Preliminary safety and efficacy results from a 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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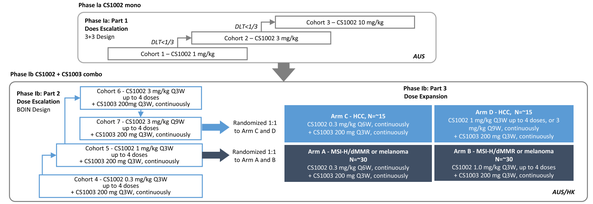
Background

- 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 Chinese Society of Clinical Oncology 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] The combination of CS1002 and CS1003 was evaluated in subcutaneous M38 murine colorectal cancer syngeneic model in CTLA-4 HuGEMM mice[5] and demonstrated significant efficacy.

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 dosing regimen of the combination that may provide similar efficacy but a better safety profile, a lower dose of CS1002 (0.3 mg/kg Q6W) was evaluated in addition to the more convention dosing schedule of anti-CTLA4 (1 mg/kg Q3W, up to 4 doses) in patients with MSI-H/dMMR tumors and melanoma. Here we present the safety of part 2, and safety and anti-tumor activity in Arm A and Arm B (MSI-H/dMMR tumors and melanoma) of part 3 as of data cut-off 01 March 2021. There was no patient enrolled for Arm C and Arm D (hepatocellular carcinoma) by 01 March 2021.

Figure 1. CS1002-101 Study Schema



Abbreviations: DLT = dose limiting toxicity; HCC = hepatocellular carcinoma; MSI-H/dMMR = high microsatellite instability /mismatch repair deficient; Q3W = once every three weeks.

Methods

In part 2, eligible patients were enrolled to receive CS1002 at 4 dose regimens (0.3 mg/kg Q3W, 1 mg/kg Q3W, 3 mg/kg Q3W and 3 mg/kg Q9W, up to 4 doses) in combination with CS1003 200 mg fixed dose Q3W, continuously. In part 3, patients with anti-PD-(L)1-naïve, pretreated MSI-H/dMMR (high microsatellite instability /mismatch repair deficient) tumors or anti-PD-(L)1-refractory melanoma were randomized and treated with CS1002 (Arm A: CS1002 0.3 mg/kg Q6W, continuously; Arm B: CS1002 1 mg/kg Q3W, up to 4 doses) and CS1003 200 mg fixed dose Q3W continuously.

Table 1. Key Inclusion and Exclusion Criteria

Key inclusion criteria	Key exclusion criteria
• ECOG PS 0-1	• Prior therapy with an anti-CTLA-4 agent
• At least one measurable lesion per RECIST Version 1.1	• Active or prior autoimmune diseases
• Patients must have advanced/metastatic, relapsed or refractory solid tumors (part 2) ; Patients must have pretreated MSI-H/dMMR tumors or anti-PD-1/PD-L1 refractory melanoma (part 3)	• Patient have MSI-H/dMMR tumors with prior anti-PD-1/PD-L1 therapy (Part 3); Patients have melanoma with prior anti-PD-1/PD-L1 therapy and experienced Grade 3 and higher irAE (Part 2 and Part 3)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; irAE = immune-related adverse event; MSI-H/dMMR = high microsatellite instability /mismatch repair deficient.

Endpoints

Part 2

Primary Endpoints
- Safety and tolerability-The incidence rate and characteristics of DLTs; The incidence and severity of adverse events (AEs) and SAEs

Secondary Endpoints
- PK parameters
- Anti-tumor activity-Objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), duration of response (DOR) and overall survival (OS)
- Immunogenicity (Anti-CS1002 antibody and anti-CS1003 antibody)

Part 3

Primary Endpoints
- Anti-tumor activity-ORR

Secondary Endpoints
- Safety, tolerability and efficacy-The incidence and severity of AEs and SAEs; DCR, PFS, DOR and 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 (± 7 days) in the first year and approximately every 12 weeks (± 7 days) thereafter.
- AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) V4.03

References

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Results

Part 2

Demographics

Table 2. Demographics and Baseline Characteristics in Part 2 (Safety Analysis Set)

	CS1002 0.3 mg/kg Q3W + CS1003 (N=3)	CS1002 1 mg/kg Q3W + CS1003 (N=3)	CS1002 3 mg/kg Q3W + CS1003 (N=9)	CS1002 3 mg/kg Q9W + CS1003 (N=3)	ALL (N=18)
Mean age, years (Min, Max)	68.0 (62, 72)	69.7 (61, 84)	60.1 (50, 74)	67.3 (46, 82)	64.2 (46, 84)
Age group (years), n (%)					
< 65 Years	1 (33.3%)	2 (66.7%)	6 (66.7%)	1 (33.3%)	10 (55.6%)
≥ 65 Years	2 (66.7%)	1 (33.3%)	3 (33.3%)	2 (66.7%)	8 (44.4%)
Sex, n (%)					
Male	2 (66.7%)	2 (66.7%)	5 (55.6%)	1 (33.3%)	10 (55.6%)
Female	1 (33.3%)	1 (33.3%)	4 (44.4%)	2 (66.7%)	8 (44.4%)
Race					
White	3 (100.0%)	2 (66.7%)	7 (77.8%)	3 (100.0%)	15 (83.3%)
Asian	0	1 (33.3%)	2 (22.2%)	0	3 (16.7%)
ECOG PS, n (%)					
0	3 (100.0%)	3 (100.0%)	7 (77.8%)	1 (33.3%)	14 (77.8%)
1	0	0	2 (22.2%)	2 (66.7%)	4 (22.2%)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status
Safety analysis set (SAS): Patients who received at least one dose of investigational product.

- The majority of patients (14/18, 77.8%) had ECOG score of 0. Ten patients (55.6%) were male and 15 patients (83.3%) were white (**Table 2**).

Safety

Table 3. Summary of Treatment Emergent Adverse Events of CS1002 and CS1003 in Part 2 (Safety Analysis Set)

	CS1002 0.3 mg/kg Q3W + CS1003 (N=3)	CS1002 1 mg/kg Q3W + CS1003 (N=3)	CS1002 3 mg/kg Q3W + CS1003 (N=9)	CS1002 3 mg/kg Q9W + CS1003 (N=3)	ALL (N=18)
Number of patients with at least one TEAE	**3 (100.0%)**	**3 (100.0%)**	**9 (100.0%)**	**3 (100.0%)**	**18 (100.0%)**
TEAE related to CS1002/CS1003	3 (100.0%)	3 (100.0%)	7 (77.8%)	1 (33.3%)	14 (77.8%)
Grade ≥3 TEAE	1 (33.3%)	1 (33.3%)	7 (77.8%)	3 (100.0%)	12 (66.7%)
Grade ≥3 TEAE related to CS1002/CS1003	1 (33.3%)	1 (33.3%)	6 (66.7%)	0	8 (44.4%)
SAE	1 (33.3%)	0	7 (77.8%)	2 (66.7%)	10 (55.6%)
SAE related to CS1002/CS1003	0	0	6 (66.7%)	0	6 (33.3%)
Immune-related AE	2 (66.7%)	2 (66.7%)	6 (66.7%)	0	10 (55.6%)
Infusion-related Reaction	1 (33.3%)	0	0	0	1 (5.6%)
TEAE Leading to CS1002/CS1003 permanently discontinuation	0	0	4 (44.4%)*	0	4 (22.2%)
TEAE Leading to death	0	0	1 (11.1%)	0	1 (5.6%)

Abbreviations: TEAE = treatment emergent adverse event.
*Four patients experienced serious TRAEs leading to discontinuation of CS1002 and CS1003 in cohort 6, therefore, cohort 7 (CS1002 3mg/kg Q9W + CS1003 200mg Q3W) was opened to determine the safety and tolerability of the combination using a less frequency dosing schedule of CS1002.

- No DLT was observed and MTD was not reached.
- Eighteen (100%) patients experienced at least one AE, of whom 14 (77.8%) patients had treatment-related AEs (TRAEs) (**Table 3**). Serious TRAEs were reported in 6 (33.3%) patients and immune-related AEs (irAEs) occurred in 10 (55.6%) patients. CTCAE Grade ≥3 CS1002 and CS1003-related AEs occurred in 8 (44.4%) patients. Four (22.2%) patients experienced serious TRAEs leading to discontinuation of both CS1002 and CS1003 in cohort 6 (CS1002 3 mg/kg Q3W + CS1003 200 mg fixed dose, Q3W). One case (5.6%) of AE leading to death was observed in cohort 6, not related to CS1002/CS1003.

Part 3

Demographics

Table 4. Demographics and Baseline Characteristics in Part 3 (Intent-to-Treat Set)

	MSI-H/dMMR tumors[a] or Melanoma		
	CS1002 0.3 mg/kg Q6W + CS1003 (N=16)	CS1002 1 mg/kg Q3W + CS1003 (N=17)	ALL (N=33)
Mean age, years (range)	**64.3 (44, 87)**	**66.9 (39, 89)**	**65.6 (39, 89)**
Age group (years)			
< 65 Years	8 (50.0%)	6 (35.3%)	14 (42.4%)
≥ 65 Years	8 (50.0%)	11 (64.7%)	19 (57.6%)
Sex			
Male	6 (37.5%)	11 (64.7%)	17 (51.5%)
Female	10 (62.5%)	6 (35.3%)	16 (48.5%)
Race			
White	15 (93.8%)	15 (88.2%)	30 (90.9%)
Asian	1 (6.3%)	2 (11.8%)	3 (9.1%)
ECOG PS, n (%)			
0	9 (56.3%)	9 (52.9%)	18 (54.5%)
1	7 (43.8%)	8 (47.1%)	15 (45.5%)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status
Intent-to-treat (ITT) set (Part 3 only): all randomized patients in Part 3.
[a]MSI-H/dMMR tumors included colorectal cancer (n=8), endometrial cancer (n=3) and others (n=10).

- Eighteen (18/33, 54.5%) patients had ECOG score of 0. Seventeen (17/33, 51.5%) patients are male. The majority of patients (n=30, 90.9%) were white (**Table 4**).

Safety

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

	MSI-H/dMMR tumors or Melanoma		
	CS1002 0.3 mg/kg Q6W + CS1003 (N=16)	CS1002 1 mg/kg Q3W + CS1003 (N=17)	ALL (N=33)
Number of patients with at least one TEAE	**13 (81.3%)**	**16 (94.1%)**	**29 (87.9%)**
TEAE related to CS1002/CS1003	10 (62.5%)	11 (64.7%)	21 (63.6%)
Grade ≥3 TEAE	3 (18.8%)	6 (35.3%)	9 (27.3%)
Grade ≥3 TEAE related to CS1002/CS1003	2 (12.5%)	3 (17.6%)	5 (15.2%)
SAE	4 (25.0%)	7 (41.2%)	11 (33.3%)
SAE related to CS1002/CS1003	3 (18.8%)	3 (17.6%)	6 (18.2%)
Immune-related AE	4 (25.0%)	7 (41.2%)	11 (33.3%)
Infusion-related Reaction	1 (6.3%)	2 (11.8%)	3 (9.1%)
TEAE Leading to CS1002/CS1003 permanently discontinuation	1 (6.3%)	1 (5.9%)	2 (6.1%)
TEAE Leading to death	0	0	0

Abbreviations: TEAE: treatment-emergent adverse event.

- In total, 29 (87.9%) patients experienced at least one AE, of whom 21 (63.6%) patients had TRAEs (**Table 5**). CTCAE Grade ≥3 AEs related to CS1002 and CS1003 occurred in 5 (15.2%) pts (2 pts in Arm A and 3 patients in Arm B). Serious TRAEs were reported in 6 (18.2%) patients and irAEs occurred in 11 (33.3%) patients. Two (6.1%) patients experienced serious TRAEs leading to discontinuation of both CS1002 and CS1003, including one polyarthritis in Arm A and one Stevens-Johnson syndrome in Arm B. No death due to AEs was reported.

Table 6. Treatment-Related TEAEs in Part 3 (occurred in ≥ 5% patients) (Safety Analysis Set)

	MSI-H/dMMR tumors or Melanoma		
MedDRA Preferred Term	Arm A: CS1002 0.3 mg/kg Q6W + CS1003 (N=16)	Arm B: CS1002 1 mg/kg Q3W + CS1003 (N=17)	ALL (N=33)
Number of patients with at least one event related to CS1002/CS1003	**10 (62.5%)**	**11 (64.7%)**	**21 (63.6%)**
Diarrhoea	4 (25%)	3 (17.6%)	7 (21.2%)
Fatigue	2 (12.5%)	5 (29.4%)	7 (21.2%)
Rash	1 (6.3%)	4 (23.5%)	5 (15.2%)
Hyperthyroidism	1 (6.3%)	2 (11.8%)	3 (9.1%)
Arthralgia	2 (12.5%)	0	2 (6.1%)
Back pain	1 (6.3%)	1 (5.9%)	2 (6.1%)
Chills	1 (6.3%)	1 (5.9%)	2 (6.1%)
Nausea	2 (12.5%)	0	2 (6.1%)
Pruritus	1 (6.3%)	1 (5.9%)	2 (6.1%)
Rash maculo-papular	1 (6.3%)	1 (5.9%)	2 (6.1%)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

- The most common CS1002-related or CS1003-related AEs (≥15%) were diarrhoea and fatigue (7 patients each, 21.2%), rash (5 patients, 15.2%) (**Table 6**).

Table 7. All reported SAEs in Part 3 (Safety Analysis Set)

	MSI-H/dMMR tumors or Melanoma		
MedDRA Preferred Term	Arm A: CS1002 0.3 mg/kg Q6W + CS1003 (N=16)	Arm B: CS1002 1 mg/kg Q3W + CS1003 (N=17)	ALL (N=33)
Number of patients with at least one event	**4 (25%)**	**7 (41.2%)**	**11 (33.3%)**
Back pain	0	1 (5.9%)	1 (3%)
Diarrhoea	0	1 (5.9%)	1 (3%)
Groin pain	1 (6.3%)	0	1 (3%)
Hyperthyroidism	0	1 (5.9%)	1 (3%)
Pneumonitis	1 (6.3%)	0	1 (3%)
Polyarthritis	1 (6.3%)	0	1 (3%)
Pyrexia	0	1 (5.9%)	1 (3%)
Salmonella bacteraemia	0	1 (5.9%)	1 (3%)
Stevens-Johnson syndrome	0	1 (5.9%)	1 (3%)
Transaminases increased	1 (6.3%)	0	1 (3%)
Urinary tract infection	0	1 (5.9%)	1 (3%)
Vaginal haemorrhage	1 (6.3%)	0	1 (3%)

Abbreviations: SAE = serious adverse event

- Eleven patients (33.3%) experienced at least one SAE, including 4 patients (25%) in Arm A and 7 patients (41.2%) in Arm B (**Table 7**)

Efficacy

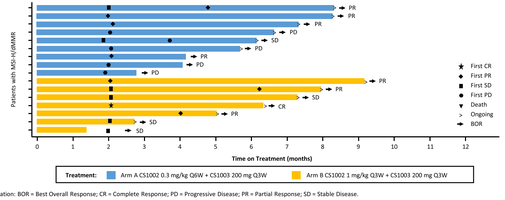
Table 8. Summary of Objective Response in Part 3 (Efficacy Analysis Set)

	Arm A: CS1002 0.3 mg/kg Q6W + CS1003		Arm B: CS1002 1 mg/kg Q3W + CS1003	
n (%) [95% CI (%)]	MSI-H/dMMR tumors (N=9)	Melanoma (N=4)	MSI-H/dMMR tumors (N=7)	Melanoma (N=4)
Objective Response Rate	4 (44.4) [13.7, 78.8]	2 (50.0) [6.8, 93.2]	4 (57.1) [18.4, 90.1]	2 (50.0) [6.8, 93.2]
Confirmed Objective Response Rate	4 (44.4) [13.7, 78.8]	1 (25.0) [0.6, 80.6]	2 (28.6) [3.7, 71.0]	0
Best Overall Response				
Complete Response (CR)	0	0	1 (14.3) [0.4, 57.9]	0
Partial Response (PR)	4 (44.4) [13.7, 78.8]	2 (50.0) [6.8, 93.2]	3 (42.9) [9.9, 81.6]	2 (50.0) [6.8, 93.2]
Stable Disease (SD)	1 (11.1) [0.3, 48.2]	2 (50.0) [6.8, 93.2]	3 (42.9) [9.9, 81.6]	2 (50.0) [6.8, 93.2]
Progressive Disease (PD)	4 (44.4) [13.7, 78.8]	0	0	0
Not evaluable (NE)	0	0	0	0
Not applicable (NA)	0	0	0	0
Disease Control Rate (CR+PR+SD)	5 (55.6) [21.2, 86.3]	4 (100.0) [39.8, 100.0]	7 (100.0) [59.0, 100.0]	4 (100.0) [39.8, 100.0]

Efficacy analysis set (EAS) : Patients with measurable baseline disease who 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.

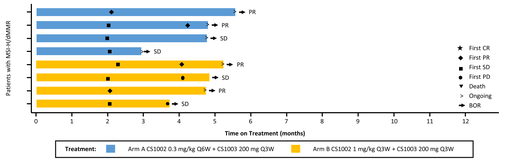
- As of 01 March 2021, of the 9 and 7 evaluable patients with MSI-H/dMMR tumors in Arms A and B, ORR was 44.4% and 57.1%, respectively (**Figure 2**, **Figure 4**, **Table 8**). Four (44.4%) patients in Arm A achieved partial response (PR). In Arm B, 1 (14.3%) patient had complete response, and 3 (42.9%) patients had PR. Among 4 patients with melanoma each in Arms A and B, ORR was both 50% with 2 patients each achieving PR (**Figure 3**, **Figure 5**, **Table 8**).

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



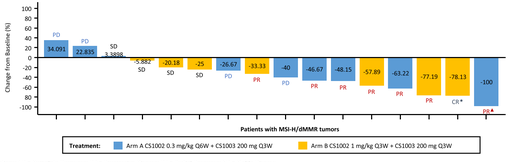
Abbreviation: BOR = Best Overall Response; CR = Complete Response; PD = Progressive Disease; PR = Partial Response; SD = Stable Disease.

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



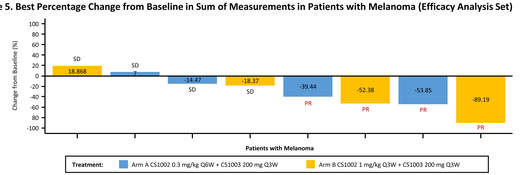
Abbreviation: BOR = Best Overall Response; PR = Partial Response; SD = Stable Disease.

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



Abbreviations: CR = Complete Response; PD = Progressive Disease; PR = Partial Response; SD = Stable Disease.
*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 .
* The only non-target lesion remained non-CR/non-PD, thus the best overall response was evaluated as PR per RECIST v1.1.

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



Abbreviations: PR = Partial Response; SD = Stable Disease.

Conclusion

- The combination of CS1002 and CS1003 demonstrated a well-managed safety profile at two dose regimens of CS1002.
  - In Part 3 of the study, TRAE were reported in 63.6% patients, most frequently reported TRAE were diarrhoea, fatigue and rash; 15.2% patients were reported as ≥ Grade 3 TRAE;
  - Comparing with Arm B, a slightly lower frequency of AEs was observed in Arm A when CS1002 was given as 0.3mg/kg Q3W;
- Promising preliminary anti-tumor activity of CS1002 in combination with CS1003 was observed in 24 evaluable patients with MSI-H/dMMR solid tumors and anti-PD-(L)1 refractory melanoma;
  - The combination regimen demonstrated durable responses in patients with MSI-H/dMMR tumors irrespective of dose regimen of CS1002.
  - Combination of CS1002 and CS1003 also demonstrated encouraging clinical activities in patients with anti-PD-(L)1 refractory melanoma.
- Current data indicates the combination of CS1002 and CS1003 associated with encouraging clinical activities in both immunotherapy naive MSI-H/dMMR solid tumors and PD(L)1 refractory melanoma, supporting further clinical development of CS1002 in combination with CS1003.

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Disclosures

- Dr. S. Bishnoi declares to own stocks of Telix Pharmaceutical Ltd. and Regeneron Pharmaceutical Ltd.
- Dr. R. Cosman declares to be principal investigator in a number of studies at Kinghorn Cancer Center, St Vincent's Hospital, Sydney, Australia.
- Dr. M. Moore declares to be advisory board member of Roche and Merck.
- Dr. R. Eek declares to own investment portfolio in Novartis and Gilead.
- Dr. 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.
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- Dr. P. Li declares to have stocks of CStone Pharmaceuticals as an employee.
- Dr. A. N. Tse declares to be Chief Scientific Officer in CStone pharmaceuticals and own CStone stock.

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