Sugemalimab versus placebo after concurrent or sequential chemoradiotherapy in patients with locally advanced, unresectable, stage III non-small-cell lung cancer in China (GEMSTONE-301): interim results of a randomised, double-blind, multicentre, phase 3 trial

Qing Zhou, Ming Chen*, Ou Jiang, Yi Pan, Desheng Hu, Qin Lin, Gang Wu, Jiuwei Cui, Jianhua Chang, Yufeng Cheng, Cheng Huang, Anwen Liu, Nong Yang, Youling Gong, Chuan Zhu, Zhiyong Ma, Jian Fang, Gongyan Chen, Jun Zhao, Anhui Shi, Yingcheng Lin, Guanghui Li, Yunpeng Liu, Dong Wang, Rong Wu, Xinhua Xu, Jianhua Shi, Zhihua Liu, Na Cui, Jingru Wang, Qiang Wang, Ran Zhang, Jason Yang, Yi-Long Wu*

Summary

Background A substantial proportion of patients with unresectable stage III non-small-cell lung cancer (NSCLC) cannot either tolerate or access concurrent chemoradiotherapy, so sequential chemoradiotherapy is commonly used. We assessed the efficacy and safety of sugemalimab, an anti-PD-L1 antibody, in patients with stage III NSCLC whose disease had not progressed after concurrent or sequential chemoradiotherapy.

Methods GEMSTONE-301 is a randomised, double-blind, placebo-controlled, phase 3 trial in patients with locally advanced, unresectable, stage III NSCLC, done at 50 hospitals or academic research centres in China. Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 who had not progressed after concurrent or sequential chemoradiotherapy. We randomly assigned patients (2:1, using an interactive voice–web response system) to receive sugemalimab 1200 mg or matching placebo, intravenously every 3 weeks for up to 24 months. Stratification factors were ECOG performance status, previous chemoradiotherapy, and total radiotherapy dose. The investigators, trial coordination staff, patients, and study sponsor were masked to treatment allocation. The primary endpoint was progression-free survival as assessed by blinded independent central review (BICR) in the intention-to-treat population. Safety was assessed in all participants who received at least one dose of assigned study treatment. The study has completed enrolment and the results of a preplanned analysis of the primary endpoint are reported here. The trial is registered with ClinicalTrials.gov, NCT03728556.

Findings Between Aug 30, 2018 and Dec 30, 2020, we screened 564 patients of whom 381 were eligible. Study treatment was received by all patients randomly assigned to sugemalimab (n=255) and to placebo (n=126). At data cutoff (March 8, 2021), median follow-up was 14·3 months (IQR 6·4–19·4) for patients in the sugemalimab group and 13·7 months (7·1–18·4) for patients in the placebo group. Progression-free survival assessed by BICR was significantly longer with sugemalimab than with placebo (median 9·0 months [95% CI 8·1–14·1] *vs* 5·8 months [95% CI 4·2–6·6]; stratified hazard ratio 0·64 [95% CI 0·48–0·85], p=0·0026). Grade 3 or 4 treatment-related adverse events occurred in 22 (9%) of 255 patients in the sugemalimab group versus seven (6%) of 126 patients in the placebo group, the most common being pneumonitis or immune-mediated pneumonitis (seven [3%] of 255 patients in the sugemalimab group *vs* one [<1%] of 126 in the placebo group). Treatment-related serious adverse events occurred in 38 (15%) patients in the sugemalimab group and 12 (10%) in the placebo group. Treatment-related deaths were reported in four (2%) of 255 patients (pneumonia in two patients, pneumonia with immune-mediated pneumonitis in one patient, and acute hepatic failure in one patient) in the sugemalimab group and none in the placebo group.

Interpretation Sugemalimab after definitive concurrent or sequential chemoradiotherapy could be an effective consolidation therapy for patients with stage III NSCLC whose disease has not progressed after sequential or concurrent chemoradiotherapy. Longer follow-up is needed to confirm this conclusion.

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Introduction

Approximately 30% of patients diagnosed with non-small cell lung cancer (NSCLC) present with tumour stages IIIA to IIIC, the majority of which are unresectable.[1] Platinum-based chemotherapy concurrent with radiotherapy was the standard of care for patients with stage III NSCLC for more than 10 years.[2] In 2018, on the basis of an interim analysis of data from the PACIFIC

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

*Contributed equally

Guangdong Lung Cancer Insitute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China (Prof Y-L Wu MD, Prof Q Zhou MD, Prof Y Pan MD); **The Cancer Hospital of the University of Chinese Academy of Sciences, Hangzhou, China** (Prof M Chen MD); **Sun Yat-sen University Cancer Centre, Guangzhou, China** (Prof M Chen); **The Second People's Hospital of Neijiang, Neijiang, China** (Prof O Jiang MD); **Hubei Cancer Hospital, Wuhan, China** (Prof D Hu BM); **The First Affiliated Hospital of Xiamen University, Xiamen, China** (Q Lin PhD); **Cancer Centre, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China** (Prof G Wu MD); **The First Hospital of Jilin University, Changchun, China** (Prof J Cui MD); **Fudan University Cancer Centre, Shanghai, China** (Prof J Chang MD); **Cancer Hospital, Chinese Academy of Medical Sciences, Shenzhen Centre, Shenzhen, China** (Prof J Chang MD); **Qilu Hospital of Shandong University, Jinan, China** (Prof Y Cheng MD); **Fujian Medical University,**

Fujian Provincial Cancer Hospital, Fuzhou, China (Prof C Huang PhD)**; The Second Affiliated Hospital of Nanchang University, Nanchang, China** (Prof A Liu MD)**; Hunan Cancer Hospital, Changsha, China** (Prof N Yang MSc)**; West China Hospital of Sichuan University, Chengdu, China** (Prof Y Gong MD)**; Chongqing University Three Gorges Hospital, Chongqing, China** (Prof C Zhu BM)**; The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China** (Prof Z Ma MM)**; Beijing Cancer Hospital, Beijing, China** (Prof J Fang MD, J Zhao MD, A Shi MD)**; Harbin Medical University Cancer Hospital, Harbin, China** (Prof G Chen MD)**; Cancer Hospital of Shantou University Medical College, Shantou, China** (Prof Y Lin PhD)**; Xinqiao Hospital of Army Medical University, Chongqing, China** (G Li MD)**; The First Hospital of China Medical University, Shenyang, China** (Prof Y Liu PhD)**; Army Medical Centre of PLA, Chongqing, China** (Prof D Wang MD)**; Shengjing Hospital of China Medical University, Shenyang, China** (Prof R Wu MD)**; The First College of Clinical Medical Science, China Three Gorges University, Yichang Central People's Hospital, Yichang, China** (Prof X Xu PhD)**; Linyi Cancer Hospital, Linyi, China** (Prof J Shi MSc)**; Jiangxi Cancer Hospital, Nanchang, China** (Z Liu MD)**; CStone Pharmaceuticals Suzhou, Shanghai, China** (N Cui PhD, J Wang PhD, Q Wang MM, R Zhang MSc, J Yang MD).

Correspondence to:
Prof Yi-Long Wu, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, China
syylwu@live.cn

Research in context

Evidence before this study

Concurrent chemoradiotherapy followed by immunotherapy is the recommended treatment for patients with unresectable stage III non-small-cell lung cancer (NSCLC). However, many such patients have one or more contraindications for, or challenges in accessing, concurrent chemoradiotherapy. Sequential chemoradiotherapy is used widely in clinical practice globally and is recommended in international treatment guidelines as an option for patients who cannot tolerate or access concurrent chemoradiotherapy, but there remains a need to improve outcomes for these patients. We searched PubMed and international oncology congress proceedings, without language restrictions, for articles and abstracts published between July 1, 2015 and July 1, 2021, about chemoradiotherapy as a treatment for stage III NSCLC, using the search terms "chemoradiotherapy" OR "chemoradiation" AND "stage III non-small-cell lung cancer" AND "concurrent" OR "sequential" AND "consolidation" AND "immune checkpoint inhibitor" OR "PD-1 antibody" OR "PD-L1 antibody" AND "treatment guidelines" AND "observation study". We also searched the ClinicalTrials.gov website for clinical studies using chemoradiotherapy regimens in stage III NSCLC. We identified one phase 3 trial of durvalumab after concurrent chemoradiotherapy (PACIFIC) which showed the value of an anti-PD-L1 antibody as consolidation therapy for stage III NSCLC.

Added value of this study

Before our study, the ability of an anti-PD-1 or anti-PD-L1 drug to improve outcomes after sequential chemoradiotherapy in patients with unresectable stage III NSCLC was unknown. To our knowledge, GEMSTONE-301 is the first randomised, phase 3 clinical trial to evaluate an immune checkpoint inhibitor in patients with unresectable stage III NSCLC who had received either concurrent or sequential chemoradiotherapy. Progression-free survival was the primary endpoint and we found that sugemalimab as a consolidation therapy resulted in a statistically significant and clinically meaningful improvement in progression-free survival in patients with unresectable stage III NSCLC without disease progression after concurrent or sequential chemoradiotherapy, compared with placebo.

Implications of all the available evidence

Overall, efficacy and safety data from GEMSTONE-301 support the potential use of sugemalimab as an effective consolidation therapy for patients with unresectable stage III NSCLC, whose disease has not progressed after sequential or concurrent chemoradiotherapy. Longer follow-up is needed to confirm this conclusion.

trial,[3] durvalumab was approved for the treatment of unresectable, stage III NSCLC in patients whose disease had not progressed after concurrent chemoradiotherapy. This regimen quickly became the new standard of care for these patients. An updated survival analysis from PACIFIC[4] suggested substantially longer overall survival with durvalumab than with placebo (5-year overall survival 43% *vs* 33%). Notably, the PACIFIC trial only evaluated patients who had received concurrent chemoradiotherapy, a regimen associated with substantial toxicity and a high rate of treatment-related mortality.[5,6] Many patients are unable to tolerate concurrent chemoradiotherapy and its use is restricted to patients with a good Eastern Cooperative Oncology Group (ECOG) performance status.[7,8]

Although comorbidities often prevent the use of concurrent chemoradiotherapy, in some countries restricted access also limits its use.[9] Access to concurrent chemoradiotherapy is particularly poor in regions with few multidisciplinary teams and hospital resources.[10] Sequential chemoradiotherapy is therefore widely used in clinical practice throughout the world as an option for patients who cannot tolerate or access concurrent chemoradiotherapy. The use of sequential chemoradiotherapy is recommended in international treatment guidelines as a valid and effective alternative to concurrent chemoradiotherapy for locally advanced, unresectable, stage III NSCLC (eg, US National Comprehensive Cancer Network,[11] European Society for Medical Oncology [ESMO],[12] and the Pan-Asian adaptation of the ESMO guidelines[13]). However, the ability of an anti-PD-1 or anti-PD-L1 drug to prolong survival in patients with unresectable stage III NSCLC who have not progressed after sequential chemoradiotherapy is unknown.

Sugemalimab (formerly CS1001) is a full-length, fully human immunoglobulin G4 (IgG4, s228p) monoclonal antibody that targets PD-L1.[14] In-vitro studies suggest that, unlike other antibodies that block Fc-null PD-L1 (eg, durvalumab), sugemalimab retains binding to Fcγ receptor I and therefore could efficiently induce antibody-dependent cellular phagocytosis through cross-linking of PD-L1-positive tumour cells with macrophages that are prevalent in the tumour microenvironment,[15] and might further enhance tumour antigen presentation. In the phase 3 GEMSTONE-302 trial[16] of patients with chemotherapy-naive stage IV NSCLC, adding sugemalimab to chemotherapy significantly improved progression-free survival compared with adding placebo, and this benefit was seen both in patients with squamous NSCLC and in those with non-squamous NSCLC.

The aim of this preplanned interim analysis of a randomised, double-blind, placebo-controlled, phase 3 trial (GEMSTONE-301) was to compare sugemalimab versus placebo as a consolidation therapy in patients with locally advanced, unresectable, stage III NSCLC who had not progressed after receiving either concurrent or sequential platinum-based chemoradiotherapy.

Methods

Study design and participants

GEMSTONE-301 is a randomised, double-blind, placebo-controlled, phase 3 trial in patients with locally advanced, unresectable, stage III NSCLC, and done at 50 hospitals or academic research centres in China.

Eligible patients were aged at least 18 years and had histologically or cytologically confirmed locally advanced, unresectable, stage III NSCLC according to the International Association for the Study of Lung Cancer classification, eighth edition.[17] Patients must have received at least two cycles of platinum-based chemotherapy, either concurrently or sequentially, with definitive radiotherapy. Chemotherapy regimens (defined according to local practice) must have contained one or more of etoposide, vinorelbine, vinblastine, pemetrexed, taxanes, or gemcitabine (gemcitabine was not allowed in concurrent chemoradiotherapy), plus cisplatin, carboplatin, or nedaplatin. Radiotherapy had to have reached a total dose of 54–66 Gy, with either the mean dose to the lung not exceeding 20 Gy or the volume of lung parenchyma that received 20 Gy or more not exceeding 35%. For sequential chemoradiotherapy regimens, the interval between the end of a chemotherapy cycle and the initiation of radiotherapy must not have exceeded 35 days. Additional inclusion criteria were no disease progression after concurrent or sequential chemoradiotherapy, an ECOG performance status score of 0 or 1, and completion of chemoradiotherapy within 1–42 days before study drug administration.

Patients had to have a life expectancy of at least 12 weeks. Eligible patients also had to have adequate organ function, as assessed by the following laboratory tests (patients must not have received any blood transfusion, erythropoietin, granulocyte colony-stimulating factor, or other medical supportive treatment during the 7 days before the experimental drug was given): absolute neutrophil count of 1500 cells per μL or higher; platelet count of 100 000/μL or higher; haemoglobin concentration of 9·0 g/dL or higher; international normalised ratio or prothrombin time of 1·5×upper limit of normal (ULN) or lower; aspartate aminotransferase and alanine aminotransferase 3×ULN or less; serum bilirubin 1·5×ULN or lower (not applicable for patients with Gilbert syndrome); and serum creatinine 1·5×ULN or lower.

Patients were excluded if they had previous exposure to antibodies or other drugs that targeted T-cell co-regulatory proteins (including anti-PD-1 and anti-PD-L1 antibodies); known sensitising *EGFR*, *ALK*, or *ROS1* gene alterations; had received another investigational drug within the 28 days before the first dose; active or previous autoimmune disease; evidence of uncontrolled concomitant diseases (eg, uncontrolled congestive heart failure or hypertension) or active infection; unresolved pneumonitis of grade 2 or worse caused by previous chemoradiotherapy; or symptomatic interstitial lung disease. Full inclusion and exclusion criteria are shown in the protocol (appendix 2).

See Online for appendix 2

Patients provided archived tumour tissue samples for PD-L1 and tumour mutation burden testing, which was optional and not required for study enrolment.

The study protocol and all amendments were approved by the appropriate ethics committees at each study site. The study was done in accordance with the Declaration of Helsinki and the Good Clinical Practice guideline as defined by the International Conference on Harmonisation. An independent data monitoring committee did regular assessments of safety data and did the efficacy interim analysis. Before enrolment, all patients provided written informed consent to participate in the trial. The complete study protocol is provided in appendix 2.

Randomisation and masking

Eligible patients were randomly assigned (2:1) to sugemalimab or placebo. Random assignment was done by the investigators using an interactive voice-response system or interactive web-response system (Calyx, NC, USA) that stratified patients by ECOG performance status (0 *vs* 1), previous chemoradiotherapy (concurrent *vs* sequential, in which no more than 40% of patients received sequential chemoradiotherapy), and total radiotherapy dose (<60 Gy *vs* ≥60 Gy). The randomisation sequence was generated by Calyx by using the block randomisation method with random block sizes of three and six. The system ensured that the randomisation treatment assignment sequence was concealed until the treatment allocation was completed. Sugemalimab and placebo were packaged and labelled identically, to ensure study personnel remained masked to treatment assignment. The investigators, trial coordination staff, patients, and study sponsor were masked to treatment allocation.

Procedures

Patients received a fixed dose of sugemalimab 1200 mg intravenously, or matching placebo, once every 3 weeks as consolidation therapy for up to 24 months. 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 80). Treatment was continued until confirmed disease progression, occurrence of unacceptable toxicity, or withdrawal of consent. At the discretion of the study investigator, patients could continue treatment after initial disease progression if there was no clinical deterioration or rapid disease progression, and if the patient remained tolerant to treatment with a stable ECOG performance status.

After discontinuation or completion of the trial regimen, patients were followed up for assessment of safety outcomes (for 90 days after the last dose of study drug or until initiation of a new anti-cancer therapy, whichever came first) and survival (assessed every 12 weeks). Crossover between the treatment groups was

not permitted; however, at the investigator's discretion, patients could receive subsequent immunotherapy. The discontinuation of study treatment followed the protocol.

Tumours were assessed using CT or MRI scans at baseline, at approximately every 9 weeks after the first treatment dose for the first 12 months, and then every 12 weeks until disease progression, death, or the end of the study, whichever occurred first. 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 of any intensity. All adverse events were assessed at baseline, continuously while on treatment, at the treatment discontinuation visit, and at the safety follow-up visit. Incidence, nature, and severity of adverse events were graded in accordance with US National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Details of laboratory assesments are presented in the the protocol (appendix 2).

Outcomes

The primary endpoint was progression-free survival (according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1), assessed by blinded independent central review (BICR). Progression-free survival was defined as the time from randomisation to disease progression or all-cause death, whichever occurred first. Secondary endpoints were: progression-free survival assessed by the investigators; overall survival, objective response rate, duration of response, and time to death or distant metastasis, all assessed by BICR and by the investigators; and pharmacokinetics and immunogenicity. Overall survival was defined as the time from randomisation to all-cause death. The objective response rate was defined as complete or partial tumour response according to RECIST version 1.1. Duration of response was defined as the time from the earliest qualified response to progression of disease or all-cause death, whichever occurred first. Time to death or distant metastasis was defined as the time from randomisation to distant metastasis or death, whichever occurred first. Previously irradiated lesions could be considered measurable and could be selected as target lesions, provided that they fulfilled the other criteria for measurability (see protocol in appendix 2). Safety assessments included treatment-emergent adverse events, adverse events of special interest, vital signs, and physical and laboratory examinations. Treatment-emergent adverse events were defined as any adverse event that occurred or worsened on or after the initiation of study drug treatment. Adverse events of special interest were sponsor-assessed immune-related adverse events and were defined using a list of preferred categories of terms specified by the sponsor. Time to death or distant metastasis, pharmacokinetics, and immunogenicity are not reported in this manuscript owing to data immaturity.

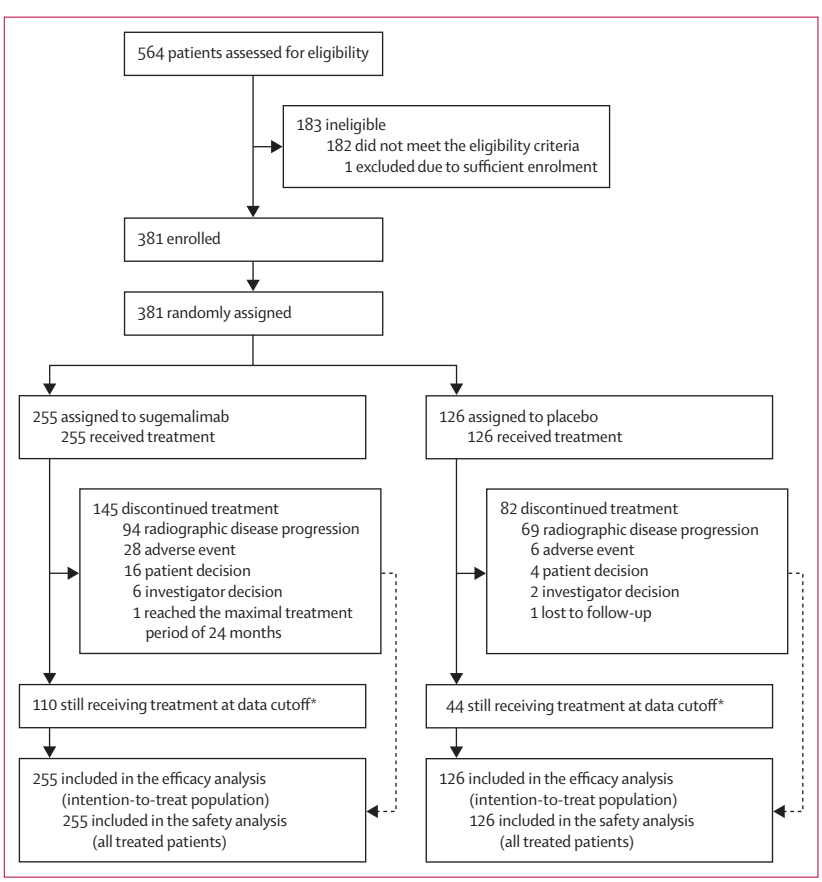

Figure 1: **Trial profile**
*Data cutoff was on March 8, 2021.

Statistical analysis

It was estimated that the study would have a power of 97·6% to detect a progression-free survival hazard ratio of 0·6, corresponding to an extension of the median progression-free survival from 6 months to 10 months, based on a log-rank test with a two-sided significance level of 5%. Approximately 262 progression-free survival events were needed; 368 patients were planned for 2:1 randomisation in this trial (in which no more than 40% of patients had received sequential chemoradiotherapy), with an expected dropout rate of 5% over 12 months. An interim analysis of progression-free survival was planned when approximately 194 events had occurred in the overall population or when the last patient had enrolled, whichever came later. Final progression-free survival analysis would be done when approximately 262 progression-free survival events had occurred. Here, we present the results at the time of the prespecified interim analysis (data cutoff March 8, 2021); 197 events (disease progression or death) were observed. The p value boundary for declaring superiority for progression-free survival at

the interim analysis was 0·0195, based on the 197 actual events. The O'Brien–Fleming method was used to control the two-sided overall type I error.

If the progression-free survival analysis was positive, the key secondary endpoint (ie, overall survival) was to be tested using a sequential testing method with a log-rank test at a two-sided We estimated that the study would have a power of 83% to detect the overall survival hazard ratio (HR) of 0·67, corresponding to an extension of median overall survival from 22 months to 32·8 months. Interim overall survival analysis would be done when 175 deaths (67% of data information) occurred. The final overall survival analysis would be done when approximately 260 deaths had been observed, with an expected dropout rate of 2% over 12 months. The Lan–DeMets method with an approximation Pocock boundary would be used to control type I error of less than 0·05. This analysis has not yet been done.

Progression-free survival, overall survival, and time to death or distant metastasis were assessed in the intention-to-treat population, which included all patients who had been randomly assigned. 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. Safety was assessed in all participants who had received at least one dose of the assigned study treatment. Progression-free survival was estimated using the Kaplan–Meier method, and between-group differences were tested with a log-rank test, stratified according to ECOG performance status, previous chemoradiotherapy, and total radiotherapy dose. HRs and 95% CIs were calculated using a stratified Cox regression model. Progression-free survival rates at different timepoints were estimated by Kaplan-Meier method and the 95% CIs were calculated using the Brookmeyer–Crowley method.

Overall survival was analysed with the same analysis method as for progression-free survival. Survival curves for each group were estimated with the Kaplan-Meier method, and non-proportionality was assessed visually. Prespecified key subgroup analyses (sex [female or male], age [<65 years or ≥65 years], smoking history [never, former, or current], ECOG performance status [0 or 1], chemoradiotherapy type [sequential or concurrent], radiotherapy dose [<60 Gy or ≥60 Gy], histology type [squamous, non-squamous, or missing], best response to previous chemoradiotherapy [complete response, partial response, or stable disease], cancer stage before chemoradiotherapy [IIIA, IIIB, or IIIC]) for progression-free survival were done to assess the consistency of treatment effects in patient subgroups. Subgroup analyses used an unstratified Cox proportional hazards model with treatment as a covariate. The Clopper–Pearson method was used to calculate the 95% CI for objective response rate in each treatment group, and between-group differences were assessed using a stratified Mantel–Haenszel test. The duration of response for each group was analysed by Kaplan–Meier method, and the treatment comparisons were descriptive.

An independent data monitoring committee evaluated the safety data every 6 months after the first patient enrolment. This committee monitored the data for

	Sugemalimab group (n=255)	Placebo group (n=126)
Sex		
Male	236 (93%)	115 (91%)
Female	19 (7%)	11 (9%)
Age, years		
Median	61 (56–65)	60 (55–65)
<65	182 (71%)	94 (75%)
≥65	73 (29%)	32 (25%)
Smoking history		
Never smoked	42 (16%)	16 (13%)
Former or current smoker	213 (84%)	110 (87%)
Eastern Cooperative Oncology Group performance status		
0	78 (31%)	38 (30%)
1	177 (69%)	88 (70%)
Chemoradiotherapy type		
Sequential	86 (34%)	41 (33%)
Concurrent	169 (66%)	85 (67%)
Radiotherapy dose		
<60 Gy	43 (17%)	20 (16%)
≥60 Gy	212 (83%)	106 (84%)
Disease stage		
IIIA	74 (29%)	32 (25%)
IIIB	146 (57%)	65 (52%)
IIIC	33 (13%)	28 (22%)
Other	2 (1%)	1 (1%)
Tumour histological type		
Squamous cell carcinoma	177 (69%)	86 (68%)
Non-squamous cell carcinoma	76 (30%)	40 (32%)
Missing data	2 (1%)	0
Previous platinum treatment*		
Cisplatin	130 (51%)	61 (48%)
Carboplatin	82 (32%)	47 (37%)
Nedaplatin	56 (22%)	20 (16%)
Best response to chemoradiotherapy		
Complete response	4 (2%)	2 (2%)
Partial response	172 (67%)	77 (61%)
Stable disease	79 (31%)	47 (37%)
PD-L1 expression†		
<1%	51 (20%)	29 (23%)
≥1%	72 (28%)	23 (18%)
Missing	132 (52%)	74 (59%)

Data are median (IQR) or n (%). PD-L1=programmed death ligand-1. *Some patients had more than one type of platinum treatment. †Assessment of baseline PD-L1 expression was not mandatory for study enrolment, therefore PD-L1 status was missing for more than half of the randomly assigned patients.

Table 1: **Baseline characteristics of patients in the intention-to-treat population**

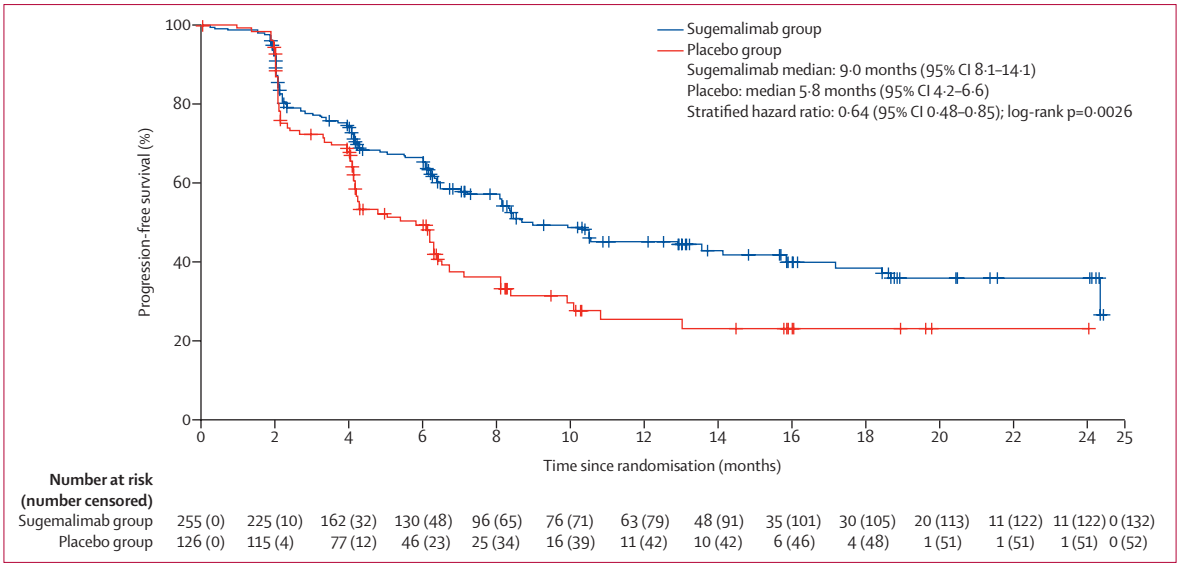

Figure 2: **Kaplan–Meier estimates of progression-free survival according to blinded independent central review**
The stratified variables were Eastern Cooperative Oncology Group performance status, type of chemoradiotherapy, and total dose of radiotherapy. At data cutoff, there were 184 patients (132 [72%] sugemalimab and 52 [28%] placebo) censored for the progression-free survival analysis, among whom 48 patients (37 sugemalimab and 11 placebo) discontinued study treatment and were less likely to have further tumour assessments.

interim progression-free survival analysis and make recommendations to the sponsor according to the p value boundary of 0·0195 with 197 observed progression-free survival events. Statistical analyses were done using SAS (version 9.4 or higher). This trial is registered with ClinicalTrials.gov (NCT03728556) and is ongoing.

Role of the funding source

The funders of the study participated in the study design, data collection, data analysis, data interpretation, and writing of the report, in collaboration with the investigators.

Results

Between Aug 30, 2018, and Dec 30, 2020, 564 patients were screened for eligibility, 183 of whom were excluded (figure 1). Between Oct 26, 2018, and Dec 30, 2020, we randomly assigned 381 patients (the intention-to-treat population) to sugemalimab (n=255) or placebo (n=126); 100% of whom received treatment and were included in the intention-to-treat and safety populations. 145 (57%) of 255 patients in the sugemalimab group and 82 (65%) of 126 patients in the placebo group discontinued study treatment. No patients discontinued treatment because of compliance issues during this clinical trial. All baseline characteristics were well balanced between the treatment groups (table 1). The median age of all patients was 61 years (IQR 56–65) and the majority were men (351 [92%] of 381) and current or former smokers (323 [85%] of 381). Most patients had an ECOG performance status of 1 (265 [70%] of 381), one-third had received previous sequential chemoradiotherapy (127 [33%]), and most had squamous cell carcinoma (263 [69%]). More than half of patients (211 [55%] of 381) had stage IIIB disease and 61 (16%) had stage IIIC disease.

At the data cutoff date (March 8, 2021) for the interim analysis, the median duration of follow-up (ie, time from randomisation to last follow-up) was 14·3 months (IQR 6·4–19·4) for sugemalimab and 13·7 months (7·1–18·4) for placebo. The median duration of follow-up for patients who had received concurrent chemoradiotherapy was shorter than for patients who had received sequential chemoradiotherapy (9·4 months [5·1–16·7] *vs* 17·9 months [15·2–21·7]), owing to a slower enrolment rate. The median number of infusions was 9·0 (IQR 4·0–16·0) for sugemalimab and 8·0 (5·0–12·0) for placebo (appendix 2 p 7). 110 (43%) of 255 patients in the sugemalimab group and 44 (35%) of 126 in the placebo group were still receiving study treatment at data cutoff. 30 (24%) of 126 patients in the placebo group and 11 (4%) of 255 patients in the sugemalimab group had received PD-1 or PD-L1 inhibitors as subsequent anti-cancer treatment (data not shown); detailed subsequent anti-cancer treatment data are shown in appendix 2 (pp 8–9).

At data cutoff for this interim analysis, 123 (48%) of 255 patients in the sugemalimab group and 74 (59%) of 126 in the placebo group had disease progression or died. Progression-free survival as assessed by BICR was significantly longer with sugemalimab than with placebo (median 9·0 months [95% CI 8·1–14·1] *vs* 5·8 months [4·2–6·6]; stratified hazard ratio [HR] 0·64, 95% CI 0·48–0·85; p=0·0026; figure 2). The 12-month progression-free survival rate was 45·4% (95% CI 38·2–52·4) with sugemalimab and 25·6% (16·2–36·1) with placebo. The Kaplan-Meier plots were assessed visually for proportional hazards and no strong evidence of non-proportionality

	Number of events/ number of patients (%)		Median progression-free survival, months (95% CI)		Unstratified HR (95% CI)
	Sugemalimab (n=255)	Placebo (n=126)	Sugemalimab (n=255)	Placebo (n=126)	
Sex					
Male	111/236 (47%)	67/115 (58%)	10·45 (8·15–15·80)	5·39 (4·17–6·37)	0·61 (0·45–0·82)
Female	12/19 (63%)	7/11 (64%)	3·94 (2·07–8·12)	6·11 (2·10–NR)	1·40 (0·55–3·57)
Age, years					
<65	86/182 (47%)	49/94 (52%)	8·97 (7·03–15·80)	6·24 (4·27–9·92)	0·75 (0·52–1·06)
≥65	37/73 (51%)	25/32 (78%)	8·67 (5·52–18·66)	4·07 (2·07–6·21)	0·40 (0·23–0·67)
Smoking history					
Never smoked	18/42 (43%)	11/16 (69%)	10·55 (6·14–NR)	5·39 (2·07–NR)	0·44 (0·20–0·96)
Former or cucrrent smoker	105/213 (49%)	63/110 (57%)	8·61 (7·03–15·80)	5·82 (4·17–6·57)	0·67 (0·49–0·92)
ECOG performance status					
0	27/78 (35%)	19/38 (50%)	NR (8·67–NR)	6·37 (4·17–13·01)	0·47 (0·26–0·86)
1	96/177 (54%)	55/88 (63%)	8·12 (6·11–10·35)	5·39 (4·07–6·24)	0·71 (0·51–0·99)
Chemoradiotherapy type					
Sequential	58/86 (67%)	35/41 (85%)	8·08 (3·98–10·35)	4·07 (2·14–6·11)	0·59 (0·39–0·91)
Concurrent	65/169 (38%)	39/85 (46%)	10·51 (8·12–NR)	6·37 (4·27–9·92)	0·66 (0·44–0·99)
Radiotherapy dose					
<60 Gy	22/43 (51%)	13/20 (65%)	10·51 (8·12–NR)	6·21 (4·04–13·01)	0·55 (0·27–1·12)
≥60 Gy	101/212 (48%)	61/106 (58%)	8·44 (6·41–14·13)	5·39 (4·17–6·57)	0·66 (0·48–0·90)
Histology type					
Squamous cell carcinoma	91/177 (51%)	57/86 (66%)	8·31 (6·31–12·88)	4·21 (3·58–6·21)	0·57 (0·41–0·80)
Non-squamous cell carcinoma	30/76 (39%)	17/40 (43%)	24·35 (8·44–NR)	9·92 (5·82–NR)	0·77 (0·42–1·40)
Missing	2/2 (100%)	0/0 (NR)	3·02 (1·87–NR)	NR (NR–NR)	NA
Best response to previous chemoradiotherapy					
Complete response	3/4 (75%)	1/2 (50%)	5·82 (0·36–NR)	NR (6·24–NR)	NA
Partial response	81/172 (47%)	41/77 (53%)	8·67 (7·03–13·54)	6·24 (4·17–9·92)	0·73 (0·50–1·06)
Stable disease	39/79 (49%)	32/47 (68%)	13·54 (6·41–18·66)	4·21 (2·33–6·21)	0·48 (0·30–0·78)
Non-complete response or non-progressive disease	0/0 (NR)	0/0 (NR)	NR (NR–NR)	NR (NR–NR)	NA
Cancer stage before chemoradiotherapy					
Stage IIIA	31/74 (42%)	17/32 (53%)	10·51 (6·47–NR)	6·21 (4·17–NR)	0·74 (0·41–1·34)
Stage IIIB	75/146 (51%)	41/65 (63%)	8·44 (7·03–15·80)	5·82 (3·94–6·57)	0·55 (0·37–0·81)
Stage IIIC	17/33 (52%)	16/28 (57%)	8·61 (4·07–NR)	5·39 (4·11–8·08)	0·73 (0·36–1·48)
Other	0/2 (0%)	0/1 (0%)	NR (NR–NR)	NR (NR–NR)	NA
All patients	**123/255 (48%)**	**74/126 (59%)**	**8·97 (8·08–14·13)**	**5·82 (4·17–6·57)**	**0·64 (0·48–0·85)**

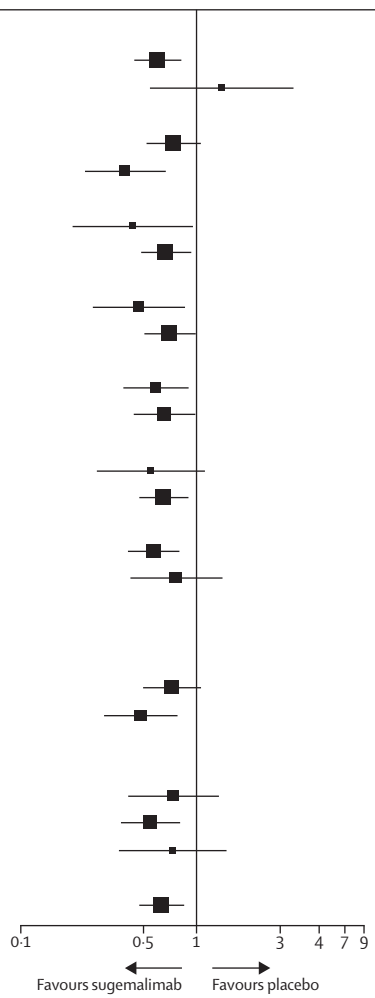

Figure 3: **Subgroup analysis of progression-free survival**
ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. NA=not applicable. NR=not reached.

was observed. Progression-free survival, as assessed by the investigators, was consistent with that assessed by BICR (appendix 2 p 4). A progression-free survival benefit with sugemalimab compared with placebo according to BICR was seen across most prespecified subgroups (figure 3), including in patients who had received concurrent chemoradiotherapy and those who had received sequential radiotherapy (figure 3, appendix 2 p 5).

BICR-assessed objective response rates were similar between groups (appendix 2 p 10). Objective response rates and duration of response assessed by the investigators were consistent with those assessed by the BICR (data not shown). The median duration of response had not been reached in patients who received sugemalimab (not reached [NR]; 95% CI 8·5–NR) and was 6·0 (2·2–NR) months in patients who received placebo (appendix 2 p 10). At data cutoff, the number of events required for a preplanned interim analysis of overall survival had not been reached, and the data remain immature. A total of 32 (13%) of 255 patients in the sugemalimab group and 32 (25%) of 126 in the placebo group had died. The results of a preliminary analysis of overall survival are shown in figure 4.

Treatment-emergent adverse events of any grade related to the study drug occurred in 193 (76%) of 255 patients with sugemalimab and 73 (58%) of 126 with placebo (table 2). Grade 3 or 4 treatment-emergent adverse events related to study drug occurred in 22 (9%) of 255 with sugemalimab versus seven (6%) of 126 with placebo, the most common being pneumonitis or

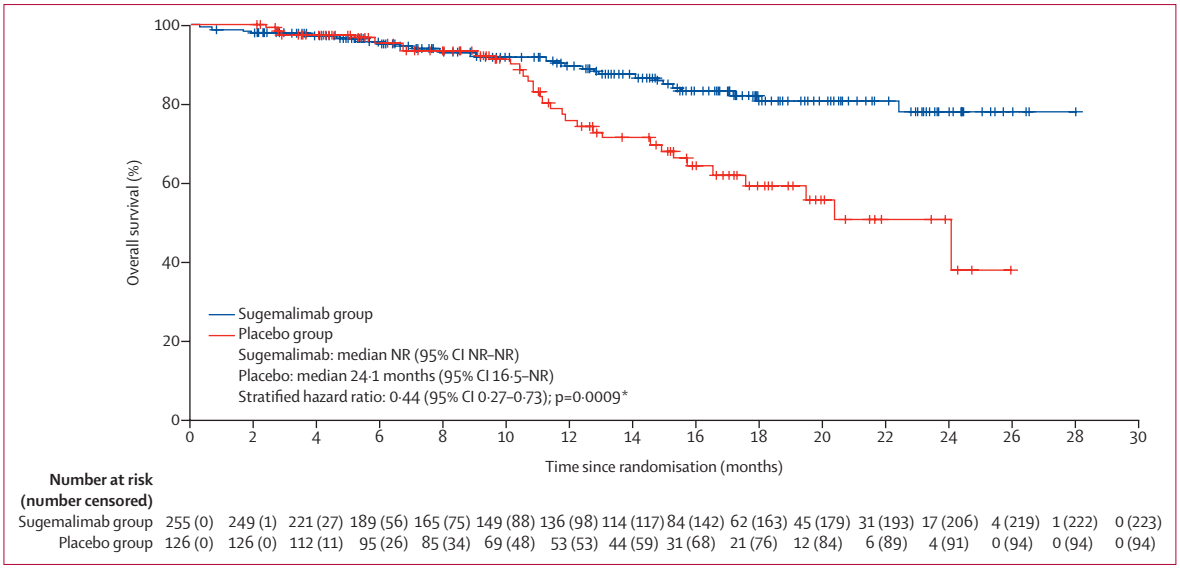

Figure 4: **Kaplan-Meier estimates of overall survival**

Data for the secondary outcome of overall survival were immature at data cutoff. At data cutoff, there were 317 patients (223 [70%] sugemalimab and 94 [30%] placebo) censored for the overall survival analysis; only seven patients (six in the sugemalimab group and one in the placebo group) were censored owing to the end of the study and the remainder are still in follow up. NR=not reached. *Prespecified overall survival time not reached yet; overall survival were immature at data cutoff date.

immune-mediated pneumonitis (seven [3%] of 255 patients in the sugemalimab group *vs* one [1%] of 126 in the placebo group). Treatment-related serious adverse events were reported in 38 (15%) of 255 patients with sugemalimab and 12 (10%) of 126 with placebo; the most frequently reported treatment-related serious adverse events in both groups (appendix 2 pp 12–13) were pneumonitis or immune-mediated pneumonitis (23 [9%] of 255 *vs* nine [7%] of 126), pneumonia (six [2%] *vs* one [<1%]), and interstitial lung disease (four [2%] *vs* two [2%]). Discontinuation of study drug owing to treatment-emergent adverse events was reported for 29 (11%) of 255 patients with sugemalimab versus six (5%) of 126 with placebo and drug discontinuation because of adverse events attributed to treatment was recorded in 24 (9%) of 255 with sugemalimab versus four (3%) of 126 with placebo (appendix 2 p 13). The most frequently reported adverse events leading to treatment discontinuation in both groups were pneumonitis or immune-mediated pneumonitis (16 [2%] of 255 *vs* two [2%] of 126), pneumonia (three [1%] *vs* one [<1%]), and interstitial lung disease (two [<1%] *vs* 0; appendix 2 p 13). 12 deaths occurred in total, four (2%) treatment-related deaths occurred in the sugemalimab group (pneumonia two [1%] of 255, pneumonia with immune-mediated pneumonitis one [<1%], and acute hepatic failure one [<1%]; table 2). Adverse events of special interest of any grade occurred in 109 (43%) of 255 patients in the sugemalimab group versus 17 (13%) of 126 in the placebo group, with grade 3 or 4 events in 11 (4%) versus one (1%); appendix 2 (p 11). The most common grade 3 or 4 adverse event of special interest was pneumonitis (six [2%] *vs* one [1%]). One death (<1%) owing to an adverse event of special interest (pneumonitis) was reported in the sugemalimab group and none occurred in the placebo group.

Discussion

The results of this preplanned interim analysis of the GEMSTONE-301 study showed that among patients with locally advanced, unresectable, stage III NSCLC who had not progressed after concurrent or sequential chemoradiotherapy, a statistically significant and clinically meaningful improvement in progression-free survival was observed with sugemalimab compared with placebo. This benefit was durable, as a higher proportion of patients treated with sugemalimab than with placebo remained progression free at 12 months (45% *vs* 26%). Median progression-free survival was longer with sugemalimab compared with placebo in patients who had received previous concurrent or sequential chemoradiotherapy. The observed narrow gaps during the first 4 months in the Kaplan–Meier plots were because of delayed treatment effects, which is common in immunotherapy clinical studies. Overall survival data were immature, but initial analysis shows an HR of 0·4, favouring sugemalimab; follow-up of patients for overall survival is ongoing. The safety profile was consistent with that previously reported for sugemalimab monotherapy,[14] with no new safety signals observed.

5-year survival outcomes from the PACIFIC trial[4] indicated a long-term benefit of durvalumab treatment compared with placebo after concurrent chemoradiotherapy. At a median follow-up period of 34·3 months,[4] updated overall survival data remained consistent with the results from the primary analysis (median

	Sugemalimab (n=255)				Placebo (n=126)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Number of patients with at least one treatment-related adverse event	167 (66%)	20 (8%)	2 (1%)	4 (2%)	66 (52%)	5 (4%)	2 (2%)	0
Grade 1–2 treatment-related adverse events occurring in at least 10% patients in either group and all grade 3–5 treatment-related adverse events								
Pneumonitis or immune-mediated pneumonitis	40 (16%)	5 (2%)	2 (1%)	1 (<1%)	20 (16%)	1 (1%)	0	0
Hypothyroidism	41 (16%)	2 (1%)	0	0	10 (8%)	0	0	0
Hyperthyroidism	37 (15%)	0	0	0	5 (4%)	0	0	0
Alanine aminotransferase increased	32 (13%)	0	0	0	11 (9%)	0	0	0
Aspartate aminotransferase increased	29 (11%)	1 (<1%)	0	0	6 (5%)	0	0	0
Rash	17 (7%)	2 (1%)	0	0	4 (3%)	0	0	0
Pruritus	15 (6%)	1 (<1%)	0	0	2 (2%)	0	0	0
Anaemia	14 (6%)	0	0	0	4 (3%)	1 (1%)	0	0
Gamma-glutamyltransferase increased	11 (4%)	1 (<1%)	0	0	1 (1%)	0	0	0
Hypertriglyceridaemia	9 (4%)	2 (1%)	0	0	4 (3%)	1 (1%)	0	0
Blood cholesterol increased	9 (4%)	1 (<1%)	0	0	3 (2%)	0	0	0
Lymphocyte count decreased	7 (3%)	1 (<1%)	0	0	1 (1%)	0	0	0
Platelet count decreased	6 (2%)	0	0	0	0	0	1 (1%)	0
Pneumonia	0	3 (1%)	0	2 (1%)	0	1 (1%)	0	0
Bilirubin conjugated increased	4 (2%)	1 (<1%)	0	0	0	0	0	0
Radiation pneumonitis	4 (2%)	0	0	0	0	1 (1%)	0	0
Hyponatraemia	1 (<1%)	1 (<1%)	0	0	2 (2%)	0	0	0
Maculopapular rash	1 (<1%)	1 (<1%)	0	0	1 (1%)	0	0	0
Hypercalcaemia	1 (<1%)	0	0	0	0	0	1 (1%)	0
Hypophosphataemia	1 (<1%)	0	0	0	0	0	1 (1%)	0
Acute hepatic failure	0	0	0	1 (<1%)	0	0	0	0
CD4 lymphocytes increased	0	1 (<1%)	0	0	0	0	0	0
CD8 lymphocytes increased	0	1 (<1%)	0	0	0	0	0	0
Metabolic acidosis	0	0	1 (<1%)	0	0	0	0	0
Respiratory alkalosis	0	0	1 (<1%)	0	0	0	0	0
T-lymphocyte count increased	0	1 (<1%)	0	0	0	0	0	0

Data are n (%). The safety population included all patients who received study treatment.

Table 2: **Treatment-related adverse events**

47·5 months with durvalumab *vs* 29·1 months with placebo; stratified HR 0·72 [95% CI 0·59–0·89]).[4] To our knowledge, no clinical trial has shown that an anti-PD-1 or anti-PD-L1 antibody as consolidation treatment can improve survival outcomes following sequential chemoradiotherapy. The GEMSTONE-301 study showed the benefit of a PD-L1 inhibitor as consolidation treatment after either concurrent or sequential chemoradiotherapy treatment. In terms of the populations enrolled, differences exist between the two studies in terms of ECOG performance status 1 (70% GEMSTONE-301 *vs* 51% PACIFIC[4]), squamous histology (69% *vs* 46%), and stage IIIB or stage IIIC disease (71% *vs* 45%). Also, GEMSTONE-301 excluded patients with known *EGFR* mutations, or *ALK* and *ROS1* rearrangements, which are important in East Asian countries because the prevalence of *EGFR* mutations in patients with NSCLC is higher in Asian than in White patients (approximately 50% *vs* 15%).[18–20] However, patients with *EGFR*-mutated NSCLC did not appear to derive benefit from durvalumab and had a high frequency of immune-related adverse events in the PACIFIC trial.[21,22] Therefore, compared with the PACIFIC study,[4] the GEMSTONE-301 study enrolled a broader population of patients with stage III NSCLC, and thus might be more representative of the populations encountered in clinical practice.

Despite the baseline population differences, key data from GEMSTONE-301 showed a clinical benefit of sugemalimab as consolidation treatment after concurrent chemoradiotherapy, which was similar to that seen with durvalumab in PACIFIC,[4] although further survival follow-up is needed. Initial data from the PACIFIC trial in 2017[3] showed that median progression-free survival was 16·8 months with durvalumab consolidation

treatment, suggesting that 12 months of treatment might not be adequate for patients to benefit from the study drug. During the same period, trials of PD-1 or PD-L1 inhibitors in advanced-stage NSCLC disease selected a 24-month treatment period as the maximum number of cycles (KEYNOTE-024,[23] KEYNOTE-189,[24]) or no treatment cycle limitation (IMpower150[25]). In GEMSTONE-301, the patient could receive sugemalimab treatment for up to 24 months.

In the current study, median progression-free survival was longer with sugemalimab than with placebo, regardless of patient age, smoking history, ECOG performance status, radiotherapy dose, squamous or non-squamous histology, and disease stage. Efficacy results were inconclusive for female patients because of low enrolment numbers, similar to another phase 3 study (NCT01015443) of stage III NSCLC in an East-Asian population. This imbalance between sexes at baseline might have been because patients who tested positive for driver mutations were excluded from the study, and fewer women than men smoke in China. A similar sex distribution was seen in other trials in Chinese patients with NSCLC.[26,27] However, results of the PACIFIC trial[3] of durvalumab in stage III NSCLC and the GEMSTONE-302 trial with sugemalimab in stage IV NSCLC have not shown sex differences in efficacy outcomes.[16]

A limitation of our study is that data for PD-L1 expression are not included at present because this was not a preplanned stratification factor and was instead an exploratory endpoint. We will assess the association between PD-L1 expression and efficacy outcomes after longer follow-up of the patients. Analyses of additional biomarkers (eg, GLUT1, *KRAS*, HLA class I loss, and *p53*) would improve understanding of the mechanisms of resistance to immune checkpoint inhibitors in the tumour microenvironment,[28,29] factors that predict response to treatment with immune checkpoint inhibitors,[30] and mechanisms that lead to sensitisation or resistance to radiotherapy.[31,32] Another potential limitation is the tumour measurement bias; however, the study design was double-blind and the primary endpoint of progression-free survival was assessed by BICR to further reduce potential bias.

The interim analysis of this randomised, controlled, phase 3 trial showed a significant and clinically meaningful improvement in progression-free survival with sugemalimab versus placebo after either concurrent or sequential chemoradiotherapy. The results suggest that sugemalimab is an effective consolidation therapy for patients with locally advanced, unresectable, stage III NSCLC without disease progression after chemoradiotherapy.

Contributors

Y-LW, QZ, MC, OJ, YP, NC, JW, JY provided substantial contributions to the conception and design of the study. JW, NC, QW, and RZ collected, acquired, or generated data. DH, QL, GW, JiuC, JiaC, YC, CH, AL, NY, CZ, ZM, JF, GC, JZ, AS, YiL, GL, YuL, DW, RW, XX, JS, YG, and ZL enrolled and treated patients. Y-LW, QZ, JW, NC, QW, and RZ verified the data. All authors had access to the study data, reviewed the data analyses, contributed to data interpretation and to drafting and revising the manuscript for important content, approved the final version of the submitted Article, and agreed to be accountable for all aspects of the work. The corresponding author had the final responsibility for the decision to submit for publication.

Declaration of interests

Y-LW reports advisory services for AstraZeneca, Boehringer Ingelheim, Novartis, and Takeda; personal fees from AstraZeneca, Beigene, Boehringer Ingelheim, Bristol Meyer Squibb, Eli Lilly, MSD, Pfizer, Roche, and Sanofi; grants from AstraZeneca, Boehringer Ingelheim, BMS, Hengrui, and Roche, outside of the submitted work. QZ reports honoraria from AstraZeneca, Boehringer Ingelheim, Bristol Meyer Squibb, Eli Lilly, MSD, Pfizer, Roche, and Sanofi, outside the submitted work. NC, JW, QW, RZ, and JY are employed by CStone Pharmaceuticals and NC, JW, QW, 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 dictionaries). The study protocol and statistical analysis plan are available in appendix 2.

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