Preliminary Results of a Phase 2 Clinical Study Evaluating the Anti-Tumor Activity and Safety of CS1001 Monotherapy in Patients with Relapsed or Refractory Extranodal Natural Killer/T Cell Lymphoma (rr-ENKTL)

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INTRODUCTION

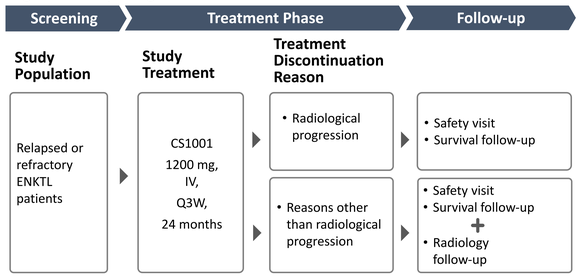
- Extranodal natural killer/T cell lymphoma (ENKTL) is a rare disease which shows a geographic predilection for Asian and South American populations, it consists of 3-10% of non-Hodgkin lymphoma, whereas less than 1% in Western countries[1]
- Current standard of care is asparaginase-based regimen. Patients failing asparaginase-based regimen have no known salvage therapy and are almost invariably fatal, with median overall survival of only several months[2]
- For ENKTL patient, complete response (CR) of meaningful magnitude and duration is associated with longer overall survival (OS)[3,4]. Current approved targeted therapy has a CR rate of less than 10%[5,6]
- Epstein-Barr virus (EBV) infection is one of the mechanisms and characteristics of ENKTL, which induces immune tolerance of tumor by upgrading PD-L1 expression in tumor cells. Blocking the PD-1/PD-L1 pathway could, therefore, be an effective treatment for ENKTL
- CS1001 is the first full-length, fully human programmed death ligand-1 (PD-L1) targeted immunoglobin G4 (IgG4, s228p) monoclonal antibody (mAb)
- Here, we report the safety and efficacy data from the ongoing Phase 2 trial of patients with relapsed or refractory ENKTL (rr-ENKTL)

STUDY DESIGN

Primary Objective:
- To evaluate the efficacy of CS1001 monotherapy in rr-ENKTL as measured by objective response rate (ORR) evaluated by independent radiological review committee (IRRC)

Secondary Objectives:
- To evaluate the efficacy of CS1001 monotherapy in rr-ENKTL as measured by investigator evaluated ORR; OS, progression-free survival (PFS), etc
- To evaluate the safety of CS1001 monotherapy in rr-ENKTL
- To evaluate PK of CS1001
- To evaluate the immunogenicity of CS1001

Figure 1. Study Design



ENKTL: extranodal natural killer/ T cell lymphoma; IV: intravenous; Q3W: once every 3 weeks

Tumor Assessments:
- According to Lugano 2014 by IRRC and investigators respectively
  - Enhanced Computed Tomography (CT): at screening and every 12 weeks after first dose of CS1001;
  - Positron Emission Tomography (PET)/CT: at screening and at Weeks 12 and 24; and every 12 weeks thereafter for patients without measurable lesion;
  - Bone marrow aspiration/biopsy: screening and when achieving radiological CR

Table 1. Key Eligibility

Key Inclusion Criteria	Key Exclusion Criteria
• Age 18-75 • Histologically confirmed ENKTL at study site • Relapsed or refractory ENKTL after prior asparaginase-based chemotherapy or chemo radiotherapy • ECOG PS of 0 or 1 • At least one evaluable or measurable lesion per Lugano 2014 classification • Adequate organ function and bone marrow function	• Invasive natural killer leukemia • Concomitant with hemophagocytic syndrome • Immunosuppressive therapy within 14 days prior to the first dose of CS1001 • Prior chemotherapy, immune therapy, biological therapy as systemic treatment for cancer, within 28 days prior to the first dose of CS1001 • Prior therapy with anti-PD-1, anti-PD-L1 or anti-CTLA-4 monoclonal antibody

CTLA-4: cytotoxic T lymphocyte-associated antigen-4; ECOG PS: Eastern Cooperative Oncology Group performance status; ENKTL: extranodal natural killer/ T cell lymphoma; PD-1: programmed death-1; PD-L1: programmed death ligand-1

RESULTS

Patient Characteristics

- As of October 08, 2019, 32 patients were enrolled and treated with CS1001
- 13 (40.6%) patients' treatment is ongoing, with 19 (59.4%) patients discontinued from CS1001 treatment
- Most treatment discontinuation (12 patients, 37.5%) was due to radiographic disease progression, 4 (12.5%) were due to AE, 3 (9.4%) were due to symptomatic deterioration without radiographic evidence

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

Patient Characteristics		Total N=32
Age (years), Median (range)		47.0 (30, 74)
Sex, n (%)	Male	19 (59.4)
	Female	13 (40.6)
ECOG PS, n (%)	0	9 (28.1)
	1	23 (71.9)
Prior systemic therapy, n (%)	1 line	16 (50.0)
	2 lines	9 (28.1)
	≥3 lines	7 (21.9)
Stage of rr-ENKTL at screening, n (%)	Stage I	2 (6.3)
	Stage II	4 (12.5)
	Stage IV	24 (75.0)
	Missing	2 (6.3)
Plasma EBV DNA at screening, n (%)	Negative	14 (43.8)
	Positive	17 (53.1)
	Missing	1 (3.1)

DNA: deoxyribonucleic acid; EBV: Epstein-Barr virus; ECOG PS: Eastern Cooperative Oncology Group performance status; rr-ENKTL: relapsed or refractory extranodal natural killer/ T cell lymphoma

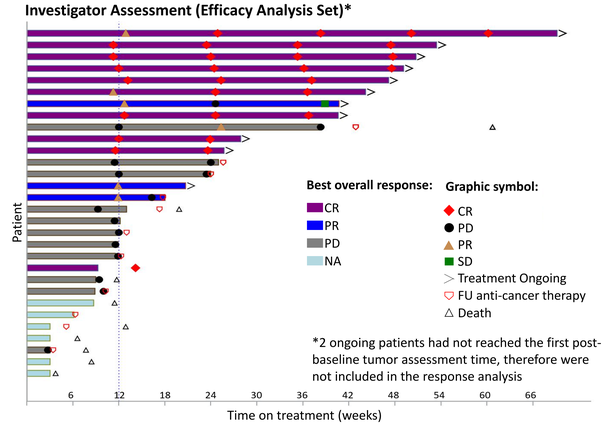
Efficacy Results

Table 3. Summary of Investigator–Assessed Objective Response and Overall Survival (Efficacy Analysis Set)

Best Overall Response	N=30*
Complete Response (CR), n (%)	10 (33.3)
(95% CI)	(17.3%, 52.8%)
Partial Response (PR), n (%)	3 (10.0)
Stable Disease (SD), n (%)	0
Progressive Disease (PD), n (%)	11 (36.7)
NA, n (%)**	6 (20.0)
ORR (CR+PR), n (%)	13 (43.3)
(95% CI)	(25.5%, 62.6%)
Disease Control Rate (DCR=CR+PR+SD), n (%)	13 (43.3)
Duration of Response (DoR, Months), Median (Range)	NR (0.03+ to 10.91+)
1-year OS rate (95% CI)***	72.4% (52.0%, 85.2%)

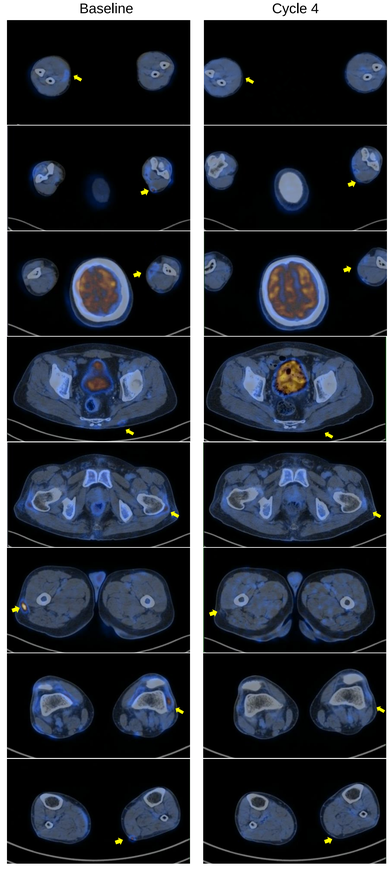
CI: confidence interval; NA: not applicable; ORR: overall response; OS: overall survival; NR: not reached
*2 ongoing patients have not reached first post-baseline tumor assessment time, therefore not included in the response analysis
**6 discontinued patients did not have any tumor assessment post-baseline and were regarded as non-responders (NA in this table)
***Safety analysis set (n=32) was applied to analyze OS rate

Figure 2. Duration of Treatment and Best Overall Response and Progression–Investigator Assessment (Efficacy Analysis Set)*



*2 ongoing patients had not reached the first post-baseline tumor assessment time, therefore were not included in the response analysis

Figure 3. PET/CT Image for a Patient with ENKTL



A 58-year-old Asian male patient was with a Stage IV ENKTL at baseline.

He received 2 lines of prior anti-cancer therapies, which were discontinued due to progression disease.

He achieved CR after 4 cycles of CS1001 treatment. At the time of data cutoff, the patient had a total of 17 cycles of CS1001 treatment and was still in complete response.

Safety Results

- As of October 08, 2019, median duration of CS1001 treatment was 12.6 (range, 3.0-69.1) weeks
- 30 (93.8%) out of 32 patients reported treatment-emergent adverse events (TEAEs). The most common TEAE was pyrexia (40.6%). 3 patients had Grade 5 AEs, which were not related to CS1001
- A total of 24 (75.0%) patients reported CS1001-related AEs (TRAEs), and the most frequently reported TRAE was pyrexia (21.9%) (**Table 5**). 3 (9.4%) patients reported Grade 3/4 TRAEs
- 7 (21.9%) patients reported serious TEAEs (SAEs), 2 SAEs (Grade 4 sinus node dysfunction and Grade 1 myositis) were considered as CS1001-related, and both have resolved
- 5 (15.6%) patients had immune-related AEs (irAEs), with only one Grade 3 rash reported, the rest were of Grade 1

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

	N=32 n (%)
Number of patients with at least one	
TEAE	30 (93.8)
CS1001-related TEAE	24 (75.0)
Grade 3-5 TEAE	9 (28.1)
CS1001-related Grade 3-5 TEAE	3 (9.4)
SAE	7 (21.9)
CS1001-related SAE	2 (6.3)
TEAE leading to CS1001 discontinuation	4 (12.5)
CS1001-related TEAE leading to CS1001 discontinuation	2 (6.3)
Immune-related TEAE	5 (15.6)
TEAE leading to death	3 (9.4)*
Infusion-related reaction	1 (3.1)

TEAE: treatment-emergent adverse event; SAE: serious adverse event
* Not related to CS1001

Table 5. Treatment-Related Adverse Events (Safety Analysis Set)

MedDRA Preferred Term	All Grade, Incidence Rate ≥ 10% N=32, n (%)
Pyrexia	7 (21.9)
White blood cell count decreased	5 (15.6)
Blood thyroid stimulating hormone increased	4 (12.5)
Rash	4 (12.5)

MedDRA=Medical Dictionary for Regulatory Activities

CONCLUSION

- CS1001 demonstrated encouraging anti-tumor activity in rr-ENKTL, with a CR rate of 33.3% and an ORR of 43.3%, as assessed by the investigators. The response is durable with median duration of response not achieved; 1-year OS rate is 72.4% that is significantly higher than historical reference
- CS1001 was well-tolerated in patients with rr-ENKTL with only 9.4% Grade 3 and above TRAE and no treatment-related death reported
- The promising safety and efficacy data presented suggest that CS1001 could be an effective treatment for rr-ENKTL patients

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DISCLOSURES
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  There are no relevant conflicts of interest to disclose
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  They are employees of CStone Pharmaceuticals

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