

Supplementary Online Content

Duan J, Cui L, Zhao X, et al. Use of immunotherapy with programmed cell death 1 vs programmed cell death ligand 1 inhibitors in patients with cancer: a systematic review and meta-analysis. Published online December 26, 2019. *JAMA Oncol*. doi:10.1001/jamaoncol.2019.5367

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

eTable 1. Search strategy.

Database	Keywords
PUBMED	
#1	nivolumab OR opdivo OR ono-4538 OR MDX-1106 OR BMS-936558 OR nivo OR pembrolizumab OR lambrolizumab OR keytruda OR SCH900475 OR MK-3475 OR atezolizumab OR tecentriq OR RO5541267 OR RG7446 OR MPDL3280A OR durvalumab OR imfinzi OR MEDI-4736 OR MEDI4736 OR avelumab OR barvencik OR MSB0010718C OR cemiplimab OR libtayo OR REGN2810
#2	Programmed death-1 OR PD-1 OR PD1 OR Programmed death ligand-1 OR PD-L1 OR PDL1 OR checkpoint inhibitor OR checkpoint blockade
#3	#1 or #2
#4	(((((randomized controlled trial) OR controlled clinical trial)) OR random*) OR groups)) AND (((clinical trials as topic[MeSH Terms]) OR (clinical AND trial AND topic)) OR clinical trials as topic) OR trial)
#5	#3 and #4
#6	2000/01/01[PDAT] : 2019/03/01[PDAT]
#7	#5 AND #6
EMABASE	
#1	nivolumab OR opdivo OR 'ono 4538' OR 'mdx 1106' OR 'bms 936558' OR nivo OR pembrolizumab OR lambrolizumab OR keytruda OR sch900475 OR 'mk 3475' OR atezolizumab OR tecentriq OR ro5541267 OR rg7446 OR mpdl3280a OR durvalumab OR imfinzi OR 'medi 4736' OR medi4736 OR avelumab OR barvencik OR msb0010718c OR cemiplimab OR libtayo OR regn2810
#2	'programmed death-1' OR 'pd-1' OR 'pd1' OR 'programmed death ligand-1' OR 'pd-l1' OR 'pdl1' OR 'checkpoint inhibitor' OR 'checkpoint blockade'
#3	#1 OR #2
#4	'clinical trials as topic' OR trial
#5	'randomized controlled trial' OR 'controlled clinical trial' OR 'random*' OR groups
#6	#4 NAD #5
#7	#3 AND #6
#8	#3 AND #6 AND [randomized controlled trial]/lim AND [humans]/lim AND [2000-2019]/py
CENTRAL	
#1	nivolumab OR opdivo OR 'ono 4538' OR 'mdx 1106' OR 'bms 936558' OR nivo OR pembrolizumab OR lambrolizumab OR keytruda OR sch900475 OR 'mk 3475' OR atezolizumab OR tecentriq OR ro5541267 OR rg7446 OR mpdl3280a OR durvalumab OR imfinzi OR 'medi 4736' OR medi4736 OR avelumab OR barvencik OR msb0010718c OR cemiplimab OR libtayo OR regn2810 OR 'programmed death-1' OR 'pd-1' OR 'pd1' OR 'programmed death ligand-1' OR 'pd-l1' OR 'pdl1' OR 'checkpoint inhibitor' OR 'checkpoint blockade'
#2	AND ('clinical trials as topic' OR trial)
#3	AND ('randomized controlled trial' OR 'controlled clinical trial' OR 'random*' OR groups)
#4	Publication Date: Jan 2000 to Mar 2019

1 **eTable 2 Trial characteristics.**

Author	Year	NCT Number	Clinical trial	Phase	Tumor type	Line	PD-L1 status	Intervention type
Brahmer	2015	NCT01642004	CheckMate 017	III	NSCLC sq	2	nonselective	MONO
Borghaei	2015	NCT01673867	CheckMate 057	III	NSCLC non-sq	2	nonselective	MONO
Wu	2019	NCT02613507	CheckMate 078	III	NSCLC	2	nonselective	MONO
Rittmeyer	2016	NCT02008227	OAK	III	NSCLC	2	nonselective	MONO
Fehrenbacher	2016	NCT01903993	POPLAR	II	NSCLC	2	nonselective	MONO
Herbst	2015	NCT01905657	KEYNOTE-010 (10mg)	II/III	NSCLC	2	PD-L1 \geq 1%	MONO
Herbst	2015	NCT01905657	KEYNOTE-010 (2mg)	II/III	NSCLC	2	PD-L1 \geq 1%	MONO
Barlesi^a	2018	NCT02395172	JAVELIN Lung 200	III	NSCLC	2	PD-L1 \geq 1%	MONO
Kang	2017	NCT02267343	ATTRACTION-2	III	GC/GEJC	3	nonselective	MONO
Bang	2018	NCT02625623	JAVELIN Gastric 300	III	GC/GEJC	3	nonselective	MONO
Bellmunt	2017	NCT02256436	KEYNOTE-045	III	UC	2	nonselective	MONO
Powles	2017	NCT02302807	IMvigor211	III	UC	2	nonselective	MONO
Langer	2016	NCT02039674	KEYNOTE-021	II	NSCLC non-sq	1	nonselective	COMBO
Gandhi	2018	NCT02578680	KEYNOTE-189	III	NSCLC non-sq	1	nonselective	COMBO
Cappuzzo	2018	NCT02367781	IMpower130	III	NSCLC non-sq	1	nonselective	COMBO
Barlesi^b	2018	NCT02657434	IMpower132	III	NSCLC non-sq	1	nonselective	COMBO
Paz-Ares	2018	NCT02775435	KEYNOTE-407	III	NSCLC sq	1	nonselective	COMBO
Jotte	2018	NCT02367794	IMpower131	III	NSCLC sq	1	nonselective	COMBO
Motzer	2019	NCT02684006	JAVELIN Renal 101	III	RCC	1	nonselective	COMBO
Rini	2019	NCT02853331	KEYNOTE-426	III	RCC	1	nonselective	COMBO

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First Author	Treatment	Control	Treatment				Control			
			Male n (%)	Total	Median Age (range)	ECOG PS=0 n (%)	Male n (%)	Total	Median Age (range)	ECOG PS=0 n (%)
Brahmer	Nivo	DOC	111 (82)	135	62 (39-85)	27 (20)	97 (71)	137	64 (42-84)	37 (27)
Borghaei	Nivo	DOC	151 (52)	292	61 (37-84)	84 (29)	168 (58)	290	64 (21-85)	95 (33)
Wu	Nivo	DOC	263 (78)	338	60 (27-78)	47 (14)	134 (81)	166	60 (38-78)	21 (13)
Rittmeyer	Ate	DOC	261 (61)	425	63 (33-82)	155 (36)	259 (61)	425	64 (34-85)	160 (38)
Fehrenbacher	Ate	DOC	93 (65)	144	62 (42-82)	46 (32)	76 (53)	143	62 (36-84)	45 (32)
Herbst	Pem	DOC	213 (62)	346	63 (56-69)	112 (33)	209 (61)	343	62 (56-69)	116 (34)
Herbst	Pem	DOC	212 (62)	344	63 (56-69)	120 (35)	209 (61)	343	62 (56-69)	116 (34)
Barlesi^a	AVE	DOC	182 (69)	264	64 (59-70)	96 (36)	185 (70)	265	63 (56-69)	91 (34)
Kang	Nivo	Placebo	229 (69)	330	62 (54-69)	95 (29)	119 (73)	163	61 (53-68)	48 (29)
Bang	AVE	PTX/IRI	140 (76)	185	59 (29-86)	66 (36)	127 (68)	186	61 (18-82)	62 (33)
Bellmunt	Pem	PTX/DOC/VIN	200 (74)	270	67 (29-88)	119 (44)	202 (74)	272	65 (26-84)	106 (39)
Powles	Ate	PTX/DOC/VIN	357 (76)	467	67 (33-88)	218 (47)	361 (78)	464	67 (31-84)	207 (45)
Langer	Pem+C+Pemex	C+Pemex	22 (37)	60	62.5 (54-70)	24 (40)	26 (41)	63	63.2 (58-70)	29 (46)
Gandhi	Pem+C/Cis+Pemex	C/Cis+Pemex	254 (62)	410	65 (34-84)	186 (45)	109 (53)	206	63.5 (34-84)	80 (39)
Cappuzzo	Ate+CnP	CnP	266 (59)	451	NA	189 (42)	134 (59)	228	NA	91 (40)
Barlesi^b	Ate+C/Cis+Pemex	C/Cis+Pemex	192 (66)	292	64 (31-85)	126 (43)	192 (67)	286	63 (33-83)	114 (40)
Paz-Ares	Pem+C(n)P	C(n)P	220 (79)	278	65 (29-87)	73 (26)	235 (84)	281	65 (36-88)	90 (32)
Jotte	Ate+CnP	CnP	279 (81)	343	65 (23-83)	115 (34)	278 (82)	340	65 (38-86)	110 (32)
Motzer	AVE+AXI	SUN	316 (72)	442	62 (29-83)	279 (63)	344 (78)	444	61 (27-88)	281 (63)
Rini	Pem+AXI	SUN	308 (71)	432	62 (30-89)	NA	320 (75)	429	61 (26-90)	NA

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First Author	Follow-up (month)	Progression free survival			Overall survival		
		Hazard ratio	95% CI lower limit	95% CI upper limit	Hazard ratio	95% CI lower limit	95% CI upper limit
Brahmer	11.0 (minimum)	0.62	0.47	0.81	0.59	0.44	0.79
Borghaei	13.2 (minimum)	0.92	0.77	1.11	0.73	0.60	0.89
Wu	ICI:10.4/Ctl:8.8 (median)	0.77	0.62	0.95	0.68	0.54	0.86
Rittmeyer	21.0 (median)	0.95	0.82	1.10	0.73	0.62	0.87
Fehrenbacher	ICI:14.8/Ctl:15.7 (median)	0.94	0.72	1.23	0.73	0.53	0.99
Herbst	13.1 (median)	0.79	0.66	0.94	0.61	0.49	0.75
Herbst	13.1 (median)	0.88	0.74	1.05	0.71	0.58	0.88
Barlesi^a	11.7 (minimum)	1.01	0.81	1.26	0.90	0.73	1.11
Kang	ICI:8.9/Ctl:8.6 (median)	0.60	0.49	0.75	0.63	0.51	0.78
Bang	ICI:10.6/Ctl:10.6 (median)	1.73	1.40	2.20	1.10	0.90	1.40
Bellmunt	14.1 (median)	0.98	0.81	1.19	0.73	0.59	0.91
Powles	17.3 (median)	NA	NA	NA	0.85	0.73	0.99
Langer	10.6 (median)	0.53	0.31	0.91	0.90	0.42	1.91
Gandhi	10.5 (median)	0.52	0.43	0.64	0.49	0.38	0.64
Cappuzzo	ICI:18.5/Ctl:19.2 (median)	0.64	0.54	0.77	0.79	0.64	0.98
Barlesi^b	ICI:18.9/Ctl:17.8 (median)	0.60	0.49	0.72	0.81	0.64	1.03
Paz-Ares	7.8 (median)	0.56	0.45	0.70	0.64	0.49	0.85
Jotte	12.8 (minimum)	0.74	0.62	0.87	0.92	0.76	1.12
Motzer	ICI:11.6/Ctl:10.7 (median)	0.69	0.56	0.84	0.78	0.55	1.08
Rini	12.8 (median)	0.69	0.57	0.84	0.53	0.38	0.74

8 Abbreviations: COMBO: Combination Therapy, UC: Urothelial Carcinoma, NSCLC: Non-Small Cell Lung Cancer, sq: squamous, Nsq: non-squamous, RCC: Renal Cell Carcinoma, C:
9 Carboplatin, Cis: Cisplatin, (n)P: (nab-)Paclitaxel, Niv: Nivolumab; Pem: Pembrolizumab; Ate: Atezolizumab; AXI: Axitinib; SUN: Sunitinib; AVE: Avelumab; DOC: Docetaxel; PTX:
10 Paclitaxel; Pemex: Pemetrexed; VIN: Vinflunine; IRI: Irinotecan; HR: Hazard Ratio; NA: Not available, ICI: Immune checkpoint inhibitor; Ctl: Control. a/b: Represents the same authors
11 in different studies.

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eTable 3. Risk of bias for each included study.

Clinical trial	Randomization	Allocation concealment	Blinding of participants and staff	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
ATTRACTION-2	low	low	low	low	low	low	low
CheckMate 017	low	low	high	high	low	low	low
CheckMate 057	low	low	high	high	low	low	low
CheckMate 078	low	low	high	high	low	low	low
IMpower130	low	low	high	high	low	low	low
IMpower131	low	low	high	high	low	low	low
IMpower132	low	low	high	high	low	low	low
IMvigor211	low	low	high	high	low	low	low
JAVELIN Gastric 300	low	low	high	low	low	low	low
JAVELIN Lung 200	low	low	high	low	low	low	low
JAVELIN Renal 101	low	low	high	low	low	low	low
KEYNOTE-010	low	low	high	low	low	low	low
KEYNOTE-021	low	low	high	low	low	low	low
KEYNOTE-045	low	low	high	low	low	low	low
KEYNOTE-189	low	low	low	low	low	low	low
KEYNOTE-407	low	low	low	low	low	low	low
KEYNOTE-426	low	low	high	low	low	low	low
OAK	low	low	high	high	low	low	low
POPLAR	low	low	high	high	low	low	low

Low indicates no risk, high indicates high risk and unclear indicates unknown risk.

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15 **eTable 4. Sensitivity analysis OS results with frequentist approach.**
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Omitted tumor type	HR 95%CI
NSCLC	0.70 [0.54, 0.92]
GC/GEJC	0.79 [0.70, 0.89]
UC	0.73 [0.62, 0.85]
RCC	0.75 [0.64, 0.87]

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19 **eTable 5. Meta-regression analysis.**

	P value	P value
	(univariable model)	(multivariable models)
Age	0.79	0.74
PS_0 percent	0.42	0.40

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21 **eTable 6. Sensitivity analysis PFS results with frequentist approach.**

Omitted tumor type	HR 95%CI
NSCLC	0.59 [0.21, 1.67]
GC/GEJC	0.84 [0.75, 0.95]
RCC	0.69 [0.51, 0.93]

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23 **eTable 7. Model fit statistics with OS, fixed- and random-effects model.**

Tumor	Line of treatment	Studies of PD-1 inhibitors	Studies of PD-L1 inhibitors	DIC Random	DIC Fixed
Monotherapy					
Gastric carcinoma	≥ 3	ATTRACTION-2	JAVELIN Gastric 300	3.987939	3.998393
Non-small cell lung cancer	≥ 2	CheckMate 017/057/078	POPLAR/OAK	7.064503	5.409897
Non-small cell lung cancer (PD-L1+)	≥ 2	KEYNOTE-010	JAVELIN Lung 200	4.018677	3.993914
Urothelial carcinoma	≤ 3	KEYNOTE-045	IMvigor211	4.009894	3.983779
		Pooled HR (subgroup)		5.882423	4.931239
Combination therapy					
Nonsquamous non-small cell lung cancer	1	KEYNOTE-021/189	IMpower130/132	7.230631	6.23982
Squamous non-small cell lung cancer	1	KEYNOTE-407	IMpower131	4.005628	3.989342
Renal cell carcinoma	1	KEYNOTE-426	JAVELIN Renal 101	4.003938	4.00256
		Pooled HR (subgroup)		3.409448	2.081451
		Pooled HR		9.256699	8.453085

Abbreviations: DIC: Deviance information criteria.

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27 **eTable 8. Model fit statistics with PFS, fixed- and random-effects model.**

Tumor	Line of treatment	Studies of	Studies of	DIC	DIC
		PD-1 inhibitors	PD-L1 inhibitors	Random	Fixed
Monotherapy					
Gastric carcinoma	≥ 3	ATTRACTION-2	JAVELIN Gastric 300	3.989376	3.999893
Non-small cell lung cancer	≥ 2	CheckMate 017/057/078	POPLAR/OAK	9.454495	9.723526
Non-small cell lung cancer (PD-L1+)	≥ 2	KEYNOTE-010	JAVELIN Lung 200	3.9786	4.008446
		Pooled HR (subgroup)		5.37054	4.61229
Combination therapy					
Nonsquamous non-small cell lung cancer	1	KEYNOTE-021/189	IMpower130/132	5.818888	4.240688
Squamous non-small cell lung cancer	1	KEYNOTE-407	IMpower131	3.991861	3.989388
Renal cell carcinoma	1	KEYNOTE-426	JAVELIN Renal 101	3.992372	3.997307
		Pooled HR (subgroup)		3.510448	2.65747
		Pooled HR		7.270352	5.38697

28 Abbreviations: DIC: Deviance information criteria.

29 **eTable 9. Sensitivity analysis OS results with Bayesian approach.**

Omitted tumor type	HR 95% CrI
NSCLC	0.79 [0.64, 0.99]
GC/GEJC	0.79 [0.71, 0.89]
UC	0.77 [0.68, 0.88]
RCC	0.80 [0.71, 0.89]

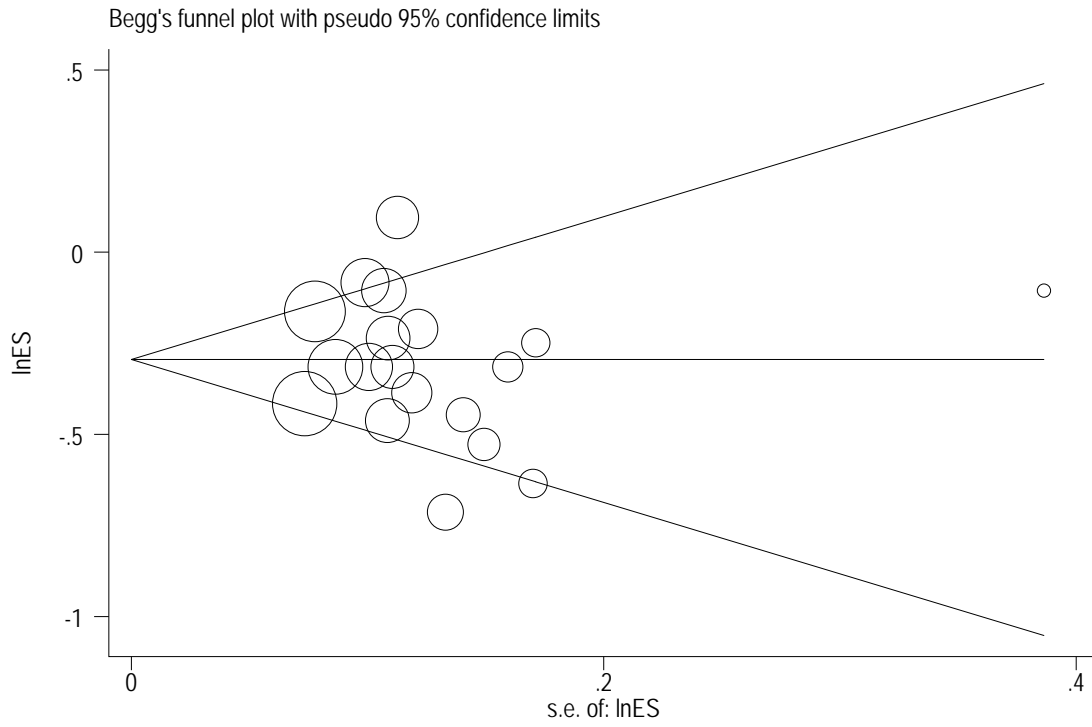
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32 **eTable 10. Sensitivity analysis PFS results with Bayesian approach.**

Omitted tumor type	HR 95% CrI
NSCLC	0.65 [0.21, 1.85]
GC/GEJC	0.82 [0.71, 0.95]
RCC	0.79 [0.68, 0.92]

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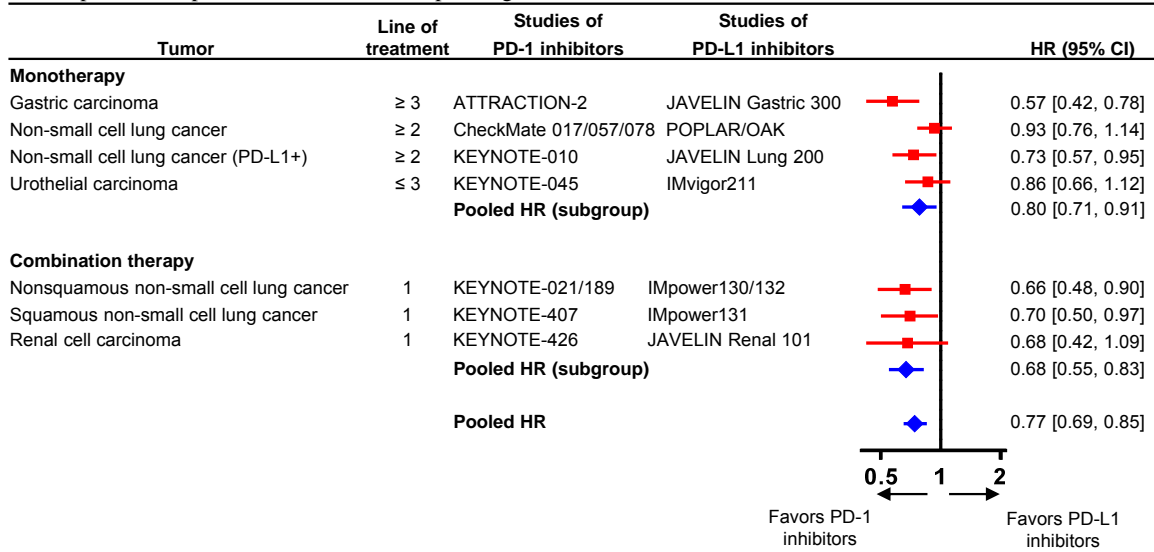
35 **eFigure1. Begg's test for publication bias.**



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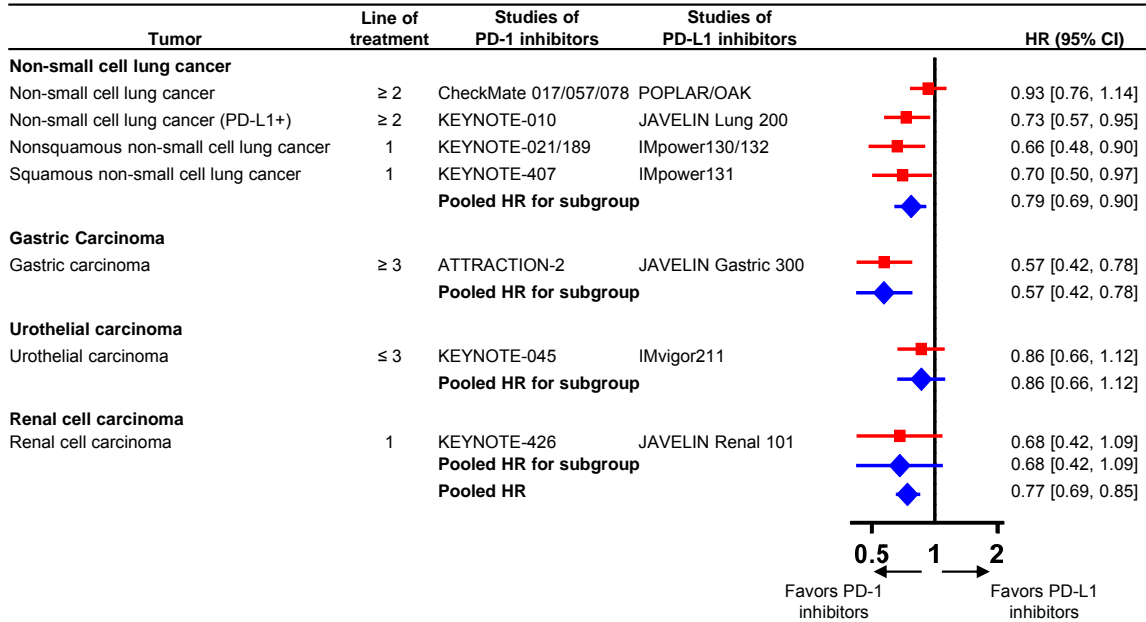
38 **eFigure 2. Forest plot of relative hazard ratios from indirect comparison of**
 39 **overall survival outcomes in patients who received therapies based on anti-**
 40 **PD-1 versus those based on anti-PD-L1 with frequentist fixed-effects model.**

41 Squares represent adjusted indirect effect size (HR). Horizontal lines indicate the 95% CIs. Diamonds indicate the meta-
 42 analytic pooled HRs, calculated separately in monotherapy and combination therapy subgroup, and the overall pooled
 43 HRs in pan-cancer patients, with their corresponding 95% CIs. HR, hazard ratio; CI, confidence interval.



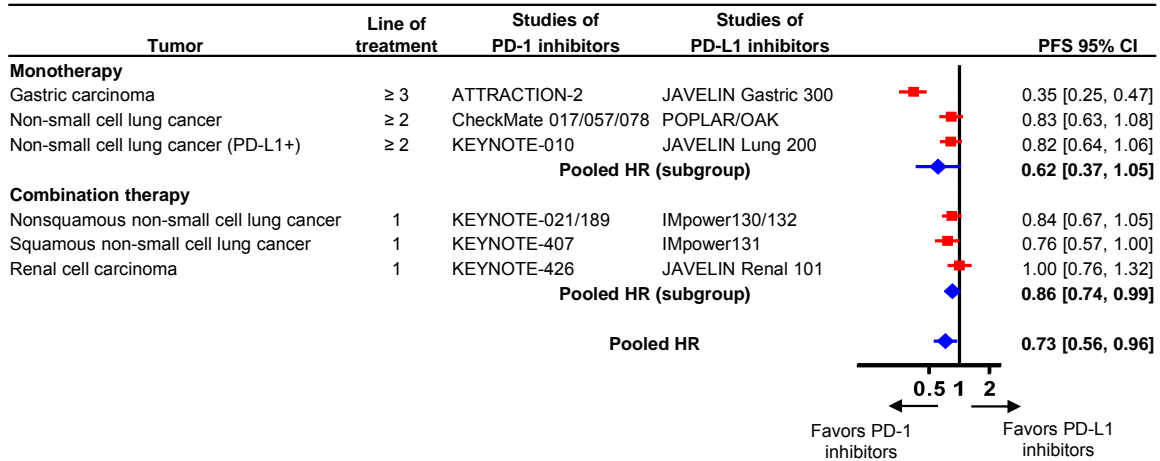
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47 **eFigure 3. Forest plot of pooled hazard ratios of overall survival outcomes**
 48 **for anti-PD-1 versus those based on anti-PD-L1 stratified by tumor types with**
 49 **frequentist fixed-effects model.** Squares represent subgroup-specific pooled hazard ratios (HRs).
 50 Horizontal lines indicate the 95% CIs. Diamonds indicate the meta-analytic pooled HRs, calculated separately in tumor
 51 types, and the overall pooled HRs in pan-cancer patients, with their corresponding 95% CIs. HR, hazard ratio; CI, confidence
 52 interval.



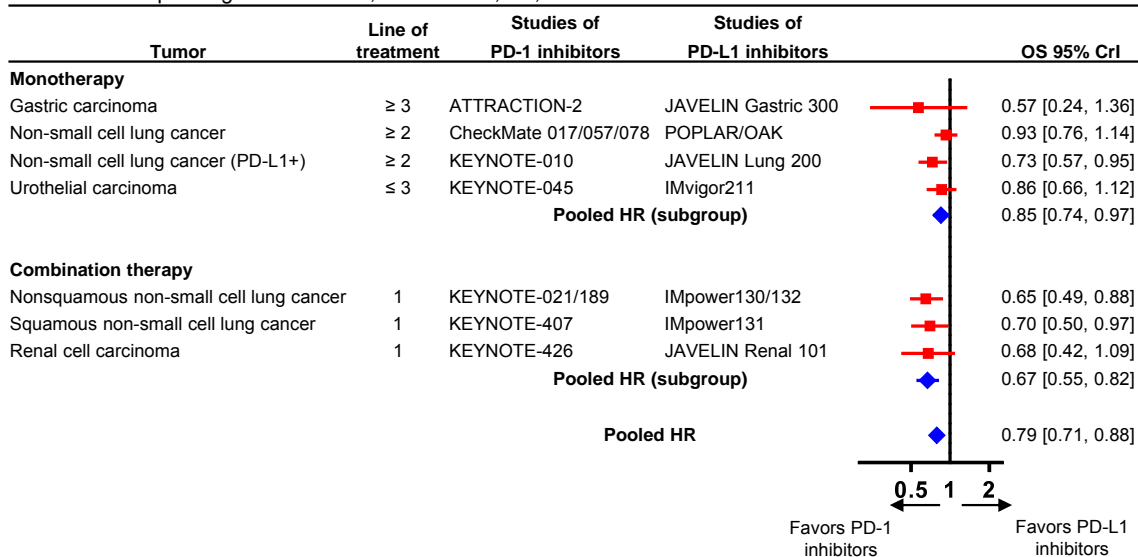
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55 **eFigure 4. Forest plot of relative hazard ratios from indirect comparison of**
 56 **progression free survival in patients who received therapies based on anti-**
 57 **PD-1 versus those based on anti-PD-L1.** Squares represent adjusted indirect effect size (HR).
 58 Horizontal lines indicate the 95% CIs. Diamonds indicate the meta-analytic pooled HRs, calculated separately in
 59 monotherapy and combination therapy, and the overall pooled HRs in pan-cancer patients, with their corresponding 95%
 60 CIs. HR, hazard ratio; CI, confidence interval.



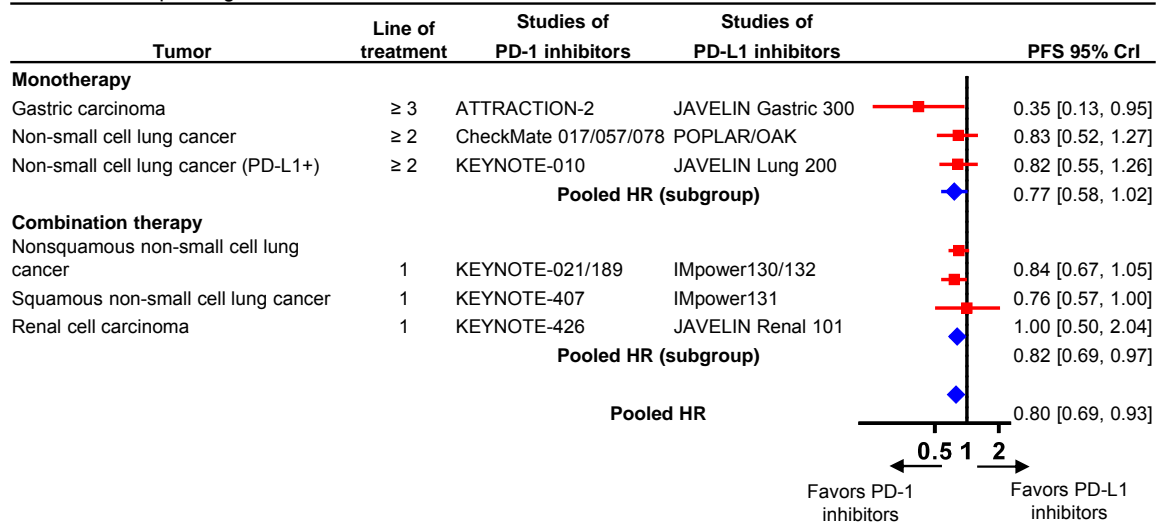
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64 **eFigure 5. Forest plot of relative hazard ratios from indirect comparison of**
 65 **overall survival outcomes in patients who received therapies based on anti-**
 66 **PD-1 versus those based on anti-PD-L1 with Bayesian approach.** Squares represent
 67 adjusted indirect effect size (HR). Horizontal lines indicate the 95% CrIs. Diamonds indicate the meta-analytic pooled HRs,
 68 calculated separately in monotherapy and combination therapy subgroup, and the overall pooled HRs in pan-cancer patients,
 69 with their corresponding 95% CrIs. HR, hazard ratio; CrI, credible interval.



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73 **eFigure 6. Forest plot of relative hazard ratios from indirect comparison of**
 74 **progression free survival in patients who received therapies based on anti-**
 75 **PD-1 versus those based on anti-PD-L1 with Bayesian approach.** Squares represent
 76 adjusted indirect effect size (HR). Horizontal lines indicate the 95% CrIs. Diamonds indicate the meta-analytic pooled HRs,
 77 calculated separately in monotherapy and combination therapy subgroup, and the overall pooled HRs in pan-cancer patients,
 78 with their corresponding 95% CrIs. HR, hazard ratio; CrI, credible interval.



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