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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 We performed a systematic review and meta-analysis to evaluate the risks of ophthalmic adverse events (AEs) associated with immune checkpoint inhibitors (ICIs) in patients with solid tumors.Methods Eligible studies were selected after a comprehensive search of multiple databases including phase II/III randomized controlled trials (RCTs) investigating ICIs in patients with the solid tumor. The data was analyzed by R software.Results After exclusion of ineligible studies, 21 RCTs met our strict inclusion criteria for the meta-analysis, included 11930 patients. Compared with chemotherapy, the odds ratio of all-grade ophthalmic treatment-related adverse events (trAEs) were significantly lower for PD-L1 inhibitors (OR: 0.18; 95% CI: 0.08-0.39; p<0.0001) and PD-1 inhibitors (OR 0.44, 95% CI: 0.23-0.83, p<0.050). The combination therapy of PD-1 plus CTLA-4 inhibitors significantly increased the risks of all-grade ophthalmic trAEs (OR 5.29, 95% CI: 1.59-17.57, p<0.05) and all-grade ophthalmic immune-related AEs (irAEs) (OR: 3.67; 95%CI: 1.08-12.50; p<0.05) compared with PD-1 or CTLA-4 inhibitors monotherapy. The combination therapy of ICIs plus chemotherapy also significantly increased the risks of all-grade ophthalmic trAEs (OR, 3.44; 95%CI, 1.72-6.88; p<0.001) and all-grade ophthalmic irAEs (OR: 3.69; 95%CI: 1.32-10.32; p<0.05) compared with chemotherapy. The risks of high-grade ophthalmic AEs had no difference in any subgroup compared with control.Conclusions Our meta-analysis demonstrated that compared with chemotherapy, PD-L1/PD-1 inhibitors had lower risks of all-grade ophthalmic trAEs and non-specific ophthalmic trAEs (NS-trAEs) but had the same risk of ophthalmic irAEs. Combination therapy of ICIs plus chemotherapy had higher risks of all-grade ophthalmic trAEs and irAEs. Compared with PD-1 or CTLA-4 inhibitors monotherapy, PD-1 plus CTLA-4 inhibitors combination therapy had significantly higher risks of all-grade ophthalmic trAEs and irAEs.

Introduction

Immuno-oncology is a growing field of treatment for quite a few solid tumors in the past decade. Immune checkpoints acted as regulators of the immune system, they protected tumor cells from the immune system’s destruction through the modulation of the immune system activation and the suppression of anti-tumor T-cell responses. Immune checkpoint inhibitors (ICIs), a new kind of

immunologic agents, will alleviate tumor-induced immunosuppression of T-cells and thereby enhance antitumor immunity after bounding 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) [1, 2].

Several ICIs 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[3, 4], then Nivolumab (PD-1 inhibitors), pembrolizumab (PD-1 inhibitors), and atezolizumab, (PD-L1 inhibitors) are approved by Food and Drug Administration (FDA) for treatments in patients with advanced NSCLC. ICIs had demonstrated remarkable improvement and benefits in overall survival (OS) in patients with malignant melanoma (MM) [3-5], non-small-cell lung cancer (NSCLC) [6-9], urothelial carcinoma[10], head-neck squamous cell carcinoma (HNSCC)[11], and malignant mesothelioma[12]. But, it is alarming that ICIs have been associated with several treatment-related adverse events (trAEs) such as immune-related adverse events (irAEs) notedly. IrAEs were considered to be the result of cross-reactive tissue damage, through the activation and the infiltration of T-cells into noncancerous tissues[13, 14], increasing levels of preexisting autoantibodies, inflammatory cytokines, and enhanced complement-mediated inflammation [15].

Ophthalmic irAEs are rare, but they have been reported in less than 1% of patients treated with Ipilimumab [16]. Ophthalmic toxicities can't be ignored as they were visual threatening if not recognized and treated in time with appropriate measures thus affecting the living quality of the patients.

Here, we have performed the meta-analysis of phase II/III RCTs focused on all types of ophthalmic AEs in patients treated with ICIs. To 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. This will be helpful for ophthalmologists and oncologists to recognize potential ophthalmic toxicities better when using ICIs clinically.

Materials And Methods

Our meta analysis was conducted according to the guidelines of the Cochrane Handbook for

Systematic Reviews of Interventions [17], and reported on the basis of the PRISMA Statement [18]. We followed the same method of our study.[19, 20]

2.1 Search strategy

We searched all the RCTs related to solid tumors, PD-1, PD-L1, and CTLA-4 inhibitors from following databases: PubMed, Embase, and https://clinicaltrials.gov. The time range of the intended RCTs was until October 2017. The medical subject heading (MeSH) terms included for searching the relevant studies contained one term means cancer: (neoplasm, carcinoma, cancer, or tumor, etc); one term means ICIs (anti-CTLA-4, anti-PD-1, anti-PD-L1, ipilimumab, tremelimumab, pembrolizumab, nivolumab, durvalumab atezolizumab, or avelumab), and one term means RCTs, We used “and” to connect them. (***Supplementary Table S1***)

2.2 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.

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 which ophthalmic AEs could not be confirmed due to insufficient data; (4) studies whose experimental method was substantially different from other selected RCTs.

2.3 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. Access a study considered to be appropriate for meta-analysis evaluated by using a patient, intervention, comparison, and outcome (PICO) chart [21]. We extracted the following information from the selected studies: year of publication, author's family name, methods of trails, 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. Cases of

disagreement were resolved with third reviewer (**Q.S.**).

2.4 Data analysis

In our study, the risk of bias analysis was performed by using Review Manager 5.3 software (Cochrane Collaboration 2014, Nordic Cochrane Center, and Copenhagen, Denmark). Two reviewers (Y.L.H. and Q.S.) independently assessed 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 [22] were used for the data analysis. was used for meta-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. In addition, the I^2 statistics was applied to assess the heterogeneity among the RCTs. I^2 values of <30%, 30%–59%, 60%–75%, and >75% were classified as low, moderate, substantial, and considerable heterogeneity respectively [23]. We used the random-effects model (REM) described by DerSimonian and Laird [24] 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.

2.5 Quality Assessment

Firstly, our meta-analysis was strictly performed by the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions. **Secondly,** 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. **Thirdly,** we paid much attention to the heterogeneity among the RCTs by using subgroup analysis. In the other hand, the REM was also employed for our meta-analysis to test and verify the statistical results.

Results

3.1 Selection of studies and characteristics

Using the search terminology, we initially identified 3445 studies from our databases searching.

Among those 3445 studies, 21 RCTs met our strict inclusion criteria (***Supplementary Figure S1***). All the 21 included trials were evaluated and compared side effects of ICIs therapies with other controlled treatments (e.g. chemotherapy, placebo, or ICI) in solid tumors representing data from a total of 11930 patients.

Among the studies (**Table 1**), two involved PD-L1 (Atezolizumab: 751 patients) [7, 8]; seven involved PD-1 (Nivolumab: 4 studies [6, 11, 25, 26], 997 patients; Pembrolizumab: 3 studies [9, 10, 27], 1305 patients); four involved CTLA-4 (Tremelimumab: 2 studies [12, 28], 705 patients; Ipilimumab: 2 studies [29, 30] 864 patients); and three studies compared combination therapy of PD-1 plus CTLA-4 inhibitors with ICI monotherapy (835 patients, Nivolumab + Iipilimumab or Pembrolizumab + Ipilimumab) [31-33]. Four studies compared combination therapy of chemotherapy plus ICIs with chemotherapy [4, 34-36]. Additionally, one study compared Pembrolizumab with Iipilimumab [37]. Eight studies had data from malignant melanoma(MM) patients[4, 25-29, 32, 33]; Six from non-small cell lung cancer (NSCLC) patients[6-9, 34, 36]; Other 6 studies from other cancers including small cell lung cancer (SCLC)[31, 35], mesothelioma[12],urothelial cancer[10], prostate cancer[30], and head-neck squamous cell carcinoma[11].

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

3.2 Risk of overall ophthalmic treatment-related adverse events

Across 20 eligible studies, 135 cases of overall ophthalmic trAEs were observed among 7588 ICI-treated patients (**Table 1**). The predicted incidences of overall **all-grade** ophthalmic trAEs were 3.32% for chemotherapy, 4.32% for combination therapy of PD-1 plus CTLA-4, 1.08% for the PD-L1 inhibitor, 1.16% for the PD-1 inhibitor, and 1.2% for the CTLA-4 inhibitor (**Table 2**).

The OR of **all-grade** ophthalmic trAEs in patients with PD-1/PD-L1 inhibitors were 0.44 (95% CI: 0.23-

0.83) and 0.18 (95% CI: 0.08-0.39) respectively, and it was statistically lower than chemotherapy ($p<0.05$). There was no significant difference between CTLA-4 inhibitor and control (chemotherapy or placebo) (OR, 1.28; 95%CI, 0.21-7.84; $p>0.05$). 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 5.29, 95% CI: 1.59-17.57, $p<0.01$,) or chemotherapy (OR, 3.44; 95%CI, 1.72-6.88; $p<0.001$).

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**)

3.3 Risk of immune-related ophthalmic adverse events

Across enrolled 14 studies, 53 cases of irAEs were observed among the 6001 ICI-treated patients (**Table 1**). The predicted incidences of **all-grade** ophthalmic irAEs were 0.8% for chemotherapy, 2.24% for combination therapy of PD-1 plus CTLA-4, 0.16% for the PD-L1 inhibitor, 0.94% for the PD-1 inhibitor, 0.53% 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, 3.67; 95%CI: 1.08-12.50; $p<0.05$), as well as patients with combination therapy (ICI plus chemotherapy) compared with chemotherapy **(**OR, 3.69; 95%CI: 1.32-10.32; $p<0.05$), 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 ($p>0.05$). Meanwhile, the risks of ophthalmic irAEs between PD-1 and CTLA-4 inhibitors were similar ($p>0.05$). (**Figure 3**)

3.4 Risk of non-specific treatment-related ophthalmic adverse events

Across enrolled 10 studies, NS-trAEs were observed among the 3957 ICI-treated patients (**Table 1**). The predicted incidences of ophthalmic NS-trAEs were shown in **Table 2.**

The risks of **all-grade** ophthalmic NS-trAEs inPD-1/ PD-L1inhibitors were significantly lower than chemotherapy (OR: 0.18; 95%CI: 0.04-0.72; $p< 0. 05$ and OR: 0.16; 95%CI: 0.07-0.36; $p<0.001$), but no concern **high-grade**. Meanwhile, the risks between PD-1 and CTLA-4 inhibitors were similar

(p>0.05) (**Figure 4**).

Discussion

Although a previous meta-analysis showed that, generally, ICIs are associated with increased risks of ocular toxicities compared with control [38], our study is the first meta-analysis in our knowledge to compare the incidences and risks of such ophthalmic trAEs and irAEs associated each with different ICI regimen, and the first to include trials with PD-L1 inhibitors and combination therapy. Theoretically, ICIs-related ophthalmic AEs were not fatal, but they might lead to blindness therefore deteriorate the quality of life, and finally affect the compliance of ICI treatment. Compared with standard chemotherapy, patients with PD-1/ PD-L1 inhibitors had a substantially lower risk of **all-grade** ophthalmic trAEs. Although combination therapy of PD-1 plus CTLA-4 inhibitors provided additional antitumor therapeutic benefit, the patients, unfortunately, had a higher risk of **all-grade** ophthalmic trAEs than with PD-1 or CTLA-4 inhibitors alone[31-33]. The combination therapy of ICI plus chemotherapy also provided additional antitumor therapeutic benefit, but a higher risk of **all-grade** ophthalmic trAEs than chemotherapy [4, 35, 36]. It is an inevitable result that multiagent treatments may lead to unpredictable AEs or overlapping toxicities. Given the high risk of ophthalmic trAEs in combination therapy, a baseline ophthalmologic examination was recommended before treatment [39]. Most of the ophthalmic trAEs were mild (grade 1-2) and were generally manageable. In summary, as our other study[40], ICIs demonstrate a clinically meaningful survival benefit, with an improved safety profile than chemotherapy.

The eye is an organ that’s susceptible to immune system disorders. Unlike trAEs, irAEs were the T-lymphocyte mediated process. ICIs may prompt a T-lymphocyte mediated immune attack on other parts of the body not limited to cancer tissues, release excessive inflammatory factors such as interferon-a (IFN-a), tumor necrosis factor (TNF), interleukin-23 (IL-23), and lead to uveitis, dacryoadenitis (dry eye syndrome), scleritis, myositis of extraocular muscles etc[41-44]. The incidence of uveitis ranged from 0.3-6%, and dry eyes ranged from 1.2-24.2% in the previous reports [38]. Thyroid eye disease or Graves’ ophthalmopathy were often observed in patients with ICI’s thyroid toxicity, which was the most common endocrine irAEs of ICIs [45]. IrAEs were not frequently

observed in chemotherapy [46]. Most chemotherapy-induced ophthalmic AEs were caused by stromal fibrosis [47], optic neurotoxicity[48], the breakdown of the retinal blood-ocular barrier[49], toxic effect on Müllercells [50] etc. Until now, the specific mechanism of ophthalmic irAEs induced by ICIs was largely unknown.

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 episcleritis[16, 51]. However, the risk of ophthalmic irAEs was not higher than chemotherapy in patients with PD-1 inhibitor. When ICIs were combined with chemotherapy, the risk increased significantly compared to chemotherapy alone. PD-1 plus CTLA-4 inhibitors combination therapy also had a significantly higher risk of ophthalmic irAEs than ICI monotherapy. Furthermore, the majority of ophthalmic irAEs induced by ICIs were of grade 3-4 in the involved RCTs [8, 26, 27, 29, 30, 32, 33], and patients may need treatment interruptions or discontinuation. ‘Multi-hit’ mechanism may offer some explanation to the high-grade irAEs in combination therapy [52]. Mild ophthalmic irAEs can be treated with topical steroids, whereas severe cases were treated with systemic corticosteroids.

Ophthalmic NS-trAEs were reported in many clinical trials [6-8, 10, 11, 25, 30, 33, 36]. Obviously, these ophthalmic NS-trAEs, which made patients feel uncomfortable in the treatment process, were subjective for patients and even clinicians. As the overall ophthalmic trAEs in our paper, we found that patients treated with PD-1/PD-L1 inhibitors were significantly less likely to experience non-specific ophthalmic symptoms versus chemotherapy. The mechanisms are still unclear for now.

Limitations

As such type of meta-analysis, our study had several limitations. Firstly, owing to rare incidence, we could only acquire limited data on some ophthalmic toxicity associated with ICIs. Secondly, we could not verify each case accurately because some ophthalmic AEs were subjective for patients and clinicians to judge. Thirdly, 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 non-specific ophthalmic trAEs (NS-trAEs), but had same risk of ophthalmic irAEs. Combination therapy of ICIs plus chemotherapy had higher risks of **all-grade** ophthalmic trAEs and irAEs. Compared with PD-1 or CTLA-4 inhibitors monotherapy, PD-1 plus CTLA-4 inhibitors combination therapy had significantly 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 of this new class of drugs by both oncologist and ophthalmologist.

Abbreviations List

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: non-specific 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

PICO: patient, intervention, comparison and outcome

Versus: VS

Chem: cheotherapy

95%CI: 95% confidence interval

FEM: fixed-effects model

REM: random-effects model

NA: not applicable

MeSH: medical subject heading

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

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 1: search performed in Pubmed and Embase).

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

Competing interests:

The authors declare no competing interests in preparing this article.

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Authors' contributions:Y.L.H. and D.Y.W., had access to all the data included in the study and are responsible for the completeness of the data and the accuracy of our analysis. Q.S., and Y.L.W. 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., Y.L.W., and M.N.B. approved the final manuscript.

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References

1. Pardoll DM. **The blockade of immune checkpoints in cancer immunotherapy**. *Nature Reviews Cancer.* 2012; **12**(4):252-264.

2. Sharma P, Wagner K, Wolchok JD, Allison JP. **Novel cancer immunotherapy agents with survival benefit: recent successes and next steps**. *Nature Reviews Cancer.* 2011; **11**(11):805-812.

3. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC *et al.***Improved survival with ipilimumab in patients with metastatic melanoma**. *The New England journal of medicine.* 2010; **363**(8):711-723.

4. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, Lebbe C, Baurain JF, Testori A, Grob JJ *et al*. **Ipilimumab plus dacarbazine for previously untreated metastatic melanoma**. *The New England journal of medicine.* 2011; **364**(26):2517-2526.

5. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, Dummer R, Garbe C, Testori A, Maio M *et al.* **Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation**. *New England Journal of Medicine.* 2011; **364**(26):2507-2516.

6. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E *et al.* **Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer**. *The New England journal of medicine.* 2015; **373**(17):1627-1639.

7. Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, Park K, Smith D, Artal-Cortes A, Lewanski C *et al.* **Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial**. *The Lancet.* 2016; **387**(10030):1837-1846.

8. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gadgeel SM,

Hida T, Kowalski DM, Dols MC *et al*. **Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial**. *The Lancet.* 2017; **389**(10066):255-265.

9. Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, Molina J, Kim J-H, Arvis CD, Ahn M-J *et al*. **Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial**. *The Lancet.* 2016; **387**(10027):1540-1550.

10. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, Vogelzang NJ, Climent MA, Petrylak DP, Choueiri TK *et al.* **Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma**. *The New England journal of medicine.* 2017; **376**(11):1015-1026.

11. Ferris RL, Blumenschein G, Jr., Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C *et al.* **Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck**. *The New England journal of medicine.* 2016; **375**(19):1856-1867.

12. Maio M, Scherpereel A, Calabrò L, Aerts J, Perez SC, Bearz A, Nackaerts K, Fennell DA, Kowalski D, Tsao AS *et al.* **Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial**. *The Lancet Oncology.* 2017; **18**(9):1261-1273.

13. Bosch X, Saiz A, Ramos-Casals M, Group BS. **Monoclonal antibody therapy-associated neurological disorders**. *Nature reviews Neurology.* 2011; **7**(3):165-172.

14. Min L, Vaidya A, Becker C. **Thyroid autoimmunity and ophthalmopathy related**

to melanoma biological therapy. *European journal of endocrinology.* 2011; **164**(2):303-307.

15. Postow MA, Sidlow R, Hellmann MD. **Immune-Related Adverse Events Associated with Immune Checkpoint Blockade**. *The New England journal of medicine.* 2018; **378**(2):158-168.

16. Della Vittoria Scarpati G, Fusciello C, Francesco Perri F, Sabbatino F, Carlomagno C, Pepe S, Ferrone S. **Ipilimumab in the treatment of metastatic melanoma: management of adverse events**. *OncoTargets and Therapy.* 2014:203.

17. **Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 The Cochrane Collaboration, 2011**

18. Moher D, Liberati A, Tetzlaff J, Altman DG. **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement**. *PLoS medicine.* 2009; **6**(7):e1000097.

19. Su Q, Zhang XC, Wang DY, Zhang HR, Zhu C, Hou YL, Liu JL, Gao ZH. **The risk of immune-related endocrine disorders associated with anti-PD-1 inhibitors therapy for solid tumors: A systematic review and meta-analysis**. *International immunopharmacology.* 2018; **59**:328-338.

20. Su Q, Zhang XC, Zhang CG, Hou YL, Yao YX, Cao BW. **Risk of Immune-Related Pancreatitis in Patients with Solid Tumors Treated with Immune Checkpoint Inhibitors: Systematic Assessment with Meta-Analysis**. *Journal of immunology research.* 2018; **2018**:1027323.

21. Huang X, Lin J, Demner-Fushman D. **Evaluation of PICO as a knowledge representation for clinical questions**. *AMIA Annual Symposium proceedings AMIA Symposium. 2006;* 2006:359-363.

22. Viechtbauer W. **Conducting Meta-Analyses in R with the metafor Package**.

Journal of Statistical Software. 2010; **36**(3).

23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. **Measuring inconsistency in meta-analyses**. *BMJ (Clinical research ed).* 2003; **327**(7414):557-560.

24. DerSimonian R, Laird N. **Meta-analysis in clinical trials revisited**. *Contemporary clinical trials.* 2015; **45**(Pt A):139-145.

25. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, Hassel JC, Rutkowski P, McNeil C, Kalinka-Warzocha E *et al*. **Nivolumab in previously untreated melanoma without BRAF mutation**. *The New England journal of medicine.* 2015; **372**(4):320-330.

26. Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, Hoeller C, Khushalani NI, Miller WH, Lao CD *et al*. **Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial**. *The Lancet Oncology.* 2015; **16**(4):375-384.

27. Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, Hodi FS, Schachter J, Pavlick AC, Lewis KD *et al*. **Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial**. *The Lancet Oncology.* 2015; **16**(8):908-918.

28. Ribas A, Kefford R, Marshall MA, Punt CJA, Haanen JB, Marmol M, Garbe C, Gogas H, Schachter J, Linette G *et al.* **Phase III Randomized Clinical Trial Comparing Tremelimumab With Standard-of-Care Chemotherapy in Patients With Advanced Melanoma**. *Journal of Clinical Oncology.* 2013; **31**(5):616-622.

29. Eggermont AMM, Chiarion-Sileni V, Grob J-J, Dummer R, Wolchok JD, Schmidt H, Hamid O, Robert C, Ascierto PA, Richards JM *et al*. **Adjuvant ipilimumab versus**

placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *The Lancet Oncology.* 2015; **16**(5):522-530.

30. Kwon ED, Drake CG, Scher HI, Fizazi K, Bossi A, van den Eertwegh AJM, Krainer M, Houede N, Santos R, Mahammedi H *et al.* **Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial**. *The Lancet Oncology.* 2014; **15**(7):700-712.

31. Antonia SJ, López-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, Jäger D, Pietanza MC, Le DT, de Braud F *et al*. **Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial**. *The Lancet Oncology.* 2016; **17**(7):883-895.

32. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, Lao CD, Wagstaff J, Schadendorf D, Ferrucci PF *et al*. **Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma**. *The New England journal of medicine.* 2017; **377**(14):1345-1356.

33. Hodi FS, Chesney J, Pavlick AC, Robert C, Grossmann KF, McDermott DF, Linette GP, Meyer N, Giguere JK, Agarwala SS *et al*. **Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial**. *The Lancet Oncology.* 2016; **17**(11):1558-1568.

34. Ramaswamy Govindan, Aleksandra Szczesna, Myung-Ju Ahn, Claus-Peter Schneider, Pablo Fernando Gonzalez Mella, Fabrice Barlesi, Baohui Han, Doina Elena Ganea, Joachim Von Pawel, Vladimir Vladimirov *et al*. **Phase III Trial of Ipilimumab**

Combined With Paclitaxel and Carboplatin in Advanced Squamous Non–Small-Cell Lung Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2017; **35**(30):3449-3457.

35. Reck M, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, Sebastian M, Lu H, Cuillerot JM, Lynch TJ. **Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial**. *Annals of oncology : official journal of the European Society for Medical Oncology.* 2013; **24**(1):75-83.
36. Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Jalal SI *et al*. **Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study**. *The Lancet Oncology.* 2016; **17**(11):1497-1508.
37. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M *et al*. **Pembrolizumab versus Ipilimumab in Advanced Melanoma**. *The New England journal of medicine.* 2015; **372**(26):2521-2532.
38. Abdel-Rahman O, Oweira H, Petrausch U, Helbling D, Schmidt J, Mannhart M, Mehrabi A, Schob O, Giryes A. **Immune-related ocular toxicities in solid tumor patients treated with immune checkpoint inhibitors: a systematic review**. *Expert Rev Anticancer Ther.* 2017; **17**(4):387-394.
39. Agustoni F, Platania M, Vitali M, Zilembo N, Haspinger E, Sinno V, Gallucci R, de Braud F, Garassino MC. **Emerging toxicities in the treatment of non-small cell lung cancer: ocular disorders**. *Cancer treatment reviews.* 2014; **40**(1):197-203.
40. Su Q, Sun Z, Zhang C, Hou Y, Cao B. **PD-1/PD-L1 antibodies efficacy and safety**

versus docetaxel monotherapy in advanced NSCLC patients after first-line treatment option: systems assessment. *Oncotarget.* 2017; **8**(35):59677-59689.

41. Coutzac C, Adam J, Soularue E, Collins M, Racine A, Mussini C, Boselli L, Kamsukom N, Mateus C, Charrier M *et al.* **Colon Immune-Related Adverse Events: Anti-CTLA-4 and Anti-PD-1 Blockade Induce Distinct Immunopathological Entities**. *Journal of Crohn's & colitis.* 2017; **11**(10):1238-1246.

42. Fleischer V, Sieber J, Fleischer SJ, Shock A, Heine G, Daridon C, Dorner T. **Epratuzumab inhibits the production of the proinflammatory cytokines IL-6 and TNF-alpha, but not the regulatory cytokine IL-10, by B cells from healthy donors and SLE patients**. *Arthritis research & therapy.* 2015; **17**:185.

43. Gaffen SL, Jain R, Garg AV, Cua DJ. **The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing**. *Nature reviews Immunology.* 2014; **14**(9):585-600.

44. Lubberts E. **The IL-23-IL-17 axis in inflammatory arthritis**. *Nature reviews Rheumatology.* 2015; **11**(7):415-429.

45. Ryder M, Callahan M, Postow MA, Wolchok J, Fagin JA. **Endocrine-related adverse events following ipilimumab in patients with advanced melanoma: a comprehensive retrospective review from a single institution**. *Endocrine-related cancer.* 2014; **21**(2):371-381.

46. Weber JS, Kahler KC, Hauschild A. **Management of immune-related adverse events and kinetics of response with ipilimumab**. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2012; **30**(21):2691-2697.

47. Esmaeli B, Hidaji L, Adinin RB, Faustina M, Coats C, Arbuckle R, Rivera E, Valero V, Tu SM, Ahmadi MA. **Blockage of the lacrimal drainage apparatus as a side effect of docetaxel therapy**. *Cancer.* 2003; **98**(3):504-507.

48. Capri G, Munzone E, Tarenzi E, Fulfaro F, Gianni L, Caraceni A, Martini C, Scaioli V. **Optic nerve disturbances: a new form of paclitaxel neurotoxicity**. *Journal of the National Cancer Institute.* 1994; **86**(14):1099-1101.

49. Georgakopoulos CD, Makri OE, Vasilakis P, Exarchou A. **Angiographically silent cystoid macular oedema secondary to paclitaxel therapy**. *Clinical & experimental optometry.* 2012; **95**(2):233-236.

50. Joshi MM, Garretson BR. **Paclitaxel maculopathy**. *Archives of ophthalmology (Chicago, Ill : 1960).* 2007; **125**(5):709-710.

51. Robinson MR, Chan CC, Yang JC, Rubin BI, Gracia GJ, Sen HN, Csaky KG, Rosenberg SA. **Cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma: a new cause of uveitis**. *Journal of immunotherapy (Hagerstown, Md : 1997).* 2004; **27**(6):478-479.

52. van Gaalen F, Ioan-Facsinay A, Huizinga TW, Toes RE. **The devil in the details: the emerging role of anticitrulline autoimmunity in rheumatoid arthritis**. *Journal of immunology (Baltimore, Md : 1950).* 2005; **175**(9):5575-5580.

Tables

Table 1: Characteristics of the eligible RCTs included in the meta-analysis.

Study[year]	Study Type	Histology	Primary Endpoint	Treatment Regimen	Patients (n)	(al
Anti-PD-L1 vs chemotherapy						
Rittmeyer[2017]	RCT III	NSCLC	OS	atezolizumab	609	
				chemotherapy	578	
Fehrenbacher[2016]	RCT II	NSCLC	OS	atezolizumab	142	
				chemotherapy	135	
Anti-PD-1 vs chemotherapy						
Ferris[2016]	RCT III	carcinoma of head & neck	OS	nivolumab	236	
				chemotherapy	111	
Weber[2015]	RCT III	melanoma	OS, ORR	nivolumab	268	
				chemotherapy	102	
Robert1[2015]	RCT III	melanoma	OS	nivolumab	206	

				chemotherapy	205
Borghaei[2015]	RCT III	NSCLC	OS	nivolumab	287
				chemotherapy	268
Bellmunt[2017]	RCT III	urothelial carcinoma	OS, PFS	pembrolizumab	266
				chemotherapy	255
Herbst[2016]	RCT II/III	NSCLC	OS, PFS	pembrolizumab2mg/kg	339
				pembrolizumab10mg/kg	343
				chemotherapy	309
Ribas[2015]	RCT II	melanoma	PFS, OS	pembrolizumab 2mg/kg	178
				pembrolizumab 10mg/kg	179
				chemotherapy	171
Anti-CTLA-4 vs chemotherapy or placebo					
Maio[2017]	RCT II	mesothelioma	OS	tremelimumab	380
				placebo	189
Eggermont[2015]	RCT III	melanoma	RFS	ipilimumab	471
				placebo	474
Kwon[2014]	RCT III	prostate cancer	OS	ipilimumab	393
				placebo	396
Ribas[2013]	RCT III	melanoma	OS	tremelimumab	325
				chemotherapy	319
Anti-PD-1+Anti-CTLA-4 vs Anti-PD-1 or Anti-CTLA-4					
Hodi[2016]	RCT II	melanoma	ORR	nivolumab+ipilimumab	94
				ipilimumab	46
Antonia[2016]	RCT I/II	SCLC	ORR	nivolumab1mg/kg+ipilimumab3mg/kg	61
				nivolumab3mg/kg+ipilimumab1mg/kg	54
				nivolumab	98
Wolchok[2017]	RCT III	melanoma	PFS, OS	nivolumab+ipilimumab	313
				nivolumab	313
				ipilimumab	311
Anti-CTLA-4 or Anti-PD-1+chemotherapy vs chemotherapy					
Govindan[2017]	RCT III	NSCLC	OS	ipilimumab+chemotherapy	475
				chemotherapy	473
Reck[2013]	RCT II	SCLC	PFS	ipilimumab+chemotherapy	84
				chemotherapy	44
Robert[2011]	RCT III	melanoma	OS	ipilimumab+chemotherapy	247

				chemotherapy	251
Langer[2016]	RCT II	NSCLC	ORR	pembrolizumab+chemotherapy	59
				chemotherapy	62
Anti-PD-1 vs Anti-CTLA-4					
Robert[2015]	RCT III	advanced melanoma	PFS,OS	pembrolizumab 10mg/kg q2w	278
				pembrolizumab 10mg/kg q3w	277
				ipilimumab 3mg/kg q3w	256

RCT: randomized controlled trial; MM: melanoma; HNSCC: head-neck squamous cell carcinoma; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; OS: overall survival; PFS: progression-free survival; ORR: objective response rate; trAE: treatment-related adverse event irAE: immune-related adverse events NS-trAE: non-specific ophthalmic treatment-related adverse event

Table 2: Incidence of ophthalmic adverse events

Drugs	trAEs(G1-4) I,95%CI(%)	trAEs(G3-4) I,95%CI(%)	irAEs(G1-4) I,95%CI(%)	irAEs(G3-4) I,95%CI(%)
Chemotherapy	3.32[1.81;6.03]	0.56[0.30;1.03]	0.80[0.22;2.83]	0.41[0.17;0.99]
PD-L1	1.08[0.54;2.15]	0.21[0.04;1.04]	0.16[0.02;1.16]	0.16[0.02;1.16]
PD-1	1.16[0.54;2.46]	0.39[0.21;0.72]	0.94[0.61;1.46]	0.32[0.14;0.71]
CTLA4	1.2[0.55;2.61]	0.59[0.32;1.08]	0.53[0.26;1.05]	0.53[0.26;1.05]
PD-1+CTLA4	4.32[1.07;5.87]	0.78[0.29;2.07]	2.24[0.56;8.52]	0.78[0.29;2.07]
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]
Nivolumab	0.55[0.26;1.14]	0.36[0.15;0.87]	0.35[0.11;1.07]	0.35[0.11;1.07]
Pembrolizumab	2.39[0.96;5.86]	0.42[0.18;0.98]	1.12[0.70;1.80]	0.25[0.06;0.98]
Ipilimumab	1.12[0.67;1.86]	0.69[0.37;1.30]	0.58[0.28;1.18]	0.58[0.28;1.18]

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: non-specific ophthalmic treatment-related adverse event; I: incidence; 95%CI: 95% confidence interval; NA: not applicable

Supplementary Materials

Supplementary file (including Supplementary TableS1-S2 and Supplementary Figure S1-S2)

Figures

Figure 1

Quality assessment of included studies (risk of bias) (A): Bar chart comparing the percentage risk of bias for each included RCT. Low risk of bias (Green), high risk of bias (Red), and unclear risk of bias (Yellow). (B): Risk of bias for each included RCT, representing a low risk of bias (+), high risk of bias (-), and unclear risk of bias (?).

Anti-PD-1 vs CHEM(G1-4)

Ferris(2016)	2	236	7	111	0.13	[0.03; 0.62]
Weber(2015)	1	268	0	102	1.15	[0.05; 28.45]
Robert(2015)	0	206	4	205	0.11	[0.01; 2.03]
Borghaei(2015)	2	287	14	268	0.13	[0.03; 0.57]
Bellmunt(2017)	20	266	17	255	1.14	[0.58; 2.23]
Herbst1(2015)	4	339	9	309	0.40	[0.12; 1.31]
Herbst2(2015)	7	343	9	309	0.69	[0.26; 1.89]
Ribas1(2015)	1	178	3	171	0.32	[0.03; 3.07]
Ribas2(2015)	2	179	3	171	0.63	[0.10; 3.83]
Random effects model		**2302**		**1901**	**0.44**	**[0.23; 0.83]**

Heterogeneity: I^2 = 42%, τ^2 = 0.3599, p = 0.09

Anti-PD-1 vs CHEM(G3-4)

Ferris(2016)	1	236	1	111	0.47	[0.03; 7.55]
Weber(2015)	1	268	0	102	1.15	[0.05; 28.45]
Robert(2015)	0	206	4	205	0.11	[0.01; 2.03]
Borghaei(2015)	1	287	0	268	2.81	[0.11; 69.31]
Bellmunt(2017)	2	266	0	255	4.83	[0.23; 101.09]
Herbst1(2015)	0	339	0	309		
Herbst2(2015)	0	343	0	309		
Ribas1(2015)	1	178	0	171	2.90	[0.12; 71.64]
Ribas2(2015)	1	179	0	171	2.88	[0.12; 71.24]
Random effects model		**2302**		**1901**	**1.20**	**[0.38; 3.82]**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.58

Anti-CTLA4 vs CHEM(G1-4)

Maio(2017)	0	380	1	189	0.17	[0.01; 4.07]
Eggermont(2015)	4	471	0	474	9.13	[0.49; 170.14]
Kwon(2014)	4	393	11	396	0.36	[0.11; 1.14]
Robias(2013)	13	325	3	319	4.39	[1.24; 15.55]
Random effects model		**1569**		**1378**	**1.28**	**[0.21; 7.84]**

Heterogeneity: I^2 = 74%, τ^2 = 2.3062, p < 0.01

Anti-CTLA4 vs CHEM(G3-4)

Maio(2017)	0	380	1	189	0.17	[0.01; 4.07]
Eggermont(2015)	4	471	0	474	9.13	[0.49; 170.14]
Kwon(2014)	3	393	7	396	0.43	[0.11; 1.67]
Robias(2013)	0	325	0	319		
Random effects model		**1569**		**1378**	**0.78**	**[0.10; 6.34]**

Heterogeneity: I^2 = 55%, τ^2 = 1.9074, p = 0.11

Anti-PD-1+Anti-CTLA4 vs Anti-PD-1 or Anti-CTLA4(G1-4)

Hodi(2016)	12	94	0	46	14.09	[0.82; 243.47]
Antonia1(2016)	2	61	0	98	8.28	[0.39; 175.37]
Antonia2(2016)	5	54	0	98	21.89	[1.19; 403.88]
Wolchok1(2017)	2	313	1	311	1.99	[0.18; 22.10]
Wolchok2(2017)	2	313	1	313	2.01	[0.18; 22.24]
Random effects model		**835**		**866**	**5.29**	**[1.59; 17.57]**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.58

Anti-PD-1+Anti-CTLA4 vs Anti-PD-1 or Anti-CTLA4(G3-4)

Hodi(2016)	1	94	0	46	1.49	[0.06; 37.34]
Antonia1(2016)	1	61	0	98	4.88	[0.20; 121.83]
Antonia2(2016)	0	54	0	98		
Wolchok1(2017)	2	313	1	311	1.99	[0.18; 22.10]
Wolchok2(2017)	2	313	1	313	2.01	[0.18; 22.24]
Random effects model		**835**		**866**	**2.23**	**[0.57; 8.70]**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.96

Anti-PD-1 or Anti-CTLA4+CHEM vs CHEM(G1-4)

Figure 2

Risk of overall ophthalmic trAEs during the treatment with different ICI regimens trAEs: treatment-related adverse events; ICI: immune checkpoint inhibitors; CHEM: chemotherapy; G: grade.

Figure 3

Risk of ophthalmic irAEs during the treatment with different ICI regimens. irAEs: immune-related adverse events; ICI: Immune checkpoint inhibitors; CHEM: chemotherapy; G: grade.

Study	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%−CI
Anti-PD-L1 vs CHEM(G1-4)						
Rittmeyer(2017)	6	609	33	578	0.16	[0.07; 0.40]
Fehrenbacher(2016)	1	142	7	135	0.13	[0.02; 1.07]
Random effects model		751		713	0.16	[0.07; 0.36]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.84$						
Anti-PD-L1 vs CHEM(G3-4)						
Rittmeyer(2017)	0	609	0	578		
Fehrenbacher(2016)	0	142	0	135		
Random effects model		751		713		
Heterogeneity: not applicable						
Anti-PD-1 vs CHEM(G1-4)						
Ferris(2016)	2	236	7	111	0.13	[0.03; 0.62]
Borghaei(2015)	1	287	14	268	0.06	[0.01; 0.49]
Herbst1(2015)	0	339	8	309	0.05	[0.00; 0.91]
Herbst2(2015)	1	343	8	309	0.11	[0.01; 0.88]
Bellmunt(2017)	20	266	17	255	1.14	[0.58; 2.23]
Robert(2015)	0	206	2	205	0.20	[0.01; 4.13]
Random effects model		1677		1457	0.18	[0.04; 0.72]
Heterogeneity: $I^2 = 73\%$, $\tau^2 = 2.0310$, $p < 0.01$						
Anti-PD-1 vs CHEM(G3-4)						
Ferris(2016)	1	236	1	111	0.47	[0.03; 7.55]
Borghaei(2015)	0	287	0	268		
Herbst1(2015)	0	339	0	309		
Herbst2(2015)	0	343	0	309		
Bellmunt(2017)	2	266	0	255	4.83	[0.23;101.09]
Robert(2015)	0	206	2	205	0.20	[0.01; 4.13]
Random effects model		1677		1457	0.74	[0.12; 4.63]
Heterogeneity: $I^2 = 13\%$, $\tau^2 = 0.3462$, $p = 0.32$						
Anti-CTLA4 vs CHEM(G1-4)						
Robias(2013)	13	325	3	319	4.39	[1.24; 15.55]
Kwon(2014)	2	393	5	396	0.40	[0.08; 2.07]
Random effects model		718		715	1.41	[0.13; 14.69]
Heterogeneity: $I^2 = 80\%$, $\tau^2 = 2.3113$, $p = 0.02$						
Anti-CTLA4 vs CHEM(G3-4)						
Robias(2013)	0	325	0	319		
Kwon(2014)	1	393	2	396	0.50	[0.05; 5.56]
Random effects model		718		715	0.50	[0.05; 5.56]
Heterogeneity: not applicable						
Anti-PD-1 vs Anti-CTL-A4(G1-4)						
Robert1(2015)	3	256	1	278	3.28	[0.34; 31.78]
Robert2(2015)	3	256	3	277	1.08	[0.22; 5.41]
Random effects model		512		555	1.57	[0.42; 5.83]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.43$						
Anti-PD-1 vs Anti-CTL-A4(G1-4)						
Robert1(2015)	0	256	0	278		
Robert2(2015)	0	256	0	277		
Random effects model		512		555		
Heterogeneity: not applicable						

Figure 4

Risk of developing non-specific ophthalmic trAEs during the treatment with different ICI regimens. treatment-related adverse events; ICI: immune checkpoint inhibitors; CHEM: chemotherapy; G: grade.

Supplementary Files

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