Search Strategy

Source	MEDLINE
Type of Study	Overview of Systematic Reviews (OsSRs)
Language	English
Date of search	29/10/2018
Search Terms	immune checkpoint inhibitors or ipilimumab or nivolumab or pembrolizumab or avelumab or atezolizumab) AND (side effects or safety or adverse drug reactions or toxicities or immune-related adverse events)
Restrictions/filters	English, systematic review, published as of 30/06/2018
References	1451
Inclusion criteria	Systematic Reviews of randomized controlled trials (RCTs), comparing immune checkpoint inhibitors with other anticancer drugs, providing incidence rates (quality assessment) and/or measure of risk estimate (quantitative assessment)
Additional procedure undertaken	Snowballing of systematic reviews
Exclusion criteria	Meta-analysis without systematic reviews (e.g., letters to the editor), meta-analysis on safety without specifying types of adverse events, network-meta-analysis, full text not available, review articles, commentaries/correspondence
Quality criteria	AMSTAR tool

Supplementary Table S1. Synopsis of the literature appraisal (PICO and main results).

STUDY	PATIENT	INTERVENTION	COMPARISON	GENERAL OUTCOME	SPECIFIC OUTCOME(S)	MAIN RESULTS
1.	NSCLC	ICI Nivolumab Permbrolizumab Atezolizumab Durvalumab Avelumab	Anti PD-1 and Anti PD-L1 treatment naive and previously treated patients	Respiratoy AEs	All Grade Pneumonitis	Incidence (All Grade Pneumonitis) PD-1 3.6% (95% CI: 2.4%-4.9%) Incidence (All Grade Pneumonitis) PD-L1 1.3% (95% CI: 0.8%-1.9%)
2.	Previously treated advanced NSCLC	ICI Nivolumab	PD-L1positive cohort PD-L1 negative cohort	Immune-related AEs	All Grade AEs	Incidence (Fatigue) 28% (95% CI: 9%–33%) Incidence (Decreased appetite) 13% (95% CI: 9%–17%) Incidence (Nausea) 12% (95% CI: 9%–16%) Incidence (Asthenia) 10% (95% CI: 8%–13%)
3.	Advanced NSCLC	ICI Nivolumab Ipilimumab Atezolizumab	Docetaxel Placebo Carboplatin plus Paclitaxel Chemotherapy	Immune-related AEs	Blood AEs Gastrointestinal AEs	↓Neutropenia RR=0.03 (95%CI: 0.00–0.49) ↓Leukopenia RR=0.07 (95%CI: 0.01–0.83) →Anemia RR=0.34 (95%CI: 0.07–1.72) →Diarrhea RR=0.81 (95%CI: 0.25–2.64) →Asthenia/Fatigue RR=0.27 (95%CI: 0.06–1.24) →Nausea/Vomiting RR=0.96 (95%CI: 0.32–2.90)
4.	Melanoma NSCLC RCC Ovarian cancer	ICI Nivolumab plus Ipilimumab Pembrolizumab	Tumor types comparisons	Respiratory AEs	Respiratory AEs	NSCLC vs Melanoma OR=2.85 (95%CI: 1.60-5.08) Monotherapy vs Combination OR=2.86 (95%CI: 1.79- 4.35)

5.	Melanoma RCC NSCLC	ICI Nivolumab Nivolumab plus Ipilimumab Tremelimumab Pembrolizumab	Decarbazine Gp100 Placebo Everolimus Chemotherapy	General AEs	High Grade Fatigue	↑ CTLA4 vs Chemotherapy OR= 1.72 (95% CI: 1.26-2.33) ↓PD-1 vs Chemotherapy OR= 0.36 (95% CI: 0.23-0.56)
6.	Melanoma	ICI Ipilimumab Tremelimumab Nivolumab Pembrolizumab	Conventional chemotherapy Control	Immune-related AEs	High Grade AEs	Incidence (High grade AEs) ICI vs Control RR=6.74 (95%CI: 4.65-9.75)
7.	Melanoma RCC Pancreas Colorectal cancer	ICI Ipilimumab Tremelimumab	ICI safety profile comparisons	Immune-related AEs	High Grade AEs	Incidence (High grade skin AEs) Ipilimumab 1.5% (95%CI: 0.7 %-2.4%) Incidence (High grade skin AEs) Tremelimumab 0.5% (95%CI: 0%-3%) Incidence (High grade Gastro AEs) Ipilimumab 11% (95%CI: 8%-14.5%) Incidence (High grade Gastro AEs) Tremelimumab 9% (95%CI: 4%-13%) Incidence (High grade Hepatic AEs) Ipilimumab 2% (95%CI: 0.6%-3%) Incidence (High grade Hepatic AEs) Tremelimumab 4% (95%CI: 0%-10%)
8.	Solid and Hematologic tumor patients	Targeted therapy (mTor inhibitor bcr-abl inhibitor) Ipilimumab (CTLA4 inhibitor)	Control therapy	Immune-related AEs	Skin AEs	Targeted therapy vs Control (All grade Pruritus) RR= 2.90 (95% CI: 1.76–4.77) Targeted therapy vs Control (High grade Pruritus) RR= 2.13 (95% CI: 0.61–7.44)

9.	Urothelial carcinoma Melanoma RCC NSCLC Pancreatic	Ipilimumab	Ipilimumab plus Decarbazine Paclitaxel plus Carboplatin Placebo plus Dacarbazine	Skin AEs	High grade Rash All grade Rash	→ Ipilimumab vs Control RR= 3.31 (95%CI: 0.70-15.76) ↑Ipilimumab vs Control RR=4.00 (95%CI: 2.63-6.08)
10.	Urothelial carcinoma Prostate cancer RCC	ICI Pembrolizumab Durvalumab Atezolizumab Nivolumab	Non Genitourinary cancer patients	Immune-related AEs	Immune-related AEs	AEs incidence in Genitourinary and non-Genitourinary (GU/non-GU) clinical trials subgroups. Incidence (All grade Pneumonitis) in GU trials 0-2% Incidence (All grade Pneumonitis) in non-GU trials 0.25-1.9%
11.	Melanoma NSCLC	ICI Ipilimumab Tremelimumab Pembrolizumab Nivolumab Atezolizumab	Non immune checkpoint inhibitors	Eye disorders AEs	Immune-related ocular toxicities	↑ICI VS Control OR=3.40 (95% CI: 1.32- 8.71) [Uveitis and dry eyes mentioned but no result given]
12.	Advanced stage cancers Metastatic melanoma	ICI Ipilimumab alone Ipilimumab+ - Decarbazine - Radiation - Carboplatin - Peptide vaccine Nivolumab	Conventional chemotherapy	Musculoskeletal AEs Endocrine AEs Gastrointestinal AEs	Arthralgia Myalgia Thyroid dysfunction Colitis	Arthralgia prevalence in clinical trials 1–43%. Myalgia reported in 2–20%. Thyroid dysfunction occurs in as many as 22% of patients treated. Colitis has been reported more commonly from ipilimumab than nivolumab in melanoma patients, with rates of about 5% compared to 1%

13.	Metastatic melanoma Lung cancer Prostate cancer Bladder cancer	ICI Ipilimumab Pembrolizumab Nivolumab	None (description of case reports)	Immune related AEs	Gastrointestinal AEs Dermatological AEs Endocrine AEs Respiratory AEs Hematological AEs Ophthalmological AEs Musculoskeletal AEs Neurological AEs	The most frequent irAEs reported with anti-PD1 agents were: -Dermatitis for pembrolizumab -Thyroid disease and pneumonitis for nivolumab.
14.	Melanoma Metastatic melanoma	ICI Ipilimumab Vemurafenib INF-alfa2, dacarbazine IL-2	None	Immune-related AEs	Respiratory AEs Gastrointestinal AEs Hepatic AEs	Incidence (Respiratory disease)= 0.0001 Cases/100 Person-years Incidence (Diarrhea and colitis) = 0.0017 Cases/100 Person-years Incidence (Liver toxicities)= 0.0006 Cases/100 Person-years [Incidences are evaluated in terms of Cases/100 Person-years with no comparison]
15.	Advanced melanoma Advanced NSCLC	ICI Pembrolizumab	Different dose schedules	Immune-related AEs	Hepatitis Rash Vitiligo Diarrhea Hypothyroidism Nephritis Pneumonitis	OR Hepatitis (2 versus 10 mg/kg every 3 weeks) = 1.86 (95% CI: 0.91–3.79; p = 0.09) OR Rash (2 versus 10 mg/kg every 3 weeks)= 0.83 (95% CI: 0.58-1.18) OR Vitiligo (2 versus 10 mg/kg every 3 weeks)= 1.27 (95% CI: 0.62-2.61) OR Diarrhea (2 versus 10 mg/kg every 3 weeks)= 0.94 (95%CI: 0.63-1.42) OR Hypothyroidism (2 versus 10 mg/kg every 3 weeks)= 0.97 (95%CI: 0.63-1.50) OR Nephritis (2 versus 10 mg/kg every 3 weeks)= 0.88 (95%CI: 0.32-2.44) OR pneumonitis (2 versus 10 mg/kg every 3 weeks) = 1.17 (95% CI: 0.62–2.23) [Above mentioned OR come from dose comparisons/no chemo comparison]

16.	NSCLC Advanced melanoma RCC	Nivolumab	Decarbazine Docetaxel Coventional Chemotherapy	General AEs	Fatigue Headache Dysgeusia Vertigo and anxiety Paresthesia and peripheral neuropathy	→ Nivolumab vs chemotherapy RR= 0.91(95%CI: 0.72-1.14) →Nivolumab vs chemotherapy RR= 0.84(95%CI: 0.61-1.17) →Nivolumab vs chemotherapy RR= 0.42(95%CI: 0.13-1.36) →Nivolumab vs chemotherapy RR= 0.76(95%CI: 0.48-1.22) →Nivolumab vs chemotherapy RR= 0.41(95%CI: 0.23-0.73)
17.	Melanoma Prostate cancer NSCLC	Ipilimumab	Non Ipilimumab based therapy or Placebo	Immune-related AEs	FAEs (fatal adverse events)	Incidence FAEs (Ipilimumab)= 0.99% (95%CI: 0.48%-1.69%) RR (Ipilimumab vs Non ipilimumab based therapy) =2.16 (95%CI: 1.03-4.54) [No specific AEs mentioned nor comparison with chemotherapy]
18.	Advanced cancer Melanoma Squamous /non squamous NSCLC	ICI Nivolumab Pembrolizumab Atezolizumab	Docetaxel Conventional Chemotherapy	Immune-related AEs	Respiratory AEs Gastrointestinal AEs Endocrine AEs Hepatic AEs Skin AEs	PD-1/PD-L1 vs Chemotherapy ↑High-grade Pneumonitis RR= 3.21(95%CI: 1.33–7.75) ↑High-grade Colitis RR= 3.51(95%CI: 1.12–10.98) ↑All-grade Hypothyroidism RR=15.05 (95%CI: 6.14–36.90) ↑All-grade Hyperthyroidism RR=5.13 (95%CI: 2.14–12.30) →All-grade Hyperthyroidism RR=2.52 (95%CI: 0.42–14.95) ↑All-grade AST elevation RR=2.02 (95%CI: 1.01–4.03) ↑All-grade ALT elevations RR=2.08 (95%CI: 1.10–3.95) ↑All-grade Rash RR=2.32 (95%CI: 1.47–3.66)

19.	Prostate cancer, Melanoma SCLC NSCLC	ICIs Ipilimumab Pembrolizumab Atezolizumab Nivolumab	Non-ICI arms Gp-100 Decarbazine Everolimus Conventional chemotherapy	Immune-related AEs	Gatrointestinal AEs Hepatic AEs Skin AEs Respiratory AEs Endocrine AEs	↑ High grade Colitis RR=5.85 (95%CI: 2.66–12.80) ↑ High grade Increased AST RR=2.79 (95%CI: 1.23–6.32) ↑ All grade Rash RR= 2.50 (95%CI: 1.65–3.78) ↑ All grade Pneumonitis RR= 4.14 (95%CI: 1.37–12.50) ↑ All grade Hypothyroidism RR= 6.81 (95%CI: 4.20-11.00)
20.	Advanced NSCLC	ICI Pembrolizumab Atezolizumab Nivolumab	Docetaxel	Immune-related AEs	Pooled AEs	High grade pooled AEs (ICI vs Control) OR= 0.18 (95%CI: 0.14-0.22)
21.	Advanced melanoma RCC SCC NSCLC Non SCC NSCLC	ICI Nivolumab Pembrolizumab Ipilimumab	Docetaxel Everolimus Decarbazine plus placebo	Immune-related AEs	Endocrine AEs Hepatic AEs Skin AEs	↑ Hypothyroidism RR= 6.79 (95%CI: 3.10-14.84) ↑ Hyperthyroidism RR=3.44 (95%CI: 1.98-5.99) ↑ Elevated AST and/or ALT RR=1.48 (95%CI: 1.04-2.11) ↑ Pruritus RR=2.01 (95%CI: 1.05-3.85) ↑ Vitiligo RR= 4.92 (95%CI: 2.07-11.69)
22.	HCC NSCLC RCC Ovarian cancer Melanoma Glioblastoma Hematological cancer	ICI Nivolumab	Chemotherapy	Immune-related AEs	General AEs Skin AEs Gastrointestinal AEs Hepatic AEs Respiratory AEs Blood AEs	Incidence rate (High Grade AEs) Fatigue 0.019 (95%CI 0.014–0.026) Rash 0.009 (95%CI 0.005–0.017) Pruritus 0.008 (95%CI 0.003–0.018) Diarrhea 0.014 (95%CI 0.010–0.020) Nausea 0.007 (95%CI 0.003–0.013) ALT increased 0.014 (95%CI 0.008–0.027) Dyspnea 0.007 (95%CI 0.003–0.017) Pneumonitis 0.020 (0.013–0.031) Lymphopenia 0.021 (95%CI 0.008–0.054)

23.	Melanoma NSCLC RCC	ICI Nivolumab Pembrolizumab	Chemotherapy or everolimus control	Hepatic AEs	All-grade ALT All-grade AST High-grade ALT High-grade AST	PD1 vs control ↑RR= 2.08 (95%CI: 1.10-3.95) PD1 vs control ↑ [RR=2.02 (95%CI: 1.01-4.03)] PD1 vs control →RR=1.47 (95%CI: 0.45-4.85) PD1 vs control →RR=1.51 (95%CI: 0.43-5.27)
24.	Advanced NSCLC	ICI Nivolumab Atezolizumab	Docetaxel	General AEs Gastrointetinal AE Muscoloskeletal AEs Blood AEs Respiratory AEs Endocrine AEs	Fatigue Nausea Asthenia Diarrhea Myalgia Neutropenia Pneumonitis Hypothyroidism	PD1-PDL1 vs Docetaxel ↓OR=0.53 (95%CI: 0.38-0.74) PD1-PDL1 vs Docetaxel ↓OR=0.44 (95%CI 0.30-0.63) PD1-PDL1 vs Docetaxel ↓OR=0.61 (95%CI: 0.41-0.93) PD1-PDL1 vs Docetaxel ↓OR=0.35 (95%CI 0.23-0.53) PD1-PDL1 vs Docetaxel ↓OR=0.20 (0.10-0.41) PD1-PDL1 vs Docetaxel ↓OR=0.02 (0.00-0.06) PD1-PDL1 vs Docetaxel ↑OR=9.20 (95%CI: 1.71-49.64) PD1-PDL1 vs Docetaxel ↑OR=23.71 (3.19-176.19)
25.	Advanced Melanoma	Nivolumab Nivolumab plus Ipilimumab	Dacarbazine Decarbazine plus Paclitaxel	Skin AEs	Pruritus all grade	↑Nivlumab vs decarbazine RR=4.96 (95%CI: 1.47–16.72)
26.	Advanced Melanoma	ICI Nivolumab Nivolumab plus Ipilimumab Permbrolizumab Atezolizumab	Chemotherapy or placebo	Immune-related AEs	Fatigue Asthenia Hematologic toxicities Gastrointestinal toxicities Skin disorders	↓PD1 inhibitors vs chemotherapy RR=0.23 (95%CI: 0.09-0.54) ↓PD1 inhibitors vs chemotherapy RR= 0.03 (95%CI: 0.01-0.09) ↓PD1 inhibitors vs chemotherapy RR=0.32 (95%CI 0.16-0.62) →PD1 inhibitors vs chemotherapy RR=3.50 (95%CI 0.42-28.83)

27.	Solid tumors	ICI Ipilimumab+ Paclitaxel Gp100 Dacarbazine Nivolumab Permbrolizumab Atezolizumab	Chemotherapy or placebo	Endocrine AEs	Hypothyroidism Hyperthyroidism Hypophysitis Adrenal insufficiency	↑ICI vs chemotherapy RR= 8.26 (95%CI:4.67-14.62); ↑ICI vs chemotherapy RR=5.48 (95%CI: 1.33-22.53); ↑ICI vs chemotherapy RR=22.03 (95%CI: 8.52-56.94); ↑ICI vs chemotherapy RR=3.87 (95%CI: 1.12-13.41)
28.	Melanoma Advanced SCC Prostate cancer	ICI Nivolumab Ipilimumab Ipilimumab+ -Paclitaxel -Gp100 Atezolizumab	Chemotherapy or Placebo	Gastrointestinal AEs	Diarrhea Vomiting Colitis	↑ICI vs Control RR= 4.46 (95% CI: 1.46–13.57) →ICI vs Control RR= 0.98(95% CI: 0.56–1.73) ↑ICI vs Control RR= 15.81 (95% CI: 6.34-39.42)
29.	NSCLC Prostate cancer Melanoma	ICI Nivolumab Tremelimumab Ipilimumab	Docetaxel or investigator choice chemotherapy	Hepatic AEs	High-grade ALT elevation High-grade AST elevation	↑ICI vs Control RR=4.90 (95%CI: 2.97-8.09) ↑ICI vs Control RR=6.85 (95%CI: 3.37-13.93)
30.	Melanoma Small cell lung cancer	ICI Ipilimumab Nivolumab Tremelimumab Pembrolizumab	Chemotherapy or Placebo	SKin AEs	Rash High grade Vitiligo All grade Pruritus High grade	↑ICI vs Control RR= 4.81 (95%CI: 1.93–12.02) ↑ICI vs Control RR=16.30 (95%CI: 3.21–82.80) →ICI vs Control RR=1.66 (95%CI: 0.64–4.30)
31.	Melanoma Prostate cancer NSCLC Renal cell carcinoma	ICI Ipilimumab Nivolumab Pembrolizumab	Docetaxel Decarbazine Conventional chemotherapy	Respiratory AEs	Pneumonitis High grade Pneumonitis All grade	→ ICI vs Control OR=2.87 (95% CI: 0.90–9.20) ↑ICI vs Control OR= 3.96 (95%CI: 2.02-7.79)

32.	Squamous /non squamous NSCLC	ICI Nivolumab Pembrolizumab	Conventional chemotherapy Docetaxel	Endocrine AEs	Hypothyroidism	↑Nivolumab or Pembrolizumab vs chemotherapy OR=3.21 (95% CI: 1.47-7.04) Pembrlizumab vs chemotherapy OR= 17.50 (95%CI: 3.43-89.30) Nivolumab vs chemotherapy OR=11.98 (95%CI: 0.82-175.96)
				Respiratory AEs	Pneumonitis	↑Nivolumab or Pembrolizumab vs chemotherapy OR=15.55 (95%CI: 4.28-56.57) Pembrolizumab vs chemotherapy OR=2.40 (95%CI: 0.99-5.82) Nivolumab vs chemotherapy OR=9.28(95%CI: 1.71-50.32)
33.	NSCLC Melanoma	ICI Nivolumab Pembrolizumab	Conventional chemotherapy	Endocrine AEs	Hypothyroidism	↑Nivolumab vs chemotherapy OR= 10.07 (95%CI: 3.37-30.11) Pembrolizumab vs chemotherapy OR= 7.73 (95%CI: 3.86-15.49)
					Hyperthyroidism	↑Anti PD1 vs chemotherapy OR= 4.87 (95%CI: 2.50-9.49) Anti PD1+CTLA4 vs chemotherapy OR= 3.79 (95%CI: 1.91-7.53) ↑Nivolumab vs chemotherapy OR= 4.29 (95%CI: 1.13-16.30) ↑Pembrolizumab vs chemotherapy OR= 5.09 (95%CI: 2.36-10.97)
34.	Cancer patients with recurrent or metastatic disease.	ICI Nivolumab Pembrolizumab Atezolizumab	Conventional chemotherapy	Gastro AEs	Colitis	↑Anti PD1 vs chemotherapy OR= 3.39 (95%ci: 1.45-7.95)
				Skin AEs	Rash	↑Anti PD1 vs chemotherapy OR=2.87 (95%CI: 2.25-3.68)
				Respiratory AEs	Pneumonitis	↑Anti PD1 vs chemotherapy OR=5.37 (95%ci: 2.73-10.56)
				Endocrine AEs	Hypothyroidism	↑Anti PD1 vs chemotherapy OR=9.85 (95%ci: 4.41-22.01)
					Hypophysitis	↑Anti PD1 vs chemotherapy OR=3.88 (95%CI: 1.08-13.91)

35.	NSCLC Melanoma RCC Urothelial carcinoma CEC	ICI Nivolumab Pembrolizumab Ipilimumab	Conventional chemotherapy	Hematologic AEs	Anemia Thrombocytopenia Leukopenia Neutropenia	↓Anti PD1 monotherapy vs chemotherapy OR= 0.12 (95%CI: 0.08-0.18) Anti PD1 combination vs chemotherapy OR=0.02 (95%CI: 0.01-0.05) ↓Anti PD1 monotherapy vs chemotherapy OR= 0.06 (95%CI: 0.02-0.19) Anti PD1 combination vs chemotherapy OR= 0.04 (95%CI: 0.01-0.05) ↓Anti PD1 monotherapy vs chemotherapy OR= 0.06 (95%CI: 0.02-0.18) Anti PD1 combination vs chemotherapy OR=0.01 (95%CI: 0.00-0.05) ↓Anti PD1 monotherapy vs chemotherapy OR= 0.01 (95%CI: 0.01-0.04) Anti PD1 combination vs chemotherapy OR= 0.02 (95%CI:0.01-0.07)
36.	Lung Melanoma NSCLC SCLC Prostate	ICI Nivolumab Pembrolizumab Ipilimumab Tremelimumab Atezolizumab	Conventional chemotherapy	Investigation AEs	Lipase increased	↑Ipilimumab vs chemotherapy OR=1.50 (95%CI: 1.01-2.24)
37.	Melanoma Squamous /non squamous NSCLC Prostate	ICI Nivolumab Pembrolizumab Atezolizumab Ipilimumab	Conventional chemotherapy	Gastrointestinal AEs General AEs Skin AEs Endocrine AE Hepatobiliary dis AEs Respiratory AEs	Diarrhea or colitis Nausea or vomiting Rash Endocrinopathy Hepatic disfunction Pneumonitis	↓ Anti PD1 PDL1 vs chemotherapy OR=0.72 (95% CI: 0.57-0.64) ↓ Anti PD1 PDL1 vs chemotherapy OR= 0.72 (95% CI: 0.60-0.66) ↑Anti PD1 PDL1 vs chemotherapy OR=3.04 (95%CI: 1.83-2.36) ↑Anti PD1 PDL1 vs chemotherapy OR=12.03 (95%CI: 7.49-19.31) →Anti PD1 PDL1 vs chemotherapy OR=1.88 (95%CI: 1.00-1.37) ↑Anti PD1 PDL1 vs chemotherapy OR=7.75 (95%CI: 2.63-4.52) *In the original study there is a disagreement in the data between forest plot and actual reported values

38.	Advanced melanoma patients	ICI Nivolumab Nivolumab+ Ipilimumab Pembrolizumab	Conventional chemotherapy	Blood AEs General AEs	Hematological reactions Neutropenia Trombocytopenia Anemia Fatigue	↓Anti PD1 vs chemotherapy OR= 0.03 (95%CI: 0.01-0.04) OR= 0.04 (95%CI: 0.01-0.25) OR= 0.09 (95%CI: 0.02-0.31) ↓Anti PD1 vs chemotherapy OR= 0.19 (95%CI: 0.07-0.51)
39.	NSCLC Melanoma RCC HNSCC	ICI Nivolumab Nivolumab+ Ipilimumab Pembrolizumab Lambrolizumab Ipilimumab	Chemotherapy or everolimus control	Gastrointestinal AEs	All grade Diarrhea High grade Diarrhea All grade Colitis High grade Colitis	↓Anti PD1 vs chemotherapy OR= 0.66 (95%CI: 0.50-0.87) →Anti PD1 vs chemotherapy OR= 0.58 (95%CI: 0.30-1.11) ↑Anti PD1 vs chemotherapy OR= 4.31 (95%CI: 1.11-16.79) ↑Anti PD1 vs chemotherapy OR= 3.36 (1.25-9.04)
40.	Solid tumor	ICI	None	Skin AEs	All grade pigmentary changes of skin All grade pigmentary changes of hair	↑RR= 93.7(95% CI, 5.86-1497.164; P <0 .001) ↑RR= 20.1 (95% CI, 8.35-48.248; P <0.001)
41.	Melanoma NSCLC Prostate SCLC	ICI Ipilimumab alone Ipilimumab+ Paclitaxel Carboplatin Gp100	Chemotherapy or placebo	Gastrointestinal AEs Cardiac AEs Hepatic AEs Respiratory AEs	Gastrointestinal AEs Cardiac AEs Hepatic AEs Pulmonary AEs	↑Ipilimumab vs chemotherapy OR= 4.46 (95%CI: 1.47–13.55) →Ipilimumab vs chemotherapy OR= 3.19 (95%CI: 0.78–13.08) →Ipilimumab vs chemotherapy OR= 1.85 (95%CI: 0.38–8.92) →Ipilimumab vs chemotherapy OR= 3.60 (95%CI: 0.42–30.83)

42.	NSCLC cancer patients	ICI Nivolumab Pembrolizumab Atezolizumab, Avelumab Durvalumab	Chemotherapy Docetaxel	Skin AEs Cardiac AEs Respiratory AEs	Severe skin reactions Cardiorespiratory arrest Cardiac failure Myocardial infarction Stroke All grade Pneumonitis	↓Anti PD1-PDL1 vs chemotherapy OR=0.02 (95%CI: 0.01-0.04) ↓ Anti PD1-PDL1 vs chemotherapy OR= 0.01 (95%CI: 0.00-0.02) OR= 0.02 (95%CI: 0.01-0.06) OR= 0.01 (95%CI: 0.00-0.04) OR= 0.02 (95%CI: 0.00-0.15) ↑Anti PD1-PDL1 vs chemotherapy OR= 2.35 (95%CI: 1.32-4.20)
43.	Melanoma Prostate NSCLC	ICI Nivolumab, Pembrolizumab, Ipilimumab, Tremelimumab, Atezolizumab	Conventional chemotherapy	Hepatobiliary AEs	High grade AST elevation High grade ALT elevation High Grade Hepatitis	↑ICI vs Controls OR= 10.4 (95%CI: 5.47– 19.75) ↑ICI vs Controls OR= 3.77 (95%CI: 1.04–13.70) ↑ICI vs Controls OR= 4.97 (95%CI: 1.11– 22.31)
44.	NSCLC	ICI Nivolumab Ipilimumab Pembrolizumab Atezulizumab Durvalumab	Chemotherapy Or Placebo	Hepatobiliary AEs Gastrointestinal AEs Skin AEs	ALT/AST increased Diarrhea Pruritis Rash	↑ICI vs Control therapies RR= 4.45 (95%CI: 1.77-11.14) →ICI vs Control therapies RR= 1.64 (95%CI: 0.95-2.82) →ICI vs Control therapies RR= 2.38 (95%CI: 0.46-12.44) →ICI vs Control therapies RR= 2.54 (95%CI: 0.96-6.74)
45.	Cancer patients	Nivolumab	Placebo	Hepatobiliary AEs	High grade AST elevation High grade ALT elevation	Nivolumab vs Placebo RR= 2.18 (95%CI: 1.03-4.10) Nivolumab vs Placebo RR= 1.82 (95%CI: 0.89-3.74)

46.	Advanced melanoma	ICI Ipilimumab Atezolizumab Durvalumab Nivolumab Pembrolizumab Tremelimumab Lambrolizumab	Combination or monotherapy with antiCTLA4/PD1	Gastrointestinal AEs	Diarrhea Colitis	Nivolumab+ipilimumab vs ipilimumab RR= 1.31 (95%CI: 1.09-1.57) Nivolumab+ipilimumab vs ipilimumab RR= 1.21 (95%CI: 0.73-1.99)
47.	Solid tumor patients	ICI Nivolumab Pembrolizumab Atezulizumab	Control therapies	Respiratory AEs	All grade pulmonary toxicity High grade pulmonary toxicity	→Anti PD1 vs Control OR= 2.65 (95%CI: 0.98-7.20) →Anti PD1 vs Control OR= 1.40 (95%CI: 0.79-2.50)
48.	Melanoma Lung Kidney Prostate cancer	ICI Ipilimumab Nivolumab Tremelimumab Pembrolizumab	24 50 4 8 3 6 2 4 2 4	Melanoma vs non-Melanoma AntiCTLA4 versus antiPD-1/PD-L1	Gastrointestinal AEs Respiratory AEs	Colitis Pneumonitis	CTLA-4 versus PD-1/PD-L1 OR= 3.12 (95%CI: 1.06–9.24) Melanoma vs non-Melanoma OR= 0.85 (95%CI: 0.28–2.57) CTLA-4 versus PD-1/PD-L1 OR= 0.03 (95%CI: 0.007–0.148) Melanoma vs non-Melanoma OR= 0.51 (95%CI: 0.11–2.41)
49.	Advanced solid tumor	ICI Ipilimumab Nivolumab Atezolizumab Pembrolizumab	Anti PD-1/PD-L1 versus antiCTLA4	Endocrine AEs	Hypophysitis Hyperthyroidism	Incidence Hypophysitis Combination vs monotherapy OR= 3.81 (95%CI: 2.10 - 6.91) Incidence Hyperthyroidism Combination vs monotherapy OR= 5.07 (95%CI: 2.45 - 10.52)
50.	Squamous cell NSCLC Melanoma Prostate Ovarian cancer	ICI Pembrolizumab Nivolumab	Conventional chemotherapy	Skin AEs	Dermatologic toxicities	Rash, Pruritus, Vitiligo (pooled) ↑Pembrolizumab vs chemotherapy RR= 2.95 (95% CI: 1.50-5.70) ↑Nivolumab vs chemotherapy RR= 2.30 (95% CI: 1.30-4.10)

Supplementary Table S2. Summary of quality assessment according to AMSTAR tool.

AMSTAR Score *	**0-6 (Low)**	**7-8 (Intermediate)**	**9-10 (High)**	**10 (Optimal)**
Total studies: 50	8	17	25	8
% over total n° of studies	16	34	50	16

***** Please note that the maximum score is 10. In fact, AMSTAR item n°8 ("*Was the scientific quality of the included studies used appropriately in formulating conclusion?")* was not assessed because:

- only rarely was the scientific quality considered to draw conclusion and formulate recommendations in the majority of systematic reviews (with the exception of Cochrane reviews), especially due to the reduced number of studies;

- we did not used the conclusions posted in the manuscript by the authors in the text, but instead we interpreted reported results according to our methodological criteria.

Details on the assessment

Question 3 * YES=at least two databases with the list of keywords used

Question 4 ± YES=clinicaltrials.gov or abstract/proceedings or websites of regulatory agencies must be quoted

Question 7 ‡ YES= provided for individual studies (e.g., high/low or +/-, although reasons for judging are not mandatory) or at least described in the results

Question 10 † YES= formally quantified (it is not sufficient to state that no publication bias was identified through visual inspection or statistical test).

Supplementary Table S3. Details of quality assessment according to AMSTAR tool. In bold, systematic reviews receiving the maximum score.

Reference	1) Was an 'a priori' design provided ?	2) Was there duplicate study selection and data extraction ?	3)* Was a comprehensive literature search performed?	4) ± Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5) Was a list of studies (included and excluded) provided?	6) Were the characteristics of the included studies provided?	7) ‡ Was the scientific quality of the included studies assessed and documented?	9) Were the methods used to combine the findings of studies appropriate?	10) † Was the likelihood of publication bias assessed?	11) Was the conflict of interest included?	Total Score
[1]	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	9/10
[2]	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	9/10
[3]	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	9/10
[4]	YES	YES	NO	YES	NO	YES	NO	YES	YES	YES	7/10
[5]	YES	NO	YES	NO	YES	YES	NO	YES	YES	NO	6/10
[6]	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	9/10
[7]	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**10/10**
[8]	YES	NO	YES	YES	YES	YES	NO	YES	NO	YES	7/10
[9]	YES	NO	YES	YES	YES	YES	NO	YES	NO	YES	7/10
[10]	YES	NO	YES	YES	YES	YES	NO	NO	NO	YES	6/10
[11]	YES	NO	NO	YES	YES	YES	YES	YES	NO	YES	7/10
[12]	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	8/10

Reference	1) Was an 'a priori' design provided ?	2) Was there duplicate study selection and data extraction ?	3)* Was a comprehensive literature search performed?	4) ± Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5) Was a list of studies (included and excluded) provided?	6) Were the characteristics of the included studies provided?	7) ‡ Was the scientific quality of the included studies assessed and documented?	9) Were the methods used to combine the findings of studies appropriate?	10) † Was the likelihood of publication bias assessed?	11) Was the conflict of interest included?	Total Score
[13]	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES	7/10
[14]	YES	NO	YES	NO	YES	YES	NO	NO	NO	YES	5/10
[15]	YES	NO	NO	NO	NO	YES	YES	YES	YES	YES	6/10
[16]	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	9/10
[17]	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**10/10**
[18]	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**10/10**
[19]	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	9/10
[20]	YES	YES	YES	YES	YES	YES	NO	YES	NO	YES	8/10
[21]	YES	NO	NO	NO	YES	YES	NO	YES	YES	YES	6/10
[22]	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**10/10**
[23]	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**10/10**
[24]	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	9/10

Reference	1) Was an 'a priori' design provided ?	2) Was there duplicate study selection and data extraction ?	3)* Was a comprehensive literature search performed?	4) ± Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5) Was a list of studies (included and excluded) provided?	6) Were the characteristics of the included studies provided?	7) ‡ Was the scientific quality of the included studies assessed and documented?	9) Were the methods used to combine the findings of studies appropriate?	10) † Was the likelihood of publication bias assessed?	11) Was the conflict of interest included?	Total Score
[25]	YES	NO	YES	NO	YES	YES	YES	YES	NO	YES	7/10
[26]	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	9/10
[27]	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	9/10
[28]	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	9/10
[29]	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	9/10
[30]	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	9/10
[31]	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	9/10
[32]	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**10/10**
[33]	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	9/10
[34]	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	9/10
[35]	YES	YES	NO	NO	YES	YES	NO	YES	YES	YES	7/10
[36]	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**10/10**

Reference	1) Was an 'a priori' design provided ?	2) Was there duplicate study selection and data extraction ?	3)* Was a comprehensive literature search performed?	4) ± Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5) Was a list of studies (included and excluded) provided?	6) Were the characteristics of the included studies provided?	7) ‡ Was the scientific quality of the included studies assessed and documented?	9) Were the methods used to combine the findings of studies appropriate?	10) † Was the likelihood of publication bias assessed?	11) Was the conflict of interest included?	Total Score
[37]	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	9/10
[38]	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	9/10
[39]	YES	YES	YES	NO	NO	YES	YES	YES	YES	YES	8/10
[40]	YES	NO	NO	YES	NO	NO	NO	YES	NO	YES	4/10
[41]	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**10/10**
[42]	YES	YES	NO	NO	YES	YES	NO	YES	NO	YES	6/10
[43]	YES	NO	YES	NO	YES	YES	NO	YES	YES	YES	7/10
[44]	YES	YES	YES	NO	YES	NO	NO	YES	NO	YES	6/10
[45]	YES	YES	NO	YES	YES	YES	NO	YES	YES	YES	8/10
[46]	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	8/10
[47]	YES	YES	YES	YES	YES	NO	YES	YES	NO	YES	8/10
[48]	YES	YES	YES	NO	YES	YES	NO	YES	NO	YES	7/10
[49]	YES	YES	NO	YES	YES	YES	NO	YES	YES	NO	7/10
[50]	YES	YES	NO	YES	YES	YES	NO	YES	NO	YES	7/10

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