Sugemalimab versus placebo, in combination with platinum-based chemotherapy, as first-line treatment of metastatic non-small-cell lung cancer (GEMSTONE-302): interim and final analyses of a double-blind, randomised, phase 3 clinical trial

Caicun Zhou, Ziping Wang, Yuping Sun, Lejie Cao, Zhiyong Ma, Rong Wu, Yan Yu, Wenxiu Yao, Jianhua Chang, Jianhua Chen, Wu Zhuang, Jiuwei Cui, Xueqin Chen, You Lu, Hong Shen, Jingru Wang, Peiqi Li, Mengmeng Qin, Dongmei Lu, Jason Yang

Summary

Background PD-1 inhibitor plus chemotherapy had been shown to be an effective first-line treatment for patients with metastatic non-small-cell lung cancer (NSCLC). However, there was no robust evidence showing a PD-L1 inhibitor combined with chemotherapy benefited patients with squamous and non-squamous NSCLC. GEMSTONE-302 aimed to evaluate the efficacy and safety of a PD-L1 inhibitor, sugemalimab, plus chemotherapy for patients with metastatic squamous or non-squamous NSCLC.

Methods This randomised, double-blind, phase 3 trial was done in 35 hospitals and academic research centres in China. Eligible patients were aged 18–75 years, had histologically or cytologically confirmed stage IV squamous or non-squamous NSCLC without known *EGFR* sensitising mutations, *ALK*, *ROS1*, or *RET* fusions, no previous systemic treatment for metastatic disease, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were randomly assigned (2:1) to receive sugemalimab (1200 mg, intravenously, every 3 weeks) plus platinum-based chemotherapy (carboplatin [area under the curve (AUC) 5 mg/mL per min, intravenously] and paclitaxel [175 mg/m², intravenously] for squamous NSCLC, or carboplatin [AUC 5 mg/mL per min, intravenously] and pemetrexed [500 mg/m², intravenously] for non-squamous NSCLC; sugemalimab group) or placebo plus the same platinum-based chemotherapy regimens for squamous or non-squamous NSCLC as in the sugemalimab group; placebo group) for up to four cycles, followed by maintenance therapy with sugemalimab or placebo for squamous NSCLC, and intravenous sugemalimab 500 mg/m² or matching placebo plus pemetrexed for non-squamous NSCLC. Randomisation was done by an interactive voice–web-response system via permuted blocks (block size was a mixture of three and six with a random order within each stratum) and stratified by ECOG performance status, PD-L1 expression, and tumour pathology. The investigators, patients, and the sponsor were masked to treatment assignment. The primary endpoint was investigator-assessed progression-free survival in the intention-to-treat population. Safety was analysed in all patients who received at least one treatment dose. Results reported are from a prespecified interim analysis (ie, when the study met the primary endpoint) and an updated analysis (prespecified final analysis for progression-free survival) with a longer follow-up. This study is registered with ClinicalTrials.gov (NCT03789604), is closed to new participants, and follow-up is ongoing.

Findings Between Dec 13, 2018, and May 15, 2020, 846 patients were assessed for eligibility; 367 were ineligible, and the remaining 479 patients were randomly assigned to the sugemalimab group (n=320) or placebo group (n=159). At the preplanned interim analysis (data cutoff June 8, 2020; median follow-up 8·6 months [IQR 6·1–11·4]), GEMSTONE-302 met its primary endpoint, with significantly longer progression-free survival in the sugemalimab group compared with the placebo group (median 7·8 months [95% CI 6·9–9·0] *vs* 4·9 months [4·7–5·0]; stratified hazard ratio [HR] 0·50 [95% CI 0·39–0·64], p<0·0001]). At the final analysis (March 15, 2021) with a median follow-up of 17·8 months (IQR 15·1–20·9), the improvement in progression-free survival was maintained (median 9·0 months [95% CI 7·4–10·8] *vs* 4·9 months [4·8–5·1]; stratified HR 0·48 [95% CI 0·39–0·60], p<0·0001). The most common grade 3 or 4 any treatment-related adverse events were neutrophil count decreased (104 [33%] of 320 with sugemalimab *vs* 52 [33%] of 159 with placebo), white blood cell count decreased (45 [14%] *vs* 27 [17%]), anaemia (43 [13%] *vs* 18 [11%]), platelet count decreased (33 [10%] *vs* 15 [9%]), and neutropenia (12 [4%] *vs* seven [4%]). Any treatment-related serious adverse events occurred in 73 (23%) patients in the sugemalimab group and 31 (20%) patients in the placebo group. Any treatment-related deaths were reported in ten (3%) patients in the sugemalimab group (pneumonia with respiratory failure in one patient; myelosuppression with septic shock in one patient; pneumonia in two patients; respiratory failure, abdominal pain, cardiac failure, and immune-mediated pneumonitis in one patient each; the other two deaths had an unspecified cause) and in two (1%) patients in the placebo group (pneumonia and multiple organ dysfunction syndrome).

Lancet Oncol 2022

Published Online
January 14, 2022
https://doi.org/10.1016/S1470-2045(21)00650-1

See Online/Comment
https://doi.org/10.1016/S1470-2045(21)00698-7

For the Chinese translation of the abstract see Online for appendix 1

Department of Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China (Prof C Zhou MD); Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education, Beijing), Department of Thoracic Oncology, Peking University Cancer Hospital and Institute, Beijing, China (Prof Z Wang MD); Department of Oncology, Jinan Central Hospital, Jinan, China (Prof Y Sun MD); Phase I Clinical Research Center, Shandong Cancer Hospital and Institute, Jinan, China (Prof Y Sun); Department of Respiratory Medicine, The First Affiliated Hospital of University of Science and Technology of China, Division of Life Sciences and Medicine, University of Science and Technology of China, Anhui Provincial Hospital, Hefei, China (Prof L Cao MMed); Department of Respiratory Medicine, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China (Prof Z Ma MMed); Department of Oncology, Shengjing Hospital of China Medical University, Huaxiang Branch Hospital, Shenyang, China (Prof R Wu MD); Department of Respiratory Medicine, Harbin

Medical University Cancer Hospital, Harbin, China (Prof Y Yu MD); Thoracic Oncology, Sichuan Cancer Hospital and Institute, Chengdu, China (Prof W Yao MD); Department of Oncology, Fudan University Shanghai Cancer Centre, Shanghai, China (Prof J Chang MD); Department of Oncology, Cancer Hospital Chinese Academy of Medical Sciences Shenzhen Centre, Shenzhen, China (Prof J Chang); Department of Thoracic Oncology, Hunan Cancer Hospital, Changsha, China (Prof J Chen MMed); Department of Thoracic Oncology, Fujian Provincial Cancer Hospital, Fuzhou, China (W Zhuang BM); Pharmacology Base, The First Hospital of Jilin University, Changchun, China (Prof J Cui MD); Department of Thoracic Oncology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Zhejiang University Cancer Centre, Hangzhou, China (Prof X Chen MMEd); Department of Thoracic Oncology, West China Hospital, Sichuan University, Chengdu, China (Prof Y Lu MD); Department of Oncology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China (H Shen MD); Clinical Development, CStone Pharmaceuticals, Suzhou, China (J Wang PhD, P Li MD, M Qin MMed, D Lu MSc, J Yang MD)

Correspondence to: Prof Caicun Zhou, Department of Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Yangpu District, Shanghai 200433, China
caicunzhoudr@163.com

Interpretation **Sugemalimab plus chemotherapy showed a statistically significant and clinically meaningful progression-free survival improvement compared with placebo plus chemotherapy, in patients with previously untreated squamous and non-squamous metastatic NSCLC, regardless of PD-L1 expression, and could be a new first-line treatment option for both squamous and non-squamous metastatic NSCLC.**

Funding **CStone Pharmaceuticals.**

Introduction

Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer death worldwide, accounting for 11·4% of new cancers and 18% of cancer deaths each year.[1] Approximately 80–90% of primary lung cancers are non-small-cell lung cancer (NSCLC), which is commonly diagnosed as metastatic disease, a stage associated with a poor prognosis.[2] Squamous-cell carcinoma accounts for 20–30% of NSCLC and is associated with even shorter survival relative to non-squamous NSCLC owing to its distinct biology and disease characteristics.[3]

Anti-PD-1 or anti-PD-L1 antibodies in combination with chemotherapy have shown varying degrees of benefit in progression-free survival, overall survival, or both, as first-line therapy in patients with advanced squamous or non-squamous NSCLC in several phase 3 trials.[2,4] KEYNOTE-189[5] and KEYNOTE-407[6] reported that the addition of pembrolizumab, an anti-PD-1 antibody, to chemotherapy resulted in statistically significantly longer overall survival and progression-free survival than placebo plus chemotherapy for systemic therapy of treatment-naive non-squamous[5] and squamous NSCLC.[6] Conversely, atezolizumab, an anti-PD-L1 antibody, showed uncertain survival benefit for NSCLC in several phase 3 trials. In IMpower131,[7] atezolizumab plus either carboplatin–paclitaxel or carboplatin–nab-paclitaxel as first-line treatment for patients with squamous NSCLC met only one of the coprimary endpoints (progression-free survival) and there was no improvement in overall survival. Similarly, atezolizumab plus either carboplatin–pemetrexed or cisplatin–pemetrexed as first-line treatment for patients with non-squamous NSCLC did not improve overall survival in the IMpower132 trial.[8] The POSEIDON trial[9] met its primary endpoint by showing a statistically significant improvements in progression-free survival with durvalumab plus chemotherapy versus chemotherapy alone, but no improvement in overall survival. Therefore, the efficacy of PD-L1 inhibitors plus chemotherapy as first-line therapy for

Research in context

Evidence before this study

We searched PubMed and major oncology congress websites (ie, American Society of Clinical Oncology, European Society of Medical Oncology, and World Conference on Lung Cancer) on Sept 24, 2021, for phase 3 clinical trials of anti-PD-L1 or anti-PD-1 antibodies plus chemotherapy as first-line treatment to treat patients with non-small-cell lung cancer (NSCLC) that were published before Dec 13, 2018, using the search terms "immunotherapy", "anti-PD-1", "anti-PD-L1", "chemotherapy", "non-small-cell lung cancer", "pembrolizumab", "nivolumab", and "atezolizumab" (both spelt out in full and abbreviations). No language preferences were specified. At the time of the start of the GEMSTONE-302 study (Dec 13, 2018), there were five published phase 3 clinical trials of the PD-1 or PD-L1 inhibitors pembrolizumab and atezolizumab in combination with chemotherapy for first-line treatment of patients with metastatic NSCLC. All five studies evaluated a single histologically unique NSCLC. Since then, several clinical trials have assessed anti-PD-1 or anti-PD-L1 antibodies in combination with chemotherapy versus chemotherapy alone in first-line settings of metastatic NSCLC. During the GEMSTONE-302 study period, PD-1 or PD-L1 inhibitors combined with platinum-based chemotherapy were shown in other studies to improve survival outcomes in patients with non-squamous metastatic NSCLC, whereas only PD-1 inhibitor combinations successfully showed survival improvements in squamous metastatic NSCLC.

Added value of this study

To our knowledge, GEMSTONE-302 is the first randomised, double-blind, phase 3 study to show a significant progression-free survival benefit of a PD-L1 inhibitor (sugemalimab) plus chemotherapy across both squamous and non-squamous NSCLC, regardless of PD-L1 expression, as a first-line treatment in the same trial.

Implications of all the available evidence

Our findings suggest that sugemalimab can be an option for patients with treatment-naive metastatic NSCLC, including in non-squamous NSCLC as an anti-PD-L1 immunotherapy option plus carboplatin and pemetrexed, and in squamous NSCLC as the only anti-PD-L1 immunotherapy plus chemotherapy. Sugemalimab in combination with chemotherapy is now approved in China for the first-line treatment of patients with metastatic non-squamous NSCLC with no *EGFR* and *ALK* genomic tumour aberrations and of patients with metastatic squamous NSCLC. Sugemalimab has also been studied in stage III NSCLC and studies are ongoing in gastric, oesophageal, and haematological malignancies.

advanced non-squamous and squamous NSCLC warrants further evaluation and validation.

Sugemalimab (formerly CS1001) is a full-length, fully human immunoglobulin G4 (IgG4, s228p) monoclonal antibody that targets PD-L1. Preclinical studies suggest that sugemalimab retains binding affinity to the Fcγ receptor I domain,[10] which could induce antibody-dependent cellular phagocytosis by crosslinking PD-L1-expressing tumour cells with macrophages in the tumour microenvironment,[11] and might further enhance tumour antigen presentation. Phase 1a/1b studies of sugemalimab showed that monotherapy, or combination with platinum-based chemotherapy, produced promising anti-tumour activity in a range of tumours, including both non-squamous and squamous NSCLC.[12,13] Here, we report the findings of the GEMSTONE-302 trial,[14] both at a prespecified progression-free survival interim analysis and at the final progression-free survival timepoint, which aimed to further evaluate the efficacy and safety of adding sugemalimab to first-line platinum-based chemotherapy in patients with non-squamous or squamous metastatic NSCLC.

Methods

Study design and participants

GEMSTONE-302 is a randomised, double-blind, phase 3 trial done at 35 hospitals and academic research centres in China. The primary objective was to compare the efficacy of sugemalimab versus placebo, each in combination with platinum-based chemotherapy, as first-line treatment of patients with metastatic NSCLC.

Eligible patients were aged 18–75 years, had histologically or cytologically confirmed stage IV squamous or non-squamous NSCLC without known *EGFR* sensitising mutations, or *ALK, ROS1,* or *RET* fusions, and had received no previous systemic treatment for metastatic disease. Patients had to have at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1,[15] an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and to provide a tumour sample for evaluation of PD-L1 expression status. Other inclusion criteria included a life expectancy of at least 12 weeks, adequate organ function as assessed in the following laboratory tests (and patients must not have had any blood transfusion, apheresis component infusion, erythropoietin, granulocyte colony-stimulating factor, or other medical supportive treatment during the 14 days before the experimental drug was given): an absolute neutrophil count of 1500 cells per μL or higher; a platelet count of 100 000 per μL or higher; haemoglobin concentration of 9 g/dL or higher; international normalised ratio (INR) or prothrombin time of 1·5×upper limit of normal (ULN) or lower; aspartate aminotransferase and, alanine aminotransferase 2·5×ULN (5×ULN for patients with hepatic metastases) or lower; serum bilirubin 1·5×ULN or lower (not applicable for patients with Gilbert syndrome); and serum creatinine clearance of 50 mL/min or higher. Patients were also excluded if they had pathologically confirmed small-cell lung cancer or tumours with a small-cell component, symptomatic central nervous system metastases, or autoimmune disease, or if they had received previous treatment with immune-checkpoint blockade therapies (appendix 2 p 6). Full inclusion and exclusion criteria are shown in appendix 2 (pp 5–8).

See Online for appendix 2

The study was done in accordance with the International Committee on Harmonisation Guidelines on Good Clinical Practice, and the Declaration of Helsinki, and was approved by the ethics committees at each participating centre. Each patient provided written informed consent before enrolment. The complete study protocol is provided in appendix 2.

Randomisation and masking

Eligible patients were randomly assigned (2:1) to sugemalimab plus platinum-based chemotherapy (sugemalimab group) or placebo plus platinum-based chemotherapy (placebo group). Permuted-block randomisation (block size was a mixture of three and six with random order within each stratum) was done using an interactive voice-response system or integrated web-response system and stratified according to ECOG performance status (0 *vs* 1), PD-L1 expression (tumour proportion score <1% *vs* ≥1%) and tumour pathology (squamous *vs* non-squamous). The investigators or designated personnel registered patients and assigned them according to the randomisation code obtained from the interactive voice–web-response system. Sugemalimab and placebo were packaged and labelled identically to each other, to ensure study personnel remained masked to treatment assignment. Investigators, patients, and the sponsor were masked to treatment assignment, and the assignment was unmasked to the sponsor after interim analysis completion and maintained for investigators and patients. Throughout the study, investigators and the sponsor were masked to PD-L1 expression.

Procedures

Patients with non-squamous NSCLC received sugemalimab (1200 mg, intravenously) or placebo, plus carboplatin (area under the concentration–time curve [AUC] 5 mg/mL per min) and pemetrexed (500 mg/m²) intravenously on day 1 of every 3-week cycle, for up to four cycles, followed by maintenance treatment with pemetrexed plus either sugemalimab or placebo. Patients with squamous NSCLC received sugemalimab (1200 mg) or placebo, plus carboplatin (AUC 5 mg/mL per min) and paclitaxel (175 mg/m²) intravenously on day 1 of every 3-week cycle, for up to four cycles, followed by maintenance treatment with sugemalimab or placebo. Sugemalimab or placebo treatment was administered for up to 35 cycles, or until disease progression or unacceptable toxicity. Sugemalimab or placebo dose adjustments were not permitted; if necessary, treatment could be withheld for up to 12 weeks or discontinued

according to prespecified criteria (appendix 2 p 9). Dose modifications for chemotherapy were permitted (see protocol in appendix 2). Patients in the placebo group who had radiographic disease progression and met the eligibility criteria (appendix 2 pp 9–10) could crossover to receive sugemalimab monotherapy for up to 35 treatment cycles.

Patients had tumour assessments at baseline with a CT scan (contrast enhanced unless contraindicated) or MRI of the thorax and abdomen. Brain MRI (or enhanced CT, if MRI was contraindicated) was done at screening if a brain CT or MRI had not been done within the previous 4 weeks. For patients who had no brain metastasis at baseline, brain CT or MRI scanning was done if clinically indicated on the basis of new specific symptoms. Subsequent tumour assessment was done at 6 and 12 weeks after the first treatment dose, then every 9 weeks for the first year, and then every 12 weeks until progressive disease, loss to follow-up, death, or study end.

Laboratory tests included hepatitis B virus, hepatitis C virus, and HIV tests, and *EGFR* and other tests for driver gene mutation were done within 28 days before the first dose. Coagulation function and serum human chorionic gonadotropin pregnancy testing were done within 7 days before the first dose. Chemistry and haematology tests were done within 7 days before the first dose and within 3 days before the subsequent doses at each cycle, and then every two cycles from cycle 12 onwards. Thyroid function tests and urinalysis were done within 7 days before the first dose, and then every two cycles from cycle 3 onwards in the first year, and then every four cycles from cycle 17 onwards.

The tumour samples were collected from irradiated sites at or after diagnosis of stage IV NSCLC. PD-L1 expression was assessed at a central laboratory by immunohistochemistry using the Ventana PD-L1 (SP263) assay on a BenchMark autostainer assay (Roche Tissue Diagnostics, Oro Valley, AZ, USA) according to the manufacturer's instructions. PD-L1 expression was scored as the percentage of tumour cells with membranous staining at any intensity.

Adverse events were monitored throughout the study and graded according to the US National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.[16] Adverse events of special interest were sponsor-assessed immune-related adverse events, defined on the basis of a sponsor-specified list of preferred categories of terms. All safety reviewers were masked to the randomised treatment assignment.

Outcomes

The primary endpoint was investigator-assessed progression-free survival (ie, time from randomisation to disease progression according to RECIST version 1.1 or death from any cause, whichever occurred first) in the intention-to-treat population. Secondary endpoints were overall survival (time from randomisation to death from any cause), investigator-assessed progression-free survival in patients with PD-L1 expression of at least 1%, progression-free survival assessed by a blinded independent central review committee (BICR), investigator-assessed objective response rate (per RECIST version 1.1), duration of response, safety, pharmacokinetics, and immunogenicity of sugemalimab, and anti-tumour activity of sugemalimab in patients in the placebo group who crossed over and received sugemalimab monotherapy as a second-line treatment. Objective response rate was defined as the percentage of patients who achieved an objective response (ie, complete or partial response). Duration of response was defined as the time between the date of the earliest documented complete or partial response and the date of documented progression of disease or all-cause death, whichever occurred first. Data for the crossover phase and the pharmacokinetics and immunogenicity of sugemalimab were not mature at the recent data cutoff; therefore those outcomes are not reported here and will be reported subsequently.

Statistical analysis

A sample size of 480 patients, to achieve 360 progression-free survival events and 360 overall survival events in both groups combined, would provide 89% power with an assumed progression-free survival HR of 0·70 and a two-sided α value of 0·05, and 80% power with an assumed overall survival HR of 0·72. An interim progression-free survival analysis and an interim overall survival analysis were planned for when 252 progression-free survival events and 252 overall survival events, had been observed or the last patient had been randomly assigned (whichever occurred later). For the interim analysis of progression-free survival reported in this Article, we planned to test the investigator-assessed progression-free survival and descriptively analysed the BICR-assessed progression-free survival to provide supporting evidence. We planned to do the final analysis of progression-free survival when 360 progression-free survival events had been observed, which is reported here, and for overall survival when 360 overall survival events had been seen (which will be reported in a future publication). Full details of the statistical analysis are shown in appendix 2 (pp 10–11). The trial is being continued to collect the overall survival data and to do formal statistical testing for overall survival in all patients.

Progression-free survival and overall survival were analysed in the intention-to-treat population, which included all randomly assigned patients. The objective response rate was analysed among all randomly assigned patients with any measurable baseline lesion. Duration of response was analysed among patients who achieved an objective response. The safety population was all randomly assigned patients who received at least one dose of study treatment.

For the primary endpoint of investigator-assessed progression-free survival, a stratified Cox model was used to estimate hazard ratios (HRs) with 95% CIs. The stratification factors were the same as those for randomisation. The Kaplan-Meier method was used to estimate median progression-free survival with a 95% CI and a stratified log-rank test was used to calculate p values. The Kaplan-Meier method was also used to estimate landmark progression-free survival rates at 12 months and their 95% CIs were estimated using the Brookmeyer Crowley method. The Kaplan-Meier plots were constructed and non-proportionality was assessed visually. Secondary endpoints, including overall survival, progression-free survival assessed by BICR, and progression-free survival in patients with PD-L1 of at least 1%, were analysed in the same way as the primary endpoint. The landmark overall survival rates at 12 months and 24 months and their 95% CIs were estimated using the same method as for the primary endpoint. The differences in objective response rate between groups were analysed using stratified Mantel–Haenszel tests; the method was used to calculate the objective response rate and 95% CI for each group, and normal approximation to a binomial distribution was used to calculate the 95% CI for the difference in objective response rate between groups. The duration of response was analysed by the Kaplan-Meier method and all statistical analyses were descriptive. Prespecified key subgroup analyses (age [<65 years *vs* ≥65 years], sex, smoking status, ECOG performance status [0 *vs* 1], tumour pathological type [squamous *vs* non-squamous], brain metastases [yes *vs* no], liver metastases [yes *vs* no], and PD-L1 expression [<1%, ≥1%, 1–49%, and ≥50%]) were done for progression-free survival and overall survival to assess the consistency of treatment effects in patient subgroups. Subgroup analysis were done on the basis of unstratified Cox proportional hazards models.

Following the interim progression-free survival analysis, given that the analysis was successful, we planned to use sequential testing method to control overall type I error, and secondary endpoints were to be tested in the following order: overall survival, progression-free survival in patients with PD-L1 of at least 1%, and objective response rate. Progression-free survival assessed by BICR was not specified as an endpoint to be formally tested. The Lan–DeMets method with an approximate O'Brien–Fleming boundary was used to control for type I error to account for a preplanned interim analysis of progression-free survival.[17] The two-sided α boundary was 0·0188 (calculated according to the number of events observed at the interim progression-free survival analysis) for claiming the success of the primary objective at the interim analysis, when 268 progression-free survival events were observed at data cutoff on June 8, 2020. In this Article, we first report data for the primary endpoint investigator-assessed progression-free survival at interim progression-free survival analysis, to show that the primary objective was successfully achieved. BICR-assessed progression-free survival at the interim progression-free survival analysis was also reported (analysed descriptively). The remainder of the reported results were based on the final progression-free survival analysis. Because the number of overall survival events had not been reached to do prespecified formal overall survival analysis, the key secondary endpoints of overall survival and progression-free survival in patients with PD-L1 of at least 1% were analysed descriptively at the interim and final progression-free survival analyses.

Post-hoc analysis was done for investigator-assessed progression-free survival in different pathological subtypes by PD-L1 expression (squamous NSCLC with PD-L1 <1%, squamous with PD-L1 ≥1%, non-squamous with PD-L1 <1%, and non-squamous with PD-L1 ≥1%), investigator-assessed intracranial progression-free survival in patients with baseline brain metastases, and investigator-assessed incidence rate of new brain lesion development in patients with or without baseline brain metastases. For the intracranial progression-free survival analysis, the unstratified HR was calculated using the Fine–Gray regression model,[18] in which systemic progression of disease without intracranial progression was considered to be an event of competing risk.

An independent data-monitoring committee evaluated the safety data collected in the trial every 6 months after the first patient was enrolled, and monitored the data for interim progression-free survival analysis and made recommendations to the sponsor according to the predefined boundaries. The statistical analysis for interim progression-free survival analysis before the trial unmasking was done by the independent data coordinating centre, where external data analysts prepared unmasked data summary reports. The final progression-free survival analysis was done by a contract research organisation under the sponsor's oversight according to the statistical analysis plan. A two-sided α value of 0·05 was used as the significance level and a sequential testing method was used to control the overall type I error. Statistical analysis was done using SAS (version 9.4). All data reported here were based on the interim and final analysis of progression-free survival. This trial is registered with ClinicalTrials.gov, NCT03789604, and is closed to new participants.

Role of the funding source

The funder participated in the data collection, data analysis, and data interpretation in collaboration with the authors, and contributed to the writing of the report by funding professional medical writing assistance.

Results

Between Dec 13, 2018, and May 15, 2020, 846 patients were screened, of whom 367 (43%) patients were excluded before randomisation, most commonly because they did not meet the eligibility criteria (figure 1); the main reasons for exclusion were positive *EGFR* mutation, physician decision, tumour tissue sample not available

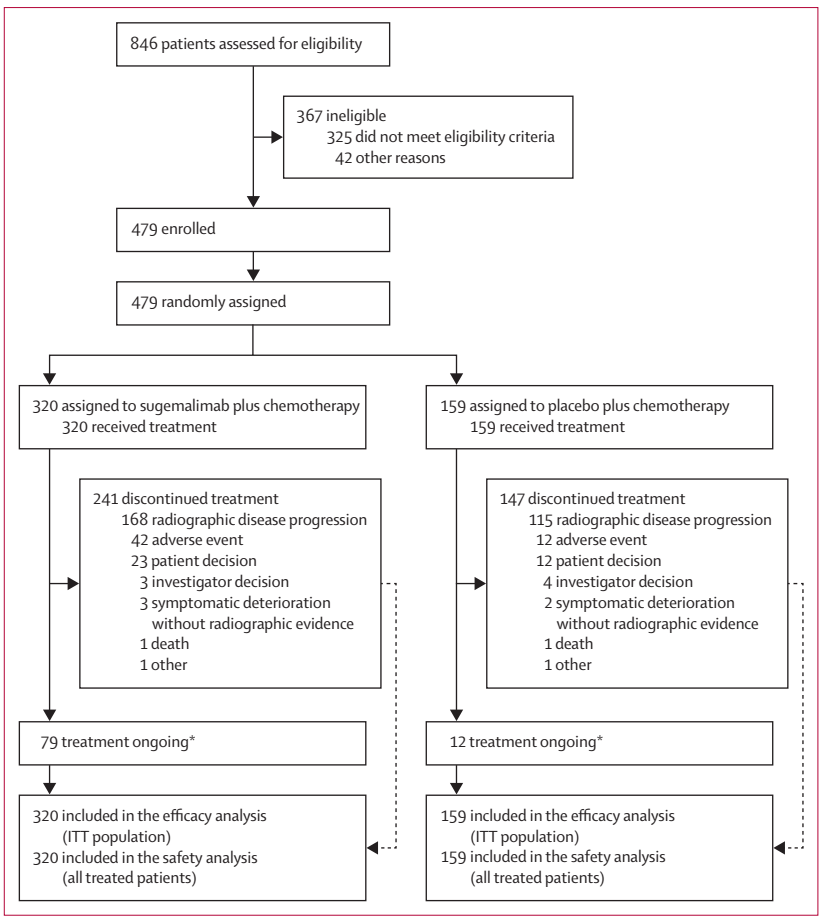


Figure 1: **Trial profile**
Data cutoff was March 15, 2021. *Includes all patients who received any dose of sugemalimab, placebo, carboplatin, pemetrexed, or paclitaxel. ITT=intention-to-treat.

	Sugemalimab plus chemotherapy (n=320)	Placebo plus chemotherapy (n=159)
Sex		
Male	254 (79%)	129 (81%)
Female	66 (21%)	30 (19%)
Age, years		
Median	62·0 (56·0–67·0)	64·0 (56·0–68·0)
<65	202 (63%)	91 (57%)
≥65	118 (37%)	68 (43%)
Eastern Cooperative Oncology Group performance status		
0	59 (18%)	25 (16%)
1	261 (82%)	134 (84%)
Smoking status		
Never smoked	88 (27%)	40 (25%)
Current or former smoker	232 (73%)	119 (75%)
Tumour pathological subtype		
Squamous	129 (40%)	63 (40%)
Non-squamous	191 (60%)	96 (60%)
PD-L1 expression		
<1%	124 (39%)	64 (40%)
≥1%	196 (61%)	95 (60%)
Baseline metastases		
Liver	39 (12%)	18 (11%)
Brain	50 (16%)	17 (11%)

Data are median (IQR) or n (%).

Table 1: **Baseline demographic and clinical characteristics (intention-to-treat population)**

for PD-L1 testing, patient withdrawal, and inadequate organ function (appendix 2 p 13). 479 patients were randomly assigned, 320 (67%) to sugemalimab and 159 (33%) to placebo, in addition to platinum-based chemotherapy, and all were included in the intention-to-treat and safety populations (figure 1). Demographic and baseline disease characteristics were well balanced in the two groups (table 1).

We report here, for the intention-to-treat population, the primary endpoint for investigator-assessed progression-free survival from the prespecified interim progression-free survival analysis with a median follow-up of 8·6 months (IQR 6·1–11·4) as of the data cutoff on June 8, 2020, and at the final progression-free survival analysis after an additional 9·2 months of follow-up (data cutoff March 15, 2021; median follow-up 17·8 months [IQR 15·1–20·9]). The data cutoff for the following parameters was March 15, 2021. 241 (75%) of 320 patients in the sugemalimab group and 147 (93%) of 159 patients in the placebo group discontinued their assigned treatment, principally because of disease progression (168 [53%] *vs* 115 [72%]), and 79 (25%) of 320 patients in the sugemalimab group and 12 (8%) of 159 in the placebo group were still receiving treatment (figure 1). Reasons for discontinuation of chemotherapy are summarised in appendix 2 (p 14). Overall, 257 (80%) of 320 patients in the sugemalimab group and 124 (78%) of 159 in the placebo group completed four cycles of chemotherapy (appendix 2, p 15). Median duration of study treatment was 7·2 months (IQR 4·2–15·4) with sugemalimab and 4·6 months (2·8–6·9) with placebo (appendix 2 p 15). 141 (44%) of 320 patients in the sugemalimab group and 99 (62%) of 159 in the placebo group had received at least one follow-up anti-cancer therapy (appendix 2 p 16). In the placebo group, 44 (28%) of 159 patients crossed over to receive at least one dose of sugemalimab monotherapy and 20 (13%) of 159 received subsequent immunotherapy other than sugemalimab (appendix 2, p 16). Data collection on the use of subsequent anti-cancer therapy is ongoing.

At the prespecified interim analysis (data cutoff June 8, 2020) for progression-free survival, GEMSTONE-302 met the primary endpoint of statistically significantly improved investigator-assessed progression-free survival in patients treated with sugemalimab plus chemotherapy compared with those treated with placebo plus chemotherapy. Progression or death events occurred in 155 (48%) of 320 patients with sugemalimab and 113 (71%) of 159 with placebo. Median progression-free

survival was 7·8 months (95% CI 6·9–9·0) with sugemalimab versus 4·9 (4·7–5·0) with placebo (stratified HR 0·50 [95% CI 0·39–0·64], p<0·0001 (appendix 2 p 29).

The improvement in progression-free survival was maintained at the prespecified progression-free survival final analysis (data cutoff March 15, 2021), with disease progression or death events occurring in 223 (70%) of 320 patients with sugemalimab and 135 (85%) of 159 with placebo: median progression-free survival was 9·0 months (95% CI 7·4–10·8) with sugemalimab versus 4·9 months (4·8–5·1) with placebo (stratified HR 0·48, 95% CI 0·39–0·60; p<0·0001; figure 2). The estimated 12-month progression-free survival rates were 36·4% (95% CI 31·0–41·8) with sugemalimab versus 14·8% (9·7–21·1) with placebo (appendix 2 p 17). Similar improvements with sugemalimab were seen in progression-free survival as assessed by the BICR at the interim and final analysis (appendix 2 pp 30–31). Prespecified subgroup analysis of investigator-assessed progression-free survival also showed similar improvements in the sugemalimab group versus the placebo group (figure 2, figure 3, appendix 2 p 32). Post-hoc analysis suggested that progression-free survival improvement was independent of PD-L1 expression for both squamous and non-squamous subgroups (appendix 2 p 33).

Post-hoc analysis suggested that among those patients with baseline brain metastases, sugemalimab plus chemotherapy, compared with placebo, improved intracranial investigator-assessed progression-free survival (appendix 2 p 18). The addition of sugemalimab, as compared with placebo, also led to a lower incidence rate of new brain lesions among patients with or without baseline brain metastases (appendix 2 p 19).

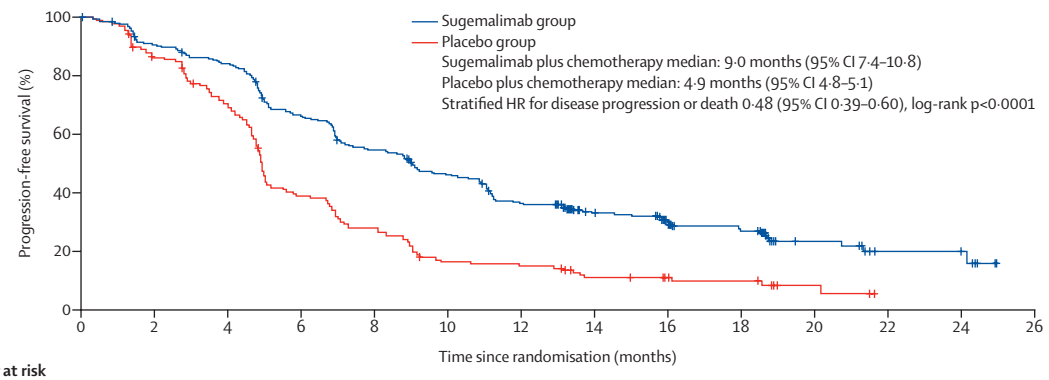
As of March 15, 2021, 198 patients had died (121 [38%] of 320 in the sugemalimab group and 77 [48%] of 159 in the placebo group), which were 55% of the preplanned number of events for the prespecified overall survival final analysis, and thus the data were not mature enough for the predefined formal analysis of overall survival. Preliminary analysis showed the median overall survival was longer with sugemalimab than with placebo (figure 4). Survival rates were 72·4% (95% CI 67·0–77·0%) at 12 months and 47·1% (37·2–56·4) at 24 months with sugemalimab versus 62·0% (53·6–69·3) at 12 months and 38·1% (27·2–49·0) at 24 months with placebo (appendix 2 p 17).

The objective response rate was higher in the sugemalimab group than in the placebo group (appendix 2 p 20). Improvement in response rates and duration of response favouring sugemalimab were seen across different subgroups defined by NSCLC subtype or tumour cell PD-L1 expression (appendix 2 p 20).

Treatment-emergent adverse events were reported in 319 (>99%) of 320 patients in the sugemalimab group and 157 (99%) of 159 patients in the placebo group (appendix 2 p 21). Rates of treatment-emergent adverse events, grade 3–4 treatment-emergent adverse events, and fatal treatment-emergent adverse events were generally similar between the two groups (table 2, appendix 2 pp 21–22). Any treatment-related adverse events occurred in 317 (99%) of 320 patients in the sugemalimab group and 153 (96%) of 159 patients in the placebo group (table 2). All reported grade 3–4 adverse events related to any treatment are listed in table 2 and occurred in 172 (54%) of 320 patients in the sugemalimab group and 89 (56%) of 159 patients in the placebo group, with the most common being neutrophil count decreased (in 104 [33%] of 320 *vs* 52 [33%] of 159), white blood cell count decreased (45 [14%] *vs* 27 [17%]), anaemia (43 [13%] *vs* 18 [11%]), platelet count decreased (33 [10%] *vs* 15 [9%]), and neutropenia (12 [4%] *vs* seven [4%]; table 2, appendix 2 [pp 23–24]). Any treatment-related serious adverse events occurred in 73 (23%) of 320 patients in the sugemalimab and 31 (20%) of 159 patients in the placebo group (appendix 2 p 25). The most common serious adverse events related to any treatment were anaemia (11 [3%] of 320 with sugemalimab *vs* five [3%] of 159 with placebo), pneumonia (ten [3%] *vs* seven [4%]), and platelet count decreased (ten [3%] *vs* four [3%]; appendix 2 p 25). Adverse events related to any treatment that led to discontinuation of any treatment occurred in 46 (14%) of 320 with sugemalimab and 14 (9%) of 159 with placebo. The most common any treatment-related adverse events leading to treatment discontinuation were anaemia (six [2%] *vs* three [2%]), pneumonia (five [2%] *vs* three [2%]), and abnormal hepatic function (three [1%] *vs* one [1%]; appendix 2 [p 26]). The proportion of patients experiencing adverse events leading to chemotherapy dose reduction was 46 (14%) of 320 with sugemalimab versus 29 (18%) of 159 with placebo (appendix 2 p 21). Deaths from adverse events irrespective of attribution occurred in 19 (6%) of 320 patients in the sugemalimab group and nine (6%) of 159 in the placebo group. Details of all fatal adverse events are provided in appendix 2 (p 27). Fatal adverse events attributed to any treatment were reported in ten (3%) of 320 patients in the sugemalimab group (pneumonia with respiratory failure in one patient; myelosuppression with septic shock in one patient; pneumonia in two patients; respiratory failure, abdominal pain, cardiac failure, and immune-mediated pneumonitis in one patient each; the other two deaths had an unspecifed cause) and two (1%) of 159 with placebo (pneumonia and multiple organ dysfunction syndrome; appendix 2 p 28).

Immune-related treatment-emergent adverse events—ie, adverse events of special interest as assessed by the sponsor—occurred in 80 (25%) of 320 patients with sugemalimab and five (3%) of 159 with placebo (appendix 2 p 21), most of which were grade 1–2 (table 2). The most common immune-related treatment-emergent adverse events by category were hypothyroidism (34 [11%] of 320 *vs* one [1%] of 159), hyperthyroidism (23 [7%] *vs* two [1%]), and non-severe skin adverse reaction (23 [7%] *vs* one [1%]).

A



Number at risk (number censored)													
Sugemalimab group	320 (0)	283 (7)	263 (8)	204 (10)	168 (11)	139 (14)	107 (17)	75 (40)	52 (55)	38 (66)	15 (85)	8 (90)	5 (93)	0 (97)
Placebo group	159 (0)	132 (6)	103 (9)	57 (10)	41 (10)	23 (11)	21 (11)	13 (14)	10 (17)	8 (18)	3 (22)	0 (24)	..	..

B

	Number of events/number of patients (%)		Median progression-free survival, months (95% CI)		HR (95% CI)
	Sugemalimab group (n=320)	Placebo group (n=159)	Sugemalimab group (n=320)	Placebo group (n=159)	
Age, years					
<65	142/202 (70%)	78/91 (86%)	9·2 (7·2–11·0)	4·9 (4·5–5·1)	0·48 (0·36–0·63)
≥65	81/118 (69%)	57/68 (84%)	8·6 (6·9–10·4)	4·9 (4·8–6·9)	0·53 (0·38–0·75)
Sex					
Male	176/254 (69%)	111/129 (86%)	9·0 (7·4–11·0)	4·9 (4·6–5·1)	0·48 (0·38–0·62)
Female	47/66 (71%)	24/30 (80%)	9·0 (6·9–11·1)	5·5 (3·7–8·9)	0·60 (0·37–0·99)
Smoking status					
Never smoked	65/88 (74%)	34/40 (85%)	9·0 (6·9–11·1)	4·9 (3·7–7·1)	0·55 (0·36–0·83)
Current or former smoker	158/232 (68%)	101/119 (85%)	9·0 (7·2–11·0)	4·9 (4·7–5·2)	0·48 (0·37–0·62)
ECOG performance status					
0	41/59 (70%)	19/25 (76%)	10·9 (6·8–14·5)	4·9 (4·2–8·9)	0·59 (0·34–1·02)
1	182/261 (70%)	116/134 (87%)	8·9 (7·1–10·4)	4·9 (4·7–5·2)	0·48 (0·38–0·61)
Tumour pathological type					
Non-squamous	128/191 (67%)	78/96 (81%)	9·6 (8·3–11·0)	5·8 (4·9–7·1)	0·59 (0·45–0·79)
Squamous	95/129 (74%)	57/63 (91%)	8·3 (6·9–10·9)	4·8 (4·2–4·9)	0·34 (0·24–0·48)
PD-L1 expression					
<1%	100/124 (81%)	57/64 (89%)	7·4 (6·8–9·0)	4·9 (4·0–5·8)	0·56 (0·40–0·77)
≥1%	123/196 (63%)	78/95 (82%)	10·9 (8·9–11·3)	4·9 (4·7–5·8)	0·46 (0·35–0·62)
1–49%	66/92 (72%)	39/48 (81%)	8·8 (6·9–10·9)	4·8 (4·6–5·1)	0·53 (0·35–0·79)
≥50%	57/104 (55%)	39/47 (83%)	12·9 (9·2–17·9)	5·1 (4·5–7·1)	0·41 (0·27–0·62)
Brain metastases					
Yes	33/50 (66%)	17/17 (100%)	8·9 (5·1–13·7)	4·5 (2·8–5·0)	0·29 (0·15–0·56)
No	190/270 (70%)	116/140 (83%)	9·0 (7·4–10·9)	4·9 (4·8–6·7)	0·54 (0·43–0·68)
Liver metastases					
Yes	30/39 (77%)	16/18 (89%)	6·0 (4·0–8·9)	3·9 (2·8–5·6)	0·54 (0·29–1·02)
No	193/281 (69%)	119/141 (84%)	9·2 (8·3–11·0)	4·9 (4·8–5·8)	0·49 (0·39–0·61)
All patients	**223/320 (70%)**	**135/159 (85%)**	**9·0 (7·4–10·8)**	**4·9 (4·8–5·1)**	**0·48 (0·39–0·60)**

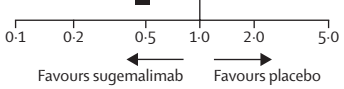


Figure 2: **Kaplan–Meier plot of investigator-assessed progression-free survival and forest plot showing the subgroup analysis of progression-free survival**
Patients in both groups also received chemotherapy. (A) Investigator-assessed progression-free survival in the intention-to-treat population. The HR was calculated using a stratified Cox regression model. (B) Subgroup analysis of progression-free survival. HRs were calculated using an unstratified Cox regression model. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio.

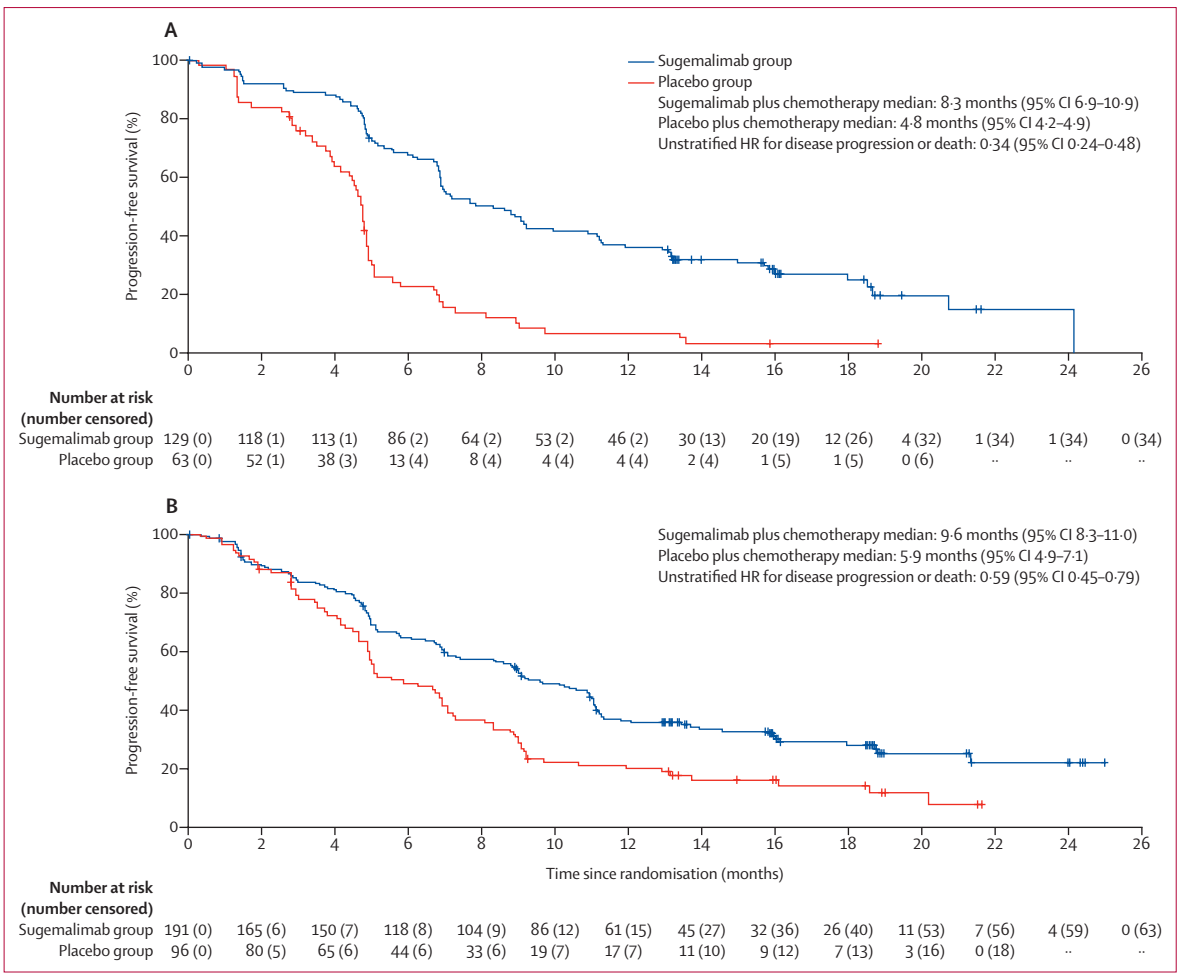


Figure 3: **Kaplan–Meier plots of investigator-assessed progression-free survival of patients by tumour pathological type**
Patients in both groups also received chemotherapy. Progression-free survival of patients with squamous non-small-cell lung cancer (A) and non-squamous non-small-cell lung cancer (B) at data cutoff on March 15, 2021. HR=hazard ratio.

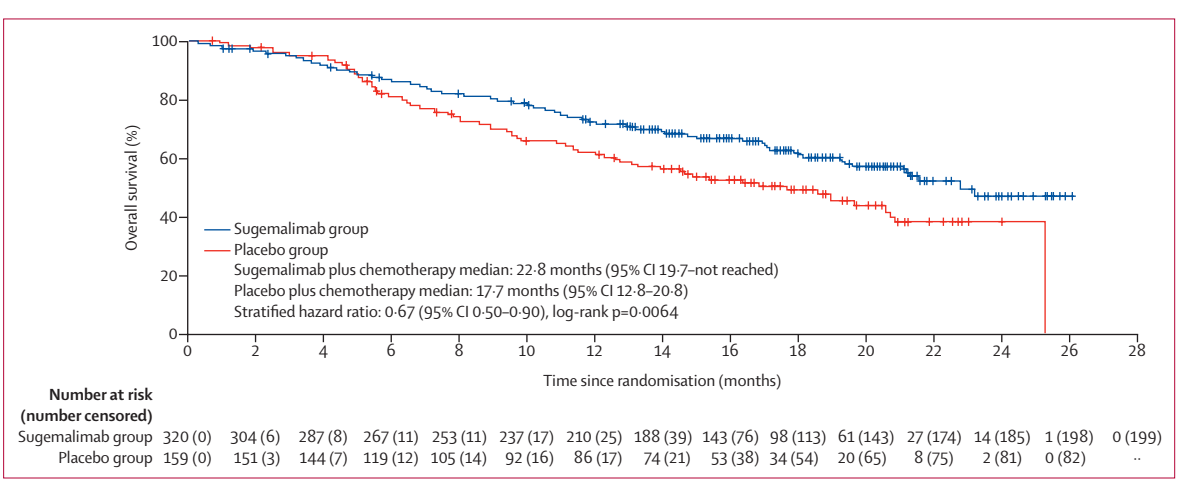


Figure 4: **Kaplan–Meier plot of overall survival**
Preliminary analysis at data cutoff on March 15, 2021, with a median follow-up of 17·8 months (IQR 15·1–20·9) and 55% of number of events for the prespecified final overall survival analysis.

	Sugemalimab plus chemotherapy (n=320)				Placebo plus chemotherapy (n=159)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
All adverse events	114 (36%)	138 (43%)	48 (15%)	19 (6%)	59 (37%)	57 (36%)	32 (20%)	9 (6%)
Adverse event leading to discontinuation of any treatment	16 (5%)	24 (8%)	4 (1%)	13 (4%)	6 (4%)	4 (3%)	4 (3%)	4 (3%)
Adverse event leading to discontinuation of sugemalimab or placebo	9 (3%)	16 (5%)	4 (1%)	13 (4%)	2 (1%)	2 (1%)	4 (3%)	4 (3%)
Any treatment-related adverse events	135 (42%)	126 (39%)	46 (14%)	10 (3%)	62 (39%)	55 (35%)	34 (21%)	2 (1%)
Any treatment-related adverse event leading to discontinuation of any treatment	16 (5%)	19 (6%)	3 (1%)	8 (3%)	5 (3%)	4 (3%)	4 (3%)	1 (1%)
Any treatment-related adverse event leading to discontinuation of sugemalimab or placebo	9 (3%)	12 (4%)	3 (1%)	8 (3%)	1 (1%)	2 (1%)	4 (3%)	1 (1%)
Grade 1–2 any treatment-related adverse events occurring in at least 10% patients in either group and all grade 3–5 any treatment-related adverse events								
Anaemia	191 (60%)	43 (13%)	0	0	91 (57%)	17 (11%)	1 (1%)	0
Neutrophil count decreased	81 (25%)	70 (22%)	34 (11%)	0	41 (26%)	27 (17%)	25 (16%)	0
White blood cell count decreased	135 (42%)	39 (12%)	6 (2%)	0	66 (42%)	26 (16%)	1 (1%)	0
Platelet count decreased	74 (23%)	25 (8%)	8 (3%)	0	45 (28%)	12 (8%)	3 (2%)	0
Aspartate aminotransferase increased	104 (33%)	1 (<1%)	0	0	39 (25%)	2 (1%)	0	0
Alanine aminotransferase increased	100 (31%)	3 (1%)	0	0	48 (30%)	3 (2%)	0	0
Appetite decreased	75 (23%)	0	0	0	36 (23%)	1 (1%)	0	0
Nausea	69 (22%)	1 (<1%)	0	0	39 (25%)	3 (2%)	0	0
Alopecia	59 (18%)	1 (<1%)	0	0	31 (20%)	0	0	0
Asthenia	48 (15%)	2 (1%)	0	0	26 (16%)	3 (2%)	0	0
Rash	47 (15%)	2 (1%)	0	0	13 (8%)	0	0	0
γ-glutamyltransferase increased	35 (11%)	6 (2%)	1 (<1%)	0	14 (9%)	2 (1%)	1 (1%)	0
Vomiting	36 (11%)	3 (1%)	0	0	21 (13%)	1 (1%)	0	0
Constipation	38 (12%)	0	0	0	21 (13%)	0	0	0
Fatigue	35 (11%)	3 (1%)	0	0	5 (3%)	1 (1%)	0	0
Leukopenia	27 (8%)	5 (2%)	1 (<1%)	0	12 (8%)	2 (1%)	0	0
Hypothyroidism	32 (10%)	0	0	0	2 (1%)	0	0	0
Hypoalbuminaemia	29 (9%)	0	0	0	16 (10%)	0	0	0
Neutropenia	15 (5%)	10 (3%)	2 (1%)	0	6 (4%)	5 (3%)	2 (1%)	0
Blood creatinine increased	22 (7%)	1 (<1%)	0	0	6 (4%)	0	0	0
Thrombocytopenia	17 (5%)	4 (1%)	0	0	8 (5%)	0	1 (1%)	0
Blood bilirubin increased	19 (6%)	1 (<1%)	0	0	16 (10%)	0	0	0
Diarrhoea	17 (5%)	3 (1%)	0	0	10 (6%)	0	0	0
Hyponatraemia	17 (5%)	3 (1%)	0	0	1 (1%)	1 (1%)	0	0
Blood alkaline phosphatase increased	16 (5%)	3 (1%)	0	0	4 (3%)	0	0	0
Hyperglycaemia	18 (6%)	1 (<1%)	0	0	5 (3%)	0	1 (1%)	0
Malaise	18 (6%)	0	0	0	7 (4%)	2 (1%)	0	0
Hepatic function atypical	10 (3%)	6 (2%)	0	0	2 (1%)	1 (1%)	1 (1%)	0
Lymphocyte count decreased	12 (4%)	3 (1%)	1 (<1%)	0	4 (3%)	2 (1%)	1 (1%)	0
Blood lactate dehydrogenase increased	15 (5%)	0	0	0	3 (2%)	0	1 (1%)	0
Hypokalaemia	14 (4%)	1 (<1%)	0	0	4 (3%)	1 (1%)	0	0
Pneumonia	8 (3%)	3 (1%)	0	3 (1%)	2 (1%)	5 (3%)	0	1 (1%)
Transaminases increased	11 (3%)	2 (1%)	0	0	2 (1%)	0	0	0
Abdominal pain upper	11 (3%)	1 (<1%)	0	0	1 (1%)	0	0	0
Mouth ulceration	11 (3%)	1 (<1%)	0	0	0	0	0	0
Pain	12 (4%)	0	0	0	5 (3%)	1 (1%)	0	0
Peripheral oedema	10 (3%)	1 (<1%)	0	0	1 (1%)	0	0	0
Hypertriglyceridaemia	8 (3%)	2 (1%)	0	0	4 (3%)	0	0	0
Bilirubin conjugated increased	7 (2%)	1 (<1%)	0	0	1 (1%)	0	0	0

(Table 2 continues on next page)

	Sugemalimab plus chemotherapy (n=320)				Placebo plus chemotherapy (n=159)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Blood cholesterol increased	7 (2%)	1 (<1%)	0	0	2 (1%)	0	0	0
Febrile neutropenia	0	5 (1·6%)	2 (1%)	0	0	1 (1%)	0	0
Amylase increased	2 (1%)	3 (1%)	0	0	1 (1%)	0	0	0
Dyspnoea	4 (1%)	1 (<1%)	0	0	0	0	0	0
Myelosuppression	0	2 (1%)	2 (1%)	1 (<1%)	1 (1%)	2 (1%)	1 (1%)	0
Stomatitis	3 (1%)	2 (1%)	0	0	0	0	0	0
Upper respiratory tract infection	4 (1%)	1 (<1%)	0	0	0	0	0	0
Urinary tract infection	4 (1%)	1 (<1%)	0	0	2 (1%)	0	0	0
Abdominal pain	2 (1%)	1 (<1%)	0	1 (<1%)	1 (1%)	0	0	0
Haemoptysis	3 (1%)	1 (<1%)	0	0	1 (1%)	1 (1%)	0	0
Hypertension	3 (1%)	1 (<1%)	0	0	2 (1%)	0	0	0
Immune-mediated pneumonitis	1 (<1%)	2 (1%)	0	1 (<1%)	0	0	0	0
Lipase increased	1 (<1%)	2 (1%)	1 (<1%)	0	0	0	0	0
Anaphylactic reaction	2 (1%)	1 (<1%)	0	0	1 (1%)	0	0	0
Cardiac failure	0	2 (1%)	0	1 (<1%)	0	0	1 (1%)	0
Maculopopular rash	2 (1%)	1 (<1%)	0	0	0	0	0	0
Renal failure	2 (1%)	1 (<1%)	0	0	0	0	0	0
Autoimmune dermatitis	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Death	0	0	0	2 (1%)	0	0	0	0
Dyspnoea exertional	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Eczema	1 (<1%)	1 (<1%)	0	0	1 (1%)	0	0	0
Liver injury	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Lymphopenia	1 (<1%)	1 (<1%)	0	0	1 (1%)	0	0	0
Respiratory failure	0	0	0	2 (1%)	0	0	0	0
Type 2 diabetes	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Acute kidney injury	0	1 (<1%)	0	0	0	0	0	0
Ascites	0	1 (<1%)	0	0	0	0	0	0
Cystitis	0	1 (<1%)	0	0	0	0	0	0
Granulocytopaenia	0	1 (<1%)	0	0	0	0	0	0
Immune-mediated hepatitis	0	0	1 (<1%)	0	0	0	0	0
Nephritis	0	1 (<1%)	0	0	0	0	0	0
Neutrophil percentage decreased	0	1 (<1%)	0	0	0	0	0	0
Septic shock	0	0	0	1 (<1%)	0	0	0	0
Skin infection	0	1 (<1%)	0	0	0	0	0	0
Uterine haemorrhage	0	1 (<1%)	0	0	0	0	0	0
Agranulocytosis	0	0	0	0	0	0	1 (1%)	0
Bone marrow failure	0	0	0	0	0	1 (1%)	0	0
Lower gastrointestinal haemorrhage	0	0	0	0	0	0	1 (1%)	0
Malnutrition	0	0	0	0	0	1 (1%)	0	0
Multiple organ dysfunction syndrome	0	0	0	0	0	0	0	1 (1%)
Rhabdomyolysis	0	0	0	0	0	1 (1%)	0	0
Immune-related adverse events*								
Hypothyroidism	34 (11%)	0	0	0	1 (1%)	0	0	0
Hyperthyroidism	23 (7%)	0	0	0	2 (1%)	0	0	0
Skin adverse reaction, non-severe	23 (7%)	0	0	0	1 (1%)	0	0	0
Skin adverse reaction, severe	0	3 (1%)	0	0	0	0	0	0
Pneumonitis	3 (1%)	2 (1%)	0	1 (<1%)	1 (1%)	0	0	0
Hepatitis	0	4 (1%)	1 (<1%)	0	0	0	0	0
Nephritis, including renal failure	2 (1%)	1 (<1%)	0	0	0	0	0	0

(Table 2 continues on next page)

	Sugemalimab plus chemotherapy (n=320)				Placebo plus chemotherapy (n=159)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Arthritis	2 (1%)	0	0	0	0	0	0	0
Diabetes	2 (1%)	0	0	0	0	0	0	0
Thyroiditis	2 (1%)	0	0	0	1 (1%)	0	0	0
Colitis	1 (<1%)	0	0	0	0	0	0	0
Myocarditis	1 (<1%)	0	0	0	0	0	0	0
Ocular toxicities	1 (<1%)	0	0	0	0	0	0	0
Pancreatitis	0	0	1 (<1%)	0	0	0	0	0

Data are n (%). *Immune-related adverse events were defined on the basis of a list of preferred categories of terms specified by the sponsor and included in the analysis regardless of whether the events were attributed to treatment by the investigator.

Table 2: **Summary of adverse events for all patients who received treatment (safety population)**

Discussion

In the GEMSTONE-302 study, the combination of sugemalimab plus platinum-based chemotherapy resulted in statistically significant and clinically meaningful improvements in progression-free survival versus placebo plus platinum-based chemotherapy in metastatic NSCLC. Subgroup analysis suggested these benefits were maintained regardless of PD-L1 expression and NSCLC subtype. In combination with chemotherapy, sugemalimab also reduced tumour burden in more patients than placebo did, as shown by higher objective response rates with durable responses.

Squamous and non-squamous NSCLC have been shown to differ markedly in their tumour microenvironment and genomic drivers, which might translate into differences in their response to immune checkpoint therapy and subsequent prognosis.[19,20] Compared with non-squamous NSCLC, squamous NSCLC has a poorer prognosis and fewer therapeutic options.[21] In terms of immunotherapy, pembrolizumab plus chemotherapy is the only PD-1 inhibitor currently recommended in the US National Comprehensive Cancer Network guidelines as the preferred first-line therapy for both metastatic non-squamous and squamous NSCLC.[22] In Chinese patient populations, the combination of PD-1 inhibitor with chemotherapy also showed improved progression-free survival, overall survival, or both in several studies.[23–27] By contrast, PD-L1 inhibitor combination therapies that include atezolizumab are only recommended for a subgroup of patients with non-squamous NSCLC, and no PD-L1 inhibitor combinations have been recommended for squamous NSCLC.[22] There are few data on the combination of a PD-L1 inhibitor and chemotherapy in Chinese NSCLC patients. In the GEMSTONE-302 study, which investigated the PD-L1 inhibitor sugemalimab in combination with chemotherapy in both squamous and non-squamous NSCLC, there was improved progression-free survival observed with sugemalimab plus chemotherapy across pathologies, especially in the squamous NSCLC subgroup, compared with placebo plus chemotherapy. These results suggest that sugemalimab could be an option for treatment-naive metastatic NSCLC patients, including in patients with non-squamous NSCLC as an anti-PD-L1 immunotherapy option with carboplatin and pemetrexed, and also in patients with squamous NSCLC as the only anti-PD-L1 immunotherapy plus chemotherapy option. Another study, CheckMate 9LA,[28] which was also done in both squamous and non-squamous NSCLC, showed a median progression-free survival of 6·7 months with nivolumab plus ipilimumab combined with chemotherapy compared with 5·3 months with chemotherapy alone (HR 0·67, 95% CI 0·56–0·79) with a minimum follow-up of 2 years. Thus, the regimen has been approved in the USA, the EU, and several other countries as first-line treatment for both squamous and non-squamous metastatic NSCLC. In the CheckMate 9LA study[28] more pronounced progression-free survival benefit was seen in the squamous NSCLC subgroup (HR 0·57, 95% CI 0·42–0·78) than in the non-squamous NSCLC subgroup (0·74, 0·60–0·92) after treatment with nivolumab plus ipilimumab with two cycles of chemotherapy. This result was similar to the findings in the GEMSTONE-302 study. Furthermore, our triplet combination of sugemalimab plus carboplatin and paclitaxel chemotherapy offered similar progression-free survival benefits and provided patients with a more convenient drug regimen compared with the quadruplet combination of PD-1, CTLA-4 inhibitors, and carboplatin and paclitaxel chemotherapy in CheckMate 9LA.

Additionally, the progression-free survival benefit was also seen in all the other preplanned subgroups in GEMSTONE-302, including in patients with all PD-L1 expression levels (<1%, ≥1%, 1–49%, and ≥50%) and in patients with brain or liver metastases, for whom therapeutic options are few and the prognosis is poor.[29] Furthermore, the intracranial progression-free survival was also improved with sugemalimab plus chemotherapy in patients who had baseline brain metastases, which was consistent with the systemic progression-free survival, and the addition of sugemalimab also reduced

the development of new brain lesions in patients with or without baseline brain metastases.

Data from the phase 3 IMpower131[7] and IMpower132[8] trials showed that atezolizumab in combination with chemotherapy, compared with chemotherapy alone, led to a statistically significant but clinically moderate improvement in progression-free survival (median 6·3 months *vs* 5·6 months, HR 0·71, 95% CI 0·60–0·85; p=0·0001[7] and 7·6 months *vs* 5·2 months; HR 0·60, 0·49–0·72; p<0·0001[8]). The POSEIDON trial[9] also showed statistically significant improvements in progression-free survival with durvalumab plus chemotherapy versus chemotherapy alone (median progression-free survival 5·5 months [95% CI 4·7–6·5] *vs* 4·8 months [4·6–5·8]; HR 0·74 [0·62–0·89]; p=0·00093). However, in all three PD-L1 trials, the progression-free survival benefit did not translate into an overall survival benefit (IMpower131 median overall survival 14·2 months [95% CI 12·3–16·8] *vs* 13·5 months [12·2–15·1]; HR 0·88, 95% CI 0·73–1·05, p=0·16;[7] IMpower132 17·5 months [13·2–19·6] *vs* 13·6 months [11·0–15·7]; HR 0·86, 0·71–1·06, p=0·1546;[8] POSEIDON 13·3 months [11·4–14·7] *vs* 11·7 months [10·5–13·1]; HR 0·86, 0·72–1·02, p=0·7581[9]). Conversely, in KEYNOTE-189[5] and KEYNOTE-407,[6] pembrolizumab plus chemotherapy showed statistically significant progression-free survival improvements and overall survival benefits in all subgroups (such as age, sex, ECOG performance score, and PD-L1 expression) compared with placebo among patients with metastatic non-squamous and squamous NSCLC. With similar progression-free survival benefits across all subgroups observed in GEMSTONE-302, sugemalimab plus chemotherapy could be a potential new option as a first-line treatment for patients with metastatic NSCLC. The immature overall survival data analysis of GEMSTONE-302 showed an HR of 0·67 with crossover permitted, which could negatively affect the overall survival results; notably, crossover was not permitted in other PD-L1 trials.[7–9] The overall survival will be followed up continuously and the preplanned overall survival formal analysis, with a longer follow-up and more events accrued, will be reported subsequently.

This study showed that sugemalimab plus chemotherapy was well tolerated. The addition of sugemalimab did not appear to increase the frequency of adverse events commonly associated with chemotherapy regimens. The incidence of most immune-mediated treatment-emergent adverse events was not higher with sugemalimab plus chemotherapy than with sugemalimab monotherapy.[12,13] No unexpected safety signals were found. Of special interest, immune-related treatment-emergent adverse event profiles in the sugemalimab group were mostly grade 1–2 and generally consistent with the known profiles of products in the same class.[30–32]

To our knowledge, this study is the first to show a PD-L1 inhibitor plus chemotherapy benefiting patients with both metastatic non-squamous and squamous NSCLC in the same trial. At the time of the design of this study, PD-1 or PD-L1 inhibitors in combination with chemotherapy had been shown to be effective in studies with a specific pathology,[5] and a similar benefit was observed in squamous and non-squamous NSCLC.[9] However, no PD-1 or PD-L1 inhibitors were approved for first-line treatment of NSCLC patients in China at that time. By combining two pathologies in one study, patients randomised 2:1 to receive treatment reduced the total sample size required and the number of patients receiving placebo, which increased patients' compliance and benefits.

One limitation of this study is that the overall survival data are not mature enough to do the formal analysis. With longer follow-up, increased patients in the placebo group are expected to receive subsequent anti-cancer immunotherapy, which will continuously affect the results of overall survival. A prespecified formal overall survival analysis will be done to show the survival improvement ultimately.

In conclusion, the addition of sugemalimab to platinum-based chemotherapy showed statistically significant and clinically meaningful improvement in progression-free survival compared with placebo plus chemotherapy, irrespective of NSCLC pathologies and PD-L1 expression, supporting its application as a new first-line treatment option for patients with metastatic NSCLC.

Contributors

CZ, ZW, YL, ZM, JCha, HS, JW, DL, and JY provided substantial contributions to the conception and design of the study. CZ, ZW, YS, LC, ZM, RW, YY, WY, JCha, JChe, WZ, JCu, XC, YL, and HS enrolled and treated patients. DL did the statistical analysis and generated data. CZ, JW, DL, MQ, PL, and JY analysed and interpreted the data. CZ, JW, DL, MQ, PL, and JY drafted the manuscript and provided critical revision of the manuscript. CZ, JW, MQ, and DL verified the data. All authors had full access to all the data in the study, reviewed the data, contributed to the development of the manuscript, approved the final version, and had final responsibility for the decision to submit for publication.

Declaration of interests

CZ reports speaker honoraria from CStone Pharmaceuticals during the course of this study and, outside of this study, reports speaker honoraria from Lilly China, Sanofi, Boehringer Ingelheim, Roche, MSD, Qilu Pharmaceutical, Hengrui Therapeutics, Innovent Biologics, Luye Pharma Group, TopAlliance Biosciences, and Amoy Diagnostics; and is an advisor for Innovent Biologics, Hengrui Therapeutics, Qilu Pharmaceutical, and TopAlliance Biosciences. JW, JY, PL, MQ, and DL are paid employees of CStone Pharmaceuticals and JW and JY declare stock ownership in the company. All other authors declare no competing interests.

Data sharing

Individual participant data will not be available (including data dictionary). The study protocol is available in appendix 2.

Acknowledgments

We thank all the patients and their families for participating in the study, and the investigators who participated in the study. We also thank Hao Wang, Shuo Chi from CStone Pharmaceuticals, and Xin Wang from IQVIA (funded by CStone Pharmaceuticals) for assistance with the statistical analysis of this study. Medical writing assistance was funded by CStone Pharmaceuticals and provided by Julie Smith and Susan Neville from Parexel on an earlier draft of the manuscript, and by Rumei Chen and Mingjue Zhao from CStone Pharmaceuticals.

References

1 Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; **71:** 209–49.

2 Dafni U, Tsourti Z, Vervita K, Peters S. Immune checkpoint inhibitors, alone or in combination with chemotherapy, as first-line treatment for advanced non-small cell lung cancer. A systematic review and network meta-analysis. *Lung Cancer* 2019; **134:** 127–40.

3 Socinski MA, Obasaju C, Gandara D, et al. Current and emergent therapy options for advanced squamous cell lung cancer. *J Thorac Oncol* 2018; **13:** 165–83.

4 Gogishvili M, Melkadze T, Makharadze T, et al. LBA51 EMPOWER-lung 3: cemiplimab in combination with platinum doublet chemotherapy for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC). European Society for Medical Oncology Congress 2021; Sept 19, 2021; mini oral session: NSCLC, metastatic. *Ann Oncol* 2021; **32** (suppl 5)**:** S1283–346.

5 Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018; **378:** 2078–92.

6 Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med* 2018; **379:** 2040–51.

7 Jotte R, Cappuzzo F, Vynnychenko I, et al. Atezolizumab in combination with carboplatin and nab-paclitaxel in advanced squamous NSCLC (IMpower131): results from a randomized phase III trial. *J Thorac Oncol* 2020; **15:** 1351–60.

8 Nishio M, Barlesi F, West H, et al. Atezolizumab plus chemotherapy for first-line treatment of nonsquamous NSCLC: results from the randomized phase 3 IMpower132 trial. *J Thorac Oncol* 2021; **16:** 653–64.

9 Johnson ML, Cho BC, Luft A, et al. Durvalumab + tremelimumab + chemotherapy as first-line treatment for mNSCLC: results from the phase 3 POSEIDON study. International Association for the Study of Lung Cancer 2021 World Conference on Lung Cancer; Sept 8–14, 2021 (abstract PL02.01).

10 Lee HT, Lee SH, Heo YS. Molecular interactions of antibody drugs targeting PD-1, PD-L1, and CTLA-4 in immuno-oncology. *Molecules* 2019; **24:** 1190.

11 Zhang J, Li Z, Tang L, et al. The preclinical characterization of CS1001, an anti-PD-L1 IgG4 monoclonal antibody and its activity beyond T cell regulation. American Association for Cancer Research Annual Meeting 2020; April 27–28 and June 22–24, 2020 (abstract 3260).

12 Shen L, Li J, Xu N, et al. A phase 1a/1b trial of the anti-programmed death-ligand 1 (PD-L1) human monoclonal antibody (mAb), CS1001, in patients (pts) with advanced solid tumors or lymphomas. European Society for Medical Oncology Congress 2019; Sept 27–Oct 1, 2019. *Ann Oncol* 2019; **30** (suppl 5)**:** v475–532 (abstract 1268P).

13 Shen L, Li J, Miao Z, et al. CS1001, an anti-PD-L1 antibody, combined with standard of care (SOC) chemotherapy for first line (1L) advanced GC/GEJ and ESCC: preliminary results from 2 phase Ib cohorts of CS1001–101 study. European Society for Medical Oncology Congress 2020; Sept 19–21, 2020. *Ann Oncol* 2020; **31** (suppl 4)**:** S841–73 (abstract 1445P).

14 Zhou C, Wang Z, Sun Y, et al. GEMSTONE-302: a phase III study of platinum-based chemotherapy (chemo) with placebo or CS1001, an anti-PDL1 antibody, for first-line (1L) advanced non-small cell lung cancer (NSCLC). European Society for Medical Oncology Asia Virtual Congress 2020; Nov 20–22, 2020. *Ann Oncol* 2020; **31** (suppl 6)**:** S1386–406 (abstract 397P).

15 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45:** 228–47.

16 US Department of Health and Human Services, National Institutes of Health and National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. June 14, 2010. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (accessed Nov 19, 20).

17 Upton G, Cook I. A dictionary of statistics, second edn. Oxford: Oxford University Press, 2008.

18 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94:** 496–509.

19 Meng X, Gao Y, Yang L, et al. Immune microenvironment differences between squamous and non-squamous non-small-cell lung cancer and their influence on the prognosis. *Clin Lung Cancer* 2019; **20:** 48–58.

20 Relli V, Trerotola M, Guerra E, Alberti S. Abandoning the notion of non-small cell lung cancer. *Trends Mol Med* 2019; **25:** 585–94.

21 Morgensztern D, Campo MJ, Dahlberg SE, et al. Molecularly targeted therapies in non-small-cell lung cancer annual update 2014. *J Thorac Oncol* 2015; **10** (suppl 1)**:** S1–63.

22 Ettinger DS, Wood DE, Aisner DL, et al. NCCN guidelines insights: non-small cell lung cancer, version 2.2021. March 2, 2021. https://jnccn.org/view/journals/jnccn/19/3/article-p254.xml (accessed June 17, 2021).

23 Zhou C, Chen G, Huang Y, et al. Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naive patients with advanced non-squamous non-small-cell lung cancer (CameL): a randomised, open-label, multicentre, phase 3 trial. *Lancet Respir Med* 2021; **9:** 305–14.

24 Zhou C, Wu L, Fan Y, et al. Sintilimab plus platinum and gemcitabine as first-line treatment for advanced or metastatic squamous NSCLC: results from a randomized, double-blind, phase 3 trial (ORIENT-12). *J Thorac Oncol* 2021; **16:** 1501–11.

25 Yang Y, Wang Z, Fang J, et al. Efficacy and safety of sintilimab plus pemetrexed and platinum as first-line treatment for locally advanced or metastatic nonsquamous NSCLC: a randomized, double-blind, phase 3 study (Oncology pRogram by InnovENT anti-PD-1-11). *J Thorac Oncol* 2020; **15:** 1636–46.

26 Wang J, Lu S, Yu X, et al. Tislelizumab plus chemotherapy *vs* chemotherapy alone as first-line treatment for advanced squamous non-small-cell lung cancer: a phase 3 randomized clinical trial. *JAMA Oncol* 2021; **7:** 709–17.

27 Lu S, Wang J, Yu Y, et al. Tislelizumab plus chemotherapy as first-line treatment for locally advanced or metastatic nonsquamous NSCLC (RATIONALE 304): a randomized phase 3 trial. *J Thorac Oncol* 2021; **16:** 1512–22.

28 Reck M, Ciuleanu T-E, Cobo M, et al. First-line nivolumab (NIVO) plus ipilimumab (IPI) plus two cycles of chemotherapy (chemo) versus chemo alone (4 cycles) in patients with advanced non-small cell lung cancer (NSCLC): two-year update from CheckMate 9LA. 2021 ASCO Annual Meeting I. Session: lung cancer—non-small cell metastatic. *Proc Am Soc Clin Oncol* 2021; **39** (suppl)**:** 9000 (abstract).

29 Sperduto PW, Yang TJ, Beal K, et al. Estimating survival in patients with lung cancer and brain metastases: an update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). *JAMA Oncol* 2017; **3:** 827–31.

30 Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2018; **36:** 1714–68.

31 Thompson JA, Schneider BJ, Brahmer J, et al. Management of immunotherapy-related toxicities, version 1.2019. *J Natl Compr Canc Netw* 2019; **17:** 255–89.

32 Wang Y, Zhou S, Yang F, et al. Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: a systematic review and meta-analysis. *JAMA Oncol* 2019; **5:** 1008–19.