Treatment-related adverse events of PD-1/PD-L1 inhibitors combined with CTLA-4 inhibitors in clinical trials: a meta-analysis

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Aim: PD-1/PD-L1 inhibitors in combination with CTLA-4 inhibitors are being tested in a number of ongoing clinical trials. As a result, it is critical to fully comprehend the toxicity characteristics of adverse events in combination therapy. This study aims to extensively compare the incidences and ORs of treatment-related adverse events between two combination strategies.

Methods: The eligible articles were searched from PubMed, EMBASE and Cochrane databases for studies published between 1 January 2010 and 1 May 2021, investigating PD-1/PD-L1 inhibitors plus CTLA-4 inhibitor-based combined clinical therapies. The mean incidences and pooled ORs of all-grade and grade 3 or higher adverse events were calculated by random-effects model using Stata 12.1. Heterogeneity between studies was assessed with I² statistics and Chi square-based Q statistic. The overall risk of bias was assessed by Review Manager 5.3.

Results: A total of 26 eligible studies of 3607 patients were selected; 2852 patients developed at least one all-grade adverse event. PD-L1 inhibitors plus CTLA-4 inhibitors regimen (incidence 0.67, 95% CI: 0.57–0.77) had marked advantage over PD-1 inhibitors plus CTLA-4 inhibitors regimen (incidence 0.89, 95% CI: 0.86–0.93).

Conclusion: PD-L1 inhibitors plus CTLA-4 inhibitors shows better safety in treatment-related adverse events than PD-1 inhibitors plus CTLA-4 inhibitors.

1. Introduction

Since first PD-1 immune checkpoint inhibitor pembrolizumab was approved in 2014, immune checkpoint blockade treatment has developed rapidly, mainly involving anti-CTLA-4 treatment, anti-PD-1 and anti-PD-L1 checkpoint blockade treatment [1]. Previous studies has indicated satisfying performance of immune checkpoint inhibitors (ICI) in various metastatic tumour, and thereby they have been applied widely in clinical practice. Mono-checkpoint blockade exerts modest effect on tumour while ICI combination therapy shows better efficacy, suggesting that the further studies focussed on ICI combination therapies is necessary [2]. Compared with conventional therapies, randomized clinical trials that applies combination strategies shows longer overall survival (OS) and progressive-free survival (PFS), leading to the approval of CTLA-4 inhibitors plus PD-1/PD-L1 inhibitors for the treatment of advanced melanoma, renal cell carcinoma, colorectal cancer and so on [3–5]. PD-1 inhibitors plus CTLA-4 inhibitors (APC) in combination: Nivolumab (PD-1 inhibitor) plus ipilimumab (CTLA-4 inhibitor) are the first APC therapy granted FDA approval [6]. Nivolumab plus ipilimumab has been studied in melanoma [7], NSCLC [8], sarcoma [9], etc. Pembrolizumab plus ipilimumab has been tested in melanoma [10] and NSCLC [11] with better response rate and improved overall survival. Pembrolizumab (PD-1 inhibitor) plus quavonlimab (CTLA-4 inhibitor) is mainly tested in NSCLC [12] and has shown better ORR and duration response than pembrolizumab alone. PD-L1 inhibitors plus CTLA-4 inhibitors (APLCL in combination: Durvalumab (PD-L1 inhibitor) plus tremelimunab (CTLA-4 inhibitor) are the most prevalent PD-L1 inhibitors plus CTLA-4 inhibitors combination therapy in clinical trials. Durvalumab plus tremelimunab in combination is the most wildly used APLC strategy in current clinical trials and has been mainly studied in NSCLC [13], biliary tract carcinoma [14], pleural or peritoneal mesothelioma [15]. These drugs reactivate T-cell-mediate anti-tumour immunity by blocking the immune checkpoint and their
downstream pathway. The combined use of ICIs has been reported to cause more autoimmune disorders than the use of ICIs alone [16]. Although PD-1 inhibitors or PD-L1 inhibitors is generally well tolerated and widely used in clinical practice, the side-effects of APC and APLC treatments have raised growing concerns about severe or even fatal treatment-related adverse events (AEs) [17–19]. The obvious increase in toxicity and AEs has become important challenge for the development of APC or APLC therapy [20], especially given the growing number of clinical trials testing combination strategies [21]. Hence, it is necessary to systematically analyse the toxicity of APC and APLC strategies, using standardized statistic methods, which may guide the clinicians to better manage potential treatment-related risks and AEs [22].

Here, we investigated ORs and incidence of AEs associated with the two combination therapies, analysing the differences in incidences of treatment-related AEs in this meta-analysis, which may provide a guide to clinicians in choosing a more appropriate ICI combination therapy in clinical practice.

2. Methods

2.1. Search methods and study selection

We identified published clinical trials using APC or APLC therapy through a systematic search. Literature search was conducted in the Web of Science, PubMed and Cochrane database using the terms PD-1 inhibitors plus CTLA-4 inhibitors and PD-L1 inhibitors plus CTLA-4 inhibitors. Eligible included studies were all published in English between 1 January 2010 and 1 May 2021. We also searched references of relevant retrospective studies to supplement the eligible studies. The included studies met all of the following standards: (1) clinical trials of tumour immune checkpoint blockade therapy; (2) published in English; (3) participants were treated with APC or APLC therapy and (4) reported tabulated data on AEs and immune-related AEs (irAEs: all the irAEs are treatment-related). Studies that did not match the selection criteria were excluded. Other exclusion criteria were as follows: (1) studies in which combined therapy employed additional ICI therapy and (2) studies in which the number of participants were less than 6. Z.M. and Y.S.Z. performed the literature search, study selection and data extraction independently. This study followed the Preferred Reporting Items for Meta-analyses (PRISMA) guidelines and registered online (ID: CRD42021256531).

2.2. Data extraction

The study name, publication year, cancer type, number of patients, name of inhibitors used, dose, all-grade AEs/immune-related AEs and grade 3 or higher AEs/immune-related AE data were obtained from the included studies.

2.3. Statistical analysis

All data analysis was calculated with the software Stata 12.1. OR (odds ratio) and incidence were employed to compare the outcomes between the two types of combined therapy. Due to the inherent heterogeneity among the included AEs, we used the random-effects model for the calculation of ORs and 95% confidence intervals. Heterogeneity among the different treatment groups was assessed by the I² statistics and Chi square-based Q statistic. The overall risk of bias was assessed by Review Manager 5.3.

3. Results

3.1. Literature search results and characteristics of the eligible studies

As shown in Figure 1, 5493 records were identified in our systematic search. Twenty-six studies of 3607 patients were
eligible for inclusion and reported the overall incidence of specific treatment-related AEs, including AEs and immune-related AEs. An evaluation of the risk of bias for each study is presented in the supporting information. All studies included could be sorted into two classes: APC (n = 18) therapy and APLC (n = 8) therapy.

The 26 eligible studies reported over 50 types of treatment-related AEs. A total of 2852 of 3592 patients from 26 studies developed at least 1 AE of all-grade (Table 1). For this meta-analysis, we selected treatment-related AEs and irAEs that were both reported by at least 10% of the included studies. The overall risk of bias by quality assessment is summarized in Figure 2 and Supplementary Figure S1, which shows that the study quality of the included studies was good. The characteristics of the included studies are shown in Table 1, and the profile of all-grade AEs shown in Figure 3 shows the incidence of all-grade AEs. Our study analysed the ORs and incidences of AEs and irAEs in APC and APLC therapy.

| Study | Year | Cancer type | Number | Number of 3 or higher AE | Dose | Median overall survival (month) |
|-------|------|-------------|--------|--------------------------|------|--------------------------------|
| D'Angelo et al. [9] | 2018 | Sarcoma | 42 | 42 | NA | niv 3 mg/kg + ipi 1 mg/kg | 14.3 |
| Armand et al. [23] | 2021 | Lymphoma | 65 | 51 | 19 | niv 3 mg/kg + ipi 1 mg/kg | NA |
| Blank et al. [7] | 2018 | Melanoma | 10 | 10 | NA | niv 1 mg/kg + ipi 3 mg/kg | NA |
| Gubens et al. [11] | 2019 | NSCLC | 51 | 35 | NA | pem 2 mg/kg + ipi 1 mg/kg | pem 10.9 |
| Hodi et al. [24] | 2016 | Melanoma | 95 | 86 | 52 | niv 1 mg/kg + ipi 3 mg/kg | NA |
| Larkin et al. [25] | 2015 | Melanoma | 314 | 299 | 215 | niv 1 mg/kg + ipi 3 mg/kg | 11.5 |
| Patel et al. [26] | 2020 | Neuroendocrine neoplasm | 32 | 27 | 16 | niv 240 mg + ipi 1 mg/kg | 11 |
| Perets et al. [12] | 2021 | NSCLC | 173 | 144 | 63 | qua 25 mg + pem 200 mg + qua 75 mg + pem 200 mg + qua 25 mg + pem 200 mg | NA |
| Pollack et al. [10] | 2018 | Melanoma | 80 | 80 | NA | niv 1 mg/kg + ipi 3 mg/kg | pem 2 mg/kg | NA |
| Scherpereel et al. [27] | 2019 | Pleural mesothelioma | 61 | 54 | 16 | niv 3 mg/kg + ipi 1 mg/kg | 15.9 |
| Schoenfeld et al. [28] | 2020 | Oral cavity squamous cell carcinoma | 15 | NA | NA | niv 3 mg/kg + ipi 1 mg/kg | NA |
| Wolchok et al. [29] | 2013 | Melanoma | 53 | 52 | NA | niv 0.3 mg + ipi 3 mg + niv 1 mg + ipi 3 mg | NA |
| Antonia et al. [30] | 2016 | SCLC | 115 | 88 | 28 | niv 1 mg/kg + ipi 3 mg/kg + niv 3 mg/kg | 13.7 |
| Hellmann et al. [8] | 2019 | Melanoma | 576 | 442 | 189 | niv 3 mg/kg + ipi 1 mg/kg | 17.1 |
| Motzer et al. [31] | 2019 | Melanoma | 574 | 514 | 255 | niv 3 mg/kg + ipi 1 mg/kg | NA |
| Tawbi et al. [32] | 2018 | Melanoma | 94 | 91 | 52 | niv 1 mg/kg + ipi 3 mg/kg | NA |
| Janjigian et al. [33] | 2018 | Esophagogastric cancer | 100 | 80 | NA | niv 1 mg/kg + ipi 3 mg/kg | NA |
| Zimmer et al. [34] | 2020 | Melanoma | 55 | 55 | NA | niv 1 mg/kg + ipi 3 mg/kg | NA |
| Antonia et al. [13] | 2016 | NSCLC | 184 | 82 | NA | dur 3 mg/kg + tre 1 mg/kg + dur 10 mg/kg + tre 1 mg/kg | NA |
| Boileve et al. [14] | 2021 | Biliary tract carcinoma | 10 | 7 | NA | dur 1500 mg + tre 1 mg/kg | 16.6 |
| Calabro et al. [15] | 2018 | Pleural or peritoneal mesothelioma | 40 | 30 | NA | dur 20 mg/kg + tre 1 mg/kg | 7.6 |
| Chen et al. [35] | 2020 | Colorectal cancer | 118 | 75 | 75 | dur 1500 mg + tre 75 mg | 6.6 |
| Siu et al. [36] | 2019 | Neck squamous cell carcinoma | 133 | 77 | 21 | dur 20 mg/kg + tre 1 mg/kg | 7.6 |
| Powles et al. [37] | 2020 | Urothelial carcinoma | 342 | 255 | 93 | dur 1500 mg + tre 75 mg | 15.1 |
| Gao et al. [38] | 2020 | Urothelial carcinoma | 28 | 26 | 6 | dur 1500 mg + tre 75 mg | NA |
| Ferris et al. [39] | 2020 | Head and neck squamous cell carcinoma | 247 | 150 | 40 | dur 20 mg/kg + tre 1 mg/kg | 7.8 |

AE: adverse event; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; PD-1 inhibitor: niv: nivolumab; pem: pembrolizumab; PD-L1 inhibitor: dur: durvalumab; CTLA-4 inhibitor: ipi: ipilimumab, tre: tremelimumab, qua: quavonlimab; NA: not available.
Figure 2. Methodological quality assessed by the quality assessment of diagnostic accuracy studies.

Figure 3. Mean incidences of overall all-grade adverse events (anti-PD-1/PD-L1 plus anti-CTLA-4 therapy).
### 3.2. OR of adverse events

The possibility of developing AEs was lower in the APLC group. The ORs of AEs and irAEs were higher in the APC group, which indicated that in that group, the incidence of AEs and irAEs was also higher. As illustrated in Figure 4, we compared the most frequent all-grade AEs in both two treatments (APC and APLC): anorexia (pooled OR 1.55, 95% CI: 1.15–2.08), colitis (pooled OR 6.07, 95% CI: 3.18–11.60), diarrhoea (pooled OR 1.65, 95% CI: 1.37–1.98), fatigue (pooled OR 0.91, 95% CI: 0.76–1.09), hypothyroidism (pooled OR 1.94, 95% CI: 1.45–2.60), increased ALT (pooled OR 1.66, 95% CI: 1.28–2.17), increased AST (pooled OR 1.29, 95% CI: 1.00–1.66), nausea (pooled OR 0.91, 95% CI: 0.72–1.14), pruritus (pooled OR 1.43, 95% CI: 1.17–1.76) and rash (pooled OR 6.48, 95% CI: 4.87–8.62). Some AEs seems more likely to develop to grade 3 or higher (Figure 4). The most common grade 3 or higher AEs were colitis (pooled OR 3.88, 95% CI: 2.01–7.50), diarrhoea (pooled OR 1.38, 95% CI: 0.92–2.06), fatigue (pooled OR 0.80, 95% CI: 0.47–1.35), increased alkaline phosphatase (pooled OR 0.32, 95% CI: 0.16–0.64), increased ALT (pooled OR 4.45, 95% CI: 2.45–8.10), increased AST (pooled OR 2.93, 95% CI: 1.66–5.17), increased lipase (pooled OR 0.66, 95% CI: 0.41–1.06), nausea (pooled OR 3.54, 95% CI: 1.06–11.79) and rash (pooled OR 1.75, 95% CI: 1.01–3.05).

### 3.3. OR of immune-related adverse events

APC and APLC therapies can block immune checkpoints and reactivate cellular immunity, causing irAEs. In this study, we analysed the ORs of all-grade irAEs between these two types of treatments. As shown in Figure 5, the most frequent irAEs of all-grade were anorexia (pooled OR 1.55, 95% CI: 1.15–2.08), colitis (pooled OR 6.07, 95% CI: 3.18–11.60), diarrhoea (pooled OR 1.65, 95% CI: 1.37–1.98), hypothyroidism (pooled OR 1.94, 95% CI: 1.45–2.60), increased alkaline phosphatase (pooled OR 0.32, 95% CI: 0.16–0.64), increased ALT (pooled OR 4.45, 95% CI: 2.45–8.10), increased AST (pooled OR 2.93, 95% CI: 1.66–5.17), increased lipase (pooled OR 0.66, 95% CI: 0.41–1.06), nausea (pooled OR 3.54, 95% CI: 1.06–11.79) and rash (pooled OR 1.75, 95% CI: 1.01–3.05).
(pooled OR 1.66, 95% CI: 1.28–2.17), increased AST (pooled OR 1.29, 95% CI: 1.00–1.66), increased lipase (pooled OR 0.51, 95% CI: 0.36–0.71), pruritus (pooled OR 1.43, 95% CI: 1.17–1.76) and rash (pooled OR 6.48, 95% CI: 4.87–8.62). As shown in Figure 5, the most common grade 3 or higher irAEs were colitis (pooled OR 3.88, 95% CI: 2.01–7.50), diarrhoea (pooled OR 1.38, 95% CI: 0.92–2.06), increased alkaline phosphatase (pooled OR 0.32, 95% CI: 0.16–0.64), increased ALT (pooled OR 4.45, 95% CI: 2.45–8.10), increased AST (pooled OR 2.93, 95% CI: 1.66–5.17) and increased lipase (pooled OR 0.66, 95% CI: 0.41–1.06).

### 3.4. Subgroup analysis

We performed subgroup analysis by the type of inhibitor regimen, investigating the potential for heterogeneity (Figure 6). Subgroup analysis showed that durvalumab plus tremelimumab regimen (incidence 0.67, 95% CI: 0.57–0.77) had a great advantage over the nivolumab plus ipilimumab regimen (incidence 0.91, 95% CI: 0.87–0.95), which was consistent with the overall analysis. Two types of combination regimen were excluded from subgroup analysis for only used in one study.

### 4. Discussion

We included 26 eligible studies in this meta-analysis analysing the incidence and ORs of AEs in APC and APLC therapy. Current clinical trials shows that PD-1/PD-L1 inhibitors are mostly used with chemotherapy, radiotherapy, and immunotherapy in combination. The most frequent combination therapy is anti-CTLA-4 therapy among numerous combination strategies. Longer PFS and OS has been shown in clinical trials using combination therapies but these therapies also result in more severe AEs. Treatment-related AEs are crucial considerations in clinical practice. Early attention of relevant symptoms of AEs can help clinicians alter treatment strategy [40]. Thus, a thorough analysis of APC/APLC-related AEs reported in previous clinical trials is critical, since these findings may be an essential guidance for the clinic. This meta-analysis showed that APC presents higher incidences of AEs/irAEs than APLC [41].

Several results from this meta-analysis are significant for clinical practice. Nearly four of five patients treated with APC or APLC had at least one AE, and one in three patients developed at least one grade 3 or higher AE. These results are critical to inform patients before they begin combination therapy. Diarrhoea was the most common all-grade AE (21.8%), grade 3 or higher AE (3.6%), all-grade irAE (21.8%) and grade 3 or higher irAE (3.6%). We summarized these AEs and irAEs, which can improve clinical vigilance for early intervention. Understanding the common AEs and irAEs is critical for improving clinical awareness which is crucial for effective cancer care.

From the perspective of combined therapy, this meta-analysis is also crucial as a reference for clinical treatment. From the results of this meta-analysis, APC treatment had a higher treatment risk than APLC treatment. In particular, the incidences of irAEs associated with APC treatment were...
almost all higher than those associated with APLC treatment. For all-grade AEs, APC were more likely to cause colitis (pooled OR 6.07, 95% CI: 3.18–11.60) than APLC treatment. To avoid developing severe colitis, clinical monitoring is required for early diagnosis and intervention. T-cell receptor sequence analysis demonstrated that some CD8⁺ T cells, which are closely associated with colitis originated from tissue-resident populations and explained the frequency of colitis symptoms from treatment commencement [42]. For grade 3 or higher AEs, APC was more likely to cause colitis (pooled OR 3.88, 95% CI: 2.01–7.50), increased ALT (pooled OR 4.45, 95% CI: 2.45–8.10), increased AST (pooled OR 2.93, 95% CI: 1.66–5.17), nausea (pooled OR 3.88, 95% CI: 2.01–7.50) and Rash (pooled OR 1.75, 95% CI: 1.01–3.05). For all-grade irAEs, APC might lead to lower incidence of increased alkaline phosphatase (pooled OR 0.07, 95% CI: 0.04–0.12) and increased lipase (pooled OR 0.51, 95% CI: 0.36–0.71). For grade 3 or higher irAEs, APLC was more likely to cause increased alkaline phosphatase but lower incidences of colitis (pooled OR 3.88, 95% CI: 2.01–7.50) and less likely to cause elevation of ALT (pooled OR 4.45, 95% CI: 2.45–8.10) and AST (pooled OR 2.93, 95% CI: 1.66–5.17) than APC therapy, but the mechanism and clinical significance are still unclear.

When compared to current available treatment options for patients with malignant tumours, the higher safety and tolerability results of APLC are clinically meaningful. In previous study, high-grade AEs could develop life-threatening autoimmune disorders, which is closely linked to treatment-related death. Therefore, this meta-analysis may be helpful for decreasing the incidence of AEs and AEs-related death in future clinical practice.

There are several restrictions in this meta-analysis. First, missing data is common in meta-analysis because clinical trials do not always present all of the data that are required in statistic analysis, which is especially true for AEs. Second, each study reported several AEs, and we only included AEs or irAEs that were both reported by at least 10% of the clinical studies. Finally, most of the research were single arm, thus these studies did not apply blinding or randomization. The different types of CTLA-4 inhibitors, PD-1/PD-L1 inhibitors and distinct cancer types also contributed a lot to the heterogeneity [43].

This meta-analysis summarized profiles of the most common AEs and irAEs in APC and APLC therapy. APC therapy was associated with a higher risk of developing AEs/irAEs than APLC therapy. This comprehensive analysis of AEs in

| Study                        | Incidence (95% CI) | % Weight |
|------------------------------|--------------------|----------|
| **Nivolumab + Ipilimumab**   |                    |          |
| Angelo 2018                  | 0.99 (0.96, 1.02)  | 4.77     |
| Armand 2021                  | 0.78 (0.68, 0.88)  | 4.08     |
| Blank 2018                   | 0.99 (0.93, 1.05)  | 4.53     |
| Hodi 2016                    | 0.91 (0.85, 0.97)  | 4.57     |
| Larkin 2015                  | 0.95 (0.93, 0.97)  | 4.80     |
| Patel 2020                   | 0.84 (0.71, 0.97)  | 3.72     |
| Pollack 2018                 | 0.99 (0.97, 1.01)  | 4.81     |
| Scherperelle 2019            | 0.88 (0.80, 0.96)  | 4.31     |
| Wolchok 2013                 | 0.98 (0.94, 1.02)  | 4.73     |
| Antonia 2016                 | 0.77 (0.69, 0.85)  | 4.37     |
| Hellmann 2019                | 0.77 (0.74, 0.80)  | 4.75     |
| Motzer 2019                  | 0.90 (0.88, 0.92)  | 4.80     |
| Tawbi 2018                   | 0.97 (0.94, 1.00)  | 4.75     |
| Janjigian 2018               | 0.80 (0.72, 0.88)  | 4.35     |
| Zimmer 2020                  | 0.99 (0.96, 1.02)  | 4.79     |
| **Subgroup, DL (I²= 93.2%, p=0.000)** |    |          |
| **Durvalumab + Tremelimumab**|                    |          |
| Antonia 2016                 | 0.45 (0.38, 0.52)  | 4.42     |
| Boileve 2021                 | 0.70 (0.42, 0.98)  | 1.93     |
| Calabro 2018                 | 0.75 (0.62, 0.88)  | 3.63     |
| Chen 2020                    | 0.64 (0.55, 0.73)  | 4.25     |
| Siv 2019                     | 0.58 (0.50, 0.66)  | 4.29     |
| Powles 2020                  | 0.75 (0.70, 0.80)  | 4.67     |
| Gao 2020                     | 0.93 (0.84, 1.02)  | 4.16     |
| Ferris 2020                  | 0.61 (0.55, 0.67)  | 4.54     |
| **Subgroup, DL (I²= 91.9%, p=0.000)** |    |          |
| **Overall, DL (I²= 96.6%, p=0.000)** |    |          | 0.83 (0.78, 0.88)  | 100.00 |

**Figure 6.** Mean incidences of overall all-grade adverse events by combination types.
APC and APLC therapy may be useful as a clinical reference for future applications.

**Author contributions**
Ze Mi: study design, data extraction, literature search, study selection, manuscript writing, revision of manuscript; Yunsu Zhang: literature search, study selection, data extraction, data analysis, draw figure, manuscript writing, revision of manuscript; Pengfei Rong: study design, manuscript writing, revision of manuscript; Zhenguof Liu: manuscript writing, revision of manuscript, statistic analysis for heterogeneity and bias; Zhichao Feng and Jiahao Liu: data analysis, manuscript writing, revision of manuscript; Jianmin Wu, Hongpei Tan and Xiaqian Ma: data analysis, manuscript writing, revision of manuscript.

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**Data availability statement**
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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