

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

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# Thorax

## 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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**3778 words**

## 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.

## 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.

### 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

$x \geq 31$ 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



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

1  
2  
3 for death among patients receiving nivolumab, pembrolizumab or atezolizumab compared to  
4 chemotherapy was 0.75 (95% CI 0.69 – 0.81,  $p < 0.00001$ ) (Figure 3A). Typically, average  
5 survival was approximately 3 months longer with immunotherapy, with pembrolizumab being  
6 associated with longest average OS (13.6 months; Supplementary Figure 1). However, the  
7 associated confidence intervals for these data overlap rendering this evidence unclear.  
8

9  
10 Among RCTs with medium-term follow up, patients receiving immunotherapy survived longer  
11 and had a lower risk of death. The pooled HR for death among patients receiving nivolumab,  
12 pembrolizumab or atezolizumab compared to chemotherapy was 0.72 (95% CI 0.65 – 0.80,  $p$   
13  $< 0.00001$ ) (Figure 3B). Typically, average survival was around 5 months longer with  
14 immunotherapy compared to chemotherapy. OS was not reached among patients receiving  
15 durvalumab (Supplementary Figure 1); the risk of death was 0.68 (99.73% CI 0.47 – 1.00)  
16 [43].  
17

18 RCTs with long-term follow up reported similar results. The pooled HR for death was 0.70  
19 (95% CI 0.59 – 0.82,  $p < 0.00001$ ) (Figure 4C). Only CheckMate017 and 057 reported OS  
20 between three- and four-year follow up. There was no change in median OS in either study  
21 arm of these two cohorts [46].  
22

23 OS in observational studies and RCTs were similar (Supplementary Figure 1). The similarity  
24 in OS between observational studies and RCTs was supported by data from observational  
25 studies with an unknown length of follow up, and abstracts.  
26

### 27 Progression-free survival

28  
29 17 RCT studies reported PFS from up to three-years patient follow up [31-42, 44, 45, 94-96].  
30 52 observational studies with short-term follow up reported PFS [48-59, 63-72, 74-76, 78-85,  
31 87-90, 92, 93, 97-104]. Heterogeneity in the meta-analysed studies tended to be high; the  $I^2$   
32 statistics for short-term follow up studies of nivolumab and pembrolizumab were 69% and 91%  
33 respectively.  
34

35 In RCTs with short-term follow up, patients receiving immunotherapy had a lower risk of  
36 progression or death than patients receiving chemotherapy. The pooled HR for progression  
37 or death among patients receiving nivolumab, pembrolizumab or atezolizumab compared to  
38 chemotherapy was 0.87 (95% CI 0.76 – 0.99,  $p = 0.03$ ) (Figure 5A). There was no evidence  
39 of a difference in average PFS among patients receiving nivolumab, pembrolizumab or  
40 atezolizumab and those receiving chemotherapy, albeit with some inconsistency within the  
41 results (Supplementary Figure 2) [94].  
42  
43

44 Among RCTs with medium or long-term follow up, patients receiving immunotherapy did not  
45 have a consistent benefit to PFS. At three-year follow up, the risk of progression or death  
46 among patients receiving nivolumab or pembrolizumab compared to chemotherapy was 0.82  
47 (95% CI 0.74 – 0.90,  $p < 0.00001$ ) (Figure 5B). However, there were no clinically significant  
48 differences in average PFS between these three agents and chemotherapy in medium or long  
49 term follow up studies (Supplementary Figure 2). In PACIFIC, the PFS was 17.3 months (95%  
50 CI 13.1 – 23.9) with durvalumab, compared to 5.6 months (95% CI 4.6 – 7.7) on placebo [43].  
51  
52

53 Similar PFS results were reported in observational studies including those with an unknown  
54 length of follow up, and abstracts (Supplementary Figure 2).  
55

### 56 Adverse effects and hospitalisations

57 20 RCT studies reported AEs [31-39, 42-44, 47, 94, 95, 105, 106]. 53 observational full texts  
58 reported AEs among patients receiving pembrolizumab, nivolumab and atezolizumab, of  
59 which 44 investigated nivolumab.  
60

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 <sup>†</sup>
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.

<sup>†</sup>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 <sup>†</sup>
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)

<sup>†</sup>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 ( $\sigma$  0.177) with durvalumab and 0.012 ( $\sigma$  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

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  $\geq 5\%$  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  $\geq 1\%$  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  $\geq 1\%$  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 2<sup>nd</sup> 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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3 We extended previous systematic reviews by looking at other outcomes in detail; however,  
4 benefits to PFS, AEs and QoL were less clear. While risk of progression or death was reduced  
5 by immunotherapy, benefits to average PFS were variable. Additionally, although a benefit to  
6 trAE incidence was observed among patients receiving immunotherapy, the overall profile of  
7 AEs was similar between immunotherapy and chemotherapy. Furthermore, immune-related  
8 AEs were more common among patients using PD1-targeting treatments. Compared to RCTs,  
9 the incidence of AEs among patients using immunotherapy in observational studies was lower,  
10 although a broader range of AEs was reported in these studies. The impact of PD1 and PDL1  
11 immunotherapy on patient QoL was variable, and highly dependent on the choice of  
12 instrument used in each study. There was a notable lack of QoL data, particularly among  
13 observational studies.  
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16 These results highlight the importance of distinguishing between the biological impact of PD1  
17 and PDL1 immunotherapy and the impact of study design on results. Differentiating these may  
18 improve study designs to capture these effects.  
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20 The absence of a clear association between OS and PFS could be explained by pseudo-  
21 progression, which is a phenomenon in which immune cells infiltrate the primary tumour  
22 causing an increase to tumour size that mimics tumour growth [118]. Although there is limited  
23 evidence to support this theory, Li et al. found that mice with induced lung tumours exposed  
24 to anti-PD1 therapy accumulated tumour-infiltrating-lymphocytes within their tumours [119].  
25 Since the included studies measured progression via the RECIST 1.1 criteria, which relies  
26 upon changes in tumour diameter, they were potentially unable to distinguish pseudo-  
27 progressions from true disease progression [120]. However, this explanation less probable,  
28 given the consistent effect of immunotherapy on the risk of progression or death. More likely,  
29 the lack of association may be explained by aspects of study design. Particularly, some of the  
30 included trials may be affected by bias introduced by calculating PFS from censored data  
31 [121]. Furthermore, many studies recruited patients from multiple therapy lines. Patients  
32 receiving later lines are more likely to have a shorter PFS, which may have meant studies  
33 investigating these reported lower median survival results.  
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36 The variability of AEs between drugs and study designs may also be explained by the effect  
37 of study design. Given all four therapies have a similar molecular basis, it is unlikely the  
38 differences in AE incidence between drugs are attributable to pharmacological effects.  
39 However, the lack of restriction of patients based on ECOG PS in observational studies may  
40 have contributed to the broader range of AEs observed, as patients with a higher ECOG PS  
41 could have a greater propensity to develop AEs. Furthermore, the retrospective nature of  
42 many observational studies may have allowed greater flexibility in detecting AEs compared to  
43 RCTs.  
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46 The choice of QoL tool impacted QoL results. While EQ-5D, a non-specific tool, was  
47 associated with minimal changes to QoL, patients assessed via more lung cancer-specific  
48 tools such as LCSS experienced greater benefits, suggesting this therapy may yet impact QoL  
49 when the correct tool is used. There is currently little research investigating impact of choice  
50 of QoL instrument on results [122]. Some studies have argued that lower AE incidence is  
51 indicative of improved QoL. However, given that QoL is a proxy measure of patient  
52 experiences with their wellbeing and care, assessments of QoL should reflect this and not rely  
53 solely upon the absence of disease.  
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56 We also extend current knowledge of factors influencing patient prognosis. Increasing PDL1  
57 expression was associated with a lower risk of death, and risk of progression or death.  
58 However, the significance of the current PDL1 threshold for accessing this therapy,  $\geq 1\%$   
59 expression, was unclear. Presence of metastases and ECOG PS2 were associated with worse  
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3 survival outcomes, while the impact of therapy line was not clear. It is unsurprising that  
4 presence of metastases and ECOG PS, which reflect patient health, were associated with  
5 poorer survival outcomes. However, it was more unexpected that having  $\geq 1\%$  expression did  
6 not confer a significant survival benefit. A potential reason for this may be that PDL1  
7 expression is known to vary within tumours, and so samples of the tumour may not reflect  
8 overall tumour PDL1 expression. Therefore, there may have been insufficient PDL1  
9 expression overall to experience a benefit among some patients, despite having  $\geq 1\%$   
10 expression in their samples. This suggests more research is required to find the optimum  
11 threshold by which to stratify patients, or better ways to quantify PDL1 expression.  
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14 There are several limitations to the study. Firstly, some relevant abstract and ClinicalTrials.gov  
15 protocols could not be included due to the lack of methods and outcome data needed for  
16 analysis. Secondly, risk of publication bias among observational studies could not be  
17 assessed because too few studies reported HRs to be able to construct a funnel plot. The  
18 potential for publication bias limits the extent to which we can be confident results from  
19 observational studies represent patients in real clinical practice, as it is unknown whether  
20 outcomes of patients who do not benefit are underreported in available literature. Thirdly, the  
21 lack of comparative RCTs meant it was not possible to directly compare and confirm survival  
22 benefits observed between immunotherapies. Fourthly, it was not possible to meta-analyse  
23 the results from single arm observational studies, which prevented us from generating a  
24 summary estimate of treatment effectiveness from these studies. Finally, the study is hindered  
25 by the heterogeneity of the patient population. While we have explored some factors likely to  
26 affect patient outcomes, the variability in reporting the lines of therapy used in each study  
27 precluded our ability to fully explore the impact of this important factor. While our study had  
28 potential to be limited by comparing this therapy to chemotherapy solely recognised by NICE,  
29 we believe this is unlikely because NICE recommends a range of chemotherapy options in  
30 line with internationally accepted guidelines and evidence [13, 123, 124].  
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34 To conclude, among patients with aNSCLC, immunotherapy improved overall survival and  
35 incidence of treatment-related AEs compared to chemotherapy. Benefits to progression-free  
36 survival and QoL were less consistent. The variable effectiveness of this therapy to some  
37 outcomes and the expenses associated with its use suggest determining patients most likely  
38 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.



## References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
2. Cancer Research UK. Lung Cancer Incidence Statistics [Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#heading=Two>].
3. Cancer Research UK. Lung Cancer Mortality Statistics 2019 [Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/mortality#heading=Zero>].
4. Broggio J, Wong K, Gildea C, Emmet M, Finnigan S. Cancer survival in England: adult, stage at diagnosis and childhood – patients followed up to 2018. 2019.
5. Caul S, Broggio J. Cancer registration statistics, England: 2017: Office for National Statistics; 2019 [Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2017#main-points>].
6. Thomas R. Cancer incidence in Wales, 2001 – 2016: Welsh Cancer Intelligence and Surveillance Unit; 2019 [Available from: [www.wcisu.wales.nhs.uk/cancer-incidence-in-wales-1](http://www.wcisu.wales.nhs.uk/cancer-incidence-in-wales-1)].
7. Northern Ireland Cancer Registry. Lung Cancer. Queen's University Belfast.
8. Information Service Division Scotland. Cancer Incidence and Prevalence in Scotland (to December 2017). 2019.
9. Cancer Research UK. Types of Lung Cancer [Available from: <https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types>].
10. Stahel R, Peters S, Baas P, Brambilla E, Cappuzzo F, De Ruyscher D, et al. Strategies for improving outcomes in NSCLC: a look to the future. *Lung Cancer*. 2013;82(3):375-82.
11. Intlekofer AM, Thompson CB. At the bench: preclinical rationale for CTLA-4 and PD-1 blockade as cancer immunotherapy. *J Leukoc Biol*. 2013;94(1):25-39.
12. Hamanishi J, Mandai M, Matsumura N, Abiko K, Baba T, Konishi I. PD-1/PD-L1 blockade in cancer treatment: perspectives and issues. *Int J Clin Oncol*. 2016;21(3):462-73.
13. National Institute of Health and Care Excellence. Lung cancer: diagnosis and management. NICE guideline [NG122]. London 2019. [cited 2019]. Available from: <https://www.nice.org.uk/guidance/ng122/chapter/Recommendations#treatment>.
14. National Institute of Health and Care Excellence. Nivolumab for previously treated squamous non-small-cell lung cancer. Technology appraisal [TA483]. 4 – Committee discussion. 2017 [Available from: <https://www.nice.org.uk/guidance/ta483/chapter/4-Committee-discussion>].
15. National Institute of Health and Care Excellence. Nivolumab for previously treated non-squamous non-small-cell lung cancer. Technology appraisal guidance [TA484]. 4 –

1  
2  
3 Committee discussion. 2017 [Available from:  
4 <https://www.nice.org.uk/guidance/ta484/chapter/4-Committee-discussion>.  
5

6 16. National Institute of Health and Care Excellence. Atezolizumab for treating locally  
7 advanced or metastatic non-small-cell lung cancer after chemotherapy. Technology appraisal  
8 guidance [TA520]. 3 – Committee discussion. 2018 [  
9

10 17. National Institute of Health and Care Excellence. Durvalumab for treating locally  
11 advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation.  
12 Technology appraisal guidance [TA578]. 3 – Committee discussion. 2019 [Available from:  
13 <https://www.nice.org.uk/guidance/ta578/chapter/3-Committee-discussion>.  
14

15 18. National Institute of Health and Care Excellence. Pembrolizumab for untreated PD-L1-  
16 positive metastatic non-small-cell lung cancer. Technology appraisal guidance [TA531]. 3 –  
17 Committee discussion. 2018 [Available from:  
18 <https://www.nice.org.uk/guidance/ta531/chapter/3-Committee-discussion>.  
19

20 19. Chen R, Tao Y, Xu X, Shan L, Jiang H, Yin Q, et al. The efficacy and safety of  
21 nivolumab, pembrolizumab, and atezolizumab in treatment of advanced non-small cell lung  
22 cancer. *Discov*. 2018;26(143):155-66.  
23

24 20. Hsu JC, Chen YT, Lo J, Yang SC, Lee YC, Lin PC. Comparative efficacy and safety of  
25 immune checkpoint inhibitors for untreated and treated advanced non-small cell lung cancer:  
26 Meta-analysis and meta-regression analysis. *Pharmacoepidemiology and Drug Safety*.  
27 2019;28 (Supplement 2):126.  
28

29 21. Jiang Q, Xie M, He M, Yan F, Zhang X, Yu S. Anti-PD-1/PD-L1 antibodies versus  
30 docetaxel in patients with previously treated non-small-cell lung cancer. *Oncotarget*.  
31 2018;9(7):7672-83.  
32

33 22. Huang G, Sun X, Liu D, Zhang Y, Zhang B, Xiao G, et al. The efficacy and safety of  
34 anti-PD-1/PD-L1 antibody therapy versus docetaxel for pretreated advanced NSCLC: A meta-  
35 analysis. *Oncotarget*. 2018;9(3):4239-48.  
36

37 23. Peng TR, Wu TW. Efficacy of PD-1/PD-L1 inhibitors in patients with advanced non-  
38 small cell lung cancer: A meta-analysis of randomized clinical trials. *Thorac Cancer*.  
39 2019;10(5):1176-81.  
40

41 24. Cao D, Xu H, Xu X, Guo T, Ge W. A reliable and feasible way to predict the benefits  
42 of Nivolumab in patients with non-small cell lung cancer: a pooled analysis of 14 retrospective  
43 studies. *Oncolmmunology*. 2018;7(11).  
44

45 25. Bao M, Pan YJ, Wang R, Li SL, Liang J, Yung JM, et al. The efficacy of nivolumab for  
46 the treatment of advanced non-small cell lung cancer: A systematic review and meta-analysis  
47 of clinical trials. *International Journal of Clinical and Experimental Medicine*. 2017;10(1):153-  
48 61.  
49

50 26. Chen S, Hu B, Li H. A meta-analysis of nivolumab for the treatment of advanced non-  
51 small-cell lung cancer. *OncoTargets and Therapy*. 2018;11:7691-7.  
52

53 27. Liu J, Zhong Y, Peng S, Zhou X, Gan X. Efficacy and safety of PD1/PDL1 blockades  
54 versus docetaxel in patients with pretreated advanced non-small-cell lung cancer: A meta-  
55 analysis. *OncoTargets and Therapy*. 2018;11:8623-32.  
56  
57  
58  
59  
60

- 1  
2  
3 28. Abdel-Rahman O, Oweira H, Giryas A. Health-related quality of life in cancer patients  
4 treated with PD-(L)1 inhibitors: a systematic review. *Expert Rev Anticancer Ther.*  
5 2018;18(12):1231-9.  
6
- 7 29. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).  
8 PRISMA flow diagram [Available from: <http://prisma-statement.org/>].  
9
- 10 30. Spigel D, de Marinis F, Giaccone G, Reinmuth N, Vergnenegre A, Barrios CH, et al.  
11 Impower110: Interim overall survival (OS) analysis of a phase III study of atezolizumab (atezo)  
12 vs platinum-based chemotherapy (chemo) as first-line (1L) treatment (tx) in PD-L1–selected  
13 NSCLC. *European Society of Medical Oncology 2019 Congress Abstracts.* 2019.  
14
- 15 31. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al.  
16 Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N*  
17 *Engl J Med.* 2015;373(2):123-35.  
18
- 19 32. Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al. First-Line  
20 Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. *N Engl J Med.*  
21 2017;376(25):2415-26.  
22
- 23 33. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab  
24 versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *New England*  
25 *Journal of Medicine.* 2015;373(17):1627-39.  
26
- 27 34. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab  
28 versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer  
29 (KEYNOTE-010): A randomised controlled trial. *The Lancet.* 2016;387(10027):1540-50.  
30
- 31 35. Mok TSK, Wu YL, Kowalski DM, Turna HZ, Laktionov KK, Lubiniecki GM, et al.  
32 Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally  
33 advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-  
34 label, controlled, phase 3 trial. *The Lancet.* 2019;393(10183):1819-30.  
35
- 36 36. Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, et  
37 al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung  
38 cancer (POPLAR): A multicentre, open-label, phase 2 randomised controlled trial. *The Lancet.*  
39 2016;387(10030):1837-46.  
40
- 41 37. Wu YL, Lu S, Cheng Y, Zhou C, Wang J, Mok T, et al. Nivolumab Versus Docetaxel in  
42 a Predominantly Chinese Patient Population With Previously Treated Advanced NSCLC:  
43 CheckMate 078 Randomized Phase III Clinical Trial. *J Thorac Oncol.* 2019;14(5):867-75.  
44
- 45 38. Horn L, Spigel DR, Vokes EE, Holgado E, Ready N, Steins M, et al. Nivolumab Versus  
46 Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-  
47 Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and  
48 CheckMate 057). *Journal of Clinical Oncology.* 2017;35(35):3924-33.  
49
- 50 39. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Updated  
51 analysis of KEYNOTE-024: Pembrolizumab versus platinum-based chemotherapy for  
52 advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater.  
53 *Journal of Clinical Oncology.* 2019;37(7):537-46.  
54
- 55 40. Fehrenbacher L, von Pawel J, Park K, Rittmeyer A, Gandara DR, Ponce Aix S, et al.  
56 Updated Efficacy Analysis Including Secondary Population Results for OAK: A Randomized  
57 Phase III Study of Atezolizumab versus Docetaxel in Patients with Previously Treated  
58  
59  
60

1  
2  
3 Advanced Non-Small Cell Lung Cancer. *Journal of Thoracic Oncology: Official Publication of*  
4 *the International Association for the Study of Lung Cancer.* 2018;13(8):1156-70.  
5

6 41. Hida T, Kaji R, Satouchi M, Ikeda N, Horiike A, Nokihara H, et al. Atezolizumab in  
7 Japanese Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer: A  
8 Subgroup Analysis of the Phase 3 OAK Study. *Clin Lung Cancer.* 2018;19(4):e405-e15.  
9

10 42. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al.  
11 Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer  
12 (OAK): a phase 3, open-label, multicentre randomised controlled trial. *The Lancet.*  
13 2017;389(10066):255-65.  
14

15 43. Antonia SJ, Ozguroglu M. Durvalumab in Stage III Non-Small-Cell Lung Cancer. *The*  
16 *New England Journal of Medicine.* 2018;378(9):869-70.  
17

18 44. Vokes EE, Ready N, Felip E, Horn L, Burgio MA, Antonia SJ, et al. Nivolumab versus  
19 docetaxel in previously treated advanced non-small-cell lung cancer (CheckMate 017 and  
20 CheckMate 057): 3-year update and outcomes in patients with liver metastases. *Ann Oncol.*  
21 2018;29(4):959-65.  
22

23 45. Herbst RS, Baas P, Perez-Gracia JL, Felip E, Kim DW, Han JY, et al. Use of archival  
24 versus newly collected tumor samples for assessing PD-L1 expression and overall survival:  
25 An updated analysis of keynote-010 trial. *Ann Oncol.* 2019;30(2):281-9.  
26

27 46. Antonia SJ, Borghaei H, Ramalingam SS, Horn L, De Castro Carpeno J, Pluzanski A,  
28 et al. Four-year survival with nivolumab in patients with previously treated advanced non-  
29 small-cell lung cancer: a pooled analysis. *The Lancet Oncology.* 2019;20(10):1395-408.  
30

31 47. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al.  
32 Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N*  
33 *Engl J Med.* 2016;375(19):1823-33.  
34

35 48. Crino L, Bidoli P, Delmonte A, Grossi F, De Marinis F, Ardizzoni A, et al. Italian Cohort  
36 of Nivolumab Expanded Access Program in Squamous Non-Small Cell Lung Cancer: Results  
37 from a Real-World Population. *Oncologist.* 2019.  
38

39 49. Crino L, Bronte G, Bidoli P, Cravero P, Minenza E, Cortesi E, et al. Nivolumab and  
40 brain metastases in patients with advanced non-squamous non-small cell lung cancer. *Lung*  
41 *Cancer.* 2019;129:35-40.  
42

43 50. Garassino MC, Crino L, Catino A, Ardizzoni A, Cortesi E, Cappuzzo F, et al. Nivolumab  
44 in never-smokers with advanced squamous non-small cell lung cancer: Results from the Italian  
45 cohort of an expanded access program. *Tumour Biology.* 2018;40(11):1010428318815047.  
46

47 51. Liu J, Li S, Zhang S, Liu Y, Ma L, Zhu J, et al. Systemic immune-inflammation index,  
48 neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio can predict clinical outcomes in  
49 patients with metastatic non-small-cell lung cancer treated with nivolumab. *Journal of Clinical*  
50 *Laboratory Analysis.* 2019;(no pagination).  
51

52 52. Oya Y, Yoshida T, Kuroda H, Mikubo M, Kondo C, Shimizu J, et al. Predictive clinical  
53 parameters for the response of nivolumab in pretreated advanced non-small-cell lung cancer.  
54 *Oncotarget.* 2017;8(61):103117-28.  
55

56 53. Schouten RD, Muller M, de Gooijer CJ, Baas P, van den Heuvel M. Real life experience  
57 with nivolumab for the treatment of non-small cell lung carcinoma: Data from the expanded  
58  
59  
60

- 1  
2  
3 access program and routine clinical care in a tertiary cancer centre-The Netherlands Cancer  
4 Institute. *Lung Cancer*. 2018;126:210-6.  
5
- 6 54. Tiu AC, Potdar R, Djibo DA, Masab M, Dourado C. Clinical outcomes of African  
7 American patients with advanced or metastatic non-small cell lung cancer on Nivolumab in a  
8 single community-based cancer center. *Medical Oncology*. 2018;35(7):109.  
9
- 10 55. Yoo SH, Keam B, Kim M, Kim SH, Kim YJ, Kim TM, et al. Low-dose nivolumab can be  
11 effective in non-small cell lung cancer: Alternative option for financial toxicity. *ESMO Open*.  
12 2018;3(5).  
13
- 14 56. Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, et al. Association of  
15 immune-related adverse events with nivolumab efficacy in non-small cell lung cancer. *JAMA*  
16 *Oncology*. 2018;4(3):374-8.  
17
- 18 57. Ksienski D, Wai ES, Croteau N, Fiorino L, Brooks E, Poonja Z, et al. Efficacy of  
19 Nivolumab and Pembrolizumab in Patients With Advanced Non-Small-Cell Lung Cancer  
20 Needing Treatment Interruption Because of Adverse Events: A Retrospective Multicenter  
21 Analysis. *Clin Lung Cancer*. 2019;20(1):e97-e106.  
22
- 23 58. Zhuo M, Chen H, Zhang T, Yang X, Zhong J, Wang Y, et al. The potential predictive  
24 value of circulating immune cell ratio and tumor marker in atezolizumab treated advanced non-  
25 small cell lung cancer patients. *Cancer Biomark*. 2018;22(3):467-76.  
26
- 27 59. Haratani K, Hayashi H, Tanaka T, Kaneda H, Togashi Y, Sakai K, et al. Tumor immune  
28 microenvironment and nivolumab efficacy in EGFR mutation-positive non-small-cell lung  
29 cancer based on T790M status after disease progression during EGFR-TKI treatment. *Ann*  
30 *Oncol*. 2017;28(7):1532-9.  
31
- 32 60. Katsura H, Suga Y, Araya T, Kita T, Yoneda T, Tanaka N, et al. Efficacy and safety of  
33 nivolumab in patients with advanced non-small-cell lung cancer and poor performance status.  
34 *Journal of Cancer*. 2019;10(10):2139-44.  
35
- 36 61. Ravanelli M, Agazzi GM, Milanese G, Roca E, Silva M, Tiseo M, et al. Prognostic and  
37 predictive value of histogram analysis in patients with non-small cell lung cancer refractory to  
38 platinum treated by nivolumab: A multicentre retrospective study. *European Journal of*  
39 *Radiology*. 2019;118:251-6.  
40
- 41 62. Brustugun OT, Sprauten M, Helland Å. Real-world data on nivolumab treatment of non-  
42 small cell lung cancer. *Acta Oncologica*. 2017;56(3):438-40.  
43
- 44 63. Dudnik E, Moskovitz M, Daher S, Shamai S, Hanovich E, Grubstein A, et al.  
45 Effectiveness and safety of nivolumab in advanced non-small cell lung cancer: The real-life  
46 data. *Lung Cancer*. 2018;126:217-23.  
47
- 48 64. Geier M, Descourt R, Quere G, Corre R, Leveiller G, Lamy R, et al. Real life second-  
49 line nivolumab in advanced non-small-cell-lung cancer: Europe observational multicenter  
50 study of 259 patients. *Journal of Thoracic Oncology*. 2017;12 (11 Supplement 2):S2427.  
51
- 52 65. Grossi F, Crino L, Logroscino A, Canova S, Delmonte A, Melotti B, et al. Use of  
53 nivolumab in elderly patients with advanced squamous non-small-cell lung cancer: results  
54 from the Italian cohort of an expanded access programme. *European Journal of Cancer*.  
55 2018;100:126-34.  
56  
57  
58  
59  
60

- 1  
2  
3 66. Ksienski D, Wai ES, Croteau N, Freeman AT, Chan A, Fiorino L, et al. Pembrolizumab  
4 for advanced nonsmall cell lung cancer: Efficacy and safety in everyday clinical practice. *Lung*  
5 *Cancer*. 2019;133:110-6.  
6  
7 67. Passaro A, Mancuso P, Gandini S, Spitaleri G, Labanca V, Guerini-Rocco E, et al. Gr-  
8 MDSC-linked asset as a potential immune biomarker in pretreated NSCLC receiving  
9 nivolumab as second-line therapy. *Clinical and Translational Oncology*. 2019.  
10  
11 68. Sabatier R, Nicolas E, Paciencia M, Jonville-Bera AP, Madroszyk A, Cecile M, et al.  
12 Nivolumab in routine practice for older patients with advanced or metastatic non-small cell  
13 lung cancer. *Journal of Geriatric Oncology*. 2018;9(5):494-500.  
14  
15 69. Tournoy KG, Thomeer M, Germonpre P, Derijcke S, De Pauw R, Galdermans D, et al.  
16 Does nivolumab for progressed metastatic lung cancer fulfill its promises? An efficacy and  
17 safety analysis in 20 general hospitals. *Lung Cancer*. 2018;115:49-55.  
18  
19 70. Weis TM, Hough S, Reddy HG, Daignault-Newton S, Kalemkerian GP. Real-world  
20 comparison of immune checkpoint inhibitors in non-small cell lung cancer following platinum-  
21 based chemotherapy. *Journal of Oncology Pharmacy Practice*. 2019.  
22  
23 71. Tamiya M, Tamiya A, Hosoya K, Taniguchi Y, Yokoyama T, Fukuda Y, et al. Efficacy  
24 and safety of pembrolizumab as first-line therapy in advanced non-small cell lung cancer with  
25 at least 50% PD-L1 positivity: a multicenter retrospective cohort study (HOPE-001).  
26 *Investigational New Drugs*. 2019.  
27  
28 72. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab  
29 for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372(21):2018-28.  
30  
31 73. Ricciuti B, Genova C, Bassanelli M, De Giglio A, Brambilla M, Metro G, et al. Safety  
32 and Efficacy of Nivolumab in Patients With Advanced Non-small-cell Lung Cancer Treated  
33 Beyond Progression. *Clin Lung Cancer*. 2019;20(3):178-85.e2.  
34  
35 74. Ricciuti B, Genova C, De Giglio A, Brambilla M, Bassanelli M, Dal Bello MG, et al.  
36 Impact of Immune-Related Adverse Events on Survival in Patients with Advanced Non-Small  
37 Cell Lung Cancer Treated with Nivolumab. *Journal of Thoracic Oncology*. 2018;13 (10  
38 Supplement):S390-S1.  
39  
40 75. Leighl NB, Hellmann MD, Hui R, Carcereny E, Felip E, Ahn MJ, et al. Pembrolizumab  
41 in patients with advanced non-small-cell lung cancer (KEYNOTE-001): 3-year results from an  
42 open-label, phase 1 study. *The Lancet Respiratory Medicine*. 2019;7(4):347-57.  
43  
44 76. Garon EB, Hellmann MD, Rizvi NA, Carcereny E, Leighl NB, Ahn MJ, et al. Five-Year  
45 Overall Survival for Patients With Advanced Non-Small-Cell Lung Cancer Treated With  
46 Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. *Journal of clinical oncology*  
47 : official journal of the American Society of Clinical Oncology. 2019;37(28):2518-27.  
48  
49 77. Alama A, Coco S, Genova C, Rossi G, Fontana V, Tagliamento M, et al. Prognostic  
50 Relevance of Circulating Tumor Cells and Circulating Cell-Free DNA Association in Metastatic  
51 Non-Small Cell Lung Cancer Treated with Nivolumab. *J Clin Med*. 2019;8(7).  
52  
53 78. Bagley SJ, Kothari S, Aggarwal C, Bauml JM, Alley EW, Evans TL, et al. Pretreatment  
54 neutrophil-to-lymphocyte ratio as a marker of outcomes in nivolumab-treated patients with  
55 advanced non-small-cell lung cancer. *Lung Cancer*. 2017;106:1-7.  
56  
57  
58  
59  
60

- 1  
2  
3 79. Dumenil C, Massiani MA, Dumoulin J, Giraud V, Labrune S, Chinet T, et al. Clinical  
4 factors associated with early progression and grade 3-4 toxicity in patients with advanced non-  
5 small-cell lung cancers treated with nivolumab. *PLoS ONE*. 2018;13(4).  
6
- 7 80. Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W, et al. Neutrophil-to-  
8 Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in  
9 patients with non-small cell lung cancer (NSCLC) treated with nivolumab. *Lung Cancer*.  
10 2017;111:176-81.  
11
- 12 81. Garde-Noguera J, Martin-Martorell P, De Julian M, Perez-Altozano J, Salvador-  
13 Coloma C, Garcia-Sanchez J, et al. Predictive and prognostic clinical and pathological factors  
14 of nivolumab efficacy in non-small-cell lung cancer patients. *Clin Transl Oncol*.  
15 2018;20(8):1072-9.  
16
- 17 82. Kaderbhai CG, Richard C, Fumet JD, Aarnink A, Ortiz-Cuaran S, Perol M, et al.  
18 Response to first line chemotherapy regimen is associated with efficacy of nivolumab in non-  
19 small-cell lung cancer. *Oncolmmunology*. 2017;6(9).  
20
- 21 83. Lacerenza LG, Messuti L, Deligianni M, Chioni A, Bindi M, Guidi O, et al. Non-small  
22 cell lung cancer treated second-line with Nivolumab: Analysis of clinical outcomes and  
23 correlation between PD-L1 and response to therapy. *Observational register REGNIVO*.  
24 [Italian]. *Giornale Italiano di Farmacia Clinica*. 2019;33(2):68-76.  
25
- 26 84. Merino Almazan M, Duarte Perez JM, Marin Pozo JF, Ortega Granados AL, Muros De  
27 Fuentes B, Quesada Sanz P, et al. A multicentre observational study of the effectiveness,  
28 safety and economic impact of nivolumab on non-small-cell lung cancer in real clinical  
29 practice. *Int J Clin Pharm*. 2019;41(1):272-9.  
30
- 31 85. Montana M, Garcia ME, Ausias N, Jeanpierre M, Meiffren M, Giorgi R, et al. Efficacy  
32 and safety of nivolumab in patients with non-small cell lung cancer: a retrospective study in  
33 clinical practice. *J Chemother*. 2019;31(2):90-4.  
34
- 35 86. Naqash AR, Stroud CRG, Butt MU, Dy GK, Hegde A, Muzaffar M, et al. Co-relation of  
36 overall survival with peripheral blood-based inflammatory biomarkers in advanced stage non-  
37 small cell lung cancer treated with anti-programmed cell death-1 therapy: results from a single  
38 institutional database. *Acta Oncologica*. 2018;57(6):867-72.  
39
- 40 87. Passiglia F, Galvano A, Castiglia M, Incorvaia L, Calo V, Listi A, et al. Monitoring blood  
41 biomarkers to predict nivolumab effectiveness in NSCLC patients. *Therapeutic Advances in*  
42 *Medical Oncology*. 2019;11(no pagination).  
43
- 44 88. Sekine K, Kanda S, Goto Y, Horinouchi H, Fujiwara Y, Yamamoto N, et al. Change in  
45 the lymphocyte-to-monocyte ratio is an early surrogate marker of the efficacy of nivolumab  
46 monotherapy in advanced non-small-cell lung cancer. *Lung Cancer*. 2018;124:179-88.  
47
- 48 89. Shamaï S, Merimsky O. Efficacy and safety of nivolumab in non-small cell lung cancer  
49 patients in tel-aviv tertiary medical center: Facing the reality. *Molecular and Clinical Oncology*.  
50 2018;9(4):419-22.  
51
- 52 90. Kawachi H, Fujimoto D, Morimoto T, Hosoya K, Sato Y, Kogo M, et al. Early depth of  
53 tumor shrinkage and treatment outcomes in non-small cell lung cancer treated using  
54 Nivolumab. *Investigational New Drugs*. 2019.  
55
- 56 91. Passiglia F, Cappuzzo F, Alabiso O, Bettini AC, Bidoli P, Chiari R, et al. Efficacy of  
57 nivolumab in pre-treated non-small-cell lung cancer patients harbouring KRAS mutations. *Br*  
58 *J Cancer*. 2019;120(1):57-62.  
59  
60

- 1  
2  
3 92. Lisberg A, Andrew Tucker D, Goldman JW, Wolf B, Carroll J, Hardy A, et al. Treatment-related adverse events predict improved clinical outcome in nsclc patients on KEYNOTE-001 at a single center. *Cancer Immunology Research*. 2018;6(3):288-94.
- 4  
5  
6  
7 93. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, et al. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. *Annals of oncology : official journal of the European society for medical oncology*. 2017;28(3):583-9..
- 8  
9  
10  
11  
12 94. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *N Engl J Med*. 2017;377(20):1919-29.
- 13  
14  
15  
16 95. Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. *N Engl J Med*. 2018;378(22):2093-104.
- 17  
18  
19  
20 96. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. *The New England Journal of Medicine*. 2019;28.
- 21  
22  
23  
24 97. Gauvain C, Vauleon E, Chouaid C, Le Rhun E, Jabot L, Scherpereel A, et al. Intracerebral efficacy and tolerance of nivolumab in non-small-cell lung cancer patients with brain metastases. *Lung Cancer*. 2018;116:62-6.
- 25  
26  
27  
28 98. Krefting F, Basara N, Schutte W, Spath-Schwalbe E, Alt J, Thiel S, et al. Clinical Experience of Immunotherapy Treatment: Efficacy and Toxicity Analysis of the Compassionate Use Program of Nivolumab in Patients with Advanced Squamous Cell Non-Small Cell Lung Cancer. *Oncol Res Treat*. 2019;42(5):243-55.
- 29  
30  
31  
32  
33 99. Edahiro R, Kanazu M, Kurebe H, Mori M, Fujimoto D, Taniguchi Y, et al. Clinical outcomes in non-small cell lung cancer patients with an ultra-high expression of programmed death ligand-1 treated using pembrolizumab as a first-line therapy: A retrospective multicenter cohort study in Japan. *PLoS ONE*. 2019;14(7).
- 34  
35  
36  
37  
38 100. Kanai O, Kim YH, Demura Y, Kanai M, Ito T, Fujita K, et al. Efficacy and safety of nivolumab in non-small cell lung cancer with preexisting interstitial lung disease. *Thorac Cancer*. 2018;9(7):847-55.
- 39  
40  
41  
42 101. Kobayashi H, Omori S, Nakashima K, Wakuda K, Ono A, Kenmotsu H, et al. Response to the treatment immediately before nivolumab monotherapy may predict clinical response to nivolumab in patients with non-small cell lung cancer. *Int J Clin Oncol*. 2017;22(4):690-7.
- 43  
44  
45  
46 102. Kobayashi K, Nakachi I, Naoki K, Satomi R, Nakamura M, Inoue T, et al. Real-world Efficacy and Safety of Nivolumab for Advanced Non-Small-cell Lung Cancer: A Retrospective Multicenter Analysis. *Clin Lung Cancer*. 2018;19(3):e349-e58.
- 47  
48  
49  
50 103. Takeda T, Takeuchi M, Saitoh M, Takeda S. Neutrophil-to-lymphocyte ratio after four weeks of nivolumab administration as a predictive marker in patients with pretreated non-small-cell lung cancer. *Thorac Cancer*. 2018;9(10):1291-9.
- 51  
52  
53  
54 104. Teraoka S, Fujimoto D, Morimoto T, Kawachi H, Ito M, Sato Y, et al. Early Immune-Related Adverse Events and Association with Outcome in Advanced Non-Small Cell Lung Cancer Patients Treated with Nivolumab: A Prospective Cohort Study. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer*. 2017;12(12):1798-805.
- 55  
56  
57  
58  
59  
60



- 1  
2  
3 105. Nosaki K, Saka H, Hosomi Y, Baas P, de Castro G, Reck M, et al. Safety and efficacy  
4 of pembrolizumab monotherapy in elderly patients with PD-L1-positive advanced non-small-  
5 cell lung cancer: Pooled analysis from the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-  
6 042 studies. *Lung Cancer*. 2019;135:188-95.  
7  
8 106. von Pawel J, Bordoni R, Satouchi M, Fehrenbacher L, Cobo M, Han JY, et al. Long-  
9 term survival in patients with advanced non-small-cell lung cancer treated with atezolizumab  
10 versus docetaxel: Results from the randomised phase III OAK study. *Eur J Cancer*.  
11 2019;107:124-32.  
12  
13 107. Manrique MCA, Martinez JM, Gonzalez JG, Afonso FJA, Quintela ML, Nunez NF, et  
14 al. Real world data of nivolumab for previously treated non-small cell lung cancer patients: A  
15 Galician lung cancer group clinical experience. *Translational Lung Cancer Research*.  
16 2018;7(3):404-15.  
17  
18 108. Reck M, Brahmer J, Bennett B, Taylor F, Penrod JR, DeRosa M, et al. Evaluation of  
19 health-related quality of life and symptoms in patients with advanced non-squamous non-small  
20 cell lung cancer treated with nivolumab or docetaxel in CheckMate 057. *European Journal of*  
21 *Cancer*. 2018;102:23-30.  
22  
23 109. Brahmer JR, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al.  
24 Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced,  
25 PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label  
26 phase 3 trial. *Lancet Oncol*. 2017;18(12):1600-9.  
27  
28 110. Hui R, Özgüroğlu M, Villegas A, Daniel D, Vicente D, Murakami S, et al. Patient-  
29 reported outcomes with durvalumab after chemoradiotherapy in stage III, unresectable non-  
30 small-cell lung cancer (PACIFIC): a randomised, controlled, phase 3 study. *Lancet Oncol*.  
31 2019;20(12):1670-80.  
32  
33 111. Bordoni R, Ciardiello F, von Pawel J, Cortinovis D, Karagiannis T, Ballinger M, et al.  
34 Patient-Reported Outcomes in OAK: A Phase III Study of Atezolizumab Versus Docetaxel in  
35 Advanced Non-Small-cell Lung Cancer. *Clin Lung Cancer*. 2018;19(5):441-9.  
36  
37 112. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of  
38 life. *Health Policy*. 1990;16(3):199-208.  
39  
40 113. Hollen PJ, Gralla RJ, Kris MG, Potanovich LM. Quality of life assessment in individuals  
41 with lung cancer: testing the Lung Cancer Symptom Scale (LCSS). *Eur J Cancer*. 1993;29A  
42 Suppl 1:S51-8.  
43  
44 114. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13:  
45 a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use  
46 in lung cancer clinical trials. EORTC Study Group on Quality of Life. *Eur J Cancer*.  
47 1994;30A(5):635-42.  
48  
49 115. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The  
50 European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life  
51 Instrument for Use in International Clinical Trials in Oncology. *JNCI Journal of the National*  
52 *Cancer Institute*. 1993;85(5):365-76.  
53  
54 116. Genova C, Boccardo S, Mora M, Rijavec E, Biello F, Rossi G, et al. Correlation  
55 between B7-H4 and Survival of Non-Small-Cell Lung Cancer Patients Treated with Nivolumab.  
56 *J Clin Med*. 2019;8(10).  
57  
58  
59  
60

- 1  
2  
3 117. Gadgeel SM, Lukas RV, Goldschmidt J, Conkling P, Park K, Cortinovis D, et al.  
4 Atezolizumab in patients with advanced non-small cell lung cancer and history of  
5 asymptomatic, treated brain metastases: Exploratory analyses of the phase III OAK study.  
6 Lung Cancer. 2019;128:105-12.  
7
- 8 118. Somarouthu B, Lee SI, Urban T, Sadow CA, Harris GJ, Kambadakone A. Immune-  
9 related tumour response assessment criteria: a comprehensive review. Br J Radiol.  
10 2018;91(1084):20170457.  
11
- 12 119. Li HY, McSharry M, Bullock B, Nguyen TT, Kwak J, Poczobutt JM, et al. The Tumor  
13 Microenvironment Regulates Sensitivity of Murine Lung Tumors to PD-1/PD-L1 Antibody  
14 Blockade. Cancer Immunol Res. 2017;5(9):767-77.  
15
- 16 120. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New  
17 response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J  
18 Cancer. 2009;45(2):228-47.  
19
- 20 121. Fleming TR, Rothmann MD, Lu HL. Issues in using progression-free survival when  
21 evaluating oncology products. J Clin Oncol. 2009;27(17):2874-80.  
22
- 23 122. Hussain S, Turner AM, Woolhouse I. Determinants of patient experiences during the  
24 lung cancer pathway: a systematic review. PROSPERO 2019 CRD42019126574. 2019.  
25
- 26 123. Besse B, Adjei A, Baas P, Meldgaard P, Nicolson M, Paz-Ares L, et al. 2nd ESMO  
27 Consensus Conference on Lung Cancer: non-small cell lung cancer first-line/second and  
28 further lines of treatment in advanced disease. Ann Oncol. 2014;25(8):1475-84.  
29
- 30 124. PDQ® Adult Treatment Editorial Board. PDQ Non-Small Cell Lung Cancer Treatment.  
31 Bethesda, MD: National Cancer Institute, 2020. [Available at:  
32 <https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq>].  
33  
34  
35  
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37  
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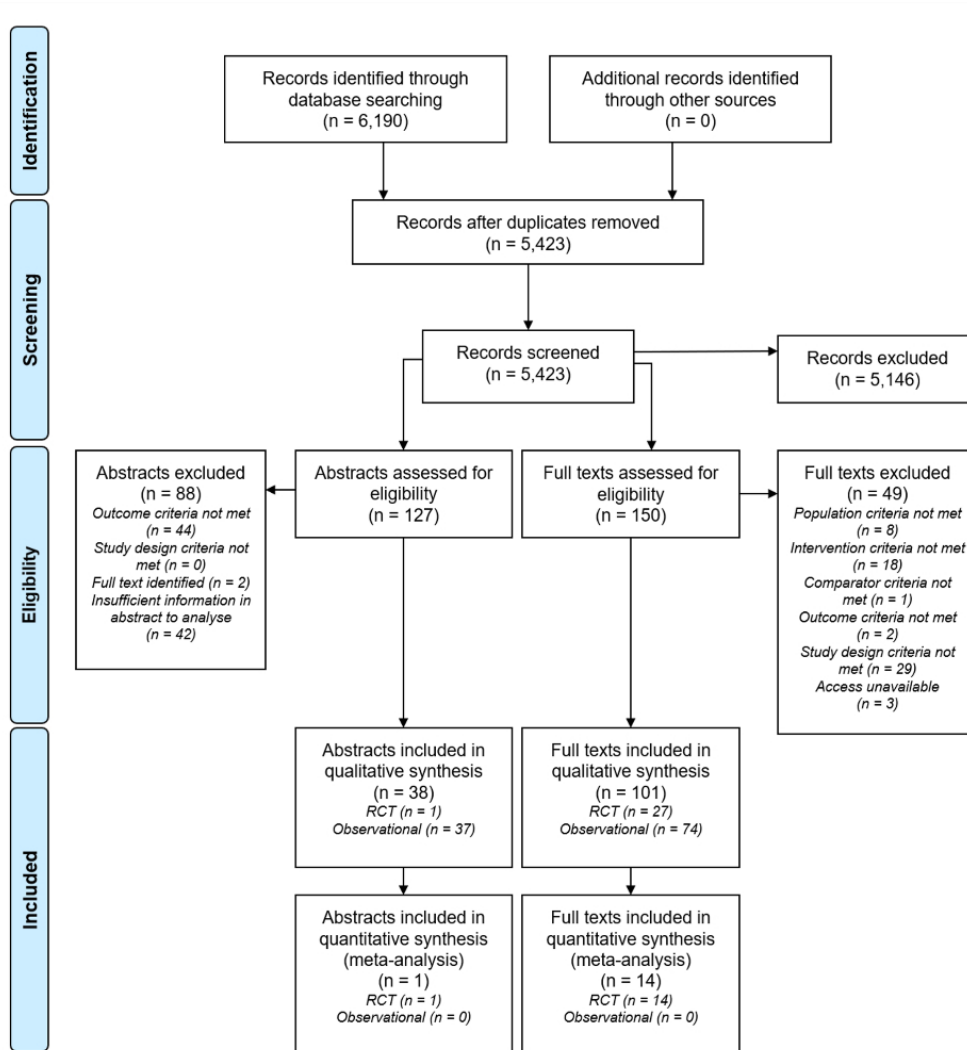


Figure 1 – PRISMA flow diagram of review Adapted from [29].

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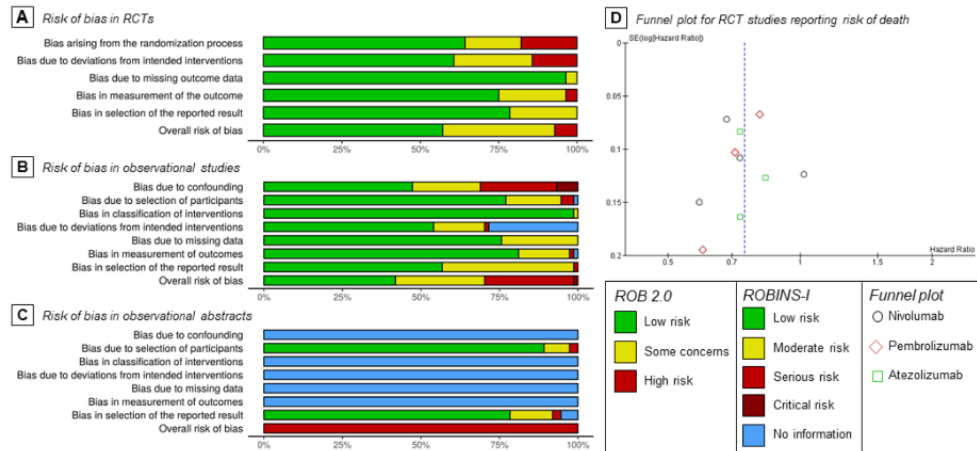


Figure 2 – Risk of Bias Assessment Summary A) Risk of bias summary bar chart for all included RCTs full texts and abstracts, assessed by ROB 2.0, B) Risk of bias summary bar chart for all included observational full texts, assessed by ROBINS-I, C) Risk of bias summary bar chart for all included observational 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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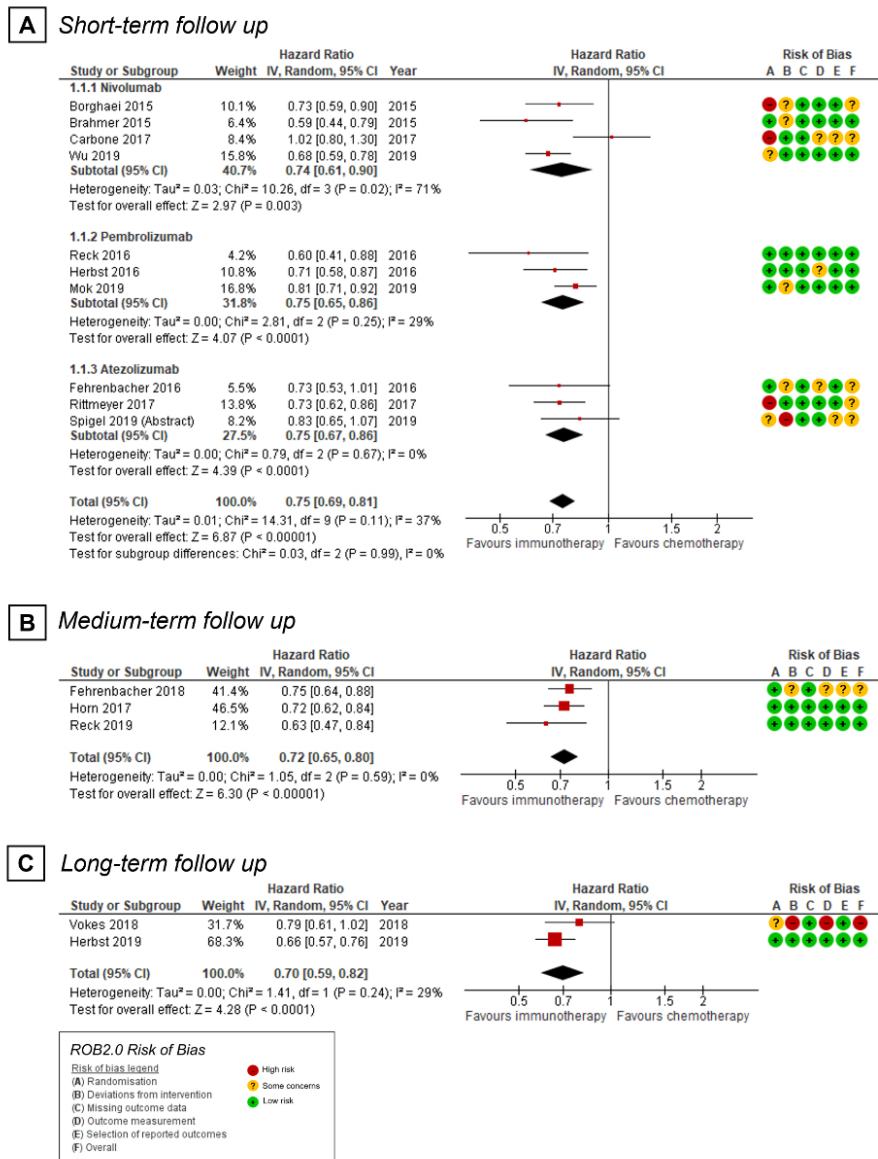


Figure 3 – Meta-analysed risk of death in RCTs A) Meta-analysed risk of death in studies with short-term follow up [30-37, 42, 47]. B) Meta-analysed risk of death in studies with medium-term follow up [38-40]. C) Meta-analysed risk of death in studies with long-term follow up [44, 45].

80x104mm (300 x 300 DPI)

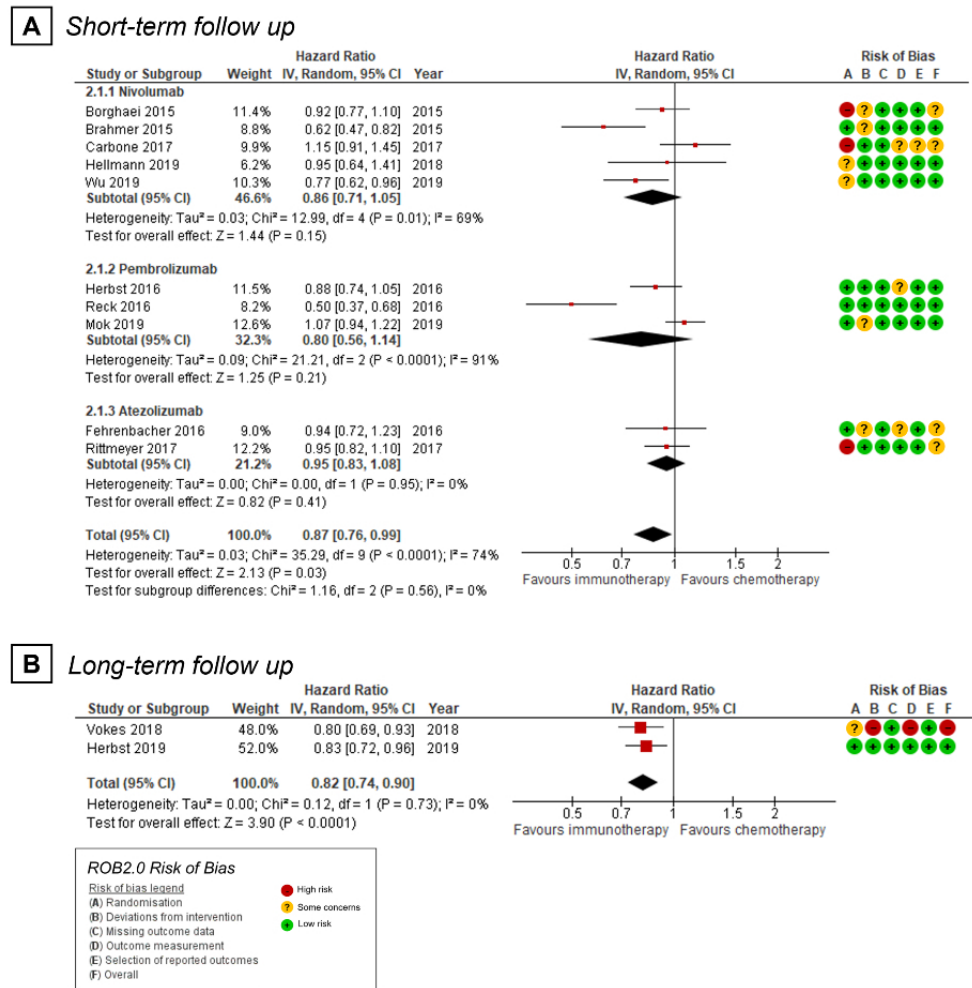


Figure 4 – Meta-analysed risk of progression or death in RCTs A) Meta-analysed risk of progression or death in RCTs with a short-term follow up [31–37, 42, 47, 96]. B) Meta-analysed risk of progression or death in RCTs with a long-term follow up [44, 45].

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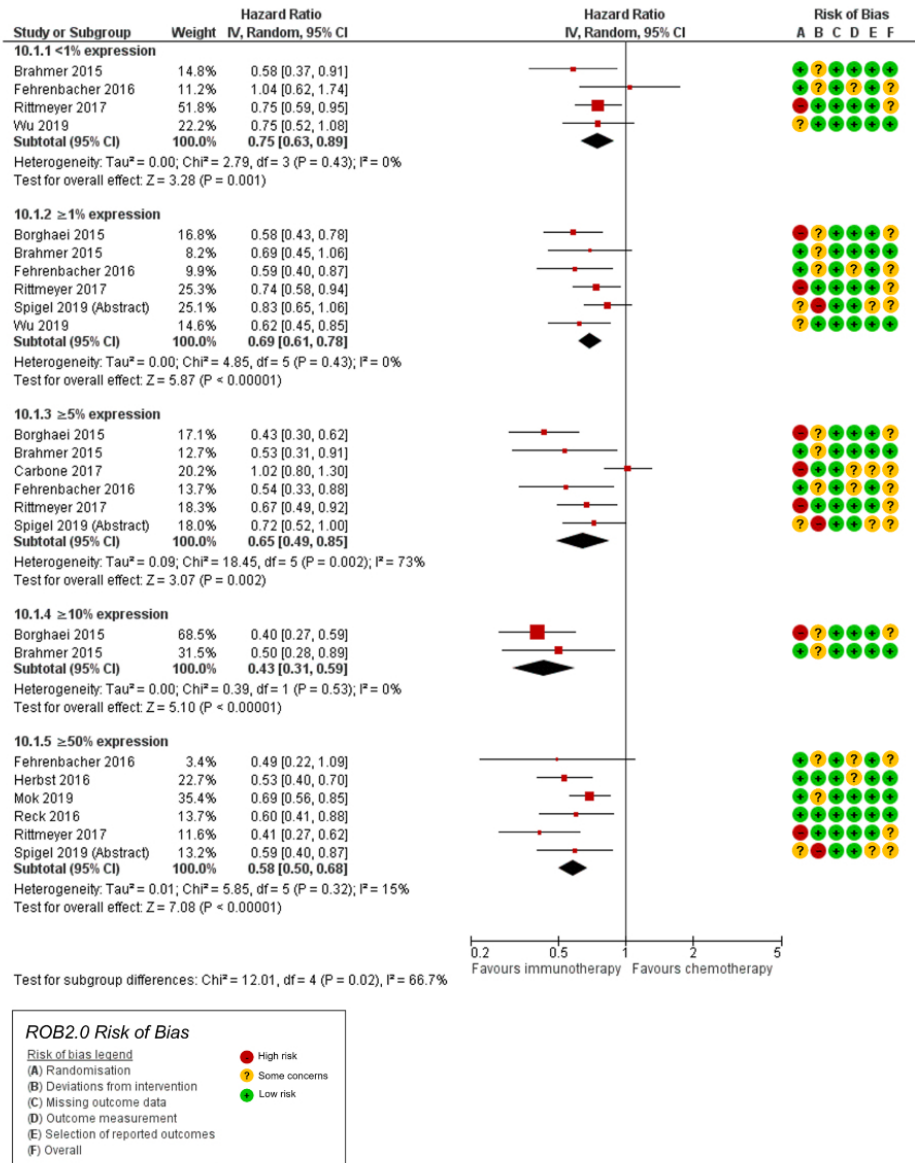


Figure 5 - Meta-analysis of risk of death by PDL1 expression status for patients receiving nivolumab, pembrolizumab or atezolizumab in included RCTs [30 – 37, 42, 47] Pembrolizumab data from patients with less than 50% expression could not be included, because a breakdown of survival outcomes was not 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 Figure 7*..... 68

**Supplementary References (continued from main reference list)**..... **69**

Confidential: For Review Only

## 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

## 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	<ul style="list-style-type: none"> <li>Age group filtered to 'Adult (18 – 64)' and 'Older Adult (65+)'</li> <li>No filters applied to sex</li> <li>'Accepts Healthy Volunteers' not selected</li> </ul>
Targeted search	<ul style="list-style-type: none"> <li>'Intervention/treatment' defined as 'Nivolumab', 'Pembrolizumab', 'Atezolizumab' or 'Durvalumab'</li> <li>No other search specifications</li> </ul>
Locations	No filters applied
Additional criteria	No filters applied

*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

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

## Supplementary Results

### Characteristics of Included Studies

#### Included RCT studies

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

<sup>1</sup> Median and range unless otherwise specified

<sup>2</sup> Squamous

<sup>3</sup> 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, 2 <sup>nd</sup> line	582	52	61 (37-84)	91	NSq = 100%	IIIB, IV	Not specified	QoL, AEs
		Docetaxel 75mg/m <sup>2</sup> per 3 weeks, 2 <sup>nd</sup> line		58	64(21-85)	92				
CheckMate 017+057	Horn et al, 2017 [38]	Nivolumab 3mg/kg per 2 weeks, 2 <sup>nd</sup> line	854	Reported previously [31, 33]			IIIB, IV	24.2 minimum	OS, PFS, AEs (2-year outcomes)	
		Docetaxel 75mg/m <sup>2</sup> per 3 weeks, 2 <sup>nd</sup> line								
	Vokes et al, 2018 [44]	Nivolumab 3mg/kg per 2 weeks, 2 <sup>nd</sup> line or later	418	Reported previously [31, 33]			IIIB, IV	36.0 minimum	OS, PFS, AEs (3-year outcomes)	
		Docetaxel 75mg/m <sup>2</sup> per 3 weeks, 2 <sup>nd</sup> line or later	.							

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, 2 <sup>nd</sup> 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 <sup>2</sup> per 3 weeks, 2 <sup>nd</sup> line					Sq = 32% NSq = 68%			
CheckMate 026	Carbone et al, 2017 [32]	Nivolumab 3mg/kg per 2 weeks, 1 <sup>st</sup> 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, 1 <sup>st</sup> line		55	65 (29-87)					



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, 1 <sup>st</sup> or 2 <sup>nd</sup> 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 <sup>2</sup> per 3 weeks, 1 <sup>st</sup> – 3 <sup>rd</sup> line		81	60 (38-78)		Sq = 40% NSq = 60%			
CheckMate 227	Hellmann et al, 2018 [95]	Nivolumab 240mg per 2 weeks, 1 <sup>st</sup> 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, 1 <sup>st</sup> line		65.5	64 (29-87)		Sq = 29.2% NSq = 70.8%			
	Hellmann et al, 2019 [96]	Nivolumab 240mg per 2 weeks, 1 <sup>st</sup> line	793	68.7	64 (27-85)		Sq = 29.5% NSq = 70.5%	IV, recurrent	29.3 minimum	OS, PFS
		Chemotherapy according to histology, 1 <sup>st</sup> line		65.5	64 (29-87)		Sq = 29.2% NSq = 70.8%			

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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> line or later					Sq = 23% NSq = 71%			
		Docetaxel 75mg/m <sup>2</sup> per 3weeks, 2 <sup>nd</sup> line or later					Sq = 19% NSq = 70%			
	Herbst et al, 2019 [45]	Pembrolizumab, 2 or 10mg/kg per 3 weeks, 1 <sup>st</sup> 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 <sup>2</sup> per 3 weeks, 1 <sup>st</sup> line or later		Sq = 19% NSq = 70%								

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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, 1 <sup>st</sup> line	305	59.7	64.5 (33-90)	.	Sq = 18.8% NSq = 81.2%	IV	11.2 median	OS, AEs
		Investigator's choice chemotherapy, 1 <sup>st</sup> line		62.9	66.0 (38-85)	.	Sq = 17.9% NSq = 82.1%			
	Reck et al, 2019 [39]	Pembrolizumab 200mg per 3 weeks, 1 <sup>st</sup> 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, 1 <sup>st</sup> line		62.9	66.0 (38-85)	.	Sq = 17.9% NSq = 82.1%			
	Brahmer et al, 2017 [109]	Pembrolizumab 200mg per 3 weeks, 1 <sup>st</sup> line	305	Reported previously [47]				Advanced	6.0 minimum	QoL, deaths
		Investigator's choice chemotherapy, 1 <sup>st</sup> line								

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, 1 <sup>st</sup> 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 <sup>2</sup> ) OR Pemetrexed (500mg/m <sup>2</sup> ), 1 <sup>st</sup> line		71	66.0 (38-85)	.	Sq = 39% NSq = 61%			
OAK	Rittmeyer et al, 2017 [42]	Atezolizumab 1200mg per 3 weeks, 2 <sup>nd</sup> or 3 <sup>rd</sup> 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 <sup>2</sup> per 3 weeks, 2 <sup>nd</sup> or 3 <sup>rd</sup> 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, 2 <sup>nd</sup> 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 <sup>2</sup> per 3 weeks, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> line or later	850	Reported previously [42]				Locally advanced and metastatic	.	QoL
		Docetaxel 75mg/m <sup>2</sup> per 3 weeks, 2 <sup>nd</sup> line or later								
	Hida et al, 2018 [41]	Atezolizumab 1200mg per 3 weeks, 2 <sup>nd</sup> line or 3 <sup>rd</sup> 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 <sup>2</sup> per 3 weeks, 2 <sup>nd</sup> line or 3 <sup>rd</sup> 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		
OAK	Gadgeel et al, 2019 [117]	Atezolizumab 1200mg per 3 weeks, 2 <sup>nd</sup> or 3 <sup>rd</sup> line	850	62.4	63.5 (33-82)	.	Sq = 28.3% NSq = 71.7%	21.0 median	OS, AEs
		Docetaxel 75mg/m <sup>2</sup> per 3 weeks, 2 <sup>nd</sup> or 3 <sup>rd</sup> line		62.3	64.0 (34-95)	.	Sq = 28.1% NSq = 71.9%		
POPLAR	Fehrenbacher et al, 2016 [36]	Atezolizumab 1200mg per 3 weeks, 2 <sup>nd</sup> or 3 <sup>rd</sup> line	287	65.0	62.0 (42-82)	.	Sq = 34% NSq = 66%	14.8 median	OS, PFS, AEs, deaths
		Docetaxel 75mg/m <sup>2</sup> per 3 weeks, 2 <sup>nd</sup> or 3 <sup>rd</sup> line		53.0	62.0 (36-84)	.	Sq = 34% NSq = 66%	15.7 median	

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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> 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, 1 <sup>st</sup> -3 <sup>rd</sup> 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, 1 <sup>st</sup> -3 <sup>rd</sup> line		65.1	62.0 (31-74)	68.6	Sq = 28.0% NSq = 68.6%			
		Platinum-based chemotherapy, patients ≥75yrs, 1 <sup>st</sup> -3 <sup>rd</sup> line		63.5	77.0 (75-90)	61.7	Sq = 24.3% NSq = 70.4%			
		Platinum-based chemotherapy, patients <75yrs. 1 <sup>st</sup> -3 <sup>rd</sup> 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, <sup>45</sup> , 2 <sup>nd</sup> or 3 <sup>rd</sup> 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, 2 <sup>nd</sup> or 3 <sup>rd</sup> line		66.0	64.0 (33-82)	74.0	Sq = 30% NSq = 70%			
		Docetaxel 75mg/m <sup>2</sup> per 3 weeks, LTS, 2 <sup>nd</sup> or 3 <sup>rd</sup> line		58.0	62.0 (41-84)	68.0	Sq = 16% NSq = 84%			
		Docetaxel 75mg/m <sup>2</sup> per 3 weeks, LTS, 2 <sup>nd</sup> or 3 <sup>rd</sup> line		62.0	64.0 (34-85)	73.0	Sq = 30% NSq = 70%			

<sup>5</sup> 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, 1 <sup>st</sup> 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, 1 <sup>st</sup> line or later	.	OS, PFS, AEs
Bins et al, 2018 [128]	Cohort study	161	67	64, $\sigma$ 8.1 <sup>6</sup>	Holland, 2 centres	Sq = 29%, Ad <sup>7</sup> = 60%, LC <sup>8</sup> = 9%, Ud <sup>9</sup> = 1%	Previously untreated	Nivolumab 3mg/kg per 2 weeks, 1 <sup>st</sup> line or later	~4.2	AEs, deaths, impact of SNPs

<sup>6</sup> Mean (standard deviation)<sup>7</sup> Adenocarcinoma<sup>8</sup> Large cell carcinoma<sup>9</sup> Undifferentiated

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, 2 <sup>nd</sup> 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, 1 <sup>st</sup> 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, 2 <sup>nd</sup> 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)	Switzerland, 1 centre	Sq = 35%, Ad = 58%	Metastatic, previously treated	Nivolumab 3mg/kg per 2 weeks, 1 <sup>st</sup> 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 <sup>10</sup> = 6%	Advanced, mostly stage IV or recurrent	Nivolumab 3mg/kg per 2 weeks, 2 <sup>nd</sup> 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, 1 <sup>st</sup> or 2 <sup>nd</sup> 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, 2 <sup>nd</sup> line	.	Impact of tumour histology, NLR, ALC, and ANC

<sup>10</sup> Not otherwise specified

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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, 1 <sup>st</sup> 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, 2 <sup>nd</sup> line or later	.	AEs
Fukihara et al, 2019 [136]	Cohort study	170	73.5	With IRP: 67.0 (58-73) No IRP: 70.0 (63-73)	Japan, 3 centres	Sq = 30% NSq = 70%  Sq = 36% NSq = 64%	Advanced or recurrent	Nivolumab 3mg/kg per 2 weeks, 1 <sup>st</sup> line or later Pembroli-zumab 200mg per 3 weeks, 1 <sup>st</sup> line or later	9.9 median	Impact of drug used on risk of IRP <sup>11</sup>

<sup>11</sup> Immune-related pneumonitis

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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> line	7.1 median	OS, PFS, deaths, AEs
Garde-Noguera et al, 2018 [81]	Cohort study	175	73.1	61.5 <sup>12</sup>	Spain, 14 centres	Sq = 22.9%, NSq = 77.1%	Stage III, IVA, or IVB	Nivolumab 3mg/kg, 2 <sup>nd</sup> line or later	.	OS, PFS, deaths and AEs, impact of histology, ECOG PS, metastases

<sup>12</sup> No range provided



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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, 2 <sup>nd</sup> 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 <sup>13</sup> : 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, 1 <sup>st</sup> 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%				

<sup>13</sup> 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, $\sigma$ 8.4 <sup>14</sup>	France, 2 centres	Sq = 16%, Ad = 82%	Advanced or metastatic	Nivolumab 3mg/kg per 2 weeks, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> 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 <sup>15</sup> = 4%	Stage IIIB, IV or recurrent; EGFR-mutation positive	Nivolumab, 1 <sup>st</sup> – 3 <sup>rd</sup> line	7.3 median	OS, PFS, impact of T790 mutation and PDL1 TPS

<sup>14</sup> Mean (standard deviation)

<sup>15</sup> Adeno-squamous

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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, 2 <sup>nd</sup> 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) <sup>16</sup>	Switzerland, 1 centre	Sq = 35%, Ad = 57%	Metastatic	Nivolumab 3mg/kg per 2 weeks, 1 <sup>st</sup> 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, unresectable	Nivolumab 3mg/kg per 2 weeks, 2 <sup>nd</sup> – 4 <sup>th</sup> lines	.	Deaths, AEs, impact of ECOG PS and CRP /albumin

<sup>16</sup> Mean (range)

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, $\sigma$ 10 <sup>17</sup>	France, 3 centres	Sq = 36.4%, Ad = 60%, LC = 1.7%	Stage IIIB or IV, previously treated	Nivolumab 3mg/kg per 2 weeks, 1 <sup>st</sup> line	.	OS, PFS, impact of initial best response to 1 <sup>st</sup> 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, 2 <sup>nd</sup> line or later	.	PFS, AEs
Karantanos et al, 2019 [137]	Cohort study	22	54.5	62, $\sigma$ 9.37 <sup>18</sup>	USA, 1 centre	Sq = 45.5%, Ad = 54.5%	Stage III or IV, pre-treated	Nivolumab 3mg/kg per 2 weeks, 2 <sup>nd</sup> –4 <sup>th</sup> line	.	OS <sup>19</sup>

<sup>17</sup> Mean (standard deviation)

<sup>18</sup> Mean (standard deviation)

<sup>19</sup> 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, 2 <sup>nd</sup> 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 <sup>20</sup> : 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, 2 <sup>nd</sup> line or later	.	OS, PFS

<sup>20</sup> Palliative care patients

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, 1 <sup>st</sup> 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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> 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, 1 <sup>st</sup> line or later	6.1 median	OS, PFS, deaths, AEs, impact of ECOG PS

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, 1 <sup>st</sup> 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, 1 <sup>st</sup> 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, 2 <sup>nd</sup> line	.	OS, PFS, AEs, Impact of PDL1 expression on OS

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, 1 <sup>st</sup> 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, 1 <sup>st</sup> 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, 1 <sup>st</sup> 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, 1 <sup>st</sup> line or later		



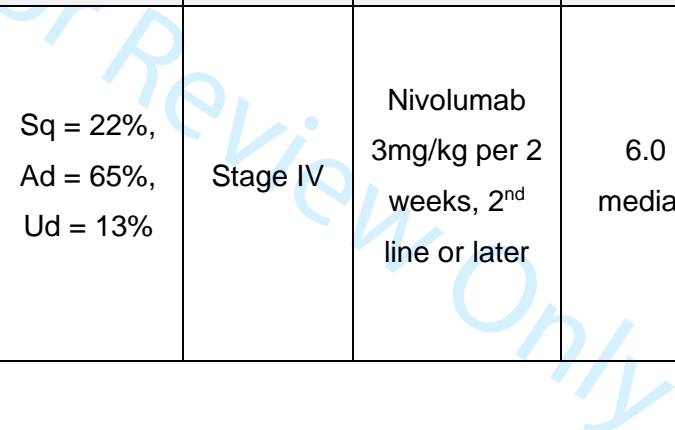
Author	Study design	Population						Intervention	Follow up (months)	Reported Outcomes
		Patients	%male	Age (yrs)	Location	Histology	Disease features			
Liu et al, 2019 [51]	Cohort study	44	75.0	60.0 (43-74)	China, 1 centre	Sq = 29.5%, Ad = 70.5%	Stage IIIB or IV	Nivolumab 3mg/kg per 2 weeks, 2 <sup>nd</sup> 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, 1 <sup>st</sup> – 6 <sup>th</sup> line	.	OS, PFS, deaths, hospitalisations, AEs, impact of ECOG PS
Merino Almazan et al, 2019 [84]	Cohort study	221	77.0	64.5 ( $\sigma$ 9.2) <sup>21</sup>	Spain, 15 centres	Sq = 59.7%, NSq = 40.3%	Stage I, II, III and IV	Nivolumab 3mg/kg per 2 weeks, 1 <sup>st</sup> line or later	.	OS, PFS, cost-effectiveness, deaths, AEs, impact of ECOG PS

<sup>21</sup> Mean and standard deviation

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, 1 <sup>st</sup> – 4 <sup>th</sup> 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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> 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	No thyroid disorder: 63.0 (35-93)	USA, 1 centre	No thyroid disorder: Ad = 85%	Stage IV	Pembrolizumab 2mg/kg per 3 weeks, 1 <sup>st</sup> line or later	.	OS, PFS, AEs
			Thyroid disorder: 50.0	Thyroid disorder: 59.0 (39-80)		Thyroid disorder: Ad = 70%				
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, 2 <sup>nd</sup> line or later	6.0 median	OS, PFS, deaths. Impact of PDL1, EGFR, KRas, LDH, CRP and histology



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, 1 <sup>st</sup> 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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> – 3 <sup>rd</sup> 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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> line or later	26.0 median	OS, PFS, AEs, impact of irAEs

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 $\geq$ 70 only	Nivolumab 3mg/kg per 2 weeks, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> 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) <sup>22</sup>	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

<sup>22</sup> Mean and range

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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 <sup>23</sup> 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, 1 <sup>st</sup> 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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> line or later		PFS, AEs, impact of NLR

<sup>23</sup> 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, 1 <sup>st</sup> 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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> 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, 1 <sup>st</sup> line or later	5.6 median	OS, PFS, deaths, AEs, impact of ethnicity



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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> 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%		Atezolizumab 1200mg per 3 weeks, 2 <sup>nd</sup> 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	Atezolizumab 1200mg per 3 weeks, 2 <sup>nd</sup> line or later	4.8 median	OS, PFS

## 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, 2 <sup>nd</sup> 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, 1 <sup>st</sup> 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, 2 <sup>nd</sup> 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

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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> line or later	.	AEs
Dixmier et al, 2018 [149]	Cohort study	1394	69.2	66.0 (35-91)	186 centres	.	.	Nivolumab, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> line or later	.	PFS, AEs
García et al, 2018 [153]	Cohort study	129	.	.	Spain, 5 centres	.	Pre-treated, advanced	Nivolumab, 2 <sup>nd</sup> 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, 1 <sup>st</sup> 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, 2 <sup>nd</sup> 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, 3 <sup>rd</sup> 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, 2 <sup>nd</sup> line or later	.	PFS, deaths, AEs
Mielgo et al, 2016 [159]	Cohort study	11	90	65.0 (40-78) <sup>24</sup>	Spain, 1 centre	Sq = 27%, Ad = 73%	Advanced	Nivolumab 3mg/kg per 2 weeks, 2 <sup>nd</sup> line or later	.	AEs

<sup>24</sup> 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, 2 <sup>nd</sup> line or later	.	OS, AEs
Moor et al, 2018 [161]	Cohort study	214	.	67.0 (42-84)	Australia, 7 centres	.	Pre-treated, advanced	Nivolumab, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> 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



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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, 2 <sup>nd</sup> 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, 1 <sup>st</sup> 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, 1 <sup>st</sup> -4 <sup>th</sup> , 8 <sup>th</sup> 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, 2 <sup>nd</sup> 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%	Stage IIIB and IV	Nivolumab, 2 <sup>nd</sup> line	.	OS, PFS
						Sq = 14.3%, NSq = 85.7%		Pembro-lizumab, 1 <sup>st</sup> line		
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 <sup>25</sup> 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, 2 <sup>nd</sup> 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

<sup>25</sup> Absolute neutrophil count/absolute lymphocyte count ratio

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[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, 1 <sup>st</sup> – 5 <sup>th</sup> 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, 2 <sup>nd</sup> 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, 2 <sup>nd</sup> line	.	AEs, impact of age

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Risk of bias assessment

	Risk of bias domains					Overall	Reasons for overall bias assessment from two reviewers
	D1	D2	D3	D4	D5		
Brahmer 2015	+	-	+	+	+	+	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.
Carbone 2017	X	+	+	-	-	-	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.
Borghaei 2015	X	-	+	+	+	-	Open-label trial, so potential for crossover is high
Wu 2019	-	+	+	+	+	+	Randomisation process specified, but no intention-to-treat analysis mentioned.
Reck 2018	X	X	+	-	+	X	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.
Heilmann 2018	-	+	+	+	+	-	Randomisation process specified, but no intention-to-treat analysis mentioned.
Heilmann 2019	-	+	+	+	+	-	Randomisation process specified, but no intention-to-treat analysis mentioned.
Antonia 2019	X	X	+	+	+	-	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.
Horn 2017	+	+	+	+	+	+	Randomisation process outlined clearly. Equal distribution of withdrawals and causes of withdrawals between trial arms. Intention-to-treat analysis was used.
Vokes 2019	-	X	+	X	+	X	The distribution of reasons for stopping treatment were not described. No intention-to-treat analysis used
Herbst 2016	+	+	+	-	+	+	Adverse effects were solely patient reported; potential for subjectivity depending on patient coping mechanisms and intuition to report.
Herbst 2019	+	+	+	+	+	+	Open-label trial, so potential for crossover is high. However, intention-to-treat analysis was used.
Brahmer 2017	+	+	+	+	+	+	Clear description of unbiased randomisation process. Consistent reporting of compliance to quality of life questionnaires. Several quality of life tools used.
Reck 2016	+	+	+	+	+	+	Open-label trial, so potential for crossover is high. However, intention-to-treat analysis is used. Blinded independent central radiological review used.
Reck 2019	+	+	+	+	+	+	Open-label trial, so potential for crossover is high. However, intention-to-treat analysis is used.
Mok 2019	+	-	+	+	+	+	Clear description of unbiased randomisation process. Adverse effects were described as leading to discontinuation; however, impact of patient characteristics not discussed.
Nosaki 2019	+	-	+	-	-	-	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.
Bordoni 2018	+	+	+	+	-	+	Several types of analyses conducted without explanation of reasoning behind analysis plan or the results presented
Fehrenbacher 2018	+	-	+	-	-	-	No information about intervention deviations due to experimental context. Pooled analysis of two populations, as protocol was amended. May be differences between populations.
Gadgeel 2019	+	+	+	+	-	+	Reason for point of step down of follow up not justified in the context of natural history of progression of disease.
Hida 2018	+	+	-	+	+	+	No information about losses to follow up. However, intention-to-treat analysis was used.
Rittmeyer 2017	X	+	+	+	+	-	Open-label and allocation unmasked, so very possible for crossover to occur. However, intention-to-treat-analysis was used.
Von Pawel 2019	+	-	+	+	+	+	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.
Antonia 2017	+	+	+	+	+	+	Patients blinded to intervention or placebo. Clear specification of randomisation process. Intention-to-treat analysis used.
Antonia 2018	+	+	+	+	+	+	Patients blinded to intervention or placebo. Clear specification of randomisation process. Intention-to-treat analysis used.
Hui 2019	+	+	+	+	+	+	Clear description of unbiased randomisation process. Patients blinded to intervention or placebo. Intention-to-treat analysis used.
Fehrenbacher 2016	+	-	+	-	+	-	Open-label; however, intention-to-treat analysis was used. Withdrawals mentioned, but impact of patient characteristics not discussed. Concern regarding focus on intervention
Spigel 2019	-	X	+	+	-	-	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.

	Risk of bias domains							Overall	Reasons for overall bias assessment from two reviewers
	D1	D2	D3	D4	D5	D6	D7		
Alama 2019	+	-	+	+	-	-	-	-	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.
Bagley 2017	+	+	+	+	-	-	+	+	Lack of information regarding whether participants were excluded due to missing information and how survival outcomes were ascertained
Bins 2018	+	+	+	+	-	-	+	-	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.
Brustugun 2016	-	+	+	+	-	-	+	-	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.
Crino 2019a	-	+	+	+	+	-	-	-	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.
Crino 2019b	-	+	+	+	+	+	+	+	No methods for accounting for confounding factors mentioned.
Dlem 2017	+	-	+	+	-	-	+	-	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.
Dudnik 2018	+	+	-	+	-	-	+	-	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.
Dumenil 2018	+	+	+	+	+	-	+	+	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.
Dusselier 2019	+	-	+	-	+	-	+	-	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.
Edahiro 2019	+	-	+	+	+	-	-	-	Lack of information regarding whether participants were excluded due to missing information and how survival outcomes were ascertained
Fujita 2019	+	+	+	?	+	+	+	+	No information regarding intervention deviations.
Fukihara 2019	+	+	+	-	-	+	+	+	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.
Fukul 2018	+	+	+	-	-	+	+	-	No information provided about missing data among patients or deviations, and any potential exclusions resulting from this.
Garassino 2018	+	+	+	✗	-	+	+	-	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.
Garde-Noguera 2018	+	+	+	-	-	+	+	+	Lack of information regarding whether participants deviated from their intended interventions and how survival outcomes were ascertained.
Garon 2015	-	+	+	-	-	-	+	-	Only PDL1 expression was accounted for in the main text. No information on deviations from intervention beyond expectation.
Garon 2019	-	+	+	+	-	-	+	-	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.
Gauvain 2018	+	+	+	-	-	+	+	+	Lack of information regarding whether participants deviated from their intended interventions and how survival outcomes were ascertained.
Geier 2018	+	-	+	+	-	+	-	-	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.
Genova 2019	+	+	+	+	+	+	-	+	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.
Grossi 2018	+	+	+	+	+	+	+	+	No notable problems
Haratani 2017	+	-	+	+	-	+	-	-	Selection of EGFR mutation positive patients on record only. The proportion of participants who had to be censored is not stated.
Haratani 2018	-	+	+	?	-	+	-	-	No information regarding deviations from interventions
Hasan Ali 2016	+	+	+	?	+	+	-	+	No information regarding deviations from interventions
Inoue 2018	+	+	+	-	-	+	+	+	Little information regarding the proportion of participants who deviated from the intervention or for whom there was missing data.
Kaderbhal 2017	+	+	+	+	+	+	+	+	No notable problems.
Kanal 2018	+	+	+	+	+	+	+	+	No notable problems.
Karantanos 2018	+	+	+	?	+	+	+	+	No notable problems, although there was no information regarding patient deviations from interventions.
Katsura 2019	-	+	+	-	+	+	-	-	Potential for confounding from factors potentially influencing patient outcomes; little information regarding deviations from intervention
Kawachi 2019	-	+	+	+	+	+	+	+	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.
Kobayashi 2017	+	-	+	?	+	+	+	+	No information regarding deviations from interventions
Kobayashi 2018	+	+	+	+	+	+	-	+	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
Krefting 2019	-	+	+	+	+	+	+	+	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.
Ksienski 2019a	+	+	+	-	+	+	+	+	Little information regarding deviations from interventions
Ksienski 2019b	+	+	+	+	+	+	+	+	No notable problems.

	Risk of bias domains							Overall	Reason for bias assessment
	D1	D2	D3	D4	D5	D6	D7		
Lacerenza 2019	+	+	+	?	+	+	+	-	No confounders were controlled for as declared in this study. No information regarding deviations from intervention.
Leight 2019	-	+	+	+	+	+	+	+	While more potential confounders are accounted for in this text, it is unclear how complete the control of these confounders is.
Lisberg 2018	+	-	+	?	+	+	+	+	When analysing the impact of trAEs on patient outcomes, no comparisons were made to validate findings in the non-trAE groups. No information regarding deviations from intervention
Liu 2019	+	+	+	+	+	+	+	+	No notable problems.
Manrique 2018	+	+	+	-	+	+	+	+	Little information regarding deviation from intervention.
Merino Almazan 2019	+	+	+	-	+	+	+	+	Little information regarding deviation from intervention.
Montana 2019	+	+	+	-	+	+	+	+	Little information regarding deviation from intervention.
Naqash 2018	+	+	+	?	+	+	+	+	No information regarding deviations from intervention.
Nomizio 2017	+	-	+	+	+	+	+	-	No confounders were controlled for as declared in this study.
Okuma 2018	-	+	+	+	+	+	+	+	There is potential for confounding from factors potentially influencing patient outcomes, such as smoking history and ECOG PS.
Ocorio 2016	-	+	+	+	+	+	+	+	There is potential for confounding from factors potentially influencing patient outcomes, such as smoking history and ECOG PS.
Oya 2017	+	-	+	+	+	+	+	+	No confounders were controlled for as declared in this study.
Oyanagi 2019	-	+	+	+	+	+	+	-	There is potential for confounding from factors potentially influencing patient outcomes, such as smoking history and ECOG PS.
Passaro 2019	-	+	+	?	+	+	+	-	No information regarding deviations from intervention
Passiglia 2019a	-	+	+	+	+	+	+	+	There is potential for confounding from factors potentially influencing patient outcomes, such as smoking history and ECOG PS.
Passiglia 2019b	+	-	+	+	+	+	+	+	No confounders were controlled for as declared in this study.
Ramos-Levi 2019	+	+	+	+	+	+	+	-	No confounders were controlled for as declared in this study.
Ravanelli 2019	+	+	+	+	+	+	+	-	No confounders were controlled for as declared in this study.
Ricciuti 2019a	+	+	+	+	+	+	+	-	No confounders were controlled for as declared in this study.
Ricciuti 2019b	-	+	+	?	+	?	+	+	There is potential for confounding from factors influencing patient outcomes. No information regarding deviations from intervention, or details of outcome assessment.
Russo 2018	+	+	+	+	+	+	+	-	No confounders were controlled for as declared in this study. Minimal details regarding outcome assessment.
Sabatier 2018	+	+	+	?	+	+	+	-	No confounders were controlled for as declared in this study; no information regarding deviations from intervention. Minimal details regarding outcome assessment.
Sarocchi 2016	+	-	+	?	+	+	+	+	No confounders were controlled for as declared in this study; no information regarding deviations from intervention.
Sato 2018	+	+	+	?	+	+	+	-	No confounders were controlled for as declared in this study; no information regarding deviations from intervention. Minimal details regarding outcome assessment.
Schouten 2017	+	+	+	?	+	+	+	-	No information regarding deviations from intervention. Minimal details regarding outcome assessment.
Sekine 2018	+	+	+	+	+	+	+	-	Heavily restricted recruitment of patients receiving nivolumab, some of which may have had implications on results.
Shamal 2018	+	-	+	+	-	+	+	-	No confounders were controlled for as declared in this study. Minimal details regarding outcome assessment.
Shroyama 2018	+	+	+	?	+	+	+	-	No confounders were controlled for as declared in this study; no information regarding deviations from intervention.
Takeda 2018	+	+	+	?	+	+	+	+	No confounders were controlled for as declared in this study; no information regarding deviations from intervention.
Tamiya 2019	+	+	+	?	+	+	+	-	No confounders were controlled for as declared in this study; no information regarding deviations from intervention.
Tanizaki 2017	+	+	+	?	+	+	+	-	No confounders were controlled for as declared in this study; no information regarding deviations from intervention
Teraoka 2017	+	+	+	?	+	+	+	-	No confounders were controlled for as declared in this study; no information regarding deviations from intervention
Tlu 2018	+	+	+	?	+	+	+	-	Confounders not controlled for due to incomplete record keeping among population studied. No information regarding deviations from intervention.
Toi 2018	+	?	+	+	+	+	+	-	No confounders were controlled for as declared in this study. No information regarding participant recruitment.
Tournoy 2018	+	+	+	+	+	+	+	-	No confounders were controlled for as declared in this study.
Weis 2019	+	+	+	+	+	+	+	-	No confounders were controlled for as declared in this study.
Yoo 2018	+	+	+	?	+	+	+	-	No confounders were controlled for as declared in this study; no information regarding deviations from intervention.
Zhuo 2018	+	+	+	+	+	+	+	-	No confounders were controlled for as declared in this study.

**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.



	Risk of bias domains							Overall	Reason for bias assessment
	D1	D2	D3	D4	D5	D6	D7		
Araujo 2017	?	+	?	?	?	?	+	⊗	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.
Arduzzoni 2017	?	+	?	?	?	?	-	⊗	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.
Bennati 2017	?	+	?	?	?	?	+	⊗	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.
Canova 2016	?	+	?	?	?	?	+	⊗	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.
Cappuzzo 2017	?	+	?	?	?	?	+	⊗	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.
De Pietro 2017	?	+	?	?	?	?	+	⊗	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.
Dixmier 2018	?	+	?	?	?	?	+	⊗	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.
Elvarathnam 2017	?	+	?	?	?	?	+	⊗	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.
Emiliani 2016	?	+	?	?	?	?	+	⊗	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.
Fernandez 2017	?	+	?	?	?	?	+	⊗	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.
Garcia 2018	?	+	?	?	?	?	+	⊗	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.
Honda 2018	?	+	?	?	?	?	+	⊗	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.
Hosoya 2018	?	+	?	?	?	?	+	⊗	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.
Kim 2017	?	+	?	?	?	?	+	⊗	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.
Lampaki 2017	?	+	?	?	?	?	+	⊗	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.
Lopez Flores 2017	?	+	?	?	?	?	+	⊗	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.
Mielgo 2016	?	+	?	?	?	?	⊗	⊗	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
Migliorino 2017	?	-	?	?	?	?	?	⊗	Very little information regarding methods to make assessments. Participant selection appears to be clear, but this is not certain.
Moor 2018	?	+	?	?	?	?	+	⊗	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.
Moreno 2017	?	+	?	?	?	?	+	⊗	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.
Nakamura 2018	?	+	?	?	?	?	+	⊗	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.
Ota 2018	?	+	?	?	?	?	+	⊗	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.
Paglalunga 2017	?	⊗	?	?	?	?	-	⊗	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
Rapaport 2019	?	+	?	?	?	?	+	⊗	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.
Rodriguez-Cid 2017	?	+	?	?	?	?	+	⊗	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.
Sajjo 2018	?	+	?	?	?	?	+	⊗	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.
Sakaguchi 2017	?	+	?	?	?	?	+	⊗	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.
Sanoyan 2017	?	+	?	?	?	?	+	⊗	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.
Saravia 2017	?	+	?	?	?	?	+	⊗	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.
Shaverdian 2019	?	-	?	?	?	?	-	⊗	Very little information regarding methods to make assessments. From the methods available, participant selection appears to be consistent and fair, and reported outcomes were reasonably assessed from appropriate analyses.
Shibata 2018	?	+	?	?	?	?	+	⊗	Very little information regarding methods to make assessments. From the methods available, participant selection was consistent and fair, and reported outcomes appear to be reasonably assessed from appropriate analyses.
Tanimura 2017	?	-	?	?	?	?	-	⊗	Very little information regarding methods to make assessments. From the methods available, participant selection was consistent and fair, and reported outcomes appear to be reasonably assessed from appropriate analyses.
Tarruella 2018	?	+	?	?	?	?	+	⊗	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.
Tay 2018	?	+	?	?	?	?	?	⊗	Very little information regarding methods to make assessments. From the methods available, participant selection was consistent and fair.
Watanabe 2017	?	+	?	?	?	?	+	⊗	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.
Yamaguchi 2017	?	+	?	?	?	?	-	⊗	Very little information regarding methods to make assessments. From the methods available, participant selection was consistent and fair, and reported outcomes appear to be reasonably assessed from appropriate analyses.
Yamane 2018	?	+	?	?	?	?	+	⊗	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.

**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	<b>HR 0.75</b> (0.69 to 0.81) [Risk of death]
Risk of death Follow-up: range 18 months to 31 months	3 RCTs	⊕⊕⊕⊕ High	<b>HR 0.72</b> (0.65 to 0.81) [Risk of death]
Risk of death Follow-up: range 31 months to as far as reported	3 RCTs	⊕⊕⊕○ Moderate	<b>HR 0.70</b> (0.59 to 0.82) [Risk of death]
Risk of progression or death Follow-up: range 0 months to 18 months	10 RCTs	⊕⊕○○ Low	<b>HR 0.87</b> (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	<b>HR 0.82</b> (0.74 to 0.90) [Risk of progression or death]
Incidence of treatment-related adverse events assessed with: Mean percentage incidence	9 RCTs	⊕⊕⊕⊕ High	<b>Not pooled</b>
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	<b>Not estimable</b>
Time to deterioration in quality of life assessed with: LCSS ASBI	1 RCT	⊕⊕○○ Low	<b>Not estimable</b>
Time to deterioration in quality of life assessed with: EORTC-QLQ-C30	1 RCT	⊕⊕⊕○ Moderate	<b>Not estimable</b>
<b>CI:</b> confidence interval; <b>HR:</b> hazard ratio			
<b>GRADE Working Group grades of evidence</b>			
<b>High certainty:</b> we are very confident that the true effect lies close to that of the estimate of the effect.			
<b>Moderate certainty:</b> 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.			
<b>Low certainty:</b> our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.			
<b>Very low certainty:</b> we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.			

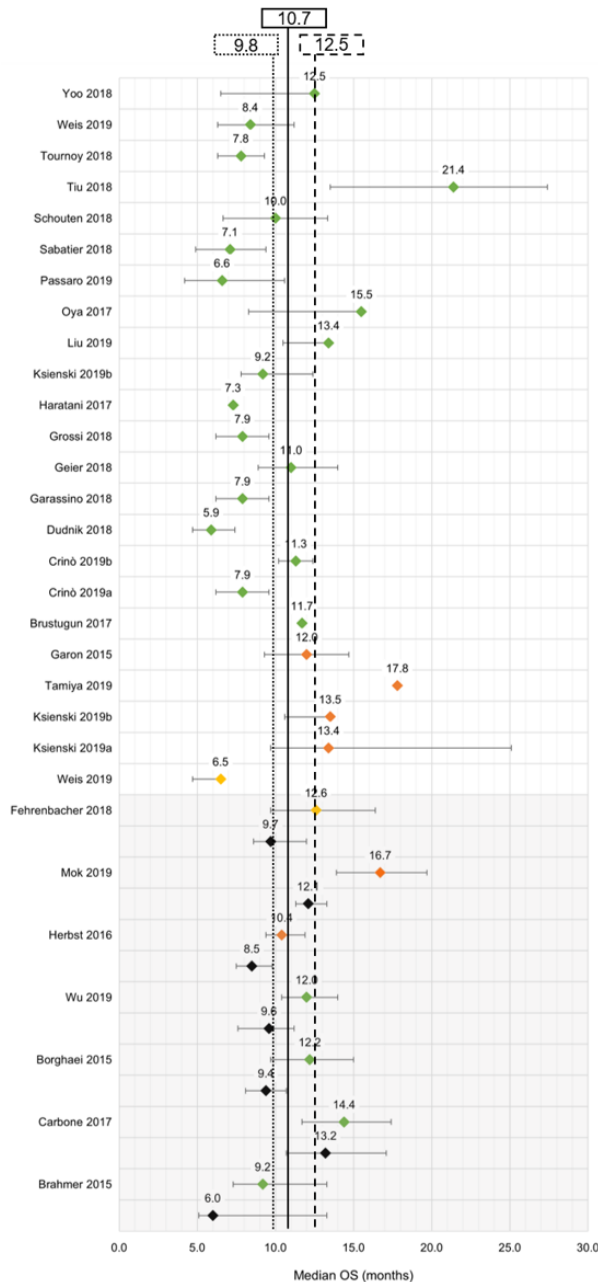
*Durvalumab compared to placebo for managing advanced NSCLC*

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

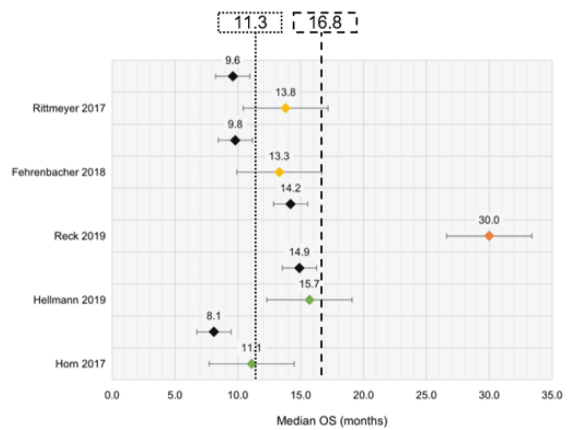
Outcomes	No of studies	Certainty of the evidence (GRADE)	Relative effect (95% CI)
Risk of death Follow-up: median 25.2 months	1 RCT	⊕⊕⊕⊕ High	<b>Not estimable</b>
Progression-free survival Follow-up: median 25.2 months	1 RCT	⊕⊕⊕⊕ High	<b>Not estimable</b>
Incidence of treatment-related adverse events assessed with: Percentage incidence Follow-up: median 25.2 months	1 RCT	⊕⊕⊕⊕ High	<b>Not estimable</b>
Time to deterioration in quality of life assessed with: EORTC-QLQ-C30 Follow-up: median 25.2 months	1 RCT	⊕⊕⊕○ Moderate	<b>Not estimable</b>
<b>CI:</b> confidence interval			
<b>GRADE Working Group grades of evidence</b>			
<b>High certainty:</b> we are very confident that the true effect lies close to that of the estimate of the effect.			
<b>Moderate certainty:</b> 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.			
<b>Low certainty:</b> our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.			
<b>Very low certainty:</b> we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.			

Supplementary analyses

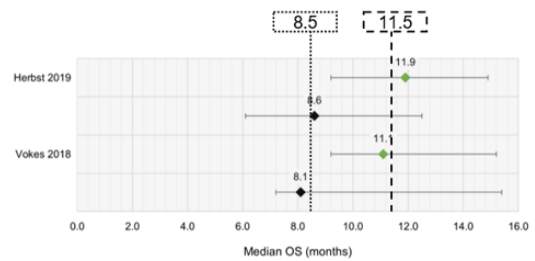
**A** Short-term follow up



**B** Medium-term follow up



**C** Long-term follow up

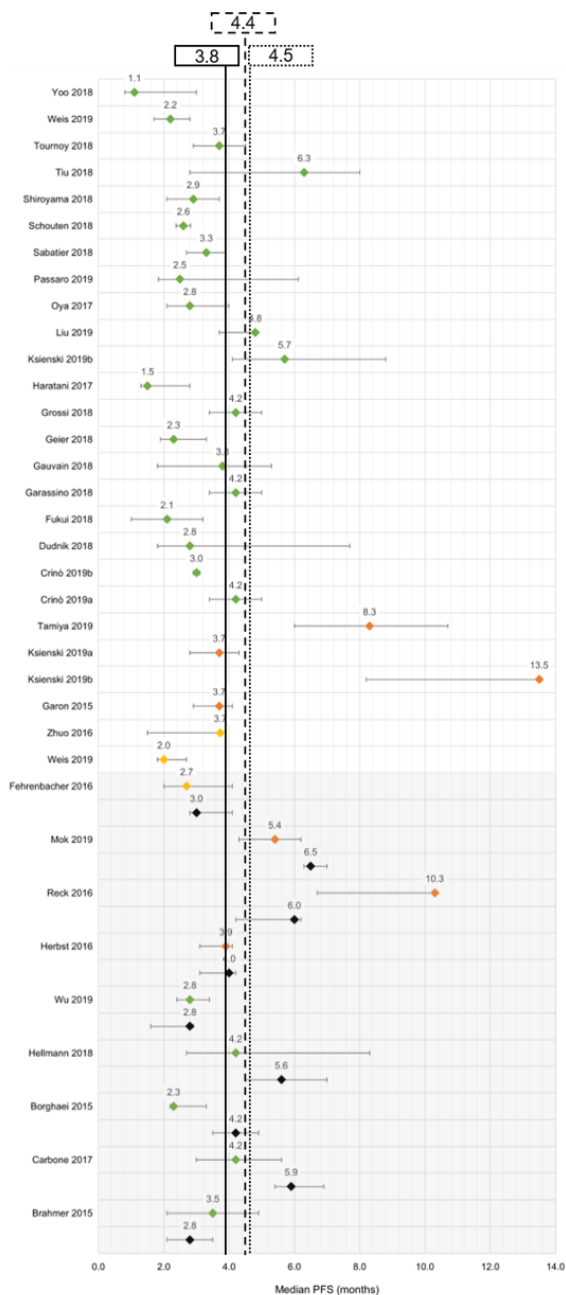


Key	
<span style="color: green;">◆</span>	Nivolumab
<span style="color: orange;">◆</span>	Pembrolizumab
<span style="color: yellow;">◆</span>	Atezolizumab
<span style="color: black;">◆</span>	Chemotherapy
<span style="border: 1px dashed black; padding: 2px;">x</span>	Mean of median OS times, immunotherapy arm (RCTs)
<span style="border: 1px solid black; padding: 2px;">x</span>	Mean of median OS times, immunotherapy arm (observational studies)
<span style="border: 1px dotted black; padding: 2px;">x</span>	Mean of median OS times, chemotherapy arm (RCTs)

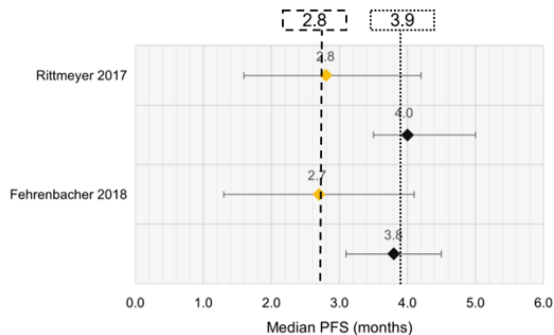
Supplementary Figure 1 – Median OS results

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].

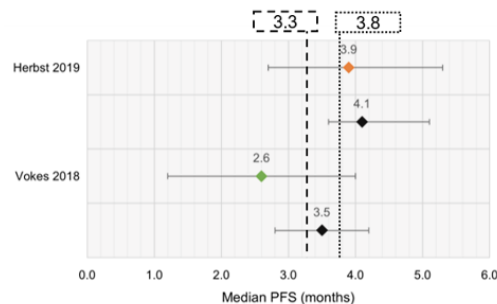
**A** Short-term follow up



**B** Medium-term follow up



**C** Long-term follow up



Key	
	Nivolumab
	Pembrolizumab
	Atezolizumab
	Chemotherapy
	Mean of median OS times, immunotherapy arm (RCTs)
	Mean of median OS times, immunotherapy arm (observational studies)
	Mean of median OS times, chemotherapy arm (RCTs)

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].

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	
	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
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	Crino 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., 2016	Gauvain et al., 2018	Geier et al., 2018	Grossi et al., 2018	Haraani et al., 2018	Kobayashi et al., 2018	Krefling et al., 2019	Ksieniski 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	Sabalier 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	Ksieniski et al., 2019a	Lisberg et al., 2018	Oscro et al., 2017	Tamiya et al., 2019				
	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	N	A	P	P	P	P	P		
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	N	N	N	N	N	N	N	N	
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				
Fatigue			3	6	11	100	60		6	11						18					25	5	20	18									38	37	20		10	2			
Asthenia				8					6		42	8	6								50																				
Rash			5	8	3	27	4	33	8					8	25	7					15	7	11	9	10			11	2	25		79	2	10	9	10		23	6		
Pruritus			5			27	6	37							12																										
Hypothyroidism	5	40		3	2	15	4	10	3		5	14				13	5	14			7	5	21	20	18	20	11	7	7	13	21		3	2	7	7	6	16			
Hyperthyroidism																																									
Nausea or vomiting				<1	4	24		19													8	6	25	4	4									9	7	10					
Arthralgia			2				7	37																																	
Myalgia												7																													
Neurological								63			11										<1	1																			
Pneumonitis	3	5	7	1	2		3	13	1					1	4						3	7		8	9		13	4	8		18	7	5	7	4	5	6	4	5		
Anaemia				2	1				2		14			2		3						5																			
Diarrhoea		4	9	5	5	19	1	13	5		14		5	7	3						11	12				7															
Decreased appetite				2	4				2				3			10					7	2																			
Pyrexia				3	4		15	6	3				3																												
Chills																																									
Constipation									33																																
Oedema									17																																
Mucosal inflammation									12					2																											
Hepatitis											2																														
Colitis																																									
Dermatitis																																									
Skin toxicity										10																															
Adrenal insufficiency																																									
Weight loss																																									
Headache																																									
Alopecia									4																																
Dry skin																																									
Dyspnoea																																									
Infusion related reaction																																									
Nephritis																																									
Cough																																									
Abdominal pain																																									
Hepatotoxicity																																									
T1 diabetes mellitus																																									
Thrombosis																																									
Polymyalgia rheumatica																																									
Pericarditis																																									
Neutropenia																																									
Cholangitis																																									
Hypophysitis																																									
Myocarditis																																									
ITP																																									
Pneumonia																																									
Nephrotoxicity																																									



### *Immune-related adverse effects*

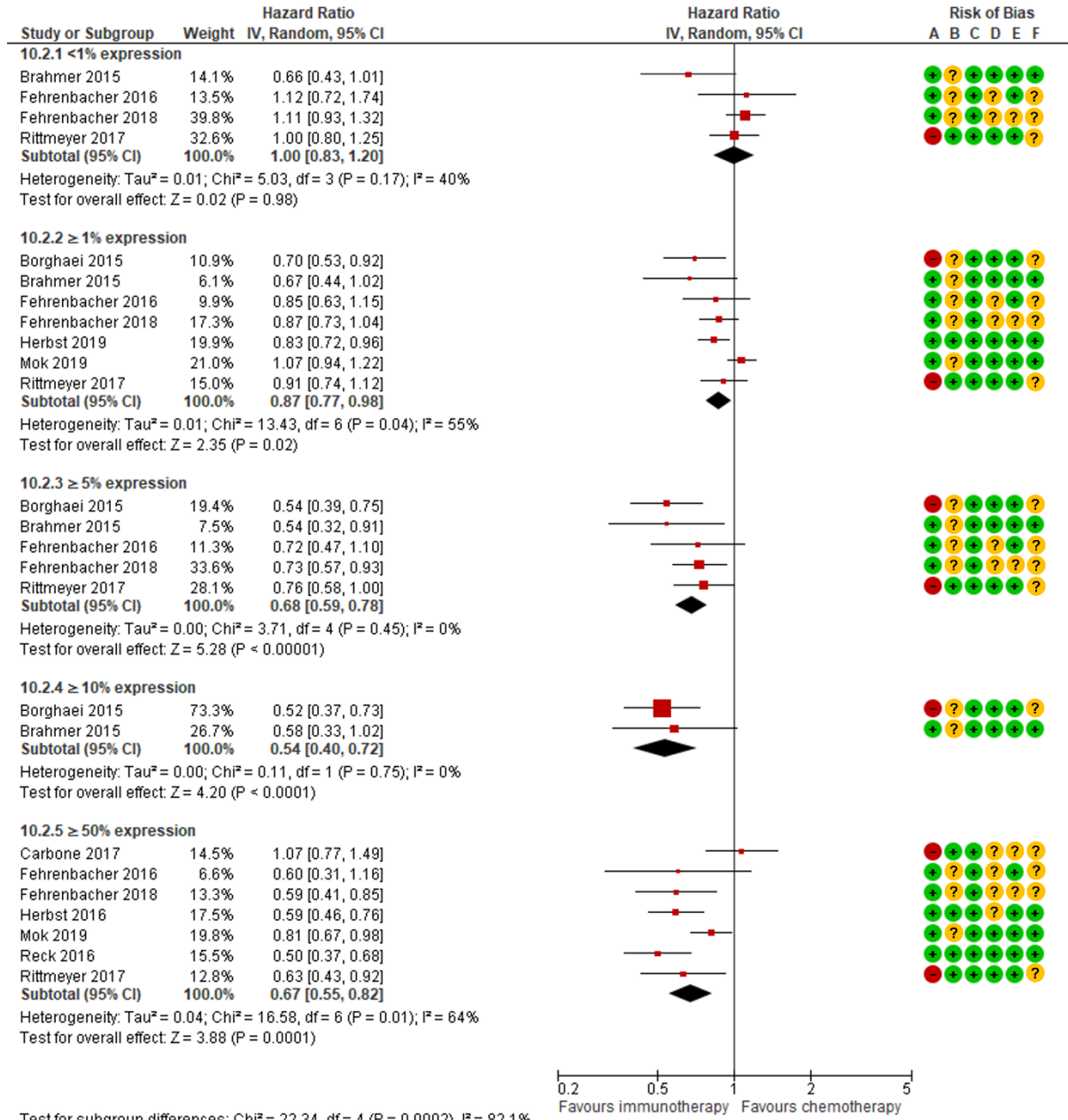
Immune-related adverse effects (irAEs) were more common among patients using an intervention compared to chemotherapy and less frequent than trAEs. The mean incidence of irAEs among patients receiving pembrolizumab in RCTs was 24.1% (range 19.0% – 29.2%). Similarly, the mean incidence of irAEs was 27.9% (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%).



**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%.



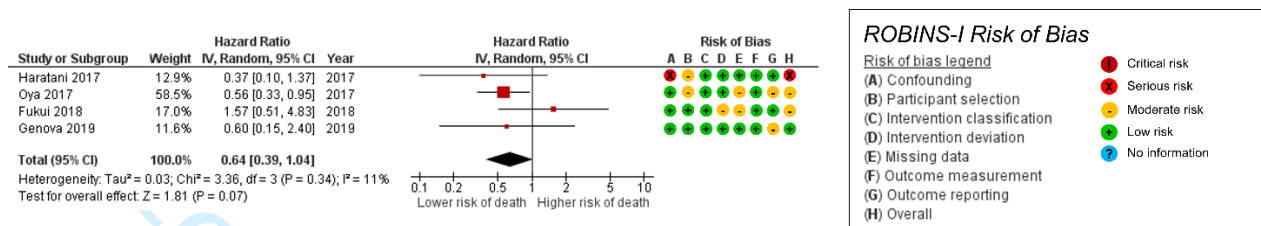
**ROB2.0 Risk of Bias**

Risk of bias legend

- (A) Randomisation
- (B) Deviations from intervention
- (C) Missing outcome data
- (D) Outcome measurement
- (E) Selection of reported outcomes
- (F) Overall

● High risk  
? Some concerns  
+ Low risk

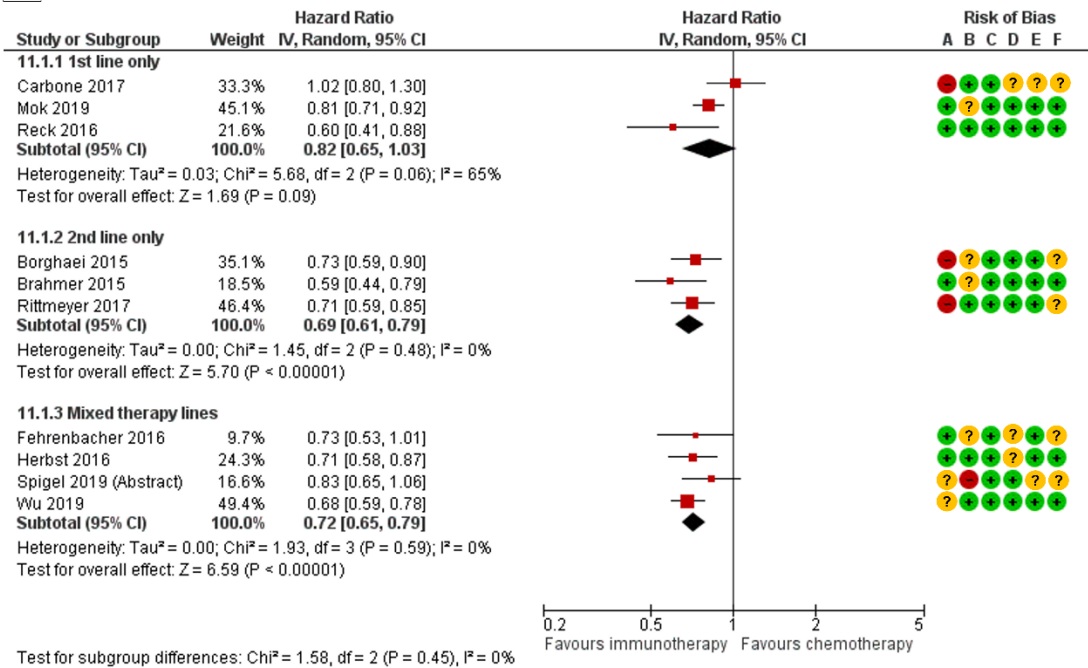
Supplementary Figure 6 – Meta-analysis comparing risk of death among patients with ≥1% and <1% PDL1 expression who received nivolumab in included observational studies [52, 104, 116, 125]



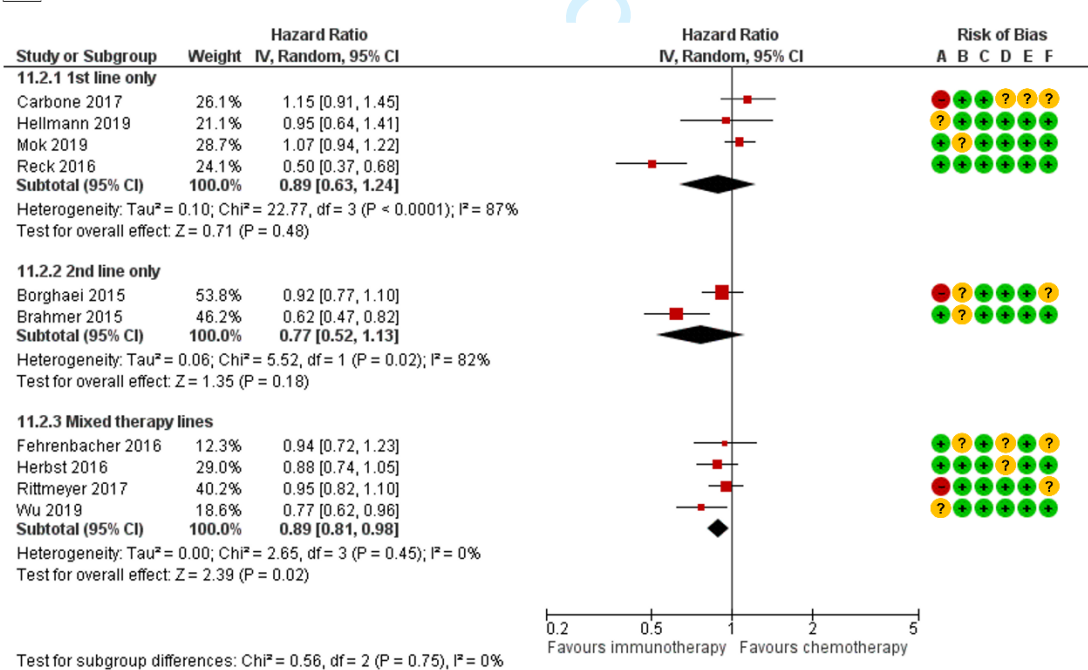
Confidential: For Review Only

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



**ROB2.0 Risk of Bias**

Risk of bias legend

- High risk
- Some concerns
- Low risk

(A) Randomisation  
 (B) Deviations from intervention  
 (C) Missing outcome data  
 (D) Outcome measurement  
 (E) Selection of reported outcomes  
 (F) Overall

**Supplementary References (continued from main reference list)**

125. Fukui T, Okuma Y, Nakahara Y, Otani S, Igawa S, Katagiri M, et al. Activity of Nivolumab and Utility of Neutrophil-to-Lymphocyte Ratio as a Predictive Biomarker for Advanced Non-Small-Cell Lung Cancer: A Prospective Observational Study. *Clin Lung Cancer*. 2019;20(3):208-14.e2.
126. Shiroyama T, Suzuki H, Tamiya M, Tamiya A, Tanaka A, Okamoto N, et al. Pretreatment advanced lung cancer inflammation index (ALI) for predicting early progression in nivolumab-treated patients with advanced non-small cell lung cancer. *Cancer Med*. 2018;7(1):13-20.
127. Hasan Ali O, Diem S, Markert E, Jochum W, Kerl K, French LE, et al. Characterization of nivolumab-associated skin reactions in patients with metastatic non-small cell lung cancer. *Oncol Immunology*. 2016;5(11).
128. Bins S, Basak EA, El Bouazzaoui S, Koolen SLW, Oomen De Hoop E, Van Der Leest CH, et al. Association between single-nucleotide polymorphisms and adverse events in nivolumab-treated non-small cell lung cancer patients. *Br J Cancer*. 2018;118(10):1296-301.
129. Inoue T, Tamiya M, Tamiya A, Nakahama K, Taniguchi Y, Shiroyama T, et al. Analysis of Early Death in Japanese Patients With Advanced Non-small-cell Lung Cancer Treated With Nivolumab. *Clin Lung Cancer*. 2018;19(2):e171-e6.
130. Ramos-Levi AM, Rogado J, Sanchez-Torres JM, Colomer R, Marazuela M. Nivolumab-induced thyroid dysfunction in patients with lung cancer. *Endocrinol*. 2019;66(1):26-34.
131. Sarocchi M, Grossi F, Arboscello E, Bellodi A, Genova C, Dal Bello MG, et al. Serial Troponin for Early Detection of Nivolumab Cardiotoxicity in Advanced Non-Small Cell Lung Cancer Patients. *Oncologist*. 2018;23(8):936-42.
132. Sato K, Akamatsu H, Murakami E, Sasaki S, Kanai K, Hayata A, et al. Correlation between immune-related adverse events and efficacy in non-small cell lung cancer treated with nivolumab. *Lung Cancer*. 2018;115:71-4.
133. Toi Y, Sugawara S, Kawashima Y, Aiba T, Kawana S, Saito R, et al. Association of Immune-Related Adverse Events with Clinical Benefit in Patients with Advanced Non-Small-Cell Lung Cancer Treated with Nivolumab. *Oncologist*. 2018;23(11):1358-65.
134. Dusselier M, Deluche E, Delacourt N, Ballouhey J, Egenod T, Melloni B, et al. Neutrophil-to-lymphocyte ratio evolution is an independent predictor of early progression of second-line nivolumab-treated patients with advanced non-small-cell lung cancers. *PLoS ONE*. 2019;14(7).
135. Fujita K, Kim YH, Kanai O, Yoshida H, Mio T, Hirai T. Emerging concerns of infectious diseases in lung cancer patients receiving immune checkpoint inhibitor therapy. *Respiratory Medicine*. 2019;146:66-70.
136. Fukihara J, Sakamoto K, Koyama J, Ito T, Iwano S, Morise M, et al. Prognostic Impact and Risk Factors of Immune-Related Pneumonitis in Patients With Non-Small-Cell Lung Cancer Who Received Programmed Death 1 Inhibitors. *Clinical Lung Cancer*. 2019.

- 1  
2  
3 137. Karantanos T, Karanika S, Seth B, Gignac G. The absolute lymphocyte count can  
4 predict the overall survival of patients with non-small cell lung cancer on nivolumab: a clinical  
5 study. *Clin Transl Oncol*. 2019;21(2):206-12.  
6
- 7 138. Nomizo T, Ozasa H, Tsuji T, Funazo T, Yasuda Y, Yoshida H, et al. Clinical Impact of  
8 Single Nucleotide Polymorphism in PD-L1 on Response to Nivolumab for Advanced Non-  
9 Small-Cell Lung Cancer Patients. *Sci*. 2017;7:45124.  
10
- 11 139. Okuma Y, Wakui H, Utsumi H, Sagawa Y, Hosomi Y, Kuwano K, et al. Soluble  
12 Programmed Cell Death Ligand 1 as a Novel Biomarker for Nivolumab Therapy for Non-  
13 Small-cell Lung Cancer. *Clin Lung Cancer*. 2018;19(5):410-7.e1.  
14
- 15 140. Oyanagi J, Koh Y, Sato K, Mori K, Teraoka S, Akamatsu H, et al. Predictive value of  
16 serum protein levels in patients with advanced non-small cell lung cancer treated with  
17 nivolumab. *Lung Cancer*. 2019;132:107-13.  
18
- 19 141. Tanizaki J, Haratani K, Hayashi H, Chiba Y, Nakamura Y, Yonesaka K, et al.  
20 Peripheral Blood Biomarkers Associated with Clinical Outcome in Non-Small Cell Lung  
21 Cancer Patients Treated with Nivolumab. *Journal of Thoracic Oncology: Official Publication*  
22 *of the International Association for the Study of Lung Cancer*. 2018;13(1):97-105.  
23
- 24 142. Russo A, Franchina T, Ricciardi GRR, Battaglia A, Scimone A, Berenato R, et al.  
25 Baseline neutrophilia, derived neutrophil-to-lymphocyte ratio (dNLR), platelet-to-lymphocyte  
26 ratio (PLR), and outcome in non small cell lung cancer (NSCLC) treated with Nivolumab or  
27 Docetaxel. *J Cell Physiol*. 2018;233(10):6337-43.  
28
- 29 143. Araujo LH, Baldotto C, Martins C, Zukin M. Local experience in an expanded access  
30 program of nivolumab in advanced non-small cell lung cancer in Brazil. *Journal of Thoracic*  
31 *Oncology*. 2017;12 (1 Supplement 1):S1303.  
32
- 33 144. Ardizzoni A, Bidoli P, Chiari R, Bonomi L, Turci D, Landi L, et al. Nivolumab in  
34 advanced non-squamous NSCLC patients with KRAS mutations: Results from the Italian  
35 expanded access program (EAP). *Journal of Thoracic Oncology*. 2017;12 (11 Supplement  
36 2):S1804.  
37
- 38 145. Bennati C, D'Arcangelo M, Minuti G, Vecchiarelli S, Landi L, Mazza V, et al.  
39 Programmed cell death ligand 1 and neutrophil to lymphocyte ratio to predict response to  
40 nivolumab in non-small cell lung cancer. *Journal of Thoracic Oncology*. 2017;12 (11  
41 Supplement 2):S2390-S1.  
42
- 43 146. Canova S, Bidoli P, Lissoni P, Abbate MI, Capici S, Casiraghi S, et al. Predictive role  
44 of absolute lymphocyte count (ALC) and neutrophil/lymphocyte ratio (NLR) in patients with  
45 metastatic non small cell lung cancer (NSCLC) treated with nivolumab: Results of a  
46 retrospective monocentric study. *Annals of Oncology Conference: 18th National Congress of*  
47 *Medical Oncology Italy*. 2016;27(Supplement 4).  
48
- 49 147. Cappuzzo F, Delmonte A, Capici S, Crino L, Logroscino AF, Sandri P, et al.  
50 Treatment beyond progression in patients with advanced squamous NSCLC participating in  
51 the Expanded Access Programme (EAP). *Journal of Thoracic Oncology*. 2017;12 (1  
52 Supplement 1):S667-S8.  
53
- 54 148. De Pietro L, Vitiello F, Gilli M, Letizia A, Tortoriello A, Hengeller M, et al. Nivolumab  
55 in non-small cell lung cancer: Is there an upper age limit? *Ann Oncol*. 2017;28 (Supplement  
56 6):vi60.  
57  
58  
59  
60

- 1  
2  
3 149. Dixmier A, Debieuvre D, Raspaud C, Auliac JB, Benoit N, Bombaron P, et al. EVIDENS: An observational study of nivolumab-treated patients in advanced non-small cell  
4 lung cancer (NSCLC) in a real-world setting: Initial results on 1394 patients. *Ann Oncol.*  
5 2018;29 (Supplement 8):viii532.  
6  
7  
8 150. Elvarathnam S, Chouaid C, Thiriart N, Jabot L, Rousseau-Bussac G, Jaskowiec C, et  
9 al. Immunochic: A prospective nivolumab monotherapy cohort in advanced non-small cell  
10 lung cancer patients in routine clinical practice. *Journal of Thoracic Oncology.* 2017;12 (1  
11 Supplement 1):S1332-S3.  
12  
13 151. Emiliani A, Prete AA, Prelaj A, Del Bene G, Speranza I, Seminara P, et al. Nivolumab  
14 in non small cell lung cancer: General and immune-related toxicities in the real life. *Annals of*  
15 *Oncology Conference: 18th National Congress of Medical Oncology Italy.*  
16 2016;27(Supplement 4).  
17  
18 152. Fernandez PR, Alcala MM, Ruiz JCP, Garcia YG, Macias I, Cardona MF. Experience  
19 with nivolumab in compassionate use in non-small lung carcinoma patients who have  
20 progressed to one or more prior lines of chemotherapy. *Journal of Thoracic Oncology.*  
21 2017;12 (1 Supplement 1):S1302.  
22  
23 153. Garcia M, Calles A, Lobo M, Alvarez Alvarez R. Clinical Characteristics of Long-Term  
24 Survivors With Nivolumab in Pretreated Advanced NSCLC from Real-World Data (RWD).  
25 *Journal of Thoracic Oncology.* 2018;13 (10 Supplement):S612.  
26  
27 154. Honda N, Akagi K, Oshima K, Gytoku H, Senjyu H, Takemoto S, et al. Analysis of  
28 advanced or postoperative recurrent non-small cell lung cancer cases treated with  
29 nivolumab at hospitals in Nagasaki, Japan. *Respirology.* 2018;23 (Supplement 2):288.  
30  
31 155. Hosoya K, Fujimoto D, Tamiya M, Tamiya A, Suzuki H, Hirano K, et al. Association  
32 between early immune-related adverse events and clinical outcomes in patients with  
33 advanced non-small cell lung cancer treated with pembrolizumab as first-line therapy: A  
34 retrospective multicenter cohort study. *Ann Oncol.* 2018;29 (Supplement 8):viii511.  
35  
36 156. Kim SW, Cho BC, Kang JH, Ahn MJ, Lee KH, Kim DW, et al. Safety of nivolumab in  
37 patients with advanced or metastatic non-small cell lung cancer who have received at least  
38 one prior systemic regimens: Expanded access program in Korea (ONO-4538-X04). *Ann*  
39 *Oncol.* 2017;28 (Supplement 10):x135-x6.  
40  
41 157. Lampaki S, Boutsikou E, Zarogoulidis P, Spyrtos D, Eleftheriadou E, Ioannidou D,  
42 et al. Immunotherapy with nivolumab in NSCLC patients: One centre preliminary results.  
43 *Journal of Thoracic Oncology.* 2017;12 (1 Supplement 1):S1341.  
44  
45 158. Lopez Flores M, Diz Tain P, Delgado Sillero I, Sanchez Cousido L, Lopez Gonzalez  
46 A, Pedraza Lorenzo M, et al. Nivolumab after progression to platinum-based chemotherapy  
47 in advanced non-small-cell lung cancer (NSCLC). *Journal of Thoracic Oncology.* 2017;12  
48 (11 Supplement 2):S1917-S8.  
49  
50 159. Mielgo X, Toro P, Ruiz-Gimenez L, Olier C, Perez M, Rosero A, et al. Nivolumab  
51 monotherapy in patients with previously treated advanced non-small cell lung cancer  
52 (NSCLC) in routine clinical practice in a Spanish center. *Journal of Thoracic Oncology.*  
53 2016;11(4):S135.  
54  
55 160. Migliorino MR, Gelibter A, Grossi F, Fagnani D, Bordi P, Franchina T, et al. Use of  
56 nivolumab in elderly patients with advanced non-squamous NSCLC: Results from the Italian  
57 expanded access program (EAP). *Ann Oncol.* 2017;28 (Supplement 5):v471.  
58  
59  
60

- 1  
2  
3 161. Moor R, Roberts K, Ladwa R, Miles K, O'Byrne K. Clinical and Radiological  
4 Predictors of Efficacy to Nivolumab in NSCLC: A Multi-Institutional, Retrospective Cohort  
5 Study. *Journal of Thoracic Oncology*. 2018;13 (10 Supplement):S895.  
6  
7 162. Martinez Moreno E, Irigoyen Medina A, Martinez Barroso K, Borregon Rivilla M,  
8 Alvarez Cabellos R, Cardenas JD, et al. Nivolumab experience in patients with previously  
9 treated advanced non small cell lung cancer (NSCLC) in Toledo, Spain. *Journal of Thoracic  
10 Oncology*. 2017;12 (11 Supplement 2):S2430.  
11  
12 163. Nakamura M, Sugihara K, Xu C, Sakai T, Ishioka K, Takahashi S, et al. NLR and its  
13 relative change early during nivolumab treatment could be useful to predict outcome in  
14 advanced NSCLC. *Ann Oncol*. 2018;29 (Supplement 7):VII80.  
15  
16 164. Ota T, Kirita K, Udagawa H, Umemura S, Matsumoto S, Yoh K, et al. Efficacy of  
17 second-line nivolumab after early time to progression on first-line cytotoxic chemotherapy in  
18 patients with advanced nonsmall cell lung cancer (NSCLC). *Ann Oncol*. 2018;29  
19 (Supplement 8):viii535.  
20  
21 165. Paglialonga L, Bellezza G, Gili A, Ricciuti B, Minotti V, Chiari R, et al. Immunotherapy  
22 against non-small cell lung cancer (NSCLC): Looking for predictive factors to avoid an  
23 untargeted shooting. *Journal of Thoracic Oncology*. 2017;12 (1 Supplement 1):S1317-S8.  
24  
25 166. Rapoport BL, Vorobiof DA, Langenhoven L, Hall JM, Van Eeden RI, Smit T, et al.  
26 Prognostic significance of neutrophil/lymphocyte ratio in patients undergoing treatment with  
27 nivolumab for recurrent non-small cell lung cancer. *Ann Oncol*. 2019;30 (Supplement 2):ii61.  
28  
29 167. Rodriguez-Cid J, Bonilla-Molina D, Martinez-Barreda L, Diaz-Rico J, Arellanes-  
30 Herrera P, Del Olmo Gil E, et al. Nivolumab for patients with non-small cell lung carcinoma in  
31 patients with progression to one or more lines of chemotherapy in Mexican population.  
32 *Journal of Thoracic Oncology*. 2017;12 (11 Supplement 2):S2153.  
33  
34 168. Saijo N, Inagaki Y, Abe Y, Kono S, Taniguchi Y, Otsuka K, et al. Efficacy and Safety  
35 of Pembrolizumab in Non-Small Cell Lung Cancer in Our Institution: A Retrospective Study.  
36 *Journal of Thoracic Oncology*. 2018;13 (10 Supplement):S900.  
37  
38 169. Sakaguchi T, Hataji O, Suzuki Y, Saiki H, Ito K, Nishii Y, et al. A retrospective study  
39 of the efficacy and safety of nivolumab in our clinical practice: A single institutional  
40 experience. *Journal of Thoracic Oncology*. 2017;12 (1 Supplement 1):S1340.  
41  
42 170. Sanoyan DA, Siebenhuner A, Delaloye R, Bankel L, Paulino TDL, Curioni A. Real-life  
43 experience with nivolumab and pembrolizumab in patients(pts) with advanced non-small cell  
44 lung cancer (NSCLC): Efficacy and safety analysis at the University Hospital Zurich. *Ann  
45 Oncol*. 2017;28 (Supplement 11):xi7.  
46  
47 171. Saravia D, Laderian B, Park W, Desai A, Vargas F, Elias R, et al. Complete blood  
48 count parameters as predictive factors in patients with advanced non-small cell lung cancer  
49 treated with nivolumab. *Journal of Thoracic Oncology*. 2017;12 (1 Supplement 1):S1327.  
50  
51 172. Shaverdian N, Zhang Z, Lobaugh S, Deasy JO, Offin M, Preeshagul I, et al. Real-  
52 World Evaluation of Consolidative Durvalumab in Locally Advanced Non-Small-Cell Lung  
53 Cancer Treated with Definitive Chemoradiation. *International Journal of Radiation Oncology  
54 Biology Physics*. 2019;105 (1 Supplement):E531.  
55  
56 173. Shibata E, Yokoi T, Takahashi R, Mikami K, Kanemura S, Koda Y, et al. Prognostic  
57 Value of Changes in Neutrophil-To-Lymphocyte Ratio in Patients with Lung Cancer Treated  
58 with Nivolumab. *Journal of Thoracic Oncology*. 2018;13 (10 Supplement):S708.  
59  
60

- 1  
2  
3 174. Tanimura K, Yamada T, Tamiya N, Kaneko Y, Uchino J, Takayama K. The impact of  
4 neutrophil/lymphocyte ratio as the predictive marker to anti-PD-1 antibody treatment in  
5 NSCLC patients. *Journal of Thoracic Oncology*. 2017;12 (11 Supplement 2):S2013.  
6  
7 175. Rodriguez-Abreu D, Campillo J, Grau F, Carcereny E, Bernabe R, Garcia Y, et al.  
8 NIVEX TRIAL (GECp 1605): Nivolumab in the Real World: Spanish Expanded Access  
9 Program Experience in Pretreated Advanced NSCLC Patients. *Journal of Thoracic  
10 Oncology*. 2018;13 (10 Supplement):S827.  
11  
12 176. Tay RY, Chiramel J, Montague E, Wilson F, Summers Y, Blackhall FH, et al. Impact  
13 of blood-based biomarkers on survival outcomes with pembrolizumab in pre-treated  
14 advanced non-small cell lung cancer (NSCLC) patients (pts). *Ann Oncol*. 2018;29  
15 (Supplement 8):viii529.  
16  
17 177. Watanabe S, Goto Y, Motoi N, Goto K, Shiraishi H, Itahashi K, et al. Nivolumab in  
18 elderly or poor performance status patients with advanced non-small cell lung cancer.  
19 *Journal of Thoracic Oncology*. 2017;12 (1 Supplement 1):S1338-S9.  
20  
21 178. Yamaguchi T, Oya Y, Kagawa Y, Furuta H, Watanabe N, Shimizu J, et al. Efficacy  
22 and safety of nivolumab in non-small cell lung cancer patients who relapse after thoracic  
23 radiotherapy. *Journal of Thoracic Oncology*. 2017;12 (11 Supplement 2):S2426.  
24  
25 179. Yamamoto T, Nomizo T, Ozasa H, Tsuji T, Yasuda Y, Yoshida H, et al. Clinical  
26 impact of hypothyroidism and PD-L1 SNPs in patients with non-small cell lung cancer  
27 treated with nivolumab. *Ann Oncol*. 2018;29 (Supplement 8):viii428.  
28  
29 180. Yamane K, Takeda K, Yanai M, Tanaka N, Izumi H, Sakamoto T, et al. Efficacy and  
30 tolerability of nivolumab in elderly patients with advanced non-small cell lung cancer. *Journal  
31 of Thoracic Oncology*. 2017;12 (11 Supplement 2):S1919.  
32  
33 181. Unknown. GRADEpro 2021 [Available from: <https://www.grade-pro.org/>]  
34  
35  
36  
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41  
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44  
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