Preliminary safety and efficacy results from phase Ib study of the anti-CTLA-4 monoclonal antibody (mAb) CS1002 in combination with the anti-PD-1 mAb CS1003 in patients with advanced solid tumors

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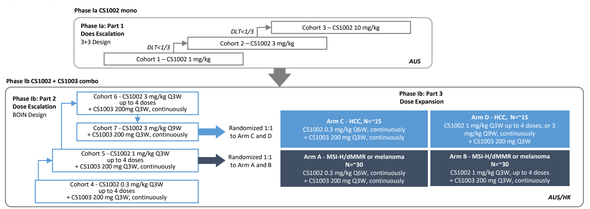
Background

- Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a negative regulator of T-cell responses following T-cell stimulation.[1] CS1002 is a human IgG1 monoclonal antibody (mAb) that binds to CTLA-4 and blocks the interaction between CTLA-4 and its ligands, CD80/CD86, thus augments T-cell activation and proliferation. Phase Ia of CS1002-101 study (NCT03523819) reported at CSCO 2019 showed up to 10 mg/kg with no dose-limiting toxicities (DLTs) and treatment-related serious adverse events (SAEs) observed in patients with solid tumors.[2]
- The programmed cell death protein 1 (PD-1) is an immune checkpoint that negatively regulates the immune system to avoid collateral damage to self-tissues.[3] CS1003 is a humanized, recombinant IgG4 monoclonal antibody against PD-1.
- The combination of anti-PD-1 and anti-CTLA-4 antibodies has shown enhanced efficacy in different types of tumors.[4] Phase Ib of CS1002-101 study (NCT03523819) reported at ESMO 2021 showed the combination of CS1002 and CS1003 had a well-managed safety profile and a promising preliminary anti-tumor activity in patients with anti-PD-(L)1-naive, pretreated MSI-H/dMMR (high microsatellite instability/mismatch repair deficient) tumors or anti-PD-(L)1-refractory melanoma at two dose regiments of CS1002 (0.3 mg/kg Q6W and 1 mg/kg Q3W).[5]
- Here we present the updated results of MSI-H/dMMR tumors and melanoma cohorts and the first report of hepatocellular carcinoma (HCC) cohort in part 3.

Objectives

CS1002-101 is a multi-center, open-label, dose escalation, and dose expansion phase Ia/Ib study to evaluate the clinical safety, tolerability, pharmacokinetics (PK), and preliminary antitumor efficacy of CS1002 as monotherapy and in combination with CS1003. The study is composed of two stages: phase Ia (part 1-CS1002 monotherapy dose escalation), and phase Ib (part 2-CS1002 and CS1003 combination therapy dose escalation and part 3-CS1002 and CS1003 combination therapy dose expansion) (Figure 1). To identify a dose regimen of the combination that may provide similar efficacy but a better safety profile, a lower dose of CS1002 (0.3 mg/kg Q6W, continuously) was evaluated in addition to the more convention dosing schedule of anti-CTLA4 (1 mg/kg Q3W, up to 4 doses and 3 mg/kg Q9W, continuously) in patients with MSI-H/dMMR tumors, Melanoma and HCC. Here we present anti-tumor activity and safety in Arm A, Arm B (MSI-H/dMMR tumors and melanoma) and Arm C, Arm D (HCC) of part 3 with the median duration of follow-up 5.26 (95% CI : 3.81, 6.54) months as of data cut-off 06 Aug 2021.

Figure 1. CS1002-101 Study Schema.



Abbreviation: BOIN = Bayesian optimal interval design; DLT = Dose Limiting Toxicity; HCC = Hepatocellular Carcinoma; MSI-H/dMMR = High microsatellite instability /mismatch repair deficient; QnW = once every n weeks.

Methods

In part 3, patients with anti-PD-(L)1-naïve, pretreated MSI-H/dMMR tumors or anti-PD-(L)1-refractory melanoma were randomized and treated with CS1002 (Arm A: CS1002 0.3 mg/kg Q6W, intravenous [iv.], continuously; Arm B: CS1002 1 mg/kg Q3W, iv., up to 4 doses) and CS1003 200 mg fixed dose Q3W iv., continuously; Patients with anti-PD-(L)1-refractory HCC were randomized and treated with CS1002 (Arm C: CS1002 0.3 mg/kg Q6W, iv., continuously; Arm D: CS1002 3 mg/kg Q9W, iv., continuously) and CS1003 200 mg fixed dose Q3W iv., continuously.

Table 1. Key Inclusion and Exclusion Criteria

Key inclusion criteria	Key exclusion criteria
• ECOG PS 0-1 • At least one measurable lesion per RECIST V1.1 • Pretreated MSI-H/dMMR tumors or anti-PD-1/PD-L1 refractory melanoma (Arm A and Arm B) • A Child-Pugh score of 6 points or less and anti-PD-1/PD-L1 refractory HCC (Arm C and Arm D)	• Prior therapy with an anti-CTLA-4 agent • Active or prior autoimmune diseases • MSI-H/dMMR tumors with prior anti-PD-1/PD-L1 therapy or Melanoma with prior anti-PD-1/PD-L1 therapy and experienced Grade 3 and higher irAE • HCC with prior anti-PD-1/PD-L1 therapy and experienced Grade 3 and higher irAE; HCC with Radiographic evidence of portal vein tumor thrombus (VP4), vena cava or heart involvement

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; HCC = Hepatocellular Carcinoma; irAE = immune-related adverse event; MSI-H/dMMR = high microsatellite instability /mismatch repair deficient; RECIST = Response Evaluation Criteria in Solid Tumors.

Endpoints and Assessments

Primary Endpoint

- Anti-tumor activity - Objective Response Rate (ORR)

Secondary Endpoints

- Safety, tolerability and efficacy-The incidence and severity of AEs and SAEs
- Disease Control Rate (DCR), Progression Free Survival (PFS), Duration of Response (DOR), Overall Survival (OS)
- PK parameters
- Immunogenicity (Anti-CS1002 antibody and anti-CS1003 antibody)

Assessments

- Tumor assessment was assessed per RECIST V1.1 by investigators, approximately every 9 weeks in the first year and approximately every 12 weeks thereafter
- AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) V4.03

References

1. Thompson, Craig B., and James P. Allison. "The emerging role of CTLA-4 as an immune attenuator." Immunity 7.4 (1997): 445-450.
2. S. Bishnoi, R. Cosman, M. Moore, etc. A phase Ia/Ib, open-label, dose-escalation and dose-expansion study of the anti-CTLA-4 monoclonal antibody CS1002 as monotherapy and in combination with anti-PD-1 monoclonal antibody CS1003 in subjects with advanced solid tumors., 2019, CSCO.
3. Francisco, Loise M., Peter T. Sage, and Arlene H. Sharpe. "The PD-1 pathway in tolerance and autoimmunity." Immunological reviews 236.1 (2010): 219-242.
4. Rotte, Anand. "Combination of CTLA-4 and PD-1 blockers for treatment of cancer." Journal of Experimental & Clinical Cancer Research 38.1 (2019): 1-12.
5. S. Bishnoi, R. Cosman, M. Moore, etc. Preliminary safety and efficacy results from phase Ib study of the anti-CTLA-4 monoclonal antibody (mAb) CS1002 in combination with anti-PD-1 mAb CS1003 in patients with advanced solid tumors, 2021, ESMO.

Results

Demographic

Table 2. Demographics and Baseline Characteristics in Part 3 Dose Expansion (Intent-to-treat-Set)

	MSI-H/dMMR tumors[*] or Melanoma		Hepatocellular Carcinoma		ALL (N=56)
	CS1002 0.3 mg/kg Q6W + CS1003 (N=21)	CS1002 1 mg/kg Q3W + CS1003 (N=22)	CS1002 0.3 mg/kg Q6W + CS1003 (N=7)	CS1002 3 mg/kg Q9W + CS1003 (N=6)	
Mean age, years (range)	65.6 (44, 87)	68.1 (39, 89)	61.3 (40, 75)	59.5 (40, 71)	65.4 (39, 89)
Age group, n (%)					
< 65 Years	10 (47.6)	7 (31.8)	4 (57.1)	4 (66.7)	25 (44.6)
≥ 65 Years	11 (52.4)	15 (68.2)	3 (42.9)	2 (33.3)	31 (55.4)
Sex, n (%)					
Male	9 (42.9)	16 (72.2)	6 (85.7)	4 (66.7)	35 (62.5)
Female	12 (57.1)	6 (27.3)	1 (14.3)	2 (33.3)	21 (37.5)
Race, n (%)					
White	20 (95.2)	19 (86.4)	2 (28.6)	0	41 (73.2)
Asian	1 (4.8)	3 (13.6)	5 (71.4)	6 (100.0)	15 (26.8)
ECOG PS, n (%)					
0	13 (61.9)	12 (54.5)	3 (42.9)	3 (50.0)	31 (55.4)
1	8 (38.1)	10 (45.5)	4 (57.1)	3 (50.0)	25 (44.6)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status.
Intent-to-treat (ITT) set: all randomized patients in Part 3.
*MSI-H/dMMR tumors included colorectal cancer (n=9), endometrial cancer (n=4) and others (n=14).

- A total of 56 patients were randomized, 54 of whom were treated by CS1002 and CS1003. As of 06 Aug 2021, 32 (57.1%) patients treatment was ongoing.

Efficacy

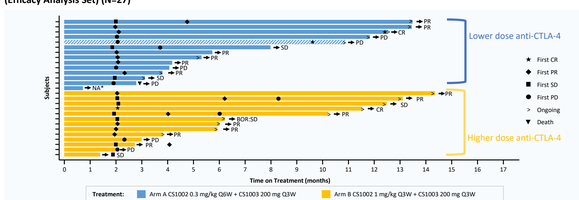
Table 3. Best Overall Response Assessed by Investigator in Part 3 (Efficacy Analysis Set)

	MSI-H/dMMR tumors (n=27)		Melanoma (N=12)		Hepatocellular Carcinoma (N=9)		
n (%) [95% CI (%)]	Arm A: CS1002 0.3 mg/kg Q6W + CS1003 (N=14)	Arm B: CS1002 1 mg/kg Q3W + CS1003 (N=13)	Arm A: CS1002 0.3 mg/kg Q6W + CS1003 (N=5)	Arm B: CS1002 1 mg/kg Q3W + CS1003 (N=7)	Arm C: CS1002 0.3 mg/kg Q6W + CS1003 (N=5)	Arm D: CS1002 3 mg/kg Q9W + CS1003 (N=4)	ALL (N=48)
ORR	7 (50.0) [23.0, 77.0]	8 (61.5) [31.6, 86.1]	1 (20.0) [0.5, 71.6]	3 (42.9) [9.9, 81.6]	0 [0.0, 52.2]	1 (25.0) [0.6, 80.6]	20 (41.7) [27.6, 56.8]
Confirmed ORR*	6 (42.9) [17.7, 71.1]	4 (30.8) [9.1, 61.4]	1 (20.0) [0.5, 71.6]	2 (28.6) [3.7, 71.0]	0 [0.0, 52.2]	1 (25.0) [0.6, 80.6]	14 (29.2) [17.0, 44.1]
CR	1 (7.1) [0.2, 33.9]	1 (7.7) [0.2, 36.0]	0 [0.0, 52.2]	1 (14.3) [0.4, 57.9]	0 [0.0, 52.2]	0 [0.0, 60.2]	3 (6.3) [1.3, 17.2]
PR	6 (42.9) [17.7, 71.1]	7 (53.8) [25.1, 80.8]	1 (20.0) [0.5, 71.6]	2 (28.6) [3.7, 71.0]	0 [0.0, 52.2]	1 (25.0) [0.6, 80.6]	17 (35.4) [22.2, 50.5]
SD	2 (14.3) [1.8, 42.8]	3 (23.1) [5.0, 53.8]	3 (60.0) [14.7, 94.7]	2 (28.6) [3.7, 71.0]	1 (20.0) [0.5, 71.6]	0 [0.0, 60.2]	11 (22.9) [12.0, 37.3]
PD	4 (28.6) [8.4, 58.1]	2 (15.4) [1.9, 45.4]	0 [0.0, 52.2]	1 (14.3) [0.4, 57.9]	3 (60.0) [14.7, 94.7]	3 (75.0) [19.4, 99.4]	13 (27.1) [15.3, 41.8]
NE	0	0	0	0	0	0	4 (8.3)
NA**	1 (7.1)	0	1 (20.0)	1 (14.3)	1 (20.0)	0	4 (8.3)
DCR (CR+PR+SD)	9 (64.3) [35.1, 87.2]	11 (84.6) [54.6, 98.1]	4 (80.0) [28.4, 99.5]	5 (71.4) [29.0, 96.3]	1 (20.0) [0.5, 71.6]	1 (25.0) [0.6, 80.6]	31 (64.6) [49.5, 77.8]

Abbreviations: CR = Complete Response; DCR = Disease Control Rate; ORR = Objective Response Rate; PD = Progressive Disease; PR = Partial Response; SD = Stable Disease; NA = Not applicable; NE = Not evaluable. Efficacy analysis set (EAS) : Patients with received at least one dose of investigational product. However, patients, who are still on treatment at the time of data cut-off but have not yet reached the first post-baseline tumor assessment, will be excluded.
*The subject has demonstrated CR/PR after CS1002 and CS1003 therapy as defined by RECIST Version 1.1, which was subsequently confirmed by a second assessment in the next scheduled tumor assessment visit to ensure responses identified were not the result of measurement error.
**Patients were classified as not applicable if no post-baseline response assessments were available.

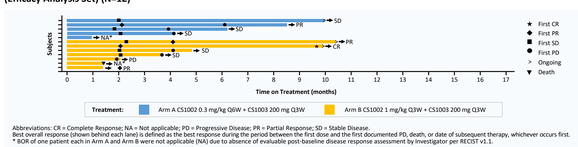
- As of 06 Aug 2021, of the 14 evaluable patients with MSI-H/dMMR tumor in Arm A, and 13 in Arm B, ORRs were 50.0% and 61.5%, respectively. Of the 5 evaluable patients with melanoma in Arm A and 7 in Arm B, ORRs were 20.0% and 42.9% respectively. Of the 9 evaluable patients with HCC, ORR was 11% (Table 3). As of 06 Aug 2021, the DOR for responders was not reached.

Figure 2. Swimmer Plot of Treatment Durations, Best Overall Response and Progression of Patients with MSI-H/dMMR Tumors (Efficacy Analysis Set) (N=27)



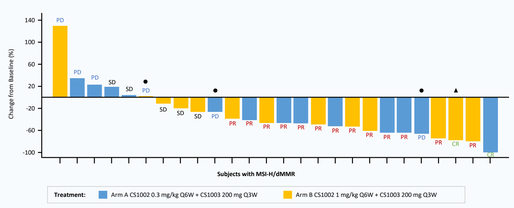
Abbreviations: CR = Complete Response; NA = Not applicable; PD = Progressive Disease; PR = Partial Response; SD = Stable Disease.
Best overall response (shown behind each lane) is defined as the best response during the period between the first dose and the first documented PD, death, or date of subsequent therapy, whichever occurs first.
*BOR of one patient in Arm A was not applicable (NA) due to absence of evaluable post-baseline disease response assessment by investigator per RECIST v1.1.
It is allowed to continue study treatment per the protocol for the subject having documented PD per RECIST1.1 which was suspected as pseudo-progression and judged as clinically stable by the investigator.

Figure 3. Swimmer Plot of Treatment Durations, Best Overall Response and Progression in Patients with Melanoma (Efficacy Analysis Set) (N=12)



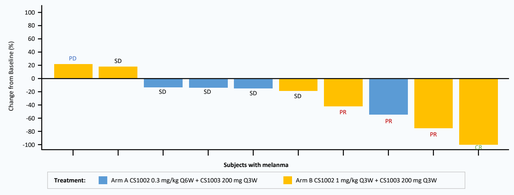
Abbreviations: CR = Complete Response; NA = Not applicable; PD = Progressive Disease; PR = Partial Response; SD = Stable Disease.
Best overall response (shown behind each lane) is defined as the best response during the period between the first dose and the first documented PD, death, or date of subsequent therapy, whichever occurs first.
* BOR of one patient each in Arm A and Arm B were not applicable (NA) due to absence of evaluable post-baseline disease response assessment by investigator per RECIST v1.1.

Figure 4. Best Percentage Change from Baseline in Sum of Measurements in Patients with MSI-H/dMMR Tumors (Efficacy Analysis Set) (N=26*)



Abbreviations: CR = Complete Response; PD = Progressive Disease; PR = Partial Response; SD = Stable Disease.
* one patient in Arm A was not included due to absence of evaluable post-baseline disease response assessment by Investigator per RECIST v1.1.
◆ Both of target lesions were lymph nodes and reduced to <10 mm in short axis; the only non-target lesion was also lymph node and disappeared. Therefore, the best overall response was evaluated as CR per RECIST v1.1, despite not a 100% target-lesion reduction.
★ Tumor assessment of three patients were progressive disease (PD) due to the new tumor lesions, although there was no tumor size increase or an increase of less than 20%.

Figure 5. Best Percentage Change from Baseline in Sum of Measurements in Patients with Melanoma (Efficacy Analysis Set) (N=10*)



Abbreviations: CR = Complete Response; PD = Progressive Disease; PR = Partial Response; SD = Stable Disease.
* One patient each in Arm A and Arm B was not included due to absence of evaluable post-baseline disease response assessment by Investigator per RECIST v1.1.

Table 4: Time to Event Summary for Progression-Free Survival Assessed by Investigator in Part 3 (Intent-to-treat Set)

	MSI-H/dMMR tumors (N=30)		Melanoma (N=13)		Hepatocellular Carcinoma (N=13)		ALL (N=56)
Months [95% CI (%)]	Arm A: CS1002 0.3 mg/kg Q6W + CS1003 (N=15)	Arm B: CS1002 1 mg/kg Q3W + CS1003 (N=15)	Arm A: CS1002 0.3 mg/kg Q6W + CS1003 (N=6)	Arm B: CS1002 1 mg/kg Q3W + CS1003 (N=7)	Arm C: CS1002 0.3 mg/kg Q6W + CS1003 (N=7)	Arm D: CS1002 3 mg/kg Q9W + CS1003 (N=6)	
PFS	- [2.04, -]	- [2.60, -]	5.14 [3.98, -]	4.11 [1.41, -]	1.94 [1.08, -]	1.95 [1.91, -]	6.05 [2.60, -]

Abbreviations: mFU = median Follow Up; PFS = Progression Free Survival.
Intent-to-treat (ITT) set: all randomized patients in Part 3.

Safety

Table 5. Summary of Treatment-Emergent Adverse Events (TEAE) of CS1002 and CS1003 in Part 3 (Safety Analysis Set)

	MSI-H/dMMR tumors or Melanoma		Hepatocellular Carcinoma		
n (%)	Arm A: CS1002 0.3 mg/kg Q6W + CS1003 (N=21)	Arm B: CS1002 1 mg/kg Q3W + CS1003 (N=21)	Arm C: CS1002 0.3 mg/kg Q6W+ CS1003 (N=6)	Arm D: CS1002 3 mg/kg Q9W+ CS1003 (N=6)	ALL (N=54)
Number of patients with at least one TEAE	19 (90.5)	20 (95.2)	4 (66.7)	5 (83.3)	48 (88.9)
TEAE related to CS1002/CS1003	13 (61.9)	16 (76.2)	3 (50.0)	4 (66.7)	36 (66.7)
Grade ≥3 TEAE	7 (33.3)	11 (52.4)	1 (16.7)	1 (16.7)	20 (37.0)
Grade ≥3 TEAE related to CS1002/CS1003	4 (19.0)	4 (19.0)	0	1 (16.7)	9 (16.7)
SAE	6 (28.6)	13 (61.9)	1 (16.7)	2 (33.3)	22 (40.7)
SAE related to CS1002/CS1003	3 (14.3)	3 (14.3)	0	1 (16.7)	7 (13.0)
Immune-related AE	6 (28.6)	9 (42.9)	0	1 (16.7)	16 (29.6)
Infusion-related Reaction	1 (4.8)	2 (9.5)	0	0	3 (5.6)
TEAE Leading to CS1002/CS1003 permanently discontinuation	2 (9.5)	3 (14.3)	0	0	*5 (9.3)
TEAE Leading to death	0	1 (4.8)	0	0	1 (1.9)

Abbreviation: TEAE = Treatment-Emergent Adverse Event.
*One patient permanently discontinued CS1002 and CS1003 due to death with unknown cause.

- In total, 48 (88.9%) patients experienced at least one TEAE, of whom 36 (66.7%) patients had treatment-related AEs (TRAEs). Nine (16.7%) patients occurred CTCAE Grade ≥3 treatment-related AE that were related to both CS1002 and CS1003. Twenty-two (40.7%) patients experienced at least one SAE and serious TRAEs occurred in 7 (13.0%) patients. IrAEs occurred in 16 (29.6%) patients (Table 5). Four (7.4%) patients experienced TRAEs leading to discontinuation of both CS1002 and CS1003, including one blood creatinine increased and one polyarthritis in Arm A and one diarrhoea and one Stevens-Johnson syndrome in Arm B. No death due to TRAEs was reported.

Table 6. Treatment-Related TEAEs (TRAE) in Part 3 (Occurred in ≥ 5% Patients) (Safety Analysis Set)

	MSI-H/dMMR tumors or Melanoma		Hepatocellular Carcinoma		
MedDRA Preferred Term, n (%)	Arm A: CS1002 0.3 mg/kg Q6W + CS1003 (N=21)	Arm B: CS1002 1 mg/kg Q3W + CS1003 (N=21)	Arm C: CS1002 0.3 mg/kg Q6W + CS1003 (N=6)	Arm D: CS1002 3 mg/kg Q9W + CS1003 (N=6)	ALL (N=54)
Number of patients with at least one event related to CS1002/CS1003	**13 (61.9)**	**16 (76.2)**	**3 (50.0)**	**4 (66.7)**	**36 (66.7)**
Fatigue	3 (14.3)	7 (33.3)	3 (50.0)	1 (16.7)	14 (25.9)
Rash	3 (14.3)	5 (23.8)	1 (16.7)	1 (16.7)	10 (18.5)
Diarrhoea	5 (23.8)	4 (19.0)	0	0	9 (16.7)
Nausea	2 (9.5)	1 (4.8)	1 (16.7)	0	4 (7.4)
Pruritus	1 (4.8)	2 (9.5)	0	0	3 (5.6)
Hyperthyroidism	1 (4.8)	2 (9.5)	0	0	3 (5.6)
Arthralgia	2 (9.5)	1 (4.8)	0	0	3 (5.6)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.

- The most common CS1002-related or CS1003-related AE (≥ 5%) was fatigue, rash, diarrhoea, nausea, pruritus, hyperthyroidism, arthralgia (Table 6) .

Table 7 . Grade ≥ 3 Treatment-Related TEAEs (TRAEs) in Part 3 (Safety Analysis Set)

	MSI-H/dMMR tumors or Melanoma		Hepatocellular Carcinoma		
MedDRA Preferred Term, n (%)	Arm A: CS1002 0.3 mg/kg Q6W + CS1003 (N=21)	Arm B: CS1002 1 mg/kg Q3W + CS1003 (N=21)	Arm C: CS1002 0.3 mg/kg Q6W+ CS1003 (N=6)	Arm D: CS1002 3 mg/kg Q9W+ CS1003 (N=6)	ALL (N=54)
Number of patients with at least one event related to CS1002/CS1003	4 (19.0)	4 (19.0)	0	1 (16.7)	9 (16.7)
Amylase increased	1 (4.8)	0	0	0	1 (1.9)
Blood creatinine increased	1 (4.8)	0	0	0	1 (1.9)
Lipase increased	1 (4.8)	0	0	0	1 (1.9)
Liver function test abnormal	0	0	0	1 (16.7)	1 (1.9)
Transaminases increased	1 (4.8)	0	0	0	1 (1.9)
Glucocorticoid deficiency	0	0	0	1 (16.7)	1 (1.9)
Hyperthyroidism	0	1 (4.8)	0	0	1 (1.9)
Conjunctivitis	0	1 (4.8)	0	0	1 (1.9)
Rash pustular	0	1 (4.8)	0	0	1 (1.9)
Rash	1 (4.8)	0	0	0	1 (1.9)
Stevens-Johnson syndrome	0	1 (4.8)	0	0	1 (1.9)
Diarrhoea	0	1 (4.8)	0	0	1 (1.9)
Polyarthritis	1 (4.8)	0	0	0	1 (1.9)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.

- Nine (16.7%) patients developed CTCAE Grade ≥3 TRAEs that were related to both CS1002 and CS1003, including 4 patients (19.0%) in Arm A, 4 patients (19.0%) in Arm B and 1 patient (16.7%) in Arm D (Table 7) .

Table 8. Treatment-Related SAEs in Part 3 (Safety Analysis Set)

	MSI-H/dMMR tumors or Melanoma		Hepatocellular Carcinoma		
MedDRA Preferred Term, n (%)	Arm A: CS1002 0.3 mg/kg Q6W + CS1003 (N=21)	Arm B: CS1002 1 mg/kg Q3W + CS1003 (N=21)	Arm C: CS1002 0.3 mg/kg Q6W + CS1003 (N=6)	Arm D: CS1002 3 mg/kg Q9W + CS1003 (N=6)	ALL (N=54)
Number of patients with at least one event related to CS1002/CS1003	3 (14.3)	3 (14.3)	0	1 (16.7)	7 (13.0)
Glucocorticoid deficiency	0	0	0	1 (16.7)	1 (1.9)
Hyperthyroidism	0	1 (4.8)	0	0	1 (1.9)
Diarrhoea	0	1 (4.8)	0	0	1 (1.9)
Transaminases increased	1 (4.8)	0	0	0	1 (1.9)
Polyarthritis	1 (4.8)	0	0	0	1 (1.9)
Pneumonitis	1 (4.8)	0	0	0	1 (1.9)
Stevens-Johnson syndrome	0	1 (4.8)	0	0	1 (1.9)

Abbreviation: SAE=serious adverse event.

- Seven (13.0%) patients experienced at least one treatment-related SAE that were related to both CS1002 and CS1003, including 3 patients (14.3%) in Arm A, 3 patients (14.3%) in Arm B and 1 patient (16.7%) in Arm D (Table 8) .

Conclusion

- The combination of CS1002 and CS1003 shows promising anti-tumor responses in patients with anti-PD-(L)1-naive, pretreated MSI-H/dMMR tumors, anti-PD-(L)1-refractory melanoma and anti-PD-(L)1-refractory HCC.
  - Combination of CS1002 and CS1003 demonstrated encouraging clinical activities in patients with MSI-H/dMMR tumors and anti-PD-(L)1 refractory Melanoma. Notable response rates were observed with the two dosing schedules of CS1002; while there appeared to be a somewhat dose-response seen with the higher CS1002 dose.
  - Response was also observed in 9 evaluable patients with anti-PD-(L)1-refractory HCC, though for small sample size and limited duration of follow-up.
  - Combination of CS1002 and CS1003 also achieved durable antitumor activity.
- The combination of CS1002 and CS1003 demonstrated a well-managed safety profile among a broad dosing range of CS1002 (0.3 mg/kg Q6W-3 mg/kg Q9W) cross different tumor types.
  - In Part 3 of the study, any grade TRAEs were reported in 66.7% patients, with the most common (≥10%) TRAEs being fatigue, rash and diarrhoea; Grade ≥ 3 TRAEs were reported in 16.7% patients.
  - Patients receiving CS1002 at 1 mg/kg Q3W in Arm B had numerically higher frequencies of TRAEs and irAEs than those receiving CS1002 at 0.3mg/kg Q6W in Arm A, whereas Grade ≥ 3 TRAEs and treatment-related SAEs were similar between the two dose levels.
- The combination of CS1002 and CS1003 demonstrates an encouraging anti-tumor activity in patients with immunotherapy naive pre-treated MSI-H/dMMR solid tumors, PD(L)1 refractory melanoma and PD(L)1 refractory HCC, supporting further clinical development of CS1002 in combination with CS1003.

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Disclosures

- S. Bishnoi declares to own stocks of Telix Pharmaceutical Ltd and Regeneron Pharmaceutical Ltd.
- R. Cosman declares to be principal investigator in a number of studies at Kinghorn Cancer Center, St Vincent's Hospital, Sydney, Australia.
- M. Moore declares to be advisory board member of Roche and Merck.
- R. Eek declares to own investment portfolio in Novartis and Gilead.
- R. Zielinski declares to have received honoraria as a speaker in Bristol Myers Squibb, Astra Zeneca, MSD and a member of advisory board in Roche and Pfizer; Astra Zeneca and BMS grant to institution; Chair of the Regional and Rural Executive Group of Clinical Oncology Society of Australia.
- S. Chan declares to have received honoraria for speaker in Eisai, AstraZeneca, MSD, Roche, Ipsen, BMS, Bayer, and direct research funding as a principal investigator and receive financial support by Eisai, MSD, Ipsen.
- P. Li declares to be an employee of CStone Pharmaceuticals and own CStone stock.
- A. N. Tse declares to be Chief Scientific Officer at CStone Pharmaceuticals and own CStone stock.
- B. Hu, H. Wang and Y. Ma declare to be employees of CStone Pharmaceuticals.

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