PD-(L)1 inhibitors for first-line treatment of extensive-stage small-cell lung cancer in Asian and non-Asian patients: a meta-analysis

Francesco Passiglia,[1] Nir Peled,[2] Vladmir Claudio Cordeiro de Lima,[3] Ji-Youn Han,[4] Sheng Xu,[5] Na Zhao,[5] Kirsha Naicker,[6] Eugenia Priedane,[6] Mesha Austin Taylor,[7] Diego Cortinovis[8]

[1]Azienda Ospedaliera Universitaria San Luigi Gonzaga, Orbassano-Torino, Italy; [2]Shaare Zedek Medical Center, Jerusalem, Israel; [3]A.C. Camargo Cancer Center, São Paolo, Brazil; [4]National Cancer Center, Goyang-si, South Korea; [5]BeOne Medicines Ltd, Shanghai, China; [6]BeOne Medicines Ltd, London, UK; [7]BeOne Medicines Ltd, Cambridge, MA, USA; [8]Ospedale San Gerardo Monza, Monza, Italy

CONCLUSIONS

- This meta-analysis of randomized phase 3 clinical studies demonstrates the comparability in efficacy of PD-(L)1 inhibitors plus chemotherapy for 1L ES-SCLC in both Asian and non-Asian patients
- PD-(L)1 inhibitors plus chemotherapy were tolerable in both Asian and non-Asian patients
- The consistency in clinical benefit shown in this meta-analysis is important when considering the use of drugs that were initially developed in an Asian population, such as tislelizumab, for use in a wider population, or for global regulatory and reimbursement submissions
- Real-world data at the regional and country level will confirm long-term clinical benefits and tolerability in specific patient populations

INTRODUCTION

- Extensive-stage small cell lung cancer (ES-SCLC) accounts for most SCLC cases[1] and is associated with poor prognosis[2]
- PD-(L)1 inhibitors in combination with platinum-based chemotherapy have improved overall survival (OS) and progression-free survival (PFS) over chemotherapy alone[3] and are established treatments for first-line (1L) ES-SCLC[4,5]
- The impact of immunotherapy treatments in Asian versus non-Asian patients with ES-SCLC is not well understood
- A systematic literature review (SLR) and meta-analysis were conducted and efficacy and safety of PD-(L)1 inhibitor combination therapy as 1L treatment of ES-SCLC in Asian versus non-Asian patients are presented

METHODS

- The SLR and meta-analysis were conducted on October 7, 2024 in accordance with published guidance[6,7]
- Literature searches were performed using the Ovid SP® platform
- A review was also conducted of relevant conference proceedings and registry databases

Selection

- Patients aged ≥18 years with histologically or cytologically confirmed ES-SCLC who received no prior systemic treatment for ES-SCLC were included; comparators included chemotherapy or placebo
- Randomized, controlled phase 3 studies that reported subgroup analyses of Asian patients defined by ethnicity or region were selected
- Studies were summarized using the Population, Intervention, Comparison, Outcomes, and Study (PICOS) design framework
- Exclusion criteria included the absence of a platinum-based chemotherapy in the control arm, study populations judged to be unsuitable for platinum-based chemotherapy, or studies in which the primary analysis population did not meet PICOS criteria

Extraction

- Results from the electronic database searches were downloaded into Covidence®, where duplicates were removed. Covidence® was used to manage citation screening during the title/abstract and full-text screening phases
- Data from the relevant publications were extracted using Microsoft Excel®
- Quality was evaluated using the Cochrane Risk of Bias tool (RoB 2.0),[8] and publication bias was evaluated for study-level OS and PFS; funnel plot and Egger's test showed no significant publication bias across studies

Outcomes

- Hazard ratios (HRs) for OS and PFS were synthesized using fixed or random effects models based on the heterogeneity evaluated by Cochrane's Q test
- Safety outcomes were described if reported

RESULTS

Study Population

- In all, the SLR screened 5517 records and identified seven randomized, controlled phase 3 1L studies (four global, three in China) enrolling 3339 patients with ES-SCLC. Most studies showed low risk of bias
- In all, 1766 patients were treated with a PD-(L)1 inhibitor plus chemotherapy and 1573 patients received chemotherapy in the control arm
- Asian patients in global studies ranged from 14.5% to 68.5%; three of the seven studies enrolled only Chinese patients
- Across studies, patients were predominantly male and had high prevalence of ever smokers (75.5%-97.0%); baseline Eastern Cooperative Oncology Group performance score was ≥1 in 64.8%-86.4% of patients. A low prevalence of patients with brain metastases (≤2%) were enrolled at baseline in Asia-only studies, aligning with regional medical practice for patients with 1L ES-SCLC

Overall Survival

- OS favored PD-(L)1 inhibitor plus chemotherapy versus control in overall populations across all studies (HR=0.73; 95% confidence interval [CI]: 0.67-0.79; **Figure 1**)
- The magnitude of OS benefit was similar in Asian (HR=0.75; 95% CI: 0.68-0.83) and non-Asian (HR=0.73; 95% CI: 0.63-0.84) patients (**Figure 2**)

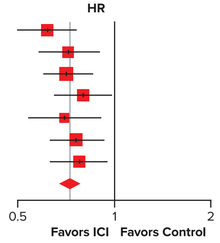
Progression-Free Survival

- PFS favored PD-(L)1 inhibitor plus chemotherapy versus control in overall populations across all studies (HR=0.67; 95% CI: 0.59-0.76; **Figure 3**)
- The magnitude of PFS benefit was comparable in Asian (HR=0.68; 95% CI: 0.61-0.76) and non-Asian (HR=0.72; 95% CI: 0.58-0.90) patients (**Figure 4**)

Figure 1. OS in the overall population across all studies

Study	logHR	SE (logHR)	HR (95% CI)	Weight
ASTRUM-005	-0.4780	0.1068	0.62 (0.50-0.76)	14.0%
CAPSTONE-1	-0.3285	0.1121	0.72 (0.58-0.90)	12.7%
CASPIAN	-0.3425	0.0918	0.71 (0.60-0.86)	18.9%
EXTENTORCH	-0.2231	0.1047	0.80 (0.65-0.98)	14.6%
IMpower133	-0.3567	0.1331	0.70 (0.54-0.91)	9.0%
KEYNOTE-604	-0.2744	0.0994	0.76 (0.63-0.93)	16.2%
RATIONALE-312	-0.2485	0.1048	0.78 (0.63-0.95)	14.6%
Common effect model			**0.73 (0.67-0.79)**	**100.0%**

Heterogeneity: I^2 = 0.0%, τ^2 = 0, p = 0.6954



Abbreviations: ICI, immune checkpoint inhibitor; SE, standard error.

Figure 2. OS in Asian versus non-Asian study populations

Study	logHR	SE (logHR)	HR (95% CI)	Weight
Race/region: Asian				
ASTRUM-005	-0.4308	0.1273	0.65 (0.51-0.84)	10.8%
CAPSTONE-1	-0.3285	0.1121	0.72 (0.58-0.90)	14.0%
CASPIAN	-0.2107	0.2398	0.81 (0.50-1.28)	3.1%
EXTENTORCH	-0.2231	0.1047	0.80 (0.65-0.98)	16.0%
IMpower133 (Japan)	-0.3285	0.4296	0.72 (0.31-1.67)	1.0%
IMpower133 (China)	-0.0726	0.2216	0.93 (0.60-1.43)	3.6%
KEYNOTE-604	-0.3285	0.2538	0.72 (0.44-1.19)	2.7%
RATIONALE-312	-0.2485	0.1048	0.78 (0.63-0.95)	16.0%
Common effect model			**0.75 (0.68-0.83)**	**67.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.8865				
Race/region: non-Asian				
ASTRUM-005	-0.6733	0.2227	0.51 (0.33-0.79)	3.5%
CASPIAN	-0.3425	0.1034	0.71 (0.58-0.87)	16.4%
KEYNOTE-604	-0.1744	0.1170	0.84 (0.67-1.06)	12.8%
Common effect model			**0.73 (0.63-0.84)**	**32.8%**
Heterogeneity: I^2 = 51.3%, τ^2 = 0.0179, p = 0.1285				
Common effect model			**0.75 (0.69-0.81)**	**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.7060
Test for subgroup differences: χ^2_1 = 0.12, df = 1 (p = 0.7315)

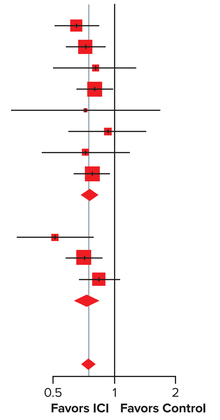


Figure 3. PFS in the overall population across all studies

Study	logHR	SE (logHR)	HR (95% CI)	Weight
ASTRUM-005	-0.7550	0.1079	0.47 (0.38-0.58)	14.0%
CAPSTONE-1	-0.4005	0.1097	0.67 (0.54-0.83)	13.8%
CASPIAN	-0.2231	0.0956	0.80 (0.66-0.96)	15.3%
EXTENTORCH	-0.4005	0.1066	0.67 (0.54-0.82)	14.1%
IMpower133	-0.2614	0.1115	0.77 (0.62-0.96)	13.7%
KEYNOTE-604	-0.3567	0.1019	0.70 (0.57-0.85)	14.6%
RATIONALE-312	-0.4463	0.1034	0.64 (0.52-0.78)	14.5%
Random effects model			**0.67 (0.59-0.76)**	**100.0%**

Heterogeneity: I^2 = 62.9%, τ^2 = 0.0187, p = 0.0128

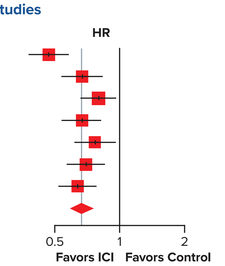
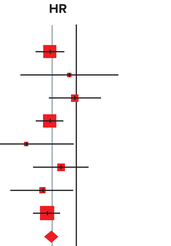


Figure 4. PFS in Asian versus non-Asian study populations

Study	logHR	SE (logHR)	HR (95% CI)	Weight
Race/region: Asian				
CAPSTONE-1	-0.4005	0.1097	0.67 (0.54-0.83)	19.6%
CASPIAN (Japan)	-0.1054	0.3777	0.90 (0.43-1.89)	1.7%
CASPIAN (China)	-0.0305	0.1990	0.97 (0.66-1.44)	6.0%
EXTENTORCH	-0.4005	0.1066	0.67 (0.54-0.82)	20.8%
IMpower133 (Japan)	-0.7550	0.3645	0.47 (0.23-0.96)	1.8%
IMpower133 (China)	-0.2357	0.2133	0.79 (0.52-1.20)	5.2%
KEYNOTE-604	-0.5108	0.2406	0.60 (0.37-0.95)	4.1%
RATIONALE-312	-0.4463	0.1034	0.64 (0.52-0.78)	22.1%
Common effect model			**0.68 (0.61-0.76)**	**81.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.5509				
Race/region: non-Asian				
KEYNOTE-604	-0.3285	0.1121	0.72 (0.58-0.90)	18.8%
Common effect model			**0.69 (0.63-0.76)**	**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.6367
Test for subgroup differences: χ^2 = 0.19, df = 1 (p = 0.6641)



Safety and Tolerability

- Treatment-related treatment-emergent adverse event (TRAE) data were obtained from six studies (EXTENTORCH did not report TRAEs)
- Overall, TRAE and immune-mediated adverse event (imAE) rates were numerically higher in some Asian sub-populations than in the overall populations
- Trend toward higher incidence of grade ≥3 TRAEs in Asian populations (CAPSTONE-1 China, 85.7%; IMpower133 Japan, 95.0%; RATIONALE-312 China, 85.5%) compared with global populations (ASTRUM-005, 33.2%; CASPIAN, 47.9%; KEYNOTE-604, 66.4%)

Limitations

- Some limitations exist that are inherent to meta-analysis design, including heterogeneity of study populations and follow-up durations
- Variations may be related to differences in reporting patterns between regions and over different time periods, making direct comparisons between subgroups difficult
- Egger's test may have low power due to the small number of studies; therefore, results should be interpreted with caution

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DISCLOSURES

FP reports consulting fees from Amgen, Johnson & Johnson, PharmaMar, Gilead, and Roche; honoraria from Pfizer and ThermoFisher Scientific; meeting and travel support from BeOne Medicines Ltd, Pfizer, Johnson & Johnson, and ThermoFisher Scientific; and participation in data safety monitoring or advisory boards from Amgen, Johnson & Johnson, Regeneron, Bristol Myers Squibb, Daichii Sankyo, and Merck Sharpe & Dohme.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers.
This study was sponsored by BeOne Medicines Ltd. Medical writing was provided by Tricia Gallagher, MS, MBA of Amiculum, and supported by BeOne Medicines Ltd.

CORRESPONDENCE: Francesco Passiglia: francesco.passiglia@unito.it

Presented at ELCC, Copenhagen, Denmark, March 25-28, 2026