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The incidence risk of programmed cell death-1/programmed cell death ligand 1 inhibitor-related alopecia for cancer patients

A systematic review and meta-analysis

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Abstract

Purpose: To evaluate the incidence risk of programmed cell death-1/programmed cell death ligand 1 (PD-1/PD-L1) inhibitor-related alopecia for cancer patients, the meta-analysis was put into practice.

Method: The meta-analysis was designed and put into practice according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

Results: After rigorous screening and verification, 22 clinical trials involving PD-1/PD-L1 inhibitors were collected for the final comprehensive analysis. The incidence risk of alopecia for all-grade in the PD-1/PD-L1 group was significantly lower than that in the control chemotherapy group (odds ratio [OR] = 0.01, 95% confidence interval [CI]: [0.01, 0.04], $I^2 = 86\%$, $Z = 8.73$ [$P < .00001$]). Similar to the above, the incidence risk of alopecia for grade 3–5 related to PD-1/PD-L1 was obvious lower than the control group (OR = 0.17, 95% CI:[0.05, 0.55], $I^2 = 0\%$, $Z = 2.97$ [$P = .003$]). When 7 clinical trials (PD-1/PD-L1 + Chemotherapy vs Chemotherapy) were taken to evaluate the risk of alopecia for all-grade and grade 3–5, no statistically significant results were found.

Conclusion: The incidence risk of alopecia caused by PD-1/PD-L1 is significantly lower than chemotherapy, and there is no statistical significant evidence that PD-1/PD-L1 combined with chemotherapy would increase the incidence risk of alopecia.

Abbreviations: CI = confidence interval, FE = fixed effect, HR = hazard ratios, OR = odds ratio, PD-L1 = programmed cell death ligand 1, PD-1 = programmed cell death-1, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RD = risk difference, RE = random effect, RR = risk ratio.

Keywords: aolpecia, cancer, meta-analysis, programmed cell death-1/programmed cell death ligand 1

1. Introduction

Alopecia is a common side effect of chemotherapy.[1–4] It is commonly found in the process of antitumor treatment related to chemotherapy drugs such as doxorubicin and paclitaxel.[1–4] Severe alopecia can even lead to irreversible results.[5] Although alopecia is not life-threatening, it has a serious impact on the quality of patients' life.[1–5] In clinical work, alopecia caused by drugs used in anti-tumor therapy is the problem that patients are mostly concerned about.[3] Whether in clinical trials or in clinical work, alopecia was regarded as a common adverse events that

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ML and LH authors have contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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was recorded in the patient's medical records and the prognosis of alopecia was needed to be explained to cancer patients carefully.[6,7]

Programmed cell death-1/programmed cell death ligand 1 (PD-1/PD-L1) inhibitor, considered as an immunotherapy anti-tumor drug, had achieved pleased and satisfied therapeutic effects for solid tumors in many clinical trials.[8–29] It was reported that PD-1 inhibitor induced alopecia areata in some former published case reports and meta-analysis.[30–32] With the completion of some new PD-1/PD-L1 related clinical trials in recent years, various drug toxicity reactions had also been reported, and alopecia was the drug toxicity reaction that was frequently reported.[8–29] PD-1/PD-L1 related treatment regimens were different in different PD-1/PD-L1 related clinical trials, and the incidence rate of PD-1/PD-L1 related alopecia was also various.[8–29] The role of PD-1/PD-L1 inhibitors on the incidence of alopecia in different tumors and different treatment options remained to be further clarified by our detailed analysis.[8–29] In order to clarify the relationship between incidence risk of alopecia and PD-1/PD-L1 inhibitors, the meta-analysis was designed and put into practice.

2. Method

The meta-analysis was designed and performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[33,34]

2.1. Types of enrolled studies

Phase III and randomized controlled clinical trials with the information of alopecia and published in English will be given priority, followed by phase I, phase II, and phase IV clinical trials. At least, one of PD-1 or PD-L1 inhibitors was prescribed for participants, diagnosed with solid malignant tumors rather than hematological malignancy.[34] For all included clinical trials, at least one control group is necessary. If >1 control group are involved in the enrolled clinical trial, only the control group involving alopecia will be used for the final comprehensive analysis.

2.2. Search strategy

The literature search of the meta-analysis was performed on March 27, 2020, using the following key words in PubMed: "neoplasm," "cancer," "tumor," "PD1/PD-L1," "nivolumab," "Opdivo," "pembrolizumab," "Keytruda," "Imfinzi," "MK-3475," "atezolizumab," "Tecentriq," "avelumab," "MPDL3280A," "Bavencio," "durvalumab," "BMS-963558." Original clinical trials involving PD1/PD-L1 inhibitors for cancer patients, reported between March 27, 2010 and March 27, 2020, were checked by a systematic search of PubMed. The following keywords will were used for the literature search.[34] Involving clinical trials for human beings, reported in full text, abstract, or poster form, were collected and checked by 4 members of our team (ML, LH, YT, LY). Other 5 members (XR, LL, QS, LL, and XW) were responsible for checking eligibility and duplicate independently by screening titles and abstracts of relevant studies.[34] If alopecia was mentioned in the published article, no specific data were presented. We would contact the corresponding author of this article to further determine whether specific data on alopecia were available, otherwise this article would be excluded from the final comprehensive analysis. The basic characteristics involving all enrolled clinical trials would be summarized and displayed in a table (Table 1).

2.3. Assessment of study quality and publication bias

Just as proposed by the Cochrane Collaboration, Funnel plot, Egger test, and Newcastle-Ottawa scale, were used for evaluating the bias of the enrolled trials.[33,35–38] Four members of our team (ML, LH, YT, LY) were designated to give comprehensive evaluation for study quality. The evaluation results, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting, proposed by the Cochrane Collaboration, would be summarized in a single figure.[33–38]

2.4. Outcome and exposure of interest

The clinical trial name, NCT number, year of publication, phase, tumor type, treatment regimens, number of participants (experimental group and control group), number of alopecia, and previous therapy were collected and summarized in a table (Table 1). Alopecia, including all-grade and grade 3–5, was used for the final comprehensive meta-analysis.[34]

2.5. Assessment of heterogeneity and statistical analysis

The heterogeneity among all enrolled clinical trials was screened and assessed by Cochrane Q statistic and the I^2 statistic, which were proposed by Higgins et al.[33,39] The range of I^2 values was used for evaluating the grade of heterogeneity (low: I^2 values <25%; moderate 25–50%; high >50%). Odds ratio (OR) and 95% confidence interval (CI) were taken into account for dealing with all the data and calculated by random effect (RE).[34,40] Fixed effect (FE) model was only used for the calculation of funnel plot.[34,40] $P < .05$ was deemed to be of statistically significance difference. All involving statistical tests of the meta were all 2-sided. In order to solve the problems encountered in the calculation process, we would perform enough subgroup analysis for all relevant data. All the data consolidation and analysis were performed by the software of Review Manager 5.3.

3. Results

3.1. Literature search results

The searching process was provided in the Supplemental Digital Content (supplemental material I, http://links.lww.com/MD/E965). Five hundred twenty four records were identified according to the preliminary searching principle set by us (Fig. 1). After rigorous screening and verification, 22 clinical trials involving PD-1/PD-L1 inhibitors were collected for the final comprehensive analysis.[8–29] The screening process for all enrolled clinical trials was shown in the form of flow diagram (Fig. 1). Risk of bias summary, review authors judgement about each risk of bias item for each included study, was displayed in (Fig. 2).[8–29]

3.2. Characteristics of identified trials

The basic characteristics of all the enrolled clinical trials were collected and gathered in (Table 1).[8–29] All enrolled clinical trials were reported to be randomized controlled trial (RCT). The specific PD-1/PD-L1 inhibitors involved in the meta-analysis were shown below: nivolumab (PD-1, n = 5),[21,24–27] pembrolizumab (PD-1, n = 8),[8,9,13,15,18,20,23,29] atezolizumab (PD-L1, n = 7),[10–12,16,17,19,22] avelumab (PD-L1, n = 1),[14] durvalumab (PD-L1, n = 1).[28] Among all enrolled clinical trials, 19 were reported to be phase

Table 1

Basic characteristics of 22 clinical trials.

NO	Reference	NCT number/ trial name	Drug name	Treatment regimen	Experimental group	Control group	Number of aolpecia	Previous therapy	Phase	Involving tumor type
1	Mok et al, 2019[8]	NCT02220894 (KEYNOTE-042)	Pembrolizumab (PD-1)	Pembrolizumab vs Platinum-based Chemotherapy	636	615	138	No	3	Locally advanced or metastatic NSCLC
2	Cohenet al, 2019[9]	NCT02252042 (KEYNOTE-040)	Pembrolizumab (PD-1)	Pembrolizumab vs Methotrexate, Docetaxel, or Cetuximab	246	234	26	Platinum containing treatment	3	Recurrent or metastatic HNSCC
3	Schmid et al, 2018[10]	NCT02425891 (IMpassion130)	Atezolizumab (PD-L1)	Atezolizumab + Nab-paclitaxel vs Nab-paclitaxel	452	438	507	No	3	Advanced TNBC
4	Horn et al, 2018[11]	NCT02763579 (IMpower133)	Atezolizumab (PD-L1)	Atezolizumab + Etoposide + Carboplatin vs Etoposide + Carboplatin	198	196	135	No	3	Extensive-stage SCLC
5	Socinski et al, 2018[12]	NCT02366143 (IMpower150)	Atezolizumab (PD-L1)	Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel vs Bevacizumab + Carboplatin + Paclitaxel	393	394	356	No	3	Metastatic Nonsquamous NSCLC
6	Paz-Ares et al, 2018[13]	NCT02775435 (KEYNOTE-407)	Pembrolizumab (PD-1)	Pembrolizumab + Carboplatin + Paclitaxel vs Carboplatin + Paclitaxel	278	280	230	No	3	Metastatic, Squamous NSCLC
7	Barlesi et al, 2018[14]	NCT02395172 (JAVELIN Lung 200)	Avelumab (PD-L1)	Avelumab vs Docetaxel	393	365	97	Platinum containing regimen	3	Stage IIIB or IV or recurrent NSCLC
8	Shitara K et al, 2018[15]	NCT02370498 (KEYNOTE-061)	Pembrolizumab (PD-1)	Pembrolizumab vs Paclitaxel	294	276	112	A platinum and fluoropyrimidine	3	Advanced gastric or gastro-oesophageal junction cancer
9	Powles et al, 2018[16]	NCT02302807 ((IMvigor211))	Atezolizumab (PD-L1)	Atezolizumab vs Chemotherapy (physician's choice: Vinflunine, Paclitaxel or Docetaxel)	459	443	153	Platinum-based chemotherapy	3	Locally advanced or metastatic UC
10	Hida et al, 2018[17]	NCT02008227 (OAK)	Atezolizumab (PD-L1)	Atezolizumab vs Docetaxel	56	45	28	Platinum-based chemotherapy	3	Locally advanced/metastatic NSCLC
11	Bellmunt et al, 2017[18]	NCT02256436 (KEYNOTE-045)	Pembrolizumab (PD-1)	Pembrolizumab VS Chemotherapy	266	255	95	Platinum-based chemotherapy	3	Advanced UC
12	Rittmeyer et al, 2017[19]	NCT02008227 (OAK)	Atezolizumab (PD-L1)	Atezolizumab vs Docetaxel	609	578	205	Platinum based combination therapies	3	Stage IIIB or IV NSCLC

(*continued*)

Table 1

(continued).

NO	Reference	NCT number/ trial name	Drug name	Treatment regimen	Experimental group	Control group	Number of aolpecia	Previous therapy	Phase	Involving tumor type
13	Langer et al, 2016[20]	NCT02039674 (KEYNOTE-021)	Pembrolizumab (PD-1)	Pembrolizumab + Carboplatin + Pemetrexed vs Carboplatin + Pemetrexed	59	62	10	No	2	Stage IIIB or IV, non-squamous NSCLC
14	Ferris et al, 2016[21]	NCT02105636 (CheckMate 141)	Nivolumab (PD-1)	Nivolumab vs (Methotrexate, Docetaxel, or Cetuximab)	236	111	14	Platinum-based chemotherapy	3	Recurrent Squamous-Cell Carcinoma of the Head and Neck (HNSCC)
15	Fehrenbacher et al, 2016[22]	NCT01903993 (POPLAR)	Atezolizumab (PD-L1)	Atezolizumab vs Doctaxel	142	135	53	Post-platinum Chemotherapy	2	Advanced or metastatic NSCLC
16	Herbst et al, 2016A[23]	NCT01905657 (KEYNOTE-010)	Pembrolizumab (PD-1)	Pembrolizumab vs Docetaxel	339	101	104	Platinum-doublet Chemotherapy	2/3	PD-L1-positive, advanced NSCLC
16	Herbst et al, 2016B[23]				343	101	103			
17	Borghaeiet al, 2015[24]	NCT01673867 (CheckMate 057)	Nivolumab (PD-1)	Nivolumab VS Docetaxel	287	268	68	Platinum-based doublet chemotherapy	3	Advanced Non squamous NSCLC
18	Brahmer et al, 2015[25]	NCT01642004 (CheckMate 017)	Nivolumab (PD-1)	Nivolumab vs Docetaxel	131	129	29	Platinum-containing regimen	3	Stage IIIB or IV advanced Squamous-Cell NSCLC
19	Kato et al, 2019[26]	NCT02569242 (ATTRACTION-3)	Nivolumab (PD-1)	Nivolumab vs Chemotherapy (paclitaxel or docetaxel)	209	208	101	Fluoropyrimidine and platinum-based chemotherapy	3	Advanced oesophageal squamous cell carcinoma (OSCC)
20	Weber et al, 2015[27]	NCT01721746 (CheckMate 037)	Nivolumab (PD-1)	Nivolumab vs Chemotherapy ICC (Dacarbazine or Paclitaxel + Carboplatin)	268	102	29	Ipilimumab, or ipilimumab and a BRAF inhibitor	3	Advanced Melanoma
21	Paz-Ares et al, 2019[28]	NCT03043872 (CASPIAN)	Durvalumab (PD-L1)	Durvalumab + Platinum-etoposide VS platinum-etoposide	265	266	174	No	3	Extensive-stage SCLC
22	Schmidet al2020[29]	NCT03036488 (KEYNOTE-522)	Pembrolizumab (PD-1)	Pembrolizumab + Paclitaxel + Carboplatin vs Paclitaxel + Carboplatin	784	390	691	NO	3	Stage II or stage III TNBC

HNSCC = head-and-neck squamous cell carcinoma; NSCLC = non small cell lung cancer, OSCC = oesophageal squamous cell carcinoma, SCLC = small cell lung cancer, TNBC = triple-negative breast cancer, UC = urothelial carcinoma.

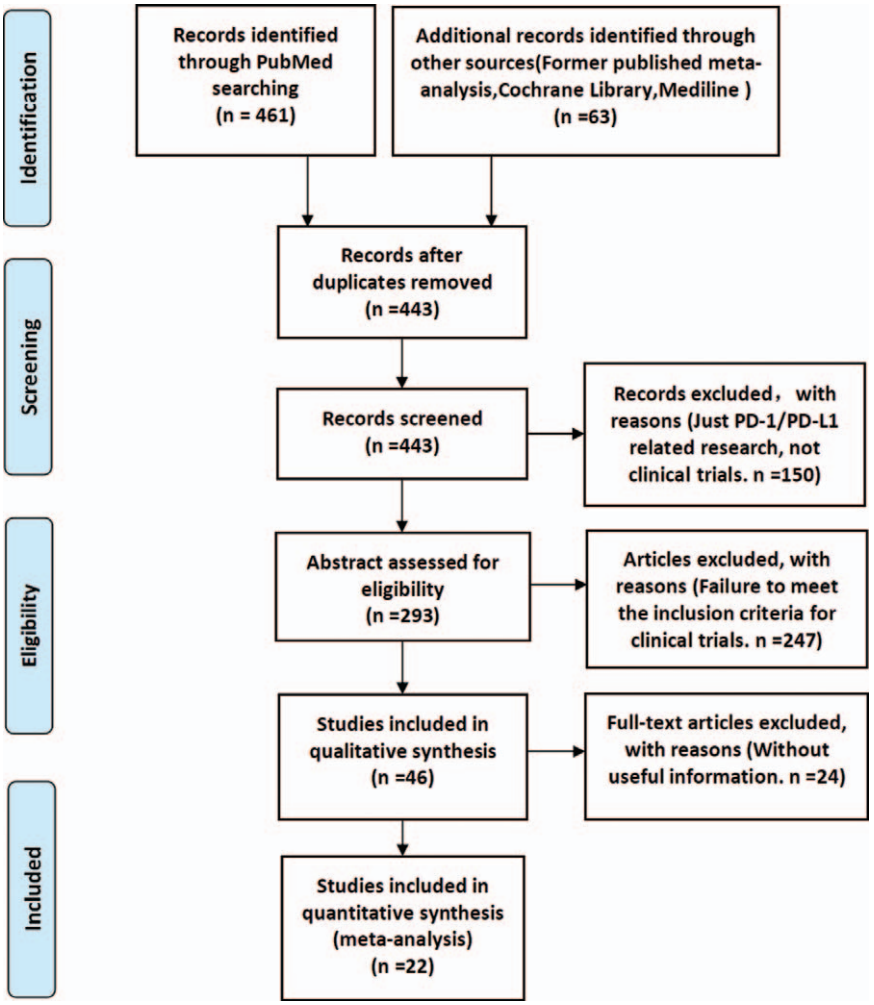

Figure 1. Flow diagram of enrolled clinical trials.

III,[8–19,21,24–29] 2 were reported to be phase II,[20,22] and 1 was reported to be phase II/III.[23] The involving tumor types among 22 enrolled trials were non small cell lung cancer (NSCLC) (n = 11),[8,12–14,17,19,20,22–25] small cell lung cancer (SCLC) (n = 2),[11,28] urothelial cancer (UC) (n = 2),[16,18] triple-negative breast cancer (TNBC) (n = 2),[10,29] head-and-neck squamous cell carcinoma (HNSCC) (n = 2),[9,21] advanced gastric or gastro-oesophageal junction cancer (n = 1),[15] oesophageal squamous cell carcinoma (OSCC) (n = 1),[26] and melanoma (n = 1).[27]

Among 14 enrolled clinical trials with previous treatments,[9,14–19,21–27] 13 of them underwent previous platinum-containing regimens before PD-1/PD-L1 inhibitors.[9,14–19,21–26] In other 8 clinical trials, PD-1/PD-L1 inhibitors were used for the first line therapy choice.[8,10–13,20,28,29] PD-1 inhibitors were prescribed in 13 clinical trials,[8,9,13,15,18,20,21,23–27,29] while PD-L1 inhibitors were used for the other 9 clinical trials.[10–12,14,16,17,19,22,28]

3.3. Risk of bias

Newcastle-Ottawa scale was taken into account for the assessment of study quality and risk of bias among enrolled clinical trials.[38] The evaluation results, including random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias), proposed by the Cochrane Collaboration, were summarized in a single figure (Fig. 2).[8–29] Publication bias, checked by Harbord test,[33] was shown in the form of funnel plots (Supplemental Digital Content; S Figure 1, http://links.lww.com/MD/E961, S Figure 2, http://links.lww.com/MD/E962, S Figure 3, http://links.lww.com/MD/E963 and S Figure 4, http://links.lww.com/MD/E964).[8–29]

3.4. Incidence risk of alopecia (PD-1/PD-L1 vs chemotherapy)

All the data were divided into 2 groups according to the treatment regimen of the experimental group and the control group. These 2 groups are shown separately as follows: Group A (PD-1/PD-L1 vs chemotherapy),[8,9,14–19,21–27] Group B (PD-1/PD-L1 + chemotherapy vs chemotherapy).[10–13,20,28,29] Then, a full subgroup analysis in each group was performed according to the specific treatment plan, or tumor type, or drug type, or specific drug name (Figs. 3 and 4).[8–29,34]

The overall analysis result of alopecia for all-grade relating to Group A was shown in the form of forest plot and gathered at the bottom of Fig. 3 (OR = 0.01, 95% CI: [0.01, 0.04], $I^2 = 86\%$, $Z =$

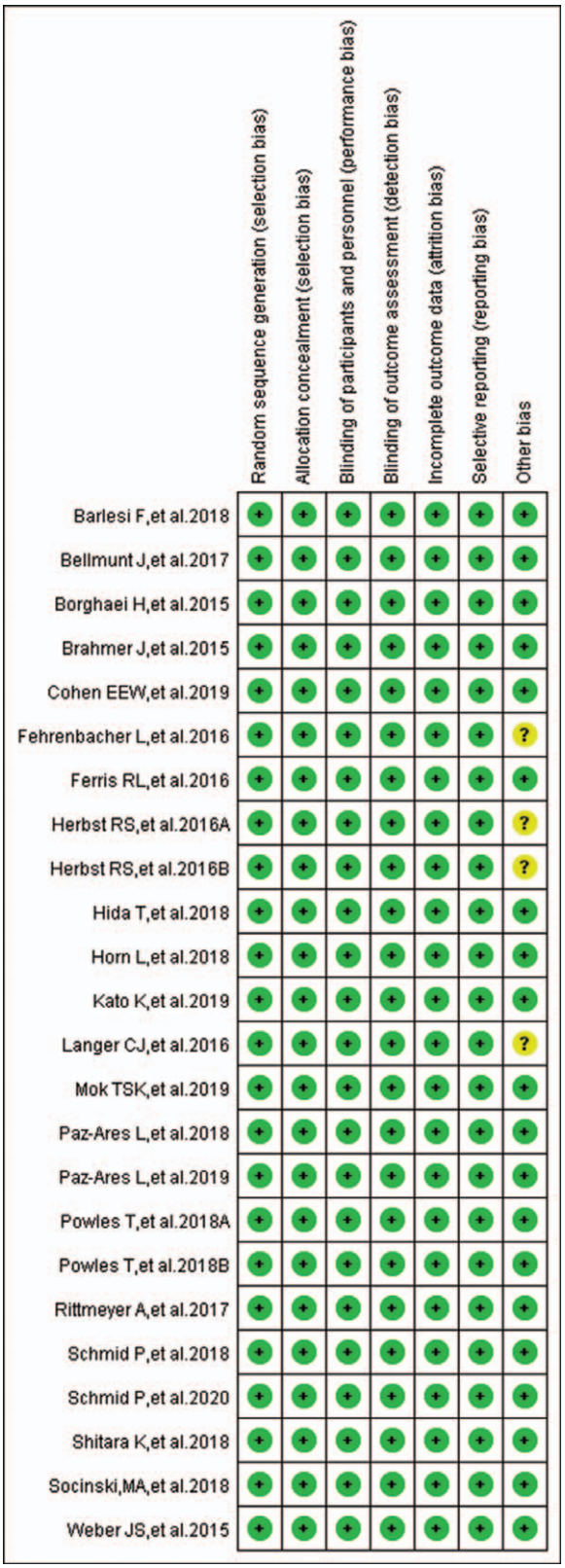

Figure 2. Risk of bias summary: review authors' judgement about each risk of bias item for each enrolled study.

8.73 [$P < .00001$]).[8,9,14–19,21–27] The existence of high heterogeneity could be found ($I^2 = 86\%$). Through subgroup analysis, it could be inferred that the heterogeneity might mainly originate from these 2 clinical trials involving UC.[16,18] Publication bias was evaluated in the form of funnel plot, which was shown in Supplemental Digital Content (S Figure 1, http://links.lww.com/MD/E961).[8,9,14–19,21–27] The existence of asymmetry was found through the funnel chart (Supplemental Digital Content, S Figure 1, http://links.lww.com/MD/E961).[8,9,14–19,21–27] Through subgroup analysis, it could be inferred that publication bias mainly came from the clinical trial of UC (Bellmunt et al).[18]

Similar to the above trend, the incidence risk of alopecia for grade 3–5 was obvious lower than the control group (OR = 0.17, 95% CI: [0.05, 0.55], $I^2 = 0\%$, $Z = 2.97$ [$P = .003$], Fig. 5).[8,15,18,19,21,23,25] No heterogeneity was found among all enrolled clinical trials ($I^2 = 0\%$, Fig. 5).[8,15,18,19,21,23,25] The funnel plot was provided in Supplemental Digital Content (S Figure 2, http://links.lww.com/MD/E962).[8,15,18,19,21,23,25] No publication bias was found through it.

3.5. Incidence risk of alopecia (PD-1/PD-L1 + chemotherapy vs chemotherapy)

Seven clinical trials were collected and analyzed for the incidence risk of alopecia for all grade.[10–13,20,28,29] No statistically significant difference in the incidence risk of alopecia was found between the experimental and control groups (OR = 1.11, 95% CI: [0.95, 1.30], $I^2 = 34\%$, $Z = 1.29$ [$P = .20$]; Fig. 4).[10–13,20,28,29] The existence of moderate heterogeneity could be found ($I^2 = 34\%$) among all the data.[10–13,20,28,29] Through subgroup analysis, it could be concluded that the heterogeneity might mainly originate from these 2 clinical trials involving NSCLC ($I^2 = 48\%$).[13,20] Publication bias was evaluated in the form of funnel plot, which was shown in Supplemental Digital Content (S Figure 3, http://links.lww.com/MD/E963).[10–13,20,28,29] No obvious publication bias was found among all enrolled clinical trials Supplemental Digital Content (S Figure 3, http://links.lww.com/MD/E963).[10–13,20,28,29]

Four clinical trials with the information of alopecia for grade 3–5 were put into practice for further analysis.[10,13,28,29] Similar to the above results, no statistically significant difference in the incidence risk of alopecia was found between the experimental and control groups (OR = 0.97, 95% CI: [0.48, 1.97], $I^2 = 0\%$, $Z = 0.08$ [$P = .93$]; Fig. 6).[10,13,28,29] No heterogeneity was found ($I^2 = 0\%$) among all enrolled data.[10,13,28,29] The funnel plot was shown in Supplemental Digital Content (S Figure 4, http://links.lww.com/MD/E964).[10,13,28,29] No obvious publication bias was found.

4. Discussion

Alopecia is a common side effect of chemotherapy. It is commonly found in the process of antitumor treatment related to chemotherapy drugs such as doxorubicin and paclitaxel.[1–4] Severe alopecia can even lead to irreversible results.[5] Although the occurrence of alopecia has been reported in some studies involving targeted drugs combined with chemotherapy,[6,41] it is not a common drug side effect of targeted anti-tumor drugs. Severe alopecia was rarely reported to be caused by targeted drugs alone.[8,15,18,19,21,23,25] In order to clarify the relationship between alopecia and PD-1/PD-L1 inhibitors, the meta-analysis was designed and put into practice.

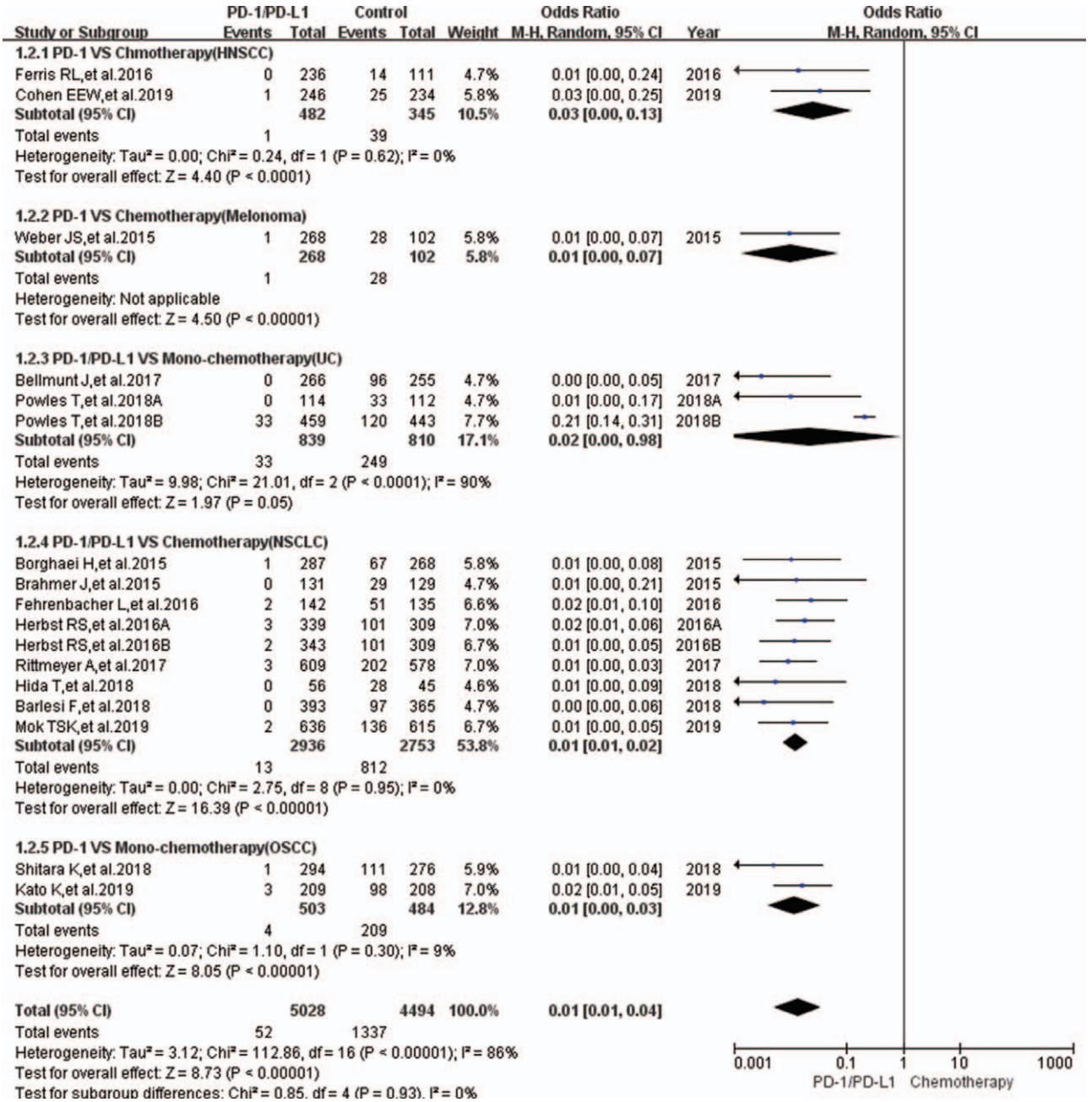

Figure 3. Forest plots of all-grade aolpecia for Group A (PD-1/PD-L1 vs chemotherapy). Subgroup analysis was put into practice based on tumor types and treatment regimen of the control group. All the data were calculated by random effect (RE) model. Involving statistical tests of the meta were 2-sided. PD-1/PD-L1 = programmed cell death-1/programmed cell death ligand 1.

After rigorous screening and verification, 22 clinical trials involving PD-1/PD-L1 inhibitors were collected for the final comprehensive analysis.[8–29] The screening process for all enrolled clinical trials was shown in the form of flow diagram (Fig. 1). Risk of bias summary, review authors judgement about each risk of bias item for each included study, was displayed in (Fig. 2).[8–29] After evaluation, all enrolled clinical trials were of high quality.[8–29]

After calculation and analysis, we found that the incidence risk of alopecia for all-grade in the PD-1/PD-L1 group was significantly lower than that in the control chemotherapy group (OR = 0.01, 95% CI: [0.01, 0.04], $I^2 = 86\%$, $Z = 8.73$ [$P < 0.00001$]; Fig. 3).[8,9,14–19,21–27] This lower incidence trend could also be seen in each subgroup analysis (HNSCC subgroup, Melonoma subgroup, UC subgroup, NSCLC subgroup, and OSCC subgroup) (Fig. 3).[8,9,14–19,21–27] Therefore, we can infer that whether it is PD-1 or PD-L1, compared with chemotherapy, the incidence risk of alopecia for all-grade in the PD-1/PD-L1 group is significantly lower than that in the chemotherapy group.[8,9,14–19,21–27] Through subgroup analysis, we concluded that the existence obvious heterogeneity ($I^2 = 86\%$) might mainly originate from those 2 clinical trials involving UC.[16,18] For the

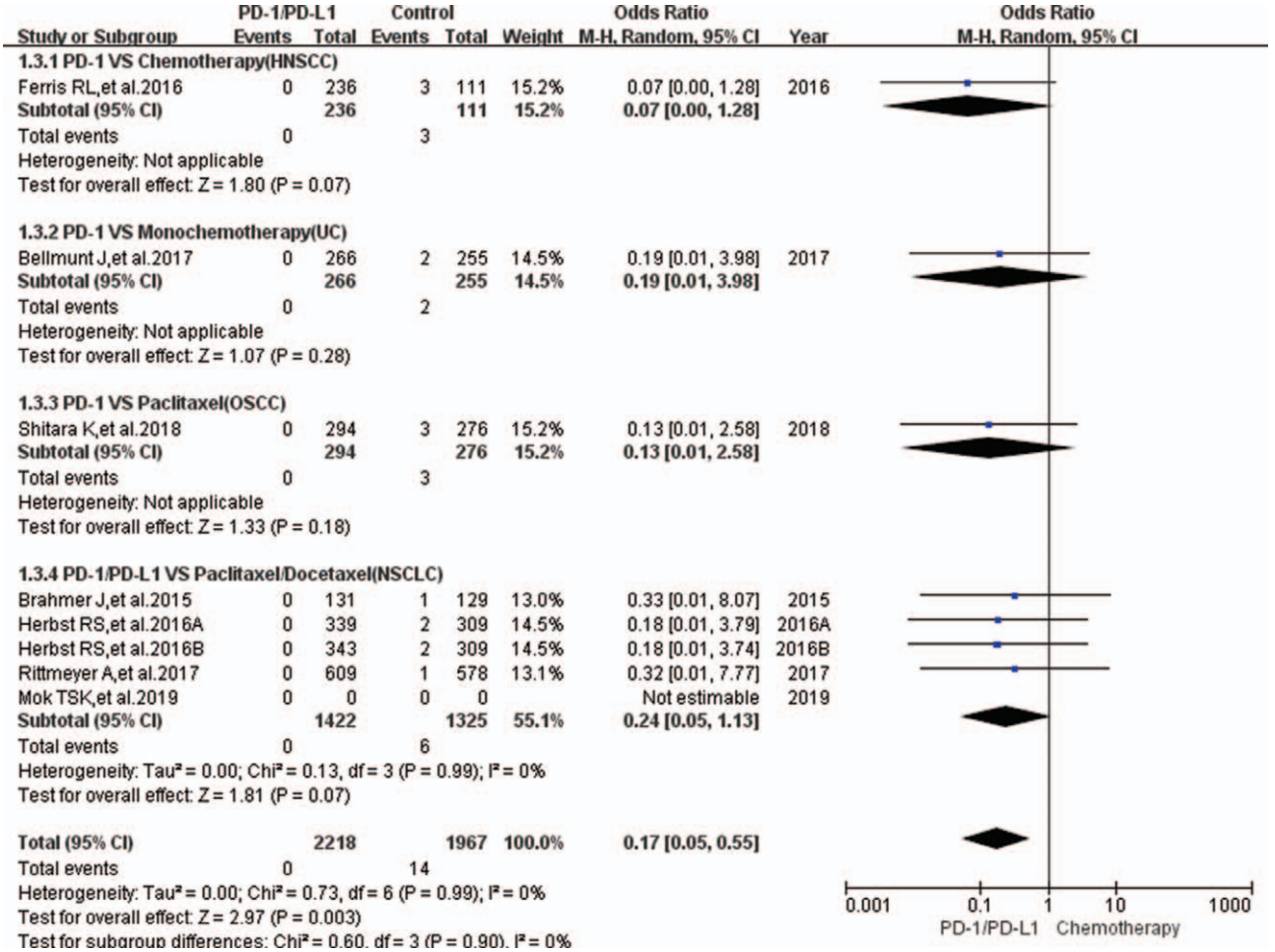

Figure 4. Forest plots of all-grade aolpecia for Group B (PD-1/PD-L1 + chemotherapy vs chemotherapy). Subgroup analysis was put into practice based on tumor types and treatment regimen of the control group. All the data were calculated by random effect (RE) model. Involving statistical tests of the meta were 2-sided. PD-1/PD-L1 = programmed cell death-1/programmed cell death ligand 1.

funnel plot, we found that there was a enrolled clinical trial that clearly deviated from the center of symmetry, suggesting the existence of publication bias. Through subgroup analysis, it could be inferred that publication bias might mainly originate from the clinical trial of UC (Bellmunt et al).[18] Similar incidence trend of alopecia for grade 3–5 could also be seen (OR = 0.17, 95% CI: [0.05, 0.55], $I^2 = 0\%$, $Z = 2.97$ [$P = .003$], Fig. 5) without any heterogeneity or publication bias.[8,15,18,19,21,23,25]

When 7 clinical trials of Group B (PD-1/PD-L1 + chemotherapy vs chemotherapy) were taken to evaluate the risk of alopecia for all-grade, no statistically significant results were found (OR = 1.11, 95% CI: [0.95, 1.30], $I^2 = 34\%$, $Z = 1.29$ [$P = .20$]; Fig. 4).[10–13,20,28,29] In other words, when PD-1/PD-L1 was combined with chemotherapy in the process of anti-tumor therapy, the incidence risk of alopecia was not increased.[10–13,20,28,29] The existence of moderate heterogeneity could be found ($I^2 = 34\%$).[10–13,20,28,29] Through subgroup analysis, it could be concluded that the heterogeneity might mainly originate from those 2 clinical trials involving NSCLC ($I^2 = 48\%$).[13,20] No obvious publication bias was found among all enrolled clinical trials (Supplemental Digital Content; S Figure 3, http://links.lww.com/MD/E963).[10–13,20,28,29] Similar to the above results, no statistically significant difference in the incidence risk of alopecia for grade 3–5 was found between the experimental and control groups (OR = 0.97, 95% CI: [0.48, 1.97], $I^2 = 0\%$, $Z = 0.08$ [$P = .93$]; Fig. 6).[10,13,28,29] No heterogeneity and obvious publication bias was found ($I^2 = 0\%$) among all enrolled data.[10,13,28,29]

As safety and satisfactory clinical efficacy in the process of anti-tumor therapy, more and more clinical trials involving PD-1/PD-L1 inhibitors have been putting into practice.[8–29,42–44] Moreover, alopecia was rarely reported in those clinical trials related to PD-1/PD-L1 without chemotherapy.[44–47] Among the clinical trials enrolled in this study, when PD-1/PD-L1 was used alone, no occurrence of alopecia above grade 2 was found.[8,15,18,19,21,23,25] In other words, PD-1/PD-L1 will not cause severe alopecia. Therefore, in the process of anti-tumor therapy, if severe alopecia was encountered, it should be considered to be caused by chemotherapy rather than PD-1/PD-L1 inhibitors. This finding is helpful to guide us to explain the side effects of treatment to patients in clinical work and improve the quality of life of patients.

In a word, the incidence risk of alopecia caused by PD-1/PD-L1 is significantly weaker than chemotherapy, and there is no

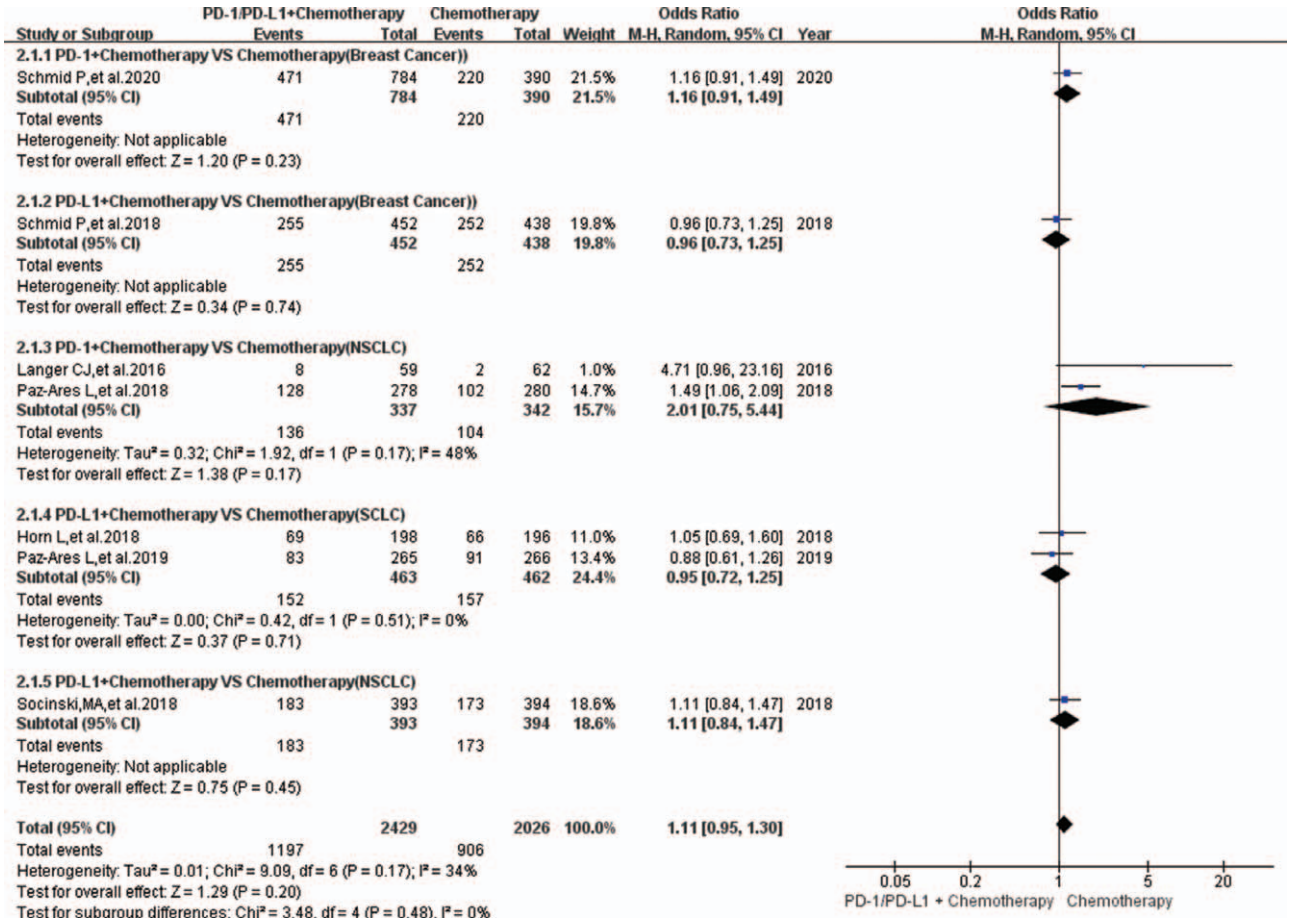

Figure 5. Forest plots of Grade 3–5 aolpecia for Group A (PD-1/PD-L1 vs chemotherapy). Subgroup analysis was put into practice based on tumor types and treatment regimen of the control group. All the data were calculated by random effect (RE) model. Involving statistical tests of the meta were 2-sided. PD-1/PD-L1 = programmed cell death-1/programmed cell death ligand 1.

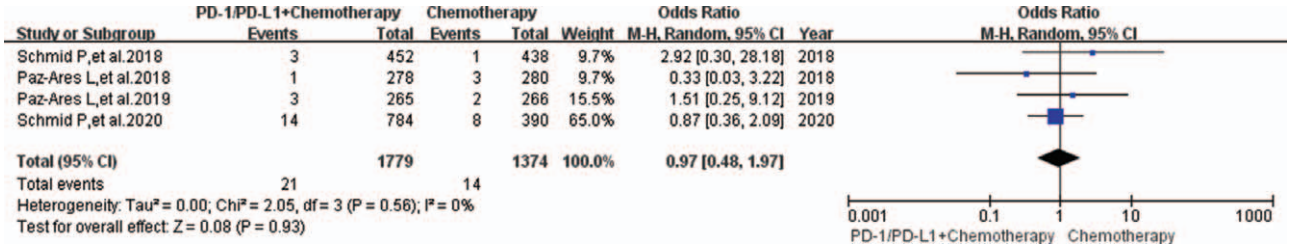

Figure 6. Forest plots of Grade 3–5 aolpecia for Group B (PD-1/PD-L1 + chemotherapy vs chemotherapy). Subgroup analysis was put into practice based on tumor types and treatment regimen of the control group. All the data were calculated by random effect (RE) model. Involving statistical tests of the meta were 2-sided. PD-1/PD-L1 = programmed cell death-1/programmed cell death ligand 1.

evidence that PD-1/PD-L1 combined with chemotherapy would increase the incidence risk of aolpecia.

5. Conclusions

The incidence risk of alopecia caused by PD-1/PD-L1 is significantly lower than chemotherapy, and there is no statistical significant evidence that PD-1/PD-L1 combined with chemotherapy would increase the incidence risk of alopecia.

Author contributions

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Writing – original draft: Fuli Mi.
Writing – review & editing: Fuli Mi.

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