

Gandhi et al, 2018	0.43 [0.31; 0.60]	B
Brahmer et al, 2015	0.52 [0.36; 0.76]	
Robert et al, 2015	0.52 [0.32; 0.85]	
Paz-Ares et al, 2018	0.52 [0.34; 0.80]	
Motzer et al, 2018 Herbst et al, 2016	0.53 [0.40; 0.71]	
Ferris et al, 2016	0.63 [0.50; 0.79] 0.64 [0.46; 0.90]	
Hodi et al, 2010	0.65 [0.47; 0.90]	
Robert et al, 2011	0.70 [0.55; 0.90]	
Hodi et al, 2010	0.70 [0.54; 0.90]	
Bellmunt et al, 2017	0.75 [0.53; 1.06]	
Kang et al, 2017	0.76 [0.58; 1.00]	
Shitara et al, 2018	0.77 [0.58; 1.02]	
Motzer et al, 2015	0.78 [0.60; 1.01]	
Rittmeyer et al, 2017	0.80 [0.64; 1.00]	
Borghaei et al, 2015	0.81 [0.63; 1.05]	
Govindan et al, 2017 Barlesi et al, 2018	0.82 [0.64; 1.05]	
Maio et al, 2017	0.84 [0.63; 1.12] 0.87 [0.64; 1.19]	
Ribas et al, 2013	0.88 [0.72; 1.07]	
Horn et al, 2018	0.92 [0.64; 1.32]	
Cohen et al, 2017	0.94 [0.73; 1.21]	
Reck et al, 2016	1.08 [0.90; 1.30]	
Carbone et al, 2017	1.13 [0.83; 1.54]	
Larkin et al, 2018	1.17 [0.84; 1.63]	
Bang et al, 2018	1.22 [0.90; 1.66]	
Total (fixed effect) Total (random effects)	0.79 [0.75; 0.83]	<u> </u>
Heterogeneity: χ^2_{25} = 72.76 (P	0.77 [0.70; 0.85] < 001) $l^2 = 66\%$	
Elderly patients (age \geq		
Robert et al, 2015	0.44 [0.24; 0.81]	
Horn et al, 2018	0.53 [0.36; 0.78]	
Kang et al, 2017	0.53 [0.38; 0.74]	
Brahmer et al, 2015	0.56 [0.34; 0.92]	
Cohen et al, 2017 Hodi et al, 2010	0.57 [0.37; 0.87]	
Larkin et al, 2018	0.61 [0.38; 0.98] 0.62 [0.41; 0.94]	
Borghaei et al, 2015	0.63 [0.45; 0.89]	
Motzer et al, 2015	0.64 [0.45; 0.91]	
Gandhi et al, 2018	0.64 [0.43; 0.95]	
Rittmeyer et al, 2017	0.66 [0.52; 0.83]	
Hodi et al, 2010	0.69 [0.47; 1.01]	
Paz-Ares et al, 2018 Bellmunt et al, 2017	0.74 [0.51; 1.07] 0.76 [0.56; 1.03]	
Herbst et al, 2016	0.76 [0.57; 1.03]	
Motzer et al, 2018	0.86 [0.58; 1.27]]
Ribas et al, 2013	0.87 [0.64; 1.19]	
Shitara et al, 2018	0.90 [0.63; 1.29]	
Robert et al, 2011	0.91 [0.64; 1.29]	
Ferris et al, 2016	0.93 [0.56; 1.54]	
Bang et al, 2018	0.95 [0.65; 1.38]	
Barlesi et al, 2018 Maio et al, 2017	0.98 [0.71; 1.35] 0.99 [0.77; 1.27]	
Carbone et al, 2017	1.04 [0.77; 1.41]	
Govindan et al, 2017	1.06 [0.82; 1.38]	
Reck et al, 2016	1.14 [0.87; 1.49]	{ - ■
Total (fixed effect)	0.79 [0.74; 0.84]	÷
Total (random effects)	0.77 [0.70; 0.8	*
Heterogeneity: $\chi^2_{25} = 50.15 (P)$ Elderly patients (age \geq		
Govindan et al, 2017	0.85 [0.51; 1.42]	
Borghaei et al, 2015	0.90 [0.43; 1.88]	
Motzer et al, 2018	0.97 [0.48; 1.96]	
Barlesi et al, 2018	1.16 [0.54; 2.48]	
Motzer et al, 2015	1.23 [0.66; 2.30]	
Brahmer et al, 2015	1.85 [0.76; 4.51]	**
Total (fixed effect)	1.05 [0.80; 1.39]	
Total (random effects) Heterogeneity: $\chi_5^2 = 2.73$ (P = .	1.05[0.80; 1.39] 74) $l^2 = 0\%$	
Total (fixed effect)	0.79 [0.76; 0.83]	
Total (random effects)	0.78 [0.73; 0.83]	\
Heterogeneity: χ^2_{57} = 129.76 (P	$< .001), I^2 = 56\%$	
	0.	
		HR (95% CI)
Test for subard	oup differences (fixed	d effect): $\chi_2^2 = 4.13 (P = .13)$

Test for subgroup differences (fixed effect): χ_2^2 = 4.13 (*P* = .13) Test for subgroup differences (random effects): χ_2^2 = 4.70 (*P* = .10)

Progression-free survival forest plot

	P	
Source	HR (95% CI)	7 7
Younger patients (age < 65)	
Ribas et al, 2015	0.42 [0.30; 0.59]	
Antonia et al, 2018	0.43 [0.32; 0.57]	
Gandhi et al, 2018	0.43 [0.33; 0.57]	
Ribas et al, 2015	0.47 [0.34; 0.65]	
Paz-Ares et al, 2018	0.50 [0.37; 0.68]	——————————————————————————————————————
Hellmann et al, 2018	0.51 [0.34; 0.77]	i
Reck et al, 2016	0.61 [0.40; 0.93]	
Brahmer et al, 2015	0.62 [0.44; 0.88]	
Horn et al, 2018	0.76 [0.57; 1.01]	
Schmid et al, 2018	0.84 [0.70; 1.01]	- <u>-</u>
Herbst et al, 2016	0.84 [0.69; 1.02]	
Borghaei et al, 2015	0.89 [0.70; 1.13]	
Carbone et al, 2017	1.17 [0.88; 1.56]	
Bang et al, 2018	1.96 [1.43; 2.68]	
Barlesi et al. 2018	3.40 [2.48; 4.66]	
Total (fixed effect)	0.78 [0.73; 0.84]	▲
Total (random effects)		
	$7.66 (P < .001), I^2 = 93\%$	
Elderly patients (a	ne > 65)	
Reck et al, 2016	0.45 [0.29; 0.70]	
Brahmer et al, 2015	0.51 [0.32; 0.82]	
Ribas et al, 2015	0.60 [0.41; 0.88]	
Hellmann et al, 2018	0.62 [0.40; 0.97]	
Paz-Ares et al, 2018	0.63 [0.47; 0.84]	
Schmid et al. 2018	0.69 [0.51; 0.94]	
Ribas et al, 2015	0.70 [0.48; 1.02]	
Antonia et al, 2018	0.74 [0.54; 1.01]	
Gandhi et al, 2018	0.75 [0.55; 1.02]	
Horn et al, 2018	0.76 [0.56; 1.03]	
Herbst et al, 2016	0.93 [0.72; 1.20]	
Borghaei et al, 2015	0.94 [0.69; 1.28]	
Carbone et al, 2017	1.21 [0.91; 1.61]	
Bang et al, 2018	1.38 [0.94; 2.03]	
Barlesi et al, 2018	4.20 [2.42; 7.27]	>
Total (fixed effect)	0.82 [0.75; 0.89]	★
Total (random effects)		
Heterogeneity: $\chi^2_{14} = 70$.82 ($P < .001$), $I^2 = 80\%$	
Elderly patients (a		
Hellmann et al, 2018		
Barlesi et al, 2018	0.91 [0.42; 1.97]	
Borghaei et al, 2015	0.97 [0.49; 1.94]	
Brahmer et al, 2015	1.76 [0.77; 4.04]	
Total (fixed effect)	0.98 [0.65; 1.48]	
Total (random effects)	0.98 [0.64; 1.50]	
Heterogeneity: $\chi_3^2 = 4.1$		<u></u>
Total (fixed effect)	0.80 [0.75; 0.84]	
Total (random effects)	$4.26 (P < .001), I^2 = 88\%$	
Herei ugeneity. $\chi_{33} = 27$	4.20 (P < .001), 7 = 88% 0.2	0.5 1 2
	0.2	Hazard Ratio (95% Cl)

Test for subgroup differences (fixed effect): $\chi_1^2 = 0.58 \ (P = .45)$ Test for subgroup differences (random effects): $\chi_1^2 = 0.23 \ (P = .63)$

Supplementary Figure 2 Α

Overall survival forest plot

Source Younger patients (Gandhi et al, 2018 Brahmer et al, 2015 Robert et al, 2015 Paz-Ares et al, 2018 Motzer et al, 2018 Herbst et al, 2016 Ferris et al, 2016 Hodi et al, 2010 Robert et al, 2011 Hodi et al, 2010 Bellmunt et al, 2017 Kang et al, 2017 Motzer et al, 2015 Rittmeyer et al, 2015 Horn et al, 2018 Total (fixed effect) Total (random effects) Heterogenety: $\chi_{15}^2 = 23.7$	$\begin{array}{c} 0.43 \ [0.31, 0.60] \\ 0.52 \ [0.36; 0.76] \\ 0.52 \ [0.32; 0.85] \\ 0.52 \ [0.32; 0.85] \\ 0.52 \ [0.34; 0.80] \\ 0.53 \ [0.40; 0.71] \\ 0.63 \ [0.50; 0.79] \\ 0.64 \ [0.46; 0.90] \\ 0.65 \ [0.47; 0.90] \\ 0.70 \ [0.55; 0.90] \\ 0.70 \ [0.55; 0.90] \\ 0.70 \ [0.55; 0.90] \\ 0.70 \ [0.55; 0.90] \\ 0.75 \ [0.53; 1.06] \\ 0.76 \ [0.58; 1.00] \\ 0.78 \ [0.60; 1.01] \\ 0.80 \ [0.64; 1.32] \\ 0.68 \ [0.63; 0.73] \\ 0.67 \ [0.61; 0.74] \\ 74 \ (P = .07), I^2 = 37\% \end{array}$		
Elderly patients (a Robert et al, 2015	ge ≥ 65) 0.44 [0.24; 0.81] -		
Horn et al. 2018	0.53 [0.36; 0.78]		
Kang et al, 2017	0.53 [0.38; 0.74]		
Brahmer et al, 2015	0.56 [0.34; 0.92]		
Hodi et al, 2010	0.61 [0.38; 0.98]		
Borghaei et al, 2015	0.63 [0.45; 0.89]		
Motzer et al, 2015	0.64 [0.45; 0.91]		
Gandhi et al, 2018	0.64 [0.43; 0.95]		
Rittmeyer et al, 2017	0.66 [0.52; 0.83]	— — —	
Hodi et al, 2010	0.69 [0.47; 1.01]		
Paz-Ares et al, 2018	0.74 [0.51; 1.07]		
Bellmunt et al, 2017	0.76 [0.56; 1.03]	3	
Herbst et al, 2016	0.76 [0.57; 1.02]		
Motzer et al, 2018 Robert et al, 2011	0.86 [0.58; 1.27]		
Robert et al, 2011 Ferris et al, 2016	0.91 [0.64; 1.29] 0.93 [0.56; 1.54]		
Total (fixed effect)	0.68 [0.62; 0.74]	<u></u>	
Total (random effects)		4	
Heterogeneity: $\chi^2_{15} = 13.8$			
Total (fixed effect)	0.68 [0.64; 0.72]	\$	
Total (random effects)	0.68 [0.64; 0.72]		_
Heterogeneity: $\chi^2_{31} = 37.6$	52 (P = .19), / ² = 18%	1 1	
	0.2	0.5 1	2
		Hazard Ratio (95% CI)	

Progression-free survival forest plot

В

Source Younger patients (a Ribas et al, 2015 Antonia et al, 2018 Gandhi et al, 2018 Ribas et al, 2018 Paz-Ares et al, 2018 Hellmann et al, 2018 Reck et al, 2016 Brahmer et al, 2015 Horn et al, 2018 Schmid et al, 2018 Herbst et al, 2016 Borghaei et al, 2015 Total (fixed effect) Total (random effects) Heterogeneity: $\chi_{11}^2 = 52.4$	0.42 [0.30; 0.59] 0.43 [0.32; 0.57] 0.43 [0.33; 0.57] 0.47 [0.34; 0.65] 0.50 [0.37; 0.68] 0.51 [0.34; 0.77] 0.61 [0.40; 0.93] 0.62 [0.44; 0.88] 0.76 [0.57; 1.01] 0.84 [0.70; 1.01] 0.84 [0.70; 1.02] 0.69 [0.70; 1.13] 0.65 [0.60; 0.70] 0.60 [0.50; 0.71] $6 (P < .001), I^2 = 79\%$		
Elderly patients (ag			
Reck et al, 2016	0.45 [0.29; 0.70]		
Brahmer et al, 2015 Ribas et al, 2015	0.51 [0.32; 0.82] 0.60 [0.41; 0.88]		
Helimann et al. 2018			
Paz-Ares et al. 2018	0.63 [0.47; 0.84]		
Schmid et al. 2018	0.69 [0.51; 0.94]		
Ribas et al. 2015	0.70 [0.48; 1.02]		
Antonia et al, 2018	0.74 [0.54; 1.01]		
Gandhi et al, 2018	0.75 [0.55; 1.02]		
Horn et al, 2018	0.76 [0.56; 1.03]		
Herbst et al, 2016	0.93 [0.72; 1.20]	·	
Borghaei et al, 2015	0.94 [0.69; 1.28]	· · · · · · · · · · · · · · · · · · ·	
Total (fixed effect)	0.72 [0.65; 0.79]	~	
Total (random effects)	0.71 [0.63; 0.80]	*	
Heterogeneity: $\chi^2_{11} = 15.8$	(P = .15), I ² = 30%		
Total (fixed effect)	0.68 [0.64; 0.72]	\$	
Total (random effects)		<u> </u>	-
Heterogeneity: $\chi^2_{23} = 70.9$			
	0.2	0.5 1	2
		Hazard Ratio (95% CI)	

Supplementary Table 1. PRISMA 2020 Checklist

Section and Topic	ltem #	Checklist item	Location where item is reported			
TITLE						
Title	1	Identify the report as a systematic review.	Page 1			
ABSTRACT						
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2			
INTRODUCTION						
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3			
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3-4			
METHODS Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4 and Figure 1			
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4			
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4			
Selection process	8					
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5			
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5 and Table 1-2			
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5 and Table 1-2			
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6 and Supplementary table 2			
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 5-6			
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6			
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not applicable			
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 6 and Figure 2			
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 6-7			
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 6 and			

Section and Topic	ltem #	Checklist item	Location where item is reported
			Table 3-4-5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 7-8 and Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Page 7-8 and Table 1-2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 8 and Supplementary table 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 8-9 and Table 1-2 and Figure 2
Results of	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 8-11
syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 8-11 and Table 3-4-5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 9-10 and Table 1-5
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 11-12
	23b	Discuss any limitations of the evidence included in the review.	Page 12-13
	23c	Discuss any limitations of the review processes used.	Page 12-13
	23d	Discuss implications of the results for practice, policy, and future research.	Page 13
OTHER INFORMA	TION		
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 4
protocol	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 4

Section and Topic	ltem #	Checklist item	Location where item is reported
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 14
Competing interests	26	Declare any competing interests of review authors.	Page 14
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 4

C	DL	Tumor tuno	T • .	NT	Turnet	Genterl	Median age	Median	N ((%)	OS, HR (95% CI)		
Source	Phase	Tumor type	Line	Ν	Treatment	Control	(years)	follow-up (months)	<65 y	<u>≥</u> 65 y	All	<65 y	<u>≥</u> 65 y
Gandhi, 2018 ²⁴	3	NSCLC	1	616	Pembrolizumab + Platinum	Placebo, Platinum	Int: 65 (34–84); cont: 64(34-84)	10.5 (0.2-20.4)	312 (51)	304 (49)	0.49 (0.38–0.64)	0.43 (0.31–0.61)	0.64 (0.43–0.95)
Barlesi, 2018 ²⁵	3	NSCLC	>1	264	Avelumab	Docetaxel	Int: 64 (58–59); cont: 63 (57-69)	18.3 (IQR, 13.2–22.7)	134 (51)	130 (49)	0.90 (0.72–1.12)	0.84 (0.63–1.13)	0.98 (0.71–1.34)
Paz-Ares, 2018 ²⁶	3	NSCLC	1	559	Pembrolizumab + ICC	Placebo + ICC	Int: 65 (29–87); cont: 65 (36-88)	7.8 (0.1–19.1)	254 (45)	305 (55)	0.64 (0.49–0.85)	0.52 (0.34–0.80)	0.74 (0.51–1.07)
Horn, 2018 ²⁹	3	SCLC	1	403	Atezolizumab + carboplatin + etoposide	Placebo + carboplatin + etoposide	Int: 64 (28–90); cont: 64 (26–87)	13.9 (NR)	217 (54)	186 (46)	0.70 (0.54–0.91)	0.92 (0.64–1.32)	0.53 (0.36–0.77)
Larkin, 2018 ³⁰	3	Melanoma	>1	405	Nivolumab	Placebo	61 (23–88)	24 (NR)	257 (63)	148 (37)	0.92 (0.71–1.18)	1.17 (0.84–1.63)	0.62 (0.41–0.94)
Shitara, 2018 ³²	3	Gastric or GE junction carcinoma	2	395	Pembrolizumab	Paclitaxel	62.5 (54–70)	7.9 (IQR, 3.4–14.6)	232 (59)	163 (41)	0.82 (0.66–1.03)	0.77 (0.58–1.02)	0.90 (0.63–1.29)
Bang, 2018 ³³	3	Gastric or GE junction carcinoma	3	371	Avelumab	CTx	59 (29–86)	8.0 weeks* (2–66)	230 (62)	141 (38)	1.1 (0.9–1.4)	1.22 (0.89–1.65)	0.95 (0.65–1.38)
Motzer, 2018 ³⁴	3	ccRCC	1	847	Nivolumab + ipilimumab	Sunitinib	Int: 62 (26–85); cont: 51 (21–85)	25.2 (NR)	524 (62)	323 (38)	0.66 (0.53–0.82)	0.53 (0.40–0.71)	0.86 (0.58–1.27)
Govindan, 2017 ⁶²	3	NSCLC	1	749	Ipilimumab + docetaxel + carboplatin	Placebo + docetaxel + carboplatin	64 (28–85)	Int: 12.5(NR); Cont: 11.8(NR)	380 (51)	369 (49)	0.91 (0.77–1.07)	0.82 (0.64–1.04)	1.06 (0.81–1.37)
Carbone, 2017 ³⁶	3	NSCLC	1	541	Nivolumab	ICC	64 (29–89)	13.5 (NR)	281 (52)	260 (48)	1.08 (0.87–1.34)	1.13 (0.83–1.54)	1.04 (0.77–1.41)
Rittmeyer, 2017 ³⁷	3	NSCLC	1	850	Atezolizumab	Docetaxel	64 (33–85)	21 (NR)	453 (53)	397 (47)	0.73 (0.62-0.87)	0.80 (06.4-1.00)	0.66 (0.52-0.83)
Cohen, 2017 ³⁸	3	HNSCC	2	495	Pembrolizumab	ICC	60 (19–85)	7.3	332 (67)	163 (33)	0.80 (0.65–0.98)	0.94 (0.73–1.20)	0.57 (0.37–0.87)
Bellmunt, 2017 ³⁹	3	Urothelial carcinoma	>1	542	Pembrolizumab	ICC	66 (26–88)	14.1 (9.9–22.1)	230 (52)	312 (48)	0.73 (0.59–0.91)	0.75 (0.53–1.05)	0.76 (0.56–1.02)
Kang, 2017 ⁴⁰	3	Gastric or GE junction carcinoma	>1	493	Nivolumab	Placebo	62 (IQR, 53–69)	Int: 8.87 (IQR, 6.57–12.37); cont: 8.59 (IQR, 5.65–11.37)	284 (58)	209 (42)	0.65 (0.53–0.80)	0.76 (0.58–1.00)	0.53 (0.38–0.74)
Maio, 2017 ⁴¹	3	Mesothelio ma	>1	571	Tremelimumab	Placebo	67 (IQR, 60–73)	NR	237 (42)	334 (58)	0.92 (0.76–1.12)	0.87 (0.64–1.20)	0.99 (0.77–1.26)
Ferris, 2016 ⁴²	3	HNSCC	>1	361	Nivolumab	ICC	60 (28–83)	5.1 (0–16.8)	248 (69)	113 (31)	0.69 (0.53–0.91)	0.64 (0.45–0.89)	0.93 (0.56–1.54)

Supplementary Table 2. Baseline characteristics of 26 randomized controlled studies for overall survival.

Herbst, 2016 ⁴⁴	2,3	NSCLC	>1	103 3	Pembrolizumab	Docetaxel	63 (IQR, 54–70)	13.1 (IQR, 8.6–17.7)	604 (58)	429 (42)	0.67 (0.56–0.80)	0.63 (0.50–0.79)	0.76 (0.57–1.02)
Reck, 2016 ⁴³	3	SCLC	1	954	Ipilimumab + etoposide + platinum	Placebo + etoposide + platinum	63 (35–85)	Int: 10.5 (NR); cont: 10.2 (NR)	576 (60)	378 (40)	0.94 (0.81–1.09)	1.08 (0.9–1.31)	1.14 (0.87–1.49)
Brahmer, 2015 ⁴⁶	3	NSCLC	>1	272	Nivolumab	Docetaxel	63 (39–85)	11.0 (NR)	152 (56)	120 (44)	0.59 (0.44–0.78)	0.52 (0.35–0.75)	0.56 (0.34–0.91)
Borghaei, 2015 ⁴⁷	3	NSCLC	>1	582	Nivolumab	Docetaxel	62 (21–88)	13.2 (NR)	339 (58)	243 (42)	0.75 (0.62–0.91)	0.81 (0.62–1.04)	0.63 (0.45–0.89)
Robert, 2015 ⁴⁸	3	Melanoma	1	418	Nivolumab	Dacarbazine	65 (18–87)	Int:8.9 (NR); cont:6.8 (NR)	200 (48)	218 (52)	0.42 (0.30–0.59)	0.52 (0.32–0.85)	0.44 (0.24–0.81)
Motzer, 2015 ⁴⁹	3	ccRCC	>1	821	Nivolumab	Everolimus	62 (23-88)	NR	497 (61)	324 (39)	0.76 (0.62–0.92)	0.78 (0.60–1.01)	0.64 (0.45–0.91)
Ribas, 2013 ⁶³	3	Melanoma	1	655	Tremelimumab	ICC	57 (22–90)	NR	455 (69)	200 (31)	0.88 (0.75–1.04)	0.88 (0.72–1.07)	0.87 (0.64–1.19)
Robert, 2011 ⁵³	3	Melanoma	1	502	Ipilimumab + Dacarbazine	Placebo + Dacarbazine	56.9 (NR)	54 (NR)	342 (68)	160 (32)	0.72 (0.59–0.87)	0.70 (0.55–0.90)	0.91 (0.64–1.28)
Hodi, 2010 ⁵²	3	Melanoma	>1	273	Ipilimumab	gp100	56.8 (NR)	21.0 (ipilimumab + gp100),	189 (69)	84 (31)	0.64 (0.49–0.84)	0.65 (0.47–0.90)	0.61 (0.38–0.99)
Hodi, 2010 ⁵²	3	Melanoma	>1	539	Ipilimumab + gp100	gp100	56.2 (NA)	27.8 (ipilimumab), 17.2 (gp100)	385 (71)	154 (29)	0.69 (0.56–0.85)	0.70 (0.54–0.90)	0.69 (0.47–1.01)

#subgroup of patients with PD-L1+

Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; HNSCC, head and neck squamous cell carcinoma; RT, radiotherapy; CTx, chemotherapy; GE, gastroesophageal; ccRCC, clear cell renal cell carcinoma; Cont, control group, PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ICC, investigator's choice of chemotherapy; int, intervention; group; IQR, interquartile range; NR, not reported; N, number; CI, confidence interval

G		- 	-	•	- 		Median age	Median	N	(%)		PFS, HR (95% CI)	
Source	Phase	Tumor type	Line	Ν	Treatment	Control	(years)	follow-up (months)	<65 y	<u>≥</u> 65 y	All	<65 y	<u>≥</u> 65 y
Gandhi, 2018 ²⁴	3	NSCLC	1	616	Pembrolizumab + Platinum	Placebo, Platinum	Int: 65 (34–84); cont: 64 (34-84)	10.5 (0.2-20.4)	312 (51)	304 (49)	0.52 (0.43–0.64)	0.43 (0.32–0.56)	0.75 (0.55–1.02)
Barlesi, 2018 ²⁵	3	NSCLC	>1	264	Avelumab	Docetaxel	Int: 64 (58–59); cont: 63 (57-69)	18.3 (IQR, 13.2-22.7)	134 (51)	130 (49)	3.4 (2.7–4.9)	3.4 (2.5-4.7) [#]	4.2 (2.1-6.3) [#]
Paz-Ares, 2018 ²⁶	3	NSCLC	1	559	Pembrolizumab + ICC	Placebo + ICC	Int: 65 (29–87); cont: 65 (36-88)	7.8 (0.1–19.1)	254 (45)	305 (55)	0.56 (0.45–0.70)	0.50 (0.37-0.69)	0.63 (0.47-0.84)
Antonia, 2018 ²⁷	3	NSCLC	>1	713	Durvalumab	Placebo	64 (23–90)	25.2 (0.2–43.1)	391 (55)	322 (45)	0.55 (0.45–0.68)	0.43 (0.32-0.57)	0.74 (0.54-1.01)
Hellmann, 2018 ²⁸	3	NSCLC	1	326	Nivolumab + ipilimumab	CTx	64 (41–87)	NR	156 (48)	170 (52)	0.58 (0.43–0.77)	0.51 (0.34-0.77)	0.62 (0.40-0.97)
Horn, 2018 ²⁹	3	SCLC	1	403	Atezolizumab + carboplatin + etoposide	Placebo + carboplatin + etoposide	Int: 64 (28–90); cont: 64 (26–87)	13.9 (NR)	217 (54)	186 (46)	0.77 (0.62–0.96)	0.76 (0.57–1.01)	0.76 (0.56–1.03)
Schmid, 2018 ³¹	3	Breast cancer	1	902	Atezolizumab + nab-paclitaxel	Placebo + nab-paclitaxel	55 (20-82)	12.9	68 3 (76)	219 (24)	0.81 (0.70–0.93)	18–40yr: 0.79 (0.53–1.16), 41-64yr: 0.84 (0.70–1.01)	0.69 (0.51–0.94)
Bang, 2018 ³³	3	Gastric or GE junction carcinoma	3	371	Avelumab	CTx	59 (29–86)	8.0 weeks* (2–66)	230 (62)	141 (38)	1.73 (1.4–2.2)	1.96 (1.43–2.67)	1.38 (0.94–2.04)
Carbone, 2017 ³⁶	3	NSCLC	1	541	Nivolumab	ICC	64 (29–89)	13.5 (NR)	281 (52)	260 (48)	1.19 (0.97–1.46)	1.17 (0.88–1.56)	1.21 (0.91–1.62)
Reck, 2016 ⁴³	3	NSCLC	1	305	Pembrolizumab	ICC	65 (33–90)	11.2 (6.3–19.7)	141 (46)	164 (54)	0.50 (0.37–0.68)	0.61 (0.40–0.92)	0.45 (0.29–0.70)
Herbst, 2016 ⁴⁴	2,3	NSCLC	>1	103 3	Pembrolizumab	Docetaxel	63 (IQR, 54–70)	13.1 (IQR, 8.6–17.7)	604 (58)	429 (42)	0.85 (0.73–0.98)	0.84 (0.69–1.02)	0.93 (0.72–1.19)
Brahmer, 2015 ⁴⁶	3	NSCLC	>1	272	Nivolumab	Docetaxel	63 (39–85)	11.0 (NR)	152 (56)	120 (44)	0.63 (0.48–0.82)	0.62 (0.44–0.89)	0.51 (0.32–0.82)
Borghaei, 2015 ⁴⁷	3	NSCLC	>1	582	Nivolumab	Docetaxel	62 (21–88)	13.2 (NR)	339 (58)	243 (42)	0.91 (0.76–1.09)	0.89 (0.70–1.13)	0.94 (0.69–1.27)
Ribas, 2015 ⁵⁰	2	Melanoma	>1	359	Pembrolizumab 2mg/kg	CTx	62 (15–87)	NR	200 (56)	159 (44)	0.57 (0.45–0.73)	0.47 (0.34–0.66)	0.70 (0.48–1.01)
Ribas, 2015 ⁵⁰	2	Melanoma	>1	360	Pembrolizumab 10mg/kg	CTx	60 (27–89)	NR	204 (57)	156 (43)	0.50 (0.37–0.64)	0.42 (0.30–0.59)	0.60 (0.41–0.88)

Supplementary Table 3. Baseline characteristics of 15 randomized controlled studies for progression-free survival.
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#subgroups of patients with PD-L1-positive

Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; HNSCC, head and neck squamous cell carcinoma; RT, radiotherapy; CTx, chemotherapy; GE, gastroesophageal; ccRCC, clear cell renal cell carcinoma; Cont, control group, PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ICC, investigator's choice of chemotherapy; int, intervention; group; IQR, interquartile range; NR, not reported; N, number; CI, confidence interval

Study (Year)	Randomization	Blinding	Account	Jadad Score
Barlesi et al, 2018	2	0	1	3
Bellmunt et al, 2017	2	0	1	3
Borghaei et al, 2015	2	0	1	3
Brahmer et al, 2015	2	0	1	3
Carbone et al, 2017	2	0	1	3
Ferris et al, 2016	2	0	1	3
Herbst et al, 2016	2	0	1	3
Larkin et al, 2018	2	0	1	3
Motzer et al, 2015	2	0	1	3
Motzer et al, 2018	2	0	1	3
Reck et al, 2016	2	0	1	5
Ribas et al, 2013	2	0	1	3
Rittmeyer et al, 2017	2	0	1	5
Robert et al, 2015	2	0	1	3
Coehn et al, 2017	2	0	1	3
Bang et al, 2018	2	0	1	3
Ribas et al, 2015	2	0	1	3
Shitara et al, 2018	2	0	1	3
Hellmann et al, 2018	2	0	1	3
Schmid et al, 2018	2	0	1	3
Antonia et al, 2018	2	2	1	5
Gandhi et al, 2018	2	2	1	5
Govindan et al, 2017	2	2	1	5
Horn et al, 2018	2	2	1	5
Kang et al, 2017	2	2	1	5
Maio et al, 2017	2	2	1	5
Paz-Arez et al, 2018	2	2	1	5
Reck et al, 2016	2	2	1	5
Robert et al, 2011	2	2	1	5
Hodi et al, 2010	2	2	1	5

Supplementary Table 4. Summary of Jadad score by randomization, blinding, and account. A score of 0–2 is considered low, and a score of 3–5 is defined as high quality.

Variables	Number	Number of participants		Pooled HR (95% CI)			Test for Difference	
		all	<65	≥65	all	<65	≥65	P value
All	16	9,111	5,230	3,881	0.67 (0.64, 0.71)	0.67 (0.61, 0.74)	0.68 (0.62, 0.74)	0.85
Primary disease site								
NSCLC	7	4,454	2,344	2,110	0.67 (0.60, 0.74)	0.64 (0.53, 0.77)	0.69 (0.61, 0.78)	0.50
melanoma	4	1,732	1,116	616	0.62 (0.51, 0.77)	0.67 (0.58 0.78)	0.69 (0.52, 0.90)	0.89
Other tumors	5	2,925	1,770	1,155	0.69 (0.63, 0.77)	0.71 (0.59, 0.85)	0.66 (0.53, 0.81)	0.59
Type of immunotherapy								
anti-PD-1/PD-L1 antibody	12	6,950	3,790	3,160	0.66 (0.61, 0.72)	0.68 (0.60, 0.77)	0.66 (0.59, 0.72)	0.69
Anti-CTLA-4 antibody	3	1,314	916	398	0.69 (0.61, 0.78)	0.69 (0.59, 0.80)	0.75 (0.59, 0.96)	0.54
Combination treatment	1	847	524	323	-	-	-	-
Line of treatment								
0	9	4,916	2,928	1,988	0.69 (0.64, 0.74)	0.70 (0.64, 0.77)	0.67 (0.60, 0.76)	0.61
1	7	4,195	2,302	1,893	0.63 (0.55, 0.72)	0.62 (0.51, 0.77)	0.69 (0.59, 0.80)	0.44

Supplementary Table 5. Subgroup analysis of immunotherapy efficacy in terms of overall survival (OS) between younger age (<65 years old) and older age (≥65 years old) in clinical trials with positive outcomes.

Abbreviations: NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval

Variables	Number	Number of participants			Test for Difference			
		all	<65	≥65	all	<65	≥65	P value
All	12	6,430	3,653	2,777	0.64 (0.56, 0.73)	0.60 (0.50, 0.71)	0.71 (0.63, 0.80)	0.11
Primary disease site								
NSCLC	8	4,406	2,349	2,057	0.63 (0.53, 0.75)	0.59 (0.48, 0.73)	0.71 (0.59, 0.84)	0.20
melanoma	2	719	404	315	0.53 (0.45, 0.64)	0.44 (0.35, 0.56)	0.65 (0.50, 0.85)	0.04*
Other tumors	2	1,305	900	405	0.80 (0.71, 0.90)	0.82 (0.70, 0.95)	0.72 (0.58, 0.90)	0.38
Type of immunotherapy								
anti-PD-1/PD-L1 antibody	11	6,104	3,497	2,607	0.65 (0.56, 0.74)	0.60 (0.50, 0.73)	0.71 (0.63, 0.81)	0.14
Anti-CTLA-4 antibody	0	-	-	-	-	-	-	-
Combination treatment	1	326	156	170	-	-	-	-
Line of treatment								
0	6	3,319	1,890	1,429	0.66 (0.54, 0.81)	0.59 (0.45, 0.78)	0.75 (0.63, 0.90)	0.15
1	6	3,111	1,763	1,348	0.62 (0.52. 0.74)	0.60 (0.48, 0.76)	0.67 (0.58, 0.76)	0.45

Supplementary Table 6. Subgroup analysis of immunotherapy efficacy in terms of progression-free survival (PFS) between younger age (\leq 65 years old) and older age (\geq 65 years old) in clinical trials with positive outcomes.

Abbreviations: NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval

*P<0.05

Supplementary Table 7. Meta-regression analysis to evaluate the impact of covariates on the overall survival and progression-free survival in clinical trials with positive outcomes.

	Overall surv	vival	Progression-free survival		
Covariates	Log HR estimate (CI bound)	P value	Log HR estimate (CI bound)	P value	
Age group	0.013 (-0.128 ~ 0.155)	0.852	0.153 (-0.030 ~ 0.335)	0.101	
Line of therapy	-0.045 (-0.191 ~ 0.102)	0.550	-0.294 (-0.534 ~ -0.053)	0.017*	
Tumor type (NSCLC)	-0.001 (-0.224 ~ 0.221)	0.990	0.332 (0.051 ~ 0.612)	0.021*	
Tumor type (Other tumors)	0.018 (-0.188 ~ 0.223)	0.864	0.668 (0.273 ~ 1.063)	0.001**	
Type of immunotherapy	0.017 (-0.136 ~ 0.170)	0.827	0.007 (-0.201 ~ 0.216)	0.946	

Abbreviations: NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval

P*<0.05; *P*<0.01;

Supplementary Table 8. Meta-regression analysis to evaluate the impact of covariates on the overall survival and progression-free survival, including different age cut-offs.

	Overall surv	vival	Progression-free survival		
Covariates	Log HR estimate (CI bound)	P value	Log HR estimate (CI bound)	<i>P</i> value	
Age group (age≥65)	-0.004 (-0.142 ~ 0.134)	0.958	0.099 (-0.247 ~ 0.447)	0.573	
Age group (age≥75)	0.310 (-0.029 ~ 0.649)	0.073	0.116 (-0.581 ~ 0.814)	0.744	
Line of therapy	< 0.001 (-0.154 ~ 0.155)	0.999	-0.467 (-0.861 ~ -0.073)	0.020*	
Tumor type (NSCLC)	0.042 (-0.164~ 0.247)	0.691	0.648 (0.093 ~ 1.204)	0.022*	
Tumor type (Other tumors)	0.110 (-0.078 ~ 0.299)	0.252	0.917 (0.251 ~ 1.589)	0.007**	
Type of immunotherapy	0.049 (-0.097 ~ 0.196)	0.509	-0.101 (-0.423 ~ 0.222)	0.541	

Abbreviations: NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval

P*<0.05; *P*<0.01;