Preliminary pharmacokinetics (PK), safety and efficacy of two dosing regimens of CS1003 (anti-PD-1) in solid tumors: 200 mg every 3-week (Q3W) and 400 mg every 6-week (Q6W)

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B. Markman[1, 12], D. Day[1], J. Park[2], J. Coward[3], S. Bishnoi[4], D. Kotasek[4, 13], R. Eek[5], M.P. Brown[6], C. Lemech[7, 14], J. Kuo[7, 15], A. Prawira[8], R. Strother[9], Q. Zhang[10], L. Wang[11], R. Chen[11], Y. Ma[11], Z. Qin[11], A. Tse[10]

1 Oncology, Monash Medical Centre, Clayton, VIC, Australia; 2 Department of Clinical Medicine, Macquarie University, North Ryde, NSW, Australia; 3 Medical Oncology, Icon Cancer Centre, South Brisbane, QLD, Australia; 4 Medical Oncology, Ashford Cancer Centre Research and University of Adelaide, Adelaide, SA, Australia; 5 Medical Oncology, Border Medical Oncology, East Albury, NSW, Australia; 6 Medical Oncology, Royal Adelaide Hospital, Adelaide, SA, Australia; 7 Scientia Clinical Research Ltd, Randwick, NSW, Australia; 8 Medical Oncology, St. Vincent's Hospital, Darlinghurst, NSW, Australia; 9 Medical Oncology, Christchurch Hospital, Christchurch, New Zealand; 10 Translational Medicine and Early Development, CStone Pharmaceuticals (Su Zhou) Co., Ltd., Suzhou, China; 11 Clinical Department, CStone Pharmaceuticals (Su Zhou) Co., Ltd., Suzhou, China; 12 Alfred Hospital, Melbourne, VIC, Australia; 13 Adelaide Cancer Centre, Tennyson Centre, SA, Australia; 14 Prince of Wales Clinical School, UNSW, Sydney, NSW, Australia; 15 University of New South Wales, Sydney, NSW, Australia

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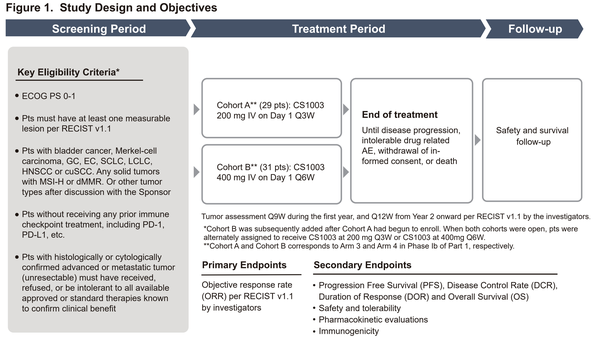
BACKGROUND

- CS1003 is a novel humanized IgG4 anti-PD-1 monoclonal antibody (mAb) developed to disrupt the PD-1 interaction with PD-L1/PD-L2 to restore or improve T-cell function as stand-alone therapy or in combination with other anticancer reagents [1].
- CS1003 demonstrated comparable binding affinities across species against human, cynomolgus monkey, and mouse PD-1, and this allows rapid evaluation of the anti-tumor effect in syngeneic mouse tumor models, including that of proposed combinational therapies [1].
- Alternative dosing regimens of different commercial anti-PD-1 mAbs have been evaluated using modeling and simulation, and have recently been validated in clinical trials [2, 3, 4].
- In Phase Ib part of the first-in-human study of CS1003 (NCT03475251), anti-tumor activities of 2 dosing schedules of CS1003, at 200 mg Q3W and at 400 mg Q6W were evaluated in patients (pts) with selected tumor types. Herein, we present the pharmacokinetic (PK), efficacy and safety data of these different dosing regimens.

METHODS

- Pts were enrolled in cohort A (200 mg Q3W) or cohort B (400 mg Q6W) to receive CS1003 intravenously in Part 1 Phase 1b of this study. Safety, preliminary anti-tumor activity (objective response rate per RECIST v1.1 by investigators), and PK were assessed.

Figure 1. Study Design and Objectives



Tumor assessment Q9W during the first year, and Q12W from Year 2 onward per RECIST v1.1 by the investigators.

*Cohort B was subsequently added after Cohort A had begun to enroll. When both cohorts were open, pts were alternately assigned to receive CS1003 at 200 mg Q3W or CS1003 at 400mg Q6W.
**Cohort A and Cohort B corresponds to Arm 3 and Arm 4 in Phase Ib of Part 1, respectively.

Primary Endpoints	Secondary Endpoints
Objective response rate (ORR) per RECIST v1.1 by investigators	• Progression Free Survival (PFS), Disease Control Rate (DCR), Duration of Response (DOR) and Overall Survival (OS) • Safety and tolerability • Pharmacokinetic evaluations • Immunogenicity

Abbreviations: AE: adverse event; cuSCC: cutaneous squamous cell carcinoma; dMMR: deficient mismatch repair; EC: esophageal carcinoma; ECOG: Eastern Cooperative Oncology Group; GC: gastric cancer; HNSCC: head and neck squamous cell carcinoma; IV: intravenous; LCLC: large-cell lung cancer; MSI-H: microsatellite instability; PS: performance status; QD: once daily; Q3W: once every 3 weeks; Q6W: once every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SCLC: small-cell lung cancer.

Assessments:

- PK parameters including but not limited to C_{max} and C_{trough} were calculated using the non-compartmental analysis model of Phenix WinNonlin® V8.2.
- Tumor response was assessed per RECIST V1.1 by investigators, approximately every 9 weeks (± 5 days) in the first year and approximately every 12 weeks (± 5 days) thereafter.
- AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) V4.03.
- Data cut-off date for evaluation of PK was 22 Jul 2020, and cut-off date for efficacy and safety analyses was 15 Jul 2020.

REFERENCE
1. Li F., et al., American Association for Cancer Research (AACR), 2019
2. Bi Y., et al., Annals of Oncology, 2019
3. Lala M., et al., Eur J Cancer, 2020
4. Lala M., et al., American Association for Cancer Research (AACR), 2020

RESULTS

Patient Demographics

Table 1. Demographics and Baseline Characteristics (Safety Analysis Seta)

Parameter	Cohort A 200mg Q3W (N=29)	Cohort B 400mg Q6W (N=31)
Age (Years), Median (range)	64.0 (36, 84)	68.0 (37, 83)
Sex, n(%)		
Male/Female	18 (62.1%) / 11 (37.9%)	22 (71.0%) / 9 (29.0%)
Race, n(%)		
White	27 (93.1%)	27 (87.1%)
Asian	1 (3.4%)	4 (12.9%)
Other	1 (3.4%)	0
ECOG Performance Status, n(%)		
0	14 (48.3%)	18 (58.1%)
1	15 (51.7%)	13 (41.9%)
Initial Diagnosis, n(%)		
SCLC	7 (24.1%)	5 (16.1%)
cuSCC	5 (17.2%)	4 (12.9%)
EC	1 (3.4%)	5 (16.1%)
GC	0	1 (3.2%)
Other	16 (55.2%)	16 (51.6%)
MSI-H/dMMR status, n(%)		
Yes	5 (17.2%)	5 (16.1%)
No	7 (24.1%)	9 (29.0%)
Unknown	17 (58.6%)	17 (54.8%)
Metastases Diagnosed, n(%)		
Yes	28 (96.6%)	27 (87.1%)
No	1 (3.4%)	4 (12.9%)
No. of prior systemic cancer therapy regimens, Median (Range)	1 (0, 9)	1 (0, 5)
Prior systemic therapy, n(%)		
0 regimen	7 (24.1%)	9 (29.0%)
1 regimen	15 (51.7%)	12 (38.7%)
2 regimens	4 (13.8%)	5 (16.1%)
≥3 regimens	3 (10.3%)	5 (16.1%)
Prior radiotherapy, n(%)		
Yes	19 (65.5%)	18 (58.1%)
No	10 (34.5%)	13 (41.9%)
Prior Cancer-Related Surgery / Procedure, n(%)		
Yes	15 (51.7%)	20 (64.5%)
No	14 (48.3%)	11 (35.5%)

Abbreviations: cuSCC: cutaneous squamous cell carcinoma; dMMR: deficient mismatch repair; EC: esophageal carcinoma; GC: gastric cancer; MSI-H: microsatellite instability; n: number of pts with an observation; N: number of pts in the analysis set; SCLC: small-cell lung cancer.
[a] Safety Analysis Set (SAS): consists of all pts who received at least one dose of study drug. It will be the analysis set for pt disposition, demographic, baseline characteristic and safety.

Pharmacokinetics

- PK exposure parameters (C_{avg}, C_{max} and C_{trough}) at steady state of 400 mg Q6W are comparable to that of 200 mg Q3W.

Figure 2. Mean (±SD) Serum Concentration vs. Time Profiles of CS1003 in Patients Following IV Administration of 200 mg Q3W (A) or 400 mg Q6W (B)

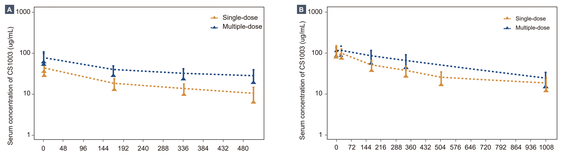
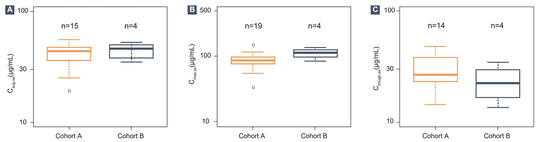


Table 2. Summary of Statistics of Serum PK Parameters After of two dosing regimens (Pharmacokinetic Analysis Set[a]) Single-dose and Multiple-dose

Parameter (unit)	Statistic	Cohort A 200 mg Q3W		Cohort B 400 mg Q6W	
		Single-dose	Multiple-dose	Single-dose	Multiple-dose
$AUC_{0-t_{last}}$ (day*ug/mL)	n	27	15	-	-
	GeoMean (CV %)	391 (28.6)	841 (29.6)	-	-
AUC_{0-tau} (day*ug/mL)	n	-	-	19	4
	GeoMean (CV %)	-	-	1290 (36.5)	1840 (17.9)
C_{max} (ug/mL)	n	-	15	-	4
	GeoMean (CV %)	-	40.0 (29.6)	-	43.7 (17.9)
C_{max} (ug/mL)	n	29	19	23	8
	GeoMean (CV %)	44.4 (22.4)	83.4 (32.6)	105 (43.1)	95.1 (52.2)
C_{trough} (ug/mL)	n	-	14	-	4
	GeoMean (CV %)	-	27.2 (38.2)	-	22.0 (41.1)
T_{max} (h)	n	29	19	23	8
	Median (Min-Max)	2.02 (1.45-2.50)	0.767 (0.583-2.17)	2.03 (1.45-505)	12.0 (0.583-1010)
CL (L/day)	n	24	10	18	4
	GeoMean (CV %)	0.340 (40.4)	0.240 (21.9)	0.237 (48.6)	0.218 (17.9)
$T_{1/2}$ (day)	n	24	-	18	-
	Mean (SD)	15.5 (5.18)	-	19.3 (12.0)	-
Racc (AUC)	n	-	15	-	4
	GeoMean (CV %)	-	2.04 (25.7)	-	1.48 (57.9)

Abbreviations: AUC: area under the plasma concentration-time curve; C_{av}: average plasma concentration; CL: oral clearance; C_{max}: maximun plasma concentration; C_{trough}: trough plasma concentration; $Racc_{(AUC)}$: accumulation index (based on AUC); T_{max}: time to maximal plasma concentration; $t_{1/2}$: terminal elimination half life.
[a] Pharmacokinetic Analysis Set (PKAS): consists of all pts who received at least one dose of study drug and had at least one post-baseline pharmacokinetic assessment.
• The difference in the n (number of observations), if any, across the PK parameters in a given cohort is due to insufficient data to estimate the particular PK parameter.
• The parameter being "-" indicates it is not available or suitable for the cohort or the dosing period.
• $Racc_{(AUC)}$ calculated as AUC_{0-t1} at Cycle 4/ AUC_{0-t1} at Cycle 1 for Cohort A and AUC_{0-tau} at Cycle 7/ AUC_{0-tau} at Cycle 1 for Cohort B.

Figure 3. C_{avg}, C_{max} and C_{trough} comparison between Cohort A and Cohort B at steady state



Efficacy

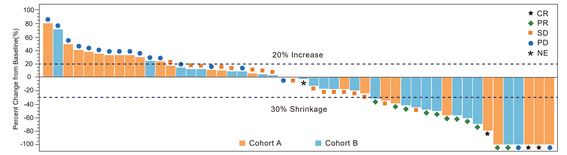
- As of 15 Jul 2020, the median duration of follow up in Cohort A and Cohort B were 11.7 months (mo) (range: 0.9-15.4) and 6.9 mo (range: 0.9-9.7), respectively.
- The median duration of treatment were 15.0 weeks (range: 3.0-67.0) for Cohort A and 27.4 weeks (range: 4.0-44.3) for Cohort B.
- Best ORR (including unconfirmed responses) in Cohort A and Cohort B were 24.1% and 32.3%, respectively
  - Confirmed ORR in Cohort A and Cohort B were 20.7% and 25.8%, respectively.
- The median duration of response (DoR) in both Cohort A and Cohort B had not been reached.
- The median PFS were 2.2 mo (95% Confidence Interval [CI]: 2.0-8.2) in Cohort A and 6.3 mo (95% CI: 2.1-not estimable) in Cohort B respectively.
- The median OS in both Cohort A and Cohort B had not been reached as of the analysis date.

Table 3. Summary of Objective Response of Cohort A and Cohort B (Efficacy Analysis Set[a])

Parameter, n(%)	Cohort A 200mg Q3W (N=29)	Cohort B 400mg Q6W (N=31)
ORR	7 (24.1%)[c]	10 (32.3%)[c]
Best Overall Response		
CR	3 (10.3%)	0
PR	4 (13.8%)	10 (32.3%)
SD	5 (17.2%)	9 (29.0%)
PD	12 (41.4%)	8 (25.8%)
Not Evaluable	0	1 (3.2%)
Not Applicable[d]	5 (17.2%)	3 (9.7%)
Confirmed ORR	6 (20.7%)	8 (25.8%)
DCR (CR+PR+SD)	12 (41.4%)	19 (61.3%)

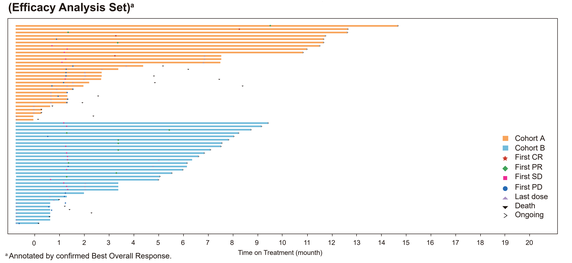
Abbreviations: 95% CI: 95% Confidence Interval; CR: complete response; n: number of pts with an observation; N: number of pts of each cohort in the efficacy analysis set; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease.
[a] Efficacy Analysis Set (EAS): consists of all pts with measurable baseline disease who received at least one dose of study drug. However, pts, 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. It will be the primary analysis set for efficacy in this study.
[b] As of 15 Jul 2020, unconfirmed ORR in Cohort A was 24.1% (7/29), with 3 confirmed CRs, 3 confirmed PRs, and 1 additional unconfirmed PR.
[c] AS of 15 Jul 2020, unconfirmed ORR in Cohort B was 32.3% (10/31), with 8 confirmed PRs and 2 additional unconfirmed PRs.
[d] Not applicable: Pts were classified as not applicable if no post-baseline response assessments were available.

Figure 4. Percentage Change from Baseline in Sum of Diameters of Cohort A[a] and Cohort B[b] (Efficacy Analysis Set)[c]



[a] 5 pts in Cohort A did not have any post-baseline target lesion assessment.
[b] 5 pts in Cohort B did not have any post-baseline target lesion assessment, with 1 pt being observed to have new lesions.
[c] Annotated by confirmed Best Overall Response.

Figure 5. Duration of Treatment and Tumor Assessment by RECIST V1.1 of Cohort A and Cohort B (Efficacy Analysis Set)[a]



[a] Annotated by confirmed Best Overall Response.

Safety

- As of 15 Jul 2020, a total of 60 pts were enrolled and received at least one dose of CS1003 in either Cohort A (29 pts) or Cohort B (31 pts) for safety analysis.
- 96.6% and 96.8% pts from Cohort A and B, respectively, reported at least one treatment-emergent AE (TEAE).
- Most treatment-related TEAEs were of Grade (G) 1-2 (Cohort A: 44.8% vs. Cohort B: 45.2%); G3-5 treatment-related TEAEs in Cohort A and Cohort B were 0 and 9.7%, respectively.
- The incidence of immune-related AEs were comparable between Cohort A (34.5%) and Cohort B (32.3%).

Table 4. Summary of Adverse Events (Safety Analysis Set)

AE, n(%)	Cohort A 200mg Q3W (N=29)	Cohort B 400mg Q6W (N=31)
Number of patients with ≥ 1 event	28 (96.6%)	30 (96.8%)
Treatment-related TEAE	13 (44.8%)	17 (54.8%)
Serious TEAE	14 (48.3%)	10 (32.3%)
Treatment-related serious TEAE	1 (3.4%)	3 (9.7%)
Grade 3-5 TEAE	13 (44.8%)	13 (41.9%)
Treatment-related Grade 3-5 TEAE	0	3 (9.7%)[a]
Immune-related TEAE	10 (34.5%)	10 (32.3%)
Infusion-related Reaction	2 (6.9%)	3 (9.7%)
TEAE Leading to Infusion Interruption	0	2 (6.5%)
TEAE Leading to Drug Permanently Discontinued	1 (3.4%)	2 (6.5%)
TEAE Leading to Treatment Cycle Delay	6 (20.7%)	5 (16.1%)
TEAE Leading to Death	0	1 (3.2%)[b]

Abbreviations: n: number of pts with an observation; N: number of pts of each cohort in the safety analysis set.
[a] 3 pts each experienced a Grade 4 treatment-related Type 1 diabetes mellitus, a Grade 3 treatment-related hepatitis and a Grade 3 treatment-related dermatitis, respectively.
[b] One patient had a grade 5 cardiac failure, which was assessed to be unrelated to study treatment by investigator.

Table 5.Treatment-Related TEAE occurred in ≥ 5% patients (Safety Analysis Set)

Preferred Term, n(%)	Cohort A 200mg Q3W (N=29) All Grades	Cohort B 400mg Q6W (N=31) All Grades
Number of patients with ≥ 1 event	13 (44.8%)[a]	17 (54.8%)[a]
Abdominal pain	2 (6.9%)	0
Alanine aminotransferase increased	2 (6.9%)	0
Arthralgia	1 (3.4%)	4 (12.9%)
Aspartate aminotransferase increased	2 (6.9%)	0
Diarrhoea	2 (6.9%)	1 (3.2%)
Dry mouth	0	2 (6.5%)
Fatigue	4 (13.8%)	3 (9.7%)
Hypothyroidism	1 (3.4%)	3 (9.7%)
Pruritus	2 (6.9%)	5 (16.1%)
Rash	2 (6.9%)	2 (6.5%)

[a] All treatment-related TEAEs in Cohort A were of Grades 1 to 2.
[b] Most treatment-related TEAEs in Cohort B were of Grades 1 to 2; 3 pts from Cohort B each experienced a Grade 4 treatment-related Type 1 diabetes mellitus, a Grade 3 treatment related hepatitis and a Grade 3 treatment related dermatitis, respectively.

CONCLUSIONS

- Similar to CS1003 200 mg Q3W, CS1003 400 mg Q6W is also a safe and effective dosing regimen in treating patients with solid tumors.
  - PK exposure parameters (C_{avg}, C_{max} and C_{trough}) at steady state of 400 mg Q6W are comparable to that of 200 mg Q3W.
  - Preliminary efficacy is generally similar between the two groups.
  - The safety profile of 400 mg Q6W regimen is generally comparable to that of 200 mg Q3W, though G3-4 treatment related TEAEs is higher in cohort B (9.7%).
- In addition to 200 mg Q3W dosing regimen, CS1003 dosing regimen at 400 mg Q6W offers a convenient and flexible dosing option, for patients and physicians.
- First-in-human data also support further explorations of CS1003 alone or in combination in solid tumors (including NCT03809767, NCT03523819, NCT04194775).

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DISCLOSURE
- Dr. B. Markman declares to be an advisory board member of Amgen and Novatis.
- Q. Zhang, L. Wang, R. Chen, Y. Ma, Z. Qin, and A. Tse are employees of CStone Pharmaceuticals.

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Contact corresponding author: TMED@cstonepharma.com

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