Clinical Study Report	
Drug Substance	Durvalumab
Study Code	D419BR00018
Edition Number	1.0
Date	16Oct 2023
NCT Number	NCT04449861

An Open Label, Multicenter Study of First-Line Durvalumab plus Platinum-Based Chemotherapy in Chinese Patients with Extensive Stage Small-Cell Lung Cancer (Oriental)

Study dates:	First subject enrolled: 7 December 2020 Last subject last visit: 30 March 2023 The analyses presented in this report are based on a clinical data lock date of 31 May 2023
Phase of development:	Therapeutic use (IIIb)
Co-ordinating Investigator:	
Sponsor's Responsible Medical Officer:	

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study centre(s)

This study was conducted at 32 centres that enrolled participants in China.

Publications

Cheng et al 2022

Cheng Y, Wang J, Yu Y, et al. Phase IIIb study of durvalumab plus platinum-etoposide in first-line treatment of Chinese extensive-stage small-cell lung cancer (ORIENTAL): preliminary safety and efficacy results. Annals of Oncology (2022) 16 (suppl_1): 100102-100102.

Cheng Y, Wang J, Cang S, et al. An open label, multicenter, phase IIIb study of first-line durvalumab plus platinum-based chemotherapy in Chinese patients with extensive stage small cell lung cancer (ES-SCLC). Journal of Thoracic Oncology (2021). VOLUME 16, ISSUE 4, SUPPLEMENT, S727-S728

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of durvalumab + EP in patients with performance status 0-2	• Incidence of Grade ≥ 3 AEs • Incidence of imAEs
Secondary	
• To assess the efficacy of durvalumab + EP in terms of PFS, ORR and OS • To assess the safety and tolerability profile of durvalumab + EP	• PFS, APF12, ORR, DoR using site Investigator assessment and OS, OS12 • Incidence of AEs, SAEs, AESIs, AEs resulting in treatment discontinuation

AE Adverse event; AESI adverse event of special interest; APF12 Proportion of patients alive and progression free at 12 months after first dose of study treatment; DoR Duration of Response; EP Etoposide and platinum-based chemotherapy; imAE Immune-mediated adverse event; ORR Objective response rate; OS Overall survival; OS12 Overall survival at 12 months after first dose of study treatment; PFS Progression free survival.

Study design

This was an open-label, single-arm, multicentre, Phase IIIb study to determine the safety of durvalumab + etoposide and cisplatin or carboplatin (EP) as first-line treatment in patients with extensive stage small-cell lung cancer (ES-SCLC). Participants who fulfilled all the inclusion criteria and none of the exclusion criteria were enrolled and received treatment with durvalumab + etoposide and either cisplatin or carboplatin for 4 to 6 cycles, followed by durvalumab maintenance. Durvalumab was administered at a dose of [redacted] every 3 weeks (Q3W) with first-line chemotherapy (EP) and continued to be administered as monotherapy every 4 weeks (Q4W) post-chemotherapy until progressive disease (PD) or intolerable toxicity. Prophylactic cranial irradiation (PCI) was allowed at the investigators' discretion as per standard of care (SoC) guidance for ES-SCLC. Participants attended a safety follow up visit 90 days after last dose of durvalumab.

Target population and sample size

Adult patients (aged ≥ 18 years) with histologically or cytologically documented extensive stage SCLC (stage IV [T any, N any, M1 a/b/c], or with T3-4 due to multiple lung nodules that were too extensive or have tumour/nodal volume that was too large to be encompassed in a tolerable radiation plan according to American Joint Committee on Cancer Stage (8th edition). Patients must have World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2; patients with PS2 were limited to 20% of the total study population.

Sample size:

Planned: 300 participants

Actual enrolled: 166 participants

Evaluated: 165 participants

Investigational product and comparator(s): dosage, mode of administration and batch numbers

[redacted] was administered via intravenous (IV) infusion concurrently with etoposide and platinum-based chemotherapy (Investigator choice of cisplatin or carboplatin) Q3W starting on Week 0 for 4 to 6 cycles. Durvalumab monotherapy was continued Q4W post-chemotherapy until disease progression.

[redacted]

Duration of treatment

Unless specific treatment discontinuation criteria were met, participants enrolled continued durvalumab therapy until disease progression or intolerable toxicity, as per investigator assessment.

EP was administered for 4 to 6 cycles for participants per investigator clinical decision.

Statistical methods

Approximately 300 participants were enrolled to this study. All participants who received at least 1 dose of study treatment were included in the safety analysis set, which was the primary analysis set for all analyses.

Safety data was summarized descriptively overall, by seriousness, by causality, and by maximum National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) grade (v5.0) based on the safety analysis set. Continuous

variables were summarised by the number of observations (n), mean, standard deviation (Std), median, quartiles (Q1 and Q3), minimum, and maximum. Categorical variables were summarised by frequency counts and percentages for each category. The Clopper-Pearson 2-sided 95% confidence intervals (CIs) around incidence also was reported for Grade ≥ 3 AEs, for each imAE, and where appropriate, for other AE types.

The efficacy of first-line durvalumab + EP was assessed as secondary objectives, in terms of PFS, APF12, ORR, DoR, OS, OS12. Time-to-event data was summarized using Kaplan-Meier estimates of the median event time and quartiles together with their 95% CIs; data was reported for patients overall and separately for patients based on performance status (0 to 1 and 2). ORR (based on Investigator assessment) was summarized descriptively, and the 95% CIs using Clopper-Pearson method was reported.

There was no formal interim analysis in this study.

Study population

According to the protocol, enrolment was closed as soon as the product received China marketing authorization as first line treatment for ES-SCLC or total 300 sample size was achieved, whichever came first. Durvalumab as first line treatment for ES-SCLC received NMPA's approval on 14 July 2021, so the enrolment was closed on 07 August 2021. A total of 193 participants were screened, among which, 166 participants (86.0%) were successfully screened and enrolled into the study from 32 study sites. Among the 166 enrolled participants, 165 of them (99.4%) received study treatment, and thus were included into the safety set (SS). The safety set was used as the efficacy analysis set. At data cut-off (DCO), no participant remained on study treatment and all 166 participants discontinued the study.

Summary of efficacy results

The safety analysis set was used for the efficacy analysis set. Among the 165 participants in the SS, the median PFS was 6.3 (95% CI: 5.6, 6.5) months, and APF12 was 17.6% (95% CI: 12.0%, 24.1%). ORR was 76.4% (95% CI: 69.1%, 82.6%), DCR was 89.1% (95% CI: 83.3%, 93.4%). The median DoR was 5.1 (95% CI: 4.7, 5.7) months. The median OS was 14.8 (95% CI: 13.2, 16.0) months, and the OS12 was 60.8% (95% CI: 52.8%, 67.9%).

Summary of safety results

The median intended and actual duration of durvalumab were 182.0 and 176.0 days, respectively. The mean relative dose intensity of durvalumab was 96.94%. The median total number of cycles received of durvalumab, carboplatin, cisplatin and etoposide were 7.0 (IQR: 5.0, 10.0), 5.0 (IQR: 4.0, 6.0), 4.0 (IQR: 1.0, 4.0) and 5.0 (IQR: 4.0, 6.0), respectively. In the SS, 161 participants (97.6%) reported 1534 AEs. There were 164 Grade ≥ 3 AEs occurred in 82 participants (49.7%), and 159 Grade 3 or 4 AEs occurred in 79 participants (47.9%). There were 70 participants (42.4%) reported 130 SAEs, 66 participants (40.0%) reported 118 AESIs, 40 participants (24.2%) reported 81 imAEs, and 11 participants (6.7%) reported 18 infusion reaction AEs. There were 50 participants (30.3%) interrupted the study treatment due to AEs, 20 participants (12.1%) discontinued permanently due to AEs. AEs leading to death were reported in 5 participants (3.0%), 2 of the events were related to study treatment.

Conclusion(s)

This study is the largest study to evaluate the safety and efficacy of durvalumab plus platinum-etoposide in Chinese ES-SCLC patients to date. . The efficacy results of this study had showed that durvalumab plus platinum-etoposide was effective for Chinese patients with ES-SCLC. The overall safety findings in this study remained consistent with the known safety profiles of durvalumab and platinum-etoposide. No new safety concern was identified. Overall, the benefit-risk balance was positive for durvalumab plus platinum-etoposide as first-line treatment in real-world like population of Chinese patients with ES-SCLC and consistent with CASPIAN study findings, further supporting durvalumab as preferred standard of care in ES-SCLC.