

Figure S1. Flow chart of study selection [8]. RCTs = randomized controlled trials * Other studies included pooled analyses, post-marketing studies, clinical trial protocols, patient-reported outcome assessments and any study on biomarkers/gene profiling. ** Updates published for the clinical trials KEYNOTE-024 [19,39,41] and KEYNOTE-042 [18,42] were considered in the analysis.

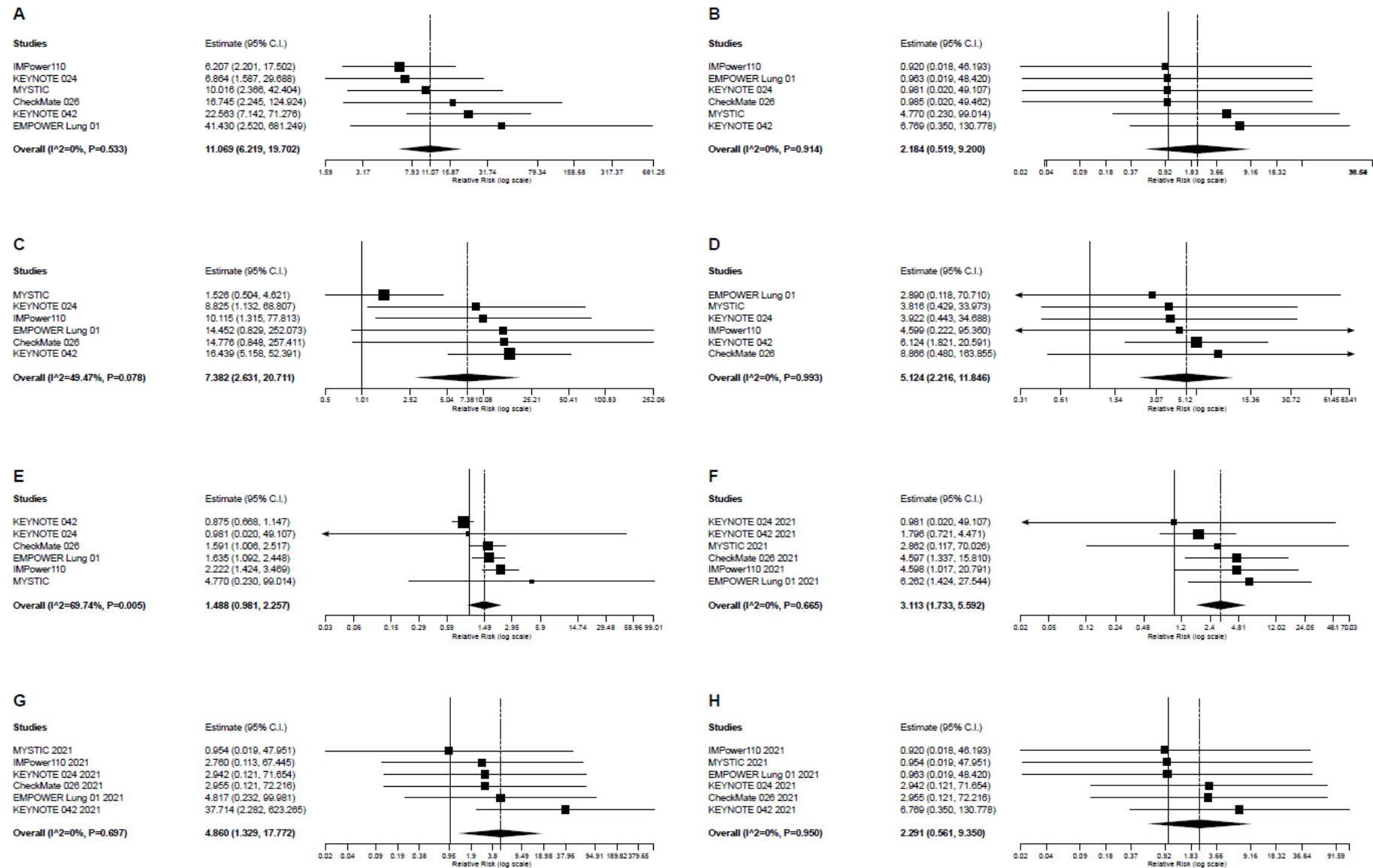


Figure S2. Forest plot of pooled risk ratios (RR) for clinically relevant irAEs in patients who received antiPD-1 or antiPD-L1 immunotherapy compared to platinum-based chemotherapy alone. (A) hypothyroidism any grade; (B) hypothyroidism grade 3-4 (C) pneumonitis any grade; (D) pneumonitis grade 3-4; (E) transaminases increased any grade; (F) transaminases increased grade 3-4; (G) nephritis any grade; and (H) nephritis grade 3-4. Estimate, RR; CI, confidence interval.

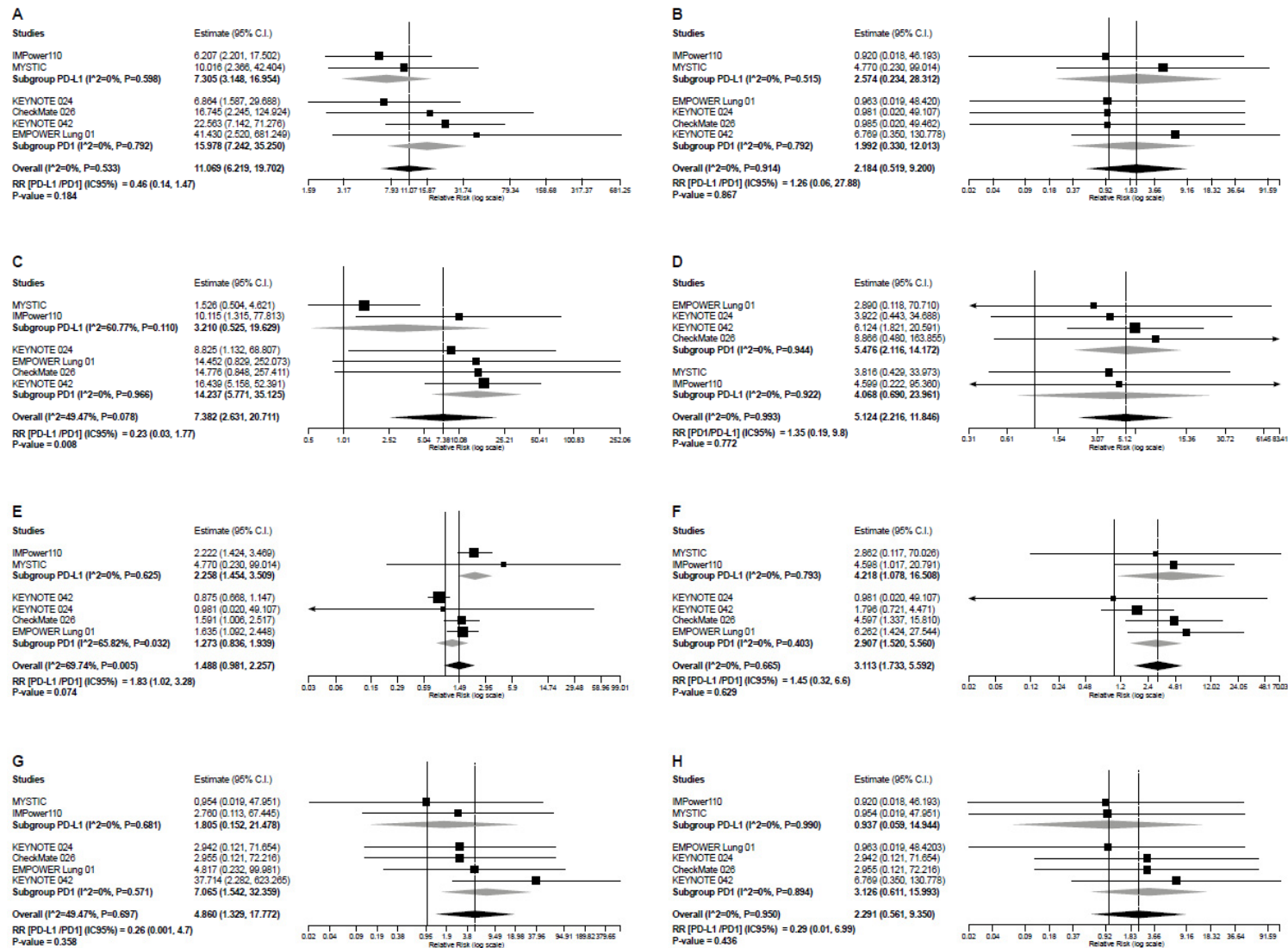


Figure S3. Forest plots of pooled risk ratios (RR) for clinically relevant irAEs in the subgroup analysis (antiPD-L1 versus PD-1 inhibitors) (A) hypothyroidism any grade; (B) hypothyroidism grade 3-4 (C) pneumonitis any grade; (D) pneumonitis grade 3-4; (E) transaminases increased any grade; (F) transaminases increased grade 3-4; (G) nephritis any grade; and (H) nephritis grade 3-4. Estimate, RR; CI, confidence interval.

Table S1. League table showing the RRs and CI 95% for hypothyroidism any grade between immunotherapy treatments.

	KEYNOTE-024	KEYNOTE-042	CheckMate-026	IMPower110	MYSTIC	EMPOWER Lung-01
KEYNOTE-024		3,29	2,44	0,90	1,46	6,04
Lower limit		0,51	0,20	0,11	0,19	0,26
Upper limit		21,16	29,32	7,64	11,40	142,21
KEYNOTE-042	0,30		0,74	0,28	0,44	1,84
Lower limit	0,05		0,07	0,06	0,04	0,09
Upper limit	1,96		7,52	1,29	4,58	37,88
CheckMate-026	0,41	1,35		0,37	0,60	2,47
Lower limit	0,03	0,13		0,04	0,05	0,05
Upper limit	4,93	13,65		3,56	7,10	134,10
IMPower110	1,11	3,64	2,70		1,61	6,67
Lower limit	0,13	0,77	0,28		0,27	0,34
Upper limit	9,34	17,10	25,88		9,54	132,14
MYSTIC	0,69	2,25	1,67	0,62		4,14
Lower limit	0,09	0,22	0,14	0,10		0,18
Upper limit	5,35	23,24	19,84	3,66		96,50
EMPOWER-Lung 01	0,17	0,54	0,40	0,15	0,24	
Lower limit	0,01	0,03	0,01	0,01	0,01	
Upper limit	3,90	11,24	21,91	2,97	5,64	

RR>1 indicates increased risk of AE for the column treatment as compared to the row treatment. Lower and upper limit of the IC95% are shown. All possible indirect comparisons are presented. Statistically significant results are highlighted in blue and underlined.

Table S2. League table showing the RRs and CI 95% for hypothyroidism grade 3-4 between immunotherapy treatments.

	KEYNOTE-024	KEYNOTE-042	CheckMate 026	IMPower110	MYSTIC	EMPOWER-Lung 01
KEYNOTE-024		0,70	0,14	0,14	0,15	0,14
Lower limit		0,01	0,00	0,01	0,00	0,00
Upper limit		48,85	18,70	2,84	19,44	19,45
KEYNOTE-042	1,42		0,19	0,21	0,21	0,20
Lower limit	0,02		0,00	0,00	0,01	0,00
Upper limit	98,38		27,69	28,58	4,34	28,79
CheckMate 026	7,36	5,18		1,07	1,07	1,05
Lower limit	0,05	0,04		0,00	0,00	0,02
Upper limit	1012,57	744,39		270,07	271,95	54,16
IMPower110	6,90	4,86	0,94		1,00	0,98
Lower limit	0,35	0,03	0,00		0,00	0,00
Upper limit	135,39	675,76	237,53		247,71	247,15
MYSTIC	6,87	4,84	0,93	1,00		0,98
Lower limit	0,05	0,23	0,00	0,00		0,00
Upper limit	918,19	101,82	237,24	245,70		246,86
EMPOWER-Lung 01	7,03	4,95	0,96	1,02	1,02	
Lower limit	0,05	0,03	0,02	0,00	0,00	
Upper limit	960,90	706,45	49,43	256,48	258,26	

RR>1 indicates increased risk of AE for the column treatment as compared to the row treatment. Lower and upper limit of the IC95% are shown. All possible indirect comparisons are presented. Statistically significant results are highlighted in blue and underlined.

Table S3. League table showing the RRs and CI 95% for pneumonitis any grade between immunotherapy treatments.

	KEYNOTE-024	KEYNOTE-042	CheckMate 026	IMPower110	MYSTIC	EMPOWER-Lung 01
KEYNOTE-024		1,86	1,67	1,15	0,17	1,64
Lower limit		0,18	0,05	0,06	0,02	0,05
Upper limit		19,69	56,52	20,72	1,78	55,30
KEYNOTE-042	0,54		0,90	0,62	<u>0,09</u>	0,88
Lower limit	0,05		0,04	0,06	<u>0,03</u>	0,04
Upper limit	5,67		19,64	6,43	<u>0,30</u>	19,21
CheckMate 026	0,60	1,11		0,68	0,10	0,98
Lower limit	0,02	0,05		0,02	0,00	0,02
Upper limit	20,16	24,30		22,93	2,21	40,77
IMPower110	0,87	1,63	1,46		0,15	1,43
Lower limit	0,05	0,16	0,04		0,01	0,04
Upper limit	15,77	16,98	48,93		1,54	47,88
MYSTIC	5,78	<u>10,77</u>	9,68	6,63		9,47
Lower limit	0,56	<u>3,35</u>	0,45	0,65		0,44
Upper limit	59,64	<u>34,66</u>	207,56	67,55		203,11
EMPOWER-Lung 01	0,61	1,14	1,02	0,70	0,11	
Lower limit	0,02	0,05	0,02	0,02	0,00	
Upper limit	20,62	24,86	42,61	23,45	2,26	

RR>1 indicates increased risk of AE for the column treatment as compared to the row treatment. Lower and upper limit of the IC95% are shown. All possible indirect comparisons are presented. Statistically significant results are highlighted in blue and underlined.

Table S4. League table including RR and CI 95% for pneumonitis grade 3-4 between immunotherapy treatments

	KEYNOTE-024	KEYNOTE-042	CheckMate 026	IMPower110	MYSTIC	EMPOWER-Lung 01
KEYNOTE-024		1,56	2,26	1,17	0,97	0,74
Lower limit		0,13	0,06	0,09	0,04	0,02
Upper limit		18,93	86,23	14,50	21,33	35,36
KEYNOTE-042	0,64		1,45	0,75	0,62	0,47
Lower limit	0,05		0,06	0,03	0,12	0,02
Upper limit	7,77		34,07	19,65	3,13	14,43
CheckMate 026	0,44	0,69		0,52	0,43	0,33
Lower limit	0,01	0,03		0,01	0,01	0,02
Upper limit	16,87	16,25		34,80	16,46	6,68
IMPower110	0,85	1,33	1,93		0,83	0,63
Lower limit	0,07	0,05	0,03		0,02	0,01
Upper limit	10,54	34,85	129,34		34,82	51,51
MYSTIC	1,03	1,60	2,32	1,21		0,76
Lower limit	0,05	0,32	0,06	0,03		0,02
Upper limit	22,53	8,06	88,88	50,57		36,44
EMPOWER-Lung 01	1,36	2,12	3,07	1,59	1,32	
Lower limit	0,03	0,07	0,15	0,02	0,03	
Upper limit	65,13	64,81	62,90	130,44	63,54	

RR>1 indicates increased risk of AE for the column treatment as compared to the row treatment. Lower and upper limit of the IC95% are shown. All possible indirect comparisons are presented. Statistically significant results are highlighted in blue and underlined.

Table S5. League table showing the RRs and CI 95% for transaminases increased any grade between immunotherapy treatments.

	KEYNOTE-024	KEYNOTE-042	CheckMate 026	IMPower110	MYSTIC	EMPOWER-Lung 01
KEYNOTE-024		0,89	1,62	2,27	4,86	1,67
Lower limit		0,02	0,03	0,04	0,03	0,03
Upper limit		44,16	81,72	115,08	675,76	83,47
KEYNOTE-042	1,12		<u>1,82</u>	<u>2,54</u>	<u>5,45</u>	<u>1,87</u>
Lower limit	0,02		<u>1,07</u>	<u>1,51</u>	<u>1,46</u>	<u>1,15</u>
Upper limit	55,51		<u>3,10</u>	<u>4,27</u>	<u>20,34</u>	<u>3,04</u>
CheckMate 026	0,62	<u>0,55</u>		1,40	3,00	1,03
Lower limit	0,01	<u>0,32</u>		0,74	0,14	0,62
Upper limit	31,07	<u>0,94</u>		2,65	64,36	1,71
IMPower110	0,44	<u>0,39</u>	0,72		2,15	0,74
Lower limit	0,01	<u>0,23</u>	0,38		0,10	0,40
Upper limit	22,43	<u>0,66</u>	1,36		45,99	1,34
MYSTIC	0,21	<u>0,18</u>	0,33	0,47		0,34
Lower limit	0,00	<u>0,05</u>	0,02	0,02		0,02
Upper limit	28,58	<u>0,68</u>	7,16	9,98		7,30
EMPOWER-Lung 01	0,60	<u>0,54</u>	0,97	1,36	2,92	
Lower limit	0,01	<u>0,33</u>	0,59	0,75	0,14	
Upper limit	30,05	<u>0,87</u>	1,62	2,48	62,15	

RR>1 indicates increased risk of AE for the column treatment as compared to the row treatment. Lower and upper limit of the IC95% are shown. All possible indirect comparisons are presented. Statistically significant results are highlighted in blue and underlined.

Table S6. League table showing RR and CI 95% for transaminases increased grade 3-4 between immunotherapy treatments.

	KEYNOTE-024	KEYNOTE-042	CheckMate 026	IMPower110	MYSTIC	EMPOWER-Lung 01
KEYNOTE-024		1,83	4,69	4,69	2,92	6,38
Lower limit		0,03	0,08	0,08	0,02	0,10
Upper limit		99,80	278,28	279,77	449,50	411,06
KEYNOTE-042	0,55		2,56	2,56	1,59	3,49
Lower limit	0,01		0,55	0,44	0,48	0,61
Upper limit	29,77		11,89	14,93	5,29	19,86
CheckMate 026	0,21	0,39		1,00	0,62	1,36
Lower limit	0,00	0,08		0,14	0,02	0,19
Upper limit	12,67	1,81		7,03	19,17	9,97
IMPower110	0,21	0,39	1,00		0,62	1,36
Lower limit	0,00	0,07	0,14		0,02	0,16
Upper limit	12,73	2,28	7,03		21,35	11,28
MYSTIC	0,34	0,63	1,61	1,61		2,19
Lower limit	0,00	0,19	0,05	0,05		0,06
Upper limit	52,81	2,08	49,46	55,11		74,18
EMPOWER-Lung 01	0,16	0,29	0,73	0,73	0,46	
Lower limit	0,00	0,05	0,10	0,09	0,01	
Upper limit	10,09	1,63	5,37	6,08	15,49	

RR>1 indicates increased risk of AE for the column treatment as compared to the row treatment. Lower and upper limit of the IC95% are shown. All possible indirect comparisons are presented. Statistically significant results are highlighted in blue and underlined.

Table S7. League table showing the RRs and CI 95% for nephritis any grade between immunotherapy treatments.

	KEYNOTE-024	KEYNOTE-042	CheckMate 026	IMPower110	MYSTIC	EMPOWER-Lung 01
KEYNOTE-024		12,82	1,00	0,94	0,32	1,64
Lower limit		0,18	0,01	0,04	0,00	0,02
Upper limit		897,45	91,87	24,83	50,68	133,71
KEYNOTE-042	0,08		0,08	0,07	0,03	0,13
Lower limit	0,00		0,00	0,00	0,00	0,00
Upper limit	5,46		5,50	5,14	0,43	7,95
CheckMate 026	1,00	12,76		0,93	0,32	1,63
Lower limit	0,01	0,18		0,01	0,00	0,05
Upper limit	91,06	896,47		85,70	50,60	51,31
IMPower110	1,07	13,66	1,07		0,35	1,75
Lower limit	0,04	0,19	0,01		0,00	0,02
Upper limit	28,22	959,90	98,24		54,18	143,00
MYSTIC	3,08	39,53	3,10	2,89		5,05
Lower limit	0,02	2,35	0,02	0,02		0,04
Upper limit	481,97	665,41	485,45	453,45		715,31
EMPOWER-Lung 01	0,61	7,83	0,61	0,57	0,20	
Lower limit	0,01	0,13	0,02	0,01	0,00	
Upper limit	49,88	487,47	19,31	46,95	28,06	

RR>1 indicates increased risk of AE for the column treatment as compared to the row treatment. Lower and upper limit of the IC95% are shown. All possible indirect comparisons are presented. Statistically significant results are highlighted in blue and underlined.

Table S8. League table showing the RRs and CI 95% for nephritis increased grade 3-4 between immunotherapy treatments.

	KEYNOTE-024	KEYNOTE-042	CheckMate 026	IMPower110	MYSTIC	EMPOWER-Lung 01
KEYNOTE-024		2,30	1,00	0,31	0,32	0,33
Lower limit		0,03	0,01	0,01	0,00	0,00
Upper limit		178,98	91,87	7,76	50,68	51,53
KEYNOTE-042	0,43		0,44	0,14	0,14	0,14
Lower limit	0,01		0,01	0,00	0,01	0,00
Upper limit	33,81		34,07	18,70	2,77	19,45
CheckMate 026	1,00	2,29		0,31	0,32	0,33
Lower limit	0,01	0,03		0,00	0,00	0,01
Upper limit	91,06	178,77		49,47	50,60	8,08
IMPower110	3,20	7,36	3,21		1,04	1,05
Lower limit	0,13	0,05	0,02		0,00	0,00
Upper limit	79,32	1012,57	510,38		267,00	271,31
MYSTIC	3,08	7,10	3,10	0,96		1,01
Lower limit	0,02	0,36	0,02	0,00		0,00
Upper limit	481,97	139,62	485,45	248,31		258,37
EMPOWER-Lung 01	3,06	7,03	3,07	0,96	0,99	
Lower limit	0,02	0,05	0,12	0,00	0,00	
Upper limit	480,95	960,90	76,08	247,62	253,57	

RR>1 indicates increased risk of AE for the column treatment as compared to the row treatment. Lower and upper limit of the IC95% are shown. All possible indirect comparisons are presented. Statistically significant results are highlighted in blue and underlined.