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

Fausto Petrelli1 · Anna Maria Morelli2 · Andrea Luciani1 · Antonio Ghidini3 · Cinzia Solinas4

Accepted: 11 June 2021 / Published online: 5 July 2021
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2021

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].
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...
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 (Chi²) test and the I-square (I²) statistic. We used a P value threshold of 0.10 to determine statistical significance for the Chi² test and considered an I² 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...
| 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                     |
| 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   | 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   | 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   | 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   | 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  | 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   | 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   | 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     | 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           |
| 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 |
| 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           |
Risk of Infection with Immune Checkpoint Inhibitors 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, comitant steroid use, previous bacteremia or infection with

| Table 1 (continued) |
|---------------------|
| Author/year        | Zimmer 2020       |
| No. of patients    | 167               |
| Type of infection  | Respiratory tract, conjunctivitis, genital herpes, hepatitis viral, nasopharyngitis, pharyngitis, rash pustular |
| G1–2 (%) (exp vs. ctr arms) | NA 0 vs. 0 |
| G3–4 (%) (exp vs. ctr arms) | 0 vs. 0 |
| G5 (%) (exp vs. ctr arms) | NA not available |
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 ICI-s 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/ \text{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

| Table 2  Summary of the findings with the GRADE of evidence |
|---------------------------------|-----------------|-------------------|---------------------|-------------------|
| **Outcome**                     | **Absolute effects (rate of events in exp vs. ctr arms)** | **Relative risk (studies)** | **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) | 21,451 (36 RCTs) | ⊕⊕⊕ ⊕ MODERATE | 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) | 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) | 11,703 (18 RCTs) | ⊕⊕⊕ ⊕ MODERATE | 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 1.23–1.90) | 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) | 20,359 (35 RCTs) | ⊕⊕⊕ ⊕ MODERATE | 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, **I** downgraded because the heterogeneity was high

*a*Random-effect model

*b*Fixed-effect model
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.
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.
Risk of Infection with Immune Checkpoint Inhibitors

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.

△ Adis
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11523-021-00824-3.

Declarations

Funding No external funding was used in the preparation of this article.

Conflict of interest Fausto Petrelli, Anna Maria Morelli, Andrea Luciani, Antonio Ghidini, and Cinzia Solinas declare that they have no conflicts of interest that might be relevant to the contents of this article.

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.

References

1. Kaderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer. 2006;106(10):2258-66. https://doi.org/10.1002/cncr.21847.

2. Klastersky J, Paesmans M. The multinational association for supportive care in cancer (MASCC) risk index score: 10 years of use for identifying low-risk febrile neutropenic cancer patients. Support Care Cancer. 2013;21(5):1487-95. https://doi.org/10.1007/s00520-013-1758-y.

3. Barber DL, Sakai S, Kudchadkar RR, Fling SP, Day TA, Vergara JA, et al. Tuberculosis following PD-1 blockade for cancer immunotherapy. Sci Transl Med. 2019;11(475):eaat2702. https://doi.org/10.1126/scitranslmed.aat2702.

4. Picchi H, Mateus C, Chouaid C, Besse B, Marabelle A, Michot JM, et al. Infectious complications associated with the use of immune checkpoint inhibitors in oncology: reactivation of tuberculosis after anti PD-1 treatment. Clin Microbiol Infect. 2018;24(3):216-8. https://doi.org/10.1016/j.cmi.2017.12.003.

5. Del Castillo M, Romero FA, Argüello E, Kyi C, Postow MA, Redelman-Sidi G. The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. Clin Infect Dis. 2016;63(11):1490-3. https://doi.org/10.1093/cid/ciw539.

6. Magee DE, Hird AE, Klaassen Z, Sridhar SS, Nam RK, Wallis CDJ, et al. Adverse event profile for immunotherapy agents compared with chemotherapy in solid organ tumors: a systematic review and meta-analysis of randomized clinical trials. Ann Oncol. 2020;31(1):50-60. https://doi.org/10.1016/j.annonc.2019.10.008.

7. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097.

8. André T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab in microsatellite-instability–high advanced colorectal cancer. N Engl J Med. 2020;383(23):2207–18. https://doi.org/10.1056/NEJMoA176999.

9. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med. 2017;377(20):1919-29. https://doi.org/10.1056/NEJMoA1709937.

10. Barlesi F, Vansteenkiste J, Spigel D, Ishii H, Garassino M, de Marinis F, et al. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomized, phase 3 study. Lancet Oncol. 2018;19(11):1468–79. https://doi.org/10.1016/S1470-2045(18)306739.

11. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373(17):1627–39. https://doi.org/10.1056/NEJMoA1507643.

12. Cohen EEW, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomized, open-label, phase 3 study. Lancet. 2019;393(10167):156–67. https://doi.org/10.1016/S0140-6736(19)31999-8.

13. Emens LA, Esteva FJ, Beresford M, Saura C, De Laurentiis M, Kim SB, et al. Trastuzumab emtansine plus avelumab versus trastuzumab emtansine plus placebo in previously treated, HER2-positive advanced breast cancer (KATE2): a phase 2, multicentre, randomized, double-blind trial. Lancet Oncol. 2020;21(10):1283–95. https://doi.org/10.1016/S1470-2045(20)30465-4.

14. Eng C, Kim TW, Bendell J, Argüelles G, Tebbutt NC, Di Bartolomeo M, et al. Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomized, controlled trial. Lancet Oncol. 2019;20(6):849–61. https://doi.org/10.1016/S1470-2045(20)30027-0.

15. Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazières J, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomized controlled trial. Lancet. 2016;387(10030):1837–46. https://doi.org/10.1016/S0140-6736(16)30878-0.

16. Ferris RL, Blumenschein G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016;375(19):1856–67. https://doi.org/10.1056/NEJMoA1704520.

17. Fraudet Y, Bellmunt J, Vaughan DJ, Lee JL, Fong L, Vogelzang NJ, et al. Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of > 2 years of follow-up. Ann Oncol. 2019;30(9):970–6. https://doi.org/10.1093/annonc/mdz127.

18. Galsky MD, Mortazavi A, Milowsky MI, George S, Gupta S, Fleming MT, et al. Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients with metastatic urothelial cancer. J Clin Oncol. 2020;38(16):1797–806. https://doi.org/10.1200/JCO.20.03091.

19. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer (KEYNOTE-040): a randomized, open-label, phase 3 study. Lancet. 2018;392(10160):1507–17. https://doi.org/10.1016/S0140-6736(18)31640-3.

20. Goldman JW, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab, with or without tremelimumab, plus...
platinum–etoposide versus platinum–etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPian): updated results from a randomized, controlled, open-label, phase 3 trial. Lancet Oncol. 2021;22(1):51–65. https://doi.org/10.1016/S1470-2045(20)30539-8.

21. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomized controlled trial. Lancet. 2016;387(10027):1540–50. https://doi.org/10.1016/S0140-6736(15)01281-7.

22. Herbst RS, Giaccone G, de Marinis F, Reinmuth N, Vergnenegre A, Barrios CH, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. N Engl J Med. 2020;383(14):1328–39. https://doi.org/10.1056/NEJmoa1917346.

23. Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379(23):2220–9. https://doi.org/10.1056/NEJMoa1809064.

24. Jotte R, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Rodriguez-Arceu D, Hussein M, et al. Atezolizumab in combination with carboplatin and nab-paclitaxel in advanced squamous non-small-cell lung cancer (IMpower131): Results from a randomized phase III trial. J Thorac Oncol. 2020;15(8):1351–60. https://doi.org/10.1016/j.jto.2020.03.028.

25. Kato K, Cho BC, Takahashi M, Okada M, Lin CY, Chin K, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomized, open-label, phase 3 trial. Lancet Oncol. 2019;20(11):1506–17. https://doi.org/10.1016/S1470-2045(19)30626-6.

26. Kwon ED, Drake CG, Scher HI, Fizazi K, Bossi A, van der Eerden MO, et al. Pembrolizumab plus axitinib versus sunitinib in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2014;15(7):700–12. https://doi.org/10.1016/S1470-2045(14)70189-5 (Epub 2014 May 13).

27. Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomized, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016;17(11):1497–508. https://doi.org/10.1016/S1470-2045(16)30498-3.

28. Loibl S, Untch M, Burchardi N, Huober J, Sinn BV, Blohmmer J-U, et al. A randomized phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol. 2019;30(8):1279–88. https://doi.org/10.1093/annonc/mdz158.

29. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373(2):123–35. https://doi.org/10.1056/NEJMoa1504627 (Epub 2015 May 31).

30. Mittendorf EA, Zhang H, Barrios CH, Saji S, Jung KH, Hegg R, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): A randomized, double-blind, phase 3 trial. Lancet. 2020;396(10257):1090–100. https://doi.org/10.1016/S0140-6736(20)31953-X.

31. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomized, open-label, controlled, phase 3 trial. Lancet. 2019;393(10183):1819–30. https://doi.org/10.1016/S0140-6736(18)32409-7.

32. Powles T, Durán I, van der Heijden MS, Loriot Y, Vogelzang NJ, De Giorgi U, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2017;6736(17):1–11. https://doi.org/10.1016/S0140-6736(17)33297-X.

33. Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med. 2020;383(13):1218–30. https://doi.org/10.1056/nejmoa2002788.

34. Powles T, van der Heijden MS, Castellano D, Galsky MD, Loriot Y, Petrylak DP, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomized, open-label, multicentre, phase 3 trial. Lancet Oncol. 2020;21(12):1574–88. https://doi.org/10.1016/S1470-2045(20)30541-6.

35. Reck M, Luft A, Szczesna A, Havel L, Kim S-W, Akerley W, et al. Phase III randomized trial of ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. J Clin Oncol. 2016;34(31):3740–8. https://doi.org/10.1200/JCO.2016.67.6601.

36. Ribas A, Keeford R, Marshall MA, Punt CJ, Haanen JB, Marmol M, et al. Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J Clin Oncol. 2013;31(5):616–22. https://doi.org/10.1200/JCO.2012.44.6112.

37. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380(12):1116–27. https://doi.org/10.1056/nejmoa1816714.

38. Rizvi NA, Cho BC, Reinmuth N, Lee KH, Luft A, Ahn MJ, et al. Durvalumab with or without tremelimumab vs. standard chemotherapy in first-line treatment of metastatic non-small-cell lung cancer: the MYSTIC phase 3 randomized clinical trial. JAMA Oncol. 2020;6(5):661–74. https://doi.org/10.1001/jamaoncol.2020.0237.

39. Rudin CM, Awad MM, Navarro A, Gottfried M, Peters S, Čsösz T, et al. Pembrolizumab on placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 Study. J Clin Oncol. 2020;38(21):2369–79. https://doi.org/10.1200/JCO.20.00793.

40. Schmid P, Adams S, Rugo HS, Schneweiss A, Barrios CH, Iwata H, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018;379(22):2108–21. https://doi.org/10.1056/nejmoa1809615.

41. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Mogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018;378(24):2288–301. https://doi.org/10.1056/nejmoa1716948.

42. West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conroy T, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380(12):1116–27. https://doi.org/10.1056/nejmoa1816714.

43. Zimmer L, Livingston E, Hassel JC, Fluck M, Eigentler T, Loquai C, et al. Adjuvant nivolumab plus ipilimumab or nivolumab monotherapy versus placebo in patients with resected stage IV melanoma with no evidence of disease (IMMUNED): a
44. Cochrane Handbook for Systematic Reviews of Interventions. 2019. https://doi.org/10.1002/9781119536604.
45. Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64(12):1311-6. https://doi.org/10.1016/j.jclinepi.2011.06.004.
46. Belluomini L, Caldart A, Avancini A, Dodi A, Trestini I, Kadrija D, et al. Infections and immunotherapy in lung cancer: a bad relationship? Int J Mol Sci. 2021;22(1):42. https://doi.org/10.3390/ijms22010042.
47. Gambichler T, Reuther J, Scheel CH, Susok L, Kern P, Becker JC. Cancer and immune checkpoint inhibitor treatment in the era of SARS-CoV-2 infection. Cancers. 2020;12(11):3383. https://doi.org/10.3390/cancers12113383.
48. Gambichler T, Reuther J, Scheel CH, Becker JC. On the use of immune checkpoint inhibitors in patients with viral infections including COVID-19. J Immunother Cancer. 2020;8(2):e001145. https://doi.org/10.1136/jitc-2020-001145.
49. Petrelli F, Ardito R, Borgenovo K, Lonati V, Cabiddu M, Ghilardi M, et al. Haematological toxicities with immunotherapy in patients with cancer: a systematic review and meta-analysis. Eur J Cancer. 2018;103:7-16. https://doi.org/10.1016/j.ejca.2018.07.129.
50. de Naurois J, Novitzky-Basso I, Gill MJ, Marti FM, Cullen MH, Roila F. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. Ann Oncol. 2010;21(Suppl_5):v252-6. https://doi.org/10.1093/annonc/mdq196.
51. Thompson JA, Schneider BI, Brahmer J, Andrews S, Armand P, Bhatia S, et al. Management of immunotherapy related toxicities. NCCN Clin Pract Guidel Oncol. 2020;17:255–89.