RESEARCH ARTICLE

The landscape of immune checkpoint inhibitor therapy in advanced lung cancer

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Abstract

Background: The advent of immune checkpoint inhibitors (ICIs) therapy has resulted in significant survival benefits in patients with non-small-cell lung cancer (NSCLC) without increasing toxicity. However, the utilisation of immunotherapy for small-cell lung cancer (SCLC) remains unclear, with a scarcity of systematic comparisons of therapeutic effects and safety of immunotherapy in these two major lung cancer subtypes. Herein, we aimed to provide a comprehensive landscape of immunotherapy and systematically review its specific efficacy and safety in advanced lung cancer, accounting for histological types.

Methods: We identified studies assessing immunotherapy for lung cancer with predefined endpoints, including overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and treatment-related adverse events (TRAE), from PubMed, Embase, Medline, and Cochrane library. A random-effects or fixed-effect model was adopted according to different settings.

Results: Overall, 38 trials with 20,173 patients with lung cancer were included in this study. ICI therapy resulted in a significantly prolonged survival in both patients with NSCLC and SCLC when compared with chemotherapy (hazard ratio [HR] = 0.74; 95% confidence interval [CI], 0.70–0.79] and [HR = 0.82; 95% CI, 0.75–0.90], respectively). The magnitude of disease control and survival benefits appeared superior with ICI plus standard of care (SOC) when compared with SOC alone. OS and PFS advantages were observed only when immunotherapy was employed as the first-line treatment in patients with SCLC.

Conclusion: ICI therapy is a promising therapeutic option in patients with NSCLC and SCLC. ICI plus SOC can be recommended as the optimal first-line treatment for patients with SCLC, and double-target ICIs combined with SOC are recommended in patients with NSCLC as both the first and subsequent lines of treatment. Additionally, non-first-line immunotherapy is not recommended in patients with SCLC.

Keywords: Immune checkpoint inhibitor, Efficacy, Non-small-cell lung cancer, Small-cell lung cancer

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Introduction

Lung cancer is the primary cause of cancer-related mortality and incidence, resulting in a significant economic burden [1]. Regarding histological types, lung cancer can be categorised into small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). SCLC accounts for only 15% of lung cancers, with first-line treatment mainly restricted to chemotherapy or radiotherapy and presenting a worse prognosis than NSCLC [2]. In contrast, NSCLC constitutes approximately 85% of lung cancers and presents a relatively superior prognosis, given the rapid development of therapeutic techniques, including surgery, chemotherapy, radiotherapy, and targeted therapy [3, 4]; however, the actual 5-year overall survival (OS) of NSCLC remains poor. Standard of care (SOC) therapies include chemotherapy and radiotherapy for patients with lung cancer lacking specific therapeutic targets, whereas targeted therapy can be administered to those with corresponding mutated genes.

One main hypothesis for tumour invasion and metastasis is immune evasion, controlled by a combination of inhibitory or stimulatory receptors and corresponding ligands [5]. Among them, cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death 1 (PD-1) pathways are promising therapeutic targets, also known as immune checkpoints [6, 7]. Tumour cells can escape the immune system attack via forming immune checkpoints. Accordingly, blocking such immune checkpoints can activate the immune system and prevent tumour cell evasion. Currently, immune checkpoint inhibitors (ICIs) developed to treat malignant tumours, including lung cancer, can be classified into anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies.

Accumulating evidence has reported that ICIs have higher efficacy than SOC in both NSCLC and SCLC, indicating their superior therapeutic potential. In patients with advanced NSCLC, anti-PD-1 monotherapy can achieve a median OS of 11.9 months, which was significantly superior to that with a SOC at 9.5 months (hazard ratio [HR]: 0.75; 95% confidence interval [CI]: 0.61–0.93). Furthermore, the incidence of treatment-related adverse events (TRAE) in the ICI group was reportedly lower than in the SOC group [8]. In patients with SCLC, anti-PD-L1 therapy as first-line treatment has demonstrated a better OS than platinum-etoposide treatment [9].

However, clinical trials evaluating the efficiency and safety of ICI therapy have mainly focused on NSCLC in recent years, neglecting any specific data analysis for SCLC. More importantly, systematic studies comparing ICI therapy among NSCLC patients with SCLC remain scarce.

A pooled analysis not restricted to patients with SCLC or NSCLC could provide valuable clinical information regarding anti-PD-1/PD-L1 and CTLA-4 treatments. In the present study, we aimed to validate whether immunotherapy could result in more manageable TRAEs and better efficacy than SOC in patients with advanced NSCLC or SCLC. Moreover, we compared the distinct benefits and risks of immunotherapy between patients with NSCLC and SCLC. We anticipate that our results could benefit the development of immunotherapy in lung cancer and offer practical solutions for routine clinical practice using immunotherapy in patients with NSCLC or SCLC.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [10].

Search strategy and study selection

We performed a search for eligible randomised controlled trials (RCTs) from January 2010 to May 2021 in Medline, PubMed, Embase, and the Cochrane Central Register of Controlled Trials, using the following key words: ICIs (PD-1, PD-L1, or CTLA-4), specific ICI drug names (toripalimab, sintilimab, camrelizumab, tilelizumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, ipilimumab, and tremelimumab), and lung cancer. For further identifying unpublished studies, we retrieved abstracts from the American Society of Clinical Oncology, the European Society of Medical Oncology, the American Association for Cancer Research, and the World Conference on Lung Cancer. (Table S1).

Exclusion and inclusion criteria were predefined. Eligible RCTs were required to meet the following criteria: (a) population: diagnosed with lung cancer (NSCLC or SCLC) pathologically; (b) intervention: treatment with PD-1/PD-L1 or CTLA-4 inhibitors (toripalimab, sintilimab, camrelizumab, tislelizumab, nivolumab, pembroliatezolizumab, zumab, durvalumab, avelumab, ipilimumab and tremelimumab); (c) control: treated with chemotherapy or radiotherapy; (d) type of study: phase II and III clinical trials. Exclusion criteria were as follows: (a) the study was not a randomised controlled trial; (b) data regarding PFS/OS measured by HRs, objective response rate (ORR), or TRAEs was unavailable; (c) duplicate articles.

Data extraction and quality assessment

For all included trials, we extracted the name of the trial, year of publication, trial phase, line of treatment, age and number of patients, OS/PFS/ORR, and TRAEs of grade \geq 3 and any grade. We adopted the Cochrane Risk of Bias Tool, consisting of allocation concealment, random sequence generation, blinding of outcome assessment, blinding protocol, selective reporting, and

incomplete outcome data, to methodologically assess the quality of the enrolled RCTs [11]. The items adjudged as "low risk" were regarded as applicable. Two authors independently performed data extraction and quality assessment. Discrepancies were resolved by reaching a consensus.

Statistical analysis

Heterogeneity was identified by the Q test and quantified using the I² and Q statistics [12]. If I² was more than 50%, the random effect model was applied; otherwise, the fixed-effect model was selected [13]. The primary outcomes in the present study were OS and PFS, measured as HRs, 95% CIs, and *p*-values. ORR, grade \geq 3 TRAEs, and Grade 1–5 TRAEs were presented as risk ratios (RRs). The Q test was used to detect heterogeneity between the subgroups and assess differences between histological types. Prespecified subgroup analyses were performed to evaluate the potential association between individual or methodological factors and immunotherapy efficacy in each histological type of lung cancer. Egger's and Begg's tests were used to assess the publication bias for included RCTs. Stata 16.0 software (Stata Corp, College Station, TX) was used to perform all analyses. Statistical significance was set at p < 0.05.

Result

Literature search results

The initial literature search identified 30,284 related studies (Fig. 1). In total, 38 RCTs, including 41 studies with 20,173 patients with lung cancer, were included for quantitative analyses [6–8, 14–48]. Eight studies explored the efficacy of ICI versus SOC in patients with SCLC (three studies on ipilimumab, two on atezolizumab, one on nivolumab, one about durvalumab, and one assessing tremelimumab plus durvalumab). The remaining 33 studies were performed efficiency and



safety comparisons between ICIs and SOC in patients with NSCLC.

Characteristics of identified trials

The main characteristics of the 38 trials are listed in Table 1. All included trials were performed in patients with relapsed or extensive SCLC and advanced NSCLC. In total, 20,173 patients were included, of which 17,250 (85.5%) were diagnosed with NSCLC and 2923 (14.5%) with SCLC. Regarding age, most patients were \geq 70 years old. All eligible trials were phase II or III studies, with 31 phase III trials, 6 phase II, and 1 phase II/III. Among these trials, 22 employed ICIs as first-line therapy, and the remaining trials were in a non-first-line setting. Overall, all studies, except for 17 (44.7%), confirmed improvements in OS in patients receiving immunotherapy when compared with those receiving SOC. Except for PEMBRO-RT and IFCT-1603, all trials reported total TRAEs in patients. Furthermore, several RCTs were uniquely designed, necessitating further explanation. KEYNOTE-010 evaluated the efficiency of different pembrolizumab doses (2 mg/kg and 10 mg/kg), accordingly divided into KEYNOTE-010, a and KEYNOTE-010, b. OAK established two different cohorts, ITT850 and ITT1225, both of which were treated as independent studies. Likewise, ARCTIC and CASPIAN were considered independent studies. CA184-041 was a phase II study focusing on different medication orders, which was considered four studies based on histological type and order of medication. Trials were generated through a random sequence and at low risk of selection bias, presenting good quality (Table S2). The reduced selection bias was attributed to low attrition and thorough reporting without missing cases. The funnel plot (Fig. S1), as well as Egger's and Begg's tests, all indicated no sign of publication bias.

Efficiency

In summary, ICI treatment presented a significant advantage over SOC, with a reduction in mortality (HR, 0.76; 95% CI, 0.72-0.80) (Fig. 2) and successful control of disease progression in patients with lung cancer (HR, 0.77; 95% confidence interval [CI], 0.71-0.83) (Fig. 3). Furthermore, immunotherapy yielded superior efficacy in terms of objective response in patients with lung cancer when compared with chemotherapy or radiotherapy (RR, 1.21; 95% CI, 1.13-1.30; Fig. 4). Regarding different histological types, greater improvements in PFS following ICI therapy were observed in patients with NSCLC than in patients with SCLC ([HR = 0.74; 95% CI, 0.67-0.80] and [HR = 0.95; 95% CI, 0.77–1.13]; difference *p* = 0.02; Fig. 3), similar findings were documented in terms of ORR ([RR = 1.28; 95% CI, 1.18–1.39] and [RR = 1.00; 95% CI, 0.92–1.08]; difference p < 0.01; Fig. 4). In contrast, equivalent OS benefits from ICI therapy were observed in both patients with NSCLC and SCLC ([HR = 0.74; 95% CI, 0.70–0.79] and [HR = 0.82; 95% CI, 0.75–0.90]; difference p = 0.07; Fig. 2). Remarkably, disease progression was retarded in patients with NSCLC treated with ICIs when compared with patients treated with SOC ([HR = 0.74; 95% CI, 0.67–0.80], Fig. 3), risk of death ([HR = 0.74; 95% CI, 0.70–0.79], Fig. 2), and increased ORR ([RR = 1.28; 95% CI, 1.18–1.39], Fig. 4). However, the benefit of ICI therapy in patients with SCLC was only indicated by OS ([HR = 0.82; 95% CI, 0.75–0.90], Fig. 2).

Safety

Compared with SOC alone, immunotherapy for patients with lung cancer reduced the risk of Grade 3–5 TRAEs (RR, 0.76; 95% CI, 0.64–0.89, Fig. 5) and Grade 1–5 TRAEs (RR, 0.95; 95% CI, 0.92–0.98, Fig. 6). In terms of Grade 3–5 TRAEs, no significant difference in risk reduction was observed among patients with different subtypes of lung cancer receiving ICI treatment when compared with SOC ([RR = 0.75; 95%, CI, 0.63–0.90] and [RR = 0.76; 95% CI, 0.48–1.18], respectively; difference p = 0.98; Fig. 5). The risk of Grade 1–5 TRAEs was equivalent among patients with different subtypes of lung cancer treated with ICIs and SOC ([RR = 0.95; 95% CI, 0.92–0.98] and [RR = 0.96; 95% CI, 0.87–1.07], respectively; p = 0.78; Fig. 6).

Subgroup analysis

Table 2 and Table S3 display differences in the efficiency of ICI therapy between patients with NSCLC and SCLC. Importantly, as indicated by PFS, patients with NSCLC presented greater benefits following ICI therapy plus SOC than those with SCLC, when corresponding ICItreated patients were used as a standard for comparison ([HR, 0.63; 95% CI, 0.57-0.69] and [HR, 0.83; 95% CI, 0.76–0.90], respectively, difference p < 0.01); similar results were observed following ICI monotherapy ([HR, 0.82; 95% CI, 0.73-0.91] and [HR, 1.68; 95% CI, 0.90-2.45], respectively; p = 0.03). Moreover, we further assessed differences on efficiency between patients with NSCLC and SCLC when immunotherapy was employed as the first or subsequent line of treatment. We detected an advantage in terms of PFS in patients with NSCLC when compared with patients with SCLC in both the first ([HR, 0.68; 95% CI, 0.60-0.76] and [HR, 0.83; 95% CI, 0.76–0.90], respectively, difference p = 0.01) and subsequent line of therapy ([HR, 0.83; 95% CI, 0.73-0.92] and [HR, 1.68; 95% CI, 0.90-2.45], respectively, *p* = 0.03). However, further subgroup analyses of sex, age, drug target, and Eastern Cooperative Oncology Group Performance Status (ECOG PS) score showed no statistically significant differences on PFS between patients

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Table 1	Clinical characteristics	and outcomes of the included	randomized controlled trials

Trials	Trial	Line of	Intervention	Control (No.)	Age,	Efficiency			TRAEs	
	phase	treatment	(No.)		Median (Range)	OS (95% CI)	PFS (95% CI)	ORR	Grade 3–5	Grade 1–5
NSCLC										
KEYNOTE-407, 2018	III	1	PEM plus PBC (278)	PBC plus placebo (281)	Int:65 (29– 87) Con:65 (36– 88)	0.64 (0.49– 0.85)	0.56 (0.45– 0.70)	161/ 278 108/ 281	194/ 278 191/ 280	273/ 278 274/ 280
KEYNOTE-021, 2016	II	1	PEM plus PBC (60)	PBC (63)	Int:62.5 (54– 70) Con:63.2 (58–70)	0.56 (0.32– 0.95)	0.53 (0.33– 0.86)	33/ 60 18/ 63	24/59 17/62	55/59 57/62
OAK ITT850 2017, 2019	III	> 1	ATE (425)	DOC (425)	Int:63.5 (33– 77) Con:58.5 (34–79)	0.75 (0.64– 0.88)	0·95 (0·82– 1·10)	58/ 425 57/ 425	90/609 248/ 578	390/ 609 496/ 578
CheckMate 026 2017	III	1	NIV (271)	PBC (270)	Int:63 (32– 89) Con:65 (29– 87)	1.08 (0.87– 1.34)	1.19 (0.97– 1.46)	55/ 211 71/ 212	47/267 133/ 263	190/ 267 243/ 263
OAK ITT1225 2018	III	> 1	ATE (613)	DOC (612)	Int:63 (25– 84) Con:64 (34– 85)	0.80 (0.70– 0.92)	0.96 (0.85– 1.08)	84/ 613 72/ 612	243/ 609 322/ 578	574/ 609 557/ 578
JAVELIN Lung 200, 2018	III	> 1	Avelumab (396)	DOC (396)	Int:64 (58– 69) Con:63 (57– 69)	0·90 (0·75– 1·08)	1·16 (0·97– 1·40)	59/ 396 44/ 396	39/393 180/ 365	251/ 393 254/ 365
KEYNOTE-189, 2018	III	1	PEM plus PBC (410)	PBC plus placebo (206)	Int:65 (34– 84) Con:63 (34– 84)	0.49 (0.38– 0.64)	0.52 (0.43– 0.64)	195/ 410 39/ 206	272/ 405 133/ 202	404/ 405 200/ 202
KEYNOTE-042, 2019	III	1	PEM (637)	PBC (637)	Int:63 (57– 69) Con:63 (57– 69)	0.81 (0.71– 0.93)	1.07 (0.94– 1.21)	174/ 637 169/ 637	113/ 636 252/ 615	399/ 636 553/ 615
KEYNOTE-010, a, 2016	/	> 1	PEM (344)	DOC (172)	Int:63 (56– 69) Con:62 (56– 69)	0.71 (0.58– 0.88)	0.88 (0.74– 1.05)	62/ 344 16/ 172	43 /339 55/155	215/ 339 126/ 155
KEYNOTE-010, b, 2016	/	> 1	PEM (346)	DOC (171)	Int:63 (56– 69) Con:62 (56– 69)	0.61 (0.49– 0.75)	0.79 (0.66– 0.94)	64/ 346 16/ 171	55/343 54/154	226/ 343 125/ 154
POPLAR, 2016	Ι	> 1	ATE (144)	DOC (143)	Int:62 (42– 82) Con:62 (36– 84)	0.73 (0.53– 0.99)	0.94 (0.72– 1.23)	21/ 144 21/ 143	57/142 71/135	95/142 119/ 135
PACIFIC 2017, 2018	III	> 1	DUR (476)	PBC plus Placebo (237)	Int:64 (31– 84) Con:64 (23– 90)	0.68 (0.47– 0.997)	0.52 (0.42– 0.65)	126/ 443 34/ 123	142/ 475 61/234	460/ 475 222/ 234
KEYNOTE- 024, 2016, 2019	III	1	PEM (154)	PBC (151)	Int:64.5 (33– 90) Con:66.0 (38–85)	0.63 (0.47– 0.86)	0.50 (0.37– 0.68)	69/ 154 42/ 151	48/154 80/150	118/ 154 135/ 150
CheckMate 017 2015	III	> 1	NIV (135)	DOC (137)	Int:62 (39– 85) Con:64 (42– 84)	0.59 (0.44– 0.79)	0.62 (0.47– 0.81)	27/ 135 12/ 137	9/131 71/129	76/131 111/ 129

Trials	Trial	Line of	Intervention	Control (No.)	Age, Median (Range)	Efficiency			TRAEs		
	phase	treatment	: (No.)			OS (95% CI)	PFS (95% CI)	ORR	Grade 3–5	Grade 1–5	
IMpower110 2020	III	1	ATE (277)	PBC (277)	Int:64 (30– 81) Con:65 (30– 87)	0.83 (0.65– 1.07)	0.77 (0.63– 0.94)	81/ 277 88/ 277	97/286 149/ 263	258/ 286 249/ 263	
CheckMate 057 2015	III	> 1	NIV (292)	DOC (290)	Int:61 (37– 84) Con:64 (21– 85)	0.73 (0.59– 0.89)	0.92 (0.77– 1.11)	56/ 292 36/ 290	30/287 144/ 268	199/ 287 236/ 268	
IMpower150 2018	III	1	ATE plus PBC (400)	PBC (400)	Int:63 (31– 89) Con:63 (31– 90)	0.78 (0.64– 0.96)	0.61 (0.52– 0.72)	224/ 353 159/ 331	230/ 393 197/ 394	371/ 393 376/ 394	
CheckMate 078 2020	III	> 1	NIV (338)	DOC (166)	Int:60 (27 to 78) Con:60 (38 to 78)	0.75 (0.61– 0.93)	: 0.79 (0.65– 0.98)	59/ 338 7/ 166	41/337 74/156	219/ 337 131/ 156	
IMpower130 2019	III	1	ATE plus PBC (483)	PBC (240)	Int:64 (18– 86) Con:65 (38– 85)	0·80 (0·65– 0·99)	0.65 (0·54– 0·77)	220/ 447 72/ 226	354/ 473 141/ 232	455/ 473 215/ 232	
ARCTIC, a, 2020	III	> 1	DUR (62)	Erlotinib, gemcitabine, or vinorelbine) (64)	Int:63.5 (35– 79) Con:62.0 (41–81)	0.63 (0.42– 0.93)	0.71 (0.49– 1.04)	22/ 62 8/64	25/62 41/63	60/62 63/63	
ARCTIC, b 2020	III	> 1	DUR plus TRE (174)	Erlotinib, gemcitabine, or vinorelbine) (118)	Int:62.5 (26– 81) Con:65 (42– 83)	0.80 (0.61– 1.05)	0.77 (0.59– 1.01)	26/ 174 8/ 118	74/173 57/110	160/ 173 105/ 110	
CameL 2020	III	1	CAM plus PBC (205)	PBC (207)	Int:59 (54– 64) Con:61 (53– 65)	0.73 (0.53– 1.02)	0.60 (0.45– 0.79)	124/ 205 80/ 207	78/205 63/207	146/ 205 132/ 207	
CheckMate 227 2019	III	1	NIV plus IPI (583)	PBC (583)	Int:64 (26– 87) Con:64 (29– 87)	0.73 (0.64– 0.84)	0.79 (0.69– 0.91)	199/ 583 162/ 583	189/ 576 205/ 570	442/ 576 467/ 570	
CheckMate 9LA 2021	III	1	NIV plus IPI plus PBC (361)	PBC (358)	Int:65 (59– 70) Con:65 (58– 70)	0·69 (0·55– 0·80)	0·68 (0·57– 0·82)	138/ 361 89/ 358	168/ 358 132/ 349	327/ 358 303/ 349	
CA184–041, a 2012	II	1	Concurrent IPI plus PBC (70)	PBC (33)	Int:59 (36– 82) Con:62 (36– 82)	0.99 (0.67– 1.46)	0.88 (0.61– 1.27)	15/ 70 6/33	40/71 13/32	52/71 23/32	
CA184–041, b 2012	ll	1	Phased IPI plus PBC (68)	PBC (33)	Int:61 (36– 82) Con:62 (36– 88)	0.87 (0.59– 1.28)	0.69 (0.48– 1.00)	22/ 68 6/33	36/67 13/33	49/67 23/33	
CA184–104 2017	III	1	IPI plus PBC (388)	PBC plus placebo (361)	Int:64 (28– 84) Con:64 (28– 85)	0.91 (0.77– 1.07)	0.87 (0.75– 1.01)	171/ 388 170/ 361	205/ 388 129/ 361	344/ 388 292/ 361	
IMpower132 2020	III	1	ATE plus PBC (292)	PBC (286)	Int:64 (31– 85) Con:63 (33– 83)	0.86 (0.71– 1.06)	0.60 (0.49– 0.72)	137/ 292 92/ 286	208/ 291 166/ 274	287/ 291 266/ 274	
PEMBRO-RT 2019	II	> 1	PEM plus Radiotherapy (36)	Radiotherapy (40)	lnt:62 (35– 78)	0.66 (0.37–	0.71 (0.42–	13/ 36	12/35 6/37	NA	

Table 1 Clinical characteristics and outcomes of the included randomized controlled trials (Continued)

Trials	Trial	Line of	Intervention (No.)	Control (No.)	Age, Median	Efficiency			TRAEs	
	phase	treatment			Median (Range)	OS (95% CI)	PFS (95% CI)	ORR	Grade 3–5	Grade 1–5
					Con:62 (38– 78)	1.18)	1.18)	7/40		
IMpower131 2020	III	1	ATE plus PBC (343)	PBC (340)	Int:65 (23– 83) Con:65 (38– 86)	0.88 (0.73– 1.05)	0.71 (0.60– 0.85)	170/ 343 139/ 340	231/ 334 195/ 334	316/ 334 303/ 334
EMPOWER- Lung 1 2021	III	1	CEM (283)	PBC (280)	Int:63 (58– 69) Con:64 (58– 70)	0.57 (0.42– 0.77)	0.54 (0.43– 0.68)	111/ 283 57/ 280	50/355 134/ 342	204/ 355 303/ 342
RATIONALE 307, a 2021	III	1	TIS plus PBC (120)	PBC (61)	Int:60 (41– 74) Con:62 (34– 74)	\	0.52 (0.37– 0.74)	87/ 120 30/ 61	103/ 120 47/59	119/ 120 59/59
RATIONALE 307, b 2021	III	1	TIS plus PBC (119)	PBC (60)	Int:63 (38– 74) Con:62 (34– 74)	١	0.48 (0.34– 0.68)	89/ 119 30/ 60	99/118 47/58	117/ 118 58/58
SCLC										
CASPIAN, a 2021	III	1	TRE plus DUR plus PBC (268)	PBC (269)	Int:63 (58– 68) Con:63 (57– 68)	0·82 (0·68– 1·00)	0·84 (0·70– 1·01)	156/ 267 78/ 134	196/ 266 86/133	264/ 266 129/ 133
CASPIAN, b 2021	III	1	DUR plus PBC (268)	PBC (269)	Int:62 (58– 68) Con:63 (57– 68)	0.75 (0.62– 0.91)	0·80 (0·66– 0·96)	182/ 268 78/ 135	171/ 265 87/133	260/ 265 129/ 133
IFCT-1603 2019	II	> 1	ATE (49)	PBC (24)	Int:65.9 (51.1–85.5) Con:63.5 (51.8–81.0)	0.84 (0.45– 1.58)	2.26 (1.30– 3.39)	1/43 2/20	2/48 18/24	NA
IMpower133 2018		1	ATE plus PBC (201)	PBC plus placebo (202)	Int:64 (28– 90) Con:64 (26– 87)	0.70 (0.54– 0.91)	0.77 (0.62– 0.96)	121/ 201 130/ 202	115/ 198 113/ 196	188/ 198 181/ 198
CA184–041, a 2013	II	1	Concurrent IPI plus PBC (43)	PBC plus placebo (23)	Int:57 (44– 80) Con:58 (42– 82)	0.95 (0.59– 1.54)	0.93 (0.59– 1.48)	14/ 43 11/ 23	19/42 10/22	29/42 18/22
CA184–041, b 2013	II	1	Phased IPI plus PBC (42)	Placebo plus PBC (22)	Int:59 (43– 80) Con:58 (42– 82)	0.75 (0.46– 1.23)	0.93 (0.59– 1.45)	24/ 42 11/ 22	22/42 9/22	33/42 18/22
CA184–156, 2016	III	1	IPI plus PBC (478)	Placebo plus PBC (476)	Int:62 (39– 85) Con:63 (36– 81)	0.94 (0.81– 1.09)	0.85 (0.75– 0.97)	297/ 478 296/ 476	231/ 478 214/ 476	391/ 478 361/ 478
CheckMate 331 2021		> 1	NIV (284)	PBC (285)	Int:62 (37– 85) Con:61 (34– 82)	0.86 (0.72– 1.04)	1.41 (1.18– 1.69)	39/ 284 47/ 285	39/282 194/ 265	156/ 282 239/ 265

Table 1 Clinical characteristics and outcomes of the included randomized controlled trials (Continued)

Abbreviations: ATE atezolizumab, AVE avelumab, DOC docetaxel, TRAE treatment-related adverse event, IPI ipilimumab, NIV nivolumab, DUR durvalumab, TRE tremelimumab, CAM camrelizumab, CEM Cemiplimab, TIS Tislelizumab, ORR objective response rate, OS overall survival, PBC platinum-based chemotherapy, PEM pembrolizumab, PFS progression-free survival

		HR	
Trial		with 95% CI	
NSCLC			
KEYNOTE-407, 2018		0.64 [0.46, 0.82]	
KEYNOTE-021, 2016		0.56 [0.25, 0.88]	
OAK ITT850, 2019		0.75 [0.63, 0.87]	
CheckMate 026, 2017		 1.08 [0.85, 1.32] 	
OAK ITT1225, 2018		0.80 [0.69, 0.91]	
JAVELIN Lung 200, 2018		0.90 [0.73, 1.06]	
KEYNOTE-189, 2018		0.49 [0.36, 0.62]	
KEYNOTE-042, 2019		0.81 [0.70, 0.92]	
KEYNOTE-010, a, 2016		0.71 [0.56, 0.86]	
KEYNOTE-010, b, 2016		0.61 [0.48, 0.74]	
POPLAR, 2016		0.73 [0.50, 0.96]	
PACIFIC, 2017, 2018		0.68 [0.42, 0.94]	
KEYNOTE- 024, 2016, 2019		0.63 [0.43, 0.83]	
CheckMate 017, 2015		0.59 [0.41, 0.76]	
IMpower110, 2020		0.83 [0.62, 1.04]	
CheckMate 057, 2015	_ _	0.73 [0.58, 0.88]	
IMpower150, 2018		0.78 [0.62, 0.94]	
CheckMate 078, 2020		0.75 [0.59, 0.91]	
IMpower130, 2019	_	0.80 [0.63, 0.97]	
ARCTIC, a, 2020		0.63 [0.37, 0.89]	
CameL, 2020	_	0.73 [0.49, 0.98]	
ARCTIC, b, 2020		0.80 [0.58, 1.02]	
CheckMate 227, 2019		0.73 [0.63, 0.83]	
CheckMate 9LA, 2021		0.69 [0.56, 0.81]	
CA184-041, a, 2012		0.99 [0.59, 1.39]	
CA184-041, b, 2012		0.87 [0.53, 1.22]	
CA184-104, 2017		0.91 [0.76, 1.06]	
IMpower132, 2020		0.86 [0.69, 1.03]	
PEMBRO-RT, 2019		0.66 [0.26, 1.06]	
IMpower131, 2020		0.88 [0.72, 1.04]	
EMPOWER-Lung 1, 2021		0.57 [0.39, 0.74]	
Heterogeneity: $\tau^2 = 0.01$, $I^2 = 49.46\%$, $H^2 = 1.98$	•	0.74 [0.70, 0.79]	
Test of $\theta_i = \theta_j$: Q(30) = 57.93, p = 0.00			
SCLC			
CASPIAN, b, 2021		0.75 [0.60, 0.90]	
CASPIAN, a, 2021		0.82 [0.66, 0.98]	
IFCT-1603, 2019		0.84 [0.27, 1.41]	
IMpower133, 2018		0.70 [0.51, 0.88]	
CA184-041, a, 2013		0.95 [0.47, 1.42]	
CA184-041, b, 2013		0.75 [0.36, 1.14]	
CA184-156, 2016		0.94 [0.80, 1.08]	
CheckMate 331, 2021		0.86 [0.70, 1.02]	
Heterogeneity: τ^2 = 0.00, I ² = 14.97%, H ² = 1.18	•	0.82 [0.75, 0.90]	
Test of $\theta_i = \theta_j$: Q(7) = 5.98, p = 0.54	·		
Overall	•	0.76 [0.72, 0.80]	
Heterogeneity: $\tau^2 = 0.01$, $I^2 = 47.16\%$, $H^2 = 1.89$	•	-	
Test of $\theta_i = \theta_i$: Q(38) = 68.96, p = 0.00			
Tool of around ifferences: $O(4) = 2.02 = -0.07$			
rest of group differences. $\omega_{b}(1) = 3.22$, $p = 0.07$		1 15	
Dondom offenia DENI model	JU .5	1 1.5	
Fig. 2 Forest plots of HRs comparing overall survival of immunotherap	by between NSCLC and	d SCLC	

Trial		HR with 95% CI
NSCLC		
KEYNOTE-407, 2018	-	0.56 [0.44, 0.69]
KEYNOTE-021, 2016		0.53 [0.26, 0.79]
OAK ITT850, 2019	-	0.95 [0.81, 1.09]
CheckMate 026, 2017		
OAK ITT1225_2018	-	0.96[0.84,1.07]
	_	
KETNOTE 042 2010		
KETNOTE 010 a 2016		
		0.54 [0.69, 1.19]
PACIFIC, 2017, 2018		
RETNOTE- 024, 2016, 2019		0.50 [0.34, 0.66]
		0.62 [0.45, 0.79]
IMpower110, 2020		0.77 [0.61, 0.92]
CheckMate 057, 2015		0.92 [0.75, 1.09]
IMpower150, 2018	-	0.61 [0.51, 0.71]
CheckMate 078, 2020		0.79 [0.63, 0.96]
IMpower130, 2019	-	0.65 [0.53, 0.76]
ARCTIC, a, 2020		0.71 [0.44, 0.98]
CameL, 2020		0.60 [0.43, 0.77]
ARCTIC, b, 2020		0.77 [0.56, 0.98]
CheckMate 227, 2019	+	0.79 [0.68, 0.90]
CheckMate 9LA, 2021	-	0.68 [0.56, 0.81]
CA184-041, a, 2012		0.88 [0.55, 1.21]
CA184-041, b, 2012		0.69 [0.43, 0.95]
CA184-104, 2017	-	0.87 [0.74, 1.00]
IMpower132, 2020	-	0.60 [0.49, 0.72]
PEMBRO-RT, 2019		0.71 [0.33, 1.09]
IMpower131, 2020	-	0.71 [0.58, 0.83]
EMPOWER-Lung 1, 2021	-	0.54 [0.42, 0.67]
RATIONALE 307, a, 2021		0.52 [0.33, 0.70]
RATIONALE 307, b, 2021		0.48 [0.31, 0.65]
Heterogeneity: $\tau^2 = 0.03$, $I^2 = 83.29\%$, $H^2 = 5.99$	•	0.74 [0.67, 0.80]
Test of $\theta_i = \theta_j$: Q(32) = 180.70, p = 0.00		
SCLC		
CASPIAN, b, 2021		0.80 [0.65, 0.95]
CASPIAN, a, 2021		0.84 [0.68, 0.99]
IFCT-1603, 2019		
IMpower133, 2018		0.77 [0.60, 0.94]
CA184-041, a, 2013		0.93 [0.48, 1.38]
CA184-041, b, 2013		0.93 [0.50, 1.36]
CA184-156, 2016	-	0.85 [0.74, 0.96]
CheckMate 331, 2021		1.41 [1.15, 1.67]
Heterogeneity: $\tau^2 = 0.04$, $I^2 = 81.16\%$, $H^2 = 5.31$	•	0.95 [0.77, 1.13]
Test of $\theta_i = \theta_j$: Q(7) = 26.60, p = 0.00	•	
Overall	•	0.77 [0.71, 0.83]
Heterogeneity: $\tau^2 = 0.03$, $I^2 = 84.14\%$, $H^2 = 6.31$		
Test of $\theta_i = \theta_j$: Q(40) = 226.72, p = 0.00		
Test of group differences: $Q_b(1) = 5.03$, p = 0.02		
	0 1	2 3
Random-effects REML model		
. 3 Forest plots of HRs comparing progression-free survival of immu	notherapy betwee	en NSCLC and SCLC

Trial	Treat Events	ment Total	Cor Events	ntrol Total		Risk Ratio with 95% Cl	Weight (%)
NSCLC							. ,
KEYNOTE-407, 2018	161	278	108	281	+	1.32 [1.08, 1.62]	3.80
KEYNOTE-021, 2016	33	60	18	63		1.60 [0.98, 2.61]	1.52
OAK ITT850, 2019	58	425	57	425		1.02 [0.72, 1.43]	2.41
CheckMate 026, 2017	55	211	71	212	-	0.82 [0.60 1.12]	2.69
OAK ITT1225 2018	84	613	72	612	_	1 14 [0.85, 1.54]	2.81
IAV/ELIN Lung 200, 2018	59	306	12	396		1.14[0.00, 1.04]	2.01
KEYNOTE 180, 2018	105	410	20	206		2.02 [1.48 2.76]	2.20
KETNOTE 042, 2010	174	607	160	200		2.02 [1.40, 2.70]	2.03
KETNOTE-042, 2019	174	037	109	470		1.02 [0.65, 1.23]	3.97
	62	344	10	172	_	1.79[1.06, 3.02]	1.39
REYNOTE-010, b, 2016	64	346	16	171		1.82 [1.08, 3.07]	1.40
POPLAR, 2016	21	144	21	143		0.99 [0.56, 1.75]	1.23
PACIFIC, 2017, 2018	126	443	34	123		1.02 [0.73, 1.43]	2.48
KEYNOTE- 024, 2016, 2019	69	154	42	151		1.42 [1.02, 1.98]	2.51
CheckMate 017, 2015	27	135	12	137		2.07 [1.09, 3.93]	1.01
IMpower110, 2020	81	277	88	277	-	0.94 [0.72, 1.22]	3.12
CheckMate 057, 2015	56	292	36	290		1.46 [0.99, 2.15]	2.07
IMpower150, 2018	224	353	159	331	-	1.20 [1.02, 1.41]	4.25
CheckMate 078, 2020	59	338	7	166		- 3.67 [1.71, 7.88]	0.75
IMpower130, 2019	220	447	72	226	-	1.37 [1.09, 1.72]	3.50
ARCTIC, a, 2020	22	62	8	64		2.36 [1.12, 4.97]	0.78
CameL, 2020	124	205	80	207	-	1.35 [1.07, 1.71]	3.46
ARCTIC, b. 2020	26	174	8	118		2.05 [0.96, 4.38]	0.76
CheckMate 227, 2019	199	583	162	583		1 17 [0 98 1 40]	4 04
CheckMate 9I A 2021	138	361	89	358	-	1 39 [1 10 1 75]	3 44
CA184-0.41 = 2012	15	70	6	33		1.00 [1.10, 1.70]	0.60
CA184.041 b 2012	22	60	6	22		1.15[0.40, 2.75]	0.00
CA184-041, b, 2012	474	200	170	33		1.59 [0.70, 3.61]	0.00
CA184-104, 2017	1/1	388	170	301		0.96 [0.80, 1.14]	4.10
Impower132, 2020	137	292	92	286		1.31 [1.05, 1.64]	3.54
PEMBRO-RT, 2019	13	36	7	40		1.78 [0.78, 4.07]	0.65
IMpower131, 2020	170	343	139	340	÷	1.14 [0.95, 1.38]	3.98
EMPOWER-Lung 1, 2021	111	283	57	280		1.67 [1.25, 2.21]	2.93
RATIONALE 307, a, 2021	87	120	30	61		1.27 [0.91, 1.78]	2.49
RATIONALE 307, b, 2021	89	119	30	60		1.28 [0.92, 1.79]	2.51
Heterogeneity: τ^2 = 0.02, I^2 =	52.40%, H	$H^2 = 2.1$	C		•	1.28 [1.18, 1.39]	
Test of $\theta_i = \theta_j$: Q(32) = 66.94,	p = 0.00						
SCLC							
CASPIAN, b, 2021	182	268	78	135	-	1.10 [0.90, 1.36]	3.72
CASPIAN, a, 2021	156	267	78	134	+	1.00 [0.81, 1.24]	3.64
IFCT-1603, 2019	1	43	2	20 —		0.25 [0.02, 2.61]	0.09
IMpower133, 2018	121	201	130	202	÷	0.96 [0.79, 1.17]	3.89
CA184-041, a, 2013	14	43	11	23		0.76 [0.39, 1.48]	0.95
CA184-041, b, 2013	24	42	11	22		1.09 [0.61, 1.95]	1.19
CA184-156, 2016	297	478	296	476	1	1.00 [0.88. 1.13]	4.67
CheckMate 331, 2021	30	284	47	285		0.85[0.57, 1.27]	2 04
Heterogeneity: $\tau^2 = 0.00$ $l^2 =$	о оо% н ²	² = 1 00		200			2.01
Test of $\theta_i = \theta_j$: Q(7) = 3.74, p =	= 0.81	1.00				1.00 [0.02, 1.00]	
Overall					1	121 112 1201	
Hotorogopoitur $r^2 = 0.00$ $r^2 = -$	54 790/ ·	J ² – 0.0	1		Y	י.בין ו.וס, ו.סט]	
Test of $\theta_i = \theta_j$: Q(40) = 88.97,	p = 0.00	1 = 2.2	I				
Test of group differences: Q ₆ ((1) = 18.24	4, p = 0.	00			_	
5 1					- I I I	_	
Random-effects RFMI model				1/32	1/8 1/2 2		

	T · · ·	Treatr	nent	Cor	itrol		Risk Ratio	Weight
		Events	lotal	Events	lotal	:	with 95% CI	(%)
	NSCLC							
	KEYNOTE-407, 2018	194	278	191	280	*	1.01 [0.87, 1.18]	2.69
	KEYNOTE-021, 2016	24	59	17	62		1.34 [0.78, 2.30]	2.12
	OAK ITT850, 2019	90	609	248	578	-	0.43 [0.34, 0.53]	2.62
	CheckMate 026, 2017	47	267	133	163		0.33 [0.25, 0.45]	2.53
	OAK ITT1225, 2018	243	609	322	578	-	0.80 [0.69, 0.91]	2.70
	JAVELIN Lung 200, 2018	39	393	180	365		0.27 [0.20, 0.38]	2.49
	KEYNOTE-189, 2018	272	405	133	202		1.01 [0.86, 1.19]	2.68
	KEYNOTE-042, 2019	113	636	252	615	-	0.52 [0.43, 0.63]	2.65
	KEYNOTE-010, a, 2016	43	339	55	155		0.43 [0.30, 0.62]	2.43
	KEYNOTE-010, b, 2016	55	343	54	154		0.53 [0.38, 0.74]	2.47
	POPLAR, 2016	57	142	71	135		0.83 [0.62, 1.11]	2.54
	PACIFIC, 2017, 2018	142	475	61	234	-	1.11 [0.85, 1.45]	2.57
	KEYNOTE- 024, 2016, 2019	48	154	80	150		0.68 [0.50, 0.93]	2.52
	CheckMate 017, 2015	9	131	71	129	_ -	0.18 [0.09, 0.35]	1.90
	IMpower110, 2020	97	286	149	263		0.70 [0.57, 0.87]	2.63
	CheckMate 057, 2015	30	287	144	268		0.27 [0.19, 0.39]	2.42
	IMpower150, 2018	230	393	197	394	—	1.11 [0.95, 1.29]	2.69
	CheckMate 078, 2020	41	337	74	156		0.34 [0.24, 0.48]	2.45
	IMpower130, 2019	354	473	141	232		1.13 [0.97, 1.32]	2.69
	ARCTIC, a, 2020	25	62	41	63		0.73 [0.48, 1.10]	2.35
	CameL. 2020	78	205	63	207		1.18 [0.89, 1.57]	2.54
	ABCTIC b. 2020	74	173	57	110		0.88 [0.66, 1.17]	2.54
	CheckMate 227 2019	189	576	205	570	-	0.93[0.79, 1.11]	2 67
	CheckMate 9I A 2021	168	358	132	349	-	1 16 [0 96 1 41]	2.65
	CA184-041 = 2012	40	71	13	32		1.10 [0.00, 1.11]	2.00
	CA184-041 b 2012	36	67	13	33		1.20 [0.73, 2.10]	2.10
	CA184-104 2017	205	388	129	361		1 31 [1 09 1 58]	2.66
	Mpower132, 2020	200	201	166	274		1.01 [1.03, 1.30]	2.00
		12	251	100	274		- 1 92 [0 75 / //5]	1.52
		221	224	105	224			1.52
		231	334	195	334		0.44[0.32,0.50]	2.09
	ENFOWER-Lung 1, 2021	102	100	134	542		1.04 [0.93, 0.39]	2.55
	RATIONALE 307, 8, 2021	103	120	47	59		1.04 [0.01, 1.35]	2.50
	RATIONALE 307, b, 2021	99	118 2 - 40	47	96		1.02 [0.79, 1.32]	2.56
	Heterogeneity: $t = 0.25$, $I = 5$	4.80%, H	= 19.	23			0.75[0.63, 0.90]	
	Test of $\theta_i = \theta_j$: Q(32) = 394.12,	p = 0.00						
	SCI C							
	CASPIAN & 2021	171	265	87	122		0991081 1241	2 64
	CASPIAN 2 2021	106	200	90	122			2.04
	UTUT ITN, a, 2021	190 0	∠00 ∕10	10	100			2.00
	IMpowor133, 2019	∠ 115	40 100	10	24 - 106			2.64
	111100001133, 2018	115	190	113	190			∠.0 4
	CA 184-041, a, 2013	19	42	10	22			1.90
	CA184-041, b, 2013	22	42	9	22		1.18 [0.62, 2.26]	1.93
	CA184-156, 2016	231	4/8	214	4/6		1.05 [0.90, 1.22]	2.09
	CheckMate 331, 2021	39	282	194	265	-	0.29 [0.21, 0.39]	2.50
	Heterogeneity: $\tau^2 = 0.35$, $I^2 = 9$	95.25%, H	- = 21.	07			0.76 [0.48, 1.18]	
	Fest of $\theta_i = \theta_j$: Q(7) = 70.56, p	= 0.00						
	o "						0.701.001.000	
			2				U.76[U.64, 0.89]	
	Heterogeneity: $\tau^2 = 0.25$, $I^2 = 9$	94.75%, H	⁻ = 19.	06				
	Test of $\theta_i = \theta_j$: Q(40) = 467.28,	p = 0.00						
	Test of group differences: Q _b (1) = 0.00,	p = 0.9	8				
	Random-effects REML model				1	//32 1/8 1/2 2	_	
Fig. 5 Forest pla	ts of RRs comparing Grade 3–	5 TRAFs	of im	munoth	neranv I	between NSCLC and SCL	_C	
J Brest plo							-	

$\begin{aligned} \begin{array}{c c c c c c c c c c c c c c c c c c c $									
Trial Events Total with 65% Cl (%) NSGLC KEWNOTE-407, 2016 273 278 274 200 1001 0.06, 113 3.35 KEWNOTE-407, 2016 55 69 57 62 1001 0.07, 1132 1.13 3.55 OAK ITTSS0, 2019 390 609 466 578 0.871 0.75 0.851 0.76 0.981 0.71			Trea	tment	Co	ntrol		Risk Ratio	Weight
NSCLC KEYNOTE-01, 2016 KEYNOTE-01, 2016 KEYNOTE-01, 2016 CheckMate 028, 2017 OAK (ITT350, 2019 JAVELIN Lung O2, 0216 JAVELIN LUNG O2, 0217 JAVELIN LUNG		Trial	Events	Total	Events	Total		with 95% CI	(%)
$ \begin{array}{c} KEYNOTE_{42}, 2016 & 57 & 99 & 57 & 62 & 100 & [0.87, 1.33 & 1.35 \\ CheckMote 026, 2017 & 930 & 600 & 496 & 578 & 0.85 & [0.76, 0.57, 1.00] & 2.78 \\ OAK, ITT_{520, 2018 } & 574 & 609 & 557 & 578 & 0.95 & [0.87, 1.07, 1.02] & 1.27 \\ OAK, ITT_{520, 2018 } & 574 & 609 & 557 & 578 & 0.95 & [0.87, 1.07, 1.02] & 2.78 \\ OAK, ITT_{520, 2018 } & 574 & 609 & 557 & 578 & 0.95 & [0.87, 1.03] & 2.79 \\ OAK, ITT_{520, 2018 } & 574 & 609 & 557 & 578 & 0.95 & [0.87, 1.03] & 2.78 \\ OAK, ITT_{520, 2018 } & 574 & 609 & 557 & 578 & 0.95 & [0.87, 1.03] & 2.78 \\ OAK, ITT_{520, 2018 } & 574 & 609 & 557 & 578 & 0.95 & [0.87, 1.03] & 2.78 \\ NEYNOTE_{-010, 2010 & 216 & 215 & 339 & 126 & 155 & 0.87 & [0.74, 0.03] & 3.93 \\ KEYNOTE_{-010, 2016 & 216 & 215 & 339 & 126 & 155 & 0.87 & [0.74, 0.03] & 1.12 & 2.24 \\ NEYNOTE_{-010, 2010 & 216 & 226 & 343 & 125 & 154 & 0.86 & [0.70, 1.02 & 1.73 \\ POR-IAR, 2016 & 707 & [1.08 & 114 & 135 & 150 & 0.92 & [0.76, 1.02 & 1.17 & 1.14 & 115 & 150 & 0.92 & [0.76, 1.02 & 1.17 & 1.14 & 1.17 & 0.98 & [0.70, 1.02 & 1.17 & 1.14 & 1.15 & 1.14 & 1.17 & 0.98 & [0.70, 1.02 & 1.17 & 1.14 & 1.15 & 0.98 & [0.80, 1.11 & 3.17 & 0.98 & [0.80, 1.11 & 3.17 & 0.98 & [0.80, 1.11 & 3.17 & 0.98 & [0.80, 1.11 & 3.17 & 0.98 & [0.80, 1.11 & 3.17 & 0.98 & [0.80, 1.11 & 3.17 & 0.98 & [0.80, 1.11 & 2.14 & 1.14 & 3.46 & 0.98 & [0.80, 1.11 & 3.17 & 0.98 & [0.80, 1.11 & 2.14 & 1.14 & 3.46 & 0.98 & [0.80, 1.11 & 2.14 & 1.14 & 3.46 & 0.98 & [0.80, 1.11 & 2.14 & 1.14 & 3.46 & 0.98 & [0.80, 1.10 & 2.24 & 1.10 & [0.80, 1.11 & 2.14 & 1.14 & 3.46 & 0.98 & [0.80, 1.11 & 2.14 & 0.14 & 0.14 & 2.14 & 2.14 & 2.12 & 2.24 & 1.10 & [0.80, 1.17 & 2.14 & 1.14 & 2.14 & 2.12 & 2.24 & 1.10 & [0.80, 1.17 & 2.14 & 1.14 & 2.14 & 2.24 & 1.14 & 2.14 & 2.24 & 1.14 & 2.14 & 2.24 & 1.14 & 2.14 & 2.24 & 1.14 & 2.14 & 2.24 & 1.14 & 2.24 & 1.14 & 2.24 & 1.14 & 2.24 & 1.14 & 2.24 & 1.14 & 2.24 & 1.14 & 2.24 & 1.14 & 2.24 & 1.14 & 2.24 & 1.14 & 1.24 & 0.98 & [0.84, 1.17 & 2.14 & 1.14 & 2.14 & 2.24 & 1.14 & $		NSCLC							
$ \begin{array}{c} KEWNCE_{221,2016} & 55 & 59 & 57 & 62 & 1011 [0.7, 15.0 & 27.8 \\ CARCHTR80,026,2017 & 50 & 69 & 496 & 57.8 & 0.991 [0.51, 10.0] & 27.8 \\ CARCHTR80,02018 & 251 & 333 & 254 & 365 & 0.991 [0.51, 10.0] & 27.8 \\ CARCHTR80,02018 & 251 & 333 & 254 & 365 & 0.991 [0.51, 10.0] & 28.1 & 33.2 \\ KEWNCE-102,02018 & 251 & 339 & 128 & 155 & 0.671 [0.73, 10.2] & 22.8 \\ KEWNCE-010,0,2016 & 251 & 339 & 128 & 155 & 0.671 [0.73, 10.2] & 22.8 \\ KEWNCE-010,0,2016 & 251 & 223 & 343 & 125 & 154 & 0.991 [0.51, 10.0] & 2.31 \\ POFLAR,2016 & 95 & 122 & 124 & 101 [0.70, 10.6] & 1.31 \\ POFLAR,2016 & 91 & 124 & 113 & 150 & 0.98 [0.70, 10.6] & .31 \\ POCHAR,2016 & 215 & 222 & 234 & 0.991 [0.51, 10.0] & 2.31 \\ POCHAR,2016 & 215 & 339 & 128 & 155 & 0.671 [0.73, 10.2] & 228 \\ KEWNCE-010,0,2016 & 251 & 222 & 234 & 0.991 [0.51, 10.0] & 2.31 \\ POCHAR,2016 & 201 & 218 & 213 & 111 & 129 & 0.991 [0.51, 10.0] & 2.31 \\ POCHAR,2016 & 201 & 218 & 218 & 150 & 0.991 [0.51, 10.0] & 2.31 \\ POCHAR,2016 & 201 & 218 & 228 & 249 & 253 & 0.991 [0.61, 10.0] & 2.31 \\ POCHAR,2016 & 201 & 218 & 224 & 228 & 0.991 [0.61, 10.0] & 2.31 \\ POCHAR,2020 & 129 & 273 & 344 & 0.991 [0.61, 10.0] & 3.83 \\ CheckMate 07,2015 & 173 & 215 & 232 & 0.991 [0.61, 10.0] & 3.83 \\ CheckMate 07,201 & 455 & 473 & 215 & 232 & 0.991 [0.61, 11.0] & 3.83 \\ CheckMate 207,2019 & 442 & 576 & 467 & 570 & 0.981 [0.71, 10.2] & 1.15 \\ CARH-10,202 & 146 & 77 & 23 & 247 & 0.981 [0.61, 1.72 & 1.15 \\ CARH-10,202 & 146 & 77 & 23 & 247 & 0.981 [0.61, 1.72 & 1.15 \\ CARH-10,202 & 126 & 576 & 467 & 570 & 0.981 [0.61, 1.72 & 1.15 \\ CARH-10,202 & 127 & 738 & 303 & 349 & 0.991 [0.71, 11.5] & 3.42 \\ ARCTC,0,202 & 160 & 173 & 105 & 110 & 0.981 [0.87, 1.72 & 1.15 \\ CARH-10,202 & 172 & 738 & 303 & 349 & 0.981 [0.87, 1.71 & 1.15 \\ CARH-10,202 & 127 & 238 & 303 & 349 & 0.981 [0.87, 1.71 & 1.15 \\ CARH-10,202 & 126 & 276 & 129 & 133 & 0.911 [0.67, 1.71 & 2.59 \\ CARH-10,20 & 0.01 & 7-44 & 388 & 1292 & 0.98$		KEYNOTE-407, 2018	273	278	274	280		1.00 [0.89, 1.13]	3.35
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		KEYNOTE-021, 2016	55	59	57	62		1.01 [0.77, 1.32]	1.13
CheckMate 028, 2017 CAR ITT1225, 2018 CAR ITT1225, 2018 KEYNOTE-148, 2018 KEYNOTE-402, 2018 KEYNOTE-402, 2019 KEYNOTE-402, 2019 KEYNOTE-010, b, 2016 226 KEYNOTE-010, b, 2016 226 KEYNOTE-010, b, 2016 228 KEYNOTE-010, b, 2017 228 KEYNOTE-010, b, 2016 228 KEYNOTE-010, b, 2017 228 KEYNOTE-010, b, 2017 228 KEYNOTE-010, b, 2017 228 KEYNOTE-010, b, 2017 228 KEYNOTE-010, b, 2017 228 229 40 40 40 40 40 40 40 40 40 40		OAK ITT850, 2019	390	609	496	578		0.85 [0.76, 0.94]	3.88
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		CheckMate 026, 2017	190	267	243	263		0.87 [0.75, 1.00]	2.78
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		OAK ITT1225, 2018	574	609	557	578		0.99 [0.91, 1.07]	4.46
$ \begin{array}{c} KEYNOTE-169, 2019 \\ KEYNOTE-042, 2019 \\ KEYNOTE-042, 2019 \\ KEYNOTE-042, 2019 \\ KEYNOTE-010, a, 2016 \\ L^{21} \\ L^{21} \\ KEYNOTE-010, a, 2016 \\ L^{22} \\ L^{21} \\ KEYNOTE-010, a, 2016 \\ L^{22} \\ L^{21} \\ KEYNOTE-010, a, 2016 \\ L^{22} \\ L^{21} \\ L^{$		JAVELIN Lung 200, 2018	251	393	254	365		0.95 [0.83, 1.09]	2.93
$ \begin{array}{c} KEYNOTE- 0.2016 & 215 & 339 & 126 & 155 & & & & 0.81 [0.74, 0.90] & 2.88 \\ KEYNOTE- 0.0, 2.2016 & 215 & 339 & 126 & 155 & & & & 0.85 [0.73, 1.02] & 2.28 \\ KEYNOTE- 0.0, 2.2016 & 95 & 142 & 119 & 135 & & & 0.86 [0.75, 1.01] & 2.01 \\ POPLAR, 2016 0.95 & 142 & 119 & 135 & & & 0.92 [0.76, 1.10] & 2.01 \\ CheckMate 017, 2015 76 & 131 & 111 & 129 & & & 0.92 [0.76, 1.10] & 2.01 \\ CheckMate 057, 2015 199 & 287 & 236 & 268 & & & & 0.87 [0.76, 1.01] & 2.78 \\ IMpower150, 2018 371 & 393 & 376 & 394 & & & 0.98 [0.86, 1.07, 1.28] & 2.28 \\ CheckMate 057, 2015 199 & 287 & 236 & 268 & & & 0.87 [0.76, 1.01] & 2.78 \\ IMpower150, 2018 371 & 393 & 376 & 394 & & & 0.98 [0.87, 1.01] & 2.84 \\ IMpower150, 2019 455 & 473 & 215 & 222 & & & 102 [0.91, 1.16] & 3.42 \\ ARCTIC, a, 2020 60 & 62 & 63 & 63 & & & & 0.98 [0.77, 1.26] & 1.25 \\ Caramel, 2020 160 & 173 & 105 & 110 & & & & 0.98 [0.87, 1.17] & 2.18 \\ CheckMate 9LA, 2021 327 & 358 & 303 & 349 & & & & & & 0.98 [0.87, 1.07] & 0.89 [2.82, 1.17] & 2.11 \\ CheckMate 9LA, 2021 42 & 576 & 467 & 570 & & & & & & & & & & & & & & & & & & &$		KEYNOTE-189, 2018	404	405	200	202		1.00 [0.89, 1.13]	3.32
$ \begin{array}{c} KEYNOTE-010, a, 2016 \\ KEYNOTE-010, b, 2016 \\ KEYNOTE-010, b, 2016 \\ CPOPLAR, 2017, 2018 \\ CPOPLAR, 2017, 2018 \\ CPOPLAR, 2017, 2015 \\ CPAPLAR, 2018 \\ CPAPLAR, 2018 \\ CPAPLAR, 2020 \\ CPAPLAR, 2021 \\ CP$		KEYNOTE-042, 2019	399	636	553	615		0.81 [0.74, 0.90]	3.98
$ \begin{array}{c} KEYNOTE-10, b, 2016 & 226 & 343 & 125 & 154 \\ POPLAR, 2017 & 018 & 60 & 475 & 222 & 234 \\ POPLAR, 2017 & 2018 & 2019 & 118 & 154 & 135 & 150 \\ CheckMate 017, 2015 & 76 & 131 & 111 & 129 \\ CheckMate 017, 2015 & 76 & 131 & 111 & 129 \\ CheckMate 037, 2015 & 199 & 227 & 238 & 268 \\ Mpower150, 2020 & 126 & 226 & 244 & 263 \\ Mpower150, 2020 & 193 & 371 & 136 \\ CheckMate 057, 2019 & 455 & 473 & 215 & 232 \\ CheckMate 057, 2019 & 455 & 473 & 215 & 232 \\ ARCTIC, a, 2020 & 60 & 62 & 63 & 63 \\ CameL, 2020 & 160 & 173 & 105 & 110 \\ CheckMate 054, 2021 & 217 & 358 & 303 & 49 \\ CameL, 2020 & 160 & 173 & 105 & 110 \\ CheckMate 212, 2020 & 160 & 173 & 105 & 110 \\ CheckMate 214, 2021 & 227 & 738 & 303 & 349 \\ CA184-041, a, 2012 & 527 & 12 & 23 & 333 \\ CheckMate 227, 2019 & 442 & 576 & 467 & 570 \\ CA184-041, a, 2012 & 527 & 112 & 333 \\ CA184-041, a, 2012 & 527 & 112 & 333 \\ CA184-041, a, 2012 & 247 & 714 & 23 & 323 \\ CA184-041, a, 2012 & 257 & 112 & 333 \\ CA184-041, a, 2012 & 267 & 212 & 268 & 274 \\ Mpower131, 2020 & 316 & 334 & 303 & 334 \\ Mpower131, 2020 & 316 & 334 & 303 & 334 \\ Mpower131, 2020 & 216 & 117 & 118 & 58 & 58 \\ Mpower132, 2020 & 316 & 334 & 303 & 334 \\ Mpower133, 2018 & 148 & 198 & 181 & 198 \\ CA184-041, a, 2013 & 33 & 42 & 18 & 22 \\ CA184-041, a, 2013 & 33 & 42 & 18 & 22 \\ CA184-041, a, 2013 & 33 & 42 & 18 & 22 \\ CA184-041, a, 2013 & 33 & 42 & 18 & 22 \\ CA184-041, a, 2013 & 33 & 42 & 18 & 22 \\ CA184-041, a, 2013 & 33 & 42 & 18 & 22 \\ CA184-041, a, 2013 & 33 & 42 & 18 & 22 \\ CA184-041, a, 2013 & 33 & 42 & 18 & 22 \\ CA184-041, a, 2013 & 33 & 42 & 18 & 22 \\ CA184-041, a, 2013 & 33 & 42 & 18 & 22 \\ CA184-041, a, 2013 & 33 & 42 & 18 & 22 \\ CA184-041, a, 2013 & 33 & 42 & 18 & 22 \\ CA184-041, a, 2013 & 33 & 42 & 18 & 22 \\ CA184-041, a, 2013 & 33 & 42 & 18 & 22 \\ CA184-041, a, 2016 & 328, p = 0.04 \\ Ca184-041, a$		KEYNOTE-010, a, 2016	215	339	126	155		0.87 [0.73, 1.02]	2.28
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		KEYNOTE-010, b, 2016	226	343	125	154		0.89 [0.75, 1.05]	2.31
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		POPLAR, 2016	95	142	119	135		0.86 [0.70, 1.05]	1.73
$ \begin{array}{c} KEYNOTE- 024, 2016, 2019 & 118 & 154 & 135 & 150 \\ CheckMale 017, 2015 & 76 & 131 & 111 & 129 \\ IMpower10, 2020 & 258 & 286 & 249 & 253 \\ IMpower10, 2020 & 19 & 337 & 394 \\ IMpower10, 2020 & 219 & 337 & 311 & 156 \\ CheckMale 067, 2020 & 119 & 327 & 314 & 156 \\ CheckMale 067, 2020 & 146 & 205 & 132 & 207 \\ ARCTIC, a, 2020 & 166 & 173 & 105 & 110 \\ CheckMale 927, 2019 & 442 & 576 & 467 & 570 \\ CheckMale 927, 2019 & 442 & 576 & 467 & 570 \\ CheckMale 927, 2019 & 442 & 576 & 467 & 570 \\ CheckMale 927, 2019 & 442 & 576 & 467 & 570 \\ CheckMale 927, 2019 & 442 & 576 & 467 & 570 \\ CheckMale 927, 2019 & 442 & 576 & 467 & 570 \\ CheckMale 927, 2019 & 442 & 576 & 467 & 570 \\ CheckMale 92, 2021 & 227 & 358 & 303 & 349 \\ CA184-041, a, 2012 & 29 & 729 & 123 & 32 \\ CA184-041, a, 2012 & 29 & 729 & 1266 & 274 \\ IOP(0, 173) & 10, 22, 1.15 & 3.50 \\ CA184-041, a, 2012 & 297 & 291 & 266 & 274 \\ IOP(0, 173) & 10, 22, 1.15 & 3.50 \\ CA184-041, a, 2012 & 207 & 277 & 291 & 23 & 32 \\ CA184-041, a, 2012 & 297 & 291 & 266 & 274 \\ IOP(0, 170, 1.47) & 0.681 \\ IOP(0, 0, 1.13) & 3.06 & 314 & 303 & 334 \\ IOP(0, 0, 1.13) & 3.06 & 1.19 & 1.16 \\ IOP(0, 0, 1.29 & 1.53 & 303 & 324 \\ IOP(0, 0, 1.29 & 1.53 & 304 & 100 & 10.06 & 1.29 & 1.53 \\ IOP(0, 0, 1.29 & 1.53 & 314 & 305 & 334 & 324 \\ IOP(0, 0, 1.29 & 1.53 & 1.00 & 10.00 & 1.29 & 1.51 \\ IOP(0, 0, 1.29 & 1.53 & 1.00 & 10.00 & 1.29 & 1.51 \\ IOP(0, 0, 1.29 & 1.53 & 3.42 & 0.95 & 1.00 & 10.00 & 1.29 & 1.51 \\ IOP(0, 0, 0, 1.24 & 1.51 & 0.95 & 1.29 & 1.00 & 10.00 & 1.24 & 1.51 \\ IOP(0, 0, 0, 1.24 & 1.51 & 0.95 & 1.29 & 0.95 & 0.32 & 0.98 & 0.75 & 0.64 & 0.88 & 2.48 \\ IOP(0, 1, 0, 0, 1.51 & 3.50 & 0.75 & 0.64 & 0.88 & 2.48 \\ IOP(0, 0, 0, 0, 1, 0, 0, 0, 1, 14 & 3.50 & 0.55 & 0.95 $		PACIFIC, 2017, 2018	460	475	222	234		1.01 [0.90, 1.13]	3.47
CheckMate 017, 2015 Npower10, 2020 CheckMate 07, 2015 CheckMate 07, 2015 CheckMate 07, 2015 CheckMate 07, 2015 CheckMate 07, 2012 CheckMate 07, 2012 CheckMate 07, 2012 CheckMate 07, 2012 CheckMate 07, 2012 CheckMate 07, 2012 CheckMate 07, 2020 CheckMate 227, 2019 CheckMate 227, 2020 CheckMate 227, 2020 CheckMate 30, 2021 CheckMate 30, 2021 CheckMate 30, 2021 CheckMate 30, 2021 CheckMate 30, 2021 CheckMate 31, 2021 CheckMate 331, 2021 CheckMate		KEYNOTE- 024, 2016, 2019	118	154	135	150		0.92 [0.76, 1.10]	2.01
IMpower10, 2020 258 286 249 263 0.98 [0.86, 1.11] 3.17 CheckMate 057, 2015 199 287 236 0.87 [0.76, 1.01] 2.78 IMpower130, 2019 455 473 215 232 0.86 [0.73, 1.02] 2.34 IMpower130, 2019 455 473 215 232 0.98 [0.86, 1.17] 3.17 CheckMate 076, 2020 160 173 105 110 0.88 [0.82, 1.17] 2.11 CheckMate 227, 2019 442 576 467 570 0.99 [0.87, 1.06] 400 CheckMate 227, 2019 442 576 473 33 1.03 [0.70, 1.47] 0.68 0.88 [0.82, 1.17] 2.11 CheckMate 24, 2021 127 356 303 349 1.03 [0.92, 1.15] 3.50 CA184-041, a, 2012 52 71 23 32 1.01 [0.70, 1.47] 0.68 CA184-041, a, 2012 204 355 303 344 1.03 [0.94, 1.18] 3.66 IMpower132, 2020 287 291 266 274 1.05 [0.94, 1.18] 3.66		CheckMate 017, 2015	76	131	111	129		0.79 [0.63, 0.99]	1.48
CheckMate 057, 2015 IMpower150, 2018 CheckMate 057, 2020 CheckMate 078, 2020 CheckMate 078, 2020 CheckMate 227, 2019 CheckMate 237, 2020 CheckMate 237, 2020 CheckMate 237, 2020 CheckMate 237, 2020 CheckMate 237, 2020 CheckMate 237, 2020 CheckMate 237, 2021 CheckMate 237, 2021 CheckMate 237, 2021 CheckMate 237, 2021 CheckMate 237, 2012 CheckMate 237, 2012 CheckMate 237, 2012 CheckMate 237, 2012 CheckMate 237, 2013 CheckMate 237, 2016 CheckMate 237, 2016 CheckMate 237, 2016 CheckMate 237, 2021 CheckMate 237, 2021 CheckMate 237, 2021 CheckMate 237, 2021 CheckMate 237, 2016 CheckMate 237, 2016 CheckMate 231, 2021 CheckMate 2		IMpower110, 2020	258	286	249	263		0.98 [0.86, 1.11]	3.17
		CheckMate 057, 2015	199	287	236	268		0.87 [0.76, 1.01]	2.78
CheckMate 078, 2020 219 337 131 156 Mpower130, 2019 455 473 215 232 ARCTIC, a, 2020 160 62 63 63 CameL, 2020 160 173 105 110 CheckMate 227, 2019 442 576 467 570 CheckMate 227, 2019 443 88 292 361 105 [0.94, 1.18] 3.46 1005 [0.94, 1.14] 3.50 EMPOWER-Lung 1, 2021 260 265 129 133 1001 [0.87, 1.17] 2.59 CASPIAN, a, 2021 260 265 129 133 1001 [0.87, 1.17] 2.59 CASPIAN, b, 2021 177 118 58 1000 [0.80, 1.24] 1.51 1000 [0		IMpower150, 2018	371	393	376	394		0.99 [0.90, 1.10]	3.83
$ \begin{array}{c} Mpower130, 2019 & 455 & 473 & 215 & 232 & & & & 1.02 \left[0.91, 1.15 \right] 3.42 \\ ARCTIC, a, 2020 & 160 & 173 & 105 & 110 & & & & & & & & & & & & & & & & &$		CheckMate 078, 2020	219	337	131	156		0.86 [0.73, 1.02]	2.34
ARCTIC, a, 2020 60 62 63 63 0.98 [0.77, 1.26] 1.25 CameL, 2020 146 205 132 207 1.07 [0.88, 1.28] 202 ARCTIC, b, 2020 160 173 105 110 0.98 [0.87, 1.16] 4.00 CheckMate 9LA, 2021 327 358 303 349 1.03 [0.70, 1.47] 0.61 CA184-041, a, 2012 52 71 23 32 1.01 [0.70, 1.47] 0.63 CA184-041, b, 2012 49 67 23 33 1.03 [0.92, 1.15] 3.50 CA184-041, 2017 344 388 292 361 1.05 [0.94, 1.18] 3.46 IMpower131, 2020 216 343 303 334 1.02 [0.91, 1.14] 3.50 RATIONALE 307, a, 2021 119 120 59 59 1.00 [0.80, 1.24] 1.51 RATIONALE 307, b, 2021 117 118 58 58 1.00 [0.80, 1.24] 1.51 RATIONALE 307, b, 2021 260 265 129 133 1.01 [0.87, 1.17] 2.59 CASPIAN, a, 2021 26		IMpower130, 2019	455	473	215	232		1.02 [0.91, 1.15]	3.42
CameL, 2020 ARCTIC, b, 2020 ARCTIC, b, 2020 CheckMate 227, 2019 CheckMate 237, 2020 CheckMate 230, 2020 CheckMate 231, 2020 CheckMate 231, 2021 CheckMate 230, b, 2021 CheckMate 231, 2021		ARCTIC, a, 2020	60	62	63	63		0.98 [0.77, 1.26]	1.25
ARCTIC, b, 2020 160 173 105 110 0 0 98 0.82 1.17 2.11 CheckMate 227, 2019 442 576 467 570 0 96 0.87, 1.06 4.00 CheckMate 9LA, 2021 327 358 303 349 103 0.92 1.15 3.50 CA184-041, b, 2012 52 71 23 32 1.01 0.70 1.03 0.70 0.00 0.00 1.14 3.50 0.00 1.14 3.50 0.00 1.14 3.50 0.00 1.14 3.50 0.00 0.00 1.14 3.50 0.00 1.14 3.50 0.00 0.00 1.14 3.50 0.00 0.00 1.14 3.50 0.00 0.00 1.14 3.50 0.00 0.00 1.14 3.50 0.00 0.00 0.00 1.14 3.50 0.00 0.00 0.00 0.00 0.00 0.00 0.00		CameL, 2020	146	205	132	207		1.07 [0.89, 1.28]	2.02
CheckMate 227, 2019 442 576 467 570 CheckMate 227, 2019 442 576 467 570 CheckMate 9LA, 2021 327 358 303 349 CA184-041, a, 2012 52 71 23 32 CA184-041, b, 2012 49 67 23 33 CA184-041, b, 2012 349 67 23 33 CA184-041, b, 2012 368 292 361 Into [0.87, 1.07] 1.50 0.61 Into [0.90, 1.13] 3.60 IMpower131, 2020 267 291 266 274 Into [0.90, 1.14] 3.50 EMPOWER-Lung 1, 2021 204 355 303 342 CA184-041, a, 2021 119 120 59 59 RATIONALE 307, a, 2021 119 120 59 59 RATIONALE 307, a, 2021 117 118 58 58 RATIONALE 307, a, 2021 117 118 58 58 Into [0.80, 1.24] 1.51 Heterogeneity: $r^2 = 0.00$, $l^2 = 40.20\%$, $H^2 = 1.67$ Test of $\theta_1 = \theta_1$ (Q(31) = 48.77, p = 0.02 SCLC CASPIAN, a, 2021 260 265 129 133 CA184-041, a, 2013 29 42 18 22 CA184-041, a, 2013 29 42 18 22 CA184-041, b, 2013 33 42 18 22 CA184-041, b, 2013 33 42 18 22 CA184-041, b, 2013 156 282 239 265 CA184-041, b, 2014, l^2 58.62\%, H^2 = 1.76 Test of $\theta_1 = \theta_1 O([\theta_1 = 13.26, p = 0.04]$ Corral Heterogeneity: $r^2 = 0.01, l^2 = 58.62\%, H^2 = 1.76$ Test of $\theta_1 = \theta_1 O([\theta_1 = 13.26, p = 0.04]$ Corral Heterogeneity: $r^2 = 0.01, l^2 = 58.62\%, H^2 = 1.76$ Tes		ARCTIC, b, 2020	160	173	105	110		0.98 [0.82, 1.17]	2.11
CheckMate 9LA, 2021 327 358 303 349 CA184-041, a, 2012 52 71 23 32 CA184-041, b, 2012 49 67 23 33 CA184-104, 2017 344 388 292 361 IMpower132, 2020 287 291 266 274 I.05 [0.94, 1.18] 3.46 IMpower131, 2020 316 334 303 334 I.05 [0.94, 1.18] 3.46 IMpower131, 2020 316 334 303 334 I.00 [0.80, 1.24] 1.51 RATIONALE 307, a, 2021 119 120 59 59 RATIONALE 307, b, 2021 117 118 58 58 Heterogeneity: $r^2 = 0.00$, $l^2 = 40.20\%$, $H^2 = 1.67$ Test of $\theta_i = \theta_i$ Q(31) = 48.77, p = 0.02 SCLC CASPIAN, a, 2021 264 266 129 133 I.00 [0.80, 1.24] 1.51 IMpower133, 2018 188 198 181 198 I.00 [0.88, 1.18] 2.67 CA184-041, a, 2013 29 42 18 22 O.91 [0.58, 1.41] 0.46 CA184-041, a, 2013 29 42 18 22 O.91 [0.58, 1.41] 0.46 CA184-041, b, 2013 33 42 18 22 O.95 [0.92, 0.98] CheckMate 331, 2021 166 282 239 265 CheckMate 331, 2021 165 282 239 265 CheckMate 331, 2021 156 2		CheckMate 227, 2019	442	576	467	570		0.96 [0.87, 1.06]	4.00
CA184-041, a, 2012 52 71 23 32 CA184-041, b, 2012 49 67 23 33 CA184-041, b, 2012 49 67 23 33 CA184-041, b, 2012 49 67 23 33 (A1000 0.00, 1.50) 0.61 CA184-104, 2017 344 388 292 361 1.05 0.94, 1.18] 3.46 IMpower132, 2020 287 291 266 274 1.01 0.90, 1.13] 3.36 IMpower132, 2020 316 334 303 344 CA184-041, 2021 204 355 303 342 RATIONALE 307, a, 2021 119 120 59 59 RATIONALE 307, a, 2021 117 118 58 58 Test of $\theta_1 = \theta_1$: Q(31) = 48.77, p = 0.02 SCLC CASPIAN, a, 2021 260 265 129 133 CA184-041, a, 2013 29 42 18 22 CA184-041, b, 2013 33 42 18 22 CA184-041, b, 2013 29 42 18 22 CA184-041, b, 2013 33 42 18 22 CA184-156, 2016 391 478 361 478 CA184-156, 2016 391 478 361 478 CA184-156, 2016 391 478 361 478 CA184-156, 2016 1391 478 361 478 CA184-156, 2016 391 478 361 478 CA184-156, 2016 1392, 0.98] Heterogeneity: $r^2 = 0.00, l^2 = 43.05\%, H^2 = 1.76$ Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.01 Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.01 Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.01 Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.01 Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.01 Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.01 Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.01 Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.01 Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.01 Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.04 0.95 [0.92, 0.98] Heterogeneity: $r^2 = 0.00, l^2 = 43.05\%, H^2 = 1.76$ Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.78 CA184-041, b, 203 = 62.68, p = 0.78 CA184-041,		CheckMate 9LA, 2021	327	358	303	349		1.03 [0.92, 1.15]	3.50
CA184-041, b, 2012 49 67 23 33 CA184-104, 2017 344 388 292 361 IMpower132, 2020 287 291 266 274 IMpower131, 2020 316 334 303 334 IMpower131, 2020 316 334 303 334 IMpower131, 2020 21 204 355 303 342 RATIONALE 307, a, 2021 117 118 58 58 RATIONALE 307, a, 2021 117 118 58 58 Test of $\theta_1 = \theta_1$: Q(31) = 48.77, p = 0.02 SCLC CASPIAN, a, 2021 264 266 129 133 IMpower133, 2018 188 198 181 198 CA184-041, b, 2013 29 42 18 22 CASPIAN, a, 2021 264 266 129 133 IMpower133, 2018 188 198 181 198 CA184-041, b, 2013 29 42 18 22 CA184-041, b, 2013 33 42 18 22 CA184-041, b, 2016 391 478 361 478 Heterogeneity: $\tau^2 = 0.01, t^2 = 58.62\%, H^2 = 2.42$ Test of $\theta_1 = \theta_1$: Q(3) = 62.68, p = 0.04 Overall Heterogeneity: $\tau^2 = 0.01, t^2 = 43.05\%, H^2 = 1.76$ Test of $\theta_1 = \theta_1$: Q(3) = 62.68, p = 0.04 Overall Heterogeneity: $\tau^2 = 0.01, t^2 = 58.62\%, H^2 = 2.42$ Test of $\theta_1 = \theta_1$: Q(3) = 62.68, p = 0.04 Overall Heterogeneity: $\tau^2 = 0.01, t^2 = 43.05\%, H^2 = 1.76$ Test of $\theta_1 = \theta_1$: Q(3) = 62.68, p = 0.04 Overall Heterogeneity: $\tau^2 = 0.01, t^2 = 43.05\%, H^2 = 1.76$ Test of $\theta_1 = \theta_1$: Q(3) = 62.68, p = 0.04 Overall Heterogeneity: $\tau^2 = 0.01, t^2 = 43.05\%, H^2 = 1.76$ Test of $\theta_1 = \theta_1$: Q(3) = 62.68, p = 0.04 Overall Heterogeneity: $\tau^2 = 0.01, t^2 = 58.62\%, H^2 = 2.42$ Test of $\theta_1 = \theta_1$: Q(3) = 62.68, p = 0.04 Overall Heterogeneity: $\tau^2 = 0.01, t^2 = 58.62\%, H^2 = 2.42$ Test of $\theta_1 = \theta_1$: Q(3) = 62.68, p = 0.04 Overall Heterogeneity: $\tau^2 = 0.01, t^2 = 58.62\%, H^2 = 1.76$ Test of $\theta_1 = \theta_1$: Q(3) = 62.68, p = 0.04 Overall Heterogeneity: $\tau^2 = 0.01, t^2 = 58.62\%, H^2 = 2.42$ Test of $\theta_1 = \theta_1$: Q(3) = 62.68, p = 0.04 Overall Heterogeneity: $\tau^2 = 0.01, t^2 = 58.62\%, H^2 = 2.42$ Test of $\theta_1 = \theta_1$: Q(3) = 62.68, p = 0.04 Overall Heterogeneity: $\tau^2 = 0.01, t^2 = 58.62\%, H^2 = 2.42$ Test of $\theta_1 = \theta_1$: Q(3) = 62.68, p = 0.04 Overall Heterogeneity: $\tau^2 = 0.01, t^2 = 58.62\%, H^2 = 1.76$ Test of group differences: Q(1) = 0.08, p = 0.78 Heterog		CA184-041, a, 2012	52	71	23	32		- 1.01 [0.70, 1.47]	0.63
CA184-104, 2017 344 388 292 361 Mpower132, 2020 287 291 266 274 1.05 0.94, 1.18] 3.46 1.01 0.90, 1.13] 3.36 IMpower131, 2020 316 334 303 334 EMPOWER-Lung 1, 2021 204 355 303 342 EMPOWER-Lung 1, 2021 119 120 59 59 RATIONALE 307, b, 2021 117 118 58 58 Heterogeneity: $r^2 = 0.00$, $l^2 = 40.20\%$, $H^2 = 1.67$ Test of $\theta_1 = \theta_1$: Q(31) = 48.77, p = 0.02 SCLC CASPIAN, b, 2021 260 265 129 133 IMpower133, 2018 188 198 181 198 CA184-041, a, 2013 29 42 18 22 OA184-041, b, 2013 33 42 18 22 OA184-156, 2016 391 478 361 478 CA184-041, b, 2013 13 3 42 18 22 OA184-156, 2016 391 478 361 478 CA184-041, b, 2013 13 3 42 18 22 OA184-156, 2016 391 478 361 478 CheckMate 331, 2021 156 282 239 265 OA5E [0.92, 0.98] Heterogeneity: $r^2 = 0.00$, $l^2 = 43.05\%$, $H^2 = 1.76$ Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.01 Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.01 Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.78 Random-effects REML model ig. 6 Forest plots of RRs comparing Grade 1–5 TRAEs of immunotherapy between NSCLC and SCLC		CA184-041, b, 2012	49	67	23	33		- 1.03 [0.70, 1.50]	0.61
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		CA184-104, 2017	344	388	292	361		1.05 [0.94, 1.18]	3.46
$\begin{array}{c} \text{Impower131, 2020} & 316 & 334 & 303 & 334 \\ \text{EMPOWER-Lung 1, 2021} & 204 & 355 & 303 & 342 \\ \text{EMPOWER-Lung 1, 2021} & 204 & 355 & 303 & 342 \\ \text{RATIONALE 307, a, 2021} & 119 & 120 & 59 & 59 \\ \text{RATIONALE 307, b, 2021} & 117 & 118 & 58 & 58 \\ \text{Heterogeneity: } t^2 = 0.00, t^2 = 40.20\%, tt^2 = 1.67 \\ \text{Test of } \theta_1 = \theta_1; Q(31) = 48.77, p = 0.02 \\ \end{array}$		IMpower132, 2020	287	291	266	274		1.01 [0.90, 1.13]	3.36
$ \begin{array}{c} EMPOWER-Lung 1, 2021 \\ EMPOWER-Lung 1, 2021 \\ RATIONALE 307, a, 2021 \\ RATIONALE 307, a, 2021 \\ RATIONALE 307, b, 2021 \\ Rational 11, 118 \\ S8 \\ S9 \\ $		IMpower131, 2020	316	334	303	334		1.02 [0.91, 1.14]	3.50
RATIONALE 307, a, 2021 119 120 59 59 RATIONALE 307, b, 2021 117 118 58 58 Heterogeneity: $\tau^2 = 0.00$, $t^2 = 40.20\%$, $H^2 = 1.67$ Test of $\theta_1 = \theta_1$, Q(31) = 48.77, p = 0.02 SCLC CASPIAN, b, 2021 260 265 129 133 CASPIAN, a, 2021 264 266 129 133 I.01 [0.87, 1.17] 2.59 CASPIAN, a, 2021 264 266 129 133 I.01 [0.87, 1.18] 2.60 IMpower133, 2018 188 198 181 198 CA184-041, a, 2013 29 42 18 22 CA184-041, b, 2013 33 42 18 22 CA184-041, b, 2013 33 42 18 22 CA184-041, b, 2013 33 42 18 22 CA184-156, 2016 391 478 361 478 CheckMate 331, 2021 156 282 239 265 CheckMate 331, 2021 156 282 100 CheckMate 331, 2021 156 282 239 265 CheckMate 331, 2021 282 CheckMate 331, 2021 282 CheckMate 331, 2021 28		EMPOWER-Lung 1, 2021	204	355	303	342	_	0.78 0.68. 0.891	2.90
RATIONALE 307, b, 2021 117 118 58 58 Heterogeneity: $t^2 = 0.00$, $l^2 = 40.20\%$, $H^2 = 1.67$ Test of $\theta_i = \theta_i$: Q(31) = 48.77, p = 0.02 SCLC CASPIAN, b, 2021 260 265 129 133 CASPIAN, a, 2021 264 266 129 133 I.01 [0.87, 1.17] 2.59 CASPIAN, a, 2021 264 266 129 133 I.01 [0.87, 1.18] 2.60 IMpower133, 2018 188 198 181 198 O.21 [0.88, 1.18] 2.67 CA184-041, a, 2013 29 42 18 22 O.91 [0.58, 1.41] 0.46 CA184-041, b, 2013 33 42 18 22 O.91 [0.58, 1.41] 0.46 CA184-156, 2016 391 478 361 478 CheckMate 331, 2021 156 282 239 265 O.75 [0.64, 0.88] 2.48 Heterogeneity: $t^2 = 0.01$, $l^2 = 58.62\%$, $H^2 = 2.42$ Test of $\theta_i = \theta_i$: Q(6) = 13.26, p = 0.04 Overall Heterogeneity: $t^2 = 0.00$, $l^2 = 43.05\%$, $H^2 = 1.76$ Test of $\theta_i = \theta_i$: Q(3) = 62.68, p = 0.01 Test of group differences: Q ₀ (1) = 0.08, p = 0.78 Random-effects REML model 0.58 1.50 Ig. 6 Forest plots of RRs comparing Grade 1–5 TRAEs of immunotherapy between NSCLC and SCLC		RATIONALE 307, a, 2021	119	120	59	59		1.00 [0.80, 1.24]	1.53
Heterogeneity: $r^2 = 0.00$, $l^2 = 40.20\%$, $H^2 = 1.67$ Test of $\theta_i = \theta_i$; Q(31) = 48.77, p = 0.02 SCLC CASPIAN, a, 2021 260 265 129 133 1.01 [0.87, 1.17] 2.59 CASPIAN, a, 2021 264 266 129 133 1.01 [0.87, 1.18] 2.60 IMpower133, 2018 188 198 181 198 1.02 [0.88, 1.18] 2.67 CA184-041, a, 2013 29 42 18 22 0.91 [0.58, 1.41] 0.46 CA184-041, b, 2013 33 42 18 22 0.98 [0.64, 1.50] 0.49 CA184-156, 2016 391 478 361 478 1.05 [0.94, 1.16] 3.69 CheckMate 331, 2021 156 282 239 265 0.75 [0.64, 0.88] 2.48 Heterogeneity: $r^2 = 0.01$, $l^2 = 58.62\%$, $H^2 = 2.42$ Test of $\theta_i = \theta_i$: Q(38) = 62.68, p = 0.01 Test of $\theta_i = \theta_i$: Q(38) = 62.68, p = 0.01 Test of $\theta_i = \theta_i$: Q(38) = 62.68, p = 0.01 Test of $\theta_i = \theta_i$: Q(38) = 62.68, p = 0.78 Random-effects REML model ig. 6 Forest plots of RRs comparing Grade 1–5 TRAEs of immunotherapy between NSCLC and SCLC		RATIONALE 307, b, 2021	117	118	58	58		1.00 [0.80, 1.24]	1.51
Test of $\theta_1 = \theta_1$: Q(31) = 48.77, p = 0.02 SCLC CASPIAN, a, 2021 260 265 129 133 1.01 [0.87, 1.17] 2.59 CASPIAN, a, 2021 264 266 129 133 1.01 [0.87, 1.18] 2.60 IMpower133, 2018 188 198 181 198 1.02 [0.88, 1.18] 2.67 CA184-041, a, 2013 29 42 18 22 0.91 [0.58, 1.41] 0.46 CA184-041, b, 2013 33 42 18 22 0.91 [0.58, 1.41] 0.46 CA184-041, b, 2013 33 42 18 22 0.98 [0.64, 1.50] 0.49 CA184-156, 2016 391 478 361 478 1.05 [0.94, 1.16] 3.69 CheckMate 331, 2021 156 282 239 265 0.75 [0.64, 0.88] 2.48 Heterogeneity: $\tau^2 = 0.01$, $t^2 = 58.62\%$, $H^2 = 2.42$ 0.96 [0.87, 1.07] Test of $\theta_1 = \theta_1$: Q(6) = 13.26, p = 0.04 Overall Heterogeneity: $\tau^2 = 0.00$, $t^2 = 43.05\%$, $H^2 = 1.76$ Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.01 Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.01 Test of group differences: Q ₆ (1) = 0.08, p = 0.78 Random-effects REML model i.50 i.50 i.50 i.50		Heterogeneity: $\tau^2 = 0.00$. $I^2 = 4$	0.20%.	$+^2 = 1.6$	7		▲	0.95 [0.92. 0.98]	
SCLC CASPIAN, b, 2021 260 265 129 133 101 [0.87, 1.17] 2.59 CASPIAN, a, 2021 264 266 129 133 101 [0.87, 1.18] 2.60 IMpower133, 2018 188 198 181 198 10.2 [0.88, 1.18] 2.67 CA184-041, a, 2013 29 42 18 22 0.91 [0.58, 1.41] 0.46 CA184-041, b, 2013 33 42 18 22 0.91 [0.58, 1.41] 0.46 CA184-041, b, 2013 33 42 18 22 0.98 [0.64, 1.50] 0.49 CA184-156, 2016 391 478 361 478 1.05 [0.94, 1.16] 3.69 CheckMate 331, 2021 156 282 239 265 0.75 [0.64, 0.88] 2.48 Heterogeneity: $\tau^2 = 0.01$, $l^2 = 58.62\%$, $H^2 = 2.42$ Test of $\theta_i = \theta_i$; Q(6) = 13.26, p = 0.04 Overall Heterogeneity: $\tau^2 = 0.00$, $l^2 = 43.05\%$, $H^2 = 1.76$ Test of $\theta_i = \theta_i$; Q(38) = 62.68, p = 0.01 Test of group differences: Q ₆ (1) = 0.08, p = 0.78 Random-effects REML model ig. 6 Forest plots of RRs comparing Grade 1–5 TRAEs of immunotherapy between NSCLC and SCLC		Test of $\theta_i = \theta_i$: Q(31) = 48.77, p	o = 0.02				•		
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CASPIAN, b, 2021 260 265 129 133 1.01 [0.87, 1.17] 2.59 CASPIAN, a, 2021 264 266 129 133 1.01 [0.87, 1.17] 2.59 CASPIAN, a, 2021 264 266 129 133 1.01 [0.87, 1.18] 2.60 IMpower133, 2018 188 198 181 198 1.02 [0.88, 1.18] 2.67 CA184-041, b, 2013 29 42 18 22 0.91 [0.58, 1.41] 0.46 CA184-041, b, 2013 33 42 18 22 0.91 [0.58, 1.41] 0.46 CA184-041, b, 2013 33 42 18 22 0.91 [0.58, 1.41] 0.46 CA184-156, 2016 391 478 361 478 1.05 [0.94, 1.16] 3.69 CheckMate 331, 2021 156 282 239 265 0.75 [0.64, 0.88] 2.48 Heterogeneity: $\tau^2 = 0.01$, $I^2 = 58.62\%$, $H^2 = 2.42$ Test of $\theta_1 = \theta_1$; Q(6) = 13.26, p = 0.04 Overall 0.95 [0.92, 0.98] Heterogeneity: $\tau^2 = 0.00$, $I^2 = 43.05\%$, $H^2 = 1.76$ Test of $g_1 = \theta_1$; Q(38) = 62.68, p = 0.01 Test of group differences: $Q_b(1) = 0.08$, p = 0.78 Random-effects REML model 0.58 1.50 Fig. 6 Forest plots of RRs comparing Grade 1–5 TRAEs of immunotherapy between NSCLC and SCLC		SCLC							
CASPIAN, a, 2021 264 266 129 133 IMpower133, 2018 188 198 181 198 CA184-041, a, 2013 29 42 18 22 CA184-041, b, 2013 33 42 18 22 CA184-041, b, 2013 33 42 18 22 CA184-156, 2016 391 478 361 478 CheckMate 331, 2021 156 282 239 265 CheckMate 331, 2021 150 CheckMate 331,		CASPIAN, b, 2021	260	265	129	133		1.01 [0.87, 1.17]	2.59
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		CASPIAN, a, 2021	264	266	129	133		1.01 [0.87, 1.18]	2.60
CA184-041, a, 2013 CA184-041, b, 2013 CA184-041, b, 2013 CA184-041, b, 2013 CA184-156, 2016 CA184-156, 2016 CA184-041, b, 2013 CA184-156, 2016 CA184-041, b, 2013 CA184-156, 2016 CA184-041, b, 2013 CA184-156, 2016 CA184-041, b, 2013 CA184-041, b, 2013 CA184-156, 2016 CA184-041, b, 2013 CA184-041, b, 2013 CA184-04, 1.50 CA184-041, b, 2013 CA184-04, 0.88 CA184-04 CA184-04 CA184-04, 0.88 CA184-04 CA184		IMpower133, 2018	188	198	181	198		1.02 [0.88, 1.18]	2.67
CA184-041, b, 2013 33 42 18 22 CA184-156, 2016 391 478 361 478 CheckMate 331, 2021 156 282 239 265 CheckMate 331, 2021		CA184-041, a, 2013	29	42	18	22 -		0.91 [0.58, 1.41]	0.46
CA184-156, 2016 391 478 361 478 CheckMate 331, 2021 156 282 239 265 Heterogeneity: $\tau^2 = 0.01$, $l^2 = 58.62\%$, $H^2 = 2.42$ Test of $\theta_i = \theta_i$: Q(6) = 13.26, p = 0.04 Overall Heterogeneity: $\tau^2 = 0.00$, $l^2 = 43.05\%$, $H^2 = 1.76$ Test of $\theta_i = \theta_i$: Q(38) = 62.68, p = 0.01 Test of group differences: Q _b (1) = 0.08, p = 0.78 Random-effects REML model 0.58 1.50 1.50 1.50 1.50		CA184-041, b, 2013	33	42	18	22		- 0.98 [0.64, 1.50]	0.49
CheckMate 331, 2021 156 282 239 265 0.75 [0.64, 0.88] 2.48 Heterogeneity: $\tau^2 = 0.01$, $I^2 = 58.62\%$, $H^2 = 2.42$ Test of $\theta_i = \theta_i$: Q(6) = 13.26, p = 0.04 Overall 0.95 [0.92, 0.98] Heterogeneity: $\tau^2 = 0.00$, $I^2 = 43.05\%$, $H^2 = 1.76$ Test of $\theta_i = \theta_i$: Q(38) = 62.68, p = 0.01 Test of group differences: Q _b (1) = 0.08, p = 0.78 Random-effects REML model 0.58 1.50 Fig. 6 Forest plots of RRs comparing Grade 1–5 TRAEs of immunotherapy between NSCLC and SCLC		CA184-156, 2016	391	478	361	478		1.05 [0.94, 1.16]	3.69
Heterogeneity: $\tau^2 = 0.01$, $l^2 = 58.62\%$, $H^2 = 2.42$ Test of $\theta_i = \theta_j$: Q(6) = 13.26, p = 0.04 Overall Heterogeneity: $\tau^2 = 0.00$, $l^2 = 43.05\%$, $H^2 = 1.76$ Test of $\theta_i = \theta_j$: Q(38) = 62.68, p = 0.01 Test of group differences: Q _b (1) = 0.08, p = 0.78 Random-effects REML model 0.58 1.50 Fig. 6 Forest plots of RRs comparing Grade 1–5 TRAEs of immunotherapy between NSCLC and SCLC		CheckMate 331, 2021	156	282	239	265		0.75 [0.64, 0.88]	2.48
Test of $\theta_i = \theta_j$: Q(6) = 13.26, p = 0.04 Overall 0.95 [0.92, 0.98] Heterogeneity: $\tau^2 = 0.00$, $I^2 = 43.05\%$, $H^2 = 1.76$ Test of $\theta_i = \theta_j$: Q(38) = 62.68, p = 0.01 Test of group differences: Q _b (1) = 0.08, p = 0.78 Random-effects REML model 0.58 1.50 Fig. 6 Forest plots of RRs comparing Grade 1–5 TRAEs of immunotherapy between NSCLC and SCLC		Heterogeneity: $\tau^2 = 0.01$, $I^2 = 5$	8.62%, I	$H^2 = 2.42$	2		-	0.96 [0.87, 1.07]	
Overall 0.95 [0.92, 0.98] Heterogeneity: $\tau^2 = 0.00$, $i^2 = 43.05\%$, $H^2 = 1.76$ 0.95 [0.92, 0.98] Test of $\theta_1 = \theta_1$: Q(38) = 62.68, p = 0.01 0.58 Test of group differences: $Q_b(1) = 0.08$, p = 0.78 0.58 Random-effects REML model 0.58 Forest plots of Rs comparing Grade 1–5 TRAEs of immunotherapy between NSCLC and SCLC		Test of $\theta_i = \theta_j$: Q(6) = 13.26, p	= 0.04					-	
Heterogeneity: $\tau^2 = 0.00$, $l^2 = 43.05\%$, $H^2 = 1.76$ Test of $\theta_l = \theta_j$: Q(38) = 62.68, p = 0.01 Test of group differences: Q _b (1) = 0.08, p = 0.78 Random-effects REML model 0.58 1.50 Forest plots of RRs comparing Grade 1–5 TRAEs of immunotherapy between NSCLC and SCLC		Overall					•	0.95 [0.92, 0.98]	
Test of $\theta_i = \theta_j$: Q(38) = 62.68, p = 0.01Test of group differences: Q _b (1) = 0.08, p = 0.78Random-effects REML model0.581.50 ig. 6 Forest plots of RRs comparing Grade 1–5 TRAEs of immunotherapy between NSCLC and SCLC		Heterogeneity: $\tau^2 = 0.00$, $I^2 = 4$	3.05%, I	$H^2 = 1.7$	6				
Test of group differences: $Q_b(1) = 0.08$, $p = 0.78$ Random-effects REML model0.581.50 ig. 6 Forest plots of RRs comparing Grade 1–5 TRAEs of immunotherapy between NSCLC and SCLC		Test of $\theta_i = \theta_j$: Q(38) = 62.68, p	0 = 0.01						
Random-effects REML model 0.58 1.50 ig. 6 Forest plots of RRs comparing Grade 1–5 TRAEs of immunotherapy between NSCLC and SCLC		Test of group differences: $Q_b(1)$) = 0.08	, p = 0.7	8	_			
ig. 6 Forest plots of RRs comparing Grade 1–5 TRAEs of immunotherapy between NSCLC and SCLC		Random-effects REMI model				0.5	8	1.50	
	Fig. 6 Forest plot	s of RRs comparing Grade 1–	5 TRAE	s of imi	munotł	nerapy b	etween NSCLC and SCL	C	

Variable	Study	Test for Difference								
		NSCLC	SCLC	χ²	P Value					
Overall	41	0.74 [0.67; 0.80]	0.95 [0.77; 1.13]	5.03	0.02					
Sex										
Male	18	0.63 [0.56; 0.69]	0.87 [0.64; 1.10]	3.16	0.08					
Female	18	0.69 [0.57; 0.82]	0.59 [0.37; 0.81]	0.67	0.41					
Age										
< 65 yr	18	0.62 [0.54; 0.70]	0.76 [0.54; 0.98]	1.40	0.24					
≥ 65 yr	14	0.67 [0.58; 0.77]	0.76 [0.53; 0.99]	0.44	0.51					
Line of therapy										
First	26	0.68 [0.60; 0.76]	0.83 [0.76; 0.90]	7.68	0.01					
Subsequent	15	0.83 [0.73; 0.92]	1.68 [0.90; 2.45]	4.59	0.03					
Research methodology										
ICI vs non-ICI	20	0.82 [0.73; 0.91]	1.68 [0.90; 2.45]	4.66	0.03					
ICI + non-ICI vs non-ICI	21	0.63 [0.57; 0.69]	0.83 [0.76; 0.90]	15.28	< 0.01					
Drug target										
Anti-PD-1/PD-L1	31	0.73 [0.56; 0.81]	1.16 [0.64; 1.68]	2.61	0.11					
Anti-CTLA-4	6	0.84 [0.73; 0.95]	0.86 [0.76; 0.96]	0.07	0.80					
Anti-PD-1/PD-L1 + CTLA-4	4	0.75 [0.66; 0.83]	0.84 [0.68; 0.99]	1.12	0.29					
ECOG PS										
0	17	0.64 [0.54; 0.75]	0.84 [0.53; 1.15]	1.42	0.23					
1	17	0.64 [0.57; 0.71]	0.72 [0.53; 0.92]	0.54	0.46					
Trial phase										
II	8	0.75 [0.59; 0.91]	1.23 [0.54; 1.91]	1.17	0.18					
III	33	0.73 [0.66; 0.81]	0.92 [0.71; 1.13]	2.65	0.10					

Table 2 Differences in PFS benefits of Immunotherapy in NSCLC and SCLC by subgroups

with NSCLC and SCLC. In addition, we conducted subgroup analyses, including sex, age, smoking status, line of therapy, research methodology, drug target, and ECOG PS score, for OS and found no statistically significant differences in OS among patients with NSCLC and SCLC in all subgroups (Table S3).

Discussion

The present study is the first systematic review and meta-analysis to evaluate the association between ICIs and long-term outcomes in patients with NSCLC and SCLC. We used published data from 38 RCTs of high quality, including more than 20,000 patients with lung cancer, revealing that ICIs were associated with a better therapeutic effect on reducing the risk of death in patients with NSCLC and SCLC without increasing TRAEs when compared with SOC. However, in terms of ORR and control of disease progression, benefits were primarily observed in patients with NSCLC, who showed significant improvements when compared with patients with SCLC. Compared with SOC, immunotherapy resulted in significantly prolonged PFS in patients with NSCLC than in patients with SCLC, with a significant difference noted between the two subgroups. Furthermore, among the treatment strategies, ICIs plus SOC led to a better improvement in PFS than ICI monotherapy in both patients with NSCLC and SCLC patients; accordingly, it is recommended for patients with advanced lung cancer as a preferential option. However, $I^2 > 50\%$ in PFS analyses of NSCLC and SCLC indicated heterogeneity. In terms of NSCLC, we conducted subgroup analysis for drug targets, revealing that I^2 of CTLA-4 and PD-1/ PD-L1 plus CTLA-4 groups was 0 and 10.17% after grouping; however, the heterogeneity for the PD-1/ PD-L1 group persisted (Fig. S2). On carefully comparing therapeutic regimens, we observed that the CTLA-4 and PD-1/PD-L1 plus CTLA-4 groups adopted similar ICI regimens among different trials. Nevertheless, the number of ICIs in the PD-1/PD-L1 group reached eight, with some employed in only one trial. Therefore, we believe that variations in ICIs possibly accounted for the heterogeneity. For SCLC, we found only two trials that assessed non-first-line treatment. Accordingly, we conducted a subgroup analysis for the line of therapy and observed that the I^2 for first-line treatment became 0; this suggested that the different non-first-line treatments were sources of heterogeneity (Fig. S3).

Furthermore, the current study indicated that the magnitude of immunotherapy treatment effects was related to the ICI drug targets. Based on the checkpoints, ICIs are roughly classified as anti-PD-1/ PD-L1 and anti-CTLA-4 drugs. Some researchers have highlighted that combining anti-PD-1/ PD-L1 with anti-CTLA-4 might lead to additive antitumour effects [16]. Herein, we demonstrated that, among different drug targets, the combination of anti-PD-1/PD-L1 and anti-CTLA-4 decreased the risk of death by 28% in patients with NSCLC, which was only 26% in the anti-PD-1/PD-L1 group and 9% in the anti-CTLA-4 group, consistent with the former hypothesis. Similarly, the magnitude of PFS benefits seemed to favour anti-PD-1/PD-L1 plus anti-CTLA-4 treatment in both patients with NSCLC and SCLC. Nevertheless, the magnitude of OS benefits favoured the anti-PD-1/PD-L1 group most in patients with SCLC, revealing that the combination of anti-PD-1/ PD-L1 and anti-CTLA-4 treatment has better therapeutic effects in patients with NSCLC. Given the limited number of clinical trials, additional research is needed to comprehensively evaluate the efficiency of drug combinations. Nevertheless, there is a potential explanation for the promising effects of combined anti-PD-1/PD-L1 with anti-CTLA-4 treatment. Although the anti-PD-1/PD-L1 and anti-CTLA-4 antibodies are distinct ICIs, they may play a synergistic role. More precisely, anti-PD-1/PD-L1 antibodies restore the antitumour function of T cells, whereas anti-CTLA-4 antibodies activate antitumour Tcell responses and induce the proliferation of T-cells involving memory T cells [49].

In addition, we observed that therapy with ICIs plus SOC conferred greater treatment benefits than ICI monotherapy. This finding was in line with findings reported by Wang and colleagues, which revealed that ICI plus SOC results in significantly prolonged PFS when compared with monotherapy with immunotherapy [50]. However, we compared both NSCLC and SCLC rather than just NSCLC. In theory, chemotherapy or radiotherapy can induce the expression of immune checkpoints on infiltrating immune cells and tumour cells, which might enhance the curative effects of ICI therapy [50]. Thus, a combination of ICIs and SOCs should be adopted as the optimal treatment for SCLC and NSCLC. For NSCLC, we recommended a combination of SOC and anti-PD-1/PD-L1 plus anti-CTLA-4 antibodies. Furthermore, although men and women exhibited distinct immunological responses to antigens, no significant association of sex in terms of survival and disease control advantages was detected in patients with NSCLC and SCLC, in agreement with a previous study by Wallis et al. [51].

Currently, no RCTs comparing the therapeutic effects of ICIs in patients with NSCLC and SCLC patients have been reported. In the past decade, most drugs were found to be ineffective in SCLC management, in contrast to the success in the NSCLC field. In 2018, the IMpower133 trial revealed that the combination of atezolizumab and chemotherapy significantly prolonged OS and PFS when compared with chemotherapy alone for patients with advanced-stage SCLC [19]; this challenged the traditional chemotherapy-based treatment strategies for patients with SCLC. Subsequently, atezolizumab was adopted as the first-line treatment for SCLC. To date, only one study has compared first-line treatment strategies for SCLC, which only included two studies of ICI therapy, while most other trials in the SCLC field were limited in chemotherapy subtypes [52]. Another novelty of our study lies in the subgroup analyses according to individual conditions and treatment methods. Herein, we demonstrated that for patients with SCLC, ICI plus SOC therapy confers superior advantages over SOC, as indicated by OS and PFS. Furthermore, our study revealed that patients with NSCLC presented greater PFS benefits than SCLC patients receiving ICI monotherapy and ICI plus SOC therapy regarding different lung cancer subtypes. In terms of the line of therapy, patients with NSCLC benefited more from ICI treatment than patients with SCLC in both the first and subsequent lines of therapy, with significant differences between groups. These findings indicate that NSCLC might benefit more from ICI treatment than SCLC, regardless of the methodology of drug administration.

Implications of the study

Providing optimal treatment strategies for patients with lung cancer

Our study had several clinical implications. We recommend treatment strategies for patients with lung cancer based on sufficient evidence. With the development and gradual maturity of ICI treatment, it is necessary for oncologists, respiratory physicians, and thoracic surgeons to navigate multiple treatment strategies, including various ICI therapies, and to determine the optimal treatment for patients with lung cancer. Therefore, we recommend that patients with SCLC undergo ICI plus SOC therapy based on findings in the present study. For patients with NSCLC, a combination of anti-PD-1/PD-L1 and anti-CTLA-4 antibodies and SOC could serve as the optimal treatment strategy.

Discovering novel therapeutic regimen for SCLC

In addition, our research provides a new approach for SCLC therapy. The median OS for SCLC, especially for

extensive-stage SCLC, is less than 10 months, emphasising the need for novel promising treatments [2]. However, several clinical trials, including targeted drugs, have declared treatment failure for SCLC in the past few decades. In 2013 and 2016, CA184-041 and CA184-156 were conducted by Reck et al. to evaluate the therapeutic effect of ipilimumab in patients with SCLC patients. The authors reported that ipilimumab had no significant efficacy when compared with traditional chemotherapy [20, 21]. Recently, IMpower133 and CASPIAN assessed anti-PD-1/PD-L1 antibodies with or without anti-CTLA-4 antibodies as the first-line of therapy for patients with SCLC, revealing better therapeutic effects in prolonging OS and PFS in patients with SCLC than chemotherapy [16, 19], which indicated a major development in SCLC therapy. However, IFCT-1603 and CheckMate 331 used anti-PD-1/PD-L1 antibodies as first-line therapy when compared with traditional chemotherapy and observed no significant difference in prolonging OS. In terms of PFS, immunotherapy led to worse results than chemotherapy [17, 18]. In the current study, we systematically analysed data from these RCTs and validated that ICI therapy could prolong OS in patients with SCLC. Considering these discrepancies, we conducted subgroup analyses in line with therapy and drug targets, which recommended ICI treatment as the first-line therapy for SCLC, affording better OS and PFS than with the subsequent line of therapy. Among different drug targets, anti-PD-1/PD-L1 antibodies with or without anti-CTLA-4 antibodies presented a superior advantage in reducing the risk of death; this indicated that anti-PD-1/PD-L1 antibodies with or without anti-CTLA-4 antibodies should be adopted as the first-line therapy for patients with SCLC. Moreover, additional trials should be conducted to further validate the treatment effects of anti-PD-1/PD-L1 antibodies with or without anti-CTLA-4 antibodies as the first-line therapy for SCLC.

Landscape of ICI treatment efficacy among lung cancer

Another clinical implication of our study is that NSCLC might benefit more from ICI therapy than SCLC among different histological subtypes. Currently, available studies are insufficient to compare the treatment effects of ICIs in patients with NSCLC and SCLC. However, we conducted the first analysis to evaluate differences in ICI treatment between patients with NSCLC and SCLC. The results revealed that patients with NSCLC benefited more from immunotherapy than patients with SCLC in almost all subgroups, regardless of treatment methodology and individual patient conditions. Notably, ICI treatment presented a statistically significant advantage in terms of therapeutic efficiency in patients with NSCL C when compared with patients with SCLC, irrespective of first or subsequent line of therapy and treatment methodology (ICIs alone or ICIs plus SOC). In terms of PFS and ORR, patients with SCLC receiving immunotherapy showed no difference from those on SOC regimens, both of which were significantly lower than in patients with NSCLC. Thus, the above results demonstrated that although the OS of patients with SCLC could benefit from immunotherapy, PFS and ORR fail to demonstrate promising effects equivalent to those in patients with NSCLC.

Strengthens and weaknesses of this study

First, this is the first study to comprehensively review the relative benefits and risks of ICI treatment between patients with NSCLC and SCLC and indirectly compare the efficiency of treatment methodology in each histological lung cancer subtype, including the largest number of trials and patients. As few studies have analysed the efficiency and safety of ICI treatment in patients with SCLC, and no comparison directly included patients with SCLC versus those with NSCLC, to a certain extent, we bridged the gap in efficiency and safety data for ICI therapy among patients with NSCLC and SCLC. Previously, Maung et al. have shown that ICIs conferred better survival benefits than chemotherapy in both NSCLC and SCLC [53]. However, their conclusions were mainly based on qualitative analysis, without data analysis of clinical trials. In contrast, the quantitative analysis in our study could lead to more accurate and convincing results. Furthermore, our findings confirmed that immunotherapy could better benefit patients with NSCLC in prolonging PFS and increasing ORR than patients with SCLC. Given that the therapeutic effects of ICI treatment for SCLC remain controversial, we conducted a comprehensive assessment to compare its efficacy with chemotherapy. We observed that ICIs could undoubtedly reduce the risk of death in patients with SCLC, with a statistically significant difference, which has compensated for the lack of assessments of immunotherapy in the SCLC field. Second, one of the distinct strengths of our study is the data quality involved in our analyses. We employed 38 well-designed RCTs, gathered data from more than 20,000 patients with lung cancer, and carried out analyses according to predefined primary endpoints of OS and PFS and second endpoints of TRAEs with different grades. Our study was the largest scale of ICI analyses in patients with lung cancer. Under most circumstances, one essential factor in reducing statistical errors in a meta-analysis involves a largescale quantity of subjects with high quality. Third, this study recommends optimal ICI treatment strategies in patients with NSCLC and SCLC. For NSCLC, the combination of anti-PD-1/PD-L1 and anti-CTLA-4 antibodies plus SOC is recommended for both first and subsequent lines of immunotherapy. In patients with

SCLC, we only recommend the first-line treatment as anti-PD-1/PD-L1 plus SOC with or without anti-CTLA-4 antibodies.

Despite these strengths, several limitations exist in the present study. First, differences in risks and benefits between patients with NSCLC and SCLC were determined and compared through indirect analyses. To date, no RCTs have directly compared the efficiency and safety of immunotherapy between patients with SCLC and patients with NSCLC. Therefore, our results remain suggestive but not conclusive. Second, although our study is based on the largest scale of ICI analysis for lung cancer, more research is needed to comprehensively investigate the efficiency of immunotherapy in SCLC. Third, in selecting immunotherapy, the risk of toxicity is as important as the therapeutic effect, which should be thoroughly investigated. However, we only considered TRAEs of grade \geq 3 and any grade, as information regarding TRAEs stratified by predefined subgroups was unavailable. Furthermore, additional factors should be used to evaluate toxicity.

Conclusion

In conclusion, for patients with NSCLC and SCLC, ICI therapies are promising therapeutic options with advantages in terms of survival and toxicity over SOC. Furthermore, ICIs plus SOC are recommended as the optimal first-line therapy for patients with SCLC. Anti-PD-1/PD-L1 plus SOC with anti-CTLA-4 antibodies is recommended for patients with NSCLC without mutated gene targets in both the first and subsequent lines of therapy. In addition, immunotherapy as a subsequent line is not recommended as a standard strategy for patients with SCLC.

Abbreviations

ATE: Atezolizumab; CI: Confidence interval; CTLA-4: Cytotoxic T lymphocyteassociated antigen 4; DOC: Docetaxel; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: Hazard ratio; ICI: Immune checkpoint inhibitor; IPI: Ipilimumab; NIV: Nivolumab; DUR: Durvalumab; TRE: Tremelimumab; CAM: Camrelizumab; CEM: Cerniplimab; TIS: Tislelizumab; SCLC: Small-cell lung cancer; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; OS: Overall survival; PBC: Platinumbased chemotherapy; PD-1: Programmed cell death 1; PD-L1: Programmed cell death 1 ligand 1; PEM: Pembrolizumab; PFS: Progression-free survival; RCT: Randomised controlled trial; RR: Risk ratio; TRAEs: Treatment-related adverse events; SOC: Standard of care

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-021-08662-2.

Additional file 1: Fig. S1 Funnel plot of the effect size for each trial. Fig. S2 Drug targets analysis for NSCLC. Fig. S3 Therapeutic scheme analysis for SCLC. Table S1 Search strategies. Table S2 The methodological quality of included RCTs. Table S3 Differences in OS benefits of Immunotherapy in NSCLC and SCLC by subgroups

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Not applicable.

Authors' contributions

Y. L. and H. G. designed the study. C. W. and J. L. collected the data and analyzed the data. C. W. and J. L. wrote the initial manuscript. C. W., J. W., Q. Z., Y. X., and L. S. participated in the manuscript correcting and data analyses. All authors participated in the manuscript writing and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files]. All the data were available from the corresponding authors for reasonable request.

Declarations

Ethics approval and consent to participate

All analyses were based on previously published studies, thus no ethical approval and patient consent are required.

Consent for publication

Not applicable.

Competing interests

All authors declared that there was no conflict of interests.

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