A Phase 1b study of the PD-1 antagonist CS1003 plus lenvatinib (LEN) in Chinese patients (pts) with the first-line (1L) unresectable hepatocellular carcinoma (uHCC)

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BACKGROUND

- Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver[1] and China accounts for more than 50% of global liver cancer cases, of which 70% to 85% are HCC[2].
- Sorafenib and lenvatinib (LEN) are the currently recommended first line (1L) treatments for advanced unresectable HCC (uHCC)[3].
- IMbrave150 was the first randomized phase III study that shows a significant survival improvement of atezolizumab plus bevacizumab vs sorafenib as 1L treatment in patients (pts) with uHCC[4].
- Combination of pembrolizumab with LEN as 1L treatment in Ph1b trial has recently demonstrated promising anti-tumor activity and manageable safety in pts with uHCC in United States, Europe and Japan[5].
- 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 monotherapy or in combination with other anti-cancer reagents[6].
- 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[6].
- In Phase Ib part of this study (NCT03809767), anti-tumor activities of CS1003 at 200 mg Q3W, as confirmed in Phase Ia part, were evaluated as monotherapy or in combination with chemotherapies or targeted therapies in pts with selected tumor types, including uHCC (Arm 5).
- Herein, we present the efficacy and safety data of 1L treatment of CS1003 + LEN in Chinese uHCC pts.

METHODS

In this open-label Phase 1b study, Chinese pts with 1L uHCC, BCLC stage B or C, Child-Pugh class A, and ECOG PS ≤ 1 received 200 mg CS1003 intravenously once every 3 weeks and LEN orally (body weight ≥ 60 kg: 12 mg; < 60 kg: 8 mg) daily.

Figure 1. Study Design of Phase Ib Arm 5 and Objectives

Key Eligibility Criteria
- ECOG PS 0-1
- Histologically confirmed diagnosis of HCC
- Patients must have at least one measurable lesion per RECIST v1.1
- Patients with advanced HCC
  - a) Patients with histologically confirmed diagnosis of HCC
  - b) Patients with BCLC Stage B or C disease that is not suitable for radical surgery and/or locoregional therapy, or the disease progresses after surgery and/or local treatment
  - c) No prior systemic treatment for advanced HCC
  - d) Child Pugh score ≤ 6

* Subject body weight ≥ 60 kg: 12 mg, once daily, orally; subject body weight <60 kg: 8 mg, once daily, orally

Primary Endpoints
Objective response rate (ORR) per RECIST v1.1 by investigators

Secondary Endpoints
- Progression Free Survival (PFS), Disease Control Rate (DCR), Duration of Response (DOR) and Overall Survival (OS)
- Safety and tolerability
- Pharmacokinetic evaluations
- Immunogenicity

Tumor assessment Q9W during the first year, and Q12W from Year 2 onward per RECIST V1.1 by the investigators.

Abbreviations: AE: adverse event; BCLC: Barcelona Clinic Liver Cancer; ECOG:Eastern Cooperative Oncology Group; HCC: hepatocellular carcinoma; IV: intravenous; PS: performance status; QD: once daily; Q3W: once every 3 weeks; RECIST:Response Evaluation Criteria in Solid Tumors.

Assessments

- Tumor assessment 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 efficacy and safety analyses was 22 Jun 2020.

RESULTS

Patient Demographics and Baseline Disease Characteristics

- As of 22 Jun 2020, a total of 20 Chinese uHCC pts were enrolled.
- The majority of pts were male (90%), have ECOG status score 1 (75%), have BCLC stage C HCC (90%), and have HBV infection (65%).

Table 1. Demographics and Baseline Characteristics (Safety Analysis Set*)

Parameter	CS1003 + LEN (N=20)
Age (Years), Median (range)	54.5 (19, 70)
Age Category, n(%)	
<65 Years	16 (80.0%)
≥65 Years	4 (20.0%)
Gender, n(%)	
Male/Female, n(%)	18 (90.0%) / 2 (10.0%)
Race, n(%)	
Asian	20 (100.0%)
ECOG Performance Status, n(%)	
0	5 (25.0%)
1	15 (75.0%)
BCLC stage at study entry, n(%)	
B	2 (10.0%)
C	18 (90.0%)
Serum AFP level, n(%)	
<200 ng/ml	12 (60.0%)
200-400 ng/ml	2 (10.0%)
≥400 ng/ml	6 (30.0%)
Viral infection (present/history) , n(%)	
HBV	13 (65.0%)
HCV	3 (15.0%)
Non-viral infected	4 (20.0%)
Prior radiotherapy, n(%)	
Yes	2 (10.0%)
No	18 (90.0%)
Prior cancer-related surgery/procedure, n(%)	
Yes	18 (90.0%)
No	2 (10.0%)

Abbreviations: AFP: alpha fetoprotein; HBV: hepatitis B virus; HCV: hepatitis C virus.
* 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.

Patient Disposition

- As of 22 Jun 2020, 20 uHCC pts without prior systemic anti-tumor therapy were enrolled in this Phase Ib study and received CS1003 + LEN as 1L treatment.
- Median durations of treatment of CS1003 and LEN were 26.9 weeks (range: 9.9-40.7) and 26.9 weeks (range: 9.1-40.7), respectively.
- At the time of data cut-off, 13 pts were still on treatment of CS1003 in combination with LEN, while 7 pts ended study treatment due to radiographic disease progression.
- There was no death case as of the analysis date.
- Due to the difficulty of on-site visits during the outbreaks of Coronavirus disease 2019 (COVID-19), there were in total 13 pts whose dosing were impacted and missed for at least one dose of CS1003.
  - median number of dose missing (range) was 2 (1-6) for these 13 pts.
- LEN administrations were rarely impacted during COVID-19 as a result of the success of drug delivery under a strict instruction and monitoring.
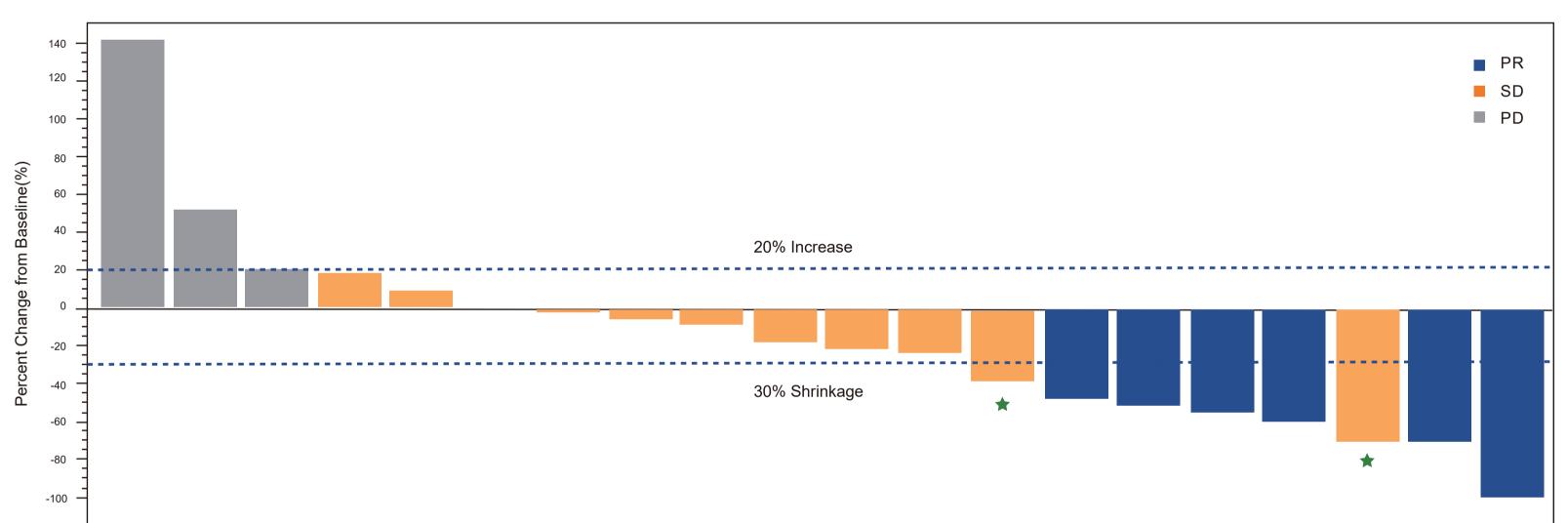
Preliminary Anti-tumor Activity

- As of 22 Jun 2020, a total of 20 pts were enrolled for evaluating preliminary anti-tumor activity.
- A total of 6 pts achieved a confirmed partial response (PR), 2 additional pts had unconfirmed PR awaiting further confirmation (Table 2).
- Median follow up duration was 6.2 months (range: 2.9-9.4).
- Median PFS was 8.4 months (95% Confidence Interval [CI]: 6.2-not estimable); 6-month PFS rate was 83.1%.
- Median OS was not reached; 6-month OS rate was 100%.
- Median duration of response (DoR) was not reached.

Table 2. Summary of Objective Response (Efficacy Analysis Set*)

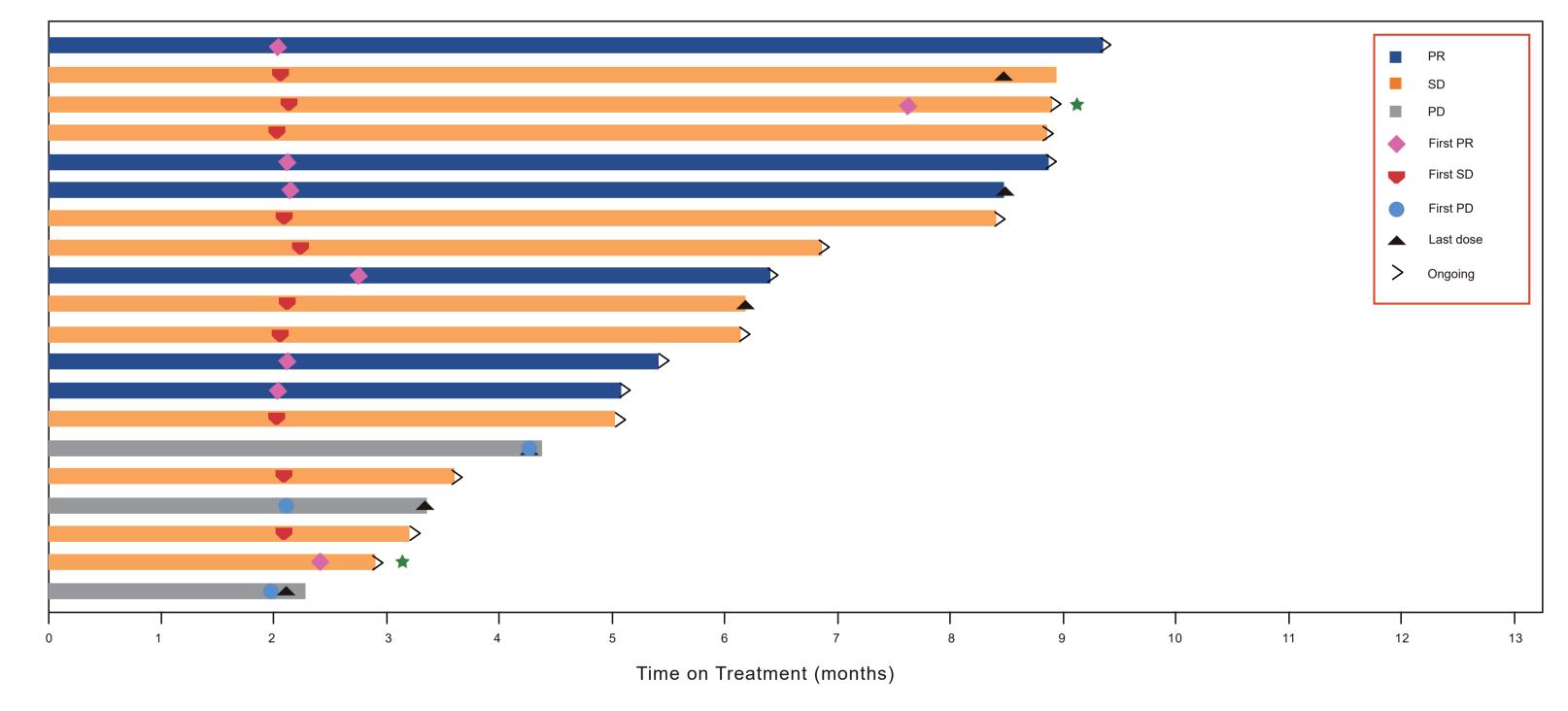| Parameter, n(%)	CS1003 + LEN (N=20)
ORR, n(%)	8 (40.0%)**
Best Overall Response	
CR	0
PR	8 (40.0%)
SD	9 (45.0%)
PD	3 (15.0%)
Confirmed ORR	6 (30.0%)
DCR (CR+PR+SD)	17 (85.0%)

Abbreviations: CR: complete response; DCR: disease control rate; n: number of pts with an observation; N: number of pts in the efficacy analysis set; PD: progressive disease; PR: partial response; SD: stable disease.
*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.
**As of 22 Jun 2020, unconfirmed ORR was 40.0% (8/20), with 6 confirmed PRs, and 2 additional unconfirmed PRs that both have recently been confirmed in the next tumor assessment after the cut-off date.

Figure 2. Waterfall Plot of Maximum Target Lesion Shrinkage by RECIST V1.1 (Efficacy Analysis Set)[a]

★ As of cut-off date, these two pts epereineced unconfirmed PRs that both have recently been confirmed in the next tumor assessment after the cut-off date.
[a]Annotated by confirmed Best Overall Response.

Figure 3. Duration of Treatment and Tumor Assessment by RECIST V1.1 (Efficacy Analysis Set)[a]

★ As of cut-off date, these two pts epereineced unconfirmed PRs that both have recently been confirmed in the next tumor assessment after the cut-off date.
[a]Annotated by confirmed Best Overall Response.

Safety

- As of 22 Jun 2020, all 20 patients received any dosage of combination treatment and were evaluable for safety assessment.
- The most common any treatment-related treatment emergent AE (TEAE) of any grade was blood bilirubin increased (35%), protein urine present (30%) and proteinuria (30%).
- 5 pts each had a Grade 3 any treatment-related TEAE, including: hypertension (5%), bilirubin conjugated increased (5%), diarrhoea (5%), diabetes mellitus (5%), and hypophosphataemia (5%).
- No pt had Grade 4 and above any treatment-related TEAE.

Table 3. Summary of Adverse Events (Safety Analysis Set)

AE, n(%)	CS1003 + LEN (N=20)
Number of pts with ≥ 1 event	20 (100.0%)
TEAE related to any drug*	20 (100.0%)
TEAE related to CS1003*	19 (95.0%)
Grade 3-5 TEAE	7 (35.0%)
Grade 3-5 TEAE related to any drug*	5 (25.0%)
Grade 3-5 TEAE related to CS1003*	2 (10.0%)
Serious TEAE	2 (10.0%)
Serious TEAE related to any drug*	1 (5.0%)
Serious TEAE related to CS1003*	1 (5.0%)
Immune-related TEAE	14 (70.0%)
Infusion-related Reaction	1 (5.0%)
TEAE Leading to CS1003 rate of infusion modification	0
TEAE Leading to CS1003 drug interruption	0
TEAE Leading to CS1003 drug permanently discontinuation	0
TEAE Leading to CS1003 treatment cycle delay	3 (15.0%)
TEAE Leading to LEN reduction	1 (5.0%)
TEAE Leading to LEN interruption	4 (20.0%)
TEAE Leading to LEN permanently discontinuation	0
TEAE Leading to death	0

Abbreviations: n: number of pts with an observation; N: number of pts in the safety analysis set; TEAE: treatment emergent adverse event.
a Refer to any of the following study treatments: CS1003 and LEN.
b Refer to CS1003 only.

Table 4. Most common any treatment-related TEAE, Grade 3 or 4 treatment-related TEAE, and most common CS1003-related TEAE (Safety Analysis Set)

Preferred Term, n(%)	CS 1003 + LEN (N=20)		
Most Common (≥ 20% of pts) any treatment-related TEAE	All-grade	Grade 1-2	Grade 3-4*
Blood bilirubin increased	7 (35.0%)	7 (35.0%)	0
Protein urine present	6 (30.0%)	6 (30.0%)	0
Proteinuria	6 (30.0%)	6 (30.0%)	0
Aspartate aminotransferase increased	5 (25.0%)	5 (25.0%)	0
Blood thyroid stimulating hormone increased	5 (25.0%)	5 (25.0%)	0
Platelet count decreased	5 (25.0%)	5 (25.0%)	0
Hypothyroidism	4 (20.0%)	4 (20.0%)	0
Hypertension	4 (20.0%)	3 (15.0%)	1 (5.0%)
Any treatment-related TEAE, Grade 3 or 4 (≥ 5% of pts)	All-grade	Grade 1-2	Grade 3-4*
Hypertension	4 (20.0%)	3 (15.0%)	1 (5.0%)
Bilirubin conjugated increased	2 (10.0%)	1 (5.0%)	1 (5.0%)
Diarrhoea	2 (10.0%)	1 (5.0%)	1 (5.0%)
Diabetes mellitus	1 (5.0%)	0	1 (5.0%)
Hypophosphataemia	1 (5.0%)	0	1 (5.0%)
Most Common (≥ 20% of pts) CS1003-related TEAE	All-grade	Grade 1-2	Grade 3-4
Blood bilirubin increased	5 (25.0%)	5 (25.0%)	0
Blood thyroid stimulating hormone increased	5 (25.0%)	5 (25.0%)	0
Hypothyroidism	4 (20.0%)	4 (20.0%)	0
Proteinuria	4 (20.0%)	4 (20.0%)	0

* One pt had a Grade 3 bilirubin conjugated increased that was attributed to both CS1003 and LEN; one pt had a Grade 3 diabetes mellitus only attributed to CS1003; 3 additional pts each had a Grade 3 hypertension, a Grade 3 diarrhoea, and a Grade 3 hypophosphataemia that were only related to LEN; no pt had any Grade 4 or 5 TEAE that was related to any treatment.

CONCLUSIONS

- The CS1003 + LEN combination therapy shows promising anti-tumor activity and a manageable safety profile in Chinese pts with uHCC as 1L treatment.
- A multi-regional, double-blinded, randomized Phase III trial is ongoing to further evaluate the efficacy and safety of CS1003 + LEN vs. placebo + LEN as 1L treatment of uHCC (NCT04194775).

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