

Supplementary material

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Supplementary Table S1: Search terms used in our meta-analysis

#	Search
1	"immunotherapy"[MeSH Terms] OR "immunotherapy"[All Fields] OR "immunotherapies"[All Fields] OR "immunotherapy s"[All Fields]
2	"anti"[All Fields] AND "pd1"[All Fields]
3	"anti pd1"[All Fields]
4	"anti"[All Fields] AND "ctla4"[All Fields]
5	2 OR 3 OR 4
6	"atezolizumab"[Supplementary Concept] OR "atezolizumab"[All Fields]
7	"ipilimumab"[MeSH Terms] OR "ipilimumab"[All Fields]
8	"durvalumab"[Supplementary Concept] OR "durvalumab"[All Fields]
9	"nivolumab"[MeSH Terms] OR "nivolumab"[All Fields] OR "nivolumab s"[All Fields]
10	"pembrolizumab"[Supplementary Concept] OR "pembrolizumab"[All Fields]
11	"cemiplimab"[Supplementary Concept] OR "cemiplimab"[All Fields]
12	"avelumab"[Supplementary Concept] OR "avelumab"[All Fields]
13	6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
14	1 OR 5 OR 13
15	"cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]
16	14 AND 15

Supplementary Table S2: Quality of included studies using A) Cochrane Collaboration’s tool for assessing risk of bias in randomized trials for quality assessment of randomized clinical trials (RCTs) and B) The Newcastle-Ottawa Quality Assessment Scale (NOS) for non-RCTs

A							
	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS
	Altorki 2021	+	+	+	+	+	+
	Amaria 2018	+	?	-	+	+	+
	Arrieta 2020	+	+	?	+	+	+
	Cascone 2021	+	+	+	?	+	+
	Duska 2020	+	+	+	+	+	+
	Ferrarotto 2020	+	+	?	+	+	+
	Lee 2013	+	?	+	+	+	+
	Liu 2020	+	+	+	+	+	+
	Mahmood 2021	+	+	+	+	+	+

Pakkala 2020	+	+	+	?	+	+	+
Sundahl 2019	+	+	+	+	+	+	+
Tobin 2018	+	+	?	+	+	+	+
Voorwerk 2019	+	+	-	+	+	+	+
Welsh 2020	+	+	+	+	+	+	+
Zhu 2022	+	+	-	-	+	+	+

+	Low Risk
?	Uncertain
-	High Risk

B				
Study	Selection	Comparability	Outcome	Total
Aamdal 2021	***	*	***	*****
Ariyan 2018	***	*	***	*****
Awada 2020	****	**	***	*****
Ben-Ami 2017	***	*	***	*****
Bjoern 2016	***	*	***	*****
Boutros 2020	***	**	***	*****

Brastianos 2020	***	*	***	*****
Brustugun 2017	***	*	***	*****
Calabrò 2013	***	*	***	*****
Calabrò 2015	****	*	***	*****
Calabrò 2018	***	*	***	*****
Chalmers 2019	***	*	***	*****
Chang 2021	****	**	***	*****
Chintakuntlawar 2019	***	*	***	*****
Cho 2019	****	*	***	*****
Chu 2021	***	*	***	*****
Chung 2019	***	*	***	*****
Da Gama Duarte 2018	***	*	***	*****
DAngelo 2017	****	*	***	*****
Di Giacomo 2011	***	**	***	*****
Di Giacomo 2019	****		***	*****
Di Noia 2021	***	**	***	*****
Disselhorst 2019	****	*	***	*****
Duffy 2017	****	*	***	*****
Edenfield 2021	***	*	***	*****
Eichhorn 2021	***	*	***	*****
Elbers 2020	***	*	***	*****

Feng 2020	***	*	***	*****
Ferrarotto 2021	***	*	***	*****
Feun 2019	***	**	***	*****
Freeman-Keller 2016	***	**	***	*****
Frumovitz 2020	***	*	***	*****
Gao J. 2020	***	*	***	*****
Gao S. 2020	***	*	***	*****
Giaccone 2018	***	*	***	*****
Goldberg 2016	****		***	*****
Goldberg 2020	***	*	***	*****
Graff 2016	***	*	***	*****
Graff 2020	***	*	***	*****
Gray 2019	****	*	***	*****
Haag 2018	***	*	***	*****
Habra 2019	***	*	***	*****
Hamanishi 2015	****	*	***	*****
Hasan Ali 2019	***	*	***	*****
Hodi 2014	****		***	*****
Horinouchi 2015	****	*	***	*****
Huang 2019	***	*	***	*****
Kamath 2020	***	*	***	*****
Kanda 2016	****		***	*****

Kanda 2020	****	*	***	*****
Kawazoe 2020	***	*	***	*****
Kelly 2020	***	*	***	*****
Kim 2020	***	*	***	*****
Kitano 2021	****	*	***	*****
Kluger 2019	***	*	***	*****
Lam 2021	***	*	***	*****
Lin 2020	***	*	***	*****
Lisberg 2018	***	*	***	*****
Luke 2018	***	*	***	*****
Ma 2021	***	*	***	*****
Madan 2012	***	**	**	*****
Mahalingam 2020	***	*	***	*****
Maity 2018	****		***	*****
Maity 2021	****	*	***	*****
Majd 2020	***	*	***	*****
Maker 2005	***	*	***	*****
Maker 2006	***	*	***	*****
Marcq 2021	***	**	**	*****
Massarelli 2019	***	**	**	*****
McNeel 2012	****		***	*****
Mego 2019	***	*	***	*****

Merchant 2016	****	**	***	*****
Miyamoto 2019	***		**	*****
Music 2020	***	*	***	*****
Naing 2020	***	*	***	*****
ONeill 2020	***	*	***	*****
Parikh 2018	****	*	***	*****
Patel 2017	***	*	***	*****
Pelster 2021	***	*	***	*****
Perez 2021	***	*	***	*****
Postow 2020	****		***	*****
Qiao 2019	****	*	***	*****
Qin 2017	***	**	***	*****
Ralph 2010	***	*	***	*****
Ratnayake 2020	***	*	***	*****
Ray 2016	***	*	***	*****
Reilley 2017	****		***	*****
Reschke 2021	****	*	**	*****
Reuben 2006	***	*	***	*****
Rodriguez 2020	****	*	***	*****
Ross 2020	***	*	***	*****
Royal 2010	***	*	***	*****
Rozeman 2020	****		***	*****

Sahebjam 2021	****	*	***	*****
Sakamuri 2018	***	*	***	*****
Sarfaty 2021	***	*	***	*****
Schoenfeld 2020	****		***	*****
Schweizer 2020	****	*	***	*****
Shah 2020	****	*	***	*****
Shenderov 2021	****	*	***	*****
Shoushtari 2018	***	*	***	*****
Strauss 2018	****		***	*****
Sundahl 2019	***	*	***	*****
Suresh 2019	****		***	*****
Takahashi 2020	***	**	***	*****
Tang 2019	***	**	***	*****
Thomas 2019	***	*	***	*****
Tree 2018	***	**	**	*****
Tsimberidou 2021	***	*	***	*****
van Dijk 2020	****		***	*****
Wang 2020	****	*	***	*****
Weber 2013	****		***	*****
Weber 2016	***	*	***	*****
Wei 2020	****		***	*****
Weide 2017	***	*	***	*****

Weiss 2017	***	*	***	*****
Weiss 2018	***	*	***	*****
Welsh 2019	***	*	***	*****
Welsh JW 2020	***	*	***	*****
Welsh J.W. 2020	***	*	***	*****
Wilgenhof 2016	***	*	***	*****
Wilky 2019	***	*	***	*****
Xie C. 2020	****		***	*****
Xie L. 2020	***	**	***	*****
Yamamoto 2017	***	*	***	*****
Yang 2007	****		***	*****
Yang 2018	****	*	**	*****
Yarchoan 2020	***	*	***	*
Yuan 2021	***	**	***	*****
Zamarin 2020	***	*	***	*****
Zhang 2021	***	*	***	*****
Zimmer 2019	***	*	***	*****

Supplementary Table S3: Criteria of included studies,

Author/year	Stud	Pati	Country	Cancer type	Mea	Male	Pathology (commonest	Unde	Re	Re	ITH drug	Target	Mean follow-	Overall	Progression-	AE
Lam 2021 (1)	P	40	China	Lung cancer	61.5	20	Lung cancer	N/A	13	9	atezolizuma	PD-L1	17.8 months	Median	9.4 (95%	2
Edenfield 2021 (2)	P	49	USA	Rare solid cancers	62	22	Cholangiocarcinoma 12 (24%)	N/A	N/A	0	N/A	N/A	18 months	N/A	N/A	N/A
Ferrarotto 2021 (3)	P	20	USA	Skin Cancer	68	17	SCC	17	13	13	pembrolizu mab	PD-1	44.1 months	8.31 months	2.04 months	N/A
Zhu 2022 (4)	RCT	170	China	Pancreatic cancer	N/A	105	ADC	N/A	N/A	N/A	pembrolizu	PD-1	23.3 months	24.9 months	18.3 months	N/A
Reschke 2021 (5)	P	17	Germany	Skin Cancer	70	9	Melanoma	N/A	2	2			Follow-up of patients was after at least 6 months (maximum 18	N/A	N/A	N/A
Chang 2021 (6)	P	25	Taiwan	solid cancers	54	21	Not specified	N/A	17	25	pembrolizu mab	PD-1	Not reported	8.5 months (95% CI, 6.6~ not reached) for	1.9 months (95% CI, 1.9 ~ 6) by RECIST and 2.0	N/A
Zhang 2021 (7)	RCT	20	China	Esophageal cancer	64	12	SCC	N/A	20	N/A	camrelizum ab	PD-1	31.0 months	16.7 months	11.7 months	N/A
Tsimberidou 2021 (8)	P	12	USA	Germ cell tumors	35	83.3	Testicular germ cell tumor, 7(58.3%)	0	0	12	pembrolizu mab	PD-1	N/A	10.6 (95% CI, 4.6–27.1)	2.4 (95% [CI], 1.5–4.5)	6
Marcq 2021 (9)	P	8	Canada	Bladder Cancer	68	75	Bladder Cancer	8	8	8	atezolizuma b	PD-L1	N/A	N/A	N/A	5
Altorki 2021 (10)	RCT	60	USA	Lung cancer	70.5	51.6	ADC: 34(56.6%)	52	30	N/A	durvalumab	PD-L1	16.9 months	N/A	N/A	11

Di Noia 2021 (11)	RCT	42	Italy	Lung cancer	70.5	71	Non-SCC: 36 (86%)	0	24	0	pembrolizu mab	PD-1	18.5 mo	Not reached in group 1&2 Group 3: 7.2 (95% CI 5.6	Median PFS for all groups : 8 (95% CI: 4.4–17.4)	1
Aamdal 2021 (12)	P	12	Norway	Melanoma	57	58	Melanoma	0	0	4	ipilimumab	CTLA-4	61.0 months	not reached	6.7	5
Shenderov 2021 (13)	P	30	USA	Prostate Cancer	67	100	ADC	0	0	30	N/A	N/A	9.9 (range, 2.3 –17.3)	9.5 (8.1, 11.4)	3.0 (2.7, 5.5)	12
Sahebjam 2021 (14)	P	32	USA	High grade Gliomas	52.5	65.6	Glioblastoma: 90.6%	14	32	32	pembrolizu mab	PD-1	Group A: 3.7 months Group B: 3.1 months	Group A: 13.45 months Group B: 9.3 months	Group A: 7.92 months Group B: 6.54 months	12
Chu 2021 (15)	P	22	China	Lung cancer	64.5	95.5	SCC 54.5%	0	0	0	sintilimab	PD-1	15.8 months	N/A	15 months	12
Ma 2021 (16)	P	39	China	Melanoma or nasopharyngeal carcinoma	48	72	Nasopharyngeal carcinoma: 76%	23	19	25	ipilimumab	CTLA-4	Group A: 4.9 Group B: 4.8	Group A: Not reached Group B: 76.6%	Group A: 10.1 Group B: 14.3%	0

Cascone 2021 (17)	RCT	44	USA	Lung cancer	65.6	64	ADC: 59%	39	4	17	Nivolumab & Ipilimumab	PD-1 & CTLA-4	22.2 months	Group A: 22 patients alive at end of follow up Group B: 21 Patients alive	Group A: 19 Patients progression free Group B: 16 Patients Progression free	5
Eichhorn 2021 (18)	P	15	Germany	Lung cancer	59.8	46.6	ADC: 86.6%	12	0	0	pembrolizu mab	PD-1	N/A	N/A	N/A	3
Pelster 2021 (19)	P	35	United States.	Skin Cancer	62	12	Melanoma	N/A	N/A	1	N/A	N/A	13.0 months	19.1 months.	5.5 months	0
Sarfaty 2021 (20)	P	13	United States.	carcinoma of the urinary tract	57	10	SCC ADC	5	N/A	21	N/A	N/A	7.38 months	6.97 months	1.8 months	N/A
Yuan 2021 (21)	P	16	United States.	Breast cancer	64	0	Triple -ve Breast cancer	16	15	N/A	pembrolizu mab	PD-1	24.9 months	2.6 months	25.5 months	N/A
Perez 2021 (22)	P	21	USA	Lung cancer	66	62	SCLC	0	21	21	N/A	N/A	N/A	11.7 months	4.5 months	16
Maity 2021	P	22	USA	Melanoma	N/A	77.2	Melanoma	0	22	11	ipilimumab	CTLA-4	89.2 months	10.7 months	3.6 months	3
Kitano 2021 (24)	P	13	Japan	Lung: 15.4% Bladder: 7.7% Breast: 7.7) Urethra: 1 (7.7%) Uterus: 1 (7.7%) Ovary: 1 (7.7%) prostate: 1 (7.7%) pancreas: 1 (7.7%)	62	38.4	N/A	9	7	12	cemiplimab	PD-1	8.11 (range 2.0–26.1).	N/A	N/A	4
Mahmood 2021 (25)	RCT	20	USA	Adenoid Cystic Carcinoma	64.5	20	Adenoid Cystic Carcinoma	19	17	9	pembrolizu mab	PD-1	19.8 months	Not reached	Arm A: 4.5 months (95%[CI], 2.4-20.6) Arm B: 3.16 months (95%[CI], 1.4-5.0)	1
Pakkala 2020 (26)	RCT	18	USA	Lung Cancer	70.00	61.1	SCLC	0	0	18	Durvalumab + Tremelimum	PD-L1 & CTLA-4	N/A	Median OS:3.9	Median PFS: 3.16.00	N/A

Majd 2020 (27)	P	4	USA	Pituitary carcinoma	27.5	50	corticotroph adenoma: 3 Lactotroph adenoma : 1	3	3	4	pembrolizu mab	PD-1	N/A	80	8	0
van Dijk 2020 (28)	P	24	Netherland s	Urinary Bladder Cancer	65	75	Urothelial Carcinoma	24	0	0	N/A	N/A	8.3 months	Obtained from Kaplan Meier curve	Obtained from Kaplan Meier curve	13
Gao 2020 (29)	P	28	USA	Urinary Bladder Cancer	71	71	Pure urothelial carcinoma 21 (75%)	24	0	0	N/A	N/A	19.2	88.8%	82.8%	6
Welsh 2020 (30)	P	40	USA	Lung cancer	64	40	SCLC: 36 (90%)	0	40	40	pembrolizu mab	PD-1	23.1 months	39.5 months	19.7 months	N/A
Duska 2020 (31)	RCT	52	USA	Cancer Cervix	49	0	squamous cell carcinoma	0	52	52	pembrolizu mab	PD-1	4.8 months	N/A	N/A	34
Schweizer 2020 (32)	P	104	Germany	HNSCC 44 (42%) Lung Cancer 46 (44%)	N/A	73	Squamous cell Carcinoma 64 (65%)	0	50	6	N/A	N/A	8.3 months.	22.8 months	7.8 months	4
Takahashi 2020 (33)	P	57	Japan	Melanoma	58	49.1	Melanoma	0	0	0	N/A	N/A	6.75 months	14 months	3.3 months	32
Awada 2020 (34)	P	54	Belgium	Glioblastoma	55	63	Glioblastoma	45	45	43	avelumab	PD-L1	24.9	26.6	Cohort 1: 12.0	N/A
Welsh 2020 (35)	RCT	100	USA	Lung cancer	65	64	ADC: 77(77%)	0	18	37	pembrolizu mab	PD-1	20.4 (1.4– 30.2)	N/A	SBRT Group: 20.8 RT Group: 6.8 Pembrolizuma b Alone: 6.8	17

Wang 2020 (36)	P	41	China	Lung Cancer	59	70.7	ADC: 29 (70.7%) SCC: 10 (24.4%)	14	20	41	toripalimab	PD-1	14.9 (3.2-22.5) months	13.8 months (95% CI, 10.0	2.8 (95% CI, 2.7 to 4.6)	1
Schoenfeld 2020 (37)	P	29	USA	HNSCC	65.2	62.1	SCC	29	0	0	N/A	N/A	14.2 months	89%	85%	N/A
ONeill 2020 (38)	P	10	USA	Pancreatic Cancer	62	40	Adenocarcinoma	10	N/A	10	nivolumab	PD-1	12 Months	18.0 months	6.8 months	7
Frumovitz 2020 (39)	P	7	USA	Gynecologic small cell neuroendocrine carcinoma	41	0	Small cell Neuroendocrine Carcinoma	0	N/A	N/A	pembrolizu mab	PD-1	N/A	N/A	2.1 months (Median)	2
Ratnayake 2020 (40)	P	24	Austrialia	Melanoma	66.8	79	N/A	0	24	0	N/A	N/A	28 months	16.9 months	2.2 months	N/A
Boutros 2020 (41)	P	19	France	Melanoma	58	53	N/A	N/A	19	N/A	ipilimumab	CTLA-4	5.8 years (Q1=4.5; Q3=6.8)	0.9 years (0.5–2)	0.4 (0.2–1.4)	N/A
Kawazoe 2020 (42)	P	29	Japan	Gastric and esophageal	70	90	Intestinal: 15 (52%)	6	0	15	pembrolizu mab	PD-1	12.6 (10.5-14.3)	not reached	7.1 (5.4-13.7)	14
Wei 2020 (43)	P	25	China	Solid tumors	52	80	N/A	N/A	N/A	25	toripalimab	PD-1	5mo (1.5-19.8)	N/A	N/A	0
Brastianos 2020 (44)	P	20	USA	Solid tumors	51.5	0	N/A	10	18	20	pembrolizu mab	PD-1	N/A	3.6 months	N/A	8
Kim 2020 (45)	P	9	USA	lung cancer or high grade neuroendocrine	61	44	SCLC: 6 (67%)	0	3	9	nivolumab	PD-1	6.8 mos	N/A	N/A	5
Graff 2020 (46)	P	28	USA	Prostate	72	100	Not specified	11	8	4	pembrolizu mab	PD-1	37 months	21.9 months	N/A	N/A
Ferrarotto 2020 (47)	RCT	28	USA	Oropharyngeal	N/A	97	N/A	0	9	0	N/A	N/A	15.8 months	100% still alive	N/A	4
Postow 2020 (48)	P	20	USA	Melanoma	60	60	N/A	0	10	N/A	N/A	N/A	19.4 months	1 year OS 56.3%	N/A	7

Zamarin 2020 (49)	P	27	USA	Ovarian	64	0	High grade serous: 23 (85.2%)	0	0	27	durvalumab	PD-L1	29 months	21 months	2.8 months	N/A
Feng 2020 (50)	P	32	China	Hepatobiliary	60	56	N/A	21	10	7	nivolumab	PD-1	12.8 months	8.5 months	6.1 months	N/A
Kanda 2020 (51)	P	24	Japan	Lung Cancer	63	70.8	ADC: 79.2%	N/A	N/A	N/A	nivolumab	PD-1	N/A	N/A	N/A	2
Arrieta 2020 (52)	RCT	78	Mexico	Lung Cancer	50.1	41	ADC: 88%	0	0	43	pembrolizu mab	PD-1	8.9 months	14.8	9.5 months	2
Rozeman 2020 (53)	P	38	Netherland s	Melanoma	62	59	N/A	N/A	N/A	N/A	ipilimumab	CTLA-4	N/A	12.4	3 mos	16
Xie 2020 (54)	P	59	USA	pancreatic	61	63	N/A	0	0	59	durvalumab	PD-L1	N/A	A1: 3.3 mos (1.2-6.6) A2: 9 (5-18.4)	A1: 1.7mos (0.8-2.0) A2: 2.5 (0.1-	18
Music 2020 (55)	P	78	Canada	solid tumors	61	45	High Grade serous ovarian carcinoma	N/A	N/A	N/A	pembrolizu mab	PD-1	N/A	23.8 mo	N/A	7
Liu 2020 (56)	RCT	40	China	Breast	45.5	0	Triple negative	N/A	N/A	30	camrelizum ab	PD-1	N/A	8.1 mos (4.0-not reached)	3.7 mos (2.0-6.4)	10
Xie 2020 (57)	P	43	China	Osteosarcoma	19	73	N/A	0	0	43	camrelizum	PD-1	11.3 (7.1-	11.3 mos	6.2 mos(4-	30
Goldberg 2020 (58)	P	42	USA	Lung Cancer	60	33	ADC: 86%	N/A	N/A	27	pembrolizu mab	PD-1	8.3 mos (4.5-26.2)	1yr OS 40% (30-64%)	1.9 (1.8-3.7)	7
Gao 2020 (59)	P	40	China	Lung Cancer	59.8	82.5	SCC: 82.5%	0	0	0	sintilimab	PD-1	3.2 mos(1.2-12.1)	N/A	N/A	4.0 0
Kamath 2020 (60)	P	21	USA	Pancreatic Cancer	66	38	ADC: 86%	8	4	14	ipilimumab	CTLA-4	N/A	6.9 mos (2.6-9.6)	2.78mos (1.6-4.8)	16. 00
Naing 2020 (61)	P	127	USA	Multiple solid tumor	56	54	N/A	N/A	N/A	127	pembrolizu mab	PD-1	N/A	N/A	N/A	11. 00
Kelly 2020 (62)	P	20	USA	Sarcoma	63.5	40	N/A	0	0	19	pembrolizu mab	PD-1	56 weeks	74.7wks (49-n/a)	17.1 wks (12.6-n/a)	4
Ross 2020 (63)	P	12	USA	Prostate	65.5	100	N/A	0	0	0	pembrolizu mab	PD-1	31.3 mos (18.1-39.3)	N/A	17.5mos (not specified)	0

Rodriguez 2020 (64)	P	50	USA	HEENT	60.5	78	N/A	0	0	25	pembrolizu mab	PD-1	12.6 mo	12.6mos (8.1-not reached)	4.5 mos (4.1- 8.4)	N/A
Shah 2020 (65)	P	30	USA	Breast	51	0	HR+, HER-, or triple negative	0	0	23	pembrolizu mab	PD-1	N/A	15.4 mos (8.2-20.3)	4.0 mos (2- 6.4)	N/A
Yarchoan 2020 (66)	P	12	USA	Colorectal	58	35	N/A	0	11	12	pembrolizu mab	PD-1	N/A	213 days (179-441)	82 days (48- 97)	2
Lin 2020 (67)	P	40	USA	Lung Cancer	67	68	ADC: 55%	0	0	0	atezolizuma b	PD-L1	part I: 22.5mos (19.0-29.1) Part II: 15.3 mos (10.9- 20.3)	part I: 22.8 Part II: not reached	Part I: 12.5mo Part II: 13.2mos	32. 00
Welsh 2020 (68)	P	38	USA	Lung Cancer	62	61	Small cell neuroendocrine: 91%	0	0	38	pembrolizu mab	PD-1	7.3mos (1-13)	8.4 (6.7-10.1)	6.1mos (4.1- 8.1)	2.0 0
Mahalingam 2020 (69)	P	11	USA	Pancreatic	64	27	N/A	4	11	7	pembrolizu mab	PD-1	N/A	3.1 mos (0- 8.7)	2.0 mos (0- 6.8)	2.0 0
Elbers 2020 (70)	P	10	Netherland s	HNSCC	69	8	SCC of the oral cavity, oropharynx, hypopharynx or larynx	N/A	9	N/A	avelumab	PD-L1	12 (8–26)	N/A	N/A	4
Di Giacomo 2019 (71)	P	19	Italy	melanoma	58	16	N/A	N/A	N/A	N/A	ipilimumab	CTLA-4	26.3 months	26.2 months (95% CI, 3.5– 48.9);	5.6 months (95% CI, 4.5– 6.6)	16
Welsh 2019 (72)	P	106	USA	Non Melanoma metastatic cancer	60	50	ADC 57, SCC 13, Neuroendocrine 9, Sarcoma 7, Adrenocortical 5, Other 15	N/A	106	N/A	ipilimumab	CTLA-4	10.5 months	median overall survival time was not	2.9 months	N/A
Gray 2019 (73)	P	33	USA	Lung Cancer	68	22	ADC 25, Adenosquamos Carcinoma 1, Squamos cell carcinoma 7	N/A	N/A	27	pembrolizu mab	PD-1	18.2 months	Immunothera py Refractoty: 6.8 (95% CI,	Immuntherapy Refractory: 2.8 (95% CI, 1.8—not	7.0 0
Qiao 2019 (74)	P	11	China	pancreatic, gastric, colorectal, cervical, endometrial cancer and peritoneal cancer	N/A	45	pancreatic: 1 gastric: 1 colorectal: 4 cervical:2 endometrial: 2 Peritoneal: 1	6	3	7	pembrolizu mab	PD-1	N/A	N/A	N/A	0

Chintakuntlawar 2019 (75)	P	3	USA	Anaplastic thyroid cancer	56	33	Anaplastic thyroid cancer: Sarcomatoid: 1 (33%) Epithelial: 1 (33%) Unspecified: 1 (33%)	2	3	3	pembrolizumab	PD-1	N/a	2.76 months	N/A	3
Feun 2019 (76)	P	29	USA	Hepatocellular Carcinoma	67	25	N/A	N/A	1	N/A	pembrolizumab	PD-1	17 months	13 months	4.5 months	3
Habra 2019 (77)	P	16	USA	adrenocortical carcinoma	48	8	ACC	N/A	N/A	N/A	pembrolizumab	PD-1	N/A	N/A	N/A	1
Cho 2019 (78)	P	33	Korea	Thymoma=7, Thymic carcinoma=26	57	21	73.1% SCC	11	12	33	pembrolizumab	PD-1	14.9 months	N/A	6.1 months (5.3-6.9)	0
Chalmers 2019 (79)	P	14	USA	Lung Cancer (NSCLCs)	N/A	N/A	N/A	N/A	N/A	N/A	ipilimumab	CTLA-4	n/a	> 42.3 months	24.1 month	5
Mego 2019 (80)	P	8	Slovakia	Germ cell tumor	29	100	1 embryonal carcinoma, 1 choriocarcinoma, 1 yolk sac tumor, 1 immature	0	0	8	avelumab	PD-L1	2.6 (0.3 to 14.4)	2.7 months (95% CI 1.0–3.3)	0.9 months (95% CI 0.5–1.9)	0
Thomas 2019 (81)	P	20	USA	Lung Cancer mall Cell Lung Cancer	64	45	N/A	1	9	20	durvalumab	PD-L1	11.1 months	4.1 months	1.8 months	N/A
Zimmer 2019 (82)	P	9	USA	7 ovarian/1 endometrial/1 triple negative breast cancer	59	0	OvCa (HGSOC/Clear cell/Mixed Mullerian/ Mixed Serous and Endometrioid) 6 (2/2/1/1) Platinum sensitivity in OvCa (sensitive/resistant) 2/5 Primary Peritoneal cancer (platinum-resistant) 1 Endometrial carcinoma (MSI low) 1 Triple Negative Breast Cancer 1	0	0	2	durvalumab	PD-L1	8 months	N/A	N/A	N/A

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Kluger 2019 (94)	P	23	USA	melanoma	65	65	N/A	12	12	N/A	pembrolizu mab	PD-1	34 months	17 months	2 months	N/A
Massarelli 2019 (95)	P	24	USA	22 (92) oropharyngeal cancer, Cervix1 (4) Anus1 (4)	60	83	N/A	N/A	N/A	N/A	nivolumab	PD-1	12.2	17.5 months	2.7 months	N/A
Parikh 2018 (96)	P	12	USA	urothelial carcinoma, recurrent or advanced disease	66	8	urothelial carcinoma	N/A	N/A	2	pembrolizu mab	PD-1	Arm A 5.7 months, Arm B 3.7 months	N/A	4.8 months	7.0 0
Maity 2018 (97)	P	24	USA	Melanoma and others (pancreas and breast)	59.7	10.42	N/A	18	15	N/A	pembrolizu mab	PD-1	N/A	N/A	N/A	8
Amaria 2018 (98)	RCT	53	USA	Melanoma	52	35.8	Superficial spreading (42%)	8	1		Nivolumab: + Ipilimumab	PD-1 & CTLA-4	15.0 months	100% at 24.4 months with I+N versus 76% (31–94%) at 22.6 mo with N, p=0.18	82% at 17.2 months (mo) with I+N versus 58% (27–80%) at 22.6 mo with N	9
Tobin 2018 (99)	RCT	10	USA	Melanoma	52.1	40	N/A	0	0	0	ipilimumab	CTLA-4	group 1 318 days group 2 365 days	N/A	N/A	5
Tree 2018 (100)	P	5	UK	Urinary Bladder			N/A	N/A	N/A	5	pembrolizu mab	PD-1	N/A	N/A	N/A	2.0 0
Lisberg 2018 (101)	P	11	USA	Lung Cancer	58.7	36.3	Squamous 1 Non squamos 10	0	0	0	pembrolizu mab	PD-1	233 days	N/A	N/A	1

Calabrò 2018 (102)	P	40	Italy	pleural or peritoneal mesothelioma	64	73	epithelioid: 32 (80%) Sarcomatoid: 2 (5%) Biphasic: 5 (13%)	N/A	N/A	N/A	N/A	N/A	N/A	16.6 months	5.7 moths	7
Luke 2018 (103)	P	73	USA	Ovarian 9, Lung Cancer 7, breast 6, cholangiocarcinoma 6, endometrial 6, colorectal 5, head and neck 4, others	62	39.7	N/A	0	69	73	pembrolizu mab	PD-1	5.5 months	9.6 months	PFS was 3.1 months	50
Strauss 2018 (104)	P	19	Germany	adenoid cystic carcinoma 2, anal 2, Appendiceal 1, bronchopulmonary carcinoid 1, cervix 4, chordoma 1, colorectal 2	56	52.6	N/A	0	0	19	m7824	PD-L1	N/A	N/A	N/A	4
Da Gama Duarte 2018 (105)	P	5	Australia	Melanoma	59	60	Melanoma	0	0	3	ipilimumab	CTLA-4	study terminated due to	study terminated due to	study terminated due to	2
Giaccone 2018 (106)	P	40	USA	Thymic carcinoma	57	70	SCC 48% , Poorly differentiated 32%. Neuroendocrine 15% Not specified 5%	21	23	40	pembrolizu mab	PD-1	20 months (IQR 14–26)	24.9 months (15.5–not reached)	4.2(95% CI 2.9–10.3)	N/A
Yang 2018 (107)	P	13	USA	Lung Cancer	61.4	38	ADC:62%, SCC:38%	13	0	13	ipilimumab	CTLA-4	N/A	29.2 (95% CI: 22.1 to not reached)	N/A	5
Sakamuri 2018 (108)	P	36	USA	Melanoma, Thyroid, Adrenocortical cancer, Adenoid cystic cancer, Leiomyosarcoma, Hodgkin Lymphoma, Renal cancer, Others	56	33	Hodgkin Lymphoma 7 (19%)	N/A	N/A	N/A	ipilimumab	CTLA-4	N/A	N/A	N/A	N/A
Ariyan 2018 (109)	P	26	USA	Melanoma	N/A	62	Melanoma	N/A	N/A	26	ipilimumab	CTLA-4	36 Months	N/A	N/A	10

Haag 2018 (110)	P	25	Germany	Melanoma	64	80	Melanoma	24	5	9	ipilimumab	CTLA-4	4.56(2.2---14.2)	22.7 (95% CI 9.5-Not reached)	2.9 (95% CI 2.5e8.1)	9
Weiss 2018 (111)	P	17	USA	Pancreatic Cancer	55	35.3	ADC	2	1	4	pembrolizu mab	PD-1	N/A	15 (95%CI, 6.8----22.6)	9.1(95%CI, 4.9---15.3)	12
Shoushtari 2018 (112)	P	64	USA	Melanoma	56	50	Melanoma	3	3	N/A	N/A	N/A	14 months	N/A	N/A	38
Patel 2017 (113)	P	64	USA	Melanoma	62	70	Melanoma	0	0	N/A	ipilimumab	CTLA-4	20 months (2–60)	Not reached	5	N/A
Ben-Ami 2017 (114)	P	12	Israel	Uterus	54.5	N/A	Leiomyosarcoma	N/A	N/A	N/A	nivolumab	PD-1	Not reported	Because of the small sample size	1.8 months (95% CI 0.1-3.5)	N/A
Qin 2017 (115)	P	24	USA	Lung	64	24	NSCLC	N/A	18	24	pembrolizu mab	PD-1	9.2 months	Not reported	Not reported	N/A
Weiss 2017 (116)	P	49	USA	Breast, pancreatic, NSCLC, Sarcoma, SCLC, ovarian cancer, and other	55	13	Breast cancer	19	16	2	pembrolizu mab	PD-1	N/A	10.46 months	N/A	N/A
DAngelo 2017 (117)	P	28	USA	Gastric	56	17	GIST & other sarcomas	N/A	N/A	N/A	ipilimumab	CTLA-4	17.5 months	13.5 months	2.8 months	N/A
Reilley 2017 (118)	P	35	USA	Gastric, Renal, Skin & Lung	57.5	23	Melanoma	N/A	N/A	N/A	ipilimumab	CTLA-4	Not reported	Not reported	N/A	N/A
Weide 2017 (119)	P	15	Germany	Skin	54	9	Melanoma	N/A	N/A	4	ipilimumab	CTLA-4	231 days	12 months	N/A	N/A
Yamamoto 2017 (120)	P	17	Japan.	Colorectal. Lung	N/A	10	ADC	12	5	16	nivolumab	PD-1	24 months	Not reported	N/A	N/A

Brustugun 2017 (121)	P	58	Norway	Lung cancer	64.6	28	ADC 32 (55.2)	N/A	N/A	N/A	nivolumab	PD-1	14.3 months	11.7 months	N/A	N/A
Duffy 2017 (122)	P	32	USA	Liver cancer	61	28	Hepatocellular carcinoma	5	5		tremelimum ab	CTLA-4	18.8 months	12.3 months	Six and 12-month tumor	N/A
Kanda 2016 (123)	P	24	Japan	Lung cancer	63	17	NSCLC	N/A	N/A	N/A	nivolumab	PD-1	6.23 months (range, 2.04–	Not reported	6.28 months in arm A, 9.63	N/A
Ray 2016 (124)	P	12	United	Skin cancer	63.5	6	Melanoma	N/A	N/A	N/A	ipilimumab	CTLA-4	N/A	>31 months	N/A	N/A
Graff 2016 (125)	P	10	USA	prostate cancer	72	10	ADC	N/A	N/A	N/A	pembrolizu mab	PD-1	7.5 months	N/A	Three patients remain free of	N/A
Bjoern 2016 (126)	P	10	Denmark	Skin cancer	51.1	8	Melanoma	N/A	N/A	N/A	ipilimumab	CTLA-4	N/A	N/A	N/A	N/A
Goldberg 2016 (127)	P	36	USA	skin and lung cancer	62	18	Melanoma and NSCLC	24	9	N/A	pembrolizu mab	PD-1	Melanoma>> 11.6 months. NSCLC>> 11.6 months.	Melanoma was not	N/A	N/A
Wilgenhof 2016 (128)	P	39	Netherland	skin cancer	46	23	Melanoma	N/A	22	18	ipilimumab	CTLA-4	36 months	14.75 months	6.75 months	N/A
Weber 2016 (129)	P	126	USA	Skin cancer	60	60	Melanoma	N/A	N/A	47	nivolumab	PD-1	16 months	20.6 months	5.3 months	N/A
Merchant 2016 (130)	P	33	USA	Metastatic skin cancer from many solid tumors.	N/A	14	Melanoma Sarcoma Renal/bladder carcinoma	N/A	17	23	ipilimumab	CTLA-4	Not reported	irAE n= 14 >> 100 % 3months,	N/A	N/A
Freeman-Keller 2016 (131)	P	159	USA	Skin	N/A	N/A	Melanoma	N/A	N/A	N/A	nivolumab	PD-1	35months	16.8 months	N/A	N/A
Hamanishi 2015 (132)	P	20	Japan	Ovarian cancer	61.1	0	Serous>	N/A	N/A	20	nivolumab	PD-1	11.0 months	20 months.	3.5 months	N/A
Horinouchi 2015 (133)	P	15	Japan.	Lung cancer	61	12	NSCLC	N/A	N/A	N/A	ipilimumab	CTLA-4	N/A	9 months	N/A	N/A

Calabrò 2015 (134)	P	29	Italy.	Lung cancer	65	20	Mesothelioma	N/A	N/A	15	tremelimum ab	CTLA-4	21·3 months	11.3 months	6.2 months	2
Hodi 2014 (135)	P	46	USA	Skin cancer	58	28	Melanoma	N/A	20	29	ipilimumab	CTLA-4	17.3 months	25.1 months.	N/A	N/A
Weber 2013 (136)	P	90	USA	Skin cancer	N/A	58	Melanoma	N/A	N/A	N/A	nivolumab	PD-1	8.1 months	N/A	N/A	N/A
Calabrò 2013 (137)	P	29	Italy.	Skin cancer	64	21	Mesothelioma.	N/A	N/A	25	tremelimum ab	CTLA-4	27 months	10.7 months	6.2 months	N/A
Le 2013 (138)	RCT	30	USA	Pancreatic cancer	62	20	ADC.	N/A	N/A	28	ipilimumab	CTLA-4	25 months	4.3 months	Not reported	N/A
McNeel 2012 (139)	P	11	USA	Prostatic cancer	63	11	ADC.	9	6	N/A	tremelimum ab	CTLA-4	15 months	N/A	N/A	N/A
Madan 2012 (140)	P	30	USA	Prostatic cancer	69	30	ADC.	N/A	N/A	6	ipilimumab	CTLA-4	Not reported.	34·4 months	3·9 months	N/A
Di Giacomo 2011 (141)	P	27	Italy.	Skin cancer	55	14	Melanoma	N/A	N/A	N/A	ipilimumab	CTLA-4	8.5 months	9.6 months	29 months	N/A
Royal 2010 (142)	P	27	USA	Pancreatic cancer	55	15	ADC.	24	12	20	ipilimumab	CTLA-4	N/A	10.9 months	N/A	N/A
Ralph 2010 (143)	P	18	UK	Gastric/esophageal	56	14	ADC	N/A	N/A	18	tremelimum ab	CTLA-4	N/A	Median survival for	N/A	N/A
Yang 2007 (144)	P	40	USA	Renal cancer	N/A	28	RCC	39	N/A	2	ipilimumab	CTLA-4	N/A	N/A	N/A	17
Maker 2006 (145)	P	46	USA	Skin Cancer	48	32	Melanoma	46	14	28	ipilimumab	CTLA-4	N/A	N/A	N/A	N/A
Reuben 2006 (146)	P	30	USA	Skin Cancer	58	19	Melanoma	2	11	17	ticilimumab	CTLA-4	N/A	N/A	N/A	N/A
Maker 2005 (147)	P	36	USA	Skin Cancer	47.1	22	Melanoma	36	7	8	ipilimumab	CTLA-4	N/A	N/A	N/A	N/A

ACC: adenoid cystic carcinoma, ADC: Adenocarcinoma, CTH: chemotherapy, HEENT: Head, Eyes, Ears, Nose, & Throat, HNSCC: Head & Neck squamous cell carcinoma, HCC: hepatocellular carcinoma, NSCLC: Non-small cell lung cancer, NOS: Not Otherwise Specified, P: Prospective, RCT: Randomized Controlled Trial, R: Retrospective SCC: squamous cell carcinoma, TC: thymic carcinoma, UC: Urothelial carcinoma.

Supplementary Table S4: Summary of criteria of different variables included in meta-analysis

	Average	SD	Median	Min	Max
Study period (years)	1.75	1.16	1.42	0.25	7.33
Age	59.22	8.44	60.75	19	72
Males (%)	47.64	-	-	0	100
Underwent surgery (%)	31.2	-	-	0	100
Underwent radiotherapy (%)	17.2	-	-	0	100
Underwent chemotherapy (%)	16.15	-	-	0	100

Supplementary Table S5: List of the 45 excluded studies for the sensitivity analysis

Aamdal 2021	Awada 2020	Bjoern 2016	Chalmers 2019	Chang 2021
Chu 2021	Chung 2019	DAngelo 2017	Da Gama Duarte 2018	Di Giacomo 2019
Duffy 2017	Graff 2020	Graff 2016	Gray 2019	Haag 2018
Hodi 2014	Kawazoe 2020	Kelly 2020	Kim 2020	Kitano 2021
Lam 2021	Le 2013	Liu 2020	Madan 2012	Mahalingam 2020
Maker 2005	Massarelli 2019	ONeill 2020	Ray 2016	Reilley 2017
Rodriguez 2020	Rozeman 2020	Sahebjam 2021	Sakamuri 2018	Shenderov 2021
Thomas 2019	Weber 2013	Weide 2017	Wilgenhof 2016	Wilky 2019
Xie 2020	Yarchoan 2020	Yuan 2021	Zamarin 2020	Zimmer 2019

*Studies in gray were added to the first 33 excluded studies (in white)

Supplementary Table S6: Subgroup analysis of pooled events rates in A) adverse events (AE) 3-4 and B) AE 5 by ITH drugs

A) AE 3-4				B) AE 5			
ITH drug	N. Studies	PER (95% CI)	Subgroup difference	ITH drug	N. Studies	PER (95% CI)	Subgroup difference
Pembrolizumab	33	20.73% (13.92-29.71) ¶	p=0.1160	Pembrolizumab	38	2.90% (1.96-4.29) ¶¶	p=0.9798
Ipilimumab	13	42.20% (31.14-54.12) ¶		Ipilimumab	24	2.50% (1.47-4.23) ¶¶	
Nivolumab	5	21.92% (4.80-60.99)		Nivolumab	10	2.95% (0.98-8.56)	
Atezolizumab	3	42.40% (5.44-90.41)		Atezolizumab	3	2.54% (0.63-9.61)	
Toripalimab	3	10.78% (0.32-82.18)		Camrelizumab	3	1.49% (0.30-7.04)	
Avelumab	2	21.94% (2.80-73.28)		Durvalumab	3	1.07% (0.22-5.12)	
Camrelizumab	2	46.87% (11.70-85.46)		Tremelimumab	3	3.02% (0.75-11.34)	
Durvalumab	2	24.32% (14.30-38.24)		Avelumab	2	2.22% (0.31-14.28)	
Sintilimab	2	27.14% (3.49-79.31)		Sintilimab	2	4.84% (1.57-13.97)	
Cemiplimab	1	30.77% (12.04-59.07)		Toripalimab	2	1.51% (0.21-9.97)	
M7824	1	21.05% (8.13-44.55)		Cemiplimab	1	3.57% (0.22-38.39)	
Tremelimumab	1	6.9% (1.73-23.75)		M7824	1	2.50% (0.15-29.81)	

¶ Subgroup analysis of AE 3-4 of Pembrolizumab and Ipilimumab was p=0.0030

¶¶ Subgroup analysis of AE 5 of Pembrolizumab and Ipilimumab was p=0.6563

AE: adverse events, PER: pooled events rate

Supplementary Table S7: Subgroup analysis of pooled events rates A) adverse events (AE) 3-4 and B) AE 5 by ITH class

	A) AE 3-4			B) AE 5		
ITH drug	N. Studies	PER (95% CI)	Subgroup difference	N. Studies	PER (95% CI)	Subgroup difference
Anti PD-1	46	22.16% (15.81-30.15)	p=0.0610	56	3.17% (2.31-4.35)	p=0.4817
Anti PD-L1	8	30.15% (14.43-52.49)		9	1.90% (0.79-4.49)	
Anti CTLA-4	14	38.64% (27.39-51.26)		27	2.56% (1.56-4.18)	

AE: adverse events, CTL A-4: cytotoxic T lymphocyte antigen 4, PD-1: programmed cell death 1 and PD-L1: programmed cell death 1 ligand 1, PER: pooled events rate

Supplementary Table S8: Subgroup analysis of primary outcomes on lung cancer only vs pancreatic cancer only vs all other cancers

Outcome	Group	Patients	Studies	PER (95%CI)	Heterogeneity (I ² , p-value)	Subgroup, p-value
Any grade irAE	Lung	545	17	74.81% [61.90; 84.45]	83.8%, p<0.0001	0.0113
	Pancreatic	97	4	96.19% [87.59; 98.90]	0%, p=0.5642	
	Others	1341	44	79.48% [70.03; 86.52]	87.1%, p<0.0001	
Grade 3-4 irAE	Lung	762	22	18.26% [11.13; 28.48]	84.5%, p<0.0001	0.0207
	Pancreatic	118	5	53.17% [28.56; 76.33]	81.0%, p=0.0003	
	Others	1414	49	29.48% [23.05; 36.83]	81.1%, p<0.0001	
Grade 5 irAE	Lung	734	22	2.38% [1.43; 3.95]	0%, p=0.9995	0.9134
	Pancreatic	315	7	3.28% [0.80; 12.50]	61.3%, p=0.0166	
	Others	2227	71	2.51% [1.85; 3.39]	0%, p=0.9996	
Cardiac-related irAE	Lung	961	29	2.76% [1.58; 4.77]	34.2%, p=0.0383	0.6213
	Pancreatic	345	8	1.73% [0.65; 4.53]	0%, p=0.8948	
	Others	3004	95	2.85% [2.19; 3.72]	7.6%, p=0.2758	
Pulmonary-related irAE	Lung	961	29	7.42% [5.17; 10.53]	41.1%, p=0.0120	0.0059
	Pancreatic	345	8	1.91% [0.80; 4.52]	0%, p=0.8980	
	Others	3004	95	4.53% [3.71; 5.52]	0%, p=0.5814	

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