# Review Article

# **Risk of Rash in PD-1 or PD-L1-Related Cancer Clinical Trials: A** Systematic Review and Meta-Analysis

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*Background*. Given that immune-related rash was the most frequently reported PD-1 or PD-L1-related skin toxicity, this systematic review and meta-analysis were conducted to elucidate its incidence risk. *Methods*. The meta-analysis was carried out according to the PRISMA guidelines. The random effect model was used in the process of all analyses. Skin rash of all grades and grades 3–5 were calculated and gathered in the final comprehensive analyses. *Results*. The study included 86 clinical trials classified into 15 groups. Compared with chemotherapy, PD-1 or PD-L1 inhibitors significantly strengthened the risk of developing rash across all grades (OR = 1.66, 95% CI: [1.31, 2.11]; p < 0.0001). This trend was significantly strengthened the control group was placebo (OR = 2.62, 95% CI: [1.88, 3.65]; p < 0.00001). Similar results were observed when PD-1 or PD-L1 inhibitors were given together with chemotherapy (OR = 1.87, 95% CI: [1.59, 2.20]; p < 0.00001), even in patients with grades 3–5. As with other combination therapies, the risk of developing rash for all grades was enhanced when PD-1 or PD-L1 was given together with chemotherapy as the second-line option (OR = 2.98, 95% CI: [1.87, 4.75]; p = 0.05). No statistically significant differences could be found in skin rash between the PD-1 and PD-L1-related subgroups. *Conclusion*. Whether PD-1 or PD-L1 inhibitors were given alone or together with others, the risk of developing rash would be enhanced. Furthermore, the risk of developing rash appeared to be higher when PD-1 or PD-L1 inhibitors together with other antitumor drugs were given as the second-line options. No statistically significant results of developing rash between PD-1 and PD-L1 subgroups were obtained owing to the participation of PD-1 or PD-L1 inhibitors.

#### 1. Introduction

Due to tobacco cessation, advancements in early diagnosis and treatment, the death rate of various cancers has been falling year after year in the United States, while the survival rate has been improving, particularly for non-small-cell lung cancer (NSCLC) [1]. Among the several therapeutic options available, cancer immunotherapy is extremely successful in increasing cancer patients' survival rates, particularly when PD-1 or PD-L1 inhibitors are given [2]. On the basis of research into the mechanisms of immune escape, PD-1 or PD-L1 inhibitors have reshaped the therapy landscape for cancer by activating the immune system, while also gradually reporting plenty of treatment-related side effects [3]. Although the association between some adverse events and PD-1 or PD-L1 inhibitors has been extensively examined and documented [4-9], many toxicities remain unexplored, including skin toxicities [3].

Skin toxicities, such as rash, pruritus, vitiligo, palmarplantar erythrodysasthesia (PPE), erythema, eczema, urticaria, dermatitis, dry skin, and maculopapular rash, were frequently observed in cancer patients treated with PD-1 or PD-L1 [3, 10, 11]. Additionally, autoimmune skin toxicities associated with PD-1 or PD-L1 have been reported to be significantly more prevalent in patients with NSCLC who are in complete or partial remission [10]. This pattern may also be observed in other types of tumors [11, 12]. Correlations between adverse events and clinical benefit are not uncommon [13-15]. However, the correlations between the risk of developing skin toxicities and PD-1 or PD-L1 inhibitors, as well as their effect on patient prognosis, remain unknown. Therefore, the rash with the highest rate of occurrence among PD-1 or PD-L1-related skin toxicities was chosen for the comprehensive analysis. To begin, subgroup analysis would be used to assess the difference in rash risk between the PD-1 and PD-L1 subgroups; second, the effect of different administration timing on rash would be assessed; and then, detailed subgroup analysis would be used to elucidate the source of heterogeneity.

#### 2. Methods

The design and specific procedures of the meta-analysis were carried out step-by-step as recommended by the PRISMA [16].

2.1. Eligibility Screening for All Clinical Trials. Phase III clinical trials involving PD-1 or PD-L1 inhibitors with control groups would be preferred. Other clinical trials with control groups would be placed in an alternate location. With the exception of hematological malignancies, the types of solid tumors would not be limited. All data involving rash would be extracted and recorded in preparation for the subsequent adequate subgroup analysis. Four authors were appointed for eligibility screening.

2.2. Formulation and Implementation of Literature Search Strategy. According to the principle of PICOS (participants, interventions, comparisons, outcomes, and study design), the specific strategy of literature search was specified and implemented by all authors [16]. First, neoplasm was firstly searched as the MeSH keyword, not limited to specific solid tumor types. Then, all kinds of PD-1 or PD-L1 inhibitors, including common names, trade names, and abbreviations, would be searched as keywords and the search results would be unioned.

The publication time of relevant studies would be limited from July 09, 2013, to September 14, 2021. If one clinical trial was repeatedly reported several times, only the one with full detailed data could be selected for the analysis.

2.3. Quality Evaluation and Publication Bias Screening. The revised Cochrane Collaboration tool was adopted for bias risk screening in all selected trials [17], and the Funnel plot and Egger's test were used for publication bias assessments [18]. A p value < 0.05 was considered as the evidence for the existence of publication bias.

The quality screening of all the enrolled clinical trials were also carried out by the above four authors. The screening criteria were listed as the following 5 items: (a) selection bias, (b) performance bias, (c) detection bias, (d) attrition bias, and (e) reporting bias [17].

2.4. Screening of Results. The main outcome measure was the risk of PD-1 or PD-L1 involving rash across all grades, while the second was the rash for grades 3–5. The main information of all trials would be extracted and summarized in the single table (Table 1). The main content included in the table was listed as the following items: the first author's name, publication years, trial title, registered trial number, therapies lines, treatment regimens, participants, phase, tumor type, RCT, and the number of rash events.

2.5. Heterogeneity Screening and Statistical Analyses. Cochrane's Q and I<sup>2</sup> statistics were used for heterogeneity screening, as described by Higgins and colleagues [16, 19], while the Harbord test was used for publication bias evaluation [19]. Three grades of heterogeneity were defined according to the I<sup>2</sup> value: The two separation thresholds were 25% and 50%, respectively [20]. Using Review Manager 5.3, odds ratios (OR) and 95% confidence intervals (CI) across all enrolled clinical trials using the random effect (RE) method were calculated [21], whereas funnel plots were constructed using the fixed effect (FE) model. All statistical tests were two-sided, and p < 0.05 was taken as a statistically significant result. In the process of analyses, adequate subgroup evaluations would be carried out according to the actual situation.

ial.	Reference	NCT number	LABLE Drug	1: basic information of all selected clinical trials. Treatment Regimens	Involving Patients	Rash	Previous therapy	Phase	Tumor Type
1	Borghaei H, et al 2015 [22]	NCT01673867 (CheckMate 057)	Nivolumab (PD- 1)	Nivolumab versus Docetaxel	555	35	Yes	III	Advanced non- sonamons NSCLC
	Weber JS, et al. 2015 [23]	NCT01721746 (CheckMate 037)	Nivolumab (PD- 1)	Nivolumab versus Dacarbazine/Paclitaxel plus Carbonlatin	370	30	No	III	Advanced melanoma
	Brahmer J, <i>et al.</i> 2015 [24]	NCT01642004 (CheckMate 017)	Nivolumab (PD- 1)	Nivolumab versus Docetaxel	260	13	Yes	III	Advanced squamous cell NSCLC
	Motzer RJ, <i>et al.</i> 2015 [25]	NCT01668784 (CheckMate 025)	Nivolumab (PD- 1)	Nivolumab versus Everolimus	803	120	Yes	III	Advanced RCC
	Herbst RS, <i>et al.</i> 2016A [26]			Pembrolizumab 2 mg/kg versus Pembrolizumab 10 mg/kg		73			
	Herbst RS, et al. 2016B [26]	NCT01905657 (KEYNOTE-010)	Pembrolizumab (PD-1)	Pembrolizumab 2 mg/kg versus Docetaxel	166	43	Yes	III/II	Advanced NSCLC
	Herbst RS, et al. 2016C [26]			Pembrolizumab 10 mg/kg versus Docetaxel		58			
	Langer C), <i>et al.</i> 2016 [27] Awad MM, <i>et al.</i>	NCT02039674 (KEYNOTE-021)	Pembrolizumab (PD-1)	Pembrolizumab plus Carboplatin plus Pemetrexed versus Carboplatin plus Pemetrexed	121	25	No	Π	Advanced nonsquamous NSCLC
	2021 [28] Antonia SJ, <i>et al.</i> 2016 [29]	NCT01928394 (CheckMate 032)	Nivolumab (PD- 1)	Nivolumab versus Nivolumab plus Ipilimumab	152	9	Yes	II/II	Recurrent SCLC
	Ferris RL, et al. 2016 [30]	NCT02105636 NCT02105636 (CheckMate 141)	Nivolumab (PD- 1)	Nivolumab versus (Methotrexate, Docetaxel, or Cetuximab)	347	23	Yes	III	Recurrent HNSCC
	Hodi FS, <i>et al.</i> 2016 [31]	NCT01927419 (CheckMate 069)	Nivolumab (PD- 1)	Nivolumab plus Ipilimumab versus Ipilimumab	140	54	No	II	Advanced melanoma
	Bellmunt J, <i>et al.</i> 2017 [32]	NCT02256436 (KEYNOTE-045)	Pembrolizumab (PD-1)	Pembrolizumab versus Chemotherapy	531	45	Yes	III	Advanced UC
	Kang YK, <i>et al.</i> 2017 [33]	NCT02267343 (ONO- 4538-12, ATTRACTION-2)	Nivolumab (PD- 1)	Nivolumab versus Placebo	491	24	Yes	III	Advanced gastric or GJC
	Schachter J, et al. 2017A [34]			Pembrolizumab every 2 weeks versus Pembrolizumab every 3 weeks		92			
	Schachter J, et al. 2017B [34]	NCT01866319 (KEYNOTE-006)	Pembrolizumab (PD-1)	Pembrolizumab every 2 weeks versus Ipilimumab	811	84	Yes	III	Advanced melanoma
	Schachter J, et al. 2017C [34]	~	~	Pembrolizum <sup>1</sup> b every 3 weeks versus Ipilimumab		88			
	Antonia SJ, <i>et al.</i> 2017 [35]	NCT02125461 (PACIFIC)	Durvalumab (PD-L1)	Durvalumab versus Placebo	209	50	Yes	III	Advanced, unresectable, stage III NSCLC
	Socinski MA, et al. 2018 [36]	NCT02366143 (IMpower150)	Atezolizumab (PD-L1)	Atezolizumab plus Bevacizumab plus Carboplatin plus Paclitaxel (ABCP) versus Bevacizumab plus Carboplatin plus Paclitaxel (BCP)	787	72	No	III	Metastatic nonsquamous NSCLC

TABLE 1. Basic information of all selected clinical trials

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Tumor Type	Squamous NSCLC	Extensive-stage SCLC	Stage III NSCLC	Metastatic nonsquamous NSCLC	Advanced/metastatic NSCLC	Resected stage III melanoma	Unresectable locally advanced or metastatic TNBC	Stage IV or recurrent NSCLC Locally advanced or metastatic UC
Phase	III	III	III	II	III	III	Ξ	
Previous therapy	No	No	Yes	No	Yes	No	No	No YSE No
Rash	79	57	76	105	22	136	113	139 125 72 139 139 125 20 61 61
Involving Patients	558	394	709	607	101	1011	890	1537 1128 531
Treatment Regimens	Pembrolizumab plus chemotherapy versus chemotherapy	Atezolizumab plus Carboplatin plus Etoposide versus Carboplatin plus Etoposide	Durvalumab versus Placebo	Pembrolizumab plus Pemetrexed plus A platinum-based drug versus Pemetrexed plus A platinum-based drug	Atezolizumab versus Docetaxel	Pembrolizumab versus Placebo	Atezolizumab plus Nab-paclitaxel versus Nab- paclitaxel	Nivolumab plus Ipilimumab versus Nivolumab Nivolumab plus Ipilimumab versus Chemotherapy (platinum doublet) Nivolumab versus Chemotherapy (platinum doublet) Nivolumab plus Ipilimumab versus Nivolumab Nivolumab plus Ipilimumab versus Chemotherapy (platinum Nivolumab versus Chemotherapy (platinum doublet) Nivolumab versus Chemotherapy (vinflumine paclitaxel or docetaxel) Durvalumab blus FP versus FP
Drug	Pembrolizumab (PD-1)	Atezolizumab (PD-L1)	Durvalumab (PD-L1)	Pembrolizumab (PD-1)	Atezolizumab (PD-L1)	Pembrolizumab (PD-1)	Atezolizumab (PD-L1)	Nivolumab (PD- 1) Atezolizumab (PD-L1) Durvalumab
NCT number	NCT02775435 (KEYNOTE-407)	NCT02763579 (IMpower133)	NCT02125461 (PACIFIC)	NCT02578680 (KEYNOTE-189)	NCT02008227 (OAK)	NCT02362594	NCT02425891 (IMpassion130)	NCT02477826 (CheckMate 227) (CheckMate 227) (IMvigor211) NCT03043872
Reference	Paz-Ares L, <i>et al.</i> 2018 [37]	Horn L, <i>et al.</i> 2018 [38]	Antonia SJ, <i>et al.</i> 2018 [39]	Gandhi L, <i>et al.</i> 2018 [40] Gadgeel S, <i>et al.</i> 2020 [41] Rodríguez- Abreu D, <i>et al.</i> 2021 [42]	Hida T, <i>et al.</i> 2018 [43]	Eggermont AMM, et al. 2018 [44]	Schmid P, <i>et al.</i> 2018 [45] Emens LA, <i>et al.</i> 2021 [46]	Hellmann MD, et al. 2018A [47] Hellmann MD, et al. 2018B [47] Hellmann MD, et al. 2018C [47] Reck M, et al. 2021A [48] Reck M, et al. 2021B [48] Reck M, et al. 2021C [48] Powles T, et al. 2018B [49] Paz-Ares L, et al.
Trial no.	15	16	17	18	19	20	21	24 23 22 24

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Trial no.	Reference	NCT number	Drug	Treatment Regimens	Involving Patients	Rash	Previous therapy	Phase	Tumor Type
25	Motzer RJ, et al. 2019 [51] Motzer RJ, et al. 2020 [52]	NCT02684006 (JAVELIN Renal 101)	Avelumab (PD- L1)	Avelumab plus Axitinib versus Sunitinib	873	96	Yes	Ξ	Advanced RCC
26	West H, <i>et al.</i> 2019 [53]	NCT02367781 (IMpower130)	Atezolizumab (PD-L1)	Atezolizumab plus Carboplatin plus Nab- paclitaxel versus Carboplatin plus Nab-paclitaxel	705	25	No	III	Metastatic nonsquamous NSCLC
27	Kato K, <i>et al.</i> 2019 [54]	NCT02569242 (ATTRACTION-3)	Nivolumab (PD- 1)	Nivolumab versus Paclitaxel/Docetaxel	417	54	Yes	Ш	Advanced OSCC
28	2019 [55] 2019 [55]	NCT02231749 (CheckMate 214)	Nivolumab (PD- 1)	Nivolumab plus Ipilimumab versus Sunitinib	1082	193	No	III	Advanced RCC
29	Rini BI, <i>et al.</i> 2019 [56]	NCT02420821 (IMmotion151)	Atezolizumab (PD-L1)	Atezolizumab plus Bevacizumab versus Sunitinib	206	128	No	III	Metastatic RCC
30	Sullivan RJ, <i>et al.</i> 2019 [57]	NCT01656642	Atezolizumab (PD-L1)	Atezolizumab plus Vemurafenib versus Atezolizumab plus Cobimetinib plus Vemurafenib	56	20	No	ſŀ	BRAF-mutated melanoma
	Hellmann MD, et al 2019A [58]			Nivolumab plus Ipilimumab versus Nivolumab		139			
31	Hellmann MD, et al. 2019B [58]	NCT02477826 (CheckMate 227)	Nivolumab (PD- 1)	Nivolumab plus Ipilimumab versus Chemotherapy (platinum doublet)	1537	125	No	III	Advanced NSCLC
	Hellmann MD, et al. 2019C [58]			Nivolumab versus Chemotherapy (platinum doublet)		72			
32	Wu YL, <i>et al.</i>	NCT02613507	Nivolumab (PD-	Nivolumab versus Docetaxel	493	43	Yes	III	Advanced NSCLC
33	Cohen EEW, et al. 2019 [60]	NCT02252042 (KEYNOTE-040)	Pembrolizumab (PD-1)	Pembrolizumab versus (Methotrexate, Docetaxel, or Cetuximab)	480	53	Yes	III	Recurrent or metastatic HNSCC
	Mok TSK, <i>et al.</i> 2019 [61]	NCT02220894	Pembrolizumah						Locally advanced or
34	Wu YL, <i>et al.</i>	(KEYNOTE-042)	(PD-1)	Pembrolizumab versus Chemotherapy	1251	73	No	II	metastatic NSCLC
	Burtness B, et al.			Pembrolizumab versus Pembrolizumab plus		59			
35	2012A [03] Burtness B, <i>et al.</i> 2019B [63]	NCT02358031 (KEYNOTE-048)	Pembrolizumab (PD-1)	Dembrolizumab versus Cetuximab plus Chemotherapy	863	141	No	III	Recurrent or Metastatic HNSCC
	Burtness B, <i>et al</i> . 2019C [63]	~		Pembrolizumab plus Chemotherapy versus Cetuximab plus Chemotherapy		140			
36	Finn RS, <i>et al.</i> 2020 [64]	NCT03434379	Atezolizumab (PD-L1)	Atezolizumab plus Bevacizumab versus Sorafenib	485	68	No	III	Unresectable hepatocellular carcinoma
37	Gutzmer R, <i>et al.</i> 2020 [65]	NCT02908672 (IMspire150)	Atezolizumab (PD-L1)	Atezolizumab plus Vemurafenib plus Cobimetinib versus Vemurafenib plus Cobimetinib	511	209	No	III	Unresectable advanced BRAFV600 mutation- positive melanoma
38	Mittendorf EA, et al. 2020 [66]	NCT03197935 (IMpassion031)	Atezolizumab (PD-L1)	Atezolizumab + Chemotherapy versus Chemotherapy	331	88	No	III	Early stage TNBC

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	NCT number	Drug	Treatment Regimens	Involving Patients	Rash	Previous therapy	Phase	e Tumor Type
	NCT02388906 (CheckMate 238)	Nivolumab (PD- 1)	Nivolumab versus Ipilimumab	905	197	No	III	Resected stage IIIB–C and stage IV Melanom
	NCT02409342 (IMpower110)	Atezolizumab (PD-L1)	Atezolizumab versus Chemotherapy (platinum- based)	549	63	No	III	PD-L1-selected NSCLC
	NCT02924883 (KATE2)	Atezolizumab (PD-L1)	Atezolizumab plus Trastuzumab emtansine versus Trastuzumab emtansine	200	34	Yes	Π	HER2-positive advanced breast cance
	NCT03099382 (ESCORT)	Camrelizumab (PD-1)	Camrelizumab versus Chemotherapy (Docetaxel or Irinotecan)	448	189	Yes	III	Advanced or metastati OSCC
	NCT02603432 (JAVELIN Bladder 100)	Avelumab (PD- L1)	Avelumab versus Best Supportive Care (BSC)	689	44	Yes	III	Advanced or metastati UC
	NCT02563002 (KEYNOTE-177)	Pembrolizumab (PD-1)	Pembrolizumab versus Chemotherapy (5- fluorouracil-based therapy with or without bevacizumab or cetuximab)	296	36	No	III	Colorectal cancer
	NCT03036488 (KEYNOTE-522)	Pembrolizumab (PD-1)	Pembrolizumab plus Chemotherapy (Paclitaxel plus Carboplatin) versus Placebo plus Chemotherany (Paclitaxel alue Cochonletin)	1170	229	No	III	Stage II or stage III TNBC
	NCT02367794 (IMbower131)	Atezolizumab (PD-L1)	Atezolizumaby (racinaxer pus Caroopaun) Atezolizumab plus Carboplatin plus Nab- paclitaxel versus Carboplatin plus Nab-paclitaxel	668	38	Yes	III	Advanced squamous NSCLC
	NCT03134872 (CameL)	Camrelizumab (PD-1)	Camrelizumab plus Carboplatin plus Pemetrexed versus Carboplatin plus Pemetrexed	412	36	No	III	Nonsquamous NSCLC
~			Nivolumab plus Ipilimumab versus Nivolumab		6			
	NCT02523313 (IMMUNED)	Nivolumab (PD- 1)	Nivolumab plus Ipilimumab versus Placebo	162	N/A	Yes	II	Resected stage IV melanoma
_ :			Nivolumab versus Placebo		N/A			
5			Atezolizumab plus Chemotherapy (platinum- hseed) yarense Atezolizumab		75			
_	NCT02807636	Atezolizumab	Atezolizumab plus Chemotherapy versus		0		111	Locally advanced or
_	(IMvigor130)	(PD-L1)	Chemotherapy	1203	80	No	II	metastatic UC
_			Atezolizumab versus Placebo plus Chemotherapy		41			
	NCT07516241	Durvalumah	Durvalumab versus Durvalumab plus Tremelimumab		73			IInresectable advances
	(DANUBE)	(PD-L1)	Durvalumab versus Chemotherapy (gemcitabine plus cisplatin/carboplatin)	998	34	No	III	or metastatic UC
	NCT03066778 (KEYNOTE-604)	Pembrolizumab (PD-1)	Pembrolizumab plus EP versus Placebo plus EP	446	43	No	III	Extensive-stage SCLC

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Trial no.	Reference	NCT number	Drug	Treatment Regimens	Involving Patients	Rash	Previous therapy	Phase	Tumor Type
	Shitara K, <i>et al.</i> 2020A [80]			Pembrolizumab versus Pembrolizumab plus Chemotherapy (Cisplatin plus Fluorouracil/ Capecitabine)		43			
52	Shitara K, <i>et al.</i> 2020B [80]	NCI 02494583 (KEYNOTE-062)	Pembrolizumab (PD-1)	Pembrolizumab versus Chemotherapy	748	26	No	III	Advanced GC
	Shitara K, <i>et al.</i> 2020C [80]			Pembrolizumab plus Chemotherapy versus Chemotherapy		37			
	Ribas A, <i>et al.</i> 2020A [81]			Durvalumab plus Dabrafenib plus Trametinib versus Durvalumab plus Trametinib		16			
53	Ribas A, <i>et al.</i> 2020B [81]	NCT02027961	Durvalumab (PD-L1)	(concurrent) Durvalumab plus Dabrafenib plus Trametinib versus Durvalumab plus Trametinib (sequential)	68	20	Yes	Ι	Advanced melanoma
	Ribas A, <i>et al.</i> 2020C [81]			Durvalumab plus Trametinib (concurrent) versus Durvalumab plus Trametinib (sequential)		18			
54	Winer EP, et al. 2021 [82]	NCT02555657 (KEYNOTE-119)	Pembrolizumab (PD-1)	Pembrolizumab versus Single-drug Chemotherany	601	8	Yes	III	Metastatic TNBC
55	Lee NY, <i>et al.</i> 2021 [83]	NCT02952586	Avelumab (PD-	Avelumab plus Chemorad and Avelumab versus nlacebo nlus Chemoradiotherany	692	56	No	III	Locally advanced HNSCC
56	Miles D, <i>et al.</i> 2021 [84]	NCT03125902 (IMpassion131)	Atezolizumab (PD-L1)	Atezolizumab plus Paclitaxel versus Placebo plus Paclitaxel	649	207	No	III	Locally advanced/ metastatic TNBC
57	Ren Z, <i>et al.</i> 2021 [85]	NCT03794440 (ORIENT-32)	Sintilimab (PD-1)	Sintilimab plus Bevacizumab biosimilar (IBI305) versus sorafenib	565	49	No	III-II	Unresectable hepatocellular carcinoma
	Powles T, <i>et al.</i> 2021A [86]			Pembrolizumab versus Chemotherapy		64			
58	Powles T, <i>et al.</i> 2021B [86]	NCT02853305 (KEYNOTE-361)	Pembrolizumab (PD-1)	Pembrolizumab plus Chemotherapy versus Chemotherapy	993	107	No	Ш	Advanced UC
	Powles T, <i>et al.</i> 2021C [86]			Pembrolizumab versus Pembrolizumab plus Chemotherapy		123			
59	Bajorin DF, et al. 2021 [87]	NCT02632409 (CheckMate 274)	Nivolumab (PD- 1)	Nivolumab (Adjuvant) versus placebo	669	72	Yes	III	Muscle-invasive UC
	Brufsky A, <i>et al.</i> 2021A [88]			Cobimetinib plus atezolizumab plus paclitaxel versus Cobimetinib plus paclitaxel	152	32			
60	Brufsky A, <i>et al.</i> 2021B [88]	NCT02322814 (COLET)	Atezolizumab (PD-L1)	Cobimetinib plus atezolizumab plus paclitaxel versus Cobimetinib plus atezolizumab plus Nab- paclitaxel		28	No	II	Advanced or metastatic TNBC
	Brufsky A, et al. 2021C [88]			Cobimetinib plus paclitaxel versus Placebo plus paclitaxel		25			

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Tumor Type		Advanced RCC		Muscle-invasive UC	Advanced RCC	Advanced NSCLC	Stage IV or recurrent NSCLC	Unresectable malignant pleural mesothelioma		Extensive-stage SCLC			Platinum-resistant or platinum-refractory OC		Resected esophageal or GJC	Stage IIIB/IV or recurrent nonsquamous NSCLC	NC	Extensive-stage SCLC
Phase		III		III	III	III	III	III		III			Π		III	III	III	III/I
Previous therapy		No		No	No	No	No	No		No			Yes		Yes	No	No	No
Rash	143	184	135	101	95	26	78	58	26	46	52	61	54	25	62	121	72	61
Involving Patients		1047		787	640	697	707	584		797			546		792	548	263	394
Treatment Regimens	Lenvatinib plus Pembrolizumab versus Sunitinib	Lenvatinib plus Pembrolizumab versus Lenvatinib plus Everolimus	Lenvatinib plus Everolimus versus Sunitinib	Atezolizumab versus Observation	Nivolumab plus Cabozantinib versus Sunitinib	Cemiplimab versus Chemotherapy (platinum- doublet)	Nivolumab plus Ipilimumab plus Chemotherapy versus Chemotherapy	Nivolumab plus Ipilimumab versus Chemotherapy	Durvalumab plus EP versus EP	Durvalumab plus Tremelimumab (CTLA-4) plus EP versus EP	Durvalumab plus Tremelimumab (CTLA-4) plus EP versus Durvalumab plus EP	Avelumab plus PLD (Pegylated Liposomal Doxorubicin) versus PLD	Avelumab plus PLD versus Avelumab	Avelumab versus PLD	Nivolumab versus Placebo	Nivolumab versus Placebo	Camrelizumab plus Gemcitabine plus Cisplatin versus Gemcitabine plus Cisplatin	Atezolizumab plus CP/ET versus Placebo plus CP/ET
Drug		Pembrolizumab (PD-1)		Atezolizumab (PD-L1)	Nivolumab (PD- 1)	Cemiplimab (PD- 1)	Nivolumab (PD- 1)	Nivolumab (PD- 1)		Durvalumab (PD-L1)			Avelumab (PD- L1)		Nivolumab (PD- 1)	Nivolumab (PD- 1)	Camrelizumab (PD-1)	Atezolizumab (PD-L1)
NCT number		NCT02811861 (CLEAR)		NCT02450331 (IMvigor010)	NCT03141177 (CheckMate 9ER)	NCT03088540 (EMPOWER-Lung 1)	NCT03215706 (CheckMate 9LA)	NCT02899299 (CheckMate 743)		NCT03043872 (CASPIAN)			NCT02580058 (JAVELIN Ovarian 200)		NCT02743494 (CheckMate 577)	NCT03117049 (ONO- 4538-52/TASUKI-5)	NCT03707509 (CAPTAIN-1st)	NCT02763579 (IMpower133)
Reference	Motzer R, et al. 2021A [89]	Motzer R, <i>et al.</i> 2021B [89]	Motzer R, <i>et al.</i> 2021C [89]	Bellmunt J, <i>et al</i> . 2021 [90]	Choueiri TK, et al. 2021 [91]	Sezer A, <i>et al.</i> 2021 [92]	Paz-Ares L, <i>et al.</i> 2021 [93]	Baas P, <i>et al.</i> 2021 [94]	Goldman JW, et al 2021 A [95]	Goldman JW, et al. 2021B [95]	Goldman JW, et al. 2021C [95]	Pujade-Lauraine E, <i>et al</i> . 2021A [96]	Pujade-Lauraine E, <i>et al.</i> 2021B [96]	Pujade-Lauraine E, <i>et al.</i> 2021C [96]	Kelly RJ, <i>et al.</i> 2021 [97]	Sugawara S, et al. 2021 [98]	Yang Y, <i>et al.</i> 2021 [99]	Liu SV, <i>et al.</i> 2021 [100]
Trial no.		61		62	63	64	65	99		67			68		69	70	71	72

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Trial no.	Reference	NCT number	Drug	Treatment Regimens	Involving Patients	Rash	Previous therapy	Phase	Tumor Type
	Monk BJ, <i>et al.</i> 2021A [101]			Avelumab plus Chemotherapy + Avelumab (maintenance) versus Chemotherapy		91			
73	Monk BJ, <i>et al.</i> 2021B [101]	NCT02718417 (JAVELIN Ovarian 100)	Avelumab (PD- L1)	Avelumab plus Chemotherapy plus Avelumab (maintenance) versus Chemotherapy plus Avelumab (maintenance)	166	125	No	III	Stage III–IV epithelial OC
	Monk BJ, <i>et al.</i> 2021C [101]	×		Chemotherapy plus Avelumab (maintenance) versus Chemotherapy		84			
74	Choueiri TK, et al. 2021 [102]	NCT03142334 (KEYNOTE-564)	Pembrolizumab (PD-1)	Pembrolizumab versus Placebo	984	151	No	III	Clear-cell, advanced RCC
75	Moore KN, <i>et al.</i> 2021 [103]	(NCT03038100) (IMagyn050/GOG 3015/ENGOT-OV39)	Atezolizumab (PD-L1)	Atezolizumab plus CP plus Bevacizumab versus Placebo plus CP plus Bevacizumab	1285	252	No	III	Stage III or IV OC
76	Gogas H, <i>et al.</i> 2021 [104] Ourseileoleo TV	NCT03273153 (IMspire170)	Atezolizumab (PD-L1)	Cobimetinib plus Atezolizumab versus Pembrolizumab	436	118	No	III	BRAFV600 wild-type melanoma
	CWOILIKOKU 1.N. $et al. 2021A$ [105]			Nivolumab plus Ipilimumab versus Nivolumab		82			
77	Owonikoko TK, <i>et al.</i> 2021B [105]	NCT02538666 (CheckMate 451)	Nivolumab (PD- 1)	Nivolumab plus Ipilimumab versus Placebo	830	76	Yes	III	Extensive-disease SCLC
	Owonikoko TK, et al. 2021C			Nivolumab versus Placebo		28			
78	[105] Luo H, <i>et al.</i> 2021 [106]	NCT03691090 ((ESCORT-1st)	Camrelizumab (PD-1)	Camrelizumab plus Chemotherapy versus Chemotherapy	595	22	No	III	Advanced or metastatic ESCC
	Colombo N, et al. 2021A [107]	NICT03635567	Demhrolizumuh	Pembrolizumab plus Chemotherapy plus Bevacizumab versus Chemotherapy plus Bevacizumad	389	65			Persistent, recurrent, or
79	Colombo N, et al. $2021B$ [107]	(KEYNOTE-826)	(PD-1)	Pembrolizumab plus Chemotherapy versus Chemotherapy	227	17	No	III	metastatic cervical cancer
80	Fennell DA, et al. 2021 [108]	NCT03063450 (CONFIRM)	Nivolumab (PD- 1)	Nivolumab versus Placebo	332	1	Yes	III	Malignant mesothelioma
81	Pusztai L, <i>et al.</i> 2021 [109]	(NCT01042379) (I- SPY2)	Durvalumab (PD-L1)	Durvalumab plus Olaparib plus Paclitaxel (DOP) versus Paclitaxel	372	63	No	II	HER2-negative stage II/III breast cancer
82	Zhu X, <i>et al.</i> 2021 [110]	NCT02704156	Pembrolizumab (PD-1)	SBRT plus Pembrolizumab plus Trametinib versus SBRT plus Gemcitabine	170	22	Yes	II	Locally recurrent pancreatic cancer after surgical resection
83	Sun JM, <i>et al.</i> 2021 [111]	NCT03189719 (KEYNOTE-590)	Pembrolizumab (PD-1)	Pembrolizumab plus Chemotherapy versus Placebo plus Chemotherapy	740	47	No	III	Advanced esophageal cancer
84	Mai HQ, <i>et al.</i> 2021 [112]	NCT03581786	Toripalimab (PD- 1)	Toripalimab plus GP versus Placebo plus GP	289	71	No	Ш	Advanced NC

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rious Phase Tumor Type apy	es III Resected stage IB-Li NSCLC						io III Advanced melanon						
ash Prev the	02 Y	67	62	43	65	61	40 N	67	62	43	07	83	28
Involving <sub>R:</sub> Patients	990 1	1	1	1	1	1	937 1	1	1	1	2	1	2
Treatment Regimens	Atezolizumab versus BSC	Nivolumab plus Ipilimumab versus Nivolumab	Nivolumab plus Ipilimumab versus Ipilimumab	Nivolumab versus Ipilimumab	Nivolumab plus Ipilimumab versus Nivolumab	Nivolumab plus Ipilimumab versus Ipilimumab	Nivolumab versus Ipilimumab	Nivolumab plus Ipilimumab versus Nivolumab	Nivolumab plus Ipilimumab versus Ipilimumab	Nivolumab versus Ipilimumab	Nivolumab versus Nivolumab plus Ipilimumab	Nivolumab versus Ipilimumab	Nivolumab plus Ipilimumab versus Ipilimumab
Drug	Atezolizumab (PD-L1)						Nivolumab (PD- 1)						
NCT number	NCT02486718 (IMpower010)						NCT01844505 (CheckMate 067)						
Reference	Felip E, <i>et al.</i> 2021 [113]	Larkin J, <i>et al.</i> 2019A [114]	Larkin J, <i>et al.</i> 2019B [114]	Larkin J, <i>et al.</i> 2019C [114]	Wolchok JD, et al. 2017A [115]	Wolchok JD, et al. 2017B [115]	Wolchok JD, et al. 2017C	Hodi FS, <i>et al.</i> 2018A [116]	Hodi FS, <i>et al.</i> 2018B [116]	Hodi FS, <i>et al.</i> 2018C [116]	Larkin J, <i>et al.</i> 2015A [117]	Larkin J, <i>et al.</i> 2015B [117]	Larkin J, <i>et al.</i> 2015C [117]
Trial no.	85						86						

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#### 3. Results

3.1. Literature Search Results. After a preliminary PubMed search, 522 studies were retrieved (Figure 1). After criteria screened, 95 studies involving 86 clinical trials, including 55207 participants, were used for the final comprehensive analyses [22-25], [26-30], [31-35], [36-40], [41-45], [46-50], [51-55], [56-60], [61-65], [66-70], [71-75], [76-80], [81-85], [86-90], [91-95], [96-110], [111-115], [116, 117]. According to the PICOS guidelines, the detailed process of literature screening was provided in the form of PRISMA flow diagram (Figure 1). All types of literature included in the quality checking were finished by the four authors independently and finally summarized by the corresponding author and then plotted as the (S Figure 1) [22-25], [26-30], [31-35], [36-40], [41-45], [46-50],[51-55], [56-60], [61-65], [66-70], [71-75], [76-80], [81-85], [86-90], [91-95], [96-110], [111-115], [116, 117].

3.2. Basic Information for All Included Clinical Trials. Basic characteristics of 86 clinical trials included in the study were extracted and shown in Table 1 [5], [22-25], [26-30], [31-35], [36-40], [41-45], [46-50], [51-55], [56-60],[61-65], [66-70], [71-75], [76-80], [81-85], [86-90], [91-95], [96-110], [111-115], [116, 117]. 6 clinical trials, including KEYNOTE-021 [27, 28], KEYNOTE-189 [40-42], CheckMate 227 [47, 48], JAVELIN Renal 101 [51, 52], KEYNOTE-042 [61, 62], and CheckMate 067 [114-117], were repeatedly reported multiple times by different reporters, and only one with the detailed data could be selected for the final analyses. Among them, there were 72 Phase III, 8 Phase II, 2 Phase II/III, 1 Phase I/II, 1 Phase I/III, 1 Phase Ib, and 1 Phase I clinical trials. In 55 clinical trials, PD-1 or PD-L1 inhibitors were given alone or together with other antitumor drugs as the first-line regimens [23, 27, 28, 31], [36-38, 40-42], [44-48, 50, 53], [55-58], [61-68],[72, 73, 75], [77-80, 83-86], [88-95], [98-104], [106, 107, 109, 111, 112], [114-117], while previous therapies were found in the other 31 clinical trials [22, 24-26, 29, 30, 32-35, 39, 43, 49, 51, 52, 54, 59, 60, 69-71, 74, 76, 81, 82, 87, 96, 97, 105, 108, 110, 113]. Among the tumor types involved in all enrolled clinical trials, NSCLC accounted for the highest proportion (n = 22) [22, 24, 26–28, 35-37, 39-43, 47, 48, 53, 58, 59, 61, 62, 68, 74, 75, 92, 93, 98, 113], followed by melanoma (n = 11)[23, 31, 34, 44, 57, 65, 67, 76, 81, 104, 114-117], urothelial carcinoma (n = 8) [32, 49, 71, 77, 78, 86, 87, 90], renal cell carcinoma (n = 7) [25, 51, 52, 55, 56, 89, 91, 102], SCLC (n=7) [29, 38, 50, 79, 95, 100, 105], triple-negative breast cancer (n=6) [46, 66, 73, 82, 84, 88], and head and neck squamous cell carcinoma (n = 4) [30, 60, 63, 84].

All enrolled clinical trials were classified into 15 groups in view of the treatment regimens of all the control groups, which were listed as follows: Group A (PD-1 or PD-L1 versus Chemotherapy) [22–24, 26, 32, 43, 47, 49, 54, 59, 61, 68, 77, 78, 80, 82, 86, 92, 96], Group B (PD-1 or PD-L1 plus Chemotherapy versus Chemotherapy) [27, 37, 41, 45, 53, 66, 73, 74, 77, 79, 80, 84, 86, 95, 96, 100, 101, 103, 107, 111, 112],

Group C (Camrelizumab plus Chemotherapy versus Chemotherapy) [75, 99, 106], Group D (PD-1 or PD-L1 plus Chemotherapy plus Bevacizumab versus Chemotherapy plus Bevacizumab) [36, 107], Group E (PD-1 or PD-L1 versus Placebo) [33, 39, 44, 71, 87, 90, 91, 97, 98, 105, 108], Group F (PD-1 or PD-L1 plus Chemotherapy versus PD-1 or PD-L1) [63, 77, 80, 96], Group G (PD-1 or PD-L1 plus CTLA-4 versus PD-1 or PD-L1) [29, 47, 76, 78, 105, 118], Group H (PD-1 or PD-L1 versus CTLA-4) [34, 67, 117], Group I (PD-1 or PD-L1 plus CTLA-4 versus Chemotherapy) [47, 94], Group J (PD-1 or PD-L1 plus CTLA-4 plus Chemotherapy versus Chemotherapy) [93, 95], Group K (PD-1 or PD-L1 plus Bevacizumab versus Sorafenib) [64, 85], Group L (PD-1 or PD-L1 plus CTLA-4 versus CTLA-4) [31, 117], Group M (PD-1 or PD-L1 versus Methotrexate/docetaxel/cetuximab) [30, 60], and Group N (PD-1 or PD-L1 plus Antineoplastic Drug versus Sunitinib) [51, 55, 56, 89, 91]. The others would just be used for the 34, 57, systematic review [25, 26, 63, 65. 69, 72, 81, 83, 88, 89, 95, 101, 104, 105, 109, 110]. Within each group, the differences between the PD-1 and PD-L1 subgroups would be assessed firstly, followed by the treatment lines.

3.3. Risk of Bias. 86 clinical trials, involving 95 literatures, were all screened for 5 relevant bias risks, and the results were shown in the (S Figure 1) [22-25], [26-30], [31-35], [36-40], [41-45], [46-50], [51-55], [56-60], [61-65], [66-70], [71-75], [76-80], [81-85], [86-90], [91-95], [96-110], [111-115], [116, 117]. Data with high bias would not be adopted for the final meta-analysis (S Figure 1) [57, 114-116]. The funnel plots for publication bias assessments were constructed and shown in the corresponding figures (S Figures 2–6).

3.4. Risk Assessments of Rash for All Grades in Group A (PD-1 or PD-L1 versus Chemotherapy). Reactive cutaneous capillary endothelial proliferation (RCCEP) was the characteristic rash of camrelizumab, so the clinical trials including camrelizumab were evaluated separately [70]. 19 clinical trials in Group A were summarized and prepared for the final analyses [22–24, 26, 32, 43, 47, 49, 54, 59, 61, 68, 77, 78, 80, 82, 86, 92, 96]. Among all tumor types, NSCLC was the most common one (n=10) [22, 24, 26, 43, 47, 59, 61, 68, 92], followed by UC (n=5) [32, 49, 77, 78, 86].

Through analyses, we found that PD-1 or PD-L1 inhibitors significantly increased the risk of developing rash for all grades (OR = 1.66, 95% CI: [1.31, 2.11]; I<sup>2</sup> = 57%, Z = 4.19, p < 0.0001; Figures 2(a)–2(d)). Compared with the PD-L1 subgroup, the risk of developing rash appeared to be higher in PD-1 subgroup (OR = 1.92, 95% CI: [1.48, 2.50]; I<sup>2</sup> = 46%, Z = 4.86, p = 0.03; Figure 2(a)). Similar trend was also found when subgroup was divided based on the treatment lines (OR = 1.82, 95% CI: [1.48, 2.24]; I<sup>2</sup> = 0%, Z = 5.67, p < 0.00001; Figure 2(b)). However, no statistically significant subgroup differences were found in the above two subgroups (Chi<sup>2</sup> = 2.62, p = 0.11, I<sup>2</sup> = 61.8%, Figure 2(a); Chi<sup>2</sup> = 0.46, p = 0.50, I<sup>2</sup> = 0%, Figure 2(b)).



FIGURE 1: The flow diagram of all enrolled clinical trials.

High heterogeneity ( $I^2 = 57\%$ ) could be found in the analysis results (Figures 2(a)-2(d)). After adequate subgroup analyses, it was found that this high degree of heterogeneity stemmed mainly from the two clinical trials of NSCLC ( $I^2 = 76\%$ , Figure 2(c);  $I^2 = 83\%$ , Figure 2(d)) [22, 24]. The funnel plots of them are shown in S Figures 2(a)-2(d).

3.5. Risk Assessments of Rash for All Grades in Group B, Group C, and Group D. 21 clinical trials in Group B were enrolled for the final analysis [27, 37, 41, 45, 53, 66, 73, 74, 77, 79, 80, 84, 86, 95, 96, 100, 101, 103, 107, 111, 112]. Among all enrolled clinical trials, clinical trials involving NSCLC (n=5) still accounted for the highest proportion [27, 37, 41, 53, 74], followed by triple-negative breast cancer (TNBC) (n=4) [45, 66, 73, 84], small cell lung cancer (SCLC) (n=3) [79, 95, 100], ovarian cancer (OC) (n=3) [96, 101, 103], and urothelial carcinoma (UC) (n=2) [77, 86].

Compared with chemotherapy in Group B, it was found that PD-1 or PD-L1 together with chemotherapy significantly increased the risk of rash for all grades (OR = 1.87, 95% CI: [1.59, 2.20];  $I^2 = 53\%$ , Z = 7.50, p < 0.00001; Figures 3(a)–3(d)), even in each evaluable subgroups (Figures 3(c) and 3(d)). Similar to the former analysis result of Group A, the PD-1 subgroup appeared to have a higher risk of rash (OR = 2.01, 95% CI: [1.63, 2.47]; Figure 3(a)) with no statistical significant differences [27, 37, 41, 73, 79, 80, 86, 107, 111, 112], when it was

compared to the PD-L1 subgroup (Chi<sup>2</sup> = 0.66, p = 0.42; Figure 3(a)) [45, 53, 66, 74, 77, 84, 95, 96, 100, 101, 103]. Different from the previous analyses (Figure 2(b)), the incidence risk of rash was higher when PD-1 or PD-L1 together with chemotherapy was given as the second-line option (OR = 2.98, 95% CI: [1.87, 4.75]; Chi<sup>2</sup> = 3.95, p = 0.05; Figure 3(b)) [74, 96]. Subgroup analyses indicated that the incidence risk of rash was different among different tumor types, especially in UC subgroup (OR = 2.66, 95% CI: [1.73, 4.09]; I<sup>2</sup> = 61%, Z = 4.48, p < 0.00001; Figure 3(c)) [77, 86]. Through subgroup analyses (Figures 3(c) and 3(d)), it was found that the high heterogeneity (I<sup>2</sup> = 53%) might be mainly derived from the clinical trial KEYNOTE-361 (Figure 3(d)) [86].

Similar to the analysis result in Group B, the incidence risk of rash was also significantly increased when camrelizumab was given together with chemotherapy (OR = 2.30, 95% CI: [1.54, 3.44];  $I^2 = 0\%$ , Z = 4.04, p < 0.0001; Figure 3(e)) [75, 99, 106]. However, when PD-1 or PD-L1 was given with bevacizumab and chemotherapy, no statistically significant analysis result was found (OR = 1.90, 95% CI: [0.86, 4.20];  $I^2 = 77\%$ , Z = 1.60, p = 0.11; Figure 3(e)). All the corresponding funnel lots are shown in S Figures 3(a)– 3(f).

3.6. Risk Assessments of Rash for All Grades in Groups E and F. 11 clinical trials in Group E were enrolled for the final analyses [33, 39, 44, 71, 87, 90, 91, 97, 98, 105, 108]. Among



FIGURE 2: Forest plots of comparison in Group A (PD-1 or PD-L1 versus Chemotherapy). (a) The OR of rash for all grades calculated by the random effect (RE) model: subgroup analyses were performed according to the types of immune checkpoint inhibitors (PD-1 or PD-L1). (b) The OR of rash for all grades calculated by the random effect (RE) model: subgroup analyses were performed according to the treatment lines (first or second line). (c) The OR of rash for all grades calculated by the random effect (RE) model: subgroup analyses were performed based on drug name, tumor type, and immune checkpoint type. (d) The OR of rash for all grades calculated by the random effect (RE) model: subgroup analyses were performed based on drug name, tumor type, immune checkpoint type, and I2 value.

all clinical trials, clinical trials involving UC (n=3) accounted for the highest proportion [71, 87, 90], followed by NSCLC (n=2) [39, 98]. In 5 clinical studies [44, 90, 91, 98, 108], PD-1 or PD-L1 inhibitors were given as the first-line choice, whereas they were utilized as second-

line or alternative therapeutic choices in the other 6 trials [33, 39, 71, 87, 97, 105].

Compared with placebo, it was found that PD-1 or PD-L1 inhibitors significantly increased the risk of developing rash for all grades (OR = 2.62, 95% CI: [1.88, 3.65];  $I^2 = 69\%$ ,

(d)

PD-1/PE Study or Submourn	-L1+Chem	otherapy	Ch	emother	upy Total Wa	O Indet (%) M H I	ids Ratio	Odds Ratio	PD-1/PI	D-L1+Chemothe	rapy C	hemother	apy Travil	Wataba (W)	Odds Ratio	Odds Ratio
2.1.1 PD-1+Chemotherapy VS Chemother	rapy	101		ents	iotai we	igni (%) 31-ri. r	andom. 95%	M-H, Kandoli, 55% Cl	2.3.1 PD-1/PD-L1+Chemotherapy VS Ch	emotherapy (Fir	st Line)	vents	lotai	weight (%)	M-H. Random, 95% CI	M-H, Random, 95% Cl
Gadgeel S, et al.2021B	82	405	5 2	3	202	2.0 2.02 5.0 1.98	0.72, 5.65]	<u> </u>	Colombo N, et al.2021B Gadgeel S, et al.2020	11 82	111 405	6 23	116 202	2.0 5.0	2.02 [0.72, 5.65] 1.98 [1.20, 3.25]	<b>—</b>
Langer CJ, et al.2016 Mai HQ, et al.2021	16 40	59 146	5 3	9	62 143	2.4 2.19 4.6 1.36	0.88, 5.45] 0.80, 2.34]		Gaisky MD, et al.2020B Goldman JW, et al.2021A	57 16	453 265	23 10	390 266	4.9 2.8	2.30 [1.39, 3.80] 1.64 [0.73, 3.69]	<u>↓</u>
Paz-Ares L, et al.2018 Powles T, et al.2021B	47 83	278	3 3 9 2	4	280 342	5.1 1.58 5.2 4 13	0.97, 2.56] 2.55, 6.70]		Langer CJ, et al.2016 Liu SV, et al.2021	16 40	59 198	9 21	62 196	2.4 4.4	2.19 [0.88, 5.45] 2.11 [1.19, 3.73]	
Powles T, et al.2021C Rudin CM, et al.2020	83 30	345	9 4 3 1	0 3	302 223	5.8 2.04 3.6 2.51	1.35, 3.09] 1.27, 4.95]		Mai HQ, et al.2021 Miles D, et al.2021	40 141	146 432	31 66	143 217	4.6 6.5	1.36 [0.80, 2.34] 1.11 [0.78, 1.58]	<b>*</b>
Schmid P, et al.2020 Shitara K, et al.2020C	27	781 250	1 5 ) 1	9	389 244	6.8 1.56 3.2 2.83	1.12, 2.15] 1.34, 5.99]		Mittendorf EA, et al.2020 Monk BJ, et al.2021A	46 66	164 329	42 25	167 334	5.1 5.1	1.16 [0.71, 1.89] 3.10 [1.90, 5.06]	
Sun JM, et al.2021 Subtotal (95% CI)	29	370	) 1 1	8	370 2673	4.1 1.66 47.9 2.01	0.91, 3.05] 1.63, 2.47]	•	Moore KN, et al.2021 Paz-Ares I., et al.2018	153 47	642 278	99 32	644 280	7.3 5.1	1.72 [1.30, 2.28] 1.58 [0.97, 2.56]	_ <b>∓</b> _
Total events Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 15.49, (	618 if = 10 (P =	0.12); I <sup>2</sup> =	2£ 35%	55					Powles T, et al.2021B Powles T, et al.2021C	83 83	349 349	24 40	342 302	5.2 5.8	4 13 [2.55, 6.70] 2.04 [1.35, 3.09]	
Test for overall effect: Z = 6.61 (P < 0.0000	1)								Rudin CM, et al.2020 Schmid P. et al.2018	30 59	223 452	13 54	223 438	3.6 6.0	2.51 [1.27, 4.95] 1.07 [0.72, 1.58]	
2.1.2 PD-L1+Chemotherapy VS Chemoth Gaisky MD, et al.2020B	erapy 57	453	3 2	3	390	4.9 2.30	1.39, 3.80]		Schmid P, et al.2020 Shitara K, et al.2020C	170 27	781 250	59 10	389 244	6.8 3.2	1.56 [1.12, 2.15] 2.83 [1.34, 5.99]	
Goldman JW, et al.2021 A Jotte R, et al.2020	16 27	265 334	5 1 1 1	0	266 334	2.8 1.64 3.3 2.58	0.73, 3.69] 1.26, 5.30]	T	Sun JM,et al.2021 West H. et al.2019	29 18	370 473	18 7	370 232	4.1 2.5	1.66 [0.91, 3.05] 1.27 [0.52, 3.09]	
Liu SV, et al.2021 Miles D, et al.2021	40 141	198 432	8 2 2 6	6	196 217	4.4 2.11 6.5 1.11	1.19, 3.73] 0.78, 1.58]	+	Subtotal (95% CI) Total events	1214	6729	612	5557	92.6	1.80 [1.53, 2.13]	•
Mittendorf EA, et al.2020 Monk BJ, et al.2021A	46 66	164 325	4 4 9 2	2 5	167 334	5.1 1.16 5.1 3.10	0.71, 1.89] 1.90, 5.06]	<b>₩</b>	Heterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 40.02, Test for overall effect: Z = 6.93 (P < 0.000	df = 19 (P = 0.00 01)	03); I² = 539					
Moore KN, et al.2021 Pujade-Lauraine E, et al.2021	153 45	642 182	2 9	9 6	644 177	7.3 1.72 4.0 3.31	1.30, 2.28] 1.79, 6.11]	<del>*</del>	2.3.2 PD-1/PD-L1+Chemotherapy VS Ch	emotherapy (See	cond or Oth	ers)				
Schmid P, et al.2018 West H, et al.2019	59 18	452 473	2 5	4	438 232	6.0 1.07 2.5 1.27	0.72, 1.58] 0.52, 3.09]	- <b>T</b>	Jotte R, et al.2020 Pujade-Lauraine E, et al.2021A	27 45	334 182	11 16	334 177	3.3 4.0	2.58 [1.26, 5.30] 3.31 [1.79, 6.11]	
Subtotal (95% CI) Total events	668	392	4 37	74	3395	52.1 1.76	1.37, 2.25]	•	Subtotal (95% CI) Total events	72	516 27		511	7.4	2.98 [1.87, 4.75]	•
Heterogeneity: Tau <sup>2</sup> = 0.10; Chi <sup>2</sup> = 27.19, Test for overall effect: Z = 4.41 (P< 0.0001)	f = 10 (P =	0.002); I <sup>2</sup> =	- 63%						Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.26, d Test for overall effect: Z = 4.58 (P < 0.000	f = 1 (P = 0.61); 01)	I <sup>2</sup> = 0%					
Total (95% CI)		724	5		6068	100.0 1.87	1.59, 2.20]	•	Total (95% CI)		7245		6068	100.0	1.87 [1.59, 2.20]	•
Total events Heterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 45.16, a	1286 if = 21 (P =	0.002); I <sup>2</sup> =	- 53%	39					Total events Heterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 45.16,	1286 df = 21 (P = 0.00	02); I <sup>2</sup> = 539	639				
Test for overall effect: Z = 7.50 (P < 0.0000 Test for subgroup differences: Chi <sup>2</sup> = 0.66,	1) df = 1 (P =	0.42); I <sup>2</sup> = 0	196				0	02 0.1 1 10 100 PD-1/PD-L1+Chemotherapy Chemotherapy	Test for overall effect: Z = 7.50 (P < 0.000 Test for subgroup differences: Chi <sup>2</sup> = 3.95	01) . df = 1 (P = 0.05	5): I <sup>2</sup> = 74.75	6			0.02	0.1 1 10 50 PD-1/PD-L1+Chemotherapy Chemotherapy
											,.					
					(a)								(	b)		
PD 1/05-1	1+Chemos	herapy	Chemoth	erapy		Odds Rotio		Odds Ratio		PD.I1+Chare-P	berate: -	hare at			Odde Patio	Odde Ratie
Study or Subgroup	Events	Total 1	Events	Total V	Veight (%)	M-H. Random.	5% CI Year	M-H, Random, 95% CI	Study or Subgroup	Events	Total F	vents	Total	Weight (%)	M-H. Random. 95% CI	M-H, Random, 95% CI
Langer CJ, et al.2016 Paz-Ares L, et al.2018	16 47	59 278	9 32	62 280	2.4 5.1	2.19 [0.88, 5.4 1.58 [0.97, 2.5	5] 2016 5] 2018	<b></b>	Gadgeel S, et al.2020	82	405	23	202	5.0	1.98 [1.20, 3.25]	<u> </u>
West H, et al.2019 Jotte R, et al.2020	18 27	473 334	7	232 334	2.5	1.27 [0.52, 3.0 2.58 [1.26, 5.3	9] 2019 0] 2020	+	Langer CJ, et al.2016 Paz-Ares L, et al.2018 Subtoral (95% CI)	16 47	59 278	9 32	62 280	2.4 5.1	2.19 [0.88, 5.45] 1.58 [0.97, 2.56]	T T
Gadgeel S,et al.2020 Sabtotal (95% CI)	82	405 1549	23	202 1110	5.0 18.4	1.98 [1.20, 3.2 1.84 [1.39, 2.4	5] 2020 4]	<b>*</b>	Total events	145	/42	64	544	12.6	1.81 [1.31, 2.50]	-
Total events Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.13, df Tota for source II official 2 = 4.28 (D = 0.0001)	190 = 4 (P = 0.7	1); I <sup>2</sup> = 0%	82						Test for overall effect: Z = 3.59 (P = 0.0003	r = 2 (P = 0.74); : i)	1* = 0%					
2.2.2 PD-WDL1aChemotherapy VS Cheine	otherany (S	an							2.2.2 PD-L1+Chemotherapy VS Chemoth	erapy (NSCLC)						
Rudin CM, et al.2020 Liu SV,et al.2021	30 40	223 198	13 21	223 196	3.6 4.4	2.51 [1.27, 4.5 2.11 [1.19, 3.7	5] 2020 3] 2021		Jotte R, et al.2020 West H, et al.2019	18	473	7	232	2.5	2.58 [1.26, 5.30] 1.27 [0.52, 3.09]	
Goldman JW,et al.2021 A Subtotal (95% CI)	16	265 686	10	266 685	2.8 10.8	1.64 (0.73, 3.6 2.11 (1.44, 3.1	9] 2021A 9]	<b>•</b>	Subtotal (95% CI) Total events	45	807	18	566	5.8	1.90 [0.96, 3.79]	
Total events Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.62, df	86 = 2 (P = 0.7	44 4); I <sup>2</sup> = 0%							Heterogeneity: Tau <sup>2</sup> = 0.08; Chi <sup>2</sup> = 1.48. dt Test for overall effect: Z = 1.84 (P = 0.07)	f = 1 (P = 0.22);	I² = 32%					
Test for overall effect: Z = 3.80 (P = 0.0001)		DUD(2)							2.2.3 PD-1+Chemotherapy VS Chemother	rapy (SCLC)						
Schmid P, et al.2018 Schmid P, et al.2020	59 170	452 781	54 59	438 389	6.0 6.8	1.07 [0.72, 1.5	8] 2018 5] 2020	+	Rudin CM, et al.2020 Subtotal (95% CI)	30	223 223	13	223 223	3.6 3.6	2.51 [1.27, 4.95] 2.51 [1.27, 4.95]	-
Mittendorf EA, et al.2020 Miles D, et al.2021	46 141	164 432	42 66	167 217	5.1 6.5	1.16 [0.71, 1.8 1.11 [0.78, 1.5	9] 2020 8] 2021	+-	Total events Heterogeneity: Not applicable	30		13				
Subtotal (95% CI) Total events	416	1829	221	1211	24.5	1.24 [1.03, 1.5	1	•	Test for overall effect: Z = 2.66 (P = 0.008)							
Heterogeneity: Tau <sup>2</sup> = 0.00; Chl <sup>2</sup> = 2.89, df - Test for overall effect: Z = 2.24 (P = 0.03)	- 3 (P = 0.4	1); 12 = 0%							2.2.4 P D-L1+Chemotherapy VS Chemoth Goldman JW, et al.2021A	herapy (SCLC) 16	265	10	266	2.8	1.64 [0.73, 3.69]	<b>+</b> ••
2.2.4 PD-1/PD-L1+Chemotherapy VS Chei Gaisky MD, et al 2020B	notherapy ( 57	(UC) 453	23	390	4.9	2.30 [1.39. 3.8	0] 2020	-	Liu SV,et al.2021 Subtotal (95% CI)	40	198 463	21	196 462	4.4 7.2	2.11[1.19, 3.73] 1.94 [1.22, 3.10]	<b>*</b>
Powles T, et al.2021B Powles T, et al.2021C	83 83	349 349	24 40	342 302	5.2 5.8	4.13 [2.55, 6.7 2.04 [1.35, 3.0	0] 2021B 9] 2021C		Total events Heterogeneity: Tau <sup>2</sup> = 0.00: Chi <sup>2</sup> = 0.24. dt	56 f = 1 (P = 0.62);	I <sup>2</sup> = 0%	31				
Subtotal (95% CI) Total events	223	1151	87	1034	16.0	2.66 (1.73, 4.0	9Ĵ	•	Test for overall effect: Z = 2.79 (P = 0.005)							
Heterogeneity: Tau' = 0.09; Chi' = 5.08, dt - Test for overall effect: Z = 4.48 (P < 0.00001	- 2 (P = 0.0 )	8); 1' = 61%							2.2.5 P D-1/PD-L1+Chemotherapy VS Ch Miles D. et al.2021	emotherapy (T? 141	NBC) 432	66	217	6.5	1.11 [0.78, 1.58]	-
2.2.5 PD-1/PD-L1+Chemotherapy VS Cher Puiade-Lauraine E. et al.2021A	notherapy ( 45	Ovarian Ca 182	ancer) 16	177	4.0	3.31 [1.79. 6.1	1] 2021		Mittendorf EA, et al.2020 Schmid P. et al.2018	46 59	164 452	42 54	167 438	5.1 6.0	1.16 [0.71, 1.89] 1.07 [0.72, 1.58]	
Moore KN, et al.2021 Monk BJ, et al.2021A	153 66	642 329	99 25	644 334	7.3 5.1	1.72 [1 30, 2.2 3.10 [1.90, 5.0	8] 2021 5] 2021A	<b>*</b>	Schmid P, et al.2020 Subtotal (95% CI)	170	781 1829	59	389 1211	6.8 24.5	1.56 [1.12, 2.15] 1.24 [1.03, 1.50]	<b>▲</b>
Subtotal (95% CI) Total events	264	1153	140	1155	16.5	2.47 [1.55, 3.9	4	-	Total events Heterogeneity: Tau <sup>2</sup> = 0.00: Chi <sup>2</sup> = 2.89, dt	416 f = 3 (P = 0.41);	l² = 0%	221				
Heterogeneity: Tau' = 0.12; Chi' = 6.44, dt = Test for overall effect: Z = 3.80 (P = 0.0001)	2 (P = 0.04	l); 1° = 69%							Test for overall effect: Z = 2.24 (P = 0.03)							
2.2.6 PD-1+Chemotherapy VS Chemothera Shitara K, et al.2020C	py (Gastric 27	Cancer) 250	10	244	3.2	2.83 [1.34, 5.5	9] 2020		2.2.6 PD-1+Chemotherapy VS Chemother Powles T et al 2021B	rapy (UC) 83	349	74	347	5.2	413 [255 6 70]	
Subtotal (95% CI) Total events	27	250	10	244	3.2	2.83 [1.34, 5.9	9)	•	Povdes T, et al.2021C Subtotal (95% CI)	83	349	40	302	5.8	2.04 [1.35, 3.09]	
Heterogeneity: Not applicable Testfor overall effect: Z = 2.73 (P = 0.006)									Total events Heterogeneity: Tau <sup>2</sup> = 0.20: Chi <sup>2</sup> = 4.73. dt	166 f = 1 (P = 0.03):	I <sup>2</sup> = 79%	64				
2.2.7 PD-1+Chemotherapy VS Chemothera Colombo N et al 2021B	py (Cervic	al Cancer)	6	116	2.0	2 02 [0 72 5 6	5] 2021B		Test for overall effect: Z= 3.00 (P = 0.003)							
Sabtotal (95% CI) Total events	11	111	6	116	2.0	2.02 (0.72, 5.6	6	-	2.2.7 PD-L1+Chemotherapy VS Chemoth Gaisky MD, et al.2020B	erapy (UC) 57	453	23	390	4.9	2.30 [1.39, 3.80]	
Heterogeneity: Not applicable Testfor overall effect: Z = 1.33 (P = 0.18)									Subtotal (95% CI) Total events	57	453	23	390	4.9	2.30 [1.39, 3.80]	•
2.2.8 PD-1+Chemotherapy VS Chemothera	py (Oesopl	nageal)	10	770		1 66 (0.01. 3 6	1 2021		Heterogeneity: Not applicable Test for overall effect: Z = 3 23 (P = 0.001)							
Subtotal (95% CI) Total events	29	370	18	370	4.1	1.66 (0.91, 3.0	5) 2021	•	2.2.8 PD-1+Chemotherany VS Chemother	rapy (Oesonhoo	cal)					
Heterogeneity: Not applicable Testfor overall effect: Z = 1.64 (P = 0.10)									Sun JM, et al.2021 Subtotal (95% CI)	29	370 370	18	370 370	4.1	1.66 [0.91, 3.05] 1.66 [0.91 3.05]	-
2.2.9 PD-1+Chemotherapy VS Chemothera	py (Nasopł	aryngeal)	71	1/2	44	1 36 10 00 -	(1 2027	L	Total events Heterogeneity: Not applicable	29		18				
Subtotal (95% CI) Total events	40	146	31	143	4.6	1.36 [0.80, 2.3 1.36 [0.80, 2.3	i) 2021	•	Test for overall effect: Z = 1.64 (P = 0.10)							
Heterogeneity: Not applicable Test for overall effect: Z = 1.13 (P = 0.26)									2.2.9 PD-1+Chemotherapy VS Chemother Mai HO, et al.2021	rapy (Nasophary 40	(ngeal) 146	31	143	4.6	1.36 (0.80 2 34)	<b>↓</b>
Total (95% CI)		7245		6068	100.0	1.87 [1.59, 2.2	ŋ	•	Subtotal (95% CI) Total events	40	146	31	143	4.6	1.36 [0.80, 2.34]	+
Iotai events Heterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 45.16, dt Tactfor correll affacts 7 = 7.50 (b + 5.50)	1286 = 21 (P = 0	0.002); I <sup>2</sup> = !	639 53%				5		Heterogeneity: Not applicable Test for overall effect: Z = 1.13 (P = 0.76)			51				
Testfor subgroup differences: Chi <sup>2</sup> = 21.26,	df = 8 (P =	0.006); I <sup>z</sup> =	62.4%				0.0	D1 0.1 1 10 100 PD-1/PD-L1+Chemotherapy Chemotherapy	2.2.10 PD 1aChemotherany VS Chemoth	arany (Carrical)	Concer					
									Colombo N, et al.2021B Subtotal (95% C7)	11 11	111	6	116	2.0	2.02 [0.72, 5.65]	
									Total events	11		6	110	2.0	2.02 (0.72, 5305)	-
									Test for overall effect: Z = 1.33 (P = 0.18)							
									2.2.11 PD-1+Chemotherapy VS Chemoth- Shitara K et al 2020	erapy (Gastric C	ancer)	10	7.0.4	3.7	2 83 [1 34 5 00]	_ <b>_</b>
									Subtotal (95% CI) Total events	27	250	10	244	3.2	2.83 [1.34, 5.99]	-
									Heterogeneity: Not applicable	2/		10				
									10% for overall effect: Z = 2.73 (P = 0.006)	hamothe	mariar C.	-wr)				
									Monk BJ, et al.2021A	66	329	25	334	5.1	3.10 [1.90, 5.06]	<b>_</b>
									Pujade-Lauralne E, et al.2021 A	45	182	99 16	644	4.0	3.31 [1.79, 6.11]	
									Total events Heterocometry Tory 0.12 (bit 1.11)	264	1133	140	1155	10.5	2.47 [1.55, 3.94]	-
									Test for overall effect: Z= 3.80 (P = 0.0001)	)	0.976					
									Total (95% CI) Total events	1794	7245	630	6068	100.0	1.87 [1.59, 2.20]	•
									Heterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 45.16, o Test for overall effort: Z= 7.50 (B < 0.000)	1286 df = 21 (P = 0.00	12); I² = 53%	6.59			1	
									Test for subgroup differences: Chi <sup>2</sup> = 20.84	4, df = 11 (P = 0:	04); P = 47.	2%			0.002	PD-1/PD-L1+Chemotherapy Chemotherapy

(c)

FIGURE 3: Continued.



FIGURE 3: Forest plots of comparison in combination regimens. (a) The OR of rash for all grades checked using the random effect (RE) model in Group B (PD-1 or PD-L1 plus Chemotherapy versus Chemotherapy): subgroup analyses were carried out according to the types of immune checkpoint inhibitors (PD-1 or PD-L1). (b) The OR of rash for all grades checked using the random effect (RE) model in Group B (PD-1 or PD-L1 plus Chemotherapy versus Chemotherapy): subgroup analyses were carried out according to the treatment lines (first or second line). (c) The OR of rash for all grades checked using the random effect (RE) model in Group B (PD-1 or PD-L1 plus Chemotherapy versus Chemotherapy): subgroup analyses were carried out based on tumor type. (d) The OR of rash for all grades checked using the random effect (RE) model in Group B (PD-1 or PD-L1 plus Chemotherapy versus Chemotherapy): subgroup analyses were carried out based on tumor type and immune checkpoint type. (e) The OR of rash for all-grade checked using the random effect (RE) model in Group C (Camrelizumab plus Chemotherapy versus Chemotherapy). (f) The OR of rash for all-grade checked using the random effect (RE) model in Group D (PD-1 or PD-L1 plus Chemotherapy). (f) The OR of rash for all-grade checked using the random effect (RE) model in Group D (PD-1 or PD-L1 plus Chemotherapy). (f) The OR of rash for all-grade checked using the random effect (RE) model in Group D (PD-1 or PD-L1 plus Chemotherapy). (f) The OR of rash for all-grade checked using the random effect (RE) model in Group D (PD-1 or PD-L1 plus Chemotherapy). (f) The OR of rash for all-grade checked using the random effect (RE) model in Group D (PD-1 or PD-L1 plus Chemotherapy). (f) The OR of rash for all-grade checked using the random effect (RE) model in Group D (PD-1 or PD-L1 plus Chemotherapy). (f) The OR of rash for all-grade checked using the random effect (RE) model in Group D (PD-1 or PD-L1 plus Chemotherapy). (f) The OR of rash for all-grade checked using the random effect (RE) model in

Z=5.71, p < 0.00001; Figures 4(a)–4(d)), especially for UC (OR=5.81, 95% CI: [2.78, 12.15]; I<sup>2</sup>=71%, Z=4.68, p < 0.00001; Figure 4(d)) [71, 87, 90]. Subgroup comparison indicated that the risk of developing rash was higher in the PD-L1 subgroup and first-line subgroup (Figures 4(a)–4(d)), which no statistical subgroup difference could be found. Overall heterogeneity in high degree (I<sup>2</sup>=69%) could be found, which was mainly caused by the clinical trial CheckMate 274 (I<sup>2</sup>=0%, Figure 4(c); I<sup>2</sup>=71%, Figure 4(d)) [87]. The corresponding funnel plots are shown in S Figures 4(a)–4(d).

4 clinical trials in Group F were enrolled for the final analyses [63, 77, 80, 96]. For PD-1/PD-L1 alone, the risk of rash was significantly increased when they were given with chemotherapy (OR = 2.33, 95% CI: [1.15, 4.75];  $I^2 = 81\%$ , Z = 2.34, p = 0.02; Figures 4(e) and 4(f)). Furthermore, this trend was much more pronounced when PD-L1 was combined with chemotherapy (OR = 4.02, 95% CI: [1.70, 9.53];  $I^2 = 71\%$ , Z = 3.16, p = 0.002; Figure 4(e)) or prescribed as the second line (OR = 6.50, 95% CI: [3.07, 13.75]; Figure 4(f)). Through subgroup analysis, it could be indicated that the high degree heterogeneity might be caused by the clinical trial JAVELIN Ovarian 200 (Figures 4(e) and 4(f)) [96]. The corresponding funnel plots were constructed and are shown in S Figures 4(e) and 4(f).

3.7. The Incidence Risk of Rash for All Grades in Groups G–N. 6 clinical trials in Group G were used for the final analysis [29, 47, 76, 78, 105, 118]. In 3 clinical trials [47, 78, 118], PD-1 or PD-L1 inhibitors were given as the first-line choice, while they were used as second-line or other treatment options in the other 3 trials [29, 76, 105]. Compared with the adoption of PD-1 or PD-L1 inhibitor alone, the combination regimen (PD-1 or PD-L1 plus CTLA-4) significantly increased the risk of developing rash (OR = 2.39, 95% CI: [1.67, 3.42];  $I^2 = 54\%$ , Z = 4.79, p < 0.00001; Figures 5(a)–5(c)). Subgroup analysis suggested that the risk of rash in SCLC was higher than that in other tumor types (OR = 4.61, 95% CI: [2.70, 7.88];  $I^2 = 0\%$ , Z = 5.59, p < 0.00001; Figure 5(b)). Furthermore, the incidence risk of rash was higher when PD-1 or PD-L1 together with CTLA-4 was given as the second-line choice (OR = 4.31, 95% CI: [2.58, 7.20];  $I^2 = 0\%$ , Z = 5.59, p < 0.00001; Figure 5(c)). By comprehensively evaluating the results of various subgroup analyses (Figures 5(a)-5(c)), we inferred that the high degree of heterogeneity might be mainly caused by the clinical trial CheckMate 227 [47]. The corresponding funnel plots are shown in S Figures 5(a)-5(c).

3 clinical trials in Group H (PD-1 or PD-L1 versus CTLA-4) were selected for the final meta-analysis [34, 67, 117]. The risk of developing rash caused by PD-1 was found to be significantly lower than that of CTLA-4 only in the first-line therapy subgroup (OR = 0.51, 95% CI: [0.26, 0.99];  $I^2 = 87\%$ , Z = 1.99, p = 0.05; Figure 5(e)), whereas the overall effect was not statistically significant (OR = 0.73, 95% CI: [0.43, 1.22];  $I^2 = 86\%$ , Z = 1.20, p = 0.23; Figure 5(d)). The subgroup analysis suggested that the high heterogeneity might be mainly caused by CheckMate 238 and CheckMate 067 [67, 117]. The corresponding funnel plots are shown in S Figures 5(d) and 5(e).

For chemotherapy alone, PD-1 or PD-L1 together with CTLA-4 (Group I) [47, 94], or together with chemotherapy on this basis (Group J) [93, 95], would significantly increase the risk of developing rash (Figures 5(f) and 5(g)). However, the conclusion was still controversial due to few studies included in those analyses (Figures 5(f) and 5(g)). The corresponding funnel plots are shown in (S Figures 5(f) and 5(g)).

For sorafenib (Group K), the risk of developing rash was lower (OR = 0.60, 95% CI: [0.41, 0.89];  $I^2 = 0\%$ , Z = 2.52, p = 0.01; Figure 5(h)). When PD-1 or PD-L1 was given with CTLA-4 (Group L), the risk of developing rash was higher than that of CTLA-4 subgroup (OR = 1.43, 95% CI: [1.06, 1.93];  $I^2 = 0\%$ , Z = 2.32, p = 0.02; Figure 5(i)). When PD-1 was compared with chemotherapy (Group M), no statistical significant result was found (OR = 0.87, 95% CI: [0.25, 2.98];  $I^2 = 78\%$ , Z = 0.23, p = 0.82; Figure 5(j)). The corresponding funnel plots are shown in S Figures 5(k)–5(m).

In 5 of the 6 clinical trials of renal cell carcinoma, the control group was sunitinib [51, 55, 56, 89, 91]. In these 5 clinical trials, we found that PD-1 or PD-L1 increased the incidence risk of rash regardless of which antitumor drug was used in combination [51, 55, 56, 89, 91]. However, the



(e)

(f)

FIGURE 4: Forest plots of different comparison groups. (a) The OR of rash for all grades checked using the random effect (RE) model in Group E (PD-1 or PD-L1 versus Placebo): subgroup analyses were carried out according to the types of immune checkpoint inhibitors (PD-1 or PD-L1). (b) The OR of rash for all grades checked using the random effect (RE) model in Group E (PD-1 or PD-L1 versus Placebo): subgroup analyses were carried out according to the treatment lines (first or second line). (c) The OR of rash for all grades checked using the random effect (RE) model in Group E (PD-1 or PD-L1 versus Placebo): subgroup analyses were carried out based on tumor type. (d) The OR of rash for all grades checked using the random effect (RE) model in Group F (PD-1 or PD-L1 versus Placebo): subgroup analyses were carried out based on tumor type and I2 value. (e) The OR of rash for all grades checked using the random effect (RE) model in Group F (PD-1 or PD-L1) plus Chemotherapy VS PD-1 or PD-L1): subgroup analyses were carried out according to the types of immune checkpoint inhibitors (PD-1 or PD-L1). (f) The OR of rash for all grades checked using the random effect (RE) model in Group F (PD-1 or PD-L1). (f) The OR of rash for all grades checked using the random effect (RE) model in Group F (PD-1 or PD-L1). (f) The OR of rash for all grades checked using the random effect (RE) model in Group F (PD-1 or PD-L1). (f) The OR of rash for all grades checked using the random effect (RE) model in Group F (PD-1 or PD-L1). (f) The OR of rash for all grades checked using the random effect (RE) model in Group F (PD-1 or PD-L1).



(a)

98 3.8 279 19.1 56 3.8 433 26.6

(c)

0.73 (0.43, 1.22

(i)

1.62 | 1.93 | 2.59 |

43 391 25.6 81 313 27.4 22 345 20.4 1049 73.4

 313
 102
 311
 26.0

 452
 136
 453
 26.2

 765
 764
 52.2

277 40 256 24.0 278 40 256 23.8 555 512 47.8

1276 100.

81 61

> 48 44

Search of Subgroup	1.10.111.0	10144	1.10.10.0	10.75 200	maight ( )	() M1-11. Residential. 2070 4		M-11, Paintoni, 5570 Gi
5.3.1 PD-1+CTLA-4 VS PD-I (SO	LC)							
Antonia SJ, et al.2016	4	54	2	98	3.8	3.84 [0.68, 21.69]	2016	
Owonikoko TK, et al.2021A	65	278	17	279	19.1	4.70 [(2.68, 8.26]	2021A	
Subtotal (95% CI)		332		377	22.9	4.61 [2.70, 7.88]		•
Total events	69		19					
Heterogeneity: Tau2 = 0.00; Chi2	= 0.05, df =	1 (P = 0.	83); I <sup>2</sup> = 0%					
Test for overall effect: Z = 5.59 (P	< 0.00001)							
5.3.2 PD-1+CTLA4 VS PD-1 (Me	elanoma)							
Larkin Let al 2015A	126	313	81	313	27.4	1 93 [1 37 2 71]	2015A	+
Zimmer L et al 2020A	4	55	2	56	3.8	2 12 [0 37 12 06]	2020	
Subtotal (95% CI)		368		369	31.2	1.94 [1.39, 2.70]		•
Total events	130		83					1.
Heterogeneity: Tau2 = 0.00: Chi2	= 0.01. df =	1 (P = 0.	92); I <sup>2</sup> = 0%					
Test for overall effect: Z = 3.89 (P	< 0.0001)							
5.3.3 PD-1+CTLA-4 VS PD-1 (N	SCLC)							
Hellmann, MD, et al.2018A	96	576	43	391	25.6	1.62 [1.10, 2.38]	2018	
Subtotal (95% CI)		576		391	25.6	1.62 [1.10, 2.38]		•
Total events	96		43					
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.45 (P	= 0.01							
5.3.4 PD-L1+CTLA-4 VS PD-L1	(UC)							
Powles T, et al.2020A	51	340	22	345	20.4	2.59 [1.53, 4.38]	2020	
Subtotal (95% CI)		340		345	20.4	2.59 [1.53, 4.38]		•
Total events	51		22					
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.56 (P	= 0.0004)							
Total (95% CI)		1616		1487	100.0	2 39 [1 67 3 42]		•
Total events	346		167					
Heterogeneity: Tau2 = 0.09: Chi2	= 10.79, df -	- 5 (P = 0	0.06); I <sup>2</sup> = 5	4%			_	
Test for overall effect: Z = 4.79 (P	< 0.00001)						0.01	0.1 1 10 100
Test for subgroup differences: Ch	i <sup>2</sup> = 10.70, d	lf = 3 (P	- 0.01); I <sup>2</sup> -	72.0%				PD-1/PD-L1 CTLA-4 PD-1/PD-L1
p 4			//-					

(b)

Study or Subgroup	PD-1/PD- Events	L1 Total	CTLA-4 Events	Total	Weight (%)	Odds Ratio M-H. Random. 959	6 CI	Odds M-H, Randi	tatio m, 95% CI	
7.1.1 PD-1 VS CTLA-4 (Melan	toma)									
Ascierto PA, et al.2020	61	452	136	453	26.2	0.36 [0.26, 0.51]		-		
Larkin J, et al.2015B	81	313	102	311	26.0	0.72 [0.51, 1.01]		+		
Schachter J, et al.2017B	44	278	40	256	23.8	1.02 [0.64, 1.62]		-	-	
Schachter J, et al.2017C	48	277	40	256	24.0	1.13 [0.72, 1.79]	i	-	÷	
Subtotal (95% CI)		1320		1276	100.0	0.73 [0.43, 1.22]		+		
Total events	234		318							
Heterogeneity: Tau <sup>2</sup> = 0.24; Ch	ni² = 20.86,	if = 3 (F	= 0.0001)	I <sup>2</sup> = 86	%					
Test for overall effect: Z = 1.20	(P = 0.23)									
Total (95% CI)		1320		1276	100.0	0.73 [0.43, 1.22]		-		
Total events	234		318							
Heterogeneity: Tau <sup>2</sup> = 0.24; Ch	ni² = 20.86,	if = 3 (F	= 0.0001)	I <sup>2</sup> = 86	%		1			
Test for overall effect: Z = 1.20	(P = 0.23)						0.005	0.1 1	10	200
Test for subgroup differences:	Not applica	ole						PD-1/PD-1	1 CTLA-4	

(d)

	PD-1/PD-L1+CT	LA-4	Chemot	therapy		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight (%)	M-H. Random. 95% C	I Year	M-H, Rand	om, 95% CI	
8.1.1 PD-1+CTLA-4 VS C	hemotherapy (NS	CLC)								
Hellmann MD, et al.2019/	98	576	30	570	67.3	3.69 [2.41, 5.66]	2019A			
Subtotal (95% CI)		576		570	67.3	3.69 [2.41, 5.66]			•	
Total events	98		30							
Heterogeneity: Not applica	ible									
Test for overall effect: Z =	5.99 (P < 0.00001)									
8.1.2 PD-1+CTLA-4 VS C	hemotherapy (Me	sothelio	rna)							
Baas P, et al. 2021	43	300	15	284	32.7	3.00 [1.63, 5.53]	2021			
Subtotal (95% CI)		300		284	32.7	3.00 [1.63, 5.53]			-	
Total events	43		15							
Heterogeneity: Not applica	ible									
Test for overall effect: Z =	3.52 (P = 0.0004)									
Total (95% CI)		876		854	100.0	3.45 [2.43, 4.90]			+	
Total events	141		45							
Heterogeneity: Tau2 = 0.00	: Chi <sup>2</sup> = 0.30. df =	-1 (P= 0	.59); J <sup>2</sup> = (	3%				-		
Test for overall effect: Z = (	5.93 (P < 0.00001)						0.05	0.2	1 5	20
Test for subgroup different	ces: Chi² = 0.30, d	f = 1 (P -	= 0.59); I <sup>2</sup>	= 0%			PD-1	/PD-L1 CTLA	-4 Chemotherap	у

(j)

(e)	(1)
PD-1/PD-L1+ CTLA-4+Chemo Chemotherapy Odds Ratio Odds Ratio	PD-1/PD-11+8evacizumab Sorafenib Odds Ratio Study or Subgroup Events Total Events Total Weight (%) M-H. Random. 95% CI Year 2
hug or Shapeyon         Borner         Total         Weight (%)         M.H. Random, 19% CI           J. 12. Nonlaunds - Minimum Channellergery         Description         Description         Description           J. 12. Nonlaunds - Minimum Channellergery         Description         Description         Description           Jointa of Minimum Channellergery         Description         Description         Description         Description           Joint of Minimum Channellergery         Description         Description         Description         Description           Joint or Minimum Channellergery         Description         Description         Description         Description         Description           Joint or Minimum Channellergery         Description         Description         Description         Description         Description           Joint or Minimum Channellergery         Description	9.1.1 Accolumnab Hencimumb VS confemb Fran Ki, et al. 2010 4 229 27 156 55.6 0.06 [0.01, 113] 2020 Total events C1 4 229 27 156 55.6 0.06 [0.01, 123] Total events C2 4 229 27 156 55.6 0.06 [0.01, 123] Heterogenerity Not applicable Total for oreall effect Z - 14.10 (= 0.13) 9.1.2 Smithmab Accountable VS confemb
badman (V) e zl 20210 % 56 66 10 266 64.3 4.01 [154, 2.3] 20210 deal (75%, 2.3) 56 10 266 64.3 4.01 [154, 2.3] 20210 deal (75%, 2.3) 56 10 266 64.3 4.01 [154, 4.2] deal (75%, 4.2) 56 10 26 10	Ren Z, et al. 2021         26         380         23         185         44.4         0.52 [0.29, 0.39]         2021           Subdeal (95% CI)         380         185         44.4         0.52 [0.29, 0.33]         1021           Total events         26         23         185         44.4         0.52 [0.29, 0.33]           Text for overall effect Z = 219 (P = 0.03)         100         100         100         100
sial (984C) sial	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$
(g)	(h)
PD-1+CTLA-4 CTLA-4 Odds Ratio Odds Ratio Study or Subgroup Events Total Events Total Weight (%) M-H. Random, 95% CI Year M-H, Random, 95% CI	(methotrexate, docetaxel, PD-1 or cetuximab) Odds Ratio
Larkin J, et al. 2015C 126 313 102 311 84.0 1.38 [1.00, 1.92] 2015C Hold FS, et al. 2016 40 94 14 46 16.0 1.69 [0.80, 3.58] 2016	Study or Subgroup         Events         Total         Weight (%)         M.H. Random, 95% (2)         Year         M           Ferris RL, et al. 2016         18         236         5         111         44.5         1.7.7 (06.3, 4.84)         2016           Cohen EEW, et al. 2019         19         246         34         234         55.5         0.49 (0.27, 0.89)         2019
Statel (958 CJ)         467         357         100.0         1.43 [1.06, 1.93]           Statel (958 CJ)         166         116           Heterogrenoly: Tair = 0.00; Cli = 0.34, d = (1 p = 0.32); U = 0%         0.1         1         1         10         100	$ \begin{array}{c} \mbox{Total} (95\% (C)) & 462 & 345 & 100.0 & 0.87 & [0.25, 2.98] \\ \mbox{Total} = (cont) & 37 & 39 & 100.0 & 0.87 & [0.25, 2.98] \\ \mbox{Hetrogeneity: } \mbox{Total} = 0.83 & (Ch^2 = 4.47, d = 1 & (P = 0.03); l^2 = 78\% & 0.01 & 0.1 \\ \mbox{Total} = 0.63 & (Ch^2 = 0.42) & (P = 0.23) & (P = 1.02) \\ \mbox{Total} = 0.63 & (Ch^2 = 0.42) & (P = 0.02) & (P = 1.02) \\ \mbox{Total} = 0.63 & (Ch^2 = 0.42) & (P = 0.02) & (P = 0.02) \\ \mbox{Total} = 0.63 & (Ch^2 = 0.42) & (P = 0.02) & (P = 0.02) \\ \mbox{Total} = 0.63 & (Ch^2 = 0.02) & (Ch^2 = 0.02) & (P = 0.02) \\ \mbox{Total} = 0.63 & (Ch^2 = 0.02) & (P = 0.02) & (P = 0.02) \\ \mbox{Total} = 0.63 & (Ch^2 = 0.02) & (P = 0.02) & (P = 0.02) & (P = 0.02) \\ \mbox{Total} = 0.63 & (Ch^2 = 0.02) & (P = 0.02) & (P$

FIGURE 5: Forest plots of comparison groups (Groups G-M). (a) The OR of rash for all grades checked using the random effect (RE) model in Group G (PD-1 or PD-L1 plus CTLA-4 versus PD-1 or PD-L1): subgroup analyses were carried out according to the types of immune checkpoint inhibitors (PD-1 or PD-L1). (b) The OR of rash for all grades checked using the random effect (RE) model in Group G (PD-1 or PD-L1 plus CTLA-4 versus PD-1 or PD-L1): subgroup analyses were carried out based on tumor type. (c) The OR of rash for all grades checked using the random effect (RE) model in Group G (PD-1 or PD-L1 plus CTLA-4 versus PD-1 or PD-L1): subgroup analyses were carried out according to the treatment lines (first or second line). (d) The OR of rash for all grades checked using the random effect (RE) model in Group H (PD-1 or PD-L1 versus CTLA-4). (e) The odds ratio of rash for all grades calculated by the random effect (RE) model in Group H (PD-1 or PD-L1 versus CTLA-4). (e) The odds ratio of rash for all grades calculated by the random effect (RE) model in Group H (PD-1 or PD-L1 versus CTLA-4). (e) The odds ratio of rash for all grades calculated by the random effect (RE) model in Group H (PD-1 or PD-L1 versus CTLA-4). (e) The odds ratio of PD-L1 plus CTLA-4 versus Chemotherapy): subgroup analyses were carried out based on tumor type. (g) The OR of rash for all grades checked using the random effect (RE) model in Group J (PD-1 or PD-L1 plus CTLA-4 versus Chemotherapy): subgroup analyses were carried out based on treatment regimens. (h) The OR of rash for all grades checked using the random effect (RE) model in Group K (PD-1 or PD-L1). (i) The odds ratio of rash for all-grade checked using the random effect (RE) model in Group J (PD-1 or PD-L1). (i) The odds ratio of rash for all-grade checked using the random effect (RE) model in Group J (PD-1 or PD-L1) plus CTLA-4 versus CTLA-4). (j) The odds ratio of rash for all grades checked using the random effect (RE) model in Group J (PD-1 or PD-L1). (i) The odds ratio of rash for

meta-analysis could not be performed due to the lack of consistency in the experimental groups in these 5 clinical trials [51, 55, 56, 89, 91]. The types of combination therapy regimens involving PD-1 or PD-L1 have been increasingly used in different tumors [26, 34, 57, 63, 65, 69, 72, 81, 83, 88, 95, 101, 104, 105, 109, 110]. In those combined treatment regimens, rash has been reported, which further verified the correlation between PD-1 or PD-L1 and the incidence of rash [26, 34, 57, 63, 65, 69, 72, 81, 83, 88, 95, 101, 104, 105, 109, 110].

3.8. Risk Assessments of Rash for Grades 3–5. The risk of developing rash for grades 3–5 was reported in 18 clinical trials (Group A) [22–24, 26, 32, 47, 54, 59, 61, 68, 70, 72, 77, 78, 82, 86, 92, 96]. Through analyses, statistically significant result was found only in NSCLC (OR = 2.51, 95% CI: [1.03, 6.11]; I<sup>2</sup> = 0%, Z = 2.02, p = 0.04; Figure 6(a)) [22, 24, 47, 59, 61, 64, 68, 92], while the overall effect across all tumor types was not statistically different (OR = 1.73, 95% CI: [0.91, 3.31]; I<sup>2</sup> = 0%, Z = 1.66, p = 0.10; Figure 6(a)).

Similar to the risk of rash for all grades in Group B, the risk of developing rash was significantly higher than that of the control chemotherapy group [27, 36, 38, 41, 45, 53, 66, 73-75, 79, 80, 84, 86, 96, 101, 103, 107, 111, 112], when PD-1 or PD-L1 was given together with chemotherapy (OR = 2.61, 95% CI: [1.67, 4.08]; I<sup>2</sup> = 0%, Z = 4.20, p < 0.0001; Figure 6(b)), especially for ovarian cancer (OR = 4.34, 95%) CI: [1.89, 9.96];  $I^2 = 0\%$ , Z = 3.46, p = 0.0005; Figure 6(b)) [96, 101, 103]. The positive result could also be found in Group C (OR = 3.42, 95% CI: [1.49, 7.85];  $I^2 = 0\%$ , Z = 2.89, p = 0.004; Figure 6(c)), Group G (OR = 3.39, 95% CI: [1.54, [7.49];  $I^2 = 0\%$ , Z = 3.02, p = 0.002; Figure 6(d)), and Group J  $(OR = 9.64, 95\% CI: [1.22, 76.16]; I^2 = 0\%, Z = 2.15, p = 0.03;$ Figure 6(i) [39, 44, 47, 77, 78, 81, 90, 91, 93, 95, 98, 105, 117]. However, when PD-1 or PD-L1 plus bevacizumab were compared with sorafenib, the risk of developing rash was lower than that of the control group (OR = 0.13, 95% CI: [0.02, 0.83];  $I^2 = 0\%$ , Z = 2.16, p = 0.03; Figure 6(h)). In the other groups, no statistical significant results could be found (Figures 6(e)-6(g)). All the corresponding funnel plots were constructed and are shown in S Figures 6(a)-6(i).

#### 4. Discussion

Among several therapeutic options available, cancer immunotherapy is extremely successful in increasing tumor patients' survival rates, particularly with PD-1/PD-L1 inhibitors [2]. Currently, PD-1 or PD-L1 inhibitors are extensively employed in the treatment of many types of malignancies, and the combination regimens using PD-1 or PD-L1 inhibitors are diversified [22–25], [26–30], [31–35], [36–40], [41–45], [46–50], [51–55], [56–60], [61–65], [66–70], [71–75], [76–80], [81–85], [86–90], [91–95], [96–110], [111–115], [116, 117], [118]. As with cetuximab [119, 120], rash associated with therapeutic benefit was one of the most frequently reported skin toxicities associated with PD-1 or PD-L1 inhibitors [13–15]. The correlation between rash and PD-1 or PD-L1 inhibitors, on the other hand, has to be further clarified in detail, particularly in diverse combination treatment regimens. Therefore, a systematic review and meta-analysis were conducted with the guidelines of the PRISMA criteria (Figure 1) [16].

After quality screening (S Figure 1), 86 clinical trials with complete data were adopted for the final comprehensive analyses [22–25], [26–30], [31–35], [36–40], [41–45], [46-50], [51-55], [56-60], [61-65], [66-70], [71-75], [76-80], [81-85], [86-90], [91-95], [96-110], [111-115], [116, 117], which avoided the high risk of attrition bias. With the development of clinical research, PD-1 or PD-L1 inhibitors have been increasingly prescribed as the first-line antitumor options (*n* = 51) [23, 27, 28], [31, 36–38], [40–42], [44-48], [50, 53], [55-58], [61-68], [72, 73], [75, 77-80], [83-86], [88-95], [98-104], [106, 107, 109], [111, 112], [114-117], especially for PD-1 or PD-L1 combined regimens [27, 36, 38, 41, 45, 53, 66, 73, 75, 79, 80, 84, 86, 99, 101, 103, 107, 111, 112], which also increase the difficulty of elucidating the relationship between PD-1 or PD-L1 and the risk of rash. Therefore, it is necessary for us to conduct this meta-analysis.

According to the compositions of all the control groups, all the enrolled clinical trials were firstly classified into different groups (Groups A-N), and then, analyses were carried out for each group (Figures 2–6 and S Figures 2–6). Through the analyses, it was found that PD-1 or PD-L1 inhibitors raised the risk of developing rash (Figure 2, Figures 4(a)-4(d), and Figure 6(a)), whether compared with chemotherapy or placebo alone (Group A and Group E) [22-24, 26, 32, 33, 39, 43, 44, 47, 49, 54, 59, 61, 68, 71, 77, 78, 80, 82, 86, 87, 90-92, 96-98, 105, 108]. However, this effect was weaker than CTLA-4 with no statistical significance (Group H) (Figures 5(d)–5(e) and 6(f)) [34, 67, 117]. In the combined antitumor treatment regimens containing PD-1 or PD-L1 inhibitors (Group B, Group C, Group D, and Group L) [27, 31, 36, 37, 41, 45, 53, 66, 73-75, 77, 79, 80, 84, 86, 95, 96, 99–101, 103, 106, 107, 111, 112, 117], it was also found that the risk of rash was increased due to the involvement of PD-1 or PD-L1 inhibitors (Figure 3, Figures 5(a)-5(c), Figure 6(b), S Figure 3, S Figure 5(a)-5(c), and S Figure 6(b)). Similar trend was also found in other PD-1 or PD-L1 inhibitor-based combination regimens (Group F, Group G, Group I, and Group G) (Figures 4(e) and 4(f); Figures 5(a)-5(c), 5(f), 5(g), 6(d), 6(e), and 6(i); S Figures 4(e)-4(f); S Figures 5(a)-5(c), 5(f), 5(g), 6(d), 6(e), and 6(i)) [29, 47, 63, 76–78, 80, 93–96, 105, 117]. In the other clinical trials for which meta-analysis could not be performed, the experimental group of PD-1 or PD-L1 inhibitors involved also indicated an increased risk of rash [25, 26, 34, 51, 55-57, 63, 65, 69, 72, 81, 83, 88, 89, 91, 95, 101, 104, 105, 109, 110]. From the above, it could be concluded that the risk of rash would be increased when PD-1 or PD-L-1 inhibitors were given alone or together with other antitumor regimens.

For the lack of head-to-head contrast between PD-1 and PD-L1 [22–25], [26–30], [31–35], [36–40], [41–45], [46–50], [51–55], [56–60], [61–65], [66–70], [71–75], [76–80], [81–85], [86–90], [91–95], [96–110], [111–115], [116, 117], we tried to investigate the differences between PD-1 and PD-

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	PD-1/PD	)-L1	Chemot	herapy		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight (%	) M-H. Random. 95% C	I Year	M-H, Random, 95% CI
1.6.1 PD 1/PD L1 VS Chamotha	rong (NSC)	LC)						
Brahmer L et al 2015	napy (1450)	121	2	179	4.5	0.19 [0.01 4.09]	2015	
Branner J, et al. 2015		151	2	129	4.5	0.19 [0.01, 4.08]	2015	
Hordent Df. et al 2016 D	-	20/	0	208	4.1	2.81 [0.11, 69.31]	2015	
Herost R5, et al.2016B	1	339	0	309	4.1	2./4 [0.11, 6/.38]	2016	
Herbst RS, et al.2016C	1	343	0	309	4.1	2.71 [0.11, 66.79]	2016	
Hellmann, MD,et al.2018C	3	391	0	570	4.8	10.28 [0.53, 199.56]	2018	
Mok TSK, et al.2019	3	636	0	615	4.8	6.80 [0.35, 131.94]	2019	
Wu YL, et al.2019	3	337	0	156	4.7	3.28 [0.17, 63.79]	2019	
Herbst RS, et al.2020	3	286	2	263	13.0	1.38 [0.23, 8.34]	2020	
Sezer A. et al.2021	3	355	0	342	4.8	6.80 [0.35, 132,16]	2021	
Wu YL et al 2021	1	128	0	125	4.1	2 95 [0 12 73 18]	2021	
Colored (and CD)		1111	-	1000	C3.6	351 (103 6 11)		-
Subibilit (95% CI)	10	3233		3080	32.8	2.51 [1.05, 0.11]		-
iour evenis	19							
Heterogeneity: Tau* = 0.00; C.m*	= 4.93, dI -	-9(P-	0.84); 1-	- 0%				
Test for overall effect: Z = 2.02 (F	= 0.04)							
1.6.2 PD-1/PD-L1 VS Chemothe	rapy (UC)							
Bellmunt J, et al.2017	1	266	0	255	4.1	2.89 [0.12, 71.20]	2017	
oalsky MD, et al.2020C	2	354	0	390	4.5	5.54 [0.27, 115,77]	2020	
Pondes Tet al 2020B	2	345	0	313	4.5	4 56 [0 22 95 42]	2020	
Pondes Tet al 2021 A	0	302	2	347	4.5	0.23 [0.01 4.71]	2021A	
Colored (and CD)	-	13/7	-	1100	17.7	1 00 (0 41 0 10)		-
Subibilit (95% CI)		1207		1300	17.7	1.59 [0.43, 5.30]		
lotal events								
Heterogeneity: Tau <sup>2</sup> = 0.00; C.m <sup>2</sup>	= 2.76, dI -	- 3 (P -	0.43); 1*	- 0%				
Test for overall effect: Z = 0.88 (F	= 0.38)							
1.6.3 PD-1 VS Chemotherapy (or	esophageal	)						
Kato K, et al.2019	1	209	2	208	7.2	0.50 [0.04, 5.50]	2019	
Huang L et al.2020	1	228	0	220	4.1	2.91 [0.12, 71,76]	2020	
Subtatal (95% CI)		437		478	113	0.94 [0.14.6.43]		-
Total exents	2		2					
Heterogeneity: Toul - 0.00; Chil	- 0.75 df -	- 1 (P -	0 10) 11	- 0%				
Preterogeneity: Tau- = 0.00; Cili-	= 0.75, di =		0.39); 1-	= 0%				
lest for overall effect: Z = 0.07 (F	= 0.95)							
1.6.4 PD-L1 VS Chetnotherapy (	Ovarian Ca	incer)						
Pujade-Lauralne E, et al.2021C	0	187	3	177	4.7	0.13 [0.01, 2.59]	2021	
Subtotal (95% CI)		187		177	4.7	0.13 [0.01, 2.59]		
Total events	0		3					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.33 (F	= 0.18							
	,							
1.6.5 PD 1 VS Chainotherony (C	olometal C	ancer)						
A she T at al 2020	otorectar C	ancer)		1.47		0.03 [0.07, 17,08]	2020	
Andro 1, et al.2020	1	155		145	3.4	0.93 [0.06, 13.08]	2020	
Subtotal (95% CI)		153		143	5.4	0.93 [0.06, 15.08]		
Total events	1		1					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.05 (F	= 0.96)							
1.6.6 PD-1 VS Chemotherapy (T	NBC)							
Winer FP et al 2021	1	309	0	292	4.1	2 84 [0 12 70 10]	2021	
Colored (and CD)		300	-	202		3 54 (0 13 70 10)		
Subibilit (95% CI)		309		292	4.1	2.84 [0.12, 70.10]		
lotal events	1		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.64 (F	= 0.52)							
1.6.7 PD-1 VS Chemotherapy (N	(elanoma)							1
Weber JS, et al.2015	1	268	0	102	4.1	1.15 [0.05, 28.45]	2015	
Subtotal (95% CI)		268		102	41	1 15 10 05 28 451		
Total events	1	2.00	0	- 04	*			1
Haterogenaity: Not applicable								1
meaning way, Not applicable								
test for overall effect: Z = 0.09 (F	= u.93)							1
								la .
Total (95% CI)		5854		5528	100.0	1.73 [0.91, 3.31]		-
Total events	29		12					
Heterogeneity: Tau2 = 0.00; Chi2	= 12.72, df	= 19 (	P = 0.85);	$I^{2} = 0\%$	5		-	— <del>————</del>
Test for overall effect: Z = 1.66 (F	= 0.10						0.001	0.1 1 10 1000
Test for subgroup differences: Ch	i <sup>2</sup> = 4.30, d	lf = 6 (l	P = 0.64;	$I^{2} = 0\%$				PD-1/PD-L1 Chemotherapy
				_				

(a)

	PD-1/PD-L1		Placebo			Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight (?	6) M-H. Random. 95% C	. N	d-H, Random, 95% CI
4.4.1 PD-1/PD-L1 VS Placebo (NS	CLC)							
Antonia SJ, et al.2018	1	475	0	234	6.7	1.48 [0.06,36.53]	-	
Sugawara S, et al.2021	13	273	1	275	16.6	13.70 [1.78,105.47]		
Subtotal (95% CI)		748		509	23.4	6.37 [0.78,52.25]		
Total events	14		1					
Heterogeneity: Tau2 = 0.67; Chi2 =	1.36. df = 1 (P	= 0.24	l); I <sup>z</sup> = 265	6				
Test for overall effect: Z = 1.72 (P =	0.08)							
4.4.2 PD-1 VS Placebo (SCLC)								
Owonikoko TK, et al.2021 A	1	278	1	279	9.0	1.00 [0.06. 16.13]	-	
Subtotal (95% CI)		278		279	9.0	1.00 [0.06, 16.13]	-	
Total events	1		1					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P =	1.00)							
4.4.3 PD-1/PD-L1 VS Placebo (UC	5							
Bajorin DF, et al.2021	2	351	0	348	7.5	4.99 [0.24, 104.23]		
Bellmunt J, et al.2021	7	390	0	397	8.4	15.55 [0.88, 273.16]		
Powles, et al.2020	1	344	0	345	6.7	3.02 [0.12, 74.33]		<u> </u>
Subtotal (95% CI)		1085		1090	22.7	6.55 [1.14, 37.63]		-
Total events	10		0					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> =	0.64, df = 2 (P	= 0.73	3); I <sup>2</sup> = 0%					
Test for overall effect: Z = 2.11 (P =	0.04)							
4.4.4 MPA 1 MC Blanch - (Parashanna)			1 how estimate	C				
4.4.4 PD-1 VS Placebb (Esophigea	or Gastroesop	nuge.	i junction	200	·	1.00 (0.33, 17.04)		
Keny KJ, et al. 2021		532	1	260	14.4	1.96 [0.22, 17.64]		
Total mante	4	332	1	200	24.4	1.90 [0.22, 17.04]		
Haterogeneity: Not applicable								
Text for overall effect: 7 = 0.60 (P =	0.55)							
104 101 OTTAIL CIRCL. 2 0.00 (1 -	0.00)							
4.4.5 PD-1 VS Placebo (Melanoma	)							
Eggermont AMM, et al.2018		509	0	502	6.7	2.96 [0.12, 72,95]		
Subtotal (95% CI)		509		502	6.7	2.96 [0.12, 72,95]		
Total events	1		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.66 (P =	0.51)							
4.4.6 PD-1 VS Placebo(RCC)								
Choueirl TK, et al.2021	4	488	2	496	23.9	2.04 [0.37, 11.20]		
Subtotal (95% CI)		488		496	23.9	2.04 [0.37, 11.20]		
Total events	4		2					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.82 (P =	0.41)							
Total (95% CI)	3	1640		3136	100.0	3.42 [1.49, 7.85]		
Total events	34		5					-
Heterogeneity: Tau2 = 0.00; Chi2 =	4.88, df = 8 (P	= 0.75	7); I <sup>z</sup> = 0%					1
Test for overall effect: Z = 2.89 (P =	0.004)						0.002 0	1 10 500
Test for subgroup differences: Chi2	= 2.19, df = 5 (	(P = 0)	.82); I <sup>2</sup> = 0	196			0.002 0	PD-1/PD-L1 Placebo

(c)

Study or Subgroup	PD-1/PI Chemot Events	D-L1+ herapy Total	PD-1/I Events	PD-L1 Total	Weight (%)	Odds Ratio M-H. Random. 95% C	I Year	Odds M-H, Rand	Ratio om, 95% CI	
631 PD L1+Chemotherany VS	D I I									
Gaisky MD et al 2020A		453	2	354	23.8	0.16[0.01.3.25]	2020		_	
Puiade, Lauralne E. et al 2021B	Ű.	182	0	187	25.2	25 15 [1 47 429 95]	2021		-	
Subtatal (95% CI)		635		541	48.9	2 04 0 01 321 551				
Total events	11		2							
Heterogeneity: Tau <sup>2</sup> = 11.09; Chi <sup>2</sup> Test for overall effect: Z = 0.28 (P	= 5.93, df = = 0.78)	- 1 (P = )	0.01); I <sup>2</sup>	- 83%						
6 3 2 PD-1+Chemotherany VS PI	2.1									
Burtness B et al 2019A		276	2	300	78.4	0.54 [0.05.6.01]	2019A			
Shitara K et al 2020A	- i	250	0	254	22.6	3.06 [0.12, 75,48]	2020	-+		
Subtotal (95% CI)		526		554	51.1	1.01 (0.15, 6.93)				
Total events	2		2							
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> - Tect for coverall effect: Z = 0.01 (P	= 0.72, df =	1 (P = 0.	40); I <sup>2</sup> =	0%						
ich ist oreran encer. z. = 0.01 (i	- 0.77)									
Total (95% CI)		1161		1095	100.0	1.57 [0.17, 14.67]				
Total events	13		4							
Heterogeneity: Tau2 = 3.08; Chi2 -	- 7.38, df =	3 (P = 0.	06); I <sup>2</sup> =	59%						
Test for overall effect: Z = 0.39 (P	= 0.69)						0.001	0.1 1	10	100
Test for subgroup differences: Chi	2 = 0.06. df	= 1 (P =	0.80); I <sup>2</sup>	- 0%			PD-1	/PD-L1+Chemothe	rapy Chemoth	herapy

(e)

	PD-1/PI	D-L1	Placebo			Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight (%)	M-H. Random. 95% CI	Year	M-H, Random, 95% CI	
Fenis RL, et al.2016	0	236	1	111	42.8	0.16 [0.01, 3.85]	2016		
Cohen EEW, et al.2019	1	246	1	234 5	7.2	0.95 (0.06, 15.29)	2019	Т	
Total (95% CI)		482		345	100.0	0.44 (0.05, 3.58)		-	
Total events	1		2						
Heterogeneity: Tau2 = 6	0.00; Chi²	= 0.70,	if = 1 (P =		0.001	0.1 1 10 1000			
Test for overall effect: 2	$^{2} = 0.44$					PD-1 (methotrexate, decetaxel, or cet)			

(g)

Study or Subgroup Events	110016110016	fotal Events	Total	7 Weight (%	) M-H. Random. 95% C	I Year	M-H, Random, 95% CI
2.5.1 PD-1/PD-L1+Chemotherapy	VS Chemothe	rapy (NSCL	C)				
Langer CJ, et al.2016	1	59 0	62	1.9	3.21 (0.13, 80.25)	2016	
Socins MMA, et al.2018	5 3	393 0	394	2.4	1 1.17 [0.62, 202.69]	2018	
West H, et al.2019	1 .	473 0	232	19	1.48 [0.06, 36.38]	2019	
Zhou C, et al.2020	3	205 0	207	2.3	7.17 [0.37, 139.74]	2020	
Jotte R, et al.2020		334 1	3.54	3.5	2.01 [0.18, 22.23]	2020	
Subtoted (05% CT)		403 3	1421	22.7	2.14 (0.84, 5.46)	2020	-
Total events	19	4	1431	22.7	2.14 (0.84, 3.40)		-
Heterogeneity: Tau2 = 0.00: Chi2 = 2	2.91. df = 5 (P	= 0.71); I <sup>2</sup> =	0%				
Test tor overall effect: Z = 1.59 (P =	0.11)						
		10.01.0					
2.5.2 PD-1/PD-L1+Cnemotherapy	vs Chemothe	rapy (SCLC,	100		0.00 [0.40, 170,07]	2016	
Pudin CM at al 2020	- 1	222 0	221	2.3	7 10 0 36 139 16	2018	
Subtotal (95% CI)		421	419	4.6	8 05 [1 00 64 72]	1010	
Total events	7	0					-
Heterogeneity: Tau2 = 0.00; Chi2 = 0	0.01, df = 1 (P	= 0.91); I <sup>z</sup> =	0%				
Test for overall effect: Z = 1.96 (P =	0.05)						
2.5.3 PD 1/PD L1aChamotharane	VS Chamotha	rome (TNRC					
Schmid D at al 2019	2	457 2	429	5.7	0.97 [0.14 6.91]	2018	
Schmid P et al 2020		781 1	3.89	4.5	3 51 [0 43 28 62]	2020	
Nittendorf EA, et al 2020	4	164 1	167	4.1	4.15 0.46. 37.53	2020	
Miles D, et al.2021	4 .	432 2	217	6.9	1.00 [0.18, 5.53]	2021	
Subtotal (95% CI)	1	1829	1211	20.7	1.74 (0.65, 4.64)		-
Total events	17	8					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1	1.80, df = 3 (P	= 0.61); I <sup>z</sup> =	0%				
lest for overall effect: Z = 1.10 (P =	0.27)						
2.5.4 PD-L1+Chemotherapy VS Ch	emotherapy (	Ovarian Car	icer)				
Pujade-Lauralne E, et al 2021A	11	182 3	177	11.9	3.73 [1.02, 13.61]	2021	
Moore KN, et al.2021	13	642 3	644	12.6	4.42 [1.25, 15.57]	2021	
Monk BJ, et al 2021A	6	329 1	334	4.4	6.19 [0.74, 51.66]	2021A	
Subtolai (95% C1)	70	153 7	1155	29.0	4.34 [1.89, 9.96]		-
Haterogeneity: Tun2 - 0.00. Chi2 - 1	116 df = 7 (P)	- 0.97)-12-	025				
Test for overall effect: Z = 3.46 (P =	0.0005)	- 0.72),1 -	0.0				
2.5.5 PD-1+Chemotherapy VS Che	motherapy (N	lasopharyng	cal)				
Mai HO, et al 2021	5	146 3	143	95	1.65 [0.39, 7.06]	2021	
Subtolai (95% C1)	-	140	143	9.5	1.65 [0.39, 7.06]		
Haterogeneity: Not applicable	3	3					
Test for overall effect: Z = 0.68 (P =	0.50)						
2.5.6 PD-1+Chemotherapy VS Che	motherapy (G	astric Cance	r)				
Shifara K, et al.2020C.		250 0	244	1.9	2.94 [0.12, 72.52]	2020	
Total mante	1 1	230 0	244	1.9	2.54 [0.12, 72.32]		
Heterogeneity: Not applicable		0					
Test for overall effect: Z = 0.66 (P =	0.51)						
		~					
2.5.7 PD-1+chemotherapy VS Cher	notherapy (U)	240 2	143		2 47 (0 46 12 62)	2020	
Subtotal (05% CT)	3	249 2	242	7.4	2.47 [0.48, 12.82]	2020	
Total events	5	2			2.47 [0.40, 12.04]		-
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.08 (P =	0.28)						
2.5.8 MOLTS Character WE Ch		Constant Con					
Colombo N at al 2021 B	emomerapy (	111 0	116	2.2	5 32 (0 25 112 05)	2021B	
Subtated (05% CT)	0		116	2.2	5 12 (0 25 112 05)	20210	
Total events	2	0					
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.07 (P =	0.28)						
2.5.9 PO-1+Chemotherany VS Che	motherany (O	(esophages)					
Sun IM et al 2021	0	370 1	370	19	0 33 (0 01 8 19)	2021 -	
Subtotal (95% CI)		370	370	1.9	0.33 [0.01, 8.19]		
Total events	0	1			(,)		
Heterogeneity: Not applicable							
Test for overall effect Z= 0.67 (P = 0	(50)						
Total (95% CI)	6	498	5437	100.0	261 [167 408]		•
Total events	86	23					1.
Heterogeneity Tau2 = 0.00, Chi2 = 1	0.44, df = 19 (	$P = 0.94$ ; $I^2$	= 0%			7	1 1 1 1
Test for overall effect: Z = 4.20 (P <	0.0001)	0.000				0.002	U.1 1 10 500
test for subgroup differences: Chi*-	= 5.56, df = 8	(r = 0.69); I	0%			rD-1/PL	2-11+Cnemomerapy Chemotherapy

#### (b)

	PD-1/PD	-L1						
	+CTLA-	4	PD-1/F	D-L1		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight (%)	M-H. Random. 95% CI	Year	M-H, Random, 95% CI
5.4.1 Nivolurnab+lpilimumab VS	Nivoluma	b (NSCI	LC)					
Hellmann MD, et al.2018A	9	576	3	391	36.4	2.05 [0.55, 7.63]	2018	
Subtotal (95% CI)		576		391	36.4	2.05 (0.55, 7.63)		-
Total events	9		3					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.07 (P	= 0.28)							
5.4.2 Nivolumah+Inilimumah VS	Nivoluma	- ISCLC	5					
Owonikoko TK, et al.2021A	5	278	″ 1	279	13.5	5.09 [0.59, 43.86]	2021A	
Subtotal (95% CT)		278		279	13.5	5 09 10 59 43 861		-
Total events	5		1					
Heterogeneity Not applicable								
Test for overall effect: Z = 1.48 (P	= 0.14							
5.4.3 Durvalumab+tremelimumab	VS Durvi	alumab (	(UC)					
Powles T, et al.2020A	4	340	2	345	21.6	2.04 [0.37, 11.22]	2020	
Subtotal (95% CI)		340		345	21.6	2.04 [0.37, 11.22]		
Total events	4		2					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.82 (P	= 0.41							
5.4.4 Nivolulia0+ipalinalia0 v S	NNOtuma 15	o (Meiai	noma)		20.5	7 63 [1 77 34 63]	2015.4	
Subtatel (195% CT)	13	313	-	212	28.5	7.83 [1.77, 34.32]	201504	-
Tatal monte	10	515		515	20.0	7.00 [1.77, 54.04]		-
Lotare events	15		-					
Test for overall effects Z = 2.72 (R	- 0.007)							
10x 101 010111 01000 2 2.72 (1	- 0.007)							
Total (95% CI)		1507		1328	100.0	3.39 [1.54, 7.49]		•
Total events	33		8					
Heterogeneity Tau2 = 0.00; Chi2 =	2.31, df =	3(P = 0	1.51); I <sup>2</sup> =	- 0%				
Test for overall effect: Z = 3.02 (P	= 0.002							DD 1/PD 11+CTLA 4 PD 1/PD 11
Test for subgroup differences: Chi	i² = 2.26, d	f = 3 (P	= 0.52);	[² = 09				10-010-010-010-010-010-01

(d)

Study or Subgroup	PD-1/P Events	D-L1 Total	Placeb Events	o Total	Weight (%	Odds Ratio ) M-H. Random. 95%	CI Year		Od M-H, Ra	ds Ratio adom, 95% CI	
Larkin J, et al.2015B	2	313	6	311	79.9	0.33 [0.07, 1.63]	2015B			+	
Ascierto PA, et al.2020	0	452	1	453	20.1	0.33 [0.01, 8.20]	2020	_			
Total (95% CI)		765		764	100.0	0.33 [0.08, 1.38]			-	-	
Total events	2		7								
Heterogeneity: Tau <sup>2</sup> = 0.	00; Chi² =	0.00, 6	f = 1 (P	= 0.99	); I <sup>z</sup> = 0%					+	
Test for overall effect: Z -	- 1.52 (P -	- 0.13)						0.01	0.1	1 10	0 100
									PD-1/PD-L1	Chemotherapy	r -

(f)





FIGURE 6: Forest plots of comparison groups for grades 3–5. (a) The OR of rash for grades 3–5 checked using the random effect (RE) model in Group A (PD-1 or PD-L1 versus Chemotherapy): subgroup analyses were carried out based on tumor types. (b) The OR of rash for grades 3–5 checked using the random effect (RE) model in Group B (PD-1 or PD-L1 plus Chemotherapy versus Chemotherapy): subgroup analyses were carried out based on tumor types. (c) The OR of rash for grades 3–5 checked using the random effect (RE) model in Group E (PD-1 or PD-L1 versus Placebo): subgroup analyses were carried out based on tumor types. (d) The OR of rash for grades 3–5 checked using the random effect (RE) model in Group G (PD-1 or PD-L1 plus CTLA-4 versus PD-1 or PD-L1): subgroup analyses were carried out based on tumor types. (e) The OR of rash for grades 3–5 checked using the random effect (RE) model in Group G (PD-1 or PD-L1 plus CTLA-4 versus PD-1 or PD-L1): subgroup analyses were carried out based on the types of immune checkpoint inhibitors (PD-1 or PD-L1). (f) The OR of rash for grades 3–5 checked using the random effect (RE) model in Group F (PD-1 or PD-L1). (g) The odds ratio of rash for grades 3–5 checked using the random effect (RE) model in Group K (PD-1 or PD-L1). (g) The odds ratio of rash for grades 3–5 checked using the random effect (RE) model in Group K (PD-1 or PD-L1 plus Bevacizumab versus Sorafenib): subgroup analyses were carried out based on the name of immune checkpoint inhibitors. (i) The OR of rash for grades 3–5 checked using the random effect (RE) model in Group K (PD-1 or PD-L1 plus Bevacizumab versus Sorafenib): subgroup analyses were carried out based on the name of immune checkpoint inhibitors. (i) The OR of rash for grades 3–5 checked using the random effect (RE) model in Group J (PD-1 or PD-L1 plus CTLA-4 plus Chemotherapy versus Chemotherapy): subgroup analyses were carried out based on the name of immune checkpoint inhibitors. (i) The OR of rash for grades 3–5 checked using the random effect (RE) mod

L1 subgroups and indirectly observe the differences of rash risk. Although the analyses indicated that the risk of rash differed between PD-1 and PD-L1-related subgroups (Figures 2(a), 3(a) and 4(a)), no statistically significant results were found due to the involvement of PD-1 or PD-L1 inhibitors [22–24], [26, 27, 32], [33, 37, 39], [41, 43–45], [47, 49, 53], [54, 59, 61, 66], [68, 71–74], [77–80], [82, 84, 86], [87, 90–92], [95–98], [100, 101, 103], [105, 107, 108], [111, 112]. However, compared with the PD-1 involved subgroup (Figure 4(e)), the participation of chemotherapy significantly increased the risk of rash in the PD-L1 subgroup (p = 0.03) [63, 77, 80, 96].

The similar strategy was used to elucidate the influence of PD-1 or PD-L1 involved treatment lines on the risk of developing rash (Figures 2(b), 3(b), 4(b), 4(f), 5(c), and 5(e)). Subgroup studies revealed an increased risk of rash when PD-1 or PD-L1 inhibitors were given together with other antitumor agents as the second-line choice (Figure 3(b), 4(f), and 5(c)) [27, 29, 37, 41, 45, 47, 53, 63, 66, 73, 74, 76–80, 84, 86, 95, 96, 100, 101, 103, 105, 107, 111, 112, 117]. When PD-1 or PD-L1 inhibitors were given alone, this incidence trend was only seen in Group H (Figure 5(e)) [34, 67, 117]. The reasons leading to the above results might be related to the combined treatment drugs, and the specific reasons were still need to be further studied.

The formation of heterogeneity is inevitable in the course of detailed examination (Figures 2–6). By conducting adequate subgroup analyses and comparing the results of rash between all grades and grades 3–5, the clinical trials responsible for the heterogeneity were identified, and further analyses revealed that the heterogeneity might be primarily due to the data themselves (Figure 6), implying that it would have little effect on the overall analysis results. Additionally, no noticeable publication bias was detected using funnel plots (S Figures 2–6). This further increased the reliability and rigor of this meta-analysis. Although the correlation between skin toxicities and tumor regression had been reported frequently in some studies [10–12], no such data were found in all the enrolled clinical trials [22–25], [26–30], [31–35], [36–40], [41–45], [46–50], [51–55], [56–60], [61–65], [66–70], [71–75], [76–80], [81–85], [86–90], [91–95], [96–110], [111–115], [116, 117]. Therefore, to elucidate the correlation between the rash risk and tumor prognosis, more and more relevant clinical trials should be put into practice [13–15]. Furthermore, researchers needed to pay more attention to this kind of data and report it in a timely manner. In clinical work, we need to use treatment-related rashes cautiously to judge the treatment response and prognosis of patients.

#### 5. Conclusions

The risk of developing rash would be enhanced whether PD-1 or PD-L1 inhibitors were given alone or together with others. Furthermore, the incidence risk of rash appeared to be higher when PD-1 or PD-L1 inhibitors together with other antitumor drugs were given as the second-line choice. No statistically significant differences in the results of the rash between the PD-1 and PD-L1 subgroups were found due to the involvement of PD-1 or PD-L1 inhibitors.

#### Abbreviations

PRISMA:	Preferred Reporting Items for Systematic
	Reviews and Meta-Analyses
PICOS:	Participants, interventions, comparisons,
	outcomes, and study design
RCT:	Randomized controlled trial
N/A:	Not available
PD-1:	Programmed cell death-1
PD-L1:	Programmed cell death ligand 1
HR:	Hazard ratios

0 1 1

0 D

OK:	Odds ratio
RD:	Risk difference
CI:	Confidence interval
RE:	Random effect
NSCLC:	Non-small-cell lung cancer
SCLC:	Small-cell lung cancer
NC:	Nasopharyngeal carcinoma
OC:	Ovarian cancer
TNBC:	Triple-negative breast cancer
HNSCC:	Head and neck squamous cell carcinoma
UC:	Urothelial carcinoma
GC/GJC:	Gastric or gastro-oesophageal junction cancer
RCC:	Renal cell carcinoma
ESCC:	Esophageal squamous cell carcinoma.

#### **Data Availability**

The data used to support the findings of this study are included within the article.

#### **Ethical Approval**

The study was not carried out in any human subjects, and no ethical issues were involved; hence, ethical approval was not needed.

#### **Conflicts of Interest**

The authors declare that they have no conflicts of interest.

#### **Authors' Contributions**

Yuan Tian designed and wrote the draft of the manuscript. Chi Zhang, Qi Dang, Qian Liu, and Kaiyong Wang were responsible for PubMed search and data collection; all the data selection and analyses were carried out by Yuan Tian, Hongmei Liu, Heli Shang, Junyan Zhao, Yuedong Xu, Tong Wu, and Wei Liu; all authors reviewed the final draft and approved its submission. Yuan Tian was responsible for all the disagreement, controversy, and inconsistency. Mohammed Safi was appointed for grammar and sentence modification. Yuan Tian, Chi Zhang, Qi Dang, and Kaiyong Wang contributed equally to this work.

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#### **Supplementary Materials**

S Figure 1: a summary table of review authors' judgements for each risk of bias item for each study. S Figure 2: funnel plots of comparison in Group A (PD-1 or PD-L1 versus Chemotherapy). A: the OR of rash for all-grade checked using the fixed effect (FE) model: Subgroup analyses were carried out according to the types of immune checkpoint inhibitors (PD-1 or PD-L1). B: the OR of rash for all-grade checked using the fixed effect (FE) model: subgroup

analyses were carried out according to the treatment lines (first or second line). C: the OR of rash for all grades checked using the fixed effect (FE) model: Subgroup analyses were carried out based on drug name, tumor type, and immune checkpoint type. D: the OR of rash for all grades checked using the fixed effect (FE) model: subgroup analyses were carried out based on drug name, tumor type, immune checkpoint type, and  $I^2$  value. S Figure 3: funnel plots of comparison in combination regimens. A: the odds ratio of rash for all grades checked using the fixed effect (FE) model in Group B (PD-1 or PD-L1 plus Chemotherapy versus Chemotherapy): subgroup analyses were carried out according to the types of immune checkpoint inhibitors (PD-1 or PD-L1). B: the odds ratio of rash for allgrade checked using the fixed effect (FE) model in Group B (PD-1 or PD-L1 plus Chemotherapy versus Chemotherapy): subgroup analyses were carried out according to the treatment lines (first or second line). C: the odds ratio of rash for all grades checked using the fixed effect (FE) model in Group B (PD-1 or PD-L1 plus Chemotherapy versus Chemotherapy): subgroup analyses were carried out based on tumor type. D: the odds ratio of rash for all grades checked using the fixed effect (FE) model in Group B (PD-1 or PD-L1 plus Chemotherapy versus Chemotherapy): subgroup analyses were carried out based on tumor type and immune checkpoint type. E: the odds ratio of rash for all grades checked using the fixed effect (FE) model in Group C (Camrelizumab plus Chemotherapy versus Chemotherapy). F: the odds ratio of rash for all-grade checked using the fixed effect (FE) model in Group D (PD-1 or PD-L1 plus Chemotherapy plus Bevacizumab versus Chemotherapy plus Bevacizumab). S Figure 4: funnel plots of different comparisons. A: the OR of rash for all-grade checked using the fixed effect (FE) model in Group E (PD-1 or PD-L1 versus Placebo): subgroup analyses were carried out according to the types of immune checkpoint inhibitors (PD-1 or PD-L1). B: the OR of rash for all grades checked using the fixed effect (FE) model in Group E (PD-1 or PD-L1 versus Placebo): subgroup analyses were carried out according to the treatment lines (first or second line). C: the OR of rash for all grades checked using the fixed effect (FE) model in Group E (PD-1 or PD-L1 versus Placebo): subgroup analyses were carried out based on tumor type. D: the OR of rash for all grades checked using the fixed effect (FE) model in Group E (PD-1 or PD-L1 versus Placebo): subgroup analyses were carried out based on tumor type, and I<sup>2</sup> value. E: the OR of rash for all grades checked using the fixed effect (FE) model in Group F (PD-1 or PD-L1 plus Chemotherapy versus PD-1 or PD-L1): subgroup analyses were carried out according to the types of immune checkpoint inhibitors (PD-1 or PD-L1). F: the OR of rash for all grades checked using the fixed effect (FE) model in Group F (PD-1 or PD-L1 plus Chemotherapy versus PD-1 or PD-L1): subgroup analyses were carried out according to the treatment lines (first or second line). S Figure 5: funnel plots of comparison groups (Groups G-M). A: the OR of rash for all grades checked using the fixed effect (FE) model in Group G (PD-1 or PD-L1 plus CTLA-4 versus PD-1 or PD-L1): subgroup analyses were carried out according to

the types of immune checkpoint inhibitors (PD-1 or PD-L1). B: the OR of rash for all grades checked using the fixed effect (FE) model in Group G (PD-1 OR PD-L1 plus CTLA-4 versus PD-1 or PD-L1): subgroup analyses were carried out based on tumor type. C: the OR of rash for all grades checked using the fixed effect (FE) model in Group G (PD-1 or PD-L1 plus CTLA-4 versus PD-1 or PD-L1): subgroup analyses were carried out according to the treatment lines (first or second line). D: the OR of rash for all grades checked using the fixed effect (FE) model in Group H (PD-1 or PD-L1 versus CTLA-4). E: the OR of rash for all grades checked using the fixed effect (FE) model in Group H (PD-1 or PD-L1 versus CTLA-4): subgroup analyses were carried out according to the treatment lines (first or second line). F: the OR of rash for all grades checked using the fixed effect (FE) model in Group I (PD-1 or PD-L1 plus CTLA-4 versus Chemotherapy): subgroup analyses were carried out based on tumor type. G: the OR of rash for all grades checked using the fixed effect (FE) model in Group J (PD-1 or PD-L1 plus CTLA-4 plus Chemotherapy versus Chemotherapy): subgroup analyses were carried out based on treatment regimens. H: the OR of rash for all grades checked using the fixed effect (FE) model in Group K (PD-1 or PD-L1 plus Bevacizumab versus Sorafenib): subgroup analyses were carried out according to the types of immune checkpoint inhibitors (PD-1 or PD-L1). I: the OR of rash for all grades checked using the fixed effect (FE) model in Group L (PD-1 or PD-L1 plus CTLA-4 versus CTLA-4). J: the OR of rash for all grades checked using the fixed effect (FE) model in Group M (PD-1 or PD-L1 versus Methotrexate/docetaxel/cetuximab). S Figure 6: funnel plots of comparison groups for grades 3-5. A: the OR of rash for grades 3-5 checked using the fixed effect (FE) model in Group A (PD-1 or PD-L1 versus Chemotherapy): subgroup analyses were carried out based on tumor types. B: the OR of rash for grades 3-5 checked using the fixed effect (FE) model in Group B (PD-1 or PD-L1 plus Chemotherapy versus Chemotherapy): subgroup analyses were carried out based on tumor types. C: The OR of rash for grades 3-5 checked using the fixed effect (FE) model in Group E (PD-1 or PD-L1 versus Placebo): subgroup analyses were carried out based on tumor types. D: the OR of rash for grades 3-5 checked using the fixed effect (FE) model in Group G (PD-1 or PD-L1 plus CTLA-4 versus PD-1 or PD-L1): subgroup analyses were carried out based on tumor types. E: the OR of rash for grades 3–5 checked using the fixed effect (FE) model in Group F (PD-1 or PD-L1 plus Chemotherapy versus PD-1 or PD-L1): subgroup analyses were carried out based on the types of immune checkpoint inhibitors (PD-1 or PD-L1). F: the OR of rash for grades 3-5 checked using the fixed effect (FE) model in Group H (PD-1 or PD-L1 versus CTLA-4). G: the OR of rash for grades 3-5 checked using the fixed effect (FE) model in Group M (PD-1 or PD-L1 versus Methotrexate/docetaxel/cetuximab). H: the OR of rash for grades 3-5 checked using the fixed effect (FE) model in Group K (PD-1 or PD-L1 plus Bevacizumab versus Sorafenib): subgroup analyses were carried out based on the name of immune checkpoint inhibitors. I: the OR of rash for grades 3-5 checked using the fixed effect

(FE) model in Group J (PD-1 or PD-L1 plus CTLA-4 plus Chemotherapy versus Chemotherapy): subgroup analyses were carried out based on treatment regimens. (*Supplementary Materials*)

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