**Sintilimab versus placebo in combination with chemotherapy as first line treatment for locally advanced or metastatic oesophageal squamous cell carcinoma (ORIENT-15): multicentre, randomised, double blind, phase 3 trial**

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**ABSTRACT**

**OBJECTIVE**

To evaluate sintilimab versus placebo in combination with chemotherapy (cisplatin plus paclitaxel or cisplatin plus 5-fluorouracil) as first line treatment of unresectable locally advanced, recurrent, or metastatic oesophageal squamous cell carcinoma.

**DESIGN**

Multicentre, randomised, double blind, phase 3 trial.

**SETTING**

66 sites in China and 13 sites outside of China between 14 December 2018 and 9 April 2021.

**PARTICIPANTS**

659 adults (aged ≥18 years) with advanced or metastatic oesophageal squamous cell carcinoma who had not received systemic treatment.

**INTERVENTION**

Participants were randomised 1:1 to receive sintilimab or placebo (3 mg/kg in patients weighing ≥60 kg or 200 mg in patients weighing ≥60 kg) in combination with cisplatin 75 mg/m² plus paclitaxel 175 mg/m² every three weeks. The trial was amended to allow investigators to choose the chemotherapy regimen: cisplatin plus paclitaxel or cisplatin plus 5-fluorouracil (800 mg/m² continuous infusion on days 1-5).

**MAIN OUTCOME MEASURES**

Overall survival in all patients and in patients with combined positive scores of ≥10 for expression of programmed cell death ligand 1.

**RESULTS**

659 patients were randomly assigned to sintilimab (n=327) or placebo (n=332) with chemotherapy. 616 of 659 patients (93%) received sintilimab or placebo in combination with cisplatin plus paclitaxel and 43 of 659 patients (7%) received sintilimab or placebo in combination with cisplatin plus 5-fluorouracil. At the interim analysis, sintilimab with chemotherapy showed better overall survival compared with placebo and chemotherapy in all patients (median 16.7 vs 12.5 months, hazard ratio 0.63, 95% confidence interval 0.51 to 0.78, P<0.001) and in patients with combined positive scores of ≥10 (17.2 vs 13.6 months, 0.64, 0.48 to 0.85, P<0.002).

Sintilimab and chemotherapy significantly improved progression free survival compared with placebo and chemotherapy in all patients (7.2 vs 5.7 months, 0.56, 0.46 to 0.68, P<0.001) and in patients with combined positive scores of ≥10 (8.3 vs 6.4 months, 0.58, 0.45 to 0.75, P<0.001). Adverse events related to treatment occurred in 321 of 327 patients (98%) in the sintilimab-chemotherapy group versus 326 of 332 (98%) in the placebo-chemotherapy group.

Rates of adverse events related to treatment, grade ≥3, were 60% (196/327) and 55% (181/332) in the sintilimab-chemotherapy group versus 326 of 332 (7%) in the placebo-chemotherapy group, respectively.

**CONCLUSIONS**

Compared with placebo, sintilimab in combination with cisplatin plus paclitaxel showed significant benefits in overall survival and progression free survival as first line treatment in patients with advanced or metastatic oesophageal squamous cell carcinoma. Similar benefits of sintilimab with cisplatin plus 5-fluorouracil seem promising.

**TRIAL REGISTRATION**

ClinicalTrials.gov NCT03748134.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

First line systemic treatments for advanced or metastatic oesophageal squamous cell carcinoma have historically been limited to platinum based doublet chemotherapy according to standard guidelines. The prognosis of first line chemotherapy is unsatisfactory. In some randomised controlled clinical trials, PD-1 monoclonals have shown single agent activity in patients with oesophageal squamous cell carcinoma who progressed after first line chemotherapy.

**WHAT THIS STUDY ADDS**

This trial showed the general applicability of sintilimab with two different chemotherapy regimens, based on different regional clinical practices. The association between efficacy and expression of PD-L1 based on the combined positive score or tumour proportion score was reported in one trial. Compared with placebo with chemotherapy, sintilimab with chemotherapy as first line treatment of advanced oesophageal squamous cell carcinoma significantly prolonged median overall survival by more than four months with a 37% reduction in the risk of death.

**Introduction**

Oesophageal squamous cell carcinoma is the predominant subtype of oesophageal cancer in Asian populations, occurring in 90% of patients, whereas...
adenocarcinoma is more common in North America and western Europe.\textsuperscript{1,2} China has more than half of the number of patients with oesophageal squamous cell carcinoma globally.\textsuperscript{3}

Currently, first-line treatment for patients with advanced or metastatic oesophageal squamous cell carcinoma is limited to platinum-based chemotherapy. Platinum plus paclitaxel is commonly used in China whereas platinum plus 5-fluorouracil is preferred in other countries.\textsuperscript{4,5} Median overall survival, however, is <12 months in patients with advanced or metastatic oesophageal cancer receiving platinum doublets as first-line chemotherapy. Therefore, an effective first-line strategy in these populations is needed.

Treatment with immune checkpoint inhibitors that target programmed death protein 1 (PD-1) or programmed death ligand 1 (PD-L1) is a new approach for the immunotherapy of tumours, which can reverse the immune evasion of cancer.\textsuperscript{6} Binding of the PD-1 receptor to its ligands negatively regulates the antitumour immune response by inhibiting T cell proliferation, cytokine production, and cytotoxic functions, and facilitates immune escape of tumours. PD-1 antibodies can specifically bind to PD-1 and inhibit the apoptosis of antigen-specific T cells, thereby reducing regulatory T cell apoptosis by blocking activation of PD-L1.

Sintilimab, a fully recombinant human IgG4 anti-PD-1 monoclonal antibody, and with other PD-1 monoclonals, showed single-agent activity in patients with oesophageal squamous cell carcinoma who progressed after first-line chemotherapy.\textsuperscript{7-10} Sintilimab has been approved for the treatment of classical Hodgkin’s lymphoma, non-small-cell lung cancer, and hepatocellular carcinoma by the National Medical Products Administration of China.\textsuperscript{11-14} Only about 10-20% of patients with oesophageal squamous cell carcinoma had a response to monotherapy, however,\textsuperscript{11-16} but PD-1/PD-L1 treatment combined with chemotherapy has shown benefits in several tumour types.\textsuperscript{11-18} Therefore, combining PD-1/PD-L1 treatment with chemotherapy as first-line treatment in oesophageal squamous cell carcinoma could be effective.

When we conducted our trial, several similar trials were ongoing: KEYNOTE-590 (A Randomized, Double-blind, Placebo-controlled Phase III Clinical Trial of Pembrolizumab (MK-3475) in Combination With Cisplatin and 5-Fluorouracil Versus Placebo in Combination With Cisplatin and 5-Fluorouracil as First-line Treatment in Subjects With Advanced/Metastatic Esophageal Carcinoma), CHECKMATE-648 (A Randomized Phase 3 Study of Nivolumab Plus Ipilimumab or Nivolumab Combined With Fluorouracil Plus Cisplatin Versus Fluorouracil Plus Cisplatin in Subjects With Unresectable Advanced, Recurrent or Metastatic Previously Untreated Esophageal Squamous Cell Carcinoma), ESCORT-1st (PD-1 Antibody SHR-1210 Combined With Paclitaxel and Cisplatin Versus Placebo Combined With Paclitaxel and Cisplatin in First-line Therapy for Advanced Esophageal Cancer: a Randomized, Double-blinded, Controlled, Multi-center Phase III Trial), and JUPITER-06 (A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center Study to Compare Toripalimab Injection (JS001) Combined With Standard Chemotherapy Versus Placebo Combined With Standard Chemotherapy in Treatment of Advanced or Metastatic Esophageal Squamous Cell Cancer Without Previous Systemic Chemotherapy). We began our study to evaluate the antitumour activity of sintilimab in combination with cisplatin plus paclitaxel versus cisplatin plus paclitaxel only. Because the preferred chemotherapeutic regimen for oesophageal squamous cell carcinoma in the West is based on 5-fluorouracil, we amended our trial to include cisplatin plus 5-fluorouracil as a chemotherapy option for global investigators. Also, we halved the dose of paclitaxel during the first cycle on days 1 and 8 to reduce the incidence of oesophageal fistula, based on our previous clinical findings.

Methods

Trial design

ORIENT-15 was a multicentre, double-blind, randomised, phase 3 clinical trial conducted at 79 sites in five countries (China, France, Spain, US, and Australia; table S2). The ORIENT-15 trial was started in China in December 2018. While our study was ongoing, other studies that enrolled patients with oesophageal squamous cell carcinoma globally reported that anti-PD-1 monoclonal antibodies prolonged overall survival in those who progressed after first-line chemotherapy,\textsuperscript{8,9} and therefore we expanded our trial to include western countries. Based on communications with the US Food and Drug Administration, the chemotherapy regimen of cisplatin plus 5-fluorouracil, used globally, was added as a chemotherapy option in our trial. In February 2020, our trial was amended to a multinational trial and the number of patients enrolled was increased to 676. We enrolled 62% of patients (420/676) before February 2020 but the first patient outside of China was enrolled on 25 November 2020 because of the covid-19 pandemic. At that time, 95% of the target number of patients (640/676) had been enrolled in China.

In January 2021, one of the primary endpoints of the trial was changed from overall survival in patients with tumour proportion scores ≥10% for expression of programmed death ligand 1 (PD-L1 TPS), to overall survival in patients with combined positive scores ≥10 for expression of programmed death ligand 1 (PD-L1 CPS). This change was based on the results of KEYNOTE-181 (A Phase III Randomized Open-label Study of Single Agent Pembrolizumab vs Physicians’ Choice of Single Agent Docetaxel, Paclitaxel, or Irinotecan in Subjects With Advanced/Metastatic Adenocarcinoma and Squamous Cell Carcinoma of the Esophagus That Have Progressed After First-line Standard Therapy) and KEYNOTE-590, suggesting that the combined positive score might be better associated with the benefits of anti-PD-1 treatment than the tumour proportion score.\textsuperscript{8,19} Up to January 2021, 95% of patients (646/676) had been enrolled in the trial based on the tumour proportion score as one of the
stratification factors, and therefore the stratification factor during enrolment could not be changed from the tumour proportion score to the combined positive score. After January 2021, enrolment outside of China was ongoing whereas enrolment in China had ended when one of the primary endpoints of the trial was changed from overall survival in patients with PD-L1 TPS≥10% to overall survival in patients with PD-L1 CPS≥10.

Based on the positive results of the interim analysis, sintilimab in combination with chemotherapy significantly prolonged the overall survival of patients compared with placebo in combination with chemotherapy. But only 19 patients outside of China had been randomised before 9 April 2021 (cut-off date of the interim analysis). Enrolment in the randomisation phase was still ongoing outside of China. To further evaluate the efficacy and safety of sintilimab in combination with chemotherapy in patients representing western populations with advanced or metastatic oesophageal squamous cell carcinoma, a single arm open label extension phase will be conducted outside of China after completion of enrolment in the randomisation phase. Seventy patients will receive sintilimab combined with chemotherapy in the open label phase. The protocol was amended after the interim analysis in August 2021.

The trial was done according to Good Clinical Practice and the Declaration of Helsinki. The protocol and amendments were approved by the institutional review board or ethics committee at each site.

Participants
Eligible patients were ≥18 years of age with histologically confirmed unresectable locally advanced, recurrent, or metastatic oesophageal squamous cell carcinoma; were unsuitable for curative intent surgery or definite concomitant chemoradiotherapy; had received no previous systemic treatment (patients who had progressed >6 months after adjuvant or neoadjuvant chemotherapy or definitive chemoradiotherapy were eligible); could provide a fresh or archival tumour sample to evaluate expression of PD-L1; had at least one measurable lesion, based on the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, assessed by the investigators; had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; and had adequate haematological and organ function. Key exclusion criteria were tumour invasion in the aorta or trachea, hepatic metastasis of >50% of the total volume of the liver, a diagnosis of other malignant tumours, active autoimmune disease or a history of other malignant, active autoimmune disease, and interstitial lung disease requiring corticosteroids. Full eligibility criteria are available in the protocol (appendix 2, clinical protocol).

Randomisation and blinding
All eligible patients were randomly assigned (1:1) with an interactive web response system. Randomisation was stratified by expression of PD-L1 (tumour proportion score <10% or ≥10%), ECOG performance status score (0 or 1), chemotherapy regimen (cisplatin plus paclitaxel or cisplatin plus 5-fluorouracil), and hepatic metastasis (yes or no). Patients, investigators, and the sponsor’s study team were blinded to the allocation of treatment.

Intervention
Every three weeks, all patients received sintilimab or placebo combined with chemotherapy. The chemotherapy regimen was chosen by the investigator: cisplatin plus paclitaxel or cisplatin plus 5-fluorouracil. Sintilimab or placebo was given intravenously at a dose of 3 mg/kg in patients weighing <60 kg or 200 mg in patients weighing ≥60 kg on day 1 of each cycle. Cisplatin (75 mg/m² on day 1 of each cycle) plus paclitaxel (87.5 mg/m² on day 1 and day 8 of cycle 1; 175 mg/m² on day 1 of the other cycles) or 5-fluorouracil (800 mg/m² continuous administration on days 1-5 of each cycle) were also given intravenously. A maximum of six cycles was recommended for chemotherapy. Treatment with sintilimab or placebo was continued until progressive disease, intolerable toxicity, the start of new antitumour treatment, withdrawal of consent, lost to follow-up, death, completion of treatment, or any other reasons determined by the investigators for stopping treatment, whichever occurred first.

Sintilimab or placebo was continued for a maximum of 24 months. Sintilimab or placebo was used alone if chemotherapy was intolerable, or when six cycles of chemotherapy had been given. The choice of chemotherapy regimen (cisplatin plus paclitaxel or cisplatin plus 5-fluorouracil) could not be switched during the study. Appendix 2 provides more details of the study design.

Assessments of the tumours were performed by the investigators according to RECIST version 1.1 at baseline, once every six weeks for 48 weeks, and then once every 12 weeks. Adverse events were assessed up to 90 days after the last dose and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 5.0). Survival was assessed every 60 days during follow-up.

Expression of PD-L1 in fresh or archival tumour sample was assessed during screening at a central laboratory (Covance, Shanghai, China) with the PD-L1 immunohistochemistry 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA). The combined positive score was defined as the number of PD-L1 staining cells (tumour cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells. The tumour proportion score was defined as the percentage of viable tumour cells showing partial or complete membrane staining.

Outcomes
The primary endpoint was overall survival, defined as the time from randomisation until death from any cause, in all patients and in patients with PD-L1 CPS ≥10. Secondary endpoints were objective response rate (proportion of patients with a complete or partial
response), assessed by the investigators according to RECIST version 1.1; progression free survival (time from randomisation to the first reported tumour progression or death), assessed by the investigators according to RECIST version 1.1; disease control rate (proportion of patients with a complete response, partial response, or stable disease); duration of response (time from the first reported complete or partial response until disease progression or death) in all patients and in patients with PD-L1 CPS ≥10; and safety profile. Exploratory endpoints included health related quality of life. Appendix 3 provides full details of the statistical analysis plan.

Statistical analysis
All efficacy endpoints were assessed in the intention-to-treat population of patients who were randomised. Safety was assessed in all patients who received at least one dose of the study treatment. The statistical analysis plan specified one interim analysis and a final analysis.

Median overall survival, progression free survival, duration of response, and corresponding 95% confidence intervals were estimated by the Kaplan-Meier method, and survival curves were plotted. A stratified log rank test was used to compare overall survival and progression free survival between treatment groups. Hazard ratios (95% confidence intervals) were estimated with a stratified Cox proportional hazards model where the stratification factors were PD-L1 CPS, ECOG performance status score, chemotherapy regimen, and hepatic metastasis. The objective response rate and disease control rate with corresponding 95% confidence intervals for each treatment group were estimated with normal approximation. Differences and 95% confidence intervals in objective response rates between the treatment groups were calculated with Miettinen-Nurminen methods.

We estimated that enrolling 676 patients to observe 500 overall survival events, and 260 overall survival events in patients with PD-L1 CPS ≥10, would provide a power of 83% to detect a hazard ratio of 0.75 in all patients and a power of 86% to detect a hazard ratio of 0.65 in patients with PD-L1 CPS ≥10 for overall survival favouring sintilimab in combination with chemotherapy over placebo in combination with chemotherapy, respectively. The overall type I error of the hypothesis testing for the two primary endpoints of overall survival was controlled by first assigning a one sided α of 0.0125 to all patients and a one sided α of 0.0125 to patients with PD-L1 CPS ≥10. The two primary hypotheses (superiority of sintilimab with chemotherapy vs chemotherapy only for overall survival in all patients and in patients with PD-L1 CPS ≥10) were tested in parallel. If the test in any population was significant, all α values allocated to that population were transferred to the other population. If the primary analyses for both populations were significant, the key secondary endpoints were tested in the sequence of objective response rate in all patients, progression free survival in all patients, objective response rate in patients with PD-L1 CPS ≥10, and progression free survival in patients with PD-L1 CPS ≥10.

The interim analysis was planned at about 70% overall survival events in all patients (350 overall survival events) and in patients with PD-L1 CPS ≥10 (168 overall survival events). The preset 70% overall survival events, however, did not occur at the same time in all patients and in patients with PD-L1 CPS ≥10. According to the prespecified conditions in the protocol, the interim analysis was performed at 351 overall survival events (about 70% overall survival events) in all patients; there were 195 overall survival events in patients with PD-L1 CPS ≥10 at this time. On the basis of the observed number of overall survival events, the threshold of one sided α for the interim analysis of overall survival was 0.0028 in all patients and 0.0056 in patients with PD-L1 CPS ≥10. The type I error boundary for the interim analysis was determined with the Lan-DeMets spending function in combination with the O’Brien-Fleming boundary in both populations. The independent data monitoring committee confirmed that the study met the specified efficacy and safety endpoints after reviewing the results of the interim analysis by an unblinded external statistics team.

Health related quality of life was assessed by the questionnaires QLQ-C30 (quality of life questionnaire core 30), QLQ-OES18 (quality of life questionnaire-oesophageal cancer module 18), and EQ-5D-5L (five level EuroQol five dimensional questionnaire) as exploratory endpoints. Time to deterioration (defined as first decline in standard score of ≥10 from baseline) in the global health status/quality of life domain of the QLQ-C30 and the pain, eating, reflux, and dysphagia domains of the QLQ-OES18 were compared with a stratified log rank test and Cox proportional hazard model, and the Kaplan-Meier method. The change from baseline in the visual analogue scale of the EQ-5D-5L was compared with a mixed model for a repeated measures approach, with treatment group, visit, treatment-by-visit interaction, randomisation group, baseline, and baseline-by-visit interaction as covariates. Least squares means in each treatment group and differences between groups were calculated, with corresponding standard errors and 95% confidence intervals. All statistical analyses were conducted with SAS version 9.2 (or higher). An independent data monitoring committee reviewed safety and interim efficacy.

Patient and public involvement
As it was not customary in China when the trial was initially designed, no patients were involved in the design or implementation of the trial, nor did they have any input on data analysis, interpretation, or writing up of the results. Although patients and the public were not directly involved in this trial mainly because of training restrictions, we did speak to patients about the trial and we asked a member of the public to read our manuscript after submission.
Results
The results are from the interim analysis based on the data cut-off date of 9 April 2021.

Participants
Between 14 December 2018 and 9 April 2021, 1033 patients were screened for eligibility and 659 were randomly assigned to sintilimab (n=327) or placebo (n=332) combined with chemotherapy. All patients who were randomised received at least one dose of study treatment. In the sintilimab-chemotherapy group, 307 patients received the chemotherapy regimen cisplatin plus paclitaxel and 20 patients received cisplatin plus 5-fluorouracil. In the placebo-chemotherapy group, 309 patients received the cisplatin plus paclitaxel regimen and 23 patients received the cisplatin plus 5-fluorouracil regimen. Median follow-up for overall survival was 16.0 months (interquartile range 12.3–19.4) in the sintilimab-chemotherapy group and 16.9 months (11.8–20.2) in the placebo-chemotherapy group. The most frequent primary reason for stopping treatment in both groups was progressive disease (fig 1). Median duration of the use of sintilimab or placebo in the sintilimab-chemotherapy group was 28.0 weeks (range 3-105) and 20.0 weeks (range 3-106) in the placebo-chemotherapy group.

Fig 1 | Flowchart of trial design. *Positive for surface antigen of hepatitis B virus and hepatitis B virus DNA viral load ≥103 copies/mL or ≥200 IU/mL, or acute or chronic active hepatitis C (positive hepatitis C virus antibody and positive hepatitis C virus RNA). †Table S3 lists details of other reasons. ‡Tumour lesion of liver at baseline was confirmed as primary hepatocellular carcinoma after study treatment. §Other reasons included start of new antitumour treatment and non-compliance with protocol. ECOG PS=Eastern Cooperative Oncology Group performance status score.
Baseline characteristics were similar in the two groups (table 1). Of 659 patients included, 640 (97%) were from 66 sites in China and 19 (3%) were from 13 sites outside of China. Because of the covid-19 pandemic, enrolment outside of China was affected and only 19 non-Chinese patients were enrolled. All enrolled patients had oesophageal squamous cell carcinoma; 57% (188/327) and 58% (193/332) of patients had PD-L1 CPS ≥10 in the sintilimab-chemotherapy group and placebo-chemotherapy group, respectively. We found 36% (119/327) of patients with PD-L1 TPS ≥10 in the sintilimab-chemotherapy group and 36% (119/332) in the placebo-chemotherapy group (table 1). Also, of 238 patients with PD-L1 TPS ≥10, 237 patients had PD-L1 CPS ≥10 (table S4). Overall, 93% (616/659) of patients received cisplatin plus paclitaxel (table 1).

**Primary outcomes**

The trial met the primary endpoint of overall survival in all patients and in patients with PD-L1 CPS ≥10 at the interim analysis: 148 of 327 (45%) patients in the sintilimab-chemotherapy group and 203 of 332 (61%) patients in the placebo-chemotherapy group died. Overall survival was greater in all patients in the sintilimab-chemotherapy group than in the placebo-chemotherapy group (median 16.7 months, 95% confidence interval 14.8 to 21.7 v 12.5 months, 11.0 to 14.5, hazard ratio 0.63, 95% confidence interval 0.51 to 0.78, P<0.001, fig 2). In patients with PD-L1 CPS ≥10, overall survival was also significantly improved in the sintilimab-chemotherapy group compared with the placebo-chemotherapy group (17.2 months, 15.5 to not calculated v 13.6 months, 11.3 to 15.7, hazard ratio 0.64, 0.48 to 0.85, P=0.002, fig 2). For all patients, the 12 month overall survival rates were 64% versus 52% and the 24 month overall survival rates were 39% versus 16% for the sintilimab-chemotherapy and placebo-chemotherapy groups, respectively. In patients with PD-L1 CPS ≥10, the 12 month and 24 month overall survival rates were 66% versus 55% and 42% versus 18% for the sintilimab-chemotherapy and placebo-chemotherapy groups, respectively (table S5). In patients with PD-L1 TPS ≥10, overall survival favoured sintilimab with chemotherapy versus placebo with chemotherapy (median 16.8 months, 13.4 to not calculated v 11.5 months, 9.7 to 14.5, hazard ratio 0.55, 0.38 to 0.78, table S7). The hazard ratios for overall survival favoured sintilimab with chemotherapy over placebo with chemotherapy for all prespecified subgroups, except PD-L1 CPS <1, probably because of the small sample size (fig 3). The hazard ratios for overall survival for sintilimab with chemotherapy versus placebo with chemotherapy were 0.62 (95% confidence interval 0.45 to 0.85) in the subgroup PD-L1 CPS <10, 0.67 (0.52 to 0.88) in the subgroup PD-L1 CPS <10% 0.65 (0.52 to 0.80) in the cisplatin plus paclitaxel subgroup (93% of all patients), and 0.31 (0.08 to 1.20) in the cisplatin plus 5-fluorouracil subgroup (table S7 and fig S1).

**Secondary outcomes**

Based on gated sequential testing, the secondary endpoints, progression free survival and objective response rate, were also met in this trial: 193 of 327 (59%) patients in the sintilimab-chemotherapy group and 245 of 332 (74%) patients in the placebo-chemotherapy group had disease progression, assessed by investigators, or died. Sintilimab with chemotherapy was better than placebo with chemotherapy for progression free survival in all patients (median 7.2 months, 95% confidence interval 7.0 to 9.6 v 5.7 months, 5.5 to 6.8, hazard ratio 0.56,
0.46 to 0.68, P<0.001, fig 4) and in patients with PD-L1 CPS ≥10 (median 8.3 months, 6.9 to 12.4 v 6.4 months, 5.5 to 6.9, hazard ratio 0.58, 0.45 to 0.75, P<0.001, fig 4). The six month progression free survival rates were 63% versus 49% and the 12 month progression free survival rates were 38% versus 15% for all patients in the sintilimab-chemotherapy and placebo-chemotherapy groups, respectively. The six month progression free survival rates were 43% versus 18% for patients with PD-L1 CPS ≥10 in the sintilimab-chemotherapy and placebo-chemotherapy groups, respectively (table S6). In all the prespecified subgroups, sintilimab with chemotherapy was better than placebo with chemotherapy for progression free survival (fig 5, and table S8).

In all patients, the confirmed objective response rate, assessed by investigators, was 66% (216/327; 95% confidence interval 61% to 71%) for sintilimab combined with chemotherapy versus 45% (151/332;
40% to 51%) for placebo with chemotherapy. In patients with PD-L1 CPS ≥10, 68% (127/188; 61% to 74%) of patients in the sintilimab-chemotherapy group and 49% (94/193; 42% to 56%) in the placebo-chemotherapy group had an objective response. The objective response rate was significantly higher in the sintilimab-chemotherapy group than in the placebo-chemotherapy group in all patients (estimated difference 20%, 13% to 28%, P<0.001) and in patients with PD-L1 CPS ≥10 (19%, 9% to 28%, P=0.003, table 2).

Median duration of confirmed response was longer in the sintilimab-chemotherapy group than in the placebo-chemotherapy group in all patients (median 9.7 months, 7.1 to 13.7 v 6.9 months, 5.6 to 7.2, hazard ratio 0.62, 0.47 to 0.80, P<0.001) and in patients with PD-L1 CPS ≥10 (median 12.4 months, 7.2 to 15.4 v 5.7 months, 5.1 to 7.6, hazard ratio 0.59, 0.42 to 0.84, P=0.003, table 2 and figs S2 and S3).

In the sintilimab-chemotherapy group, 134 of 327 (41%) patients received subsequent systemic drug treatments compared with 179 of 332 (54%) patients in the placebo-chemotherapy group. Forty one of 327 (13%) patients in the sintilimab-chemotherapy group and 59 of 332 (18%) patients in the placebo-
Chemotherapy group received anti-PD-1 or anti-PD-L1 agents (table S9).

Adverse events

In all patients, adverse events related to treatment (sintilimab, placebo, cisplatin, paclitaxel, or 5-fluorouracil) of any grade were reported by 321 of 327 (98%) patients in the sintilimab-chemotherapy group and in 326 of 332 (98%) patients in the placebo-chemotherapy group. Adverse events related to treatment, grades 3-5, occurred in 196 of 327 (60%) patients in the sintilimab-chemotherapy group and in 181 of 332 (55%) patients in the placebo-chemotherapy group (table 3). The most frequent grade 3 or worse adverse events (occurring in ≥5% of patients in the sintilimab-chemotherapy group) were a decrease in neutrophil count (30% (98/327) in the sintilimab-chemotherapy group vs 34% (112/332) in the placebo-chemotherapy group).
Serious adverse events related to treatment occurred in 90 of 327 (28%) patients in the sintilimab-chemotherapy group versus 68 of 332 (20%) patients in the placebo-chemotherapy group. Sixty eight of 327 (21%) patients in the sintilimab-chemotherapy group and 41 of 332 (12%) patients in the placebo-chemotherapy group stopped taking a study drug because of adverse events related to treatment. Adverse events related to treatment resulted in death in nine of 327 (3%) patients in the sintilimab-chemotherapy group and six of 332 (2%) patients in the placebo-chemotherapy group (tables S10 and S12). The rates of adverse events were similar when we grouped patients by chemotherapy regimen (cisplatin plus paclitaxel regimen or cisplatin plus 5-fluorouracil, tables S14 and S15).

We found adverse events related to the immune system, as assessed by the investigators, in 155 of 327 (47%) patients in the sintilimab-chemotherapy group and in 81 of 332 (24%) patients in the placebo-chemotherapy group (table S10). The most frequent adverse events related to the immune system (in ≥5% of patients in the sintilimab-chemotherapy group) were rash (13% (42/327) v 2% (8/332)), hypothyroidism (13% (41/327) v 7% (23/332)), and hyperthyroidism (6% (19/327) v 2% (5/332)) in the sintilimab-chemotherapy and placebo-chemotherapy groups, respectively (table S16). Most of adverse events related to the immune system were grades 1-2.
Table 2 | Antitumour activity

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Patients with combined positive score ≥10</th>
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<tbody>
<tr>
<td></td>
<td>Sintilimab and chemotherapy (n=327)</td>
<td>Placebo and chemotherapy (n=332)</td>
</tr>
<tr>
<td>Confirmed objective response (No (%; 95% CI))</td>
<td>216 (66; 61 to 71)</td>
<td>151 (45; 40 to 51)</td>
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<td>Estimated difference (%) (95% CI)</td>
<td>-6 (11; -17 to 5)</td>
<td>-23 (-35 to -10)</td>
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<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Best overall response (No (%))</td>
<td>20 (13 to 28)</td>
<td>19 (9 to 28)</td>
</tr>
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</table>

Percentages might not sum to 100 because of rounding.

Chemotherapy regimen is cisplatin plus paclitaxel or cisplatin plus 5-fluorouracil.

*Confirmed objective response was defined as a response (complete or partial) confirmed by two consecutive tumour assessments according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, assessed by investigators.
†Imaging assessment was not done at the first tumour assessment (week 6) because treatment was ongoing and time of treatment was less than six weeks, or treatment was discontinued before six weeks after randomisation.

or worse adverse events related to the immune system occurred in 33 of 327 (10%) patients in the sintilimab-chemotherapy group and in eight of 332 (2%) patients in the placebo-chemotherapy group (table S10). Of the grade 3 or worse adverse events related to the immune system, only lung disease (2%, 7/327) and rash (1%, 4/327) occurred in more than 1% of patients in the sintilimab-chemotherapy group (table S16).

Health related quality of life

Mean difference and least squares mean difference between groups favoured sintilimab with chemotherapy for the visual analogue scale of the EQ-5D-5L at most time points, except weeks 18 and 30 (fig S4 and table S17). Patients in the sintilimab-chemotherapy group had a decreased risk of deterioration in quality of life compared with patients in the placebo-chemotherapy group for the global health status/quality of life domain of the of QLQ-C30 (median time to deterioration 9.7 months v 5.6 months, hazard ratio 0.81, 95% confidence interval 0.64 to 1.02, P=0.07, fig S5). Health related outcomes with first line sintilimab with chemotherapy versus chemotherapy only in patients with advanced or metastatic oesophageal squamous cell carcinoma will be published separately.

Discussion

Principal findings

In this phase 3 trial, we found that sintilimab combined with chemotherapy had a significant and clinically meaningful improvement in overall survival compared with placebo combined with chemotherapy in patients with advanced or metastatic oesophageal squamous cell carcinoma. For progression free survival, objective response rate, and duration of response, we also found a significant improvement in the sintilimab-chemotherapy group. These benefits were found in all patients and in patients with PD-1 CPS ≥10. The Kaplan-Meier curves for overall survival in all patients and in patients with PD-1 CPS ≥10 showed early separation (that is, the curves neither overlapped nor crossed), and the separation was maintained during follow-up. These results indicated a long term overall survival benefit with sintilimab in combination with chemotherapy. The estimated progression free survival rates at different follow-up time were also higher in the sintilimab-chemotherapy group than in the placebo-chemotherapy group.

Patients with advanced or metastatic oesophageal cancer commonly have a poor health related quality of life because of their disease. Our results showed that sintilimab combined with chemotherapy was associated with a reduced risk of deterioration in some health related quality of life measures compared with placebo with chemotherapy. With greater efficacy and a manageable safety profile, our results support a clinically meaningful benefit of sintilimab combined with chemotherapy in patients with advanced or metastatic oesophageal squamous cell carcinoma. Complete outcomes for health related quality of life will be published separately.

Comparison with other studies

First line treatment of oesophageal squamous cell cancer is changing rapidly, with five recent randomised phase 3 trials showing efficacy for anti PD-1 inhibitors in combination with chemotherapy. In the KEYNOTE-590 trial, pembrolizumab plus cisplatin and 5-fluorouracil showed improved survival (hazard ratio 0.72, 95% confidence interval 0.60 to 0.88) over placebo plus cisplatin and 5-fluorouracil in patients with advanced or metastatic oesophageal squamous cell carcinoma. Subsequently, nivolumab plus cisplatin and 5-fluorouracil reduced the risk of death by 26% compared with placebo plus cisplatin and 5-fluorouracil in the CHECKMATE-648 trial (hazard ratio 0.74, 0.58 to 0.96). Also, the ESCORT-1st trial, which enrolled only Chinese patients with
Table 3 | Adverse events related to treatment in patients who received sintilimab or placebo in combination with chemotherapy

<table>
<thead>
<tr>
<th>Any adverse events related to treatment*</th>
<th>Grades 1-2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sintilimab and chemotherapy (n=327)</td>
<td>125 (38)</td>
<td>134 (41)</td>
<td>53 (16)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Placebo and chemotherapy (n=332)</td>
<td>145 (44)</td>
<td>122 (37)</td>
<td>53 (16)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>204 (62)</td>
<td>41 (13)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decrease in white blood cell count</td>
<td>155 (47)</td>
<td>44 (13)</td>
<td>13 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>166 (45)</td>
<td>7 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>105 (32)</td>
<td>7 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decrease in neutrophil count</td>
<td>104 (32)</td>
<td>61 (19)</td>
<td>37 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>98 (30)</td>
<td>1 (c1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>96 (29)</td>
<td>13 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>90 (28)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypoanaesthesia</td>
<td>73 (22)</td>
<td>2 (c1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decrease in platelet count</td>
<td>60 (18)</td>
<td>6 (2)</td>
<td>2 (c1)</td>
<td>1 (c1)</td>
</tr>
<tr>
<td>Decrease in weight</td>
<td>53 (16)</td>
<td>3 (c1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>48 (15)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>45 (14)</td>
<td>4 (1)</td>
<td>1 (c1)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>37 (11)</td>
<td>4 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Increase in alanine aminotransferase</td>
<td>35 (11)</td>
<td>1 (c1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypophagia</td>
<td>33 (10)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decrease in lymphocyte count</td>
<td>30 (9)</td>
<td>8 (2)</td>
<td>2 (c1)</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>22 (7)</td>
<td>14 (4)</td>
<td>2 (c1)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoanaemia</td>
<td>21 (6)</td>
<td>2 (c1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal hepatic function</td>
<td>11 (3)</td>
<td>5 (2)</td>
<td>1 (c1)</td>
<td>0</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>8 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Immune mediated lung disease</td>
<td>7 (2)</td>
<td>4 (1)</td>
<td>3 (c1)</td>
<td>0</td>
</tr>
<tr>
<td>Increase in blood pressure</td>
<td>5 (2)</td>
<td>10 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (c1)</td>
<td>6 (2)</td>
<td>1 (c1)</td>
<td>3 (c1)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>0</td>
<td>3 (c1)</td>
<td>5 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Data are number (%).</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Chemotherapy regimen is cisplatin plus paclitaxel or cisplatin plus 5-fluorouracil.

*Adverse events related to treatment of grades 1-2 occurring in ≥10% of patients or grades 3-5 occurring in ≥1% of patients are shown. Adverse events related to treatment included any study drug. Patients who died because of adverse events related to treatment had immune mediated lung disease (n=2), immune mediated lung disease and pneumonia (n=1), pneumonitis and pneumonia (n=1), pneumonia, septic shock, and myelosuppression (n=1), arrhythmia (n=1), decrease in platelet count and cerebral haemorrhage (n=1), cardiac failure, respiratory failure, renal failure, and septic shock (n=1), and unknown cause of death (n=3), unknown cause of death (n=2), and immune mediated myositis, immune mediated myocarditis, and decreased platelet count (n=1) in the placebo-chemotherapy group.

osseous squamous cell carcinoma, found a hazard ratio for overall survival of 0.70 (0.56 to 0.88) with camrelizumab versus placebo in combination with cisplatin and paclitaxel.21 Toripalimab plus cisplatin and paclitaxel showed greater overall survival versus placebo plus cisplatin and paclitaxel in the JUPITER-06 trial (hazard ratio 0.58, 0.425 to 0.783).22 In our trial, sintilimab with a chemotherapy regimen chosen by the investigators (cisplatin plus paclitaxel or cisplatin plus 5-fluorouracil) also improved efficacy. These trials show that PD-1 inhibitors in combination with chemotherapy could improve overall survival for patients with advanced or metastatic oesophageal squamous cell carcinoma.

Preferred chemotherapy regimens differ according to local clinical practice, with cisplatin plus 5-fluorouracil preferred in non-Chinese populations and cisplatin plus paclitaxel in Chinese populations. In our trial, we evaluated the antitumour activity of sintilimab in combination with both chemotherapy regimens as first line treatment for oesophageal squamous cell carcinoma to account for different regional clinical practices and to show the general applicability of sintilimab in combination with two different chemotherapy regimens.

Although only 7% of patients (43/659) received the cisplatin plus 5-fluorouracil regimen because of the covid-19 pandemic and late enrolment of western populations, this regimen also showed a trend for survival benefit (hazard ratio for overall survival 0.31, 95% confidence interval 0.08 to 1.20, P=0.07). The results of the KEYNOTE-590 and CHECKMATE-648 trials showed that PD-1 inhibitors in combination with cisplatin and 5-fluorouracil improved overall survival for patients with untreated advanced or metastatic oesophageal squamous cell carcinoma.19 20 We found a trend for improved overall survival for sintilimab with cisplatin plus 5-fluorouracil but our trial was limited by the small sample size and the short follow-up time in the subgroup of patients who received the cisplatin plus 5-fluorouracil regimen. Future studies should determine if sintilimab with cisplatin plus 5-fluorouracil provides better overall survival. After our interim analysis, enrolment continued outside of China and our final analysis will be updated with the results of these analyses.

Median overall survival was more than 15 months in patients who received a PD-1 inhibitor with cisplatin plus paclitaxel in the ORIENT-15, ESCORT-1st, and JUPITER-06 trials. Median overall survival was about 13 months in the KEYNOTE-590 and CHECKMATE-648 trials where a PD-1 inhibitor was combined with cisplatin plus 5-fluorouracil. In the Chinese populations of KEYNOTE-590, median overall survival in the
group who received pembrolizumab in combination with cisplatin plus 5-fluorouracil was 10.5 months. Overall survival seemed to be different in these trials in patients who received a PD-1 inhibitor with cisplatin plus paclitaxel or cisplatin plus 5-fluorouracil, but a direct comparison of the chemotherapy regimens was lacking. The use of different chemotherapy regimens might cause different alterations in the tumour microenvironment, as evidenced by taxane inducing immunogenic cell death of cancer cells and causing various immunogenic actions.23-26 Also, paclitaxel could be a more convenient chemotherapy agent than 5-fluorouracil which requires continuous infusion on multiple days. Future studies should compare paclitaxel with 5-fluorouracil.

The patients enrolled in this trial had unresectable locally advanced or metastatic oesophageal squamous cell carcinoma and were unsuitable for definitive treatments, including definite concomitant chemoradiotherapy and surgery. Median overall survival in patients with locally advanced carcinoma was similar to patients with metastatic oesophageal squamous cell carcinoma (table S7). Patients with unresectable locally advanced oesophageal squamous cell carcinoma, who receive no further clinical benefit from definitive treatment, would be treated the same as patients with metastatic oesophageal squamous cell carcinoma. The proportion of these patients with unresectable locally advanced oesophageal squamous cell carcinoma in our trial was only 13% (87/659). Similarly, about 10-20% of patients had unresectable locally advanced oesophageal cancer in the KEYNOTE-590, CHECKMATE-648, ESCORT-1st, and JUPITER-06 trials.19-22

In our subgroup analysis, we showed that overall survival, assessed by prespecified baseline demographic and disease characteristics, consistently favoured sintilimab with chemotherapy versus placebo with chemotherapy across all subgroups. The different PD-L1 scoring methods, tumour proportion score and combined positive score, have been found to be markers of clinical efficacy for PD-1/PD-L1 inhibitors.27 The tumour proportion score represents the status of expression of PD-L1 in tumour issues, whereas the combined positive score represents the status of expression of PD-L1 in tumour issues and mesenchymal immune cells. Currently, expression of PD-L1 is a potential biomarker for predicting immune checkpoint inhibitors in anticaner treatment, based on basic science and clinical evidence. We found that the overall survival advantage with sintilimab in combination with chemotherapy was not related to expression of PD-L1 (hazard ratios: patients with CPS ≥10, 0.64; CPS <10, 0.62; TPS ≥10%, 0.55; and TPS <10%, 0.67). Although the hazard ratios for overall survival in patients with PD-L1 CPS ≥10 and PD-L1 CPS <10 seemed to be similar, the duration of confirmed response was longer in patients with PD-L1 CPS ≥10. The hazard ratio for overall survival in patients with PD-L1 TPS ≥10% was less than that for PD-L1 TPS <10%. The KEYNOTE-590, CHECKMATE-648, and ESCORT-1st trials found similar results, with patients with higher expression of PD-L1 deriving more clinical benefit.19-21

Sintilimab with chemotherapy was well tolerated, with similar incidences of any adverse events and grade ≥3 adverse events related to treatment compared with placebo in combination with chemotherapy. The incidence of adverse events related to treatment, grade ≥3, in patients in the sintilimab-chemotherapy group was similar to other PD-1 inhibitors with first line chemotherapy although these treatments were not directly compared.19-22 We found no new safety issues with sintilimab, and the safety profile in this trial was consistent with profiles previously established in patients with oesophageal squamous cell carcinoma and other solid tumours.10-14 28

Strengths and limitations of this study
The strengths of this randomised, double blind, placebo controlled trial were its large size and the number of participating sites. In our trial, the chemotherapy regimens cisplatin plus paclitaxel and cisplatin plus 5-fluorouracil were simultaneously chosen by the investigators based on regional clinical practice. Hence the trial showed the general applicability of sintilimab in combination with two chemotherapy regimens. The association between efficacy and expression of PD-L1 based on the combined positive score or tumour proportion score was reported in one trial.

Our trial had some limitations. Although the trial was designed to be multiregional, 640 of 659 (97%) patients from 66 sites in China and only 19 of 659 patients from 13 sites outside of China were enrolled because of the outbreak of the covid-19 pandemic. Hence the trial represented mainly Chinese patients with oesophageal squamous cell carcinoma. Also, the sample size was small in the cisplatin plus 5-fluorouracil group because in China, cisplatin plus paclitaxel is the preferred treatment. Enrolment outside of China was ongoing at the time of the interim analysis.

Conclusion
The ORIENT-15 trial recruited 97% (640/659) Chinese patients, and 93% (616/659) of patients received cisplatin plus paclitaxel as chemotherapy. Sintilimab combined with chemotherapy showed solid benefits in overall survival and progression free survival in the subgroup of patients who received the cisplatin plus paclitaxel regimen. Although the number of patients who received the cisplatin plus 5-fluorouracil regimen was small, the trends for improved outcomes were similar to those found with other PD-1 monoclonals in randomised controlled trials.

Sintilimab in combination with chemotherapy (cisplatin plus paclitaxel or cisplatin plus 5-fluorouracil) provided greater overall survival, with improved progression free survival, higher overall response rate, and a manageable safety profile compared with placebo with chemotherapy in patients.
with advanced oesophageal squamous cell carcinoma, regardless of expression of PD-L1.

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Contributors: ZLu, JW, and YS contributed equally to this trial. LS, ZLu, JW, and YS contributed to the study design. LS was the chief investigator. ZLu, JW, YS, LL, LX, LY, BW, GS, YS, GC, HLi, TC, NL, WQ, GL, YH, Hs, LX, YZ, YW, ZLu, XW, SY, YP, M-PP, AZ, and LS contributed to patient enrolment and data acquisition. HLi did the statistical analysis. ZM and YW contributed to the data interpretation and medical reviewing. LS, ZLu, ZM, and YW drafted the manuscript. All authors contributed to manuscript revision. LS, ZLu, JW, YS, and ZM, and HLi accessed and verified the raw data in the manuscript and data. The corresponding investigator has the final responsibility for the decision to submit for publication. LS is the study guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from Innoven Biologics and Eli Lilly for the submitted work; LS reports receiving research funding from Innoven Biologics, Bevegavox, Xantiom Biomedical Technology, Qilu Pharmaceutical, ZaiLab Pharmaceutical, BeiHai Kangcheng (Beijing) Medical Technology, and Jacobio Pharmaceuticals; consultant fees from MSD, Merck, Mingji Biopharmaceutical, Haichuang Pharmaceutical, Herbour Biomed, and Bi; honoraria from Hutchison Whampoa, Hengru, ZaiLab, and CSTONE Pharmaceutical; and serving as a consultant for Roeghang Pharmaceutical, ZaiLab, CSTONE Pharmaceutical, and BMS. AZ has participated in consulting boards, advisory boards, or both, for Amgen, Lilly, Merck, Roche, Sanofi, Servier, Baxter, MSD, Pierre Fabre, Havas Life, Alina Health, and Zymeworks.

Ethical approval: This study was approved by the institutional review board or ethics committee at each site (appendix 5), and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The trial was overseen by an independent trial steering committee and data monitoring and ethics committee. All patients gave written informed consent. The trial protocol was reviewed by representatives of the National Medical Products Administration of China and the US Food and Drug Administration, who provided valuable input about the design of the trial.

Data sharing: Reasonable requests for data sharing should be made to the corresponding author and will be handled in line with the data access and sharing policy of Human Genetic Resource Administration of China and other participating sites outside of China. The corresponding author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Participating sites were informed of the results. Results can be communicated to study participants who express an interest during clinic visits. Dissemination to the public will be achieved through media outreach.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Web appendix: Supplementary information