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Impact of PD1 and PDL1 immunotherapy on non-small cell lung cancer outcomes

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The impact of PD1 and PDL1 immunotherapy on non-small cell lung cancer outcomes: a systematic review

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The impact of PD1 and PDL1 immunotherapy on non-small cell lung cancer outcomes: a systematic review

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Abstract

Introduction

Despite comprising many cancer diagnoses, few treatments are suitable for patients with advanced non-small cell lung cancer (aNSCLC). Trials suggest blockade of Programmed Death 1 (PD1) or its ligand (PDL1) may be effective for these patients. However, this therapy's impact on outcomes other than survival, and outcomes of patients not in trials, remains largely unknown. Therefore, we compared the effectiveness of PD1 and PDL1 immunotherapy to chemotherapy and placebo across multiple clinical outcomes.

Methods

Six databases were searched on 12-13/10/2019 for randomised controlled trials (RCTs) and observational studies investigating nivolumab, pembrolizumab, atezolizumab or durvalumab. Study selection was performed independently by two reviewers. Data for overall survival, progression-free survival, adverse effects (AEs), and quality of life (QoL) were descriptively and meta-analysed. Factors impacting treatment outcomes, including PDL1 expression, were explored. The similarity between RCT and observational data was assessed.

Results

From 5,423 search results, 139 full texts and abstracts were included. Immunotherapy was associated with a lower risk of death than both comparators. In RCTs, the incidence of treatment-related AEs was approximately 20% lower among patients using immunotherapy compared to chemotherapy. However, no other consistent benefits were observed. Progression-free survival results were inconsistent. Improvements to QoL varied according to the instrument used; however, QoL was not recorded widely. Survival results were similar between study designs; however, AEs incidence was lower in observational studies.

Discussion

Among patients with aNSCLC, immunotherapy improved overall survival and incidence of treatment-related AEs compared to chemotherapy. Benefits to progression-free survival and QoL were less consistent.

(Word count: 249)

Key messages

What is already known on the topic?

In trials, PD1 and PDL1 immunotherapy improves overall survival, but the impact to other clinical outcomes, the extent to which trial data reflect clinical practice, and factors affecting outcomes from this therapy are less well understood.

What this study adds

We present comprehensive systematic review data from 26,581 patients, demonstrating that while this immunotherapy improves overall survival, benefits to progression-free survival and quality of life are less clear. Performance status and presence of metastases had potential influence on survival outcomes.

How this study might affect research, practice, or policy

This study may be used to provide information about multiple clinical outcomes to patients and contribute to understanding factors affecting patient outcomes, to identify those most likely to succeed with this therapy.

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Introduction

Globally and in the United Kingdom (UK), lung cancer is a major healthcare problem due to its high incidence and poor associated long-term survival [1-3]. In the UK, just 7.6% of men and 11.3% of women are predicted to survive past ten years [4]. Lung cancer incidence is strongly correlated with smoking, increasing age, and deprivation, suggesting vulnerable individuals are more susceptible [5-8].

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, comprising around 87% of cases [9]. The complex reasons for the poor prognosis associated with NSCLC have been widely studied [10]. One core reason is that many available treatments are unsuitable for patients with advanced NSCLC (aNSCLC), who comprise a large proportion of cases. Therefore, patient prognosis may be improved by identifying more treatments suitable for aNSCLC. Due to the specificity of antigen recognition within the immune system, therapies capitalising on immune checkpoint blockade, particularly Programmed Death 1 (PD1) and Programmed Death Ligand 1 (PDL1) immunotherapy, have potential to improve care of patients with aNSCLC.

PD1 and PDL1 immunotherapy consists of monoclonal antibodies that block the intra-tumoral interactions between PD1 and PDL1, restoring the cytotoxic functionality of anti-tumour immune cells [11, 12]. Based on data assimilated by the National Institute of Health and Care Excellence (NICE) from phase III randomized controlled trials (RCTs), PD1 and PDL1 immunotherapy has been recommended for the treatment of stage IIIB and stage IV NSCLC among patients expressing PDL1 [13].

However, several unanswered questions remain. Firstly, the generalisability of current NICE guidelines is questionable. This is because, by only considering trial data, the guidelines place emphasis on results from a few tightly regulated, relatively well, subsets of the population of NSCLC patients [14-18]. Secondly, available systematic reviews are limited because they focus on a single class effect, mostly related to short-term survival; assimilate data across several cancer types; and largely do not include observational data to assess real-world treatment-related outcomes [19-28]. Therefore, further systematic reviews are needed to provide a more realistic estimate of treatment effect and to investigate outcomes unrelated to survival. We aimed to establish whether PD1 and PDL1 immunotherapy is effective at improving clinical outcomes of NSCLC, compared to chemotherapy or placebo. Both RCTs and observational studies were included to assess data generalisable to a broad population. As a secondary objective, we explored potential patient and disease factors influencing patient prognosis.

Methods

The protocol is registered on PROSPERO (CRD42019153345).

Identification of relevant studies

All searches consisted of synonyms describing NSCLC, and PD1 and PDL1 immunotherapy, with database-specific subject headings where appropriate (see supplement). Studies in any language from inception to 13/10/2019 were included. Six databases were searched: Ovid Medline, Ovid EMBASE, EBSCO CINAHL, Cochrane Library, ClinicalTrials.gov and NICE Evidence Search. To check for relevant studies missed by literature searches, the reference lists of relevant systematic reviews returned from searches were compared against relevant results from title and abstract screening.

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Study screening, selection, and data extraction

Eligible studies were required to meet the criteria specified in the protocol (Table 1). Studies were excluded if there were insufficient data for analysis, or if these criteria were not met.

Population	Adults > 18 years old with squamous, large cell, or adenocarcinoma NSCLC in ≥90% of participants, or data presented separately for eligible patients.	
Intervention	Nivolumab, pembrolizumab, atezolizumab and durvalumab monotherapy administered by a healthcare professional in a secondary or tertiary healthcare setting.	
Comparator	Placebo or NICE-recommended chemotherapy administered by healthcare professionals in a secondary or tertiary setting.	
Outcomes	Overall survival (OS)	Time between initiation of treatment and death of patient
	Progression-free survival (PFS)	Time between initiation of treatment and worsening of the patient's cancer or death
	Adverse effects (AEs)	A healthcare problem that arises after initiating treatment
	Quality of life (QoL)	Patient's satisfaction with their standard of living while they are using a treatment
	Hospitalisations	
Study designs	Randomised Controlled Trials (RCTs)	Those comparing the effectiveness of PD1 and PDL1 immunotherapy to either of the two comparators were eligible. Non-comparative trials were not eligible. Abstracts permitted.
	Cohort and case control studies	Participant number ≥ 10, receiving PD1 or PDL1 immunotherapy. Abstracts permitted.
	Case series and case reports were not eligible.	

Table 1 – PICOS criteria

Search results were independently screened for relevance, and data were extracted by at least two reviewers at each stage. The data collected are outlined in the supplementary methods. When relevant data were unavailable, authors were contacted via e-mail.

Risk of bias and quality assessment

Risk of bias was assessed at a study level by one author and checked by SSK using the revised tool for Risk of Bias in randomized trials (RoB2.0) for RCTs, and the 2016 Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) as appropriate. The risk of publication bias was assessed using a funnel plot of the hazard ratios (HRs) for mortality from included RCTs, constructed in Review Manager 5.3™. Risk of bias data were visualised using the Risk Of Bias Visualisation Tool (ROBVIS). Additionally, the quality of RCT evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework; the GRADEpro™ tool was used to produce a Summary of Findings table.

Data analysis

All outcomes were analysed descriptively. Studies were grouped by follow up length for analysis (Table 2).

Reported length of follow up	**Follow up classification in review**
0 months ≤ x < 18 months	Short-term follow up
18 months ≤ x < 31 months	Medium-term follow up

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x ≥ 31 months	Long-term follow up

Table 2 – Classification of length of follow up
x = median follow up reported in study, or minimum follow up if median was unavailable. This classification was used because most primary-analysis studies reported a follow up of just over one year, which would not be a fair comparison against data collected from closer to 24 months follow-up.

Risk of death and risk of progression or death HRs from RCT studies were meta-analysed in Review Manager 5.3™ using a random effects model. Meta-analysis was precluded in observational studies due to the lack of reported HRs in these largely single arm studies. Median survival times and 95% confidence intervals (CIs) are displayed in the supplement. To aid comparison between studies, we also show the simple arithmetic mean of median survival times ('average survival') in the supplement. These mean estimates are indicative only.

AEs data were directly reported as or were converted to percentage incidence, defined as the proportion of patients within the study arm who had each AE. These data were analysed descriptively and with simple means to provide summary estimates of incidence. Detailed AEs tables are presented in the supplement.

Quality of life (QoL) results were reported directly from included studies. Meta-analysis was precluded because multiple QoL questionnaires were used among the studies.

Subgroup meta-analyses of HRs stratified by PDL1 expression, therapy line, tumour histology, presence of metastases and performance status were performed via the same methods. Where a breakdown of results by therapy line was not reported, studies were grouped into a 'mixed' category for analysis. These analyses were only possible for survival data due to a lack of HRs and stratification of results, particularly in the observational data.

Results

Characteristics of studies

After removing duplicates, 5,423 records were screened by title and abstract. Subsequently, 277 full texts and abstracts were screened. From these, 101 full texts and 38 abstracts were included (Figure 1) [29].

The 28 RCT studies included primary, extended follow up, and comparative subgroup analyses of 12 phase II or III international trials comparing immunotherapy to docetaxel, combination platinum chemotherapy or a placebo. The 111 observational studies included 74 full texts and 37 abstracts. Most observational studies were non-comparative cohort studies of a single intervention used in real clinical practice, typically nivolumab.

Across all RCTs, the total number of patients was 7,727 (range 272-1,274/study). The total number of participants across all observational studies was 18,951 (10-1,588/study). Participants in RCTs and observational studies had similar baseline characteristics (Table 3), though reporting was inconsistent among abstracts. Patients were typically men aged between 58 – 75. In RCTs, most patients were Caucasian; few observational studies reported ethnicity. Participants were recruited internationally, although few patients were from Africa.

Most patients in RCTs had stage III, IV or recurrent NSCLC, and thus had metastatic disease. Similarly, despite recruiting patients with all stages of disease, most patients in observational studies had metastatic disease. Most trials restricted recruitment by NSCLC histology, unlike the observational studies. Across both study designs, most patients had non-squamous

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disease. However, unlike the observational studies, all trial patients had an Eastern Co-Operative Oncology Group Performance Status (ECOG PS) between 0 – 1.

Median length of follow up was typically one year, with some extended follow up RCTs reporting outcomes from up to four years.

Several lines of therapy were investigated in both RCTs and observational studies. In some studies, multiple lines were investigated (see supplement).

Patient characteristic	Randomised Controlled Trials (RCTs)			Observational	
	Number of RCTs*	Mean (Range) for intervention	Mean (Range) for comparator	Number of studies*	Mean (Range)
% male	11	67.1 (52.0 – 82.0)	64.6 (53.0 – 81.0)	86	68.5 (19.6 - 90.0)
% Caucasian	6	79.1 (66.2 – 91.0)	81.8 (70.6 – 95.0)	9	65.1 (13.0 – 97.0)
Median age (yrs)	11	62.7 (60.0 – 64.5)	63.5 (60.0 – 66.0)	79	66.5 (58.0 – 75.2)
Non-squamous histology	11	65.2 (0.0 – 100.0)	67.8 (0.0 – 100.0)	87	64.6 (0.0 - 100.0)

Table 3 – Baseline characteristics of patients

*Not all studies reported all characteristics. Among the RCTs, Spigel et al did not report any baseline characteristics in their abstract [30]. Among the observational studies, absences of data largely originated from observational abstracts.

Risk of bias and quality of evidence

Overall, the risk of bias was relatively low (Figure 2A – C and supplement). Most RCTs and observational full texts were associated with a low risk of bias. The most common sources of bias in RCTs arose in domains relating to randomisation and intervention, attributable to the lack of reported compensatory mechanisms for potential crossover in open-label trials. The main source of bias in observational full texts arose from a lack of adjusting analyses for known confounders. Furthermore, approximately 40% of observational full texts did not report the implications of intervention deviations. The lack of reporting of methods in observational abstracts impacted our ability to assess risk of bias in these studies, which therefore remains unclear.

Funnel plots using HRs for death from RCTs were relatively symmetrical and are therefore unlikely to be subject to significant publication bias (Figure 2D). Our assessment gives no suggestion that conflicts of interest impacted the conduct of any of the studies included.

Using GRADE, the overall certainty of RCT evidence was moderate to high (Supplementary Results). Among studies investigating nivolumab, pembrolizumab and atezolizumab, time to deterioration in quality of life when assessed by EQ-5D-3L and LCSS ASBI were downgraded due to risk of bias, and risk of progression or death between 0 – 18 months were downgraded due to inconsistency and imprecision.

Overall survival

17 RCT studies reported OS at one- to four-years follow up [31-47]. 48 observational studies with short-term follow up reported OS [48-93]. Heterogeneity in the meta-analyses tended to be low to moderate, except for nivolumab in short-term follow up studies (I^2 = 71%).

Among RCTs with short-term follow up, patients receiving immunotherapy survived longer on average and had a lower risk of death than patients receiving chemotherapy. The pooled HR

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for death among patients receiving nivolumab, pembrolizumab or atezolizumab compared to chemotherapy was 0.75 (95% CI 0.69 – 0.81, p < 0.00001) (Figure 3A). Typically, average survival was approximately 3 months longer with immunotherapy, with pembrolizumab being associated with longest average OS (13.6 months; Supplementary Figure 1). However, the associated confidence intervals for these data overlap rendering this evidence unclear.

Among RCTs with medium-term follow up, patients receiving immunotherapy survived longer and had a lower risk of death. The pooled HR for death among patients receiving nivolumab, pembrolizumab or atezolizumab compared to chemotherapy was 0.72 (95% CI 0.65 – 0.80, p < 0.00001) (Figure 3B). Typically, average survival was around 5 months longer with immunotherapy compared to chemotherapy. OS was not reached among patients receiving durvalumab (Supplementary Figure 1); the risk of death was 0.68 (99.73% CI 0.47 – 1.00) [43].

RCTs with long-term follow up reported similar results. The pooled HR for death was 0.70 (95% CI 0.59 – 0.82, p < 0.0001) (Figure 4C). Only CheckMate017 and 057 reported OS between three- and four-year follow up. There was no change in median OS in either study arm of these two cohorts [46].

OS in observational studies and RCTs were similar (Supplementary Figure 1). The similarity in OS between observational studies and RCTs was supported by data from observational studies with an unknown length of follow up, and abstracts.

Progression-free survival

17 RCT studies reported PFS from up to three-years patient follow up [31-42, 44, 45, 94-96]. 52 observational studies with short-term follow up reported PFS [48-59, 63-72, 74-76, 78-85, 87-90, 92, 93, 97-104]. Heterogeneity in the meta-analysed studies tended to be high; the I^2 statistics for short-term follow up studies of nivolumab and pembrolizumab were 69% and 91% respectively.

In RCTs with short-term follow up, patients receiving immunotherapy had a lower risk of progression or death than patients receiving chemotherapy. The pooled HR for progression or death among patients receiving nivolumab, pembrolizumab or atezolizumab compared to chemotherapy was 0.87 (95% CI 0.76 – 0.99, p = 0.03) (Figure 5A). There was no evidence of a difference in average PFS among patients receiving nivolumab, pembrolizumab or atezolizumab and those receiving chemotherapy, albeit with some inconsistency within the results (Supplementary Figure 2) [94].

Among RCTs with medium or long-term follow up, patients receiving immunotherapy did not have a consistent benefit to PFS. At three-year follow up, the risk of progression or death among patients receiving nivolumab or pembrolizumab compared to chemotherapy was 0.82 (95% CI 0.74 – 0.90, p < 0.00001) (Figure 5B). However, there were no clinically significant differences in average PFS between these three agents and chemotherapy in medium or long term follow up studies (Supplementary Figure 2). In PACIFIC, the PFS was 17.3 months (95% CI 13.1 – 23.9) with durvalumab, compared to 5.6 months (95% CI 4.6 –7.7) on placebo [43].

Similar PFS results were reported in observational studies including those with an unknown length of follow up, and abstracts (Supplementary Figure 2).

Adverse effects and hospitalisations

20 RCT studies reported AEs [31-39, 42-44, 47, 94, 95, 105, 106]. 53 observational full texts reported AEs among patients receiving pembrolizumab, nivolumab and atezolizumab, of which 44 investigated nivolumab.

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In primary-analysis RCT studies, nivolumab, pembrolizumab and atezolizumab were associated with a lower incidence of treatment-related adverse effects (trAEs) than chemotherapy (Table 4), except one atezolizumab study [69]. Durvalumab was associated with a similar incidence of trAEs [94].

Drug	% incidence – mean (range)		
	Intervention arm, Randomised Controlled Trials (RCTs)	Intervention, observational studies	Chemotherapy arm, RCTs†
Nivolumab	65.2 (58.0 – 71.0)	50.6 (21.0 – 88.0)	87.3 (83.0 – 92.0)
Pembrolizumab	66.4 (63.0 – 73.4)	48.2 (10.0 – 71.0)	87.0 (81.0 – 90.0)
Atezolizumab	65.5 (64.0 – 67.0)	.	87.0 (86.0 – 88.0)
Overall	65.7	49.4	87.1
Drug	**% incidence**		
	Intervention arm, RCT	**Intervention, observational studies**	**Placebo arm, RCT**
Durvalumab*	67.8	.	53.4

Table 4 – Incidence of trAEs among randomised controlled trials (RCTs) and observational studies

*Only one study reported the incidence of trAEs among patients receiving durvalumab.

†Chemotherapy choices were highly variable between RCTs, but typically consisted of docetaxel or platinum-based chemotherapy combinations (see Supplementary Results).

The pattern and incidence of trAEs are summarised in Tables 5 and 6 and the supplementary results. Immune-related AEs were highly variable between studies and agents (see supplement).

Adverse effect	Number of trials	Mean % incidence	
		Immunotherapy	Chemotherapy†
Fatigue	9	15	27
Decreased appetite	9	11	21
Diarrhoea	8	11	15
Pyrexia	3	11	7
Nausea	8	10	31
Rash	6	9	4
Hypothyroidism	5	9	1
Asthenia	7	8	12
Arthralgia	3	7	8
Constipation	5	6	12

Table 5 – Top 10 trAEs with the highest mean percentage incidence among patients receiving nivolumab, pembrolizumab, or atezolizumab in primary-analysis randomised controlled trials (RCTs)

†Chemotherapy choices were highly variable between RCTs, but typically consisted of docetaxel or platinum-based chemotherapy combinations (see Supplementary Results).

Adverse effect	Number of studies	Mean % incidence
Fatigue/asthenia	24	27
Rash	25	13
Pruritus	12	11

Hypo-/hyperthyroidism	31	10
Nausea/vomiting	12	10
Arthralgia/myalgia	14	9
Diarrhoea	22	8
Neurological symptoms	10	8*
Pneumonitis	27	5
Anaemia	13	5

Table 6 – Top 10 trAEs with the highest mean percentage incidence among patients receiving nivolumab, pembrolizumab, or atezolizumab in observational studies
*The mean percentage incidence for patients experiencing neurological symptoms was heavily positively skewed by one study, which reported a percentage incidence of 63%.

Manrique et al were the only study to report hospitalisations; in this study, 5 out of 188 patients receiving nivolumab (2.7%) were hospitalised due to AEs [107].

Quality of Life

Quality of life (QoL) was reported in 4 RCTs using either EQ-5D (3L or 5L), EORTC-QLQ (LC13 or C30) or LCSS (Table 7).

Reck et al reported no significant differences to benefit in EQ-5D-3L between nivolumab and docetaxel [108]. While patients in both KEYNOTE 024 trial arms improved in EQ-5D-3L, the difference between pembrolizumab and chemotherapy was not significant [109]. Hui et al reported a mean change in EQ-5D-5L of -0.014 (σ 0.177) with durvalumab and 0.012 (σ 0.122) on placebo [110].

The proportion of patients that improved in terms of Lung Cancer Symptom Scale (LCSS) by week 12 was 17.8% with nivolumab (95% CI 13.6% – 22.7%) and 19.7% with docetaxel (95% CI 15.2% – 24.7%) [108]. The time to deterioration in average symptom burden index (ASBI) in the LCSS was prolonged with nivolumab, despite an initial worsening at week 4 [108].

EORTC-QLQ-C30 was used in studies of pembrolizumab, atezolizumab and durvalumab Patients taking pembrolizumab experienced a mean improvement of 6.9 points (95% CI 3.3 – 10.6) between baseline and week 15 [109]. By contrast, patients in the chemotherapy arm experienced mean decline of 0.9 points (95% CI -4.8 – 3.0; p = 0.002) [109]. However, there was no significant difference between atezolizumab and docetaxel or durvalumab and placebo (Table 5) [110, 111].

Beneficial effects on EORTC-QLQ-LC13 score were observed with pembrolizumab and atezolizumab compared to chemotherapy and docetaxel, respectively [109, 111]. There were no clinically important EORTC-QLQ-LC13 between-group differences between patients using durvalumab and placebo [110].

Study	Drug	QoL Tool	QoL Measure	HR	95% CI	p value
Reck et al, 2018 [108]	Nivolumab	EQ-5D-3L [112]	Time to disease-related deterioration	0.90	0.69 – 1.17	0.424
		LCSS ASBI [113]	Time to disease-related deterioration	0.65	0.49 – 0.85	0.002
Brahmer et al, 2017 [109]	Pembrolizumab	EORTC-QLQ-LC13 [114]	Time to deterioration in the composite of cough, chest pain and dyspnoea	0.66	0.44 – 0.97	0.029

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Bordoni et al, 2018 [111]	Atezolizumab	EORTC-QLQ-C30 [115]	Time to deterioration	0.94	0.72 – 1.24	0.6634
		EORTC-QLQ-LC13	Time to deterioration in chest pain	0.71	0.49 – 1.08	0.082
Hui et al, 2019 [110]	Durvalumab	EORTC-QLQ-C30	Time to deterioration	0.95	0.72 – 1.26	.

Table 7 – Time to deterioration in quality of life, comparing interventions to chemotherapy and placebo

The time to deterioration was prolonged among patients using an intervention [108-111]. The HRs have been reported directly from the included studies listed in the table.

Patient and disease factors influencing prognosis

Among 9 meta-analysable RCTs, increasing PDL1 expression was associated with a reduced risk of death (Figure 5). However, the CIs overlapped between groups, and there was significant heterogeneity among data from patients with ≥5% expression. A similar relationship was observed between PDL1 expression and risk of progression or death (Supplementary Figure 5). When considering the current PDL1 expression threshold for accessing immunotherapy, patients with ≥1% expression has a 6% lower risk of death than patients with <1% expression in these RCTs (Figure 5). However, the CIs between the two groups overlapped. Additionally, in 4 observational studies comparing this threshold among patients with nivolumab, no difference between risk of death for patients with <1% compared to ≥1% was observed (Supplementary Figure 6). This result is hindered by the fact that one of these studies recruited patients involved in a compassionate access programme [116].

Among 10 RCTs with analysable therapy line data, patients receiving immunotherapy as 2nd line therapy had a 13% lower risk of death and a 12% lower risk of progression or death (Supplementary Figure 7). However, heterogeneity was significant in these subgroups.

No consistent impact to risk of death, or risk of progression or death, was observed when comparing patients with squamous to patients with non-squamous disease in 9 RCTs. This finding was upheld among the 10 observational studies comparing these subgroups.

2 RCT studies reported that patients with CNS and liver metastases receiving immunotherapy had a similar risk of death to patients without [44, 117]. However, the meta-analysed risk of death from 5 observational studies was significantly higher among patients with metastases (HR 1.69, 95% CI 1.23 – 2.32).

Among the 14 observational studies reporting the impact of ECOG PS on risk of death, patients with PS2 were at greater risk of death than patients with PS 0 – 1. The meta-analysed risk of death in 3 observational studies comparing PS2 to PS 0 – 1 was 1.95 (95% CI 1.54 – 2.48).

Discussion

Our results suggest PD1 and PDL1 immunotherapy increases OS and reduces risk of death from aNSCLC, based on numerous RCTs and observational studies with a relatively low risk of bias. This result replicates and builds upon previous reviews by demonstrating the impact of this therapy on OS is consistent both across study designs and at extended periods of follow up.

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We extended previous systematic reviews by looking at other outcomes in detail; however, benefits to PFS, AEs and QoL were less clear. While risk of progression or death was reduced by immunotherapy, benefits to average PFS were variable. Additionally, although a benefit to trAE incidence was observed among patients receiving immunotherapy, the overall profile of AEs was similar between immunotherapy and chemotherapy. Furthermore, immune-related AEs were more common among patients using PD1-targeting treatments. Compared to RCTs, the incidence of AEs among patients using immunotherapy in observational studies was lower, although a broader range of AEs was reported in these studies. The impact of PD1 and PDL1 immunotherapy on patient QoL was variable, and highly dependent on the choice of instrument used in each study. There was a notable lack of QoL data, particularly among observational studies.

These results highlight the importance of distinguishing between the biological impact of PD1 and PDL1 immunotherapy and the impact of study design on results. Differentiating these may improve study designs to capture these effects.

The absence of a clear association between OS and PFS could be explained by pseudo-progression, which is a phenomenon in which immune cells infiltrate the primary tumour causing an increase to tumour size that mimics tumour growth [118]. Although there is limited evidence to support this theory, Li et al. found that mice with induced lung tumours exposed to anti-PD1 therapy accumulated tumour-infiltrating-lymphocytes within their tumours [119]. Since the included studies measured progression via the RECIST 1.1 criteria, which relies upon changes in tumour diameter, they were potentially unable to distinguish pseudo-progressions from true disease progression [120]. However, this explanation less probable, given the consistent effect of immunotherapy on the risk of progression or death. More likely, the lack of association may be explained by aspects of study design. Particularly, some of the included trials may be affected by bias introduced by calculating PFS from censored data [121]. Furthermore, many studies recruited patients from multiple therapy lines. Patients receiving later lines are more likely to have a shorter PFS, which may have meant studies investigating these reported lower median survival results.

The variability of AEs between drugs and study designs may also be explained by the effect of study design. Given all four therapies have a similar molecular basis, it is unlikely the differences in AE incidence between drugs are attributable to pharmacological effects. However, the lack of restriction of patients based on ECOG PS in observational studies may have contributed to the broader range of AEs observed, as patients with a higher ECOG PS could have a greater propensity to develop AEs. Furthermore, the retrospective nature of many observational studies may have allowed greater flexibility in detecting AEs compared to RCTs.

The choice of QoL tool impacted QoL results. While EQ-5D, a non-specific tool, was associated with minimal changes to QoL, patients assessed via more lung cancer-specific tools such as LCSS experienced greater benefits, suggesting this therapy may yet impact QoL when the correct tool is used. There is currently little research investigating impact of choice of QoL instrument on results [122]. Some studies have argued that lower AE incidence is indicative of improved QoL. However, given that QoL is a proxy measure of patient experiences with their wellbeing and care, assessments of QoL should reflect this and not rely solely upon the absence of disease.

We also extend current knowledge of factors influencing patient prognosis. Increasing PDL1 expression was associated with a lower risk of death, and risk of progression or death. However, the significance of the current PDL1 threshold for accessing this therapy, ≥1% expression, was unclear. Presence of metastases and ECOG PS2 were associated with worse

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survival outcomes, while the impact of therapy line was not clear. It is unsurprising that presence of metastases and ECOG PS, which reflect patient health, were associated with poorer survival outcomes. However, it was more unexpected that having ≥1% expression did not confer a significant survival benefit. A potential reason for this may be that PDL1 expression is known to vary within tumours, and so samples of the tumour may not reflect overall tumour PDL1 expression. Therefore, there may have been insufficient PDL1 expression overall to experience a benefit among some patients, despite having ≥1% expression in their samples. This suggests more research is required to find the optimum threshold by which to stratify patients, or better ways to quantify PDL1 expression.

There are several limitations to the study. Firstly, some relevant abstract and ClinicalTrials.gov protocols could not be included due to the lack of methods and outcome data needed for analysis. Secondly, risk of publication bias among observational studies could not be assessed because too few studies reported HRs to be able to construct a funnel plot. The potential for publication bias limits the extent to which we can be confident results from observational studies represent patients in real clinical practice, as it is unknown whether outcomes of patients who do not benefit are underreported in available literature. Thirdly, the lack of comparative RCTs meant it was not possible to directly compare and confirm survival benefits observed between immunotherapies. Fourthly, it was not possible to meta-analyse the results from single arm observational studies, which prevented us from generating a summary estimate of treatment effectiveness from these studies. Finally, the study is hindered by the heterogeneity of the patient population. While we have explored some factors likely to affect patient outcomes, the variability in reporting the lines of therapy used in each study precluded our ability to fully explore the impact of this important factor. While our study had potential to be limited by comparing this therapy to chemotherapy solely recognised by NICE, we believe this is unlikely because NICE recommends a range of chemotherapy options in line with internationally accepted guidelines and evidence [13, 123, 124].

To conclude, among patients with aNSCLC, immunotherapy improved overall survival and incidence of treatment-related AEs compared to chemotherapy. Benefits to progression-free survival and QoL were less consistent. The variable effectiveness of this therapy to some outcomes and the expenses associated with its use suggest determining patients most likely to benefit is a key topic for future research or evidence syntheses.

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Contributor Statement

SSK was the lead author of the study. Roles included: planning study methods; writing the PROSPERO protocol; literature searches; screening study titles and abstracts; checking inclusions and exclusions, and bias assessments of relevant studies; data analysis and writing and editing the submitted manuscript.

The roles of AT were: screening study titles and abstracts, screening relevant studies, extracting data from included studies and completing the primary risk of bias assessments.

The roles of VS and PB were: screening relevant studies, extracting data from included studies and completing the primary risk of bias assessments.

The roles of MJP were: assisting in the editing of figures, assisting in the meta-analysis of data, and editing the submitted manuscript.

AMT was the supervisor of the study. Roles included: planning study methods, editing the PROSPERO protocol, screening study titles and abstracts, and writing and editing the submitted manuscript.

All authors commented on drafts of the article and have approved the final version.

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Competing Interests

None to declare. The views expressed are those of the authors and not necessarily those of the NHS, NIHR or the Department of Health and Social Care.

Ethics Statement

Ethical approval was not required for this study, because all data sourced and analysed were previously published anonymised patient data. No human participants were directly involved.

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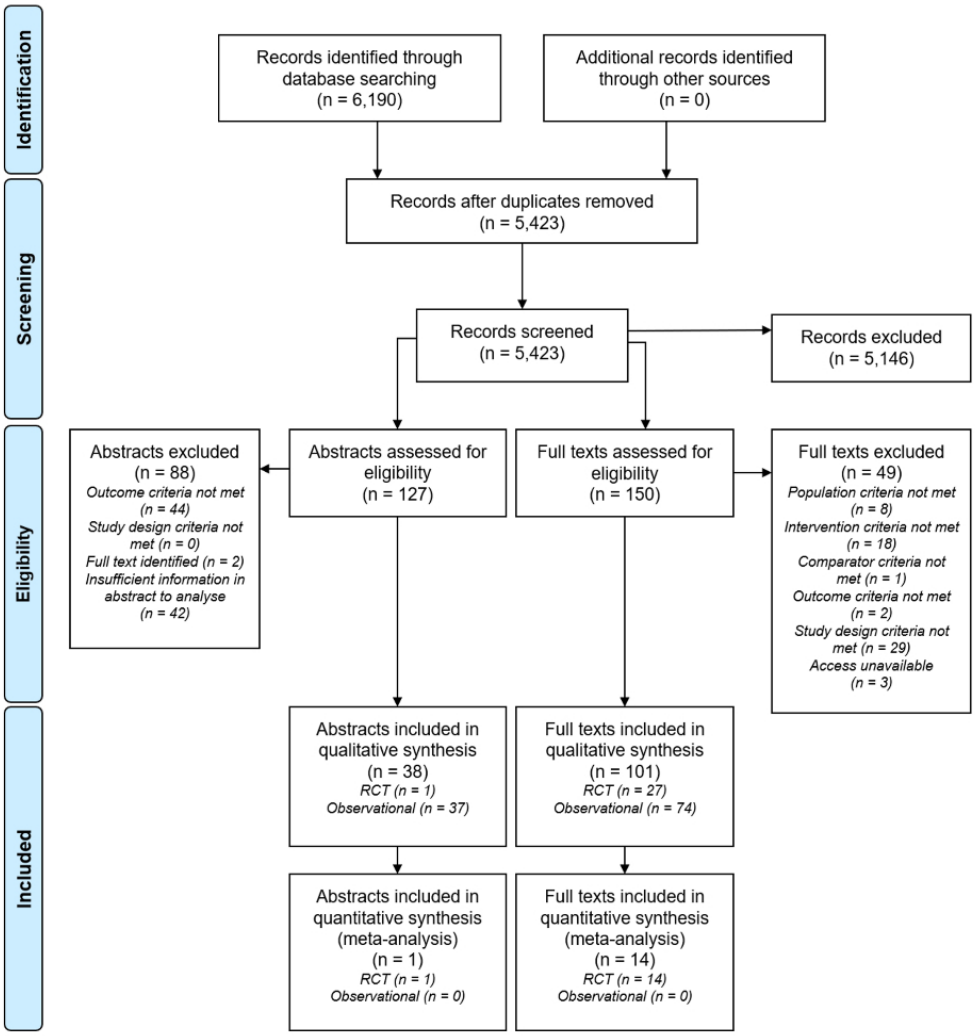

Figure 1 – PRISMA flow diagram of review Adapted from [29].

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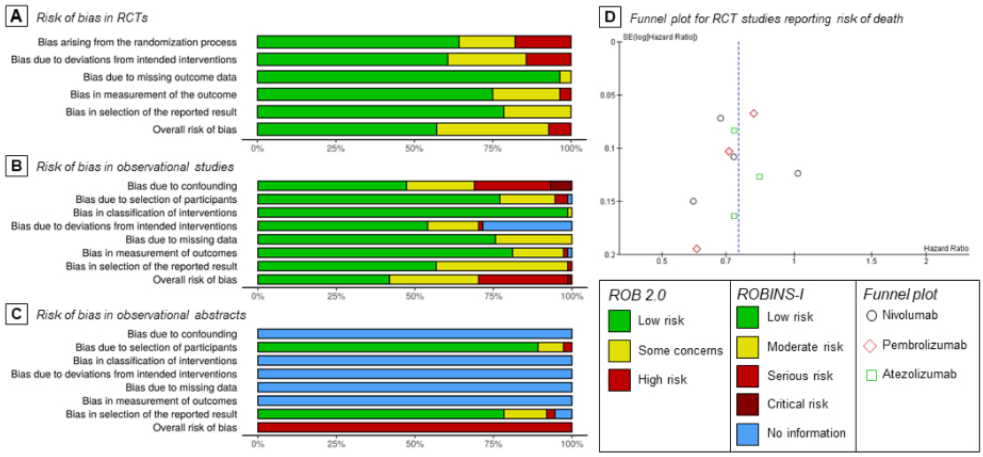

Figure 2 – Risk of Bias Assessment Summary A) Risk of bias summary bar chart for all included RCTs full texts and abstracts, assessed by ROB 2.0, B) Risk of bias summary bar chart for all included observational full texts, assessed by ROBINS-I, C) Risk of bias summary bar chart for all included observational abstracts, assessed by ROBINS-I, D) Funnel plot for publication bias, derived from HRs for overall survival at one year follow up from 10 RCTs. A 95% confidence region could not be plotted. This is because calculating a total risk from this data was not appropriate, as the included RCTs tested different interventions.

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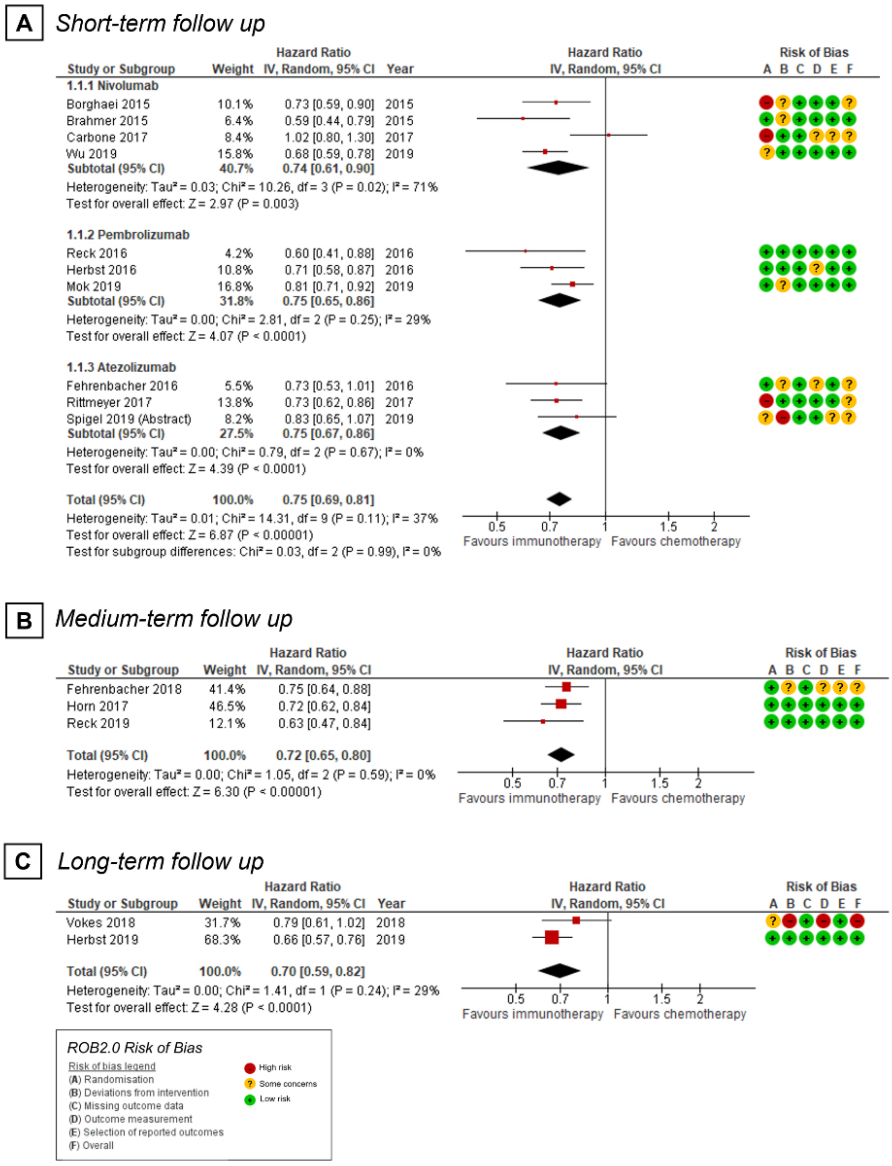

Figure 3 – Meta-analysed risk of death in RCTs A) Meta-analysed risk of death in studies with short-term follow up [30-37, 42, 47]. B) Meta-analysed risk of death in studies with medium-term follow up [38-40]. C) Meta-analysed risk of death in studies with long-term follow up [44, 45].

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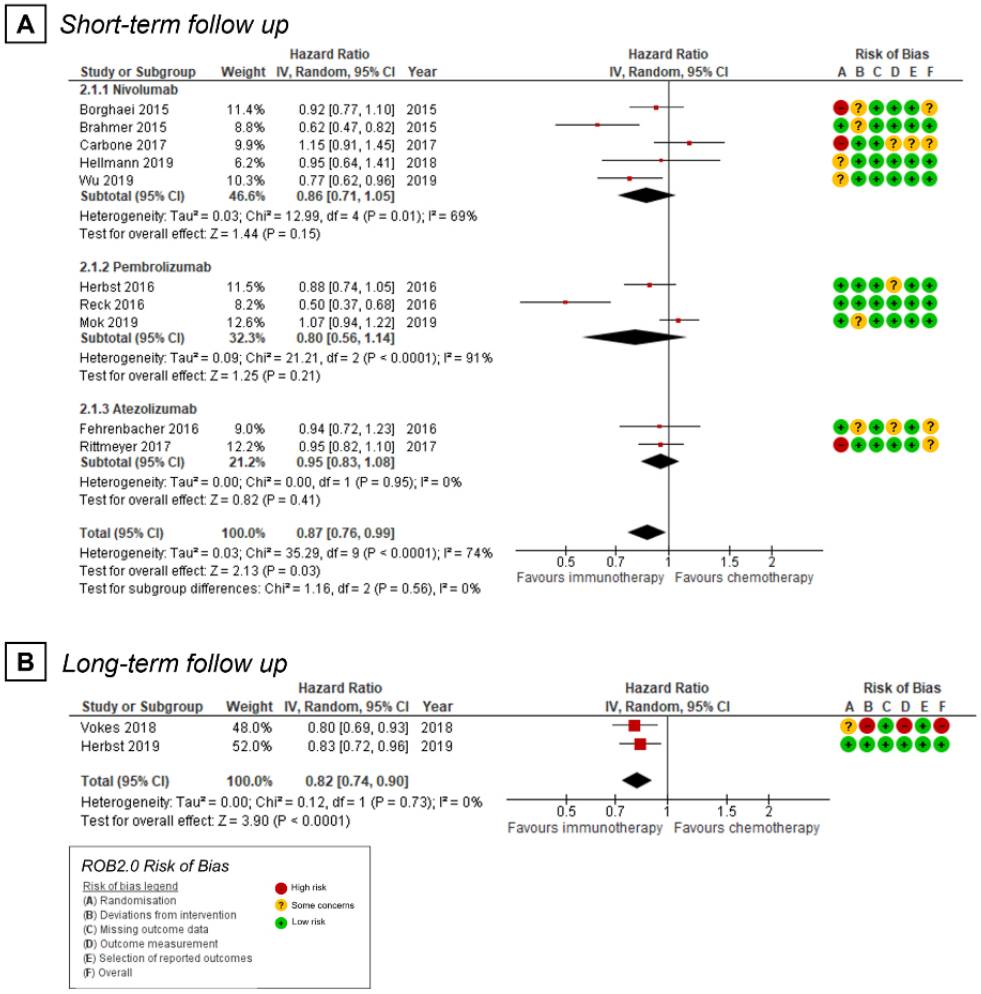

Figure 4 – Meta-analysed risk of progression or death in RCTs A) Meta-analysed risk of progression or death in RCTs with a short-term follow up [31-37, 42, 47, 96]. B) Meta-analysed risk of progression or death in RCTs with a long-term follow up [44, 45].

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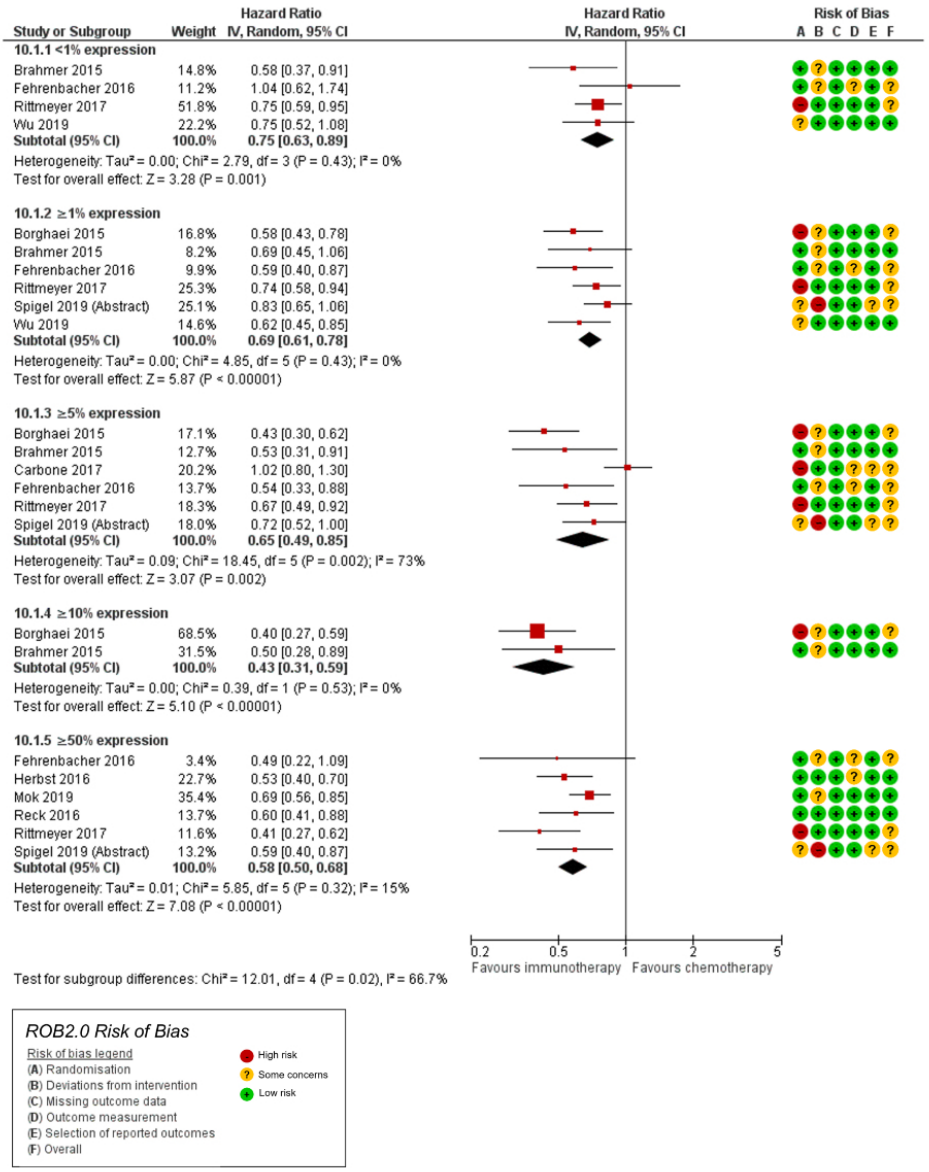

Figure 5 - Meta-analysis of risk of death by PDL1 expression status for patients receiving nivolumab, pembrolizumab or atezolizumab in included RCTs [30 – 37, 42, 47] Pembrolizumab data from patients with less than 50% expression could not be included, because a breakdown of survival outcomes was not provided between 1 – 49%.

79x98mm (300 x 300 DPI)

The impact of PD1 and PDL1 immunotherapy on NSCLC outcomes: a systematic review (Supplementary Material)

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Supplementary Methods

Literature Searches

Ovid Medline

1	("Programmed Death 1" or PD1 or PD-1 or "Programmed Death Ligand 1" or PDL1 or PD-L1).af.
2	(Immunotherap* or "Checkpoint inhibitors").af.
3	(Nivolumab or Pembrolizumab or Atezolizumab or Durvalumab).af
4	exp Lung Neoplasms/
5	((lung or pulmonary or bronchus or bronchial or bronchoalveolar or alveolar or "nonsmall cell" or "non small cell" or "non-small cell" or "non-small-cell" or "NSCLC" or squamous or "large cell") adj (cancer* or carcinom* or adenocarcinom* or malignan* or tumo$r* or neoplasm* or metasta*)).ti,ab.
6	exp Animals, Laboratory/
7	exp Animal Experimentation/
8	exp Models, Animal/
9	Or/6-8
10	1 or 2
11	4 and 5
12	3 and 10
13	11 and 12
14	13 not 9

Ovid EMBASE

1	("Programmed Death 1" or PD1 or PD-1 or "Programmed Death Ligand 1" or PDL1 or PD-L1).af.
2	(Immunotherap* or "Checkpoint inhibitors").af.
3	(Nivolumab or Pembrolizumab or Atezolizumab or Durvalumab).af
4	exp lung tumor/
5	((lung or pulmonary or bronchus or bronchial or bronchoalveolar or alveolar or "nonsmall cell" or "non small cell" or "non-small cell" or "non-small-cell" or "NSCLC" or "squamous" or "large cell") adj (cancer* or carcinom* or adenocarcinom* or malignan* or tumo$r* or neoplasm* or metasta*)).ti,ab.
6	exp experimental animal/
7	exp animal experiment/
8	exp animal model/
9	Or/6-8
10	1 or 2
11	4 and 5
12	3 and 10
13	11 and 12
14	13 not 9

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EBSCO CINAHL

S1	TX (“Programmed Death 1 OR PD1 or PD-1 OR “Programmed Death Ligand 1” OR PDL1 OR PD-L1)
S2	TX (Immunotherap* OR “Checkpoint inhibitors”)
S3	TX (Nivolumab OR Pembrolizumab OR Atezolizumab OR Durvalumab)
S4	MH (“Lung Neoplasms+”)
S5	TI (((lung or pulmonary or bronchus or bronchial or bronchoalveolar or alveolar or “nonsmall cell” or “non small cell” or “non-small cell” or “non-small-cell” or “NSCLC” or “squamous” or “large cell”) n2 (cancer* or carcinom* or adenocarcinom* or malignan* or tumo$r* or neoplasm* or metasta*))) OR AB (((lung or pulmonary or bronchus or bronchial or bronchoalveolar or alveolar or “nonsmall cell” or “non small cell” or “non-small cell” or “non-small-cell” or “NSCLC” or “squamous” or “large cell”) n2 (cancer* or carcinom* or adenocarcinom* or malignan* or tumo$r* or neoplasm* or metasta*)))
S6	MH (“Animals, Laboratory” OR “Models, Biological” OR “Animal Studies”)
S7	S1 OR S2
S8	S4 AND S5
S9	S3 AND S7
S10	S8 AND S9
S11	S10 NOT S6

Clinicaltrials.gov

Condition or disease	Non-small cell lung cancer
Other terms	None
Study type	All studies
Study results	All studies
Status	No filters applied to ‘Recruitment’ or ‘Expanded Access’
Eligibility criteria	• Age group filtered to ‘Adult (18 – 64)’ and ‘Older Adult (65+)’ • No filters applied to sex • ‘Accepts Healthy Volunteers’ not selected
Targeted search	• ‘Intervention/treatment’ defined as ‘Nivolumab’, ‘Pembrolizumab’, ‘Atezolizumab’ or ‘Durvalumab’ • No other search specifications
Locations	No filters applied
Additional criteria	No filters applied

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Cochrane Library

1	(“Programmed Death 1” or PD1 or PD-1 or “Programmed Death Ligand 1” or PDL1 or PD-L1)
2	(Immunotherap* or “Checkpoint inhibitors”)
3	(Nivolumab or Pembrolizumab or Atezolizumab or Durvalumab)
4	MeSH descriptor: [Lung Neoplasms] explode all trees
5	(lung or pulmonary or bronchus or bronchial or bronchoalveolar or alveolar or “nonsmall cell” or “non small cell” or “non-small cell” or “non-small-cell” or “NSCLC” or “squamous” or “large cell”):ti,ab,kw
6	(cancer* or carcinom* or adenocarcinom* or malignan* or tumo$r* or neoplasm* or metasta*):ti,ab,kw
7	#5 and #6
8	MeSH descriptor: [Animals, Laboratory] explode all trees
9	MeSH descriptor: [Animal Experimentation] explode all trees
10	MeSH descriptor: [Models, Animal] explode all trees
11	#8 or #9 or #10
12	#1 or #2
13	#4 and #7
14	#3 and #12
15	#13 and #14
16	#15 not #11

NICE Evidence Search

Search terms	Nivolumab, pembrolizumab, atezolizumab or durvalumab AND Non-small cell lung cancer
Filters	No filters applied on search results

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Data fields collected from included studies

Author details	Author name, conflicts of interest, funding declaration	
Population	Eligibility criteria	Patient criteria, disease criteria, previous intervention criteria, any other relevant criteria
	Baseline characteristics	Participant number, average age (including whether a mean or a median was reported), proportion of patients who were male, proportion of patients who were Caucasian or from an ethnic minority, proportion of patients with a smoking history, recruitment setting
	Disease features	Proportion of patients with squamous NSCLC, adenocarcinoma, large cell carcinoma, or undifferentiated carcinoma; stages of disease and the proportion of patients with each stage; percentage PDL1 expression, and the proportion of patients in each classification
Intervention	Drug name, drug dose, drug administration regimen, route of administration, duration of drug administration, person administering the drug and whether they were an investigator, administration setting, intervention integrity	
Comparator	Drug name, drug dose, drug administration regimen, route of administration, duration of drug administration, person administering the drug and whether they were an investigator, administration setting	
Outcomes	OS, PFS, AEs, QoL, cost-effectiveness, number of deaths and number of hospitalisations, and progression to metastases. For each outcome, the method used to ascertain the outcome and uncertainty was also collected. Free text space was used to enable collection of additional relevant but unexpected outcomes.	
Study design	For randomised controlled trials (RCTs): Method of sampling, dates of recruitment period, length of recruitment period, randomisation method, method of blinding, methods to prevent bias, length of follow up, method of data analysis, analyses to reduce potential for bias such as intention-to-treat analysis	For observational studies: Type of study, method of patient identification, dates of recruitment period, length of recruitment, methods to prevent bias, length of follow up, method of data analysis, analyses to reduce bias

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Supplementary Results

Characteristics of Included Studies

Included RCT studies

Trial	Author	Trial arms	Population						Follow up (months)	Outcomes
			Patients	%male	Age (yrs)[1]	%White	Histology	Stages		
CheckMate 017	Brahmer et al, 2015 [31]	Nivolumab 3mg/kg per 2 weeks, 2nd line	272	82	62 (39-85)	90	Sq[2] = 100%	IIIB, IV	11.0 minimum	OS, PFS, AEs
		Docetaxel 75mg/m^2 per 3 weeks, 2nd line		71	64 (42-85)	95				
CheckMate 057	Borghaei et al, 2015 [33]	Nivolumab 3mg/kg per 2 weeks, 2nd line	582	52	61 (37-84)	91	NSq[3] = 100%	IIIB, IV	13.2 minimum	OS, PFS, AEs, deaths
		Docetaxel 75mg/m^2 per 3 weeks, 2nd line		58	64(21-85)	92				

[1] Median and range unless otherwise specified
[2] Squamous
[3] Non-squamous

Trial	Author	Trial arms	Population						Follow up (months)	Outcomes
			Patients	%male	Age (yrs)	%White	Histology	Stages		
CheckMate 057	Reck et al, 2018 [108]	Nivolumab 3mg/kg per 2 weeks, 2nd line	582	52	61 (37-84)	91	NSq = 100%	IIIB, IV	Not specified	QoL, AEs
		Docetaxel 75mg/m^2 per 3 weeks, 2nd line		58	64(21-85)	92				
CheckMate 017+057	Horn et al, 2017 [38]	Nivolumab 3mg/kg per 2 weeks, 2nd line	854	Reported previously [31, 33]				IIIB, IV	24.2 minimum	OS, PFS, AEs (2-year outcomes)
		Docetaxel 75mg/m^2 per 3 weeks, 2nd line								
	Vokes et al, 2018 [44]	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	418	Reported previously [31, 33]				IIIB, IV	36.0 minimum	OS, PFS, AEs (3-year outcomes)
		Docetaxel 75mg/m^2 per 3 weeks, 2nd line or later	.							

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Trial	Author	Trial arms	Population						Follow up (months)	Outcomes
			Patients	%male	Age (yrs)	%White	Histology	Stages		
CheckMate 017+057	Antonia et al, 2019 [46]	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	854	Reported previously [31, 33]			Sq = 31% NSq = 69%	IIIB, IV	51.6 minimum	OS, PFS, AEs (4-year outcomes)
		Docetaxel 75mg/m^2 per 3 weeks, 2nd line					Sq = 32% NSq = 68%			
CheckMate 026	Carbone et al, 2017 [32]	Nivolumab 3mg/kg per 2 weeks, 1st line	541	68	63 (32-89)	.	Sq = 24% NSq = 76%	IV, recurrent	13.7 median	OS, PFS, deaths, AEs
		Investigator's-choice chemotherapy, per 3 weeks, 1st line		55	65 (29-87)					

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Trial	Author	Trial arms	Population						Follow up (months)	Outcomes
			Patients	%male	Age (yrs)	%White	Histology	Stages		
CheckMate 078	Wu et al, 2019 [37]	Nivolumab 3mg/kg per 2 weeks, 1st or 2nd line	504	78	60 (27-78)	.	Sq = 39% NSq = 61%	IIIB, IV, recurrent	11.2 median, 8.8 minimum	OS, PFS, AEs
		Docetaxel 75mg/m^2 per 3 weeks, 1st – 3rd line		81	60 (38-78)	.	Sq = 40% NSq = 60%			
CheckMate 227	Hellmann et al, 2018 [95]	Nivolumab 240mg per 2 weeks, 1st line	793	68.7	64 (27-85)	.	Sq = 29.5% NSq = 70.5%	IV, recurrent	11.2 minimum	PFS, AEs, deaths
		Chemotherapy according to histology, 1st line		65.5	64 (29-87)	.	Sq = 29.2% NSq = 70.8%			
	Hellmann et al, 2019 [96]	Nivolumab 240mg per 2 weeks, 1st line	793	68.7	64 (27-85)	.	Sq = 29.5% NSq = 70.5%	IV, recurrent	29.3 minimum	OS, PFS
		Chemotherapy according to histology, 1st line		65.5	64 (29-87)	.	Sq = 29.2% NSq = 70.8%			

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Trial	Author	Trial arms	Population						Follow up (months)	Outcomes
			Patients	%male	Age (yrs)	%White	Histology	Stages		
Keynote 010	Herbst et al, 2016 [34]	Pembrolizumab, 2mg/kg per 3 weeks, 2nd line or later	1034	62	63 (56-69)	72	Sq = 22% NSq = 70%	Advanced	13.2 median, 8.0 minimum	OS, PFS, deaths, AEs
		Pembrolizumab, 10mg/kg per 3 weeks, 2nd line or later					Sq = 23% NSq = 71%			
		Docetaxel 75mg/m^2 per 3weeks, 2nd line or later		61	62 (56-69)	73	Sq = 19% NSq = 70%			
	Herbst et al, 2019 [45]	Pembrolizumab, 2 or 10mg/kg per 3 weeks, 1st line or later	1033	62	63 (20-88)	72	Sq = 23% NSq = 70%	Locally advanced and metastatic	31.0 median	OS, PFS, AEs
		Docetaxel 75mg/m^2 per 3 weeks, 1st line or later		61	62 (33-82)	73	Sq = 19% NSq = 70%			

Trial	Author	Trial arms	Population						Follow up (months)	Outcomes
			Patients	%male	Age (yrs)	%White	Histology	Stages		
Keynote 024	Reck et al, 2016 [47]	Pembrolizumab 200mg per 3 weeks, 1st line	305	59.7	64.5 (33-90)	.	Sq = 18.8% NSq = 81.2%	IV	11.2 median	OS, AEs
		Investigator's choice chemotherapy, 1st line		62.9	66.0 (38-85)	.	Sq = 17.9% NSq = 82.1%			
	Reck et al, 2019 [39]	Pembrolizumab 200mg per 3 weeks, 1st line	305	59.7	64.5 (33-90)	.	Sq = 18.8% NSq = 81.2%	IV	25.2 median	OS, deaths, AEs (2-year outcomes)
		Investigator's choice chemotherapy, 1st line		62.9	66.0 (38-85)	.	Sq = 17.9% NSq = 82.1%			
	Brahmer et al, 2017 [109]	Pembrolizumab 200mg per 3 weeks, 1st line	305	Reported previously [47]				Advanced	6.0 minimum	QoL, deaths
		Investigator's choice chemotherapy, 1st line								

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Trial	Author	Trial arms	Population						Follow up (months)	Outcomes
			Patients	%male	Age (yrs)	%White	Histology	Stages		
Keynote 042	Mok et al, 2019 [35]	Pembrolizumab, 200mg per 3 weeks, 1st line	1274	71	63.0 (57-69)	.	Sq = 38% NSq = 62%	Locally advanced and metastatic	12.8 minimum	OS, PFS, AEs deaths
		Carboplatin (5-6mg/mL/min) + Paclitaxel (200mg/m^2) OR Pemetrexed (500mg/m^2), 1st line		71	66.0 (38-85)	.	Sq = 39% NSq = 61%			
OAK	Rittmeyer et al, 2017 [42]	Atezolizumab 1200mg per 3 weeks, 2nd or 3rd line	850	61	63.0 (33-82)	71	Sq = 26% NSq = 74%	IIIB, IV	21.0 median	OS, PFS, AEs, deaths for ITT850 population
		Docetaxel 75mg/m^2 per 3 weeks, 2nd or 3rd line		61	64.0 (34-85)	70	Sq = 26% NSq = 74%			

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Trial	Author	Trial arms	Population						Follow up (months)	Outcomes
			Patients	%male	Age (yrs)	%White	Histology	Stages		
OAK	Fehrenbacher et al, 2018 [40]	Atezolizumab 1200mg per 3 weeks, 2nd line or later	1225	61.8	63.0 (25-84)	71.5	Sq = 26.3% NSq = 73.7%	Advanced	21.0 minimum, 26.0 median	OS, PFS, AEs, deaths for ITT1225 population
		Docetaxel 75mg/m^2 per 3 weeks, 2nd line or later		61.9	64.0 (34-85)	70.6	Sq = 26.1% NSq = 73.9%			
	Bordoni et al, 2018 [111]	Atezolizumab 1200mg per 3 weeks, 2nd line or later	850	Reported previously [42]				Locally advanced and metastatic	.	QoL
		Docetaxel 75mg/m^2 per 3 weeks, 2nd line or later								
	Hida et al, 2018 [41]	Atezolizumab 1200mg per 3 weeks, 2nd line or 3rd line	64 efficacy, 101 safety	52.8	63.5 (33-77)	0	Sq = 22.2% NSq = 77.8%	Locally advanced or metastatic	19.4 minimum, 21.0 median	OS, PFS, AEs

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		Docetaxel 75mg/m^2 per 3 weeks, 2nd line or 3rd line		67.9	58.5 (34-79)	0	Sq = 21.4% NSq = 78.6%			

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Trial	Author	Trial arms	Population						Follow up (months)	Outcomes
			Patients	%male	Age (yrs)	%White	Histology	Stages		
OAK	Gadgeel et al, 2019 [117]	Atezolizumab 1200mg per 3 weeks, 2nd or 3rd line	850	62.4	63.5 (33-82)	.	Sq = 28.3% NSq = 71.7%	.	21.0 median	OS, AEs
		Docetaxel 75mg/m^2 per 3 weeks, 2nd or 3rd line		62.3	64.0 (34-95)	.	Sq = 28.1% NSq = 71.9%			
POPLAR	Fehrenbacher et al, 2016 [36]	Atezolizumab 1200mg per 3 weeks, 2nd or 3rd line	287	65.0	62.0 (42-82)	.	Sq = 34% NSq = 66%	.	14.8 median	OS, PFS, AEs, deaths
		Docetaxel 75mg/m^2 per 3 weeks, 2nd or 3rd line		53.0	62.0 (36-84)	.	Sq = 34% NSq = 66%		15.7 median	

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Trial	Author	Trial arms	Population						Follow up (months)	Outcomes
			Patients	%male	Age (yrs)	%White	Histology	Stages		
IMPower110	Spigel et al, 2019 (abstract) [31]	Atezolizumab 1200mg per 3 weeks, line not reported	572	Not reported				IV	15.7 median	OS, AEs
		Chemotherapy according to histology, line not reported								
PACIFIC	Antonia et al, 2017 [94]	Durvalumab 10mg/kg per 2 weeks, 2nd line or later	713	70.0	64.0 (23-39)	66.2	Sq = 43.0% NSq = 57.0%	IIIA, IIIB	14.5 median	PFS, AEs
		Placebo per 2 weeks, 2nd line or later		70.2	64.0 (31-84)	70.8	Sq = 47.1% NSq = 52.9%			
	Antonia et al, 2018 [43]	Durvalumab 10mg/kg per 2 weeks, line not specified	713	70.0	64.0 (23-39)	66.2	Sq = 43.0% NSq = 57.0%	IIIA, IIIB	25.2 median	OS, PFS, AEs (2-year outcomes)

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		Placebo per 2 weeks, line not specified		70.2	64.0 (31-84)	70.8	Sq = 47.1% NSq = 52.9%			
	Hui et al, 2019 [110]	Durvalumab 10mg/kg per 2 weeks, line not specified	713	Reported previously [94]				IIIA, IIIB	25.2 median	QoL
		Placebo per 2 weeks, line not specified								

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Included RCT studies with breakdown by patient characteristics

Trial	Author	Trial arms	Population						Follow up (months)	Outcomes
			Patients	%male	Age (yrs)	%White	Histology	Stages		
Keynote 010+024+042	Nosaki et al, 2019 [105]	Pembrolizumab 2 or 10mg/kg or 200mg per 3 weeks, patients ≥75yrs, 1st – 3rd line	3510	67.1	77.0 (75-90)	68.5	Sq = 36.9% NSq = 61.1%	Advanced	11.7 median	OS, AEs, deaths, comparing outcomes of elderly to younger patients
		Pembrolizumab 2 or 10 mg/kg or 200mg per 3 weeks, patients <75yrs, 1st – 3rd line		65.1	62.0 (31-74)	68.6	Sq = 28.0% NSq = 68.6%			
		Platinum-based chemotherapy, patients ≥75yrs, 1st – 3rd line		63.5	77.0 (75-90)	61.7	Sq = 24.3% NSq = 70.4%			
		Platinum-based chemotherapy, patients <75yrs. 1st – 3rd line		67.2	62.0 (20-74)	70.7	Sq = 30.9% NSq = 66.0%			

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Trial	Author	Trial arms	Population						Follow up (months)	Outcomes
			Patients	%male	Age (yrs)	%White	Histology	Stages		
OAK	Von Pawel et al, 2019 [106]	Atezolizumab 1200mg per 3 weeks, [45], 2nd or 3rd line	774	51.0	63.0 (35-81)	71.0	Sq = 16% NSq = 84%	IIIB, IV	28.0 median, 26.0 minimum	OS, PFS, AEs (2-year outcomes)
		Atezolizumab 1200mg per 3 weeks, non-LTS, 2nd or 3rd line		66.0	64.0 (33-82)	74.0	Sq = 30% NSq = 70%			
		Docetaxel 75mg/m^2 per 3 weeks, LTS, 2nd or 3rd line		58.0	62.0 (41-84)	68.0	Sq = 16% NSq = 84%			
		Docetaxel 75mg/m^2 per 3 weeks, LTS, 2nd or 3rd line		62.0	64.0 (34-85)	73.0	Sq = 30% NSq = 70%			

[5] LTS = Long-term survivors, defined as patients who lived ≥ 24 months from randomisation

Included observational studies, intervention only assessed

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Alama et al, 2019 [77]	Cohort study	89	70.8	67.0 (44-86)	Italy, 1 centre	Sq = 28.0%, Ad = 70.8%	Advanced	Nivolumab 3mg/kg per 2 weeks, 1st line or later	.	OS, deaths, impact of circulating tumour cells and cfDNA
Bagley et al, 2017 [78]	Cohort study	175	46	68.0 (33-88)	USA, 1 centre	Sq = 24%, NSq = 76%	Advanced, previously treated	Nivolumab 3mg/kg per 2 weeks, 1st line or later	.	OS, PFS, AEs
Bins et al, 2018 [128]	Cohort study	161	67	64, σ 8.1[6]	Holland, 2 centres	Sq = 29%, Ad[7] = 60%, LC[8] = 9%, Ud[9] = 1%	Previously untreated	Nivolumab 3mg/kg per 2 weeks, 1st line or later	~4.2	AEs, deaths, impact of SNPs

[6] Mean (standard deviation)
[7] Adenocarcinoma
[8] Large cell carcinoma
[9] Undifferentiated

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Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Brustugun et al, 2017 [62]	Cohort study	58	48.3	64.6 (32-88)	Norway, 1 centre	Sq = 41.4%, Ad = 55.2%, LC = 1.7%	Metastatic	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	15.6 median	OS, AEs
Crinò et al, 2019a [49]	Cohort study	1588	65	66.0 (27-89)	Italy, 153 centres	NSq = 100%	Stages IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 1st line or later	6.1 median	OS, PFS, deaths, AEs, impact of CNS metastases
Crinò et al, 2019b [48]	Cohort study	371	80	68.0 (33-88)	Italy, 96 centres	Sq = 100%	Stages IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	7.1 median	OS, PFS, deaths, AEs, impact of ECOG PS and metastases
Diem et al, 2017 [80]	Cohort study	52	56	66.2 (45.5-88.2)	Switzer-land, 1 centre	Sq = 35%, Ad = 58%	Metastatic, previously treated	Nivolumab 3mg/kg per 2 weeks, 1st line or later	0 – 14 (range only)	OS, PFS, deaths, impact of NLR and PLR

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Dudnik et al, 2018 [63]	Cohort study	260	68	67.0 (41-99)	Israel, 5 centres	Sq = 23%, NSq = 70%, NOS[10] = 6%	Advanced, mostly stage IV or recurrent	Nivolumab 3mg/kg per 2 weeks, 2nd line	8.4 median	OS, PFS, deaths, AEs, impact of ECOG PS on OS
Dumenil et al, 2018 [79]	Cohort study	67	69	68.5 (60-77)	France, 2 centres	Sq = 25%, Ad = 70%, NOS = 5%	Stage IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 1st or 2nd line	.	OS, PFS, AEs, histology, metastases, and ECOG PS
Dusselier et al, 2019 [134]	Cohort study	59	75	59.3 (30.3-87.3)	France, 2 centres	Sq = 20%, NSq = 80%	Advanced, pre-treated	Nivolumab 3mg/kg per 2 weeks, 2nd line	.	Impact of tumour histology, NLR, ALC, and ANC

[10] Not otherwise specified

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Edahiro et al, 2019 [99]	Cohort study	149	83.2	71.0 (39-87)	Japan, 11 centres	Sq = 23.5%, NSq = 76.5%	Stage III or IV	Pembro-lizumab, 1st line	.	Impact of PDL1 TPS, AEs
Fujita et al, 2019 [135]	Cohort study	32 (patient with infection only)	78.1	69.8, σ 12.2	Japan, 2 centres	NSq = 78.1%	Stage IV	Nivolumab, 2nd line or later	.	AEs
Fukihara et al, 2019 [136]	Cohort study	170	73.5	With IRP: 67.0 (58-73)	Japan, 3 centres	Sq = 30% NSq = 70%	Advanced or recurrent	Nivolumab 3mg/kg per 2 weeks, 1st line or later	9.9 median	Impact of drug used on risk of IRP[11]
				No IRP: 70.0 (63-73)		Sq = 36% NSq = 64%		Pembroli-zumab 200mg per 3 weeks, 1st line or later		

[11] Immune-related pneumonitis

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Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Fukui et al, 2018 [125]	Cohort study	52	71	69.0 (46-83)	Japan, 1 centre	Sq = 31%, Ad = 63%, NOS = 6%	Stages IIIA, IIIB, IVA, IVB or recurrent	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	10.9 median	PFS, deaths, AEs, impact of histology, ECOG PS, PDL1 TPS and NLR
Garassino et al, 2018 [50]	Cohort study	371	80	68.0 (31-91)	Italy, 96 centres	Sq = 100%	Stage IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 2nd line	7.1 median	OS, PFS, deaths, AEs
Garde-Noguera et al, 2018 [81]	Cohort study	175	73.1	61.5[12]	Spain, 14 centres	Sq = 22.9%, NSq = 77.1%	Stage III, IVA, or IVB	Nivolumab 3mg/kg, 2nd line or later	.	OS, PFS, deaths and AEs, impact of histology, ECOG PS, metastases

[12] No range provided

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Garon et al, 2015 [72]	Phase I trial akin to cohort study	495	64	64.0 (28-93)	Europe, Australia, Asia, USA	Sq = 17.2%, Ad = 1.4%, NSq = 81.0%	Advanced or metastatic	Pembro-lizumab 2mg/kg per 3 weeks, 2nd line	10.9 median	OS, PFS, AEs, impact of PDL1 TPS
Garon et al, 2019 [76]	Phase I trial akin to cohort study	550	Rx-naïve[13]: 59	Rx-naïve: 68.0 (39-93)	.	Rx-naïve: Sq = 19%, NSq = 78%, NOS = 3%	Advanced or metastatic	Pembro-lizumab 2mg/kg per 3 weeks OR 10mg/kg per 2 weeks, then 200mg per 3 weeks, 1st line or later	60.6 median	OS, deaths, AEs, impact of EGFR mutation, histology, and PDL1 TPS (5-year outcomes)
			Pre-treated: 51	Pre-treated: 62.0 (28-85)		Pre-treated: Sq = 17%, NSq = 82%, NOS = 1%				

[13] Therapy-naïve

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Gauvain et al, 2018 [97]	Cohort study	43	76	59.5, σ 8.4[14]	France, 2 centres	Sq = 16%, Ad = 82%	Advanced or metastatic	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	5.8 median	PFS, deaths, AEs
Geier et al, 2018 [64]	Cohort study	259	72.2	62.0 (29-85)	France, 9 centres	Sq = 27%, Ad = 63.7%, Ud = 6.9%	Stage IIIB or IV	Nivolumab 3mg/kg per 15 days, 2nd line	17.7 median	OS, PFS, AEs, impact of histology and irAEs
Grossi et al, 2018 [65]	Cohort study	371	80	68.0 (31-91)	Italy, 96 centres	Sq = 100%	Stage IIIB or IV	Nivolumab 3mg/kg per 2 weeks, line not reported	7.5 median	OS, PFS, AEs, impact of age and ECOG PS
Haratani et al, 2017 [59]	Cohort study	25	48	69.0 (42-78)	Japan, 3 centres	Ad = 96%, AdSq[15] = 4%	Stage IIIB, IV or recurrent; EGFR-mutation positive	Nivolumab, 1st – 3rd line	7.3 median	OS, PFS, impact of T790 mutation and PDL1 TPS

[14] Mean (standard deviation)
[15] Adeno-squamous

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Haratani et al, 2018 [56]	Cohort study	134	67	68.0 (33-85)	Japan, 4 centres	Sq = 25%, NSq = 75%	Stage IIIB, IV or recurrent	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	4 weeks, 6 weeks and 8 weeks	OS and PFS, AEs, impact of skin and endocrine AEs
Hasan Ali et al, 2016 [127]	Cohort study	40	55	65.5 (46-88)[16]	Switzer-land, 1 centre	Sq = 35%, Ad = 57%	Metastatic	Nivolumab 3mg/kg per 2 weeks, 1st line or later	.	AEs, deaths
Inoue et al, 2018 [129]	Cohort study	201	67.2	68.0 (27-87)	Japan, 3 centres	Sq = 20.9%, Ad = 70.6%	Advanced, un-resectable	Nivolumab 3mg/kg per 2 weeks, 2nd – 4th lines	.	Deaths, AEs, impact of ECOG PS and CRP /albumin

[16] Mean (range)

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Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Kaderbhai et al, 2017 [82]	Cohort study	115	77	66, σ 10[17]	France, 3 centres	Sq = 36.4%, Ad = 60%, LC = 1.7%	Stage IIIB or IV, previously treated	Nivolumab 3mg/kg per 2 weeks, 1st line	.	OS, PFS, impact of initial best response to 1st line therapy
Kanai et al, 2018 [100]	Cohort study	216	71	69.0 (30-89)	Japan, 3 centres	Sq = 27%, Ad = 62%	Advanced/recurrent, pre-treated	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	.	PFS, AEs
Karantanos et al, 2019 [137]	Cohort study	22	54.5	62, σ 9.37[18]	USA, 1 centre	Sq = 45.5%, Ad = 54.5%	Stage III or IV, pre-treated	Nivolumab 3mg/kg per 2 weeks, 2nd – 4th line	.	OS[19]

[17] Mean (standard deviation)
[18] Mean (standard deviation)
[19] Mean (standard deviation)

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Katsura et al, 2019 [60]	Cohort study	99	ECOG PS2-4: 80	ECOG P2 2-4: 69.0 (55-84)	Japan, 2 centres	ECOG PS 2-4: Sq = 45% Ad = 45%	Advanced or recurrent	Nivolumab 3mg/kg per 2 weeks, 2nd line	~3 months	OS, PFS, AEs
			ECOG PS 0-1: 84	ECOG PS 0-1: 70.0 (48-90)		ECOG PS 0-1: Sq = 42% Ad = 53%				
			PC[20]: 50	PC: 74.0 (44-91)		PC: Sq = 14% Ad = 81%				
Kawachi et al, 2019 [90]	Cohort study	31	71	69.0 (41-92)	Japan, 1 centre	Sq = 19%, Ad = 77%	Stage IIIB or IV	Nivolumab, 2nd line or later	.	OS, PFS

[20] Palliative care patients

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Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Kobayashi et al, 2017 [101]	Cohort study	50	60	67.0 (34-85)	Japan, 1 centre	Sq = 12%, NSq = 88%	Stage III, IV or recurrent	Nivolumab 3mg/kg per 2 weeks, 1st line	.	PFS
Kobayashi et al, 2018 [102]	Cohort study	142	74.6	67.0 (34-85)	Japan, 13 centres	Sq = 28.9%, Ad = 58.5%, LC = 2.8%, Ud = 6.3%	Stage III or IV	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	.	PFS, deaths, AEs, impact of EGFR or ALK mutation
Krefting et al, 2019 [98]	Cohort study	40	75.0	65.0 (59-82)	Germany	Sq = 100%	Stage IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	20.0 median	PFS, AEs
Ksienski et al, 2019a [66]	Cohort study	190	51.5	70.0 (41-91)	USA, 6 centres	Sq = 22.1%	Stage IIIB, IV or recurrent	Pembro-lizumab 2mg/kg per 3 weeks, 1st line or later	6.1 median	OS, PFS, deaths, AEs, impact of ECOG PS

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Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Ksienski et al, 2019b [57]	Retrospective cohort study	271	50.4	64.0 (39-82)	USA	Sq = 25.7%, NSq = 74.3%	Stage IV	Nivolumab 3mg/kg per 2 weeks, 1st line or later	8.1 median	OS, PFS, deaths, AEs, impact of treatment interruption and colitis
			51.2	68.0 (50-81)		Sq = 19.5%, NSq = 80.5%		Pembro-lizumab 2mg/kg per 3 weeks, 1st line or later		
Lacerenza et al, 2019 [83]	Cohort study	20	85	67.0 (43-81)	Italy	Sq = 30%, Ad = 70%	Stage IIIB or IV	Nivolumab, 2nd line	.	OS, PFS, AEs, Impact of PDL1 expression on OS

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Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Leighl et al, 2019 [75]	Phase I trial akin to cohort study	550	Rx-naïve: 59.0	Rx-naïve: 68.0 (59-74)	.	Rx-naïve: Sq = 19%, NSq = 78%, NOS = 3%	Stage IV	Pembrolizumab 2mg/kg per 3 weeks, 1st line or later	34.5 median	OS, PFS, deaths, AEs, impact of PDL1 TPS, and previous Rx, (3-year outcomes)
			Pre-treated: 51.0	Pre-treated: 62.0 (54-70)		Pre-treated: Sq = 17%, NSq = 82%, NOS = 1%		Pembrolizumab 10mg/kg per 2 weeks, 1st line or later		
Lisberg et al, 2018 [92]	Cohort study	97	trAE: 56.0	trAE: 67.0 (32-87)	USA, 1 centre	trAE: Sq = 21%	Stage IV	Pembrolizumab 2mg/kg per 3 weeks, 1st line or later	.	OS, PFS, AEs, impact of trAEs on OS and PFS
			Non-trAE: 48.0	Non-trAE: 65.0 (36-83)		Non-trAE: Sq = 19%		Pembrolizumab 10mg/kg per 2 weeks, 1st line or later		

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Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Liu et al, 2019 [51]	Cohort study	44	75.0	60.0 (43-74)	China, 1 centre	Sq = 29.5%, Ad = 70.5%	Stage IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	6.9 median	OS, PFS, deaths, AEs, impact of blood inflammation markers
Manrique et al, 2018 [107]	Cohort study	188	77.0	58.0 (45-81)	Spain, 9 centres	Sq = 35%, Ad = 60%, Ud = 5%	Stage IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 1st – 6th line	.	OS, PFS, deaths, hospital-isations, AEs, impact of ECOG PS
Merino Almazan et al, 2019 [84]	Cohort study	221	77.0	64.5 (σ 9.2)[21]	Spain, 15 centres	Sq = 59.7%, NSq = 40.3%	Stage I, II, III and IV	Nivolumab 3mg/kg per 2 weeks, 1st line or later	.	OS, PFS, cost-effectiveness, deaths, AEs, impact of ECOG PS

[21] Mean and standard deviation

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Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Montana et al, 2019 [85]	Cohort study	98	71.4	65.5 (42-85.6)	France	Sq = 21.4%, NSq = 78.6%	Stage IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 1st – 4th lines	.	OS, PFS, AEs, impact of ECOG PS on OS
Naqash et al, 2018 [86]	Cohort study	87	64.4	64.0 (35-85)	USA, 1 centre	Sq = 44.8%, Ad = 49.4%	Stage III or IV	Nivolumab, 2nd line	.	OS, AEs, impact of CRP, NLR, and prognostic scores
Nomizo et al, 2017 [138]	Cohort study	50	68	65.0 (40-80)	Japan	Sq = 20%, Ad = 80%	Stage IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 2nd line	.	PFS, impact of SNPs
Okuma et al, 2018 [139]	Cohort study	39	74.4	69.0 (50-88)	Japan, 2 centres	Sq = 17.9%, Ad = 71.8%, LC = 5.1%, Ud = 5.1%	Stage IV or recurrent	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	.	Impact of soluble PDL1 on OS

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Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Osorio et al, 2017 [93]	Cohort study	51	No thyroid disorder: 39.1 Thyroid disorder: 50.0	No thyroid disorder: 63.0 (35-93) Thyroid disorder: 59.0 (39-80)	USA, 1 centre	No thyroid disorder: Ad = 85% Thyroid disorder: Ad = 70%	Stage IV	Pembro-lizumab 2mg/kg per 3 weeks, 1st line or later	.	OS, PFS, AEs
Oya et al, 2017 [52]	Cohort study	124	70.0	66.0 (37-79)	Japan, 1 centre	Sq = 22%, Ad = 65%, Ud = 13%	Stage IV	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	6.0 median	OS, PFS, deaths. Impact of PDL1, EGFR, KRas, LDH, CRP and histology

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Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Oyanagi et al, 2019 [140]	Cohort study	38	74.0	68.5 (49-86)	Japan, 1 centre	Sq = 29%, NSq = 71%	Stage IIIB and IV	Nivolumab 3mg/kg per 2 weeks, 1st line or later	.	Impact of follastin, IP10 and RANTES
Passaro et al, 2019 [67]	Cohort study	53	62.0	64.0 (56-70)	Italy, 1 centre	Sq = 29%, Ad = 75%	Stage IIIB and IV	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	19.0 median	OS, PFS, impact of Gr-MDSC
Passiglia et al, 2019a [91]	Cohort study	530	KRas +ve: 63	KRas +ve: 66.0 (36-87)	Italy, 168 centres	NSq = 100%	Stage IIIB, IIIC or IV	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	.	OS, PFS, deaths, AEs
			KRas -ve: 67	KRas -ve: 65.0 (29-86)						
Passiglia et al, 2019b [87]	Cohort study	45	71.1	66.0 (51-80)	Italy, 2 centres	Sq = 45.5%, Ad = 55.5%	Stage IIIB, IIIC or IV	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	.	OS, deaths, impact of ECOG PS, NLR, and histology

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Ramos-Levi et al, 2019 [130]	Cohort study	40	67.5	69.0 (38-86)	Spain, 1 centre	Sq = 52.5%, NSq = 42.5%, NOS = 5.0%	Previous Rx	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	7.6 median	AEs
Ravanelli et al, 2019 [61]	Cohort study	104	66.4	67.0 (43-85)	Italy, 3 centres	Sq = 27.9%, NSq = 72.1%	Stage IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 2nd – 3rd line	~3.5 median	OS, PFS, deaths
Ricciuti et al, 2019a [73]	Cohort study	176	62.5	63.0 (30-84)	Italy, 3 centres	Sq = 18.7%, NSq = 78.5%, NOS = 2.8%	Stage IIIB, IV or recurrent	Nivolumab 3mg/kg per 15 days, 2nd line or later	28.3 months	OS, AEs, impact of Rx post-progression or discontinuation
Ricciuti et al, 2019b [74]	Cohort study	195	65.6	63.0 (30-84)	Italy, 3 centres	Sq = 21.1%, NSq = 78.9%, NOS = 2.8%	Stage IIIB, IV or recurrent	Nivolumab, 2nd line or later	26.0 median	OS, PFS, AEs, impact of irAEs

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Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Sabatier et al, 2018 [68]	Cohort study	30	73	75.2 (70-86.8)	France, 1 centre	Sq = 37%, NSq = 63%	Stage IIIB or IV, patients ≥ 70 only	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	8.2 median	OS, PFS, AEs, impact of AEs and PDL1 TPS
Sarocchi et al, 2018 [27]	Cohort study	59	69	69.0 (44-81)	Italy, 1 centre	Sq = 22%, NSq = 78%	Stage IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	.	Deaths, AEs
Sato et al, 2018 [132]	Cohort study	38	74	68.5 (49-86)	Japan, 1 centre	Sq = 26%, NSq = 74%	Stage IIIB or IV, post-operative relapse	Nivolumab 3mg/kg per 2 weeks, line not specified	~5.25 months	PFS, AEs
Schouten et al, 2018 [53]	Cohort study	248	54.8	63.0 (29-84)[22]	Holland, 1 centre	Sq = 22.2%, Ad = 66.5%, Mixed = 6.5%, NOS = 4.8%	Metastasis	Nivolumab 3mg/kg per 2 weeks, 1st line or later	4.8 median	OS, PFS, deaths, AEs, impact of histology and ECOG PS

[22] Mean and range

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Sekine et al, 2018 [88]	Cohort study	87	62.5	62.0 (34-83)	Japan, 1 centre	Sq = 11.5%, Ad = 73.6%, Other = 14.9%	Stage III or IV	Nivolumab 3mg/kg per 2 weeks, 1st line or later	.	OS, PFS, AEs, impact of LMR[23] and NLR on OS
Shamai et al, 2018 [89]	Cohort study	77	55.9	68.0 (33-90)	Israel, 1 centre	Sq = 16.9%, NSq = 83.1%	Previously treated	Nivolumab 3mg/kg per 2 weeks, 1st line or later	.	OS, PFS, deaths, AEs
Shiroyama et al, 2018 [126]	Cohort study	201	67.2	68.0 (27-87)	Japan, 3 centres	Sq = 20.4%, NSq = 79.6%	Advanced, previously treated	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	12.4 median	PFS, deaths, impact of acute lung injury and NLR
Takeda et al, 2018 [103]	Cohort study	30	63.3	71.0 (54-83)	Japan, 1 centre	Sq = 30%, Ad = 70%	Pre-treated	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	.	PFS, AEs, impact of NLR

[23] Lymphocyte-monocyte ratio

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Tamiya et al, 2019 [71]	Cohort study	213	82.6	71 (39-91)	Japan, 11 centres	Sq = 25.8%, Ad = 60.6%, NOS = 13.6%	Untreated, stage IIIB or IV	Pembroli-zumab 200mg/kg per 3 weeks, 1st line	11.0 median	OS, PFS, AEs, impact of ECOG PS, PDL1 and steroid use on PFS
Tanizaki et al, 2018 [141]	Cohort study	134	67.2	68.0 (33-85)	Japan, 4 centres	Sq = 24.6%, Ad = 67.2%, NOS = 8.2%	Stage IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	.	Impact of blood biomarkers and histology
Teraoka et al, 2017 [104]	Cohort study	43	63.0	70.0 (50-82)	Japan, 1 centre	Sq = 21%, Ad = 70%, NOS = 9%	Stage IIIB or IV	Nivolumab, 2nd line or later	.	PFS, AEs, impact of irAEs
Tiu et al, 2018 [54]	Cohort study	38	42.0	67.0 (46-84)	USA	Sq = 13%, Ad = 71%, NOS = 11%	Stage IIB, IIIA, IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 1st line or later	5.6 median	OS, PFS, deaths, AEs, impact of ethnicity

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Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Toi et al, 2018 [133]	Cohort study	70	87.0	68.0 (36-88)	Japan, 1 centre	Sq = 39%, NSq = 61%	Advanced	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	.	AEs, impact of irAEs
Tournoy et al, 2018 [69]	Cohort study	67	72.3	66.0 (41-86)	Belgium 20 centres	Sq = 26.6%, NSq = 73.4%	Stage IIIA, IIIB, or IV	Nivolumab, 2nd line or later	.	OS, PFS, AEs, impact of ECOG PS
Weis et al, 2019 [70]	Cohort study	24	48.2	64.3	USA, 1 centre	Sq = 32.1%, NSq = 60.5%, Ud = 7.4%	Stage IV or recurrent	Nivolumab 240mg OR 3mg/kg per 2 weeks, 2nd line or later	7.5 median	OS, PFS, deaths, AEs, impact of drug type and histology
			53.5	67.2		Sq = 27.9%, NSq = 67.4%, Ud = 4.7%		Atezo-lizumab 1200mg per 3 weeks, 2nd line or later		

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Yoo et al, 2018 [55]	Cohort study	47	85.1	62.0 (41-81)	South Korea, 2 centres	Sq = 14.9%, Ad = 61.7%, NOS = 23.4%	Stage IIIB, IV or recurrent	Nivolumab 3mg/kg per 2 weeks OR 20mg or 100mg per 3 weeks, 2nd line or later	5.2 median	OS, PFS, deaths, impact of use of a low dose on OS and PFS
Zhuo et al, 2018 [58]	Cohort study	10	70	64.0 (45-66)	China	Sq = 40%, Ad = 50%, AdSq = 10%	Pre-treated stage IIIB or IV	Atezo-lizumab 1200mg per 3 weeks, 2nd line or later	4.8 median	OS, PFS

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Included observational studies, intervention and comparator assessed

Author	Study design	Study arms	Population						Follow up (months)	Reported Outcomes
			Patients	%male	Age (yrs)	Location	Histology	Disease features		
Genova et al, 2019 [116]	Cohort study	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	73	73.9	70.0 (44-82)	Italy	Sq = 23.9%, NSq = 76.1%	Stage IIIB or IV	18.0 median	OS, PFS, impact of B7H4 and PDL1 expression on PFS
		Cisplatin + pemetrexed/ carboplatin, 1st line		74.1	69.0 (46-81)		NSq = 100%			
Russo et al, 2018 [142]	Cohort study	Nivolumab, 2nd line or later	62	77.0	68.0 (45-82)	Italy, 1 centre	Sq = 40%, Ad = 48%, Mixed/NOS = 12%	.	17.0 median	OS, PFS, impact of baseline neutrophilia, NLR and PLR
		Docetaxel, 2nd line or later								
Araujo et al, 2017 [143]	Cohort study	Nivolumab	287	62	64.0 (37-83)	Brazil, 1 centre	NSq = 59%	Pre-treated, advanced/ metastatic	4.9 median	OS, PFS, AEs

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Ardizzoni et al, 2017 [144]	Cohort study	Nivolumab 3mg/kg per 2 weeks	1588	.	.	Italy, 168 centres	NSq = 100%	Previously treated, stage IIIB or IV	7.7 median	OS

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Included observational abstracts

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Bennati et al, 2017 [145]	Cohort study	86	61	.	.	Ad = 76%	.	Nivolumab, lines not specified	.	OS, PFS, impact of NLR and PDL1 TPS
Canova et al, 2016 [146]	Cohort study	37	.	65.0 (54-79)	.	Sq = 56.8%, NSq = 27%	Pre-treated stage IIIA or IV	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	12.0 median	PFS
Cappuzzo et al, 2017 [147]	Cohort study	363	.	.	Italy	Sq = 100%	Pre-treated, stage IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	5.2 median	OS
De Pietro et al, 2017 [148]	Cohort study	92	.	.	.	.	Pre-treated stage IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	.	AEs
Dixmier et al, 2018 [149]	Cohort study	1394	69.2	66.0 (35-91)	186 centres	.	.	Nivolumab, 2nd line or later	.	PFS, AEs

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Elvarathnam et al, 2017 [150]	Cohort study	63	76.1	65.0 (40-78)	France, 1 centre	Sq = 33.3%	Advanced	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	.	AEs
Emiliani et al, 2016 [151]	Cohort study	33	51.5	67.0 (53-84)	.	Sq = 18%, Ad = 82%	Metastatic	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	.	AEs
Fernandez et al, 2017 [152]	Cohort study	32	87.5	.	Spain, 1 centre	Sq = 25%, Ad = 75%	Stage IIIB or IV	Nivolumab, 2nd line or later	.	PFS, AEs
García et al, 2018 [153]	Cohort study	129	.	.	Spain, 5 centres	.	Pre-treated, advanced	Nivolumab, 2nd line or later	6.0 median	OS, impact of ECOG PS
Honda et al, 2018 [154]	Cohort study	93	76.3	67.0 (31-89)	Japan, 1 centre	Sq = 30.1%, NSq = 69.9%	Advanced	Nivolumab, lines not specified	.	PFS, AEs
Hosoya et al, 2018 [155]	Cohort study	145	84.0	71.0 (39-87)	Japan, 10 centres	.	Advanced, PDL1 TPS ≥50%	Pembro-lizumab, 1st line	.	Impact of early irAEs and types of AEs

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Kim et al, 2017 [156]	Cohort study	299	68.9	.	Korea, 36 centres	Sq = 28.8%, NSq = 70.9%	Pre-treated, advanced/ metastatic	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	.	AEs
Lampaki et al, 2017 [157]	Cohort study	23	82.6	68.0	Greece, 1 centre	Sq and NSq	Pre-treated stage IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 3rd line or later	.	Deaths, AEs
Lopez Flores et al, 2017 [158]	Cohort study	25	80	64.0 (43-80)	Spain, 1 centre	Sq = 48%, Ad = 44%	Pre-treated, stage IIIA, IIIB, or IV	Nivolumab 3mg/kg per 15 days, 2nd line or later	.	PFS, deaths, AEs
Mielgo et al, 2016 [159]	Cohort study	11	90	65.0 (40-78)[24]	Spain, 1 centre	Sq = 27%, Ad = 73%	Advanced	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	.	AEs

[24] Mean and range

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Migliorino et al, 2017 [160]	Cohort study	754	.	.	Italy	NSq = 100%	Pre-treated stage IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	.	OS, AEs
Moor et al, 2018 [161]	Cohort study	214	.	67.0 (42-84)	Australia, 7 centres	.	Pre-treated, advanced	Nivolumab, 2nd line	.	OS, PFS, AEs, impact of ECOG PS
Moreno et al, 2017 [162]	Cohort study	46	86	64.0 (47-77)	Spain, 1 centre	Sq = 39%, NSq = 61%	Pre-treated, stage III or IV	Nivolumab, 2nd line or later	.	OS, PFS, AEs
Nakamura et al, 2018 [163]	Cohort study	31	.	.	Japan	.	Advanced	Nivolumab, lines not specified	.	HRs for OS and PFS, impact of NLR
Ota et al, 2018 [164]	Cohort study	51	.	.	Japan	.	Pre-treated, advanced	Nivolumab, 2nd line	.	Impact of time to progression and histology
Paglialunga et al, 2017 [165]	Cohort study	69	.	.	Italy	Sq = 23%, Ad = 77%	Advanced	Nivolumab, lines not specified	.	OS, PFS, AEs, impact of EGFR mutations

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Rapoport et al, 2019 [166]	Cohort study	56	57	65.0 (46-86)	South Africa, 5 centres	Ad = 57%	Pre-treated	Nivolumab, line not specified	.	OS, PFS, AEs, impact of NLR
Rodriguez-Abreu et al, 2018 [175]	Cohort study	664	73	61.0 (32-85)	Spain	Sq = 19.2%, NSq = 80.8%	Pre-treated, advanced	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	Median 8.2 months	OS, PFS, AEs
Rodriguez-Cid et al, 2017 [167]	Cohort study	38	35.3	.	India, 1 centre	Sq = 5.9%, Ad = 88.2%	Pre-treated, stage III or IV	Nivolumab, 1st line or later	.	OS, PFS, deaths
Saijo et al, 2018 [168]	Cohort study	51	19.6	70.0 (37-87)	Japan, 1 centre	Sq = 11.8%, Ad = 45.1%	Advanced NSCLC	Pembro-lizumab, 1st-4th, 8th lines	6.4 median	OS, PFS, AEs
Sakaguchi et al, 2017 [169]	Cohort study	50	66	69.0 (53-86)	Japan, 1 centre	Sq = 28%, Ad = 66%	Advanced or recurrent	Nivolumab 3mg/kg per 2 weeks, 2nd line or later	.	PFS, AEs

Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Sanoyan et al, 2017 [170]	Cohort study	70	.	64.5 (39-89)	Germany, 1 centre	Sq = 23.8%, NSq = 76.2% Sq = 14.3% NSq = 85.7%	Stage IIIB and IV	Nivolumab, 2nd line Pembro-lizumab, 1st line	.	OS, PFS
Saravia et al, 2017 [171]	Cohort study	114	52	67.0 (40-91)	USA	.	Advanced	Nivolumab, lines not specified	5.4 median	Impact of ANC/ALC ratio[25] and ECOG PS
Shaverdian et al, 2019 [172]	Cohort study	43	65	67.0	.	.	Pre-treated	Durvalumab 10mg/kg biweekly, lines not specified	4.6 median	Deaths, AEs, impact of NLR
Shibata et al, 2018 [173]	Cohort study	35	.	.	.	.	.	Nivolumab, 2nd line	.	AEs, impact of NLR
Tanimura et al, 2017	Cohort study	19	.	67.0	.	Sq = 47.4%, NSq =	.	Nivolumab, lines not	Median 7.2	PFS

[25] Absolute neutrophil count/absolute lymphocyte count ratio

[174]						52.6%		specified	months	

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Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Tay et al, 2018 [176]	Cohort study	58	66	67.0	UK, 1 Trust	Sq = 36%, NSq = 64%	Pre-treated, advanced	Pembroli-zumab, line not specified	Median 5.2 months	OS, PFS
Watanabe et al, 2017 [177]	Cohort study	20	Elderly: 80	Elderly: 78.0 (75-83)	Japan	Elderly: Ad = 100%	Stage III, IV and post-operative recurrent	Nivolumab, 1st – 5th line	.	PFS, AEs
			Poor PS: 60	Poor PS: 64.0 (46-72)		Poor PS: Sq = 30%, Ad = 40%				
Yamaguchi et al, 2017 [178]	Cohort study	42	88	67.5 (39-76)	.	.	Pre-treated, stage III or IV	Nivolumab, 2nd line	.	PFS, AEs

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Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Yamamoto et al, 2017 [179]	Cohort study	68	.	.	Japan, 1 centre	.	.	Nivolumab, line not specified	.	PFS, impact of hypo-thyroidism and SNPs
Yamane et al, 2017 [180]	Cohort study	34	.	64	Japan, 1 centre	.	Advanced	Nivolumab, 2nd line	.	AEs, impact of age

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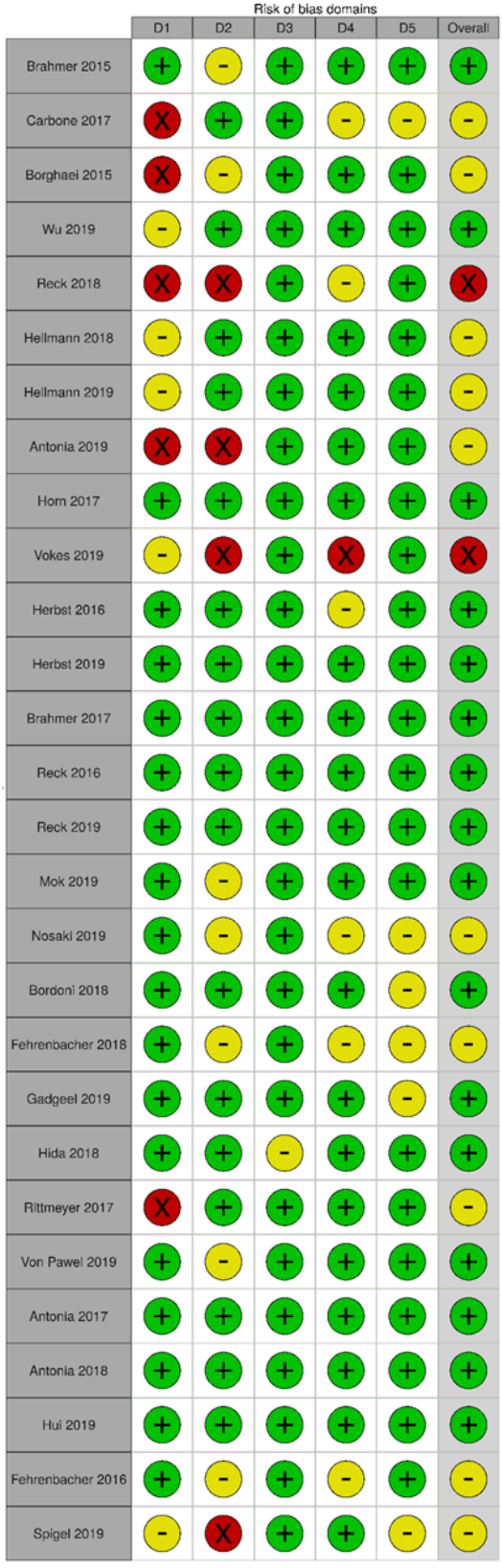
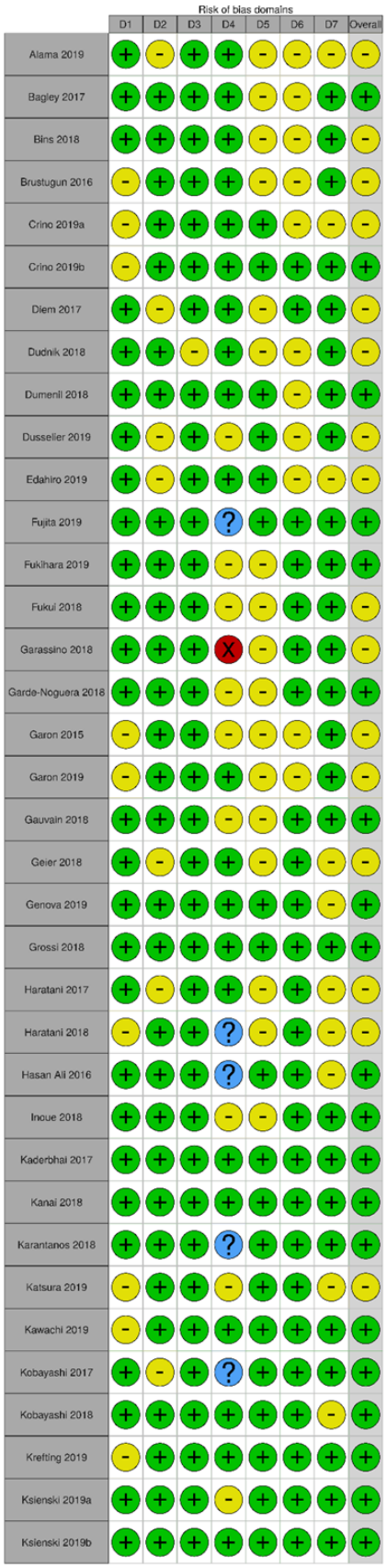
Risk of bias assessment



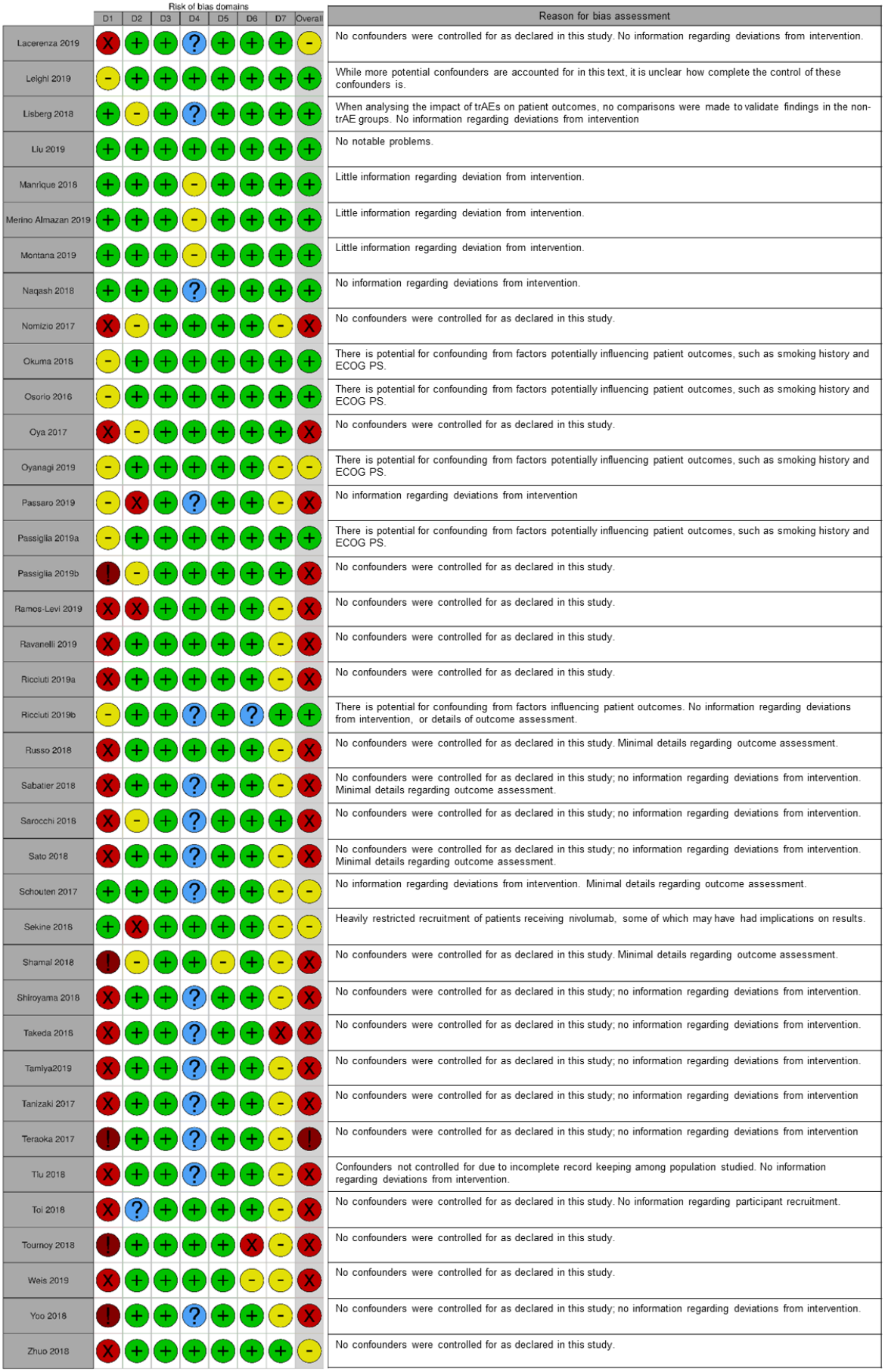
Reasons for overall bias assessment from two reviewers
Open-label, so potential for crossover is high. However, intention-to-treat analysis was used. More patients using intervention discontinued; impact of patient characteristics not discussed
Open-label trial, so potential for crossover is high. However, the primary end point of PFS was assessed by blinded central review; details of this are not specified.
Open-label trial, so potential for crossover is high
Randomisation process specified, but no intention-to-treat analysis mentioned.
Open-label trial, so potential for crossover is high. No details provided about the causes of losses to follow up, and the proportion in each treatment arm.
Randomisation process specified, but no intention-to-treat analysis mentioned.
Randomisation process specified, but no intention-to-treat analysis mentioned.
Analysis of two open-label trials, so potential for crossover is high. Adverse effects and deaths were causes of treatment cessation, but were not compared between trial arms.
Randomisation process outlined clearly. Equal distribution of withdrawals and causes of withdrawals between trial arms. Intention-to-treat analysis was used.
The distribution of reasons for stopping treatment were not described. No intention-to-treat analysis used
Adverse effects were solely patient reported; potential for subjectivity depending on patient coping mechanisms and intuition to report.
Open-label trial, so potential for crossover is high. However, intention-to-treat analysis was used.
Clear description of unbiased randomisation process. Consistent reporting of compliance to quality of life questionnaires. Several quality of life tools used.
Open-label trial, so potential for crossover is high. However, intention-to-treat analysis is used. Blinded independent central radiological review used.
Open-label trial, so potential for crossover is high. However, intention-to-treat analysis is used.
Clear description of unbiased randomisation process. Adverse effects were described as leading to discontinuation; however, impact of patient characteristics not discussed.
Open-label trial; however, intention-to-treat analysis was used. Higher rate of discontinuation due to AEs in chemotherapy group; impact of patient characteristics not discussed.
Several types of analyses conducted without explanation of reasoning behind analysis plan or the results presented
No information about intervention deviations due to experimental context. Pooled analysis of two populations, as protocol was amended. May be differences between populations.
Reason for point of step down of follow up not justified in the context of natural history of progression of disease.
No information about losses to follow up. However, intention-to-treat analysis was used.
Open-label and allocation unmasked, so very possible for crossover to occur. However, intention-to-treat-analysis was used.
No details of the extent of masking or blinding, so the impact of crossover is unknown. However, intention-to-treat analysis was used. Clear definition used for subgroup analysis.
Patients blinded to intervention or placebo. Clear specification of randomisation process. Intention-to-treat analysis used.
Patients blinded to intervention or placebo. Clear specification of randomisation process. Intention-to-treat analysis used.
Clear description of unbiased randomisation process. Patients blinded to intervention or placebo. Intention-to-treat analysis used.
Open-label; however, intention-to-treat analysis was used. Withdrawals mentioned, but impact of patient characteristics not discussed. Concern regarding focus on intervention
Very little information provided regarding randomisation, receipt of intended intervention, and justification of outcomes, due to abstract format.

ROB 2.0 assessment

The figure shows a traffic light assessment, generated using ROBVIS, and accompanying reasoning for the overall risk from the assessing authors.



Reasons for overall bias assessment from two reviewers
Lack of information on how participants were selected for the study, whether participants were excluded due to missing data, and how study outcomes were ascertained.
Lack of information regarding whether participants were excluded due to missing information and how survival outcomes were ascertained
Lack of information regarding whether participants were excluded due to missing information and how survival outcomes were ascertained. Reasoning behind 7 investigated single nucleotide polymorphisms is not explicit.
Authors did not account for the impact of smoking on patient outcomes. No information on exclusions due to missing information. Time to treatment failure was not defined, which could introduce systematic errors in assessment.
No methods for accounting for confounding factors mentioned. Lack of information regarding whether participants were excluded due to missing information and how survival outcomes were ascertained.
No methods for accounting for confounding factors mentioned.
Given the aim of the study was to investigate blood parameters as markers of effectiveness, there is potential for exclusion of patients with incomplete blood results. No discussion of this in the study.
Exclusions based on inadequate follow up may introduce a bias against patients who did not meet minimum follow up requirement due to medical reasons relating to therapy. No clarification of this within the study.
The information used in the study was highly dependent on availability in medical charts which, in turn, is dependent on completeness of clinical assessment and recording. No discussion of how this was addressed.
Given the aim of the study was to investigate blood parameters as markers of effectiveness, there is potential for exclusion of patients with incomplete blood results. No discussion of this in the study.
Lack of information regarding whether participants were excluded due to missing information and how survival outcomes were ascertained
No information regarding intervention deviations.
The study subdivided patients into groups of patients who experienced or did not experience immune related pneumonitis; likely to be differences in patient characteristics that also affect susceptibility, which were not discussed.
No information provided about missing data among patients or deviations, and any potential exclusions resulting from this.
A very high rate of discontinuation was observed in this study, which largely originated from patients who had never smoked. The authors potentially attribute this to differences in tumour mutational burden.
Lack of information regarding whether participants deviated from their intended interventions and how survival outcomes were ascertained.
Only PDL1 expression was accounted for in the main text. No information on deviations from intervention beyond expectation.
While more potential confounders are accounted for in this text, it is unclear how complete the control of these confounders is. No information on deviations from intervention beyond expectation, or patients exclusions.
Lack of information regarding whether participants deviated from their intended interventions and how survival outcomes were ascertained.
Little information regarding outcomes of all participants and exclusions. Unclear whether predictive factors of efficacy were calculated using data from responders alone, rather than contrasting to non-responders.
Many different outcome measures are investigated, and two distinct cohorts of patients were used to compare and contrast the impact of B7-H4 as a biomarker of effectiveness.
No notable problems
Selection of EGFR mutation positive patients on record only. The proportion of participants who had to be censored is not stated.
No information regarding deviations from interventions
No information regarding deviations from interventions
Little information regarding the proportion of participants who deviated from the intervention or for whom there was missing data.
No notable problems.
No notable problems.
No notable problems, although there was no information regarding patient deviations from interventions.
Potential for confounding from factors potentially influencing patient outcomes; little information regarding deviations from intervention
In spite of recording baseline characteristics of potential confounders, there is potential for confounding from factors potentially influencing patient outcomes, such as smoking history and ECOG PS.
No information regarding deviations from interventions
Several measures of survival-related outcome effectiveness measures were used, which increases the scope to detect an effect but no speculation on impact of outcome choice on results
In spite of recording baseline characteristics of potential confounders, there is potential for confounding from factors potentially influencing patient outcomes, such as smoking history and ECOG PS.
Little information regarding deviations from interventions
No notable problems.



ROBINS-I assessment of observational full texts

The figures show a traffic-light assessment, generated using ROBVIS, and accompanying reasoning for the overall risk from the assessing authors.

Reason for bias assessment
Very little information regarding methods to make assessments. From the methods available, participant selection was consistent and fair, and reported outcomes were reasonably assessed from appropriate analyses.
Very little information regarding methods to make assessments. Although participant selection appeared consistent, the results reported were chosen from patients who were KRas mutation positive; this was to be expected but does have associated risk.
Very little information regarding methods to make assessments. From the methods available, participant selection was consistent and fair, and reported outcomes were reasonably assessed from appropriate analyses.
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Very little information regarding methods to make assessments. From the methods available, participant selection was consistent and fair. However, despite several clinical outcomes being alluded to, very few of these measures were ultimately reported
Very little information regarding methods to make assessments. Participant selection appears to be clear, but this is not certain.
Very little information regarding methods to make assessments. From the methods available, participant selection was consistent and fair, and reported outcomes were reasonably assessed from appropriate analyses.
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Very little information regarding methods to make assessments. Only responders to therapy were analysed in this study, as the authors were looking to identify biomarkers. However, by excluding non-responders, they were unable to compare findings to non-responders
Very little information regarding methods to make assessments. From the methods available, participant selection was consistent and fair, and reported outcomes were reasonably assessed from appropriate analyses.
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ROBINS-I assessment of observational abstracts

The figure shows a traffic light assessment, generated using ROBVIS, and accompanying reasoning for the overall risk from the assessing authors.

GRADE Assessment of RCT Evidence

Nivolumab, pembrolizumab or atezolizumab compared to chemotherapy for managing advanced NSCLC

Adapted from table produced using the GRADEpro Guideline Development Tool (GDT) [181]

Outcomes	No of studies	Certainty of the evidence (GRADE)	Relative effect (95% CI)
Risk of death Follow-up: range 0 months to 18 months	10 RCTs	⊕⊕⊕⊕ High	**HR 0.75** (0.69 to 0.81) [Risk of death]
Risk of death Follow-up: range 18 months to 31 months	3 RCTs	⊕⊕⊕⊕ High	**HR 0.72** (0.65 to 0.81) [Risk of death]
Risk of death Follow-up: range 31 months to as far as reported	3 RCTs	⊕⊕⊕◯ Moderate	**HR 0.70** (0.59 to 0.82) [Risk of death]
Risk of progression or death Follow-up: range 0 months to 18 months	10 RCTs	⊕⊕◯◯ Low	**HR 0.87** (0.76 to 0.99) [Risk of progression or death]
Risk of progression or death Follow-up: range 18 months to 31 months	2 RCTs	⊕⊕⊕◯ Moderate	**HR 0.82** (0.74 to 0.90) [Risk of progression or death]
Incidence of treatment-related adverse events assessed with: Mean percentage incidence	9 RCTs	⊕⊕⊕⊕ High	**Not pooled**
Time to deterioration in quality of life assessed with: EORTC-QLQ-LC13	2 RCTs	⊕⊕⊕◯ Moderate	**-**
Time to deterioration in quality of life assessed with: EQ-5D-3L	1 RCT	⊕⊕◯◯ Low	**Not estimable**
Time to deterioration in quality of life assessed with: LCSS ASBI	1 RCT	⊕⊕◯◯ Low	**Not estimable**
Time to deterioration in quality of life assessed with: EORTC-QLQ-C30	1 RCT	⊕⊕⊕◯ Moderate	**Not estimable**

CI: confidence interval; **HR**: hazard ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Confidential: For Review Only

Durvalumab compared to placebo for managing advanced NSCLC
Adapted from table produced using the GRADEpro Guideline Development Tool (GDT) [181]

Outcomes	No of studies	Certainty of the evidence (GRADE)	Relative effect (95% CI)
Risk of death Follow-up: median 25.2 months	1 RCT	⊕⊕⊕⊕ High	**Not estimable**
Progression-free survival Follow-up: median 25.2 months	1 RCT	⊕⊕⊕⊕ High	**Not estimable**
Incidence of treatment-related adverse events assessed with: Percentage incidence Follow-up: median 25.2 months	1 RCT	⊕⊕⊕⊕ High	**Not estimable**
Time to deterioration in quality of life assessed with: EORTC-QLQ-C30 Follow-up: median 25.2 months	1 RCT	⊕⊕⊕◯ Moderate	**Not estimable**

CI: confidence interval

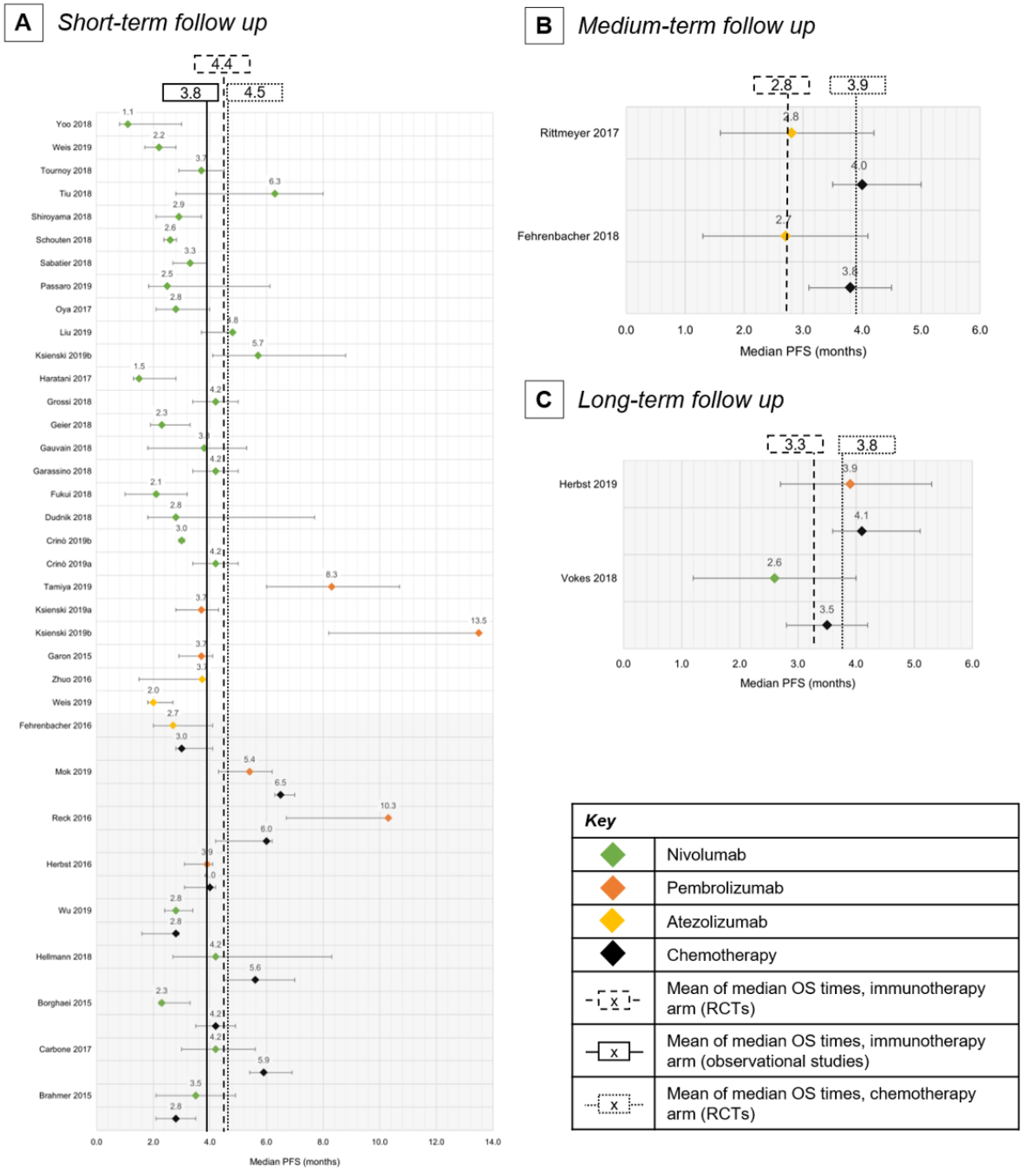
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

For Confidential Peer Review Only

Supplementary analyses

Supplementary Figure 1 – Median OS results

A) Median OS and 95% confidence intervals reported in observational and RCT studies with short-term follow up [31-35, 37, 40, 48-55, 57, 59, 62-72]. B) Median OS and 95% confidence intervals reported in observational and RCT studies with medium-term follow up [38-40, 42, 64]. C) Median OS and 95% confidence intervals reported in observational and RCT studies with long-term follow up. Shaded area denotes RCT data [44, 45].



Supplementary Figure 2 – Median PFS results

A) Median PFS and 95% confidence intervals reported in observational and RCT studies with short-term follow up [31-37, 47-59, 63-72, 95, 97, 125, 126]. B) Median PFS and 95% confidence intervals reported in observational and RCT studies with medium-term follow up [40, 42]. C) Median PFS and 95% confidence intervals reported in observational and RCT studies with long-term follow up. Shaded area denotes RCT data [44, 45].

Supplementary Figure 3 – Incidence of trAEs in primary-analysis RCTs

Table illustrating the percentage incidence of trAEs in RCTs. Each block corresponds to the proportion of patients with each AE per trial arm, expressed as a percentage. [32-35, 37-39, 42, 44, 47, 94, 95]. N = nivolumab, P = pembrolizumab, A = atezolizumab, D = durvalumab, C = chemotherapy.

	Study name	Brahmer et al., 2015		Carbone et al., 2017		Borghaei et al., 2015		Hellmann et al., 2018		Wu et al., 2019		Herbst et al., 2016			Reck et al., 2016		Mok et al., 2019		Rittmeyer et al, 2017		Antonia et al., 2017	
	Trial arm	N	C	N	C	N	C	N	C	N	C	P (2mg/kg)	P (10mg/kg)	C	P	C	P	C	A	C	D	Placebo
	Number of patients	131	129	267	263	287	268	391	570	337	156	339	343	309	154	150	636	615	609	578	475	234
AE incidence (%)	Fatigue	16	33	21	35	16	29	11	18	10	25	14	14	25	10	29	8	17	27	36	13	11
	Decreased appetite	11	19	12	28	10	16	6	19	7	23	14	10	16	9	26	6	18	24	24	6	3
	Diarrhoea	8	20	14	13	8	1	11	10	.	.	1	6	18	14	13	5	7	15	24	10	8
	Pyrexia	5	8	.	.	.	.	.	.	.	.	.	.	.	10	5	.	.	18	13	.	.
	Nausea	9	23	12	48	12	26	5	36	.	.	11	9	15	10	43	5	30	18	23	6	6
	Rash	4	6	10	6	.	.	11	1	12	3	9	13	5	.	.	7	4	.	.	8	6
	Hypothyroidism	.	.	.	.	.	.	6	0	.	.	8	8	<1	9	1	11	<1	.	.	11	<1
	Asthenia	10	14	3	11	10	18	7	13	.	.	6	6	11	.	.	4	10	19	20	6	6
	Arthralgia	5	7	.	.	.	.	.	.	.	.	.	.	.	.	.	4	7	12	10	.	.
	Constipation	.	.	3	11	.	.	2	15	.	.	.	.	.	4	11	1	11	18	14	.	.
	Vomiting	.	.	6	23	.	.	3	13	.	.	.	.	.	3	20	2	16	12	11	.	.
	Myalgia	2	10	.	.	2	11	.	.	.	.	.	.	.	.	.	3	8	6	16	.	.
	Alopecia	0	22	.	.	<1	25	.	.	<1	22	1	1	33	.	.	<1	22	<1	35	.	.
	Peripheral oedema	.	.	.	.	3	10	.	.	.	.	.	.	.	.	.	.	.	9	14	.	.
	Anaemia	2	22	3	43	2	20	3	32	4	26	3	4	13	5	42	6	37	12	24	.	.
	Leukopenia	1	6	.	.	0	10	.	.	3	17	.	.	.	.	.	2	6	.	.	.	.
	Neutropenia	1	33	0	18	<1	31	<1	17	2	20	<1	<1	14	<1	23	5	14	2	16	.	.
	Cough	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	23	18	5	2
	Febrile neutropenia	0	11	.	.	0	10	.	.	.	.	.	.	.	.	.	.	.	<1	11	.	.
	Stomatitis	.	.	.	.	.	.	.	.	.	.	4	2	14	3	12	1	5	3	11	.	.
	Peripheral neuropathy	1	12	.	.	.	.	.	.	.	.	.	.	.	.	.	<1	8	4	11	.	.
	Dyspnoea	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	19	19	6	3
	Thrombocytopenia	.	.	1	14	.	.	.	.	.	.	.	.	.	0	11	<1	9	.	.	.	.
	Dysgeusia	.	.	.	.	.	.	.	.	.	.	.	.	.	<1	10	.	.	3	10	.	.
	Back pain	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	11	7	.	.
	Musculoskeletal pain	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	11	4	.	.
	Pneumonitis	5	0	.	.	.	.	.	.	.	.	5	4	2	6	<1	7	3	.	.	9	3
	Hyperthyroidism	.	.	.	.	.	.	.	.	.	.	4	6	1	8	1	6	<1	.	.	6	1
	Pruritus	.	.	.	.	.	.	8	1	.	.	.	.	.	.	.	7	2	.	.	7	2
	Colitis	.	.	.	.	.	.	.	.	.	.	1	1	0	2	0	.	.	.	.	.	.
	Severe skin reaction	.	.	.	.	.	.	.	.	.	.	1	2	1	4	0	.	.	.	.	.	.
	Pancreatitis	.	.	.	.	.	.	.	.	.	.	1	0	0	<1	0	.	.	.	.	.	.
	Myositis	.	.	.	.	.	.	.	.	.	.	1	<1	<1	2	0	.	.	.	.	.	.
	Thyroiditis	.	.	.	.	.	.	.	.	.	.	<1	0	0	3	0	.	.	.	.	.	.
	Type 1 diabetes	.	.	.	.	.	.	.	.	.	.	<1	1	0	<1	0	.	.	.	.	.	.
	Hypophysitis	.	.	.	.	.	.	.	.	.	.	<1	<1	0	<1	0	.	.	.	.	.	.
	Autoimmune hepatitis	.	.	.	.	.	.	.	.	.	.	<1	1	0	.	.	.	.	.	.	.	.
	Adrenal insufficiency	.	.									1	1	0								
	Nephritis	.	.	.	.	.	.	.	.	.	.	.	.	.	<1	0	.	.	.	.	.	.
	Mucosal inflammation	2	9	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Key	
0% ≤ x < 10%	
10% ≤ x < 20%	
20% ≤ x < 30%	
30% ≤ x < 40%	
40% ≤ x	

Supplementary Figure 4 – Incidence of AEs in observational studies

Table illustrating the percentage incidence of AEs in observational studies. Each block corresponds to the proportion of patients with each AE in the study, expressed as a percentage. [48-51, 53, 56, 57, 62-66, 68-76, 78, 79, 81, 83-85, 88, 89, 92, 94, 96-98, 101, 107, 125, 128, 132, 133].

Study name	Bagley et al., 2017	Bins et al., 2018	Brustugun et al., 2017	Crinò et al., 2019a	Crino et al., 2019b	Dudnik et al., 2018	Dumenil et al., 2018	Fukui et al., 2018	Garassino et al., 2018	Garde-Noguera et al., 2018	Gauvain et al., 2018	Geier et al., 2018	Grossi et al., 2018	Haraani et al., 2018	Kobayashi et al., 2018	Kretting et al., 2019	Ksienski et al., 2019b	Lacerenza et al., 2019	Liu et al., 2019	Manrique et al., 2018	Merino Almazan et al., 2019	Montana et al., 2019	Ricciuti et al., 2019b	Ricciuti et al., 2019a	Sabatier et al., 2018	Sato et al., 2018	Schouten et al., 2018	Sekine et al., 2018	Shamai et al., 2018	Toi et al., 2018	Tournoy et al., 2018	Weis et al.,		Garon et al., 2015	Ksienski et al., 2019a	Lisberg et al., 2018	Osorio et al., 2017	Tamiya et al., 2019
Intervention	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	P	P	P	P	P
Number of patients	175	161	58	1588	371	260	67	52	371	175	43	259	371	134	142	40	271	20	44	188	221	98	195	176	30	38	248	87	77	70	67	24		495	190	97	51	213
AE incidence (%) Fatigue	.	.	3	6	11	100	60	.	6	11	.	.	6	5	.	18	.	.	.	25	5	.	20	18	.	.	.	.	67	.	.	38	37	20	.	10	.	2
Asthenia	.	.	.	8	.	.	.	.	.	.	42	8	.	.	.	.	.	50	.	.	39	30	.	.	.	.	.	.	.	.	.	.	.	5	.	.	.	.
Rash	.	.	5	8	3	27	4	33	8	.	.	.	8	25	7	.	.	.	5	.	7	11	9	10	.	11	2	25	.	79	2	10	9	10	.	23	6	.
Pruritus	.	.	5	.	.	27	6	37	.	.	.	.	.	12	.	.	.	.	.	15	7	.	1	2	3	.	.	.	.	.	.	.	.	11	.	3	.	.
Hypothyroidism	5	40	.	3	2	15	4	10	3	.	5	14	.	.	11	.	13	5	14	7	5	21	20	18	20	11	7	7	13	21	.	3	2	7	7	6	16	.
Hyperthyroidism	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2	.	1	.	.	.
Nausea or vomiting	.	.	.	<1	4	24	.	19	.	.	.	.	.	.	.	.	.	.	.	8	6	25	4	4	.	.	.	.	.	.	.	9	7	10	.	.	.	.
Arthralgia	.	.	2	.	.	.	7	37	.	.	.	.	.	.	.	.	4	.	.	.	7	7	.	4	.	.	.	.	.	.	.	15	5	9	3	2	10	.
Myalgia	.	.	.	.	.	.	.	.	.	.	.	7	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	5	3	.	.	.	.
Neurological	.	.	.	.	.	.	.	63	.	.	11	.	.	1	2	.	1	.	.	<1	1	.	.	.	.	.	.	.	.	.	1	.	.	.	2	.	2	.
Pneumonitis	3	5	7	1	2	.	3	13	1	.	.	.	1	4	.	.	5	.	.	3	7	.	8	9	.	13	4	8	.	18	7	5	7	4	5	6	4	5
Anaemia	.	.	.	2	1	.	.	.	2	.	14	.	2	.	3	.	.	.	.	.	5	27	<1	<1	3	.	.	.	.	.	.	.	.	4	.	.	.	<1
Diarrhoea	.	4	9	5	5	19	1	13	5	.	14	.	5	7	3	.	.	.	.	11	12	.	.	.	7	.	.	6	20	7	.	10	7	8	.	.	.	.
Decreased appetite	.	.	.	2	4	.	.	.	2	.	.	.	3	.	.	10	.	.	.	7	2	.	.	.	.	.	.	.	.	.	.	.	.	11	.	4	.	<1
Pyrexia	.	.	.	3	4	.	15	6	3	.	.	.	3	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	4	.	5	.	.
Chills	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2	.	.	.	.
Constipation	.	.	.	.	.	.	.	33	.	.	.	.	.	.	4	.	.	.	.	.	3	.	<1	<1	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Oedema	.	.	.	.	.	.	.	17	.	.	.	.	.	.	.	.	.	.	.	.	4	.	.	.	.	.	.	.	.	.	.	4	5	.	.	2	.	.
Mucosal inflammation	.	.	.	.	.	.	.	12	.	.	.	.	.	2	.	.	<1	.	.	.	1	.	.	.	3	.	.	.	.	.	.	.	.	.	.	.	.	.
Hepatitis	.	.	.	.	.	.	.	.	.	.	2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0	3	4	.	2	.
Colitis	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0	.	7	.	.	1
Dermatitis	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	3	11	.	.	.
Skin toxicity	.	.	.	.	.	.	.	.	.	10	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Adrenal insufficiency	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	10	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	<1
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Key
0% ≤ x < 10%
10% ≤ x < 20%
20% ≤ x < 30%
30% ≤ x < 40%
40% ≤ x

Immune-related adverse effects

Immune-related adverse effects (irAEs) were more common among patients using an intervention compared to chemotherapy and less frequent than trAEs. The mean incidence of irAEs among patients receiving pembrolizumab in RCTs was 24.1% (range 19.0% – 29.2%). Similarly, the mean incidence of irAEs was 27.9% (range 17.0% – 43.0%) among the 7 observational studies investigating pembrolizumab. By contrast, the mean incidence of irAEs across the chemotherapy arms of RCTs investigating pembrolizumab was 5.3%, (range 4.2% – 7.0%). Unlike the RCTs, 10 observational studies reported the incidence of irAEs among patients using nivolumab; the mean incidence of irAEs was 37.5% (range 18.1% – 62.8%).

With a mean incidence of 9.3%, the most common irAE among patients receiving pembrolizumab in RCTs was hypothyroidism. Similarly, the irAEs with the highest mean incidence among patients using pembrolizumab in observational studies were hypothyroidism (7.2%), dermatitis (6.6%) and pneumonitis (4.6%). Among patients receiving nivolumab, the irAEs with the highest mean incidence were hypothyroidism (11.1%), hyperthyroidism (10.8%) and pneumonitis (5.9%).

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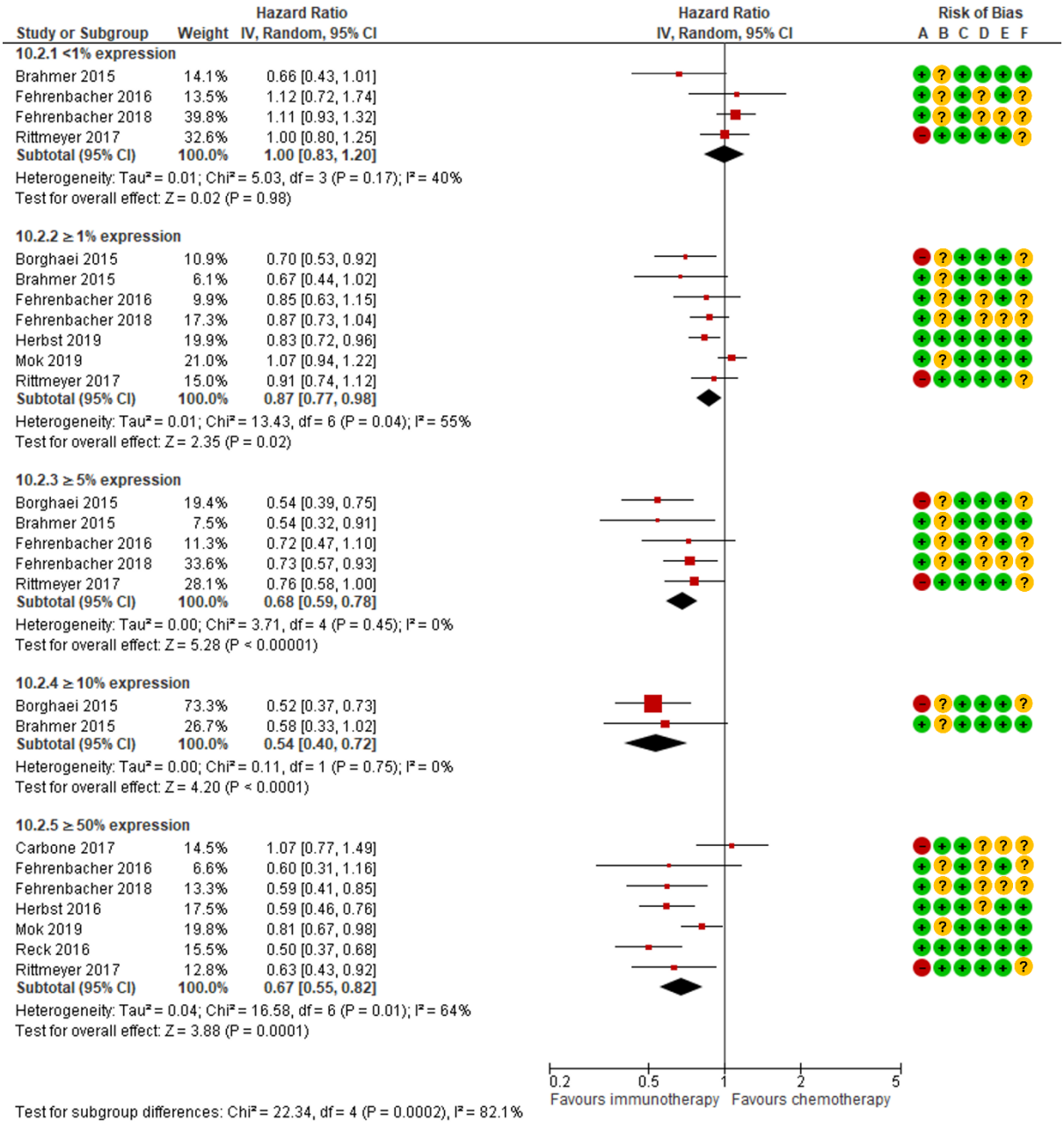
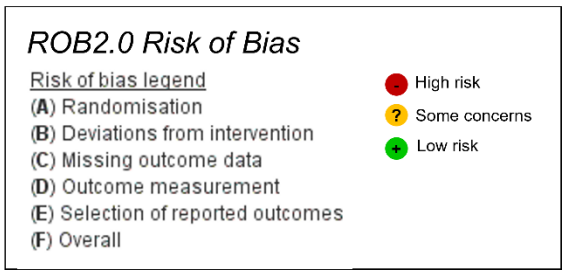
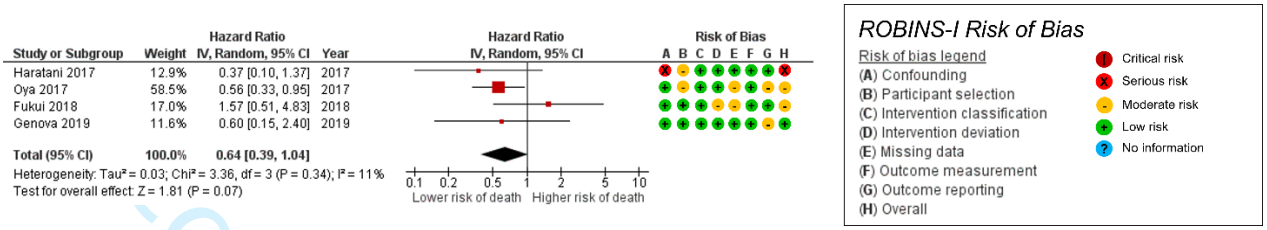
Supplementary Figure 5 – Meta-analysis risk of progression or death by PDL1 expression status for patients receiving nivolumab, pembrolizumab or atezolizumab in included RCTs [31 - 36, 40, 42]

Pembrolizumab data from patients with less than 50% expression could not be included, because a breakdown of survival outcomes was not provided between 1 – 49%.





Supplementary Figure 6 – Meta-analysis comparing risk of death among patients with ≥1% and <1% PDL1 expression who received nivolumab in included observational studies [52, 104, 116, 125]



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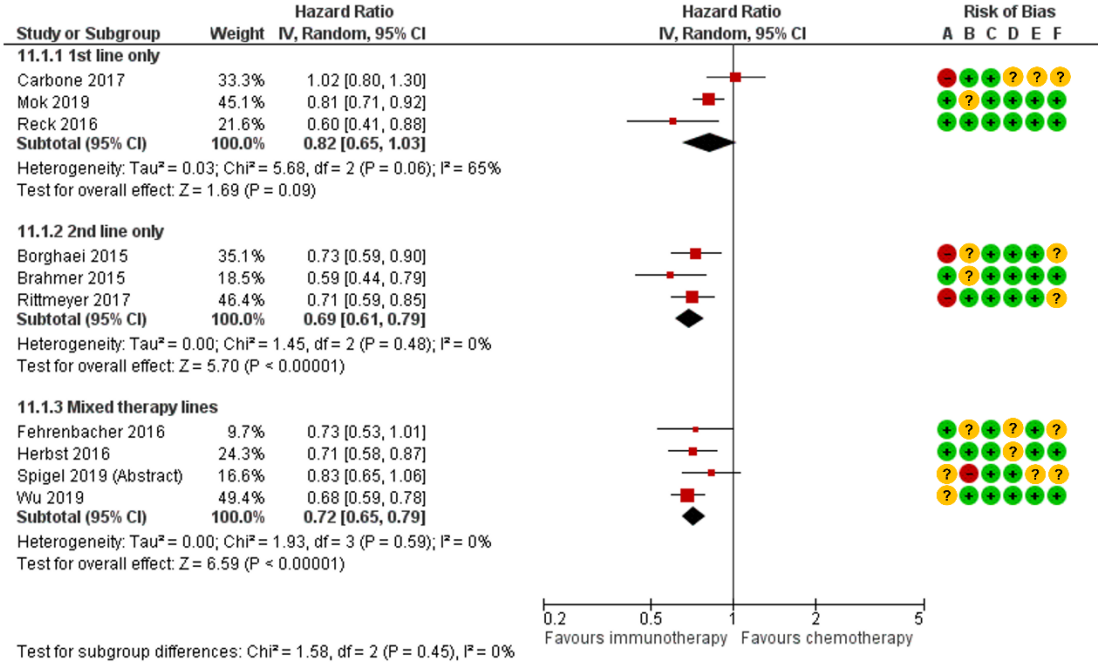
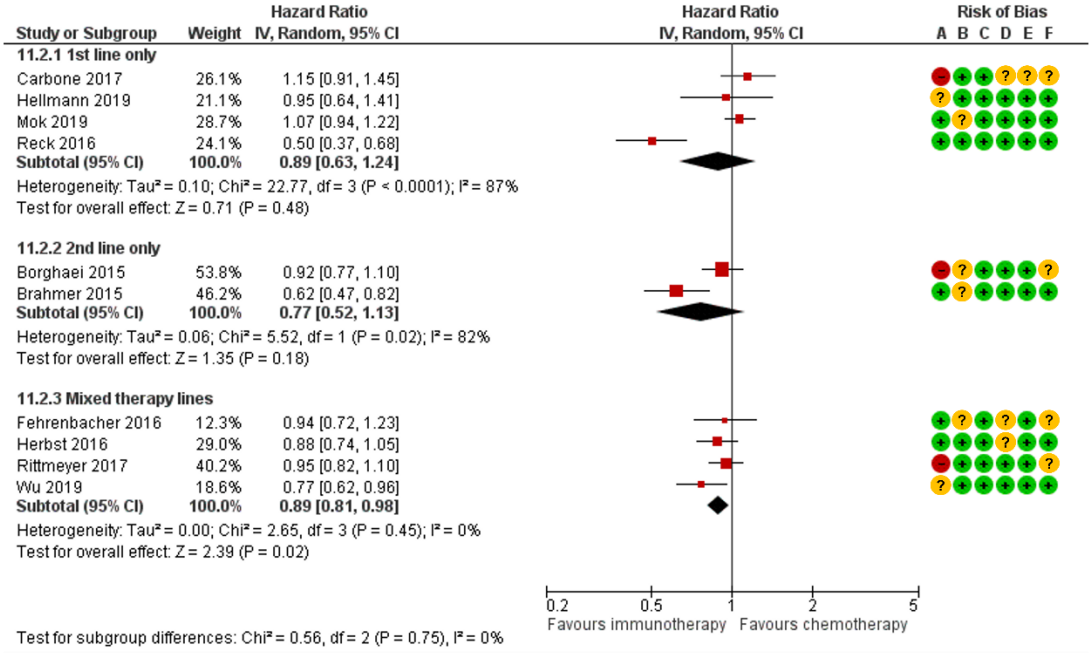
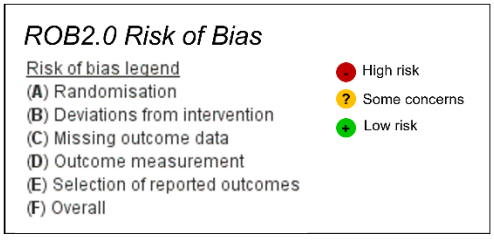
Supplementary Figure 7 – Meta-analysis of A) risk of death and B) risk of progression or death by therapy line for patients receiving nivolumab, pembrolizumab or atezolizumab in included RCTs [30 – 37, 42, 47, 96]

A *Risk of death by therapy line*



B *Risk of progression or death by therapy line*





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