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ORIGINAL RESEARCH ARTICLE

Risk of Infection with Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis

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Abstract

Background The relative risk (RR) of infection for patients treated with immune checkpoint inhibitors (ICIs) is unknown.

Objectives This study evaluated the risk of infection for patients with solid tumors undergoing ICI therapy based on a systematic review and meta-analysis.

Patients and Methods The Cochrane Library, EMBASE, and Pubmed databases were searched up to 1 December 2020. Randomized trials comparing any ICI alone, with chemotherapy (CT), or with other agents *versus* placebo, CT, or other agents were included. Three independent reviewers extracted the data. The primary outcome was the RR of all-grade (G) and G3–5 infections for patients receiving ICI-based treatments. Random or fixed-effect models were used according to statistical heterogeneity.

Results A total of 21,451 patients from $N = 36$ studies were eligible. ICIs were associated with a similar risk of all-grade infections (RR = 1.02; 95% CI 0.84–1.24; $P = 0.85$) versus non-ICI treatments (G1–5 events: 9.6 *versus* 8.3%). When the ICIs alone were compared to CT, their use was associated with 42% less risk of all-grade infections (RR = 0.58, 95% CI 0.4–0.85; $P = 0.01$). Compared to CT, the combination of ICIs and CT increased the risk of all-grade (RR = 1.37, 95% CI 1.23–1.53; $P < 0.01$) and severe infections (RR = 1.52, 95% CI 1.17–1.96; $P < 0.01$). In anti-PD-1, anti-PD-L1, anti-CTLA-4, monotherapy, and combination trials, the RR of all-grade infections was 0.72 (95% CI 0.49–1.05; $P = 0.09$), 1.18 (95% CI 0.95–1.46; $P = 0.13$), 1.74 (95% CI 1.13–2.67; $P = 0.01$), 0.97 (95% CI 0.79–1.19; $P = 0.75$) and 2.26 (95% CI 1.34–3.8; $P < 0.01$), respectively.

Conclusions Compared to CT alone, ICIs were safer and are recommended for frail patients. Conversely, CT + ICIs or ICIs combinations increased infection risk. Further studies are required to identify high-risk patients and evaluate the need for CT dose reduction or prophylactic myeloid growth factors.

1 Introduction

An impaired immune response and the loss of barrier integrity due to tumor development and treatments (e.g., those causing myelosuppression) render cancer patients more susceptible to infections. Infections and neutropenia represent some of the most common life-threatening side effects, generating higher mortality and morbidity in patients who are treated with chemotherapy (CT) [1]. Diverse clinical factors identify the patients who have a high risk of developing neutropenia. These factors include: older age, advanced disease, poor performance status, the nature of the anti-cancer treatment, concomitant steroid use, no granulocyte colony-stimulating factor (G-CSF) use, underlying chronic lung disease, and hepatic or renal insufficiency [2].

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Key Points

The use of immune checkpoint inhibitors (ICIs) in monotherapy is associated with a lower risk of all-grade infections.

Chemotherapy combined with ICIs increased the incidence of infections.

ICIs as monotherapy are recommended for frail patients (including: older age, advanced disease, and poor performance status).

Immune checkpoint inhibitors (ICIs) boost the spontaneous, pre-existing, adaptive anti-tumor immune response by rescuing the activity of the patients' dysfunctional immune cells. The most common adverse events (AEs) linked to ICIs have an autoimmune-like hyperactivation genesis. Interestingly, a *stimulus* to the function of the T helper-1 (Th1) cells could be responsible for the sporadic reactivation of tuberculosis, as found in several patients who were treated with anti-programmed cell death-1 (PD-1) antibodies [3, 4]. Additionally, a retrospective study on melanoma patients revealed that the immunosuppressive drugs employed for the management of immune-related AEs (e.g., steroids and the tumor necrosis factor-alpha (TNF-α) inhibitor infliximab) represent the main risk factors for the development of infections in patients undergoing ICIs [5]. Furthermore, a recent meta-analysis revealed that patients with solid tumors who were treated with ICIs were less likely to develop severe AEs than those receiving CT [6].

Currently, ICIs are being used either alone or in combination with other agents, such as CT, and the risk of infection in these patients is unknown. It is not clear which agents (e.g., bacteria, virus, and fungi) or which sites (e.g., lung, urinary system, gastrointestinal tract, skin, etc.) are most associated with infections in patients treated with ICIs.

We performed this systematic review and meta-analysis to evaluate the incidence, grade (G), and relative risk (RR) of infection in patients with solid tumors who were enrolled in randomized trials and receiving ICIs as single agents or in combination with CT *versus* other treatments (e.g., CT and placebo).

2 Material and Methods

This systematic review was carried out in accordance with the statement in the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [7].

2.1 Search Strategy and Study Selection

We identified all studies that prospectively evaluated the risk of infection in patients with solid tumors treated with an ICI. A systematic search on multiple electronic databases (Pubmed, EMBASE, and the Cochrane Central Register of Controlled Trials) was conducted from inception to 1 December 2020. The search strategy included the following terms: *(atezolizumab or nivolumab or pembrolizumab or avelumab or durvalumab or cemiplimab or ipilimumab or tremelimumab) and (fungal or viral or infection or infestation or flu-like symptoms or influenza-like illness or tuberculosis or pneumonia or sepsis or septic shock or infection [MeSH Terms] or abscess).* To ensure that any missing studies were included, the references from the included publications were reviewed manually to identify any additional studies.

A total of $N = 36$ randomized studies was included among the $N = 1234$ publications retrieved from a systematic search (Fig. 1) [8–43]. The study types were as follows: $N = 29$ phase III, $N = 1$ phase II–III, and $N = 6$ phase II. Thirteen trials compared CT + ICIs *versus* CT alone, $N = 18$ compared ICIs alone *versus* CT alone or other targeted therapies, and $N = 5$ compared ICIs alone *versus* no active treatment (placebo or best supportive care). A total of $N = 21{,}451$ patients were analyzed in the quantitative analysis ($N = 12{,}346$ and $N = 9305$ in the experimental and control arms, respectively).

The types of tumors that were treated in the included studies were as follows: lung cancer ($N = 18$), urothelial cancer ($N = 5$), breast cancer ($N = 4$), head and neck and esophageal cancer ($N = 3$), colorectal carcinoma ($N = 2$), melanoma ($N = 2$), prostate cancer ($N = 1$), and renal cell carcinoma ($N = 1$). The disease stages were all locally advanced or metastatic, except for $N = 2$ studies, where the ICIs were added to the standard (neoadjuvant) CT in early-stage breast cancer.

The experimental arms included nivolumab ($N = 4$), pembrolizumab ($N = 9$), durvalumab ($N = 2$), atezolizumab ($N = 9$), avelumab ($N = 2$), ipilimumab ($N = 2$), tremelimumab ($N = 1$), and a combination of two ICIs ($N = 4$; durvalumab + tremelimumab in $N = 3$ studies and nivolumab + ipilimumab in $N = 1$ study).

In $N = 3$ studies, targeted therapies were present in the experimental and control arms (atezolizumab + cobimetinib, atezolizumab + trastuzumab emtansine (TDM-1), and pembrolizumab + axitinib *versus* regorafenib, TDM-1, and sunitinib, respectively).

2.2 Inclusion Criteria

We included prospective phase II or III randomized clinical trials that reported the risk of infection in adult patients

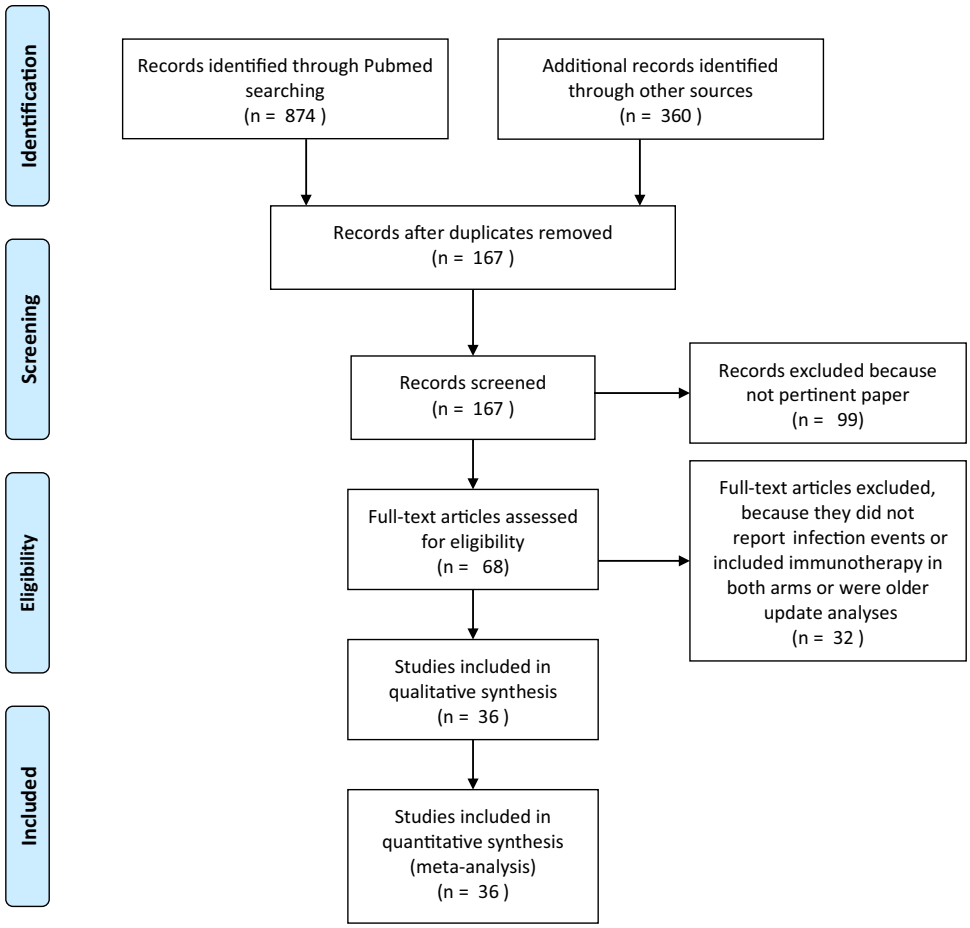

Fig. 1 Flow diagram of the included studies.

treated with the anti-PD-1 nivolumab, pembrolizumab, or cemiplimab, the anti-CTLA-4 ipilimumab or tremelimumab, or the anti-PD-L1 avelumab, atezolizumab, or durvalumab either alone or in combination with other ICIs (or CT/other agents) for any solid tumor. The incidence rates were then compared to non-ICI arms (CT or agents alone (e.g., tyrosine kinase inhibitors) or placebo/best supportive care). Studies were included if they reported toxicities according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 or 4.0. We excluded studies that included patients who had previously been exposed to the same class(es) of ICI therapy, pediatric patients, or patients with hematological malignancies.

2.3 Data Extraction and Study Quality

Two investigators (FP and AMM) independently reviewed and identified relevant studies that were eligible for inclusion and used a standardized Microsoft Word template to extract data from each of the included studies. Disagreements on study inclusion were resolved by consensus with a third investigator (CS). The following information was extracted: baseline study characteristics, including primary tumor, author, year of publication, and type of trial, type of disease, type of therapy (experimental and control arms), the incidence of any-G (G1–5), low-G (G1–2), and high-G (G3–4) and fatal-event (G5) infections, and the type of event(s).

The tools in the Cochrane handbook for evaluating randomized controlled trials were used to assess the sources of bias in each study [44]. The bias parameters included random sequence generation and allocation concealment (selection bias), the blinding of the outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. Each trial was categorized based on the risk of bias, as follows: low risk of bias (+); high risk of bias (−); and unclear (?). The publication bias was also evaluated by inspecting a funnel plot and using Begg's and Egger's tests (Table 1).

2.4 Assessment of the Certainty of Evidence (GRADE)

We used the GRADE system to rate the quality of evidence relating to the estimated treatment effects on the rates of all-grade and G3–5 infections [45]. The GRADE criteria for assessing the quality of evidence included the study design, risk of bias, inconsistency, indirectness, imprecision, suspected publication bias, and other considerations. The assessments of these criteria and corresponding justifications are provided in Table 2. We performed GRADE assessments separately for selected subgroups related to inconsistency (e.g., heterogeneity) among effect estimates for the primary endpoint.

2.5 Statistical Analysis

The number (or rate) of events was compared, and the relative risk (RR with a 95% confidence interval (CI)) was calculated. The primary endpoint was the rate of all-grade infections. The secondary endpoint was the rate of severe infections (G3–5). The following three primary subgroup analyses were performed: ICIs *versus* CT arms; ICIs *versus* control arm, including no active treatment (e.g., best supportive care or placebo); and ICIs + CT or other agents *versus* CT or other agents alone. To account for heterogeneity across the study populations and designs, the incidence of infection was determined using random- or fixed-effects models. We assessed the heterogeneity among the studies in each analysis using a visual inspection and statistically using the Chi-square (Chi^2) test and the I-square (I^2) statistic. We used a P value threshold of 0.10 to determine statistical significance for the Chi^2 test and considered an I^2 of 50% or more to be a high degree of heterogeneity. The Review Manager (RevMan) (computer program) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for the statistical analysis.

3 Results

3.1 Incidence of Infections

Overall, the risk of all-grade (G1–5) infections was 9.6% and 8.3% for ICIs and non-ICIs (all studies), respectively. These values were 16.5% in the combination and 11.2% for CT alone, 3.9% in ICIs alone and 6.3% in CT alone comparisons, and 16.2% in ICIs alone *versus* 9.4% for best supportive care or placebo (no active treatment). The risk of high G infections was 3.1% and 2.6% for ICIs and non-ICIs, respectively. When added to CT, the combination of ICIs + CT was associated with a 4.4% incidence of G3–5 infections compared to 2.4% for CT alone. G5 infections were 0.5% for the experimental and 0.5% for the control group.

3.2 Risk of All-Grade and G3–5 Infections

In the pooled analysis, the use of ICIs was associated with a similar risk of all-grade infections (RR = 1.02; 95% CI 0.84–1.24; $P = 0.85$; Fig. 2) compared to non-ICIs. Compared to non-ICI arms, the use of ICIs did not increase the risk of severe (G3–5) infections (RR = 0.99; 95% CI 0.74–1.32; $P = 0.95$; Fig. 3). Fatal infections were also lower (albeit non-significantly) for ICIs compared to non-ICIs (RR = 0.77; 95% CI 0.52–1.13; $P = 0.18$).

3.3 Subgroup Analyses

Compared to CT, the combination of ICIs and CT increased the risk of all-grade infections (RR = 1.37; 95% CI 1.23–1.53; $P < 0.01$; $N = 13$ studies; Fig. 4). When ICIs alone were compared to CT, the experimental arms were associated with 42% less risk of G1–5 infections (RR = 0.58; 95% CI 0.4–0.85; $P < 0.01$; $N = 18$ studies; Fig. 5). Conversely, compared to non-active treatments (placebo or best supportive care; $N = 5$ studies), ICIs increased the risk of all-grade infections (RR = 1.53; 95% CI 1.23–1.9; $P < 0.01$; Fig. 6).

For G3–5 infections, ICIs alone increased the risk compared to placebo or best supportive care (RR = 2.11; 95% CI 1.04–4.26; $P = 0.04$; $N = 5$ studies). Compared to CT alone, ICIs reduced the risk of G3–5 infections (RR = 0.52; 95% CI 0.34–0.78; $P < 0.01$; $N = 18$ studies). When added to CT, ICIs increased the risk of severe infection (RR = 1.52; 95% CI 1.17–1.96; $P < 0.01$; $N = 12$ studies).

In lung cancer studies, which represented 50% of the total included, the RR of G1–5, G3–5, and G5 infections was not superior in ICIs *versus* control treatment (data not shown). Similarly, the risk of infection with ICIs was not greater than the control treatments in non-lung cancer trials. In an exploratory analysis, RR was not correlated to rates of febrile neutropenia or of G3–4 neutropenia.

In anti-PD-1, anti-PD-L1, anti-CTLA-4, monotherapy, and combination trials, the RR of infections at all grades was 0.72 (95% CI 0.49–1.05; $P = 0.09$), 1.18 (95% CI 0.95–1.46; $P = 0.13$), 1.74 (95% CI 1.13–2.67; $P = 0.01$), 0.97 (95% CI 0.79–1.19; $P = 0.75$), and 2.26 (95% CI 1.34–3.8; $P < 0.01$).

3.4 Risk of Bias

A low risk of bias was observed in $N = 23$ studies for the unblinding study design (formal absence of a placebo in the control). No relevant biases were found in $N = 13$ studies. Although Egger's tests for funnel plot asymmetry indicated evidence of publication bias for the all-grade infection

Table 1 Characteristics of included studies

Author/year	Phase of the trial	No. of patients	Primary tumor	Study treatment (exp (*N*) vs. ctr arms (*N*))	Infection rate (%) (exp vs. ctr arms)	Type of infection	G1–2 (%) (exp vs. ctr arms)	G3–4 (%) (exp vs. ctr arms)	G5 (%) (exp vs. ctr arms)	Bias (ROB-2)
Andrè 2020 [8]	III	307	Colorectal cancer	Pembro vs. CT 153 vs. 154	19.60 vs. 16.78	Respiratory tract infection, urinary infection	NA	0.65 vs. 2.79	NA	Low
Antonia 2017 [9]	III	713	NSCLC	Durva vs. placebo 476 vs. 237	25.26 vs. 17.52	Respiratory tract infection, sepsis, septic shock, West Nile virus infection	NA	4.63 vs. 3.84	1.05 vs. 2.13	No
Barlesi 2018 [10]	III	792	NSCLC	Ave vs. CT 396 vs. 396	0.76 vs. 9.58	Pneumonia, sepsis, respiratory tract infection, soft tissue infection, encephalitis	0.50 vs. 3.28	0.25 vs. 4.38	0 vs. 1.91	Low
Brahmer 2015 [29]	III	272	NSCLC	Nivo vs. CT 135 vs. 137	0.76 vs. 4.65	Respiratory infection, sepsis, neutropenic infection	NA	0.76 vs. 3.87	0 vs. 0.77	Low
Borghaei 2015 [11]	III	582	NSCLC	Nivo vs. CT 292 vs. 290	0 vs. 5.59	Pneumonia, septic shock, nail infection	0 vs. 0.37	0 vs. 5.22	0 vs. 0	Low
Cohen 2019 [12]	III	495	Head and neck carcinoma	Pembro vs. CT 247 vs. 248	12.19 vs. 37.03	Respiratory tract infection, skin infection, soft tissue infection	NA	0.81 vs. 8.97	0	Low
Emens 2020 [13]	II	202	Breast cancer	Atezo + T-DM1 vs. T-DM1+ placebo 133 vs. 69	34.58 vs. 34.32	Respiratory infection, skin infection, urinary infection, sepsis, TBC	28.57 vs. 25.37	6.01 vs. 8.95	0 vs. 0	No
Eng 2019 [14]	III	363	Colorectal cancer	Atezo + cobimetinib or Atezo vs. regorafenib 273 vs. 90	14.49 vs. 12.5	Sepsis, respiratory tract infection, skin infection, urinary infection	8.17 vs. 6.25	5.57 vs. 6.25	0.74 vs. 6	Low
Fehrenbacher 2016 [15]	II	287	NSCLC	Atezo vs. CT 144 vs. 143	NA	Sepsis, pneumonia	NA	2.11 vs. NA	0.70 vs. 0.74	Low

Table 1 (continued)

Author/year	Phase of the trial	No. of patients	Primary tumor	Study treatment (exp (*N*) vs. ctr arms (*N*))	Infection rate (%) (exp vs. ctr arms)	Type of infection	G1–2 (%) (exp vs. ctr arms)	G3–4 (%) (exp vs. ctr arms)	G5 (%) (exp vs. ctr arms)	Bias (ROB-2)
Ferris 2016 [16]	III	361	Head and neck carcinoma	Nivo vs. CT 240 vs. 121	15.67 vs. 18.91	Pneumonia, sepsis, respiratory tract infection, urinary infection, device-related infection	NA	11.44 vs. 15.31	0.42 vs. 0.90	Low
Fradet 2019 [17]	III	542	Urothelial cancer	Pembro vs. CT 272 vs. 270	0 vs. 2.74	Urinary tract infection, septic shock, sepsis	NA	NA	0 vs. 1.17	Low
Galsky 2020 [18]	II	108	Urothelial cancer	Pembro vs. placebo 55 vs. 53	21.81 vs. 17.30	Respiratory infection, urinary infection	14.54 vs. 17.30	7.27 vs. 0	0 vs. 0	No
Gandhi 2018 [19]	III	616	NSCLC	Pembro + CT vs. CT 410 vs. 206	24.44 vs. 21.28	Pneumonia, sepsis, urinary infection	NA	2.22 vs. 0.49	1.72 vs. 1.48	Low
Goldman 2020 [20]	III	805	SCLC	Durva + tremelimumab + CT or durva + CT vs. CT 536 vs. 269	9.03 vs. 7.06	Pneumonia, sepsis, urinary infection, *C. difficile* colitis	NA	7.53 vs. 6.69	1.50 vs. 0.37	Low
Herbst 2015 [21]	II/III	1034	NSCLC	Pembro vs. CT 691 vs. 343	2.19 vs. 7.11	Pneumonia, respiratory tract infection, urinary infection, sepsis, TBC	NA	NA	0.29 vs. 0.32	Low
Herbst 2020 [22]	III	572	NSCLC	Atezo vs. CT 285 vs. 287	14.33 vs. 17.11	Pneumonia, respiratory tract infection, urinary infection, sepsis, TBC	9.79 vs. 9.12	4.19 vs. 6.84	0.34 vs. 1.14	Low
Horn 2018 [23]	I/III	403	SCLC	Atezo + CT vs. CT 201 vs. 202	4.04 vs. 6.12	Respiratory tract infection, septic shock, urinary infection, cytomegalovirus infection	1.51 vs. 1.02	2.02 vs. 3.06	0.50 vs. 2.04	Low

Table 1 (continued)

Author/year	Phase of the trial	No. of patients	Primary tumor	Study treatment (exp (*N*) vs. ctr arms (*N*))	Infection rate (%) (exp vs. ctr arms)	Type of infection	G1–2 (%) (exp vs. ctr arms)	G3–4 (%) (exp vs. ctr arms)	G5 (%) (exp vs. ctr arms)	Bias (ROB-2)
Jotte 2020 [24]	III	1021	NSCLC	Atezo + CT vs. CT 681 vs. 340	2.10 vs. 2.09	Sepsis, pneumonia, septic shock	0.15 vs. 0	1.05 vs. 1.49	0.90 vs. 0.59	Low
Kato 2019 [25]	III	419	Oesophageal squamous cell carcinoma	Nivo vs. CT 210 vs. 209	0.95 vs. 2.88	Pneumonia, sepsis, spinal cord abscess	NA	0 vs. 0.48	0.95 vs. 1.92	Low
Kwon 2014 [26]	III	799	Prostate cancer	Ipi vs. placebo 399 vs. 400	31.29 vs. 23.73	Respiratory tract infection, skin infection, urinary infection, sepsis, abscess	NA	10.17 vs. 5.05	1.78 vs. 0.50	No
Langer 2016 [27]	II	123	NSCLC	Pembro + CT vs. CT 60 vs. 63	8.47 vs. 1.61	Sepsis, cellulitis, pneumonia	1.69 vs. 0	5.08 vs. 0	1.69 vs. 1.61	Low
Loibl 2019 [28]	II	174	Breast cancer	Durva + CT vs. CT + placebo 88 vs. 86	54.34 vs. 47.56	Infection	NA	5.43 vs. 4.87	NA	No
Mittendorf 2020 [30]	III	333	Breast cancer	Atezo + CT vs. CT + placebo 165 vs. 168	23.17 vs. 22.75	Upper respiratory tract infection, paronychia, pneumonia	NA	23.17 vs. 22.75	0 vs. 0	No
Mok 2019 [31]	III	1274	NSCLC	Pembro vs. CT 637 vs. 637	0.31 vs. 1.30	Sepsis, *Klebsiella* infection	NA	NA	0.31 vs. 1.30	Low
Powles 2020 [32]	III	1032	Urothelial cancer	Durva or durva + tremelimumab vs. CT 688 vs. 344	0.14 vs. 0	Septic shock	0 vs. 0	0 vs. 0	0.14 vs. 0	Low
Powles 2020 [33]	III	700	Urothelial cancer	Ave vs. BSC 350 vs. 350	28.12 vs. 18.84	Sepsis, urinary tract infection, pyelonephritis, kidney infection	NA	27.08 vs. 18.84	1.04 vs. 1.04	Low
Powles 2020 [34]	III	931	Urothelial cancer	Atezo vs. CT 467 vs. 465	NA	Respiratory tract infection, sepsis, septic shock	NA	NA	0 vs. 1.12	Low
Reck 2016 [35]	III	954	SCLC	Ipi + CT vs CT+ placebo 478 vs. 476	3.81 vs. 4.91	Sepsis, pneumonia	NA	2.29 vs. 3.27	1.52 vs. 1.63	No

Table 1 (continued)

Author/year	Phase of the trial	No. of patients	Primary tumor	Study treatment (exp (*N*) vs. ctr arms (*N*))	Infection rate (%) (exp vs. ctr arms)	Type of infection	G1–2 (%) (exp vs. ctr arms)	G3–4 (%) (exp vs. ctr arms)	G5 (%) (exp vs. ctr arms)	Bias (ROB-2)
Ribas 2013 [36]	III	655	Melanoma	Tremelimumab vs. CT 328 vs. 327	0.64 vs. 0.34	Pneumonia, septic shock	NA	NA	0.64 vs. 0.34	No
Rini 2019 [37]	III	861	RCC	Pembro + Axitinib vs. Sunitinib 432 vs. 429	0.23 vs. 1.17	Pneumonia, sepsis, urinary tract infection necrotizing fasciitis	NA	NA	0.23 vs. 1.17	Low
Rizvi 2020 [38]	III	1118	NSCLC	Durva or durva + tremelimumab vs. CT 746 vs. 372	NA	Pneumonia, septic shock, sepsis	NA	NA	1.75 vs. 2.07	No
Rudin 2020 [39]	III	453	SCLC	Pembro + CT vs. CT + placebo 228 vs. 225	10.30 vs. 12.38	Pneumonia, sepsis	NA	5.57 vs. 4.86	4.48 vs. 3.13	No
Schmid 2020 [40]	III	902	Breast cancer	Atezo + CT vs. CT+ placebo 451 vs. 451	50.88 vs. 39.25	Urinary tract infection, pneumonia, septic shock	41.11 vs. 39.25	9.55 vs. 5.37	0.22 vs. 0	No
Socinski 2018 [41]	III	800	NSCLC	Atezo + beva + CT vs. beva + CT 400 vs. 400	3.77 vs. 2.12	Respiratory tract infection, sepsis, urinary tract infection, *C. difficile* colitis, *Staphylococcal* infection	0.26 vs. 0	3.50 vs. 1.59	0 vs. 0.53	No
West 2019 [42]	III	723	NSCLC	Atezo + CT vs. CT 483 vs. 240	63.05 vs. 41.30	Respiratory tract infection, sepsis, urinary tract infection, *C. difficile* colitis, cellulitis	41.18 vs. 30.43	20.16 vs. 10.86	1.69 vs. 2.17	No

Table 1 (continued)

Author/year	Phase of the trial	No. of patients	Primary tumor	Study treatment (exp (*N*) vs. ctr arms (*N*))	Infection rate (%) (exp vs. ctr arms)	Type of infection	G1–2 (%) (exp vs. ctr arms)	G3–4 (%) (exp vs. ctr arms)	G5 (%) (exp vs. ctr arms)	Bias (ROB-2)
Zimmer 2020 [43]	II	167	Melanoma	Nivo + Ipi or Nivo vs. placebo 115 vs. 52	12.84 vs. 8.16	Respiratory tract infection, conjunctivitis, genital herpes, hepatitis viral, nasopharyngitis, penile infection, pharyngitis, rash pustular	NA	0 vs. 0	NA	No

exp experimental, *ctr* control, *NSCLC* non-small cell lung cancer, *SCLC* small cell lung cancer, *RCC* renal cell carcinoma, *CT* chemotherapy, *pembro* pembrolizumab, *durva* durvalumab, *ave* avelumab, *atezo* atezolizumab, *nivo* nivolumab, *ipi* ipilimumab, *beva* bevacizumab, *BSC* best supportive care, *TBC* tuberculosis, *NA* not available.

analysis (Online Supplemental Material, Fig. 1; $P = 0.03$), it did not indicate a bias for the G3–5 infection analysis (Online Supplemental Material, Fig. 2; $P = 0.1$).

4 Discussion

This systematic review and meta-analysis of 36 randomized clinical trials suggests an association between the use of ICIs administered with CT and an increased risk of infections in patients with solid tumors. Most ICIs + CT-associated infections were pneumonitis and low respiratory tract, viral, urinary, and cutaneous infections. Sepsis was rarely described. Interestingly, our data showed the presence of three cases of tuberculosis reactivation: one in a patient with advanced HER2-positive breast cancer, and two in patients with non-small-cell lung cancer. Conversely, compared to CT alone, the ICIs reduced the risk of G3–5 infections. According to type of ICI, combinations (e.g., anti-PD-1 + anti-CTLA-4) were associated with more than double the infections compared to a single agent alone.

The increased risk of infection when ICIs were administered with CT was probably due to the synergistic effects of each agents' specific toxicities, such as pneumonitis (from ICIs), neutropenia (CT and targeted agents), the advanced stage of the disease, and the diagnosis of a lung cancer [46]. Remarkably, regarding this tumor, the occurrence of infections might influence the patient's prognosis, as shown by the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), which causes the severe Coronavirus disease 19 (COVID-19) and a higher risk of mortality. In the pandemic era, caution should be used particularly with those patients at risk of COVID-19 infection and mortality when ICI combinations or a CT + ICIs combination is planned in cancer patients. Despite this, larger studies are urgently needed to improve the evaluation of the effects of ICIs in patients with COVID-19 and the use of ICIs during the coronavirus pandemic [47, 48].

Due to the increased risk of infection observed with the association of CT and ICIs or with ICI combinations, preventive measures in this group of patients may be considered, particularly in those with a higher risk of developing neutropenia (e.g., prior CT or radiotherapy (e.g., to the lung), bone marrow involvement by the tumor, or older age), elderly or frail patients, and subjects with pulmonary, cardiovascular, and metabolic co-morbidities.

In particular, in patients at a higher risk of developing infections, the use of ICIs alone might be safer, given their low hematological toxicity [49]. These risk factors include older age, advanced disease, poor performance status, the nature of the anti-cancer treatment administered, recent surgical procedures, prior prophylactic antibiotics, concomitant steroid use, previous bacteremia or infection with

Table 2 Summary of the findings with the GRADE of evidence

Outcome	Absolute effects (rate of events in exp vs. ctr arms)	Relative risk	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
Risk of G1–5 infections (all studies)	9.6 vs. 8.3 (96 per 1000 vs. 83 per 1000)	1.02 (95% CI 0.84–1.24)[a]	21,451 (36 RCTs)	⊕⊕⊕⊖ MODERATE[1]	Heterogeneity 73% ($P < 0.01$) Two studies had regorafenib and sunitinib as comparators
Risk of G1–5 infections (CT + ICIs vs. CT)	15.8 vs. 10.7 (165 per 1000 vs. 107 per 100	1.36 (95% CI 1.22–1.52)[b]	7271 (13 RCTs)	⊕⊕⊕⊕ HIGH	Heterogeneity 13% ($P = 0.31$)
Risk of G1–5 infections (ICIs vs. CT)	3.9 vs. 6.3 (42 per 1000 vs. 64 per 1000)	0.58 (95% CI 0.4–0.85)[a]	11,703 (18 RCTs)	⊕⊕⊕⊖ MODERATE[1]	Heterogeneity 73% ($P < 0.01$) Three studies reported 0 events in experimental arms
Risk of G1–5 infections (ICIs vs. BSC/placebo)	16.2 vs. 9.4 (163 per 1000 vs. 95 per 1000)	1.53 (95% CI 1.231–90)[b]	2467 (5 RCTs)	⊕⊕⊕⊕ HIGH	Heterogeneity 0% ($P = 0.99$)
Risk of severe infections (all studies)	3.2 vs. 2.7 (32 per 1000 vs. 27 per 1000)	0.99 (95% CI 0.74–1.32)[a]	20,359 (35 RCTs)	⊕⊕⊕⊖ MODERATE[1]	Heterogeneity 54% ($P < 0.01$) Five studies did not report events in experimental and control arms

RCTs randomized controlled trials, *CT* chemotherapy, *ICIs* immune checkpoint inhibitors, *G* grade, *1* downgraded because the heterogeneity was high

[a]Random-effect model

[b]Fixed-effect model

resistant-organisms or fungal infection, no use of a G-CSF, cardiovascular disease, presence of symptoms, dehydration, hemodynamic instability, mucositis, gastrointestinal symptoms, changes in neurological or mental status, intravascular catheter infection, new pulmonary infiltrate or hypoxemia, underlying chronic lung disease, or hepatic or renal insufficiency [2, 50].

Furthermore, regarding the use of steroids, the mainstay for the management of most immune-related AEs related to ICIs should be conducted cautiously and with the awareness of creating a higher risk of infection by specific pathogens, such as *Pneumocystis jiroveci*, fungal infections, and *Herpes zoster*. In addition, in patients treated with ICIs, infliximab has been associated with the hepatitis B virus and reactivation of tuberculosis [51]. In the trials included in this meta-analysis, no cases of hepatitis B and three tuberculosis reactivations were detected in ICI groups.

Febrile neutropenia (> 38.3 °C or two consecutive readings of > 38 °C over 2 h *plus* a neutrophil count of < 500/mm^3) is a common complication of cancer CT. In around 30% of febrile episodes in cancer patients, common infections were in the intestinal tract, lungs, and skin, which cause diarrhea, pneumonia, lung infiltrates, and cellulitis, respectively [49]. Further, bacteremia was observed in around 20% of patients with febrile neutropenia. Sepsis can develop in a minority of patients. In our analysis, similar infection sites were observed; therefore, it can be assumed that the risk is likely driven by CT-induced myelosuppression.

The limitations of our work are as follows: we had difficulty finding detailed information on the precise sites of infection (e.g., infections of the respiratory tract *versus* pneumonia); there was incomplete information on the nature of the agent of the infections (e.g., viral *versus* fungal *versus* bacterial); and the use of prophylactic myeloid growth factors was not reported in the primary studies. Furthermore, the present meta-analysis was unable to include an age-stratified analysis or other subgroup analyses, as the primary studies were not focused on reporting risk factors for

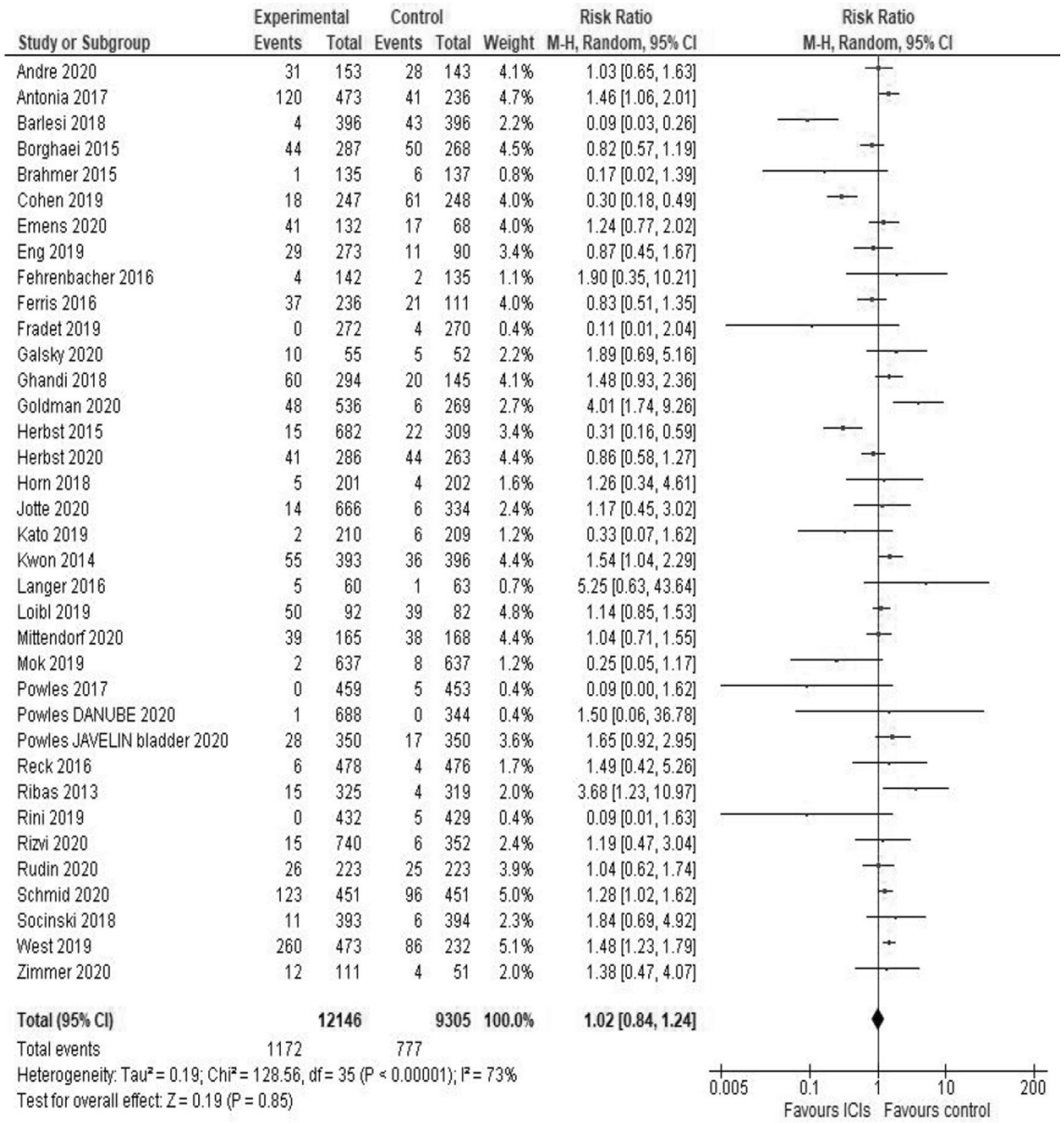

Fig. 2 Forest plot of the risk ratio for all-grade infections.

infections related to age, co-morbidities, or disease-related complications. The causative role of autoimmune AEs (e.g., pneumonitis) or the detrimental effect of steroids may not be elucidated in single publications. Finally, two-thirds of trials showed evidence of some publication bias mostly due to the unblinded randomization design and general heterogeneity explained for different diseases and stage settings.

However, our work is the first to analyze the overall risk of all infections in patients with solid tumors treated with ICIs either alone or in combination with other agents. Among its strengths, we acknowledge the inclusion of data from > 20,000 patients, the variety of tumor types, the homogeneous disease stage (locally advanced and metastatic), and the possibility of calculating the RR for the inclusion of randomized studies.

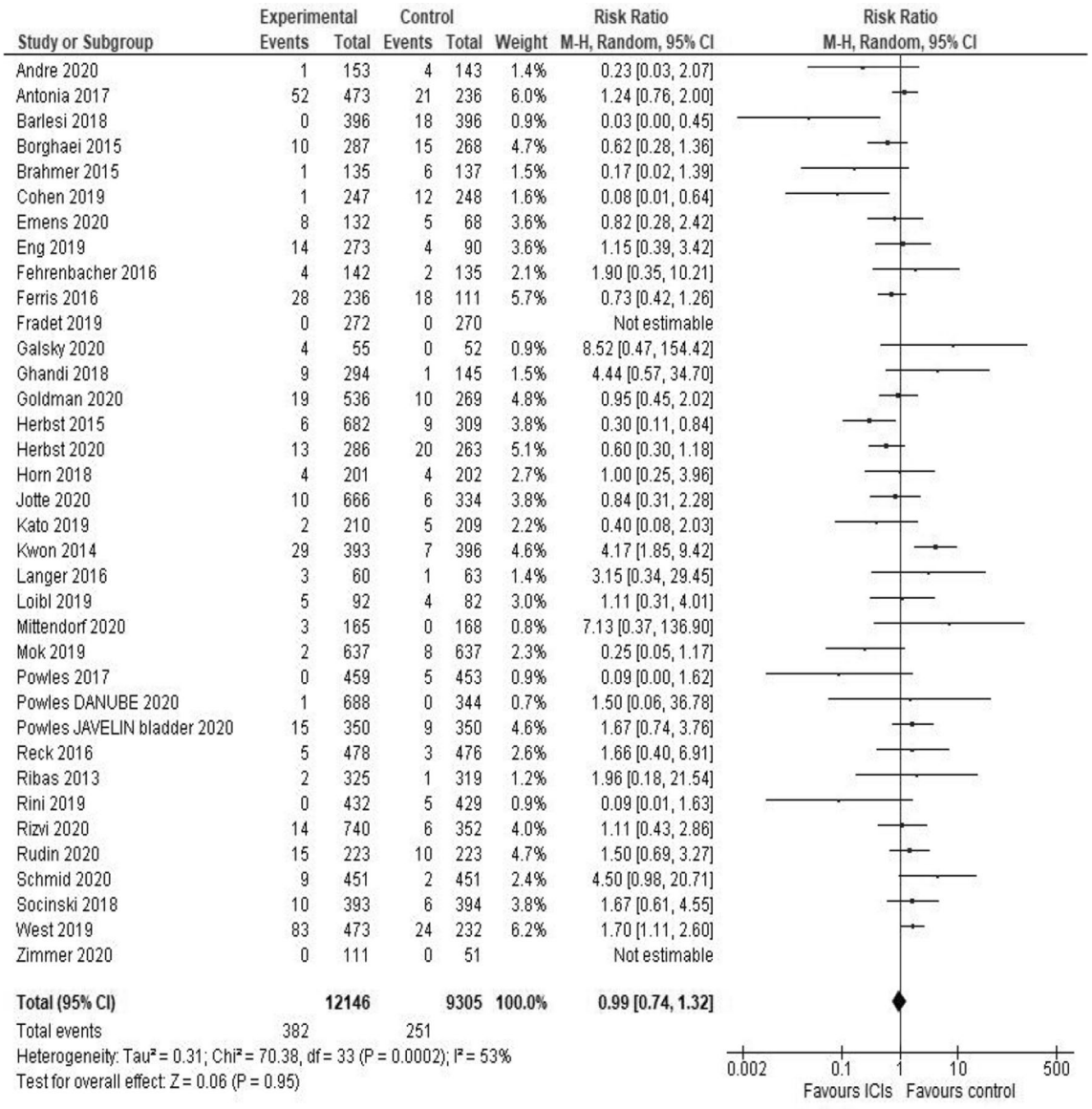

Fig. 3 Forest plot of the risk ratio for grade 3–5 infections.

However, the correlation between infections in cancer patients undergoing ICIs needs to be investigated further in dedicated trials.

The challenges for clinical practice include: correct management and differential diagnosis with the involvement of a multidisciplinary team and the aim of selecting the best treatment options (e.g., supportive drugs) for these patients, particularly those at a high risk, while maintaining the antitumor effect.

In conclusion, our study suggests that the use of ICIs may be associated with a higher risk of infection, particularly when provided in association with CT. Whenever the use of ICIs *plus* CT is indicated, we should consider the employment of myeloid growth factors and dose reductions of ICIs and/or CT.

Considering the disease's stage and prognosis and the significant improvement in overall survival provided by ICIs, the benefits may still outweigh the risk of infection in most patients.

This meta-analysis highlights the need to perform dedicated studies to identify those patients at a higher risk, as they might be candidates for prophylaxis with colony-stimulating factors or (ICI and/or CT) dose reduction. Strategies to prevent infections and identify patients at risk should be developed.

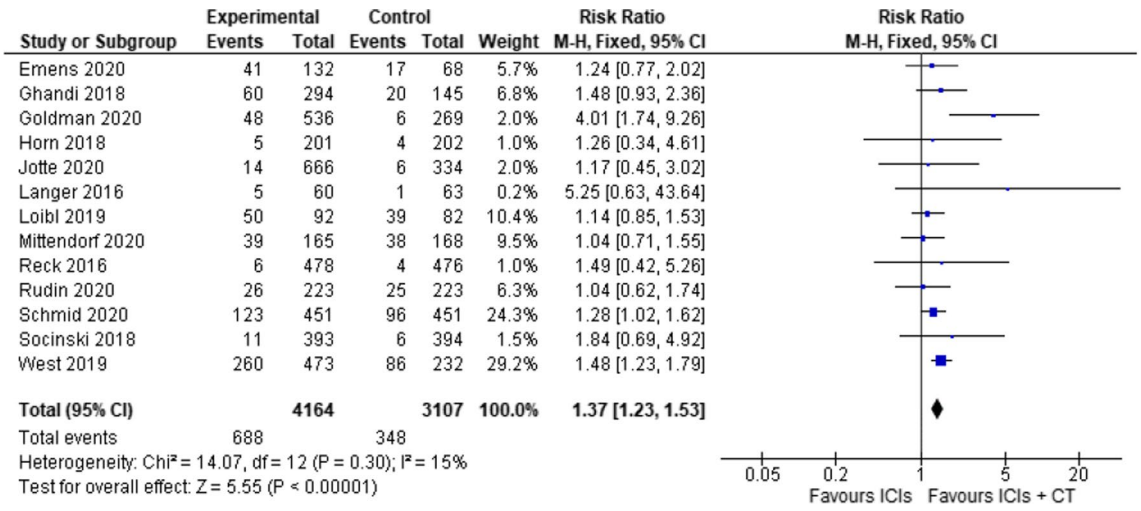

Fig. 4 Forest plot of the risk ratio for all-grade infections for chemotherapy + immune checkpoint inhibitors *versus* chemotherapy-alone studies.

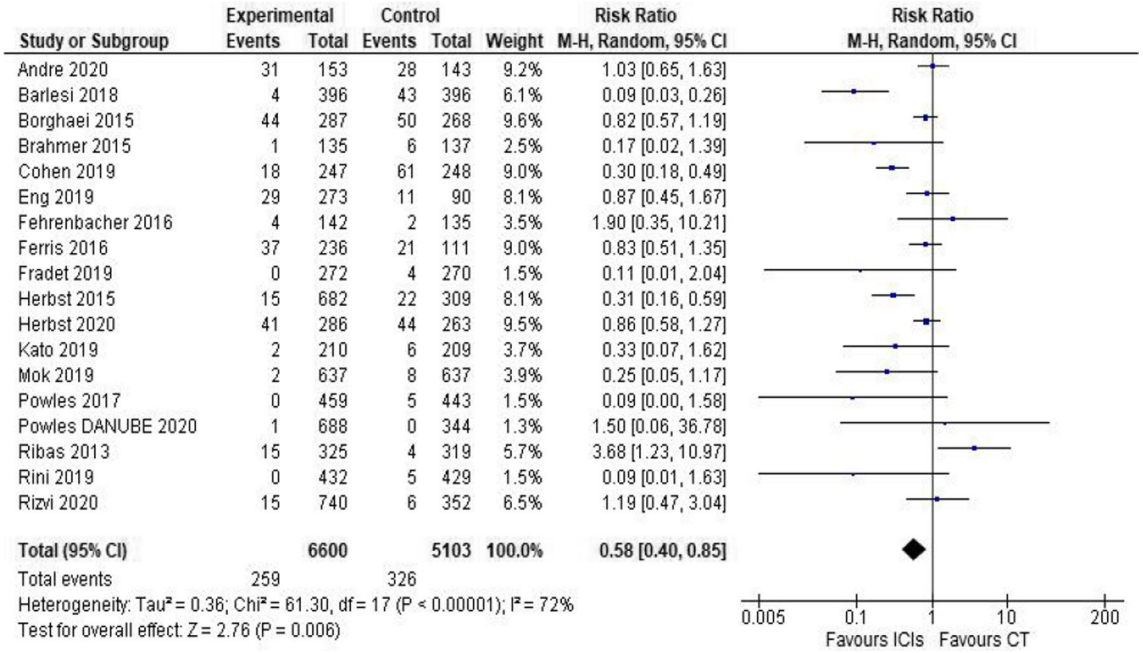

Fig. 5 Forest plot of the risk ratio for all-grade infections for immune checkpoint inhibitors *versus* chemotherapy alone studies.

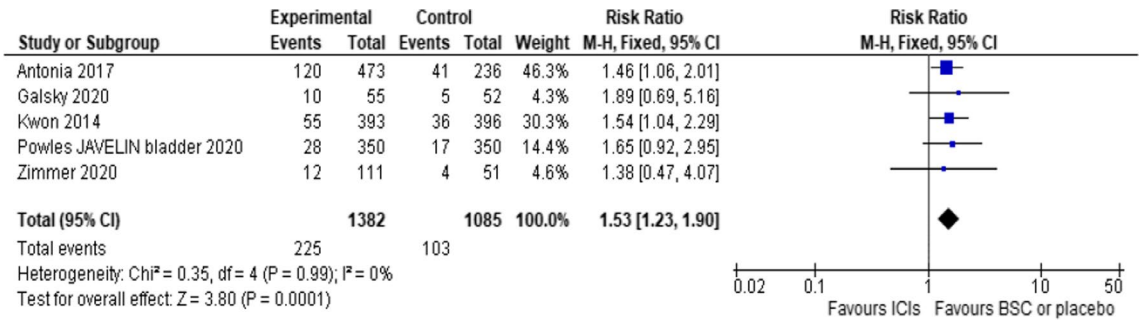

Fig. 6 Forest plot of the risk ratio for all-grade infections for immune checkpoint inhibitors *versus* placebo/best supportive care studies.

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Declarations

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Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Data availability Data and material are available on request from the corresponding author.

Code availability Not applicable.

Authors' contributions FP, AMM, and CS extracted the data; FP performed the statistical analysis; FP, AMM and CS drafted the manuscript; all coauthors participated in writing the final version of the work by providing intellectual input and approving its submission.

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