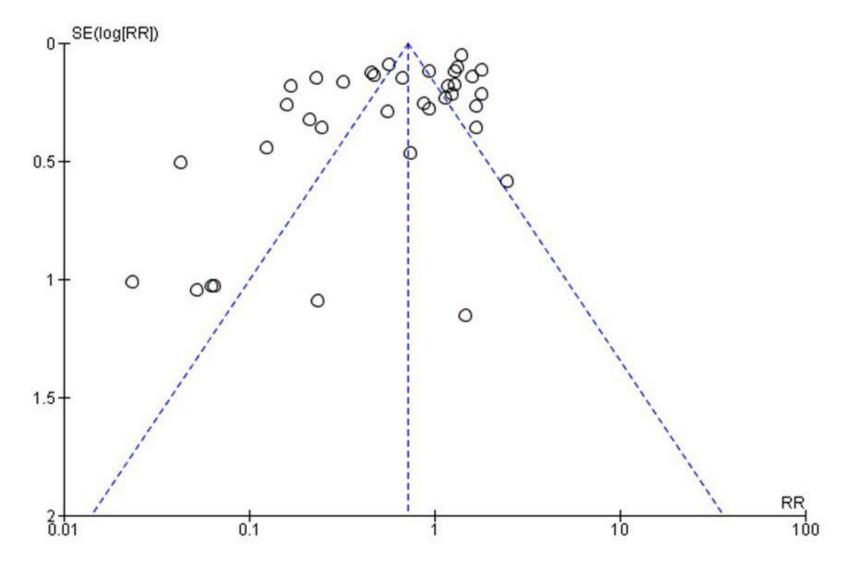
Supplemental Online Content

Farooq MZ, Aqeel SB, Lingamaneni P, et al. Association of immune checkpoint inhibitors with neurologic adverse events: a systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(4):e227722. doi:10.1001/jamanetworkopen.2022.7722

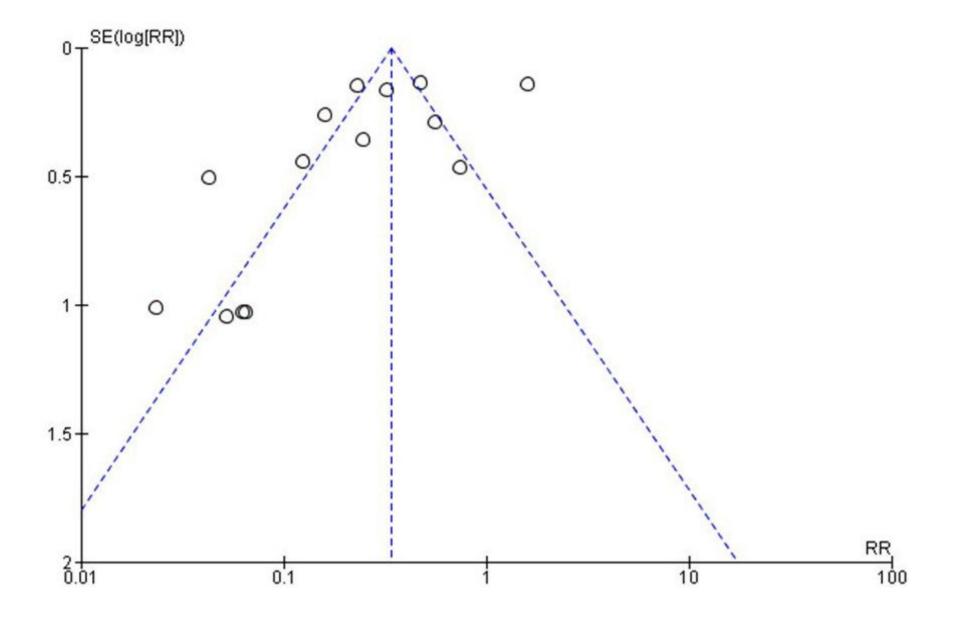
- eFigure 1. Funnel Plots for Included Trials by Subgroup
- **eFigure 2.** Overall Analysis of Incidence of Adverse Events Between Checkpoint Inhibitor and Control Arm
- **eFigure 3.** Subgroup Analysis of Adverse Events Between Checkpoint Inhibitors and Chemotherapy
- eFigure 4. Subgroup Analysis of Headache Between Checkpoint Inhibitors and Placebo
- **eFigure 5.** Overall Risk of Neurologic Adverse Events Excluding Incidence of Specific Event Between Checkpoint Inhibitors and Control Arm
- eTable 1. Quality Assessment of All Trials Using the Cochrane Collaborations Tool
- eTable 2. Pooled Characteristics of the Intention-to-Treat Population

This supplemental material has been provided by the authors to give readers additional information about their work.

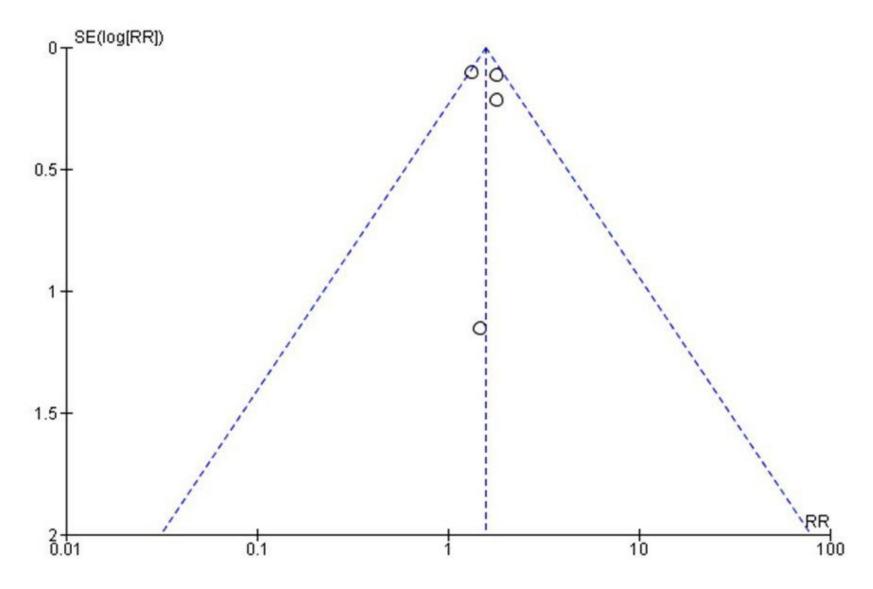
eFigure 1. Funnel Plots for Included Trials by Subgroup



A. Funnel plots for trials included in overall analysis.



B. Funnel plots for trials included in the subgroup analysis of immunotherapy versus chemotherapy.



C. Funnel plots for trials included in the subgroup analysis of immunotherapy versus placebo

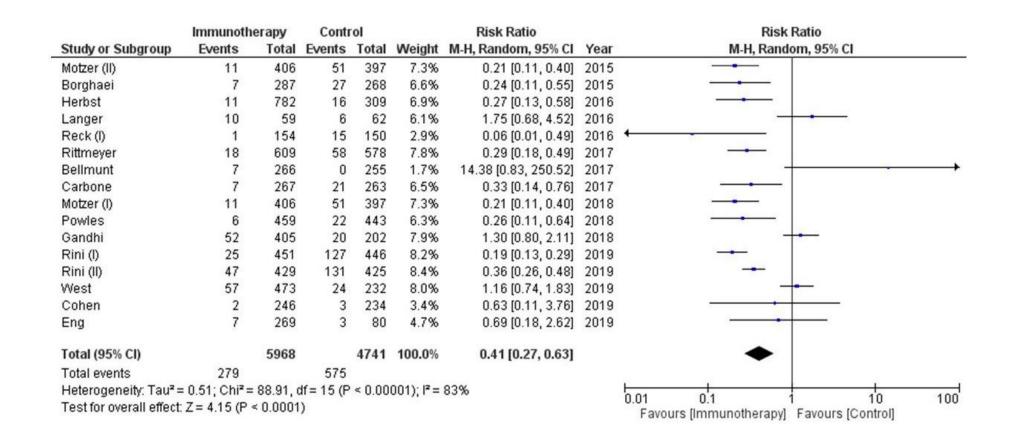
eFigure 2. Overall Analysis of Incidence of Adverse Events Between Checkpoint Inhibitor and Control Arm

	Immunoth	егару	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Reck (III)	57	84	32	44	6.0%	0.93 [0.74, 1.18]	2012	+
Kwon	5	393	8	396	4.9%	0.63 [0.21, 1.91]	2014	-
Borghaei	9	287	25	268	5.5%	0.34 [0.16, 0.71]	2015	
Fehrenbacher	1	142	15	135	3.3%	0.06 [0.01, 0.47]	2016	
Ferris	1	236	7	111	3.2%	0.07 [0.01, 0.54]	2016	
Herbst	11	782	52	309	5.6%	0.08 [0.04, 0.16]	2016	
Reck (II)	10	478	4	476	4.8%	2.49 [0.79, 7.88]	2016	 • • • • • • • • • • • • • • • • • • •
Bellmunt	3	266	59	255	4.8%	0.05 [0.02, 0.15]	2017	
Carbone	1	267	15	263	3.3%	0.07 [0.01, 0.49]	2017	
Govindan	44	388	63	361	5.9%	0.65 [0.45, 0.93]	2017	-
Hamid	3	361	14	179	4.6%	0.11 [0.03, 0.36]	2017	
Maio	1	380	1	189	2.4%	0.50 [0.03, 7.91]	2017	
Rittmeyer	24	609	65	578	5.8%	0.35 [0.22, 0.55]	2017	
Horn	6	198	4	196	4.6%	1.48 [0.43, 5.18]	2018	- •
Paz-Ares	57	278	45	280	5.9%	1.28 [0.90, 1.82]	2018	+
Powles	3	459	50	443	4.8%	0.06 [0.02, 0.18]	2018	
Shitara	1	294	40	276	3.4%	0.02 [0.00, 0.17]	2018	
Bang	1	57	0	45	2.0%	2.38 [0.10, 57.05]	2018	
Usmani	1	149	0	145	2.0%	2.92 [0.12, 71.10]	2019	
West	53	473	21	232	5.8%	1.24 [0.77, 2.00]	2019	
Cohen	1	246	11	234	3.3%	0.09 [0.01, 0.66]	2019	-
Eng	5	269	1	80	3.1%	1.49 [0.18, 12.54]	2019	
Mok	4	636	90	615	5.1%	0.04 [0.02, 0.12]	2019	
Total (95% CI)		7732		6110	100.0%	0.30 [0.17, 0.51]		•
Total events	302		622					
Heterogeneity: Tau² = Test for overall effect:				P < 0.0	0001); l²:	= 91%		0.01 0.1 1 10 10 Favours [Immunotherapy] Favours [Control]

A. Peripheral neuropathy

	Immunoth	егару	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Hodi	84	511	19	132	7.5%	1.14 [0.72, 1.81]	2010	+
Robert	40	247	33	251	8.0%	1.23 [0.80, 1.89]	2011	+-
Kwon	39	393	32	396	7.7%	1.23 [0.79, 1.92]	2014	+-
Borghaei	29	287	2	268	1.5%	13.54 [3.26, 56.20]	2015	
Eggermont (II)	152	471	86	474	11.4%	1.78 [1.41, 2.24]	2015	-
Herbst	14	782	2	309	1.4%	2.77 [0.63, 12.10]	2016	-
Maio	20	380	6	189	3.3%	1.66 [0.68, 4.06]	2017	 • -
Bellmunt	13	266	13	255	4.3%	0.96 [0.45, 2.03]	2017	
Horn	42	198	38	196	8.6%	1.09 [0.74, 1.62]	2018	
Barlesi	7	393	9	365	2.9%	0.72 [0.27, 1.92]	2018	
Gandhi	57	405	23	202	7.6%	1.24 [0.79, 1.95]	2018	+
Mateos	15	120	5	121	2.9%	3.02 [1.14, 8.06]	2019	
Rini (I)	48	451	30	446	7.9%	1.58 [1.02, 2.45]	2019	-
Rini (II)	68	429	69	425	10.1%	0.98 [0.72, 1.33]	2019	+
West	77	473	23	232	7.8%	1.64 [1.06, 2.55]	2019	
Cohen	5	246	6	234	2.1%	0.79 [0.25, 2.56]	2019	- 1
Eng	26	269	10	80	4.8%	0.77 [0.39, 1.53]	2019	
Total (95% CI)		6321		4575	100.0%	1.32 [1.10, 1.59]		◆
Total events	736		406					
Heterogeneity: Tau ² =	= 0.07; Chi2=	32.88, 0	df = 16 (P	= 0.00	8); I ² = 51	%		0.01 0.1 1 10 100
Test for overall effect:	그렇게 50~~~~ 보이면 하다 하면 하는데 살아 있다. ~							0.01 0.1 i 10 100 Favours [Immunotherapy] Favours [control]

B. Headache



C. Dysgeusia

	Immunoth	егару	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Kwon	23	393	18	396	13.2%	1.29 [0.71, 2.35]	2014	· -
Borghaei	25	287	1	268	3.7%	23.34 [3.19, 171.09]	2015	5
Herbst	11	782	5	309	8.7%	0.87 [0.30, 2.48]	2016	· ·
Langer	6	59	4	62	7.4%	1.58 [0.47, 5.31]	2016	5
Ferris	0	236	2	111	1.8%	0.09 [0.00, 1.95]	2016	s
Bellmunt	15	266	19	255	12.6%	0.76 [0.39, 1.46]	2017	·
Maio	18	380	3	189	7.4%	2.98 [0.89, 10.00]	2017	· +
Gandhi	52	405	20	202	14.5%	1.30 [0.80, 2.11]	2018	3 •
Cohen	0	246	2	234	1.8%	0.19 [0.01, 3.94]	2019	•
Mateos	15	120	30	121	13.6%	0.50 [0.29, 0.89]	2019	· · ·
West	76	473	25	232	15.2%	1.49 [0.98, 2.28]	2019	•
Total (95% CI)		3647		2379	100.0%	1.16 [0.75, 1.79]		•
Total events	241		129					1000
Heterogeneity: Tau ² =	= 0.27; Chi2=	27.99.	df = 10 (P	= 0.00	2); I ² = 64	%		ha. d
Test for overall effect	(B) 나를 살 다른 사람들이 되었다.				••			0.01 0.1 1 10 100 Favours [Immunotherapy] Favours [Control]

D. Dizziness

	Immunoth	егару	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Kwon	11	393	10	396	11.9%	1.11 [0.48, 2.58]	2014	
Borghaei	5	287	0	268	4.1%	10.27 [0.57, 184.92]	2015	
Herbst	9	782	22	309	12.3%	0.16 [0.08, 0.35]	2016	
Hamid	3	361	10	179	9.7%	0.15 [0.04, 0.53]	2017	
Maio	15	380	2	189	8.8%	3.73 [0.86, 16.14]	2017	 •
Govindan	17	388	25	361	13.0%	0.63 [0.35, 1.15]	2017	
Powles	7	459	25	443	12.0%	0.27 [0.12, 0.62]	2018	
West	41	473	12	232	12.9%	1.68 [0.90, 3.13]	2019	 • • • • • • • • • • • • • • • • • • •
Chih-Hsin Yang	1	17	3	12	6.1%	0.24 [0.03, 2.00]	2019	
Cohen	3	246	6	234	9.2%	0.48 [0.12, 1.88]	2019	
Total (95% CI)		3786		2623	100.0%	0.61 [0.31, 1.23]		
Total events	112		115					
Heterogeneity: Tau2 =	= 0.87; Chi2=	42.57,	df = 9 (P <	< 0.000	$01); I^2 = 7$	9%		
Test for overall effect	E STATE OF THE STA		,		•			0.01 0.1 1 10 100 Favours [Immunotherapy] Favours [Control]

E. Paresthesia

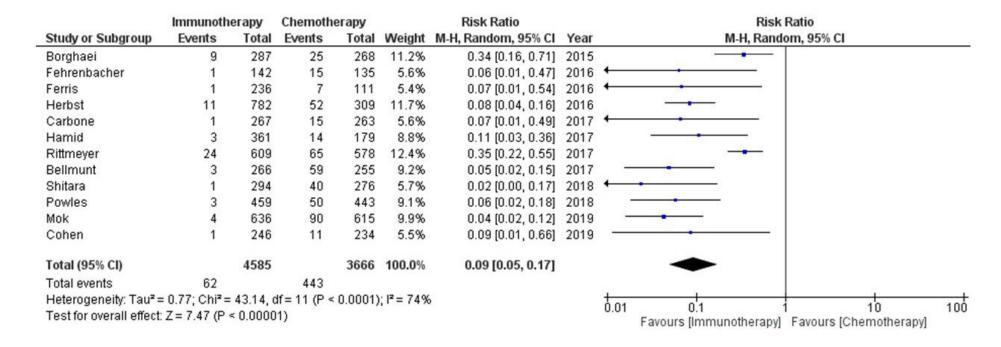
	Immunoth	егару	Contr	rol		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Rand	lom, 95% CI	
Kwon	31	393	24	396	57.2%	1.30 [0.78, 2.18]	2014	-		
Carbone	1	267	0	263	1.7%	2.96 [0.12, 72.22]	2017	-		
Maio	20	380	10	189	29.9%	0.99 [0.48, 2.08]	2017	- 10	-	
Barlesi	0	393	1	365	1.7%	0.31 [0.01, 7.58]	2018		_	
Cohen	1	246	0	234	1.7%	2.85 [0.12, 69.72]	2019	-	+	-
Eng	3	269	1	80	3.4%	0.89 [0.09, 8.46]	2019	-		
West	20	473	1	232	4.3%	9.81 [1.32, 72.65]	2019		-	
Total (95% CI)		2421		1759	100.0%	1.30 [0.85, 1.97]			•	
Total events	76		37							
Heterogeneity: Tau ² =	= 0.01; Chi ² =	6.15, df	= 6 (P =	0.41); P	= 2%			L	1 1	400
Test for overall effect								0.01 0.1 Favours [experimental]	Favours [control]	100

F. Altered mental status

	Immunoth	егару	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Kwon	31	393	0	396	5.5%	63.48 [3.90, 1033.76]	2014	
Borghaei	20	287	2	268	12.4%	9.34 [2.20, 39.57]	2015	
Herbst	4	782	6	309	13.9%	0.26 [0.07, 0.93]	2016	-
Bellmunt	16	266	19	255	19.4%	0.81 [0.42, 1.53]	2017	
Usmani	19	149	22	145	20.0%	0.84 [0.48, 1.49]	2019	
West	68	473	31	232	21.3%	1.08 [0.73, 1.60]	2019	
Cohen	3	246	1	234	7.5%	2.85 [0.30, 27.24]	2019	-
Total (95% CI)		2596		1839	100.0%	1.40 [0.66, 2.99]		
Total events	161		81					
Heterogeneity: Tau2 =	= 0.66; Chi2=	28.96,	df = 6 (P <	0.000	1); $I^2 = 79^4$	%		
Test for overall effect	Z = 0.88 (P	= 0.38)						0.01 0.1 1 10 100 Favours [Immunotherapy] Favours [Control]

G. Insomnia

eFigure 3. Subgroup Analysis of Adverse Events Between Checkpoint Inhibitors and Chemotherapy



A. Peripheral neuropathy

	Immunoth	егару	Chemoth	егару		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI		
Borghaei	7	287	27	268	16.1%	0.24 [0.11, 0.55]	2015			
Reck (I)	1	154	15	150	7.6%	0.06 [0.01, 0.49]	2016			
Herbst	11	782	16	309	16.6%	0.27 [0.13, 0.58]	2016	-		
Langer	10	59	6	62	14.9%	1.75 [0.68, 4.52]	2016			
Bellmunt	7	266	0	255	4.6%	14.38 [0.83, 250.52]	2017	 		
Carbone	7	267	21	263	15.9%	0.33 [0.14, 0.76]	2017			
Rittmeyer	609	18	578	58		Not estimable	2017			
Powles	6	459	22	443	15.4%	0.26 [0.11, 0.64]	2018			
Cohen	2	246	3	234	8.8%	0.63 [0.11, 3.76]	2019			
Total (95% CI)		2538		2042	100.0%	0.42 [0.21, 0.85]		•		
Total events	660		688					1.1 900		
Heterogeneity: Tau2:	= 0.62; Chi2=	22.22, 0	df = 7 (P = 0)	0.002); [3	= 68%					
Test for overall effect	Z= 2.43 (P=	= 0.02)						0.01 0.1 1 10 100 Favours [Immunotherapy] Favours [Chemotherapy]		

B. Dysgeusia

	Immunoth	егару	Chemoth	erapy		Risk Ratio		Risk Ratio			
Study or Subgroup	Events Total		Events	Events Total		M-H, Random, 95% CI	Year	M-H, Random, 95% CI			
Borghaei	5	287	0	268	6.6%	10.27 [0.57, 184.92]	2015		\rightarrow		
Herbst	9	782	22	309	28.3%	0.16 [0.08, 0.35]	2016	os services and the services are			
Hamid	3	361	10	179	19.6%	0.15 [0.04, 0.53]	2017				
Powles	7	459	25	443	27.1%	0.27 [0.12, 0.62]	2018				
Cohen	3	246	6	234	18.3%	0.48 [0.12, 1.88]	2019				
Total (95% CI)		2135		1433	100.0%	0.29 [0.13, 0.67]		•			
Total events	27		63								
Heterogeneity: Tau ² :	= 0.47; Chi ² =	9.64, dt	f = 4 (P = 0.	05); I²=	58%		<u> </u>	, da do	400		
Test for overall effect	Z= 2.93 (P	= 0.003)					0.0	0.1 10 Favours [Immunotherapy] Favours [Chemotherapy	100 /]		

C. Paresthesia

	Immunotherapy Chemotherap			erapy		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Rand	lom, 95% CI	
Borghaei	29	287	2	268	17.6%	13.54 [3.26, 56.20]	2015	9500		_
Herbst	14	782	2	309	17.1%	2.77 [0.63, 12.10]	2016	-	-	
Bellmunt	13	266	13	255	23.8%	0.96 [0.45, 2.03]	2017			
Barlesi	7	393	9	365	21.7%	0.72 [0.27, 1.92]	2018	-	-	
Cohen	5	246	6	234	19.9%	0.79 [0.25, 2.56]	2019		-	
Total (95% CI)		1974		1431	100.0%	1.66 [0.61, 4.46]		-		
Total events	68		32							
Heterogeneity: Tau2:	= 0.93; Chi ² =	15.92, 0	df = 4 (P = 0)	0.003); [3	= 75%		<u> </u>	24 04	1 10	400
Test for overall effect: $Z = 1.00$ (P = 0.32)						0.0		Favours [Chemotherapy]	100	

D. Headache

	Immunoth	егару	Chemoth	егару		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI	
Borghaei	20	287	2	268	24.7%	9.34 [2.20, 39.57]	2015		
Herbst	4	782	6	309	26.3%	0.26 [0.07, 0.93]	2016		
Bellmunt	16	266	19	255	30.7%	0.81 [0.42, 1.53]	2017		
Cohen	3	246	1	234	18.3%	2.85 [0.30, 27.24]	2019	- · · · · · · · · · · · · · · · · · · ·	
Total (95% CI)		1581		1066	100.0%	1.39 [0.32, 5.97]			
Total events	43		28						
Heterogeneity: Tau2:	= 1.69; Chi ² =	15.87, 0	df = 3 (P = 0)	0.001); P	= 81%		L	24 24 4	400
Test for overall effect	Z = 0.44 (P	= 0.66)					U.U	01 0.1 1 10 Favours [Immunotherapy] Favours [Chemotherapy]	100

E. Insomnia

	Immunoth	егару	Chemoth	егару		Risk Ratio			Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Rande	om, 95% CI	
Borghaei	25	287	1	268	19.0%	23.34 [3.19, 171.09]	2015			-	\longrightarrow
Ferris	0	236	2	111	12.6%	0.09 [0.00, 1.95]	2016	\leftarrow			
Herbst	11	782	5	309	26.6%	0.87 [0.30, 2.48]	2016		-	-	
Bellmunt	15	266	19	255	29.3%	0.76 [0.39, 1.46]	2017			-	
Cohen	0	246	2	234	12.5%	0.19 [0.01, 3.94]	2019	\leftarrow	•		
Total (95% CI)		1817		1177	100.0%	0.98 [0.24, 3.91]					
Total events	51		29								
Heterogeneity: Tau ² =	= 1.60; Chi2=	16.26,	df = 4 (P = 1	0.003); [2	= 75%			0.04		10	400
Test for overall effect		LOCKET PROBLET						0.01	Favours [Immunotherapy]	Favours [Chemotherapy]	100

F. Dizziness

eFigure 4. Subgroup Analysis of Headache Between Checkpoint Inhibitors and Placebo

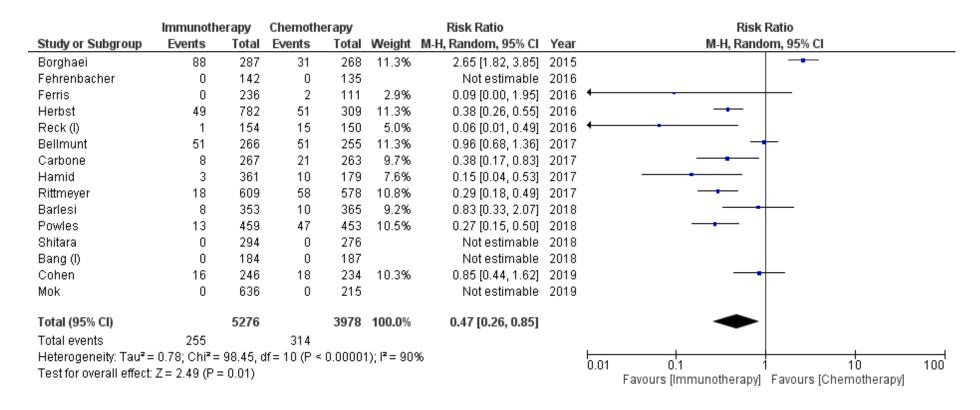
	Immunoth	nunotherapy Place		bo		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI		
Kwon	39	393	32	396	21.9%	1.23 [0.79, 1.92]	2014	-		
Eggermont (II)	152	471	86	474	72.5%	1.78 [1.41, 2.24]	2015	-		
Maio	20	380	6	189	5.6%	1.66 [0.68, 4.06]	2017			
Total (95% CI)		1244		1059	100.0%	1.63 [1.32, 2.02]		•		
Total events	211		124							
Heterogeneity: Tau2 =	= 0.00; Chi ² =	2.09, df	= 2 (P =	0.35); [= 4%			0.01 0.1 1 10 100		
Test for overall effect	Z = 4.50 (P	< 0.0000	01)					0.01 0.1 1 10 100 Favours [Immunotherapy] Favours [Placebo]		

eFigure 5. Overall Risk of Neurologic Adverse Events Excluding Incidence of Specific Event Between Checkpoint Inhibitors and Control Arm

	Immunoth		Conti			Risk Ratio		Risk Ratio
Study or Subgroup	Events		Events			M-H, Random, 95% CI		M-H, Random, 95% CI
Hodi	84	511	19	132	3.8%	1.14 [0.72, 1.81]	2010	-
Robert	40	247	33	251	3.8%	1.23 [0.80, 1.89]	2011	
Reck (III)	0	84	0	44		Not estimable	2012	
Kwon	145	393	104	396	4.1%	1.40 [1.14, 1.73]	2014	
Borghaei	88	287	32	268	3.9%	2.57 [1.78, 3.71]	2015	_
Eggermont (II)	153	471	86	474	4.1%	1.79 [1.42, 2.26]	2015	-
Motzer (II)	11	406	51	397	3.4%	0.21 [0.11, 0.40]	2015	
Fehrenbacher	0	142	0	135		Not estimable	2016	
Ferris	0	236	2	111	0.7%	0.09 [0.00, 1.95]	2016	
Herbst	49	782	51	309	3.9%	0.38 [0.26, 0.55]	2016	
Langer	16	59	10	62	3.3%	1.68 [0.83, 3.40]	2016	 • • •
Reck (I)	1	154	15	150	1.3%	0.06 [0.01, 0.49]		
Reck (II)	0	478	0	476		Not estimable	2016	
Bang (II)	Ō	57	ō	45			2017	
Antonia	3	475	1	234	1.1%	1.48 [0.15, 14.13]		
Bellmunt	51	266	51	255	4.0%	0.96 [0.68, 1.36]		+
Carbone	8	267	21	263	3.1%	0.38 [0.17, 0.83]		
Govindan	19	388	25	361	3.6%	0.71 [0.40, 1.26]	2017	
Hamid	3	361	10	179	2.2%	0.15 [0.04, 0.53]		
Maio	82	380	22	189	3.8%	1.85 [1.20, 2.87]	2017	
Rittmeyer	18	609	58	578	3.7%	0.29 [0.18, 0.49]		
Bang (I)	.0	184	0	177	3.1 70	Not estimable	2018	
Barlesi	8	393	10	365	2.8%	0.74 [0.30, 1.86]		
Eggermont (I)	Ö	509	0	502	2.0 %	Not estimable	2018	
Gandhi	161	405	63	202	4.1%	1.27 [1.01, 1.62]		
	44	198	38	196	3.9%			
Horn	31	547	180	535	4.0%	1.15 [0.78, 1.69]		
Motzer (I)	0	278		280	4.070	0.17 [0.12, 0.24]		
Paz-Ares	_		0		0.500	Not estimable		
Powles	13	459	47	443	3.5%	0.27 [0.15, 0.49]		
Shitara	0	294	0	276		Not estimable	2018	
Usmani	20	149	22	145	3.6%	0.88 [0.50, 1.55]		
West	362	473	125	232	4.2%	1.42 [1.25, 1.62]	2019	-
Chih-Hsin Yang	. 1	17	3	12	1.1%	0.24 [0.03, 2.00]		
Cohen -	16	246	18	234	3.4%	0.85 [0.44, 1.62]	2019	
Eng	42	269	15	80	3.6%	0.83 [0.49, 1.42]		 -
Mateos	30	120	18	121	3.7%	1.68 [0.99, 2.85]		
Mok	0	636	0	615		Not estimable	2019	
Rini (I)	73	451	157	446	4.1%	0.46 [0.36, 0.59]		*
Rini (II)	115	429	200	425	4.2%	0.57 [0.47, 0.69]	2019	-
Total (95% CI)		13110		10595	100.0%	0.74 [0.56, 0.97]		•
Total events	1687		1487					
Heterogeneity: Tau² =		404 27		o < U UU	001): I² =	Q3%		
received energy rad -	: Z = 2.22 (P		a 23 (I	- 0.00	001/,1 -	33.0		0.01 0.1 1 10 1

A. Excluding the Incidence of Peripheral Neuropathy

© 2022 Farooq MZ et al. JAMA Network Open.



B. Excluding the Incidence of Peripheral Neuropathy

eTable 1. Quality Assessment of All Trials Using the Cochrane Collaborations Tool

Article	Selection Bias		Performance Bias	Detection bias	Attrition bias	Reporting Bias	Other bias	
	Random Sequence Generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting	Anything else, ideally prespecified	Our evaluation
Chih-Hsin Yang	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Cohen	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Eng	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Mateos	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Mok	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Rini (1)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Rini (2)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Usmani	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
West	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Bang (1)	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Fair quality
Barlesi	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Eggermont	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Gandhi	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Horn	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Motzer	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Paz-Ares	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Powles	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Shitara	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Antonia	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Bang (2)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Fair quality
Bellmunt	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Carbone	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Fair quality
Govindan	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Fair quality
Hamid	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Maio	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Rittmeyer	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Fehrenbacher	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Ferris	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Herbst	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Langer	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Reck (I)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Reck (II)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Borghaei	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality

^{© 2022} Farooq MZ et al. JAMA Network Open.

Eggermont (II)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Article	Selection Bias		Performance Bias		Detection bias		Other bias	Our evaluation
	Random	Allocation	Blinding of	Blinding of	Incomplete	Selective	Anything else,	
	Sequence	concealment	participants	outcome	outcome	Reporting	ideally	
	Generation		and personnel	assessment	data		prespecified	
Motzer (II)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Kwon	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Reck	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Fair quality
Robert	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Hodi	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality

eTable 2. Pooled Characteristics of the Intention-to-Treat Population

Variable	Control group (All drug regimens in	Immune checkpoint inhibitor group N=12958		
	the comparison arm) N=10775			
Age	Unable to estimate	Unable to estimate		
Female sex — no. (%)	3315 (30.8)	4283 (33.1)		
Race — no. (%)				
White	3365 (31.2)	4501 (34.7)		
African American/black	56 (0.1)	91 (0.1)		
Asian	779 (7.2)	924 (7.1)		
Other	50 (<0.1)	74 (0.1)		
Unknown/not reported	6525 (60.1)	7368 (56.9)		
Region				
North America	496 (4.6)	664 (5.1)		
Europe	1353 (12.6)	1522 (11.8)		
Asia	715 (6.6)	804 (6.2)		
Latin America	192 (1.8)	205 (1.6)		
Unspecified/not reported	8019 (74.4)	9763 (75.3)		
Tumor type				
Non-small cell lung cancer	4060 (37.6)	5116 (39.5)		
Renal cell carcinoma	1847 (17.1)	1846 (14.2)		
Malignant melanoma	1548 (14.4)	2140 (16.5)		
Small cell lung cancer	723 (6.7)	764 (5.9)		
Urothelial	736 (6.8)	737 (5.7)		
Gastric/gastroesophageal junction cancer	539 (5.0)	538 (4.2)		
HNSCC	369 (3.4)	487 (3.8)		
Prostate	400 (3.7)	399 (3.1)		
Tumor Type (continued)				
Multiple myeloma	274 (2.5)	276 (2.1)		
Malignant mesothelioma	189 (1.8)	382 (2.9)		
Colorectal cancer	90 (0.1)	273 (2.1)		
ECOG performance-status score — no. (%)				
0	2890 (26.8)	3725 (28.7)		
1	4757 (44.1)	5855 (45.2)		
2	23 (0.2)	22 (0.2)		
Unknown/not reported/used Karnofsky performance status	3105 (28.8)	3356 (25.9)		
Smoking status — no. (%)				
Current or former smoker	4132 (38.3)	5105 (39.4)		
Never smoker	895 (8.3)	1109 (8.6)		
Unknown/not reported	5748 (53.3)	6744 (52.0)		

ECOG- Eastern Cooperative Oncology Group; HNSCC- Head and Neck Squamous Cell Carcinoma.