Treatment- and immune-related adverse events of immune checkpoint inhibitors in advanced lung cancer

Jun Shao†, Chengdi Wang†, Pengwei Ren†, Yuting Jiang, Panwen Tian* and Weimin Li*

1.Department of Respiratory and Critical Care Medicine, West China Medical School/West China Hospital, Sichuan University, Chengdu, China
2. Department of Clinical Research Center for Respiratory Diseases, West China Hospital, Sichuan University, Chengdu, Sichuan, China.
3. West China Medical School, Sichuan University, Chengdu, China
† Jun Shao, Chengdi Wang and Pengwei Ren are contributed equally.

Running title: The safety of immunotherapy in lung cancer

Correspondence author
Dr Weimin Li, Department of Respiratory and Critical Care Medicine, West China Medical School/West China Hospital, No. 37 Guoxue Xiang, Chengdu 610041, Sichuan China. Tel: +86 28 85423001; Fax: +86 28 85423001; E-mail: weimi003@scu.edu.cn.

Dr Panwen Tian, Department of Respiratory and Critical Care Medicine, West China Medical School/West China Hospital, No. 37 Guoxue Xiang, Chengdu 610041, Sichuan China.
Tel: +86 18980606625; Fax: +86 28 85423365; E-mail: mrascend@163.com
Abstract

Background: Immune checkpoint inhibitors (ICIs) emerged as the preferred therapy in advanced lung cancer, understanding the treatment- and immune-related adverse events of these drugs is of great significance for clinical practice.

Materials and methods: PubMed, Embase, Cochrane library and major conference proceedings were systematically searched for all randomized controlled trials (RCTs) in lung cancer using PD-1/PD-L1/CTLA-4 inhibitors. The outcomes included treatment-related adverse events (TRAEs) and several organ specific immune-related adverse events (IRAEs).

Results: 24 RCTs involving 14256 patients were included. There was a significant difference for ICI therapy in the incidence of any grade of TRAEs (RR: 0.90; 95%CI: 0.84-0.95; P=0.001) and a lower frequency of grade 3-5 of TRAEs (RR: 0.65; 95%CI: 0.51-0.82; P<0.001). Patients treated with ICI therapy in non–small-cell lung cancer (NSCLC) were less reported TRAEs than in small cell lung cancer (SCLC). A lower risk of TRAEs was favored by anti-PD-1 inhibitors over anti-PD-L1 antibodies and anti-CTLA-4 drugs. The most common organ specific IRAE was hypothyroidism which occurred 8.7%. The incidence of pneumonitis and hepatitis reached 4.5% and 4.0% respectively. Compared with patients treated in control arms, those treated with ICI drugs were at higher risk for each organ specific adverse event including colitis, hepatitis, pneumonitis, hypothyroidism and hypophysitis.

Conclusions: ICI therapy was safer than chemotherapy, especially ICI monotherapy such as anti-PD-1 antibodies in NSCLC. Compared with standard treatments, ICI drugs increased the risk of organ-specific IRAEs, although the overall incidence remained low.

Keywords: Immune checkpoint inhibitor- adverse event- chemotherapy- advanced lung cancer

Abbreviations:
ICI: immune checkpoint inhibitor; TRAE: treatment-related adverse event; IRAE: immune-related adverse event; NSCLC: non–small-cell lung cancer; SCLC: small-cell lung cancer; ES-SCLC: extensive-stage small-cell lung cancer; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; KRAS: kirsten rat sarcoma; ROS1: rat osteosarcoma; PD-1:programmed death 1; PD-L1:programmed death ligand 1; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; PD-L2:
programmed death ligand 2; RR: risk ratio; CI: confidence interval; RCT: randomized controlled trial;
CTCAE: common terms classified by clinical adverse events; FDA: Food and Drug Administration.
Introduction

Lung cancer still remains the most commonly diagnosed carcinoma type and the leading cause of cancer death globally. According to the GLOBCAN report, an estimated 2.09 million new cases were diagnosed in 2018. Non–small-cell lung cancer (NSCLC) represents 85% of all lung tumors, and the other 15% is small-cell lung cancer (SCLC). Approximately one third of patients with NSCLC have locally advanced disease at diagnosis. Conventional therapy standard of first-line care treatment for advanced NSCLC and extensive-stage small-cell lung cancer (ES-SCLC) is platinum-doublet chemotherapy. Despite over 30 years of clinical research, little progress has been made, and outcome of lung cancer remains poor. Even in the most recent large randomized clinical trials (RCTs), the median overall survival (OS) of metastatic SCLC patients receiving standardized chemotherapy was still between 9 and 11 months. The discovery of anaplastic lymphoma kinase (ALK) gene rearrangement in NSCLC in 2007 led to an understanding of its significance of disease biology and natural history. Subsequently, the targetable genetic alterations of lung cancer have been gradually identified such as epidermal growth factor receptor (EGFR) mutations, kirsten rat sarcoma (KRAS) mutations, and rat osteosarcoma (ROS1), and the development of targeted drugs greatly affected the prognosis of patients. However, only a small proportion of patients harbor these mutations, and targeted drug therapy did not significantly improve 5-year overall survival of lung cancer patients.

The rapid development of immune checkpoint inhibitor (ICI), a revolutionary form of immunotherapy, has transformed the way numerous cancer are managed. Inhibitory checkpoint molecules produced during T cell activation, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) which regulates the immune synapses between T cells and lymph node dendritic cells to inhibit T cell activation, or programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) suppressing the immune synapses between T cells and tumor cells, are currently the most relevant targets for immunotherapy.

In 2011, Food and Drug Administration (FDA) approved the first checkpoint inhibitor ipilimumab, which is a fully human anti-CTLA-4 monoclonal antibody. Later, several immune checkpoint inhibitors directed at PD-1 (nivolumab and pembrolizumab) and PD-L1 (atezolizumab, durvalumab, and avelumab) were approved for the treatment of multiple cancers. These drugs improved clinical survival outcomes of solid cancer such as lung cancer dramatically. In a review of the literature,
pembrolizumab has showed a significant survival benefit over chemotherapy when given as monotherapy or as part of combination therapy for metastatic, squamous or non-squamous NSCLC\textsuperscript{18-20}. Like chemotherapy, immunotherapy can have serious treatment-related adverse events (TRAEs) leading to low compliance, dose reduction, delayed treatment or treatment rejection, although some studies illustrated anti-PD-1 drugs were overall less toxic than standard chemotherapy\textsuperscript{21-23}. At the same time, ICI drugs have immune-related adverse events (IRAEs) reported on clinical trials. The IRAEs including colitis, hepatitis, pneumonitis, hypothyroidism, hyperthyroidism and so on affect multiple organ systems including skin, colon, endocrine organs, liver and lungs\textsuperscript{24}. Here, we performed a systematic and meta-analysis of immunotherapy safety. High quality studies focusing on adverse events are required to aid clinicians to improve early management and identify IRAEs.

Materials and methods

Search strategy

A literature search of studies published up to March 2019 was performed from major citation databases, including PubMed, Embase, Cochrane Library. The following search terms were used: immune checkpoint inhibitor, PD-1 or programmed death 1, PD-L1 or programmed death ligand 1, CTLA-4 or cytotoxic T-lymphocyte-associated protein 4, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, ipilimumab, or tremelimumab, and lung cancer, randomized controlled trial. To identify additional studies, we also searched the major international congresses’ proceedings (American Society of Clinical Oncology, the European Society of Medical Oncology and the World Conference of Lung Cancer). When duplicate publications were identified, the most recent, relevant, and comprehensive data were accepted. This study was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement\textsuperscript{25}.

Study selection

Trails were eligible for inclusion if they met several criteria:1) patients were pathologically diagnosed with lung cancer; 2) studies involving participants treated with ICI or ICI plus chemotherapy;3) trails which the control was chemotherapy alone;4) main outcome was treatment-related adverse events of any grade and grade 3-5;5) phase II or III randomized controlled trials. Studies were exclusion:1)
retrospective or prospective cohort studies; 2) reviews, letters, commentaries, irrelevant abstract, quality of life studies, cost effectiveness analyses; 3) publications did not contain detailed safety data.

**Data extraction and quality assessment**

Two investigators independently extracted data from each study with a piloted collection form: name of first author, year, trial phases, study ID, region, trial phase, types of tumor, treatment, the size of intervention and control group, TRAEs reporting rate, the frequency of specific adverse event and median follow-up time. The risk of bias was assessed by using Cochrane Risk of Bias Tool\(^2\). This scale evaluates six criteria: randomized sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting, and other bias. Each aspect was labeled as high, low or unclear. All disagreements in the study selection, data extraction, and quality assessment were resolved by consensus.

Our primary outcome was the incidence of TRAEs, which indicate the toxicity of therapy. Our secondary outcome was the incidence of commonly described organ specific adverse events (colitis, hepatitis, pneumonitis, hypothyroidism, and hypophysitis). We recorded data from full article and supplementary appendix. Common terms classified by clinical adverse events (CTCAE) were used to identify grade 3-5 as serious and grade 1-2 as other. Data from different dosing arms within the same study were extracted and reported separately.

**Statistical analysis**

For each of the included studies, we calculated the odds ratio and 95% confidence interval of event incidence between the intervention group and the control group based on the number of reported events and sample size. Risk ratio (RR) and 95% confidence interval (CI) were pooled to quantify the therapeutic effect. The heterogeneity of effect size estimates across studies was described with the \(I^2\) index and Q statistic’s \(p\) value. If significant heterogeneity was not present \( (P>0.1)\), the risk ratio was calculated with fixed effect meta-analysis; otherwise, a random effects model was applied to calculate pooled odds ratio and 95% confidence interval if significant heterogeneity was present \( (P\leq0.1)\). We used funnel plots to assess publication bias. Two-sided \(P\) values less than 0.05 were considered statistically significant. All statistical analyses were conducted using Stata version 15.0(StataCorp, College Station, TX).
Results

Eligible studies and characteristics

A total of 2993 records were initially in line based on the literature search, of which 1013 excluded because of duplications. After screening the titles, abstracts, full article, 24 randomized controlled trials (RCTs) were finally identified in strict inclusion and exclusion criteria. Data were obtained from published manuscripts and conference proceedings. The selection process was presented in Figure 1.

All 24 studies included 14,256 patients representing advanced lung cancer were international multi center studies. 21 studies evaluated NSCLC, and the other 3 studies investigated ES-SCLC. 7613 patients who received ICI monotherapy or combination therapy served as the investigational arm and 6643 patients who received chemotherapy as the control arms. KEYNOTE010 which analyzed two different doses (2 mg/kg and 10 mg/kg) compared with standard control was divided into two trails. All grades, grade 3, and grade 4 adverse events indicate complete, severe, life threatening toxicity, respectively. The main characteristics of the included studies are summarized in Table 1.

Treatment-related adverse event

In terms of ICI therapy in advanced lung cancer, there was a significant difference in the probability of any grade of TRAEs (RR: 0.90; 95%CI: 0.84-0.95; P=0.001) and a lower frequency of grade 3-5 of TRAEs (RR: 0.65; 95%CI: 0.51-0.82; P<0.001) (Figure 2). However, subgroup analysis demonstrated ICI-chemotherapy associated with the risk of TRAEs (any grade: RR: 1.03; 95%CI:1.01-1.06; P=0.017; grade 3-5: RR: 1.18; 95%CI: 1.09-1.28; P<0.001). ICI monotherapy was safer in the risk of grade 1-5 (RR:0.76; 95%CI:0.73-0.78; P<0.001) and grade 3-5 (RR:0.33; 95%CI:0.26-0.41; P<0.001) adverse events than standard control. The finding indicated that ICI therapy led to a significant difference in NSCLC for TRAEs (any grade: RR: 0.88; 95%CI:0.82-0.95; P=0.001; grade 3-5: RR: 0.60; 95%CI: 0.46-0.78; P<0.001), but no statistical significance in SCLC (any grade: RR: 1.03; 95%CI:0.97-1.10; P=0.318; grade 3-5: RR: 1.06; 95%CI:0.95-1.18; P=0.280). A lower risk of any grade(RR:0.85; 95%CI:0.74-0.97; P=0.018) or grade 3-5(RR:0.50; 95%CI:0.35-0.73; P<0.001) adverse events was favored by anti-PD-1 antibodies over anti-PD-L1 antibodies(any grade: RR: 0.92; 95%CI:0.83-1.01; P=0.090; grade 3-5: RR: 0.70; 95%CI: 0.46-1.05; P=0.086). Anti-CTLA-4 antibodies was not different
from conventional therapy in any grade TRAEs (RR: 1.05; 95% CI: 0.98-1.12; P=0.179), but less safe in grade 3-5 (RR: 1.25; 95% CI: 1.00-1.55; P=0.047) (Table 2).

**Immune-related adverse event**

Among intervention group, the most common IRAE was hypothyroidism which occurred 8.7%, while colitis, hepatitis, pneumonitis and hypophysitis occurred 1.6%, 4.0%, 4.5%, and 0.6% respectively. Looking at serious organ specific IRAEs, 1.8% patients had hepatitis, 1.5% patients had pneumonitis, 0.8% patients had colitis, 0.3% patients had hypothyroidism, and 0.3% patients had hypophysitis. Table 3 shows the rates of organ specific serious immune-related adverse events.

In the present study, compared with patients treated in control arms, those treated with ICI were at higher risk for IRAEs. Figure 3 shows that ICI therapy increased the frequency of immune-related colitis (RR: 5.54; 95% CI: 3.06-10.02; P<0.001), though events were rare., Patients treated with ICI drugs were at a higher risk for any grade hepatitis (RR: 2.49; 95% CI: 1.77-3.50; P<0.001) and pneumonitis (RR:2.57; 95% CI:1.96-3.37; P<0.001).Patients were more likely to experience hypothyroidism (RR: 6.33; 95% CI: 4.66-8.61; P<0.001) and hypophysitis (RR: 3.91; 95% CI:1.33-11.54; P=0.013) compared with patients in the chemotherapy.

**Quality of included studies and sensitivity analysis**

Risk of bias of the included RCTs was showed in Table S1. Most studies have experienced low risk, especially the generation of random sequences. Unclear risk of bias was mainly focused on performance bias (blinding of participants and personnel). To examine the stability of the combined results, we conducted a sensitivity analysis after removing conference proceedings (Figure S1). After these analyses, the results indicated that the outcome remained consistent.

**Discussion**

Included more than 14,000 patients in advanced lung cancer, the current study was performed to analyze adverse events of ICI therapy versus the standard treatment to further our understanding of the safety of this emerging class of drugs. The pooled study indicated that ICI therapy was safer than chemotherapy, especially ICI monotherapy or anti-PD-1 drug in NSCLC. But ICI-chemotherapy increased the incidence of TRAEs, and anti-CTLA-4 antibodies was less safe in grade 3-5 TRAEs.
Organ special IRAEs including colitis, hepatitis, pneumonitis, hypothyroidism and hypophysitis were uncommon but the risk was increased compared with control treatment.

Chemotherapy has always been the most commonly used class of antineoplastic drugs for advanced cancers. Traditional chemotherapeutic drugs work by killing rapidly dividing cells, whether they are tumor or healthy. Due to the long term clinical application, the toxicities of chemotherapy drugs which reduce the quality of life of patients have been clearly demonstrated. In the era of precision medicine, it is proposed that the treatment should not only cure diseases, but also restore patients' health with the maximum quality of life. Fortunately, the development of immunotherapy challenged the management of treatment-related toxic effects. Like the prior study, ICI drugs were overall less toxic than chemotherapy especially in monotherapy, and combining an ICI with chemotherapy increased the rate of grade 3 or worse severity TRAEs. Although combined therapy resulted in significantly longer overall survival and progression-free survival than chemotherapy, its cytotoxicity also improved, which should not be underestimated. Moreover, it is worth mentioning that ICI therapy was safer in risk of TRAEs for NSCLC patients, but less safe for SCLC. This may be due to the different pathogenesis of these two cancers. In terms of drugs, anti-PD-1 antibodies had the best safety profile in lung cancer, which was same with previous conclusions. Theoretically, PD-1 antibody can bind to PD-1 protein on T cells, thus blocking the binding of PD-1 to PD-L1 and PD-L2, while PD-L1 antibody can only interact with PD-L1, so it can only block the binding of PD-1 to PD-L1. All that meant PD-1 antibody emerged as the best option for treatment in advance lung cancer patients with greater survival condition and low incidence of TRAEs.

IRAEs represent the immune effect of incorrect stimulation of the immune system on normal tissues. Compared with the toxicities caused by conventional treatment, the IRAEs of ICI drugs have unique characteristics in organs involved, pathogenesis patterns and severity. A number of randomized controlled trials were summarized the general situation of IRAEs, including skin, gastrointestinal, pulmonary, hepatic, and endocrine toxicities. This study focused on five organs special IRAEs, including colitis, hepatitis, pneumonitis, hypothyroidism, and hypophysitis. For lung cancer, the most common organ specific IRAE was hypothyroidism which occurred 8.7%. The incidence of pneumonitis and hepatitis reached 4.5% and 4.0% respectively. In addition, a recent study evaluated
the risk of IRAEs in patients treated with anti-PD-1 and anti-PD-L1 drugs. Our findings regarding risk of IRAEs were similar that those treated with ICI drugs were at higher risk for each organ specific adverse event compared with patients treated in control arms. Precise explanations for these observed differences were unknown, but this high-risk situation suggests that routine thyroid function tests and chest CT examinations should be added to patients with ICI therapy.

All the results emphasized a need for increased awareness and careful monitoring of patients with lung cancer during immunotherapy for the possibility of adverse events, particularly in IRAEs. Although most IRAEs are typically manageable with supportive treatment and glucocorticoids, uncommon fatal events have been reported increasingly. The mechanism of IRAEs was still unclear. Health care providers need to maintain a high index of suspicion when patients develop worsening of symptoms and take appropriate measures to diagnose, initiate corticosteroids at the right time. Moreover, careful multidisciplinary consultation should be conducted in each case of suspected IRAEs to avoid improper disease management. In addition to advances in treatment strategies, identifying and improving the use of predictive biomarkers will also be critical for identifying patients most likely to benefit from treatment.

There were several limitations in the current study. Firstly, the follow-up time was different from included studies (range 8-24 months), and the patients may have been discharged from hospital at the time of measurement. For example, it is reported that pneumonitis occur between 7.4 and 24.3 months after taking ICI drugs. Thus the frequency of adverse events may be influenced by the confounding effect of time. Secondly, the methods for identifying adverse events has not standardized. Even in CTCAE, overlapping definitions confuse the recognizing of specific adverse events which lead to potential uncertainty about data quality. As such, recognizing adverse events which usually depends on investigators’ evaluation may cause errors. A classic example is that immune-related colitis can be classified as colitis or diarrhea. Thirdly, we combined all ICI drugs into experience group, including several therapeutic agents; however, because such a subdivision would result in more subgroups with smaller sample sizes, the cohorts were not subdivided according to these agents. Looking ahead, longer follow-up and special attention to various adverse events are needed to enhance our understanding.
Conclusions

The current study indicated that immunotherapy was superior to chemotherapy in terms of safety profiles, especially ICI monotherapy. Patients treated with ICI therapy in NSCLC were less reported TRAEs than in SCLC. A lower risk of TRAEs was favored by anti-PD-1 antibodies over anti-PD-L1 antibodies and anti-CTLA-4 antibodies. Compared with standard treatment, ICI drugs increased the risk of organ-specific IRAEs, although the overall incidence remained low. For clinicians, it was important to monitor all IRAEs in lung cancer patients treated with ICI drugs.

Authors’ contribution

C.W., P.T. and W.L. designed the research study, J.S. and C.W. performed the search, extracted the data, drew the draft and revised the manuscript, P.R. and Y.J. analyzed the data, C.W., J.S., P.T. and W.L. contributed to discussion and reviewed the manuscript. All authors have participated sufficiently in the study and approved the final version.

Conflict of interest:

The authors have declared no conflicts of interest.

Acknowledgments

This work was supported by grants 91859203, 81871890 from National Natural Science Foundation of China and Chengdu Science and Technology Program Projects (2017-CY02-00030-GX).
1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

2. Ferlay J EM, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. 2018; https://gco.iarc.fr/today.

3. Reck M, Rabe KF. Precision Diagnosis and Treatment for Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2017;377(9):849-861.

4. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010;28(13):2181-2190.

5. Network NCC. NCCN clinical practice guidelines in oncology. 2018; https://www.nccn.org.

6. Farago AF, Keane FK. Current standards for clinical management of small cell lung cancer. Transl Lung Cancer Res. 2018;7(1):69-79.

7. Jalal SI, Lavin P, Lo G, Lebel F, Einhorn L. Carboplatin and Etoposide With or Without Palifosfamide in Untreated Extensive-Stage Small-Cell Lung Cancer: A Multicenter, Adaptive, Randomized Phase III Study (MATISSE). J Clin Oncol. 2017;35(23):2619-2623.

8. Reck M, Luft A, Szczesna A, et al. Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. J Clin Oncol. 2016;34(31):3740-3748.

9. Tiseo M, Boni L, Ambrosio F, et al. Italian, Multicenter, Phase III, Randomized Study of Cisplatin Plus Etoposide With or Without Bevacizumab as First-Line Treatment in Extensive-Disease Small-Cell Lung Cancer: The GOIRC-AIFA FARM6PMFJM Trial. J Clin Oncol. 2017;35(12):1281-1287.

10. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007;448(7153):561-566.

11. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010;363(18):1693-1703.

12. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013;368(25):2385-2394.
13. Camidge DR, Pao W, Sequist LV. Acquired resistance to TKIs in solid tumours: learning from lung cancer. *Nat Rev Clin Oncol.* 2014;11(8):473-481.

14. Baxi S, Yang A, Gennarelli RL, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. *BMJ.* 2018;360:k793.

15. Postow MA, Callahan MK, Wolchok JD. Immune Checkpoint Blockade in Cancer Therapy. *J Clin Oncol.* 2015;33(17):1974-1982.

16. Gong J, Chehrazi-Raffe A, Reddi S, Salgia R. Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: a comprehensive review of registration trials and future considerations. *J Immunother Cancer.* 2018;6(1):8.

17. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med.* 2012;366(26):2443-2454.

18. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. *N Engl J Med.* 2018;378(22):2093-2104.

19. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med.* 2016;375(19):1823-1833.

20. Lopes G WY-L, Kudaba I, et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥1%: open-label, phase 3 KEYNOTE-042 study. *J Clin Oncol.* 2018;36:Suppl:LBA4. abstract.

21. Abdel-Rahman O, ElHalawani H, Fouad M. Risk of gastrointestinal complications in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. *Immunotherapy.* 2015;7(11):1213-1227.

22. De Velasco G, Je Y, Bossé D, et al. Comprehensive Meta-analysis of Key Immune-Related Adverse Events from CTLA-4 and PD-1/PD-L1 Inhibitors in Cancer Patients. *Cancer Immunol Res.* 2017;5(4):312-318.

23. Abdel-Rahman O, Fouad M. A network meta-analysis of the risk of immune-related renal toxicity in cancer patients treated with immune checkpoint inhibitors. *Immunotherapy.* 2016;8(5):665-674.

24. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol.* 2012;30(21):2691-2697.

25. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339:b2535.
26. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.

27. Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med*. 2018;379(24):2342-2350.

28. Barlesi F, Vansteenkiste J, Spigel D, et al. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study. *Lancet Oncol*. 2018;19(11):1468-1479.

29. Borghaei H, Langer CJ, Gadgeel S, et al. 24-Month Overall Survival from KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin with or without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous Non-Small Cell Lung Cancer. *J Thorac Oncol*. 2019;14(1):124-129.

30. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med*. 2015;373(17):1627-1639.

31. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med*. 2015;373(2):123-135.

32. Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. *N Engl J Med*. 2017;376(25):2415-2426.

33. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet*. 2016;387(10030):1837-1846.

34. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018;378(22):2078-2092.

35. Govindan R, Szczesna A, Ahn MJ, et al. Phase III Trial of Ipilimumab Combined With Paclitaxel and Carboplatin in Advanced Squamous Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2017;35(30):3449-3457.

36. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387(10027):1540-1550.

37. Horn L, Mansfield AS, Szczesna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. *N Engl J Med*. 2018;379(23):2220-2229.

38. Jotte RM CF, Vynnychenko I, et al. IMpower131: primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel
vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. *J Clin Oncol.* 2018;36:Suppl: LBA9000. abstract.

39. Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. *J Clin Oncol.* 2012;30(17):2046-2054.

40. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. *N Engl J Med.* 2018;379(21):2040-2051.

41. Reck M, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. *Ann Oncol.* 2013;24(1):75-83.

42. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet.* 2017;389(10066):255-265.

43. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med.* 2018;378(24):2288-2301.

44. Wu YL, Lu S, Cheng Y, et al. Nivolumab Versus Docetaxel in a Predominantly Chinese Patient Population With Previously Treated Advanced NSCLC: CheckMate 078 Randomized Phase III Clinical Trial. *J Thorac Oncol.* 2019.

45. Borghaei H DHM, G. Paz-Ares L, et al. Nivolumab (Nivo) + platinum-doublet chemotherapy (Chemo) vs chemo as first-line (1L) treatment (Tx) for advanced non-small cell lung cancer (NSCLC) with <1% tumor PD-L1 expression: results from CheckMate 227. *J Clin Oncol* 2018;36:9001.

46. Papadimitrakopoulou VA SJ, Jappe A, et al. IMpower132: PFS and safety results with 1L atezolizumab + carboplatin/cisplatin + pemetrexed in stage IV non-squamous NSCLC. *J Thorac Oncol* 2018;13:S332-S333.

47. Xu C, Chen YP, Du XJ, et al. Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis. *BMJ.* 2018;363:k4226.

48. Yang P. Maximizing quality of life remains an ultimate goal in the era of precision medicine: exemplified by lung cancer. *Precision Clinical Medicine.* 2019;2(1):8-12.

49. Zhou Y, Chen C, Zhang X, et al. Immune-checkpoint inhibitor plus chemotherapy versus conventional chemotherapy for first-line treatment in advanced non-small cell lung carcinoma: a systematic review and meta-analysis. *J Immunother Cancer.* 2018;6(1):155.
50. Wu Y, Shi H, Jiang M, et al. The clinical value of combination of immune checkpoint inhibitors in cancer patients: A meta-analysis of efficacy and safety. *Int J Cancer*. 2017;141(12):2562-2570.

51. Altorki NK, Markowitz GJ, Gao D, et al. The lung microenvironment: an important regulator of tumour growth and metastasis. *Nat Rev Cancer*. 2019;19(1):9-31.

52. Zhang Y, Zhou H, Zhang L. Which is the optimal immunotherapy for advanced squamous non-small-cell lung cancer in combination with chemotherapy: anti-PD-1 or anti-PD-L1? *J Immunother Cancer*. 2018;6(1):135.

53. Gangadhar TC, Vonderheide RH. Mitigating the toxic effects of anticancer immunotherapy. *Nat Rev Clin Oncol*. 2014;11(2):91-99.

54. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-analysis. *JAMA Oncol*. 2018;4(2):173-182.

55. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol*. 2016;17(11):1497-1508.

56. Johnson DB, Balko JM, Compton ML, et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. *N Engl J Med*. 2016;375(18):1749-1755.

57. Moslehi JJ, Salem JE, Sosman JA, Lebrun-Vignes B, Johnson DB. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. *Lancet*. 2018;391(10124):933.

58. Wang DY, Salem JE, Cohen JV, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. *JAMA Oncol*. 2018;4(12):1721-1728.

59. Havel JJ, Chowell D, Chan TA. The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. *Nat Rev Cancer*. 2019;19(3):133-150.

60. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the Immune-Related Adverse Effects of Immune Checkpoint Inhibitors: A Review. *JAMA Oncol*. 2016;2(10):1346-1353.
Table and figure legends

**Table 1** Characteristics of patients comparing ICI therapy with Chemotherapy in included randomized controlled trials

**Table 2** Risk ratios for treatment-related adverse events (TRAEs) comparing ICI therapy with Chemotherapy

**Table 3** Incidence of organ specific immune-related adverse event (IRAEs). Value are percentage (95% confidence intervals)

**Table S1** Quality assessment: risk of bias by Cochrane Collaboration’s tool

**Figure 1** Flowchart of study selection and design/study flow diagram

**Figure 2** Forest plot of all grade(A) and grade3-5(B) TRAEs in lung cancer patients treated with ICI versus Chemotherapy

**Figure 3** Forest plot of colitis (A), hepatitis (B), pneumonitis (C), hypothyroidism (D) and hypophysitis(E) in lung cancer patients treated with ICI versus Chemotherapy

**Figure S1** Sensitivity analyses of all grade TRAEs (A) and grade 3-5 TRAEs (B) after removing conference process
| First author     | Study ID    | Trial Phase | Cancer Type | Treatment          | ICI drug | NO OF Patients | TRAEs all grade | TRAEs grade 3-5 |
|------------------|-------------|-------------|-------------|--------------------|----------|----------------|-----------------|-----------------|
| Borghaei, 2018   | KEYNOTE021  | II          | NSCLC       | Pembrolizumab+Chemotherapy | PD-1     | 55             | 24              | 59              |
|                  |             |             |             | Chemotherapy       |          |                |                 |                 |
| Gandhi, 2018     | KEYNOTE189  | III         | NSCLC       | Pembrolizumab+Chemotherapy | PD-1     | 404            | 272             | 405             |
|                  |             |             |             | Chemotherapy       |          | 200            | 133             | 202             |
| Paz-Ares, 2018   | KEYNOTE407  | III         | NSCLC       | Pembrolizumab+Chemotherapy | PD-1     | 273            | 194             | 278             |
|                  |             |             |             | Chemotherapy       |          | 274            | 191             | 280             |
| Herbst, 2016     | KEYNOTE010  | II/III      | NSCLC       | Pembrolizumab 2mg/kg | PD-1     | 215            | 43              | 339             |
|                  |             |             |             | Pembrolizumab 10mg/kg | PD-1     | 226            | 55              | 343             |
|                  |             |             |             | Chemotherapy       |          | 251            | 109             | 309             |
| Reck, 2016       | KEYNOTE024  | III         | NSCLC       | Pembrolizumab       | PD-1     | 113            | 41              | 154             |
|                  |             |             |             | Chemotherapy       |          | 135            | 80              | 150             |
| Lopes, 2018      | KEYNOTE042  | III         | NSCLC       | Pembrolizumab       | PD-1     | 399            | 113             | 636             |
|                  |             |             |             | Chemotherapy       |          | 553            | 252             | 615             |
| Borghaei, 2018   | CheckMate227(a) | III      | NSCLC       | Nivolumab+Chemotherapy | PD-1     | 158            | 89              | 172             |
|                  |             |             |             | Chemotherapy       |          | 141            | 64              | 183             |
| Hellmann, 2018   | CheckMate227(b) | III     | NSCLC       | Nivolumab          | PD-1     | 42             | 30              | 391             |
|                  |             |             |             | Chemotherapy       |          | 79             | 61              | 570             |
| Brahmer, 2015    | CheckMate017 | III        | NSCLC       | Nivolumab          | PD-1     | 76             | 9               | 131             |
|                  |             |             |             | Chemotherapy       |          | 111            | 71              | 129             |
| Carbone, 2017    | CheckMate026 | III        | NSCLC       | Nivolumab          | PD-1     | 190            | 47              | 267             |
| Study                  | Treatment                  | Phase | Disease  | Agent/Combination                          | PD-L1 | Chemotherapy | CR (%) | PR (%) | SD (%) | OS (m) |
|-----------------------|----------------------------|-------|----------|--------------------------------------------|-------|--------------|--------|--------|--------|--------|
| Borghaei, 2015        | CheckMate057               | III   | NSCLC    | Nivolumab                                  | PD-1  | Chemotherapy | 199    | 30     | 287    |        |
| Wu, 2019              | CheckMate078               | III   | NSCLC    | Nivolumab                                  | PD-1  | Chemotherapy | 216    | 35     | 337    |        |
| Jotte, 2018           | IMpower131                 | III   | NSCLC    | Atezolizumab + Chemotherapy                | PD-L1 | Chemotherapy | 316    | 231    | 334    |        |
| Papadimitrakopoulou, 2018 | IMpower132             | III   | NSCLC    | Atezolizumab + Chemotherapy                | PD-L1 | Chemotherapy | 267    | 167    | 291    |        |
| Horn, 2018            | IMpower133                 | III   | ES-SCLC  | Atezolizumab + Chemotherapy                | PD-L1 | Chemotherapy | 188    | 115    | 198    |        |
| Socinski, 2018        | IMpower150                 | III   | NSCLC    | Atezolizumab + Chemotherapy                | PD-L1 | Chemotherapy | 371    | 230    | 393    |        |
| Rittmeyer, 2017       | OAK                        | III   | NSCLC    | Atezolizumab                                | PD-L1 | Chemotherapy | 390    | 90     | 609    |        |
| Fehrenbacher, 2016    | POPLAR                      | II    | NSCLC    | Atezolizumab                                | PD-L1 | Chemotherapy | 95     | 17     | 142    |        |
| Barlesi, 2018         | JAVELIN Lung 200           | III   | NSCLC    | Avelumab                                   | PD-L1 | Chemotherapy | 251    | 39     | 393    |        |
| Antonia, 2018         | PACIFIC                    | III   | NSCLC    | Durvalumab + Chemoradiotherapy             | PD-L1 | Chemotherapy | 460    | 142    | 475    |        |
| Lynch, 2012           | CA184-041(a)               | II    | NSCLC    | Ipilimumab + Chemotherapy                  | CTLA-4| Chemotherapy | 54     | 29     | 71     |        |
| Reck, 2013            | CA184-041(b)               | II    | ES-SCLC  | Ipilimumab + Chemotherapy                  | CTLA-4| Chemotherapy | 52     | 24     | 65     |        |
| Abbreviations: ICI: immune checkpoint inhibitors; TRAE: treatment-related adverse event; NSCLC: non–small cell lung cancer; ES-SCLC: extensive-stage small cell lung cancer; PD-1: programmed death 1; PD-L1: programmed death ligand 1; CTLA-4: cytotoxic T-lymphocyte-associated protein 4. |
Table 2 Risk ratios for treatment-related adverse events (TRAEs) comparing ICI therapy with Chemotherapy

|                | All grade | | Grade 3-5 | |
|----------------|-----------|---|-----------|---|
|                | No. of trials | No. of patients | RR(95%CI) | P   | No. of trials | No. of patients | RR(95%CI) | P   |
| Overall*       | 25         | 14256         | 97.1%(<0.001) | 0.90(0.84,0.95) | 0.001 | Overall       | 25         | 14256         | 96.7%(<0.001) | 0.65(0.52,0.82) | <0.001 |
| Subgroup       |            |               |             |     | Subgroup      |            |               |             |     |
| Method         |            |               |             |     | Method        |            |               |             |     |
| ICI-Chem       | 13         | 6689          | 77.4%(<0.001) | 1.03(1.01,1.06) | 0.017 | ICI-Chem      | 13         | 6689          | 61.8%(0.002) | 1.18(1.09,1.28) | <0.001 |
| ICI            | 12         | 7567          | 19.0%(0.257)  | 0.76(0.73,0.78) | <0.001 | ICI           | 12         | 7567          | 82.9%(<0.001) | 0.33(0.26,0.41) | <0.001 |
| Cancer Type    |            |               |             |     | Cancer Type   |            |               |             |     |
| NSCLC          | 22         | 12822         | 97.8%(<0.001) | 0.88(0.82,0.95) | 0.001 | NSCLC         | 22         | 12822         | 97.1%(<0.001) | 0.60(0.46,0.78) | <0.001 |
| SCLC           | 3          | 1434          | 50.0%(0.135)  | 1.03(0.97,1.10) | 0.318 | SCLC          | 3          | 1434          | 0.0%(0.460)  | 1.06(0.95,1.18) | 0.280  |
| ICI drug       |            |               |             |     | ICI drug      |            |               |             |     |
| Anti-PD-1      | 13         | 6986          | 98.8%(<0.001) | 0.85(0.74,0.97) | 0.018 | Anti-PD-1     | 13         | 6986          | 96.8%(<0.001) | 0.50(0.35,0.73) | <0.001 |
|        | RR  | CI     | p-value |        | RR  | CI     | p-value |
|--------|-----|--------|---------|--------|-----|--------|---------|
| Anti-PD-L1 |
| 8      | 5345| 96.7% (<0.001) | 0.090  | Anti-PD-L1 |
| 8      | 5345| 97.5% (<0.001) | 0.70 (0.46, 1.05) | 0.086 |
| Anti-CTLA-4 |
| 4      | 1925| 47.6% (0.126) | 1.05 (0.98, 1.12) | 0.179  |
| Anti-CTLA-4 |
| 4      | 1925| 66.6% (0.030) | 1.25 (1.00, 1.55) | 0.047  |

Abbreviations: RR: risk ratio; CI: confidence interval
| Author            | Study ID     | Intervention | Colitis | Hepatitis | Pneumonitis | Hypothyroidism | Hypophysitis |
|-------------------|--------------|--------------|---------|-----------|-------------|----------------|-------------|
|                   |              |              | All     | Serious   | All         | Serious        | All         | Serious     |
| Borghaei, 2018    | KEYNOTE021   | 59           | 1.7     | 0.0       | NA          | NA             | 6.8         | 1.7         | 15.3        | 0.0         | NA          | NA          |
| Gandhi, 2018      | KEYNOTE189   | 405          | 2.2     | 0.7       | 1.2         | 1.0            | 4.4         | 2.7         | 6.7         | 0.5         | 0.7         | 0.0         |
| Paz-Ares, 2018     | KEYNOTE407   | 278          | 2.5     | 2.2       | 1.8         | 1.8            | 6.5         | 2.5         | 7.9         | 0.4         | 1.1         | 0.7         |
| Herbst, 2016      | KEYNOTE010(a)| 339          | 1.2     | 0.9       | NA          | NA             | 4.7         | 2.1         | 8.3         | 0.0         | 0.3         | 0.3         |
| Herbst, 2016      | KEYNOTE010(b)| 343          | 0.6     | 0.3       | NA          | NA             | 4.4         | 2.0         | 8.2         | 0.0         | 0.3         | 0.3         |
| Reck, 2016        | KEYNOTE024   | 154          | 1.9     | 1.3       | NA          | NA             | 5.8         | 2.6         | 9.1         | 0.0         | 0.6         | 0.6         |
| Wu, 2019          | CheckMate078 | 337          | NA      | NA        | NA          | NA             | 3.0         | 1.2         | NA          | NA          | NA          | NA          |
| Jotte, 2018       | IMpower131   | 334          | 1.8     | 1.2       | 17.4        | 5.4            | 6.9         | 1.2         | 10.2        | 0.6         | 0.0         | 0.0         |
| Papadimitrapoulos, 2018 | IMpower132 | 291          | 1.7     | 0.7       | 4.5         | 2.4            | 5.5         | 2.1         | 7.9         | 0.7         | NA          | NA          |
| Horn, 2018        | IMpower133   | 198          | 1.5     | 1.0       | 7.1         | 3.5            | 2.0         | 0.5         | 12.6        | 0.0         | 0.5         | 0.0         |
| Socinski, 2018     | IMpower150   | 393          | 2.3     | 1.3       | 2.0         | 1.0            | 2.8         | 1.3         | 12.7        | 0.3         | 0.8         | 0.3         |
| Rittmeyer, 2017   | OAK          | 609          | 0.3     | 0.0       | 0.3         | 0.3            | 1.0         | 0.7         | NA          | NA          | NA          | NA          |
| Fehrenbacher, 2016 | POPLAR      | 142          | 1.4     | 0.7       | 0.7         | 0.0            | 2.8         | 0.7         | 5.6         | 0.7         | NA          | NA          |
| Barlesi, 2018     | JAVELIN Lung 200 | 393    | 0.3     | NA        | NA          | NA             | 2.3         | NA         | 4.8         | NA          | NA          | NA          |
| Antonia, 2018     | PACIFIC      | 475          | NA      | NA        | NA          | NA             | 10.7        | 1.7         | 9.3         | 0.2         | NA          | NA          |
| Lynch, 2012       | CA184-041(a) | 71           | NA      | NA        | NA          | NA             | NA          | NA         | 1.4         | 1.4         | NA          | NA          |

Table 3 Incidence of organ specific immune-related adverse events (IRAEs). Value are percentage (95% confidence intervals)
|                  | CA184-041(b) | 42   | 2.4  | 2.4  | 2.4  | 2.4  | NA   | NA   | NA   | NA   | 0.0  | 0.0  |
|------------------|--------------|------|------|------|------|------|------|------|------|------|------|------|
| Reck, 2013       |              |      |      |      |      |      |      |      |      |      |      |      |
| Govindan, 2017   | CA184-104    | 388  | 4.4  | 2.3  | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   |
| **TOTAL**        |              |      |      |      |      |      |      |      |      |      |      |      |
|                  | 1.6          | 4.0  | 1.8  | 4.5  | 1.5  | 8.7(7.8-9.6) | 0.3(0.2-0.5) | 0.6(0.3-1.0) | 0.3(0.1-0.6) |
|                  | (1.3-2.0)    | (3.3-4.8) | (1.3-2.4) | (3.9-5.1) | (1.2-1.9) |

All 1: includes all Common Terms classified by Clinical Adverse Events (CTCAE) grades.

Serious2: includes CTCAE grades 3,4, or 5. NA: not available
## Supplementary Appendix

| Study ID      | Random sequence generation | Allocation concealment | Blinding of participants | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|--------------|----------------------------|------------------------|---------------------------|-------------------------------|-------------------------|---------------------|------------|
| KEYNOTE021   | Low                        | Low                    | High                      | High                          | Low                     | Low                 | Low        |
| KEYNOTE189   | Low                        | Low                    | Low                       | Low                           | Low                     | Low                 | Low        |
| KEYNOTE407   | Low                        | Low                    | Low                       | Low                           | Low                     | Low                 | Low        |
| CheckMate 227(a) | Low               | Low                    | Low                       | Low                           | Low                     | Low                 | Low        |
| IMpower131   | Low                        | Low                    | unclear                   | unclear                       | High                    | Low                 | High       |
| IMpower132   | Low                        | Low                    | unclear                   | unclear                       | High                    | Low                 | High       |
| IMpower133   | Low                        | Low                    | Low                       | Low                           | High                    | Low                 | Low        |
| IMpower150   | Low                        | Low                    | Low                       | Low                           | Low                     | Low                 | Low        |
| PACIFIC      | Low                        | Low                    | Low                       | Low                           | Low                     | Low                 | Low        |
| CA184-041(a) | Low                        | Low                    | Low                       | Low                           | High                    | High                | Low        |
| CA184-041(b) | Low                        | Low                    | Low                       | Low                           | High                    | High                | Low        |
| CA184-104    | Low                        | Low                    | Low                       | Low                           | Low                     | Low                 | Low        |
| CA184-156    | Low                        | Low                    | Low                       | Low                           | Low                     | Low                 | Low        |
| Study             | Assessment 1 | Assessment 2 | Assessment 3 | Assessment 4 | Assessment 5 | Assessment 6 | Assessment 7 |
|-------------------|-------------|--------------|--------------|--------------|--------------|--------------|--------------|
| KEYNOTE010        | Low         | Low          | High         | High         | Low          | Low          | Low          |
| KEYNOTE024        | Low         | Low          | High         | High         | High         | High         | Low          |
| KEYNOTE042        | Low         | Low          | unclear      | unclear      | High         | Low          | High         |
| CheckMate017      | Low         | Low          | High         | High         | Low          | Low          | Low          |
| CheckMate026      | Low         | Low          | High         | High         | Low          | Low          | Low          |
| CheckMate057      | Low         | Low          | High         | High         | Low          | Low          | Low          |
| CheckMate078      | Low         | Low          | High         | High         | Low          | Low          | Low          |
| CheckMate227(b)   | Low         | Low          | High         | High         | Low          | Low          | Low          |
| OAK               | Low         | Low          | High         | High         | High         | High         | Low          |
| POPLAR            | Low         | Low          | High         | High         | High         | High         | Low          |
| JAVELIN Lung 200  | Low         | Low          | High         | High         | Low          | Low          | Low          |

Table S1 Quality assessment: risk of bias by Cochrane Collaboration’s tool
Records identified through database searching (n=2993)

→ Excluded (n=1013) for duplications

Records after duplicates removed (n=1980)

→ Studies excluded after screening of title and abstracts (n=1933)

Full-text articles assessed for eligibility (n=47)

→ Excluded (n=23) for reasons:
  - Not relevant outcome n=9
  - Insufficient data n=4
  - Other intervention therapy n=10

Records after duplicates removed (n=24)
**A**

| Study ID | RR (95% CI) | Weight |
|----------|-------------|--------|
| KEYNOTE021 | 1.01 (0.92, 1.12) | 4.01 |
| KEYNOTE189 | 1.01 (0.99, 1.02) | 4.46 |
| KEYNOTE407 | 1.00 (0.96, 1.03) | 4.44 |
| KEYNOTE010(a) | 0.78 (0.71, 0.86) | 4.04 |
| KEYNOTE010(b) | 0.81 (0.74, 0.89) | 4.07 |
| KEYNOTE024 | 0.82 (0.73, 0.91) | 3.94 |
| KEYNOTE042 | 0.70 (0.65, 0.74) | 4.28 |
| CheckMate 227(a) | 1.19 (1.09, 1.31) | 4.09 |
| CheckMate 227(b) | 0.78 (0.55, 1.10) | 1.85 |
| CheckMate017 | 0.67 (0.57, 0.79) | 3.44 |
| CheckMate026 | 0.77 (0.71, 0.84) | 4.14 |
| CheckMate057 | 0.79 (0.72, 0.86) | 4.10 |
| CheckMate078 | 0.77 (0.68, 0.86) | 3.96 |
| IMpower131 | 1.04 (1.00, 1.09) | 4.38 |
| IMpower132 | 1.05 (0.99, 1.11) | 4.31 |
| IMpower133 | 1.03 (0.98, 1.08) | 4.34 |
| IMpower150 | 0.99 (0.96, 1.02) | 4.42 |
| OAK | 0.75 (0.70, 0.80) | 4.25 |
| POPLAR | 0.76 (0.67, 0.87) | 3.74 |
| JAVELIN Lung 200 | 0.74 (0.68, 0.81) | 4.13 |
| PACIFIC | 1.02 (0.99, 1.06) | 4.41 |
| CA184-041(a) | 0.95 (0.80, 1.14) | 3.28 |
| CA184-041(b) | 0.92 (0.78, 1.08) | 3.42 |
| CA184-104 | 1.10 (1.03, 1.17) | 4.29 |
| CA184-156 | 1.08 (1.01, 1.15) | 4.28 |
| Overall (I-squared = 97.1%, p = 0.000) | 0.90 (0.84, 0.95) | 100.00 |

**B**

| Study ID | RR (95% CI) | Weight |
|----------|-------------|--------|
| KEYNOTE021 | 1.48 (0.89, 2.47) | 3.57 |
| KEYNOTE189 | 1.02 (0.90, 1.15) | 4.27 |
| KEYNOTE407 | 1.02 (0.92, 1.14) | 4.28 |
| KEYNOTE010(a) | 0.36 (0.26, 0.49) | 4.00 |
| KEYNOTE010(b) | 0.45 (0.34, 0.60) | 4.06 |
| KEYNOTE024 | 0.50 (0.37, 0.68) | 4.03 |
| KEYNOTE042 | 0.43 (0.36, 0.53) | 4.20 |
| CheckMate 227(a) | 1.42 (1.16, 1.89) | 4.12 |
| CheckMate 227(b) | 0.72 (0.47, 1.09) | 3.79 |
| CheckMate017 | 0.12 (0.07, 0.24) | 3.22 |
| CheckMate026 | 0.35 (0.26, 0.46) | 4.06 |
| CheckMate057 | 0.19 (0.14, 0.28) | 3.92 |
| CheckMate078 | 0.22 (0.15, 0.31) | 3.92 |
| IMpower131 | 1.20 (1.07, 1.34) | 4.28 |
| IMpower132 | 1.38 (1.16, 1.64) | 4.22 |
| IMpower133 | 1.01 (0.85, 1.19) | 4.23 |
| IMpower150 | 1.17 (1.03, 1.33) | 4.27 |
| OAK | 0.35 (0.28, 0.43) | 4.17 |
| POPLAR | 0.29 (0.18, 0.48) | 3.62 |
| JAVELIN Lung 200 | 0.20 (0.15, 0.28) | 4.00 |
| PACIFIC | 1.15 (0.89, 1.48) | 4.11 |
| CA184-041(a) | 1.11 (0.72, 1.69) | 3.77 |
| CA184-041(b) | 1.45 (0.82, 2.58) | 3.41 |
| CA184-104 | 1.48 (1.25, 1.75) | 4.23 |
| CA184-156 | 1.07 (0.94, 1.23) | 4.26 |
| Overall (I-squared = 96.7%, p = 0.000) | 0.65 (0.51, 0.82) | 100.00 |

**NOTE:** Weights are from random effects analysis
### Table A

| Study ID       | RR (95% CI)        | Weight |
|---------------|--------------------|--------|
| KEYNOTE021    | 3.15 (0.13, 75.82) | 3.67   |
| KEYNOTE189    | 9.50 (0.56, 162.41)| 5.02   |
| KEYNOTE407    | 1.76 (0.52, 5.96)  | 30.01  |
| KEYNOTE010(a) | 8.21 (0.44, 151.80)| 3.94   |
| KEYNOTE010(b) | 4.51 (0.22, 93.49) | 3.96   |
| KEYNOTE024    | 6.82 (0.36, 130.30)| 3.81   |
| IMpower131    | 13.00 (0.74, 229.84)| 3.77   |
| IMpower132    | 10.36 (0.58, 186.47)| 3.88   |
| IMpower133    | 6.93 (0.36, 133.28)| 3.78   |
| IMpower150    | 4.51 (0.98, 20.75) | 15.04  |
| OAK           | 4.75 (0.23, 98.64) | 3.86   |
| POPLAR        | 4.76 (0.23, 98.15) | 3.86   |
| JAVELIN Lung 200 | 2.79 (0.11, 68.19)| 3.90   |
| CA184-041(b)  | 3.14 (0.13, 74.98) | 3.68   |
| CA184-104     | 15.82 (2.12, 118.25)| 7.80   |
| Overall (I-squared = 0.0%, p = 0.973) | 5.54 (3.06, 10.02) | 100.00 |

### Table B

| Study ID       | RR (95% CI)        | Weight |
|---------------|--------------------|--------|
| KEYNOTE189    | 5.50 (0.31, 98.98) | 1.54   |
| KEYNOTE407    | 11.08 (0.82, 199.41)| 1.15   |
| IMpower131    | 2.00 (1.32, 3.04)  | 67.00  |
| IMpower132    | 6.12 (1.39, 26.87) | 4.76   |
| IMpower133    | 1.54 (0.36, 5.47)  | 20.90  |
| IMpower150    | 17.04 (0.99, 294.27)| 1.15   |
| OAK           | 4.75 (0.23, 98.64) | 1.19   |
| POPLAR        | 2.85 (0.12, 69.44) | 1.18   |
| CA184-041(b)  | 3.14 (0.13, 74.98) | 1.13   |
| CA184-104     | 2.49 (1.77, 3.50)  | 100.00 |

Overall (I-squared = 0.0%, p = 0.529)
| Study            | RR (95% CI)     | Weight |
|------------------|-----------------|--------|
| KEYNOTE189       | 3.50 (0.18, 67.43) | 15.71  |
| KEYNOTE407       | 7.05 (0.37, 135.86) | 11.74  |
| KEYNOTE010(a)    | 2.74 (0.11, 66.90)  | 12.32  |
| KEYNOTE010(b)    | 2.70 (0.11, 66.12)  | 12.39  |
| KEYNOTE024       | 2.92 (0.12, 71.18)  | 11.94  |
| IMpower133       | 2.97 (0.12, 72.46)  | 11.84  |
| IMpower150       | 7.02 (0.36, 135.41) | 11.77  |
| CA184-041(a)     | 2.75 (0.11, 66.34)  | 12.29  |
| CA184-041(b)     | (Excluded)       | 0.00   |
| Overall (I-squared = 0.0%, p = 0.999) | 3.91 (1.33, 11.54)  | 100.00 |
