Risk of Ophthalmic Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-analysis

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**ABSTRACT**

**Background:** Immune checkpoint inhibitors (ICls) induced adverse events (AEs) have been reported affecting almost all human organs. However, studies about ocular AEs are few. A meta-analysis was performed to evaluate the risks of ICI-related ophthalmic AEs compared to chemotherapy.

**Methods:** Eligible studies were selected from phase II/III randomized controlled trials investigating ICls. The data were analyzed by R software and Stata.

**Results:** Odds ratio of treatment-related AEs (trAEs) and nonspecific ophthalmic trAEs (NS-trAEs) were lower for PD-1/PD-L1 inhibitors than chemotherapy (OR 0.44, p < .05; OR 0.28, p < .001; OR 0.18, p < .01 respectively). Compared with monotherapy, PD-1 plus CTLA-4 inhibitors increased the risks of immune-related AEs (irAEs) (OR 4.52, p < .01); ICls plus chemotherapy increased the risks of trAEs and irAEs (OR 2.82, p < .001; OR 3.63, p < .05 respectively).

**Conclusions:** PD-L1/PD-1 inhibitors had lower risks of trAEs and NS-trAEs than chemotherapy; Compared with monotherapy, combination therapy had higher risks of ophthalmic trAEs and irAEs.

**Abbreviation:** PD-1: programmed cell death protein 1; PD-L1: programmed cell death protein ligand 1; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; ICI: immune checkpoint inhibitor; AE: adverse event; trAE: treatment-related adverse event; irAE: immune-related adverse events; NS-trAE: nonspecific ophthalmic treatment-related adverse event; RCT: randomized controlled trials; PFS: progression-free survival; OS: overall survival; ORR: objective response rate; MM: melanoma; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; HNSCC: head-neck squamous cell carcinoma; PICOL: patient, intervention, comparison, and outcome; Versus: VS; Chem: chemotherapy; 95%CI: 95% confidence interval; FEM: fixed-effects model; REM: random-effects model; NA: not applicable; MeSH: medical subject heading

The field of immune-oncology has evolved significantly over the past decade. Immune checkpoints are essentially receptors on cytotoxic T cells that work as inhibitory responses to prevent T cells from immune overactivation. However, this physiological process may be nefariously imitated by tumor cells. Tumor cells may be recognized as 'self' by the immune system and then escape from immune attack. A new kind of immunologic agents, called immune checkpoint inhibitors (ICls), alleviate the tumor-induced T cells inhibition and thereby evoke anti-tumor immunity after binding to their specific ligands: cytotoxic T-lymphocyte associated antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1).

Several ICls have already been approved and have been in use for years. Ipilimumab (CTLA-4 inhibitor) was the first inhibitor to be approved for melanoma management in 2011, then Nivolumab (PD-1 inhibitors), pembrolizumab (PD-1 inhibitors), and atezolizumab (PD-L1 inhibitors) were approved by Food and Drug Administration (FDA) for treatment in patients with advanced NSCLC. ICls have remarkable improvement and benefits in overall survival (OS) in patients with malignant melanoma (MM), non-small-cell lung cancer (NSCLC), urethral carcinoma, head-neck squamous cell carcinoma (HNSCC), and malignant mesothelioma. Unfortunately, ICls have been associated with several treatment-related adverse events (trAEs), such as immune-related adverse events (irAEs) most notably. IrAEs are considered to be the result of cross-reactive tissue damage, through the activation and the infiltration of T-cells into noncancerous tissues, preexisting auto-antibodies and inflammatory cytokines levels increase, and complement-mediated inflammation enhance.

Ophthalmic irAEs are rare, having been reported in less than 1% of patients treated with Ipilimumab. Ophthalmic toxicities however shouldn’t be ignored as they can be visually threatening without timely recognition or appropriate treatments, ultimately affect the quality of life. Here, we have performed a meta-analysis of phase II/III RCTs focused on all types of ophthalmic AEs in patients treated with ICls. To the best of our knowledge, this is the most detailed meta-analysis...
to synthesize information concerning risks and incidences of ophthalmic AEs with PD-1/PD-L1, CTLA-4 inhibitors monotherapy, or combination therapy. It will assist ophthalmologists and oncologists in recognizing potential ophthalmic toxicities in patients treated with ICIs.

Materials and methods

Our meta-analysis was conducted according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions and reported based on the PRISMA Statement. We followed the same method of our study.

Search strategy

We searched all the RCTs related to solid tumors, PD-1, PD-L1, and CTLA-4 inhibitors from the following databases: PubMed, Embase, and https://clinicaltrials.gov. The time range of the intended RCTs was until September 2020. The medical subject heading (MeSH) terms included for searching the relevant studies contained one term to indicate cancer: (neoplasm, carcinoma, cancer, or tumor, etc); one term to indicate ICIs (anti-CTLA-4, anti-PD-1, anti-PD-L1, ipilimumab, tremelimumab, pembrolizumab, nivolumab, durvalumab, atezolizumab, or avelumab), and one term to indicate RCTs. We used “and” to connect them. (Supplementary Table S1)

Inclusion and exclusion criteria

Our meta-analysis included the following information in English literature studies: (1) Phase II/III RCTs with primary endpoints such as overall survival, progression-free survival (PFS), or objective response rate (ORR); (2) histologically-confirmed solid tumors such as lung cancer, melanoma (MM), and others; (3) containing the information of ICIs (PD-1/PD-L1 inhibitors or CTLA4 inhibitor alone or PD-1 inhibitor combined with CTLA4 inhibitor), controlled therapies, and ophthalmic AEs were concerned.

However, the studies were excluded if they were: (1) reviews, duplicate reports, letters, unfinished studies, or conference reports; (2) studies conducted with animal models or cell lines or on non-solid tumors; (3) studies whose ophthalmic AEs could not be confirmed due to insufficient data; (4) studies whose experimental method was substantially different from other selected RCTs.

Data extraction

Two reviewers (Y.L.H. and D.Y.W.) independently searched all the relevant studies and read the titles, abstracts, and full texts of the identified studies. A study was deemed acceptable for inclusion in the study if PICO (Patient, Intervention, Comparison, and Outcome) criteria were met. We extracted the following information from the selected studies: year of publication, author’s family name, methods of trials, number of ICIs treatment type, number of control treatment, number of ophthalmic AEs, all-grade (grade 1–4), and high-grade (grade 3–4) respectively, number of ophthalmic treat-related AEs(trAEs), immune-related AEs(irAEs) and nonspecific treat-related AEs (NS-trAEs) respectively.

Grade of the ophthalmic AEs has been reported according to common terminology criteria for adverse events (CTCAE Version 5.0), where no grade 5(death) ophthalmic AEs had been mentioned (Supplementary Table S3). IRAEs were usually defined as any AE associated with drug exposure and consistent with an immune-mediated mechanism of action, such as uveitis, dry eye, iritis, retinopathy, etc. NS-trAEs were defined as adverse events unrelated to immune responses, such as ocular infectious diseases, or those that lack detailed clinical description (eye disorders, blurred vision, etc.). TrAEs: all ophthalmic adverse events that were associated with drugs during treatment, including irAEs and NS-trAEs. Cases of disagreement were resolved with a third reviewer (Q.S.).

Data analysis

In our study, the risk of bias analysis was performed by Review Manager 5.3 software (Cochrane Collaboration 2014, Nordic Cochrane Center, and Copenhagen, Denmark) and stata (version 15.1). Two reviewers (Y.L. H. and Q.S) independently assess the quality of the included RCTs according to the Cochrane risk of bias tool, which assesses the following seven domains: selection bias (including both random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias, and other bias. R3.4.3 (R Project) and the metafor package were used for the data analysis. Odds ratio (OR) was used to estimate ophthalmic AEs of grade 1–4 and grade 3–4. OR >1.0 indicated a higher risk of ophthalmic AEs in patients treated with ICIs. Besides, the I² statistics were applied to assess the heterogeneity among the RCTs. I² values of <30%, 30%–59%, 60%–75%, and >75% were classified as low, moderate, substantial, and considerable heterogeneity respectively. We used the random-effects model (REM) described by DerSimonian and Laird to calculate pooled OR and 95% confidence interval (CI). Sources of heterogeneity were explored using subgroup analyses mainly according to different ICI regimens. The Begg’s and Egger’s tests were used to analyze the publication bias across RCTs. All P values were 2-tailed, and a probability level <0.05 was considered statistically significant.

Quality assessment

First, our meta-analysis was strictly performed by the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions. Second, two independent reviewers searched all the relevant studies and read the titles, abstracts, and full texts of the identified studies. Any question was resolved by discussion with other reviewers until the agreement was reached. Third, we paid much attention to the heterogeneity among the RCTs by using subgroup analysis. On the other hand, the REM was also employed for our meta-analysis to verify the statistical results.
Results

Selection of studies and characteristics

Using the search terminology, we initially identified 3,445 studies from our databases search results. Among those studies, 25 RCTs met our strict inclusion criteria (Supplementary Figure S1). All the 25 included trials were evaluated and compared side effects of ICIs therapies with other controlled treatments (chemotherapy, placebo, or ICI) in solid tumors representing data from a total of 13,599 patients.

Among the studies (Table 1), four involved PD-L1 (Atezolizumab: 2 studies8,7 751 patients; Avelumab: 2 studies25,26 580 patients); seven involved PD-1 (Nivolumab: 4 studies6,11,27,28, 997 patients; Pembrolizumab: 3 studies9,10,29, 1,309 patients); four involved CTLA-4 (Tremelimunab: 2 studies12,32 705 patients; Ipilimumab: 2 studies30,31 864 patients); and three studies compared combination therapy of PD-1 plus CTLA-4 inhibitors with ICI monotherapy (1,290 patients, Nivolumab + Ipilimumab or Pembrolizumab + Ipilimumab).33–35 Six studies compared combination therapy of chemotherapy plus ICIs with chemotherapy.4,36–40 Additionally, one study compared Pembrolizumab with Ipilimumab.41 Nine studies had data from malignant melanoma(MM) patients4,27–30,32,33,35,41; Seven from non-small cell lung cancer (NSCLC) patients6,9,26,36,40; Other 9 studies from other cancers including small cell lung cancer (SCLC),13,37 mesothelioma12, urothelial cancer10, prostate cancer,31, and head-neck squamous cell carcinoma11, ovarian cancer25, Multiple Myeloma.38,39

The quality of the included studies was measured by the Cochrane risk of bias tool, and the results are in Figure 1, Supplementary Table S2, and Supplementary Figure S2. All the included studies had described the details regarding binding of outcome assessment and random sequence generation. However, some of them had described incomplete outcome data and allocation concealment. Some studies failed to mention the binding of participants, personnel, and selective reporting. Other indices of bias lacked specific description in all the included clinical studies.

Risk of overall ophthalmic treatment-related adverse events

Across 19 eligible studies, 228 cases of overall ophthalmic trAEs and 37 cases of grade 3–4 ophthalmic trAEs were observed among 11,357 involved patients (Table 1). The predicted incidences of overall all-grade ophthalmic trAEs were 2.70% for chemotherapy, 4.98% for combination therapy of PD-1 plus CTLA-4, 0.87% for the PD-L1 inhibitor, 1.28% for the PD-1 inhibitor, and 1.43% for the CTLA-4 inhibitor (Table 2).

The OR of all-grade ophthalmic trAEs in patients with PD-1/PD-L1 inhibitors was 0.44 (95% CI: 0.23–0.83 p < .050) and 0.28 (95% CI: 0.10–0.77 p < .0001) respectively, and it was statistically lower than chemotherapy (p < .05). There was no significant difference between CTLA-4 inhibitor and control (chemotherapy or placebo) (OR, 1.28; 95%CI, 0.21–7.84; p > .05). Patients with combination therapy (PD-1 plus CTLA-4 inhibitors or ICIs plus chemotherapy) have a higher risk of all-grade trAEs than CTLA-4/PD-1 inhibitor alone (OR 4.52, 95% CI: 1.67–12.24, p < .01) or chemotherapy (OR, 2.82; 95%CI, 1.45–5.46; p < .001). The risks of high-grade ophthalmic trAEs in PD-1/PD-L1/CTLA-4 inhibitors monotherapy or combination therapy had no significant difference than controls. (Figure 2)

Risk of immune-related ophthalmic adverse events

Across enrolled 14 studies, 82 cases of irAEs (grade 1–4) and 25 cases of irAEs (grade 3–4) were observed among the 8,810 involved patients (Table 1). The predicted incidences of all-grade ophthalmic irAEs were 0.86% for chemotherapy, 4.98% for combination therapy of PD-1 plus CTLA-4, 0.30% for the PD-L1 inhibitor, 1.25% for the PD-1 inhibitor, and 0.92% for the CTLA-4 inhibitor. (Table 2)

Compared with PD-1 or CTLA-4 inhibitor monotherapy, patients with ICIs combination therapy (PD-1 plus CTLA-4 inhibitors) were significantly more likely to experience all-grade ophthalmic irAEs (OR, 4.52; 95%CI: 1.67–12.24; p < .05), as well as patients with combination therapy (ICI plus chemotherapy) compared with chemotherapy (OR, 3.63; 95%CI: 1.36–9.66; p < .05), but not concern high-grade ophthalmic irAEs. Compared with chemotherapy or control, the risk of all-grade and high-grade ophthalmic irAEs in PD-1/PD-L1/CTLA-4 inhibitors had no significant difference (p > .05). (Figure 3)

Risk of nonspecific treatment-related ophthalmic adverse events

Across enrolled 10 studies, 146 cases of NS-trAEs (grade 1–4) and 12 cases of NS-trAEs (grade 3–4) were observed among the 6,480 involved patients (Table 1). The predicted incidences of ophthalmic NS-trAEs were shown in Table 2.

The risks of all-grade ophthalmic NS-trAEs in PD-1/PD-L1inhibitors were significantly lower than chemotherapy (OR: 0.18; 95%CI: 0.04–0.72; p < .05) and OR: 0.18; 95%CI: 0.08–0.40; p < .001), but no concern high-grade. (Figure 4)

Risk of ophthalmic adverse events between PD-1 and CTLA-4 inhibitors

The risks of ophthalmic trAEs/irAEs/NS- trAEs between PD-1 and CTLA-4 inhibitors were similar (p > .05). (Figure 2–4)

Discussions

A previous meta-analysis showed that, generally, irAEs (particularly uveitis and dry eyes) occur with a higher frequency in cancer patients treated ICIs compared with control.42 To the best of our knowledge, our study is the first meta-analysis to compare the incidences and risks of ophthalmic trAEs and irAEs associated with different ICI regimens and the first to include trials with PD-L1 inhibitors and combination therapy.

Although ICI-related ophthalmic AEs are not fatal and are generally manageable, they may interrupt treatment due to blindness or pain, affecting quality of life significantly. Compared with standard chemotherapy, patients with PD-1/PD-L1 inhibitors had a substantially lower risk of all-grade ophthalmic trAEs and NS-
| Study Type | Primary | Treatment | Patients | trAEs | irAEs | NS-trAEs |
|------------|---------|-----------|----------|-------|-------|----------|
| RCT III    | OS      | Nivolumab | 236      | 2     | 1     | 2        |
| III        |         | Avelumab  | 187      | 1     | 1     | 1        |
|            |         | Chemotherapy | 177 | 0 | 0 | 0 |
| iii       | OS      | Avelumab  | 393      | 1     | 1     | 1        |
| iii       |         | Chemotherapy | 365 | 1 | 0 | 0 |
| iii       | NSCLC   | Atezolizumab | 609 | 7 | 1 | 1 |
|            |         | Chemotherapy | 578 | 33 | 0 | 0 |
| ii        | NSCLC   | Atezolizumab | 142 | 1 | 0 | 1 |
|            |         | Chemotherapy | 135 | 7 | 0 | 7 |
| ii        | Carcinoma of head & neck | Nivolumab | 111 | 7 | 1 |
| ii        | Melanoma | Nivolumab | 268 | 1 | 1 | 1 |
| ii        | NSCLC   | Nivolumab | 206 | 0 | 0 | 0 |
| ii        | NSCLC   | Nivolumab | 287 | 2 | 1 | 1 |
| ii        | Urothelial carcinoma | Pembrolizumab | 266 | 20 | 2 |
| ii        | PFS     | Pembrolizumab | 255 | 17 | 0 |
| ii        | OS      | Pembrolizumab | 339 | 4 | 0 | 0 |
| ii        | NSCLC   | Pembrolizumab | 343 | 7 | 0 | 0 |
| ii        | Melanoma | Pembrolizumab | 178 | 1 | 1 | 1 |
| ii        | PFS, OS | Pembrolizumab | 179 | 2 | 1 | 2 |
| ii        | Nivolumab | Chemotherapy | 171 | 3 | 0 | 0 |
| ii        | Ipilimumab | Placebo | 380 | 0 | 0 | 0 |
| iii        | RFS     | Ipilimumab | 471 | 4 | 4 | 4 |
| iii        | ORR     | Ipilimumab | 474 | 0 | 0 | 0 |
| iii        | OS      | Ipilimumab | 393 | 4 | 3 | 1 |
| iii        | Placebo | Ipilimumab | 396 | 11 | 7 | 5 |
| iii        | Melanoma | Tremelimumab | 325 | 13 | 0 | 0 |
| iii        | Chemotherapy | Ipilimumab | 319 | 3 | 0 | 0 |
| ii        | Malherba | Placebo | 189 | 1 | 1 | 1 |
| ii        |Ipilimumab | Placebo | 46 | 2 | 0 | 0 |
| ii        | Melanoma | Nivolumab | 94 | 17 | 0 | 17 |
| iii        | SCLC    | Nivolumab | 46 | 2 | 0 | 0 |
| iii        | IPB     | Nivolumab | 61 | 2 | 1 | 2 |
| iii        | BMS     | Nivolumab | 54 | 5 | 0 | 5 |
| iii        | RS       | Nivolumab | 98 | 0 | 0 | 0 |
| iii        | SCLC    | Nivolumab | 313 | 2 | 2 | 2 |
| iii        | OS      | Nivolumab | 313 | 1 | 1 | 1 |
| iii        | Ipilimumab | Placebo | 311 | 1 | 1 | 1 |
| iii        | Ipilimumab | Placebo | 46 | 2 | 0 | 0 |
| iii        | Ipilimumab | Placebo | 61 | 2 | 1 | 2 |
| iii        | Ipilimumab | Placebo | 54 | 5 | 0 | 5 |
| iii        | Ipilimumab | Placebo | 98 | 0 | 0 | 0 |
| iii        | Ipilimumab | Placebo | 313 | 2 | 2 | 2 |
| iii        | Ipilimumab | Placebo | 313 | 1 | 1 | 1 |
| iii        | Ipilimumab | Placebo | 311 | 1 | 1 | 1 |
| iii        | Ipilimumab | Placebo | 46 | 2 | 0 | 0 |
| iii        | Ipilimumab | Placebo | 61 | 2 | 1 | 2 |
| iii        | Ipilimumab | Placebo | 54 | 5 | 0 | 5 |
| iii        | Ipilimumab | Placebo | 98 | 0 | 0 | 0 |
| iii        | Ipilimumab | Placebo | 313 | 2 | 2 | 2 |
| iii        | Ipilimumab | Placebo | 313 | 1 | 1 | 1 |
| iii        | Ipilimumab | Placebo | 311 | 1 | 1 | 1 |
| iii        | Ipilimumab | Placebo | 46 | 2 | 0 | 0 |
| iii        | Ipilimumab | Placebo | 61 | 2 | 1 | 2 |
| iii        | Ipilimumab | Placebo | 54 | 5 | 0 | 5 |
| iii        | Ipilimumab | Placebo | 98 | 0 | 0 | 0 |
| iii        | Ipilimumab | Placebo | 313 | 2 | 2 | 2 |
| iii        | Ipilimumab | Placebo | 313 | 1 | 1 | 1 |
| iii        | Ipilimumab | Placebo | 311 | 1 | 1 | 1 |
trAEs in our paper. Three issues may have contributed to the lower risk: First, traditional chemotherapy drugs generally work as cytotoxic reagents that favor killing rapid-dividing cells, whether they are tumor cells or healthy ones, thus lacking targetability and precision. PD-1/PD-L1 inhibitors activate the anti-tumor immune system specifically by releasing the already existing T cell inhibition. ICI represents one type of target therapy. Our previous analysis indicated that anti-PD-1 therapy is associated with fewer adverse events than chemotherapy, such as nausea, febrile neutropenia, diarrhea, anemia, neutropenia, fatigue, and alopecia. Second, in the ocular system, chemotherapy drugs may break the retinal blood-ocular barrier, which is crucial for protecting the eye from toxins. The ocular is an immune-privileged organ, and the blood-retinal lacks efficient lymphatics make the ocular system less affected by PD-1/PD-L1 inhibitors. Third, most chemotherapy-induced AEs were dose-dependent. TrAEs appear to be associated with their cumulative dose and cumulative cell toxicity. But there is a lesser or inconsistent dose-dependent relationship between AEs and PD-1/PD-L1 inhibitors.55

ICIs may prompt a T-lymphocyte-mediated immune attack on other parts of the body not limited to cancer tissues, such as cutaneous, endocrine, eye, etc. cause immune-related AEs. Although patients with ICIs had a 10–15% higher rate of irAE than traditional chemotherapy,16 and patients who developed colitis and diarrhea were also likely to developed uveitis or episcleara.16 However, the risk of ophthalmic irAEs was not higher than chemotherapy in patients with PD-1/PD-L1 and CTLA-4 inhibitors. Ophthalmic irAEs most frequently manifest as uveitis (1%) and dry eye (1–24%).47 Uveitis is also the most common ophthalmic irAEs of melanoma and PD-1 plus CTLA-4 inhibitors combination therapy.48,49 Thyroid eye disease or Graves’ ophthalmopathy occurs in patients with ICI’s thyroid toxicity, which is the most common endocrine irAEs of ICIs.50 The scientific rationale for the causative mechanism of immune-related ophthalmic AEs is unclear. Excessive inflammatory factors such as interferon-a (IFN-a), tumor necrosis factor (TNF), interleukin-23 (IL-23) released by T cells may lead to autoimmune uveitis,51 dacyrooadenitis (dry eye syndrome), scleritis, myositis of extraocular muscles, etc. IrAEs were not frequently observed in chemotherapy.52

Traditional chemotherapy agents involved mostly in our study include taxane (Docetaxel, Paclitaxel) and platinum (Cisplatin). Taxanes are mitotic inhibitors that restrict microtubule mobility and inhibit mitosis during cell division. Cisplatin is a heavy metal compound and has cytotoxicity. Chemotherapy agents breakdown the retinal blood-ocular barrier that affected the optic nerve or ganglion cell axonal transport, result in optic neurotoxicity.53 They lead to vascular dysregulation and potentially vasospasm in retinal and optic nerve vasculature. Fluid retention, such as intracellular fluid accumulation and subclinical extracellular fluid leakage in the retina, results in Müller cell toxicity.54 Stromal fibrosis results in canalicular and nasolacrimal duct obstruction in chemotherapy.

Combination therapy provided additional anti-tumor therapeutic benefits in patients. PD-1 plus CTLA-4 inhibitors or ICI plus chemotherapy would act synergistically. CTLA-4 inhibitors regulate T-cell activation in lymph nodes/tissues and suppress DC activity via Treg cells. PD-1 inhibitors inhibit the effector T-cell and NK cell activation in peripheral tissues and indut Treg cell

| Table 1 (Continued). | Study type | Primary | Treatment | Histology | Response rate | TrAE treatment-related adverse event |
|-----------------------|-----------|---------|-----------|-----------|---------------|-------------------------------------|
| Mateos18              | RCT III   | Multiple Myeloma | Pembrolizumab + chemotherapy | myeloma | 7/278 | 0  |
| Usmani19              | RCT II    | Multiple Myeloma | Pembrolizumab + chemotherapy | Myeloma | 1/278 | 0  |
| Langer10             | RCT III   | Multiple-Myeloma | Pembrolizumab + chemotherapy | myeloma | 1/278 | 0  |
| Anti-PD-1 vs Anti-CTLA-4 | RCT III   | NSCLC     | Pembrolizumab + chemotherapy | NSCLC | 1/278 | 0  |
| Robert28             | RCT III   | Advanced melanoma | Pembrolizumab + chemotherapy | melanoma | 1/278 | 0  |

RCT, randomized controlled trial; MM, multiple myeloma; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ORR, overall response rate; TrAE, treatment-related adverse event; irAE, immune-related adverse event; T-cell, T-lymphocyte; PD-1/PD-L1, programmed-death receptor-1 programmed-death receptor ligand-1; ICI, immune-checkpoint inhibitor.
differentiation. But, because of the combination of anti-tumor drugs, it is difficult to identify a specific agent accounting for the following ophthalmic AEs. Multiple and simultaneous factors that can lead to changes in ocular function and structure are coexisting. Unfortunately, Combination therapy had a higher risk of all-grade ophthalmic trAEs/irAEs compared with PD-1 or CTLA-4 inhibitors or chemotherapy alone. Those are inevitable results that multiagent treatments may lead to unpredictable AEs or overlapping toxicities.

Furthermore, in several RCTs of combination therapy, the majority of ICI-related ophthalmic irAEs were grade 3–4. ‘Multi-hit’ mechanism may offer some explanation to the high-grade irAEs in combination therapy. Clinically, checkpoint inhibitors result in the exacerbation of preexisting autoimmune disease. Patients with server ophthalmic irAEs (grade 3–4) may need treatment with systemic corticosteroids and interruptions or discontinuation of ICIs. Mild ophthalmic irAEs (grade 1–2) were generally manageable, can be treated

Table 2. Incidence of ophthalmic adverse events in different Icl.

| Drugs                   | trAEs(G1-4) | trAEs(G3-4) | irAEs(G1-4) | irAEs(G3-4) | NS-trAEs(G1-4) | NS-trAEs(G3-4) |
|-------------------------|-------------|-------------|-------------|-------------|----------------|----------------|
| Chemotherapy            | 2.70[1.78;4.07] | 0.55 [0.29;1.01] | 0.86 [0.54;1.36] | 0.54[0.30;1.00] | 3.20[2.05;4.96] | 0.47[0.25;0.88] |
| PD-L1                   | 0.87[0.47;1.61] | 0.29[0.10;0.82] | 0.30[0.07;1.18] | 0.30[0.07;1.18] | 0.80[0.40;1.59] | 0.21[0.05;0.83] |
| PD-1                    | 1.29[0.68;2.39] | 0.40[0.22;0.71] | 1.25[0.81;1.94] | 0.33[0.18;0.60] | 0.65[0.32;1.35] | 0.37[0.15;0.89] |
| CTLA4                   | 1.43[0.68;3.02] | 0.59[0.32;1.08] | 0.92[0.37;2.25] | 0.53[0.26;1.06] | 1.89[0.37;9.13] | 0.40[0.12;1.37] |
| PD-1+ CTLA4             | 4.98[1.25;17.86] | 0.82[0.31;2.18] | 4.98[1.25;17.86] | 0.82[0.31;2.18] | NA              | NA              |
| Atezolizumab            | 1.08[0.54;2.15] | 0.21[0.04;1.04] | 0.16[0.02;1.16] | 0.16[0.02;1.16] | 0.94[0.45;1.96] | 0.17[0.02;1.19] |
| Avelumab                | 0.37[0.09;1.46] | 0.37[0.09;1.46] | 0.53[0.08;3.70] | 0.53[0.08;3.70] | 0.25[0.04;1.78] | 0.25[0.04;1.78] |
| Nivolumab               | 0.53[0.26;1.14] | 0.35[0.14;0.87] | 0.35[0.13;0.92] | 0.35[0.12;0.93] | 0.55[0.19;1.55] | 0.29[0.07;1.17] |
| Pembrolizumab           | 2.14[1.08;4.19] | 0.52[0.22;1.19] | 1.76[1.20;5.58] | 0.33[0.13;0.83] | 0.86[0.05;13.34] | 0.44[0.14;1.34] |
| Ipilimumab              | 1.31[0.68;2.52] | 0.69[0.37;1.30] | 1.10[0.45;2.67] | 0.58[0.28;1.18] | 0.76[0.25;2.34] | 0.76[0.25;2.34] |

PD-1: programmed cell death protein 1; PD-L1: programmed cell death protein ligand 1; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; trAE: treatment-related adverse event irAE: immune-related adverse events NS-trAE: nonspecific ophthalmic treatment-related adverse event; I: incidence; 95%CI: 95% confidence interval; NA: not applicable.
with topical steroid. Dow ER et al. found 83.6% of ICI-related uveitis were diagnosed within six months. With the appropriate treatments, the majority of patients recovered within one line of baseline vision. Given the ophthalmic tRAEs in ICIs therapy, a baseline ophthalmologic examination was recommended before treatment.
Limitations

As such type of meta-analysis, our study had several limitations. First, owing to a rare incidence, we could only acquire limited data on some ophthalmic toxicity associated with ICIs. Second, we could not verify each case accurately because some ophthalmic AEs were subjective for patients and clinicians to judge. Third, our study was based on available RCTs and had no detailed data of the individual patient.
Conclusions

Our meta-analysis demonstrated that compared with chemotherapy, PD-L1/PD-1 inhibitors had lower risks of all-grade ophthalmic trAEs and NS-trAEs; None of the ICIs had a higher risk of ophthalmic irAEs. Compared with monotherapy, combination therapy (PD-1 plus CTLA-4 inhibitors vs. ICI or ICIs plus chemotherapy vs. chemotherapy) had higher risks of all-grade ophthalmic trAEs and irAEs. In the treatment of ICIs, there is a need for close monitoring of the safety profile by both oncologists and ophthalmologists.

Authors’ contributions

Y.L.H. and D.Y.W. have access to all the data included in the study. They are responsible for the completeness of the data and the accuracy of our analysis. Q.S. and H.Y.L. helped to design the study. Q.S., W.W., R.Y.T., and Y.L.H. contributed to the statistical analysis and the revision of this manuscript. Q.S. and H.Y.L. approved the final manuscript.

Acknowledgments

The working group wishes to thank Yang-Tian, LU (College Jean-de-Brebeuf, Montreal, Quebec, Canada) for their assistance in the preparation and review of this manuscript.
Funding
This research is supported by the Beijing Natural Science Foundation Program and Scientific Research Key Program of Beijing Municipal Commission of Education [Grant No. KZ202010025047] and the National Natural Science Foundation of China [Grant No. 92046015].

Availability of data and material
Firstly, all of the datasets used in our manuscript are available in the [Pubmed or Embase] repository, [https://www.ncbi.nlm.nih.gov/ Pubmed] and [http://www.embase.com/search] (See Supplementary Table S1: search performed in Pubmed and Embase).

Secondly, the datasets analyzed in our manuscript are available according to our methods part or from the corresponding author on reasonable request.

Declaration of interest
The authors declare no competing interests in preparing this article.

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