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Review article

Impact of PD-1/PD-L1 inhibitors on survival in stage III non-small-cell lung cancer: A systematic review

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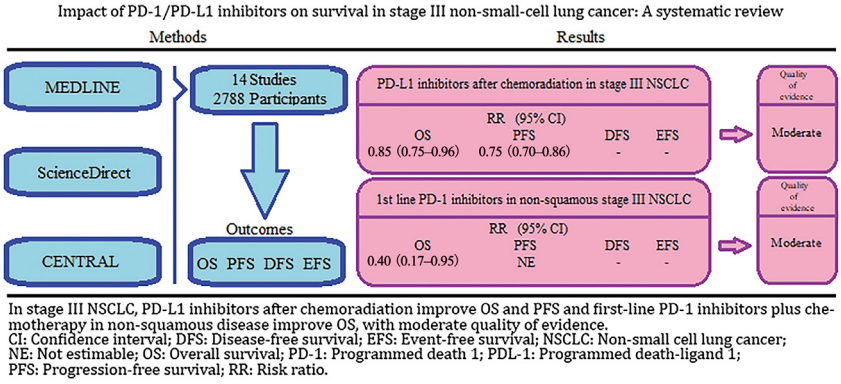
HIGHLIGHTS

- A systematic review of 14 studies and 2788 participants with stage III non-small cell lung cancer (NSCLC) was performed.
- Programmed death-ligand 1 (PD-L1) inhibitors improved overall and progression-free survival in resected stage III NSCLC after chemoradiation therapy.
- First-line PD-1 inhibitors plus chemotherapy improved overall survival in unresected non-squamous stage III NSCLC.

GRAPHICAL ABSTRACT



In stage III NSCLC, PD-L1 inhibitors after chemoradiation improve OS and PFS and first-line PD-1 inhibitors plus chemotherapy in non-squamous disease improve OS, with moderate quality of evidence.
CI: Confidence interval; DFS: Disease-free survival; EFS: Event-free survival; NSCLC: Non-small cell lung cancer; NE: Not estimable; OS: Overall survival; PD-1: Programmed death 1; PDL-1: Programmed death-ligand 1; PFS: Progression-free survival; RR: Risk ratio.

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ABSTRACT

Background: Lung cancer is the leading cause of cancer-related death, and non-small-cell lung cancer (NSCLC) is the predominant subtype. Programmed death 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors are widely used to treat stage IV NSCLC. This study systematically reviewed the literature to clarify the impact of PD-1/PD-L1 inhibitor treatment on the survival of patients with stage III NSCLC.

Methods: Randomized phase III clinical trials of PD-1/PD-L1 inhibitors administered to patients with stage III NSCLC that were written in English and published between November 2012 and November 2022 were eligible for review. The sources of information were the MEDLINE database (last consulted on December 26, 2022), ScienceDirect website (last consulted on December 26, 2022), and CENTRAL register (last consulted on December 27, 2022). The outcomes of interest were overall survival (OS), progression-free survival (PFS), disease-free survival (DFS), and event-free survival (EFS). Risk of bias assessments were performed according to the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0. The findings have been assessed for certainty according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) guidelines.

Results: Fourteen eligible studies and 2788 participants were included in the review. The key characteristics used to group the participants were disease histology, percentage of PD-L1 expression in cancer cells, and timeline of therapy. OS and PFS were improved (risk ratio [RR]: 0.85; 95% confidence interval [CI]: 0.75–0.96 and RR: 0.75; 95% CI: 0.70–0.86, respectively) based on the use of PD-L1 inhibitors after chemoradiation and OS was improved using first-line PD-1 inhibitors plus chemotherapy in non-squamous NSCLC (RR: 0.40; 95% CI: 0.17–0.95), with the GRADE results indicating moderate quality of evidence.

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Conclusion: This review highlights the OS and PFS benefits of PD-L1 inhibitors in stage III NSCLC when used after chemoradiation and OS benefits of first-line PD-1 inhibitors added to chemotherapy in non-squamous stage III disease.

Introduction

Lung cancer is one of the most common malignancies and a leading cause of cancer-related death.[1] Non-small-cell lung cancer (NSCLC) is the predominant histological subtype and accounts for approximately 85% of lung cancer cases. Most patients diagnosed with NSCLC are at an advanced stage (III or IV),[2] and the 5-year survival rate is 33% for stage III and 6% for stage IV.[3] The therapeutic options for advanced disease depend on the tumor resectability, disease histology, oncogenic driver mutations, and tumor programmed death-ligand 1 (PD-L1) expression level. Resection is suggested in resectable stage IIIA tumors after neoadjuvant concurrent chemoradiation,[4] and treatment includes adjuvant chemotherapy plus atezolizumab in the case of PD-L1 levels of at least 1%[5] or osimertinib in the case of epidermal growth factor receptor (EGFR) mutations.[6] For unresectable disease, concurrent chemoradiation followed by durvalumab is suggested.[7] The chemotherapy regimens consist of cisplatin plus pemetrexed for non-squamous carcinomas and cisplatin plus docetaxel or gemcitabine for squamous carcinomas.[8] In stage IV NSCLC, tyrosine kinase inhibitors (TKIs) are used if oncogenic driver mutations are present; otherwise, immunotherapy regimens with programmed death 1 (PD-1) and PD-L1 inhibitors are mainly used.[9] These antibodies block the PD-1-PD-L1 interaction, which induces signals in the PD-1 pathway that inhibit the cytotoxic effect of T cells and leads to tumor immune tolerance. Thus, these drugs enhance the immune response against cancer cells.[10] Anti-PD-1/PD-L1 immunotherapy in stage III NSCLC has not yet been established, and until the completion of this review, the only anti-PD-1/PD-L1 agents approved for stage III NSCLC were durvalumab as consolidation therapy in patients with unresectable tumors and without disease progression after first-line concurrent chemoradiation therapy[7] and adjuvant atezolizumab in patients with surgically removed tumors after adjuvant chemotherapy and with tumor PD-L1 expression of at least 1%.[5] This study systematically reviewed the literature to clarify the effects of PD-1/PD-L1 inhibitor treatment on the survival of patients diagnosed with stage III NSCLC.

Methods

Search strategy

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11] The sources of information were the MEDLINE database via the PubMed platform (last consulted on December 26, 2022), the Science Direct website (last consulted on December 26, 2022), and CENTRAL register (last consulted on December 27, 2022). The authors independently searched for eligible studies, applied a search strategy to each source [Supplementary File 1], screened the retrieved titles and abstracts, and read the full text of eligible studies. Any disagreements at any stage of the selection process were resolved through further discussion between the authors.

Eligibility criteria

Studies eligible for review were phase III randomized clinical trials of PD-1/PD-L1 inhibitors administered to patients with stage III NSCLC. The intervention could be used as a monotherapy, combination therapy along with chemotherapy, adjuvant therapy, or neoadjuvant therapy. Possible comparisons between the intervention and control groups included PD-1/PD-L1 inhibitors *vs.* chemotherapy, placebo, or best supportive care. The included studies were written in English and published from November 2012 to November 2022. Conference abstracts, unpublished studies, and studies that did not measure or report the results for outcomes of interest were excluded from the review. Incomplete studies meeting the eligibility criteria were also excluded from the review unless an interim analysis reporting the outcomes of interest had been published. For reports on the same study, only the most recent update was included in the review. In the case of reports that provide the results for a specific demographic subgroup of an eligible study, only the main study was included.

Outcomes

The survival outcomes of interest were overall survival (OS), defined as the time from randomization until death from any cause; progression-free survival (PFS), defined as the time from randomization until disease progression or death; disease-free survival (DFS), defined as the time from first response to treatment until tumor relapse or death; and event-free survival (EFS), defined as the time from randomization until disease progression, death, or treatment discontinuation for any reason. Progressive disease and treatment responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[12] The effect of treatment on outcomes was measured using the hazard ratio (HR) and respective 95% confidence interval (CI).

Data collection

The authors independently extracted the following data from each study: author, year of publication, study design, number of participants with stage III NSCLC, intervention and corresponding dose, comparator and corresponding dose, and results of the outcomes of interest. The data are presented in Table 1. Any disagreements were resolved through further discussion between the authors.

Risk of bias assessment

The authors independently evaluated the risk of bias in the included studies using the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.[13] Evaluations were performed in the following domains: random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. The risk of bias in each domain was characterized as "high," "low," or "unclear." Overall risk of bias was not assessed for any of the studies. Any disagreements were resolved through further discussion between the authors.

Certainty assessment

The authors independently assessed the certainty of evidence in this review according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) guidelines.[14] The results are presented in a summary of the findings in Supplementary File 3. The studies were grouped according to disease histology, percentage of PD-L1 expression in cancer cells, and timeline of therapy (after chemoradiation, adjuvant, or first-line). The quality of evidence for each outcome fell into one of the following categories: high, which corresponded to high confidence that the true effect lies close to the estimated effect; moderate, which corresponded to moderate confidence about the closeness of the true and the estimated effect; low, which corresponded to limited confidence about the closeness of the true and the estimated effect; and very

Table 1
Main characteristics of the included studies.

Study	Design	Patients	Intervention	Comparator	OS	PFS	EFS	DFS
Felip et al., 2021[5]	Phase III, randomized, multicenter, multinational, open-label	Stage IIIA:	Atezolizumab 1200 mg/21 days for 16 cycles or 1 year	BSC (regular scans for disease recurrence) after adjuvant platinum-based chemotherapy (1–4 cycles)	–	–	–	(Median, months)
	Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA NSCLC	Any PD-L1 expression:						Any PD-L1 expression:
		atezolizumab: ($n = 205$) BSC: ($n = 208$) PD-L1 $\geq$ 1%: atezolizumab: ($n = 117$) BSC: ($n = 115$)						atezolizumab: (32.3) BSC: (29.7) PD-L1 $\geq$ 1%: atezolizumab: (42.3) BSC: (26.7)

Study	Design	Patients	Intervention	Comparator	OS	PFS	EFS	DFS
Zhou et al., 2022[15]	Phase III, randomized, multicenter, double-blind	Stage IIIA:	Sugemalimab 1200 mg/21 days for up to 24 months	Placebo/21 days for up to 24 months	–	(Median, months)	–	–
	Sugemalimab after concurrent or sequential chemoradiation therapy in unresectable stage III NSCLC	Sugemalimab				Stage IIIA:		
		($n = 74$) Placebo: ($n = 32$) Stage IIIB: Sugemalimab ($n = 146$) Placebo: ($n = 65$) Stage IIIC: Sugemalimab ($n = 33$) Placebo: ($n = 28$)				Sugemalimab (10.51) Placebo: (6.21) Stage IIIB: Sugemalimab (8.44) Placebo: (5.82) Stage IIIC: Sugemalimab (8.61) Placebo: (5.39)		
Spigel et al., 2022 (update)[16]	Phase III, randomized, multicenter, multinationa double-blind		Durvalumab 10 mg/kg every 14 days for up to 12 months	Placebo every 14 days for up to 12 months	(Median, months)	(Median, months)	–	–
	Durvalumab in stage III NSCLC after 2 or more cycles with platinum-based chemoradiotherapy and without disease progression	Stage IIIA: Durvalumab:			Durvalumab: (47.5)	Durvalumab: (16.9)		
		($n = 252$) Placebo: ($n = 125$) Stage IIIB: Durvalumab: ($n = 212$) Placebo: ($n = 107$)			Placebo: (29.1)	Placebo: (5.6)		

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Study	Design	Patients	Intervention	Comparator	OS	PFS	EFS	DFS
Yang et al., 2021 (update)[17]	Phase III, randomized, multicenter double-blind Sintilimab plus chemotherapy as first-line therapy in non-squamous locally advanced or metastatic NSCLC	Stage IIIB/IIIC: Sintilimab + Chemo: ($n = 21$)	Sintilimab 200 mg + Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2 or	Placebo + Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2 or	(Events/n) Sintilimab + Chemo:	(Events/n) Sintilimab + Chemo:	–	–
		Placebo + Chemo: ($n = 15$)	Carboplatin every 21 days for 4 cycles Maintenance therapy: Sintilimab 200 mg + Pemetrexed 500 mg/m^2 every 21 days for up to 24 months	Carboplatin every 21 days for 4 cycles Maintenance therapy: Placebo + Pemetrexed 500 mg/m^2 every 21 days for up to 24 months	(5/21) Placebo + Chemo: (9/15)	(7/21) Placebo + Chemo: (13/15)		
Gogishvili et al., 2022[18]	Phase III, Randomized, multicenter, multinational double-blind Cemiplimab plus chemotherapy in NSCLC	Stage III: Cemiplimab + Chemo: ($n = 45$)	Cemiplimab 350 mg every 21 days for up to 108 weeks + four cycles of platinum-based chemotherapy, followed by maintenance therapy with Pemetrexed	Placebo every 21 days for up to 108 weeks + four cycles of platinum-based chemotherapy, followed by maintenance therapy with Pemetrexed	(Events/n) Cemiplimab + Chemo:	(Events/n) Cemiplimab + Chemo:	–	–
		Placebo + Chemo: ($n = 24$)			(16/45) Placebo + Chemo: (13/24)	(26/45) Placebo + Chemo: (23/24)		

Study	Design	Patients	Intervention	Comparator	OS	PFS	EFS	DFS
Shi et al., 2022[19]	Phase III, randomized, multicenter, open-label Sintilimab *vs.* docetaxel as second-line treatment in squamous locally advanced or metastatic NSCLC	Stage IIIB: Sintilimab: ($n = 21$) Docetaxel: ($n = 17$) Stage IIIC: Sintilimab: ($n = 7$) Docetaxel: ($n = 9$)	Sintilimab 200 mg every 21 days	Docetaxel 75 mg/m^2 every 21 days	(Events/n) Stage IIIB/IIIC: Sintilimab: (19/28) Docetaxel: (21/26)	–	–	–
Wang et al., 2023[20]	Phase III, randomized, multicenter, double-blind Toripalimab plus chemotherapy for untreated advanced NSCLC	Stage IIIB/IIIC: Toripalimab + Chemo: ($n = 49$) Placebo + Chemo: ($n = 23$)	Toripalimab 240 mg + 4–6 cycles of Chemotherapy every 21 days, followed by maintenance therapy with Toripalimab every 21 days	Placebo + 4–6 cycles of Chemotherapy every 21 days, followed by maintenance therapy with placebo every 21 days	(Median, months) Toripalimab + Chemo: (NE) Placebo + Chemo: (20.3)	(Median, months) Toripalimab + Chemo: (9.7) Placebo + Chemo: (5.5)	–	–
O'Brien et al., 2022[21]	Phase III, randomized, multicenter, multinational, triple-blind Adjuvant Pembrolizumab in resected stage IB-IIIA NSCLC	Stage IIIA: Pembrolizumab: ($n = 177$) Placebo: ($n = 162$)	Pembrolizumab 200 mg every 21 days	Placebo every 21 days	–	–	–	(Events/n) Pembrolizumab: (89/177) Placebo: (89/162)

Study	Design	Patients	Intervention	Comparator	OS	PFS	EFS	DFS
Zhou et al., 2021[22]	Phase III, randomized, multicenter, double-blind Sintilimab plus chemotherapy as first-line treatment for squamous advanced or metastatic NSCLC	Stage IIIB/IIIC: Sintilimab + Chemo: ($n = 39$) Placebo + Chemo: ($n = 44$)	Sintilimab 200 mg + 4–6 cycles Gemcitabine (1 g/m^2) + Cisplatin (75 mg/m^2)/ Carboplatin every 21 days. Maintenance therapy: Sintilimab 200 mg every 21 days for up to 24 months	Placebo + 4–6 cycles Gemcitabine (1 g/m^2) + Cisplatin (75 mg/m^2)/ Carboplatin every 21 days. Maintenance therapy: Placebo every 21 days for up to 24 months	–	(Events/n) Sintilimab + Chemo: (30/39) Placebo + Chemo: (41/44)	–	–
Lu et al., 2021[23]	Phase III, randomized, multicenter, open-label Tislelizumab plus chemotherapy as first-line treatment for non-squamous locally advanced or metastatic NSCLC	Stage IIIB: Tislelizumab + Chemo: ($n = 40$) Chemo: ($n = 21$)	Tislelizumab 200 mg + 4–6 cycles Cisplatin (75 mg/m^2)/ Carboplatin + Pemetrexed 500 mg/m^2 every 21 days. Maintenance therapy: Tislelizumab 200 mg + Pemetrexed 500 mg/m^2 every 21 days	4–6 cycles Cisplatin (75 mg/m^2)/ Carboplatin + Pemetrexed 500 mg/m^2 every 21 days. Maintenance therapy: Pemetrexed 500 mg/m^2 every 21 days	–	(Median, months) Tislelizumab + Chemo: (9.0) Chemo: (7.6)	–	–
Wang et al., 2021[24]	Phase III, randomized, multicenter, open-label Tislelizumab plus chemotherapy as first-line treatment in squamous advanced NSCLC	Stage IIIB: Tislelizumab + Paclitaxel + Carboplatin: ($n = 38$) Tislelizumab + nab-Paclitaxel + Carboplatin: ($n = 40$) Paclitaxel + Carboplatin: ($n = 44$)	Tislelizumab 200 mg + Paclitaxel 175 mg/m^2 + Carboplatin every 21 days (Intervention A) Tislelizumab 200 mg + Carboplatin every 21 days + nab-Paclitaxel 100 mg/m^2 every 7 days (Intervention B)	Paclitaxel 175 mg/m^2 + Carboplatin every 21 days	–	(Median, months) Tislelizumab + Paclitaxel + Carboplatin: (9.8) Tislelizumab + nab-Paclitaxel + Carboplatin: (11.0) Paclitaxel + Carboplatin: (5.6)	–	–
Forde et al., 2022[25]	Phase III, randomized, multicenter, multinational, open-label Neoadjuvant Nivolumab plus chemotherapy in resectable NSCLC	Stage IIIA: Nivolumab + Chemo: ($n = 113$) Chemo: ($n = 115$)	Nivolumab 360 mg + Platinum-based chemotherapy every 21 days for 3 cycles before surgery	Platinum-based chemotherapy every 21 days, for 3 cycles before surgery	–	–	Median, months) Nivolumab + Chemo: (31.6) Chemo: (15.7)	–

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Study	Design	Patients	Intervention	Comparator	OS	PFS	EFS	DFS
Sezer et al., 2021[26]	Phase III, Randomized, multicenter, multinational, open-label Cemiplimab monotherapy as first-line treatment in advanced NSCLC with PD-L1 expression of at least 50%	Stage IIIB/IIIC PD-L1 ≥ 50%: Cemiplimab: (n = 45) Chemo: (n = 42)	Cemiplimab 350 mg every 21 days	4–6 cycles Platinum-based chemotherapy	(Events/n) Cemiplimab: (9/45) Chemo: (15/42)	(Events/n) Cemiplimab: (27/45) Chemo: (28/42)	–	–
de Castro et al., 2023 (update)[27]	Phase III, randomized, multicenter, multinational, open-label Pembrolizumab for untreated PD-L1-expressing locally advanced or metastatic NSCLC	Locally advanced stage PD-L1 ≥ 1%: Pembrolizumab: (n = 69) Chemo: (n = 81)	Pembrolizumab 200 mg every 21 days for up to 35 cycles	4–6 cycles Carboplatin + Paclitaxel 200 mg/m^2 or Pemetrexed 500 mg/m^2 every 21 days	(Events/n) Totally: (128/150)	–	–	–

BSC: Best supportive care; DFS: Disease-free survival; EFS: Event-free survival; NSCLC: Non-small-cell lung cancer; OS: Overall survival; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival.

low, which corresponded to the likelihood of substantial differences between the true and the estimated effects. The factors considered for assessment were risk of bias, imprecision, inconsistency between results, indirectness of evidence, large magnitude of the effect, and confounding factors. The risk of bias was assessed and is presented in Supplementary File 2. When high risk of bias was observed, the quality of evidence was downgraded by one. The precision of the effects was assessed based on the sample size. When imprecision was observed, the quality of evidence was downgraded by one. The consistency between the results was assessed according to the absence or minimal overlapping of CIs between studies. When inconsistency was observed, the quality of evidence was downgraded by one. The directness of the evidence was assessed according to differences in the study populations and/or interventions. When indirectness was observed, the quality of evidence was downgraded by one. The magnitude of the effect was assessed using the risk ratio (RR). When a large effect magnitude (RR $<$ 0.5 or RR $>$ 2) was observed, the quality of evidence was upgraded by one. When a confounding factor that minimized the effect size was observed, the quality of evidence was upgraded by one. All randomized clinical trials were initially considered high-quality evidence. Any disagreements were resolved through further discussion between the authors.

Results

Study selection

The search strategy yielded 4615 records. After title/abstract screening, 75 records were eligible for full-text assessment. Ultimately, 14 studies[5,15–27] involving 2788 participants were included in the review. The details are shown in the flow diagram [Figure 1].

Description of the studies

All included studies were phase III randomized multicenter clinical trials. Seven were multinational studies, seven were open-label, six were double-blind, and one was triple-blind. In three studies, the intervention was a PD-L1 inhibitor, and in 11 studies, the intervention was a PD-1 inhibitor. Two studies were conducted in an adjuvant setting, and one was conducted in a neoadjuvant setting. In seven studies, the intervention was administered as a combination therapy, and in seven studies, it was administered as a monotherapy. Three studies included only patients with squamous disease, and two included only patients with non-squamous disease. Two studies were conducted based on the PD-L1 expression levels in cancer cells. Seven studies reported OS results, nine reported PFS results, one reported EFS results, and two reported DFS results. The main characteristics of these studies are listed in Table 1.

Risk of bias

Two studies had an unclear risk of selection bias; one study had an unclear risk of performance bias, and three had a high risk; two studies had a high risk of detection bias; and eight studies had a high risk of attrition bias. No reporting bias was detected in the included studies, and 10 studies had an unclear risk of other biases. A detailed risk of bias assessment is presented in Supplementary File 2.

Outcomes

Table 2 summarizes the survival outcomes of the included studies with their respective HRs and 95% CIs. Among the studies that could not be grouped together, a notable improvement in EFS (HR: 0.54; 95% CI: 0.37–0.80) was observed when nivolumab was added to neoadjuvant chemotherapy.[25] An improvement in DFS (HR: 0.62; 95% CI: 0.42–0.90) when the adjuvant atezolizumab was used after adjuvant chemotherapy in resected stage IIIA NSCLC with PD-L1 expression of at least 1%[5] has already resulted in drug approval.

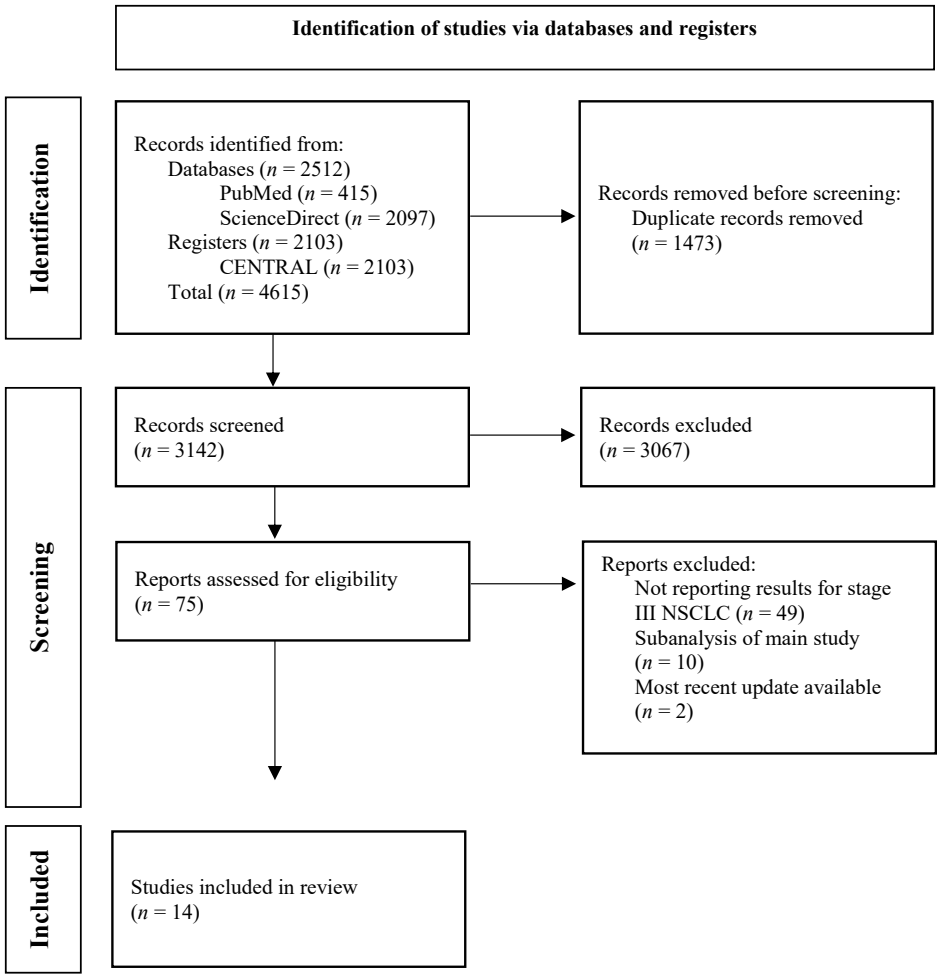

Figure 1. Flow diagram of study selection. NSCLC: Non-small cell lung cancer.

Certainty of evidence

The quality of evidence was assessed according to predetermined classifications. Two studies[15,16] on PD-L1 inhibitors after chemoradiotherapy that included 1074 participants were grouped together and showed statistically significant improvements in both OS (RR: 0.85; 95% CI: 0.75–0.96) and PFS (RR: 0.75; 95% CI: 0.70–0.86), with GRADE results indicating moderate quality of evidence. Two studies[17,23] on first-line PD-1 inhibitors as combination therapy administered for non-squamous NSCLC that included 97 participants were grouped together and showed statistically significant improvements in OS (RR: 0.40; 95% CI: 0.17–0.95), with moderate quality of evidence. Three studies[19,22,24] on PD-1 inhibitors administered for squamous NSCLC that included 259 participants were grouped together and showed statistically insignificant improvements in OS (RR: 0.84; 95% CI: 0.61–1.15), with low quality of evidence. Two studies[26,27] on PD-1 inhibitors administered for PD-L1-expressing NSCLC that included 247 participants were grouped together and showed statistically insignificant improvements in PFS (RR: 0.90; 95% CI: 0.65–1.24), with low quality of evidence. Two studies[5,21] on adjuvant PD-1/PD-L1 inhibitors administered for resected NSCLC that included 752 participants were grouped together; however, the DFS benefit could not be estimated. Eight studies[17,18,20,22–24,26,27] on first-line PD-1 inhibitors administered for advanced NSCLC that included 680 participants were grouped together; however, the OS and PFS benefits could not be estimated. A detailed assessment of the certainty of the evidence is presented in Supplementary File 3.

Discussion

In this systematic review, we aimed to provide an overall picture of the efficacy of all PD-1/PD-L1 inhibitors administered for all patients with stage III NSCLC and perform appropriate subanalyses according to the patient's histology, tumor PD-L1 expression levels, and timeline of therapy. Another systematic review highlighted the use of durvalumab as consolidation therapy after chemoradiation therapy in unresectable stage III NSCLC,[28] and the results are consistent with those of the PACIFIC trial.[7] This review provides evidence to support the previously reported benefits of consolidation therapy with a PD-L1 inhibitor after chemoradiation therapy when disease progression is not observed in stage III NSCLC and introduces the prospect of using PD-L1 inhibitors other than durvalumab, such as sugemalimab. Furthermore, this review determined the benefit of adding a first-line PD-1 inhibitor to chemotherapy according to histological subtype, and the results show that non-squamous cases are more favorable for such intervention. Similar results have only previously been reported for stage IV disease in another systematic review.[29] In another study included in this review,[25] survival benefits were observed with the addition of a PD-1 inhibitor to neoadjuvant chemotherapy. Several phase III studies have been designed to elucidate the established therapeutic regimen of anti-PD-L1 immunotherapy with durvalumab after chemoradiotherapy for stage III NSCLC. Two studies will assess the efficacy of combination immunotherapy in this setting. Durvalumab is currently being used alongside a CD73 or a killer cell lectin-like receptor C1 (KLRC1) inhibitor[30] and a T cell immunoreceptor with Ig and ITIM domain (TIGIT) inhibitor.[31] An ongoing study is

Table 2
Survival outcomes summary for the included studies.

Study	Intervention *vs.* comparator	HR (95% CI)
Felip et al., 2021[5]	Atezolizumab *vs.* BSC	Stage IIIA: DFS: 0.81 (0.61–1.06) (total) 0.62 (0.42–0.90) (PD-L1 $\geq$ 1%)
Zhou et al., 2022[15]	Sugemalimab *vs.* Placebo	PFS: Stage IIIA: 0.74 (0.41–1.34) Stage IIIB: 0.55 (0.37–0.81) Stage IIIC: 0.73 (0.36–1.48)
Spigel et al., 2022[16]	Durvalumab vs. Placebo	Stage IIIA: OS: 0.61 (0.47–0.80) PFS: 0.53 (0.40–0.69) Stage IIIB: OS: 0.86 (0.63–1.17) PFS: 0.64 (0.48–0.85)
Yang et al., 2021[17]	Sintilimab *vs.* Placebo	Stage IIIB/IIIC: OS: 0.32 (0.11–0.96) PFS: 0.17 (0.07–0.44)
Gogishvili et al., 2022[18]	Cemiplimab *vs.* Placebo	Stage III: OS: 0.54 (0.25–1.15) PFS: 0.34 (0.19–0.62)
Shi et al., 2022[19]	Sintilimab *vs.* Docetaxel	Stage IIIB/IIIC: OS: 0.80 (0.42–1.51)
Wang et al., 2023[20]	Toripalimab *vs.* Placebo	Stage IIIB/IIIC: OS: 0.57 (0.25–1.35) PFS: 0.39 (0.21–0.73)
O'Brien et al., 2022[21]	Pembrolizumab *vs.* Placebo	Stage IIIA: DFS: 0.92 (0.69–1.24)
Zhou et al., 2021[22]	Sintilimab *vs.* Placebo	Stage IIIB/IIIC: PFS: 0.53 (0.33–0.85)
Lu et al., 2021[23]	Tislelizumab + Chemo *vs.* Chemo	Stage IIIB: PFS: 0.66 (0.32–1.38)
Wang et al., 2021[24]	Tislelizumab + PC/Tislelizumab + nab-PC *vs.* PC	Stage IIIB: PFS: 0.40 (0.22–0.75) (T + PC *vs.* PC) 0.37 (0.20–0.69) (T + nab-PC *vs.* PC)
Forde et al., 2022[25]	Nivolumab + Chemo *vs.* Chemo	Stage IIIA: EFS: 0.54 (0.37–0.80)
Sezer et al., 2021[26]	Cemiplimab *vs.* Chemo	Stage IIIB/IIIC, PD-L1 $\geq$ 50%: OS: 0.48 (0.20–1.14) PFS: 0.49 (0.27–0.88)
de Castro et al., 2023[27]	Pembrolizumab *vs.* Chemo	Locally advanced stage, PD-L1 $\geq$ 1%: OS: 0.65 (0.44–0.96)

BSC: Best supportive care; CI: Confidence interval; DFS: Disease-free survival; HR: Hazard ratio; nab-PC: Nanoparticle albumin-bound paclitaxel + carboplatin; OS: Overall survival; PC: Paclitaxel + carboplatin; PFS: Progression-free survival.

comparing the combination immunotherapy of the PD-L1 inhibitor atezolizumab and a TIGIT inhibitor with durvalumab after chemoradiotherapy.[32] The combination of a PD-1 inhibitor and TIGIT inhibitor will be compared with durvalumab after chemoradiotherapy in two studies.[33,34] In the neoadjuvant setting of stage III NSCLC, two phase III studies will assess the efficacy of adding a PD-1 inhibitor to chemotherapy[35,36] and one study will assess the efficacy of adding the PD-L1 inhibitor atezolizumab to chemotherapy.[37] The small sample size of patients with stage III NSCLC and the risk of bias in the included studies constitute limitations of the evidence presented. Lack of communication with the study authors was another limitation of the review process, and it may have prevented the inclusion of additional studies. The evidence presented in this review points to the expansion of anti-PD-1/anti-PD-L1 immunotherapy in stage III NSCLC, and such therapeutic strategy could become more robust if future clinical trials of PD-1/PD-L1 inhibitors are designed to mainly include patients with stage III NSCLC according to the appropriate characteristics, such as histological subtype or PD-L1 expression levels.

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Authors contribution

Petros Roussos: conceptualization, methodology, formal analysis, investigation, writing – original draft, and visualization: Magdalini Migkou: validation, writing, review and editing, and supervision.

Ethics statement

Not applicable.

Data availability statement

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

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpt.2023.09.004.

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