A Phase Ia/Ib Trial of The Anti-PD-L1 Human Monoclonal Antibody, CS1001, in Patients with Advanced Solid Tumors or Lymphomas

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BACKGROUND

- CS1001 is the first full-length, fully human programmed death ligand-1 (PD-L1) targeted immunoglobin G4 (IgG4, s228p) monoclonal antibody (mAb) developed by the OMT transgenic rat platform. Thus CS1001 is a natural IgG4 human antibody and potentially reduces the risk of immunogenicity and toxicity in patients
- CS1001 specifically binds to PD-L1, blocking its ligation with programmed cell death protein 1 (PD-1)
- This first-in-human Phase Ia/Ib study was conducted to evaluate the safety, tolerability, pharmacokinetics (PK) profile, and anti-tumor activities of CS1001 in patients with advanced solid tumors or lymphomas
- Here we present updated safety and efficacy data from the Phase Ia dose-escalation study

METHODS

For the Phase Ia dose-escalation study, adult patients with histologically or cytologically confirmed metastatic or locally advanced solid tumor or lymphoma; who experienced progression since previous anti-cancer therapy, or for whom standard treatment is not available, not tolerated, or refused; Eastern Cooperative Oncology Group (ECOG) performance status of 0-1

Study Design

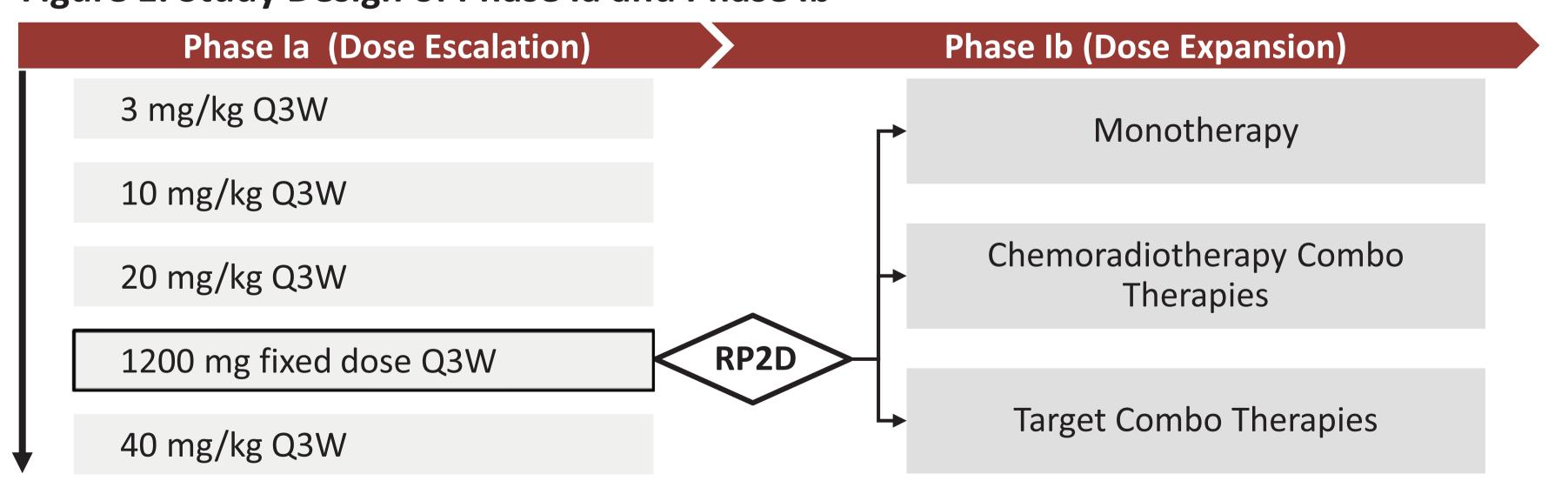
Eligibility

- This study includes 2 stages, dose escalation (Phase Ia) and dose expansion (Phase Ib)
- In Phase Ia, escalating doses of CS1001 were evaluated for safety and tolerability under a modified "3+3" design
- In Phase Ib, 20 to 30 patients with various tumor types were enrolled in each of monotherapy cohorts, chemotherapy combo cohorts or target therapy combo cohorts

Objectives

- Phase Ia: to evaluate safety and tolerability of CS1001 and to determine maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of CS1001; to characterize the PK profile and to evaluate the preliminary anti-tumor activity of CS1001
- Phase Ib: to evaluate the preliminary efficacy of CS1001 in monotherapy or combination with standard therapies

Figure 1. Study Design of Phase Ia and Phase Ib



Treatment and Assessments

- In Phase Ia, patients with advanced solid tumors or lymphomas were enrolled and treated with CS1001, once every three weeks (Q3W), at escalating doses of 3 mg/kg, 10 mg/kg, 20 mg/kg, 1200 mg fixed dose and 40 mg/kg
- Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for AE (NCI-CTCAE) v4.03
- Blood specimens were collected for PK analysis at predefined timepoints. PK parameters were derived from non-compartmental analysis from the serum concentration-time profile of CS1001
- Anti-tumor activity was assessed per RECIST v1.1 Q9W (for solid tumors) and Lugano 2014 Q12W (for lymphomas)

RESULTS

Baseline Characteristics and Patient Disposition

- At the time of data cutoff (Nov 30, 2018), 29 patients with various tumor types were enrolled
- Median age was 53 years (range, 23 to 75) (Table 1)
- 5 (17.2%) patients were diagnosed as Stage IV lymphomas and the rest were as Stage IV solid tumors

| Table 1 Demographics and Baseline Characteristics (Safety Analysis Set) | |
|---|---------------|
| Characteristics | Total (N=29) |
| Age, Years | |
| Median (range) | 53.0 (23, 75) |
| Sex n (%) | |
| Male | 18 (62.1) |
| Female | 11 (37.9) |
| ECOG Performance Status n (%) | |
| 0 | 4 (13.8) |
| 1 | 25 (86.2) |
| Prior Anti-Cancer Therapies | |
| Median (range) | 2 (0-7) |
| ECOG = Eastern Cooperative Oncology Group | |

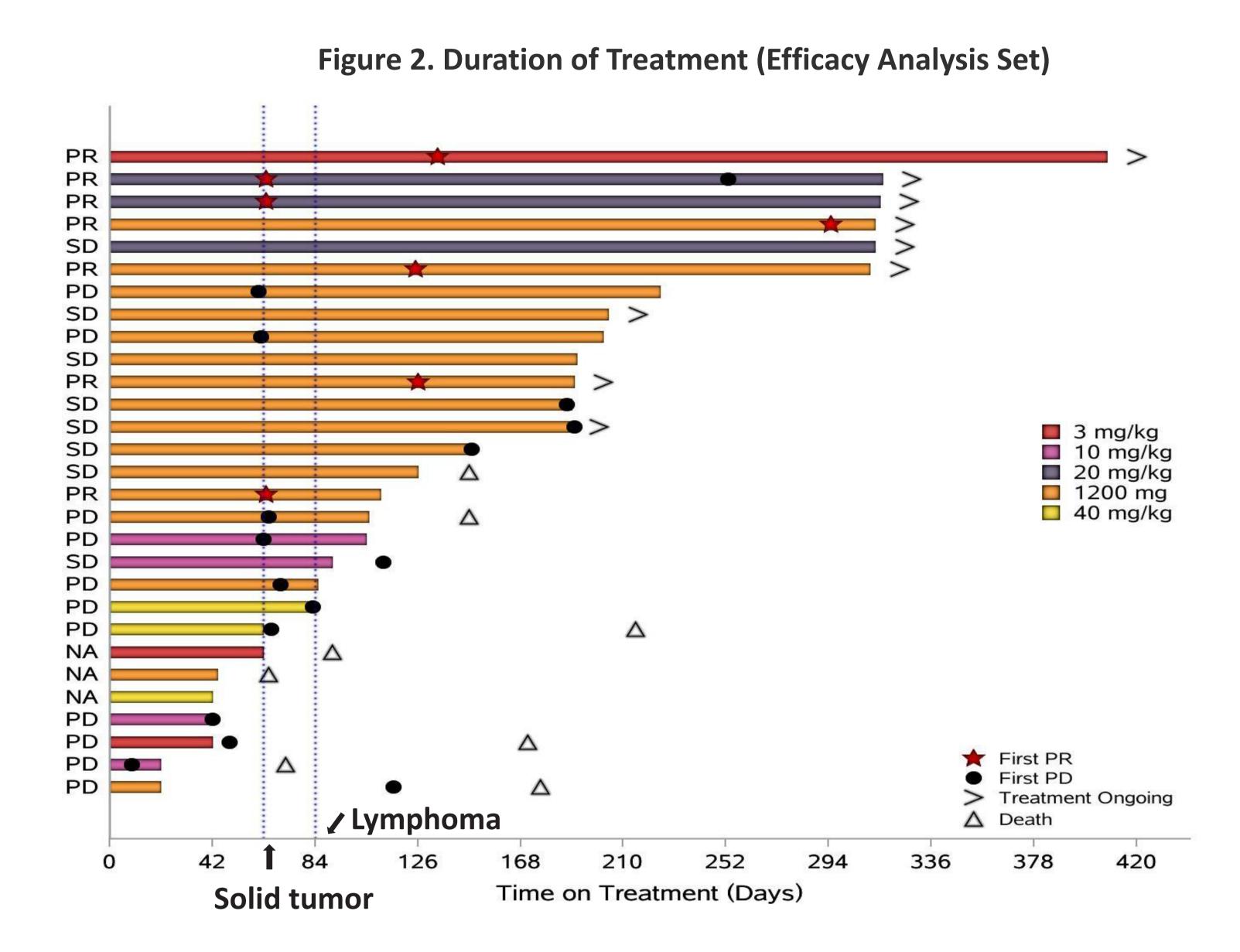
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- Median duration of treatment was 126 days (range, 21 to 408+)
- All 29 patients experienced at least one treatment-emergent adverse event (TEAE)
- Of the 29 patients, 27 (93.1%) reported at least one treatment-related AE (TRAE). The most common TRAEs were anaemia (48.3%), proteinuria (44.8%), total bilirubin increased (27.6%), alanine aminotransferase increased (24.1%), aspartate aminotransferase increased (20.7%), direct bilirubin increased (20.7%), and white blood cell count decreased (20.7%) (Table 2)
- Most of the TRAEs were Grade 1 or 2. 3 (10.3%) patients reported Grade 3 TRAEs, including platelet count decreased (n=1) and anaemia (n=2). No Grade 4 or 5 TRAEs were observed
- 6 (20.7%) patients experienced at least one serious adverse event (SAE), none of which were considered to be related to CS1001
- 7 (24.1%) patients reported at least one immune-related AE (irAE). All irAEs were of Grade 1 or 2. The most frequently reported irAE was hypothyroidism (n=4, 13.8%). 1 (3.4%) patient experienced a Grade 2 pneumonitis
- No DLTs or TRAEs leading to death were observed.
- As of Nov 30, 2018, 2 (6.9%) patients permanently discontinued the study treatment due to hepatic function abnormal (Grade 4) and pulmonary tuberculosis (Grade 3), respectively. Both AEs were considered not related to study treatment by the Investigator

Table 2 Most Frequently Reported TRAE in ≥ 20% Patients or Grade ≥3 (Safety Analysis Set) **Total (N=29)** n (%) MedDRA PT **Any Grade** Grade ≥3 3 (10.3) Number of Patients with at Least One TRAE 27 (93.1) 2 (6.9) 14 (48.3) Anaemia 13 (44.8) Proteinuria 8 (27.6) Blood bilirubin increased Alanine aminotransferase increased 7 (24.1) 6 (20.7) Aspartate aminotransferase increased Bilirubin conjugated increased 6 (20.7) 6 (20.7) White blood cell count decreased 1 (3.4) Platelet count decreased 1 (3.4) MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TRAE = treatment-related adverse event

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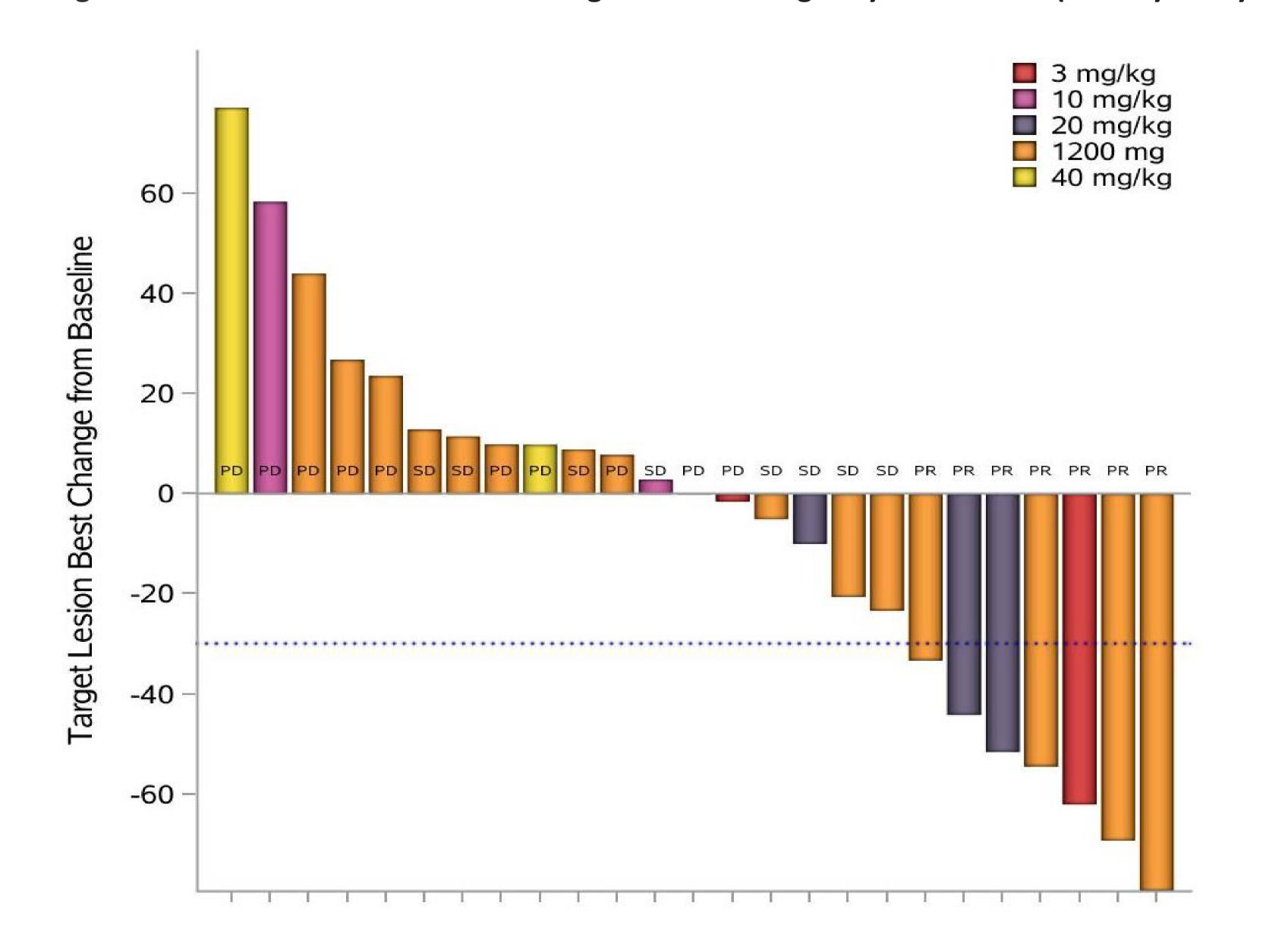
- As of Nov 30, 2018, 7 (24.1%) patients achieved a partial response (PR) as assessed by investigators per RECIST 1.1. 6 PRs were confirmed at least 4 weeks after initial response. Disease control rate (DCR) was 51.7% (**Figure 3**)
- Duration of response (DoR) ranged from 0.03+ to 8.7+ months, median DoR was not reached



NA = not applicable; PD = progressive disease; PR = partial response; SD = stable disease Tumor assessment performed every 9 weeks for solid tumors and every 12 weeks for lymphomas

As of Nov 30, 2018, 9 (31.0%) patients remained on study treatment and the rest discontinued, mostly due to progressive disease (n=14, 48.3%) (**Figure 2**), with a median duration of treatment being 126 days (range, 21 to 408+)

Figure 3. Waterfall Plot of Maximum Target Lesion Changes by RECIST V1.1 (Efficacy Analysis Set)



| Response, n (%) | Total (N=29*) | |
|--------------------------------------|---------------|---|
| Partial response (PR) | 7 (24.1) | Diagnoses of patients with PR: middle and low differentiated adenocarcinoma of ampulla with MSI-H, cholangiocarcinoma, non-small cell lung cancer (NSCLC cervical cancer, mixed histology of esophagus cancer and melanoma, nasopharyngeal cancer and Classic Hodgkir lymphoma (cHL). Note: All 29 patients were included in the efficacy analypatients who discontinued without any post baseline to assessment were not shown in the table and were regards as non-responders. |
| Stable disease (SD) | 8 (27.6) | |
| Progressive disease (PD) | 11 (37.9) | |
| Objective response rate (ORR, CR+PR) | 7 (24.1) | |
| Disease control rate (DCR, CR+PR+SD) | 15 (51.7) | |
| DoR (months) | 0.03+ to 8.7+ | |

CONCLUSION

- Based on current Phase Ia data, CS1001 appears to be generally safe and well tolerated in patients with advanced solid tumors and lymphomas at doses from 3 mg/kg to 40 mg/kg
- No DLTs were observed, and MTD was not reached
- Anti-tumor activity including 7 PRs was observed among 29 patients, (ORR=24.1%); response to CS1001 monotherapy was durable
- The preliminary safety profile and antitumor activity support continued development of CS1001 in patients with advanced solid tumors or lymphomas
- CS1001 is currently being evaluated in 5 registration trials as monotherapy or in combination with standard of care therapies

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