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Comparative risk of serious and fatal treatment-related adverse events caused by 19 immune checkpoint inhibitors used in cancer treatment: a network meta-analysis

Tingting Liu*, Bo Jin*, Jun Chen, Hui Wang, Shuiyu Lin, Jun Dang and Guang Li

Abstract

Background: This network meta-analysis assessed the comparative risk of grade 3–5 and grade 5 treatment-related adverse events (TRAEs) for immune checkpoint inhibitors (ICIs), either alone or in combination with other modalities, for cancer treatment.

Methods: PubMed, Embase, Cochrane Library, Web of Science, and recent predominant oncology congresses were searched for relevant phase II and phase III randomized controlled trials (RCTs). As outcomes, grade 3–5, and grade 5 TRAE outcomes were reported as odds ratios and 95% confidence intervals.

Results: In 67 RCTs involving 36,422 patients and 19 ICIs, the incidence of grade 3–5 and grade 5 TRAEs was 17.9% and 0.8% with ICI monotherapy and 46.3% and 1.4%, respectively, with combinatorial therapy. Pneumonitis was the most common cause of grade 5 TRAEs following either monotherapy (16.3%) or combinatorial therapy (11.4%). Regarding grade 3–5 TRAEs, atezolizumab + chemotherapy (CT) and antiangiogenic therapy (AT) (atezolizumab + CAT), pembrolizumab + CT, ipilimumab + CT, and atezolizumab + CT were more toxic than any ICI monotherapy, pembrolizumab or nivolumab + radiotherapy (RT), and ICIs dual therapy (durvalumab + tremelimumab and nivolumab + ipilimumab). Tremelimumab, ipilimumab, durvalumab, and pembrolizumab were, however, associated with higher grade 5 TRAEs than combinatorial treatments. Atezolizumab + CAT was the most toxic and nivolumab + RT was the least toxic of combinatorial treatments; among monotherapies, tremelimumab and avelumab were the most and least toxic, respectively. The toxicity ranking changed with type of grade 3–5 TRAEs.

Conclusions: Compared with combinatorial therapy, ICI monotherapy caused lower grade 3–5 TRAEs, but some monotherapies resulted in a higher incidence of fatal TRAEs. Atezolizumab + CAT and nivolumab + RT were the most and least toxic of combinatorial treatments, respectively, and tremelimumab and avelumab were the most and least toxic of the monotherapies, respectively.

Keywords: antiangiogenic therapy, chemotherapy, immune checkpoint inhibitor, network meta-analysis, radiotherapy, treatment-related adverse events

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Introduction

Immune checkpoint inhibitors (ICIs), including programmed cell death-1 (PD-1), programmed cell death ligand-1 (PD-L1), and cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitors, have revolutionized the treatment of many cancers. These agents can upregulate T cell activity, leading to an immune response against cancer cells.

However, the increased activity of T cells can also induce autoimmune toxicities by unbalancing the immune system.[1] ICIs have been reported to cause a wide spectrum of immune-related adverse events (irAEs), such as skin, gastrointestinal, endocrine, hepatic, pulmonary, and cardiovascular toxicities.[2] In general, most irAEs are mild and can be well controlled with supportive treatment and glucocorticoids. However, the incidence of irAEs appears to have increased with the rapidly growing number of patients receiving ICIs, and some irAEs are serious with fatal outcomes.

Currently, the United States Food and Drug Administration (FDA) has approved several ICIs for the treatment of various cancers, including two PD-1 inhibitors (nivolumab and pembrolizumab), three PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab), and two CTLA-4 inhibitors (ipilimumab and tremelimumab). As individual ICIs influence different immunologic mechanisms, the frequencies, severities, and profiles of the irAEs may vary.[2–6] Moreover, ICIs in combination with conventional therapy [chemotherapy (CT), antiangiogenic therapy (AT), or their combinations] or with a second ICI, are being increasingly used, and these combinations have demonstrated survival advantage over monotherapy in several tumors.[7–10] However, combinatorial therapy may also result in an increased risk of treatment-related adverse events (TRAEs). To date, evidence regarding head-to-head comparisons among ICIs is lacking, and therefore, determining which monotherapy or combinatorial therapy has the most or the least toxicity remains undefined.

Safety is the critical factor for drug evaluation. A better understanding of the comparative safety profiles between the ICIs would be helpful in clinical decision making. In this study, we performed a systematic review and network meta-analysis to assess the comparative risk of grade 3–5 and grade 5 TRAEs among 19 ICIs used in cancer treatment.

Methods

Literature search strategy

This network meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Supplemental Table S1).[11] We systematically searched PubMed, Embase, the Cochrane Library, Web of Science, and the most recent oncology congresses (American Society of Clinical Oncology, American Society of Radiation Oncology, European Society for Medical Oncology, and World Conference on Lung Cancer) for available studies published before 1 November 2019. The search strategy is detailed in Supplemental Table S2. The reference lists of all relevant publications were also assessed for additional eligible studies.

Inclusion and exclusion criteria

Studies were included if they met all of the following criteria: (a) phase II or phase III randomized controlled trials (RCTs) of patients with cancer; (b) at least one treatment arm received an FDA-approved ICI, alone or in combination with another ICI or conventional therapy; (c) reported data of grade 3–5 and/or grade 5 TRAEs in each arm; and (d) published in English. When multiple publications covered the same study population, the one with the most recent and comprehensive data was used. Studies that failed to meet the above criteria were excluded from the network meta-analysis.

Data extraction

To better assess the toxicity of ICIs, especially in combinatorial treatments, we evaluated TRAEs instead of irAEs as the outcomes of interest. Two investigators independently extracted the following data from each study: the first author or the name of the RCT, year of publication, region, cancer type, study design, follow-up time, number of patients, interventions, and the number of grade 3–5 and grade 5 TRAEs.

Quality assessment

Two investigators independently assessed the risk of bias of the included RCTs using the Cochrane Collaboration's tool,[12] which includes the following five domains: sequence generation, allocation concealment, blinding, incomplete data, and selective reporting. Blinding cannot be applied in studies with specific designs (such as open-label or cross-over) owing to unavoidable reasons. If such reasons were clearly stated in the included studies, these studies were rated as "+." An RCT was judged to have a "low risk of bias," a "high risk of bias," or an "unclear risk of bias" if all domains indicated low risk, one or more domains

indicated high risk, or more than three domains indicated as unclear risk, respectively.

Statistical analysis

The outcomes of interest were grade 3–5 and grade 5 TRAEs. Odds ratios (ORs) and their 95% confidence intervals (CIs) were used as summary statistics to estimate treatment effects. If a study reported zero grade 5 TRAEs in any arm, a half integer continuity correction (adding a 0.5 to each cell) was applied to calculate ORs. For direct comparisons, a standard pairwise meta-analysis was performed using R (version 3.5.0). The heterogeneity among studies was assessed using the chi-squared (χ^2) and *I*-squared (I^2) tests. A p value greater than 0.10 or an I^2 value greater than 50% indicated substantial heterogeneity, and a random-effects model was used; otherwise, a fixed-effects model was used.

The Bayesian network meta-analysis was conducted using a random-effects model (generalized linear model) using the Markov chain Monte Carlo method in OpenBUGS (version 3.2.3).[13] For each outcome measure, four independent Markov chains were simultaneously run for 20,000 burn-ins and 100,000 inference iterations per chain to obtain the posterior distribution. The traces plot and Gelman–Rubin method were used to assess the convergence of the model.[14] Relative toxicity rankings were assessed according to the surface under the cumulative ranking curve (SUCRA) method.[15] SUCRA equals one if the treatment is certain to be the worst, and zero if it is certain to be the best. The transitivity assumption was assessed by comparing the distribution of potential effect modifiers (sample size, median age, and median follow-up time) across treatment comparisons.[16] Global inconsistency was evaluated by comparing the fit of the consistency and inconsistency models using a design-by-treatment test[15]; local inconsistency was assessed by calculating the difference between the direct and indirect estimates in the treatment loops using the loop-specific approach,[15] and by testing between direct and indirect results within the treatment loops using node-split models[17]; $p < 0.05$ indicated significant inconsistency. We assumed a common heterogeneity parameter for all comparisons and used the between-study heterogeneity variance, τ^2, to assess the extent of heterogeneity for each outcome.[18,19] We conducted subgroup meta-regressions (sample size, treatment line, tumor type, drug dose, control arm, and study risk of bias) to search for the sources of heterogeneity.

Sensitivity analyses were conducted to assess the stability of the results by omitting studies with a high overall risk of bias, a sample size <100, or a placebo-controlled trial as well as by dividing the trials of nivolumab + ipilimumab into two dose groups [nivolumab (3 mg) + ipilimumab (1 mg) and nivolumab (1 mg) + ipilimumab (3 mg)] and the trials of pembrolizumab into three dose groups (200 mg, 2 mg/kg, 10 mg/kg). In addition, we performed subgroup analyses based on the nature and severity of TRAEs. Publication bias was examined using funnel plots.[20]

Results

Literature search results and characteristics of included RCTs

The details of our literature search and study selection process are shown in Figure 1. The initial literature search identified 38,457 studies, of which 244 were deemed potentially eligible and were thus retrieved for detailed assessment. The relevant references were also reviewed for any missed studies. Finally, 67 RCTs involving 36,422 patients and evaluating 22 treatments (including CT, AT, placebo, and 19 ICIs) were included in the network meta-analysis.[8–10,21–95] Among the 19 ICI-based treatments, 7 were monotherapies (nivolumab,[21–31] pembrolizumab,[32–43] atezolizumab,[44–47] avelumab,[48,49] durvalumab,[91,93,95] ipilimumab,[50,51] and tremelimumab[52,53]) and 12 were combinatorial therapies (nivolumab + RT,[54] pembrolizumab + AT,[55] pembrolizumab + CT,[56–61] pembrolizumab + RT,[62,63] atezolizumab + AT,[64,65] atezolizumab + CT,[66–70] atezolizumab + CT + AT (atezolizumab + CAT),[71] avelumab + AT,[72] durvalumab + CT,[73] ipilimumab + CT,[74–80] nivolumab + ipilimumab,[8–10,81–90] and durvalumab + tremelimumab[91–95]). The baseline characteristics of the included trials are shown in Table 1. A total of 46 studies (68.7%) were phase III trials, and 64 (95.5%) were multinational trials. Cancer types assessed in the trials included lung (n=30), melanoma (n=10), gastric and esophageal (n=8), head and neck (n=6), renal cell (n=5), urothelial (n=3), prostate (n=2), breast (n=1), endometrial (n=1), and malignant mesothelioma (n=1). The mean sample size for toxicity analysis was 515 participants (range, 36–1274). The mean age was 62.3 years (range, 55.5–69.5 years). The median follow-up time was 13.9 months (range, 5.1–57.7 months).

Table 1. Characteristics of included trials.

Trial/year	Region	Design	Cancer type	Treatment line	Treatment	Total No.	Toxicity analysis No.	Median follow-up (months)	G 3–5 TRAEs No.	G 5 TRAEs No.	Median age
CheckMate 067/2017[8,9]	Multicenter	II	Melanoma	First	Niv+Ipi	945	313	NR	187	2	59.3
					Niv		313		71	1	58.7
					Ipi		311		87	1	59.6
CheckMate 032-2/2019[10]	Multicenter	II	UC	Second	Niv+Ipi	274	196	NR	69	1	63.5
					Niv		78		22	1	65.5
CheckMate 026/2017[21]	Multicenter	III	NSCLC	First	Niv	423	267	13.5	49	2	63
					PC/PP/GP		263	13.5	136	3	65
CheckMate 057/2015[22]	Multicenter	III	NSCLC	Second	Niv	592	287	NR	31	1	61
					Doc		268		145	1	64
CheckMate 017/2015[23]	Multicenter	III	NSCLC	Second	Niv	272	131	NR	9	0	62
					Doc		129		74	3	64
CheckMate 078/2019[24]	Multicenter	III	NSCLC	Second	Niv	504	337	10.4	44	4	60
					Doc		156	8.8	77	3	60
CheckMate 066/2014[25,26]	Multicenter	III	Melanoma	First	Niv	418	206	38.4	31	0	64
					DTIC		205	38.5	36	0	66
CheckMate 037/2015[27,28]	Multicenter	III	Melanoma	Second	Niv	405	268	48	37	0	59
					DTIC/PC		102	48	35	0	62
CheckMate 141/2016[29]	Multicenter	III	HNC	Second	Niv	361	236	5.1	33	2	59
					Met/Doc/Cet		111	5.1	40	1	61
ATTRACTION-3/2019[30]	Multicenter	III	GEC	Second	Niv	419	209	10.5	38	2	64
					Pac/Doc		208	8	131	3	67
ATTRACTION-2/2017[31]	Multicenter	III	GEC	Second	Niv	493	330	8.9	39	5	62
					Placebo		161	8.6	9	2	61
KEYNOTE-024/2016[32,33]	Multicenter	III	NSCLC	First	Pem	205	154	11.2	48	2	64.5
					PC/PP/GP		150	11.2	80	3	66

(Continued)

Table 1. (Continued)

Trial/year	Region	Design	Cancer type	Treatment line	Treatment	Total No.	Toxicity analysis No.	Median follow-up (months)	G 3–5 TRAEs No.	G 5 TRAEs No.	Median age
KEYNOTE-042/2019[34]	Multicenter	Ⅲ	NSCLC	First	Pem	1274	636	12.8	113	13	63
					PC/PP		615	12.8	252	14	63
KEYNOTE-010/2016[35]	Multicenter	Ⅱ/Ⅲ	NSCLC	Second	Pem	991	682	13.1	98	6	63
					Doc		309	13.1	109	5	62
KEYNOTE-002/2015[36,37]	Multicenter	Ⅱ	Melanoma	Second	Pem	540	357	28	54	1	61
					PC/DTIC/Tem		171	28	45	0	63
KEYNOTE-045/2017[38]	Multicenter	Ⅲ	UC	Second	Pem	542	266	14.1	40	4	67
					Pac/Doc/Vin		255	14.1	126	4	65
KEYNOTE-181/2019[39]	Multicenter	Ⅲ	GEC	Second	Pem	628	314	7.1	57	5	NR
					Pac/Doc/Iri		296	6.9	129	5	NR
KEYNOTE-061/2018[40]	Multicenter	Ⅲ	GEC	Second	Pem	592	294	7.5	42	3	62.5
					Pac		276	7.1	96	1	60
KEYNOTE-040/2019[41]	Multicenter	Ⅲ	HNC	Mix	Pem	595	246	7.5	33	4	60
					Met/Doc/Cet		234	7.1	85	2	60
KEYNOTE-006/2015[42,43]	Multicenter	Ⅲ	Melanoma	Mix	Pem	834	555	57.7	97	1	62
					Ipi		256	57.7	50	0	62
OAK/2017[44]	Multicenter	Ⅲ	NSCLC	Second	Ate	1225	609	28	90	0	63
					Doc		578	28	248	1	64
POPLAR/2016[45]	Multicenter	Ⅱ	NSCLC	Second	Ate	144	142	14.8	17	1	62
					Doc		135	15.7	55	3	62
IMpower110/2019[46]	Multicenter	Ⅲ	NSCLC	First	Ate	572	286	15.7	37	0	NR
					PP/GP		263	15.7	117	1	NR
IMvigor211/2018[47]	Multicenter	Ⅲ	UC	Second	Ate	931	459	17.3	95	4	67
					Pac/Doc/Vin		443	17.3	198	9	67
JAVELIN Lung 200/2018[48]	Multicenter	Ⅲ	NSCLC	Second	Ave	792	393	18.3	39	4	64
					Doc		365	18.3	180	14	63

(Continued)

Table 1. (Continued)

Trial/year	Region	Design	Cancer type	Treatment line	Treatment	Total No.	Toxicity analysis No.	Median follow-up (months)	G 3–5 TRAEs No.	G 5 TRAEs No.	Median age
JAVELIN Gastric 300/2018[49]	Multicenter	Ⅲ	GEC	Second	Ave	371	184	10.6	17	0	59
					Pac/Iri		177	10.6	56	1	61
Beer/2017[50]	Multicenter	Ⅲ	PC*	First	Ipi	602	399	24	167	9	70
					Placebo		199	24	11	0	69
CA184-043/2014[51]	Multicenter	Ⅲ	PC*	Second	Ipi	799	393	9.9	105	4	69
					Placebo		396	9.3	11	0	67.5
DETERMINE/2017[52]	Multicenter	Ⅱ	MM	Second	Tre	571	380	NR	110	5	66
					Placebo		189		12	0	67
Ribas/2013[53]	Multicenter	Ⅲ	Melanoma	First	Tre	655	325	NR	NR	7	57
					Tem/DTIC		319		NR	1	56
ASCO6009/2018[54]	Single center	Ⅱ	HNC	Mix	Niv+RT	53	27	12.8	3	NR	NR
					Niv		26	12.8	4		NR
KEYNOTE-426/2019[55]	Multicenter	Ⅲ	RCC	First	Pem+Axi	861	429	12.8	270	4	62
					Sun		425	12.8	247	7	61
KEYNOTE-189/2018[56]	Multicenter	Ⅲ	NSCLC	First	Pem+PP	616	405	10.5	36()	3	65
					PP		202	10.5	9()	0	63.5
KEYNOTE-407/2019[57]	Multicenter	Ⅲ	NSCLC	First	Pem+PC/CnP	559	278	7.8	30	1	65
					PC/CnP		280	7.8	9	1	65
KEYNOTE-021/2016[58,59]	Multicenter	Ⅱ	NSCLC	First	Pem+PP	123	59	23.9	24	1	62.5
					PP		62	23.9	17	2	63.2
KEYNOTE-048/2018[60]	Multicenter	Ⅲ	HNC	First	Pem+FP	582	281	17	200	NR	NR
					Pem		301	17	51		NR
KEYNOTE-062/2019[61]	Multicenter	Ⅲ	GEC	First	Pem+FP/Cap	763	257	11.3	188	NR	NR
					Pem		256	11.3	44		NR
					FP/Cap		250	11.3	173		NR

(Continued)

Table 1. (Continued)

Trial/year	Region	Design	Cancer type	Treatment line	Treatment	Total No.	Toxicity analysis No.	Median follow-up (months)	G 3–5 TRAEs No.	G 5 TRAEs No.	Median age
ASCO9104/2019[62]	Single center	II	NSCLC	First	Pem+RT	124	36	15.4	11	0	NR
					Pem		36	15.4	5	0	NR
PEMBRO-RT/2019[63]	Multicenter	II	NSCLC	Second	Pem+RT	92	35	23.6	5	0	62
					Pem		37	23.6	11	1	62
IMmotion151/2019[64]	Multicenter	III	RCC	First	Ate+Bev	915	451	15	187	5	62
					Sun		446	15	241	1	60
IMmotion150/2018[65]	Multicenter	II	RCC	First	Ate+Bev	305	100	20.7	59	2	62
					Ate		103	20.7	17	0	61
					Sun		101	20.7	41	1	61
IMpower130/2019[66]	Multicenter	III	NSCLC	First	Ate+CnP	724	473	18.5	354	8	64
					CnP		232	19.2	141	1	65
IMpower131/2018[67]	Multicenter	III	NSCLC	First	Ate+CnP	683	334	17.1	231	4	65
					CnP		334	17.1	196	3	65
IMpower132/2018[68]	Multicenter	III	NSCLC	First	Ate+PP	578	291	14.8	167	11	64
					PP		274	14.8	114	7	63
IMpower133/2018[69]	Multicenter	III	SCLC	First	Ate+EP	403	198	13.9	115	3	64
					EP		196	13.9	113	3	64
IMpassion130/2018[70]	Multicenter	III	BC	First	Ate+nap-Pac	902	452	13	182	3	55
					nap-Pac		438	12.5	133	1	56
IMpower150/2018[71]	Multicenter	III	NSCLC	First	Ate+Bev+PC	793	393	20	234	11	63
					Ate+PC		400	20	176	4	63
JAVELIN Renal 101/2019[72]	Multicenter	III	RCC	First	Ave+Axi	886	434	11.6	246	3	62
					Sun		439	10.7	243	1	61
CASPIAN/2019[73]	Multicenter	III	SCLC	First	Dur+EP	575	265	14.2	126	5	62
					EP		266	14.2	140	2	63

(Continued)

Table 1. (Continued)

Trial/year	Region	Design	Cancer type	Treatment line	Treatment	Total No.	Toxicity analysis No.	Median follow-up (months)	G 3–5 TRAEs No.	G 5 TRAEs No.	Median age
CA184-024/2011[74,75]	Multicenter	III	Melanoma	First	Ipi+DTIC	502	247	NR	103	0	57.5
					DTIC		251		16	1	56.4
Lynch/2012[76]	Multicenter	II	NSCLC	First	Ipi+PC	204	138	NR	56	1	60
					PC		65		24	1	62
Govindan/2017[77]	Multicenter	III	NSCLC	First	Ipi+PC	749	388	12.5	205	7	64
					PC		361	12.5	129	1	64
Reck/2013[78]	Multicenter	II	SCLC	First	Ipi+PC	130	84	NR	40	1	NR
					PC		44		13	0	NR
Reck/2016[79]	Multicenter	III	SCLC	First	Ipi+EP	954	478	10.5	231	5	62
					EP		476	10.2	214	2	63
Hersh/2011[80]	Multicenter	II	Melanoma	First	Ipi+DTIC	72	35	20.9	9	1	60
					Ipi		39	16.4	6	1	66
CheckMate 227/2018[81,82]	Multicenter	III	NSCLC	First	Niv+Ipi	1537	576	28.3	221	8	NR
					Niv		391	28.3	95	2	NR
					PP/GP		570	28.3	248	6	NR
Lung-MAP Sub-Study/2019[83]	Multicenter	III	NSCLC	Second	Niv+Ipi	275	124	17.4	48	5	NR
					Niv		123	17.4	38	1	NR
CheckMate 032-1/2019[84]	Multicenter	II	SCLC	Second	Niv+Ipi	243	96	11.2	40	4	65
					Niv		147	11.9	20	1	63
CheckMate 032/2018[85]	Multicenter	II	GEC	Second	Niv+Ipi	160	101	22–28	37	1	55.5
					Niv		59	28	10	0	60
Long/2018[86]	Multicenter	II	Melanoma	First	Niv+Ipi	63	35	17	19	0	59
					Niv		25	17	4	0	63

(Continued)

Table 1. (Continued)

Trial/year	Region	Design	Cancer type	Treatment line	Treatment	Total No.	Toxicity analysis No.	Median follow-up (months)	G 3–5 TRAEs No.	G 5 TRAEs No.	Median age
CheckMate 069/2015[87,88]	Multicenter	II	Melanoma	First	Niv+Ipi	142	94	24	54	3	64
					Ipi		46	24	9	0	67
CheckMate 214/2018[89,90]	Multicenter	III	RCC	First	Niv+Ipi	1096	547	25.2	263	8	62
					Sun		535	25.2	346	4	62
MYSTIC/2018[91]	Multicenter	III	NSCLC	First	Dur+Tre	1118	373	NR	82	0	NR
					Dur		373		54	0	NR
					PP		373		126	0	NR
CONDOR/2018[92]	Multicenter	II	HNC	Second	Dur+Tre	267	133	6.5	22	1	62
					Dur		65	6	8	0	62
					Tre		65	5.2	11	0	61
EAGLE/2019[93]	Multicenter	III	HNC	Second	Dur+Tre	736	247	NR	40	NR	NR
					Dur		240		24		NR
					FP/Cet/Tax/ Met		249		60		NR
ASCO5582/2019[94]	Single center	II	EC	NR	Dur+Tre	56	27	NR	12	0	NR
					Dur		27		3	0	NR
Kelly/2019[95]	Multicenter	II	GEC	Second	Tre	88	12	9.2	5	0	64
					Dur+Tre		52	9.2	9	0	60
					Dur		24	3.5	1	0	54

Ate, atezolizumab; Ave, avelumab; Axi, axitinib; BC, breast cancer; Bev, bevacizumab; Cap, capecitabine; Cet, cetuximab; CnP, paclitaxel-nanoparticle albumin-bound-carboplatin; DOC, docetaxel; DTIC, dacarbazine; Dur, durvalumab; EC, endometrial carcinoma; EP, etoposide-cisplatin/carboplatin; FP, fluorouracil-cisplatin/carboplatin; GEC, gastric or esophageal cancer; GP, gemcitabine-cisplatin/carboplatin; HNC, head and neck cancer; Ipi, ipilimumab; Iri, irinotecan; Met, methotrexate; MM, malignant mesothelioma; Nap, nedaplatin; Niv, nivolumab; No., number; NR, not reported ; NSCLC, non-small cell lung cancer; Pac, paclitaxel; PC, paclitaxel-cisplatin /carboplatin; PC*, prostate cancer; Pem, pembrolizumab; RCC, renal cell carcinoma; RT, radiotherapy; SCLC, small cell lung cancer; Sun, sunitinib; Tax, taxane; Tem, temozolomide; TRAEs, treatment-related adverse events; Tre, tremelimumab; UC, urothelial carcinoma; Vin, vinflunine.

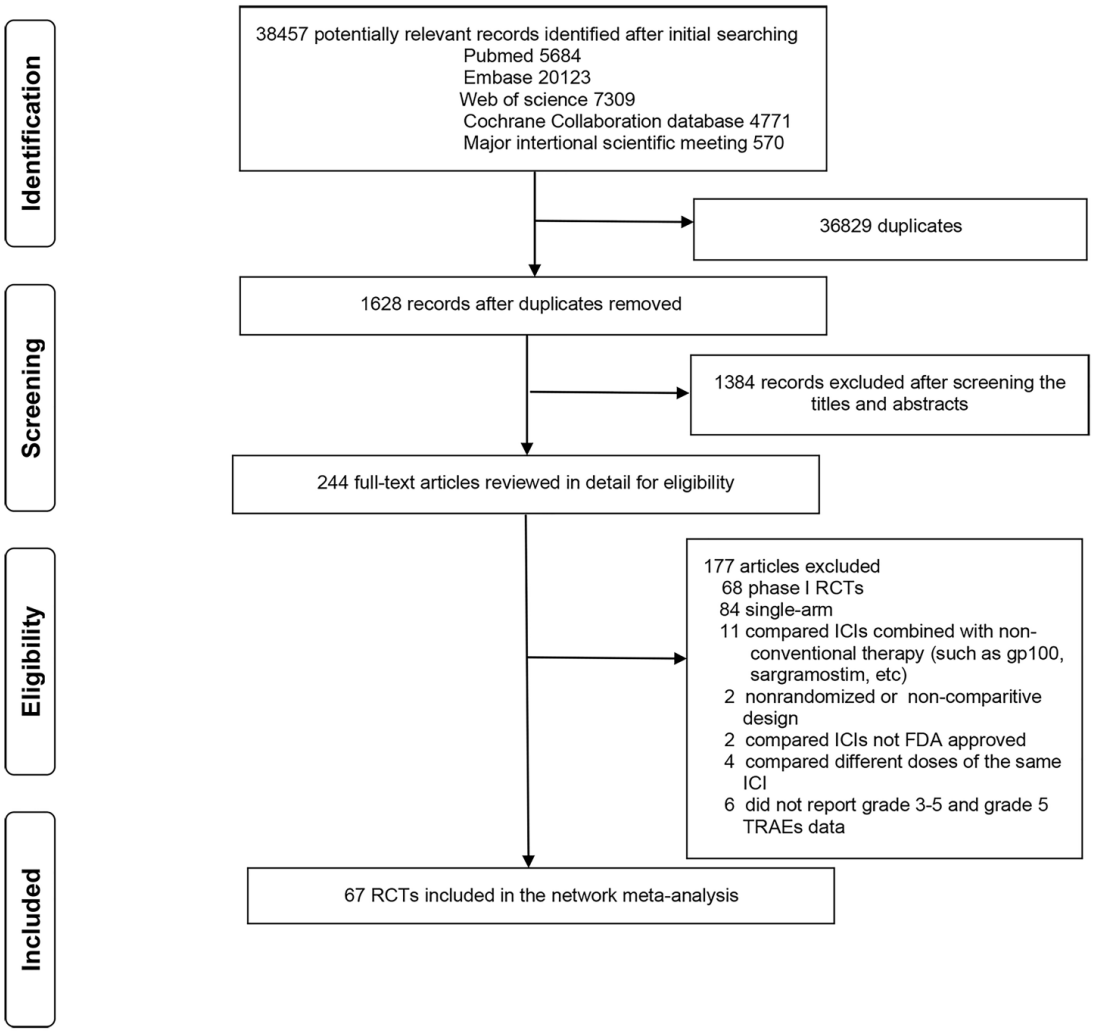


Figure 1. Literature search and selection.
FDA, United States Food and Drug Administration; ICIs, immune checkpoint inhibitors; RCTs, randomized control trials; TRAEs, treatment-related adverse events.

Assessment of included trials

The risks of bias for the included RCTs are summarized in Supplemental Figure S1. Overall, the risk of bias across studies was relatively low; 12 RCTs were rated with a high risk of bias.[22–24,35,42–45,48,55,72,86,92] The funnel plot analysis did not indicate any evident risk of publication bias for grade 5 TRAEs, but it did suggest a probability of publication bias for grade 3–5 TRAEs (Supplemental Figure S2).

Incidence of grade 3–5 and grade 5 TRAEs

The overall incidence of grade 3–5 and grade 5 TRAEs were 34.4% (12,297 of 35,778 patients from 66 studies) and 1.0% (352 of 34,288 patients from 63 studies), respectively, and, for patients receiving ICIs, the incidence rates were 30.5% (6,793 of 22,256 patients) and 1.1% (221 of 20,946 patients) for grade 3–5 and grade 5 TRAEs, respectively. Further analysis revealed that, with monotherapy, the incidence of grade 3–5 and grade 5 TRAEs were 17.9% (2220 of 12,373 patients from 47 studies) and 0.8% (98 of 11,875 patients from 44 studies), respectively, and combinatorial therapy resulted in 46.3% (4573 of 9883 from 39 studies) and 1.4% (123 of 9071 from 36 studies), respectively.

The causes of the grade 5 TRAEs are presented in Supplemental Table S3. Of the 98 cases of

grade 5 TRAEs that occurred in the monotherapy cohort, the leading causes were respiratory ($n = 36$; 36.7%), gastroenteropancreatic ($n = 10$; 10.2%), and cardiovascular ($n = 9$; 9.2%) diseases. Of the 123 cases in the combinatorial treatment cohort, the leading causes were respiratory ($n = 26$; 21.1%), cardiovascular ($n = 10$; 8.1%), and infectious ($n = 10$; 8.1%) diseases. Pneumonitis was the most common cause of grade 5 TRAEs in patients receiving either monotherapy (16 out of 98; 16.3%) or combinatorial therapy (14 out of 123; 11.4%).

Conventional pairwise meta-analysis

The results of the pairwise meta-analysis are shown in Table 2. In terms of grade 3–5 TRAEs, monotherapies, including atezolizumab (OR = 0.25, 95% CI: 0.21–0.29), avelumab (OR = 0.14, 95% CI: 0.10–0.19), durvalumab (OR = 0.34, 95% CI: 0.25–0.45), nivolumab (OR = 0.21, 95% CI: 0.13–0.34), and pembrolizumab (OR = 0.27, 95% CI: 0.20–0.36), and the combination of durvalumab + tremelimumab (OR = 0.57, 95% CI: 0.47–0.74) were safer than CT. In addition, ICIs in combination with CT, including atezolizumab + CT (OR = 1.59, 95% CI: 1.37–1.84), ipilimumab + CT (OR = 2.24, 95% CI: 1.13–4.47), and pembrolizumab + CT (OR = 1.89, 95% CI: 1.15–3.09) were more toxic than CT alone. The durvalumab + tremelimumab combination was more toxic than durvalumab monotherapy (OR = 1.76, 95% CI: 1.33–2.34), the nivolumab + ipilimumab combination was more toxic than ipilimumab monotherapy (OR = 4.04, 95% CI: 2.96–5.51) and nivolumab monotherapy (OR = 2.69, 95% CI: 1.69–4.28), and the pembrolizumab + CT combination was more toxic than pembrolizumab monotherapy (OR = 12.57, 95% CI: 9.40–16.80). Atezolizumab and avelumab caused less grade 5 TRAEs than CT alone (OR = 0.38, 95% CI: 0.15–0.98 and OR = 0.26, 95% CI: 0.09–0.76, respectively); the nivolumab + ipilimumab combination caused more grade 5 TRAEs than nivolumab monotherapy (OR = 2.64, 95% CI: 1.13–6.14). Obvious heterogeneity was observed for grade 3–5 TRAEs in avelumab *versus* CT, nivolumab *versus* CT, pembrolizumab *versus* CT, durvalumab *versus* tremelimumab, ipilimumab + CT *versus* CT, pembrolizumab + CT *versus* CT, nivolumab + ipilimumab *versus* nivolumab monotherapy, and durvalumab + tremelimumab *versus* tremelimumab monotherapy ($I^2 = 56$–90%). No heterogeneity was observed for grade 5 TRAEs in all comparisons, except atezolizumab + AT *versus* AT ($I^2 = 51\%$).

Network meta-analysis

Figure 2 shows the network of eligible comparisons for grade 3–5 and grade 5 TRAEs. Results of the network meta-analysis are presented in Figure 3. In terms of grade 3–5 TRAEs, ICIs in combination with CT (atezolizumab + CAT, pembrolizumab + CT, ipilimumab + CT, and atezolizumab + CT) were more toxic than all monotherapies (pembrolizumab, nivolumab, durvalumab, atezolizumab, avelumab, ipilimumab, and tremelimumab); pembrolizumab + AT, avelumab + AT, and nivolumab + ipilimumab were more toxic than all ICI monotherapy regimens except tremelimumab and ipilimumab; durvalumab + CT and atezolizumab + AT were more toxic than atezolizumab, nivolumab, and avelumab; and durvalumab + tremelimumab was more toxic than durvalumab and avelumab. CT was more toxic than all ICIs when used as monotherapy (except tremelimumab), and pembrolizumab + RT. Pembrolizumab + CT and ipilimumab + CT were more toxic than CT. Among the combinatorial treatments, ICIs in combination with CT (except durvalumab + CT) were more toxic than dual ICI therapy (nivolumab + ipilimumab and durvalumab + tremelimumab) as well as ICI + RT (pembrolizumab + RT and nivolumab + RT). Moreover, pembrolizumab + AT and avelumab + AT were more toxic than pembrolizumab + RT and nivolumab + RT, respectively. Among ICIs used as monotherapies, tremelimumab was more toxic than avelumab. With regard to grade 5 TRAEs, atezolizumab + CAT, ipilimumab + CT, atezolizumab + CT, and nivolumab + ipilimumab showed higher risk of grade 5 TRAEs than nivolumab, atezolizumab, and avelumab; atezolizumab + CAT also had a higher risk of grade 5 TRAEs than pembrolizumab, CT, and pembrolizumab + AT; durvalumab + CT, pembrolizumab + CT, and CT alone were associated with a higher risk of grade 5 TRAEs than atezolizumab and avelumab. Tremelimumab was more toxic than the other ICIs when used as monotherapy, except durvalumab and ipilimumab; pembrolizumab was more toxic than atezolizumab and avelumab. All results mentioned above were statistically significant with the ORs and lower limits of 95% CIs greater than 1.

Table 2. Results of direct comparison meta-analysis.

Treatment	No. of study	No. of patients (E/C)	OR(95%CI)	Heterogeneity I^2 (%)
Grade 3–5 TRAEs				
Ate *versus* CT	4	1496/1419	**0.25(0.21–0.29)**	48
Ave *versus* CT	2	577/542	**0.14(0.10–0.19)**	70
Dur *versus* CT	2	613/622	**0.34(0.25–0.45)**	0
Niv *versus* CT	9	2332/2012	**0.21(0.13–0.34)**	90
Pem *versus* CT	9	3205/2556	**0.27(0.20–0.36)**	80
Dur *versus* Tre	2	89/77	0.26(0.02–2.69)	72
Ate+CT *versus* CT	5	1748/1474	**1.59(1.37–1.84)**	43
Ipi+CT *versus* CT	5	1335/1197	**2.24(1.13–4.47)**	92
Pem+CT *versus* CT	4	999/794	**1.89(1.15–3.09)**	57
Dur+Tre *versus* CT	2	620/622	**0.57(0.44–0.74)**	0
Dur+Tre *versus* Dur	4	780/705	**1.76(1.33–2.34)**	14
Niv+Ipi *versus* Ipi	2	407/357	**4.04(2.96–5.51)**	0
Niv+Ipi *versus* Niv	7	1441/1136	**2.69(1.69–4.28)**	82
Pem+CT *versus* Pem	2	538/557	**12.57(9.40–16.80)**	0
Pem+RT *versus* Pem	2	71/73	1.04(0.16–6.91)	81
Dur+Tre *versus* Tre	2	185/77	0.73(0.37–1.44)	56
Ate+AT *versus* AT	2	552/546	**0.58(0.45–0.73)**	0
Ipi *versus* placebo	2	792/595	**12.5(8.0–19.7)**	0
Grade 5 TRAEs				
Ate *versus* CT	4	1498/1421	**0.38(0.15–0.98)**	0
Ave *versus* CT	2	577/542	**0.26(0.09–0.76)**	0
Niv *versus* CT	9	2335/2015	0.56(0.28–1.11)	0
Pem *versus* CT	8	2950/2307	0.94(0.59–1.50)	0
Dur *versus* Tre	2	91/79	0.72(0.04–11.86)	0
Ate+CT *versus* CT	5	1748/1474	1.68(0.88–3.18)	0
Ipi+CT *versus* CT	5	1337/1199	2.14(0.83–5.51)	0
Pem+CT *versus* CT	3	743/545	1.21(0.30–4.95)	0
Dur+Tre *versus* Dur	4	589/493	0.98(0.16–6.09)	0
Niv+Ipi *versus* Ipi	2	408/358	2.61(0.41–16.65)	0
Niv+Ipi *versus* Niv	7	1443/1138	**2.64(1.13–6.14)**	0
Pem+RT *versus* Pem	2	73/75	0.51(0.05–5.77)	0
Dur+Tre *versus* Tre	2	187/79	0.80(0.07–8.64)	0
Ate+AT *versus* AT	2	553/547	1.85(0.50–6.83)	51
Ipi *versus* placebo	2	794/597	**9.5(1.2–73.9)**	0

Significant results are in bold.
AT, antiangiogenic therapy; Ate, atezolizumab; Ave, avelumab; CI, confidence interval; CT, chemotherapy; Dur, durvalumab; E/C, experimental/control; Ipi, ipilimumab; Niv, nivolumab; No., number; OR, odds ratio; Pem, pembrolizumab; TRAEs, treatment-related adverse events; Tre, tremelimumab; RT, radiotherapy.

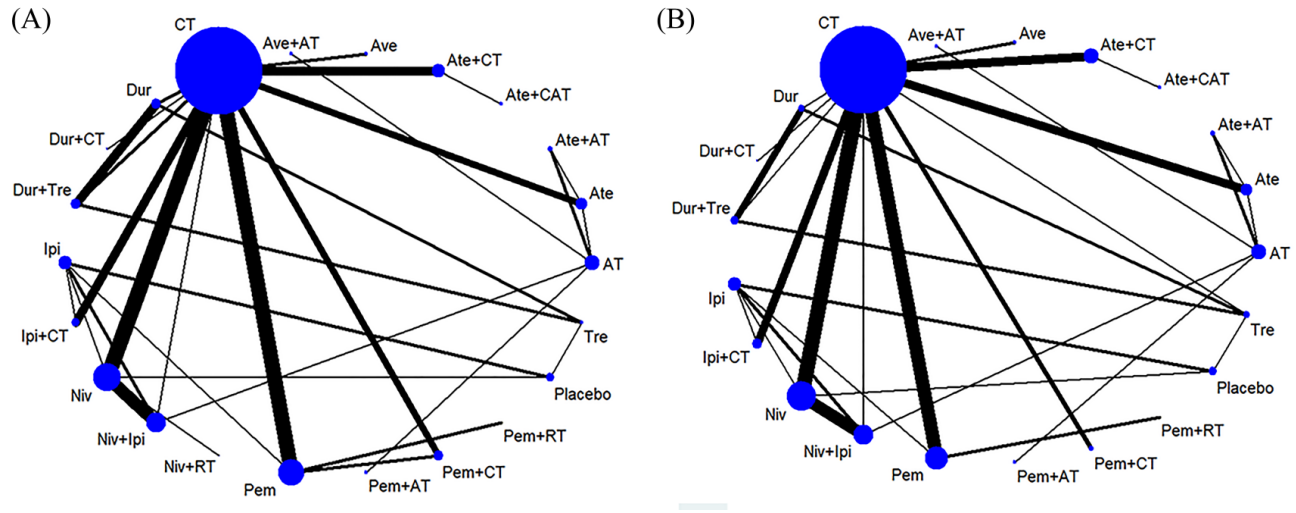


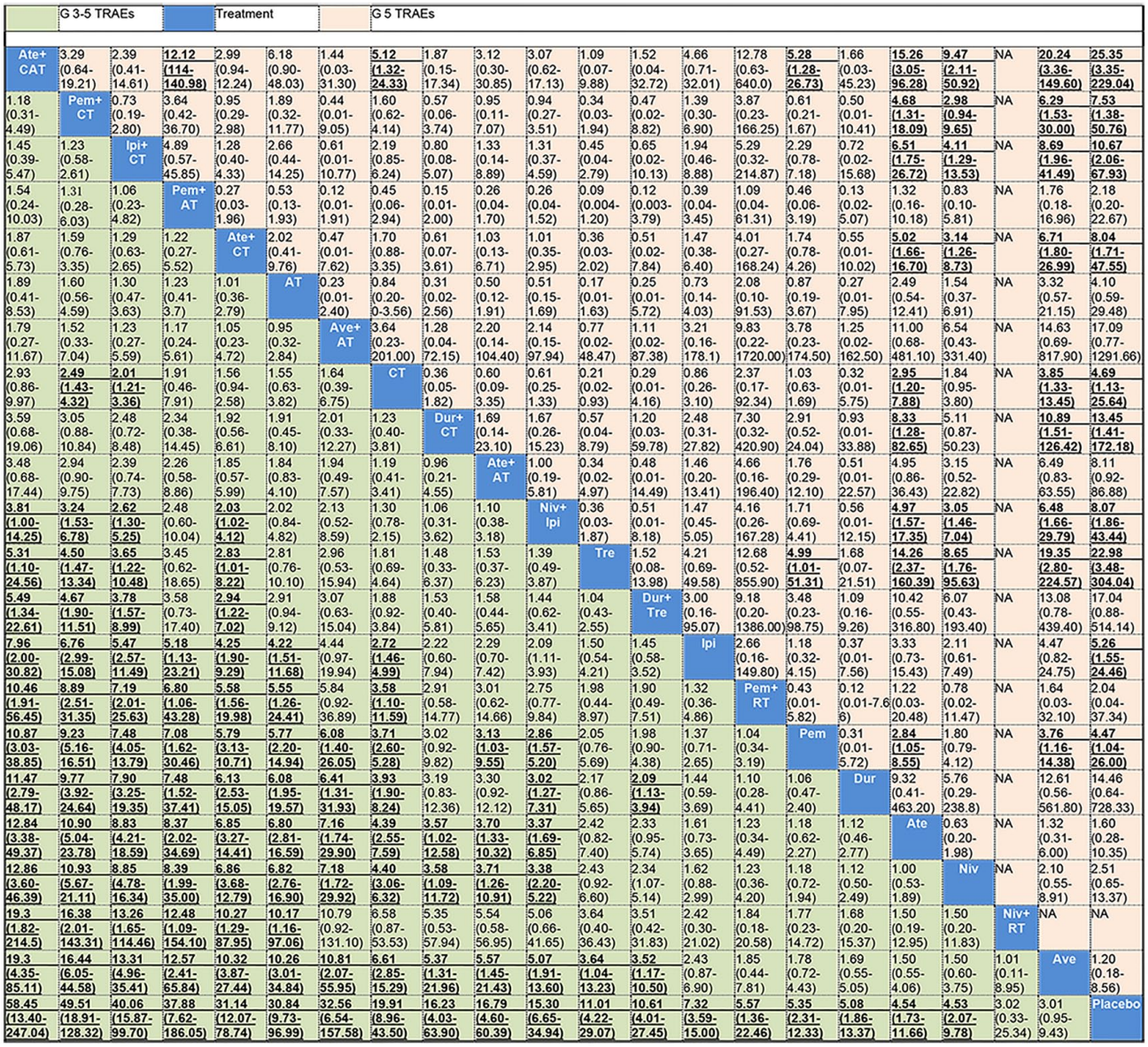
Figure 2. Network of eligible comparisons for the network meta-analysis. (A) Grade 3–5 TRAEs. (B) Grade 5 TRAEs.
AT, antiangiogenic therapy; Ate, atezolizumab; Ave, avelumab; CAT, CT+AT; CT, chemotherapy; Dur, durvalumab; Ipi, ipilimumab; Niv, nivolumab; Pem, pembrolizumab; RT, radiotherapy; TRAEs, treatment-related adverse events; Tre, tremelimumab.

Results of the toxicity ranking based on SUCRA are presented in Table 3, and ranking curves are shown in Supplemental Figure S3. Atezolizumab + CAT (91.2%) was ranked the most toxic treatment in terms of grade 3–5 TRAEs, followed by pembrolizumab + CT (90.9%), ipilimumab + CT (85.7%), pembrolizumab + AT(81.9%), and atezolizumab + CT (78.2%); avelumab (11.6%) was the least toxic treatment except placebo; and the nivolumab + RT combination was the least toxic combinatorial treatment. In terms of grade 5 TRAEs, atezolizumab + CAT (86.6%) was the most toxic treatment, followed by tremelimumab (84.5%), avelumab + AT (74.2%), durvalumab + CT (72.9%), and durvalumab + tremelimumab (72.2%); avelumab (10.6%) was also the least toxic treatment except placebo.

Transitivity, inconsistency, heterogeneity, and sensitivity analysis

Assessment of transitivity for grade 3–5 TRAEs indicated that the sample size, median age, and median follow-up times across treatment comparisons were relatively similar (Supplemental Figure S4). There were 13 independent closed loops with 32 comparisons in the network for grade 3–5 TRAEs, and 15 independent closed loops with 31 comparisons for grade 5 TRAEs. The design-by-treatment test for grade 3–5 TRAEs showed that there was no significantly global inconsistency ($p = 0.102$). However, tests of local inconsistency (loop-specific method and node-split model) showed that two of the loops (ipilimumab-nivolumab-placebo, $p = 0.003$; and pembrolizumab + CT-pembrolizumab-CT, $p = 0.009$) (Supplemental Table S4) and three of the comparisons (nivolumab + ipilimumab *versus* nivolumab, $p = 0.017$; nivolumab + ipilimumab *versus* ipilimumab monotherapy, $p = 0.005$; and ipilimumab *versus* placebo, $p = 0.018$) (Supplemental Table S5) were inconsistent. No significantly global ($p = 0.976$) or local inconsistencies (Supplemental Tables S4 and S5) were observed for grade 5 TRAEs.

The median heterogeneity, τ^2, were estimated at 0.29 (95% CI: 0.17–0.49) for grade 3–5 TRAEs, suggesting moderate heterogeneity; and 0.02 (95% CI: 0.01–0.23) for grade 5 TRAEs, suggesting low heterogeneity. The common heterogeneity standard deviation (SD) was 0.54 (95% CI: 0.41–0.70) for grade 3–5 TRAEs, and 0.14 (95% CI: 0.01–0.48) for grade 5 TRAEs. Subgroup meta-regression analyses for grade 3–5 TRAEs (Supplemental Table S6) revealed that the treatment choice and tumor type were the main sources of heterogeneity. Exclusion of patients receiving first-line therapy or including only patients with lung cancer resulted in 24.1% or 20.4%, respectively, relative reduction in heterogeneity SD. Sample size, control arm, and drug dose were also potential sources of heterogeneity. Excluding trials with a sample size <100 participants, or trials with a placebo-controlled



Ate+ CAT	3.29 (0.64-19.21)	2.39 (0.41-14.61)	**12.12 (114-140.98)**	2.99 (0.94-12.24)	6.18 (0.90-48.03)	1.44 (0.03-31.30)	**5.12 (1.32-24.33)**	1.87 (0.15-17.34)	3.12 (0.30-30.85)	3.07 (0.62-17.13)	1.09 (0.07-9.88)	1.52 (0.04-32.72)	4.66 (0.71-32.01)	12.78 (0.63-640.0)	**5.28 (1.28-26.73)**	1.66 (0.03-45.23)	**15.26 (3.05-96.28)**	**9.47 (2.11-50.92)**	NA	**20.24 (3.36-149.60)**	**25.35 (3.35-229.04)**
1.18 (0.31-4.49)	Pem+ CT	0.73 (0.19-2.80)	3.64 (0.42-36.70)	0.95 (0.29-2.98)	1.89 (0.32-11.77)	0.44 (0.01-9.05)	1.60 (0.62-4.14)	0.57 (0.06-3.74)	0.95 (0.11-7.07)	0.94 (0.27-3.51)	0.34 (0.03-1.94)	0.47 (0.02-8.82)	1.39 (0.30-6.90)	3.87 (0.23-166.25)	0.61 (0.21-1.67)	0.50 (0.01-10.41)	**4.68 (1.31-18.09)**	**2.98 (0.94-9.65)**	NA	**6.29 (1.53-30.00)**	**7.53 (1.38-50.76)**
1.45 (0.39-5.47)	1.23 (0.58-2.61)	Ipi+ CT	4.89 (0.57-45.85)	1.28 (0.40-4.33)	2.66 (0.44-14.25)	0.61 (0.01-10.77)	2.19 (0.85-6.24)	0.80 (0.08-5.07)	1.33 (0.14-8.89)	1.31 (0.37-4.59)	0.45 (0.04-2.79)	0.65 (0.02-10.13)	1.94 (0.46-8.88)	5.29 (0.32-214.87)	2.29 (0.78-7.18)	0.72 (0.02-15.68)	**6.51 (1.75-26.72)**	**4.11 (1.29-13.53)**	NA	**8.69 (1.96-41.49)**	**10.67 (2.06-67.93)**
1.54 (0.24-10.03)	1.31 (0.28-6.03)	1.06 (0.23-4.82)	Pem+ AT	0.27 (0.03-1.96)	0.53 (0.13-1.93)	0.12 (0.01-1.91)	0.45 (0.06-2.94)	0.15 (0.01-2.00)	0.26 (0.04-1.70)	0.26 (0.04-1.52)	0.09 (0.004-1.20)	0.12 (0.003-3.79)	0.39 (0.04-3.45)	1.09 (0.04-61.31)	0.46 (0.06-3.19)	0.13 (0.02-5.07)	1.32 (0.16-10.18)	0.83 (0.10-5.81)	NA	1.76 (0.18-16.96)	2.18 (0.20-22.67)
1.87 (0.61-5.73)	1.59 (0.76-3.35)	1.29 (0.63-2.65)	1.22 (0.27-5.52)	Ate+ CT	2.02 (0.41-9.76)	0.47 (0.01-7.62)	1.70 (0.88-3.35)	0.61 (0.07-3.61)	1.03 (0.13-6.71)	1.01 (0.35-2.95)	0.36 (0.03-2.02)	0.51 (0.02-7.84)	1.47 (0.38-6.40)	4.01 (0.27-168.24)	1.74 (0.78-4.26)	0.55 (0.01-10.02)	**5.02 (1.66-16.70)**	**3.14 (1.26-8.73)**	NA	**6.71 (1.80-26.99)**	**8.04 (1.71-47.55)**
1.89 (0.41-8.53)	1.60 (0.56-4.59)	1.30 (0.47-3.63)	1.23 (0.41-3.7)	1.01 (0.36-2.79)	AT	0.23 (0.01-2.40)	0.84 (0.20-3.56)	0.31 (0.02-2.56)	0.50 (0.12-1.91)	0.51 (0.15-1.69)	0.17 (0.01-1.63)	0.25 (0.01-5.72)	0.73 (0.14-4.03)	2.08 (0.10-91.53)	0.87 (0.19-3.67)	0.27 (0.01-7.95)	2.49 (0.54-12.41)	1.54 (0.37-6.91)	NA	3.32 (0.57-21.15)	4.10 (0.59-29.48)
1.79 (0.27-11.67)	1.52 (0.33-7.04)	1.23 (0.27-5.59)	1.17 (0.24-5.61)	1.05 (0.23-4.72)	0.95 (0.32-2.84)	Ave+ AT	3.64 (0.23-201.00)	1.28 (0.04-72.15)	2.20 (0.14-104.40)	2.14 (0.15-97.94)	0.77 (0.02-48.47)	1.11 (0.02-87.38)	3.21 (0.16-178.1)	9.83 (0.22-1720.00)	3.78 (0.23-174.50)	1.25 (0.02-162.50)	11.00 (0.68-481.10)	6.54 (0.43-331.40)	NA	14.63 (0.69-817.90)	17.09 (0.77-1291.66)
2.93 (0.86-9.97)	**2.49 (1.43-4.32)**	**2.01 (1.21-3.36)**	1.91 (0.46-7.91)	1.56 (0.94-2.58)	1.55 (0.63-3.82)	1.64 (0.39-6.75)	CT	0.36 (0.05-1.82)	0.60 (0.09-3.35)	0.61 (0.25-1.33)	0.21 (0.02-0.93)	0.29 (0.01-4.16)	0.86 (0.26-3.10)	2.37 (0.17-92.34)	1.03 (0.63-1.69)	0.32 (0.01-5.75)	**2.95 (1.20-7.88)**	1.84 (0.95-3.80)	NA	**3.85 (1.33-13.45)**	**4.69 (1.13-25.64)**
3.59 (0.68-19.06)	3.05 (0.88-10.84)	2.48 (0.72-8.48)	2.34 (0.38-14.45)	1.92 (0.56-6.61)	1.91 (0.45-8.10)	2.01 (0.33-12.27)	1.23 (0.40-3.81)	Dur+ CT	1.69 (0.14-23.10)	1.67 (0.26-15.23)	0.57 (0.04-8.79)	1.20 (0.03-59.78)	2.48 (0.31-27.82)	7.30 (0.32-420.90)	2.91 (0.52-24.04)	0.93 (0.01-33.88)	**8.33 (1.28-82.65)**	5.11 (0.87-50.23)	NA	**10.89 (1.51-126.42)**	**13.45 (1.41-172.18)**
3.48 (0.68-17.44)	2.94 (0.90-9.75)	2.39 (0.74-7.73)	2.26 (0.58-8.86)	1.85 (0.57-5.99)	1.84 (0.83-4.10)	1.94 (0.49-7.57)	1.19 (0.41-3.41)	0.96 (0.21-4.55)	Ate+ AT	1.00 (0.19-5.81)	0.34 (0.02-4.97)	0.48 (0.01-14.49)	1.46 (0.20-13.41)	4.66 (0.16-196.40)	1.76 (0.29-12.10)	0.51 (0.01-22.57)	4.95 (0.86-36.43)	3.15 (0.52-22.82)	NA	6.49 (0.83-63.55)	8.11 (0.92-86.88)
3.81 (1.00-14.25)	**3.24 (1.53-6.78)**	**2.62 (1.30-5.25)**	2.48 (0.60-10.04)	**2.03 (1.02-4.12)**	2.02 (0.84-4.82)	2.13 (0.52-8.59)	1.30 (0.78-2.15)	1.06 (0.31-3.62)	1.10 (0.38-3.18)	Niv+ Ipi	0.36 (0.03-1.87)	0.51 (0.01-8.18)	1.47 (0.45-5.05)	4.16 (0.26-167.28)	1.71 (0.69-4.41)	0.56 (0.01-12.15)	**4.97 (1.57-17.35)**	**3.05 (1.46-7.04)**	NA	**6.48 (1.66-29.79)**	**8.07 (1.86-43.44)**
5.31 (1.10-24.56)	**4.50 (1.47-13.34)**	**3.65 (1.22-10.48)**	3.45 (0.62-18.65)	**2.83 (1.01-8.22)**	2.81 (0.76-10.10)	2.96 (0.53-15.94)	1.81 (0.69-4.64)	1.48 (0.33-6.37)	1.53 (0.37-6.23)	1.39 (0.49-3.87)	Tre	1.52 (0.08-13.98)	4.21 (0.69-49.58)	12.68 (0.52-855.90)	**4.99 (1.01-51.31)**	1.68 (0.07-21.51)	**14.26 (2.37-160.39)**	**8.65 (1.76-95.63)**	NA	**19.35 (2.80-224.57)**	**22.98 (3.48-304.04)**
5.49 (1.34-22.61)	**4.67 (1.90-11.51)**	**3.78 (1.57-8.99)**	3.58 (0.73-17.40)	**2.94 (1.22-7.02)**	2.91 (0.94-9.12)	3.07 (0.63-15.04)	1.88 (0.92-3.84)	1.53 (0.40-5.81)	1.58 (0.44-5.65)	1.44 (0.62-3.41)	1.04 (0.43-2.55)	Dur+ Tre	3.00 (0.16-95.07)	9.18 (0.20-1386.00)	3.48 (0.23-98.75)	1.09 (0.16-9.26)	10.42 (0.55-316.80)	6.07 (0.43-193.40)	NA	13.08 (0.78-439.40)	17.04 (0.88-514.14)
7.96 (2.00-30.82)	**6.76 (2.99-15.08)**	**5.47 (2.57-11.49)**	**5.18 (1.13-23.21)**	**4.25 (1.90-9.29)**	**4.22 (1.51-11.68)**	4.44 (0.97-19.94)	**2.72 (1.46-4.99)**	2.22 (0.60-7.94)	2.29 (0.70-7.42)	2.09 (1.11-3.93)	1.50 (0.54-4.21)	1.45 (0.58-3.52)	Ipi	2.66 (0.16-149.80)	1.18 (0.32-4.15)	0.37 (0.01-7.56)	3.33 (0.73-15.43)	2.11 (0.61-7.49)	NA	4.47 (0.82-24.75)	**5.26 (1.55-24.46)**
10.46 (1.91-56.45)	**8.89 (2.51-31.35)**	**7.19 (2.01-25.63)**	**6.80 (1.06-43.28)**	**5.58 (1.56-19.98)**	**5.55 (1.26-24.41)**	5.84 (0.92-36.89)	**3.58 (1.10-11.59)**	2.91 (0.58-14.77)	3.01 (0.62-14.66)	2.75 (0.77-9.84)	1.98 (0.44-8.97)	1.90 (0.49-7.51)	1.32 (0.36-4.86)	Pem+ RT	0.43 (0.01-5.82)	0.12 (0.01-7.6 6)	1.22 (0.03-20.48)	0.78 (0.02-11.47)	NA	1.64 (0.03-32.10)	2.04 (0.04-37.34)
10.87 (3.03-38.85)	**9.23 (5.16-16.51)**	**7.48 (4.05-13.79)**	**7.08 (1.62-30.46)**	**5.79 (3.13-10.71)**	**5.77 (2.20-14.94)**	**6.08 (1.40-26.05)**	**3.71 (2.60-5.28)**	3.02 (0.92-9.82)	**3.13 (1.03-9.55)**	**2.86 (1.57-5.20)**	2.05 (0.76-5.69)	1.98 (0.90-4.38)	1.37 (0.71-2.65)	1.04 (0.34-3.19)	Pem	0.31 (0.01-5.72)	**2.84 (1.05-8.55)**	1.80 (0.79-4.12)	NA	**3.76 (1.16-14.38)**	**4.47 (1.04-26.00)**
11.47 (2.79-48.17)	**9.77 (3.92-24.64)**	**7.90 (3.25-19.35)**	**7.48 (1.52-37.41)**	**6.13 (2.53-15.05)**	**6.08 (1.95-19.57)**	**6.41 (1.31-31.93)**	**3.93 (1.90-8.24)**	3.19 (0.83-12.36)	3.30 (0.92-12.12)	**3.02 (1.27-7.31)**	2.17 (0.86-5.65)	**2.09 (1.13-3.94)**	1.44 (0.59-3.69)	1.10 (0.28-4.41)	1.06 (0.47-2.40)	Dur	9.32 (0.41-463.20)	5.76 (0.29-238.8)	NA	12.61 (0.56-561.80)	14.46 (0.64-728.33)
12.84 (3.38-49.37)	**10.90 (5.04-23.78)**	**8.83 (4.21-18.59)**	**8.37 (2.02-34.69)**	**6.85 (3.27-14.41)**	**6.80 (2.81-16.59)**	**7.16 (1.74-29.90)**	**4.39 (2.55-7.59)**	**3.57 (1.02-12.58)**	**3.70 (1.33-10.32)**	**3.37 (1.69-6.85)**	2.42 (0.82-7.40)	2.33 (0.95-5.74)	1.61 (0.73-3.65)	1.23 (0.34-4.49)	1.18 (0.62-2.27)	1.12 (0.46-2.77)	Ate	0.63 (0.20-1.98)	NA	1.32 (0.31-6.00)	1.60 (0.28-10.35)
12.86 (3.60-46.39)	**10.93 (5.67-21.11)**	**8.85 (4.78-16.34)**	**8.39 (1.99-35.00)**	**6.86 (3.68-12.79)**	**6.82 (2.76-16.90)**	**7.18 (1.72-29.92)**	**4.40 (3.06-6.32)**	**3.58 (1.09-11.72)**	**3.71 (1.26-10.91)**	**3.38 (2.20-5.22)**	2.43 (0.92-6.60)	2.34 (1.07-5.14)	1.62 (0.88-2.99)	1.23 (0.36-4.20)	1.18 (0.72-1.94)	1.12 (0.50-2.49)	1.00 (0.53-1.89)	Niv	NA	2.10 (0.55-8.91)	2.51 (0.65-13.37)
19.3 (1.82-214.5)	**16.38 (2.01-143.31)**	**13.26 (1.65-114.46)**	**12.48 (1.09-154.10)**	**10.27 (1.29-87.95)**	**10.17 (1.16-97.06)**	10.79 (0.92-131.10)	6.58 (0.87-53.53)	5.35 (0.53-57.94)	5.54 (0.58-56.95)	5.06 (0.66-41.65)	3.64 (0.40-36.43)	3.51 (0.42-31.83)	2.42 (0.30-21.02)	1.84 (0.18-20.58)	1.77 (0.23-14.72)	1.68 (0.20-15.37)	1.50 (0.19-12.95)	1.50 (0.20-11.83)	Niv+ RT	NA	NA
19.3 (4.35-85.11)	**16.44 (6.05-44.58)**	**13.31 (4.96-35.41)**	**12.57 (2.41-65.84)**	**10.32 (3.87-27.44)**	**10.26 (3.01-34.84)**	**10.81 (2.07-55.95)**	**6.61 (2.85-15.29)**	**5.37 (1.31-21.96)**	**5.57 (1.45-21.43)**	**5.07 (1.91-13.60)**	**3.64 (1.04-13.23)**	**3.52 (1.17-10.50)**	2.43 (0.87-6.90)	1.85 (0.44-7.81)	1.78 (0.72-4.43)	1.69 (0.55-5.05)	1.50 (0.55-4.06)	1.50 (0.60-3.75)	1.01 (0.11-8.95)	Ave	1.20 (0.18-8.56)
58.45 (13.40-247.04)	**49.51 (18.91-128.32)**	**40.06 (15.87-99.70)**	**37.88 (7.62-186.05)**	**31.14 (12.07-78.74)**	**30.84 (9.73-96.99)**	**32.56 (6.54-157.58)**	**19.91 (8.96-43.50)**	**16.23 (4.03-63.90)**	**16.79 (4.60-60.39)**	**15.30 (6.65-34.94)**	**11.01 (4.22-29.07)**	**10.61 (4.01-27.45)**	**7.32 (3.59-15.00)**	**5.57 (1.36-22.46)**	**5.35 (2.31-12.33)**	**5.08 (1.86-13.37)**	**4.54 (1.73-11.66)**	**4.53 (2.07-9.78)**	3.02 (0.33-25.34)	3.01 (0.95-9.43)	Placebo

Figure 3. Treatments are reported in order of risk of grade 3–5 TRAEs ranking from high to low according to SUCRAs. Comparisons should be read from left to right. Data are ORs (95% CI) in the column-defining treatment compared with the row-defining treatment. An OR over 1 favors the row-defining treatment. Significant results are in bold and underlined.
AT, antiangiogenic therapy; Ate, atezolizumab; Ave, avelumab; CAT, CT+AT; CI, confidecned interval; CT, chemotherapy; Dur, durvalumab; Ipi, ipilimumab; Niv, nivolumab; OR, odds ratio; Pem, pembrolizumab; RT, radiotherapy; SUCRA, surface under the cumulative ranking; TRAEs, treatment-related adverse events; Tre, tremelimumab.

design, or dividing treatments of nivolumab + ipilimumab into two dose groups resulted in 3.7%, 3.7%, or 5.6% relative reduction in heterogeneity SD, respectively.

Sensitivity analysis (Table 3) conducted by omitting trials with high risk of bias ($n=12$), with sample size <100 ($n=6$), or with placebo-controlled arms ($n=4$) did not affect the main results of toxicity ranking substantially for both grade 3–5 and grade 5 TRAEs. Sensitivity analysis dividing treatments of nivolumab + ipilimumab into two dose groups or pembrolizumab into three dose groups resulted in slight changes in the ranking order of nivolumab + ipilimumab or pembrolizumab for either grade 3–5 or grade 5 TRAEs, without obvious changes in the ranking order of other treatments.

Table 3. SUCRA values of grade 3–5 and grade 5 TRAEs for overall and sensitivity analysis.

Treatment	Overall	Sensitivity analysis				
		Excluding trials of high risk of bias	Excluding trials of sample size <100	Excluding trials of placebo-controlled	Dividing Niv+Ipi into two dose groups	Dividing Pem into three dose groups
Grade3–5						
Ate+CAT	91.2	91.0	90.8	91.0	93.0	92.0
Pem+CT	90.9	90.3	89.9	90.4	92.9	90.7
Ipi+CT	85.7	87.9	87.3	84.2	88.4	87.2
Pem+AT	81.9	81.6	79.5	79.8	77.8	83.8
Ate+CT	78.2	78.0	76.4	76.7	80.6	79.9
AT	78.1	77.6	74.9	75.4	73.1	80.4
Ave+AT	77.9	77.7	75.3	75.4	73.5	80.1
CT	64.7	65.3	62.3	61.4	66.1	67.3
Dur+CT	58.6	59.5	56.3	55.4	59.6	60.7
Ate+AT	58.5	56.7	54.8	54.3	53.6	61.6
Niv+Ipi	56.2	55.8	50.9	50.2	a (44.8), b (70.9)	60.1
Tre	47.8	47.4	43.0	60.5	48.8	50.6
Dur+Tre	46.5	47.4	41.5	47.4	47.0	49.0
Ipi	35.9	32.2	27.7	23.0	38.9	40.6
Pem+RT	27.9	28.5	-	23.3	27.2	25.2
Pem	25.9	26.9	23.0	21.9	24.8	c (21.0), d (32.2) e (40.4)
Dur	23.7	24.5	23.5	25.6	23.2	24.5
Ate	20.3	21.1	17.4	16.6	17.6	20.6
Niv	19.6	19.7	16.1	16.2	19.2	20.5
Niv+RT	17.9	17.9	-	14.1	17.5	18.4
Ave	11.6	12.3	9.3	7.4	10.6	11.3
Placebo	1.0	0.8	0.1	-	1.0	1.0
Grade 5						
Ate+CAT	86.6	86.9	87.2	85.1	87.1	88.0
Tre	84.5	86.2	83.9	86.6	84.7	86.7
Ave+AT	74.2	75.3	71.0	73.9	73.6	71.2
Dur+CT	72.9	73.9	72.2	71.5	72.0	74.7

(Continued)

Table 3. (Continued)

Treatment	Overall	Sensitivity analysis				
		Excluding trials of high risk of bias	Excluding trials of sample size <100	Excluding trials of placebo-controlled	Dividing Niv+Ipi into two dose groups	Dividing Pem into three dose groups
Dur+Tre	72.2	73.0	68.7	73.3	70.9	72.7
Ipi+CT	69.7	70.4	70.4	65.9	67.4	70.7
Dur	69.1	68.9	64.6	71.1	68.0	70.0
Niv+Ipi	62.2	64.6	62.5	58.9	a (63.0), b (57.5)	64.4
Ate+CT	62.1	62.7	62.3	60.5	61.6	64.9
Ate+AT	60.1	34.0	60.0	58.8	60.3	61.3
Pem+CT	59.4	59.7	58.8	57.8	59.5	61.5
Ipi	48.1	47.9	43.0	30.9	46.9	49.7
CT	42.1	42.8	41.7	40.0	41.4	44.5
Pem	41.4	42.3	41.0	39.2	40.5	c (46.3), d (30.3) e (40.4)
AT	38.3	45.2	37.4	36.7	38.2	39.6
Pem+RT	26.9	27.4	-	25.4	28.5	29.7
Niv	23.6	24.7	22.6	21.8	23.1	25.0
Pem+AT	23.2	29.2	22.5	21.9	23.0	23.8
Ate	14.3	14.5	13.9	12.5	14.2	15.4
Ave	10.6	10.8	8.8	7.9	10.0	10.0
Placebo	8.7	9.7	7.7	-	8.5	9.0

AT, antiangiogenic therapy; Ate, atezolizumab; Ave, avelumab; CAT, CT+AT; CT, chemotherapy; Dur, durvalumab; Ipi, ipilimumab; Niv, nivolumab; Pem, pembrolizumab; RT, radiotherapy; SUCRA, surface under the cumulative ranking; TRAEs, treatment-related adverse events; Tre, tremelimumab; a, Niv(3 mg)+Ipi(1 mg); b, Niv(1 mg)+Ipi(3 mg); c, Pem(200 mg); d, Pem(2 mg/kg); e, Pem(10 mg/kg).

Subgroup analysis according to the type and severity grade 3–5 TRAEs

Results of the subgroup analyses are shown in Supplemental Tables S7–14. In term of grade 3–5 respiratory TRAEs, pembrolizumab was more toxic than CT. In terms of grade 3–5 gastroenteropancreatic TRAEs, atezolizumab + CAT, pembrolizumab + CT, ipilimumab + CT, atezolizumab + CT, pembrolizumab + AT, atezolizumab + AT, avelumab + AT, nivolumab + ipilimumab, ipilimumab monotherapy, pembrolizumab monotherapy, CT, and AT were more toxic than monotherapy with nivolumab, atezolizumab, or avelumab; atezolizumab + CAT, pembrolizumab + CT, ipilimumab + CT, atezolizumab + CT, nivolumab + ipilimumab, and CT were also more toxic than pembrolizumab monotherapy; atezolizumab + CAT, pembrolizumab + CT, and ipilimumab + CT were also more toxic than durvalumab + CT; the combination of ipilimumab + CT was also more toxic than atezolizumab + CT, nivolumab + ipilimumab, CT, ipilimumab monotherapy, atezolizumab + AT, and pembrolizumab + RT; atezolizumab + AT was more toxic than avelumab monotherapy; tremelimumab was also more toxic than monotherapy with avelumab

or atezolizumab. As for grade 3–5 hepatic TRAEs, ipilimumab + CT and nivolumab + ipilimumab were more toxic than monotherapy with ipilimumab, pembrolizumab, nivolumab, avelumab, or CT; durvalumab + CT and atezolizumab + CT were more toxic than CT. Regarding grade 3–5 neurological TRAEs, atezolizumab + CT was more toxic than monotherapy with pembrolizumab, nivolumab, atezolizumab, or avelumab; CT was more toxic than monotherapy with pembrolizumab or atezolizumab. As for grade 3–5 endocrine TRAEs, durvalumab + CT, nivolumab + ipilimumab, pembrolizumab + CT, atezolizumab + CT, ipilimumab, and pembrolizumab monotherapy were more toxic than CT; nivolumab + ipilimumab and ipilimumab monotherapy were also more toxic than nivolumab monotherapy; pembrolizumab + AT was more toxic than AT. For grade 3–5 skin TRAEs, nivolumab + ipilimumab and ipilimumab + CT were more toxic than monotherapy with pembrolizumab, nivolumab, CT, and AT; ipilimumab monotherapy was also more toxic than CT. With regard to grade 3–5 hematological TRAEs, durvalumab + CT, atezolizumab + CT, pembrolizumab + CT, ipilimumab + CT, CT, and AT were more toxic than avelumab monotherapy; durvalumab + CT, atezolizumab + CT, ipilimumab + CT, and CT were also more toxic than monotherapy with nivolumab or pembrolizumab. All results mentioned above were statistically significant with the ORs and lower limits of 95% CIs greater than 1. No significant differences were observed in grade 3–5 renal TRAEs among all treatments.

The safety ranking based on SUCRA (Table 4) showed that pembrolizumab monotherapy, atezolizumab + CAT, durvalumab + CT, avelumab, nivolumab + ipilimumab, pembrolizumab + AT, atezolizumab + CT, and AT were ranked the most toxic regimens for respiratory, gastroenteropancreatic, hepatic, renal, skin, endocrine, neurological, and hematological grade 3–5 TRAEs, respectively.

Discussion

To our knowledge, this is the largest and most comprehensive network meta-analysis conducted to assess the comparative safety of ICIs. Compared with the previous meta-analysis on this subject, our network meta-analysis included more recent studies, as well as the information reported in the predominant oncology congresses of 2019, more patients, and compared nearly all ICI-based treatments used in cancers. Moreover, this network meta-analysis focused on individual ICIs rather than ICI classes, selecting TRAEs instead of irAEs as the outcome of interest, and assessing the risk of grade 3–5 and grade 5 TRAEs separately. This network meta-analysis included 67 RCTs involving 36,422 patients and compared 19 ICIs. The incidence of grade 3–5 and grade 5 TRAEs were 17.9% and 0.8%, respectively, for monotherapy with an ICI, and were 46.3% and 1.4%, respectively, for combinatorial therapy. Pneumonitis was the most common cause of grade 5 TRAEs for patients receiving either monotherapy (16 out of 98; 16.3%) or combinatorial therapy (14 out of 123; 11.4%). Most of combinatorial treatments (ICI + CT, or AT, or another ICI) showed a significantly higher risk for grade 3–5 TRAEs than most of ICI-based monotherapy regimens. However, no significant differences were observed between several monotherapy regimens (tremelimumab, ipilimumab, durvalumab, and pembrolizumab) and combinatorial treatments in risk of grade 5 TRAEs, and tremelimumab was ranked the second-most toxic treatment among all treatments. Compared with grade 3–4 TRAEs, grade 5 TRAEs are uncommon. Individual clinical trials cannot characterize these rare toxic effects comprehensively, and the comparative risk of fatal TRAEs in ICI-based therapies is still not fully understood. Our findings suggested that although monotherapy was generally safer than a combinatorial treatment, a number of them seemed to be associated with an even higher risk of grade 5 TRAEs, which suggests that monitoring for adverse events is important.

Although CTLA-4 inhibitors are generally considered to be more toxic, and PD-L1 inhibitors are generally considered to be better tolerated because of their programmed cell death ligand-2-sparing ability that preserves the normal immunological homeostasis among ICIs used as monotherapy,[3,5,96,97] the lack of head-to-head comparisons prevents us from making a firm conclusion. In a systematic analysis of the toxicity profile of PD-1 *versus* PD-L1 Inhibitors in non-small cell lung cancer,[98] patients treated with PD-1 inhibitors had an increased rate of irAEs (16% *versus* 11%, $p = 0.07$) and pneumonitis (4% *versus* 2%, $p = 0.01$) compared with patients who received PD-L1 inhibitors. However, in our network meta-analysis, no significant differences in the risk of grade 3–5 TRAEs were observed between PD-1 and PD-L1 inhibitors. Tremelimumab showed a significantly higher risk of grade 3–5 TRAEs than

Table 4. SUCRA values according to type of grade3–5 TRAEs.

Respiratory		Gastroentero-pancreatic		Hepatic		Renal		Skin		Endocrine		Neurological		Hematological	
Treatment	**SUCRA**	**Treatment**	**SUCRA**	**Treatment**	**SUCRA**	**Treatment**	**SUCRA**	**Treatment**	**SUCRA**	**Treatment**	**SUCRA**	**Treatment**	**SUCRA**	**Treatment**	**SUCRA**
Pem	81.2	Ate+CAT	90.2	Dur+CT	85.8	Ave	73.6	Niv+Ipi	87.8	Pem+AT	87.2	Ate+CT	91.9	Dur+CT	81.9
Pem+CT	68.1	Ipi+CT	88.7	Ipi+CT	84.7	Ipi+CT	72.6	Ipi+CT	84.2	Dur+CT	73.4	Ipi+CT	77	AT	79.2
Niv+Ipi	67.3	Pem+CT	79.9	Niv+Ipi	84.3	Niv+Ipi	68.4	Pem+RT	83.7	Ipi	68.6	CT	71.8	Ate+CT	76.5
Dur+CT	61.4	Pem+AT	76.3	Ate+CAT	67.2	Ate+CT	62.3	Ipi	75.4	Niv+Ipi	67.3	Niv+Ipi	42.8	CT	72.5
Pem+RT	61.1	Tre	73.4	Pem+CT	58.9	Pem+CT	55.2	Ate+CT	63.7	Pem+CT	65.7	Niv	41.7	Pem+CT	70.7
Ate+CAT	56.5	Ave+AT	70.3	Ate+CT	55.1	Pem	54.7	Ate+CAT	51.7	Ate+CAT	64.3	Pem	32.3	Ipi+CT	70.6
Niv	48.2	Ate+CT	66.1	Pem+RT	43.5	Pem+RT	51.1	Pem+CT	48.4	Ave	51	Ate	21.5	Ate+AT	48.6
Ate+CT	46.9	AT	64.6	Niv	41	Ipi	39.4	Pem	47.3	Ate+CT	48.8	Ave	21.1	Ate	42.5
Ipi	35.5	Dur+Tre	63.3	Pem	38.3	Dur+CT	39.1	Niv	46.0	Ave+AT	47.2			Ave+AT	36.6
CT	32.4	Niv+Ipi	62.9	Ipi	35.2	Niv	32.2	Dur+CT	44.3	Pem+RT	46.9			Pem+AT	34.2
Ave	25.8	CT	52.2	Ave	30.2	Placebo	25.9	Pem+AT	34.7	AT	45.5			Niv+Ipi	33.9
Placebo	15.6	Ipi	51.6	CT	15.3	CT	25.4	Placebo	34.1	Ate+AT	44.5			Ipi	32.5
		Ate+AT	41.2	Placebo	10.5			CT	31.9	Pem	44.3			Niv	31.9
		Pem	35.3					Ate+AT	27.7	Ate	39.7			Pem	30.3
		Dur+CT	31.1					Ave+AT	21.5	Placebo	33.4			Ave	8.1
		Pem+RT	27.1					AT	17.7	Niv	31.8				
		Dur	27							Ipi+CT	24.7				
		Niv	23.1							CT	15.6				
		Ave	11.1												
		Ate	9.9												
		Placebo	4.8												

AT, antiangiogenic therapy; Ate, atezolizumab; Ave, avelumab; CT, chemotherapy; Dur, durvalumab; Ipi, ipilimumab; Niv, nivolumab; Pem, pembrolizumab; RT, radiotherapy; SUCRA, surface under the cumulative ranking; TRAEs, treatment-related adverse events; Tre, tremelimumab.

avelumab. The toxicity of ICIs as monotherapy, in terms of grade 3–5 TRAEs ranked from high to low was: tremelimumab, ipilimumab, pembrolizumab, durvalumab, atezolizumab, nivolumab, and avelumab. In terms of grade 5 TRAEs, tremelimumab was more toxic than other ICIs except durvalumab and ipilimumab; and pembrolizumab was more toxic than atezolizumab and avelumab. The toxicity ranking of ICIs as monotherapy based on the risk of grade 5 TRAEs from high to low was: tremelimumab, durvalumab, ipilimumab, pembrolizumab, nivolumab, atezolizumab, and avelumab. These results suggested that tremelimumab and avelumab seemed to be the most and least toxic ICIs monotherapy, respectively, and that different ICIs in the same class might be related to different risks of serious TRAEs.

To date, few trials have directly compared the safety between ICI-based combinatorial treatments. In their network meta-analysis, Xu *et al.* concluded no significant difference was observed in the risk of all-grade and grade 3–5 TRAEs between the combination of two ICIs and one ICI with conventional therapy.[6] In our network meta-analysis, 12 combinatorial treatments were compared. There were no significant differences in either the risk of grade 3–5 or grade 5 TRAEs among combinatorial treatments with CT or AT, while two ICIs (durvalumab + tremelimumab or nivolumab + ipilimumab) showed lower risk of grade 3–5 TRAEs than ICIs in combination with CT (except durvalumab + CT). Based on toxicity rankings, atezolizumab + CAT, pembrolizumab + CT, and ipilimumab + CT were ranked the most, second-most, and third-most toxic regimens in term of grade 3–5 TRAEs, respectively. Moreover, we found that the comparative risk of grade 3–5 TRAEs for ICIs based treatments varied depending on the nature and degree of severity TRAEs. Pembrolizumab, atezolizumab + CAT, durvalumab + CT, avelumab, nivolumab + ipilimumab, pembrolizumab + AT, atezolizumab + CT, and durvalumab + CT were ranked the most toxic treatments in risk of respiratory, gastroenteropancreatic, hepatic, renal, skin, endocrine, neurological, and hematological grade 3–5 TRAEs, respectively. These findings will be helpful for physicians to tailor an ICI-based therapy strategy for patients with different clinical backgrounds. For example, although the overall risk of grade 3–5 TRAEs for pembrolizumab and avelumab monotherapy were lower than combinatorial treatments, they seemed to have the highest risk of respiratory and renal grade 3–5 TRAEs in our study respectively, and should be used with caution in patients with chronic lung or kidney diseases.

Several recent clinical trials have evaluated combinations of ICIs with RT in cancers.[54,62,63,99] The available data suggests that the combination has significantly improved survival compared with ICIs or RT alone. However, it is still not clear if combining ICIs with RT will increase the risk of TRAEs. In the present network meta-analysis, the risk of grade 3–5 TRAEs for pembrolizumab + RT or nivolumab + RT was similar to ICI monotherapy and was lower than other combinatorial treatments. Of note, current trials only represent a small fraction of the potential therapeutic combinations of ICIs with RT. Some factors such as treatment schedules of ICIs plus RT (concurrent or sequential), RT technique (SBRT or conventional RT), anatomic location irradiated (internal organs, bone, or brain), interval between treatments, and type of ICI used might affect the outcomes. Further clinical studies are needed to address these issues.

Some limitations of our network meta-analysis should be stated. First, heterogeneity was observed in the results of grade 3–5 TRAEs. Subgroup meta-regression analyses revealed that trials with a sample size <100 patients, cancer type, treatment line, and drug dose were potential sources of heterogeneity. However, sensitivity analysis showed that the main results for both grade 3–5 and grade 5 TRAEs were not markedly altered when removing trials of high risk of bias, sample size <100, or placebo-controlled, or dividing treatments of nivolumab + ipilimumab and pembrolizumab into different dose groups. Second, some trials reported TRAEs without the necessary details, and excluded reporting on TRAEs which occurred underneath a certain threshold (for example 1% or 5%). The missing information might result in bias. Moreover, different CT regimens and schedules used in individual trials might also lead to heterogeneity. Third, some of the newer data were extracted from recent conference abstracts. This could lead to a selection bias because the comprehensive toxicity data might be reported in the full publication. Fourth, TRAES refer to those adverse events which occur during the treatment, while irAEs mean those which have a putative immunological basis, and irAEs/TRAEs incidence might differ from each other. We selected TRAEs instead of

irAEs as the outcome of interest in this study because TRAEs are more suitable for identifying and describing the safety profiles of chemo-immunotherapy combinations. However, not using the irAEs profiles might result in missing/overlooking the true nature of the monotherapy safety profile (at least for clinical practice). Finally, the network meta-analysis was conducted based on results reported from trials rather than individual patient data, and they were based on indirect comparisons but not direct comparisons. Thus, interpretation of the network meta-analysis results and drawing conclusions should be done with caution.

Conclusion

Compared with ICI-based combinatorial therapy, monotherapy with an ICI had a lower risk of grade 3–5 TRAEs, but some of them resulted in an even higher risk of fatal TRAEs. Some ICIs combined with CT seemed to be more toxic than the combination with RT or combination of two ICIs. Atezolizumab + CAT seemed to be the most toxic and nivolumab + RT seemed to be the least toxic among the combinatorial treatments, and among the monotherapy regimens, tremelimumab and avelumab seemed to be the most and least toxic, respectively. The toxicity ranking of some treatments changed depending on the nature and degree of severity of grade 3–5 TRAEs.

Author contributions

DJ contributed to the conception and design, data interpretation, and statistical analysis. LT and JB contributed to data acquisition, data interpretation, and statistical analysis and drafting of the manuscript. CJ, WH, LS, and LG contributed to data acquisition, data interpretation, and drafting of the manuscript. All authors read and approved the final manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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