Incidence of Immune Checkpoint Inhibitor-Associated Diabetes: A Meta-Analysis of Randomized Controlled Studies

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Background: Immune checkpoint inhibitors (ICIs) are now an important option for more than 14 different cancers. Recent series case reports have described that ICIs are associated with new-onset diabetes in patients, yet the definitive risk is not available. We thus performed a meta-analysis of randomized controlled trials (RCTs) to assess the incidence and risk of developing new-onset diabetes following the use of ICIs.

Methods: The PubMed, EMBASE, Cochrane Library databases, and ClinicalTrials.gov for RCTs were searched. Statistical analyses were performed using STATA 15 and R language. Fifty-two RCTs were included, and 12 did not report any events of ICI-associated diabetes.

Results: A meta-analysis of 40 trials was performed, which reported at least one diabetes-related event among 24,596 patients. Although specific diabetes-related events were rare, compared with the placebo or other therapeutic strategies, the rates of serious hyperglycemia (OR 2.41, 95% CI 1.52 to 3.82), diabetes (3.54, 1.32 to 9.51), all-grade T1D (6.60, 2.51 to 17.30), and serious-grade T1D (6.50, 2.32 to 18.17) were increased with ICI drugs. Subgroup analysis according to the type of control, type of ICIs, and the combination mode suggested that ICIs plus conventional treatments significantly decreased the risks of diabetes and serious-grade hyperglycemia. There was little heterogeneity across the studies in all results except hyperglycemic events, which in part was attributable to data from everolimus-based control group.

Conclusions: New-onset diabetes is uncommon with ICIs but the risk is increased compared with placebo or another therapeutic strategy. However, more studies are warranted to substantiate these findings across ICIs.

Keywords: immune checkpoint inhibitors, diabetes, hyperglycemia, meta-analysis, safety outcomes

INTRODUCTION

Immune checkpoint inhibitor (ICI)-based treatments that block molecules such as programmed cell death protein 1 (PD-1), PD1 ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) have emerged as powerful weapons in a growing number of cancers (Temel et al., 2018). Currently, nine ICIs have been approved for the treatment of different cancers: anti-PD-1 (nivolumab,
pembrolizumab, toripalimab, sintilimab, and cemiplimab); anti-PD-L1 (atezolizumab, avelumab, and durvalumab); and anti-CTLA-4 (ipilimumab). Immune checkpoint molecules play an important role in maintaining immunological tolerance to self-antigens and preventing autoimmune disorders (Pardoll, 2012). Consequently, their blockade in cancer therapy not only promotes T cell-mediated immune destruction on tumor cells but may also facilitate autoimmune activity that affects various organ systems (Johnson et al., 2018). Thus, ICIs frequently cause toxicities related to the mechanism of action that are generally referred to as immune-related adverse events (irAEs) (Postow et al., 2018).

Among these irAEs, new-onset diabetes is receiving increased attention, as more evidence suggests the recognition of diabetes-related adverse events in patients with cancers who are treated with ICIs. A marked increase in reporting diabetes has also been seen since 2017 by analyzing the World Health Organization’s database of individual case safety reports (Wright et al., 2018). These observations raised concern as to whether ICIs treatments could be associated with an increased risk of diabetes in patients with cancer. However, there has been no report of a meta-analysis of the incidence or risk of ICI-associated diabetes among the different ICIs in different tumor subtypes.

Given the dramatic growth in the number of clinical trials testing ICI agents and their clinical benefits in the increasing list of cancer types and negative influence on life quality caused by diabetes if not promptly recognized, we performed a meta-analysis of randomized controlled trials (RCTs) with ICIs in patients with cancer and evaluated the incidence and risks of diabetes-related adverse events compared with placebo or another therapeutic strategy.

MEthODS

Search Strategy and Selection Criteria

Scientific literature searches were performed in three databases (PubMed, EMBASE, and Cochrane Central Register of Controlled Trials) from the inception of all searched databases to March 2019. Relevant text words and medical subject headings that consisted of terms including ‘phase’ and the individual drug names (details in Supporting Information Table S1) were searched. The search was limited to RCTs and English language. We also performed a manual search using reference lists from trials and review articles to identify any other relevant data. The ClinicalTrials.gov website was searched for RCTs that were labeled as ‘completed’ with available results. This meta-analysis was performed in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher et al., 2009).

Study Selection

We included RCTs that were performed in adults with cancer and compared ICI treatment to another treatment strategy. The exclusion criteria were as follows: observational and retrospective studies; studies published in a meeting abstract without published full text original articles; quality of life studies; studies with only pediatric patients; 10 or fewer patients in any group; single dosing; cost effectiveness analyses; and those that could not assess the effect of ICI, such as when the control group was a different dose of the same ICI or another type of ICI. Two authors independently screened all titles and abstracts (HM and JZ). Two of three authors reviewed and discussed the potential full text. Any disagreements were resolved by consensus with all three (JL, HM, and JZ).

Data Extraction and Quality Assessment

Data from each study that met the inclusion criteria were independently extracted by two of the three authors (JL, HM, and YL). Any disagreement was resolved by consensus with all three. The retrieved data included author name, year of publication, trial characteristics (registry number, whether it was an international study, countries involved, study sites, and study phase), patient characteristics (sex, age, and performance status), the sizes of the intervention and control groups, ICI treatment, dose, and the outcomes of interest. We detected new-onset diabetes following treatment with ICIs using the following terms: hyperglycemia, diabetes mellitus (DM), type 2 diabetes (T2D), and type 1 diabetes (T1D). For data extracted from ClinicalTrials.gov, adverse events were reported as either serious or other; for data from published reports, we identified grades 3–5 as serious and grades 1–2 as other, according to Common Terminology of Clinical Adverse Events categorization. If data were available for both sources, we prioritized data from sources where the data were more complete. If a published study did not report diabetes-related adverse events, and the corresponding registry trial from ClinicalTrials.gov reported did, we included the registry report. For multiple reports of the same trial, only the most completely reported data were used. The quality of the included studies was independently assessed using the Cochrane Risk of Bias Tool. We considered all trials at unclear risk of incomplete outcome data and selective reporting bias as these studies were not designed primarily to assess adverse events.

Data Synthesis and Analysis

The estimated event rates in the intervention group are calculated as the total number of patients with a given adverse event divided by the total number at risk. Data were transformed using the Freeman–Tukey Double Arcsine transformation to calculate event rates. This statistical analyses were performed using R statistical software (package meta, R Foundation). For risk outcome, we pooled trials and calculated odds ratios (ORs) and their associated 95% confidence intervals (CIs) in the intervention group compared with the control group based on the number of patients with a given adverse event and sample size. Given the low rates of adverse events, we used Peto’s method to pool effect estimates across studies. The \( I^2 \) statistic and \( P \) value were used to examine heterogeneity across trials for each outcome. An \( I^2 \) statistic of 0–25%, 26–75%, and 76–100% was regarded as indicating low, moderate, and high heterogeneity, respectively. A \( P \) value of less than or equal to 0.05 was defined as significant heterogeneity. If a study included more than one intervention group (e.g. different doses or different types of ICI), we separately compared each intervention group with the control group, where the number of patients or events in the control...
group would be doubled. Sensitivity analyses were performed excluding an everolimus-controlled study, which was known to cause diabetes-related adverse events, to understand the reasons for the high likelihood of differences. We conducted subgroup analyses to examine studies according to the type of control group (chemotherapy vs. immunosuppressive drug vs. targeted therapy vs. placebo), the mode of intervention treatment (monotherapy vs. add-on therapy), and the type of ICI (PD-1 vs. PD-L1 vs. CTLA4 vs. combination of ICIs). Evidence of publication bias was assessed using Egger’s and Begg’s test in addition to funnel plots, and significant publication bias defined as a $P < 0.1$. All statistical analyses were conducted with STATA, version 15.

RESULTS
Study Search
Our search from the PubMed, EMBASE, and Cochrane Central Register databases yielded a total of 8,596 potentially relevant reports (Figure 1). After screening and eligibility assessment, we retrieved 67 reports for full text screening. We also identified 117 reports with results from ClinicalTrials.gov. After our formal search, three additional large clinical trials were published.

Quality of the Included Studies
Table S2 shows the risk of bias assessment of the included studies for meta-analysis. All studies were RCTs with adequate reported randomization, and all studies were funded by the pharmaceutical industry with a high risk of sponsorship bias. Of the 40 included studies for meta-analysis, 26 (65%) were open labels with a high risk of blinding participants and personnel. None of the included studies specifically stated blinded assessment or collection of diabetes-related adverse events. We classified all trials at unclear risk of incomplete outcome data and selective reporting bias.

Incidence of Diabetes-Related Adverse Events
Of the 52 clinical controlled trials assessing the effects of ICIs, 40 trials described ICI-associated diabetes events during the course of study. Hyperglycemia events were described in 32 studies; 303 cases of all-grade hyperglycemia and 55 serious-grade hyperglycemia events occurred in 10,393 patients. Pooling the data showed that the rates of all-grade and serious-grade hyperglycemia events were 2.26% (95% CI, 1.28 to 3.48) and 0.28% (95% CI, 0.16 to 0.42), respectively. The rates of hyperglycemia events differed by the type of ICI and tumor. In particular, patients treated with ICI combination therapy were more likely to report hyperglycemia: 3.37% for all-grade hyperglycemia, 0.47% for serious-grade hyperglycemia. Patients with RCC showed a trend toward higher rates of both all-grade and serious-grade hyperglycemia, with rates of 6.82%
TABLE 1 | Characteristics of controlled trials of ICI treatment in patients.

| NCT Author (year) | International study | No. of countries involved | No. of study sites | Phase | Group type | Drug | Dose of ICI (mg/kg) | No. of patients | Age Median (range) | No (%) Male | Tumor type |
|-------------------|---------------------|---------------------------|-------------------|-------|------------|------|-------------------|----------------|-------------------|------------|------------|
| NCT00527735 (Reck et al., 2013) | Yes | 8 | NR | Phase 2 | CTLA4 | Ipilimumab, Paclitaxel/carboplatin | 10 | 113 | NR | NR | NSCLC |
| NCT00861614 (Kwon et al., 2014) | Yes | 26 | 191 | Phase 3 | CTLA4 | Ipilimumab, Placebo radiotherapy | 10 | 399 | 69 | 399 | Prostate cancer |
| NCT01673867 (Borghaei et al., 2015) | Yes | 22 | NR | Phase 3 | PD-1 | Nivolumab, Docetaxel | 3 | 292 | 61 | 151 | NSCLC |
| NCT01642004 (Brahmer et al., 2015) | Yes | 20 | NR | Phase 3 | PD-1 | Nivolumab, Everolimus | 3 | 135 | 64 | 111 | NSCLC |
| NCT00636168 (Eggermont et al., 2015) | Yes | 19 | 91 | Phase 3 | CTLA4 | Ipilimumab, Placebo | 10 | 475 | 51 | 296 | Melanoma |
| NCT01668784 (Motzer et al., 2015) | Yes | 24 | 146 | Phase 3 | PD-1 | Nivolumab, Everolimus | 3 | 410 | 62 | 315 | RCC |
| NCT01704287 (Ribas et al., 2015) | Yes | 12 | 73 | Phase 2 | PD-1 | Pembrolizumab, Carboplatin/paclitaxel | 2 | 180 | 62 | 104 | Melanoma |
| NCT01721772 (Robert et al., 2015) | Yes | 16 | 80 | Phase 3 | PD-1 | Nivolumab, Carboplatin | 3 | 210 | 64 | 121 | Melanoma |
| NCT01721746 (Weber et al., 2015) | Yes | 14 | 90 | Phase 3 | PD-1 | Nivolumab, Docetaxel | 3 | 272 | 59 | 176 | Melanoma |
| NCT01903993 (Fehrenbacher et al., 2016) | Yes | 13 | 61 | Phase 2 | PD-L1 | Atezolizumab, Carboplatin/paclitaxel | 1,200 mg/dose | 144 | 62 | 93 | NSCLC |

(Continued)
### TABLE 1 | Continued

| NCT Author (year) | International study | No. of countries involved | No. of study sites | Phase | Group type | Drug | Dose of ICI (mg/kg) | No. of patients | Age Median (range) | No (%) | Tumor type |
|-------------------|---------------------|--------------------------|--------------------|-------|------------|------|------------------|----------------|------------------|--------|------------|
| NCT02105636 (Ferris et al., 2016) | Yes | 15 | NR | Phase 3 | PD-1 | Nivolumab | 3 | 240 | 59 (29–83) | 197 (82.1) | HNSCC |
| NCT01905657 (Herbst et al., 2016) | Yes | 24 | 202 | Phase 2/3 | PD-1 | Pembrolizumab | 2 | 344 | 63 (56–69) | 212 (62) | NSCLC |
| NCT02039674 (Langer et al., 2016) | Yes | 2 | 26 | Phase 2 | PD-1 | Pembrolizumab | 200 mg/dose | 60 | 62.5 (54–70) | 22 (37) | NSCLC |
| NCT01450761 (Reck et al., 2016a) | Yes | 34 | 224 | Phase 3 | CTLA4 | Ipilimumab | 10 | 478 | 62 (39–85) | 371 (66) | SCLC |
| NCT02142738 (Reck et al., 2016b) | Yes | 16 | 142 | Phase 3 | PD-1 | Pembrolizumab | 200 mg/dose | 154 | 64.5 (33–90) | 92 (59.7) | NSCLC |
| NCT02006227 (Rittmeyer et al., 2017) | Yes | 31 | 194 | Phase 3 | PD-L1 | Atezolizumab | 1,200 mg/dose | 613 | NR | 378 (61.7) | NSCLC |
| NCT02125461 (Antonia et al., 2017) | Yes | 26 | 235 | Phase 3 | PD-L1 | Durvalumab | 10 | 476 | 64 (31–84) | 334 (70.2) | NSCLC |
| NCT01057810 (Beer et al., 2017) | Yes | 24 | NR | Phase 3 | CTLA4 | Ipilimumab | 10 | 399 | NR | 100 | Prostate cancer |
| NCT02256436 (Rogers et al., 2017) | Yes | 120 | 29 | Phase 3 | PD-1 | Pembrolizumab | 200 mg/dose | 270 | 67 (29–88) | 200 (74.1) | Urothelial carcinoma |
| NCT02041533 (Carbone et al., 2017) | Yes | 26 | NR | Phase 3 | PD-1 | Nivolumab | 3 | 271 | 63 (32–89) | 184 (68) | NSCLC |

(Continued)
| NCT Author (year) | International study | No. of countries involved | No. of study sites | Phase | Group type | Drug | Dose of ICI (mg/kg) | No. of patients | Age (range) | No (%) | Tumor type |
|-------------------|---------------------|--------------------------|-------------------|-------|------------|------|---------------------|----------------|-------------|--------|-----------|
|                   |                     |                          |                   |       |            |      |                     |                |             |         |           |
| NCT01285609       | Yes                 | 34                       | 233               | Phase 3 | CTLA4       | Ipilimumab | /                   | 270            | 65 (29-87) | 148 (55) | NSCLC     |
| (Govindan et al., 2017) |                       |                          |                   |       |            | Paclitaxel/carboplatin |            |             |         |           |
| NCT02267343       | Yes                 | 3                        | 49                | Phase 3 | PD-1       | Placebo   | /                   | 477            | NR          | NR      | GEJ       |
| (Kang et al., 2017) |                       |                          |                   |       |            | Paclitaxel/carboplatin |            |             |         |           |
| NCT01843374       | Yes                 | 19                       | 105               | Phase 2b | CTLA4      | Tremelimumab | 10                 | 382            | 66 (60-72) | 283 (74.1) | Mesothelioma |
| (Llombart-Cussac et al., 2017) |                     |                          |                   |       |            |                     |            |             |         |           |
| NCT02302867       | Yes                 | 29                       | 217               | Phase 3 | PD-L1      | Placebo   | /                   | 189            | 67 (61-73) | 151 (79.9) | Urothelial bladder |
| (Powles et al., 2018) |                       |                          |                   |       |            |                     |            |             |         |           |
| NCT02395172       | Yes                 | 31                       | 173               | Phase 3 | PD-L1      | Placebo   | /                   | 396            | 63 (67-69) | 273 (68.9) | NSCLC     |
| (Barlesi et al., 2018) |                       |                          |                   |       |            |                     |            |             |         |           |
| NCT02362594       | Yes                 | 23                       | 123               | Phase 3 | PD-1       | Placebo   | /                   | 514            | 54 (19-88) | 324 (63) | Melanoma |
| (Eggermont et al., 2018) |                       |                          |                   |       |            |                     |            |             |         |           |
| NCT02578680       | Yes                 | 16                       | 126               | Phase 3 | PD-1       | Placebo   | /                   | 505            | 54 (19-83) | 304 (60.2) | SCLC |
| (Gandhi et al., 2018) |                       |                          |                   |       |            |                     |            |             |         |           |
| NCT02231749       | Yes                 | 28                       | 175               | Phase 3 | PD-1/CTLA4 | Placebo   | /                   | 206           | 63.5 (34-84) | 109 (52.9) | RCC |
| (Motzer et al., 2018) |                       |                          |                   |       |            |                     |            |             |         |           |
| NCT02775435       | Yes                 | 17                       | 137               | Phase 3 | PD-1       | Placebo   | /                   | 281            | 65 (29-87) | 220 (79.1) | NSCLC |
| (Paz-Ares et al., 2018) |                       |                          |                   |       |            |                     |            |             |         |           |

(Continued)
| NCT Author (year) | International study | No. of countries involved | No. of study sites | Phase | Group type | Drug | Dose of ICI (mg/kg) | No. of patients | Age Median (range) | No (%) Male | Tumor type |
|-------------------|---------------------|--------------------------|-------------------|-------|------------|------|-------------------|----------------|-------------------|-------------|------------|
| NCT02370498      | Yes                 | 30                       | 148               | Phase 3 | PD-1       | Pembrolizumab | 200 mg/dose       | 296             | 62.5 (54–70)      | 202 (68)   | GEJ        |
| (Shitara et al., 2018) |                     |                          |                   |       | Control     | Pacitaxel | /                 | 296             | 60.0 (53–68)      | 208 (70)   |            |
|                   |                     |                          |                   |       | Pembrolizumab | 200 mg/dose | /                 | 247             | 60.0 (55–66)      | 207 (84)   | HNSCC      |
| NCT02252042      | Yes                 | 20                       | 97                | Phase 3 | PD-1       | Pembrolizumab | 200 mg/dose       | 247             | 62.0 (54–66)      | 206 (83)   |            |
| (Cohen et al., 2019) |                     |                          |                   |       | Control     | Methotrexate Docetaxel/ Cetuximab | /                 | 248             | 60.0 (54–66)      | 205 (83)   |            |
| NCT02788279      | Yes                 | 11                       | 73                | Phase 3 | PD-L1      | Atezolizumab | 840 mg/dose       | 183             | 60.0 (54–66)      | 107 (58)   | Colorectal cancer |
| (Eng et al., 2019) |                     |                          |                   |       | Control     | Cobimetinib | /                 | 90              | 59 (61–64)        | 59 (66)    |            |
|                   |                     |                          |                   |       | PD-L1      | Atezolizumab | 1,200 mg/dose     | 90              | 59 (61–64)        | 59 (66)    |            |
|                   |                     |                          |                   |       | Control     | Pegafenib | /                 | 90              | 59 (61–64)        | 59 (66)    |            |
| NCT02220894      | Yes                 | 32                       | 213               | Phase 3 | PD-1       | Pembrolizumab | 200 mg/dose       | 636             | 63 (56–69)        | 450 (71)   | NSCLC      |
| (Mok et al., 2019) |                     |                          |                   |       | Control     | Platinum | /                 | 615             | 63 (56–69)        | 452 (71)   |            |
| NCT02613507      | Yes                 | 3                        | 32                | Phase 3 | PD-1       | Nivolumab | 3                 | 338             | 60 (27–78)        | 236 (78)   | NSCLC      |
| (Wu et al., 2019) |                     |                          |                   |       | Control     | Docetaxel | /                 | 166             | 60 (38–78)        | 134 (81)   |            |
| NCT02454933      | No                  | 1                        | 1                 | Phase 3 | PD-L1      | Durvalumab | 10 mg/kg          | 12              | 56 (41–78)        | 6 (50)     | NSCLC      |
| (Chih-Hsin Yang et al., 2019) |                 |                          |                   |       | Control     | Osimertinib | /                 | 17              | 65 (41–80)        | 4 (24)     |            |
| NCT01585987      | Yes                 | 12                       | NR                | Phase 2 | CTLA4      | Ipilimumab | 10 mg/kg          | 57              | NR (NR)          | NR (NR)    | GEJ        |
| (Squibb, 2012)   |                     |                          |                   |       | Control     | Fluoropyrimidine | /                 | 57              | NR (NR)          | NR (NR)    |            |
| NCT01984242      | Yes                 | 9                        | NR                | Phase 2 | PD-L1      | Atezolizumab | 1,200 mg/dose     | 103             | NR (74 73.3)      | 77 (74.8)  | RCC        |
| (Roche, 2014)    |                     |                          |                   |       | Control     | Bevacizumab | 1,200 mg/dose     | 101             | NR (74 73.3)      | 77 (74.8)  |            |
| NCT02367781      | Yes                 | 36                       | NR                | Phase 3 | PD-L1      | Atezolizumab | 1,200 mg/dose     | 483             | NR (78 72.2)      | NR (78 72.2)| NSCLC      |
| (Roche, 2015b)   |                     |                          |                   |       | Control     | Nab-paclitaxel | /                 | 240             | NR (78 72.2)      | NR (78 72.2)|            |
| NCT02352948      | Yes                 | NR                       | 82                | Phase 3 | subA       | Nab-paclitaxel | /                 | 240             | NR (78 72.2)      | NR (78 72.2)|            |
| (AstraZeneca, 2015) |                     |                          |                   |       | Control     | Nab-paclitaxel | /                 | 240             | NR (78 72.2)      | NR (78 72.2)|            |
| NCT02367781      | Yes                 | NR                       | 143               | Phase 3 | subB       | Durvalumab | 10                | 62              | NR (67.7)         | 42 (67.7)  | NSCLC      |
| (Roche, 2015b)   |                     |                          |                   |       | Control     | Durvalumab | /                 | 240             | NR (67.7)         | 42 (67.7)  |            |
|                   |                     |                          |                   |       | PD-L1/CTL4 | Durvalumab | 20                | 174             | NR (66.1)         | 115 (66.1) |            |
|                   |                     |                          |                   |       | Control     | Tremelimumab | 1                | 64              | NR (75.0)         | 48 (75.0)  |            |
|                   |                     |                          |                   |       | PD-L1      | Durvalumab | 10                | 117             | NR (73.0)         | 73 (62.4)  |            |

(Continued)
| NCT Author (year) | International study | No. of countries involved | No. of study sites | Phase | Group type | Drug | Dose of ICI (mg/kg) | No. of patients | Age Median (range) | No (%) Male | Tumor type |
|-------------------|---------------------|--------------------------|--------------------|-------|------------|------|-------------------|----------------|------------------|------------|-------------|
| NCT02420821 (Roche, 2015a) | Yes | 21 | NR | Phase 3 | CTLA4 | Tremelimumab | 10 | 60 | NR | 39 (65.0) | RCC |
| NCT00094653 (Hodi et al., 2010) | Yes | 13 | 125 | Phase 3 | CTLA4 | Ipilimumab | 3 | 403 | 56.8b | 247 (61.3) | Melanoma |
| NCT00324155 (Robert et al., 2011) | Yes | NR | 25 | Phase 3 | CTLA4 | Ipilimumab | 10 | 250 | 57.5a | 152 (60.8) | Melanoma |
| NCT0257205 (Ribas et al., 2013) | Yes | 24 | 114 | Phase 3 | CTLA4 | Dacarbazine | 3 | 252 | 56.4a | 149 (59.1) | NSCLC |
| NCT02763579 (Horn et al., 2018) | Yes | 21 | 106 | Phase 3 | PD-1/ CTLA4 | Nivolumab/ipilimumab | 3 | 396 | NR | PD-L1 expression: 1% | NSCLC |
| NCT02425891 (Schmid et al., 2018) | Yes | 41 | 246 | Phase 3 | PD-1 | Nivolumab | 240 mg/dose | 396 | NR | NR |
| NCT02366143 (Socinski et al., 2018) | Yes | 26 | 240 | Phase 3 | PD-1 | Nivolumab | 3 | 187 | NR | PD-L1 expression | NSCLC |
| NCT02684006 (Motzer et al., 2019) | Yes | 21 | 144 | Phase 3 | PD-1/ CTLA4 | Nivolumab/ipilimumab | 3 | 177 | NR | <1% NSCLC | Breast cancer |

(Continued)
High dose of ICIs was not associated with high rates of hyperglycemia events (Table 2).

Due to the smaller number of other ICI-associated diabetes events, no statistical inferences of the rates were made. Overall, 13 cases of DM occurred in 5,655 patients (raw event rate 0.23%), five cases of T2D occurred in 3,117 patients (raw event rate 0.16%), and 17 cases of all-grade T1D occurred in 3,899 patients (raw event rate 0.44%), and 15 cases of serious-grade T1D events occurred in 3,603 patients (raw event rate 0.42%).

**Risk of Diabetes-Related Adverse Events**

To assess the relative rate of ICI-associated diabetes compared with those in control arms, we calculated the OR of developing diabetes in the RCTs. Pooling the data of these studies showed that patients treated with ICIs were at higher risk for serious-grade hyperglycemia (OR 2.41, 95% CI 1.52 to 3.82, Figure 2), DM (OR 3.54, 95% CI 1.32 to 9.51, Figure 3), all-grade T1D (OR 6.60, 95% CI 2.51 to 17.30, Figure S1), and serious-grade T1D (OR 6.50, 95% CI 2.32 to 18.17, Figure 4) than those treated with other regimens. ICIs showed a trend toward an increased risk of all-grade hyperglycemia (OR 1.38, 95% CI 1.15 to 1.66, Figure S2), but no increased risk of T2D (OR 0.92, 95% CI 0.24 to 3.52, Figure S3). Excluding the study in which the control group was everolimus, a drug known to cause diabetes, the risk of ICI-associated diabetes events were also higher than the control: OR 4.42 for DM, OR 1.75 for all-grade hyperglycemia, OR 2.81 for serious-grade hyperglycemia (Figures S4–S6).

**TABLE 2 | Incidence of hyperglycemia events in patients treated with immune checkpoint inhibitors. Values are percentages (95% confidence intervals).**

| Characteristic                  | All-grade hyperglycemia | Serious-grade hyperglycemia |
|---------------------------------|-------------------------|-----------------------------|
| **Total**                       | 2.26 (1.28, 3.48)       | 0.28 (0.16, 0.42)           |
| **ICI type**                    |                         |                             |
| PD-1 inhibitors                 | 4.86 (2.86, 7.32)       | 0.49 (0.26, 0.78)           |
| PD-L1 inhibitors                | 0.81 (0.07, 2.06)       |                             |
| CTLA-4 inhibitors               | 0.52 (0.09, 1.18)       | 0.06 (0.00, 0.28)           |
| Combination therapy             | 3.37 (0.00, 21.49)      | 0.47 (0.00, 2.01)           |
| **Tumor type**                  |                         |                             |
| NSCLC                           | 2.54 (1.10, 4.43)       | 0.22 (0.06, 0.45)           |
| Melanoma                        | 1.75 (0.31, 4.15)       | 0.35 (0.09, 0.73)           |
| RCC                             | 6.82 (2.00, 14.05)      | 0.66 (0.27, 1.18)           |
| Prostate cancer                 | 0.12*                   | 0.12*                       |
| Colorectal cancer               | 0.37*                   |                             |
| GEJ                             | 0.57*                   | 0.53*                       |
| HNSCC                           | 5.42*                   | 0.42*                       |
| Mesothelioma                    | 0.52*                   | 0.52*                       |
| SCLC                            | 0.63*                   | 0.63*                       |
| **Dose**                        |                         |                             |
| High dose                       | 1.33 (0.27, 2.99)       | 0.22 (0.00, 0.80)           |
| Normal dose                     | 2.52 (1.32, 4.03)       | 0.29 (0.15, 0.44)           |

GEJ, gastric and gastroesophageal junction cancer; HNSCC, head and neck squamous cell carcinomas; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; SCLC, small-cell lung cancer.

aRaw event rate.
FIGURE 2 | Risk of serious-grade hyperglycemia following the use of ICIs versus control treatment, stratified by the type of control group.

| Study | ID | OR (95% CI) | % Weight | ICIS Event/Patient | Control Event/Patient |
|-------|----|-------------|----------|-------------------|----------------------|
| Chemotherapy | Paz-Ares (2018) | 1.01 (0.06, 16.20) | 12.67 | 1/278 | 1/281 |
|          | Rock (2018) | 7.29 (0.45, 117.16) | 12.65 | 2/154 | 0/151 |
|          | Hsu (2018) | 7.33 (0.15, 328.18) | 12.34 | 1/346 | 3/434 |
|          | Muk (2019) | 7.15 (0.14, 306.49) | 6.34 | 8/1836 | 0/815 |
|          | Rock (2019) | 0.13 (0.03, 6.70) | 6.34 | 0/478 | 1/1479 |
|          | Powles (2017) | 7.34 (0.13, 370.01) | 6.34 | 1/4677 | 0/4664 |
|          | NCT02630788 ( ) | 4.47 (0.07, 288.85) | 6.34 | 1/4835 | 0/5240 |
|          | NCT02620981 ( ) | 7.43 (0.15, 375.81) | 6.34 | 1/1177 | 0/4933 |
|          | Herbst (2016) | 0.00 | 0/000 | 0/000 |
|          | NCT02325494 ( ) | 0.00 | 0/000 | 0/000 |
|          | NCT02325495 ( ) | 0.00 | 0/000 | 0/000 |
|          | Subtotal (excluded = 0.00, p = 0.759) | 2.13 (0.00, 10.89) | 62.68 |
| Immunosuppressive drug | Motzer (2015) | 0.14 (0.00, 6.64) | 6.34 | 0/410 | 1/411 |
|          | Subtotal (excluded = 0.00, p = 0.759) | 0.14 (0.00, 6.64) | 6.34 |
| Targeted therapy | NCT02402321 ( ) | 7.47 (0.13, 375.51) | 6.34 | 1/4686 | 0/451 |
|          | NCT02184242 ( ) | 7.39 (0.15, 372.38) | 6.34 | 1/1961 | 0/101 |
|          | Motzer (2018) | 7.35 (0.46, 117.64) | 12.68 | 2/550 | 0/546 |
|          | NCT02184242 ( ) | 7.39 (1.04, 52.48) | 25.36 |
|          | Subtotal (excluded = 0.00, p = 1.000) | 7.39 (1.04, 52.48) | 25.36 |
| Placebo | Beer (2017) | 20.19 (0.32, 1292.89) | 5.03 | 1/199 | 0/3099 |
|          | Subtotal (excluded = 0.00, p = 1.000) | 20.19 (0.32, 1292.89) | 5.03 |
| Chemotherapy/Targeted therapy | NCT02325494 ( ) | 0.00 | 0/000 | 0/000 |
|          | NCT02325495 ( ) | 0.00 | 0/000 | 0/000 |
|          | Subtotal (excluded = 0.00, p = 0.759) | 3.54 (1.32, 9.51) | 100.00 |

FIGURE 3 | Risk of diabetes mellitus following the use of ICIs versus control treatment, stratified by the type of control group.
Subgroup analysis for these outcomes was stratification by the type of control, the mode of treatment, and type of ICI. Regarding the type of control, there were apparent differences across subgroups for the risk of ICI-associated diabetes events. Within the placebo-controlled group, ICIs were associated with a higher risk in hyperglycemia (OR 5.81). Subgroup analysis based on the mode of treatment (monotherapy vs. add-on therapy) suggests that add-on therapy decreased the risk of ICI-associated diabetes, with OR 1.77 for DM, 1.31 for serious-grade hyperglycemia, 0.58 for T2D, and 5.83 for T1D (Figures S7–S11). The subgroup analysis by the type of ICI suggests the risk of these events was increased in the subset of trials in which anti-PD-1 or anti-PD-L1 was combined with anti-CTLA-4, with OR 7.35 for DM, 2.51 for all-grade hyperglycemia, 4.18 for serious-grade hyperglycemia (Figures S12–S17).

The funnel plot and statistical test showed no evidence of publication bias for DM (Egger’s test P = 0.994), all-grade hyperglycemia (Egger’s test P = 0.128), serious-grade hyperglycemia (Egger’s test P = 0.325), T2D (Egger’s test P = 0.310), all-grade T1D (Egger’s test P = 0.300), and serious-grade T1D (Egger’s test P = 0.334) (Table S3, Figures S18–S23). We noted no heterogeneity in the effects of ICI on DM, serious-grade hyperglycemia, T2D, all-grade T1D, and serious-grade T1D (I² = 0.0%). However, we noted substantial heterogeneity for the outcome of all-grade hyperglycemia (I² = 88.2%), which was considerably reduced in the analyses of data excluding the everolimus-controlled study (I² = 8.0%).

**DISCUSSION**

We completed a systematic analysis of new-onset diabetes following treatment with ICIs versus other therapeutic regimens to further our understanding of the safety of these agents. We used data from 40 RCTs that included 13,787 patients treated with ICIs, and also extracted data from the ClinicalTrials.gov results database to supplement the published studies. To our knowledge, this is the largest and most comprehensive meta-analysis on the incidence and risk of ICI-associated diabetes events following the use of ICI regimens published to date, although previous case series analyses showed that there is an increased reporting of rapidly progressive ICI-associated diabetes (Wright et al., 2018; Kotwal et al., 2019; Perdigoto et al., 2019). This meta-analysis shows that the risk of serious-grade hyperglycemia, DM, and T1D following ICIs is significantly higher compared with patients treated with other regimens, but provides no support that ICI treatment is associated with an increased risk of all-grade of hyperglycemia. Among patients on each different ICI regimen, patients on combination therapy were more likely to develop hyperglycemia. Although the incidence was low, T1D has emerged as the highest risk associated with ICI therapy compared with other diabetes-related adverse events. The pathogenesis of T1D in the populations of patients receiving ICIs is not currently well understood. Several case reports have shown that the presence of autoantibodies before ICIs-based therapy might be at risk of developing diabetes, particularly in treated with anti-PD-1/anti-PD-L1 (Gauci et al., 2017; Usui et al., 2017; Way et al., 2017). Further support for autoimmune-based mechanism has been shown by Clotman et al. (2018), who overviewed the reported cases and demonstrated that approximately half of the tested cases of ICI-associated T1D had detectable diabetes-related autoantibodies. Other studies have shown that anti-PD-1 resulted in a rapid progression of autoimmune diabetes in patients with a high underlying genetic predisposition to T1D.
solid tumors, which achieved synergetic effects and overcame the absolute number of T1D in patients receiving ICIs. The regimen substantially increased the risk of ICI-associated diabetes events. A sensitivity analysis excluding hyperglycemia, which strengthens the primary conclusion that ICIs increased risks of diabetes events. In summary, the use of ICIs compared with placebo or other treatment strategies was associated with an increased risk of new-onset diabetes, especially autoimmune diabetes, although the overall event rates remained low. In contrast, compared with the control group, the risk of T2D was not increased. As the widespread awareness of these events increases, additional large, well-designed randomized trials are needed to definitively determine the risks of new-onset diabetes following the use of ICIs.

DATA AVAILABILITY STATEMENT
The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS
JL, JY, and XZ conceived and designed the study. YL, HM, JZ, JL, and JW wrote the manuscript. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpharm.2019.01453/full#supplementary-material
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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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