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Immune-Related Adverse Events Associated with Anti-PD-1/PD-L1 Treatment for Malignancies: A Meta-Analysis

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Background: Treatment of cancers with programmed cell death protein 1 (PD-1) pathway inhibitors can lead to immune-related adverse events (irAEs), which could be serious and even fetal. Therefore, clinicians should be aware of the characteristics of irAEs associated with the use of such drugs.

Methods: The MEDLINE, EMBASE, and Cochrane databases were searched to find potential studies using the following strategies: anti-PD-1/PD-L1 treatment; irAEs; and cancer. R© package Meta was used to pool incidence.

Results: Forty-six studies representing 12,808 oncologic patients treated with anti-PD-1/PD-L1 agents were included in the meta-analysis. The anti-PD-1/PD-L1 agents included nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, and BMS-936559. The tumor types were melanomas, Hodgkin lymphomas, urothelial carcinomas, breast cancers, non-small cell lung cancers, renal cell carcinomas (RCC), colorectal cancers, and others. We described irAEs according to organ systems, namely, the skin (pruritus, rash, maculopapular rash, vitiligo, and dermatitis), endocrine system (hypothyroidism, hyperthyroidism, hypophysitis, thyroiditis, and adrenal insufficiency), digestive system (colitis, diarrhea, pancreatitis, and increased AST/ALT/bilirubin), respiratory system (pneumonitis, lung infiltration, and interstitial lung disease), and urinary system (increased creatinine, nephritis, and renal failure). In patients treated with the PD-1 signaling inhibitors, the overall incidence of irAEs was 26.82% (95% CI, 21.73–32.61; I^2, 92.80) in any grade and 6.10% (95% CI, 4.85–7.64; I^2, 52.00) in severe grade, respectively. The development of irAEs was unrelated to the dose of anti-PD-1/PD-L1 agents. The incidence of particular irAEs varied when different cancers were treated with different drugs. The incidence of death due to irAEs was around 0.17%.

Conclusion: The occurrence of irAEs was organ-specific and related to drug and tumor types.

Keywords: Anti-PD-1 antibodies, immune-related adverse events, immunotherapy, oncology, nivolumab

INTRODUCTION

Passive immunotherapy for cancer, which involves the transfer of tumor-targeted mono-antibodies and donor T cells, has demonstrated clinical benefits against a variety of solid and hematological malignancies. In contrast to passive immunity techniques, active immunotherapy strategies aim to augment self/anti-tumor responses (Mellman et al., 2011; Callahan et al., 2016; Michot et al., 2016). However, cancer cells always evolve to exploit multiple pathways to resist immune attack. These immunosuppressive pathways are referred to as "immune checkpoints," which terminate immune responses in the normal physiological state (Pardoll, 2012). Notably, blockade of these immune checkpoints is frequently reported to be superior to traditional treatments in improving survival of oncologic patients (Borghaei et al., 2015; Ribas et al., 2015; Fehrenbacher et al., 2016; Rittmeyer et al., 2017).

Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is expressed exclusively in T cells, where it inhibits their activation (Leach et al., 1996). Antagonistic anti-CTLA-4 antibodies, such as ipilimumab and tremelimumab with proven clinical benefits, have been developed (Pardoll, 2012; Callahan et al., 2016). Ipilimumab has been approved by the FDA (Food and Drug Administration) for the treatment of advanced or recurrent melanomas. Programmed cell death protein 1 (PD-1) and its ligand PD-L1 are immune check points that physiologically limit autoimmunity during inflammatory responses (Leach et al., 1996). Monoclonal antibodies against PD-1 or PD-L1, such as nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab, have been produced. These PD-1/PD-L1 inhibitors could result in a stable regression of malignancy (Borghaei et al., 2015; Brahmer et al., 2015; Motzer et al., 2015; Ribas et al., 2015; Weber et al., 2015; Fehrenbacher et al., 2016; Herbst et al., 2016; Rittmeyer et al., 2017). Currently, the FDA has approved the use of nivolumab for advanced melanoma, renal cell carcinoma (RCC), and non-small cell lung cancer (NSCLC), and pembrolizumab for advanced melanoma and NSCLC (Costa et al., 2017). Furthermore, combined blockade of CTLA-4 and PD-1/PD-L1 appears to achieve additional clinical benefits (Callahan et al., 2016).

Treatment with immune-checkpoint inhibitors could cause immune-related adverse events (irAEs) by unbalancing the immune system (Chen et al., 2015; Marrone et al., 2016; Kumar et al., 2017). The definition of irAEs is different from that of AEs and treatment-related AEs. AEs that occur potentially due to immunological effects were defined as irAEs. irAEs could be serious, requiring suspension of immunotherapy and possibly leading to death (Bertrand et al., 2015; Chen et al., 2015; Eigentler et al., 2016). Previous studies indicated that the occurrence of irAEs induced by anti PD-1/PD-L1 agents is related to tumor types and organs and is dose-independent (Michot et al., 2016). Additionally, there are reports of delayed occurrence of irAEs after treatment with anti PD-1/PD-L1 agents (Nishino et al., 2015). Therefore, there is a need to understand the characteristics of irAEs associated with anti PD-1/PD-L1 treatments to help us manage them appropriately.

In this study, we present a systematic review and meta-analysis and aim to assess the incidence and characteristics of irAEs in malignancies treated with anti-PD-1/PD-L1 agents.

METHODS

The protocol of this meta-analysis was registered at PROSPERO, International Prospective Register of Systematic Reviews (crd.york.ac.uk/prospero, Identifier: 42016051745).

Literature Searches

MEDLINE, EMBASE, and Cochrane databases were searched to determine potentially eligible studies from database inception to March 1, 2017. We put no restriction on language. The following search terms were used: "safety OR security OR side effects OR adverse events AND (anti-PD-1 OR anti-PD-L1 OR nivolumab OR pembrolizumab OR BMS-936559 OR atezolizumab OR avelumab OR durvalumab)" in MEDLINE and EMBASE, and "anti-PD-1 OR anti-PD-L1 OR nivolumab OR pembrolizumab OR BMS-936559 OR atezolizumab OR avelumab OR durvalumab" in Cochrane databases. We also screened the references of included studies and relevant reviews to find potential studies. There were too many medical records reporting the side effects of anti-PD-1/PD-L1 agents, and it was difficult to check all conference abstracts in the 2 years prior to this study.

Selection Criteria

Eligible studies were required to meet the following criteria: (1) Prospective clinical trials that reported irAEs, which were clearly identified as "AEs of special interest," "immune-mediated adverse events," or "selected treatment-related adverse events of special interest," but not "treatment-related AEs" or "drug-related AEs." Additionally, every corresponding author of a potential irAE-related study was e-mailed and asked to provide more information about the irAEs and (2) patients were diagnosed with malignancies that were treated with anti-PD-1/PD-L1 agents. Oncologic therapy prior to anti-PD-1/PD-L1 treatment was acceptable.

The exclusion criteria were: (1) Non-oncologic patients (e.g., hepatitis C virus-related patients) treated with anti-PD-1/PD-L1 agents; (2) Oncologic patients treated with anti-PD-1/PD-L1 agents combined with other treatments simultaneously; (3) Retrospective studies, meeting abstracts, case reports, basic research, reviews, systematic reviews and meta-analysis, letters, editorials, and expert opinions; and (4) Duplicate publications or unpublished studies.

Data Extraction

The titles and abstracts of all studies retrieved were independently reviewed by two authors. Next, the full texts of all potentially eligible studies were assessed. A standardized, pre-piloted form was used to extract relevant information from the included studies.

The primary outcomes for this meta-analysis were incidence and risk ratio (RR) of irAEs and their grade (1–5; recorded according to Version 3 or 4 of the Common Terminology Criteria for Adverse Events of the National Cancer Institute).

We considered that Grades ≥3 were evaluated as high grade or severe grade. The secondary outcome was incidence of death due to irAEs. Any discrepancies were solved by discussion. Missing data were requested from the principle investigator by e-mail.

Quality Assessment

Two independent investigators assessed the risk of bias for the included studies according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2011). The following components were assessed: sequence generation, allocation concealment, blinding, completeness of outcome data, incomplete outcome data, and other sources of bias. Disagreements were resolved by discussion among investigators until a consensus was reached.

Statistical Analysis

The incidence and RR of irAEs were estimated for the included studies in this meta-analysis. We pooled the incidence of irAEs in malignancies treated with anti-PD/PD-L1 agents. Heterogeneity between studies was assessed by Q test and I^2 statistics. If the I^2 value was less than 50%, the meta-analysis was performed using the fixed-effects model. Otherwise, the random-effects model was adopted. Potential publication bias was examined by funnel plots and Egger's test. Incidence was calculated using R software [R version 3.3.2 (2016-10-31)] with package Meta and Metaprop function. RR was calculated using Review Manager 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

Literature Search

Our search strategy identified 1,991 potential articles. Five-hundred and 51 studies were excluded owing to duplicates. The remaining articles were screened for titles and abstracts, and 1080 articles were removed based on our inclusion or exclusion criteria. Furthermore, 314 studies were dropped because they did not contain our data of interest. Finally, 46 studies were included in our meta-analysis. The study selection is shown in **Figure 1**.

Study Characteristics

The detailed information of the clinical trials is presented in **Table 1**. Overall, 46 trials comprising 12,808 oncologic patients treated with anti-PD-1/PD-L1 agents were included in this meta-analysis (**Table 1**) (Brahmer et al., 2010, 2012, 2015; Topalian et al., 2012, 2014; Robert et al., 2014, 2015a,b; Borghaei et al., 2015; Garon et al., 2015; Gettinger et al., 2015, 2016; Hamanishi et al., 2015; Larkin et al., 2015; McDermott et al., 2015, 2016; Motzer et al., 2015; Patnaik et al., 2015; Ribas et al., 2015, 2016; Rizvi et al., 2015; Weber et al., 2015, 2016; Balar et al., 2016; Chatterjee et al., 2016; Choueiri et al., 2016; Fehrenbacher et al., 2016; Ferris eta., 20as.Ld ais et aa., 20a5--0.245057(s).869306(a)-0.3599387ri1(o)080.545(e)-0.061909(t)-379.678(a)]TJ 38.626 Td (l)0.05
20d4oidy i tRR-385.835(e)-0.061909(t)-388.221(a)-0.326553(d20.0541704(.)-0.274721(,)-272.184(2)-0.215392(0)-0.217044701f)0.26311eare25.6

FIGURE 1 | Flow diagram for identification and selection of studies included in the meta-analysis.

of the treatment type. Pancreatitis was rare, with an incidence of less than 1% for either all grade or severe grade across all drug types (Table S11).

Liver

The incidence of increased aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels ranged from 4 to 5% with nivolumab treatment. This incidence of increased AST or ALT levels was around 2% in patients treated with pembrolizumab or atezolizumab. However, the incidence of elevated AST/ALT/blood bilirubin and hepatitis was $\leq$2% regardless of treatment type (Table S12).

Pulmonary

Pneumonitis was the most common irAE related to the lung. The incidence of pneumonitis of any grade was approximately 3% and that of severe grade was approximately 1% during treatment with nivolumab or pembrolizumab. Treatment with atezolizumab was less likely to be associated with pneumonitis, with an incidence of $\sim$1% for any grade and $<$1% for severe grade (Table S13).

Kidney

The incidence of any grade of nephritis was very low (less than 1%) regardless of the treatment type. There were reports of acute renal failure and renal failure only with nivolumab treatment, although the incidence was only $\sim$2% for all grade and $\sim$1% for severe grade (Table S14).

Tumor-Specific irAEs

We analyzed the incidence of irAEs with regard to the tumor being treated, including melanomas, NSCLCs, RCCs, and urothelial tumors. The highest incidence of any irAE

TABLE 1 | Characteristics of studies included for meta-analysis.

Study	Design	Cancer	Size	Target	Drug	Dose(mg/kg)	CTC for AE version[c]
Brahmer et al., 2010	Non-Randomized, open label, phase I	Melanoma, NSCLC[b], RCC[b], CRC[b], and prostate cancer	39	PD-1	Nivolumab (MDX-1106)[a]	0.3; 1; 3; 10	n/a
Topalian et al., 2012	Non-Randomized, open label, phase I	Melanoma, NSCLC, RCC, CRC, and prostate cancer	296	PD-1	Nivolumab (MDX-1106)	0.1; 0.3; 1; 3; 10	3
Topalian et al., 2014	Non-Randomized, open label, phase I	Melanoma	107	PD-1	Nivolumab	1; 3; 10	3
Brahmer et al., 2015	Randomized, open label, phase III	NSCLC	272	PD-1	Nivolumab	3	4
Gettinger et al., 2015	Non-Randomized, open label, phase I	NSCLC	129	PD-1	Nivolumab	1; 3; 10	3
Hamanishi et al., 2015	Open label, single center, phase II	Ovarian, Peritoneal	20	PD-1	Nivolumab	1; 3	4
Larkin et al., 2015	Randomized, double-blind, phase III	Melanoma	945	PD-1	Nivolumab	3	4
McDermott et al., 2015	Non-Randomized, open label, phase I	RCC	34	PD-1	Nivolumab	1; 10	3
Motzer et al., 2015	Randomized, double-blind, phase II	RCC	168	PD-1	Nivolumab	0.3; 2; 10	4
Rizvi et al., 2015	Open label, single-arm, phase II	NSCLC	117	PD-1	Nivolumab	3	4
Robert et al., 2015a	Randomized, double-blind, phase III	Melanoma	418	PD-1	Nivolumab	3	4
Weber et al., 2015	Randomized, open label, phase III	Melanoma	631	PD-1	Nivolumab	3	4
Choueiri et al., 2016	Randomized, open label, phase Ib	RCC	91	PD-1	Nivolumab	0.3; 2; 10	4
Gettinger et al., 2016	Randomized, multi-arm, phase I	NSCLC	52	PD-1	Nivolumab	3	4
Lesokhin et al., 2016	Randomized, open label, phase I	Hematologic Malignancy	81	PD-1	Nivolumab	1; 3	4
Younes et al., 2016	Open label, single-arm, phase II	Hodgkin lymphoma	80	PD-1	Nivolumab	3	4
Ferris et al., 2016	Randomized, open label, phase III	NSCLC	361	PD-1	Nivolumab	3	4
Weber et al., 2016	Non-Randomized, phase I/ II	Melanoma	126	PD-1	Nivolumab	3	4
Borghaei et al., 2015	Randomized, open label, phase III	NSCLC	582	PD-1	Nivolumab	3	4
Sharma et al., 2017	Single-arm, phase II	Urothelial	270	PD-1	Nivolumab	3	4
Morris et al., 2017	Single-arm, phase II	SCCA[b]	37	PD-1	Nivolumab	3	4
Robert et al., 2014	Randomized, phase I	Melanoma	173	PD-1	Pembrolizumab	2; 10	4
Patnaik et al., 2015	Randomized, open label, phase I	Multiple solid tumors[d]	32	PD-1	Pembrolizumab	1; 2; 3; 10	4
Chatterjee et al., 2016	Randomized, open label, phase I	NSCLC	550	PD-1	Pembrolizumab	2; 10	4
Herbst et al., 2016	Randomized, open label, phase II/III	NSCLC	1034	PD-1	Pembrolizumab	2; 10	4
Reck et al., 2016	Randomized, open label, phase III	NSCLC	305	PD-1	Pembrolizumab	n/a	4
Ribas et al., 2016	Randomized, open label, phase I	Melanoma	655	PD-1	Pembrolizumab	2; 10	4
Seiwert et al., 2016	Non-Randomized, open label, phase I	HNSCC[b]	60	PD-1	Pembrolizumab	10	4

(Continued)

TABLE 1 | Continued

Study	Design	Cancer	Size	Target	Drug	Dose(mg/kg)	CTC for AE version

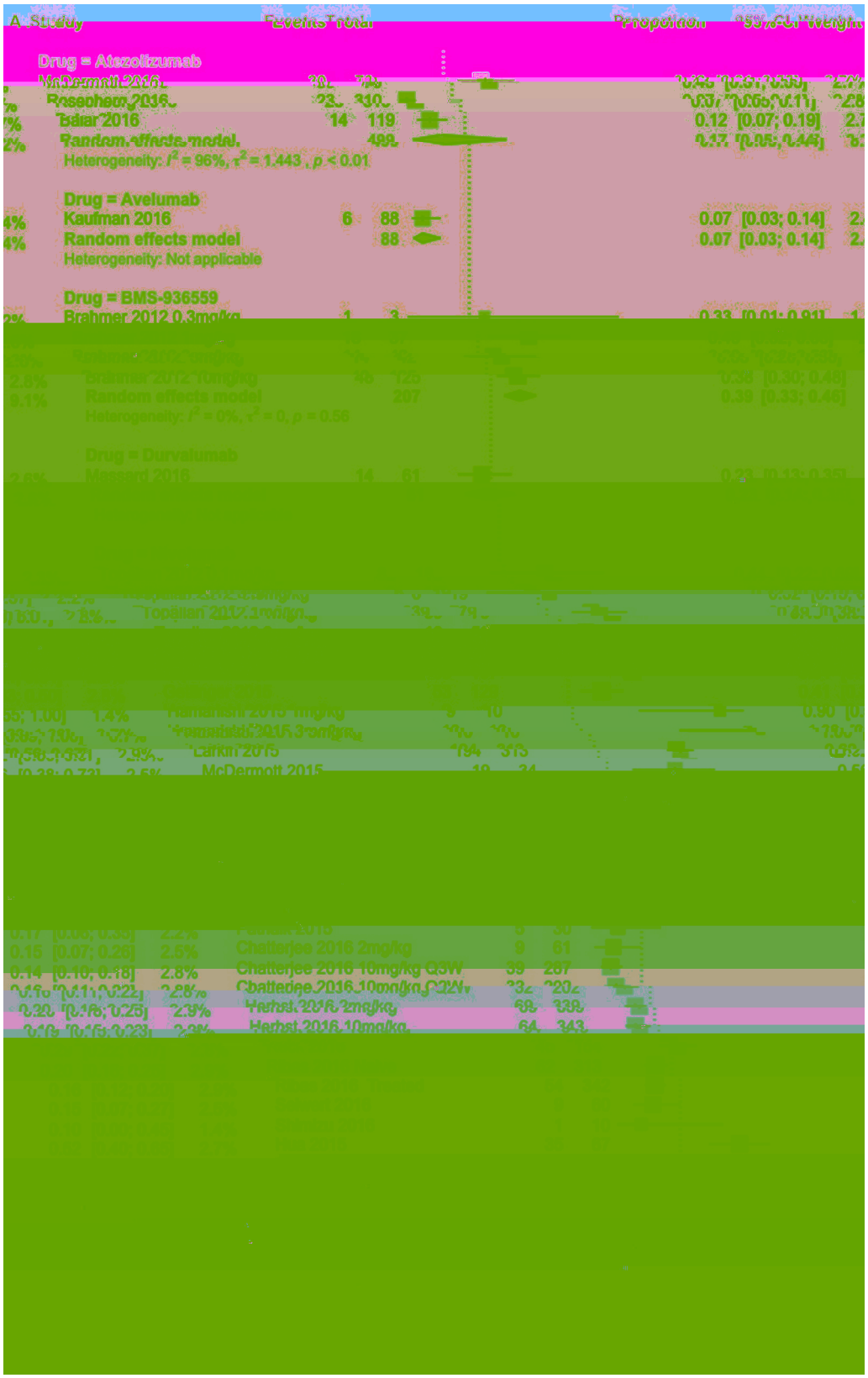

FIGURE 2 | Continued

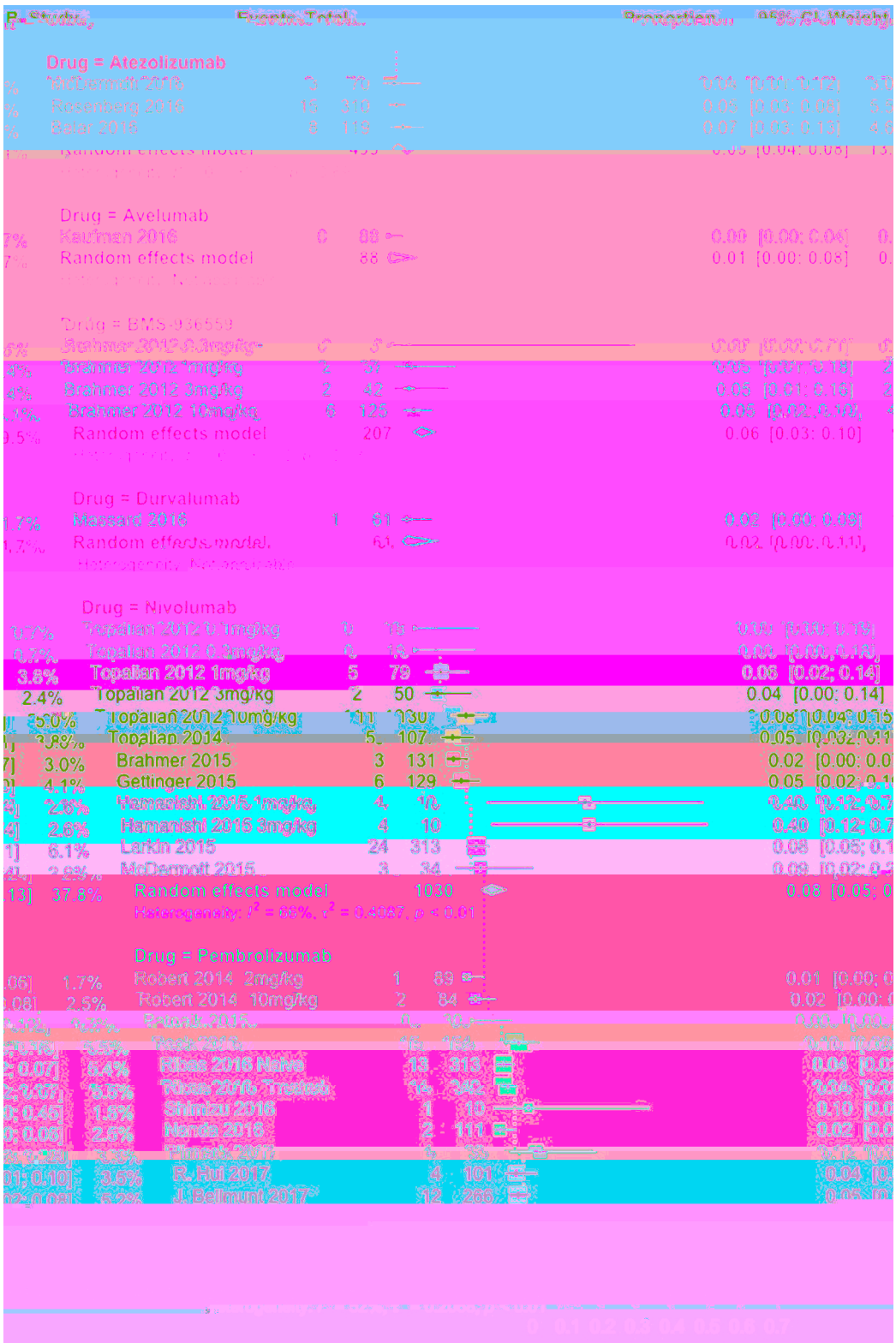

FIGURE 2 | Incidence of global immune-related adverse events (irAEs) with nivolumab (1 and 3 mg/kg), pembrolizumab (2 mg/kg, 10 mg/kg, 200 mg), atezolizumab (1,200 mg) at all dosage, any grade **(A)**, and severe grade **(B)**.

NSCLC

The most common irAEs associated with nivolumab were rash and diarrhea, and those associated with pembrolizumab were hypothyroidism and hyperthyroidism. The incidence of any grade of irAEs with pembrolizumab was higher than that with nivolumab. Severe grade irAEs were rare (Tables S21–S26).

RCC

Diarrhea and colitis were the most frequent any grade irAEs and severe grade irAEs, respectively, associated with nivolumab treatment (Tables S27–S32).

Urothelial Carcinomas

The global incidence of any grade irAEs in urothelial cancers treated with pembrolizumab and atezolizumab was 17.06% (95% CI, 13.21; 21.76; I^2, 0.00) and 9.09% (95% CI, 5, 75; 14.09; I^2, 50.60), respectively. The number of studies providing statistics on organ-specific irAEs in patients with urothelial cancer was relatively small. From the limited cases, we found that the incidence of all grade irAEs and severe grade irAEs in specific organs were very rare, with incidence of $\leq$ 1–3% (Table S33).

Dose-Dependent Analysis

The incidence of all grade irAEs in patients treated with 3 mg/kg nivolumab was 58.08% (95% CI, 34.05–78.81; I^2, 84.80), while that in patients treated with 1 mg/kg nivolumab was 70.00% (95

and diarrhea was lower in NSCLC than in melanoma and RCC during nivolumab treatment (Tables S15, S17, S21, S23, S27, and S29), confirming that the irAEs were tumor-specific. Our results correspond well with those published previously (Nishino et al., 2016) and are arguably more convincing owing to the larger number of studies involved.

In addition to the irAEs caused by anti-PD-1/PD-L1 agents, the response rate of this immunotherapy was another concern (Gibney et al., 2016; Topalian et al., 2016). Fortunately, genomic sequencing, RNA sequencing, and whole exome sequencing were of great importance in identifying predictive biomarkers for anti-

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