Original Article

A systematic literature review and meta-analysis on the efficacy and safety of PD-(L)1 inhibitors for the first- and second-line treatment of locally advanced or metastatic non-small cell lung cancer in Asian and non-Asian patients

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Background: Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide, with higher death rates in Asia than in Europe and North America. Programmed cell death protein-(ligand) 1 [PD-(L)1] inhibitors are effective in NSCLC treatment, but their comparative effectiveness in Asian *vs.* non-Asian populations is unclear. The aim of this systematic literature review (SLR) and meta-analysis was to assess the efficacy of PD-(L)1 inhibitor monotherapy or combination therapy (with platinum-based chemotherapy or cytotoxic T lymphocyte–associated protein 4 (CTLA-4) inhibitors as first-line (1L), second-line (2L), and later (2L+) treatment for locally advanced or metastatic NSCLC in Asian *vs.* non-Asian patients.

Methods: Multiregional randomized, controlled studies that included subgroup analyses for Asian patients by ethnicity or region were selected. Studies were excluded if the control arm was not platinum-based chemotherapy or if the primary population did not meet the criteria. Literature searches were undertaken from January 1, 2010, to October 25, 2024 and were performed using the Ovid SP® platform. Hazard ratios (HRs) for overall survival (OS) and progression-free survival (PFS) were extracted using random-effects models. Quality and bias were evaluated using the Cochrane Risk of Bias tool and funnel plot and Begg's test.

Results: 1,431 records were screened, and 1L (n=21) and 2L/2L+ (n=10) studies in 10,233 patients with locally advanced or metastatic squamous/non-squamous NSCLC were identified. OS favored 1L PD-(L)1 inhibitor monotherapy or combination therapy (plus platinum-based chemotherapy and/or CTLA-4 inhibitors) in both Asian [HR =0.70; 95% confidence interval (CI): 0.64–0.76] and non-Asian (HR =0.71; 95% CI: 0.65–0.77) patients. Similar findings were observed with PFS in Asian (HR =0.53; 95% CI: 0.47–0.59) and non-Asian (HR =0.58; 95% CI: 0.53–0.64) patients. 1L PD-(L)1 inhibitor monotherapy or combination therapy was extremely effective at improving OS in Asian (HR =0.50; 95% CI: 0.39–0.64) and non-Asian (HR =0.64; 95% CI: 0.55–0.76) patients with tumor cell PD-L1 expression ≥50%, and there was also a greater magnitude of effect on PFS in Asian (HR =0.38; 95% CI: 0.32–0.44) than non-Asian (HR =0.46; 95% CI: 0.37–0.56) patients with tumor cell PD-L1 expression ≥50%.

Conclusions: These data support the global use of PD-(L)1 inhibitors for Asian and non-Asian patients

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with 1L or 2L/2L+ locally advanced or metastatic NSCLC. However, it was not possible to assess outcomes in all subgroups due to lack of data (e.g., wider PD-L1 subgroups, genetic profiles), warranting further studies by ethnicity.

Keywords: Programmed cell death protein-(ligand) 1 inhibitors [PD-(L)1 inhibitors]; non-small cell lung cancer (NSCLC); systematic literature review (SLR); meta-analysis

Submitted Jun 26, 2025. Accepted for publication Oct 13, 2025. Published online Dec 29, 2025.
doi: 10.21037/tlcr-2025-746
View this article at: https://dx.doi.org/10.21037/tlcr-2025-746

Introduction

Lung cancer is the leading cause of mortality worldwide, with 1.8 million related deaths in 2022, which were higher in Asia (N=1.1 million) than in Europe and North America combined (N=526,244) (1). Non-small cell lung cancer (NSCLC) accounts for ~85% of lung cancer cases (2) and has two main histological subtypes, non-squamous (nsq; 70–80%), which also includes adenocarcinoma and large-cell lung cancer, and squamous (sq; 20–30%) (2). NSCLC carries a poor prognosis, which is exacerbated by the fact that most patients are diagnosed at an advanced stage (3). The overall 5-year relative survival rate is 28%, which increases to 65% for localized disease and decreases to 9% for metastatic disease (4).

For patients with locally advanced, unresectable (stage IIIB) NSCLC, the European Society for Medical Oncology (ESMO) guidelines recommend first-line (1L) chemoradiotherapy, while guidelines for metastatic (stage IV) NSCLC vary depending on whether the cancer is driven by programmed cell death protein-(ligand) 1 [PD-(L)1] expression and/or clinically relevant oncogene translocations (5,6). In patients with stage IV cancer, 1L standard systemic therapy may include PD-(L)1 inhibitors either alone or in combination with platinum-based chemotherapy or cytotoxic T lymphocyte–associated protein 4 (CTLA-4) inhibitors. PD-(L)1 inhibitors as monotherapy are also indicated as second-line (2L) therapy in locally advanced or metastatic NSCLC, usually after platinum-based chemotherapy.

The European Medicines Agency has approved several PD-(L)1 inhibitors for previously untreated adult patients with metastatic sq- or nsq-NSCLC (7-11). 1L options include pembrolizumab monotherapy for patients with tumor proportion score (TPS) expression ≥50% with no epidermal growth factor receptor (*EGFR*) mutations or anaplastic lymphoma kinase (*ALK*) translocations (9), atezolizumab monotherapy for patients with TPS ≥50% and no *EGFR* mutations or *ALK* translocations (7), nivolumab plus ipilimumab for patients with no *EGFR* mutations or *ALK* translocations (11), tislelizumab plus pemetrexed and platinum-based chemotherapy for nsq-NSCLC in patients with TPS ≥50% with no *EGFR* mutations or *ALK*

Highlight box

Key findings

- Twenty-one first-line (1L) and 6 second-line (2L) and later (2L+) studies including 10,233 patients with locally advanced or metastatic squamous/non-squamous non-small cell lung cancer (NSCLC) were identified. Survival outcomes favored 1L programmed cell death protein-(ligand) 1 [PD-(L)1] inhibitor monotherapy or combination therapy (with platinum-based chemotherapy and/or cytotoxic T lymphocyte–associated protein 4 inhibitors) in Asian and non-Asian patients.
- Similar findings were observed for 2L/2L+ PD-(L)1 inhibitor monotherapy on overall survival outcomes, but there was a greater magnitude of effect on progression-free survival with 2L/2L+ PD-(L)1 inhibitor monotherapy in Asian patients; this may be related to differences in treatment patterns or prior surgery.

What is known and what is new?

- Several PD-(L)1 inhibitors are approved for previously untreated adult patients with metastatic squamous or non-squamous NSCLC depending on tumor PD-(L)1 expression and presence/absence of oncogenes.
- Several meta-analyses have compared efficacy and safety outcomes with different PD-(L)1 inhibitors, but there is limited study focus on comparisons between Asian and non-Asian patients with NSCLC. This meta-analysis aims to address this unmet need.

What is the implication, and what should change now?

- These data support the global use of 1L or 2L/2L+ PD-(L)1 inhibitors in Asian and non-Asian patients with locally advanced or metastatic NSCLC. For drugs that were initially studied in an Asian patient population, such as tislelizumab, this consistency in clinical benefit is important for use in a wider population or for consideration in global regulatory submissions.

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translocations, tislelizumab plus carboplatin and either paclitaxel or nab-paclitaxel for sq-NSCLC (8,10), and cemiplimab as monotherapy (TPS ≥50%) or in combination with platinum-based doublet histotype-oriented chemotherapy (PD-L1 1–49%, no *EGFR* mutations or *ALK* translocations or *ROS1* aberrations) (8,10,12). These PD-(L)1 inhibitors (pembrolizumab, atezolizumab, nivolumab, and tislelizumab) are also indicated as 2L monotherapy (7-11). Use of PD-(L)1 inhibitors has also evolved further with the development of prognostic biomarkers to aid in treatment decision-making. PD-L1 tumor cell expression remains clinically relevant for predicting PD-(L)1 inhibitor response, and there is evidence to suggest that it may be specific enough to predict which tumors can respond in a patient depending on its presence or absence (13). Low albumin is another biomarker that is associated with increased risk of disease progression and death in patients with advanced cancer, predominantly NSCLC, treated with PD-(L)1 inhibitors (14). Neutrophil-to-eosinophil ratio is a useful non-invasive marker associated with poor survival in patients with cancer (15). These markers have enabled the development of indices, such as the cachexia index (CXI), which includes a basic laboratory test, albumin levels, and neutrophil-to-lymphocyte ratio. The CXI is used to predict survival and identify patients with high-risk disease (16).

The treatment landscape is also evolving in Asia, albeit more slowly than in non-Asian countries. PD-(L)1 inhibitors are acknowledged as treatment options in the pan-Asian adapted ESMO guidelines based on improved survival outcomes from clinical studies (17). However, these guidelines were last updated in 2020 and do not consider data from new therapies; therefore, they may differ from the more recently updated ESMO guidelines. The extent to which PD-(L)1 inhibitor strategies have been incorporated in different countries and patient groups is of great interest for aligning approaches to treatment, achieving global reduction in cancer mortality while addressing any clinical, genetic, and environmental factors (such as smoking exposure). Several meta-analyses have compared efficacy and safety outcomes with different PD-(L)1 inhibitors, but there is limited study focus on comparisons between Asian and non-Asian patients with NSCLC, and the findings are paradoxical (18-21). One analysis of 11 randomized studies (2014–2018) showed that Asian patients had better overall survival (OS) than non-Asian patients with metastatic NSCLC after receiving 1L PD-(L)1 inhibitor therapy (± chemotherapy) or 2L PD-(L)1 inhibitor monotherapy (22). A more recent meta-analysis of seven randomized studies (up to 2019) focused directly on PD-(L)1 inhibitor response in 5,465 East Asian and non–East Asian patients with advanced NSCLC (21). This meta-analysis showed that PD-(L)1 inhibitors (nivolumab ± ipilimumab, pembrolizumab ± chemotherapy, avelumab, atezolizumab + chemotherapy) were associated with OS and progression-free survival (PFS) improvements across both groups. These papers did not include safety.

We conducted an updated systematic literature review (SLR) and meta-analysis in a broader group of Asian *vs.* non-Asian patients to assess the efficacy and safety of additional PD-(L)1 inhibitors as first- and subsequent-line treatment for locally advanced or metastatic NSCLC. We present this article in accordance with the PRISMA reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-746/rc).

Methods

Search strategy

An SLR was conducted in accordance with published guidance (23-25). The literature search was undertaken from January 1, 2010, to October 25, 2024, and sought to identify 1L, 2L, or later (2L+) PD-(L)1 inhibitor treatment studies in patients with locally advanced or metastatic sq- or nsq-NSCLC. Literature searches were performed using the Ovid SP® platform, which contains the following databases: MEDLINE®, Embase®, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), and the Cochrane Library Health Technology Assessment database of effects (CLHTA). Relevant conference proceedings, registry databases (including ClinicalTrials.gov), and bibliographies of identified SLRs and meta-analyses were also reviewed. Search strategies were developed by combining free-text words and indexing terms [e.g., Medical Subject Headings (MeSH) for MEDLINE® and Emtree terms for Embase®] relevant to NSCLC, and study designs with Boolean operators (e.g., 'and', 'or', 'not') relevant to the disease area, interventions, and study design (Appendix 1).

Selection criteria

Multiregional randomized, controlled studies that included subgroup analyses of Asian patients by ethnicity or region were selected and summarized by 1L and 2L/2L+ treatment

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according to the Population, Intervention, Comparison, Outcomes, and Study (PICOS) design framework (Table S1). Only studies that were compliant with the Declaration of Helsinki, had protocols reviewed by country-specific institutional review board/independent ethics committee as required, and enrolled patients who provided written informed consent to participate were included. All data were anonymized. Studies were excluded if the control treatment was not platinum-based chemotherapy, if the patient population was not suitable for platinum-based chemotherapy, or if the primary population did not meet the criteria, i.e., if the population was not intent-to-treat or was a PD-L1 subgroup (e.g., had tumor mutational burden ≥20).

Data extraction and quality assessment

All records identified through the searches were exported to EndNote®, a bibliographic management software. After duplicates were excluded, citations were exported to DistillerSR© literature review software (26) to aid with quality checking. All retrieved studies were assessed against the eligibility (PICOS) criteria by two independent reviewers in both title/abstract and full-text review. Misalignment was resolved through 'reconciliation' (discussion between the two reviewers) or 'arbitration' by a third independent reviewer. The studies identified via conference proceedings, registry databases, and bibliographies were also screened against the PICOS criteria by a single reviewer.

Data extraction from eligible studies was conducted using a standardized template (in Microsoft Excel©). If the data were reported in graphs, software such as Automeris WebPlotDigitizer® was used to collect these data. Data extraction was performed by one independent reviewer and checked by a second reviewer. The quality of the selected studies was evaluated using the Cochrane Risk of Bias tool (RoB 2.0) (27), with assessment of five components: randomization process (D1), deviations from intended interventions (D2), missing outcome data (D3), measurement of the outcome (D4), and selection of the reported results (D5). Publication bias of selected studies was evaluated using a funnel plot and Begg's test based on the reported hazard ratios (HRs) for OS and PFS for the overall population in each study.

Statistical analysis

The primary objective of this meta-analysis was to assess the efficacy and safety of PD-(L)1 inhibitor monotherapy or combination therapy with platinum-based chemotherapy or CTLA-4 inhibitors in Asian and non-Asian patients with locally advanced or metastatic NSCLC, and to monitor any treatment differences between the two cohorts.

Most studies reported subgroup results by ethnicity. If subgroup results by ethnicity were not available, subgroup results by region were used. For studies in which results for the non-Asian subgroup were not reported, subgroup results were derived using meta-analysis of available ethnicity (or region) other than Asian based on fixed-effects models. Subgroup meta-analysis was used to derive the integrated estimate of HRs for OS and PFS for Asian and non-Asian subgroups and to compare the treatment effect between them using random-effects models. These analyses were performed by line of therapy (1L, 2L/2L+), PD-(L)1 inhibitor monotherapy and combination therapy, and high (≥50%) PD-(L)1 tumor cell expression evaluated by TPS or viable tumor cells. Study heterogeneity was accounted for by generating the interaction P value and I^2 value. The source of heterogeneity was investigated further using meta-regression based on the data for overall study populations. Initially, we used a simple regression, and any baseline characteristics with P values <0.1 were included in the meta-regression.

Summaries of treatment-related adverse events (TRAEs) and immune-mediated adverse events (imAEs) were extracted if they were reported in the study publications with both Asian and non-Asian subgroups, including summaries for any-grade TRAEs, grade ≥3 TRAEs, TRAEs leading to treatment discontinuation, TRAEs leading to death, any-grade imAEs, and grade ≥3 imAEs.

All analyses were conducted using R version 4.0.2. All reported P values were two-sided, and P<0.05 indicated statistical significance.

Results

Literature search and study selection

A total of 1,431 records were screened, and 1L (n=21) and 2L/2L+ (n=10) randomized, controlled phase 3 studies that evaluated PD-(L)1 inhibitor treatment in Asian and non-Asian patients with locally advanced or metastatic sq- or nsq-NSCLC were identified (Figure S1). Baseline and clinical characteristics of patients enrolled in these studies are shown in Table S2. Overall, 10,233 patients received PD-(L)1 inhibitor therapy (63% as 1L and 37% as 2L/2L+ therapy), and 8,498 patients received comparator (control)

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therapy (65% as 1L and 35% as 2L/2L+ therapy). The proportion of Asian patients enrolled in these studies ranged from 2% to 100% (1L) and from 3% to 100% (2L/2L+), and nine 1L studies and one 2L/2L+ study enrolled only Asian (Chinese) patients (Tables S2,S3).

All studies enrolled patients with stage IIIB/IIIC/IV or locally advanced/metastatic NSCLC, and most (n=18) included patients with either nsq or sq histology. There was a higher proportion of males enrolled across both 1L (59–94%) and 2L/2L+ (52–94%) studies. Smoking prevalence was high across all studies (62–100%). The baseline Eastern Cooperative Oncology Group performance status was ≥1% in 56–84% (1L) and 63–90% (2L/2L+) of patients. Most 1L studies were PD-(L)1 inhibitor combination studies with chemotherapy (n=14) and/or CTLA-4 inhibitor therapy (n=3). Five studies had 1L PD-(L)1 inhibitor monotherapy. All 2L/2L+ studies were PD-(L)1 monotherapy studies.

Heterogeneity and risk of bias

Most studies showed low risk of bias using RoB 2.0 (Figure S2). There was no significant evidence of overall publication bias for 1L or 2L/2L+ studies using rank-based Begg's tests, as the HR data for OS and PFS were symmetrically distributed around the integrated HR estimates for the 1L (Figure S3) and 2L/2L+ (Figure S4) analyses.

Survival outcomes with 1L PD-(L)1 inhibitor monotherapy or combination treatment

The HRs [95% confidence interval (CI)] for OS (*Figure 1*) were evaluated from 21 studies for 11 PD-(L)1 inhibitors (pembrolizumab, nivolumab, atezolizumab, durvalumab, cemiplimab, camrelizumab, penpulimab, sintilimab, sugemalimab, tislelizumab, toripalimab) used as 1L treatment in patients with locally advanced or metastatic sq- or nsq-NSCLC. OS favored 1L PD-(L)1 inhibitor treatment as monotherapy or in combination with platinum-based chemotherapy and/or CTLA-4 inhibitors, with comparable magnitude of effect in both Asian (HR =0.70; 95% CI: 0.64–0.76; 21 studies) and non-Asian (HR =0.71; 95% CI: 0.65–0.77; 11 studies) patients. There was higher study heterogeneity in the non-Asian population that was not significant and may have been impacted by the smaller number of studies (I^2=41%; P=0.06). When data were combined for all patients (irrespective of ethnicity), the magnitude of treatment effect on OS was similar to the Asian/non-Asian breakdown (HR =0.71; 95% CI: 0.67–0.75; 21 studies) (Figure S5A).

The HRs (95% CI) for PFS (*Figure 2*) were evaluated from 17 studies for 11 PD-(L)1 inhibitors (pembrolizumab, nivolumab, atezolizumab, durvalumab, cemiplimab, camrelizumab, penpulimab, sintilimab, sugemalimab, tislelizumab, toripalimab) used as 1L treatment in patients with locally advanced or metastatic sq- or nsq-NSCLC. PFS favored 1L PD-(L)1 inhibitor treatment as monotherapy or in combination with platinum-based chemotherapy and/or CTLA-4 inhibitors with comparable magnitude of effect in both Asian (HR =0.53; 95% CI: 0.47–0.59; 17 studies) and non-Asian (HR =0.58; 95% CI: 0.53–0.64; seven studies) patients. There was moderate study heterogeneity in both populations, which was significant for the Asian population (I^2=50%; P<0.006). When data were combined for all patients, the magnitude of treatment effect on PFS was also similar to the Asian/non-Asian breakdown (HR =0.59; 95% CI: 0.53–0.65; 21 studies) (Figure S5B).

Survival outcomes with 1L PD-(L)1 inhibitor combinations

The HRs (95% CI) for OS (*Figure 3*) were evaluated from 16 studies for 11 PD-(L)1 inhibitors (pembrolizumab, nivolumab, atezolizumab, durvalumab, cemiplimab, camrelizumab, penpulimab, sintilimab, sugemalimab, tislelizumab, toripalimab) used as 1L combination treatment with platinum-based chemotherapy and/or CTLA-4 inhibitors in patients with locally advanced or metastatic sq- or nsq-NSCLC. There was a comparable treatment effect on OS for both Asian (HR =0.70; 95% CI: 0.63–0.76; 16 studies) and non-Asian (HR =0.70; 95% CI: 0.62–0.79; six studies) patients. There was moderate study heterogeneity in the non-Asian analysis (I^2=52%; P=0.04).

Similar findings were observed for PFS (*Figure 4*). There was a comparable treatment effect observed with 1L PD-(L)1 inhibitors plus platinum-based chemotherapy and/or CTLA-4 inhibitors on PFS for both Asian (HR =0.53; 95% CI: 0.47–0.60; 15 studies) and non-Asian (HR =0.60; 95% CI: 0.53–0.68; five studies) patients. There was moderate study heterogeneity for both the Asian (I^2=54%; P=0.004) and non-Asian (I^2=49%; P=0.08) analyses.

Survival outcomes in patients with high PD-(L)1 expression (≥50%) treated with 1L PD-(L)1 inhibitor monotherapy or combination treatment

When data were assessed for patients with 1L sq- and nsq-

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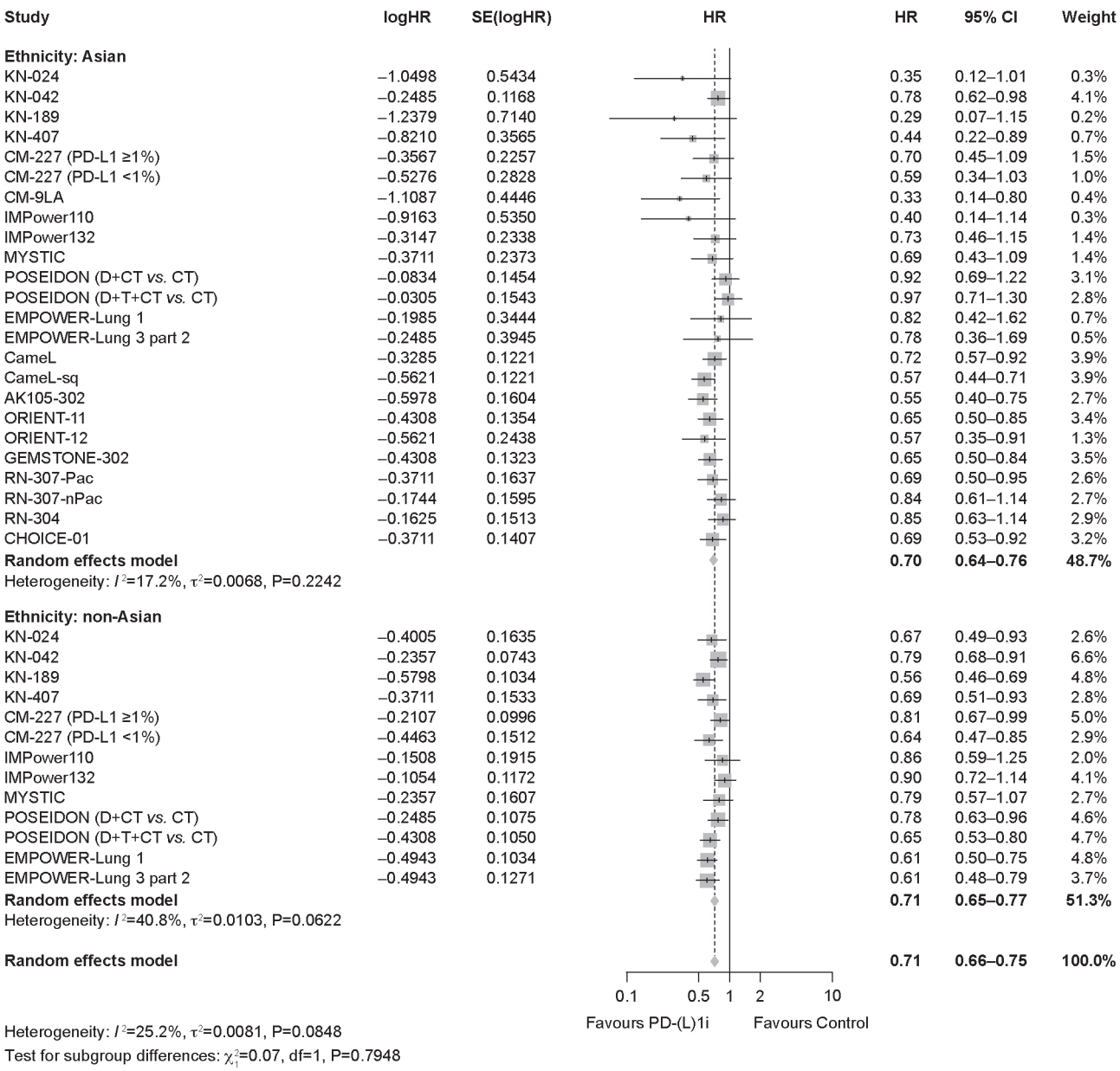


Figure 1 OS for Asian and non-Asian patients with sq- or nsq-NSCLC treated with PD-(L)1 inhibitors as 1L monotherapy or combination therapy (pooled data). 1L, first-line; CI, confidence interval; CM, CheckMate; CT, chemotherapy; D, durvalumab; HR, hazard ratio; KN, KEYNOTE; nPac, nab-paclitaxel; NSCLC, non-small cell lung cancer; nsq, non-squamous; OS, overall survival; Pac, paclitaxel; PD-(L)1, programmed cell death protein-(ligand) 1; RN, RATIONALE; SE, standard error; sq, squamous; T, tremelimumab.

NSCLC with high PD-(L)1 expression, the use of PD-(L)1 inhibitor treatment as monotherapy or in combination with platinum-based chemotherapy and/or CTLA-4 inhibitors was highly efficacious and there was a comparable treatment effect on OS for both Asian (HR =0.50; 95% CI: 0.39–0.64; nine studies) and non-Asian (HR =0.64; 95% CI: 0.55–0.76; four studies) patients. There was low study heterogeneity for these analyses [I^2=0% (Asian) and 9.9% (non-Asian)] (*Figure 5A*). There was a slightly greater magnitude of effect on PFS in Asian (HR =0.38; 95% CI: 0.32–0.44; 11 studies) than non-Asian (HR =0.46; 95% CI: 0.37–0.56; three studies) patients, but heterogeneity was moderate in the

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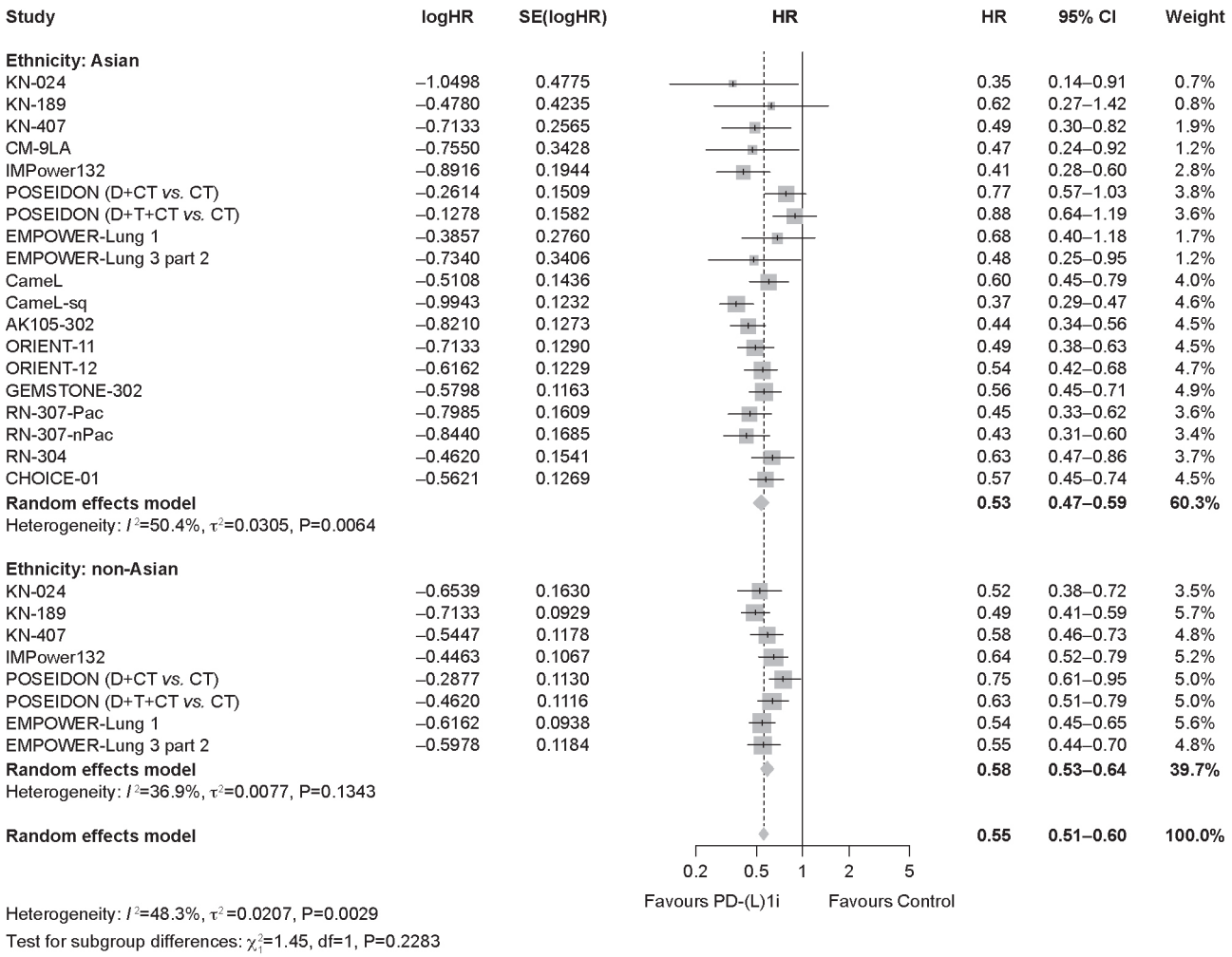


Figure 2 PFS for Asian and non-Asian patients with sq- or nsq-NSCLC treated with PD-(L)1 inhibitors as 1L monotherapy or combination therapy (pooled data). 1L, first-line; CI, confidence interval; CM, CheckMate; CT, chemotherapy; D, durvalumab; HR, hazard ratio; KN, KEYNOTE; nPac, nab-paclitaxel; NSCLC, non-small cell lung cancer; nsq, non-squamous; Pac, paclitaxel; PD-(L)1, programmed cell death protein-(ligand) 1; PFS, progression-free survival; RN, RATIONALE; SE, standard error; sq, squamous; T, tremelimumab.

non-Asian analysis, which may be a reflection of the smaller study selection (I^2=42%) (*Figure 5B*).

Survival outcomes with 2L/2L+ PD-(L)1 inhibitor monotherapy

For this analysis, data were available from six studies. For the OS analysis, there was a comparable treatment effect with 2L/2L+ PD-(L)1 inhibitor monotherapy in Asian (HR =0.73; 95% CI: 0.64–0.83; four studies) and non-Asian (HR =0.71; 95% CI: 0.64–0.78; five studies) patients (*Figure 6*). Study heterogeneity was low in both analyses. When data were combined for all patients (Asian and non-Asian patients), the magnitude of treatment effect on OS was HR =0.74 (95% CI: 0.70–0.78; 10 studies) (Figure S6A).

For the PFS analysis, both Asian and non-Asian patients derived benefit from 2L/2L+ PD-(L)1 inhibitor monotherapy treatment, but there was a greater effect in the Asian population (HR =0.57; 95% CI: 0.49–0.67; two studies) than the non-Asian population (HR =0.73; 95% CI: 0.56–0.95; three studies) (*Figure 7*). There was no evidence of study heterogeneity in the analysis for Asian patients (I^2=0%; P=0.40), but there was strong heterogeneity in the non-Asian analysis (I^2=69%; P=0.04). When data were

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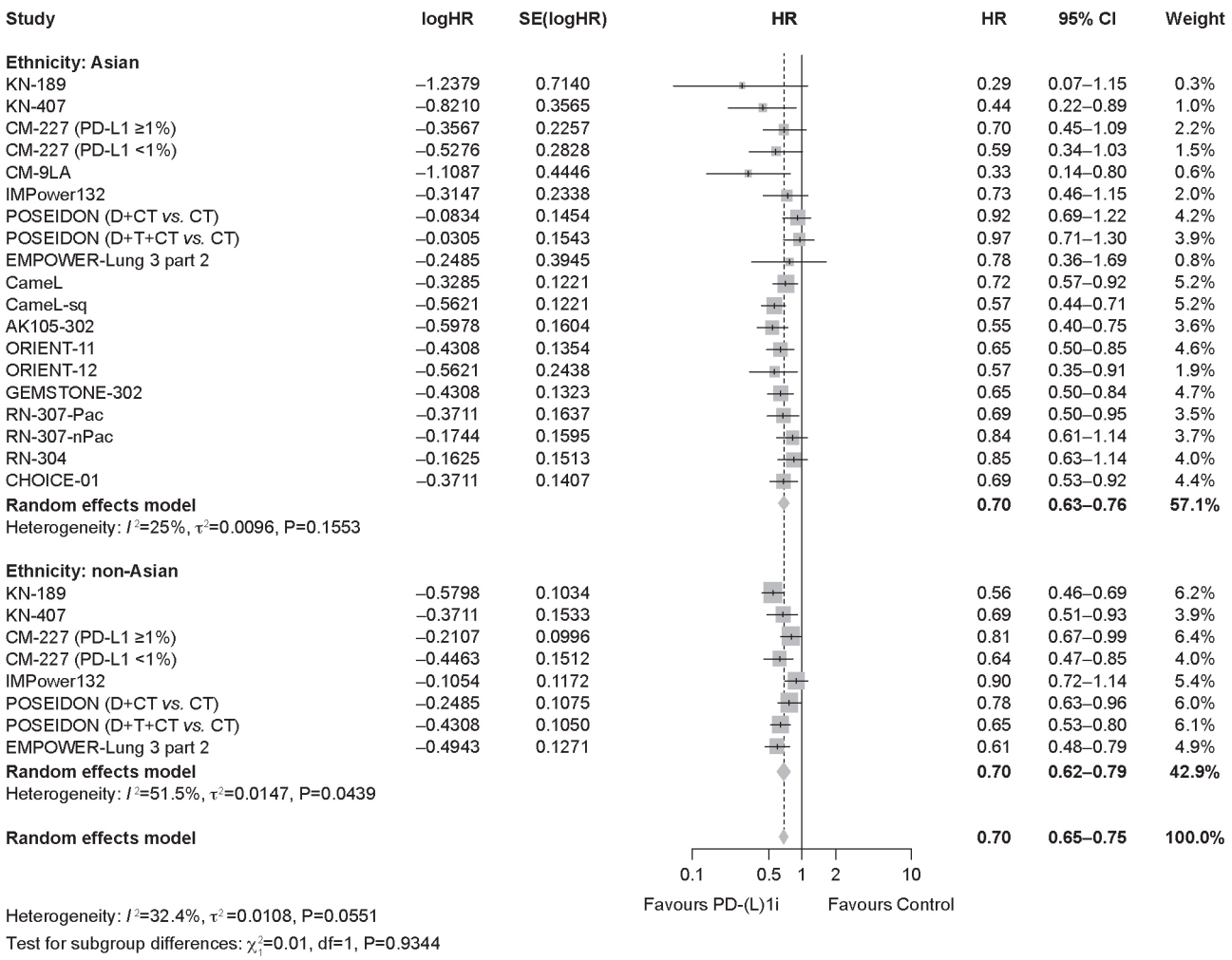


Figure 3 OS for Asian and non-Asian patients with sq- or nsq-NSCLC treated with PD-(L)1 inhibitors as 1L combination therapy. 1L, first-line; CI, confidence interval; CM, CheckMate; CT, chemotherapy; D, durvalumab; HR, hazard ratio; KN, KEYNOTE; nPac, nab-paclitaxel; NSCLC, non-small cell lung cancer; nsq, non-squamous; OS, overall survival; Pac, paclitaxel; PD-(L)1, programmed cell death protein-(ligand) 1; RN, RATIONALE; SE, standard error; sq, squamous; T, tremelimumab.

combined for all patients, the magnitude of treatment effect on PFS was comparable to that in the non-Asian population (HR =0.75; 95% CI: 0.63–0.89; seven studies) (Figure S6B), with very high study heterogeneity (I^2=79%; P<0.0001).

Safety data

Safety data were obtained from six 1L and two 2L/2L+ PD-(L)1 inhibitor studies that reported TRAEs (some studies were not included due to reporting of treatment-emergent adverse events; *Table 1*). There were some differences in TRAEs and imAEs between overall populations and Asian subpopulations within some studies; however, this may have been impacted by patient numbers. For pembrolizumab 1L studies, any and grade 3–5 TRAEs tended to be numerically higher among Asian subgroups. This difference was more noticeable in patients receiving 1L PD-(L)1 inhibitor plus platinum-based chemotherapy and/or CTLA-4 inhibitors. In KEYNOTE-407, the proportion of patients with grade 3–5 TRAEs was 57.2% in the overall population (n=278) and 81.5% in the China subpopulation (n=65) with pembrolizumab plus chemotherapy, respectively. Similarly, in CheckMate 227, the proportion of patients with grade 3–5 TRAEs was 32.8% in the overall population (n=576)

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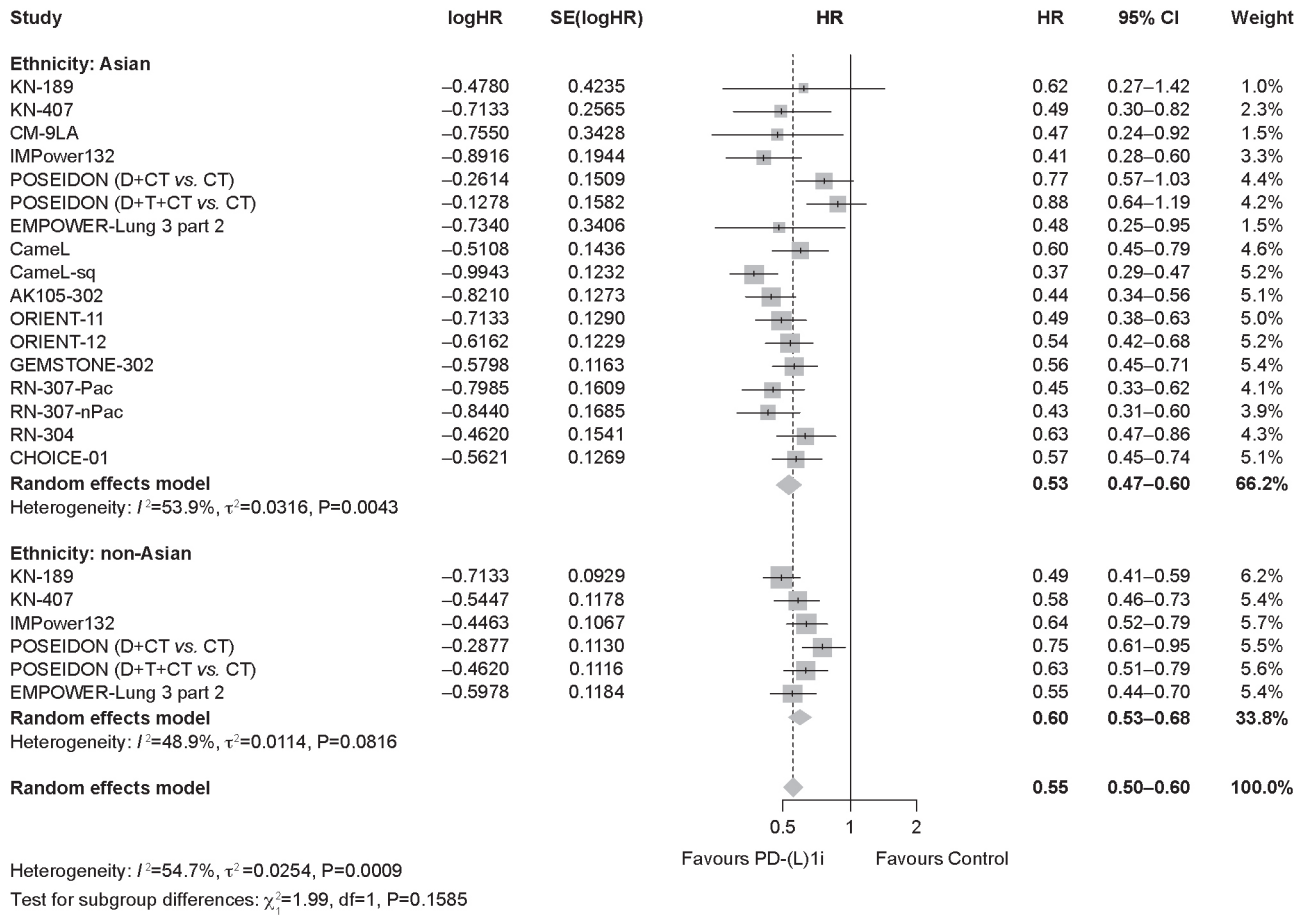


Figure 4 PFS for Asian and non-Asian patients with sq- or nsq-NSCLC treated with PD-(L)1 inhibitors as 1L combination therapy. 1L, first-line; CI, confidence interval; CM, CheckMate; CT, chemotherapy; D, durvalumab; HR, hazard ratio; KN, KEYNOTE; nPac, nab-paclitaxel; NSCLC, non-small cell lung cancer; nsq, non-squamous; Pac, paclitaxel; PD-(L)1, programmed cell death protein-(ligand) 1; PFS, progression-free survival; RN, RATIONALE; SE, standard error; sq, squamous; T, tremelimumab.

and 54.5% in the Japan subpopulation (n=66) with 1L nivolumab plus ipilimumab, and discontinuation rates (any treatment) were higher in the Japan subpopulation. In the OAK study, 2L/2L+ monotherapy with atezolizumab was associated with higher rates of TRAEs, grade 3–5 TRAEs, and discontinuations in the Japan subpopulation (n=56) than the overall population (n=609), although the overall population experienced more serious TRAEs (*Table 1*). In RATIONALE-303, TRAEs were generally comparable between Asian and non-Asian patients, except for serious TRAEs and discontinuations, which tended to be more common in the Asian population (n=423) than the non-Asian population (n=111) receiving 2L tislelizumab monotherapy.

Discussion

This meta-analysis evaluated the survival outcomes associated with PD-(L)1 inhibitors in Asian and non-Asian populations with locally advanced or metastatic NSCLC enrolled in randomized, controlled studies. We have shown that PD-(L)1 inhibitors were efficacious and safe across both populations, including the subgroup with high PD-(L)1 status (≥50%), as monotherapy and combination therapy with platinum-based chemotherapy and/or CTLA-4 inhibitors.

The findings were consistent with those of previous meta-analyses conducted in advanced NSCLC (21). One such meta-analysis showed improvements in OS and PFS

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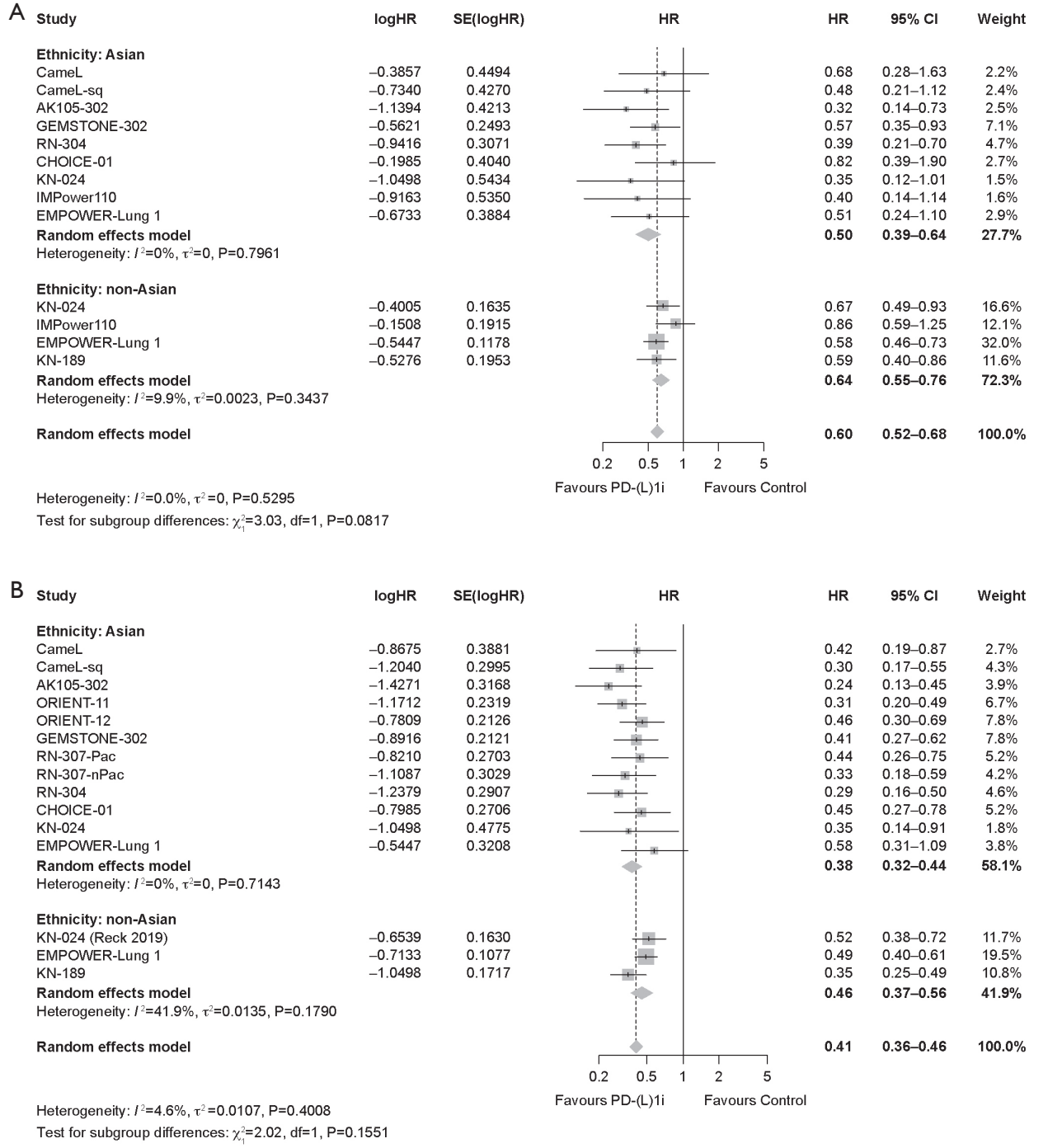


Figure 5 OS (A) and PFS (B) for Asian and non-Asian patients with sq- or nsq-NSCLC and PD-(L)1 expression ≥50% treated with 1L PD-(L)1 inhibitor monotherapy or combination therapy. 1L, first-line; CI, confidence interval; CM, CheckMate; HR, hazard ratio; KN, KEYNOTE; nPac, nab-paclitaxel; NSCLC, non-small cell lung cancer; nsq, non-squamous; OS, overall survival; Pac, paclitaxel; PD-(L)1, programmed cell death protein-(ligand) 1; PFS, progression-free survival; RN, RATIONALE; SE, standard error; sq, squamous.

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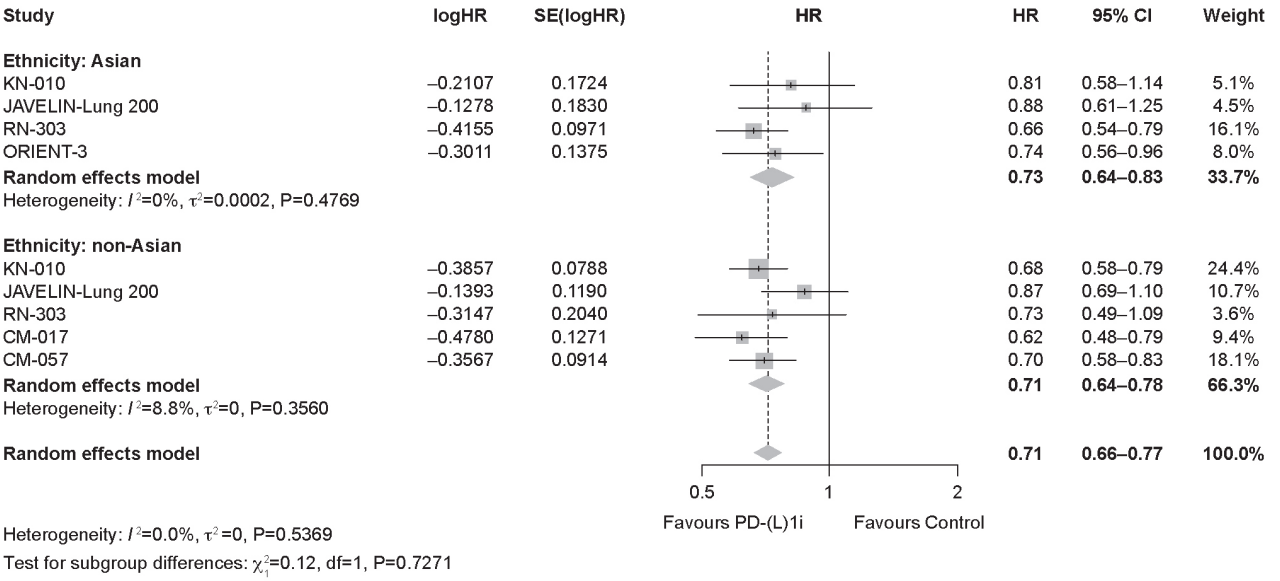


Figure 6 OS for Asian and non-Asian patients with sq- or nsq-NSCLC treated with PD-(L)1 inhibitors as 2L/2L+ monotherapy. 2L/2L+, second-line/second-line or later; CI, confidence interval; CM, CheckMate; HR, hazard ratio; KN, KEYNOTE; NSCLC, non-small cell lung cancer; nsq, non-squamous; OS, overall survival; PD-(L)1, programmed cell death protein-(ligand) 1; RN, RATIONALE; SE, standard error; sq, squamous.

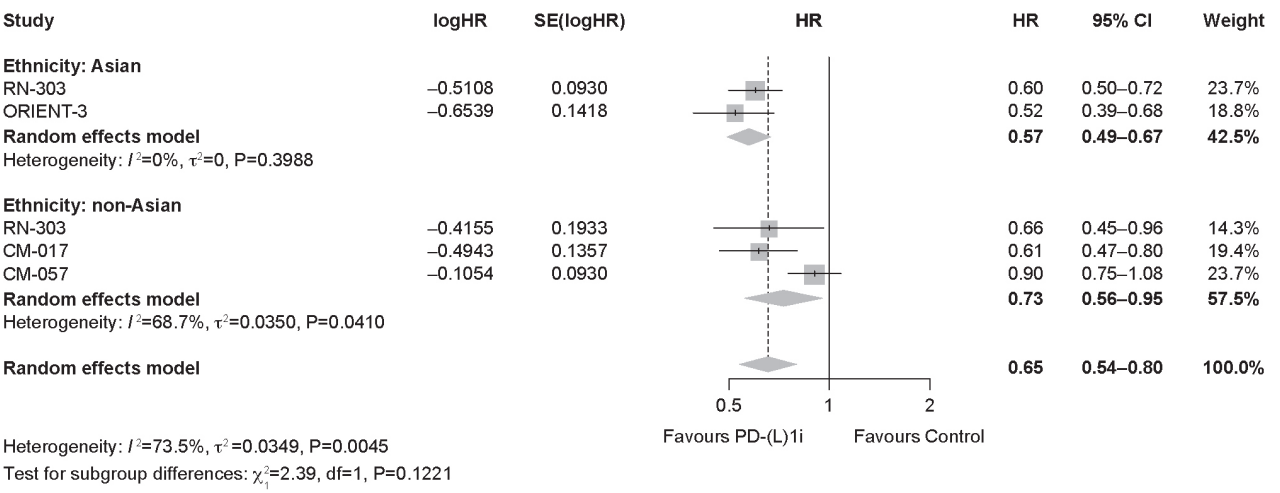


Figure 7 PFS for Asian and non-Asian patients with sq- or nsq-NSCLC treated with PD-(L)1 inhibitors as 2L/2L+ monotherapy. 2L/2L+, second-line/second-line or later; CI, confidence interval; CM, CheckMate; HR, hazard ratio; KN, KEYNOTE; NSCLC, non-small cell lung cancer; nsq, non-squamous; PD-(L)1, programmed cell death protein-(ligand) 1; PFS, progression-free survival; RN, RATIONALE; SE, standard error; sq, squamous.

for East/Southeast Asian patients (OS HR =0.74; PFS HR =0.56; n=1,740) and non-East Asian patients (OS HR =0.78; PFS HR =0.69; n=3,752) treated with PD-(L)1 inhibitors in any line of therapy (21). Similar findings were observed in another analysis in which 1L PD-(L)1 inhibitor plus chemotherapy treatment improved survival in both Asian (OS HR =0.72; PFS HR =0.72; n=286) and non-Asian patients (OS HR =0.68; PFS HR =0.62; n=2,214) (22). Another review of PD-(L)1 inhibitor studies in NSCLC found that Asian patients demonstrated comparable

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Table 1 Safety outcomes in overall and Asian/non-Asian subpopulations in PD-(L)1 inhibitor studies

PD-(L)1 inhibitor	LoT	Study	Regimen	Population	DCO	N	TRAE, %				imAE, %		
							Any grade	Grade 3–5	Serious	Led to treatment discontinuation	Led to death	Any grade	Grade 3–5
Pembrolizumab	1L	KN-024 (28,29)	Monotherapy	Overall	6/1/2020	154	76.6	31.2	22.7	13.6	1.3	34.4	13.6
				Japan	2/15/2019	21	100	38.1	NR	19.0	0	52.4	19.0
		KN-042 (30-32)	Monotherapy	Overall	4/28/2021	636	63.8	18.9	NR	9.1	2.0	27.5	8.2
				Asian	4/28/2021	269	NR	19.7	NR	NR	NR	NR	NR
				China	9/12/2022	128	82.8	19.5	NR	15.6	6.3	26.6	7.0
		KN-407 (33,34)	+ chemotherapy	Overall	2/23/2022	278	95.7	57.2	NR	20.9	4.3	35.6	13.3
				China	9/30/2020	65	100	81.5	NR	12.3	1.5	33.8	7.7
Nivolumab	1L	CM-227 (35)	+ ipilimumab	Overall	2/15/2022	576	76.7	32.8	24.5	18.1	1.4	NR	NR
				Japan	2/15/2022	66	95.5	54.5	56.1	28.8	1.5	NR	NR
		CM-9LA (36,37)	+ ipilimumab + chemotherapy	Overall	3/9/2020	358	91.3	46.9	29.3	19.3	2.0	NR	NR
				East Asian	3/9/2020	28	100	57.1	35.7	21.4	0	NR	NR
Atezolizumab	1L	IMPower132 (38)	+ chemotherapy	Overall	7/18/2019	291	91.4	58.4	34.4	NR	NR	NR	NR
				Japan	7/18/2019	48	100	72.9	35.4	NR	NR	NR	NR
				China	7/18/2019	82	97.6	64.6	31.7	NR	NR	NR	NR
Atezolizumab	2L	OAK (39,40)	Monotherapy	Overall	1/23/2017	609	64.0	14.9	32.0	7.9	0	NR	NR
				Japan	7/7/2016	56	87.5	23.2	19.6	17.9	0	NR	NR
Tislelizumab	2L	RN-303 (41)	Monotherapy	Overall	7/15/2021	534	74.9	15.7	13.5	6.7	1.5	18.9	6.6
				Asian	7/15/2021	423	77.3	16.5	14.9	7.6	1.7	18.9	6.6
				Non-Asian	7/15/2021	111	65.8	12.6	8.1	3.6	0.9	18.9	6.3

1L, first-line; 2L, second-line; CM, CheckMate; DCO, data cutoff; imAE, immune-mediated adverse event; KN, KEYNOTE; LoT, line of therapy; NR, not reported; PD-(L)1, programmed cell death protein-(ligand) 1; RN, RATIONALE; TRAE, treatment-related adverse event.

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response rates and survival benefits to non-Asian patients despite differences in epidemiologic, genetic, and molecular profiles (42). Since the publication of these meta-analyses, new PD-(L)1 inhibitors have been developed in Asian populations, reflecting the dynamic nature of this field. This updated meta-analysis allowed us to evaluate the efficacy and safety of new PD-(L)1 inhibitors in a broader Asian and non-Asian cohort using more (n=31) studies, thus demonstrating confidence in the reproducibility of outcomes. We showed a comparable magnitude of OS and PFS benefits in Asian and non-Asian patients in our analysis. Specifically, 1L PD-(L)1 inhibitor monotherapy or combination therapy was associated with an HR of 0.70 for OS and 0.53 for PFS in the Asian population compared with 0.71 for OS and 0.58 for PFS in the non-Asian population.

We observed that 2L/2L+ PD-(L)1 inhibitor monotherapy was effective in both Asian and non-Asian populations; however, there was greater improvement in PFS for Asian patients. This has been documented in previous studies (21), but the reason for this is unclear and may be related to differences in regional treatment patterns, such as prior treatment or surgery. Patients with *EGFR* mutations were excluded from our analysis; however, most enrolled patients in CheckMate 057 were *EGFR* wildtype (43). Some patients with *EGFR* mutations were allowed to receive or to be receiving an additional line of tyrosine kinase inhibitors and continue or switch to maintenance therapy with pemetrexed, bevacizumab, or erlotinib, which may have confounded any PFS benefit in this study. A late crossing of the PFS curves was noted, with a PFS rate of 19% at 1 year compared with 8% with docetaxel, representing a delay in benefit with nivolumab in the intent-to-treat population. This distinction within CheckMate 057 may explain the strong heterogeneity observed in the non-Asian patients receiving 2L/2L+ PD-(L)1 inhibitors, i.e., it was not clear if PD-(L)1 inhibitors benefited patients with *EGFR* mutations.

Taken together, these findings suggest that 1L or 2L/2L+ PD-(L)1 inhibitors are effective in Asian and non-Asian patients with locally advanced or metastatic sq- or nsq-NSCLC. For drugs that were initially studied in an Asian patient population, such as tislelizumab, this consistency in clinical benefit is important, as 1L tislelizumab plus chemotherapy showed proven efficacy and safety in patients with locally advanced or metastatic NSCLC in RATIONALE-304 and -307 (44,45).

We also examined the treatment effect in patients with 1L sq- and nsq-NSCLC with PD-L1 ≥50% status at baseline. To date, PD-L1 immunohistochemistry assays are the only approved companion diagnostic for PD-(L)1 treatment of NSCLC (46). In our analysis, improved OS was observed in Asian patients (HR =0.50) and non-Asian patients (HR =0.64) with PD-L1 ≥50% treated with PD-(L)1 inhibitor monotherapy or combination therapy. Similar findings were observed for PFS in Asian (HR =0.38) and non-Asian (HR =0.46) patients. Importantly, this may have an impact on PD-L1 testing in real-world settings. The international EXPRESS study evaluated real-world prevalence of PD-L1 expression using immunohistochemistry assays in 2,617 patients with advanced NSCLC. The overall percentage of patients with PD-L1 ≥50% expression was 22% in Europe, 22% in Asia-Pacific, and 21% in the Americas. Furthermore, 27% of patients without *EGFR* mutations/*ALK* translocations had PD-L1 ≥50%. In addition, PD-L1 testing was shown to be similar across groups and highlights that around one-quarter of these patients would benefit from PD-(L)1 inhibitors, irrespective of geographic location (47).

With respect to safety findings, PD-(L)1 inhibitors have a greater tolerability than chemotherapy in advanced cancer, and are associated with a lower risk of fatigue, anorexia, nausea, diarrhea, constipation, and sensory neuropathy but a higher incidence of imAEs (48). Consistent with previously reported data in KEYNOTE-024 (29), we observed a higher incidence of imAEs in patients from Japan compared with the overall population, though the reason for this is unknown. There was also a higher incidence of grade ≥3 TRAEs in some Asian populations compared with the overall population. These differences may be related to the reporting of adverse events over different time periods and different imAE methodologies, as seen with KEYNOTE-407 and CheckMate 227 (33,35). Such differences may have been impacted by treatment changes or available patient follow-up data, making direct comparisons between subgroups difficult. There was a trend for higher discontinuation rates in Asian populations; for example, in the OAK study, the rate of discontinuations was 17.9% (Japan) and 7.9% (overall population) (39,40). The reasons for these differences are unknown but may be related to how regional physicians handle adverse event resolution or to lack of awareness about the most common adverse events. This may explain some differences between early *vs.* later studies, particularly regarding drug class familiarity and experience and education in adverse event management.

Strengths of this meta-analysis included strict inclusion criteria and pooling of data from randomized, controlled

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studies only. The study also evaluated the treatment outcomes and safety between Asian and non-Asian patients with NSCLC receiving PD-(L)1 inhibitors as monotherapy or combination therapy and showed comparability among lines of treatment while emphasizing the benefit of personalized treatment approaches, like the PD-(L)1–high subgroup, across ethnicities. Ultimately, this methodology is the most appropriate to address our initial question, as most clinical studies are conducted globally or regionally with no objective to compare both populations; our data indicate that stratification based on ethnicity may not be relevant in immunotherapy studies.

There are, however, several limitations inherent in meta-analysis design. For the 1L sq- and nsq-NSCLC PD-L1 ≥50% population, it was not possible to assess outcomes for all patients due to lack of data from Asian and non-Asian patients. Also, subgroup meta-analysis [e.g., PD-(L)1 expression ≥50%] was based on the subgroup within a study, and any correlation between data from the same study was ignored. Furthermore, it was not possible to examine the impact of genetic profiles or other markers, such as *Notch*, *STK11*, *KEAP1*, and *TP53*, on survival outcomes. Survival outcomes may have been impacted by variation in follow-up time available from the individual studies, and we did not include other markers of treatment, such as objective response rates. All the analyses for 2L/2L+ NSCLC studies were limited by the small number of studies and observed study heterogeneity for non-Asian patients, especially for PFS; thus, these results and others from small subgroups of studies should be interpreted with caution. PD-(L)1 inhibitor treatment is usually recommended as monotherapy in the 2L+ setting, and therefore novel PD-(L)1 combinations were not included in 2L/2L+ analyses. Safety findings were also limited due to few studies with available data included. Lack of detailed information on imAE categorization also limits clinical applicability. Further meta-analysis that utilizes individual-patient–level data and addresses confounders could enable detailed investigation into interesting issues, such as the impact of prior therapies and surgery rates on treatment outcomes, and determine the association between PD-L1 inhibitors and specific imAEs, including areas where additional information may be warranted, such as hearing loss (49).

Conclusions

PD-(L)1 inhibitors as 1L or 2L/2L+ monotherapy or 1L combination therapy with chemotherapy and/or CTLA-4 inhibitors were efficacious, improving survival outcomes in Asian and non-Asian patients with locally advanced or metastatic NSCLC, with no major differences in terms of survival or safety outcomes. Based on this meta-analysis of randomized clinical studies, these data support the global use of 1L or 2L/2L+ PD-(L)1 inhibitors in Asian and non-Asian patients with locally advanced or metastatic NSCLC. More real-world evidence at the country or regional level is needed to further confirm long-term clinical benefits and tolerability in specific ethnic patient populations.

Acknowledgments

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. The authors would also like to thank IQVIA for their support with the systematic literature review, and Yu Wang for his contribution to statistical analyses. This study was sponsored by BeOne Medicines, Ltd. Medical writing support was provided by Sam Phillips, PhD, of Parexel, and supported by BeOne Medicines.

This work was presented at the International Association for the Study of Lung Cancer World Conference on Lung Cancer (IASLC WCLC), held on September 6–9, 2025, in Barcelona, Spain, and at the 36th Annual Scientific Congress of Malaysian Oncological Society (ASCOMOS), held on September 26-28, 2025, Johor, Malaysia.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-746/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-746/prf

Funding: This work was supported by BeOne Medicines, Ltd.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-746/coif). N.G. has received: grants from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, BeOne Medicines Ltd. (formerly BeiGene), Bristol Myers Squibb, Daiichi-Sankyo, Gilead Sciences Inc., Hoffmann-La Roche, Janssen, LeoPharma, Lilly, Merck Sharp & Dohme, Novartis, Sivan; consulting

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fees from AbbVie, Amgen, AstraZeneca, BeOne Medicines Ltd., Bristol Myers Squibb, Daiichi-Sankyo, Gilead Sciences Inc., Ipsen, Hoffmann-La Roche, Janssen, LeoPharma, Merck Sharp & Dohme, Mirati, Novartis, Pfizer, Sanofi, Takeda; has attended advisory board meetings for Hoffmann-La Roche, and has financial/non-financial interests with AstraZeneca. D.T. has received grants from ACM Biolabs, AstraZeneca, GlaxoSmithKline, Novartis and Pfizer; consulting fees from Amgen, AstraZeneca, Bayer, DKSH, Genmab, Merck Sharp & Dohme, Pfizer, Roche, Zymeworks; honoraria from Novartis, Pfizer, Roche, Takeda; and travel/meeting support from Boehringer Ingelheim, Pfizer, Roche. D.C. has received grants from AstraZeneca/MedImmune, Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Roche/Genentech, Seagen, and consulting fees from Amgen, AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Roche/Genentech, Seagen, Takeda. G.L. has received grants from AbbVie, Adaptimmune, AstraZeneca, Bavarian Nordic, Blueprint Medicines, Bristol Myers Squibb, EMD Serono, E.R. Squibb & Sons, LLC., G1 Therapeutics, Genentech, GlaxoSmithKline, Janssen, Lilly, Lucence Diagnostics, Merck Sharp & Dohme, Novartis, Pfizer, Rgenix, Roche, Tesaro, Xilis; consulting fees from AstraZeneca, Pfizer; honoraria from AstraZeneca, Boehringer Ingelheim, Blueprint Medicines, Janssen, Merck; travel/meeting support from AstraZeneca, Boehringer Ingelheim, Celgene, E.R. Squibb Sons, LLC., Genetics, Ibsen, Janssen, Merck Sharp & Dohme, Pfizer, Pharmacyclics, Seagen, Seattle; stock/stock options from Biomab, CDR-Life, Lucence Diagnostics, Morphometrix, Xilis; and has financial/non-financial interests with Mirati Therapeutics. P.J.V. has received: grants from AstraZeneca, Boehringer Ingelheim, BeOne Medicines Ltd., Janssen-Cilag, Johnson & Johnson, Merck KGaA, Merck Sharp & Dohme, Novartis, Roche, Viracta Therapeutics; consulting fees from Amgen, AstraZeneca, BeOne Medicines Ltd., Ipsen, Merck Sharp & Dohme, Novartis, Pfizer. M.A.T., N.G., L.Z., S.X., K.N. are employees of BeOne Medicines Ltd., and own stock/stock options with BeOne Medicines Ltd. S.P. has received: grants from Amgen, AstraZeneca, Biodesix, Bristol Myers Squibb, Boehringer Ingelheim, Illumina, Iovance Biotherapeutics, Lilly, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Phosplatin Therapeutics, Roche; consulting fees from AbbVie, Amgen, Arcus Biosciences, AstraZeneca, Bayer, Biocartis, Bioinvent, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Clovis Oncology, Daiichi Sankyo, Debiopharm Group, F-Star Biotechnology, Foundation Medicine, Genzyme, Gilead Sciences Inc., GlaxoSmithKline, Illumina, Incyte, ITeos Therapeutics, Janssen, Lilly, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, PharmaMar, Phosplatin Therapeutics, Regeneron, Roche/Genentech, Sanofi, Seagen, Takeda, Vaccibody; honoraria from AstraZeneca, Bristol Myers Squibb, Ecancer, Fishawack Facilitate, Illumina, Imedex, Incyte, Medscape, Medtoday, Mirati Therapeutics, Merck Sharp & Dohme, Novartis, Oncology Education, Peerview, PER, Pfizer, Prime Oncology, Research to Practice, RMEI Medical Education, Roche, Sanofi, Takeda; travel/meeting support from Bristol Myers Squibb, Incyte, Merck Sharp & Dohme, Roche, Sanofi; has attended advisory board meetings for Hoffmann-La-Roche, and has financial/non-financial interests with *Annals of Oncology*, ESMO, ETOP, JTO and SAMO. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Girard N, Tan D, Cortinovis D, Lopes G, Voon PJ, Taylor MA, Ghali N, Zhan L, Xu S, Naicker K, Peters S. A systematic literature review and meta-analysis on the efficacy and safety of PD-(L)1 inhibitors for the first- and second-line treatment of locally advanced or metastatic non-small cell lung cancer in Asian and non-Asian patients. Transl Lung Cancer Res 2025;14(12):5305-5322. doi: 10.21037/tlcr-2025-746

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