

Supplementary Information

Endocrine Toxicity of Immune Checkpoint Inhibitors: A Network Meta-analysis of the Current Evidence

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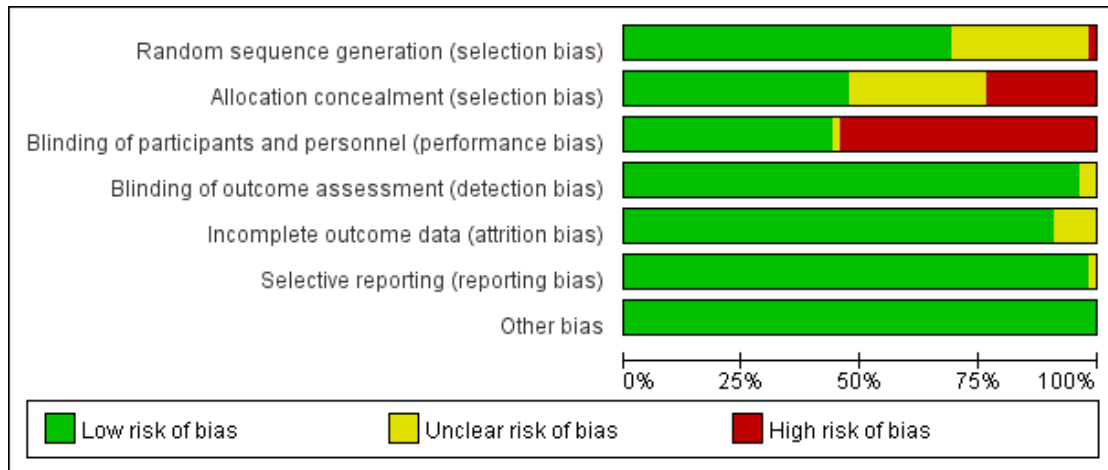


Figure S1 Risk of bias summary of the included RCTs.

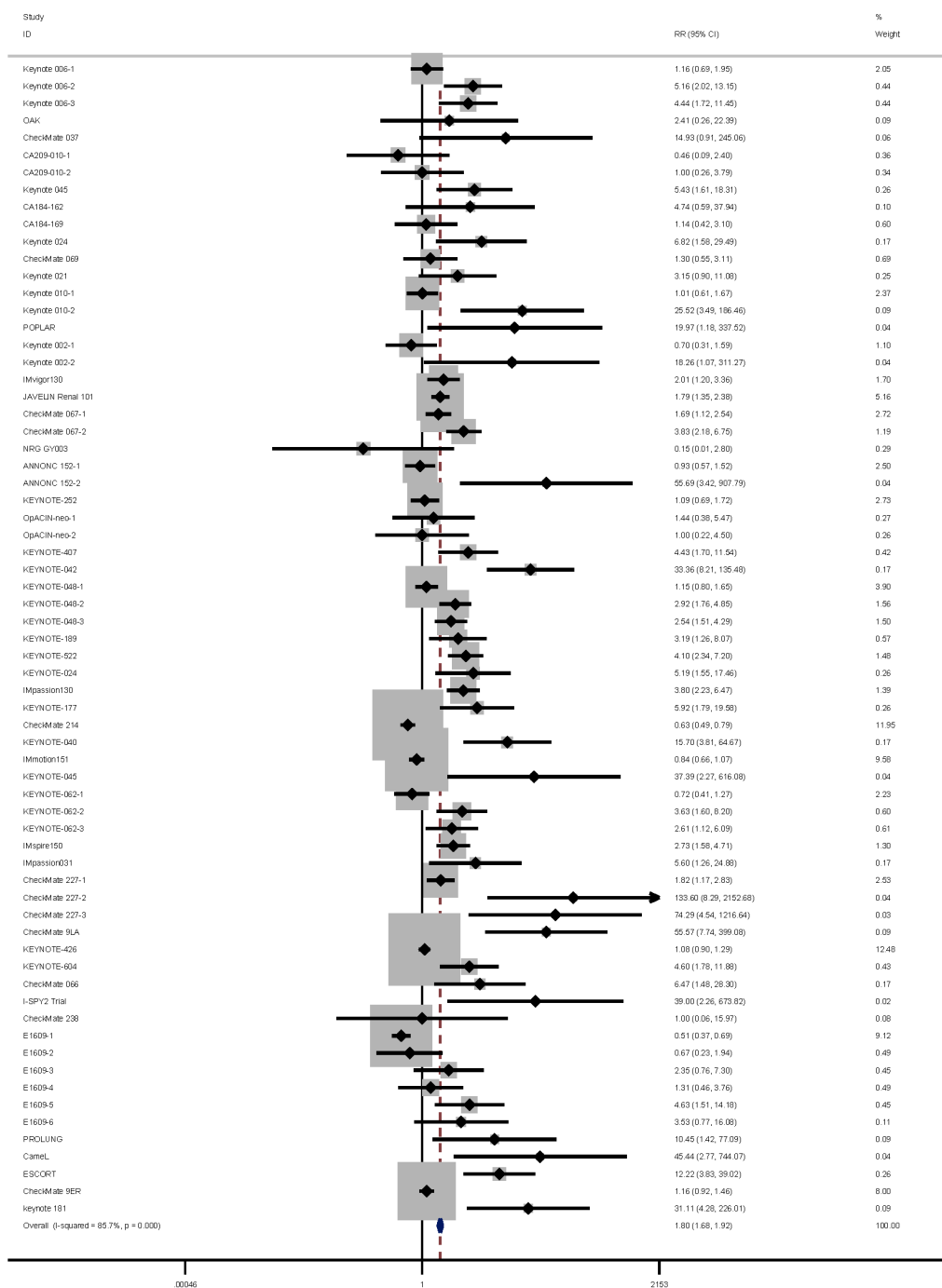


Figure S2 Forest plot of hypothyroidism, RR refers to Relative Risk, weight refers to the weight of each study in the combined Relative Risk, and I-squared (i.e., I^2) refers to the heterogeneity.

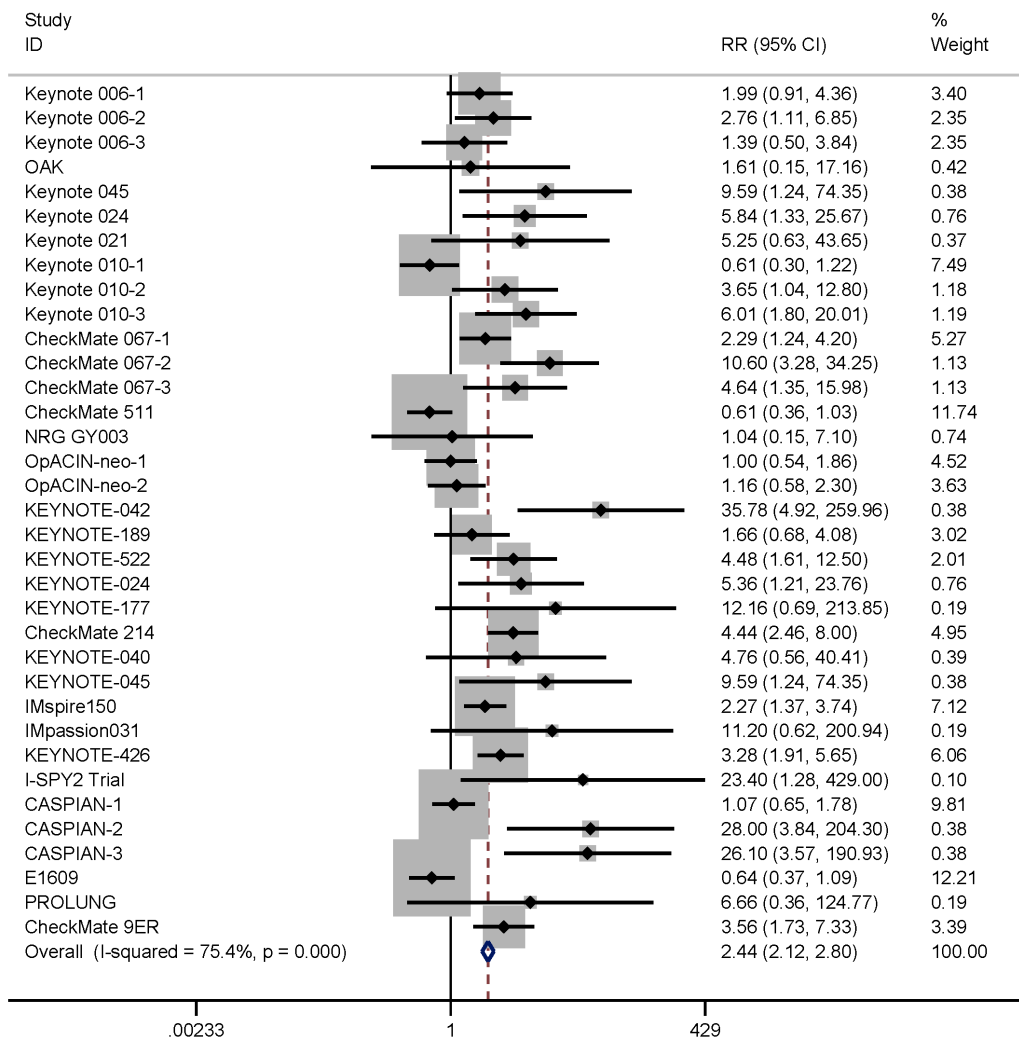


Figure S3 Forest plot of hyperthyroidism, RR refers to Relative Risk, weight refers to the weight of each study in the combined Relative Risk, and I-squared(i.e., I^2) refers to the heterogeneity.

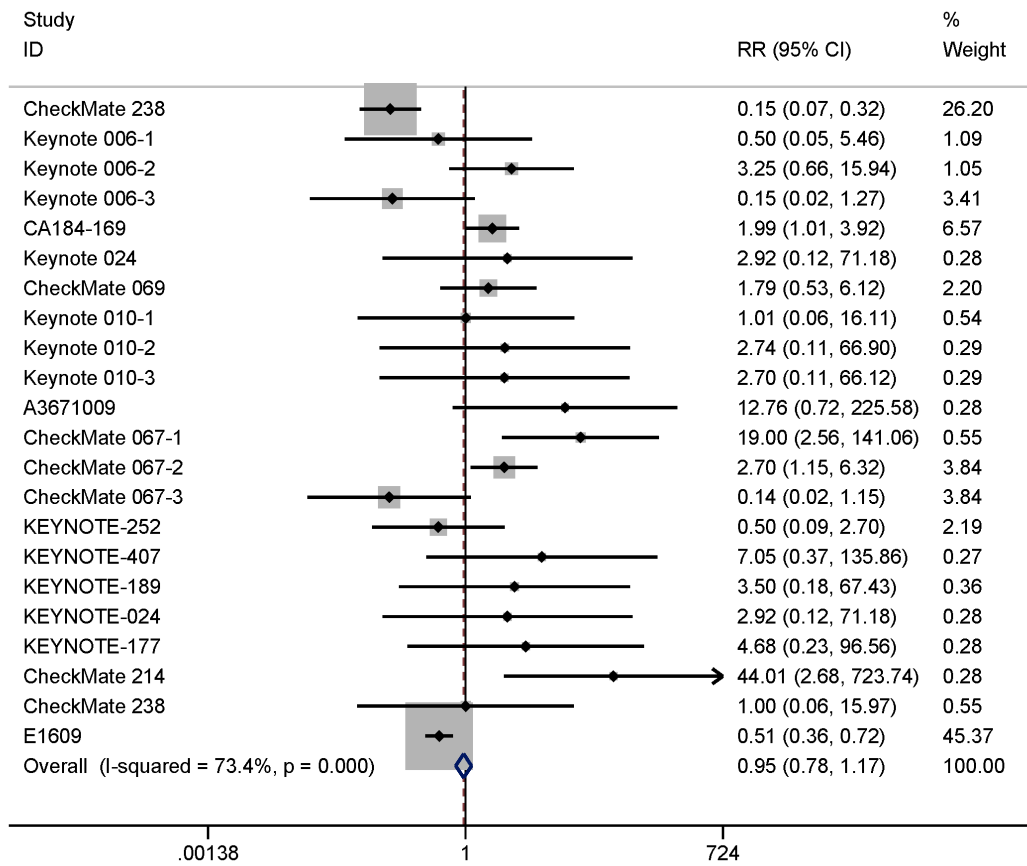


Figure S4 Forest plot of hypophysitis, RR refers to Relative Risk, weight refers to the weight of each study in the combined Relative Risk, and I-squared(i.e., I^2) refers to the heterogeneity.

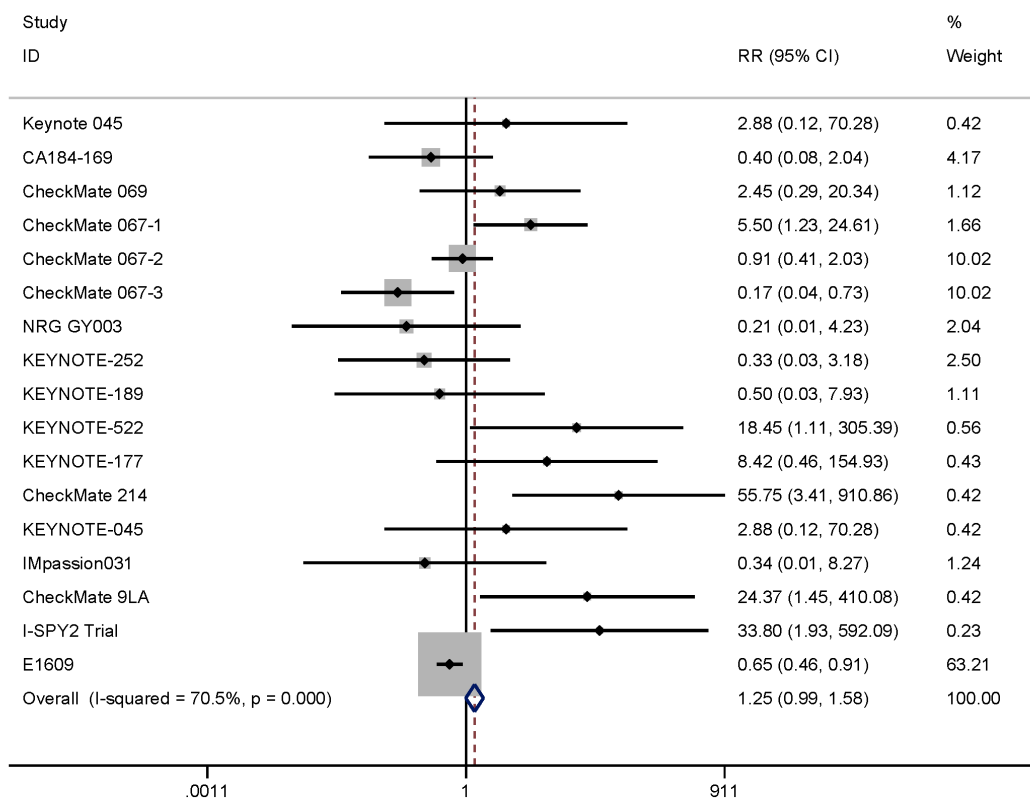


Figure S5 Forest plot of adrenal insufficiency, RR refers to Relative Risk, weight refers to the weight of each study in the combined Relative Risk, and I-squared(i.e., I^2) refers to the heterogeneity.

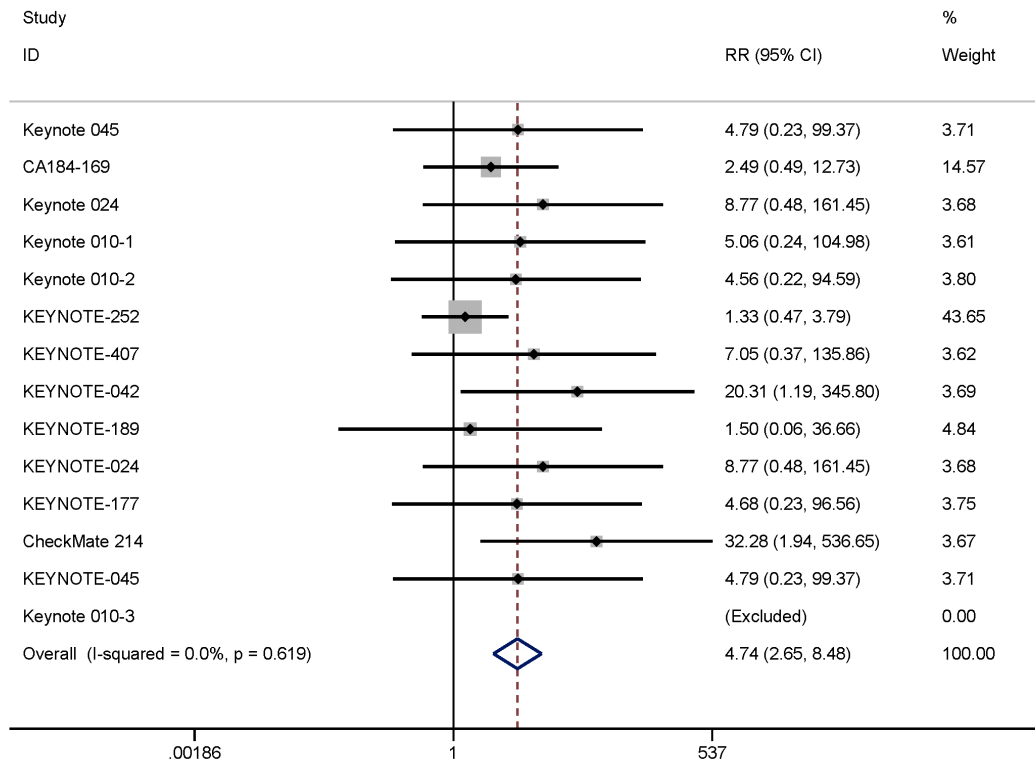


Figure S6 Forest plot of thyroiditis, RR refers to Relative Risk, weight refers to the weight of each study in the combined Relative Risk, and I-squared(i.e., I^2) refers to the heterogeneity.

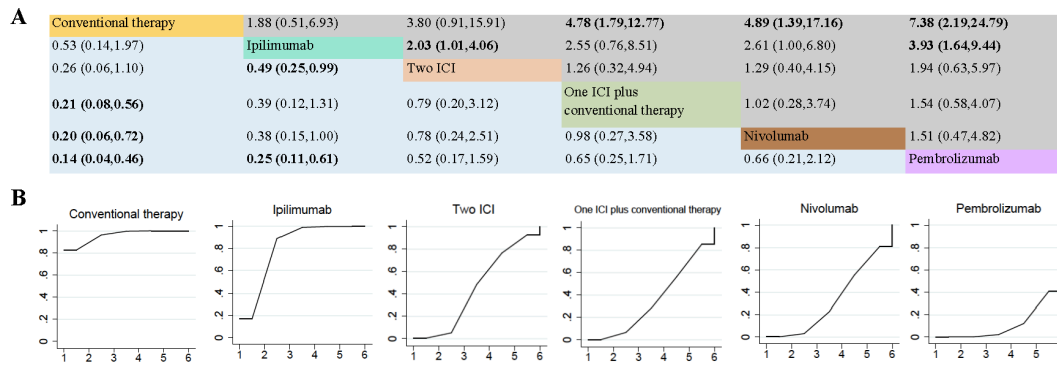


Figure S7 Subgroup Comparative Analysis of Hypothyroidism in Consistency Model-Based Network Meta-Analysis (NMA) of Melanoma. (A) League Table and (B) Probability Ranking Chart. Panel A presents a league table delineating the pooled odds ratios (OR) and corresponding 95% confidence intervals (CI) for drug-induced immune-related hypothyroidism across different treatment regimens. Statistically significant outcomes are highlighted in bold. Panel B depicts probability ranking curves, which quantify the likelihood of each treatment achieving a specified rank in terms of hypothyroidism risk reduction, ranging from the lowest to the highest. Abbreviations: ICI = Immune Checkpoint Inhibitor.

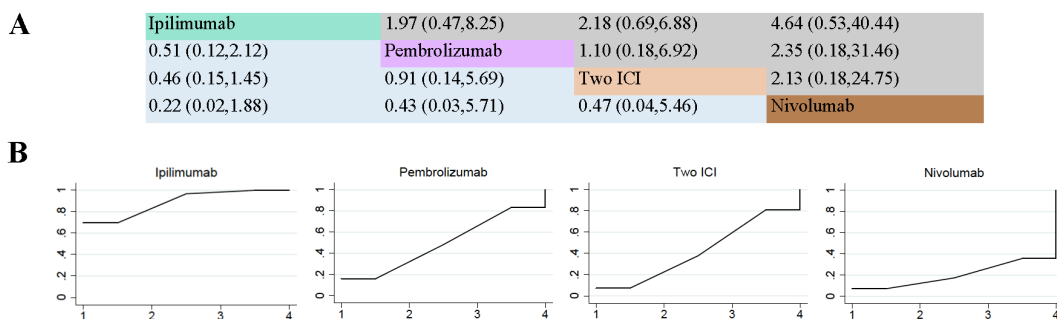


Figure S8 Subgroup Comparative Analysis of Hyperthyroidism in Consistency Model-Based Network Meta-Analysis (NMA) of Melanoma. (A) League Table and (B) Probability Ranking Chart. Panel A presents a league table delineating the pooled odds ratios (OR) and corresponding 95% confidence intervals (CI) for drug-induced immune-related hypothyroidism across different treatment regimens. Statistically significant outcomes are highlighted in bold. Panel B depicts probability ranking curves, which quantify the likelihood of each treatment achieving a specified rank in terms of hypothyroidism risk reduction, ranging from the lowest to the highest. Abbreviations: ICI = Immune Checkpoint Inhibitor.

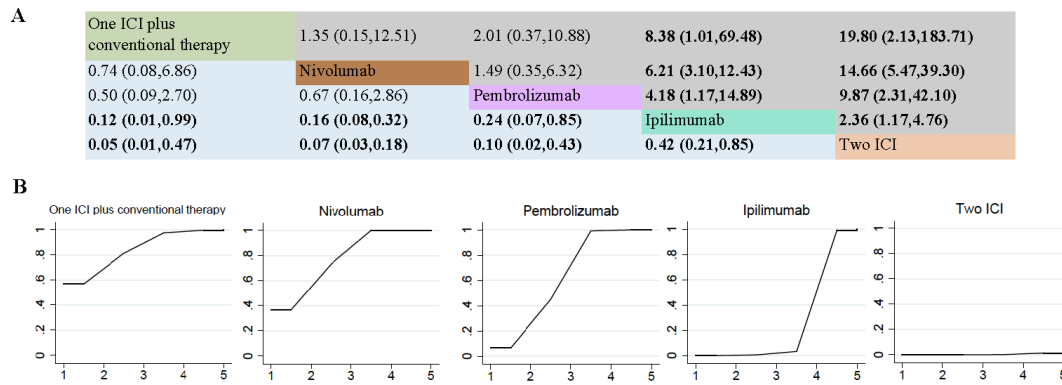


Figure S9 Subgroup Comparative Analysis of Hypophysitis in Consistency Model-Based Network Meta-Analysis (NMA) of Melanoma. (A) League Table and (B) Probability Ranking Chart. Panel A presents a league table delineating the pooled odds ratios (OR) and corresponding 95% confidence intervals (CI) for drug-induced immune-related hypothyroidism across different treatment regimens. Statistically significant outcomes are highlighted in bold. Panel B depicts probability ranking curves, which quantify the likelihood of each treatment achieving a specified rank in terms of hypothyroidism risk reduction, ranging from the lowest to the highest. Abbreviations: ICI = Immune Checkpoint Inhibitor.

A

Conventional therapy	4.36 (2.27,8.40)	5.44 (0.93,31.81)	11.32 (5.30,24.19)	25.22 (3.38,188.34)	55.57 (7.57,407.92)	74.29 (4.47,1235.63)	133.60 (8.16,2186.48)
0.23 (0.12,0.44)	One ICI plus conventional therapy	1.25 (0.19,8.06)	2.59 (1.01,6.70)	5.78 (0.70,47.87)	12.73 (1.56,103.77)	17.02 (0.95,305.20)	30.61 (1.73,540.29)
0.18 (0.03,1.08)	0.80 (0.12,5.19)	Atezolizumab	2.08 (0.31,14.11)	4.64 (0.32,67.37)	10.22 (0.71,146.53)	13.66 (0.49,377.82)	24.56 (0.90,670.23)
0.09 (0.04,0.19)	0.39 (0.15,0.99)	0.48 (0.07,3.26)	Pembrolizumab	2.23 (0.26,19.10)	4.91 (0.58,41.42)	6.56 (0.36,120.67)	11.80 (0.65,213.65)
0.04 (0.01,0.30)	0.17 (0.02,1.43)	0.22 (0.01,3.13)	0.45 (0.05,3.85)	Tremelimumab	2.20 (0.13,37.37)	2.95 (0.09,93.35)	5.30 (0.17,165.69)
0.02 (0.00,0.13)	0.08 (0.01,0.64)	0.10 (0.01,1.40)	0.20 (0.02,1.72)	0.45 (0.03,7.70)	Two ICI plus conventional therapy	1.34 (0.04,41.96)	2.40 (0.08,74.48)
0.01 (0.00,0.22)	0.06 (0.00,1.05)	0.07 (0.00,2.03)	0.15 (0.01,2.80)	0.34 (0.01,10.76)	0.75 (0.02,23.48)	Nivolumab	1.80 (0.03,94.76)
0.01 (0.00,0.12)	0.03 (0.00,0.58)	0.04 (0.00,1.11)	0.08 (0.00,1.53)	0.19 (0.01,5.91)	0.42 (0.01,12.88)	0.56 (0.01,29.30)	Two ICI

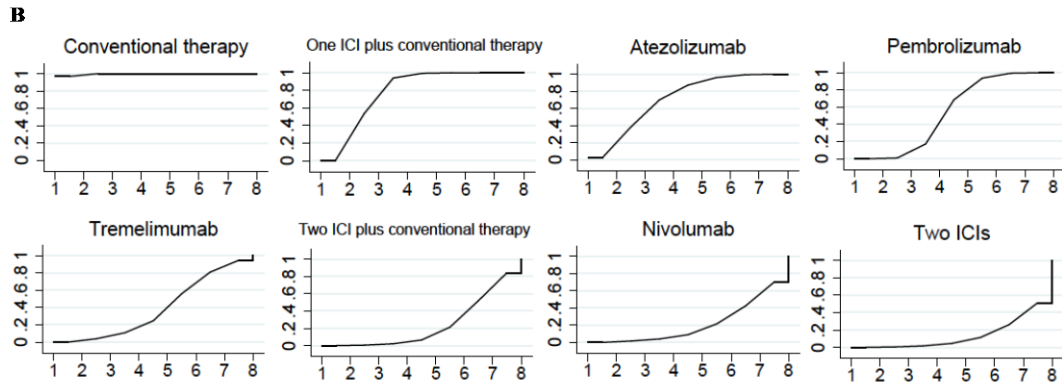


Figure S10 Subgroup Comparative Analysis of Hypothyroidism in Consistency Model-Based Network Meta-Analysis (NMA) of Non-Small Cell Lung Cancer. (A) League Table and (B) Probability Ranking Chart. Panel A presents a league table delineating the pooled odds ratios (OR) and corresponding 95% confidence intervals (CI) for drug-induced immune-related hypothyroidism across different treatment regimens. Statistically significant outcomes are highlighted in bold. Panel B depicts probability ranking curves, which quantify the likelihood of each treatment achieving a specified rank in terms of hypothyroidism risk reduction, ranging from the lowest to the highest. Abbreviations: ICI = Immune Checkpoint Inhibitor.

A

Conventional therapy	1.61 (0.15,17.16)	2.17 (0.98,4.79)	6.19 (3.28,11.66)
0.62 (0.06,6.64)	Atezolizumab	1.35 (0.11,16.38)	3.85 (0.33,44.67)
0.46 (0.21,1.02)	0.74 (0.06,9.02)	One ICI plus conventional therapy	2.86 (1.03,7.90)
0.16 (0.09,0.30)	0.26 (0.02,3.02)	0.35 (0.13,0.97)	Pembrolizumab

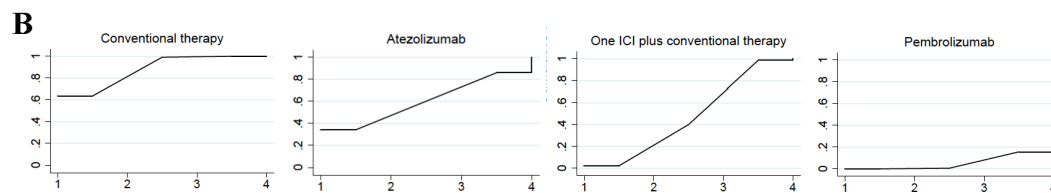


Figure S11 Subgroup Comparative Analysis of Hyperthyroidism in Consistency Model-Based Network Meta-Analysis (NMA) of Non-Small Cell Lung Cancer. (A) League Table and (B) Probability Ranking Chart. Panel A presents a league table delineating the pooled odds ratios (OR) and corresponding 95% confidence intervals (CI) for drug-induced immune-related hypothyroidism across different treatment regimens. Statistically significant outcomes are highlighted in bold. Panel B depicts probability ranking curves, which quantify the likelihood of each treatment achieving a

specified rank in terms of hypothyroidism risk reduction, ranging from the lowest to the highest.
Abbreviations: ICI = Immune Checkpoint Inhibitor.

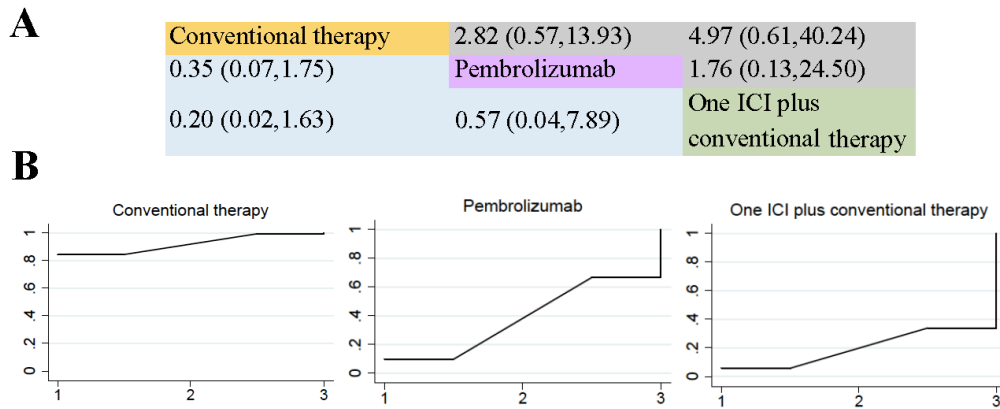


Figure S12 Subgroup Comparative Analysis of Hypophysitis in Consistency Model-Based Network Meta-Analysis (NMA) of Non-Small Cell Lung Cancer. (A) League Table and (B) Probability Ranking Chart. Panel A presents a league table delineating the pooled odds ratios (OR) and corresponding 95% confidence intervals (CI) for drug-induced immune-related hypothyroidism across different treatment regimens. Statistically significant outcomes are highlighted in bold. Panel B depicts probability ranking curves, which quantify the likelihood of each treatment achieving a specified rank in terms of hypothyroidism risk reduction, ranging from the lowest to the highest. Abbreviations: ICI = Immune Checkpoint Inhibitor.

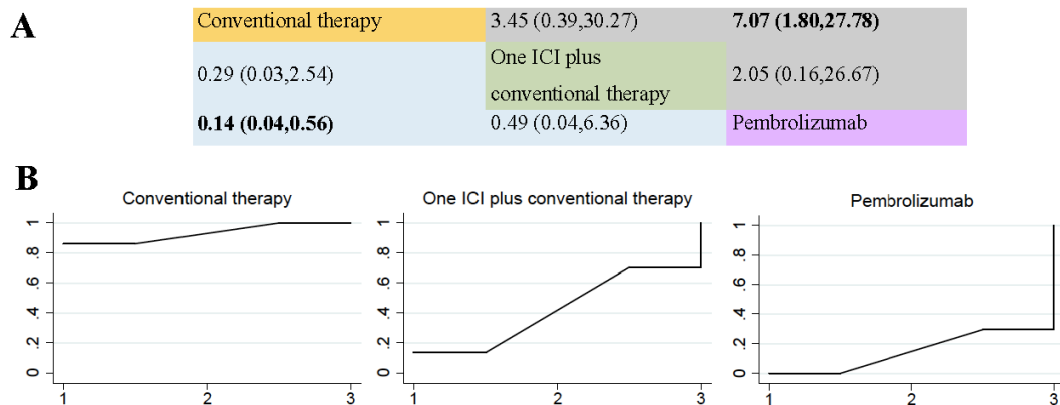


Figure S13 Subgroup Comparative Analysis of Thyroiditis in Consistency Model-Based Network Meta-Analysis (NMA) of Non-Small Cell Lung Cancer. (A) League Table and (B) Probability Ranking Chart. Panel A presents a league table delineating the pooled odds ratios (OR) and corresponding 95% confidence intervals (CI) for drug-induced immune-related hypothyroidism across different treatment regimens. Statistically significant outcomes are highlighted in bold. Panel B depicts probability ranking curves, which quantify the likelihood of each treatment achieving a specified rank in terms of hypothyroidism risk reduction, ranging from the lowest to the highest. Abbreviations: ICI = Immune Checkpoint Inhibitor.

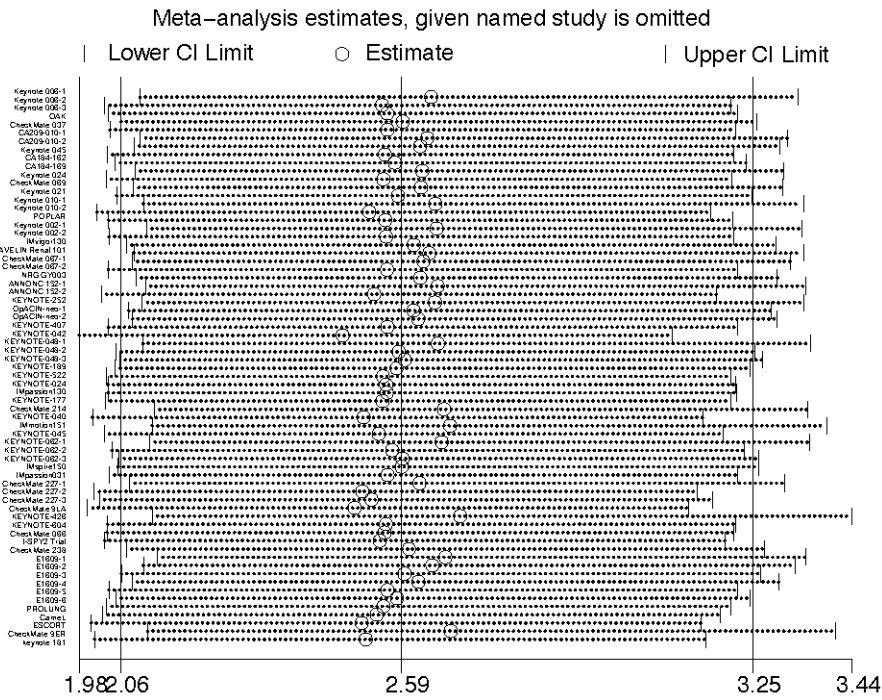


Figure S14 Sensitivity analysis of hypothyroidism in Network Meta-Analysis (NMA).

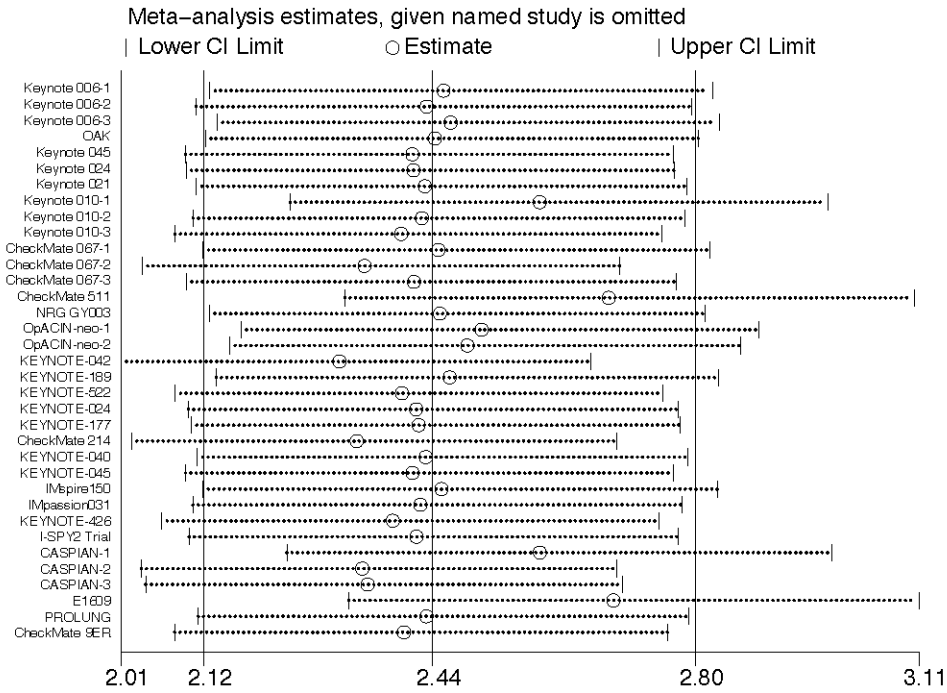


Figure S15 Sensitivity analysis of hyperthyroidism in Network Meta-Analysis (NMA).

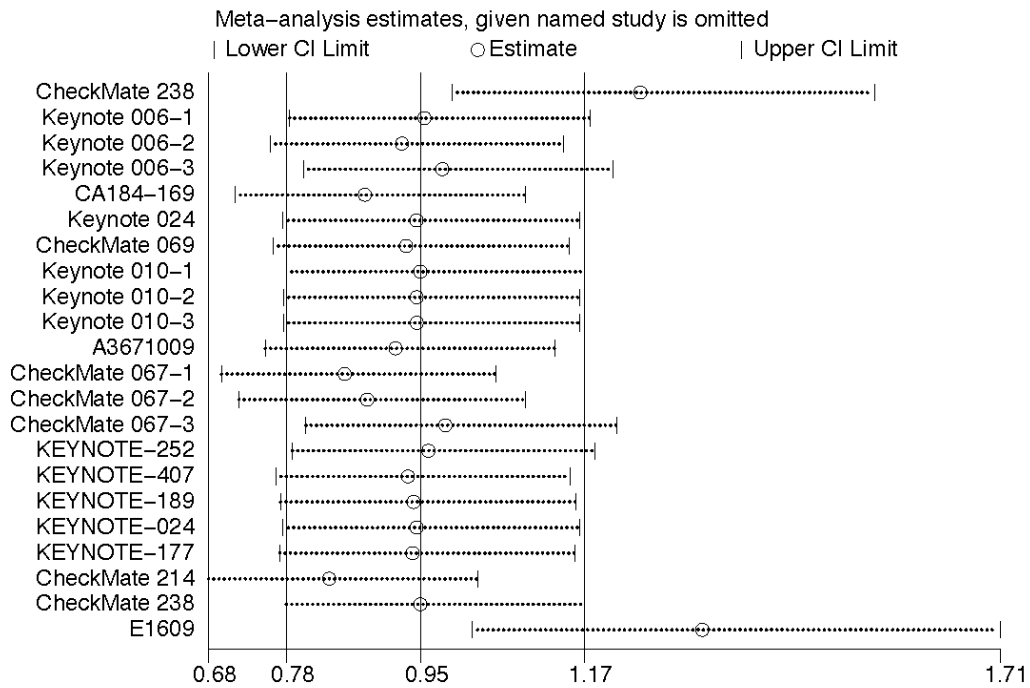


Figure S16 Sensitivity analysis of hypophysitis in Network Meta-Analysis (NMA).

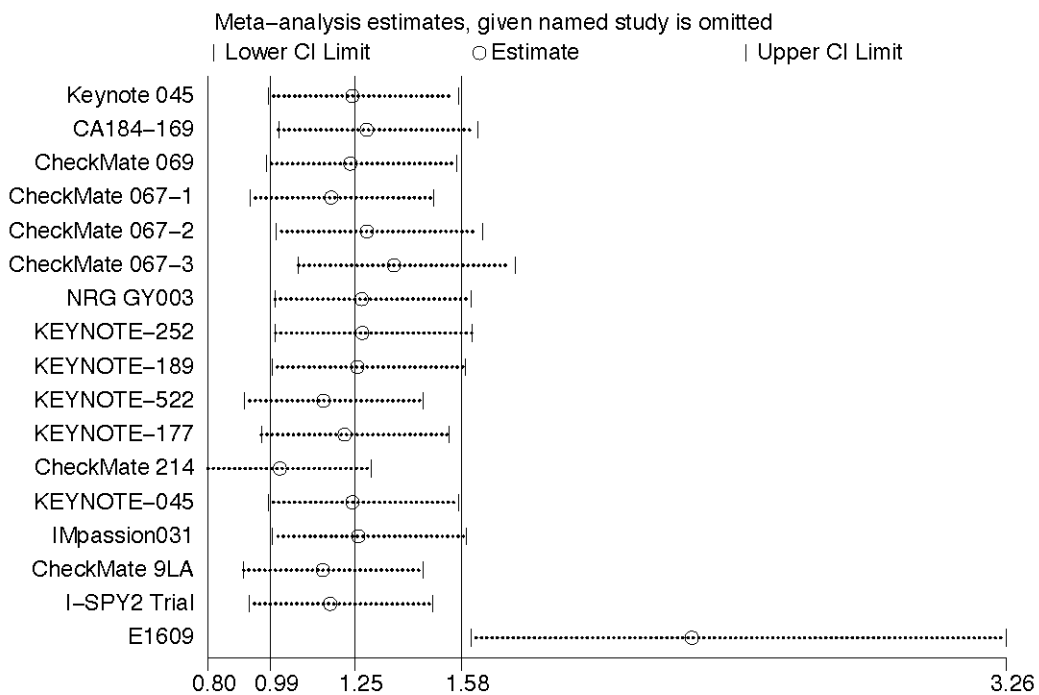


Figure S17 Sensitivity analysis of adrenal insufficiency in Network Meta-Analysis (NMA).

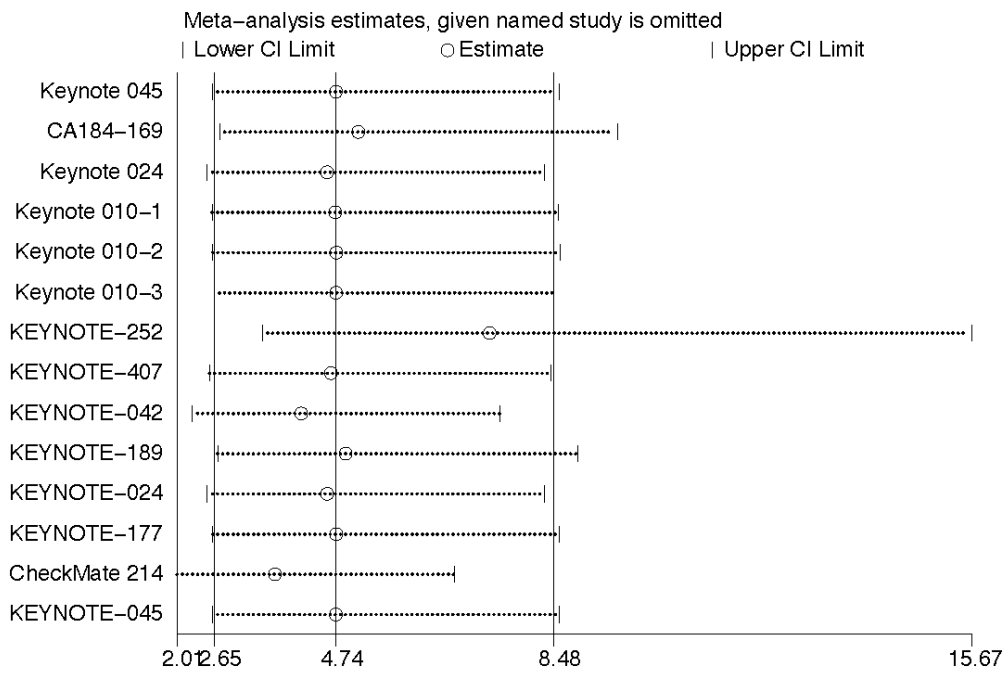


Figure S18 Sensitivity analysis of thyroiditis in Network Meta-Analysis (NMA).

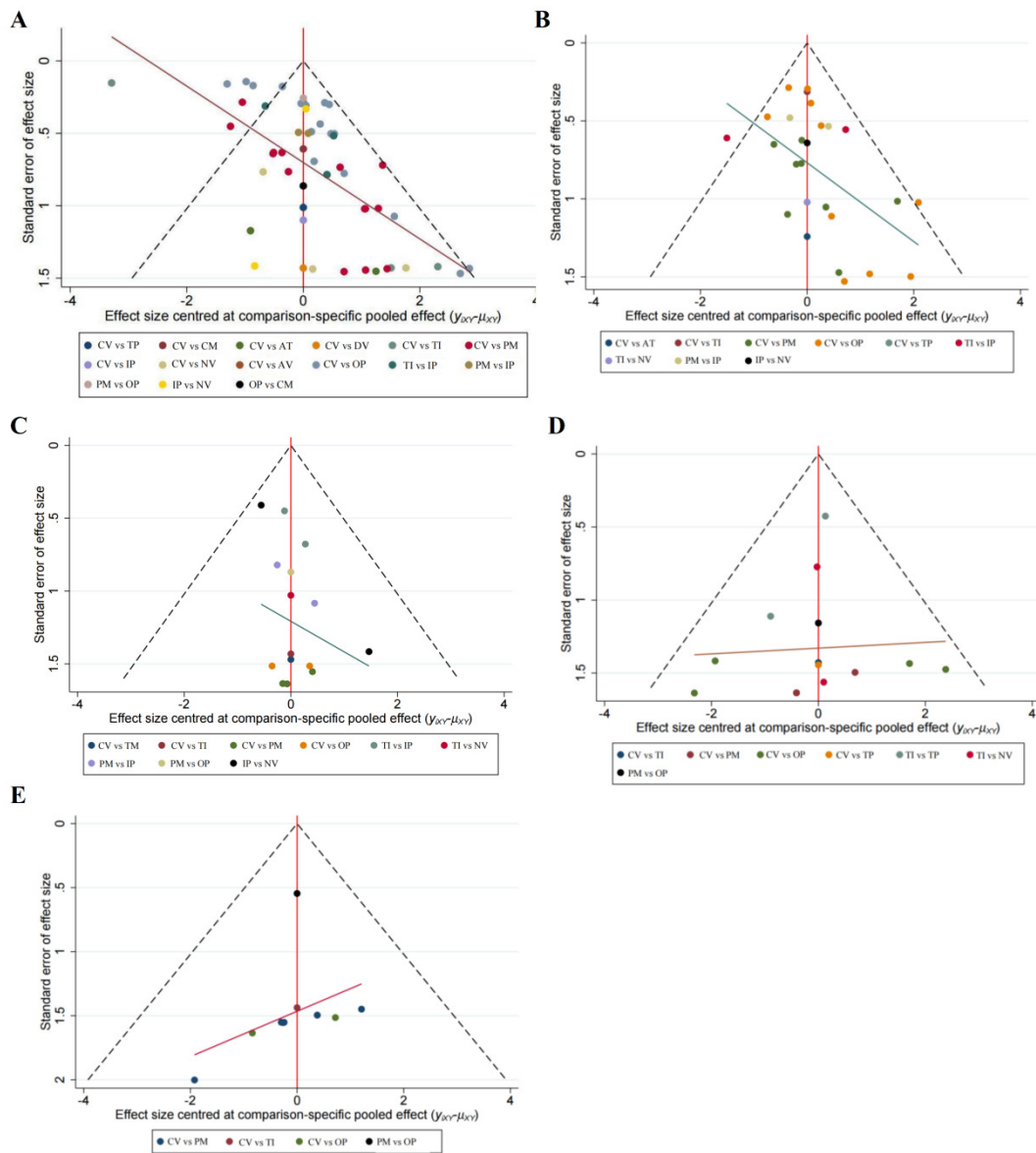


Figure S19 Funnel plot for reticulated meta-analysis of hypothyroidism (A), hyperthyroidism (B), hypophysitis (C), adrenal insufficiency (D) and thyroiditis (E). CV=conventional therapy; AT=atezolizumab; DV=durvalumab; TI=two ICI drugs combined with each other; PM=pembrolizumab; IP=ipilimumab; NV= nivolumab; AV=avelumab; OP=one ICI drug combined with conventional therapy; TP= two ICI drug combined with conventional therapy; CM=cemiplimab; TM= tislelizumab.

Table S1 The detailed search strategy.

Sources	Queries
PubMed	("Immune Checkpoint Inhibitors"[Title/Abstract] OR "checkpoint inhibitors immune"[Title/Abstract] OR "immune checkpoint inhibitor"[Title/Abstract] OR "checkpoint inhibitor immune"[Title/Abstract] OR "ICI"[Title/Abstract] OR "ICIs"[Title/Abstract] OR "Immune Checkpoint Blockers"[Title/Abstract] OR "checkpoint blockers immune"[Title/Abstract] OR "immune-checkpoint blockade"[Title/Abstract] OR "immune-checkpoint blockade"[Title/Abstract] OR "nivolumab"[Title/Abstract] OR "pembrolizumab"[Title/Abstract] OR "atezolizumab"[Title/Abstract] OR "avelumab"[Title/Abstract] OR "durvalumab"[Title/Abstract] OR "ipilimumab"[Title/Abstract] OR "tremelimumab"[Title/Abstract] OR "PD-1"[Title/Abstract] OR "PD-L1"[Title/Abstract] OR "anti-PD-1"[Title/Abstract] OR "anti-PD-L1"[Title/Abstract] OR "anti pd l 1"[Title/Abstract] OR "pd l 1"[Title/Abstract] OR "CTLA-4"[Title/Abstract] OR "anti-CTLA-4"[Title/Abstract] OR "anti-cytotoxic T-lymphocyte antigen-4"[Title/Abstract]) AND "clinical trial"[Publication Type]
Cochrane	<p><i>Title Abstract Keywords:</i></p> <p>(Immune Checkpoint Inhibitors or checkpoint inhibitors immune or immune checkpoint inhibitor or checkpoint inhibitor immune or ICI or ICIs or Immune Checkpoint Blockers or immune-checkpoint inhibitor or immune checkpoint inhibitor or immune-checkpoint blockade or immune checkpoint blockade or PD-1 or PD-L1 or PD-L1 or anti-PD-1 or anti-PD-L1 or anti pd l 1 or pd l 1 or CTLA-4 or anti-CTLA-4 or anti-cytotoxic T-lymphocyte antigen-4):ti,ab,kw AND (nivolumab or pembrolizumab or atezolizumab or avelumab or durvalumab or ipilimumab or tremelimumab):ti,ab,kw AND (clinical trial):ti,ab,kw</p>

Table S2 Global inconsistency test

Type of adverse reactions	Hypothyroidism	Hyperthyroidism	Hypophysitis	Adrenal insufficiency	Thyroiditis
P value	0.5695	0.6668	0.8973	0.5237	0.6033

Table S3 Closed-loop inconsistency test for hypothyroidism

Loop	IF	seIF	z value	p value	CI 95%	Loop Heterog tau2
A-E-I	1.251	0.786	1.592	0.111	(0.00, 2.79)	0.428
A-E-F	1.063	1.414	0.752	0.452	(0.00, 3.83)	0.396
A-D-F	0.253	2.622	0.096	0.923	(0.00, 5.39)	2.211
A-I-K	0.207	1.486	0.139	0.889	(0.00, 3.12)	0.419
A-F-G	0.044	1.299	0.034	0.973	(0.00, 2.59)	0.000

A=conventional therapy, D=two ICI drugs combined with each other, E=PEM, F=IPI, G=NIV, I= one ICI drug combined with conventional therapy, K=cemiplimab

Table S4 Closed-loop inconsistency test for hyperthyroidism

Loop	IF	seIF	z value	p value	CI 95%	Loop Heterog tau2
A-C-D-E	0.592	0.881	0.672	0.501	(0.00, 2.32)	0.183
C-E-F	0.575	2.155	0.267	0.790	(0.00, 4.80)	1.222

A=conventional therapy, C=two ICI drugs combined with each other, D=PEM, E=IPI, F=NIV

Table S5 Closed-loop inconsistency test for hypophysitis

Loop	IF	seIF	z value	p value	CI 95%	Loop Heterog tau2
A-D-G	1.163	1.558	0.747	0.455	(0.00, 4.22)	0.000
A-C-D-E	0.313	1.772	0.177	0.860	(0.00, 3.79)	0.000
C-E-F	0.256	1.207	0.212	0.832	(0.00, 2.62)	0.028

A=conventional therapy, C=two ICI drugs combined with each other, D=PEM, E=IPI, F=NIV, G=one ICI drug combined with conventional therapy

Table S6 Closed-loop inconsistency test for insufficiency

Loop	IF	seIF	z value	p value	CI 95%	Loop Heterog tau2
A-C-F	0.907	2.258	0.402	0.688	(0.00, 5.33)	1.496

A=conventional therapy, C=PEM, F=one ICI drug combined with conventional therapy

Table S7 Closed-loop inconsistency test for thyroiditis

Loop	IF	seIF	z value	p value	CI 95%	Loop Heterog tau2
A-B-D	0.864	1.355	0.638	0.524	(0.00, 3.52)	0.000

A=conventional therapy, B=PEM, D=one ICI drug combined with conventional therapy

Table S8 Node-splitting test for hypothyroidism

Node	Direct		Indirect		Difference		P> z
	Coef.	Std.Err.	Coef.	Std.Err.	Coef.	Std.Err.	
AvsD	1.139395	0.730701	1.831346	0.745139	-0.691951	1.02574	0.500
AvsE	2.300975	0.309985	1.88652	0.650815	0.414454	0.708906	0.559
AvsF	1.644123	1.364308	0.778167	0.520035	0.865956	1.460059	0.553
AvsG	2.709734	0.800451	1.310715	0.922993	1.399019	1.217184	0.250
AvsI	1.135496	0.232927	2.15324	0.766821	-1.017744	0.799916	0.203
AvsK	2.671847	1.023832	2.612703	1.215396	0.059144	1.589156	0.970
DvsF	-0.751486	0.496423	-0.059530	0.891746	-0.691955	1.02572	0.500
EvsF	-1.643979	0.685934	-1.019218	0.692709	-0.624761	0.974850	0.522
EvsI	0.095881	0.835070	-1.203184	0.364838	1.299066	0.911290	0.154
FvsG	0.688897	0.761477	2.087916	0.953894	-1.399018	1.21718	0.250
IvsK	1.386294	1.193106	1.445437	1.049723	-0.0591429	1.589157	0.970

A=conventional therapy, D=two ICI drugs combined with each other, E=PEM, F=IPI, G=NIV, I=one ICI drug combined with conventional therapy, K=cemiplimab

Table S9 Node-splitting test for hyperthyroidism

Node	Direct		Indirect		Difference		P> z
	Coef.	Std.Err.	Coef.	Std.Err.	Coef.	Std.Err.	
AvsC	1.57994	0.44722	2.193111	0.642209	-0.613170	0.782584	0.433
AvsD	1.964142	0.310025	1.350965	0.71634	0.613176	0.782572	0.433
CvsE	-0.904979	0.379876	-0.605498	0.609571	-0.299480	0.716455	0.676
CvsF	0.041672	1.058968	0.800070	0.771834	-0.758397	1.310397	0.563
DvsE	-0.725521	0.423208	-1.338699	0.656849	0.613177	0.782575	0.433
EvsF	1.570101	0.700772	0.811703	1.107276	0.758398	1.310398	0.563

A=conventional therapy, C=two ICI drugs combined with each other, D=PEM, E=IPI, F=NIV

Table S10 Node-splitting test for hypophysitis

Node	Direct		Indirect		Difference		P> z
	Coef.	Std.Err.	Coef.	Std.Err.	Coef.	Std.Err.	
AvsC	3.825513	1.431159	3.787156	0.982312	0.038357	1.735843	0.982
AvsD	1.15028	0.723780	1.944326	1.048309	-0.794045	1.273895	0.533
AvsG	1.611443	1.070753	0.497048	1.091695	1.114394	1.529153	0.466
CvsE	-0.912716	0.374709	-1.091819	0.924632	0.179103	0.997673	0.858
CvsF	-3.003862	1.029193	-2.778378	0.537819	-0.225484	1.161244	0.846
DvsE	1.449404	0.654475	1.487739	1.607732	-0.038335	1.73584	0.982
DvsG	-0.70173	0.869323	0.412663	1.25801	-1.114394	1.529154	0.466
EvsF	-1.862786	0.394150	-2.088271	1.092306	0.225485	1.161244	0.846

A=conventional therapy, C=two ICI drugs combined with each other, D=PEM, E=IPI, F=NIV, G=one ICI drug combined with conventional therapy

Table S11 Node-splitting test for insufficiency

Node	Direct		Indirect		Difference		P> z
	Coef.	Std.Err.	Coef.	Std.Err.	Coef.	Std.Err.	
AvsB	4.073385	1.445364	0.252749	882.328	3.820636	882.3292	0.997
AvsC	1.466096	0.960209	2.38522	1.485733	-0.919124	1.768676	0.603
AvsF	1.27805	0.784415	0.358925	1.585569	0.919124	1.768657	0.603
BvsD	-0.059296	0.616451	-8.099082	2376.217	8.039785	2376.217	0.997
BvsE	-1.708385	0.717245	-8.803991	3406.131	7.095606	3406.131	0.998
CvsF	-1.107172	1.261749	-0.188046	1.239391	-0.919125	1.768644	0.603

A=conventional therapy, B=two ICI drugs combined with each other, C=PEM, D=IPI, E=NIV, F=one ICI drug combined with conventional therapy

Table S12 Node-splitting test for thyroiditis

Node	Direct		Indirect		Difference		P> z
	Coef.	Std.Err.	Coef.	Std.Err.	Coef.	Std.Err.	
AvsB	1.81859	0.552040	0.954471	1.237695	0.864118	1.355226	0.524
AvsD	1.245048	1.111051	2.109166	0.776017	-0.864117	1.355226	0.524
BvsD	0.290576	0.545394	-0.573541	1.240638	0.864118	1.355226	0.524

A=conventional therapy, B=PEM, D=one ICI drug combined with conventional therapy