Efficacy of consolidation of immune checkpoint inhibitor after chemoradiation for unresectable, locally advanced PD-L1 negative non-small cell lung cancer: A systematic review and meta-analysis

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Abstract. Chemoradiotherapy (CRT) followed by consolidation of immune checkpoint inhibitors (ICIs), such as durvalumab or pembrolizumab, for patients with unresectable, locally advanced non-small cell lung cancer (NSCLC) with tumor PD-L1 expression <1% remains a topic of controversy. Previous studies from PubMed, Cochrane Library and Embase databases were searched for a meta-analysis. A total of 16 studies were included in part one of the meta-analysis and it was observed that consolidation of ICIs after CRT improved overall survival (OS) [hazard ratio (HR) 1.46; P=0.005] and progression-free survival (PFS) (HR 1.26; P=0.023) for the patients with PD-L1 expression ≥1% compared with those with PD-L1 expression <1%. Then, 15 studies were included in part two of the meta-analysis and the results indicated that the pooled 1, 2 and 3-year OS were 77% vs. 83% (P=0.07), 55% vs. 59% (P=0.327) and 38% vs. 51% (P=0.006) for CRT alone compared with CRT followed by consolidation of ICIs, respectively. The pooled 1, 2 and 3-year PFS were 51% vs. 53% (P=0.632), 29% vs. 40% (P=0.015) and 20% vs. 28% (P=0.153) for CRT alone compared with CRT followed by consolidation of ICIs, respectively. The findings of the present study highlighted that the benefits of CRT followed by consolidation of ICIs were higher compared with CRT alone in patients with unresectable, locally advanced NSCLC and PD-L1 expression <1%. Consolidation of ICIs after CRT would provide greater benefits for locally advanced NSCLC patients with PD-L1 expression ≥1% compared with those with PD-L1 expression <1%.

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Abbreviations: NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1; CRT, chemoradiotherapy; cCRT, concurrent CRT; sCRT, sequential CRT; OS, overall survival; PFS, progression-free survival; ICI, immune checkpoint inhibitors; HR, hazard ratio; CI, confidence interval

Key words: NSCLC, CRT, consolidation, immunotherapy, PD-L1

Introduction

The findings from the PACIFIC trial established durvalumab, a programmed cell death-ligand 1 (PD-L1) inhibitor, as a widely accepted standard of care for patients with stage III unresectable non-small cell lung cancer (NSCLC) who have not experienced disease progression following platinum-based chemoradiotherapy (CRT) (1). In Europe, patients must have tumors that express PD-L1 on at least 1% of tumor cells to receive this treatment, based on the results of post hoc analyses requested by the European Medicines Agency (2). The decision has raised concern about lost treatment opportunities and inequalities of care since outside the European Union, such as Canada, the United States and some Asian countries, there are no specific restrictions imposed based on PD-L1 expression status (3).

In a real-world study conducted in France that was similar to the PACIFIC study (4), a total of 567 patients who received more than 2 cycles of platinum-based concurrent CRT (cCRT) followed by consolidation of durvalumab were enrolled. The aforementioned study revealed that there was no significant difference in survival between PD-L1 positive and PD-L1 negative patients, which is consistent with the findings of another real-world study conducted in Germany (5). The phase 2 open-label KEYNOTE-799 study enrolled 216 patients and revealed that pembrolizumab plus cCRT continues to demonstrate robust and durable responses regardless of PD-L1 expression (6). Similarly, other studies exploring the efficacy of consolidation of pembrolizumab after cCRT also found no statistically significant association between survival outcomes and PD-L1 expression (7,8).

However, in the PACIFIC-6 trial, an exploratory analysis was conducted and numerical trends were observed indicating that the subgroup with PD-L1 tumor cell (TC) expression ≥1% derived greater clinical benefit from consolidation of pembrolizumab after sequential CRT (sCRT), compared with

the subgroup with PD-L1 TC expression <1% (9). A real-world multicentre study suggested that patients with PD-L1 expression ≥50% appeared to benefit the most from durvalumab therapy, with overall survival (OS) and progression-free survival (PFS) rates superior to those of patients with PD-L1 expression <50%. Notably, PD-L1 expression <1% was not associated with inferior survival outcomes in response to consolidation of durvalumab when compared with patients with PD-L1 expression ranging from 1-49% (10). The DETERRED trial revealed that patients with PD-L1 expression <1% had median PFS of 11.0 months and median OS of 26.5 months compared with those with PD-L1 expression ≥1% (27.4 months and not reached, respectively) (11). It should be noted that the sample sizes for some of these subgroups were small, which may limit interpretation.

On the basis of these conflicting studies, the role of PD-L1 expression as a predictive biomarker in this setting remains unclear. The present systematic review and meta-analysis aimed to investigate the efficacy of consolidation immune checkpoint inhibitors (ICIs) after CRT for patients with unresectable, locally advanced NSCLC with PD-L1 expression <1%, and the findings are anticipated to offer valuable insights for clinical decision-making regarding the management of these individuals.

Materials and methods

Search strategy. The present meta-analysis consisted of two parts: In part one, the pooled hazard ratios (HRs) of two groups of patients (tumor cell PD-L1 expression <1% vs. PD-L1 expression ≥1%) with unresectable, locally advanced NSCLC treated with consolidation of ICIs after CRT were investigated. In part two, the survival rates between two groups of patients (CRT alone vs. CRT followed by consolidation of ICIs) with unresectable, locally advanced NSCLC and PD-L1 expression <1% were compared.

The PubMed (https://pubmed.ncbi.nlm.nih.gov/), Cochrane Library (https://www.cochranelibrary.com/) and Embase (https://www.elsevier.com/products/embase) databases were searched for studies published before November 2023 mainly using the search terms 'NSCLC', 'PD-L1', 'consolidation', 'CRT', 'unresectable', 'locally advanced' and 'ICI' with all relevant synonyms to avoid missing literature retrieval. The references of relevant articles were also reviewed to identify any additional potentially eligible reports. The databases were independently searched by two investigators, who also screened titles and abstracts, and assessed full-text articles. The senior authors would determine whether a study should be included in the meta-analysis based on the inclusion and exclusion criteria when discrepancies were found.

Inclusion and exclusion criteria. Studies that compared the survival outcomes of patients with locally advanced unresectable NSCLC stratified by tumor PD-L1 expression (<1 and ≥1%) who were treated with consolidation of ICIs following curative-intent CRT were included. Subsequently, studies that reported the OS or PFS of patients with locally advanced unresectable NSCLC who had PD-L1 expression <1% and who were treated either with CRT alone or CRT followed by consolidation of ICIs were incorporated. English-language studies published in peer-reviewed journals were primarily considered. Retrieved studies described as case reports, clinical trials, abstracts, reviews, meta-analyses, or letters were excluded. Studies focused on patients with distant metastatic NSCLC or early-stage NSCLC were also excluded.

Data extraction and statistical analysis. In part one, the following data were collected from the eligible studies: Basic information, including first author's name, year of publication or presentation, study region, treatment time and PD-L1 diagnostic antibodies; patient characteristics in each group, including number of patients, tumor staging, histology, median age, PD-L1 status and EGFR mutation status; anticancer treatment information, including cCRT or sCRT and interval from CRT completion to ICIs initiation. The HR and associated 95% confidence interval (CI) were extracted from the literature for meta-analysis. If the HR was not reported directly, the value was estimated with methods reported in the literature (12-14). Chi-square and I^2 tests were used to assess heterogeneity.

In part two, 1, 2 and 3-year OS or PFS data were extracted from the included studies. The Enguage Digitizer software (Version 12.1) was utilized to extract OS or PFS data from the figures in studies that solely presented Kaplan-Meier survival curves. All data were transformed by logit transformation and combined using the random effect model. Chi-square test was used to compare the survival rates and $P<0.05$ was considered to indicate a statistically significant difference.

Sensitivity analysis and bias assessment. A sensitivity analysis was conducted using the leave-one-out approach, wherein each study was sequentially excluded using meta-analysis software and the pooled proportion was recalculated. The meta-analysis was reperformed after excluding studies with small sample group sizes (those with <20 participants). Publication bias was assessed by funnel plot and Egger's test. All analyses were performed using R language (The R Project for Statistical Computing; www.r-project.org).

Results

Characteristics of eligible studies. A total of 527 studies were obtained after searching the aforementioned databases. A total of 23 studies were included following screening of abstracts and full texts according to the selection criteria [Durm *et al* 2020 (7), Jabbour *et al* 2020 (8), Offin *et al* 2020 (15), McCall *et al* 2023 (16), Kartolo *et al* 2021 (17), Park *et al* 2023 (18), Jazieh *et al* 2021 (19), Landman *et al* 2021 (20), Vrankar *et al* 2021 (21), Gennen *et al* 2020 (22), Denault *et al* 2023 (23), Vrankar *et al* 2017 (24), Vrankar *et al* 2020 (25), Tufman *et al* 2021 (26), Guberina *et al* 2022 (27), Faehling *et al* 2020 (5), Paz-Ares *et al* 2021 (2), Desilets *et al* 2021 (10), Garassino *et al* 2022 (9), Liu *et al* 2022 (11), Girard *et al* 2022 (28), Nindra *et al* 2023 (29) and Raez *et al* 2022 (30)]. Among these, 16 were included in part one, and 15 were included in part two. The screening process for the studies is shown in Fig. 1. The characteristics of the studies included in part one are summarized in Table SI, and the total number of patients was 2,270. Among these patients, 591 had tumors with PD-L1 expression <1%, while 1,679 had tumors with PD-L1 expression ≥1%. The reference category was the group with PD-L1 expression ≥1%.

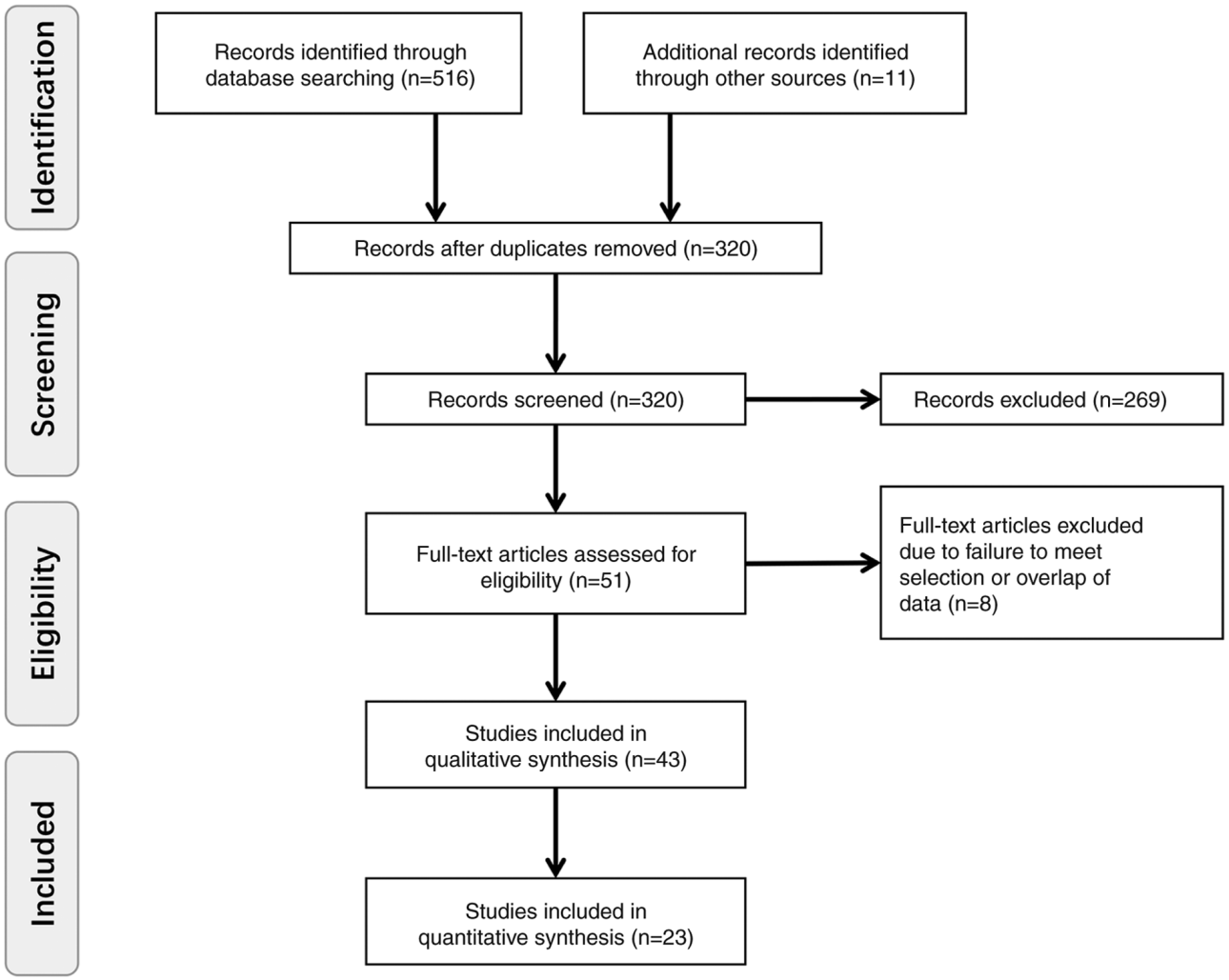

Figure 1. The screening process for the studies.

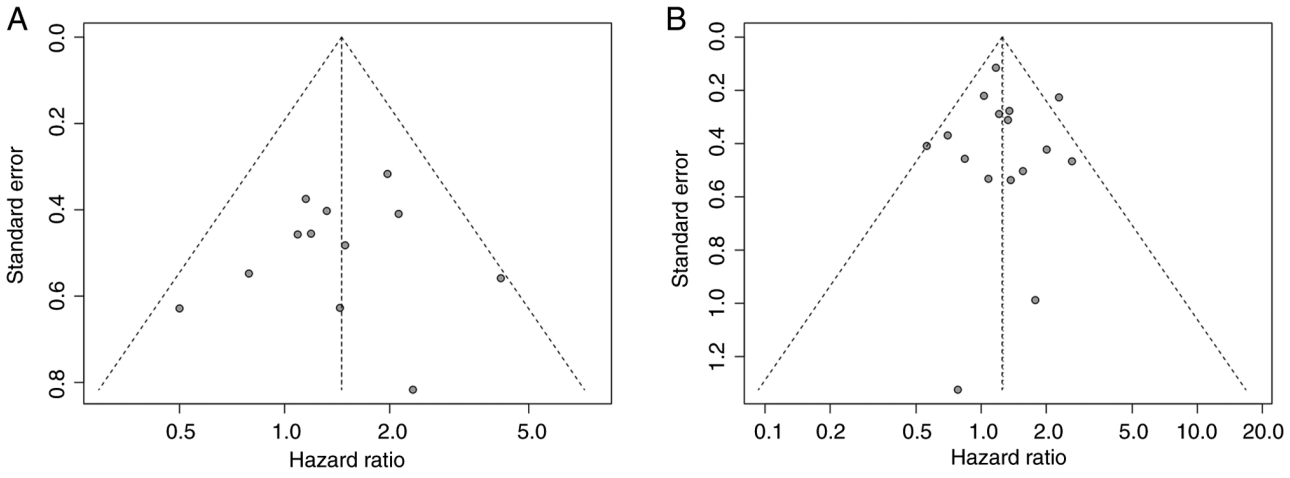

Figure 2. Funnel plots. (A) Funnel plot of HR for overall survival. (B) Funnel plot of HR for progression-free survival. HR, hazard ratio.

In part two, a total of 768 patients with locally advanced unresectable NSCLC and PD-L1 expression <1% were enrolled. Of these patients, 273 received CRT alone, and 495 received CRT followed by consolidation of ICIs. The funnel plots for OS and RFS did not provide any evidence of obvious publication bias, and no significant publication bias was detected by Egger's test (Fig. 2).

Part one: Pooled HR between PD-L1 expression <1% and PD-L1 expression ≥1% in patients treated with

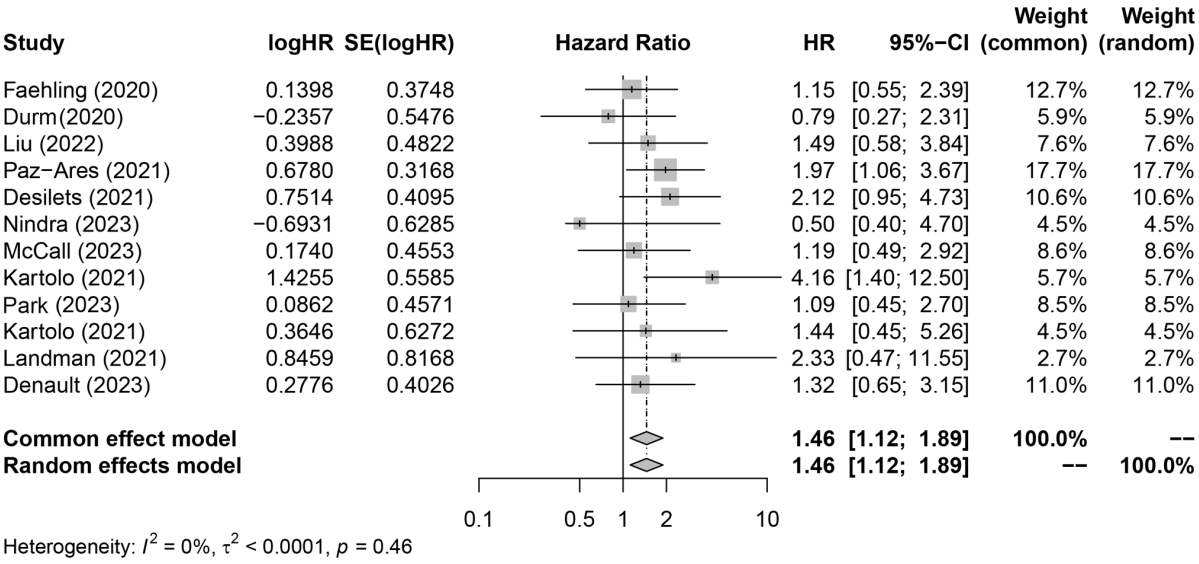

Figure 3. Forest plots of studies evaluating hazard ratio of overall survival for PD-L1 expression <1% compared with PD-L1 expression ≥1% in patients treated with consolidation of immune checkpoint inhibitors after chemoradiotherapy. PD-L1, programmed cell death-ligand 1; CI, confidence interval.

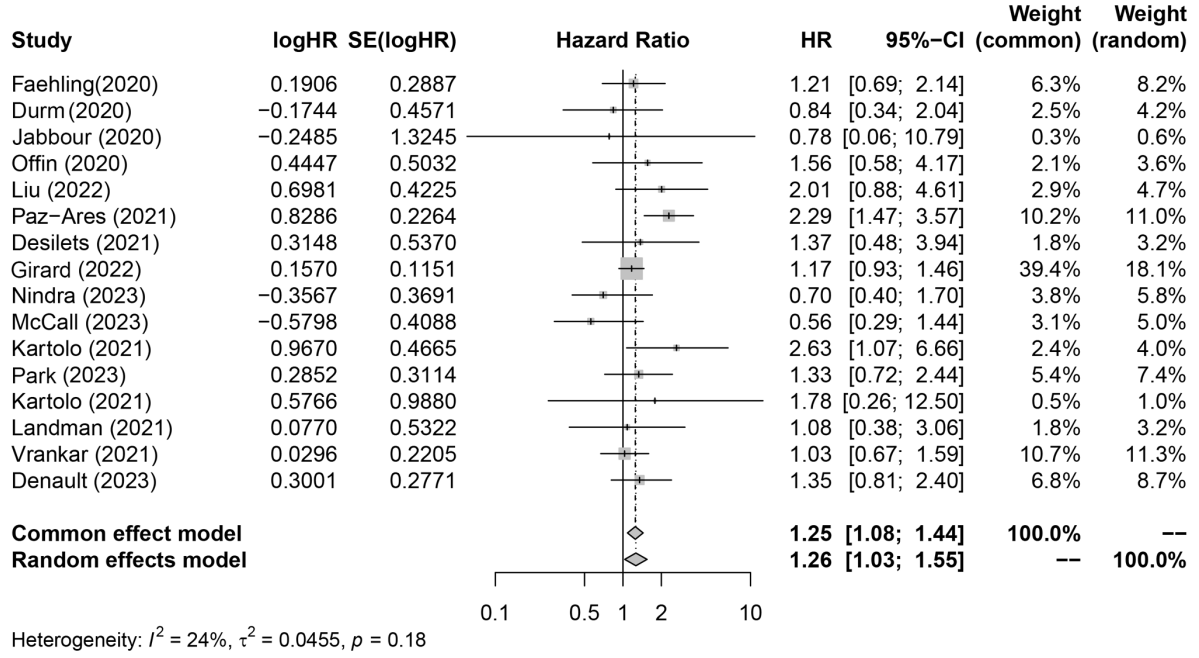

Figure 4. Forest plots of studies evaluating hazard ratio of progression-free survival for PD-L1 expression <1% compared with PD-L1 expression ≥1% in patients treated with consolidation of immune checkpoint inhibitors after chemoradiotherapy. PD-L1, programmed cell death-ligand 1; CI, confidence interval.

consolidation of ICIs after CRT. In part one, there were 12 studies included in the OS analysis of PD-L1 expression <1% vs. PD-L1 expression ≥1%. The pooled HR was 1.46 (95% CI:1.12-1.89; P=0.005) based on fixed-effects model or random-effects model (Fig. 3). There were 16 studies included in the PFS analysis of PD-L1 expression <1% vs. PD-L1 expression ≥1%. The pooled HR was 1.25 (95% CI: 1.08-1.44; P=0.002) and 1.26 (95% CI: 1.03-1.55; P=0.023) based on fixed-effects model and random-effects model, respectively (Fig. 4).

The calculation of sample size would indicate that a minimum of 100 samples is necessary to achieve more robust results, assuming an inspection level (α) of 0.5 and a power of the test statistic (1-β) of 0.8. However, the studies collected from the database are all retrospective studies and the sample size is small. If the cut off value of the group sample size for screening was set at 30, then half of the studies would have been excluded. Therefore, a sample size of 20 was chosen as the cut off value for sensitivity analysis. Meta-analysis was reperformed after excluding studies with a group sample size <20: The pooled HR of OS was 1.43 (95% CI: 1.04-1.95; P=0.025) based on fixed-effects model or random-effects model (Fig. S1), and the pooled HR of PFS was 1.24 (95% CI: 1.05-1.47; P=0.011) and 1.21 (95% CI: 0.88-1.66; P=0.238) based on fixed-effects model and random-effects model, respectively (Fig. S2). The 'leave-one-out' meta-analysis,

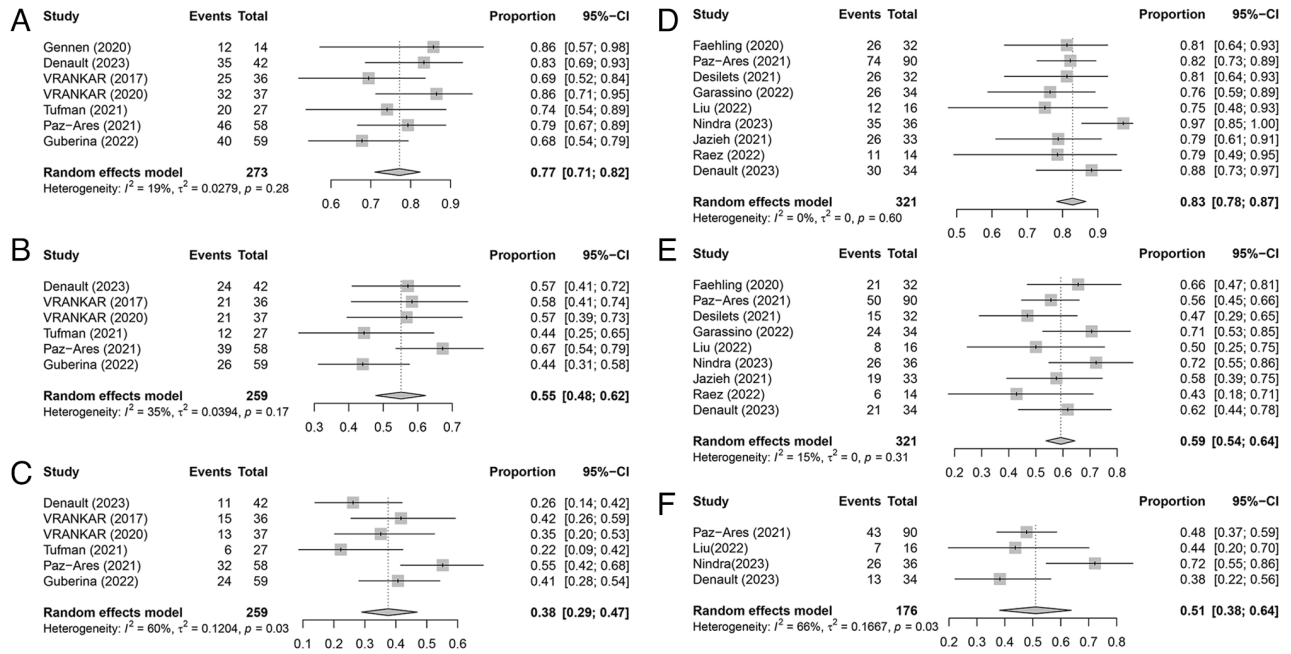

Figure 5. Forest plot for pooled OS rates of patients with locally advanced unresectable non-small cell lung cancer and programmed cell death-ligand 1 expression <1%: (A) The pooled 1-year OS rate of the patients treated with CRT alone. (B) The pooled 2-year OS rate of the patients treated with CRT alone. (C) The pooled 3-year OS rate of the patients treated with CRT alone. (D) The pooled 1-year OS rate of the patients treated with CRT followed by consolidation of ICIs. (E) The pooled 2-year OS rate of the patients treated with CRT followed by consolidation of ICIs. (F) The pooled 3-year OS rate of the patients treated with CRT followed by consolidation of ICIs. OS, overall survival; CRT, chemoradiotherapy; ICIs, immune checkpoint inhibitors.

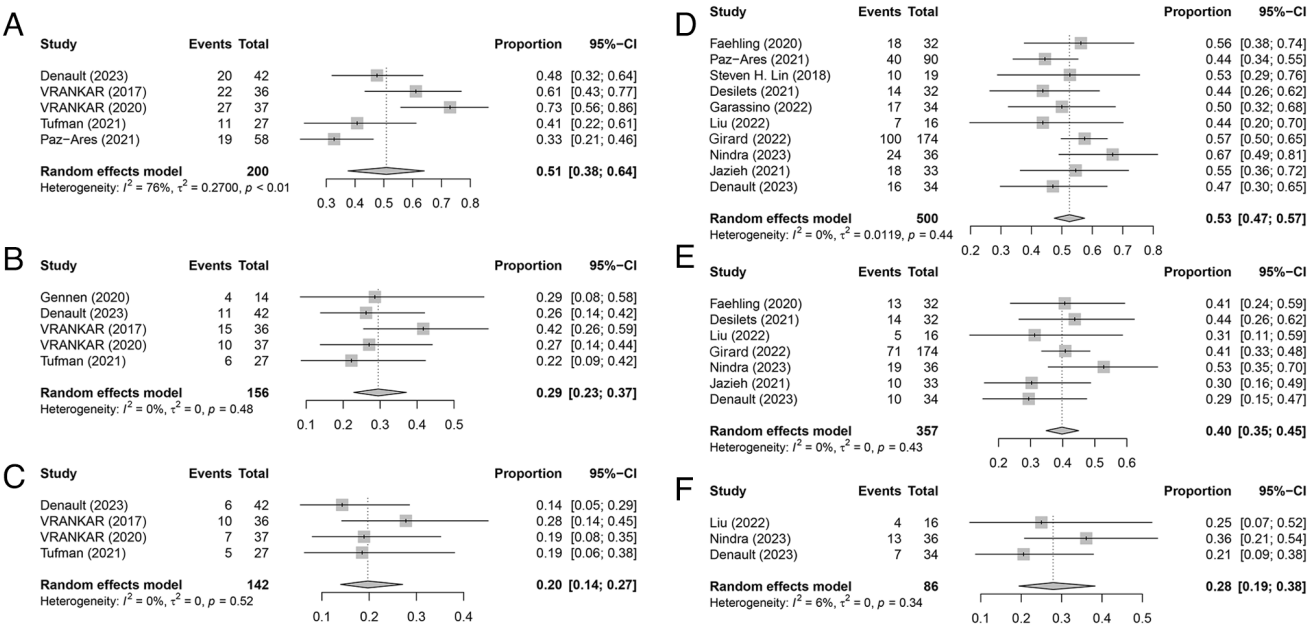

Figure 6. Forest plot for pooled PFS rates of patients with locally advanced unresectable non-small cell lung cancer and programmed cell death-ligand 1 expression <1%: (A) The pooled 1-year PFS rate of the patients treated with CRT alone. (B) The pooled 2-year PFS rate of the patients treated with CRT alone. (C) The pooled 3-year PFS rate of the patients treated with CRT alone. (D) The pooled 1-year PFS rate of the patients treated with CRT followed by consolidation of ICIs. (E) The pooled 2-year PFS rate of the patients treated with CRT followed by consolidation of ICIs. (F) The pooled 3-year PFS rate of the patients treated with CRT followed by consolidation of ICIs. PFS, progression-free survival; CRT, chemoradiotherapy; ICIs, immune checkpoint inhibitors.

depicted in Fig. S3, demonstrated favorable validity and robustness as the exclusion of any individual study did not significantly impact the outcome.

Part two: Pooled OS or PFS between CRT alone and CRT followed by consolidation of ICIs for patients with PD-L1 expression <1%. In part two, the pooled 1, 2 and 3-year OS rates were 77% vs. 83% (P=0.07), 55% vs. 59% (P=0.327) and 38% vs. 51% (P=0.006) for CRT alone compared with CRT followed by consolidation of ICIs, respectively (Fig. 5). The 1, 2 and 3-year PFS rates were 51% vs. 53% (P=0.632), 29% vs. 40% (P=0.015) and 20% vs. 28% (P=0.153) for CRT

alone compared with CRT followed by consolidation of ICIs, respectively (Fig. 6).

Meta-analysis was reperformed after excluding studies with sample size <20: The pooled 1, 2 and 3-year OS rates were 77% vs. 84% (P=0.038), 55% vs. 61% (P=0.132) and 38% vs. 53% (P=0.002) for CRT alone compared with CRT followed by consolidation of ICIs, respectively (Fig. S4). The 1, 2 and 3-year PFS rates were 51% vs. 53% (P=0.652), 30% vs. 40% (P=0.047), and 20% vs. 29% (P=0.147) for CRT alone compared with CRT followed by consolidation of ICIs, respectively (Fig. S5).

Discussion

The PACIFIC study has not definitively resolved the ongoing debate regarding the optimal mode of care for patients with unresectable, locally advanced NSCLC, particularly with PD-L1 expression <1%. A comprehensive meta-analysis was conducted by systematically gathering the available literature to address the current contentious issues for the first time. The present study compared the survival outcomes between two groups of patients (PD-L1 expression <1 and ≥1%) with unresectable, locally advanced NSCLC who received consolidation of ICIs after CRT. The present findings suggested that patients with PD-L1 expression ≥1% exhibit superior survival outcomes compared with those with PD-L1 expression <1%. To determine the survival benefit of consolidation of ICIs for NSCLC patients with PD-L1 expression <1%, a comprehensive literature search was conducted, a meta-analysis was performed and the survival rates between two treatment modalities (CRT alone and CRT followed by consolidation of ICIs) were compared in patients with unresectable, locally advanced NSCLC with PD-L1 expression <1%. The findings revealed that patients who underwent CRT followed by consolidation of ICIs exhibited significant improvements in 3-year OS and 2-year PFS. Therefore, it is considered by the authors that CRT followed by consolidation of ICIs can be used in patients with unresectable, locally advanced NSCLC and PD-L1 expression <1%, although this treatment regimen will have improved benefits in patients with PD-L1 expression ≥1%.

The efficacy of PD-1 or PD-L1 blockade treatment in reducing mortality risk has been demonstrated by numerous studies, even in patients with negative PD-L1 expression. This may be due to the upregulation of PD-L1 expression in tumor cells and surrounding cells after CRT and ICIs, which do not exert their effects solely through inhibiting the interaction between PD-1/PD-L1 (31-33).

Some studies have indicated that the survival prognosis of patients with squamous cell carcinoma is less favorable than that of patients with adenocarcinoma (5,10). However, there was a greater proportion of patients with squamous cell carcinoma in the PD-L1 expression <1% subgroup of the PACIFIC trial, which may have affected the interpretation of the survival results.

The presence of driver mutations has been observed to potentially diminish the efficacy of ICIs in certain retrospective studies examining EGFR and other driver mutations (34,35). This crucial question necessitates further investigation in future trials, although it should be noted that the collected studies included a limited number of individuals with EGFR mutations. The difference in the time interval for initiating ICIs after CRT (<42 days vs. >42 days) did not yield significant differences in terms of PFS or OS (7,10). However, the initiation of ICIs at an earlier stage may increase the likelihood of immune pneumonia, consequently impacting survival outcomes (8).

There are several limitations in the present study. All of the included studies were retrospectively designed or post hoc, and the clinical features of the two groups of patients, such as the influence of different radiotherapy doses/fractionations, irradiation target volumes and chemotherapy regimens, were not well balanced. Due to the lack of original data regarding survival statistics, these data obtained from the Kaplan-Meier survival curve may have contained some inaccuracies. Those studies were included without detailed gene mutation status into this meta-analysis due to the general lack of information on gene mutation status in the majority of the studies and the rare occurrence of gene mutations within the population. The gene mutation information of each study is presented in Table SI. The expression of PD-L1 may not serve as a reliable indicator for distinguishing between groups that benefit and those that do not. In the future, it will be imperative to integrate additional influential factors, such as microsatellite instability, mutation load and molecular biological information, to identify the specific cohorts who would benefit from consolidation of ICIs after CRT.

In conclusion, the findings of the present review highlighted that the benefits of CRT followed by consolidation of ICIs were higher compared with CRT alone in patients with unresectable, locally advanced NSCLC and PD-L1 expression <1%. The consolidation of ICIs after CRT would provide greater benefits for locally advanced NSCLC patients with PD-L1 expression ≥1% compared with those with PD-L1 expression <1%. These results are consistent with the current clinical guidelines in some countries, such as in Canada and the United States, but not with those conducted by European Medicines Agency. The aforementioned findings offer valuable insights for future research and clinical practice. In the view of limitations in the present study, the related results must be interpreted with caution.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

LHY and JS conceptualized the present study and conducted the investigation. The acquisition and extraction of data were conducted by SYR and LM. SYR and JZ carried out data analysis and drafted the manuscript. LM and JZ aided with the

statistical analysis, reviewed and edited the manuscript. SYR and LM have seen and confirm the authenticity of the raw data generated during the study. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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