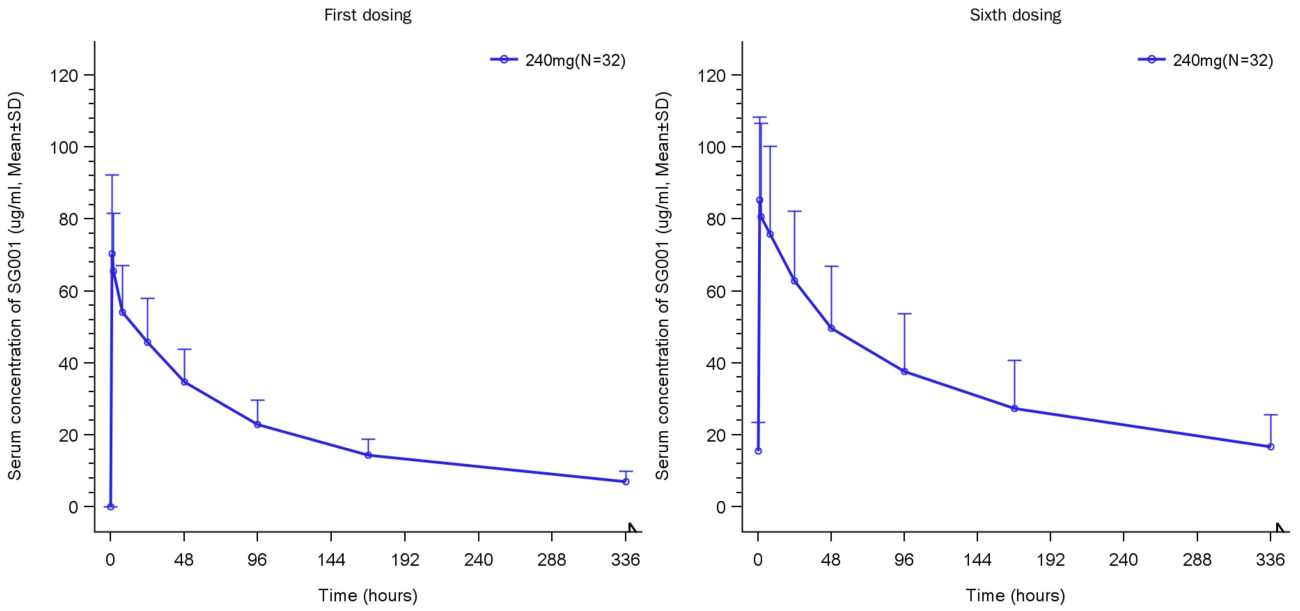

Figure 3 Concentration of SG001 following the first and sixth dosing with a dose of 240mg.

https://doi.org/10.2147/DDDT.S546663

Immunogenicity

Clinical immunogenicity was assessed in 85 patients. Two patients were SG001 ADA positive at baseline, but neither exhibited an increase in titers after baseline. Nine patients had treatment-emergent ADA, all of which were transient. The median time to positive response was 8.0 days after the first SG001 infusion. Among the 9 patients (9/85, 10.6%) with an ADA-positive response, Nabs were detected in 2 patients.

Discussion

Our results reveal that SG001 monotherapy, administered at a dose of 240mg Q2W, had an encouraging preliminary anti-tumor activity with an acceptable safety profile in patients with advanced solid tumors.

The SG001 monotherapy elicited durable, confirmed responses in patients with various advanced PD-1-positive solid tumors, including those with limited treatment options in the second-line settings and beyond (investigator-confirmed was ORR 39.4% with a median PFS of 9.6 months), indicating a potential trend toward better efficacy than other PD-1 blockade monotherapies for ≥ 2-line treatments.[18–21] Two patients in Cohort A with MSI-H solid tumors, which are known to respond more favorably to PD-1 inhibitors as previously reported,[22,23] may partially contribute to the higher ORR and longer PFS found in our study. Although the sample size is too small to draw firm conclusions specific to a tumor type, SG001 activity appears to be pronounced in NSCLC. Some ICIs targeting PD-1/PD-L1 pathways, which are the cornerstone of first-line treatments for advanced NSCLC patients without targetable mutations, have been approved by the Food and Drug Administration (FDA).[24,25] However, PD-L1-negative patients derive limited benefit from the approved PD-1 inhibitors. The KETNOTE-010 study investigating pembrolizumab, an FDA-approved PD-1-blocking humanized monoclonal IgG4 antibody for first-line therapy in advanced or metastatic NSCLC, demonstrated notable efficacy in previously treated NSCLC patients with PD-L1 expression on at least 1% of tumor cells (ORR 18%; median TTR 9 weeks; DOR not reached; OS 10.4 months; PFS 3.9 months) with a dose schedule of 2 mg/kg Q3W.[26] Furthermore, in KEYNOTE-001 study, pembrolizumab exhibited an ORR of 18%, a median PFS of 3.0 months, and a median OS of 9.3 months in previously treated PD-L1-unselected NSCLC patients.[11] Here, we reported findings suggesting the potential for relatively more favorable and durable efficacy of 240mg Q2W SG001 in both PD-1-positive (ORR 43.8%; PFS 9.6 months) and PD-1-unseclected NSCLC populations (ORR 26.1%; PFS 5.0 months). Patients with high PD-L1 expression (>50%) or non-squamous showed greater benefit from PD-1 inhibitors.[26] Therefore, the differences in the proportion of patients with high PD-L1 expression and squamous histology – data missing in our study – between populations in KETNOTE-010 and our trial may have an influence on the comparative outcomes. Nonetheless, our results align with previous findings indicating that PD-1 blockades are more effective in patients with PD-L1 expression,[11,26] and underscore the rational for further investigations of SG001 in combination with other immunotherapies and chemotherapy.

Beyond NSCLC, there remains a critical need to develop new treatment options for patients with other solid tumors. Malignant mesothelioma is known to be associated with highly aggressive disease with a poor prognosis. For several decades, the treatment of malignant mesothelioma did not significantly change, with the combination of cisplatin and pemetrexed serving as the reference therapeutic scheme for the majority of unresectable malignant mesothelioma patients.[27,28] However, the antitumor efficacy of this regimen remains unsatisfactory.[29–31] More recently, the combination of novel antineoplastic agents, nivolumab and ipilimumab, has been approved as the first-line therapy for malignant mesothelioma.[32] Furthermore, nivolumab plus ipilimumab and nivolumab monotherapy are also recommended as second-line and beyond therapeutic options for individuals who have not received first-line immunotherapy. The CONFIRM study demonstrated nivolumab monotherapy representing a benefit to patients with malignant mesothelioma who had progressed on first-line therapy, with an ORR of 11%, a median PFS of 3 months, and a median OS of 10.2 months.[33] Compared with nivolumab, our study showed a numerically slightly higher antitumor activity for SG001 monotherapy in similar patient population. Specifically, the ORR, median PFS, and median OS were 12.5%, 4.1 months, and 13.6 months, respectively. Previous study has indicated that epithelioid mesothelioma is more sensitive to PD-1 inhibitor treatment than non-epithelioid disease.[33] Additionally, PD-L1 expression of ≥25% has been demonstrated to be associated with a better ORR.[34] Further subgroup analysis, unfortunately, could not be performed in our study because of insufficient histology information.

Treatment with SG001 demonstrated an acceptable safety profile that was entirely representative of what has previously been reported for the PD-1 inhibitor class.[35–37] Although, TRAEs were reported in 78.1% patients in our study, which was comparable to the reported rate of 70%~76% in other similar studies and the percentage of patients suffered from grade ≥3 TRAEs was lower than that of other PD-1 blockades (13.8% vs 18%~26.6%).[11,19,33,38–40] This indicates that SG001-related TEAEs were predominantly of mild to moderate in severity and manageable with standard care. The incidence and severity of irAEs in our study were consistent with expectations for a PD-1 targeting checkpoint inhibitor, with no new safety signals identified.[36,41] Among the 87 pre-treated patients in this study, irAEs occurred in 29.9% of patients, with grade 3 or 4 irAEs occurring in 9.2% of patients, which is similar to rates reported for pembrolizumab (29.2%; 9.7%),[38] nivolumab (41.1%; 4.7%),[42] and a meta-analysis of 46 PD-1/PD-L1 inhibitor studies (26.8%; 6.1%).[37] Aside from the commonly recognized irAEs associated with other anti-PD-1 antibodies, no new safety signals were identified.[10,11,26,33,39,40,43–46] All cases of immune-related pneumonitis were recovered/resolved following SG001 discontinuation or interruption, and/or treatment with medications. The incidences of TRAEs leading to SG001 discontinuation (7/87) and treatment-emergent ADA (9/85) were both low.

Our findings underscore the promising developmental potential of SG001 in the treatment of solid tumors, notably in NSCLC and malignant mesothelioma. Nevertheless, this was a single-arm trial with a relatively small sample size, which represents a limitation of our study. The results obtained in this study require further validation in well-conducted randomized controlled trials with larger sample sizes and longer follow-up period.

Conclusions

Overall, SG001 monotherapy at a dose schedule of 240mg Q2W demonstrated encouraging signs of anti-tumors activity and a tolerable safety profile in patients with advanced solid tumors, particularly in NSCLC and malignant mesothelioma. Ongoing studies combining SG001 with Simmitinib or Duvelisib (NCT06132217 and NCT05508659) aim to establish its position in the treatment landscape for a broader population with solid tumors.

Data Sharing Statement

The data that support the findings of this study are not available.

Ethics Approval and Informed Consent

The study was approved by independent ethics committees or institutional review boards at each site, and adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent. ClinicalTrials.gov identifier: NCT03852823.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Silong Xiang and Xiao Zhang are employees of CSPC Zhongqi Pharmaceutical Technology (Shijiazhuang) Co., Ltd. The others have no conflicts of interest to declare for this work.

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