

Table S1. Search strategies for all sources searched.

Line #	MEDLINE (Ovid). Date searched 01/21/2022
1	(checkpoint adj3 (inhibitor* or modulator* or antibod* or block*)).ti,kf,rn.
2	(checkpoint and (inhibitor* or modulator* or antibod* or block*)).nm.
3	(immun* adj3 checkpoint adj3 (inhibitor* or modulator* or antibod* or block*)).ab.
4	((("cytotoxic T lymphocyte associated" adj3 "4") or "CTLA 4" or CTLA4).ti,kf,rn.
5	("Cytotoxic t-lymphocyte antigen" adj3 "4").ti,kf,rn.
6	("Cytotoxic t-lymphocyte antigen" or "cytotoxic T lymphocyte associated").nm.
7	(ipilimumab or "MDX CTLA 4" or Yervoy or "MDX 010" or MDX010 or "BMS-734016" or BMS734016).mp.
8	("Programmed Cell Death 1" or PD1 or "PD 1").ti,kf,rn,nm.
9	(pembrolizumab or Keytruda or Lambrolizumab or "Merck 3475" or Merck3475 or "MK 3475" or MK3475 or "Sch 900475" or Sch900475 or "HSDB 8257").mp.
10	(nivolumab or "BMS 936558" or BMS936558 or "MDX 1106" or MDX1106 or "ONO 4538" or ONO4538 or Opdivo).mp.
11	("AMP 514" or AMP514 or MEDI0680 or "MEDI 0680").mp.
12	("programmed death ligand 1" or "PD L1" or PDL1 or "B7-H1" or B7HI).ti,kf,rn,nm.
13	(atezolizumab or Tecentriq or MPDL3280A or "MPDL 3280A" or RO5541267 or RO-5541267 or RG 7446 or RG7446 or "CD274 ANTIGEN" or "CD274 protein").mp.
14	(durvalumab or imfinzi or "MEDI 4736" or MEDI4736).mp.
15	(avelumab or Bavencio or MSB0010718C or "MSB 0010718C" or MSB0010682).mp.
16	("BMS 936559" or BMS936559 or MDX1105 or "MDX 1105").mp.
17	(Cemiplimab or libtayo or REGN2810 or "REGN 2810").mp.
18	or/1-17
19	exp Neoplasms/
20	(cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta* or myeloma* or leuk?emia* or lymphoma* or sarcoma* or melanoma*).ti,ab,kf.
21	or/19-20
22	18 and 21
23	exp Influenza Vaccines/
24	((influenza* or flu or laiv) adj3 vaccin*).ti,ab,kf,rn.
25	23 or 24
26	22 and 25
	EMBASE (Ovid). Date searched 01/21/2022
1	(immun* adj3 checkpoint adj3 (inhibitor* or modulator* or antibod* or block*)).ti,ab,hw,kw.
2	((("cytotoxic T lymphocyte associated" adj3 "4") or "CTLA 4" or CTLA4).ti,ab,kw,hw.
3	("Cytotoxic t-lymphocyte antigen" adj3 "4").ti,ab,kw,hw.

4 (ipilimumab or "MDX CTLA 4" or Yervoy or "MDX 010" or MDX010 or "BMS-
 5 734016" or BMS734016).ti,ab,hw,kw,du,tn.
 6 ("Programmed Cell Death 1" or PD1 or "PD 1").ti,ab,kw,hw,du,tn.
 7 (pembrolizumab or Keytruda or Lambrolizumab or "Merck 3475" or Merck3475 or
 8 "MK 3475" or MK3475 or "Sch 900475" or Sch900475 or "HSDB
 9 8257").ti,ab,kw,hw,du,tn.
 10 (nivolumab or "BMS 936558" or BMS936558 or "MDX 1106" or MDX1106 or
 11 "ONO 4538" or ONO4538 or Opdivo).ti,ab,kw,hw,du,tn.
 12 ("AMP 514" or AMP514 or MEDI0680 or "MEDI 0680").ti,ab,kw,hw,du,tn.
 13 ("programmed death ligand 1" or "PD L1" or PDL1).ti,ab,kw,hw.
 14 (atezolizumab or Tecentriq or MPDL3280A or "MPDL 3280A" or RO5541267 or
 15 RO-5541267 or RG 7446 or RG7446 or "CD274 ANTIGEN" or "CD274
 16 protein").ti,ab,kw,hw,du,tn.
 17 (durvalumab or imfinzi or "MEDI 4736" or MEDI4736).ti,ab,kw,kw,du,tn.
 18 (avelumab or Bavencio or MSB0010718C or "MSB 0010718C" or
 19 MSB0010682).ti,ab,kw,hw,du,tn.
 20 ("BMS 936559" or BMS936559 or MDX1105 or "MDX 1105").ti,ab,kw,hw,du,tn.
 21 (Cemiplimab or libtayo or REGN2810 or "REGN 2810").ti,ab,kw,hw,du,tn.
 22 or/1-14
 23 exp malignant neoplasm/
 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*
 or myeloma* or leuk?emia* or lymphoma* or sarcoma* or melanoma*).ti,ab,kw.
 16 or 17
 15 and 18
 exp influenza vaccine/
 ((influenza* or flu or laiv) adj3 vaccin*).ti,ab,kw.
 20 or 21
 19 and 22

Web of Science (Clarivate). Date searched 01/21/2022^a

TS= (immun* NEAR/3 checkpoint NEAR/3 (inhibitor* or modulator* or antibod*
 1 or block*))
 TS=((("cytotoxic T lymphocyte associated" NEAR/3 "4") or "CTLA 4" or CT
 2 LA4)
 TS=("Programmed Cell Death 1" or PD1 or "PD 1" or "programmed death 1
 3 igand 1" or "PD L1" or PDL1)
 TS=(ipilimumab or "MDX CTLA 4" or Yervoy or "MDX 010" or MDX010
 or tremelimumab or ticilimumab or "CP 675 206" or "CP 675206" or CP67
 4 520 or pembrolizumab or Keytruda or Lambrolizumab or "Merck 3475" or
 Merck3475 or "MK 3475" or MK3475 or "Sch 900475" or Sch900475)
 TS=(nivolumab or "BMS 936558" or BMS936558 or "MDX 1106" or MDX
 1106 or "ONO 4538" or ONO4538 or Opdivo or "AMP 514" or AMP514 o
 r MEDI0680 or "MEDI 0680" or atezolizumab or tecentriq or MPDL3280A
 or "MPDL 3280A" or durvalumab or imfinzi or "MEDI 4736" or MEDI4736
 5 or avelumab or bavencio or MSB0010718C or "MSB 0010718C" or "BMS

936559" or BMS936559 or MDX1105 or "MDX 1105" or cemiplimab or lib
tayo or REGN2810 or "REGN 2810")
6 #1 OR #2 OR #3 OR #4 OR #5
TS=(cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan*
or metasta* or myeloma* or leukaemia* or leukemia* or lymphoma* or sarc
7 oma* or melanoma*)
8 #7 AND #6
9 TS=((influenza* or flu or laiv) near/3 vaccin*)
10 #9 AND #8

Cochrane Library (Wiley). Date searched 01/21/2022

((ipilimumab or "MDX CTLA 4" or Yervoy or "MDX 010" or MDX010 or
tremelimumab or ticilimumab or "CP 675 206" or "CP 675206" or CP67520 or
pembrolizumab or Keytruda or Lambrolizumab or "Merck 3475" or Merck3475 or
1 "MK 3475" or MK3475 or "Sch 900475" or Sch900475)):ti,ab,kw^b
(nivolumab or "BMS 936558" or BMS936558 or "MDX 1106" or MDX1106 or
"ONO 4538" or ONO4538 or Opdivo or "AMP 514" or AMP514 or MEDI0680 or
"MEDI 0680" or atezolizumab or Tecentriq or MPDL3280A or "MPDL 3280A" or
durvalumab or imfinzi or "MEDI 4736" or MEDI4736 or avelumab or Bavencio or
MSB0010718C or "MSB 0010718C" or "BMS 936559" or BMS936559 or
MDX1105 or "MDX 1105" or cemiplimab or libtayo or REGN2810 or "REGN
2 2810"):ti,ab,kw
((immun* near/3 checkpoint near/3 (inhibitor* or modulator* or antibod* or
3 block*)):ti,ab,kw^b
(("cytotoxic T lymphocyte associated" near/3 "4") or "CTLA 4" or
4 CTLA4):ti,ab,kw
5 ("Programmed Cell Death 1" or PD1 or "PD 1")):ti,ab,kw^b
6 ("programmed death ligand 1" or "PD L1" or PDL1)):ti,ab,kw^b
7 #1 or #2 or #3 or #4 or #5 or #6
((cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or
metasta* or myeloma* or leukaemia* or leukemia* or lymphoma* or
8 sarcoma* or melanoma*)):ti,ab,kw^b
9 #7 AND #8
10 ((influenza* or flu or laiv) NEAR/3 vaccin*):ti,ab,kw^b
11 #9 AND #10

Clinicaltrials.gov (National Library of Medicine). Date searched 01/21/2022

checkpoint OR "Programmed Cell Death 1" OR PD1 OR "PD 1" OR "programmed
death ligand 1" OR "PD L1" OR PDL1 OR "cytotoxic T lymphocyte associated"
1 OR "CTLA 4" OR CTLA4 | cancer AND (influenza OR flu) AND vaccine

^aIndexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2022

^bWord variations were also searched

Table S2. Risk of bias within studies assessed with the New-Castle Ottawa Scale^a

Study	Selection		Comparability		Outcome		Overall score
	Case definition	Case representativeness	Control selection	Control definition	Exposure ascertainment	Non-response rate	
Awadalla 2019 ^{19,20a}	*	*			*	*	6

Study	Exposed	Unexposed	Exposure	Outcome		Assessment	Follow-Up	Attrition	
Bayle 2020 ⁹	*	N/A	*		N/A	*		N/A	3
Bersanelli 2018 ^{21,22}	*	*	*	*	**	*	*	*	9
Bersanelli 2021 ²³⁻²⁵	*	*	*	*	**	*	*	*	9
Chong 2019 ^{26,27}		N/A	*	*	N/A	*	*	N/A	4
De Toma 2019 ²⁸		N/A	*	*	N/A	*		N/A	3
Erickson 2021 ²⁹		*	*	*		*			4
Failing 2019 ^{30a}		*	*	*	**	*	*	*	8
Gopalakrishnan 2018 ³¹		*	*			*	*		4
Gwynn 2019 ³²		N/A	*	*	N/A	*		N/A	3
Kanaloupitis 2017 ³³		N/A	*	*	N/A	*		N/A	3
Keam 2019 ^{34,35}		N/A	*	*	N/A	*		N/A	3
Laubli 2018 ^{36,37,40}		N/A	*	*		*		N/A	3
Munoz Burgos 2018 ⁵⁰		*	*			*			3
Reddy 2019 ³⁸		*	*		**	*			5
Roberts 2019 ³⁹		*	*			*			3
Valachis 2021 ⁴¹	*	*	*	*	**	*	*	*	9
Vutukuri 2021 ⁴²		*	*	*		*			4
Wijn 2018 ⁴³		*	*		*	*	*		5

N/A, not applicable.

^aFor uncontrolled trials and case series non-relevant items (to evaluate a control group) were marked as N/A.

Table S3. Frequency of reported immune related adverse events in vaccinated and unvaccinated patients.

Study	Adverse event	Vaccinated (%)	Unvaccinated (%)
Awadalla 2019 ^{19,20a}	Hypophysitis	4	7
	Hepatitis	4	9
	Colitis	8	9
	Dermatitis	0	8
	Neurological	4	13
	Gastritis	0	4
	Pneumonitis	12	36
	Cardiovascular death	36	72
	Complete heart block	9	19
	Cardiogenic shock	9	20
	Cardiac arrest	9	17
Bayle 2020 ⁹	Not specified	50	NA
Bersanelli 2018 ^{21,22}	NR	NR	NR
Bersanelli 2020 ²³	NR	NR	NR
Chong 2019 ^{26,27}	Endocrine (unspecified)	28	NA
	Pneumonitis	25	
	Colitis	13	
	Transaminitis	12	
De Toma 2019 ²⁸	Pneumonitis	4.8	NA
Erickson 2021 ²⁹	Cutaneous	68	40%
Failing 2019 ³⁰	Thyroiditis	38.9	32.4
	Dermatitis	5.6	21.6
	Colitis	22.2	10.8
	Pneumonitis	16.7	5.4
	Arthritis	5.6	8.1
	Hepatitis	5.6	2.7
	Adrenal insufficiency	0	5.4
	Neuritis	0	2.7
	Hypoglycemia	0	2.7
	Hyperglycemia	1	0
	Pancreatitis	0	2.7
	Thrombocytopenia	0	2.7
	Hearing loss	0	2.7
Gopalakrishnan 2018 ³¹	Pneumonitis	17.2	37.2
Gwynn 2019 ³²	Diabetes	13	NA
	Nephritis	13	
	Hypothyroidism	13	
	Myalgia	13	
	Colitis	13	
	Rash	38	
Kanaloupitis 2017 ³³	Myalgia	4	NA
Keam 2019 ^{34,35}	Hypothyroidism	2	NA
	Pneumonitis	2	
	Inflammatory arthritis	2	
	Nephritis	2	
Laubli 2018 ^{36,37,40}	Rash	13	NA
	Arthritis	13	
	Colitis	8.7	

	Encephalitis	8.7	
	Hypothyroidism	4.3	
	Pneumonitis	4.3	
	Neuropathy	4.3	
Munoz Burgos 2018 ⁵⁰	Rash	19	33
	Nephritis	5	NR
	Hypothyroidism	5	NR
	Neuritis	5	NR
	Liver dysfunction	5	NR
	Renal dysfunction	5	NR
	Psoriasis exacerbation	5	NR
Reddy 2019 ³⁸	Colitis	0	1
	Pneumonitis	9	4
	Hepatitis	3	5
Roberts 2019 ³⁹	Not specified	4.4	10.8
Valachis 2021 ⁴¹	Endocrine	11.5	6.9
	Skin toxicity	10.6	3.4
	Rheumatic	4.7	10.3
	Hepatitis	5.5	0
	Colitis	3.4	6.9
	Pneumonitis	4.3	3.4
	Neurologic	1.7	6.9
	Renal toxicity	1.3	3.4
	Other	4.3	6.9
Vutukuri 2021 ⁴²	Not specified	30.2	45
Wijn 2018 ⁴³	Endocrine (unspecified)	7	8
	Pulmonary	10	5
	Gastrointestinal	2	2
	Hepatic	2	2
	Arthritis	2	1
	Neurological	2	0
	Skin	0	1
	Other	0	2

NR, not reported; NA, not applicable

^aAwadalla et al 2019 reported rates of any type of irAEs in patients who already had myocarditis due to the immune checkpoint inhibitor.

Figure S1. Funnel plot for primary outcome (Egger test=0.55).

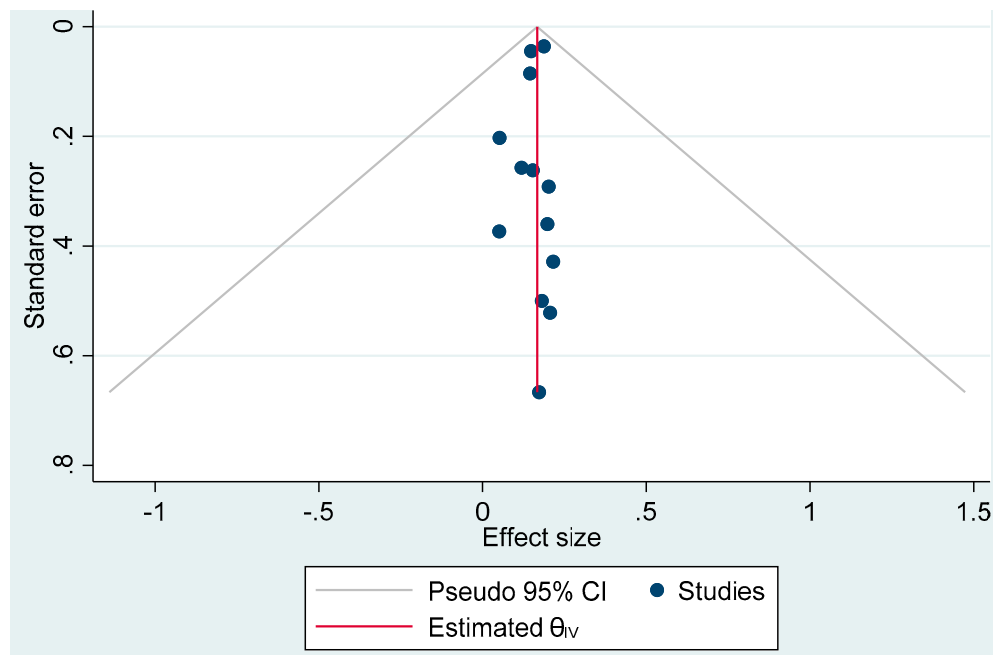


Table S4. Summary of findings table.

Outcomes	No. of participants Studies Follow-up (median time)	Quality of the evidence (GRADE)	Estimate (95% CI)	Comments
Proportion of irAEs	1334 17 studies (15 observational, 2 trials) 60 days to 31 months	⊕⊕⊕⊖ Low due to risk of bias and inconsistency ^{a,b}	Proportion 30%, 95% CI 22% to 40%	-
Risk of developing immune-related adverse events	2485 10 studies (10 observational) 107 days to 28 months	⊕⊕⊕⊖ Low due to risk of bias ^a	RR 0.90, 95% CI 0.72 to 1.1	-
Rates of vaccination among participants with irAEs	540 1 study (observational) 175 to 290 days	⊕⊖⊖⊖ Very low due to risk of bias, indirectness and publication bias ^{a,c,d}	OR 0.54 (95% CI 0.34 to 0.86)	-
Median time from vaccination to irAEs	555 4 studies (3 observational, 1 trial) 60 days to 519 days	⊕⊖⊖⊖ Very low due to risk of bias and inconsistency ^{a,b}	37 days (range 14-60) to 3.2 months (range 0- 10.6)	-

^aObservational studies without adjustment for confounding risks factors and uncontrolled case series. “In the GRADE approach to quality of evidence, observational studies without special strengths or important limitations provide low quality of evidence”¹⁸. However, for ethical reasons, no randomized controlled trials have been conducted to evaluate the benefits and harms of influenza vaccination in patients receiving ICIs.

^bInconsistency score higher than 50%.

^cSurrogate outcome (indirectly measuring the probability of irAEs).

^dResults from only one retrospective observational study.