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

Mingkai Li, BS\textsuperscript{a,*}, Linlin Huang, BS\textsuperscript{b,*}, Xihong Ren, BS\textsuperscript{c}, Lixia Liu, BS\textsuperscript{d}, Qinghong Shi, BS\textsuperscript{e}, Ling Liu, BS\textsuperscript{f}, Xiao Wang, BS\textsuperscript{a}, Yuan Tian, PhD\textsuperscript{g}, Lili Yu, BS\textsuperscript{g}, Fuli Mi, BS\textsuperscript{h}

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], \( \gamma = 0.86 \), \( Z = 8.73 [P < 0.00001] \)). 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], \( \gamma = 0.06 \), \( Z = 2.97 [P = 0.003] \)). 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: alopecia, cancer, meta-analysis, programmed cell death-1/programmed cell death ligand 1

1. Introduction

Alopecia is a common side effect of chemotherapy.\textsuperscript{[1–4]} It is commonly found in the process of antitumor treatment related to chemotherapy drugs such as doxorubicin and paclitaxel.\textsuperscript{[1–4]} Severe alopecia can even lead to irreversible results.\textsuperscript{[5]} Although alopecia is not life-threatening, it has a serious impact on the quality of patients' life.\textsuperscript{[1–5]} In clinical work, alopecia caused by drugs used in anti-tumor therapy is the problem that patients are mostly concerned about.\textsuperscript{[5]} Whether in clinical trials or in clinical work, alopecia was regarded as a common adverse events that...
was recorded in the patient’s medical records and the prognosis of alopecia was needed to be explained to cancer patients carefully.\textsuperscript{[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.\textsuperscript{[8–29]} It was reported that PD-1 inhibitor induced alopecia areata in some former published case reports and meta-analysis.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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,’ ‘PD-1/PD-L1,’ ‘nivolumab,’ ‘Opdivo,’ ‘pembrolizumab,’ ‘Keytruda,’ ‘Imfinzi,’ ‘MK-3475,’ ‘atezolizumab,’ ‘Tecentriq,’ ‘avelumab,’ ‘MPDL3280A,’ ‘Bavencio,’ ‘durvalumab,’ ‘BMS-966558.’ 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.\textsuperscript{[34]} Including 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, and XW) were responsible for checking eligibility and the bias of the enrolled trials.\textsuperscript{[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.\textsuperscript{[33–38]}

#### 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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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).\textsuperscript{[34,40]} Fixed effect (FE) model was only used for the calculation of funnel plot.\textsuperscript{[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.\textsuperscript{[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).\textsuperscript{[8–29]}

#### 3.2. Characteristics of identified trials

The basic characteristics of all the enrolled clinical trials were collected and gathered in (Table 1).\textsuperscript{[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),\textsuperscript{[21,24–27]} pembrolizumab (PD-1, n = 8),\textsuperscript{[8,9,13,15,18,20,23,29]}atezolizumab (PD-L1, n = 7),\textsuperscript{[10–12,16,17,19,22]}avelumab (PD-L1, n = 1),\textsuperscript{[14]} durvalumab (PD-L1, n = 1).\textsuperscript{[28]} Among all enrolled clinical trials, 19 were reported to be phase
| 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 | Pembrolizumab | Pembrolizumab vs Platinum-based Chemotherapy | 636 | 615 | 138 | No | 3 | Locally advanced or metastatic NSCLC |
| 2  | Cohen et al, 2019 [9] | NCT02522042 | Pembrolizumab | Pembrolizumab vs Methotrexate, Docetaxel, or Cetuximab | 246 | 234 | 26 | Platinum containing treatment | 3 | Recurrent or metastatic HNSCC |
| 3  | Schmid et al, 2018 [10] | NCT02425891 | Atezolizumab | Atezolizumab + Nab-paclitaxel vs Nab-paclitaxel | 452 | 438 | 507 | No | 3 | Advanced TNBC |
| 4  | Horn et al, 2018 [11] | NCT02763579 | Atezolizumab | Atezolizumab + Etoposide + Carboplatin vs Etoposide + Carboplatin | 198 | 196 | 135 | No | 3 | Extensive-stage SCLC |
| 5  | Socinski et al, 2018 [12] | NCT02366143 | Atezolizumab | Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel vs Bevacizumab + Carboplatin + Paclitaxel | 393 | 394 | 356 | No | 3 | Metastatic Non-squamous NSCLC |
| 6  | Paz-Ares et al, 2018 [13] | NCT02775435 | Pembrolizumab | Pembrolizumab + Carboplatin + Paclitaxel vs Carboplatin + Paclitaxel | 278 | 280 | 230 | No | 3 | Metastatic, Squamous NSCLC |
| 7  | Barlesi et al, 2018 [14] | NCT02395172 | Avelumab | Avelumab vs Docetaxel | 393 | 365 | 97 | Platinum containing regimen | 3 | Stage IIIB or IV or recurrent lung cancer |
| 8  | Shiota et al, 2018 [15] | NCT022370498 | Pembrolizumab | 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 | Avelumab | Avelumab 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 | Atezolizumab | Atezolizumab vs Docetaxel | 56 | 45 | 28 | Platinum-based chemotherapy | 3 | Locally advanced/metastatic NSCLC |
| 11 | Bellmunt et al, 2017 [18] | NCT0256436 | Pembrolizumab | Pembrolizumab vs Chemotherapy | 266 | 255 | 95 | Platinum-based chemotherapy | 3 | Advanced UC |
| 12 | Rittmeyer et al, 2017 [19] | NCT02008227 | Pembrolizumab | Pembrolizumab vs Docetaxel | 609 | 578 | 205 | Platinum based combination therapies | 3 | Stage III or IV NSCLC |
| No | Reference                  | NCT number/trial name | Drug name            | Treatment regimen                        | Experimental group | Control group | Number of alopecia | Previous therapy | Phase | Involving tumor type                  |
|----|----------------------------|-----------------------|----------------------|------------------------------------------|--------------------|---------------|-------------------|------------------|-------|---------------------------------------|
| 13 | Langer et al, 2016         | NCT02039674           | Pembrolizumab        | Pembrolizumab + Carboplatin + Pemetrexed | 59                 | 62            | 10                | No               | 2     | Stage IIB or IV, non-squamous NSCLC  |
|    | (KEYNOTE-021)              |                       |                      | Pembrolizumab + Carboplatin + Pemetrexed |                    |               |                   |                  |       |                                       |
| 14 | Ferris et al, 2016         | NCT02105636           | Nivolumab            | Nivolumab vs (Methotrexate, Docetaxel, or Cetuximab) | 236               | 111           | 14                | Platinum-based chemotherapy | 3     | Recurrent Squamous-Cell Carcinoma of the Head and Neck (HNSCC) |
|    | (CheckMate 141)            |                       |                      |                                           |                    |               |                   |                  |       |                                       |
| 15 | Fehrenbacher et al, 2016   | NCT01903933           | Atezolizumab         | Atezolizumab vs Docetaxel                | 142               | 135           | 53                | Chemotherapy      | 2     | Advanced or metastatic NSCLC         |
|    | (CheckMate 141)            |                       |                      |                                           |                    |               |                   |                  |       |                                       |
| 16 | Herbst et al, 2016A        | NCT01905657           | Pembrolizumab        | Pembrolizumab vs Docetaxel              | 339               | 101           | 104               | platinum-doublet chemotherapy | 2/3   | PD-L1-positive, advanced NSCLC       |
|    | (KEYNOTE-021)              |                       |                      |                                           |                    |               |                   |                  |       |                                       |
| 16 | Herbst et al, 2016B        | NCT01905657           | Pembrolizumab        | Pembrolizumab vs Docetaxel              | 339               | 101           | 104               | platinum-doublet chemotherapy | 2/3   | PD-L1-positive, advanced NSCLC       |
|    | (KEYNOTE-021)              |                       |                      |                                           |                    |               |                   |                  |       |                                       |
| 17 | Borghaeiet al, 2015        | NCT01673867           | Nivolumab            | Nivolumab vs Docetaxel                  | 343               | 101           | 103               | platinum-doublet chemotherapy | 3     | Advanced Non squamous NSCLC          |
|    | (CheckMate 057)            |                       |                      |                                           |                    |               |                   |                  |       |                                       |
| 18 | Brahmer et al, 2015        | NCT01642004           | Nivolumab            | Nivolumab vs Docetaxel                  | 131               | 129           | 29                | platinum-containing regimen | 3     | Stage IIB or IV advanced NSCLC       |
|    | (CheckMate 017)            |                       |                      |                                           |                    |               |                   |                  |       |                                       |
| 19 | Kato et al, 2015           | NCT0286242            | Nivolumab            | Nivolumab vs Chemotherapy (paclitaxel or docetaxel) | 209               | 208           | 101               | Fluoropyrimidine and platinum-based chemotherapy | 3     | Squamous-Cell NSCLC Advanced oesophageal squamous cell carcinoma (OSCQ) |
|    | (CheckMate 017)            |                       |                      |                                           |                    |               |                   |                  |       |                                       |
| 20 | Weber et al, 2015          | NCT01721746           | Nivolumab            | Nivolumab vs Chemotherapy (paclitaxel or docetaxel) | 268               | 102           | 29                | Ipilimumab, or ipilimumab and a BRAF inhibitor | 3     | Advanced Melanoma                     |
|    | (ATTRACTION-3)             |                       |                      |                                           |                    |               |                   |                  |       |                                       |
| 21 | Paz-Ares et al, 2015       | NCT03043872           | Durvalumab           | Durvalumab + Platinum-etoposide VS platinum-etoposide | 265               | 266           | 174               | No               | 3     | Extensive-stage SCLC                  |
|    | (CheckMate 037)            |                       |                      |                                           |                    |               |                   |                  |       |                                       |
| 22 | Schmidet al2020            | NCT03036488           | Pembrolizumab        | Pembrolizumab + Paclitaxel + Carboplatin vs Paclitaxel + Carboplatin | 784               | 390           | 691               | No               | 3     | Stage II or stage III TNBC            |
|    | (KEYNOTE-522)              |                       |                      |                                           |                    |               |                   |                  |       |                                       |

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.
II, [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), [19,21] advanced gastric or gastro-oesophageal junction cancer (n = 1), [13] 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, [8,9,15,18,20,21,23–27,29] 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. [18] 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). [18–29,34]

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], I² = 86%, Z =
8.73 \( [P < .00001] \). 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 \( (I^2 = 0\%) \).\(^{8,15,18,19,21,23,25}\) 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).\(^{10–13,20,28,29}\) No obvious publication bias was found.

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,\(^{[6,43]}\) 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.\(^{[18,15,18,19,21,23,25]}\) In order to clarify the relationship between alopecia and PD-1/PD-L1 inhibitors, the meta-analysis was designed and put into practice.

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**Figure 2.** Risk of bias summary: review authors’ judgement about each risk of bias item for each enrolled study.
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], I² = 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, Melanoma 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 (I² = 86%) might mainly originate from those 2 clinical trials involving UC.\[16,18\] For the
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], \(I^2 = 0\%\), \(Z = 2.97\) [\(P = 0.003\)], 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], \(I^2 = 34\%\), \(Z = 1.29\) [\(P = 0.20\)]; 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 (\(I^2 = 48\%\)).\(^{11,20}\) 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], \(I^2 = 0\%\), \(Z = 0.08\) [\(P = 0.93\)]; 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

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**Figure 4.** Forest plots of all-grade alopecia 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 alopecia.

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
Data curation: Linlin Huang, Xiuhong Ren, Lixia Liu, Xiao Wang.
Formal analysis: Mingkai Li, Linlin Huang, Ling Liu.
Methodology: Mingkai Li.
Resources: Mingkai Li, Qinghong Shi, Ling Liu, Xiao Wang, Lili Yu, Yuan Tian.
Software: Lili Yu.
Supervision: Xiuhong Ren, Fuli Mi.
Validation: Xiuhong Ren, Qinghong Shao, Xiao Wang, Fuli Mi. Writing – original draft: Fuli Mi. Writing – review & editing: Fuli Mi.

References

[1] Alberts DS, Durie BG, Salmon SE. Doxorubicin/B.C.N.U. chemotherapy for multiple myeloma in relapse. Lancet 1976;1:926–8.
[2] Creasey WA, McIntosh LS, Brescia T, et al. Clinical effects and pharmacokinetics of different dosage schedules of Adriamycin. Cancer Res 1976;36:216–21.
[3] Rossi A, Fortuna MC, Caro G, et al. Chemotherapy-induced alopecia: a novel observation. Australas J Dermatol 2019;60:e61–2.
[4] Hu XC, Zhang J, Xu BH, et al. Cisplatin plus gemcitabine versus paclitaxel plus gemcitabine as first-line therapy for metastatic triple-negative breast cancer (CRCSG006): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2015;16:436–46.
[5] Kim GM, Kim S, Park HS, et al. Chemotherapy-induced irreversible alopecia in early breast cancer patients. Breast Cancer Res Treat 2017;163:527–33.
[6] Manzini N, Wang X, Lim B, et al. Safety and efficacy of panitumumab plus nedaplatin chemotherapy in patients with primary HER2-negative inflammatory breast cancer. JAMA Oncol 2018;4:1207–13.
[7] International Collaborative Ovarian Neoplasm Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. Lancet 2002;360:505–15.
[8] Mok TSK, Wu YL, Kudaba I, et al. KEYNOTE-042 investigators. Pembrolizumab versus chemotherapy for previously untreated, PD-L1–expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019;393:1819–30.
[9] Cohen EEW, Soulères D, Le Tourneau C, et al. KEYNOTE-040 investigators. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. Lancet 2019;393:156–67.
[10] Schmid P, Adams S, Rugo HS, et al. IMpower133 trial investigators. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 2018;379:2220–4.
[11] Horn L, Mansi JF, Szczygieł D, et al. KEYNOTE-001 investigators. Pembrolizumab versus chemotherapy as first-line treatment for patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 2 trial. Lancet Oncol 2015;16:375–84.
[12] Pembrolizumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPian): a randomised, controlled, open-label, phase 3 trial. Lancet 2019;394:1929–39.
[13] Schmid P, Cortes J, Pusztai L, et al. KEYNOTE-522 Investigators. Pembrolizumab for early triple-negative breast cancer. N Engl J Med 2020;382:810–21.
[14] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
[15] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[16] Wells G, Shea B, O’Connel D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses; 2009. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed July 6, 2012.
[17] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[18] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[19] Huitric SA, Andre F, Jiang Z, et al. Combination of everolimus with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer (BOLOREO-1): a phase 3, randomised, double-blind, multicentre trial. Lancet Oncol 2015;16:816–29.
[20] Peters S, Félici E, Dañuf U, et al. Safety evaluation of nivolumab added concurrently to radiotherapy in a standard first line chemo-radiotherapy phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17:1497–508.
regimen in stage III non-small cell lung cancer-The ETOP NICOLAS trial. Lung Cancer 2019;133:83–7.

[44] Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1103–15.

[45] Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. N Engl J Med 2019;381:2020–31.

[46] Ready N, Hellmann MD, Awad MM, et al. First-Line Nivolumab Plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer (CheckMate 568): outcomes by programmed death Ligand 1 and tumor mutational burden as biomarkers. J Clin Oncol 2019;37:992–1000.

[47] Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol 2017;18:31–41.