Adverse Events Induced by Nivolumab Plus Ipilimumab vs. Nivolumab Monotherapy among Cancer Patients: A Systematic Review and Meta-Analysis

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ABSTRACT

A systematic review and meta-analysis of randomized controlled trials (RCTs) were performed to examine treatment-related adverse events (TRAEs) for combination of nivolumab (NIVO) and ipilimumab (IPI) compared to NIVO monotherapy among cancer patients. We searched several databases to identify relevant RCTs. Meta-analysis was performed using random-effects model. In fourteen RCTs included in the study, we found that compared to NIVO monotherapy, combination NIVO + IPI increased the risk of any grade (Risk Ratio (RR) = 1.11), and grade 3 or 4 (RR = 1.95) TRAEs. Compared to NIVO, NIVO + IPI had higher risk for any grade colitis (RR = 4.52), pneumonitis (RR = 3.06), and diarrhea (RR = 1.68).

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1. Introduction

Immunotherapy has revolutionized the treatment paradigm by providing long-term clinical benefits to patients with various cancer types (1). Immune checkpoint inhibitors (ICIs) are a type of immunotherapy drugs that increase antitumor activity by blocking either cytotoxic T-lymphocyte antigen 4 (CTLA4) or programmed cell death 1 (PD1) or ligand (PD-L1). Among these regimens, nivolumab (NIVO), a PD1 inhibitor, is approved by the US Food and Drug Administration either as monotherapy or in combination with the CTLA4 inhibitor, ipilimumab (IPI). Combination of NIVO and IPI has been approved for indications including advanced melanoma, advanced lung cancer, metastatic melanoma, advanced renal cell carcinoma, head and neck squamous cell carcinoma, hepatocellular carcinoma, metastatic and recurrent non-small cell lung cancer (NSCLC), urothelial carcinoma, colorectal carcinoma, and unresectable malignant pleural mesothelioma. Despite the clinical efficacy, ICIs are associated with a spectrum of adverse events varied in terms of tissues affected, time of onset relative to the initiation of treatment, and the severity. Some of the adverse events, such as pneumonitis, colitis, and hepatitis are potentially fatal, thereby limiting their use in many patients (2).

With the advent of ICIs, identification of which patients would be most likely to benefit from treatment has been a challenge. Several biomarkers have been described, including PD-L1, tumor mutational burden (TMB), and microsatellite instability (MSI) status (3). Unfortunately, any of the identified biomarkers alone are typically inadequate for patient selection and not sensitive enough to predict all patients who will respond to treatment (4). Interestingly, there is some evidence that low expression of PD-L1 may predict benefit to the addition of IPI with the PD-1 inhibitor, NIVO (5). When administered as monotherapy, ICIs demonstrate a manageable safety profile, but about 12–45% of patients respond to the treatment (6,7). There has been interest in combination ICIs to increase response
rates. In clinical trials, the combination of NIVO and IPI proved to be clinically beneficial and even had higher response rates as compared to NIVO monotherapy (5,6,8–10). The CheckMate 067 trial randomized 945 patients with metastatic melanoma to receive NIVO, combination of NIVO and IPI, or IPI. In this trial, the combination treatment arm showed a longer median progression-free survival (PFS) of 11.5 months for the combination treatment arms (Hazard ratio = 0.79; \( p < 0.001 \)) as compared to 6.9 months with NIVO monotherapy and 2.9 months with IPI monotherapy (HR was 0.42 for combination vs. IPI monotherapy) (6). However, combination immunotherapy may cause a series of adverse events which may result in hospitalization and put additional strain on the healthcare system or can even be fatal (11).

Considering the improved survival but increased toxicity associated with combination ICIs, it is important to recognize and monitor the unique and significant adverse events associated with immunotherapy, alone or in combination. We performed a systematic review and meta-analysis to investigate the incidence of adverse events associated with the use of a combination of NIVO and IPI compared to NIVO monotherapy in cancer patients. Findings from this study provide a basis on which providers can be informed of the potential toxicities of potential ICIs and, using their clinical expertise, justify the use of ICIs over monotherapy. NIVO monotherapy was chosen over IPI monotherapy as a comparison group because of the favorable risk-benefit ratio reported with NIVO and a more tolerable safety profile when compared with IPI (12).

2. Patients and methods

2.1. Data sources and search strategy

A comprehensive literature search was performed systematically from the date of inception through April 2021, in the following databases: PubMed, EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. We also searched for trials that were included in the conference proceedings: American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and National Comprehensive Cancer Network (NCCN). The reference lists of relevant articles were searched to find any additional publications. The search strategy focused on any terms relating to cancer, NIVO, IPI, and adverse events. The authors of the study contacted the authors of unpublished studies when full-text articles were not available. Our search was restricted to articles published in the English language. This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidance document (13).

2.2. Eligibility criteria

We included randomized controlled trials (RCTs) if they met the following criteria: (1) RCTs that included cancer patients; (2) RCTs that had a combination of NIVO and IPI in one treatment arm and NIVO monotherapy in another arm; (3) RCTs that adequately reported treatment-related adverse events (TRAEs) of any grade and/or grade 3 or 4; (4) Any phase RCTs.

2.3. Study selection

We used Covidence, an online systematic review platform for the initial screening of articles. Records were imported from various sources into Covidence (14). Two review authors (S.K., J.P) independently screened titles and abstracts of all imported articles based on the study selection criteria. After removing duplicates and irrelevant studies, we examined full-text articles for their potential eligibility. The screening process has been documented in the PRISMA flow chart of study selection (Figure 1).

2.4. Data extraction

Data extraction for each included study was performed independently by two reviewers (S.K; J.P.). A data extraction form was developed to extract information on year of publication, study identifier, country, phase of RCT, cancer type, sample size and dose of intervention and comparator arm, adverse-event reporting system used, and follow-up months. Any disagreements
were discussed and resolved by the two reviewers or by consulting a third reviewer (A.V.) if required. In case of multiple publications reporting on the same study were identified, the one with the longer follow-up period or comprehensive adverse event data was selected for data extraction.

The primary outcome of this study was TRAEs. We have also reported commonly occurring adverse reactions: gastrointestinal (diarrhea, colitis), endocrine (hypothyroidism, hyperthyroidism, and hypophysitis), respiratory (pneumonitis), hepatobiliary (increased transaminases and hepatitis), rash, fatigue, and musculoskeletal related toxicities as these events require close clinical monitoring. Adverse events assessed using the U.S. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, any grade and grade 3 or 4 (15).

2.5. Assessment of risk bias
The quality of the included studies was assessed using the Cochrane Collaboration’s Risk of Bias tool (16). The tool evaluates six domains, and each domain was labeled as ‘low’, ‘high’, and ‘unclear’ risk.

2.6. Statistical analysis
For each RCT included in the meta-analysis, the number of patients treated and the number...
of patients with adverse events were recorded for each treatment arm. RCTs containing multiple treatment arms for the combination of NIVO and IPI, the patients were analyzed in aggregate. A subgroup analysis was conducted based on the dosing in the intervention arm: NIVO 3 mg/kg + IPI 1 mg/kg (NIVO3 + IPI1) vs. NIVO (3 mg/kg); NIVO 1 mg/kg + IPI 3 mg/kg (NIVO1 + IPI3) vs. NIVO (3 mg/kg). We chose this dosing regimen only two dosing regimens are approved by FDA for combination of NIVO and IPI. As reported in the literature, the combined effect of NIVO and IPI was clinically better than monotherapies. We further investigated if there was any difference in the TRAEs of two combination therapies with different dosing regimens (NIVO3 + IPI1 vs. NIVO1 + IPI3). Additional subgroup analysis was conducted for cancer type where there were at least two studies that reported data for a cancer type. Risk ratios and the corresponding 95% confidence intervals (CIs) of any grade and grade 3 or 4 higher adverse events were calculated. The adverse events of interest included any grade and grade 3 or 4 adverse event, as these are typically associated with hospitalization. A meta-analysis for each adverse event category was performed using random-effects models with the Mantel–Haenszel method weighted by the number of patients treated (17). Heterogeneity among included studies was assessed using the Cochrane Q statistic and $I^2$ statistics. Statistical significance was measured at p values of $<0.05$. In this analysis, the $I^2$ value of 30–60% was categorized as ‘moderate heterogeneity’, 50–90% as ‘Substantial heterogeneity’ and 75–100% as ‘Considerable heterogeneity’ (18). As included studies in this meta-analysis were from different countries, various cancer types, which might cause unexplained heterogeneity, a random effect model was used for summary statistics. Meta regression was conducted to explore sources of heterogeneity in an event of at least 10 individual studies in a meta-analysis. Publication bias was assessed using funnel plots inspection and Egger’s regression test for outcomes that included at least 10 studies. All analyses were performed using Cochrane’s RevMan version 5.4 software Package (Copenhagen, Denmark; The Nordic Cochrane Center, Odense, Denmark) and RStudio version 1.4.1717 software (Boston, Massachusetts, USA) (19).

3. Results

3.1. Study selection

A total of 4705 citations were identified from the literature. We then systematically removed 1653 duplicates and further studies after the initial title and abstract screening, thus leaving 3052 studies for screening. Although 65 articles met the inclusion criteria, 38 were excluded for several reasons. Among them, seven articles were excluded due to inadequate data on adverse events; 11 articles were abstracts of published studies; 11 articles were duplicate reports; six articles were single-arm studies and did not include the combination of NIVO and IPI; two articles were pooled analysis; one article was a study protocol. In the end, 14 distinct studies with distinct citations were included in the meta-analysis (5–10, 20–27) (Figure 1).

3.2. Study characteristics

The characteristics of the included studies are listed in Table 1. Fourteen trials included a total of 2925 patients. The selected studies varied cancer types: melanoma ($n = 4$), ovarian cancer ($n = 1$), small cell lung cancer ($n = 1$), untreated squamous cell carcinoma of the oral cavity ($n = 1$), urothelial carcinoma ($n = 1$), NSCLC ($n = 2$), esophagogastric cancer ($n = 1$), sarcoma ($n = 1$), malignant glioma ($n = 1$), malignant pleural mesothelioma ($n = 1$). There was one Phase I study, seven Phase II studies, three Phase III, and three Phase I and II clinical trials.

3.3. Risk of bias within studies

Twelve of the fourteen studies were open-label RCTs and thus were at high risk of performance bias. These studies were labeled at high risk of bias. Figure 2 presents ‘risk of bias graph’ about each domain of the Cochrane risk of bias tool.
| Author name                  | Study identifier | RCT phase | Country       | Type of cancer                                                                 | Intervention and comparator arms                                                                 | No. of patients in RCT (sample size) | Age (median years) | Follow-up (in months) |
|-----------------------------|-----------------|-----------|---------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------|--------------------|----------------------|
| Gettinger et al. [20]       | NCT02785952     | III       | USA           | Stage IV squamous non-small cell lung cancer                                  | ARM 1: NIVO 3 mg/kg + IPI 1 mg/kg ARM 2: NIVO 3 mg/kg q2w                                         | 127                                | 68.1               | 29.5                 |
| Zimmer et al. [25]          | NCT02523313     | II        | Germany       | Stage IV melanoma with no evidence of disease after surgery or radiotherapy   | ARM 1: NIVO (1 mg/kg) every 3 weeks + IPI (3 mg/kg) every 3 weeks for 4 doses followed by NIVO (3 mg/kg) every 2 weeks ARM 2: NIVO (3 mg/kg) every 2 weeks + IPI placebo during 1–12 weeks | 55 NIVO1 + IPI3 = 55 NIVO3 = 56 | 58                 | 28.4                 |
| Zamarin et al. [7]          | NCT02498600     | III       | Multicountry  | Recurrent or persistent ovarian cancer or fallopian tube carcinoma             | ARM 1: NIVO (3 mg/kg) once every 2 weeks × 4 doses followed by NIVO 3mg every 2 weeks (maintenance) ARM 2: NIVO (3 mg/kg) + IPI (1 mg/kg) once every 3 weeks × 4 doses followed by NIVO 3 mg as maintenance dose every 2 weeks | 51 NIVO3 + IPI1 = 51 NIVO3 = 49 | 62 NIVO = 63 | 33                   |
| Larkin et al. [6]           | NCT01844505     | III       | Multicountry  | Unresectable or metastatic stage III or stage IV melanoma                     | ARM 1: NIVO (1 mg/kg) every 3 weeks + IPI (3 mg/kg) every 3 weeks for 4 doses followed by NIVO (3 mg/kg) every 2 weeks ARM 2: NIVO (3 mg/kg) every 2 weeks + IPI placebo ARM 3: IPI (3 mg/kg) every 3 weeks for 4 doses + NIVO matched placebo | 314 NIVO1 + IPI3 = 314 NIVO = 316 IPI = 315 | 61 NIVO = 60 | 54.6                 |
| Schoenfeld et al. [27]      | NCT02919683     | II        | USA           | Untreated squamous cell carcinoma of the oral cavity                          | ARM 1: NIVO at 3 mg/kg weeks 1 and 3 ARM 2: NIVO (3 mg/kg) + IPI (1 mg/kg) every 3 weeks for four doses followed by NIVO maintenance | 15 NIVO3 + IPI1 = 15 NIVO = 15 | 65 NIVO = 64 | 14                   |
| Sharma et al. [8]           | NCT01928394     | V/II      | Multicountry  | Platinum pretreated metastatic urothelial carcinoma                           | Arm 1: NIVO (3 mg/kg) every 2 weeks ARM 2: NIVO (3 mg/kg) + IPI (1 mg/kg) every 3 weeks for four doses followed by NIVO maintenance ARM 3: NIVO (1 mg/kg) + IPI (3 mg/kg) every 3 weeks for four doses followed by NIVO maintenance | 78 NIVO = 78 NIVO3 + IPI1 = 104 NIVO1 + IPI3 = 92 | 65 NIVO = 65.5 | 56 NIVO3: 56 NIVO3 + IPI1: 57 NIVO1 + IPI3: 26.7 |
| Hellman et al. [10]         | NCT02477826     | III       | Multicountry  | Stage IV or recurrent NSCLC and PD-L1 expression level of 1% or more          | ARM 1: NIVO (3 mg/kg)+ IPI (1 mg/kg) every 6 weeks ARM 2: NIVO (240 mg every 2 weeks) ARM 3: Platinum doublet chemotherapy every 3 weeks for upto 4 cycles | 391 NIVO3 + IPI1 = 391 NIVO = 391 CHemo = 387 | 64 NIVO = 64 | 29.3                 |
| Ready et al. [9]            | Checkmate 032   | II        | Multicountry  | Small Cell Lung Cancer                                                        | ARM 1: NIVO (1 mg/kg) every 3 weeks + IPI (3 mg/kg) every 3 weeks for 4 doses followed by NIVO (3 mg/kg) every 2 weeks ARM 2: NIVO (3 mg/kg) every 2 weeks + IPI placebo ARM 3: NIVO (3 mg/kg) every 2 weeks | 96 NIVO1 + IPI3 = 96 NIVO = 147 | 65 NIVO = 63 | 11.9                 |
| Scherpereel et al. [24]     | IFCT-1501 MAPS2  | II        | France        | Malignant pleural mesothelioma                                                 | ARM1: NIVO (3 mg/kg) ARM2: NIVO (3 mg/kg) + IPI (1 mg/kg) ARM3: NIVO (3 mg/kg Q2W) | 63 NIVO = 63 | 72.3               | 20.1                 |
| Long et al. [5]             | NCT02716272     | II        | Australia     | Active melanoma with brain metastasis                                         | ARM1: NIVO (3 mg/kg) ARM2: NIVO (3 mg/kg) + IPI (3 mg/kg) Q2W ARM3: NIVO (3 mg/kg) in patients with brain | 36 NIVO1 + IPI3 = 36 NIVO1 + IPI3 = 27 | 36 NIVO1 + IPI3 = 36 | 34                   |
|                             | NCT02734242     | II        |              |                                                                              | ARM1: NIVO (3 mg/kg) ARM2: NIVO (3 mg/kg) + IPI (3 mg/kg) Q2W ARM3: NIVO (3 mg/kg) in patients with brain | 16 NIVO (cohort): | 16 NIVO (cohort): | 16 NIVO (cohort): |

(continued)
Table 1. Continued.

| Author name     | Study identifier         | RCT phase | Country | Type of cancer                                                                 | Intervention and comparator arms                                                                 | No. of patients in each arm (sample size) | Age (median years) | Follow-up (in months) |
|-----------------|--------------------------|-----------|---------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------|--------------------|----------------------|
| Amaria et al.   | NCT02519322 (ongoing)   | II        | US      | High risk gastric, esophageal, or GEJ adenocarcinoma                           | ARM1: NIVO (3 mg/kg) Q2W ARM2: NIVO (3 mg/kg) + IPI (1 mg/kg) every 3 weeks                     | NIVO = 12, NVO3 + IPI = 11              | NIVO = 55          | NVO + IPI = 15        |
|                 |                          |           |         | locally advanced or metastatic gastric, esophageal, or GEJ adenocarcinoma      | ARM1: NIVO (3 mg/kg) every 2 weeks ARM2: NIVO (1 mg/kg) + IPI (3 mg/kg) every 3 weeks for 4 cycles | NIVO3 = 59, NVO1 + IPI = 49             | NIVO = 60          | NVO + IPI = 28        |
|                 |                          |           |         | locally advanced, unresectable, or metastatic sarcoma ≥ 1 line(s)             | ARM1: NIVO 3 mg/kg every 2 weeks ARM 2: NIVO (3 mg/kg) + IPI 1 mg/kg every 3 weeks (4 doses)    | NVO3 + IPI = 42, NVO = 43               | NVO = 56           | NVO + IPI = 13.6     |
| D’Angelo et al. | NCT02500797 (ongoing)   | II        | USA     | Grade IV malignant glioma or gliosarcoma                                      | ARM1: NIVO 3 mg/kg every 2 weeks ARM 2: NIVO(1 mg/kg) + IPI (3 mg/kg) every 2 weeks             | NIVO3 = 10, NVO1 + IPI = 10             | NIVO = 58          | NVO + IPI = 27        |
|                 |                          |           |         |                                                                                  |                                                                                                   | NVO3 + IPI = 20                         |                    |                      |

3.5.1. NIVO + IPI3 vs. NIVO and NVO3 + IPI

Compared to NIVO monotherapy, the combination of NIVO1 + IPI3 was associated with significantly higher risk of any grade and grade 3 or 4 adverse events (Table 4). Even for the other combination events, NIVO + IPI was associated with significantly higher risk of any grade and grade 3 or 4 events (NIVO3 + IPI). The risk of grade 3 or 4 events (RR = 1.80, 95% CI: 1.41–2.30; P = 0.00001) in the combination group was significantly greater as compared to NIVO monotherapy but was not significantly greater as compared to NIVO monotherapy (RR = 1.33; 95% CI: 1.19–1.49).

3.5.2. NIVO + IPI3 vs. NIVO and NVO3 + IPI

Compared to NIVO monotherapy, the combination of NIVO1 + IPI3 was associated with significantly higher risk of any grade and grade 3 or 4 adverse events (RR = 2.59; 95% CI: 2.20–3.04; P = 0.00001) in the combination group. The risk of grade 3 or 4 events (RR = 1.14; 95% CI: 1.09–1.19; P = 0.069) in the combination group was significantly greater as compared to NIVO monotherapy but was not significantly greater as compared to NIVO monotherapy (RR = 1.33; 95% CI: 1.19–1.49).

### 3.4. Synthesis of results

Combination immunotherapy was significantly associated with a higher risk of any grade (RR = 1.57; 95% CI: 1.31–1.91; P = 0.0094; P = 0.05; CI: 1.57–2.42; 9 = 0.0001; CI = 61%) compared to NIVO monotherapy (Figures 3 and 4). Combination immunotherapy-related adverse events affect a large scale of organs including endocrine gastrointestinal, respiratory, hepatic, and musculoskeletal. Incidences of any grade adverse events were 111.9% (RR = 1.03; 95% CI: 1.02–1.03; P = 0.0004).
difference in the risk of any grade events between the two groups (RR = 1.33; 95% CI: 0.88–2.01; $I^2 = 30\%$).

3.5.2. Nivo1 + IPI3 vs. NIVO3 + IPI1

For the two combination dosing regimens, there was no significant difference in the risk of any grade TRAEs between NIVO1 + IPI3 and NIVO3 + IPI1 (RR = 1.00; 95% CI: 0.92–1.09; $p = 0.88$). However, the incidence of grade 3 or 4 TRAEs was significantly higher in the NIVO1 + IPI3 group as compared to the NIVO3 + IPI1 group (RR = 1.68; 95% CI: 1.21–2.34 $p = 0.0007$) (Table 4). Compared to NIVO3 + IPI1, the risk of any grade (RR = 1.68; 95% CI: 1.21–2.34; $p = 0.02$) and grade 3 or 4 (RR = 3.16; 95% CI: 1.45–6.91; $p = 0.04$) diarrhea were higher in the NIVO1 + IPI3 group (Table 3).

3.5.3. Type of cancer

As a part of subgroup analysis, we assessed if the rate of adverse events differed for patients with melanoma (number of studies = 4) and NSCLC (number of studies = 2). Patients with advanced melanoma who received NIVO + IPI demonstrated significantly higher risk for any grade (RR = 1.16; 95% CI: 1.10–1.22) and grade 3 or 4 (RR = 2.54; 95% CI: 2.07–3.11) TRAEs (Table 4). For NSCLC patients, the risk of grade 3 or 4 AEs were significantly greater among the combination immunotherapy group compared to the NIVO...
Table 2. Pooled relative risk (RR) of any grade and grade 3 or 4 adverse events for combination immunotherapy vs. NIVO.

| Adverse event | Study or Subgroup | No. of RCT | Pooled RR | 95% CI | \(I^2\) (%) | No. of RCT | Pooled RR | 95% CI | \(I^2\) (%) |
|---------------|-------------------|------------|-----------|-------|-------------|------------|-----------|-------|-------------|
| Hyperthyroidism | Amanit 2018 | 8 | 2.45* | 1.65–3.62 | 0 | 4 | 5.32** | 1.16–24.3 | 0 |
| Hypophysitis | D'Angelo 2018 | 6 | 7.06** | 2.59–19.2 | 0 | 5 | 3.54** | 1.08–11.61 | 0 |
| Diarrhea | Janjigian 2018 | 13 | 1.78* | 1.38–2.29 | 36 | 13 | 3.31* | 1.99–5.48 | 0 |
| Colitis | Ommuro 2018 | 15 | 4.52* | 2.67–7.66 | 0 | 6 | 7.74* | 3.33–18.02 | 0 |
| Nausea and vomiting | Scherpereel 2019 | 16 | 1.56* | 1.19–2.03 | 42 | 7 | 1.62 | 0.57–4.67 | 20 |
| Pneumonitis | Hellmann 2019 | 139 | 3.06* | 1.71–5.48 | 0 | 7 | 2.31 | 0.85–6.22 | 0 |
| Increased ALT | Larkin 2019 | 186 | 3.79* | 2.64–5.43 | 0 | 10 | 5.18* | 2.84–9.43 | 0 |
| Increased AST | Sharma 2020 | 71 | 2.71* | 1.64–4.48 | 34 | 8 | 2.97* | 1.61–5.47 | 0 |
| Hepatitis | Zamarin 2020 | 34 | 2.63* | 1.51–4.60 | 0 | 5 | 3.77* | 1.53–9.26 | 0 |
| Rash | Long 2019 | 22 | 1.61* | 1.23–2.09 | 22 | 7 | 3.03* | 1.40–6.54 | 0 |
| Fatigue | Ready 2019 | 36 | 1.21** | 1.02–1.42 | 37 | 12 | 2.25** | 1.19–4.24 | 5 |
| Musculoskeletal | Zimmer 2020 | 39 | 1.31 | 0.89–1.92 | 46 | 6 | 3.08* | 1.43–6.63 | 0 |

*\(p < 0.00001\); **\(p < 0.05\).
ALT: alanine transaminase; ALT: aspartame transaminase.
\(I^2\): Statistical heterogeneity.
monotherapy group (RR = 1.57; 95% CI: 1.11–2.21).

Using multiple meta regression analysis, we found that no study-level factors (cancer type, study quality, clinical trial phase, and country) were associated with TRAE (any grade and grade 3 or 4) (p > 0.05). The test of moderators was not found to be significant (p = 0.9567 for any grade and p = 0.5588 for grade 3 or 4), thus implying that cancer type, study quality, country, and phase did not explain the observed heterogeneity between studies. No evidence of publication bias was found as the funnel plot was symmetric and with the Egger regression-based test (Supplementary material, Appendix B, Figure 2(A,B)).

### 4. Discussion

In a new generation focused on nontraditional anticancer therapies, ICIs continue to have promising results in providing patients with durable response rates to a variety of tumor burdens. Combination immunotherapy provides sustained long-term clinical benefit and is an actively growing area of clinical investigation as evidenced from the clinical trials (28,29). In CheckMate 067, the combination of NIVO and IPI showed higher overall survival rates at five years among patients with advanced melanoma with no apparent loss of quality of life as compared to NIVO monotherapy (6). The CheckMate 032 trial reported that for patients with recurrent small-cell lung cancer, the combination of NIVO and IPI showed higher objective response rate (ORR) with no significant difference in overall survival (9). However, RCTs are sometimes limited with a small sample size may not be sufficiently powered to detect a significant difference between the groups. This systematic review and meta-analysis evaluated the incidence and severity of treatment-related toxicities in association with combination of NIVO + IPI vs. NIVO monotherapy.

Similar to previously published meta-analyses, we found the pooled estimates for any grade and grade 3 or 4 TRAEs were substantially higher for the combination of NIVO and IPI as compared to NIVO monotherapy (29–31). Zhou et al. published a meta-analysis comparing NIVO + IPI to NIVO but was limited by including only four studies (30). Another study by Chen et al. investigated the efficacy and TRAEs for the combination of NIVO and IPI compared to NIVO therapy in cancer treatment. However, their search strategy was limited as they did not consider grey literature, and included 11 studies only until June 2019 (29). Previous study findings establish precedence for efficacy in favor of NIVO + IPI but when determining the use of combination therapy over monotherapy, the inclusion of patient perspective and toxicity tolerability thresholds are essential in providing holistic care.

Despite supportive therapy, common toxicities with grade 3 or higher classifications, such as diarrhea, fatigue, rash, nausea, and vomiting were much more prevalent in the combination treatment group than NIVO (31). This difference in relative risk can contribute to a higher discontinuation rate among this group. A common treatment approach for these adverse events includes cessation of the ICIs and initiation of steroids (32). When evaluating the subjective nature of QoL, a variety of factors, such as but not limited to, independent functional health, social support, and financial burden are important when making therapeutic decisions (33). A treatment-specific risk vs. benefit analysis needs to be conducted, preferably with the patient, in order to understand the totality of which regimen

### Table 4. Pooled relative risk (RR) of any grade and grade 3 or 4 adverse events from subgroup analysis.

| Adverse events | No. of trials | Pooled RR | Pooled 95% CI | $\hat{I}^2$ (%) |
|----------------|---------------|-----------|---------------|----------------|
| Treatment dosing |               |           |               |                |
| NIVO1 + IPI vs. NIVO |               |           |               |                |
| Any grade | 7 | 1.14* | 1.03–1.26 | 69 |
| Grade 3 or 4 | 7 | 2.59** | 2.20–3.04 | 37 |
| NIVO3 + IPI vs. NIVO |               |           |               |                |
| Any grade | 6 | 1.33 | 0.88–2.01 | 30 |
| Grade 3 or 4 | 10 | 1.80** | 1.41–2.30 | 68 |
| NIVO1 + IPI3 vs. NIVO3 + IPI1 |               |           |               |                |
| Any grade | 4 | 1.00 | 0.92–1.09 | 0 |
| Grade 3 or 4 | 4 | 1.68* | 1.21–2.34 | 32 |
| Type of cancer |               |           |               |                |
| NIVO + IPI vs. NIVO (melanoma) |               |           |               |                |
| Any grade | 4 | 1.16** | 1.10–1.22 | 68 |
| Grade 3 or 4 | 4 | 2.54** | 2.07–3.11 | 58 |
| NIVO + IPI vs. NIVO (NSCLC) |               |           |               |                |
| Grade 3 or 4 | 2 | 1.57* | 1.11–2.21 | 63 |

*p < 0.05; **p < 0.0001.

NSCLC: non-small cell lung cancer; NIVO3: Nivolumab 3 mg/kg; IPI3: Ipilimumab 3 mg/kg; IPI1: Ipilimumab 1 mg/kg.

$\hat{I}^2$: statistical heterogeneity.
to choose. For instance, as we evolve into more patient-centered driven care, preference in avoiding extreme fatigue or severe diarrhea may outweigh the differential efficacy and response rates between combination therapy and monotherapy, especially in patients with advanced cancer; the same might hold in evaluating financial hardships and the relative risk of debilitating adverse effects as they pertain to work productivity.

At the time of this writing, NIVO and IPI remain the only FDA approved ICI combination regimen. Regardless of the risk of TRAE associated between combination therapy and monotherapy, a significant portion of the patients receiving combination therapy received a standardized regimen of either NIVO1 + IPI3 or NIVO3 + IPI1. Although the overall survival was similar between these two groups, studies have reported that NIVO1 + IPI3 yields a higher ORR. Despite better clinical efficacy, NIVO1 + IPI3 was associated with an increased incidence of high-grade TRAEs (8,22). We have confirmed these findings in our subgroup analysis. First, compared to NIVO monotherapy, there was no significant difference in any grade TRAEs for NIVO3 + IPI1. In the subgroup analysis by two dosing regimens, NIVO1 + IPI3 demonstrated a higher risk of grade 3 or 4 events compared to NIVO3 + IPI1. Additionally, we found NIVO1 + IPI3 is significantly associated with higher risk of any grade and grade 3 or 4 diarrhea consistent with a phase I study which reported that about 70% of patients with glioblastoma experienced diarrhea in the NIVO1 + IPI3 group compared to 30% for NIVO3 + IPI1 [23]. While NIVO monotherapy was better tolerated as compared to NIVO plus IPI, the incidence of adverse events was influenced by the IPI dose possibly due to dose-related toxicity of IPI. Although NIVO1 + IPI3 had a higher incidence of higher-grade adverse events, these AEs are sometimes manageable with early recognition and appropriate treatment. This subgroup analysis can help guide anticipatory social and therapeutic supportive care, and dose reductions for patients with cancer.

Currently, several immunotherapies either as monotherapy or in combination are being evaluated for a wide range of tumors (34). When identifying single-agent dose reduction opportunities for patients experiencing grade 3 or 4 diarrhea, the evidence suggests that a reduced dose of IPI may provide some severity relief in combination therapy. Although a stronger study looking at the reduction in the severity of diarrhea is warranted between IPI and NIVO combination therapies, there is low feasibility in doing so because of the lack of financial incentives. Selecting the right immunotherapy based on specific biomarkers, dosage of selected agents, and predicting the response to these agents remains a challenge and needs to be explored further using real-world data.

4.1. Limitations

Several limitations for this meta-analysis need to be considered for appropriate interpretation. The included studies were from different countries (USA, France, Australia, and Germany), as well as different dosing for the combination therapy and various cancer types and thus we observed a high degree of heterogeneity between studies for some of the outcomes. However, we partly addressed this by conducting a subgroup analysis for NIVO plus IPI with two doses of combination immunotherapy and by cancer type.

5. Conclusion

Compared with NIVO monotherapy, the combination of NIVO and IPI increased the risk of any grade and grade 3 or 4 adverse events. Additionally, in the subgroup analysis, it was observed that the combination of NIVO1 + IPI3 had a higher incidence of grade 3 or 4 TRAEs compared to NIVO3 + IPI1. Our study findings provide healthcare providers and their patients with a deeper understanding of the quantifiable, rather than qualitative, risk in developing TRAEs. Furthermore, the frequency of the TRAEs associated with both treatment modalities should increase clarity in the importance of patient monitoring as it pertains to patient quality of life and outcomes.

Author contributions

SK: Conceptualization, Methodology, Formal Analysis, Data Curation, Investigation, Writing-Original draft, Writing-Reviewing and Editing; JP: Formal Analysis, Data curation,
Investigation, Writing-Original draft, Writing-Reviewing, and Editing; BB: Conceptualization, Data Curation, Writing-Reviewing, and Editing; AV: Conceptualization, Methodology, Data Curation, Writing-Reviewing and Editing, Investigation, Supervision.

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**Data availability statement**

Available on request due to privacy/ethical restrictions.

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