CS1001, an anti-PD-L1 antibody, combined with capecitabine and oxaliplatin (XELOX) as a first-line therapy in patients with advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJ): Updated efficacy, biomarker, and safety results

Abstract 7780

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BACKGROUND

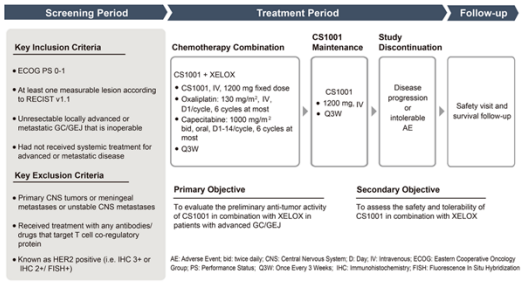
- Gastric cancer (GC) is the 2nd most common cancer in China that led to about 679,100 new cases and 498,000 deaths in 2015 [1]. Most GC patients (pts) are found to be at late stage when first diagnosed. The standard therapy for HER-2 negative advanced GC remains cytotoxic chemotherapy in the first-line setting and the median overall survival of such pts is only 10-11 months. Therefore, there is a great need for more effective treatments for advanced GC [2-6]
- CS1001 is a high-affinity, full-length, fully human anti-programmed death ligand-1 (PD-L1) immunoglobin G4 (IgG4, s228p) monoclonal antibody developed by OmniRat® transgenic platform which mirrors natural IgG4 human antibody and may potentially reduce the risk of immunogenicity and toxicity in pts
- In phase 1a of the first-in-human study (NCT03312842), CS1001 at 1200 mg fixed dose every 3 weeks (Q3W) was determined as the recommended phase 2 dose (RP2D) [6]
- Phase 1b is the dose-expansion part of the study to explore the efficacy and safety of CS1001 in multiple cohorts of selected tumor types [6]. Herein, we present the updated efficacy, biomarker, and safety data from the cohort of CS1001 in combination with chemotherapy as the first-line treatment in gastric or gastro-esophageal junction carcinoma (GC/GEJ)

METHODS

Key Eligibility:

- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
- Patients with histologically confirmed unresectable locally advanced or metastatic GC/GEJ adenocarcinoma
- Patients who had not received systemic treatment (HER2 inhibitors included) for advanced or metastatic disease

Figure 1 - Study Design and Objectives



AE: Adverse Event; bid: twice daily; CNS: Central Nervous System; D: Day; IV: Intravenous; ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; Q3W: Once Every 3 Weeks; IHC: Immunohistochemistry; FISH: Fluorescence In Situ Hybridization

Assessments:

- Tumor assessments were conducted per RECIST v1.1 by investigators every 9 weeks (Q9W) in the first year, then every 12 weeks (Q12W)
- Exploratory efficacy analyses were performed in subgroups with different PD-L1 expression evaluated by immunohistochemistry (Ventana SP263 antibody) with combined positive score (CPS)
- Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for AE (NCI-CTCAE) v4.03

Reference

1. Chen, W., et al., CA Cancer J Clin, 2016. 66(2):115-32
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3. Hui-yan Luo, et al., Chemotherapy, 2020. 56:94-100
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5. Shen, L., et al., #1165P, Presented at European Society for Medical Oncology (ESMO), 19-23 Oct, 2018, Munich, Germany
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RESULTS

Patient Disposition, Demographics, and Baseline Characteristics (Safety Analysis Set):

- As of 19 Feb 2020, 29 pts were enrolled in GC/GEJ cohort; 7 pts remained on treatment and 22 discontinued
  - Reasons of CS1001 discontinuation included progressive disease (n = 13), adverse event (n = 4), patient's withdrawal (n = 3), death (n = 1), and treatment suspension > 6 weeks (n =1)

Table 1 - Demographics and Baseline Characteristics (Safety Analysis Set)

Characteristics		GC/GEJ
		N = 29
Age (years)	Median (range)	60 (40, 73)
Sex, n (%)	Male	23 (79.3)
	Female	6 (20.7)
ECOG PS, n (%)	0	12 (41.4)
	1	17 (58.6)
Initial diagnosis	n (%)	GC: 26 (89.7) GEJ: 3 (10.3)
Time since initial diagnosis (month)	Median (range)	0.9 (0.12, 79.2)
Prior anti-cancer therapy regimen	Median (range)	0 (0, 2)*
Current cancer stage, n (%)	Stage III	1 (3.4)
	Stage IV	28 (96.6)

ECOG – Eastern Cooperative Oncology Group; PS – Performance Status
* A total of 10 patients received neoadjuvant and/or adjuvant therapy, among which 1 patient received both neoadjuvant and adjuvant therapies around curative surgery

Efficacy:

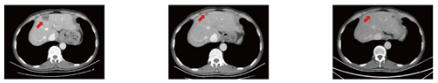
- As of 19 Feb 2020, all 29 pts from GC/GEJ cohort were included in the efficacy analysis set
- Eighteen (62.1%) pts achieved partial response (PR), including 17 confirmed PRs and 1 unconfirmed PR; 6 (20.7%) pts had stable disease (SD); 3 (10.3%) pts experienced progressive disease (PD); 2 (6.9%) pts discontinued without having any post-baseline tumor assessment (i.e. NA)

Table 2 – Summary of Objective Response, PFS, OS (Efficacy Analysis Set)

	GC/GEJ (N = 29)
ORR, n (%)	18 (62.1)
Best overall response, n (%)	
PR	18 (62.1)
SD	6 (20.7)
PD	3 (10.3)
NA	2 (6.9)
DCR, n (%)	24 (82.8)
Median DoR (month, range)	11.3 (1.0+, 14.1+)
6-month DoR rate (%, 95% CI)	76.6 (48.8, 90.4)
Median PFS (month, range)	8.3 (1.4, 16.1+)
Median OS (month, range)	17.0 (1.4, 18.7+)

NA – Not Applicable; ORR – Objective Response Rate; DCR – Disease Control Rate; DoR – Duration of Response; PFS – Progression-Free Survival; OS – Overall Survival
"+" stands for the values of censored patients

Figure 2 – Representative CT Scan Images of a Responder



Male, 58 years old, stage IV gastric cancer with liver metastasis; has completed 20 cycles of CS1001 treatment and 6 cycles of XELOX; remained on treatment as of 19 Feb 2020

Figure 3 – Waterfall Plot of Maximum Target-Lesion Shrinkage by RECIST v1.1 (Efficacy Analysis Set)

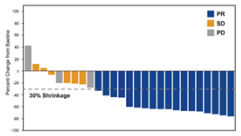
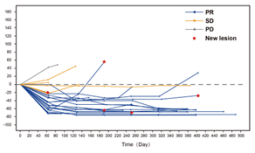
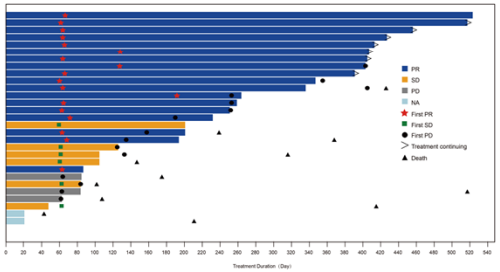


Figure 4 - Spider Plot of Percentage Change from Baseline in the Sum of Diameters (Efficacy Analysis Set)



Note: 2 patients were not shown due to lack of post-baseline tumor assessment

Figure 5 – Swimmer Plot of Treatment Duration and Tumor Assessment by RECIST v1.1 (Efficacy Analysis Set)



Biomarker Subgroup Analysis – PD-L1 Expression:

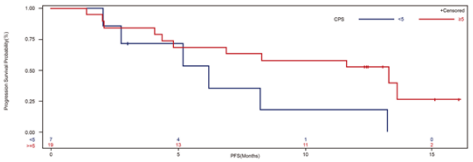
- As of 19 Feb 2020, 26 pts from efficacy analysis set were evaluable for PD-L1 expression
- ORRs were 58% and 71% in CPS ≥ 5 (n = 19) and CPS < 5 (n = 7), with median DoR being unreached and 5.0 months, respectively
- Median PFS was 13.3 months in CPS ≥ 5 (n = 19) and 6.2 months in CPS < 5 (n = 7)

Table 3 – Summary of ORR, DoR & PFS (CPS ≥ 5 vs CPS < 5)

	EAS (N = 29)	CPS ≥ 5 (n = 19)	CPS < 5 (n = 7)
ORR, n (%)	18 (62.1)	11 (57.9)	5 (71.4)
Best overall response, n (%)			
PR	18 (62.1)	11 (57.9)	5 (71.4)
SD	6 (20.7)	4 (21.1)	1 (14.3)
PD	3 (10.3)	2 (10.5)	1 (14.3)
NA	2 (6.9)	2 (10.5)	0
Median DoR (month)	11.3	NR	5.0
Median PFS (month)	8.3	13.3	6.2

EAS - Efficacy Analysis Set; NA – Not Applicable; NR – Not Reached; ORR – Objective Response Rate; DoR – Duration of Response; PFS – Progression-Free Survival; CPS – Combined Positive Score

Figure 6 – Kaplan-Meier Curve of PFS (CPS ≥ 5 vs CPS < 5)



Exposure and Safety (Safety Analysis Set):

- As of 19 Feb 2020, the median duration of CS1001 treatment was 232 (range: 21-523) days in GC/GEJ cohort
- All-grade and Grade ≥ 3 AEs related to CS1001 occurred in 28 (96.6%) pts and 14 (48.3%) pts, respectively
  - The most common (n ≥ 2) Grade ≥ 3 CS1001-related AEs included platelet count decreased (n = 6), white blood cell count decreased (n = 3), neutrophil count decreased (n = 3), anaemia (n = 3), and fatigue (n = 2)
  - Three pts each had one CS1001-related AE leading to CS1001 discontinuation: Grade 3 hypothyroidism, Grade 3 abnormal liver function, and Grade 2 pneumonia
- Immune-related AEs occurred in 21 (72.4%) pts
- No AEs leading to death or new safety signals were observed

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

	GC/GEJ (N = 29)
Number of patients with at least one below event	n (%)
TEAE	29 (100)
Grade 3/4 TEAE	20 (69.0)
TEAE related to CS1001	28 (96.6)
Grade 3/4 TEAE related CS1001	14 (48.3)
SAE	12 (41.4)
SAE related to CS1001	6 (20.7)
irAE	21 (72.4)
Grade 3/4 irAE	6 (20.7)
TEAE leading to CS1001 discontinuation	4 (13.8)
TEAE leading to discontinuation of CS1001 or chemotherapy	8 (27.6)
TEAE leading to CS1001 dose interruption	1 (3.4)
TEAE leading to treatment cycle delay	16 (55.2)
TEAE leading to death	0
Infusion-related reaction	2 (6.9)

TEAE – Treatment Emergent Adverse Event; SAE – Serious Adverse Event; irAE - Immune-related TEAE

CONCLUSIONS

- CS1001 in combination with XELOX demonstrated robust and durable anti-tumor activities with a tolerable safety profile in first-line treatment setting among patients with advanced GC/GEJ
  - ORR 62%, mDoR 11.3 months, mPFS 8.3 months, mOS 17.0 months
- Preliminary biomarker analyses suggested that tumor PD-L1 expression level may be associated with the treatment effect of CS1001 plus XELOX
- Current data support further development of CS1001 plus XELOX in advanced GC/GEJ. A double-blinded, randomized phase 3 study is ongoing in China
  - GEMSTONE-303 (CS1001-303, NCT03802591) investigating CS1001 in combination with XELOX in patients with advanced GC/GEJ

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