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# Immune checkpoint inhibitors related respiratory disorders in patients with lung cancer: A meta-analysis of randomized controlled trials

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**Background:** In recent years, immune checkpoint inhibitors (ICIs) had extremely rapid growth in anti-cancer and improved outcomes of many malignancies, specifically lung cancer. However, the incidence of ICIs-related adverse events also raised. Using this meta-analysis, ICIs-related respiratory disorders were investigated in lung cancer patients.

**Methods:** Using Cochrane Library, Embase, and PubMed databases, we performed an integrated search for randomized controlled trials (RCTs) to compare respiratory disorders among different regimens. The data was prepared with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline, and the quality of included studies was evaluated based on the Cochrane manual.

**Results:** In total, 22 RCTs were involved in this meta-analysis. Compared with ICIs, chemotherapy reduced the risk of interstitial lung disease (p = 0.03; SMD: 2.81; 95% CI: 1.08, 7.27), pleural effusion (p = 0.002; SMD: 2.12; 95% CI: 1.32, 3.42), and pneumonitis (p < 0.00001; SMD: 9.23; 95% CI: 4.57, 18.64). ICIs plus chemotherapy could provide a higher probability for patients to suffer pneumonitis than chemotherapy (p = 0.01; SMD: 1.96; 95% CI: 1.17, 3.28). In addition, single ICI brought a lower likelihood for patients suffering pneumonitis than double ICIs (p = 0.004; SMD: 2.17; 95% CI: 1.27, 3.69).

**Conclusion:** ICIs-based treatment, such as ICIs alone, ICIs plus chemotherapy and double ICIs, can raise the incidences of some respiratory disorders in patients with lung cancer. It suggests that ICIs should be conducted based on a comprehensive consideration to prevent ICIs-related respiratory disorders. To a certain degree, this study might be provided to the clinician as a reference for ICIs practice.

**Systematic review registration:** https://www.crd.york.ac.uk/prospero/display\_record.php?ID=CRD42022378901, identifier (CRD42022378901).

#### KEYWORDS

immune checkpoint inhibitors (ICI), respiratory disorders, lung cancer, meta-analysis, randomized controlled trials (RCT)

# Introduction

In most countries, cancer is currently the first or second most frequent cause of premature death. In 2022, the USA has experienced more than 1,900,000 new cancer cases and 600,000 cancer deaths, with lung cancer being the leading cause of these deaths (1). Fortunately, the survival rate of patients with lung cancer has improved, which may be related to the early screening of lung cancer. Furthermore, a significant progress in non-small cell lung cancer (NSCLC) treatment with the advent of targeted drugs, coupled with the approval of immunotherapy by the Food and Drug Administration (FDA) in 2015, has also contributed to the population-level improvement in lung cancer-specific survival (2).

Many treatments to control malignancies by mobilizing the immune system are under investigation, including cytokines, T cells (checkpoint inhibitors, co-stimulatory receptor agonists), T cell engineering, oncolytic viruses, and vaccines. Immune checkpoint inhibitor (ICI) therapy includes programmed death-1 (PD-1) and programmed cell death 1 ligand 1/2 (PD-L1/2), cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), lymphocyteactivation gene 3 (LAG3), and other potential targets. PD-1 is a transmembrane protein expressed in T, B, and NK cells and an inhibitory molecule that binds to PD-L1 and PD-L2. PD-L1 is represented on the cell surface of various tissue types, including many tumor and hematopoietic cells. Contrarily, PD-L2 is more restricted to hematopoietic cells. The combination of PD-1 and PD-L1/2 can directly inhibit tumor cell apoptosis and promote peripheral effector T cell depletion and conversion of effector T cells into Treg cells (3, 4). To date, the results of many large-scale randomized controlled trials (RCTs) of PD-1 inhibitors against lung cancer have confirmed the concept of durable antitumor responses and improved progression-free survival and overall survival (OS) (5). CTLA-4 was recognized as a negative regulator of T cell activation in the mid-1990s (6-8). CTLA-4 on the surface of CD4 + and CD8+ T cells can play a role by binding to the co-stimulatory receptors CD80 and CD86 on the surface of APCs with a higher affinity than the co-stimulatory receptor CD28 on the surface of T cells (9). Scientists believe CTLA-4 to be APC-triggered, acting as a brake on CD4+ and CD8+ T cell activation. LAG3 is expressed on B cells, specific T cells, NK cells, and tumor-infiltrating lymphocytes, where it regulates immune checkpoint pathways (10). With the deepening of the understanding of the immune mechanism, several other potential targets of immune checkpoint inhibition have been discovered, one after another, such as B and T lymphocyte attenuator, V-domain Ig suppressor of T cell activation, T cell immunoglobulin, and mucin domain-3. ICIs have become first-line treatments for various malignancies, with the addition of immunotherapy to surgery, radiotherapy, chemotherapy, and targeted therapy (11, 12).

Despite the favorable clinical benefits of checkpoint inhibition, it has side effects known as immune-related adverse events (irAEs) (13, 14). IrAEs include skin diseases, diarrhea, hepatotoxicity, and cardiotoxicity (15–19). Checkpoint inhibition may also cause fulminant or fatal toxic reactions (20). However, there is no comparative research to comprehensively discuss respiratory disorders caused by ICIs in lung cancer. Thus, we conducted this meta-analysis to identify potential respiratory diseases during ICI therapy for lung cancer to guide the selection of patients who should benefit from ICIs.

## Materials and methods

#### Reporting standards

The meta-analysis for ICIs-related respiratory disorders in patients with lung cancer was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Metaanalyses reporting guideline (21).

#### Search strategy

A competent information specialist (HL) conducted an integrated search for RCTs between January 2000 and October 2022 using the Cochrane Library, Embase, and PubMed databases. According to the PICOS (participants, interventions, comparisons, outcomes, and study design) guidelines (22), "ICIs," "PD-1," "PD-1 inhibitors," "PD-L1," "PD-L1 inhibitors," "CTLA-4," "CTLA-4 inhibitor," "atezolizumab," "avelumab," "camrelizumab," "cemiplimab," "durvalumab," "tislelizumab," "nivolumab," "tremelimumab," "lung cancer," "lung carcinoma," "neoplasms," "adverse reactions," "adverse events," and "randomized controlled trial" were entered as the Medical Subject Heading terms.

#### Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) RCT on lung cancer (phase II or III clinical trials); (2) ICI intervention, including PD-1/ PD-L1 or CTLA-4 inhibitors; and (3) comparison between singleagent ICI plus chemotherapy and chemotherapy, single-agent ICI and chemotherapy, as well as single-agent and double-agent ICIs. The exclusion criteria were as follows: (1) no report of ICIs-related respiratory disorders; (2) publications not written in English; (3) abstracts, case reports, comments, editorials, letters, and reviews; and (4) duplicate, missing, and overlapping datasets.

#### Study selection

Two investigators (SL and JJ) independently reviewed the titles and abstracts of the articles to obtain the qualified studies. Furthermore, two investigators (SW and LS) identified the potentially relevant studies to determine if they were eligible based on the inclusion and exclusion criteria. Disagreements as regards the study's selection were resolved through discussion and compromise.

## Data extraction

Two investigators (HL and JJ) independently extracted the characteristic data, including publication year, first author name, number of clinical trial, drug name, clinical trial phase, lung cancer type, regiment of intervention, enrollment, and serious adverse events (SAEs), from the eligible studies. According to the analysis of SAEs, the top 10 most frequent ICIs-related respiratory disorders, including pneumonitis, dyspnea, pulmonary embolism, pleural effusion, chronic obstructive pulmonary disease, respiratory failure, hemoptysis, interstitial lung disease, pulmonary hemorrhage, and pneumothorax, were conducted as the main outcomes (Figure 1). Disagreements as regards data extraction were resolved through discussion and compromise.

# Quality assessment

Based on the Cochrane manual, the bias risk of eligible studies, including allocation concealment, blinding of participants and personnel, blindness to outcome assessment, incomplete outcome data, random sequence generation, selective outcome reporting, and other bias, was independently evaluated by two investigators (SW and SL) (23). Funnel plot were performed to assess publication bias (24). Disagreements regarding quality assessment were resolved through discussion and compromise.

# Data synthesis and statistical analysis

All statistical analyses were calculated using Review Manager (RevMan v5.3). ICIs-related respiratory disorders, including pneumonitis, dyspnea, pulmonary embolism, pleural effusion, chronic obstructive pulmonary disease, respiratory failure,



hemoptysis, interstitial lung disease, pulmonary hemorrhage, and pneumothorax, were evaluated using the mean differences with 95% confidence intervals (CIs). Based on the Cochrane collaboration network, a fixed-effects model was used to pool studies, and the inconsistency index was used to access heterogeneity as low ( $I^2 < 30\%$ ), moderate ( $30\% \le I^2 < 50\%$ ), or high ( $I^2 \ge 50\%$ ) (25, 26). Subanalyses of the effects of the different intervention on ICIs-related respiratory disorders were conducted. A two-tailed *P*-value of <0.05 was considered statistically significant.

# Results

## Study selection

In total, 3884 potentially relevant studies were retrieved from databases as a result of the strategy performed in searching. 453 studies were recorded after duplicates removed. Then, 369 studies were excluded due to irrelevant topic, non ICIs-related or retrospective studies. The investigators removed 62 studies after screening the full texts. Four released updated results (27–30), and three did not report respiratory disorders (31–33). Finally, 22 studies were included as the flow diagram described in Figure 2 (34–55).

## Study characteristics

The characteristics of 22 RCTs from the 22 included studies are presented in Table 1. The studies ranged in year of publication from 2015 to 2021. Enrollment of 22 RCTs was 11460. Eighteen RCTs included NSCLC and four included small cell lung cancer (SCLC). PD-1 inhibitors were administered in 16 RCTs, PD-L1 inhibitors in 6, and CTLA-4 inhibitors in 4. In the treatment regimens, 9 RCTs were conducted to compare ICIs plus chemotherapy vs. chemotherapy, 10 RCTs about ICIs vs. chemotherapy, and 3 RCTs about double ICIs vs. single ICI.



NO.	First Author Publication Year	Clinical Trial	Trial Phase	Cancer Type	Drug	Treatment Regimens	Enrollment
1	Arrieta, 2020 (34)	PROLUNG (NCT02574598)	Ш	NSCLC	Pembrolizumab (PD-1)	ICIs + Chemotherapy VS. Chemotherapy	78
2	Awad, 2021 (35)	KEYNOTE-021 (NCT02039674)	Ш	NSCLC	Pembrolizumab (PD-1)	ICIs + Chemotherapy VS. Chemotherapy	121
3	Barlesi, 2018 (36)	JAVELIN Lung 200 (NCT02395172)	III	NSCLC	Avelumab (PD-L1)	ICIs VS. Chemotherapy	758
4	Borghaei, 2015 (37)	CheckMate057 (NCT01673867)	III	NSCLC	Nivolumab (PD-1)	ICIs VS. Chemotherapy	555
5	Boyer, 2021 (38)	KEYNOTE-598 (NCT03302234)	III	NSCLC	Pembrolizumab (PD-1) Ipilimumab (CTLA-4)	Double ICIs VS. single ICI	563
6	Brahmer, 2015 (39)	CheckMate 017 (NCT01642004)	III	NSCLC	Nivolumab (PD-1)	ICIs VS. Chemotherapy	260
7	Carbone, 2017 (40)	CheckMate 026 (NCT02041533)	III	NSCLC	Nivolumab (PD-1)	ICIs VS. Chemotherapy	530
8	Gadgeel, 2020 (41)	KEYNOTE-189 (NCT02578680)	III	NSCLC	Pembrolizumab (PD-1)	ICIs + Chemotherapy VS. Chemotherapy	607
9	Gettinger, 2021 (42)	Lung-MAP 1400l (NCT02785952)	III	NSCLC	Nivolumab (PD-1) Ipilimumab (CTLA-4)	Double ICIs VS. single ICI	247
10	Goldman, 2021 (43)	CASPIAN (NCT03043872)	III	SCLC	Durvalumab (PD-L1) Tremelimumab (CTLA-4)	ICIs + Chemotherapy VS. Chemotherapy	531
11	Herbst, 2020a (44)	IMpower110 (NCT02409342)	III	NSCLC	Atezolizumab (PD-L1)	ICIs VS. Chemotherapy	549
12	Herbst, 2020b (45)	KEYNOTE-010 (NCT01905657)	III	NSCLC	Pembrolizumab (PD-1)	ICIs VS. Chemotherapy	991
13	Horn, 2018 (46)	IMpower133 (NCT02763579)	III	SCLC	Atezolizumab (PD-L1)	ICIs + Chemotherapy VS. Chemotherapy	394
14	Mok, 2019 (47)	KEYNOTE-042 (NCT02220894)	III	NSCLC	Pembrolizumab (PD-1)	ICIs VS. Chemotherapy	1251
15	Nishio, 2021 (48)	IMpower132 (NCT02657434)	III	NSCLC	Atezolizumab (PD-L1)	ICIs + Chemotherapy VS. Chemotherapy	565
16	Owonikoko, 2021 (49)	CheckMate 451 (NCT02538666)	III	SCLC	Nivolumab (PD-1) Ipilimumab (CTLA-4)	Double ICIs VS. single ICI	557

(Continued)

Cancer Type     Drug     Treat       NSCLC     Pembrolizumab (PD-1)     ICIs + Chem.       NSCLC     Pembrolizumab (PD-1)     ICIs VS. Chen	Trial PhaseCancer TypeDrugTreatIIINSCLCPembrolizumab (PD-1)ICIs + ChemIIINSCLCPembrolizumab (PD-1)ICIs VS. Chei	Clinical TrialTrial PhaseCancer TypeDrugTreatKEYNOTE-407IIINSCLCPembrolizumab (PD-1)ICIs + ChemNCT02775435)IIINSCLCPembrolizumab (PD-1)ICIs VS. ChenKEYNOTE-024IIINSCLCPembrolizumab (PD-1)ICIs VS. Chen
NSCLC Pembrolizumab (PD-1) NSCLC Pembrolizumab (PD-1)	III NSCLC Pembrolizumab (PD-1) III NSCLC Pembrolizumab (PD-1)	KEYNOTE-407         III         NSCLC         Pembrolizumab (PD-1)           (NCT02775435)         III         NSCLC         Pembrolizumab (PD-1)           KEYNOTE-024         III         NSCLC         Pembrolizumab (PD-1)           (NCT02142738)         III         NSCLC         Pembrolizumab (PD-1)           CheckMate 331         III         SCTC         Pembrolizumab (PD-1)
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Cancer Type NSCLC NSCLC SCLC	Trial Phase     Cancer Type       III     NSCLC       III     NSCLC       III     SCLC	Clinical TrialTrial PhaseCancer TypeKEYNOTE-407IIINSCLCKEYNOTE-024IIINSCLCKEYNOTE-024IIINSCLCCheckMate 331IIISCLCCheckMate 331IIISCLC
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First AuthorClinical TrialPublication YearKEYNOTE-407Paz-Ares,2020 (50)KEYNOTE-407Redk, 2019 (51)NCT02775435)Redk, 2019 (51)KEYNOTE-024Spigel, 2021 (52)CheckMate 331Spigel, 2021 (52)(NCT02481830)	First Author Publication Year Paz-Ares,2020 (50) Reck, 2019 (51) Spigel, 2021 (52)	

#### Quality assessment

The quality assessment of the included studies is presented in Figure 3. In sum, all studies were randomized, with five presenting a high risk of bias in allocation concealment (selection bias). All studies showed low risks of blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), and selective reporting (reporting bias), with five studies demonstrating high risks of incomplete outcome data (attrition bias). Overall, the risk of other bias was low. The potential publication bias was evaluated through visual inspection of a funnel plot (Supplementary material).

#### Risk of ICIs-related respiratory disorders

The incidence of ICIs-related respiratory disorders in different treatment regimens is presented in Table 2. In total, the incidence rates of pneumonitis (2.14%), dyspnea (1.62%), and pulmonary embolism (1.51%) were the three highest than other respiratory disorders. Especially in double ICI treatment regimens, the incidence rates of pneumonitis and dyspnea were 6.43% and 3.65%, respectively. Compared with chemotherapy treatment regimens, the incidence rates of pneumonitis, interstitial lung disease, and pleural effusion increased by more than two-fold in ICI treatment regimens (2.84% vs. 0.22%, 0.69% vs. 0.15%, 1.68% vs. 0.83%).

## Risk of chronic obstructive pulmonary disease

The different treatment regimens on the risk of chronic obstructive pulmonary disease were presented for 18 datasets (ICIs plus chemotherapy [n = 1969] vs. chemotherapy [n = 1411]; ICIs [n = 3118] vs. chemotherapy [n = 2627]; double ICIs [n = 560] vs. single ICI [n = 560]). Compared with chemotherapy, ICIs plus chemotherapy (P= 0.67; SMD: 0.87; 95% CI: 0.46, 1.64) or ICIs (P = 0.14; SMD: 1.52; 95% CI: 0.87, 2.64) did not significantly change the incidence of chronic obstructive pulmonary disease with low evidence of heterogeneity among the studies ( $I^2$  = 0% and 10%). Double ICIs (P= 0.34; SMD: 0.45; 95% CI: 0.15, 1.30) did not significantly change the incidence of chronic obstructive pulmonary disease when compared with single ICI with low evidence of heterogeneity among the studies ( $I^2$  = 0%) (Figure 4).

## Risk of dyspnea

The different treatment regimens on the risk of dyspnea were presented for 19 datasets (ICIs plus chemotherapy [n = 2235] vs. chemotherapy [n = 1542]; ICIs [n = 3301] vs. chemotherapy [n = 2633]; double ICIs [n = 684] vs. single ICI [n = 683]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.29; SMD: 0.71; 95% CI: 0.38, 1.34) or ICIs (P = 0.36; SMD: 1.22; 95% CI: 0.80, 1.87) did not significantly change the incidence of dyspnea with low evidence of heterogeneity among the studies ( $I^2 = 0\%$  and 0%). Double ICIs (P = 0.90; SMD: 1.04; 95% CI: 0.58, 1.87) did not significantly change the

**FABLE 1** Continued



incidence of dyspnea when compared with single ICI with moderate evidence of heterogeneity among the studies ( $I^2 = 41\%$ ) (Figure 5).

#### Risk of hemoptysis

The different treatment regimens on the risk of hemoptysis were presented for 20 datasets (ICIs plus chemotherapy [n = 2235] vs. chemotherapy [n = 1542]; ICIs [n = 3455] vs. chemotherapy [n = 2783]; double ICIs [n = 560] vs. single ICI [n = 560]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.88; SMD: 1.06; 95% CI:

0.53, 2.10) or ICIs (P = 0.99; SMD: 1.00; 95% CI: 0.55, 1.83) did not significantly change the incidence of hemoptysis with low evidence of heterogeneity among the studies ( $I^2 = 0\%$  and 11%). Double ICIs (P = 1.00; SMD: 1.00; 95% CI: 0.14, 7.12) did not significantly change the incidence of hemoptysis compared with single ICI (Figure 6).

## Risk of interstitial lung disease

The different treatment regimens on the risk of interstitial lung disease were presented for 15 datasets (ICIs plus chemotherapy [n =

TABI	Ü	res

TABLE 2 The incidence of ICIs-related re	spiratory disorders in different t	reatment regimens.					
ICIs-related respiratory disorders	ICIs + Chemothe Chemother n/n (%)	erapy VS. apy	ICIs VS. Cher n/n (	%) %)	Double ICIs VS n/n (%	. single ICI 6)	Total n/n (%)
	ICIs + Chemotherapy	Chemotherapy	ICIs	Chemotherapy	Double ICIs	single ICI	
Chronic obstructive pulmonary disease	26/1969 (1.32%)	16/1411 (1.13%)	35/3118 (1.12%)	20/2627 (0.76%)	5/560 (0.89%)	11/560 (1.96%)	113/10245 (1.10%)
Dyspnea	23/2235 (1.03%)	18/1542 (1.17%)	54/3301 (1.64%)	35/2633 (1.33%)	25/684 (3.65%)	24/683 (3.51%)	179/11078 (1.62%)
Hemoptysis	21/2235 (0.94%)	12/1542 (0.78%)	22/3455 (0.64%)	18/2783 (0.65%)	2/560 (0.36%)	2/560 (0.36%)	77/11135 (0.69%)
Interstitial lung disease	7/1573 (0.45%)	4/1082 (0.37%)	18/2622 (0.69%)	3/2005 (0.15%)	2/560 (0.36%)	2/560 (0.36%)	36/8402 (0.43%)
Pleural effusion	28/2235 (1.25%)	12/1542 (0.78%)	58/3455 (1.68%)	23/2783 (0.83%)	9/684 (1.32%)	8/683 (1.17%)	138/11382 (1.21%)
Pneumonitis	56/2275 (2.46%)	20/1580 (1.27%)	98/3455 (2.84%)	6/2783 (0.22%)	44/684 (6.43%)	21/683 (3.07%)	245/11460 (2.14%)
Pneumothorax	6/2235 (0.27%)	7/1542 (0.45%)	11/3168 (0.35%)	9/2515 (0.36%)	2/406 (0.49%)	2/404 (0.50%)	37/10270 (0.36%)
Pulmonary embolism	31/1969 (1.57%)	17/1411 (1.20%)	64/3455 (1.85%)	35/2783 (1.26%)	5/560 (0.89%)	10/560 (1.79%)	162/10738 (1.51%)
Pulmonary hemorrhage	2/1029 (0.19%)	1/671 (0.15%)	9/2776 (0.32%)	10/2155 (0.46%)	3/684 (0.44%)	6/683 (0.88%)	31/7998 (0.39%)
Respiratory failure	16/2235 (0.72%)	9/1559 (0.58%)	32/3455 (0.93%)	23/2783 (0.83%)	7/684 (1.02%)	6/683 (0.88%)	93/11399 (0.82%)

1573] vs. chemotherapy [n = 1082]; ICIs [n = 2622] vs. chemotherapy [n = 2005]; double ICIs [n = 560] vs. single ICI [n= 560]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.82; SMD: 1.14; 95% CI: 0.37, 3.57) did not significantly change the incidence of interstitial lung disease with low evidence of heterogeneity among the studies  $(I^2 = 0\%)$ . ICIs (P = 0.03; SMD): 2.81; 95% CI: 1.08, 7.27) significantly increased the risk of suffering interstitial lung disease with low evidence of heterogeneity among the studies ( $I^2 = 0\%$ ). Double ICIs (P = 1.00; SMD: 1.00; 95% CI: 0.17, 5.79) did not significantly change the incidence of interstitial lung disease when compared with single ICI with low evidence of heterogeneity among the studies  $(I^2 = 0\%)$  (Figure 7).

## Risk of pleural effusion

The different treatment regimens on the risk of pleural effusion were presented for 20 datasets (ICIs plus chemotherapy [n = 2235]vs. chemotherapy [n = 2542]; ICIs [n = 3455] vs. chemotherapy [n =2783]; double ICIs [n = 684] vs. single ICI [n = 683]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.31; SMD: 1.41; 95% CI: 0.72, 2.75) did not significantly change the incidence of pleural effusion with low evidence of heterogeneity among the studies ( $I^2 = 0\%$ ). ICIs (P = 0.002; SMD: 2.12; 95% CI: 1.32, 3.42) significantly increased the risk of suffering pleural effusion with low evidence of heterogeneity among the studies ( $I^2 = 0\%$ ). Double ICIs (P = 0.82; SMD: 1.11; 95% CI: 0.44, 2.84) did not significantly change the incidence of pleural effusion when compared with single ICI with low evidence of heterogeneity among the studies  $(I^2 =$ 0%) (Figure 8).

## **Risk of pneumonitis**

The different treatment regimens on the risk of pneumonitis were presented for 22 datasets (ICIs plus chemotherapy [n = 2275]vs. chemotherapy [n = 1580]; ICIs [n = 3455] vs. chemotherapy [n = 1580]; ICIs [n = 3455]; ICIs [n = 3455]; ICIs [n = 3455] vs. chemotherapy [n = 1580]; ICIs [n = 3455]; ICIS [n = 34555]; ICIS [n = 34555]; ICIS [n = 34555]; I 2783]; double ICIs [n = 684] vs. single ICI [n = 683]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.01; SMD: 1.96; 95% CI: 1.17, 3.28) and ICIs (P < 0.00001; SMD: 9.23; 95% CI: 4.57, 18.64) significantly increased the risk of suffering pneumonitis with low evidence of heterogeneity among the studies ( $I^2 = 0\%$  and 0%). Double ICIs (P = 0.004; SMD: 2.17; 95% CI: 1.27, 3.69) significantly increased the risk of suffering pneumonitis with low evidence of heterogeneity among the studies  $(I^2 = 0\%)$  (Figure 9).

## Risk of pneumothorax

The different treatment regimens on the risk of pneumothorax were presented for 19 datasets (ICIs plus chemotherapy [n = 2235]vs. chemotherapy [n = 1542]; ICIs [n = 3168] vs. chemotherapy [n = 1542]; ICIs [n =2515]; double ICIs [n = 406] vs. single ICI [n = 404]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.28; SMD: 0.60; 95% CI: 0.24, 1.51) or ICIs (P = 0.90; SMD: 0.95; 95% CI: 0.43, 2.11) did not significantly change the incidence of pneumothorax with



low evidence of heterogeneity among the studies ( $I^2 = 0\%$  and 0%). Double ICIs (P = 0.99; SMD: 0.99; 95% CI: 0.17, 5.77) did not significantly change the incidence of pneumothorax when compared with single ICI with low evidence of heterogeneity among the studies ( $I^2 = 0\%$ ) (Figure 10).

## Risk of pulmonary embolism

The different treatment regimens on the risk of pulmonary embolism were presented for 19 datasets (ICIs plus chemotherapy [n = 1969] vs. chemotherapy [n = 1411]; ICIs [n = 3455] vs. chemotherapy [n = 2783]; double ICIs [n = 560] vs. single ICI [n = 560]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.94; SMD: 0.98; 95% CI: 0.53, 1.80) or ICIs (P = 0.06; SMD: 1.49; 95% CI: 0.98, 2.25) did not significantly change the incidence of pulmonary embolism with low evidence of heterogeneity among the studies ( $I^2 = 0\%$  and 0%). Double ICIs (P = 0.21; SMD: 0.51; 95% CI: 0.18, 1.46) did not significantly change the incidence of pulmonary embolism when compared with single ICI with low evidence of heterogeneity among the studies ( $I^2 = 0\%$ ) (Figure 11).

## Risk of pulmonary hemorrhage

The different treatment regimens on the risk of pulmonary hemorrhage were presented for 15 datasets (ICIs plus chemotherapy [n = 1029] vs. chemotherapy [n = 671]; ICIs [n =



chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

2776] vs. chemotherapy [n = 2155]; double ICIs [n = 684] vs. single ICI [n = 683]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.70; SMD: 0.68; 95% CI: 0.09, 4.82) or ICIs (P = 0.52; SMD: 0.77; 95% CI: 0.34, 1.71) did not significantly change the incidence of pulmonary hemorrhage with low evidence of heterogeneity among the studies ( $I^2 = 0\%$  and 0%). Double ICIs (P = 0.34; SMD: 0.53; 95% CI: 0.14, 1.97) did not significantly change the incidence of pulmonary hemorrhage when compared with single ICI with low evidence of heterogeneity among the studies ( $I^2 = 0\%$ ) (Figure 12).

## Risk of respiratory failure

The different treatment regimens on the risk of respiratory failure were presented for 20 datasets (ICIs plus chemotherapy [n = 2235] vs. chemotherapy [n = 1559]; ICIs [n = 3455] vs. chemotherapy [n = 2783]; double ICIs [n = 684] vs. single ICI [n = 683]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.97; SMD: 0.98; 95% CI: 0.45, 2.14) or ICIs (P = 0.52; SMD: 1.19; 95% CI: 0.70, 2.02) did not significantly change the incidence of respiratory failure with low evidence of heterogeneity among the

Study or Subgroup	Event	3	Total F	vents	Total	Weight	M-H, Fixed	95% CI	M-H. Fixed	95% CI
3.1.1 PD-1 + Chemotherapy VS.	Chemother	apy								
Awad 2021, KEYNOTE-021		1	59	0	62	3.0%	3.21 10 13	80,251		
Gadgeel 2020 KEYNOTE-189		2	405	2	202	16.7%	0 75 10 12	4 501		
Paz-Ares 2020, KEYNOTE-407		5	278	4	202	24 7%	1 26 10 34	4 761		
Vang 2020, Orient-11		2	266	0	131	1 296	3 49 10 18	68 1 3		
Subtotal (95% CI)	1.0	, ,	1008	0	675	48.6%	1 40 10 55	3 561		
Total evente	1	2	1000	6	015	40.070	1.40 [0.00]	, 0.00]		
Listeregeneits Ohi2 - 1 11 df - 1	(D = 0.77);	2 - 00/		0						
Test for overall effect: Z = 0.70 (F	r = 0.77, r = 0.48	1-= 0%								
3 1 2 DD.I 1 + Chemotherany V	Chemothe	ranv								
Goldman 2021 CASPIAN	. chemotie	alapy	265	1	266	0.4%	0 22 10 01	0 2 21		
Hom 2019 Mnoword 22			100	1	106	6.20	1 00 10 10	22 1 21		
Nichie 2021 Meguert 22		2	190		190	0.3%	1.99 [0.10,	15 1 21		
Wood 2010 Mnoword 20		2	472	2	1214	20.2%	0.94 [0.06,	15.12]		
Subtetel (05% CI)		2	4/3	3	131	29.3%	0.55 [0.14	2.22]		-
Subtotal (95% CI)	14		1227	~	807	51.470	0.75 [0.20,	, 2.00]		
I otal events		1		ь						
Test for overall effect: Z = 0.59 (F	(P = 0.78); '= 0.56)	I* = U%								
Total (95% CI)			2235		1542	100.0%	1.06 [0.53	, 2.10]	+	•
Total events	2	1		12						
Heterogeneity: Chi <sup>2</sup> = 2.91, df = 3	' (P = 0.89);	l² = 0%							0.01 0.1 1	10 10
Test for overall effect: Z = 0.16 (F	= 0.88)								Chamatharany I	Cle + Chemotherany
Test for subaroup differences: C	hi <sup>2</sup> = 0.82. d	f=1 (P=	= 0.37). P	<sup>2</sup> = 0%					chemotherapy it	Sis + Chemoulerapy
	ICIs		Chemot	nerapy		Odd	Is Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weigh	t M-H, F	ixed, 95% Cl		M-H, Fixed, 95% Cl	
3.2.1 PD-1 VS. Chemotherapy										
Borghaei 2015, CheckMate057	2	287	3	268	14.49	6 0.62	2 [0.10, 3.74]			
Brahmer 2015, CheckMate 017	1	131	2	129	9.49	6 0.49	9 [0.04, 5.45]			
Carbone 2017, CheckMate 026	0	267	1	263	7.19	6 0.33	3 [0.01, 8.07]	-	•	
Herbst 2020, KEYNOTE-010	4	682	0	309	3.29	6 4.11	[0.22, 76.49]			
Mok 2019, KEYNOTE-042	7	636	1	615	4.79	6 6.83	[0.84, 55.70]		+	
Reck 2019, KEYNOTE-024	2	154	0	150	2.39	6 4.93 [0	0.23, 103.64]			
Spigel 2021, CheckMate 331	1	282	3	265	14.49	6 0.31	1 10.03. 3.011			
Wu 2019, CheckMate 078	2	337	0	158	3.29	6 2.33	10.11.48.871			
Subtotal (95% CI)	-	2776	-	2155	58.89	6 1.44	10.70. 2.981		-	
Total events	19		10							
Heterogeneity: Chi <sup>2</sup> = 7.52, df = 3	(P = 0.38)	$^{2} = 7\%$								
Test for overall effect: Z = 0.98 (F	= 0.32)									
3.2.2 PD-L1 VS. Chemotherapy										
Barlesi 2018, JAVELIN Lung 200	3	393	4	365	19.39	6 0.69	9 [0.15, 3.12]			
Herbst 2020, IMpower110	0	286	4	263	21.99	6 0.10	0 [0.01, 1.88]	+	•	
Subtotal (95% CI)		679		628	41.29	6 0.38	[0.11, 1.32]			
Total events	3		8							
Heterogeneity: Chi <sup>2</sup> = 1.41, df = 1	(P = 0.23);	= 29%								
Test for overall effect: Z = 1.53 (F	= 0.13)									
Total (95% CI)		3455		2783	100.09	6 1.00	[0.55, 1.83]		+	
Total events	22		18							
Heterogeneity: Chi <sup>2</sup> = 10.16. df =	9 (P = 0.34)	;   <sup>2</sup> = 119	%					-		+ + + + + + + + + + + + + + + + + + + +
Test for overall effect: Z = 0.01 (F	(= 0.99)							0.01	U.1 1	10 100
Test for subaroup differences: C	hi <sup>2</sup> = 3.29 d	f=1 (P=	= 0.07). F	= 69.69	6				chemotherapy ICIs	
	Double	ICIS	Single	ICI		Odd	s Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fit	xed, 95% CI		M-H, Fixed, 95% CI	
3.3.1 PD-1 + CTL A-4 VS. PD-1										1.0
Bover 2021 KEYNOTE-599	1	282	2	281	100.0%	1.00	10 14 7 1 21			
DOYCI 2021, NETINOTE-398	1 0	202	2	201	100.0%	No.	t actimable			
Owonikoko 2021 ChookMate 44	. 0	560	U	279	100.0%	100	10 14 7 121			
Owonikoko 2021, CheckMate 45 Subtotal (95% CI)		500	-	500	100.0%	1.00	[0.14, 7.12]			
Owonikoko 2021, CheckMate 45 Subtotal (95% CI)	~		2							
Owonikoko 2021, CheckMate 45 Subtotal (95% CI) Total events	2									
Owonikoko 2021, CheckMate 45 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.00 (F	2 '= 1.00)								1	
Owonikoko 2021, CheckMate 45 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.00 (F	2 = 1.00)	560		560	100.0%	1.00	10 14 7 121			
Owonikoko 2021, CheckMate 45 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.00 (F Total (95% CI)	2 2 = 1.00)	560		560	100.0%	1.00	[0.14, 7.12]			
Owonikoko 2021, CheckMate 45 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.00 (F Total (95% CI) Total events	2 ' = 1.00) 2	560	2	560	100.0%	1.00	[0.14, 7.12]	<b>—</b>	-	
Owonikoko 2021, CheckMate 45 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.00 (F Total (95% CI) Total events Heterogeneity: Not applicable	2 '= 1.00) 2	560	2	560	100.0%	1.00	[0.14, 7.12]	L		
Owonikoko 2021, CheckMate 45 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect. Z = 0.00 (F Total events Heterogeneity: Not applicable Test for overall effect. Z = 0.00 (F	2 2 = 1.00) 2 = 1.00)	560	2	560	100.0%	1.00	[0.14, 7.12]	L	0.1 1 1 Single ICI Double ICI:	100 100

The forest plot of different treatment regimens on hemoptysis. Subgroup analyses investigated ICIs plus chemotherapy vs. chemotherapy, ICIs vs. chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

studies ( $I^2 = 0\%$  and 0%). Double ICIs (P = 0.80; SMD: 1.15; 95% CI: 0.40, 3.32) did not significantly change the incidence of respiratory failure when compared with single ICI with high evidence of heterogeneity among the studies ( $I^2 = 78\%$ ) (Figure 13).

# Discussion

As the first FDA-approved ICI on anti-cancer, ipilimumab was used to treat advanced melanoma in 2011 (56). In the next decade, the use of ICIs in cancer treatment rapidly increased, including numerous breakthroughs, expanded treatment landscape for many malignancies, and improved outcomes, specifically NSCLC (57–59). Nivolumab, a PD-1 inhibitor, brought a promising outcome when it was effectively

used as a second-line therapy for patients with advanced NSCLC. In the next phase III trials on advanced squamous and non-squamous NSCLC, nivolumab achieved inspiring results of OS and objective response rate (ORR) (37, 39). In recent years, several phase III clinical trials demonstrated a superior improvement in OS and more durable responses with ICIs or ICIs plus chemotherapy than chemotherapy (27, 29, 30, 32, 33, 44, 60, 61). The clinical choice mainly depends on disease burden, PD-L1 expression, and tumor mutation profile of the tumor. In comparison, the growth of ICIs in SCLC could be more satisfactory. ICIs merely had an achievement that PD-L1 inhibitors plus platinumbased chemotherapy conducted as first-line treatment of extensivestage SCLC (46, 62).

Based on the extremely rapid growth of ICIs, various irAEs were reported. In general, irAEs are usual due to nonspecific



ICIs vs. chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

immunostimulation, leading to autoimmunity, tissue damage, and organ-specific inflammation (63). They can be divided into cytokine release syndrome and cardiac, pulmonary, dermatologic, endocrine, neurologic, ocular, renal, rheumatologic, gastrointestinal, and hepatic toxicities (64, 65). Dermatologic, endocrine, gastrointestinal, and hepatic toxicities are shared among ICI-treated patients (65, 66). Cardiac and pulmonary toxicities are rare but potentially fatal (20, 67–70). In particular, pulmonary toxicity is rapidly progressive (71). Most of the irAEs caused by pulmonary toxicity occur during 10-12 weeks after ICI therapy, and the early symptoms are mild and nonspecific, such as cough (72). However, some ICI-treated patients may suffer severe ICIs-related respiratory disorders (SAE grade  $\geq$  3), such as chronic obstructive pulmonary disease, hemoptysis, interstitial lung disease, pleural effusion, pneumonitis, pulmonary embolism, and respiratory failure. Therefore, a broad range of diagnostic processes, including X-ray imaging, angiography, and laboratory analyses, are necessary for ICI-treated patients to distinguish pulmonary embolism, pleural effusion, pneumonitis, pneumothorax, and cancer progression.

In recent years, some researchers analyzed certain ICIs-related respiratory disorders in digestic and urologic cancer (73, 74). However, a study on comprehensive ICIs-related respiratory disorders in lung cancer is still warranted. In this study, we extracted 22 RCTs and analyzed the risk of top 10 most frequent ICIs-related respiratory disorders in patients with lung cancer. Overall, the analysis revealed that ICIs raise the risk of interstitial lung disease, pleural effusion, and pneumonitis compared with chemotherapy. Furthermore, ICIs plus chemotherapy brought a higher incidence of pneumonitis than chemotherapy. single ICI could provide a lower probability for patients to suffer pneumonitis than double ICIs. Also, other ICIs-related respiratory disorders, including chronic obstructive pulmonary disease, dyspnea, hemoptysis, pneumothorax, pulmonary embolism, pulmonary hemorrhage, and respiratory failure, were analyzed in this study.

5.11PD-11 + Chemotherapy VS. Chemotherapy 0 adaged 2020, KEYNOTE-169 6 405 4 202 34.7% 0.7 4 [0.3], 15.2 1] 0 adaged 2020, KEYNOTE-169 6 405 4 202 34.7% 0.7 4 [0.3], 15.2 1] 0 adaged 2020, KEYNOTE-169 6 405 4 202 34.7% 0.7 4 [0.3], 15.2 1] 0 adaged 2020, KEYNOTE-169 6 405 4 202 34.7% 0.7 4 [0.3], 15.2 1] 0 adaged 2020, KEYNOTE-169 6 405 4 202 34.7% 0.7 4 [0.3], 15.2 1] 0 adaged 2020, KEYNOTE-169 6 405 4 202 34.7% 0.7 4 [0.3], 15.0 1, 15.2 10, 15.2 1] 0 adaged 2020, KEYNOTE-169 7 20.8 (7 - 10.8), 1 - 0 (5	Study or Subgroup	Events		Total F	vents	Total	Weight	M-H, Fixed.	95% CI	M-H, Fixed, 95% Cl
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	5.1.1 PD-1 + Chemotherapy VS. CI	hemothera	pv							
Cadge 1220, LEYNOTE-193 6 405 4 220 347% 074 (0.1) 2.87 Parkes 2030, LEYNOTE-417 3 276 0 1 2 240 10.0% 1.52 (0.53, 15] Tail events 1 3 266 0 131 4.4% 3.49 (0.6, 6.13) Tail events 1 3 266 0 131 4.4% 3.49 (0.6, 6.13) Tail events 1 3 266 0 131 4.4% 3.49 (0.6, 6.13) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0.2 0 - 0.6) Tail events 1 20, 54 (0.7 0 - 0.3) Tail events 1 45 (0.7 0 - 0.3) Tail events 1 45 (0.7 0 - 0.3) Tail events 4 55 (0.7 0 - 0.3) Tail events 5 0 0 0 0 0 0 0 0 0 0 0 0	Awad 2021 KEYNOTE-021	3	.,	59	n	62	3.0%	7 74 10 39 1	53 211	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Gadgeel 2020, KEYNOTE-189	6		405	4	202	34 7%	0 74 10 21	2 671	
	Paz-Ares 2020, KEYNOTE-407	3		278	2	202	13.0%	1 52 10 25	9 151	
Subtail differences $Ch^{-1} = 2.65$ $d^{-1} $	Vang 2020, Orient 11	2		266	2	121	1 1 10%	2 40 10 10	60 1 21	
$ \begin{array}{c} 1000 & 0.03 & 0.03 & 0.03 & 0.04 & 0.03 & 0.04 & 0$	Subtotal (05% CI)	3		1009	0	675	4.4%	1 53 10 63	3 721	-
$ \begin{array}{c} \text{losi versitis} \\ Test or versal effect $Z = 0.84, $Z = 0\%, $Y = 0.5\%, $Y = 0\%, $Y = 0.5\%, $Y = 0.5$	Subtotal (95% CI)			1008	0	075	55.0%	1.55 [0.65	, 3.72]	
Heterogenety. Chr = 2.8, $a_1 = 3.9 = 2.0 = 0.43$ , $t = 0.95$ 51.2 DL 1 + Chemotherapy VS. Chemotherapy doman 2021, CASPIM 2 265 2 266 13.1% 1.00 [D 14, 7.16] Hom 2018, Mpower13 2 2 198 1 166 6.6% 1.99 [D 18, 22.12] Hom 2018, Mpower13 8 473 0 131 5.1% 4.80 [D 38, 33.61] West 2019, Mpower13 8 473 0 131 5.1% 4.80 [D 38, 33.76] Heterogenety. Chr <sup>2</sup> = 2.45, $dr = 3.0 = 0.65$ . Total events 3 2 12 Heterogenety. Chr <sup>2</sup> = 2.45, $dr = 3.0 = 0.65$ . Total events 2 2 Total eve	I otal events	15			6					
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Heterogeneity: Chi <sup>*</sup> = 2.65, df = 3 (f Test for overall effect: Z = 0.94 (P =	P = 0.45); P 0.35)	= 0%							
Oddman 2021, CASPIAN         2         265         2         266         11.56         1.00 [0.14, 7.18]           Ninho 2021, Mipower132         1         291         3         274         20.3%         0.31 [0.03, 30.1]           Ninho 2014, Mipower132         1         291         3         274         20.3%         0.31 [0.03, 30.1]           Ninho 2014, Mipower132         1         291         3         274         20.3%         0.31 [0.03, 30.1]           Total events         1         2.6         1.2         867         45.0%         1.26 [0.04, 3.02]           Total events         2.9         1         2.8         7         4.50%         1.26 [0.04, 3.02]           Total events         2.8         1         2.8         1.26 [0.01, 0.1         0.1         1.1         1.0           Total events         2.80         1.96%         C30 [0.6, 8.05]         0.01         0.1         1.1         1.00           Study of Study on	5.1.2 PD-L1 + Chemotherapy VS. (	Chemother	ару							
Hon 2018, Mover133 2 198 1 196 6 6.8% 1.99 [0.18, 22.12] West 2019, Mpower130 8 473 0 131 6.1% 4.09 [0.28, 32.75] Subtal (95% C) 1 1227 867 45.0% 1.28 [0.46, 3.48] Total events 1 3 6 Total events 1 3 6 Total events 2 49, df = 3 ( $P = 0.48$ ), $P = 0\%$ Test for veral effect 2 = 0.48, $P = 0.65$ Total events 1 2 235 1542 100.0% 1.41 [0.72, 2.75] Total events 1 2 235 1542 100.0% 1.41 [0.72, 2.75] Total events 1 2 8 212 Heterogeneity: Chf = 0.18, df = 1/P = 0.78, $P = 0\%$ Test for veral effect 2 = 0.48, $P = 0.65$ ; C Total events 1 2 8 219 0.05 51 (1.9% 2.52] 0.66, 9.65] Brahmer 2015, CheckMate 017 0 131 1 129 5.9% 0.33 [0.01, 6.50] Brahmer 2015, CheckMate 017 0 82 3 309 16.1% 1.06 [0.27, 4.12] Mox 2019, (EFNOTE-012 7 682 3 309 16.1% 1.08 [0.27, 4.12] Mox 2019, (EFNOTE-010 7 682 3 309 16.1% 1.08 [0.27, 4.12] Mox 2019, (EFNOTE-010 7 682 3 309 16.1% 1.08 [0.27, 4.12] Mox 2019, (EFNOTE-010 7 682 3 309 16.1% 1.08 [0.27, 4.12] Mox 2019, (EFNOTE-010 7 682 3 309 16.1% 1.08 [0.27, 4.12] Mox 2019, (EFNOTE-010 7 682 276 198 2.75] Subtal (95% C) 679 0.22, $P = 0\%$ Test for verail effect 2 = 0.10, $P = 0.37$ , $P = 0\%$ Test for verail effect 2 = 0.10, $P = 0.37$ , $P = 0\%$ Test for verail effect 2 = 0.23 ( $P = 0.02$ ) Subtal (95% C) 679 0.22, $P = 0.03$ Total events 45 7 2 248 10.9% 0.12.39 Subtal (95% C) 679 0.22, $P = 0.03$ Total events 1 3 3 Heterogeneity: Chf = 0.30, ff = 1 ( $P = 0.37$ , $P = 0\%$ Test for verail effect 2 = 0.30, $P = 0.37$ Total events 65 2 278 100.0% 2.12 [1.2, 3.42] Dot 0.1 0.1 0.1 00 Chernotherapy Bore 30.01, AVELIN Lung 200 11 393 3 365 11.9% 3.47 [0.96, 12.56] Heterogeneity: Chf = 0.30, ff = 1 ( $P = 0.37$ , $P = 0\%$ Test for verail effect 2 = 0.32 ( $P = 0.37$ ) Total events 65 7 2 262 3 281 35.4% 1.47 [0.40, 2.84] Dot 0.1 0.1 0.1 0.1 00 Chernotherapy Clis Dother Clis Subtal (95% C) 604 683 100.0\% 1.11 [0.44, 2.84] Dot 0.1 0.1 0.1 0.1 0.0 0 Chernotherapy Clis Dother Clis Subtal (95% C) 604 683 100.0\% 1.11 [0.44, 2.84] Dot 0.1 0.1 0.1 0.0 0 Chernotherapy Clis Doth	Goldman 2021, CASPIAN	2		265	2	266	13.1%	1.00 [0.14	, 7.18]	
Ninhie 2021, Mipower 132 1 201 3 274 20.3% 0.31 [0.03, 0.01] West 2019, Mipower 132 1 27 86 745.0% 1.28 [0.46, 3.48] Heterogenety. Chf= 2.49, df= 3 ( $P=0.48$ ), P= 0% Total events 1 3 6 Heterogenety. Chf= 2.19, df= 7 ( $P=0.48$ ), P= 0% Test for overall effect: Z= 0.45 ( $P=0.83$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.31$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.31$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.31$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.31$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.31$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.31$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.31$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.31$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.31$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.31$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.40 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.30 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.30 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.30 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.30 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.30 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.30 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.30 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.30 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.30 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.30 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.30 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.30 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.30 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.30 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.30 ( $P=0.33$ ), P= 0% Test for overall effect: Z= 0.30 ( $P=0$	Horn 2018, IMpower133	2		198	1	196	6.6%	1.99 [0.18,	22.12]	
West 2019, Mprover130 8 473 0 131 6.1% 4.80 [0.28, 83.75] Total events 13 6 Heterogeneity: Ch <sup>2</sup> = 2.49, df = 3 ( $P = 0.48$ ); $P = 0\%$ Test for overall effect Z = 0.45 ( $P = 0.64$ ); $P = 0\%$ Total events 28 12 Heterogeneity: Ch <sup>2</sup> = 2.49, df = 3 ( $P = 0.64$ ); $P = 0\%$ Test or overall effect Z = 1.01 ( $P = 0.64$ ); $P = 0\%$ Test or overall effect Z = 1.01 ( $P = 0.76$ ); $P = 0\%$ Study of Siboroup Events Total Events Total Weight MH, Fixed, 95% CI Att, Fixed, 95% CI Carbone 2017, CheckMate 071 0 131 122 52, 245 0, 0.08, 0.651 Events Total events 6 2 2 265 7.7% 3.00, 0.01, 0.071 Total events 7 45 0, 0.021 131 22 22 2 265 8, 11.9% 0.33 (0.18, 0.07] Carbone 2017, CheckMate 071 0 133 1 125 5.3% 0.038 (0.18, 0.07] Carbone 2017, CheckMate 073 2 237 1 156 5.3% 0.038 (0.18, 0.07] Material 2014, CheckMate 073 2 237 1 156 5.3% 0.038 (0.18, 0.07] Total events 7 45 2 20 Heterogeneity: Ch <sup>2</sup> = 2.35 ( $P = 0.02$ ) S2.2 PD-1 VS. Chemotherapy Barler 2015, CheckMate 073 2 237 1 156 5.3% 0.038 (0.18, 0.07] Total events 7 45 2 20 Heterogeneity: Ch <sup>2</sup> = 2.35 ( $P = 0.02$ ) S2.2 PD-1 VS. Chemotherapy Barler 2013, CheckMate 073 2 237 1 156 5.3% 0.038 (0.18, 0.07] Total events 7 45 2 20 Heterogeneity: Ch <sup>2</sup> = 4.75 ( $P = 0.02$ ) S2.2 PD-1 VS. Chemotherapy Barler 2013, Weitherapy Barler 2013, Weitherapy Barler 2013, Weitherapy Barler 2013, Weitherapy Barler 2014, Weitherapy Barler 2015, Weitherapy Barler 2014, Weitherapy Barler 2015, Weitherapy Barler 2015, Weitherapy Barler 2016, Weitherapy Barler 216, Weitherapy Barler 216, Weitherapy Barler 216, Weitherapy Barler 216, Weitherapy Barler 216, Weitherapy Barle	Nishio 2021, IMpower132	1		291	3	274	20.3%	0.31 [0.03	, 3.01]	
Subtal (9% C) 1227 867 45.0% 1.26 [0.46, 3.48] Heterogeneity: Ch <sup>2</sup> = 2.49, df = 3 (P = 0.48); P = 0%, Total events 2 0.45 (P = 0.68); Total events 2 0.42 (P = 0	West 2019, IMpower130	8		473	0	131	5.1%	4.80 [0.28,	83.75]	
Total events 1 3 6 Heterogeneity. Chi <sup>+</sup> = 2.49, df = 2 (43), l <sup>+</sup> = 0.43; Total (95% C) 2235 1542 100.0% 1.41 [0.72, 2.75] Heterogeneity. Chi <sup>+</sup> = 5.19, df = 7 (P = 0.43), l <sup>+</sup> = 0.5 Test for verall effect Z = 1.01 (P = 0.31) Test for subarou differences: Chi <sup>+</sup> = 0.08; df = 1 (P = 0.78), l <sup>+</sup> = 0.5 Study of Subgroup Events Total Events Total Veral ML, Fixed, 55% Cl Study of Subgroup 2 2.67 (2 2 2.63 7.7% 3.00 [0.60, 15.00] Barmer 2015, CheckMate 007 8 2.87 (2 3 206 11.9% 2.75) (0.48, 0.67) Cardone 2017, CheckMate 007 6 2.27 (2 2.63 7.7% 3.00 [0.60, 15.00] Barmer 2015, CheckMate 007 6 2.27 (2 3 300 1.16; 11.06 [0.27, 4.12] Mox 2018, KEYNOTE-042 14 6.36 5 6.15 19.6% 2.75 (0.38, 0.767) Total events 202, CheckMate 007 6 2.27 (2 2.263 7.7% 3.00 [0.60, 15.00] Subtrait (95% C) 7 2.25 7.7 (2 2.55 3.5% 0.33 (0.18, 0.77) Total events 7 45 (7 2.55 60.1% 1.15% 1.159 (0.48, 0.10, 8.10, 7.07) Total events 7 45 (7 2.276 2.276 2.25 5.5% 0.33 (0.18, 0.12, 0.5% 0.238) (0.13, 0.12, 0.5% 0.238) (0.12, 0.5% 0.138, 0.12, 0.5% 0.238) (0.13, 0.13, 0.138) (0.14, 0.13, 0.12, 0.5% 0.238) (0.13, 0.13, 0.138) (0.14, 0.138) (0.14, 0.138) (0.14, 0.138) (0.14, 0.138) (0.14, 0.138) (0.14, 0.138) (0.14, 0.148) (0.14, 0.148) (0.14, 0.148) (0.14, 0.148) (0.14, 0.148) (0.14, 0.148) (0.14, 0.148) (0.148, 0.148) (0.148, 0.148) (0.148, 0.148) (0.148, 0.148) (0.148, 0.148) (0.148, 0.148) (0.148, 0.148) (0.148, 0.148) (0.148, 0.148) (0.148, 0.148) (0.148, 0.148) (0.148, 0.148) (0.148, 0.148) (0.148, 0.148) (0.148, 0.148) (0.1	Subtotal (95% CI)			1227		867	45.0%	1.26 [0.46	, 3.48]	
Heterogeneity: $Ch^{\mu} = 2.49, (df = 2 (P = 0.48); (P = 0.68)$ Test for overall effect $Z = 0.64$ ; (P = 0.68); Total events 28 12 Heterogeneity: $Ch^{\mu} = 5.18, (df = 2 (P = 0.64); (P = 0.57); (P = 0.56);$ Test for overall effect $Z = 1.01$ (P = 0.31) Test for overall effect $Z = 1.01$ (P = 0.31) Test for overall effect $Z = 1.01$ (P = 0.31) Test for overall effect $Z = 1.01$ (P = 0.31) Test for overall effect $Z = 1.01$ (P = 0.31) Test for overall effect $Z = 1.01$ (P = 0.37); P = 0.56 South or Subtravia (D = Context Total Verialt MH, Fixed, 455: Cl MH, Fixed, 455: Cl MH, Fixed, 455: Cl MH, Fixed, 455: Cl Heterogeneity: Ch = 4.58, (df = 2 (P = 0.48); P = 0.57); South 1.195, 0.23 (0.66, 9.65) Brahmer 2015, CheckMate 017 0 131 1 129 5.9% 0.33 (0.01, 8.07) Herbs 2020, KEYNOTE-010 7 6.92 2 205 115.9% 2.75 (0.98, 7.67) Reck 2019, KEYNOTE-012 4 6 154 5 150 11.5% 1.99 (0.49, 8.09) Figure 2015, CheckMate 078 2 3.37 1 156 5.3% 0.33 (0.08, 15.02) Herbs 2020, KEYNOTE-012 4 6 154 2 200; Ke 1.5% 0.33 (0.01, 8.07) Herbs 2020, KEYNOTE-012 7 6 92.37 = 0.9% Test for overall effect $Z = 2.35$ (P = 0.82); P = 0.85 Test for overall effect $Z = 2.35$ (P = 0.82); P = 0.85 Test for overall effect $Z = 2.35$ (P = 0.82); P = 0.85 Test for overall effect $Z = 2.35$ (P = 0.82); P = 0.85 Test for overall effect $Z = 2.35$ (P = 0.82); P = 0.85 Test for overall effect $Z = 2.35$ (P = 0.82); P = 0.85 Test for overall effect $Z = 2.35$ (P = 0.82); P = 0.85 Test for overall effect $Z = 2.35$ (P = 0.48); P = 0.85 Test for overall effect $Z = 2.35$ (P = 0.48); P = 0.85 Test for overall effect $Z = 2.30$ (P = 0.48); P = 0.85 Test for overall effect $Z = 2.30$ (P = 0.48); P = 0.85 Test for overall effect $Z = 2.30$ (P = 0.48); P = 0.85 Test for overall effect $Z = 2.30$ (P = 0.49); P = 0.85 Test for overall effect $Z = 2.30$ (P = 0.49); P = 0.85 Test for overall effect $Z = 2.30$ (P = 0.49); P = 0.85 Test for overall effect $Z = 2.30$ (P = 0.49); P = 0.85 Test for overall effect $Z = 2.30$ (P = 0.49); P = 0.8	Total events	13			6					
Total (95% CI)       2235       1542       100.0%       1.41 [0.72, 2.75]         Total events       23       12         Test for overall effect $Z = 101$ ( $P = 0.31$ )       0.01       0.1       0.1       10       100         Test for overall effect $Z = 101$ ( $P = 0.31$ )       External Velocity       Odds Ratio       Odds Ratio       Odds Ratio         Study or Subproup       Forms       Total Velocity       Odds Ratio       M.H.Fixed, 95% CI         Scate Port VS.       Chemotherapy       External Velocity       M.H.Fixed, 95% CI       M.H.Fixed, 95% CI         Scate Port VS.       Chemotherapy       External Velocity       M.H.Fixed, 95% CI       M.H.Fixed, 95% CI         Scate Port VS.       Chemotherapy       External Velocity       M.H.Fixed, 95% CI       M.H.Fixed, 95% CI         Scate Port VS.       Chemotherapy       External Velocity       M.H.Fixed, 95% CI       M.H.Fixed, 95% CI         Scate Port VS.       Chemotherapy       External Velocity       100       External Velocity       M.H.Fixed, 95% CI         Scate Port VS.       Scate Port VS.       External Velocity       10.61       External Velocity       10.61       10.61       10.61         Scate Port VS.       Scate Port VS.       Scate Port VS.       Scate Port VS.       10.61 <td>Heterogeneity: <math>Chi^2 = 2.49</math>, df = 3 (f Test for overall effect: Z = 0.45 (P =</td> <td>P = 0.48); l² 0.65)</td> <td>= 0%</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Heterogeneity: $Chi^2 = 2.49$ , df = 3 (f Test for overall effect: Z = 0.45 (P =	P = 0.48); l² 0.65)	= 0%							
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Heterogeneity: $Ch^{\mu} = 5.18 (d = 7 (P = 0.8); P = 0.8$ Test for varial effect $Z = 101 (P = 0.7); P = 0.8;$ Cls Chemotherapy Cls + Chemotherapy Odds Ratio Odds Ratio O	Total events	28			12			-		
Test for overall effect Z = 1.01 ( $P = 0.31$ ) Test for subarous differences: Ch <sup>2</sup> = 0.08, df = 1 ( $P = 0.73$ ), $P = 0$ % Chemotherapy Odds Ratio Sc.1 PD-1VS. Chemotherapy Brahmer 2015, CheckMate 017 0 121 1 122 5.98, 0.33 [0.01, 8.017] Sc.1 PD-1VS. Chemotherapy Brahmer 2015, CheckMate 017 0 121 1 122 5.98, 0.33 [0.01, 8.017] Fraction 2017, CheckMate 017 0 121 1 122 5.98, 0.33 [0.01, 8.017] Herbs 2016, CheckMate 017 0 121 1 122 5.98, 0.33 [0.01, 8.017] Herbs 2016, CheckMate 017 0 121 1 122 5.98, 0.33 [0.01, 8.017] Herbs 2016, CheckMate 017 0 121 1 282 2 2 2.85 8.118, 0.080, 1.52] Mok 2019, KEPNOTE-010 7 682 3 300 16.118, 001 [0.21, 4.12] Mok 2019, KEPNOTE-024 6 154 3 150 11.55, 0.189, 0.67] Mok 2019, KEPNOTE-042 1 282 2 2.85 8.118, 0.94 [0.13, 6.72] Wo 2018, CheckMate 078 2 337 1 155 5.38, 0.33 [0.02, 10.28] Subtate (16%) C) 2.2776 2.020 Subtate (16%) C) 2.2776 2.020 S.2.2 PD-L1 VS. Chemotherapy Barlesi 2016, M-KELNL ung 200 11 33 3 365 11.9% 3.47 [0.96, 12.56] Heterogeneity, Ch <sup>2</sup> = 4.75, df = 9 (P = 0.80), P = 0% Test for overall effect Z = 2.39 (P = 0.03) Total events 1 3 Heterogeneity, Ch <sup>2</sup> = 4.75, df = 9 (P = 0.80), P = 0% Test for overall effect Z = 2.39 (P = 0.03) Total (95%) Ch 3455 2.783 100.0% 2.12 [1.32, 3.42] Double ICIs Single ICI Odds Ratio Double ICIs Single ICI Double ICIs Dist 3 0.51 (1.11, 0.44, 2.84] Double ICIs Dist 2.2.23 (P = 0.49), P = 0% Test for overall effect Z = 0.23 (P = 0.49), P = 0% Test for overall effect Z = 0.23 (P = 0.49), P = 0% Test for overall effect Z = 0.23 (P = 0.49), P = 0% Test for overall effect Z = 0.23 (P = 0.49), P = 0% Test for overall effect Z = 0.23 (P = 0.49), P = 0% Test for overall effect Z = 0.23 (P = 0.49), P = 0%	Heterogeneity: Chi <sup>2</sup> = 5.18. df = 7 (f	P = 0.64); I <sup>2</sup>	= 0%							
Test for subaroup differences: $Ch^{\mu} = 0.58$ df = 1 ( $P = 0.78$ ), $P = 0.55$ Chermotherapy Odds Ratio Study or Subaroup S2.1PD - US. Chermotherapy Odds Ratio S2.1PD - US. Chermotherapy Odds Ratio Odds Ratio MH, Fixed, 95% CI MH,	Test for overall effect: Z = 1.01 (P =	0.31)								U.U1 U.1 1 10 100
$ \begin{array}{ c c c c } \hline Che Chemother apy \\ \hline Freents Total & Veight & M-H, Fixed, 95% CI \\ \hline Carbone 2017, CheckMate 026 & 267 & 2 & 263 & 7.78 & 3.00 [0.6, 0.50 ] \\ \hline Carbone 2017, CheckMate 026 & 267 & 2 & 263 & 7.78 & 3.00 [0.6, 0.15.00 ] \\ \hline Herbst 2020, KEYNOTE-104 & 6 & 164 & 3 & 150 \\ \hline Mok 2019, KEYNOTE-042 & 14 & 636 & 5 & 615 & 19.6% & 2.75 [0.98, 7.67 ] \\ \hline Reck 2019, KEYNOTE-042 & 14 & 636 & 5 & 615 & 19.6\% & 2.75 [0.98, 7.67 ] \\ \hline Mok 2019, CheckMate 078 & 2 & 337 & 1 & 156 & 5.3\% & 0.39 [0.08, 10.23, 6.72 ] \\ \hline Muy 2019, CheckMate 078 & 2 & 337 & 1 & 156 & 5.3\% & 0.39 [0.08, 10.28 ] \\ \hline Muy 2019, CheckMate 078 & 2 & 337 & 1 & 156 & 5.3\% & 0.39 [0.08, 10.28 ] \\ \hline Heterogeneity. Chi+ = 3.68, df = 7 (P = 0.82); P = 0\% \\ \hline Test for overall effect Z = 2.35 (P = 0.02) \\ \hline Total events & 45 & 20 \\ Heterogeneity. Chi+ = 0.03, df = 1 (P = 0.80); P = 0\% \\ \hline Total events & 58 & 23 \\ Heterogeneity. Chi+ = 0.03, df = 1 (P = 0.80); P = 0\% \\ \hline Total events & 58 & 23 \\ Heterogeneity. Chi+ = 0.03, df = 1 (P = 0.80); P = 0\% \\ \hline Total events & 58 & 23 \\ Heterogeneity. Chi+ = 0.03, df = 1 (P = 0.80); P = 0\% \\ \hline Total events & 58 & 23 \\ Heterogeneity. Chi+ = 0.03, df = 1 (P = 0.80); P = 0\% \\ \hline Total events & 58 & 23 \\ Heterogeneity. Chi+ = 1.43, df = 2 (P = 0.80); P = 0\% \\ \hline Total events & 58 & 23 \\ Heterogeneity. Chi+ = 1.43, df = 2 (P = 0.80); P = 0\% \\ \hline Total events & 51 & 28 & 278 & 100.0\% \\ \hline Total events & 51 & 28 & 278 & 100.0\% \\ \hline Total events & 52 & 202 & 3 & 281 & 56.7\% & 0.59 & 10.24 \\ \hline Durble (Chi effect Z = 3.0.24); P = 0.5\% \\ \hline Total (95\% CI) & 684 & 683 & 100.0\% & 1.11 [0.44, 2.84] \\ \hline Durble (Chi effect Z = 2.0.23 (P = 0.82)) \\ \hline Total (95\% CI) & 684 & 683 & 100.0\% & 1.11 [0.44, 2.84] \\ \hline Durble (Chi effect Z = -0.23 (P = 0.82)) \\ \hline Total (95\% CI) & 684 & 683 & 100.0\% & 1.11 [0.44, 2.84] \\ \hline Durble (Chi = 1.43, df = 2 (P = 0.49)) \\ \hline Total events & 61 & 3$	Test for subaroup differences: Chi	<sup>2</sup> = 0.08. df :	= 1 (P =	= 0.78), I <sup>2</sup>	= 0%					Chemotherapy ICIs + Chemotherapy
Study of Submound         Events         Total         Weight         M.H. Fixed, 95% Cl         M.H. Fixed, 95% Cl           5.2.1 PD.1 VS. Chemotherapy         267         3         268         11.9%         2.53 [0.66, 9.65]           Brahmer 2015, CheckMate 017         0         131         1         129         5.9%         0.33 [0.01, 9.07]           Catorone 2017, CheckMate 017         0         131         1         129         5.9%         0.33 [0.01, 9.07]           Heits 1200, KEYNOTE-010         7         682         3         309         16.1%         1.06 [0.27, 4.12]           Mok 2019, KEYNOTE-042         6         154         3         150         11.5%         1.99 [0.49, 8.09]           Single 1021, CheckMate 078         2         337         1         156         5.3%         0.33 [0.02, 10.28]           Subtotal (95% Cl)         2776         2155         86.1%         1.87 [1.11, 3.17]         1.97           Total events         45         20         1.19%         3.47 [0.96, 12.56]         1.19%         1.61 [1.12, 11.88]           Total events         13         3         365         11.9%         3.64 [1.12, 11.88]         1.00 [1.1, 1.0, 1.0]         1.00           Subtotal (95% Cl)		ICIS		Chemoth	erapy		Odds	Ratio		Odds Ratio
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Study or Subgroup	Events	Total	Events	Total	Weigh	t M-H, Fix	ed, 95% CI		M-H, Fixed, 95% Cl
Borghael 2015, CheckMateOF7 8 287 3 268 11.9% 253 D66, 8.65] Brahmer 2015, CheckMate 017 0 131 1 129 5.9% 0.33 [0.01, 8.07] Carbone 2017, CheckMate 027 0 131 1 129 5.9% 0.33 [0.01, 8.07] Action 2017, CheckMate 028 6 267 2 2 263 7.7% 3.00 [0.00, 15.00] Herbs 2020, KEYNOTE-010 7 682 3 309 16.1% 1.06 [0.27, 4.12] Mok 2019, KEYNOTE-024 6 164 3 150 11.5% 1.99 [0.49, 8.09] Sipple 2021, heckMate 078 2 337 1 166 5.3% 0.39 [0.08, 10.28] Subtotal (95% CI) 2776 2 23(5 86.1% 1.87 [1.11, 3.17] Total events 45 20 Herbs 2020, KEYNOTE-020 F = 0.80; P = 0% Test for overall effect Z = 2.36 (P = 0.80; P = 0% Test for overall effect Z = 2.36 (P = 0.80; P = 0% Test for overall effect Z = 2.14 (P = 0.86); P = 0% Test for overall effect Z = 2.14 (P = 0.86); P = 0% Test for overall effect Z = 2.14 (P = 0.86); P = 0% Test for overall effect Z = 2.14 (P = 0.86); P = 0% Test for overall effect Z = 2.14 (P = 0.86); P = 0% Test for overall effect Z = 2.14 (P = 0.86); P = 0% Test for overall effect Z = 2.09 (P = 0.80; P = 0% Test for overall effect Z = 0.20 (P = 0.80; P = 0% Test for overall effect Z = 0.20 (P = 0.80; P = 0% Test for overall effect Z = 0.20 (P = 0.80; P = 0% Test for overall effect Z = 0.20 (P = 0.80; P = 0% Test for overall effect Z = 0.20 (P = 0.80; P = 0% Test for overall effect Z = 0.20 (P = 0.80; P = 0% Test for overall effect Z = 0.20 (P = 0.80; P = 0% Test for overall effect Z = 0.20 (P = 0.49); P = 0% Test for overall effect Z = 0.23 (P = 0.49); P = 0% Test for overall effect Z = 0.23 (P = 0.49); P = 0% Test for overall effect Z = 0.23 (P = 0.49); P = 0% Test for overall effect Z = 0.23 (P = 0.49); P = 0% Test for overall effect Z = 0.23 (P = 0.49); P = 0% Test for overall effect Z = 0.23 (P = 0.49); P = 0% Test for overall effect Z = 0.23 (P = 0.49); P = 0% Test for overall effect Z = 0.23 (P = 0.49); P = 0% Test for overall effect Z = 0.23 (P = 0.49); P = 0% Test for overall effect Z = 0.23 (P = 0.49); P = 0% Test for overall effect Z = 0.23 (P = 0.49); P = 0% Test for overal	5.2.1 PD-1 VS. Chemotherapy									
Brahmer 2015, CheckMate 077 0 131 1 129 5.9% 0.33 [0.01, 0.07, 0.7] Carbone 2017, CheckMate 026 6 267 2 263 7.7% 3.00 [0.60, 15.00] Herbst 200, KEYNOTE-042 14 636 5 615 19.6% 2.75 [0.98, 7.67] Reck 2019, KEYNOTE-042 6 154 3 150 11.5% 1.99 [0.49, 0.99] Shiptel 2021, CheckMate 031 2 282 2 265 81% 0.94 [0.13, 6.72] Wu 2019, CheckMate 078 2 337 1 156 5.3% 0.93 [0.08, 10.28] Subtotal (95% CI) 2776 2155 86.1% 1.87 [1.11, 3.17] Total events 45 20 Herbst 200, MAVELIN Lung 200 11 393 3 365 11.9% 3.47 [0.96, 12.56] Herbst 200, MAVELIN Lung 200 11 393 3 365 11.9% 3.47 [0.96, 12.56] Herbst 200, MAVELIN Lung 200 11 393 3 365 11.9% 3.47 [0.96, 12.56] Herbst 200, MAVELIN Lung 200 11 393 3 365 11.9% 3.47 [0.96, 12.56] Herbst 200, Mayoweri 10 2 286 0 263 2.0% 4.63 [0.22, 96.91] Subtotal (95% CI) 679 628 13.9% 3.64 [1.12, 11.88] Total events 1 3 3 Heterogeneity: Ch <sup>2</sup> = 4.75, df = 9 (P = 0.86); P = 0% Testfor overall effect Z = 2.14 (P = 0.03) Total (95% CI) 512 CIP = 0.33, df = 1 (P = 0.58); P = 0% Testfor overall effect Z = 3.09 (P = 0.08); P = 0% Testfor overall effect Z = 3.09 (P = 0.88); P = 0% Testfor overall effect Z = 3.09 (P = 0.88); P = 0% Testfor overall effect Z = 2.14 (P = 0.80); P = 0% Testfor overall effect Z = 2.02 (P = 0.48); P = 0% Testfor overall effect Z = 2.02 (P = 0.48); P = 0% Testfor overall effect Z = 2.02 (P = 0.48); P = 0% Testfor overall effect Z = 0.23 (P = 0.48); P = 0% Testfor overall effect Z = 0.23 (P = 0.48); P = 0% Testfor overall effect Z = 0.23 (P = 0.49); P = 0% Testfor overall effect Z = 0.23 (P = 0.49); P = 0% Testfor overall effect Z = 0.23 (P = 0.49); P = 0% Testfor overall effect Z = 0.23 (P = 0.49); P = 0% Testfor overall effect Z = 0.23 (P = 0.49); P = 0% Testfor overall effect Z = 0.23 (P = 0.49); P = 0% Testfor overall effect Z = 0.23 (P = 0.49); P = 0% Testfor overall effect Z = 0.23 (P = 0.49); P = 0% Testfor overall effect Z = 0.23 (P = 0.49); P = 0% Testfor overall effect Z = 0.23 (P = 0.49); P = 0% Testfor overall effect Z = 0.23 (P = 0.49);	Borghaei 2015, CheckMate057	8	287	3	268	11.9%	2.53	0.66, 9.651		
Carbone 2017, CheckMate 026 6 267 2 263 7.7% $3.00[0.60, 15.00]$ Herbs 2020, KEYNOTE-042 14 636 5 615 19.6% $7.75[0.67, 7.75]$ Reck 2019, KEYNOTE-024 6 154 3 150 11.5% $1.99[0.49, 8.09]$ Spigel 2021, CheckMate 078 2 337 1 156 5.3% $0.93[0.08, 10.28]$ Subtotal 60% CI) 2776 2155 86.1% $1.87[1.11, 3.17]$ Total events 2 20 Heterogeneity: Chi <sup>2</sup> = 3.89, df = 7 (P = 0.82); P = 0% Test for overall effect: Z = 2.50 (P = 0.02) S.2.2 PD-L1 VS. Chemotherapy Barlesi 2018, JAVELINL Lung 200 11 393 3 365 11.9% $3.47[0.96, 12.56]$ Heterogeneity: Chi <sup>2</sup> = 0.30; df = 1 (P = 0.86); P = 0% Total events 5 8 23 Total events 58 23 Total events 68 23 Total events 58 23 Total events 68 23 Total events 68 5 23 Total events 69 5 282 3 281 354% 1.67(0.40,7.07) Chermotherapy ICIs Total events 9 8 Reterogeneity: Chi <sup>2</sup> = 1.43, df = 2(P = 0.49); P = 0% Total events 9 8 Reterogeneity: Chi <sup>2</sup> = 1.43, df = 2(P = 0.49); P = 0% Total events 9 8 Reterogeneity: Chi <sup>2</sup> = 1.43, df = 2(P = 0.49); P = 0% Total events 9 8 Reterogeneity: Chi <sup>2</sup> = 1.43, df = 2(P = 0.49); P = 0% Total events 9 8 Reterogeneity: Chi <sup>2</sup> = 1.43, df = 2(P = 0.49); P = 0% Total events 9 8 Reterogeneity: Chi <sup>2</sup> = 1.43, df = 2(P = 0.49); P = 0% Total events 9 8 Reterogeneity: Chi <sup>2</sup> = 1.43, df = 2(P = 0.49); P = 0% Total events	Brahmer 2015, CheckMate 017	0	131	1	129	5.9%	6 0.33	[0.01, 8.07]	-	
Herbst 2020, KEYNOTE-010 7 682 3 309 16.1% 1.06 [0.27, 4.12] Mok 2019, KEYNOTE-042 14 636 5 615 19.6% 2.75 [0.38, 7.67] Reck 2019, KEYNOTE-042 14 636 5 615 19.6% 2.75 [0.38, 7.67] Shipted 2021, CheckMate 331 2 282 2 265 8.1% 0.94 [0.13, 6.72] Wu 2019, CheckMate 331 2 282 2 265 8.1% 0.93 [0.08] 0.028] Subtotal (95% CI) 2776 2155 86.1% 1.87 [1.11, 3.17] Total events 45 20 Heterogeneity: ChiP = 3.80, df = 7 (P = 0.82); P = 0% Test for overall effect: $Z = 2.35$ (P = 0.02) 5.2.2 PD-11 VS. Chemotherapy Barlesi 2018, LAVELIN Lung 200 11 393 3 365 11.9% 3.47 [0.96, 12.56] Herbst 2020, Mpower110 2 286 0 263 2.0% 4.63 [0.22, 96.91] Subtotal (95% CI) 679 623 2.0% 4.63 [0.22, 96.91] Total events 1 3 3 Heterogeneity: ChiP = 0.30; f = 0 (P = 0.86); P = 0% Test for overall effect: $Z = 2.14$ (P = 0.08); P = 0% Test for overall effect: $Z = 3.09$ (P = 0.002) Total (95% CI) 58 2783 100.0% 2.12 [1.32, 3.42] Total events 58 2 23 Heterogeneity: ChiP = 4.75, df = 9 (P = 0.86); P = 0% Test for overall effect: $Z = 3.09$ (P = 0.002) Total (95% CI) 58 2783 100.0% 2.12 [1.32, 3.42] Total events 58 2 23 Events Total Events 0.59 (CI 0.000, S.110, P = 1.5% Double ICIs Single ICI 0.000 K Ratio Butop Cliptic ChiP = 0.33, I = 1.03, I = 0.03, I = 0.0	Carbone 2017 CheckMate 026	6	267	2	263	7 7 9	\$ 3,00,0	60 15 001		
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Herbst 2020 KEYNOTE-010	7	682	3	300	16.19	6 1.00 [0	10 27 4 1 21		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Mok 2010 KEYNOTE-042	14	636	5	615	10.1%	0 1.00	0.27, 4.12		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Dock 2010, NETHOTE 024	14	164	0	460	14 60	4.00	0.30, 7.07]		
Shige 1021, Unexamile 331 2 202 2 2 005 6.1% 0.94 (0.13, 6.72) Wu 2019, CheckMate 078 2 337 1 156 5.3% 0.39 (0.08, 10.28) Subtoal (95% CI) 2776 2155 86.1% 1.87 [1.11, 3.17] Total events 45 20 Heterogeneity: Chi <sup>2</sup> = 3.69, df = 7 (P = 0.82); P = 0% Test for overall effect Z = 2.35 (P = 0.02) 5.2.2 PD-L1 VS. Chemotherapy Barlesi 2018, AVELIN Lung 200 11 393 3 365 11.9% 3.47 [0.96, 12.56] Herbst 2020, Mpower110 2 286 0 263 2.0% 4.63 [0.22, 96.91] Subtoal (95% CI) 679 628 13.9% 3.64 [1.12, 11.88] Total events 1 3 3 Heterogeneity: Chi <sup>2</sup> = 0.03, df = 1 (P = 0.86); P = 0% Test for overall effect Z = 2.14 (P = 0.86); P = 0% Test for overall effect Z = 0.03 (P = 0.002) Total events 5 22 Heterogeneity: Chi <sup>2</sup> = 4.75, df = 9 (P = 0.86); P = 0% Test for overall effect Z = 0.03 (P = 0.002) Test for subarous differences: Chi <sup>2</sup> = 1.01, df = 1 (P = 0.31); P = 1.5% Single ICI Subtoal (95% CI) 5 282 3 281 35.4% 1.67 [0.40, 7.07] Test for overall effect Z = 0.23 (P = 0.02) Test for overall effect Z = 0.23 (P = 0.02) Total events 1 Total Events 1 Total Events 1 Total Events 1 Total Events 5 10.0 0.01 0.1 10 100 Chemotherapy ICIs Single ICI 0 0.02 (1, 2, 74.49] Subtoal (95% CI) 684 683 100.0% 1.11 [0.44, 2.84] Total events 9 8 Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect Z = 0.23 (P = 0.82) Total (95% CI) 684 683 100.0% 1.11 [0.44, 2.84] Total events 9 8 Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect Z = 0.23 (P = 0.82) Total (95% CI) 684 683 100.0% 1.11 [0.44, 2.84] Total events 9 8 Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect Z = 0.23 (P = 0.82) Total (95% CI) 684 683 100.0% 1.11 [0.44, 2.84] Total events 1 0 9 8 Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect Z = 0.23 (P = 0.82) Total events 1 0 9 8 Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect Z = 0.23 (P = 0.82) Total events 1 0 9 8 Heterogeneity: Chi <sup>2</sup> = 0.82) T	Chinel 2021 Obsethints 201	0	104	3	150	11.5%	1.99	0.49, 8.09		
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Spiger 2021, CheckMate 331	2	282	2	265	8.1%	0 0.94	[0.13, 6.72]		
Subtotal (95% CI) 2776 2155 86.1% $1.87 [1.11, 3.17]$ Heterogeneity: Chi <sup>2</sup> = 3.69, df = 7 (P = 0.82); P = 0% Test for overall effect: Z = 2.35 (P = 0.02) 5.2.2 PD-L1 VS. Chemotherapy Barlesi 2018, JAVELIN Lung 200 11 393 3 365 11.9% 3.47 [0.96, 12.56] Herbris 2020; Mpower110 2 286 0 263 2.0% 4.63 [0.22, 96.91] Subtotal (95% CI) 679 628 13.9% 3.64 [1.12, 11.88] Total events 13 3 Heterogeneity: Chi <sup>2</sup> = 0.03, df = 1 (P = 0.86); P = 0% Test for overall effect: Z = 2.14 (P = 0.03) Total events 58 23 Heterogeneity: Chi <sup>2</sup> = 4.75, df = 9 (P = 0.86); P = 0% Test for overall effect: Z = 3.09 (P = 0.002) Test for subaroup differences: Chi <sup>2</sup> = 1.01, df = 1 (P = 0.31); P = 1.5% Single ICI Odds Ratio Study or Subgroup Events Total Weight MH, Fixed, 95% CI MH, Fixed, 95% CI Single ICI Odds Ratio Study or Subgroup Events Total Weight MH, Fixed, 95% CI MH, Fixed, 95% CI Single ICI Odds Ratio Study or Subgroup Events Total Weight MH, Fixed, 95% CI MH, Fixed, 95% CI Single ICI Odds Ratio MH, Fixed, 95% CI MH, Fixed, 95% CI Subtotal (95% CI) 684 683 100.0% 1.11 [0.44, 2.84] Total events 9 8 Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test	Wu 2019, CheckMate 078	2	337	1	156	5.3%	6 0.93 [0	0.08, 10.28]		
Total events 45 20 Heterogeneity: ChF = 3.63, df = 7 (P = 0.82); P = 0% Test for overall effect. Z = 2.35 (P = 0.02) 5.2.2 PD-L1 VS. Chemotherapy Barkesi 2018, JAVELIN Lung 200 11 393 3 365 11.9% 3.47 [0.96, 12.56] Heterost 2020, Mipower110 2 2 266 0 263 2.0% 4.63 [0.22, 96.91] Subtotal (95% Cl) 679 628 13.9% 3.64 [1.12, 11.88] Total events 13 3 Heterogeneity: ChF = 0.03, df = 1 (P = 0.86); P = 0% Test for overall effect. Z = 2.14 (P = 0.08); P = 0% Test for subarous differences: ChF = 0.48); P = 0.31). P = 1.5% Test for subarous differences: ChF = 0.48); P = 0.31). P = 1.5% Test for subarous differences: ChF = 1.01. df = 1 (P = 0.31). P = 1.5% Test for subarous differences: ChF = 1.01. df = 1 (P = 0.31). P = 1.5% Test for subarous differences: ChF = 1.01. df = 1 (P = 0.31). P = 1.5% Test for subarous differences: ChF = 1.01. df = 1 (P = 0.31). P = 1.5% Test for subarous differences: ChF = 1.01. df = 1 (P = 0.31). P = 1.5% Test for subarous differences: ChF = 1.01. df = 1 (P = 0.31). P = 1.5% Test for subarous differences: ChF = 1.01. df = 1 (P = 0.31). P = 1.5% Test for subarous differences: ChF = 1.01. df = 1 (P = 0.31). P = 1.5% Test for subarous differences: ChF = 1.01. df = 1 (P = 0.31). P = 1.5% Test for subarous differences: ChF = 1.01. df = 1 (P = 0.31). P = 1.5% Subtotal (95% Cl) 684 683 100.0% 1.11 [0.40, 7.07] Gettinger 2021, LengMAP 14001 3 124 5 123 58.7% 0.59 (D (1.2, 74.49] Subtotal (95% Cl) 684 683 100.0% 1.11 [0.44, 2.84] Total events 9 8 Heterogeneity: ChF = 1.43, df = 2 (P = 0.49); P = 0% Test for subarous file filect. Z = 0.23 (P = 0.49); P = 0% Test for subarous differences: Not apolicable Total events 9 8 Heterogeneity: ChF = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect. Z = 0.23 (P = 0.82) Test for subarous differences: Not apolicable	Subtotal (95% CI)	2	2776		2155	86.1%	§ 1.87 [	1.11, 3.17]		
Heterogeneity: Ch <sup>2</sup> = 3.69, df = 7 (P = 0.82); P = 0% Test for overall effect: Z = 2.35 (P = 0.02) 5.2.2 PD-L1 VS. Chemotherapy Barlesi 2018, JAVELIN Lung 200 11 393 3 365 11.9% 3.47 [0.96, 12.56] Herbst 2020, IMpower110 2 286 0 263 2.0% 4.63 [0.22, 96.91] Subtotal (95% CI) 679 628 13.9% 3.64 [1.12, 11.88] Total events 13 3 Heterogeneity: Ch <sup>2</sup> = 0.03, df = 1 (P = 0.86); P = 0% Test for overall effect: Z = 2.14 (P = 0.03) Total (95% CI) 3455 2783 100.0% 2.12 [1.32, 3.42] Total events 58 23 Heterogeneity: Ch <sup>2</sup> = 4.75, df = 9 (P = 0.86); P = 0% Test for overall effect: Z = 3.09 (P = 0.002) Test for overall effect: Z = 3.09 (P = 0.002) Test for subaroup differences: Ch <sup>2</sup> = 1.01. df = 1 (P = 0.31); P = 1.5% Double ICIs Single ICI Double ICIs Single ICI Odds Ratio Study or Subaroup Events Total Events Total Weight M.H. Fixed, 95% CI Study or Subaroup Events Total Events Total Weight M.H. Fixed, 95% CI Subtotal (95% CI) 684 683 100.0% 1.11 [0.44, 2.84] Total (95% CI) 684 683 100.0% 1.11 [0.44, 2.84] Total events 9 8 Heterogeneity: Ch <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall ef	Total events	45		20						
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Bartesi 2018, JAYELIN Lung 200 11 393 3 365 11.9% 3.47 (0.96, 12.56) Herbst 2020, Mpower110 2 286 0 263 2.0% 4.63 [0.22, 96.91] Total events 13 3 Heterogeneity: Chi <sup>2</sup> = 0.03, df = 1 ( $P = 0.86$ ); $P = 0\%$ Test for overall effect: $Z = 2.14$ ( $P = 0.086$ ); $P = 0\%$ Test for overall effect: $Z = 2.14$ ( $P = 0.086$ ); $P = 0\%$ Total events 58 23 Heterogeneity: Chi <sup>2</sup> = 4.75, df = 9 ( $P = 0.86$ ); $P = 0\%$ Test for overall effect: $Z = 3.09$ ( $P = 0.002$ ) Test for overall effect: $Z = 3.09$ ( $P = 0.002$ ) Test for overall effect: $Z = 3.09$ ( $P = 0.002$ ) Test for overall effect: $Z = 3.09$ ( $P = 0.002$ ) Test for overall effect: $Z = 3.09$ ( $P = 0.002$ ) Test for overall effect: $Z = 3.09$ ( $P = 0.002$ ) Test for subaroup differences: Chi <sup>2</sup> = 1.01. df = 1 ( $P = 0.31$ ). $P = 1.5\%$ Double ICIs Single ICI Odds Ratio Odds Ratio	5.2.2 PD-L1 VS. Chemotherapy									
Herbst 2020, IMpower110 2 286 0 263 2.0% 4.63 (0.22, 96.91) Subtoal (95% CI) 679 628 13.9% $3.64 [1.12, 11.88]$ Total events 13 3 Heterogeneity: Chi <sup>2</sup> = 0.03, df = 1 (P = 0.86); P = 0% Total events 58 23 Heterogeneity: Chi <sup>2</sup> = 4.75, df = 9 (P = 0.86); P = 0% Test for overall effect Z = 2.14 (P = 0.03) Total events 58 23 Heterogeneity: Chi <sup>2</sup> = 4.75, df = 9 (P = 0.86); P = 0% Test for overall effect Z = 3.09 (P = 0.002) Test for subaroup differences: Chi <sup>2</sup> = 1.01. df = 1 (P = 0.31). P = 1.5% Double ICIS Single ICI Odds Ratio Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed,	Barlesi 2018, JAVELIN Lung 200	11	393	3	365	11.9%	6 3.47 [0	0.96, 12.56]		
Subtotal (95% CI) 679 628 13.9% 3.64 [1.12, 11.88] Total events 13 3 Heterogeneify: Ch <sup>P</sup> = 0.03, df = 1 ( $P = 0.86$ ); $P = 0\%$ Test for overall effect: Z = 2.14 ( $P = 0.03$ ) Total events 58 23 Heterogeneify: Ch <sup>P</sup> = 4.75, df = 9 ( $P = 0.86$ ); $P = 0\%$ Test for overall effect: Z = 3.09 ( $P = 0.002$ ) Test for overall effect: Z = 3.09 ( $P = 0.002$ ) Test for subcroup differences: Ch <sup>P</sup> = 1.01. df = 1 ( $P = 0.31$ ), $P = 1.5\%$ Double ICIs Single ICI Odds Ratio Study or Subgroup Events Total Events Total Weight M.H. Fixed, 95% CI 53.1 PD.1+ CTLA.4 VS.PD.1 Boyer 2021, KEYNOTE-598 5 282 3 281 35.4% 1.67 [0.40, 7.07] Gettinger 2021, Lung-MAP 14001 3 124 5 123 58.7% 0.59 (0.14, 2.50] Owonikoko 2021, CheckMate 451 1 2.78 0 2.79 5.9% 3.02 [0.12, 7.44.9] Subtotal (95% CI) 684 683 100.0% 1.11 [0.44, 2.84] Total events 9 8 Heterogeneily: Ch <sup>P</sup> = 1.43, df = 2 ( $P = 0.49$ ); $P = 0\%$ Test for overall effect: Z = 0.23 ( $P = 0.82$ ) Total events 9 8 Heterogeneily: Ch <sup>P</sup> = 1.43, df = 2 ( $P = 0.49$ ); $P = 0\%$ Test for overall effect: Z = 0.23 ( $P = 0.82$ ) Total events 9 8 Heterogeneily: Ch <sup>P</sup> = 1.43, df = 2 ( $P = 0.49$ ); $P = 0\%$ Test for overall effect: Z = 0.23 ( $P = 0.82$ ) Total events 9 8 Heterogeneily: Ch <sup>P</sup> = 1.43, df = 2 ( $P = 0.49$ ); $P = 0\%$ Test for overall effect: Z = 0.23 ( $P = 0.82$ ) Total events 9 8 Heterogeneily: Ch <sup>P</sup> = 1.43, df = 2 ( $P = 0.49$ ); $P = 0\%$ Test for overall effect: Z = 0.23 ( $P = 0.82$ ) Total events 9 8 Heterogeneily: Ch <sup>P</sup> = 1.43, df = 2 ( $P = 0.49$ ); $P = 0\%$ Test for overall effect: Z = 0.23 ( $P = 0.82$ ) Total events 9 8 Heterogeneily: Ch <sup>P</sup> = 1.43, df = 2 ( $P = 0.49$ ); $P = 0\%$ Test for overall effect: Z = 0.23 ( $P = 0.82$ ) Total events 9 8 Heterogeneily: Ch <sup>P</sup> = 1.43, df = 2 ( $P = 0.49$ ); $P = 0\%$ Test for overall effect: Z = 0.23 ( $P = 0.82$ ) Total events 9 8 Heterogeneily: Ch <sup>P</sup> = 1.43, df = 2 ( $P = 0.49$ ); $P = 0\%$ Test for overall effect: Z = 0.23 ( $P = 0.82$ ) Test for overall effect: Z = 0.23 ( $P = 0.82$ ) Total events 9 8 Heterogeneily: Ch <sup>P</sup> = 1.4	Herbst 2020, IMpower110	2	286	0	263	2.0%	6 4.63 [0	0.22, 96.91]		
Total events 13 3 Heterogeneity: Chi <sup>2</sup> = 0.30, df = 1 (P = 0.86); P = 0% Test for overall effect: Z = 2.14 (P = 0.03) Total events 58 23 Test for overall effect: Z = 3.09 (P = 0.86); P = 0% Test for overall effect: Z = 3.09 (P = 0.86); P = 0% Test for subaroup differences: Chi <sup>2</sup> = 1.01, df = 1 (P = 0.31), P = 1.5% Double ICls Single ICl Odds Ratio Study or Subgroup Events Total Events Total Weight M.H. Fixed, 95% CI 5.3.1PD-1+ CTLA-4 VS. PD-1 Boyer 2021, Lucp-MAP 14001 3 124 5 123 58.7% 0.59 [0.14, 2.50] Owonikoko 2021, CheckMate 451 1 2.78 0 2.79 5.9% 3.02 [0.12, 74.49] Subtotal (95% CI) 684 683 100.0% 1.11 [0.44, 2.84] Total events 9 8 Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.82) Total events 9 8 Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.82) Total events 9 8 Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.82) Total events 9 8 Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.82) Total events 9 8 Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.82) Total events 9 8 Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.82) Total events 9 8 Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for subgroup differences: Not applicable	Subtotal (95% CI)		679		628	13.9%	6 3.64 [1	.12, 11.88]		
Heterogeneity: $Ch^{P} = 0.03$ , $df = 1$ ( $P = 0.86$ ); $P = 0\%$ Test for overall effect: $Z = 2.14$ ( $P = 0.03$ ) Total (95% CI) 3455 2783 100.0% 2.12 [1.32, 3.42] Heterogeneity: $Ch^{P} = 4.75$ , $df = 9$ ( $P = 0.86$ ); $P = 0\%$ Test for overall effect: $Z = 3.09$ ( $P = 0.002$ ) Test for overall effect: $Z = 3.09$ ( $P = 0.002$ ) Test for subaroup differences: $Ch^{P} = 1.01$ . $df = 1$ ( $P = 0.31$ ), $P = 1.5\%$ Double ICIs Single ICI Odds Ratio Single ICI Odds Ratio M.H. Fixed, 95% CI M.H. Fixed, 95%	Total events	13		3						
Total (95% CI)       3455       2783       100.0%       2.12 [1.32, 3.42]         Total events       58       23         Heterogeneity: Chi <sup>2</sup> = 4.75, df = 9 (P = 0.86); P = 0%       0.01       0.1       10       10         Test for overall effect: $Z = 3.09$ (P = 0.002)       0.011       0.1       10       100         Test for suborous differences: Chi <sup>2</sup> = 1.01. df = 1 (P = 0.31). P = 1.5%       0.014       0.014       0.1       10       100         Study or Subgroup       Events       Total       Events       Total       Weight       M.H. Fixed, 95% CI       M.H. Fixed, 95% CI         Study or Subgroup       Events       Total       Events       Total       Weight       M.H. Fixed, 95% CI       M.H. Fixed, 95% CI         Subtroal (55% CI)       684       683       100.0%       1.11 [0.44, 2.84]       0.01       0.01       0.1       10       100         Subtroal (95% CI)       684       683       100.0%       1.11 [0.44, 2.84]       0.01       0.01       0.1       10       100         Total events       9       8       8       683       100.0%       1.11 [0.44, 2.84]       0.01       0.1       10       100       100         Total events       9       8	Heterogeneity: $Chi^2 = 0.03$ , $df = 1$ (f Test for overall effect: $Z = 2.14$ (P =	P = 0.86); I <sup>2</sup> 0.03)	= 0%							
Total events       58       23         Heterogeneity: Chi <sup>2</sup> = 4.75, df = 9 (P = 0.86); P = 0%       0.01       0.1       10       100         Test for overall effect: Z = 0.30 (P = 0.002)       Double ICIs       Single ICI       Odds Ratio       Odds Ratio         Study or Subgroup       Events       Total       Events       Total       Weight       M-H, Fixed, 95% CI       M-H, Fixed, 95% CI         Study or Subgroup       Events       Total       Events       Total       Subtotal       0.01       0.1       10       100         Subtotal (95% CI)       684       683       100.0%       1.11 [0.44, 2.84]       M-H, Fixed, 95% CI       M-H, Fixed, 95% CI         Total events       9       8       8       Beterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0%       8       Int [0.44, 2.84]       M-H, Fixed, 95% CI         Total events       9       8       8       Beterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0%       8       Int [0.44, 2.84]       Meterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0%       Single ICI       Double ICIs         Test for overall effect: Z = 0.23 (P = 0.82)       8       Events       9       8       1.11 [0.44, 2.84]       Meterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0%       Single ICI       Double ICIs <t< td=""><td>Total (95% CI)</td><td></td><td>3455</td><td></td><td>2783</td><td>100.0%</td><td>6 2.12 [</td><td>[1.32, 3.42]</td><td></td><td>•</td></t<>	Total (95% CI)		3455		2783	100.0%	6 2.12 [	[1.32, 3.42]		•
Heterogeneity: Chi <sup>2</sup> = 4.75, df = 9 (P = 0.86); P = 0% Test for overall effect: $Z = 3.09$ (P = 0.002) Test for subaroup differences: Chi <sup>2</sup> = 1.01. df = 1 (P = 0.31). P = 1.5% Double ICIs Single ICI Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI 5.3.1 PD.1+ CTLA-4 VS. PD-1 Boyer 2021, Lung-MAP 1400I 3 124 5 123 58.7% 0.59 [0.14, 2.50] Owonikoko 2021, CheckMate 451 1 278 0 279 5.9% 3.02 [0.12, 74.49] Subtotal (95% CI) 684 683 100.0% 1.11 [0.44, 2.84] Total events 9 8 Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.82) Total effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for subgroup differences: Not applicable	Total events	58		23						
Test for overall effect: $Z = 3.09 (P = 0.002)$ 0.01       0.1       1       10       100         Test for subaroup differences: Chi <sup>2</sup> = 1.01. df = 1 (P = 0.31).  P = 1.5%       Double ICIs       Single ICI       Odds Ratio       Odds Ratio         Study or Subgroup       Events       Total       Events       Total       Events       Total       M-H, Fixed, 95% CI         Boyer 2021, Lung-MAP 14001       3       124       5       123       58.7%       0.59 [0.14, 2.50]         Owonikoko 2021, CheckMate 451       1       279       5.9%       3.02 [0.12, 74.49]       Image: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0%         Subtotal (95% CI)       684       683       100.0%       1.11 [0.44, 2.84]       Image: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0%         Test for overall effect: Z = 0.23 (P = 0.82)       8       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8       8       100.0%       1.11 [0.44, 2.84]       Image: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0%       1.00	Heterogeneity: Chi2 = 4.75, df = 9 (f	P = 0.86); I <sup>2</sup>	= 0%						0.01	01 1 10 100
Contention of the second of t	Test for overall effect: Z = 3.09 (P =	0.002)							0.01	Chemotherany ICIs
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	Test for subaroup differences: Chi	*= 1.01. df =	= 1 (P =	= 0.31). I <sup>2</sup>	= 1.5%					onenomerapy iois
Study or Subgroup         Events         Total         Events         Total         Weight         M.H., Fixed, 95% Cl           5.3.1 PD.1+ CTLA.4 VS. PD.1         Boyer 2021, KCYNOTE-598         5         282         3         281         35.4%         1.67 [0.40, 7.07]           Gettinger 2021, Lung-MAP 14001         3         124         5         123         58.7%         0.59 [0.14, 2.50]           Owonikoko 2021, CheckMate 451         1         278         0         279         5.9%         3.02 [0.12, 74.49]           Subtotal (95% Cl)         684         683         100.0%         1.11 [0.44, 2.84]         Image: Chi P = 1.43, df = 2 (P = 0.49); P = 0%           Test for overall effect: Z = 0.23 (P = 0.49); P = 0%         Events         683         100.0%         1.11 [0.44, 2.84]           Total events         9         8         8         1.11 [0.44, 2.84]         Image: Chi P = 1.43, df = 2 (P = 0.49); P = 0%         Image: Chi P = 1.43, df = 2 (P = 0.49); P = 0%         Image: Chi P = 1.43, df = 2 (P = 0.49); P = 0%         Image: Chi P = 1.43, df = 2 (P = 0.49); P = 0%         Image: Chi P = 1.43, df = 2 (P = 0.49); P = 0%         Image: Chi P = 1.43, df = 2 (P = 0.49); P = 0%         Image: Chi P = 1.43, df = 2 (P = 0.49); P = 0%         Image: Chi P = 0.82)		Double	ICIs	Single	ICI		Odds	Ratio		Odds Ratio
5.3.1 PD. 1 + CTLA-4 VS. PD-1 Boyer 2021, KEYNOTE-598 5 282 3 281 35.4% 1.67 [0.40, 7.07] Gettinger 2021, Lung-MAP 1400I 3 124 5 123 58.7% 0.59 [0.14, 2.50] Owonikoko 2021, CheckMate 451 1 2.78 0 279 5.9% 3.02 [0.12, 74.49] Subtotal (95% CI) 684 683 100.0% 1.11 [0.44, 2.84] Total events 9 8 Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.49); P = 0% Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for subproup differences: Not applicable	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixe	d, 95% CI		M-H, Fixed, 95% Cl
Boyer 2021, KEYNOTE-598 5 282 3 281 35.4% 1.67 [0.40, 7.07] Gettinger 2021, Lung-MAP 14001 3 124 5 123 58.7% 0.59 [0.14, 2.50] Owonikoko 2021, CheckMate 451 1 278 0 279 5.9% $3.02 [0.12, 74.49]$ Subtotal (95% CI) 684 683 100.0% 1.11 [0.44, 2.84] Total events 9 8 Heterogeneity: Chi <sup>P</sup> = 1.43, df = 2 (P = 0.49); I <sup>P</sup> = 0% Test for overall effect: Z = 0.23 (P = 0.82) Total events 9 8 Heterogeneity: Chi <sup>P</sup> = 1.43, df = 2 (P = 0.49); I <sup>P</sup> = 0% Test for overall effect: Z = 0.23 (P = 0.82) Total events 9 8 Heterogeneity: Chi <sup>P</sup> = 1.43, df = 2 (P = 0.49); I <sup>P</sup> = 0% Test for overall effect: Z = 0.23 (P = 0.82) Total events 9 8 Heterogeneity: Chi <sup>P</sup> = 1.43, df = 2 (P = 0.49); I <sup>P</sup> = 0% Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for overall effect: Z = 0.23 (P = 0.82) Test for subroup differences: Not applicable	5.3.1 PD-1 + CTLA-4 VS. PD-1									
Gettinger 2021, Lung-MAP 14001       3       124       5       123       58.7%       0.59 [0.14, 2.50]         Owonikoko 2021, CheckMate 451       1       278       0       279       5.9%       3.02 [0.12, 74.49]         Subtotal (95% CI)       684       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8         Heterogeneity: Chi <sup>P</sup> = 1.43, df = 2 (P = 0.49); P = 0%       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8       683       100.0%       1.11 [0.44, 2.84]         Test for overall effect: Z = 0.23 (P = 0.82)       8       683       100.0%       1.11 [0.44, 2.84]         Test for subgroup differences: Not applicable       8       50.01       0.01       0.1       10	Boyer 2021, KEYNOTE-598	5	282	3	281	35.4%	1.67 (0	.40, 7.071		
Owonikoko 2021, CheckMate 451       1       278       5.9       3.02 [0:12, 24.49]         Subtotal (95% CI)       684       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8         Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0%       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8         Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0%       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8       50.01       1.01       100         Test for overall effect: Z = 0.23 (P = 0.82)       50.02       50.01       50.01       50.01         Test for subgroup differences: Not applicable       50.02       50.01       50.01       50.01       50.01	Gettinger 2021 Lung-MAP 1400	3	124	5	123	58 7%	0.59 0	14 2 501		
Subtrate (95% Cl)       684       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8         Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0%       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8         Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); P = 0%       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8       683       100.0%       1.11 [0.44, 2.84]         Test for overall effect: Z = 0.23 (P = 0.82)       8       1.11 [0.44, 2.84]       100.01       1.1         Test for overall effect: Z = 0.23 (P = 0.82)       5.02 [0.10       100       100         Test for overall effect: Z = 0.23 (P = 0.82)       5.02 [0.10       5.00 [0.01       1.1       10       100         Test for subgroup differences: Not applicable       5.02 [0.10       5.00 [0.10       1.00       5.00 [0.10]       5.00 [0.10]       1.00	Owonikoko 2021 CheckMate 461	1	279	0	270	5 90%	3 0 2 10	12 74 401		
Subscription (53/8 Ci)       064       063/100.0%       1.11[0.44, 2.64]         Total events       9       8         Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); I <sup>2</sup> = 0%       683/100.0%       1.11[0.44, 2.64]         Total (95% Ci)       684       683/100.0%       1.11[0.44, 2.84]         Total events       9       8         Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); I <sup>2</sup> = 0%       8         Test for overall effect: Z = 0.23 (P = 0.82)       0.01       0.1       10         Test for overall effect: Z = 0.23 (P = 0.82)       Single ICI       Double ICIs	OWORINONU ZUZT, URECKIVALE 451	1	604	0	603	100.0%	1 44 10	14 2 041		
Total (95% CI)       684       683       100.0%       1.11 [0.44, 2.84]         Total (95% CI)       684       683       100.0%       1.11 [0.44, 2.84]         Total events       9       8         Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); I <sup>2</sup> = 0%       8         Total events       9       8         Test for overall effect: Z = 0.23 (P = 0.82)       0.01       0.1       10         Test for overall effect: Z = 0.23 (P = 0.82)       Single ICI       Double ICIs	Subtotal (05% CI)	0	084	~	085	100.0%	1.11[0	.44, 2.84]		
Total (95% Cl)         684         683         100.0%         1.11 [0.44, 2.84]           Total events         9         8           Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); I <sup>2</sup> = 0%         0.01         0.1         1         10         100           Test for overall effect: Z = 0.23 (P = 0.82)         Test for subgroup differences: Not applicable         Single ICI         Double ICIs	Subtotal (95% CI)	9	= 0%	8						
Total events         9         8           Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); i <sup>2</sup> = 0%         0.01         0.1         1         10         100           Test for overall effect: Z = 0.23 (P = 0.82)         Single ICI         Double ICIs         Single ICI         Double ICIs	Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (f Test for overall effect: Z = 0.23 (P =	P = 0.49); F 0.82)								
Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); i <sup>2</sup> = 0%         Image: Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (P = 0.49); i <sup>2</sup> = 0%         0.01         0.1         1         10         100           Test for overall effect: Z = 0.23 (P = 0.82)         0.01         0.1         1         10         100           Test for subgroup differences: Not applicable         Single ICI         Double ICIs	Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>P</sup> = 1.43, df = 2 (t Test for overall effect: Z = 0.23 (P = Total (95% Cl)	P = 0.49); P 0.82)	684		683	100.0%	1.11 [0	.44, 2.84]		+
Test for overall effect: Z = 0.23 (P = 0.82) Test for subgroup differences: Not applicable Single ICI Double ICIs	Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 1.43, df = 2 (f Test for overall effect: Z = 0.23 (P = Total (95% Cl) Total events	P = 0.49); P 0.82) 9	684	8	683	100.0%	1.11 [0	.44, 2.84]		•
Test for subgroup differences: Not applicable Single ICI Double ICIS	Subtotal (95% Cl) Total events Heterogeneity: $Chi^2 = 1.43$ , $df = 2$ (f Test for overall effect: $Z = 0.23$ (P = <b>Total (95% Cl)</b> Total events Heterogeneity: $Chi^2 = 1.43$ , $df = 2$ (f	P = 0.49); P 0.82) 9 P = 0.49); P	684 = 0%	8	683	100.0%	1.11 [0	.44, 2.84]	0.04	
	Subtotal (95% Cl) Total events Heterogeneilty: Chi <sup>2</sup> = 1.43, df = 2 (f Test for overall effect: $Z = 0.23$ (P = Total (95% Cl) Total events Heterogeneilty: Chi <sup>2</sup> = 1.43, df = 2 (f Test for overall effect: $Z = 0.23$ (P =	P = 0.49);  * 0.82) 9 P = 0.49);  * 0.82)	684 = 0%	8	683	100.0%	1.11 [0	.44, 2.84]	0.01	0.1 1 10 100

vs. chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

Still, no significant difference was observed among the different treatment regimens.

Previous studies have demonstrated that the incidence of ICIsrelated interstitial lung disease ranges from 14.5% to 18.6% (75, 76). This study showed that ICIs were more likely to cause interstitial lung disease than chemotherapy. This is similar to other studies showing that ICIs cause interstitial lung disease more frequently than other drugs used to treat NSCLC, such as pemetrexed, erlotinib, gefitinib, docetaxel, gemcitabine, or crizotinib (77–83). However, the mechanisms regulating the occurrence of ICIs-related interstitial lung disease have not been fully elucidated so far. Elevated levels of inflammatory cytokines may be involved in the pathophysiology of irAEs (84, 85). The inflammatory cytokine interleukin 6 (IL-6) induces the differentiation of naive CD4 T



chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

cells into Th17 cells, which may be related to irAE occurrence (86). Th17 cells are critical mediators of various autoimmune diseases by producing IL-17 (87, 88). Likewise, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) has been associated with irAEs, and anti-TNF- $\alpha$  antibodies were found to improve severe irAEs (89). Patients with poorer performance score and cancer cachexia status have higher levels of inflammatory cytokines, such as IL-6 and TNF- $\alpha$ , and may be

more prone to irAE-related diseases, such as ICIs-related interstitial lung disease (90, 91). PD-L1 inhibitors should be less toxic than PD1 inhibitors as they do not prevent the interaction between PD-L2 and PD1 (92). Still, we could not confirm this difference in our study due to data limitations.

In this study, a total of 81 pleural effusion events occurred in the ICIs vs. chemotherapy group, among which 58 and 23 patients



The forest plot of different treatment regimens on pneumothorax. Subgroup analyses investigated ICIs plus chemotherapy vs, chemotherapy, ICIs vs, chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

developed pleural effusion after applying ICIs and using chemotherapy, respectively; ICIs significantly increased the risk of pleural effusion compared with chemotherapy (P < 0.05). Pleural effusion has been reported as an irAE, but there are few studies on ICIs-related pleural effusion, most of which are case reports (93-95). Two patients were reported to develop recurrent pleural effusions that accumulated rapidly within days after each puncture and required multiple thoracentesis for the first 8 weeks after administration of nivolumab (95). In another study, a patient

was not initially diagnosed with pleural dissemination or malignant pleural effusion. However, cytology and radiography or thoracoscopy did not find evidence of malignancy in the pleural effusion and malignant nodules, respectively. Hypoalbuminemia and cardiac insufficiency, which may cause pleural effusion, were also excluded. And the pleural effusion responded well after corticotherapy, suggesting that this may be an irAE (94). Pleural effusion is considered to be related to the pseudo-progression of the disease (95). However, so far, there is no detailed research to explain



FIGURE 11

The forest plot of different treatment regimens on pulmonary embolism. Subgroup analyses investigated ICIs plus chemotherapy vs. chemotherapy, ICIs vs. chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

this. Moreover, the mechanism still needs to be elucidated, and further research is warranted.

In some RCTs, the incidence of ICIs-related pneumonitis was approximately 1.06% (95% CI: 0.53–2.11) for CTLA-4 inhibitors, 3.02% (95% CI: 2.31–3.93) for PD-1 inhibitors, and 7.09% (95% CI: 5.52–7.16) for PD-1 combined with CTLA-4 inhibitors (28, 30, 37, 39, 96–114). ICIs-related pneumonitis is hypothesized to be a chronic inflammatory state (114). Its symptoms are nonspecific and usually present with cough, dyspnea, shortness of breath, and hypoxia (115,

116). This study demonstrated that the risk of pneumonitis after treatment of PD-1 combined with CTLA-4 was higher than that of PD-1 alone, which is similar to the previous study (116) showing that the risks of pneumonitis (3.47-fold) and severe pneumonitis (3.48-fold) were higher with ipilimumab combined with nivolumab than nivolumab or ipilimumab alone. Therefore, the combination of CTLA-4 and PD-1 may cause a higher incidence of pneumonitis than either drug (110–112). CTLA-4 inhibitors attenuate T cell activation early in the immune response. PD-1 inhibitors can

	Cls + Chemot	herapy	Chemo	othera	ру		Odds Ratio		0	dds Ratio	
Study or Subgroup	Events	Tota	Events	s T	otal We	eight N	A-H, Fixed, 95%	6 CI	M-H,	Fixed, 95% Cl	
9.1.1 PD-L1 + Chemotherapy	VS. Chemothe	гару									
Goldman 2021, CASPIAN	0	265	5 1	0	266		Not estima	ble	_		
Nishio 2021, IMpower132	0	291	1 .	1	274 68	6.5%	0.31 [0.01, 7.	.71]			_
West 2019, IMpower130	2	473	3 1	0	131 33	3.5%	1.39 [0.07, 29.	23]			
Subtotal (95% CI)		1029	9		671 10	0.0%	0.68 [0.09, 4.	82]			
Total events	2			1							
Heterogeneity: Chi <sup>2</sup> = 0.44, df =	= 1 (P = 0.51); I	²=0%									
Test for overall effect: Z = 0.39	(P = 0.70)										
Total (95% CI)		1029	9		671 10	0.0%	0.68 [0.09, 4.	82]			
Total events	2			1							
Heterogeneity: Chi <sup>2</sup> = 0.44, df =	= 1 (P = 0.51); I	²=0%							0.01 0.1	1	10 11
Test for overall effect: Z = 0.39	(P = 0.70)								Chemother	any ICIs + C	hemotherany
Test for subaroup differences:	Not applicable	9							onemotier	apy 1013 · 0	nemourerapy
	ICIs	C	hemothe	rapy		Od	lds Ratio		Odds R	atio	
Study or Subgroup	Events T	otal E	vents	Total	Weight	t M-H,	Fixed, 95% Cl		M-H, Fixed	95% CI	
9.2.1 PD-1 VS. Chemotherapy											
Borghaei 2015, CheckMate05	7 1	287	0	268	3.8%	2.81	[0.11, 69.31]				_
Brahmer 2015, CheckMate 01	7 0	131	3	129	26.0%	6 0.1	4 [0.01, 2.69]	+	-		
Carbone 2017, CheckMate 02	6 2	267	1	263	7.4%	5 1.98	3 [0.18, 21.94]			•	-
Herbst 2020, KEYNOTE-010	1	682	2	309	20.3%	5 0.2	23 10.02. 2.501	-		_	
Mok 2019, KEYNOTE-042	4	636	2	615	14.9%	5 1.94	10.35.10.63			•	
Reck 2019 KEYNOTE-024	0	154	1	150	11.2%	6 0.3	32 [0.01, 7,98]				
Snigel 2021 CheckMate 331	ñ	282	1	265	11 4%	0.0	1 10 01 7 69	_	•		
Mu 2019 CheckMate 078	1	337	'n	156	5.0%	1 40	0 0 06 34 44				
Subtotal (95% CI)		776	v	2155	100.0%	07	7 [0 34 1 71]		-	-	
Total evente	0		10	2100	100.070		. [0:04, 11, 1]				
Hotorogonoitr Chiz-6 27 df-	- 7 (P - 0 62)-1	Z - 0%	10								
Test for overall effect: Z = 0.65	(P = 0.52)	-0%									
Total (95% CI)	2	776		2155	100.0%	6 0.7	7 [0.34, 1.71]		-	•	
Total events	9		10								
Heterogeneity: Chi <sup>2</sup> = 5.37. df=	7 (P = 0.62); I	²=0%	-							t_	
Test for overall effect: Z = 0.65	(P = 0.52)							0.01	U.1 1	10	100
Test for subaroup differences:	Not applicable	9							Chemotherapy I	CIS	
	Double	ICIS	Single	CI		Oc	lds Ratio		Odds R	atio	
Study or Subgroup	Events	Total	Events	Total	Weight	t M-H.	Fixed, 95% CI		M-H, Fixed	95% CI	
9.3.1 PD-1 + CTLA-4 VS. PD-1											
Bover 2021 KEYNOTE-598	1	282	2	281	30.9%	6 04	50 (0.04 5.51)				
Gettinger 2021   ung-MAP 14(	101 2	124	3	123	45.9%	6 01	6 (0 11 3 99)				
Owonikoko 2021, Lung-MAP 140	151 0	279	1	270	23.2%	6 0.0	33 [0 01 8 22]				
Subtotal (95% CI)		684		683	100.0%	6 0.5	3 [0.14 1 97]			-	
Total evente	2	004	e	005	100.07		0 [0.14, 1.37]				
Hotorogonoity Chi2 - 0.1.1 df	ن ۱ - ۵ م - ۵ م	2-0%	0								
Test for overall effect: Z = 0.95	(P = 0.34)	- 0 %									
Total (95% CI)		684		683	100.0%	6 0.5	3 [0.14, 1.97]			-	
Total events	3		6								
Heterogeneity: $Chi^2 = 0.14$ , df = Test for overall effect: Z = 0.95 Test for subgroup differences	= 2 (P = 0.93); I (P = 0.34)	²=0%						0.01	0.1 1 Single ICI	10 Double ICIs	100
rescion suburoup unierences.	Notabblicable	2									

inhibit T cells later in peripheral tissue immune response. Therefore, we assumed that the combined application of PD-1 and CTLA-4 may be more prone to lung toxicity than either treatment alone; however, further studies are needed to reveal this molecular mechanism. In this study, we also found that ICIs with or without chemotherapy increased the risk of pneumonitis compared with chemotherapy alone. Interestingly, studies have demonstrated that patients with NSCLC treated with PD-L1 inhibitors have a higher incidence of pneumonitis than those with other cancer types. In a study that compared data from patients with lung cancer and other solid tumors, pneumonitis was more common in patients with lung cancer (26.4% vs. 10.3%) (117). Therefore, tumor damage to lung tissue may make the lungs more prone to side effects after treatment.

With the increasing use of ICIs in more neoplastic diseases, the total burden of pneumonitis and mortality will undoubtedly increase.

This study has several limitations. First, NSCLC and SCLC were both investigated in the analysis. A retrospective study demonstrated that squamous cell cancer was a risk factor for ICIs-related pneumonitis (17). As a confounding factor, SCLC might increase heterogeneity to a certain degree. Second, there needed to be more datasets to build single-drug subgroups for certain drug analysis, such as avelumab and sintilimab. Third, the study did not involve LAG3, PD-L2, and other ICIs.

In conclusion, this study showed that ICI-based treatment, such as ICIs alone, ICIs plus chemotherapy, and double ICIs, can raise the incidences of some respiratory disorders in patients with lung

Study or Subgroup	Events	nother	Total	Events	Total	Weight	M-H. Fixed 9	5% CI	M.H. Fixe	ed. 95% CI
10.1.1 PD-1 + Chemotherapy V	S. Chemother	apy								
Awad 2021, KEYNOTE-021	0		59	0	62		Not estin	nable		
Gadgeel 2020, KEYNOTE-189	2		405	3	202	31.3%	0.33 [0.05,	1.99]		
Paz-Ares 2020, KEYNOTE-407	3		278	0	280	3.9%	7.13 [0.37, 13	8.62]		•
Yang 2020, Orient-11	2		266	0	131	5.2%	2.49 [0.12, 5	2.15]		
Subtotal (95% CI)			1008		675	40.4%	1.26 [0.39,	4.07]		
Total events	7	i		3						
Heterogeneity: Chi <sup>2</sup> = 3.64, df =	2 (P = 0.16); P	<sup>2</sup> = 45%								
Test for overall effect: Z = 0.38 (F	P = 0.70)									
10 1 2 PD I 1 + Chemotheramy	/S Chomoth	arany								
Goldman 2021 CASPIAN	13. Chemour	erapy	265	2	266	15.6%	0.50.00.05	5 551		
Horn 2018 IMnower133	1		198	2	196	15.7%	0.49 (0.04)	5 471		
Nishio 2021, Mpower132	1		291	õ	291	3.9%	3.01 /0.12.7	4.201		
West 2019, IMpower130	6		473	2	131	24.3%	0.83 [0.17.	4.15]		
Subtotal (95% CI)			1227		884	59.6%	0.80 [0.28,	2.29]	-	
Total events	9			6						
Heterogeneity: Chi2 = 0.96, df =	3 (P = 0.81); P	<sup>2</sup> = 0%								
Test for overall effect: Z = 0.42 (F	P = 0.67)									
Total (95% CI)	100		2235		1559	100.0%	0.98 [0.45,	2.14]		
Total events	16			9						
Heterogeneity: Chi <sup>2</sup> = 4.62, df =	6 (P = 0.59); P	*= 0%							0.01 0.1	1 10 10
Test for overall effect: Z = 0.04 (F	<sup>2</sup> = 0.97)		0.070						Chemotherapy	ICIs + Chemotherapy
Test for subdroub differences: C	ni* = 0.32. at	= 1 (P =	= 0.57).	horamy		Odd	le Patio		Odde Patio	
Study or Subgroup	Events	Total	Events	Total	Weigh	t M.H.E	ixed 95% Cl		M.H. Fixed, 95% (	1
10.2.1 PD-1 VS. Chemotherapy	Lycino	Total	Lventa	Total	VVCIAII		1Xeu, 35% CI		Mi-11, 11Xeu, 35% C	
Borghaei 2015 CheckMate057	6	287	4	268	16.09	6 1 41	1 10 39 5 051			
Brahmer 2015 CheckMate 017	2	131	3	129	11.79	6 0.65	5 [0.11, 3.96]			
Carbone 2017, CheckMate 026	4	267	1	263	3.99	3.98	[0.44.35.89]			
Herbst 2020, KEYNOTE-010	4	682	2	309	10.89	6 0.91	[0.16, 4.97]			
Mok 2019, KEYNOTE-042	6	636	4	615	15.99	6 1.45	5 [0.41, 5.18]			
Reck 2019, KEYNOTE-024	2	154	0	150	2.09	6 4.93 [0	0.23, 103.64]			·
Spigel 2021, CheckMate 331	2	282	2	265	8.19	6 0.94	4 [0.13, 6.72]			
Wu 2019, CheckMate 078	1	337	1	156	5.49	6 0.46	6 [0.03, 7.42]	1		_
Subtotal (95% CI)		2776		2155	73.79	6 1.33	[0.73, 2.44]		-	
Total events	27		17							
Heterogeneity: Chi <sup>2</sup> = 3.17, df =	7 (P = 0.87); P	²=0%								
Test for overall effect: Z = 0.94 (F	<sup>o</sup> = 0.35)									
10.2.2 PD I 1 VS Chemotheran										
Portoci 2019 JAVELIN Lung 20	y 6	202	6	265	20.20	0.02	2 10 27 2 221			
Herbet 2020 Minower110	5 5	292	1	262	20.27	0 0.93	1 [0.01 7 52]	_		
Subtotal (95% CI)	0	679		628	26.39	6 0.78	10.25, 2.451		-	
Total events	5	010	6	020	Loio		Torroi ruol			
Heterogeneity: Chi <sup>2</sup> = 0.40, df =	1 (P = 0.53); P	<sup>2</sup> = 0%								
Test for overall effect: Z = 0.42 (f	P = 0.67)									
	,									
Total (95% CI)		3455		2783	100.09	6 1.19	[0.70, 2.02]		+	
Total events	32		23							
Heterogeneity: Chi2 = 4.04, df =	9 (P = 0.91); P	<sup>2</sup> = 0%					1	0.01		10 100
Test for overall effect: Z = 0.64 (F	P = 0.52)							0.01	Chemotherany ICIs	10 100
Test for subaroup differences: 0	hi <sup>2</sup> = 0.66. df	= 1 (P =	= 0.42).	<sup>2</sup> = 0%					chemotherapy icis	
	Double	ICIs	Single	e ICI		Odds	s Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fix	ced, 95% Cl		M-H, Fixed, 95% CI	
10.3.1 PD-1 + CTLA-4 VS. PD-1									-	
Boyer 2021, KEYNOTE-598	0	282	-	281	70.4%	0.11	[0.01, 2.04]			
Gettinger 2021, Lung-MAP 1400	1 7	124	-	2 123	29.6%	3.62 [0	0.74, 17.78]			
Subtotal (05% CI)	0 0	278	(	693	100.0*	1 15	estimáble			
Subtotal (95% CI)	-	084		083	100.0%	1.15	0.40, 5.32]			
Laterageneits Chiz- 4.40 df-	/D - 0.02)/B	- 70%	1	)						
Tect for everall effect: 7 = 0.26 /	P = 0.03, $P = 0.03$ , $P = 0.03$	= / 8 %								
restion overall ellect. 2 = 0.20 (r	- 0.80)									
Total (95% CI)		684		683	100.0%	1.15	0.40. 3.321			
Total events	7	004	6	1			er of otor1		T	
Hotorogonoity Chiz = 4.49 df =	1 (P = 0.03): P	= 78%					F			<u>t</u>
Heterouerietty, Crit = 4.48 m =							0	.01	0.1 1	10 100
Test for overall effect: Z = 0.26 (f	P = 0.80)								Oingla ICI David	01-

The forest plot of different treatment regimens on respiratory failure. Subgroup analyses investigated ICIs plus chemotherapy vs. chemotherapy, ICIs vs. chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

cancer. It suggests that ICIs should be conducted based on a comprehensive consideration to prevent ICIs-related respiratory disorders. To a certain degree, this study might be provided to the clinician as a reference for ICI practice. Of course, more prospective and well-designed clinical trials, and larger sample size real-world studies on various ICIs are still needed to further evaluate therapeutic effects and ICIs-related adverse events.

# Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

# Author contributions

SW conducted the analysis, SL, JJ and LP collected and performed a preliminary analysis of references, HL designed the manuscript, SL and HL wrote the manuscript, LP, SW and LS revised the manuscript. All authors contributed to the article and approved the submitted version.

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# Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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# Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2023.1115305/ full#supplementary-material

#### SUPPLEMENTARY FIGURE 1

The funnel plot for accessing publication bias: chronic obstructive pulmonary diseases.

SUPPLEMENTARY FIGURE 2 The funnel plot for accessing publication bias: dyspnea.

SUPPLEMENTARY FIGURE 3 The funnel plot for accessing publication bias: hemoptysis

SUPPLEMENTARY FIGURE 4 The funnel plot for accessing publication bias: interstitial lung disease.

SUPPLEMENTARY FIGURE 5 The funnel plot for accessing publication bias: pleural effusion.

SUPPLEMENTARY FIGURE 6 The funnel plot for accessing publication bias: pneumonitis.

SUPPLEMENTARY FIGURE 7 The funnel plot for accessing publication bias: pneumothorax.

SUPPLEMENTARY FIGURE 8 The funnel plot for accessing publication bias: pulmonary embolism.

SUPPLEMENTARY FIGURE 9 The funnel plot for accessing publication bias: pulmonary hemorrhage.

SUPPLEMENTARY FIGURE 10

The funnel plot for accessing publication bias: respiratory failure.

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