A Phase III Clinical Trial of CS1001 As A Consolidation Therapy In Patients With Locally Advanced/Unresectable (Stage III) Non-Small-Cell Lung Cancer (NSCLC) Who Have Not Progressed After Prior Concurrent/Sequential Chemoradiotherapy (GEMSTONE 301)

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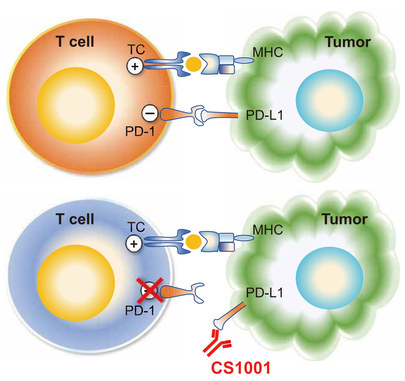
Yi-Long Wu[1], Ming Chen[2], Qing Zhou[1], Hao Li[3], Wenyi Sun[3], Tianshu Qu[3], Dongmei Lu[3]
1. Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China; 2. Zhejiang Cancer Hospital, Hangzhou, China;
3. CStone Pharmaceuticals (Su Zhou) Co., Ltd, Suzhou, China

BACKGROUND

- Lung cancer is the most common cancer in the world[1]. In 2018, about 2.1 million patients were diagnosed with lung cancer (11.6% of the total cancer incidence), and it caused 1.8 million deaths (18.4% of the total cancer-related mortalities) world-wide[2].
- Lung cancer is also the most common malignancy in China. Data published from the National Tumor Registry showed that there were 733,300 newly diagnosed lung cancer cases in 2015 (17% of the total cancer incidence), representing the highest incidence among all cancers in China. In the same year, 610,200 deaths resulted from lung cancer, which accounted for 22% of all cancer-related mortalities[3].
- 80–85% of lung cancer cases are non-small-cell lung cancer (NSCLC), among which 30% present with Stage III NSCLC[4]. Current treatment options for locally advanced/unresectable (Stage III) NSCLC are limited. Concurrent or sequential chemoradiotherapy is the main treatment modality in China, while the outcome is unsatisfactory[5].
- In the PACIFIC trial, among patients with locally advanced/unresectable NSCLC whose disease did not progress after definitive concurrent chemoradiotherapy, treatment with durvalumab (a programmed-death-ligand-1 [PD-L1] targeted monoclonal antibody [mAb]) resulted in significantly longer progression free survival (PFS) and overall survival (OS) than placebo did[6].
- CS1001 is the first full-length, fully human PD-L1 targeted immunoglobin G4 (IgG4) mAb developed by the OMT transgenic rat platform. It specifically binds to PD-L1, blocking its ligation with programmed cell death protein 1 (PD-1) (**Figure 1**).

Figure 1. CS1001 and PD-1/PD-L1 Pathway



MHC = major histocompatibility complex; PD-1 = Programmed death 1; PD-L1 = Programmed death-ligand 1; TCR = T cell receptor

- The first-in-human Phase Ia/Ib study (GEMSTONE 101, NCT03312842) demonstrated that CS1001 was well tolerated and had anti-tumor activities across a range of tumors including NSCLC.
- GEMSTONE-301 is a randomized, double-blind, Phase III study (NCT03728556) to assess the efficacy and safety of CS1001 as the consolidation therapy in Stage III locally advanced/unresectable NSCLC after concurrent or sequential chemoradiotherapy.

OBJECTIVES

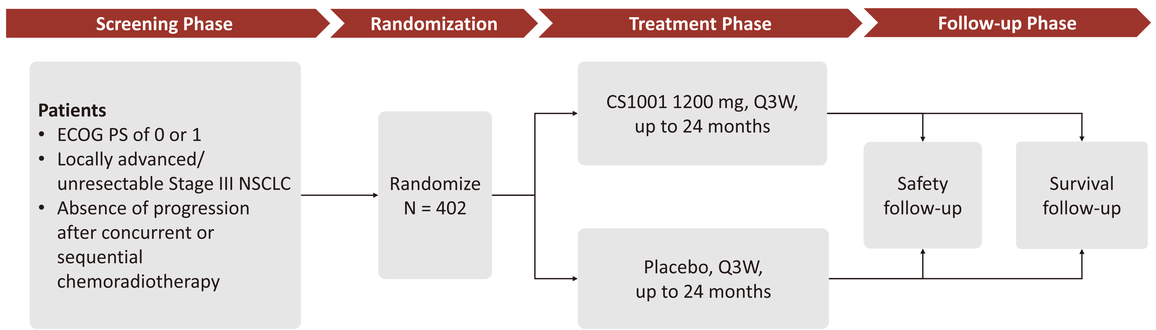
Primary Objective
- To compare the efficacy of CS1001 versus placebo in patients with locally advanced/unresectable (Stage III) NSCLC that have not progressed after prior concurrent/sequential chemoradiotherapy, as measured by investigator-assessed PFS

Secondary Objectives
- To compare the efficacy of CS1001 versus placebo, as measured by PFS based on blinded independent central review (BICR), OS, objective response rate (ORR), duration of response (DoR), and time to death/distant metastasis (TTDM)
- To compare the efficacy of CS1001 versus placebo in the subgroup of patients with tumor mutation burden ≥ 10 (TMB ≥ 10)
- To compare the safety and tolerability of CS1001 versus placebo
- To further characterize the pharmacokinetics (PK) and immunogenicity of CS1001

DESIGN

- As shown in **Figure 2**, 402 patients will be randomly assigned to receive
  - CS1001 1200 mg, every 3 weeks
  - Placebo, every 3 weeks
- Patients will receive study treatment (CS1001 or placebo) every 21 days (3 weeks) up to 24 months until confirmed disease progression, intolerable adverse events, informed consent withdrawn, lost to follow-up, death, or the end of the study (whichever occurs first)

Figure 2. Schema of Study Design



ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small-cell lung cancer; PS = Performance Status; Q3W = every 3 weeks

Patient Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Provision of written informed consent • ≥ 18 years of age on the day of signing ICF • Histologically confirmed diagnosis of locally advanced/unresectable Stage III NSCLC • The first dose of the study treatment needs to be administered within 1 - 42 days (including 42 days) after concurrent/sequential chemoradiotherapy • Received at least 2 cycles of platinum-containing chemotherapy • Absence of progression after concurrent/sequential chemoradiotherapy • ECOG PS of 0 or 1 • Life expectancy ≥ 12 weeks • With the exception of hearing loss, alopecia, and fatigue, all toxicities from prior anti-cancer treatments have recovered to baseline level or ≤ Grade 1 (according to NCI CTCAE v4.03) • Demonstrated adequate hematologic, renal, hepatic and coagulation function • Fertile men or women of childbearing potential must agree to use an effective method of birth control from the date of providing signed ICF till 180 days after the last dose of the study treatment. Women of childbearing potential must have a negative pregnancy test within 7 days prior to the first dose of the study treatment	• Histologically confirmed to have mixed small cell lung cancer component • Disease progression after concurrent/sequential chemoradiotherapy • Major surgical procedure within 28 days prior to the first dose of the study treatment • Received a live vaccine within 28 days prior to the first dose of the study treatment • Current participation in another clinical study or use of any investigational drug within 28 days prior to the first dose of the study treatment in this trial. (Participation in the overall survival follow-up of a study is allowed.) • Prior treatment of antibody/drug that targets T-cell coregulatory proteins (immune checkpoints, including PD-1, PD-L1, CTLA4, TIM3, LAG3, etc.) • Active or prior autoimmune disease. Patients with Type I diabetes, hypothyroidism treated with hormone replacement therapy only, or psoriasis not requiring systemic treatment are not exclude. • Diagnosis of immunodeficiency or received systemic corticosteroid therapy or any other immunesuppressive therapies within 14 days prior to the first dose of the study treatment • History of another malignancy within 5 years prior to the first dose of the study treatment • History of inflammatory bowel disease or active inflammatory bowel disease • History of HIV infection and/or acquired immune deficiency syndrome • Active phase of chronic hepatitis B or active hepatitis C • QTc interval > 480 millisecond as assessed by the screening ECG (as calculated by Fridericia formula)

CTCAE = Common Terminology Criteria for Adverse Events; CTLA4 = cytotoxic T lymphocyte-associated antigen-4; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; ICF = informed consent form; LAG3 = lymphocyte activation gene-3; NCI = National Cancer Institute; NSCLC = non-small-cell lung cancer; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1; PS = Performance Status; TIM3 = T cell immunoglobulin mucin-3

Assessments and Follow-up
- Baseline tumor assessment should be performed within 42 days after the last radiotherapy and within 28 days prior to the first dose
- Efficacy will be assessed by the investigators and BICR separately according to RECIST version 1.1
- Adverse events (AEs) will be monitored throughout the study and during the follow-up period and graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03
- All patients will undergo PK and immunogenicity assessments

Statistical Analysis
- Efficacy
  - Efficacy analyses will be performed using the intent-to-treat (ITT) population
  - The primary endpoint is investigator-assessed PFS, the key secondary endpoints are OS and BICR-assessed PFS
  - A stratified log-rank test will be used to compare PFS and OS between CS1001 and placebo
  - A stratified Cox regression model will be used to estimate hazard ratio and its 95% confidence interval; event rates over time will be estimated within each treatment group using Kaplan-Meier method
- Safety
  - The safety analysis population will include all patients who have received at least one dose of the study treatment
  - AEs will be summarized by severity, seriousness, and relationship to study treatment by group. Laboratory tests, electrocardiogram, and vital signs will also be summarized
  - An independent Data Monitoring Committee (iDMC) will monitor the study periodically

STATUS

- The study is ongoing. The first patient was enrolled in October 2018.
- Enrollment is expected to take place in about 34 sites across China.

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ClinicalDevelopment@cstonepharma.com
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