Supplementary Table S1. Checklist of the PRISMA extension for network meta-analysis

Section/topic	Item #	Checklist item*	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	**3–4**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	**5–8**
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**5–8**
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	**4 & 8**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	**9–10**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**9–10**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**Appendix page 5**

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**9–10**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**10–11**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**10–11**
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	**12**
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**12–13**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	**11–13**
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	**10–13**
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	**12–13**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**13**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	**13**

RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**14**
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	**14**
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	**14–15**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**15**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	**Appendix page 12–13**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	**Appendix page 29–30**
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	**15–17**
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	**16–17**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	**15–17**
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	**17–19**
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	**20**

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	**20–25**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**25**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	**26**

PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analysis. PICOS=population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Search strategy

((((((((((((((((((Immune Checkpoint Inhibitor[title] OR immune therapy[title]) OR immunotherapy[title]) OR ipilimumab[title]) OR tremelimumab[title]) OR nivolumab[title]) OR pembrolizumab[title]) OR atezolizumab[title]) OR durvalumab[title]) OR avelumab[title]) OR cytotoxic T-lymphocyte associated antigen-4[title]) OR CTLA-4[title]) OR programmed cell death protein-1[title]) OR programmed cell death protein[title]) OR PD-1[title]) OR programmed cell death-Ligand 1[title]) OR PD-L1[title])) AND ((((((((((cancer[title]) OR carcinoma[title]) OR neoplasm[Title]) OR leukemia[title]) OR lymphoma[title]) OR melanoma[title]) OR malignancy[title]) OR malignancies[title]) OR tumor[title]) OR tumors[title]) AND (((((((versus[title/abstract]) OR vs[title/abstract]) OR compare[title/abstract]) OR comparison[title/abstract]) OR comparative[title/abstract]) OR comparing[title/abstract]) OR trial[title/abstract]) OR phase[title/abstract]))) AND English[Language])) AND ("2007/01/01"[Date - Publication] : "2018/02/28"[Date - Publication]))

Establishment of the validation group

We used the head-to-head phase II–III randomized controlled trials included in our network meta-analysis to calculate the pooled incidence of all-grade/grade 3–4 treatment-related adverse events (trAEs) for all treatments. Since ICIs have obtained accelerated approval for marketing in many cancers via single-arm and placebo-controlled trials, we aimed to select corresponding high-quality studies to establish a validation group for additional meta-analysis of the pooled incidence.

Based on the search strategy described previously, we also included single-arm trials and placebo-controlled trials of any one of the five immune checkpoint inhibitors (ICIs) in cancer patients, that is, nivolumab, ipilimumab, tremelimumab, pembrolizumab, and atezolizumab. Conference abstract/poster/presentations of ongoing trials were excluded because these brief reports contained almost no detailed safety data. Trials providing a summary but no site/organ/system-level toxicity data were also excluded. High-quality trials should meet all four of the following requirements: phase II/III, multinational study, reporting detailed trAEs, and the sample size of more than 100 patients. Each requirement was assigned one score; studies with a score of 4 were eligible. Two reviewers (CX and XJD) used a standardized form independently to extract and summarize the following data: first author, year of publication, study ID, region, cancer type, study design, total number of patients, number of patients in the safety analysis, arms and treatment regimens, name and version of the criteria evaluating trAEs, follow-up time, trAE reporting rate, and the frequency of each specific all-grade/grade 3–4 trAE.

As shown in the flowchart in Figure 1, 36 potentially relevant studies were included, of which, thirty-three studies were single-arm[1-33] and three studies were placebo-controlled.[34-36] The quality assessment presented in Supplementary Table S1 showed that 6 single-arm trials[28-33] and 2 placebo-controlled trials[34,35] were evaluated as high-quality and eligible for inclusion in the validation group. Detailed baseline characteristics of all eight studies are presented in Supplementary Table S2. Tumor types studied in these trials included lung cancer (n = 2), melanoma (n = 1), urinary system cancer (n = 3), head and neck cancer (n = 1), and digestive system cancer (n = 1). ICI categories studied in these trials included nivolumab (n = 2), ipilimumab (n = 2), pembrolizumab (n = 1), and atezolizumab (n = 3). The median follow-up time was different for all included studies, ranging from 7.0 to 17.2 months.

The studies cited in Supplementary Table S2 and S3 were numbered according to the reference bibliography list. The studies cited in Supplementary Table S4 were numbered according to the order in the main text.

References

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Supplementary Table S2. Quality assessment of single-arm trials and placebo-controlled trials

First author-year	Phase II/III*	Multinational	Detailed trAEs†	No. of patients ≥100	Score
Single-arm trials					
Balar-2017[28]	Y	Y	Y	Y	4
Giaccone-2018[2]	Y	N	N	N	1
Haag-2018[4]	Y	N	N	N	1
Amin-2016[12]	Y	N	Y	N	2
Bauml-2017[29]	Y	Y	Y	Y	4
Chen-2017[13]	Y	Y	N	Y	3
Di Giacomo-2012[14]	Y	N	Y	N	2
Goldberg-2016[3]	Y	N	N	N	1
Hamanishi-2015[15]	Y	N	Y	N	2
Joshua-2015[17]	Y	N	Y	N	2
Kaufman-2016[5]	Y	Y	N	N	2
Kudo-2017[18]	Y	N	Y	N	2
Margolin-2012[6]	Y	N	N	N	1
Morris-2017[7]	Y	N	N	N	1
Nghiem-2016[8]	Y	N	N	N	1
Nishio-2016[20]	Y	N	Y	N	2
O'Day-2010[30]	Y	Y	Y	Y	4
Overman-2017[21]	Y	Y	Y	N	3
Patel-2017[9]	Y	N	N	N	1
Peters-2017[31]	Y	Y	Y	Y	4
Rizvi-2015[32]	Y	Y	Y	Y	4
Rosenberg-2016[33]	Y	Y	Y	Y	4
Sharma-2017[22]	Y	Y	N	Y	3
Yamazaki(1)-2015[23]	Y	N	Y	N	2
Yamazaki-2017[24]	Y	N	Y	N	2
Yamazaki(2)-2015[25]	Y	N	Y	N	2
Younes-2016[11]	Y	Y	N	N	2
Zimmer(1)-2015[27]	Y	N	Y	Y	3
Duffy-2017[1]	Y	N	N	N	1
Hida-2017[16]	Y	N	Y	N	2
Sangro-2013[10]	Y	N	N	N	1
Zimmer(2)-2015[26]	Y	N	Y	N	2
Maruyama-2017[19]	Y	N	Y	N	2
Placebo-controlled trials					
Kwon-2014[35]	Y	Y	Y	Y	4
Antonia-2017[36] ‡	Y	Y	Y	Y	4
Kang-2017[34]	Y	Y	Y	Y	4

TrAEs=treatment-related adverse events. No.=number. Y=yes. N=no.

* The requirement of phase II applies to single-arm trials; phase III, to placebo-controlled trials.

† "Detailed trAEs" indicates both the aggregate and site/organ/system-level data.

‡ Although this article meets the inclusion criteria, it was discarded as it studied durvalumab, which was not the research object for the network meta-analysis.

Supplementary Table S3. Baseline characteristics of high-quality single-arm (*n* = 6) and placebo-controlled trials (*n* = 2) for validation

First author-year	Study ID	Region	Cancer type	Trial phase	Total no.	Safety analysis no.	Arms and treatment regimens	Median FU time (mo)	CTCAE version	TrAE reporting rate*
Kwon-2014[35]	CA184-043	MN	Bone metastatic castration-resistant prostate cancer	III	799	393 396	Arm 1: Ipilimumab 10 mg/kg/3 wk Arm 2: Placebo	Arm 1: 9.9 Arm 2: 9.3	3.0	≥ 5%
Kang-2017[34]	ONO-4538-12	MN	Advanced gastric or gastro-esophageal junction cancer refractory to or intolerant of previous chemotherapy	III	493	330 161	Arm 1: Nivolumab 3 mg/kg/2 wk Arm 2: Placebo	Arm 1: 8.87 Arm 2: 8.59	4.0	≥ 2%
Balar-2017[28]	IMvigor210 (cohort 1)	MN	Untreated locally advanced/metastatic urothelial carcinoma	II	119	119	Atezolizumab 1200 mg/3 wk	17.2	4.0	NR
Bauml-2017[29]	Keynote 055	MN	Recurrent/metastatic HNSCC refractory to platinum and cetuximab	II	171	171	Pembrolizumab 200 mg/kg/3 wk	7.0	4.0	≥ 2%
Peters-2017[31]	BIRCH	MN	PD-L1–selected locally advanced/metastatic NSCLC	II	659	659	Atezolizumab 1200 mg/3 wk	14.6	4.0	≥ 1%
Rizvi-2015[32]	CheckMate 063	MN	Treated advanced/refractory squamous NSCLC	II	117	117	Nivolumab 3 mg/kg/2 wk	8.0	4.0	≥ 5%
Rosenberg-2016[33]	IMvigor210 (cohort 2)	MN	Treated locally advanced/metastatic urothelial carcinoma	II	310	310	Atezolizumab 1200 mg/3 wk	11.7	4.0	NR
O'Day-2010[30]	CA184-008	MN	Treated unresectable stage III/IV melanoma	II	155	155	Ipilimumab 10 mg/kg/3 wk	10.0	3.0	NR

No.=number. mo.=month. FU=follow-up. CTCAE=Common Terminology Criteria for Adverse Events. TrAE=treatment-related adverse event. MN=multinational. NSCLC=non-small-cell lung cancer. HNSCC=head and neck squamous-cell carcinoma. PD-L1=programmed death-ligand 1. wk=week. NR=not reported.

* Studies only reported the trAE with an incidence in any arm equal to or greater than the listed rate.

Supplementary Table S4. Quality assessment of the 31 studies (36 RCTs) for Bayesian network meta-analysis*

1st author-year	Adequate random sequence generation	Allocation concealment	Blinding method	Adequate assessment of each outcome	Free of selective reporting	Modified Jadad score†
Melanoma						
Weber-2017[7]	U	Y	Y	Y	Y	6
Wolchok-2017[8]/ Larkin-2015[9]	U	U	Y	Y	Y	5
Robert(1)-2015[10]/ Schachter-2017[11]	Y	Y	N	Y	Y	5
Larkin-2017[13]/ Weber-2015[14]	Y	Y	Y‡	Y	Y	7
Robert-2011[15]/ Maio-2015[16]	U	U	Y	Y	Y	5
Ascierto-2017[24]	Y	Y	Y	Y	Y	7
Postow-2015[28]/ Hodi-2016[29]	Y	Y	Y	Y	Y	7
Robert(2)-2015[32]	U	U	Y	Y	Y	5
Ribas-2015[33]	Y	Y	Y‡	Y	Y	7
Ribas-2013[37]	U	U	Y‡	Y	Y	5
Hersh-2011[40]	U	U	Y‡	Y	N	5
Hamid-2011[41]	U	U	Y	Y	Y	5
Wolchok-2010[42]	Y	Y	Y	Y	Y	7
Lung						
Rittmeyer-2017[12]	Y	N	N	Y	Y	3
Govindan-2017[18]	U	U	Y	Y	Y	5
Carbone-2017[21]	U	U	Y‡	Y	Y	5
Reck(1)-2016[25]	U	U	Y‡	Y	Y	5
Reck(2)-2016[26]	Y	Y	Y	Y	Y	7
Langer-2016[27]	Y	N	Y‡	Y	Y	5
Herbst-2016[30]	Y	N	N	Y	Y	3

Fehrenbacher-2016[31]	Y	N	N	Y	N	3
Brahmer-2015[34]	U	U	N	Y	Y	3
Borghaei-2015[35]	U	U	N	Y	Y	3
Reck-2013[38]	U	U	Y	Y	Y	5
Lynch-2012[39]	U	U	Y	Y	Y	5
Head and neck						
Ferris-2016[17]	U	U	Y‡	Y	Y	5
Urinary system						
Motzer(1)-2015[19]	U	U	Y‡	Y	Y	5
Motzer(2)-2015[20]	U	U	Y	Y	Y	5
Bellmunt-2017[22]	U	U	Y‡	Y	Y	5
Powles-2017[36]	Y	N	N	Y	Y	3
Digestive system						
Bang-2017[23]	U	U	Y‡	Y	Y	5

RCT=randomized controlled trial. U=unclear. Y=yes. N=no.

***** Quality assessment was based on the original study, possible updated study and supplementary materials, but not study protocol.

† Modified Jadad scale rates the adequacy of generation of random sequence, allocation concealment, blinding method, and drop out/loss of follow-up; high-quality study had a score ≥ 4; low-quality, ≤ 3.

‡ Application of blinding method is impracticable in these studies due to unavoidable reasons, such as special study designs (cross-over), treatment plan requiring the involvement of clinicians (investigator's choice chemotherapy), evidently different drug administration (oral medication and intravenous injection), and so on. For reasons that were clearly stated in their contents, these studies were still rated as "Y".

Supplementary Table S5. Nodesplit analysis of the dosage-based network meta-analysis

Nodes	Direct effect	Indirect effect	Overall	*P**
All-grade trAEs				
Niv-1, ICI+ICI	1.38 (0.21 to 2.55)	0.12 (-1.89 to 1.90)	1.21 (0.25 to 2.18)	0.24
Niv-1, CT	0.89 (0.46 to 1.32)	0.73 (-0.50 to 1.95)	0.87 (0.48 to 1.26)	0.79
Niv-1, Ipi-1	1.40 (0.25 to 2.54)	0.98 (0.09 to 1.86)	1.13 (0.46 to 1.81)	0.55
Niv-1, Ipi-2	-0.03 (-1.10 to 1.07)	0.92 (0.14 to 1.74)	0.55 (-0.10 to 1.25)	0.15
CT, Ipi-1	0.72 (-0.57 to 2.03)	0.06 (-0.78 to 0.91)	0.26 (-0.43 to 0.97)	0.39
CT, Pem-2	-0.62 (-1.40 to 0.16)	-0.21 (-1.57 to 1.22)	-0.52 (-1.17 to 0.15)	0.59
Ipi-1, Ipi-2	-0.35 (-1.01 to 0.36)	-1.26 (-2.43 to -0.08)	-0.58 (-1.15 to 0.04)	0.17
Ipi-2, Pem-2	-0.01 (-1.10 to 1.10)	-0.44 (-1.65 to 0.68)	-0.20 (-0.99 to 0.56)	0.58
Grade 3–4 trAEs				
Niv-1, ICI+ICI	1.68 (0.41 to 2.98)	2.12 (0.43 to 3.83)	1.94 (0.94 to 3.00)	0.66
Niv-1, CT	1.49 (1.01 to 1.99)	0.47 (-1.01 to 1.92)	1.38 (0.91 to 1.87)	0.18
Niv-1, Ipi-1	1.64 (0.29 to 2.94)	2.03 (0.96 to 3.13)	1.85 (1.07 to 2.68)	0.64
Niv-1, Ipi-2	0.35 (-0.93 to 1.66)	0.88 (-0.07 to 1.84)	0.74 (-0.04 to 1.53)	0.50
CT, Ipi-1	1.18 (-0.51 to 2.96)	0.26 (-0.72 to 1.25)	0.47 (-0.35 to 1.33)	0.35
CT, Pem-2	-0.93 (-1.88 to -0.01)	-1.64 (-3.31 to 0.06)	-1.10 (-1.91 to -0.30)	0.45
Ipi-1, Ipi-2	-1.08 (-1.93 to -0.21)	-1.27 (-2.76 to 0.15)	-1.13 (-1.84 to -0.42)	0.81
Ipi-2, Pem-2	-0.80 (-2.17 to 0.54)	-0.09 (-1.46 to 1.25)	-0.45 (-1.40 to 0.49)	0.45

TrAE=treatment-related adverse events. Niv-1=Nivolumab (2-3 mg/kg/2 wk). Ipi-1=Ipilimumab (10 mg/kg/3 wk). Ipi-2=Ipilimumab (3 mg/kg/3 wk). Pem-2=Pembrolizumab (10 mg/kg/3 wk). ICI=immune checkpoint inhibitor. CT=conventional therapy.

* $P \leq 0.05$ indicates a significant inconsistency between the direct effect and indirect effects.

Supplementary Table S6. Detailed rank and probability in the category-based network meta-analysis

Treatment	Rank of risk*							
	1	2	3	4	5	6	7	8
All-grade trAEs								
Niv	0	0	0	0	2	26	56	16
Ipi	0	2	8	25	55	8	1	0
Tre	54	21	13	5	5	1	1	0
Pem	0	0	0	2	9	55	27	8
Ate	0	0	0	0	1	7	16	76
ICI+ICI	18	27	30	14	8	2	1	0
ICI+CT	27	48	23	2	0	0	0	0
CT	0	3	26	51	20	0	0	0
Grade 3–4 trAEs								
Niv	0	0	0	0	0	8	46	46
Ipi	0	2	12	31	51	4	0	0
Tre	27	23	28	9	10	2	1	0
Pem	0	0	0	1	6	72	17	5
Ate	0	0	0	0	1	14	36	49
ICI+ICI	47	29	19	4	1	0	0	0
ICI+CT	27	45	26	2	0	0	0	0
CT	0	1	15	54	30	0	0	0

TrAE=reatment-related adverse events. Niv=Nivolumab. Ipi=Ipilimumab. Tre=Tremelimumab. Pem=Pembrolizumab. Ate=Atezolizumab. ICI=immune checkpoint inhibitor. CT=conventional therapy.

* Values are presented as probability (%).

Supplementary Table S7. Nodesplit analysis of category-based network meta-analysis

Nodes	Direct effect	Indirect effect	Overall	*P**
All-grade trAEs				
Niv, Ipi	0.66 (-0.24 to 1.59)	0.78 (-0.13 to 1.74)	0.70 (0.06 to 1.39)	0.85
Niv, ICI+ICI	1.39 (0.07 to 2.73)	0.27 (-1.85 to 2.16)	1.30 (0.23 to 2.36)	0.33
Niv, CT	0.89 (0.39 to 1.40)	1.06 (-0.20 to 2.37)	0.91 (0.47 to 1.37)	0.79
Ipi, Pem	0.16 (-1.02 to 1.35)	-1.00 (-1.98 to -0.06)	-0.52 (-1.33 to 0.23)	0.12
Ipi, ICI+CT	1.04 (-0.69 to 2.84)	0.75 (-0.22 to 1.66)	0.82 (-0.00 to 1.60)	0.77
Ipi, CT	-0.75 (-2.16 to 0.66)	0.46 (-0.28 to 1.18)	0.21 (-0.46 to 0.86)	0.13
Pem, CT	0.94 (0.31 to 1.60)	-0.23 (-1.61 to 1.16)	0.73 (0.13 to 1.35)	0.12
ICI+CT, CT	-0.58 (-1.13 to 0.00)	-0.87 (-2.89 to 1.00)	-0.61 (-1.13 to -0.06)	0.77
Grade 3–4 trAEs				
Niv, Ipi	1.00 (-0.02 to 2.05)	1.43 (0.42 to 2.49)	1.28 (0.53 to 2.04)	0.56
Niv, ICI+ICI	1.71 (0.20 to 3.15)	2.68 (0.92 to 4.51)	2.31 (1.22 to 3.42)	0.38
Niv, CT	1.49 (0.94 to 2.06)	0.70 (-0.75 to 2.11)	1.39 (0.87 to 1.91)	0.29
Ipi, Pem	-0.64 (-2.14 to 0.84)	-0.87 (-2.02 to 0.27)	-0.77 (-1.67 to 0.09)	0.80
Ipi, ICI+CT	0.73 (-1.15 to 2.66)	0.94 (-0.12 to 1.95)	0.90 (-0.01 to 1.78)	0.86
Ipi, CT	-1.18 (-3.07 to 0.60)	0.37 (-0.45 to 1.19)	0.11 (-0.67 to 0.86)	0.12
Pem, CT	0.92 (0.17 to 1.67)	0.70 (-1.06 to 2.40)	0.89 (0.24 to 1.54)	0.81
ICI+CT, CT	-0.80 (-1.42 to -0.19)	-0.59 (-2.73 to 1.47)	-0.78 (-1.37 to -0.21)	0.84

TrAE=treatment-related adverse events. Niv=Nivolumab. Ipi=Ipilimumab. Tre=Tremelimumab. Pem=Pembrolizumab. ICI=immune checkpoint inhibitor. CT=conventional therapy.

* $P \leq 0{\cdot}05$ indicates a significant inconsistency between the direct effect and indirect effects.

Supplementary Table S8. Sensitivity analysis

Groups	Rank of risk*							
	1	2	3	4	5	6	7	8
Phase III studies								
All-grade trAEs								
Niv	0	0	0	1	9	31	43	16
Ipi	0	1	4	11	49	22	9	4
Tre	39	28	20	7	3	1	1	0
Pem	0	0	1	3	16	31	28	21
Ate	0	0	0	2	9	12	19	58
ICI+ICI	23	27	30	14	4	2	1	0
ICI+CT	38	42	18	1	0	0	0	0
CT	0	3	26	60	10	1	0	0
Grade 3–4 trAEs								
Niv	0	0	0	0	1	9	38	52
Ipi	0	3	9	19	41	19	6	1
Tre	26	28	21	10	7	4	2	1
Pem	0	1	2	6	17	44	21	9
Ate	0	1	1	3	10	18	32	36
ICI+ICI	22	28	25	13	6	3	1	1
ICI+CT	51	34	12	2	1	0	0	0
CT	0	6	29	46	16	2	0	0
High-quality studies								
All-grade trAEs								
Niv	0	0	0	1	5	39	55	-
Ipi	0	4	14	28	43	10	1	-
Tre	51	20	13	6	5	3	2	-
Pem	0	0	1	4	11	44	40	-

ICI+ICI	24	27	25	12	7	3	1	-
ICI+CT	25	46	24	4	1	0	0	-
CT	0	4	22	45	28	2	0	-
Grade 3–4 trAEs								
Niv	0	0	0	0	1	26	73	-
Ipi	0	3	20	42	33	2	0	-
Tre	20	23	31	12	10	3	1	-
Pem	0	0	0	1	5	68	26	-
ICI+ICI	63	24	11	1	1	0	0	-
ICI+CT	17	50	30	3	0	0	0	-
CT	0	0	8	41	50	1	0	-
Studies explicitly reporting trAEs								
All-grade trAEs								
Niv	0	0	0	0	1	22	58	18
Ipi	0	2	7	20	61	8	1	0
Tre	63	19	9	4	3	1	0	0
Pem	0	0	0	1	9	59	24	7
Ate	0	0	0	0	2	8	15	75
ICI+ICI	22	33	28	14	6	2	1	0
ICI+CT	14	41	34	8	3	0	0	0
CT	0	5	22	52	15	0	0	0
Grade 3–4 trAEs								
Niv	0	0	0	0	0	6	57	38
Ipi	0	2	8	23	64	3	0	0
Tre	33	29	22	7	7	1	0	0
Pem	0	0	0	0	4	81	13	2
Ate	0	0	0	0	1	9	30	60
ICI+ICI	55	29	12	3	0	0	0	0

ICI+CT	12	38	44	5	1	0	0	0
CT	0	1	14	62	23	0	0	0
Studies using PD-(L)1 ICIs								
All-grade trAEs								
Niv	0	3	48	41	8	-	-	-
Pem	0	3	42	41	14	-	-	-
Ate	0	0	6	16	77	-	-	-
ICI+CT	74	21	3	2	1	-	-	-
CT	26	74	0	0	0	-	-	-
Grade 3–4 trAEs								
Niv	0	0	6	38	57	-	-	-
Pem	0	2	76	17	4	-	-	-
Ate	0	1	16	45	39	-	-	-
ICI+CT	84	13	2	1	0	-	-	-
CT	16	83	1	0	0	-	-	-
Studies using the current recommended dosage of ICIs†								
All-grade trAEs								
Niv	0	0	0	3	21	51	20	5
Ipi	1	3	6	12	39	17	13	11
Tre	56	23	11	5	3	1	0	0
Pem	0	0	1	4	10	15	28	42
Ate	0	0	0	2	7	13	37	41
ICI+ICI	13	17	26	31	8	3	2	1
ICI+CT	30	51	15	3	1	0	0	0
CT	0	6	42	40	12	0	0	0
Grade 3–4 trAEs								
Niv	0	0	0	0	3	17	43	37
Ipi	0	1	2	5	23	27	17	25

Tre	36	29	17	10	5	2	0	0
Pem	0	1	4	14	40	24	10	6
Ate	0	0	0	2	10	26	28	32
ICI+ICI	15	20	25	24	12	3	1	0
ICI+CT	48	41	10	1	0	0	0	0
CT	0	8	40	44	7	0	0	0
Studies that included previously treated patients								
All-grade trAEs						-	-	-
Niv	0	0	30	65	5	-	-	-
Ipi	97	3	0	0	0	-	-	-
Pem	0	0	68	28	4	-	-	-
Ate	0	0	2	7	92	-	-	-
CT	3	97	0	0	0			
Grade 3–4 trAEs						-	-	-
Niv	0	0	5	32	63	-	-	-
Ipi	78	18	3	0	0	-	-	-
Pem	1	4	76	15	4	-	-	-
Ate	0	1	15	52	32	-	-	-
CT	21	77	2	0	0			
Studies that included previously untreated patients								
All-grade trAEs								
Niv	2	3	4	8	11	17	55	-
Ipi	1	6	10	15	29	24	14	-
Tre	55	17	10	7	5	4	2	-
Pem	0	1	3	9	21	42	24	-
ICI+ICI	19	19	17	21	13	7	4	-
ICI+CT	22	42	23	9	3	1	0	-
CT	1	11	35	31	17	5	0	-

Grade 3–4 trAEs								
Niv	1	2	3	5	14	20	55	-
Ipi	0	5	11	18	36	21	10	-
Tre	30	22	21	11	8	5	3	-
Pem	0	0	1	4	15	47	32	-
ICI+ICI	43	25	17	10	3	1	0	-
ICI+CT	25	43	26	5	1	0	0	-
CT	0	4	21	47	23	5	0	-

TrAE=treatment-related adverse events. Niv=Nivolumab. Ipi=Ipilimumab. Tre=Tremelimumab. Pem=Pembrolizumab. Ate=Atezolizumab. ICI=immune checkpoint inhibitor. CT=conventional therapy. PD-(L)1=programmed-death-1 and its ligand.

* Values are presented as probability (%).

† According to the DailyMed website maintained by the US National Library of Medicine (https://dailymed.nlm.nih.gov/dailymed/), the current recommended dosage for ICIs is: nivolumab, 3 mg/kg/2 wk; ipilimumab, 3 mg/kg/3 wk; pembrolizumab, 200 mg/3 wk; tremelimumab, 10 mg/kg/90 days; atezolizumab, 1200 mg/3 wk.

Supplementary Table S9. Severity of toxicity and safety profile of chemotherapy strategies

Study	chemotherapy strategy	No.	Incidence (%)*															
			Grade 3-4 trAEs	All-grade trAEs	Fatigue	Pruritus	Rash	Diarrhea	Colitis	Nausea	Vomit.	ALT in.	AST in.	Pneum.	CRE in.	HoTD	HrTD	Arthralgia
Rittmeyer-2017[12]	DOC 75mg/m²/3 wk	578	42.7	85.8	35.5	-	-	24.4	-	22.7	10.7	-	-	-	-	-	-	10.0
Larkin-2017[13]/ Weber-2015[14]	ICC (DTIC 1000 mg/m²/3 wk or CBP AUC=6 + PTX 175 mg/m²/3 wk)	102	34.3	82.4	39.2	1.0	4.9	15.7	0.5	37.3	-	1.0	2.0	0.5	0.5	0.5	1.0	12.7
Robert-2011[15]/ Maio-2015[16]	DTIC 850 mg/m²	251	6.0	38.2	-	6.0	4.8	15.9	0.2	-	-	4.4	3.2	-	-	0.4	0.2	-
Ferris-2016[17]	ICC, standard single-agent (MTX 40–60 mg/m², DOC 30–40 mg/m², cetuximab 250 mg/m² after a loading dose of 400 mg/m²)	111	35.1	77.5	17.1	0.5	4.5	13.5	1.4	20.7	7.2	2.7	1.8	0.9	-	0.9	0.5	-
Govindan-2017[18]	PTX + CBP	361	35.7	80.9	16.3	2.2	3.9	10.5	-	12.7	7.2	1.1	1.7	-	-	-	-	4.4
Motzer(1)-2015[19]	Everolimus 10mg orally/day	397	36.5	87.9	33.8	16.6	19.9	21.2	-	16.6	-	-	-	14.6	-	-	-	-
Carbone-2017[21]	ICC (platinum-based chemotherapy, 6 cycles)	263	50.6	92.4	35.4	2.7	5.7	12.9	-	48.3	22.8	5.3	4.6	-	6.1	0.4	-	-
Bellmunt-2017[22]	ICC (PTX 175 mg/m²/3 wk, DOC 75 mg/m²/3 wk, or Vinflunine 320 mg/m²/3 wk)	255	62.7	98.0	33.7	5.5	6.3	18.8	-	28.6	13.3	1.6	1.2	-	5.9	1.2	-	11.8
Bang-2017[23]	Best supportive care: continuation of Fluoropyrimidine or no active maintenance treatment	45	8.9	55.6	6.7	2.2	4.4	6.7	-	17.8	2.2	-	-	-	-	1.1	-	-
Reck(1)-2016[25]	ICC (CBP/DDP + Pemetrexed, CBP/DDP + GEM, CBP + PTX)	150	53.3	90.0	28.7	-	-	13.3	0.3	43.3	20.0	-	-	0.7	13.7	1.3	1.3	-
Reck(2)-2016[26]	Etoposide + DDP/CBP	476	45.0	75.8	11.1	1.7	2.5	9.7	0.2	15.8	6.9	-	-	-	-	-	-	-
Langer-2016[27]	CBP AUC=5 + Pemetrexed 500 mg/m²/3 wk	62	22.6	87.1	40.3	3.2	14.5	11.3	-	43.5	17.7	11.3	11.3	0.8	6.5	4.8	1.6	-
Herbst-2016[30]	DOC 75 mg/m²/3 wk	309	35.3	81.2	24.6	1.6	4.5	18.1	0.2	14.6	7.8	1.3	1.0	1.9	0.2	0.3	1.0	5.8
Fehrenbacher-	DOC 75 mg/m²/3 wk	135	38.5	88.1	34.8	-	-	27.4	-	32.6	11.9	-	-	3.0	-	0.4	-	8.9

2016[31]																		
Robert(2)-2015[32]	DTIC 1000 mg/m²/3 wk	205	17.6	75.6	14.6	5.4	2.9	15.6	0.2	41.5	21.0	1.5	2.0	0.2	0.5	0.5	0.2	1.5
Ribas-2015[33]	ICC (PTX + CBP, PTX, CBP, DTIC, oral Temozolomide)	171	26.3	80.7	36.3	3.5	4.7	8.2	0.6	32.7	15.2	-	-	0.3	-	0.6	0.3	5.3
Brahmer-2015[34]	DOC 75 mg/m²/3 wk	129	55.0	86.0	32.6	0.4	6.2	20.2	0.4	23.3	10.9	0.8	0.8	0.4	1.6	0.4	-	7.0
Borghaei-2015[35]	DOC 75 mg/m²/3 wk	268	53.7	88.1	29.1	1.5	3.0	23.1	0.2	26.1	7.5	1.5	0.7	0.4	-	0.2	0.2	6.0
Powles-2017[36]	ICC (Vinflunine 320 mg/m²/3 wk, PTX 175 mg/m²/3 wk, or DOC 75 mg/m²/3 wk)	443	42.7	89.2	26.2	3.2	4.7	14.9	-	26.4	-	-	-	-	-	-	-	9.0
Ribas-2013[37]	ICC (oral Temozolomide 200 mg/m²/4 wk or DTIC 1000 mg/m²/3 wk)	319	37.3	91.5	37.0	5.0	5.3	17.6	17.6	49.5	28.8	-	-	-	-	0.6	0.6	-
Reck-2013[38]	Control regimen (PTX 175 mg/m²/3 wk or CBP AUC=6)	44	29.5	90.9	25.0	4.5	2.3	15.9	-	22.7	-	20.5	31.8	-	-	-	-	31.8
Lynch-2012[39]	Control regimen (PTX 175 mg/m²/3 wk or CBP AUC=6)	65	36.9	80.0	26.2	6.2	9.2	16.9	-	32.3	16.9	36.9	33.8	-	-	-	-	10.8

No.=number of patients. TrAE=treatment-related adverse event. Vomit.=vomiting. ALT=alanine transaminase. AST=aspartate transaminase. in.=increased. Pneum.=pneumonitis. CRE=blood creatinine. HoTD=hypothyroidism. HrTD=hyperthyroidism. ICC=investigator's choice chemotherapy. DOC=docetaxel. DTIC=dacarbazine. CBP=carboplatin. AUC=area under the curve. PTX=paclitaxel. MTX=methotrexate. DDP=cisplatin. GEM=gemcitabine. wk=week.

* All specific toxicities were limited to all-grade.

Supplementary Figure S1. Safety profile according to the dosage-based NMA results in the consistency model

Each cell of the safety profile contains the pooled ORs and 95% CrIs for all-grade trAEs (*lower triangle*) and grade 3–4 trAEs (*upper triangle*); significant results are in bold and/or underscored. For each pair of treatments, the pooled OR and 95% CrI indicate the result of the top treatment compared with the bottom treatment. NMA=network meta-analysis. ORs=odds ratios. CrIs=credibility intervals. trAE=treatment-related adverse event. Niv-1=Nivolumab 2-3 mg/kg/2 wk. Niv-2=Nivolumab 0·3 mg/kg/3 wk. Niv-3=Nivolumab 10 mg/kg/3 wk. Ipi-1=Ipilimumab 10 mg/kg/3 wk. Ipi-2=Ipilimumab 3 mg/kg/3 wk. Ipi-3=Ipilimumab 3 mg/kg/4 wk. Tre=tremelimumab 10 mg/kg/90 day. Pem-1=Pembrolizumab 10 mg/kg/2 wk. Pem-2=Pembrolizumab 10 mg/kg/3 wk. Pem-3=Pembrolizumab 2 mg/kg/3 wk. Pem-4=Pembrolizumab 200 mg/3 wk. Ate=Atezolizumab 1200 mg/3 wk. ICI=immune checkpoint inhibitor. CT=conventional therapy.

All-grade trAEs Grade 3–4 trAEs

Niv-1	4.13 (0.66 to 29.78)	1.37 (0.27 to 7.03)	**0.16 (0.07 to 0.34)**	0.48 (0.22 to 1.04)	0.24 (0.04 to 1.64)	**0.14 (0.04 to 0.52)**	0.66 (0.17 to 2.46)	0.75 (0.31 to 1.84)	0.91 (0.34 to 2.49)	0.54 (0.19 to 1.54)	0.99 (0.41 to 2.40)	**0.14 (0.05 to 0.39)**	**0.11 (0.05 to 0.23)**	**0.25 (0.15 to 0.40)**
0.68 (0.19 to 2.52)	**Niv-2**	0.33 (0.04 to 2.11)	**0.04 (0.00 to 0.28)**	**0.11 (0.01 to 0.85)**	**0.06 (0.00 to 0.83)**	**0.03 (0.00 to 0.32)**	0.16 (0.01 to 1.49)	0.18 (0.02 to 1.41)	0.22 (0.02 to 1.79)	0.13 (0.01 to 1.11)	0.24 (0.03 to 1.87)	**0.03 (0.00 to 0.28)**	**0.03 (0.00 to 0.20)**	**0.06 (0.01 to 0.40)**
0.57 (0.15 to 2.12)	0.83 (0.22 to 3.09)	**Niv-3**	**0.11 (0.02 to 0.68)**	0.35 (0.06 to 2.12)	0.17 (0.01 to 2.14)	**0.10 (0.01 to 0.82)**	0.48 (0.06 to 3.89)	0.55 (0.08 to 3.55)	0.67 (0.10 to 4.63)	0.40 (0.06 to 2.74)	0.72 (0.11 to 4.67)	**0.11 (0.01 to 0.71)**	**0.08 (0.01 to 0.49)**	0.18 (0.03 to 1.01)
0.32 (0.16 to 0.63)	0.47 (0.11 to 2.00)	0.57 (0.13 to 2.48)	**Ipi-1**	**3.08 (1.52 to 6.32)**	1.54 (0.20 to 12.06)	0.87 (0.19 to 4.06)	4.24 (1.09 to 16.39)	**4.81 (1.76 to 13.98)**	**5.87 (1.84 to 19.45)**	**3.48** (1.05 to 12.93)	**6.37 (2.11 to 19.72)**	0.92 (0.31 to 2.75)	0.72 (0.26 to 2.00)	1.60 (0.70 to 3.79)
0.58 (0.29 to 1.11)	0.84 (0.19 to 3.52)	1.01 (0.22 to 4.36)	1.78 (0.96 to 3.15)	**Ipi-2**	0.50 (0.07 to 3.90)	0.28 (0.06 to 1.27)	1.37 (0.40 to 4.73)	1.56 (0.61 to 4.06)	1.90 (0.62 to 6.05)	1.13 (0.34 to 4.05)	2.07 (0.69 to 6.39)	**0.30 (0.12 to 0.75)**	**0.24 (0.09 to 0.63)**	0.52 (0.23 to 1.20)
0.65 (0.12 to 4.13)	0.96 (0.11 to 9.22)	1.15 (0.13 to 11.25)	2.03 (0.34 to 13.92)	1.14 (0.19 to 8.06)	**Ipi-3**	0.58 (0.06 to 5.34)	2.77 (0.29 to 26.77)	3.17 (0.41 to 24.10)	3.82 (0.48 to 30.62)	2.29 (0.29 to 18.32)	4.15 (0.57 to 30.89)	0.60 (0.07 to 5.13)	0.47 (0.08 to 2.73)	1.05 (0.16 to 6.65)
0.19 (0.05 to 0.66)	0.27 (0.04 to 1.66)	0.33 (0.05 to 2.02)	0.57 (0.14 to 2.27)	0.32 (0.08 to 1.31)	0.28 (0.03 to 2.16)	**Tre**	4.80 (0.76 to 29.80)	**5.51 (1.25 to 24.87)**	**6.72 (1.43 to 32.15)**	4.01 (0.84 to 19.57)	**7.33 (1.68 to 32.14)**	1.06 (0.20 to 5.55)	0.83 (0.21 to 3.24)	1.83 (0.52 to 6.44)
0.44 (0.15 to 1.30)	0.65 (0.12 to 3.45)	0.77 (0.14 to 4.27)	1.37 (0.44 to 4.12)	0.77 (0.29 to 2.10)	0.67 (0.08 to 4.77)	2.39 (0.48 to 11.77)	**Pem-1**	1.13 (0.34 to 4.01)	1.40 (0.32 to 6.09)	0.83 (0.16 to 4.23)	1.51 (0.35 to 7.19)	**0.22 (0.05 to 0.97)**	**0.17 (0.04 to 0.72)**	0.38 (0.10 to 1.44)
0.71 (0.34 to 1.44)	1.03 (0.23 to 4.45)	1.24 (0.27 to 5.48)	2.19 (0.91 to 5.10)	1.22 (0.57 to 2.70)	1.07 (0.16 to 6.25)	3.79 (0.97 to 14.89)	1.58 (0.58 to 4.41)	**Pem-2**	1.22 (0.49 to 3.05)	0.72 (0.21 to 2.54)	1.32 (0.45 to 3.98)	**0.19 (0.06 to 0.64)**	**0.15 (0.06 to 0.40)**	**0.33 (0.15 to 0.74)**
0.91 (0.40 to 2.06)	1.33 (0.28 to 5.99)	1.60 (0.33 to 7.51)	**2.80 (1.07 to 7.40)**	1.57 (0.63 to 4.08)	1.38 (0.20 to 8.44)	**4.91 (1.17 to 20.21)**	2.04 (0.64 to 6.77)	1.29 (0.63 to 2.67)	**Pem-3**	0.60 (0.16 to 2.19)	1.09 (0.34 to 3.50)	**0.16 (0.04 to 0.61)**	**0.12 (0.04 to 0.35)**	**0.27 (0.11 to 0.68)**
1.47 (0.56 to 4.03)	2.16 (0.42 to 11.08)	2.61 (0.50 to 13.64)	**4.57 (1.46 to 14.73)**	2.56 (0.85 to 8.36)	2.25 (0.30 to 15.02)	**8.03 (1.79 to 36.88)**	3.36 (0.84 to 13.81)	2.10 (0.70 to 6.53)	1.62 (0.51 to 5.35)	**Pem-4**	1.82 (0.56 to 6.01)	0.27 (0.06 to 1.09)	**0.21 (0.07 to 0.60)**	0.46 (0.18 to 1.16)
1.50 (0.72 to 3.14)	2.19 (0.49 to 9.79)	2.64 (0.58 to 11.99)	**4.63 (1.83 to 12.03)**	**2.60** (1.05 to 6.93)	2.29 (0.34 to 13.81)	**8.10 (2.08 to 31.25)**	**3.37** (1.00 to 11.86)	2.13 (0.87 to 5.30)	1.65 (0.63 to 4.37)	1.02 (0.34 to 3.00)	**Ate**	**0.14 (0.04 to 0.53)**	**0.11 (0.05 to 0.28)**	**0.25 (0.12 to 0.53)**
0.30 (0.11 to 0.78)	0.43 (0.08 to 2.13)	0.52 (0.10 to 2.59)	0.92 (0.33 to 2.56)	0.51 (0.21 to 1.30)	0.45 (0.06 to 3.16)	1.59 (0.34 to 7.50)	0.66 (0.18 to 2.53)	0.42 (0.14 to 1.28)	0.33 (0.10 to 1.09)	**0.20 (0.05 to 0.78)**	**0.20 (0.06 to 0.64)**	**ICI+ICI**	0.79 (0.23 to 2.65)	1.74 (0.60 to 5.23)
0.23 (0.12 to 0.43)	0.33 (0.08 to 1.41)	0.40 (0.09 to 1.76)	0.70 (0.31 to 1.67)	**0.39 (0.17 to 0.98)**	0.35 (0.06 to 1.73)	1.23 (0.34 to 4.63)	0.51 (0.16 to 1.72)	**0.32 (0.15 to 0.76)**	**0.25 (0.10 to 0.62)**	**0.15 (0.05 to 0.43)**	**0.15 (0.07 to 0.34)**	0.77 (0.26 to 2.35)	**ICI+CT**	**2.22 (1.29 to 3.88)**
0.42 (0.28 to 0.62)	0.61 (0.16 to 2.33)	0.74 (0.19 to 2.93)	1.29 (0.65 to 2.63)	0.73 (0.37 to 1.51)	0.64 (0.10 to 3.36)	2.26 (0.68 to 7.67)	0.94 (0.33 to 2.84)	0.59 (0.31 to 1.16)	**0.46** (0.22 to 0.96)	**0.28 (0.11 to 0.69)**	**0.28 (0.15 to 0.52)**	1.41 (0.52 to 3.86)	**1.83 (1.12 to 2.96)**	**CT**

Supplementary Figure S2. Safety profile according to the dosage-based NMA results in the inconsistency model

Each cell of the safety profile contains the pooled ORs and 95% CrIs for all-grade trAEs (*lower triangle*) and grade 3–4 trAEs (*upper triangle*); significant results are in bold and/or underscored. For each pair of treatments, the pooled OR and 95% CrI indicate the result of the top treatment compared with the bottom treatment. NMA=network meta-analysis. ORs=odds ratios. CrIs=credibility intervals. trAE=treatment-related adverse event. Niv-1=Nivolumab 2-3 mg/kg/2 wk. Niv-2=Nivolumab 0·3 mg/kg/3 wk. Niv-3=Nivolumab 10 mg/kg/3 wk. Ipi-1=Ipilimumab 10 mg/kg/3 wk. Ipi-2=Ipilimumab 3 mg/kg/3 wk. Ipi-3=Ipilimumab 3 mg/kg/4 wk. Tre=tremelimumab 10 mg/kg/90 day. Pem-1=Pembrolizumab 10 mg/kg/2 wk. Pem-2=Pembrolizumab 10 mg/kg/3 wk. Pem-3=Pembrolizumab 2 mg/kg/3 wk. Pem-4=Pembrolizumab 200 mg/3 wk. Ate=Atezolizumab 1200 mg/3 wk. ICI=immune checkpoint inhibitor. CT=conventional therapy.

All-grade trAEs Grade 3–4 trAEs

Niv-1	4.13 (0.66 to 30.29)	1.34 (0.27 to 7.15)	**0.16 (0.06 to 0.47)**	0.52 (0.19 to 1.50)	0.23 (0.03 to 1.61)	**0.13 (0.03 to 0.53)**	0.60 (0.14 to 2.46)	0.71 (0.28 to 1.81)	0.89 (0.32 to 2.54)	0.52 (0.18 to 1.50)	0.97 (0.39 to 2.38)	**0.15 (0.05 to 0.46)**	**0.11 (0.05 to 0.23)**	**0.24 (0.15 to 0.40)**
0.67 (0.19 to 2.33)	**Niv-2**	0.33 (0.04 to 2.15)	**0.03 (0.00 to 0.29)**	**0.11 (0.01 to 0.82)**	**0.06 (0.00 to 0.83)**	**0.03 (0.00 to 0.32)**	0.15 (0.01 to 1.44)	0.17 (0.02 to 1.31)	0.22 (0.02 to 1.76)	0.13 (0.01 to 1.06)	0.23 (0.03 to 1.79)	**0.04 (0.00 to 0.31)**	**0.03 (0.00 to 0.19)**	**0.06 (0.01 to 0.39)**
0.56 (0.15 to 2.06)	0.84 (0.23 to 3.02)	**Niv-3**	**0.11 (0.01 to 0.72)**	0.32 (0.04 to 2.16)	0.17 (0.01 to 2.12)	**0.10 (0.01 to 0.81)**	0.45 (0.05 to 3.85)	0.52 (0.08 to 3.42)	0.67 (0.09 to 4.58)	0.39 (0.05 to 2.73)	0.72 (0.11 to 4.48)	**0.11 (0.01 to 0.79)**	**0.08 (0.01 to 0.49)**	**0.18 (0.03 to 0.97)**
0.29 (0.11 to 0.69)	0.52 (0.11 to 2.48)	0.62 (0.13 to 3.08)	**Ipi-1**	**3.02 (1.42 to 6.40)**	1.59 (0.20 to 13.75)	0.92 (0.18 to 4.95)	**4.18** (1.02 to 17.62)	**4.93 (1.59 to 15.71)**	**6.20 (1.71 to 24.19)**	3.67 (0.91 to 15.10)	**6.74 (1.90 to 24.88)**	1.03 (0.29 to 4.35)	0.76 (0.24 to 2.56)	1.95 (0.65 to 7.96)
0.78 (0.32 to 2.04)	0.84 (0.18 to 3.80)	1.01 (0.21 to 4.63)	1.63 (0.84 to 2.98)	**Ipi-2**	0.53 (0.07 to 4.52)	0.30 (0.06 to 1.56)	1.40 (0.39 to 4.94)	1.64 (0.60 to 4.60)	2.06 (0.61 to 7.37)	1.21 (0.32 to 4.89)	2.22 (0.65 to 8.00)	**0.30 (0.09 to 0.95)**	**0.25 (0.08 to 0.82)**	0.56 (0.21 to 1.59)
0.64 (0.12 to 3.84)	0.95 (0.12 to 8.74)	1.15 (0.14,10.62)	1.84 (0.28 to 12.93)	1.13 (0.18 to 8.06)	**Ipi-3**	0.58 (0.06 to 5.42)	2.66 (0.26 to 26.63)	3.10 (0.39 to 23.45)	3.99 (0.49 to 30.89)	2.34 (0.28 to 18.59)	4.27 (0.57 to 30.76)	0.66 (0.07 to 6.00)	0.48 (0.08 to 2.68)	1.07 (0.16 to 6.78)
0.18 (0.05 to 0.62)	0.27 (0.05 to 1.61)	0.32 (0.05 to 1.94)	0.52 (0.12 to 2.28)	0.32 (0.08 to 1.36)	0.28 (0.03 to 2.05)	**Tre**	4.59 (0.67 to 30.44)	**5.42 (1.17 to 24.60)**	**6.75 (1.41 to 32.58)**	4.03 (0.82 to 19.10)	**7.37 (1.65 to 32.26)**	1.14 (0.20 to 6.43)	0.83 (0.20 to 3.36)	1.84 (0.52 to 6.69)
0.43 (0.14 to 1.32)	0.64 (0.12 to 3.61)	0.77 (0.13 to 4.42)	1.26 (0.39 to 3.91)	0.77 (0.29 to 2.11)	0.68 (0.08 to 4.91)	2.40 (0.48 to 12.26)	**Pem-1**	1.17 (0.33 to 4.18)	1.47 (0.33 to 6.78)	0.88 (0.17 to 4.69)	1.61 (0.33 to 7.73)	0.25 (0.05 to 1.35)	**0.18 (0.04 to 0.83)**	0.40 (0.10 to 1.65)
0.69 (0.32 to 1.46)	1.03 (0.23 to 4.44)	1.24 (0.28 to 5.57)	1.99 (0.76 to 5.02)	1.22 (0.55 to 2.78)	1.09 (0.16 to 6.05)	3.85 (0.99 to 14.94)	1.58 (0.58 to 4.34)	**Pem-2**	1.26 (0.49 to 3.21)	0.75 (0.21 to 2.60)	1.37 (0.44 to 4.22)	**0.21 (0.06 to 0.83)**	**0.15 (0.06 to 0.43)**	**0.34 (0.15 to 0.80)**
0.88 (0.39 to 1.97)	1.33 (0.29 to 5.82)	1.59 (0.34 to 7.32)	2.57 (0.86 to 7.20)	1.58 (0.59 to 4.23)	1.41 (0.21 to 8.08)	**4.92 (1.24 to 19.55)**	2.04 (0.62 to 6.76)	1.29 (0.63 to 2.61)	**Pem-3**	0.59 (0.16 to 2.19)	1.09 (0.33 to 3.59)	**0.17 (0.04 to 0.71)**	**0.12 (0.04 to 0.36)**	**0.27 (0.11 to 0.69)**
1.43 (0.55 to 3.83)	2.15 (0.44 to 10.93)	2.59 (0.51 to 13.14)	**4.18 (1.16 to 14.74)**	2.55 (0.76 to 8.85)	2.25 (0.33 to 14.45)	**7.93 (1.84 to 36.27)**	3.31 (0.82 to 14.02)	2.09 (0.70 to 6.51)	1.62 (0.52 to 5.22)	**Pem-4**	1.83 (0.55 to 6.10)	0.28 (0.06 to 1.30)	**0.21 (0.07 to 0.61)**	0.46 (0.18 to 1.17)
1.46 (0.71 to 3.03)	2.19 (0.50 to 9.65)	2.64 (0.59 to 11.96)	**4.24 (1.40 to 12.32)**	2.60 (0.94 to 7.46)	2.31 (0.36 to 12.78)	**8.16 (2.16 to 30.97)**	3.39 (0.96 to 12.24)	2.13 (0.86 to 5.30)	1.65 (0.64 to 4.31)	1.02 (0.34 to 3.02)	**Ate**	**0.15 (0.04 to 0.63)**	**0.11 (0.04 to 0.29)**	**0.25 (0.12 to 0.54)**
0.30 (0.11 to 0.84)	0.45 (0.09 to 2.29)	0.53 (0.10 to 2.83)	0.86 (0.25 to 2.82)	0.73 (0.23 to 3.19)	0.47 (0.06 to 3.29)	1.66 (0.34 to 8.18)	0.68 (0.17 to 2.77)	0.43 (0.14 to 1.41)	0.34 (0.10 to 1.19)	**0.21 (0.05 to 0.82)**	**0.20 (0.06 to 0.70)**	**ICI+ICI**	0.73 (0.20 to 2.72)	1.63 (0.49 to 5.27)
0.22 (0.12 to 0.42)	0.33 (0.08 to 1.40)	0.40 (0.09 to 1.75)	0.65 (0.23 to 1.75)	0.40 (0.15 to 1.09)	0.35 (0.06 to 1.65)	1.24 (0.36 to 4.51)	0.51 (0.15 to 1.79)	**0.32 (0.14 to 0.76)**	**0.25 (0.11 to 0.61)**	**0.16 (0.06 to 0.44)**	**0.15 (0.07 to 0.34)**	0.75 (0.24 to 2.44)	**ICI+CT**	**2.22 (1.28 to 3.89)**
0.41 (0.28 to 0.61)	0.61 (0.16 to 2.34)	0.73 (0.19 to 2.89)	1.54 (0.61 to 4.51)	0.73 (0.32 to 1.69)	0.65 (0.11 to 3.22)	2.28 (0.71 to 7.42)	0.95 (0.31 to 2.92)	0.60 (0.30 to 1.16)	**0.46** (0.23 to 0.96)	**0.29 (0.11 to 0.69)**	**0.28 (0.15 to 0.52)**	1.38 (0.48 to 3.96)	**1.84 (1.12 to 2.93)**	**CT**

Supplementary Figure S3. Safety profile according to the category-based NMA results in the inconsistency model

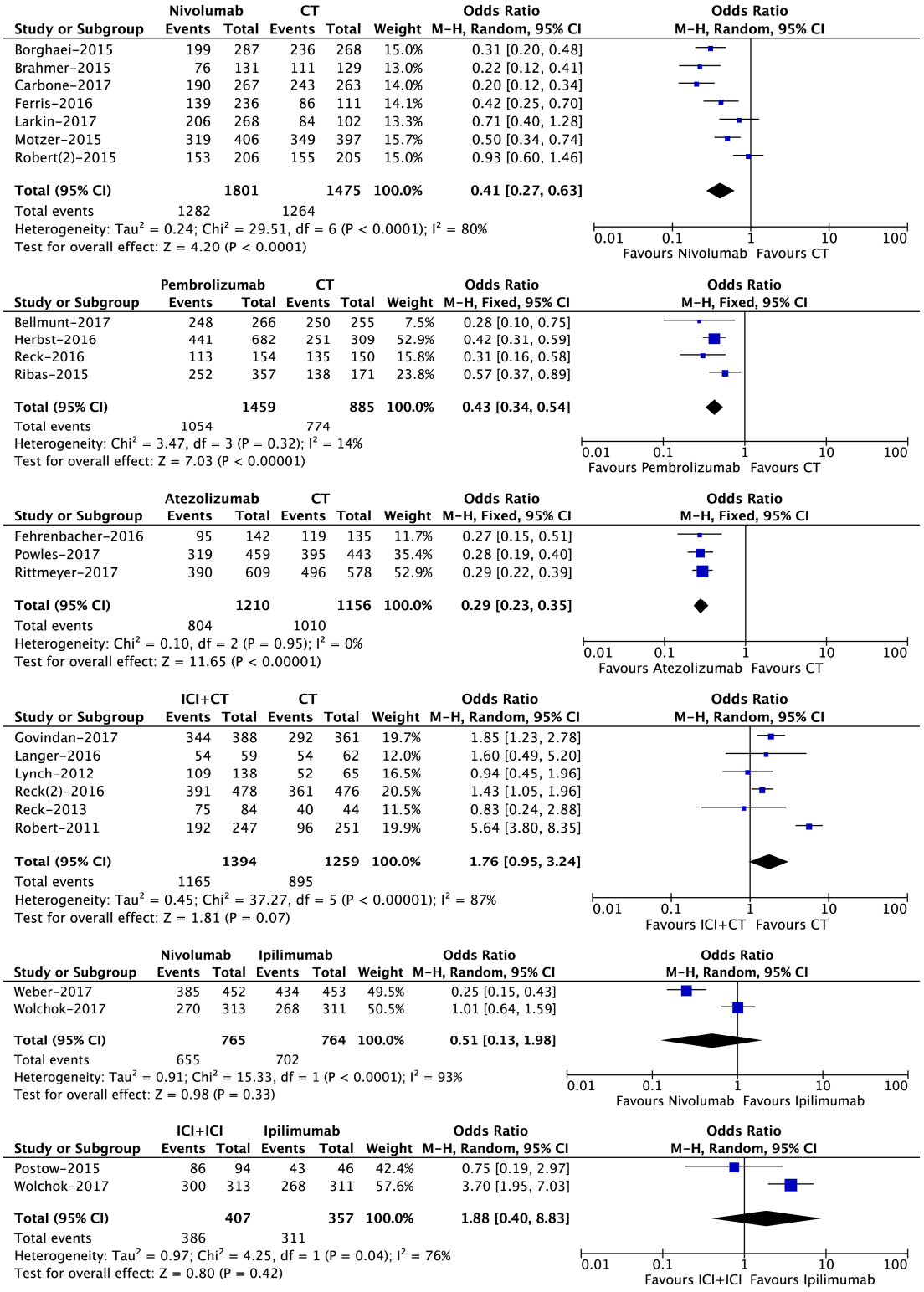
Each cell of the safety profile contains the pooled ORs and 95% CrIs for all-grade trAEs (*lower triangle*) and grade 3–4 trAEs (*upper triangle*); significant results are in bold and/or underscored. For each pair of treatments, the pooled OR and 95% CrI indicate the result of the top treatment compared with the bottom treatment. NMA=network meta-analysis. ORs=odds ratios. CrIs=credibility intervals. trAE=treatment-related adverse event. Niv=Nivolumab. Ipi=Ipilimumab. Tre=Tremelimumab. Pem=Pembrolizumab. Ate=Atezolizumab. ICI=immune checkpoint inhibitor. CT=conventional therapy.

All-grade trAEs Grade 3–4 trAEs

Niv	**0.32 (0.13 to 0.79)**	0.16 **(0.03 to 1.02)**	0.71 (0.23 to 2.45)	1.16 (0.31 to 5.00)	**0.11 (0.03 to 0.38)**	**0.13 (0.04 to 0.50)**	**0.24 (0.14 to 0.40)**
0.50 (0.24 to 1.06)	**Ipi**	0.50 (0.09 to 2.88)	2.21 (0.80 to 6.28)	3.62 (0.98 to 14.02)	0.31 (0.09 to 1.02)	0.44 (0.12 to 1.68)	1.34 (0.43 to 7.41)
0.15 (0.03 to 0.76)	0.29 **(0.06 to 1.48)**	**Tre**	4.43 (0.92 to 20.52)	**7.27 (1.39 to 36.82)**	0.62 (0.07 to 4.79)	0.83 (0.17 to 3.85)	1.84 (0.44 to 7.47)
0.73 (0.25 to 1.94)	1.44 (0.56 to 3.54)	**4.96 (1.16 to 22.13)**	**Pem**	1.65 (0.55 to 4.68)	**0.14 (0.03 to 0.64)**	**0.19 (0.08 to 0.46)**	**0.41 (0.21 to 0.81)**
1.20 (0.33 to 3.77)	2.35 (0.72 to 7.36)	**8.06 (1.77 to 37.85)**	1.62 (0.64 to 4.14)	**Ate**	**0.09 (0.01 to 0.49)**	**0.11 (0.04 to 0.32)**	**0.25 (0.11 to 0.60)**
0.24 (0.08 to 0.75)	0.70 (0.21 to 3.12)	2.46 (0.32 to 24.16)	0.48 (0.11 to 3.08)	0.30 (0.06 to 2.26)	**ICI+ICI**	1.33 (0.27 to 7.44)	2.92 (0.66 to 15.34)
0.19 (0.06 to 0.51)	0.38 (0.10 to 1.23)	1.24 (0.30 to 5.40)	**0.25 (0.11 to 0.56)**	**0.15 (0.06 to 0.38)**	0.52 (0.07 to 2.43)	**ICI+CT**	**2.20 (1.23 to 4.01)**
0.40 (0.25 to 0.63)	1.08 (0.41 to 3.85)	2.24 (0.59 to 8.90)	**0.45 (0.25 to 0.84)**	**0.28 (0.14 to 0.57)**	0.96 (0.14 to 4.01)	**1.82 (1.05 to 3.08)**	**CT**

Supplementary Figure S4. Forest plots and PWMA of head-to-head comparisons for the risk of all-grade trAEs.

Squares are the point estimates of the odds ratios with the 95% CIs indicated by horizontal bars. Diamonds are the summary estimates and 95% CIs from the pooled studies. PWMA=pairwise meta-analysis. CIs=confidence intervals. trAE=treatment-related adverse event. ICI=immune checkpoint inhibitor. CT=conventional therapy.



Supplementary Figure S5. Forest plots and PWMA of head-to-head comparisons for the risk of grade 3–4 trAEs.

Squares represent the point estimates of the odds ratios with the 95% CIs indicated by horizontal bars. Diamonds represent the summary estimates and 95% CIs from the pooled studies. PWMA=pairwise meta-analysis. CIs=confidence intervals. trAE=treatment-related adverse event. ICI=immune checkpoint inhibitor. CT=conventional therapy.