Adebrelimab or placebo plus carboplatin and etoposide as first-line treatment for extensive-stage small-cell lung cancer (CAPSTONE-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

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1. 簡述論文的概要與重大發現：

在癌症中死亡率最高為肺癌，肺癌發生率在全球的癌症中排名第二。

小細胞肺癌（small cell lung cancer, SCLC）約佔所有肺癌的 15%，是一種侵襲性神經內分泌惡性腫瘤，SCLC 的特徵是快速生長和在早期發生癌症轉移。因此大約 70%的患者在第四期才被首次診斷出患有 SCLC。儘管在開發新的治療方案做出了巨大努力，但目前鉑類藥物的化療仍然是第四期 SCLC（ES-SCLC）的標準一線治療。

近年來免疫檢查點抑制劑治療在癌症的發展有不錯的成效。在過往已有 3 期試驗評估 PD-L1 抑製劑 Atezolizumab 及 PD-L1 抑製劑 Durvalumab 和 PD-1 抑製劑 Pembrolizumab，搭配鉑類藥物聯合化療，延長了 SCLC 進展及生存率時間。根據這些研究結果讓免疫檢查點抑制劑和化療的組合被批准成為治療 ES-SCLC 的一線療法，改變了 ES-SCLC 的治療方式。

Adebrelimab 是一種針對 PD-L1 的新型人源化 IgG4 monoclonal antibody，在這次第 3 期試驗中檢驗 Adebrelimab 對 SCLC 的療效，發現 Adebrelimab 聯合化療的實驗組相較於安慰劑聯合化療對照組生存率有顯著的提高，並發現與先前其他免疫檢查點抑制劑聯合化療藥物實驗數據相比，此次實驗在不良事件中血液學事件相較多，推測亞洲人可能對免疫療法敏感性較高，另外發現相較於其他先前的實驗，對照的化療組總生存率延長，在後續治療中亦發現可能在抗血管新生藥物 anlotinib 的使用延長了生存期時間。

2. 對論文內容的提問：

此次 Adebrelimab 第三期藥物臨床試驗，參與實驗患者皆來自中國醫院的病患，針對不同地區或是不同人種，而增加收案範圍?

3. 論文的缺點與評論：

本篇作者進行 Adebrelimab 藥物第三期實驗，期望對 ES-SCLC 有更好療效並做為第一線治療藥物，增加 ES-SCLC 治療選項，延長患者生存時間。

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Summary

Background Extensive-stage small-cell lung cancer (ES-SCLC) is associated with poor prognosis and treatment options are scarce. Immunotherapy has shown robust clinical activity in ES-SCLC in previous phase 3 trials. We aimed to assess the efficacy and safety of adebrelimab (SHR-1316), a novel anti-PD-L1 antibody, with standard chemotherapy as a first-line treatment for ES-SCLC.

Methods The CAPSTONE-1 study was a randomised, double-blind, placebo-controlled, phase 3 trial, done in 47 tertiary hospitals in China. Key inclusion criteria were patients aged 18–75 years, with previously untreated histologically or cytologically confirmed ES-SCLC and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Eligible patients were randomly assigned (1:1) to receive four to six cycles of carboplatin (area under the curve of 5 mg/mL per min, day 1 of each cycle) and etoposide (100 mg/m² of body-surface area, on days 1–3 of each cycle) with either adebrelimab (20 mg/kg, day 1 of each cycle) or matching placebo, followed by maintenance therapy with adebrelimab or placebo. All treatments were given intravenously in 21-day cycles. Randomisation was done using a centralised interactive web response system with a block size of four, stratified by liver metastases, brain metastases, and lactate dehydrogenase concentration. The primary endpoint was overall survival in patients who received at least one dose of study medication. Safety was analysed in the as-treated population. This study is complete and registered with ClinicalTrials.gov, NCT03711305.

Findings Between Dec 26, 2018, and Sept 4, 2020, 462 eligible patients were enrolled and randomly assigned: 230 (50%) patients received adebrelimab plus chemotherapy (adebrelimab group) and 232 (50%) patients received placebo plus chemotherapy (placebo group). At data cutoff (Oct 8, 2021), median follow-up was 13·5 months (IQR 8·9–20·1). Median overall survival was significantly improved in the adebrelimab group (median 15·3 months [95% CI 13·2–17·5]) compared with the placebo group (12·8 months [11·3–13·7]; hazard ratio 0·72 [95% CI 0·58–0·90]; one-sided p=0·0017). The most common treatment-related grade 3 or 4 adverse events were decreased neutrophil count (174 [76%] patients in the adebrelimab group and 175 [75%] patients in the placebo group), decreased white blood cell count (106 [46%] and 88 [38%]), decreased platelet count (88 [38%] and 78 [34%]), and anaemia (64 [28%] and 66 [28%]). Treatment-related serious adverse events occurred in 89 (39%) patients in the adebrelimab group and 66 (28%) patients in the placebo group. Four treatment-related deaths were reported: two each in the adebrelimab group (respiratory failure and interstitial lung disease and pneumonia) and placebo group (multiple organ dysfunction and unknown cause of death).

Interpretation Adding adebrelimab to chemotherapy significantly improved overall survival with an acceptable safety profile in patients with ES-SCLC, supporting this combination as a new first-line treatment option for this population.

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For a Chinese translation of the summary see Online for appendix 1

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Introduction

Globally, lung cancer is the leading cause of cancer death and the second most diagnosed cancer.[1] Small-cell lung cancer (SCLC), which accounts for about 15% of all lung cancers, is an aggressive neuroendocrine malignancy.[2,3] SCLC is characterised by rapid growth and early occurrence of metastases, with approximately 70% of patients first diagnosed at the extensive stage.[4] Despite the substantial efforts into the development of new treatment regimens, for decades platinum-based (with etoposide or irinotecan) chemotherapy remained the standard first-line treatment for extensive stage SCLC (ES-SCLC), which provides a median overall survival of 9–11 months.[5]