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Review Article

Evaluation of the efficacy and safety of durvalumab combined with chemotherapy, radiotherapy, or other agents in advanced non-small cell lung cancer: a meta-analysis

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Abstract: Background: Durvalumab may improve survival in patients with advanced non-small cell lung cancer (NSCLC) when given as maintenance therapy; nevertheless, further research is required. Durvalumab and other drugs have enhanced survival rates in advanced NSCLC. The optimal therapy combination is uncertain. This trial will evaluate the effectiveness and tolerability of Durvalumab-based combination therapy for advanced NSCLC. Methods: We searched PubMed, Embase, the Cochrane Library, and Web of Science for relevant papers, obtaining information on overall response rate (ORR), median progression-free survival (mPFS), median overall survival (mOS), and adverse events (AEs). Results: 13 studies were included that involved a total of 2,277 participants. The ORR of Durvalumab combination therapy in NSCLC was 41.6%, rising to 47.1% within the radiation or chemotherapy cohort. The mPFS was 5.1 months, while the mOS was 13.5 months. The 1-year progression-free survival (PFS) rate was 49.0%, while the 2-year overall survival (OS) rate was 42.9%. In the radiation and chemotherapy subgroups, these rates rose to 53.4% and 61.1%, respectively. The prevalent adverse responses were anemia (31.3%), nausea (18.9%), and fatigue (18.6%). Conclusions: Our meta-analysis demonstrated that Durvalumab combination treatment is both effective and safe for advanced NSCLC, particularly in patients undergoing combined chemoradiotherapy. These results encourage more Phase III studies. The review agreement is recorded on PROSPERO (CRD42024622471) and is on the NIHR HTA program website.

Keywords: Durvalumab, immune checkpoint inhibitors, NSCLC

Introduction

Non-small cell lung cancer (NSCLC) is the number one cause of cancer-related mortality globally, representing 80%-85% of all lung cancer cases, with advanced NSCLC constituting over 20% of newly diagnosed cases [1, 2]. The standard treatment for advanced cancer has been concurrent chemoradiotherapy (CCRT); however, its 5-year survival rate is approximately 15% to 30%, indicating limited efficacy [3]. Recent clinical studies have shown the effectiveness of immune checkpoint inhibitors (ICIs) in treating advanced NSCLC [4-6]. Since Pacific Research in 2017, significant progress has been made in the integration of immune checkpoint inhibitors with diverse therapeutic modalities, steadily establishing an internationally recognized standard treatment protocol.

Durvalumab is a high-affinity, selective human IgG1 monoclonal antibody that enhances T cell recognition and tumor cell destruction by inhibiting the interaction between programmed cell death ligand-1 (PD-L1), programmed cell death-1 (PD-1), and CD80. The MYSTIC study indicated that the combination of Durvalumab and chemotherapy did not markedly enhance the survival rate of advanced cancer patients, with outcomes comparable to the chemotherapy-only group [7, 8]. The POSEIDON study demonstrated that the combination of Durvalumab

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and trastuzumab with platinum-based chemotherapy is better than chemotherapy alone [9]. The Pacific trial showed that the combination of Durvalumab and 12-month platinum-based chemotherapy is the global standard for stage III unresectable cancer [10-12]. Phase 2 studies in the Pacific region have shown that dulacizumab is significantly beneficial as a neo-adjuvant therapy [13-16]. Exploratory analysis of the MYSTIC trial revealed that the concomitant administration of Durvalumab and trastuzumab improved overall survival (OS) and progression-free survival (PFS) in patients with metastatic NSCLC, with significant enhancements in survival and response rates noted when bTMB surpassed 20 mut/Mb [17-20].

In the past three years, more comparable studies have emerged, and their comprehensive analysis contributed to the preliminary validation of the clinical validity of the randomized controlled trial (RCT) results. This meta-analysis aimed to assess the effectiveness of combination therapy with Durvalumab for the treatment of advanced NSCLC. The potential side effects of Durvalumab combination therapy are a key issue, as balancing efficacy and safety is critical, and our meta-analysis addressed this matter.

Methods

Literature search

We searched Embase, Scopus, PubMed, and the Web of Science up to December 4, 2024. The search strategy incorporated both MeSH terms and free-text words: “Durvalumab” AND (“Non-Small Cell Lung Cancer” OR “Lung Neoplasms” OR “Lung Cancer” OR “Pulmonary Neoplasms” OR “Adenocarcinoma” OR “Squamous Cell Carcinoma”). Searches were limited to publications in the English language. Furthermore, the citations of the listed publications were examined to uncover other pertinent research.

Study selection

Studies matching the following inclusion criteria were included in this meta-analysis: 1) Population: individuals diagnosed with advanced non-small cell lung cancer; 2) Intervention: the patient received Durvalumab combination therapy. Classification of research: prospective intervention studies, retrospective analyses, or RCTs; 3) Result: Clinical tumor outcomes of interest were recorded, embracing objective response rate (ORR), median progression-free survival (mPFS), median overall survival (mOS), one-year progression-free survival rate, one-year overall survival rate, and adverse events (AEs). They employ the Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1 to assess tumor response. They employ the Common Terminology Criteria for Adverse Events (CTCAE) to evaluate the frequency and seriousness of toxic responses. The exclusion criteria were research involving animals, cellular investigations, reviews, meta-analyses, duplicates, case reports, or correspondence.

Data extraction

Two researchers individually extracted data using standard data extraction tables in Microsoft Office Excel, while the other two authors independently checked all obtained data. The extracted information included: (1) demographic data of the study, consisting of the first author’s name, study title, publication year, randomized controlled trial phase, and sample size; (2) combination therapy methodology; and (3) primary outcomes of the study, outlining the safety and efficacy of the drug.

The quality of the included RCTs was assessed using the Jadad scale, while retrospective studies were scored with the Joanna Briggs Patient Series Key Assessment Checklist. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included non-controlled research.

Statistical analysis

This meta-analysis used STATA 14.0 software (StataCorp LP, College Station, TX, United States) for data analysis. The chi-square test and I^2 statistic were used to assess heterogeneity among studies, with *p*-values below 0.1 signifying significant differences. In cases with significant variability ($P < 0.1$ and $I^2 > 50\%$), the study applied a random effects model. A fixed-effects technique was used for situations with diminished variability. Sensitivity analyses were performed to evaluate the robustness and reproducibility of the findings. The possibility of publication bias was assessed using Begg’s and Egger’s tests.

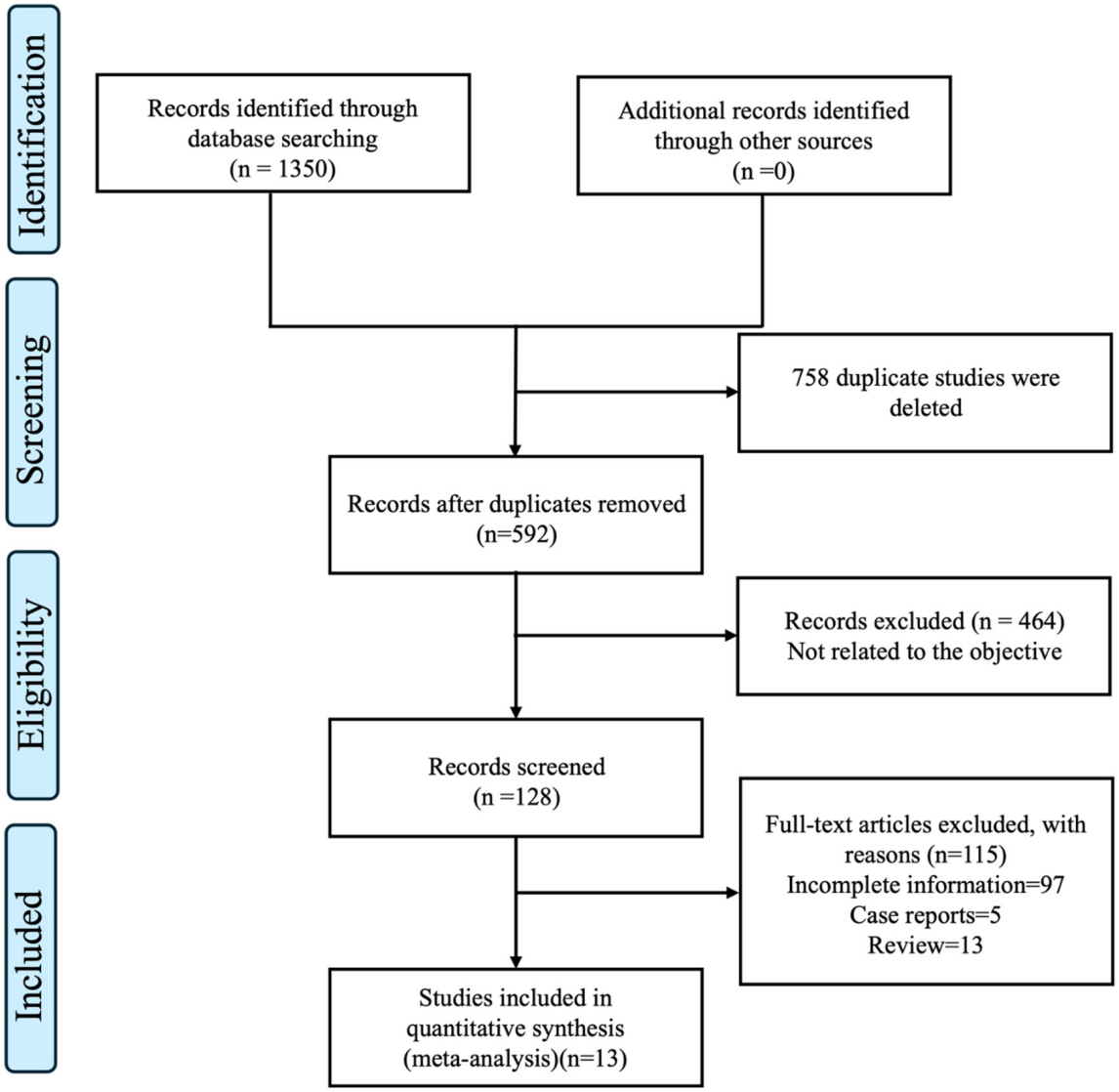


Figure 1. Flow diagram of the meta-analysis for the inclusion/exclusion of studies.

Ethics approval and consent to participate

This meta-analysis was conducted in accordance with the Helsinki Declaration. All participants in the study have signed informed consent forms, and each study has obtained permission from the relevant ethical committee. This study does not necessitate further informed permission, as it employs published data for the meta-analysis.

Results

Study selection

A comprehensive literature review produced 1,350 entries, with 758 identified as duplicates. Titles and abstracts resulted in the exclusion of 464 studies. Out of the remaining 128 papers, 115 were excluded following full-text screening: 97 due to absent data, 5 classified as case reports, and 13 classified as reviews. This meta-analysis included 13 studies with 2,277 patients who matched the inclusion criteria [14, 20-31]. The screening process is depicted in **Figure 1**, and more study data are in **Table 1**.

Study characteristics

The studies included were published from 2021 to 2024. Research was conducted on patients with confirmed advanced squamous and/or

Table 1. Characteristics of the studies included in the meta-analysis

Study ID	Country	Study design	Phase	Groups	Number	Durvalumab dosage	Follow-up (median)
Melissa L Johnson 2022	Global	RCT	III	Durvalumab plus chemotherapy	338	Durvalumab 1500 mg plus chemotherapy q3w for up to 4 cycles followed by Durvalumab 1500 mg q4w	14.75 m
Noriko Kishi 2022	Japan	Retrospective	NA	Durvalumab plus concurrent chemoradiotherapy	136	NA	24.5 months (95% CI: 19.2-30.8)
Gilberto de Castro 2023	Global	RCT	III	Durvalumab plus tremelimumab	410	Duvalumab 20 mg/kg plus 1 mg/kg tremelimumab q4w	4.6 months (95% CI: 0.1-41.1)
John V Heymach 2023	Global	RCT	III	Durvalumab plus concurrent chemoradiotherapy	366	Durvalumab 1500 mg plus chemotherapy q3w	11.7 months (95% CI: 0-46.1)
Natasha B. Leighl 2022	Global	RCT	II	Durvalumab plus tremelimumab	150	Durvalumab 1500 mg q4w plus 75 mg tremelimumab q4w	11.7 months (95% CI: 0.03-25)
Roy S Herbst 2022 1	Global	RCT	II	Durvalumab plus oleclumab	60	Durvalumab 1500 mg q4w plus oleclumab 3000 mg q2w	11.7 months (95% CI: 0.4-23.4)
Roy S Herbst 2022 2	Global	RCT	II	Durvalumab plus monalizumab	62	Durvalumab 1500 mg q4w plus monalizumab 750 mg q2w	11.7 months (95% CI: 0.4-23.4)
Myung-Ju Ahn 2022	Global	RCT	II	Durvalumab plus oleclumab	134	Durvalumab 1500 mg q4w plus oleclumab 3000 mg q2w	9.6 months (95% CI: 0-18.6)
Motoko Tachihara 2023	Japan	Single-arm	II	Durvalumab plus radiotherapy	35	Duvalumab 10 mg/kg plus q2w plus radiotherapy	22.8 months (95% CI: 4.3-31.8)
Nasser K Altorki 2021	America	Single-arm	NA	Durvalumab plus radiotherapy	30	Durvalumab 1120 mg q4w plus radiotherapy	16.9 months (95% CI: 8.3-27.7)
Michael Offin 2021	America	Retrospective	NA	Durvalumab plus chemoradiotherapy	62	NA	12 months
Naiyer A. Rizvi 2020	Global	RCT	III	Durvalumab plus tremelimumab	163	Duvalumab 20 mg/kg plus 1 mg/kg tremelimumab q4w	30.2 months (95% CI: 0.3-37.2)
Johnson, ML 2023	America	Prospective	II	Durvalumab plus mocetinostat	63	Durvalumab 1500 mg q4w plus mocetinostat 70 mg q3w	NA
Benjamin Besse 2024 1	America	Prospective	NA	Durvalumab plus ceralasertib	79	NA	28.2 months
Benjamin Besse 2024 2	America	Prospective	NA	Durvalumab plus olaparib/danvatirsen/oleclumab	189	NA	28.2 months

RCT: randomized controlled trial.

non-squamous forms of NSCLC. The chemotherapy regimen comprised pemetrexed, paclitaxel, or docetaxel, administered with or without platinum-based drugs (carboplatin or cisplatin). The ages of the participants varied from 27 to 88 years (**Table 2**).

Quality assessment

Two single-arm studies and two prospective studies were evaluated using the NOS, which includes criteria for research group selection, intergroup comparability, and exposure levels in cohort or case-control studies, assessed against eight standards. Two retrospective studies utilized the Joanna Briggs Institute Case Series Critical Assessment Checklist to evaluate eleven domains of methodological quality, including case selection, illness description, and clarity of case details. Seven randomized controlled trials were evaluated using the Jadad scale, concentrating on randomization, blinding, and the handling of absent follow-up data. **Table 3** provides detailed information regarding these quality ratings.

Newcastle-Ottawa Scale (NOS) for non-randomized studies

The numbers Q1-Q8 in the heading signs were as follows: 1, representative of the exposed cohort; 2, representative of the nonexposed cohort; 3, representative of the exposed cohort; 4, representative of the outcome of interest was present at the start of the study; 5, representative of the cohorts on the basis of the design or analysis; 6, representative of the cohort assessment; and 7, long enough for outcomes to occur; 8, adequacy of follow-up of cohorts.

JADAD scale for reporting randomized controlled trials

Numbers Q1-Q4 in heading signified: Q1: Was the study described as randomized? Q2: Was the method of randomization appropriate (e.g., computer-generated random numbers)? Q3: Was the study described as double-blind? Q4: Was there a description of withdrawals and dropouts?

JBI critical appraisal checklist for patient series for included retrospective studies

Numbers Q1-Q10 indicated the following inquiries. Q1, were criteria for inclusion in the case series clearly defined? Q2, was the condition assessed in a consistent, reliable manner for all participants in the case series? Q3, were reliable methods utilized for identifying the condition in all case series participants? Q4, did the case series include participants consecutively? Q5, was participant inclusion in the case series complete? Q6, were participant demographics in the study reported with clarity? Q7, was clinical information of the participants clearly reported? Q8, were case outcomes or follow-up findings clearly documented? Q9, was demographic information of the presenting site(s)/clinic(s) clearly documented? Q10, was the statistical analysis conducted appropriately?

Tumor response

All trials included in this analysis evaluated the efficacy of Durvalumab in combination with immunotherapy, chemotherapy, radiation, or chemoradiotherapy for the treatment of NSCLC. The observed differences in ORR among these trials are significant, ranging from 30.0% to 53.3%. In light of the minimal heterogeneity observed among studies (I^2 = 14.1%, P = 0.323), a fixed effects model was employed for the meta-analysis. The analysis indicates that the combined ORR is 41.6% (95% CI: 37.6%-45.6%). Utilizing the RCT research method for further stratification of findings revealed that the ORR for NSCLC patients in RCT studies was 40.4% (95% CI: 36.0%-44.7%). Conversely, among non-RCT NSCLC patients, the ORR is 48.9% (95% CI: 38.5%-59.2%). The findings are illustrated in **Figure 2**.

Survival

The study used a random-effects model (I^2 = 91.3%, P < 0.001) and (I^2 = 82.3%, P < 0.001), resulting in a pooled mPFS of 5.1 months (95% CI: 4.0-6.3, I^2 = 91.3%, P < 0.001, **Figure 3A**) and a pooled mOS of 13.5 months (95% CI: 11.1-15.9, I^2 = 82.3%, P < 0.001, **Figure 3B**). Following stratification based on the use of the RCT methodology, the mPFS and mOS for NSCLC patients in RCT studies were 5.7 months (95% CI: 4.7-6.7, I^2 = 78.3%, P < 0.001, **Figure 3A**) and 13.5 months (95% CI: 11.5-15.4, I^2 = 42.4%, P = 0.157, **Figure 3B**), respectively. Conversely, the mPFS and mOS for NSCLC patients in non-RCT studies were 3.7 months (95% CI: 2.2-5.3, I^2 = 88.0%, P < 0.001, **Figure 3A**) and 13.8 months (95% CI: 8.2-19.3,

Table 2. Raw data of the included studies

Study ID	Group	Number	Male (%)	Age (median)	Smoking			ECOG performance status			Tumor stage					Histopathology			
					Former	Current	Never	0	1	2	IIIA	IIIB	IIIC	IVA	IVB	SCC	ADC	ASC	Others
Melissa L Johnson 2022	Durvalumab plus chemotherapy	338	253 (74.9)	64.5 (32-87)	190 (56.2)	64 (18.9)	84 (24.9)	109 (32.2)	229 (67.8)	0	NA	NA	NA	170 (50.3)	167 (49.4)	128 (37.9)	209 (61.8)		1 (0.3)
Noriko Kishi 2022	Durvalumab plus concurrent chemoradiotherapy	136	111 (81.6)	70.0 (64-75)	117 (86.0)		19 (14.0)	87 (64.0)	43 (31.6)	6 (4.4)	57 (41.9)	68 (50.0)	11 (8.1)	0	0	55 (40.4)	62 (45.6)	19 (14.0)	
Gilberto de Castro 2023	Durvalumab plus tremelimumab	410	297 (72.4)	63.0 (27-83)	200 (48.8)	138 (33.7)	72 (17.6)	159 (38.8)	251 (61.2)	0	NA	NA	NA	NA	NA	166 (40.5)	244 (59.5)		
John V Heymach 2023	Durvalumab plus concurrent chemoradiotherapy	366	252 (68.9)	65.0 (30-88)	220 (60.1)	95 (26.0)	51 (13.9)	251 (68.6)	115 (31.4)	0	173 (47.3)	88 (24.0)	NA	NA	NA	169 (46.2)	196 (53.6)		
Natasha B. Leighl 2022	Durvalumab plus tremelimumab	150	81 (54.0)	63.0 (38-87)	101 (67.4)	35 (23.3)	14 (9.3)	45 (30.0)	105 (70.0)	0	NA	NA	NA	45 (30.0)	105 (70.0)	27 (18.0)	123 (82.0)		
Roy S Herbst 2022 1	Durvalumab plus oleclumab	60	42 (70.0)	65.0 (37-83)	54 (90.0)		6 (10.0)	33 (55.9)	26 (44.1)	1 (1.7)	27 (45.0)	29 (48.3)	4 (6.7)	NA	NA	24 (40.0)	36 (60)		
Roy S Herbst 2022 2	Durvalumab plus monalizumab	62	42 (67.7)	65.0 (44-87)	59 (95.2)		3 (4.8)	27 (44.3)	34 (55.7)	1 (1.6)	32 (51.6)	27 (43.5)	3 (4.8)	NA	NA	27 (43.5)	35 (56.5)		
Myung-Ju Ahn 2022	Durvalumab plus oleclumab	134	98 (73.1)	67.0 (24-84)	109 (81.3)		25 (18.7)	52 (38.8)	81 (60.4)	1 (0.7)	NA	NA	NA	NA	NA	58 (43.3)	76 (56.7)		
Motoko Tachihara 2023	Durvalumab plus radiotherapy	35	31 (88.6)	72.0 (44-83)	16 (45.7)	18 (51.4)	1 (2.9)	19 (54.3)	16 (45.7)	0	16 (45.7)	7 (20.0)	3 (8.6)	NA	NA	15 (42.9)	19 (54.3)	1 (2.9)	
Nasser K Altorki 2021	Durvalumab plus radiotherapy	30	15 (50.0)	70.0 (64-74)	10 (33.0)	16 (53.0)	4 (13.0)	23 (77.0)	7 (23.0)	0	12 (40.0)	NA	NA	NA	NA	12 (40.0)	18 (60.0)	0	0
Michael Offin 2021	Durvalumab plus chemoradiotherapy	62	36 (58.0)	66.0 (49-86)	60 (97.0)		2 (3.3)	33 (53.0)	29 (47.0)	0	17 (27.0)	33 (53.0)	12 (19.0)	0	0	19 (31.0)	36 (58.0)	7 (11.0)	
Naiyer A. Rizvi 2020	Durvalumab plus tremelimumab	163	118 (72.4)	65.0 (34-87)	96 (58.9)	42 (25.8)	25 (15.3)	65 (39.9)	98 (60.1)	0	NA	NA	NA	NA	NA	53 (32.5)	110 (67.5)		
Johnson, ML 2023	Durvalumab plus mocetinostat	63	33 (52.4)	68.0 (27-88)	55 (87.3)	18 (22.8)	8 (12.7)	16 (25.4)	47 (74.6)	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
Benjamin Besse 2024 1	Durvalumab plus ceralasertib	79	52 (65.8)	63.0 (42-80)	52 (65.8)		9 (11.4)	28 (35.4)	51 (64.6)	0	NA	NA	NA	NA	NA	55 (69.6)	19 (24.1)	5 (6.3)	
Benjamin Besse 2024 2	Durvalumab plus olaparib/danvatirsen/oleclumab	189	103 (54.5)	64.0 (35-85)	138 (73.0)	23 (12.2)	28 (14.8)	64 (34.0)	123 (65.4)	1 (0.5)	NA	NA	NA	NA	NA	43 (22.8)	131 (69.3)	15 (7.9)	

SCC: squamous cell carcinoma; ADC: adenocarcinoma; ASC: adenosquamous carcinoma; ECOG: Eastern Cooperative Oncology Group; NA: not available.

Table 3. Quality assessment of the studies included in the meta-analysis

JBI Critical Appraisal Checklist for Case Series for included retrospective studies											
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	TOTAL
Noriko Kishi 2022	2	0	2	2	2	0	2	2	2	2	16
Michael Offin 2021	2	0	2	2	2	0	2	2	2	2	16
Newcastle-Ottawa Scale (NOS) for non-randomized studies											
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8			
Motoko Tachihara 2023	1	0	1	1	0	1	0	1			5
Nasser K Altorki 2021	1	0	1	1	0	1	0	1			5
Benjamin Besse 2024	1	0	1	1	0	1	0	1			5
Johnson, ML 2023	1	0	1	1	0	1	0	1			5
Modified JADAD Scale for Reporting Randomized Controlled Trials											
Study	Q1	Q2	Q3	Q4							
Melissa L Johnson 2022	2	2	2	1							7
Gilberto de Castro 2023	2	2	2	1							7
John V Heymach 2023	2	2	2	1							7
Natasha B. Leighl 2022	2	2	2	1							7
Roy S Herbst 2022	2	2	2	1							7
Myung-Ju Ahn 2022	2	2	2	1							7
Naiyer A. Rizvi 2020	2	2	2	1							7

I^2 = 91.7%, P < 0.001, **Figure 3B**), respectively. Additionally, the one-year PFS rate and two-year OS rate, as per the random effects model, were 49.0% (95% CI: 27.9%-70.1%, I^2 = 97.4%, P < 0.001, **Figure 3C**) and 42.7% (95% CI: 27.2%-58.1%, I^2 = 93.6%, P < 0.001, **Figure 3D**), respectively. RCTs indicated a two-year OS rate of 28.0% (95% CI: 24.3%-31.8%, I^2 = 0.0%, P = 0.612, **Figure 3D**) and a one-year PFS rate of 30.7% (95% CI: 26.2%-35.2%, I^2 = 21.4%, P = 0.280, **Figure 3C**). The non-RCT indicated a rate of 68.8% (95% CI: 59.3%-78.3%, I^2 = 0.0%, P = 0.466, **Figure 3D**) and 76.9% (95% CI: 61.6%-92.2%, I^2 = 82.7%, P = 0.016, **Figure 3C**).

Subgroup analysis comparing combination therapies

This subgroup analysis analyzed the effects of several combination therapies on critical efficacy measures in NSCLC patients, including ORR, one-year PFS rate, and two-year OS rate.

The meta-analysis of ORR (**Figure 4**) indicated that within the chemoradiotherapy subgroup, individual research effect sizes varied from 43.3% to 53.3%, yielding a combined estimate of 47.1% (95% CI: 36.8%-57.4%), and demonstrating a substantial tumor decrease in 47.1% of patients. This subgroup had minimal heterogeneity (I^2 = 0.0%, P = 0.356), signifying consistency throughout the investigations. The non-chemoradiotherapy subgroup had individual effect sizes of 30.0% and 46.2%, yielding a combined estimate of 40.7% (95% CI: 36.3%-45.0%), indicating an average response rate of 40.7%. This subgroup exhibited minimal heterogeneity (I^2 = 17.9%, P = 0.301). No significant general heterogeneity was seen across subgroups (P = 0.262), and the aggregated ORR was 41.6% (95% CI: 37.6%-45.6%), demonstrating substantial effectiveness for both approaches, with a marginal benefit for chemoradiotherapy.

In the examination of the one-year PFS rate (**Figure 5A**), the chemoradiotherapy subgroup exhibited effect estimates of 24.4%, 72.1%, and 65.0%, with 95% confidence intervals outside 1, suggesting potential significance. The cumulative effect was 53.4% (95% CI: 18.7%-88.1%). The non-chemoradiotherapy category, including two trials, exhibited values of 25.6% and 25.8%, with 95% confidence intervals encompassing 1, signifying no significant difference. The aggregate impact for this subgroup was 25.7% (95% CI: 19.9%-31.6%). Substantial heterogeneity was noted among subgroups (P < 0.001), yielding an overall combined effect of 41.7% (95% CI: 25.2%-58.1%) and considerable heterogeneity (I^2 = 94.4%).

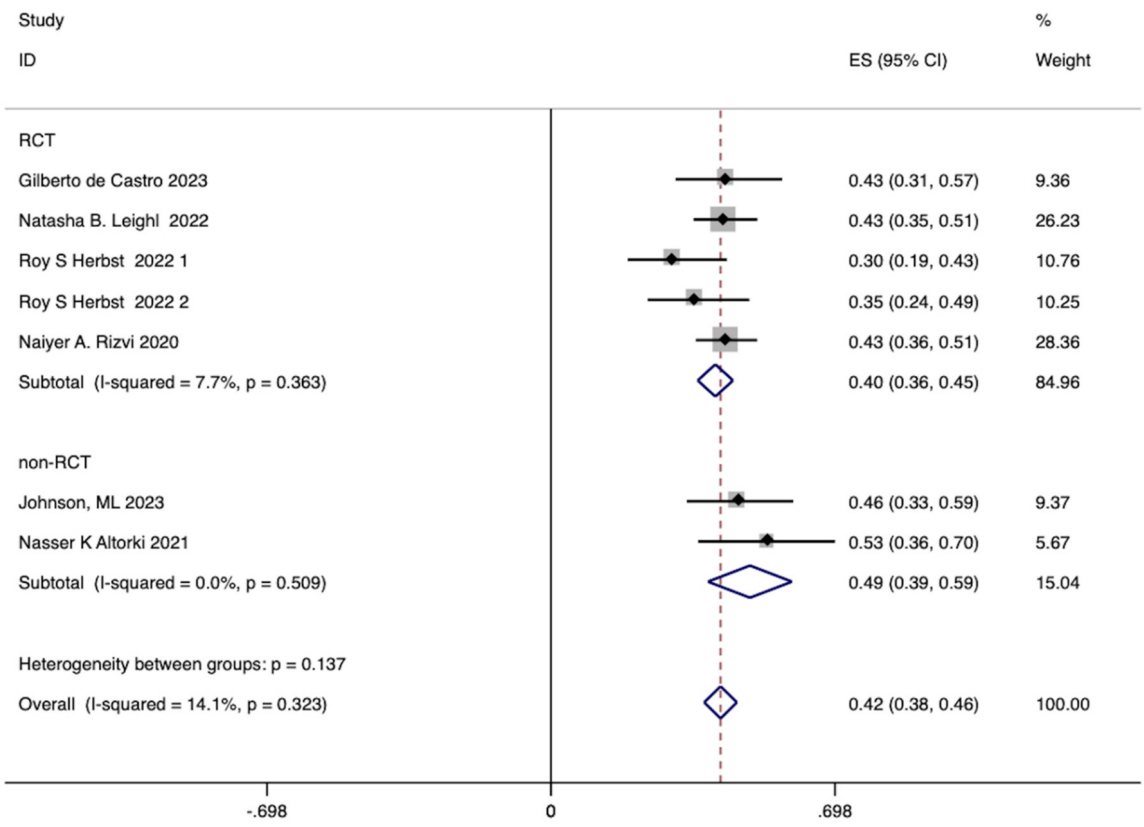


Figure 2. Forest plot of the pooled ORR. ORR, overall response rate.

The two-year OS rate analysis (**Figure 5B**) revealed that the chemoradiotherapy subgroup exhibited effect estimates between 29.6% and 85.0%, with a pooled effect of 61.1% (95% CI: 26.2%-96.1%), suggesting possible statistical significance. The non-chemoradiotherapy category, including two investigations, yielded values of 26.1% and 35.4%, with 95% confidence intervals encompassing 1, suggesting no significant difference. The aggregate impact for this subgroup was 31.5% (95% CI: 22.4%-40.5%). Substantial heterogeneity was observed among subgroups ($P < 0.001$), yielding an overall composite effect of 49.0% (95% CI: 27.9%-70.1%) and considerable heterogeneity ($I^2 = 97.4\%$).

Toxicities

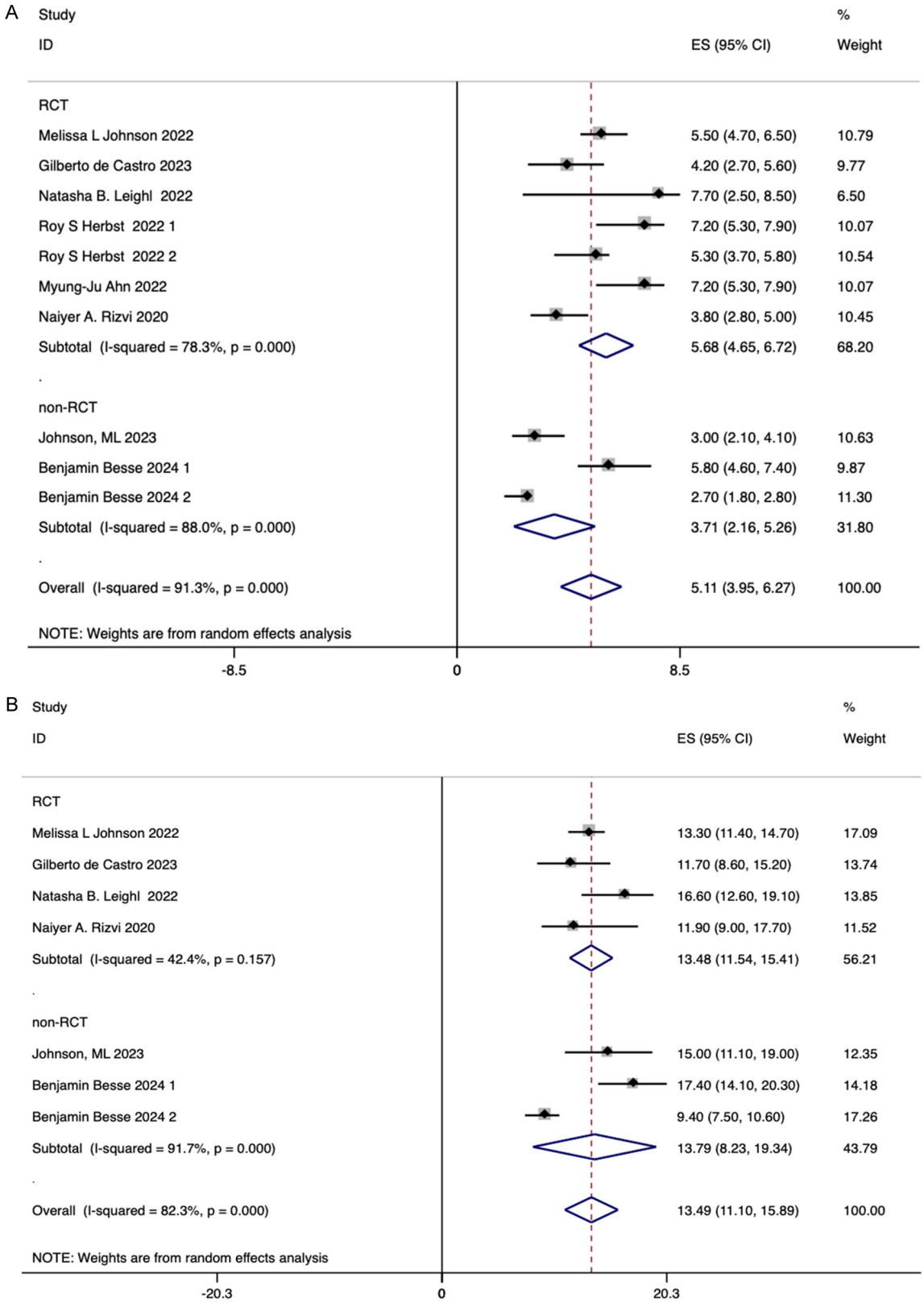
The prevalent adverse events linked to Durvalumab combination treatment for advanced non-small cell lung cancer are shown in **Table 4**. Adverse events of Grade 1-2 were the most prevalent and well-tolerated. The main adverse events were anemia (31.3%, 95% CI: 11.6%-50.9%), nausea (18.9%, 95% CI: 12.9%-25.0%), and fatigue (18.6%, 95% CI: 13.9%-23.3%). Adverse events of grade 3 or higher were few, with anemia (7.4%, 95% CI: 2.5%-12.3%), neutropenia (5.5%, 95% CI: 0.6%-10.4%), and fatigue (2.1%, 95% CI: 0.2%-3.9%) being the most common. The occurrence of adverse events resulting in mortality was 2.1% (95% CI: 0.2%-3.9%).

Sensitivity analysis

A sensitivity analysis was conducted by methodically excluding one study at a time to assess its impact on the aggregated results. The results demonstrated that the exclusion of a single investigation did not significantly affect the overall findings or their 95% confidence intervals, thereby confirming the robustness of the meta-analysis results (**Figure 6**).

Publication bias

Both Egger's and Begg's tests were applied to the meta-analysis in order to assess publica-


A
Study
ID
ES (95% CI)
%
Weight
RCT
Melissa L Johnson 2022
5.50 (4.70, 6.50)
10.79
Gilberto de Castro 2023
4.20 (2.70, 5.60)
9.77
Natasha B. Leighl 2022
7.70 (2.50, 8.50)
6.50
Roy S Herbst 2022 1
7.20 (5.30, 7.90)
10.07
Roy S Herbst 2022 2
5.30 (3.70, 5.80)
10.54
Myung-Ju Ahn 2022
7.20 (5.30, 7.90)
10.07
Naiyer A. Rizvi 2020
3.80 (2.80, 5.00)
10.45
Subtotal (I-squared = 78.3%, p = 0.000)
5.68 (4.65, 6.72)
68.20
non-RCT
Johnson, ML 2023
3.00 (2.10, 4.10)
10.63
Benjamin Besse 2024 1
5.80 (4.60, 7.40)
9.87
Benjamin Besse 2024 2
2.70 (1.80, 2.80)
11.30
Subtotal (I-squared = 88.0%, p = 0.000)
3.71 (2.16, 5.26)
31.80
Overall (I-squared = 91.3%, p = 0.000)
5.11 (3.95, 6.27)
100.00
NOTE: Weights are from random effects analysis
-8.5
0
8.5
B
Study
ID
ES (95% CI)
%
Weight
RCT
Melissa L Johnson 2022
13.30 (11.40, 14.70)
17.09
Gilberto de Castro 2023
11.70 (8.60, 15.20)
13.74
Natasha B. Leighl 2022
16.60 (12.60, 19.10)
13.85
Naiyer A. Rizvi 2020
11.90 (9.00, 17.70)
11.52
Subtotal (I-squared = 42.4%, p = 0.157)
13.48 (11.54, 15.41)
56.21
non-RCT
Johnson, ML 2023
15.00 (11.10, 19.00)
12.35
Benjamin Besse 2024 1
17.40 (14.10, 20.30)
14.18
Benjamin Besse 2024 2
9.40 (7.50, 10.60)
17.26
Subtotal (I-squared = 91.7%, p = 0.000)
13.79 (8.23, 19.34)
43.79
Overall (I-squared = 82.3%, p = 0.000)
13.49 (11.10, 15.89)
100.00
NOTE: Weights are from random effects analysis
-20.3
0
20.3

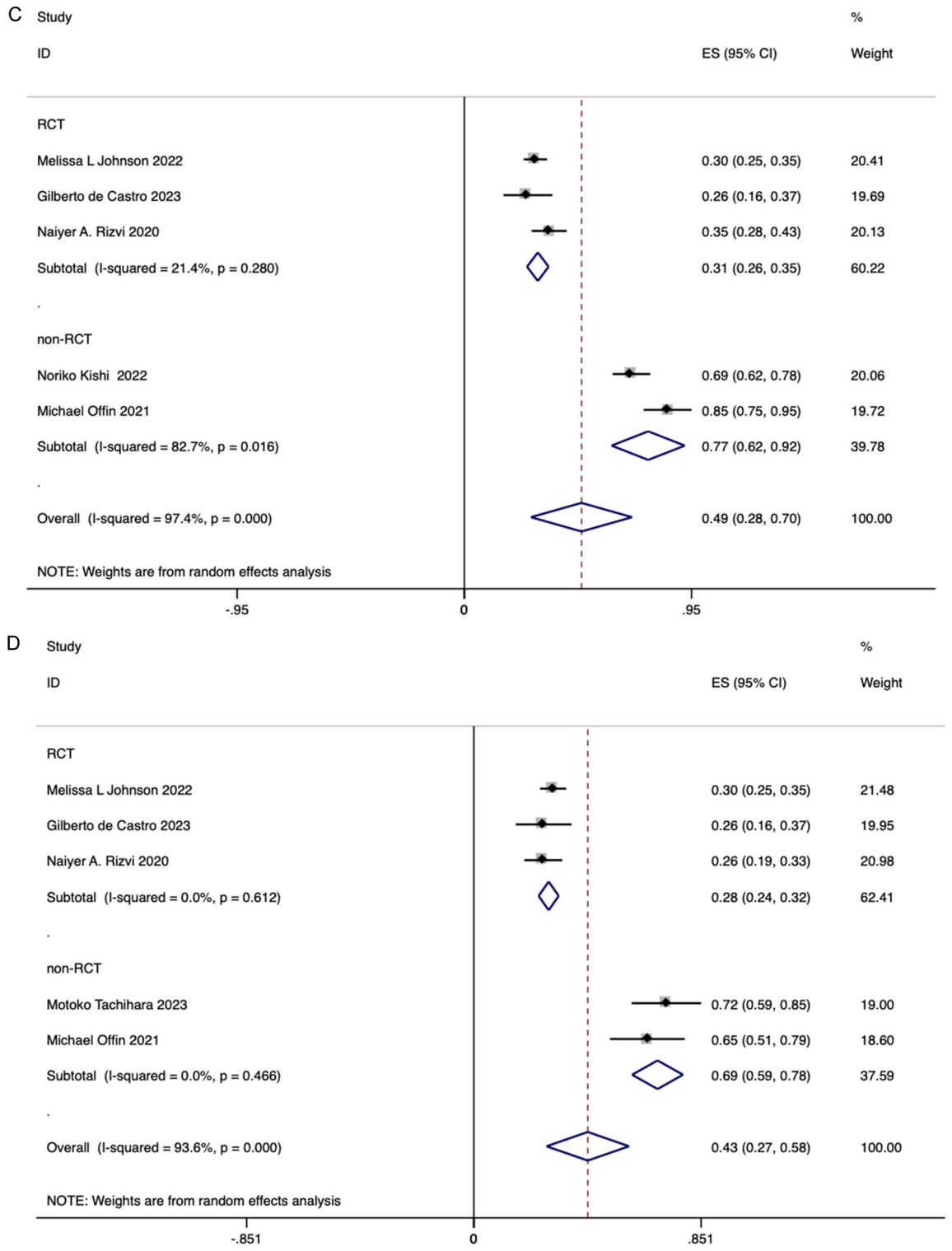


Figure 3. Forest plot of the pooled results for mPFS (A), mOS (B), one-year PFS (C), two-year OS (D) according to treatment regimen. OS, overall survival; PFS, progression-free survival; mPFS, median progression-free survival; mOS, median overall survival.

tion bias. The evaluation outcomes revealed that for the RECIST 1.1 criteria, no significant publication bias was detected in the assessment of ORR (P = 0.932 for Egger's test and

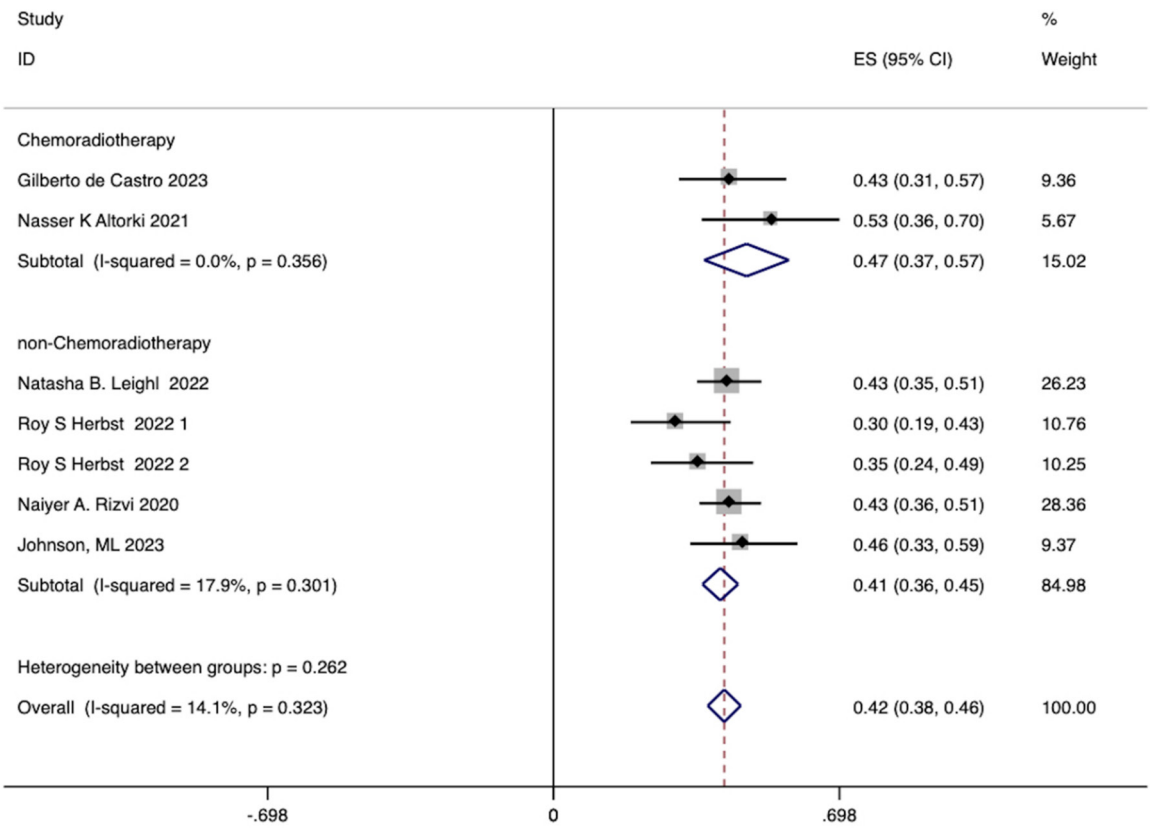


Figure 4. Forest plot of the pooled ORR based on various treatment methods. ORR, overall response rate.

P = 0.548 for Begg's test), mOS (*P* = 0.195 for Egger's test and *P* = 1.000 for Begg's test), one-year PFS rate (*P* = 0.198 for Egger's test and *P* = 0.462 for Begg's test), two-year OS rate (*P* = 0.353 for Egger's test and *P* = 0.462 for Begg's test), AEs (*P* = 0.136 for Egger's test and *P* = 0.244 for Begg's test) and AEs graded 3 or higher (*P* = 0.225 for Egger's test and *P* = 1.000 for Begg's test). No significant publication bias was observed as mentioned above. Despite this, upon scrutinizing the occurrence of severe mPFS, a notable publication bias was identified, mPFS (*P* = 0.010 for Egger's test and *P* = 0.531 for Begg's test). The potential variability of mPFS results may lead to publication bias, which may be due to differences in study design, patient characteristics, or treatment regimens.

Discussion

The efficacy of immune checkpoint inhibitors (ICIs) for controlling advanced NSCLC is based on their ability to alter the tumor microenvironment by blocking the PD-1/PD-L1 pathway, a vital method of immune evasion used by cancer cells. By inhibiting this connection, immune checkpoint inhibitors reinstate T cell-mediated anticancer immunity, resulting in improved tumor cell identification and destruction. This molecular process results in clinically meaningful enhancements in ORR, PFS, and OS. Recent trials, including AEGEAN, CheckMate-816, IMpower010, KEYNOTE-091, Neotorch, and KEYNOTE-671, have confirmed the benefits of immunotherapy as a neoadjuvant treatment in combination with chemotherapy, adjuvant therapy, or both for NSCLC [32-36]. The PACIFIC research demonstrated the efficacy of Durvalumab after chemo-radiotherapy in NSCLC, highlighting extended OS benefits and sustained improvements in progression-free survival. At five years, the OS rate was 42.9% with Durvalumab (95% CI: 38.2%-47.4%) versus 33.4% for placebo (95% CI: 27.3%-39.6%). The PFS rate was 33.1% with Durvalumab (95% CI: 28.0%-38.2%) against 19.0% for placebo (95% CI: 13.6%-25.2%). The stratified hazard ratio for OS was 0.72 (95% CI: 0.59-0.89), with a mOS of 47.5 months against 29.1 months in

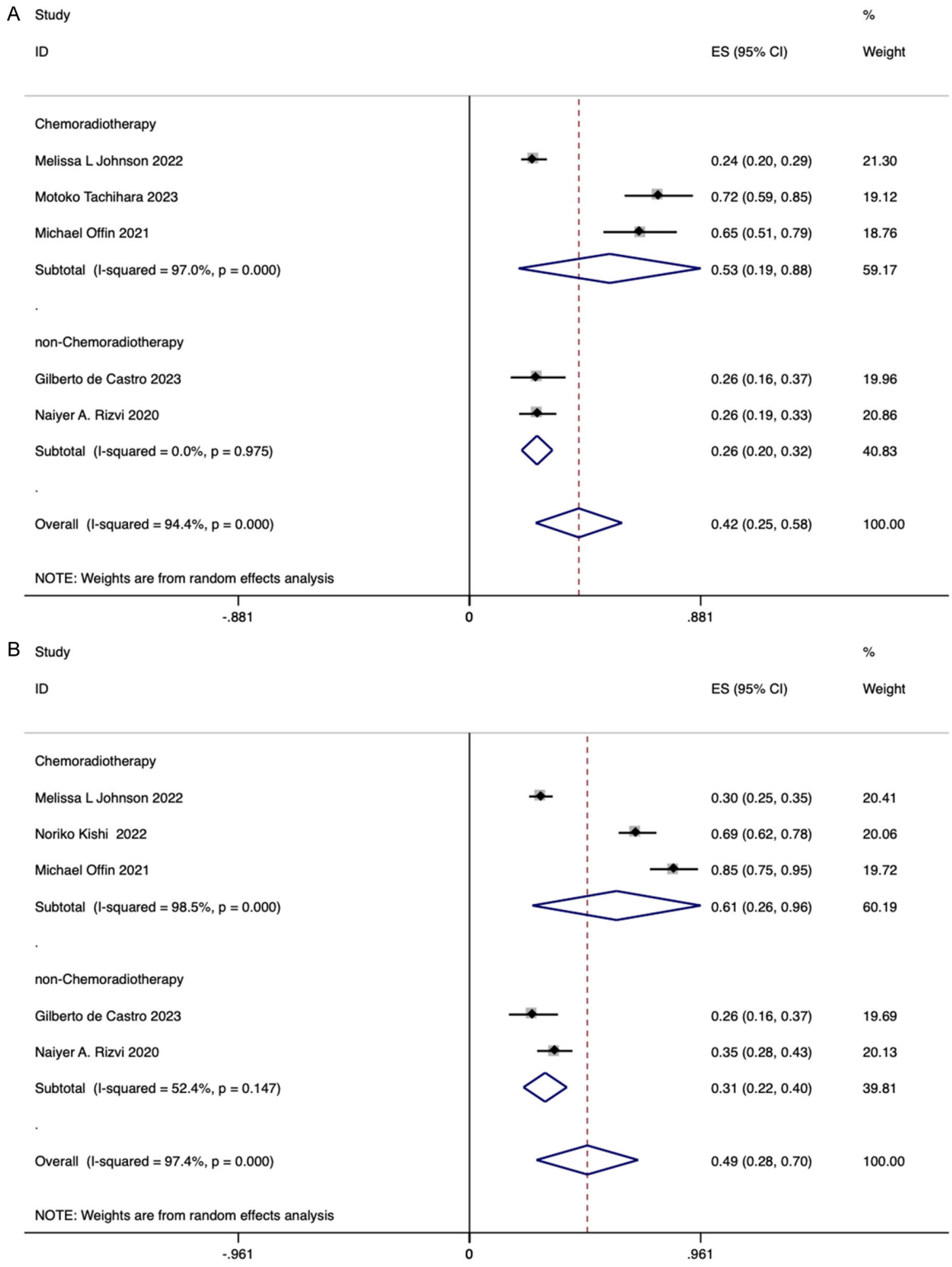


Figure 5. Forest plot of the pooled results for one-year PFS rate (A) and two-year OS rate (B) according to different treatment methods. PFS, progression-free survival; OS, overall survival.

the placebo cohort. The PFS was improved, exhibiting a median of 16.9 months in contrast to 5.6 months in the placebo group 0.55 (95% CI: 0.45-0.68). These findings highlight

Table 4. Adverse events in the studies included in the meta-analysis

AEs	All grade		≥ Grade III	
	ES, % (95% CI)	I^2, %	ES, % (95% CI)	I^2, %
Fatigue	18.6	89.6	2.1	76.5
Anemia	31.3	98.9	7.4	87.2
Nausea	18.9	94.4	0.3	0.0
Neutropenia	8.9	97.1	5.5	95.0
Decreased appetite	12.7	82.0	0.7	0.0
Thrombocytopenia	6.7	91.8	1.9	74.2
Vomiting	10.9	90.3	0.4	0.0
Alanine aminotransferase increased	8.3	76.2	1.2	62.3
Diarrhea	14.0	71.6	1.6	57.1
Constipation	6.5	92.4	NA	NA
Rash	14.2	80.6	0.8	18.8
Hypothyroidism	10.1	75.0	NA	NA
Asthenia	7.5	62.9	NA	NA
Pruritis	12.8	66.0	0.4	0.0
Alopecia	7.9	97.1	NA	NA
Fatal	3.3	55.4	NA	NA
All	89.6	97.1	36.8	92.9

AEs: adverse events.

Durvalumab's potential as a significant therapeutic advancement post-chemoradiotherapy. Although RCTs serve as the gold-standard method for generating evidence about improvements to routine care, they frequently do not accurately represent real-world clinical practice because of their restrictive inclusion criteria and relevance following regulatory approval. It is imperative to employ empirical evidence and research to substantiate the benefits or risks of innovative medical products [37]. This article provides a comprehensive review and meta-analysis of the existing evidence about the efficacy and safety of Durvalumab combination therapy in advanced NSCLC.

This meta-analysis clarifies the efficacy outcomes of Durvalumab combination therapy as a robust treatment modality, evidenced by ORR, mPFS, mOS, one-year PFS rate, and two-year OS rate. These findings address an absence in previous research that has not conclusively demonstrated the full potential of this method. The combined treatment demonstrated significant efficacy, yielding a pooled ORR of 41.6% (95% CI: 37.6%-45.6%). The mPFS and mOS for the combined therapy group were 5.1 months (95% CI: 4.0-6.3) and 13.5 months (95% CI: 11.1-15.9), respectively.

The findings demonstrate that Durvalumab combination therapy is more effective than monotherapy. In the COAST trial, the overall response rate for Durvalumab monotherapy was 17.9% (95% CI: 9.6%-29.2%) [23]. Initial findings indicated that the combination of Olanumab or Monozolizumab with Durvalumab provides enhanced therapeutic advantages, increasing ORR and extending PFS vs. Durvalumab monotherapy. The PFS curve demonstrates an initial separation effect that persists for around 2-4 months until the conclusion of the research [38-42]. This study revealed that combination therapy achieved an ORR of 41.6%, underscoring its synergistic effect in NSCLC. This research presents compelling clinical data for Durvalumab combination therapy in NSCLC, indicating a markedly enhanced ORR relative to current monotherapies and establishing it as a viable therapeutic standard.

Notable disparities were found in the effectiveness of different combination treatments. The chemoradiotherapy subgroup exhibited an ORR of 47.1% and a one-year PFS rate of 53.4%, significantly surpassing the 17.9% and 33.9% observed in the COAST study [23]. This significant enhancement indicated that the combination of Durvalumab with chemoradiotherapy

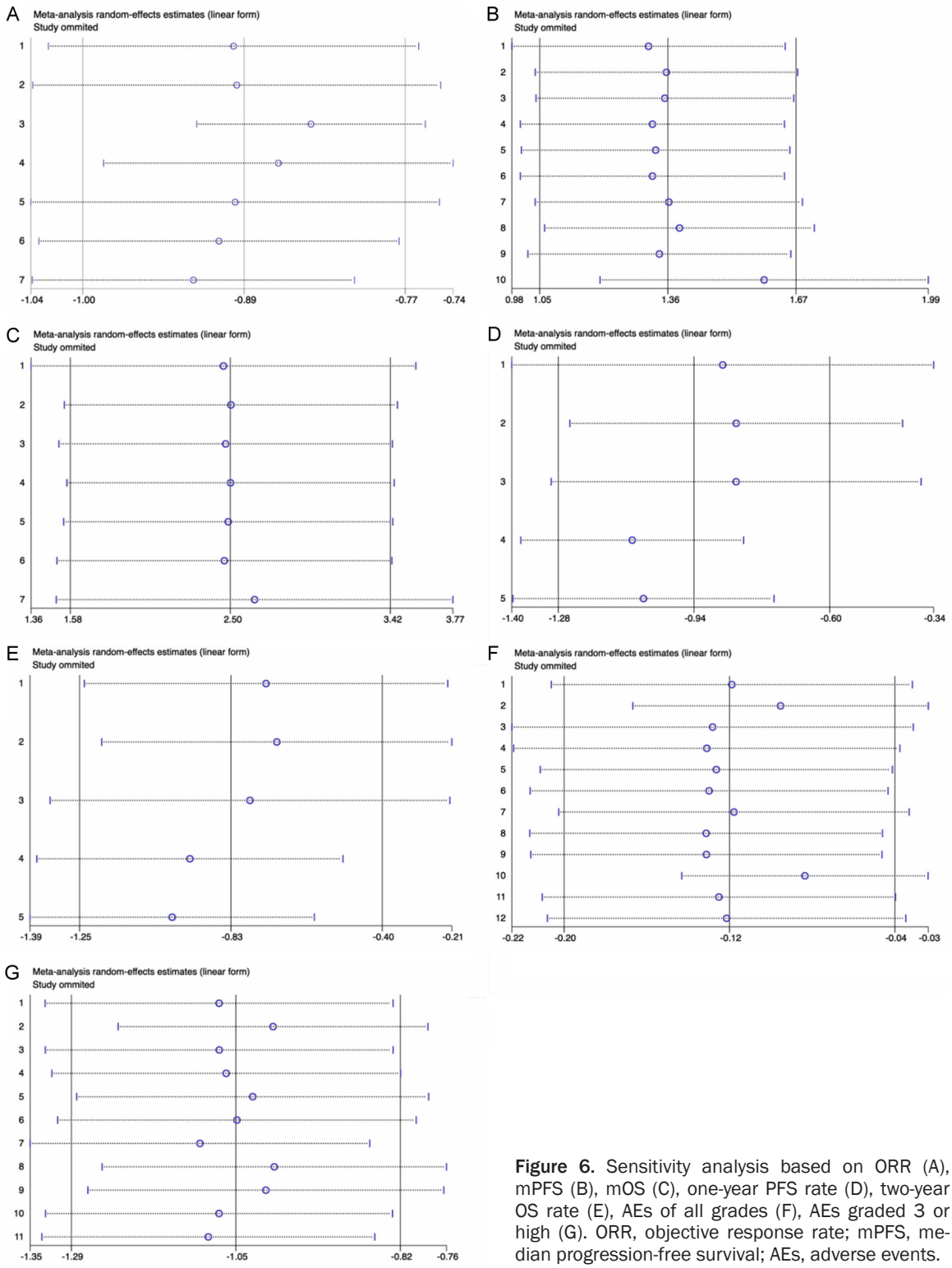


Figure 6. Sensitivity analysis based on ORR (A), mPFS (B), mOS (C), one-year PFS rate (D), two-year OS rate (E), AEs of all grades (F), AEs graded 3 or high (G). ORR, objective response rate; mPFS, median progression-free survival; AEs, adverse events.

may markedly increase treatment effectiveness. The observed advantages are probably attributable to the combined effect of localized tumor management from chemoradiotherapy and systemic immune stimulation from immunotherapy. Conversely, the non-chemoradiotherapy subgroup had an ORR of 40.7% and a one-year PFS rate of 25.7%. Notwithstanding

Table 5. AEs for subgroups and PACIFIC-6

AEs	All grade ES, % (95% CI)			*p*
	Chemotherapy	non-Chemotherapy	PACIFIC-6	
Fatigue	20.2	18.2	20.5	0.54
Nausea	22.1	17.7	13.7	0.63
Decreased appetite	14.7	12.1	10.3	0.92
Vomiting	10.1	11.4	6.8	0.75
Alanine aminotransferase increased	9.9	4.5	5.1	0.88
Diarrhea	10.0	12.2	16.2	0.60
Constipation	11.2	4.6	17.1	0.06
Rash	11.6	15.5	11.1	0.63
Pruritis	13.4	11.0	17.9	0.61
Fatal	3.8	2.6	1.7	0.69
AEs ≥ Grade III	40.3	34.0	18.8	0.63
All Grade	95.8	86.4	96.5	0.26

AEs: adverse events.

the enhancement in ORR, the PFS rate did not surpass the results obtained in the COAST study. This discrepancy may have arisen from various factors, including diminished sample sizes and differences in patient selection criteria. The COAST trial, featuring a larger cohort and varied patient characteristics, may have provided a more thorough assessment of long-term outcomes. Furthermore, variations in treatment protocols, duration of follow-up, and criteria for advancement between studies may explain these differences. These findings call for further validation through more investigations. Future research must address these deficiencies by conducting large-scale randomized controlled trials with standardized treatment methods and extended follow-up periods.

Due to the relatively recent development of the combination therapy with Durvalumab, fear of heightened side effects persists. It is essential to balance efficacy and safety when integrating Durvalumab with other treatments. The cumulative incidence rate for all levels of AEs was 89.6%. Common full-grade adverse effects include anemia (31.3%), nausea (18.9%), fatigue (18.6%), rash (14.2%), diarrhea (14.0%), pruritis (12.8%), decreased appetite (12.7%), vomiting (10.9%), and hypothyroidism (10.1%). The incidence rate of grade 3 AEs was 36.8%, with anemia (7.4%), neutropenia (5.5%), fatigue (2.1%), thrombocytopenia (1.9%), diarrhea (1.6%), and increased alanine aminotransferase (1.2%) being the most common. Overall, our meta-analysis underscores the safety of combination therapy with Durvalumab in advanced cancer. Although the incidence of grade 1-2 adverse events has increased, the incidence of grade 3 and above adverse events has not exceeded the range reported in the PACIFIC-6 trial [10], and the mortality rate for grade 5 and above events was 3.3%. Subgroup analysis showed that the overall and ≥ Grade 3 incidences of various AEs in both chemotherapy and non-chemotherapy subgroups were consistent with the results of the PACIFIC-6 trial (**Table 5**). The data suggest that the AEs associated with Durvalumab combination therapy are manageable and do not escalate in severity. Consequently, cautious patient selection is crucial before therapy. During the treatment regimen, biological markers must be diligently evaluated, drug dosages adjusted as required, and treatment-related adverse events promptly managed to alleviate their impact.

It is crucial to acknowledge the considerable heterogeneity identified in this meta-analysis. We found significant differences in PFS and OS analysis (I^2 = 91.3%, P < 0.001; I^2 = 82.3%, P < 0.001), therefore a random effects model was used. To explore potential sources of heterogeneity, we conducted subgroup analysis, taking into account factors such as study type and combination therapy approach. The results showed that the PFS and OS of patients in the RCT study group were 5.7 months (95% CI: 4.7-6.7, I^2 = 78.3%) and 13.5 months (95% CI: 11.5-15.4, I^2 = 42.4%), respectively. The two-year OS rate was 28.0% (95% CI: 24.3%-31.8%,

I^2 = 0.0%), and the one-year PFS rate was 30.7% (95% CI: 26.2%-35.2%, I^2 = 21.4%). These findings indicate that variability can result from changes in research design, as well as variations in patient demographics and treatment regimens. The sensitivity analysis, which involved the systematic exclusion of specific studies, corroborated the strength of our findings; nonetheless, the significant variability necessitates care for drawing conclusive conclusions. Future research may analyze the sources of heterogeneity using meta-regression analysis; however, the scarcity of accessible papers may limit the viability of such analyses.

This study provides the first comprehensive evaluation of the safety and efficacy of Durvalumab combination therapy in non-small cell lung cancer, based on reliable data. The effectiveness is based on the examination of four primary databases and adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure comprehensive coverage. This meta-analysis, however, possesses limitations. The restricted quantity of papers incorporated, particularly the number of randomized controlled trials, may have influenced the statistical power of the meta-analysis. Secondly, variations in the quality of the included studies and variety in patient population characteristics may have influenced the reliability and generalizability of the findings. This meta-analysis relied on published summary data, and the absence of individual patient data constrained comprehensive analysis. Nevertheless, the research supports Durvalumab combination therapy, with or without chemoradiotherapy, as a viable and safe therapeutic option, highlighting the need for additional high-quality randomized controlled trials in this area. The optimization potential for this combined therapy may be further investigated in the future. Examining the ratio, dosage, and duration of various medication combinations to enhance efficacy and minimize adverse responses. Conversely, comprehensive investigation of biomarkers and systematic screening of patient demographics that may substantially benefit from treatment might facilitate individualized therapy. Furthermore, broadening its use in early neoadjuvant therapy for lung cancer, as well as in the management of recurrent and metastatic lung cancer, is anticipated to yield more comprehensive and effective treatment strategies for lung cancer patients, thereby advancing the field of lung cancer therapy.

Conclusion

Our meta-analysis confirmed the efficacy and safety of Durvalumab combination therapy in patients with advanced non-small cell lung cancer. The chemoradiotherapy cohort exhibited improved tumor response rates and survival durations compared to the non-chemoradiotherapy group. Furthermore, the combined treatment had acceptable tolerability, with no new toxicity identified. These findings provide critical insight and show the need for comprehensive, multicenter randomized controlled trials in advanced stage III non-small cell lung cancer.

Disclosure of conflict of interest

None.

Abbreviations

NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; OS, overall survival; AEs, adverse events; mPFS, median progression-free survival; mOS, median overall survival; PD-L1, programmed cell death ligand-1; PD-1, programmed cell death protein 1; CCRT, concurrent chemoradiotherapy; ICIs, immune checkpoint inhibitors; RCTs, randomized controlled trials; RECIST, Response Evaluation Criteria for Solid Tumors; CTCAE, Common Terminology Criteria for Adverse Events; NOS, Newcastle Ottawa Scale; SCC, squamous cell carcinoma; ADC, adenocarcinoma; ASC, adenosquamous carcinoma; ECOG, Eastern Cooperative Oncology Group; NA, available; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

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