Immune Checkpoint Inhibitors Combined With Chemotherapy Compared With Chemotherapy Alone for Triple-Negative Breast Cancer: A Systematic Review and Meta-Analysis

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Background: It is still controversial whether immune checkpoint inhibitors (ICIs) can improve the curative effect when added to original standard chemotherapy treatment for triple-negative breast cancer (TNBC). We compared their antitumor efficacy and adverse effects (AEs) to make a better clinical decision.

Methods: Seven databases were searched for eligible articles. Progression-free survival (PFS), overall survival (OS), and AEs were measured as the primary outcomes.

Results: Nine randomized controlled trials (RCTs) involving 4,501 patients were included. ICI+chemotherapy treatment achieved better PFS (hazard ratio [HR]: 0.78, [0.70–0.86], p < 0.00001), OS (HR: 0.86, [0.74–0.99], p = 0.04), and complete response (584/1,106 vs. 341/825, risk ratio [RR]: 1.38, [1.01–1.89], p = 0.04). With the prolongation of survival, the survival advantage of ICI+chemotherapy increased compared with chemotherapy. Subgroup analysis suggested that the addition of ICIs might not have a better effect in Asian patients, patients with locally advanced disease, or patients with brain metastases. In the toxicity analysis, more Grade 3–5 AEs and serious AEs were found in the ICI+chemotherapy group. For Grade 3–5 AEs, more cases of diarrhea, severe skin reactions, pneumonitis, hepatitis, and adrenal insufficiency were related to the ICI+chemotherapy group.

Conclusions: ICI+chemotherapy appears to be better than chemotherapy alone for TNBC treatment, with better OS and PFS. However, its high rates of serious AEs need to be taken seriously.

Systematic Review Registration: PROSPERO Registration: CRD42021276394.

Keywords: chemotherapy, triple-negative breast cancer, meta-analysis, immune checkpoint inhibitors, systematic review
INTRODUCTION

In recent years, breast cancer has been the most common malignancy in women (1). As one of the major subtypes (15–20%), triple-negative breast cancer (TNBC) has the worst prognosis (2). In clinical practice, chemotherapy remains the standard of care (not only in neoadjuvant therapy but also in radical drug therapy) for patients with TNBC (3). However, its poor survival efficacy is not satisfactory for patients and doctors. In recent years, immune checkpoint inhibitors (ICIs) have been incorporated into cancer treatment, and their efficacy has been proven in lung cancer, hepatocellular carcinoma, and gastric cancer (4–6). However, whether ICIs can improve the curative effect when added to original standard chemotherapy treatment for TNBC is still controversial.

In the updated guidelines, ICIs+chemotherapy has been recognized as one of the treatment options for TNBC (7, 8). The KEYNOTE-522 and 1MPassion130 trials compared ICIs +chemotherapy with chemotherapy in 2,076 patients with TNBC and suggested that combination therapy prolonged progression-free survival (PFS) and increased the rates of pathological complete response (PCR) (9, 10). Similar results were confirmed by 4 other randomized controlled trials (RCTs) (11–15). However, Bachelot et al.’s, Brufsky et al.’s, and Tolaney et al.’s studies reported that ICIs+chemotherapy could not improve the survival of patients but will cause more adverse effects (AEs) and reduce the quality of life of patients (16–18).

Hence, this meta-analysis of RCTs aimed to compare the efficacy and safety between ICIs+chemotherapy and chemotherapy for TNBC.

MATERIALS AND METHODS

We conducted this study according to the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines (PRISMA) (Table S1) (19). (PROSPERO Registration: CRD42021276394).

Search Strategy

Studies were retrieved from the following databases: The Cochrane Library, PubMed, Web of Science, Scopus, EMBASE, ScienceDirect, and Ovid MEDLINE. Studies were retrieval time from inception to May 5, 2021. The MeSH terms and keywords were “Breast cancer”, “Immune checkpoint inhibitors”, and “Chemotherapy”. The search details are included in Table S2.

Selection Criteria

The inclusion criteria were as follows: (1) RCTs published in English comparing ICIs+chemotherapy with chemotherapy alone; (2) studies that enrolled patients with TNBC; and (3) the outcomes included survival indicators (OS and PFS), drug responses, and AEs.

The exclusion criteria were as follows: (1) animal studies; (2) meta-analyses and reviews; (3) conference articles; (4) case reports; and (5) studies that did not only enroll patients with TNBC.

Data Extraction

Two investigators extracted the following information independently: the publication year, first author, participant characteristics (quantity, age, etc.), tumor characteristics (histopathology, stage, etc.), antitumor efficacy (OS, PFS, etc.), and number of AEs. All disagreements were resolved by a third investigator.

Outcome Assessments

PFS and OS were the primary outcomes. The subgroup analysis of OS was performed according to age, race, Eastern Cooperative Oncology Group (ECOG) performance status, baseline disease status, metastatic sites, PD-L1 status, neoadjuvant therapy, homologous recombination deficiency (HRD), metastases (brain, bone, liver, or lung), lymph node-only disease, and previous treatment (chemotherapy, taxane, or anthracycline).

Quality Assessment

We assessed the quality of the included RCTs by using the Cochrane Risk of Bias Tool (CRBT) (20) and 5-point Jadad scale (21). We assessed the quality of the results by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (22).

Statistical Analysis

When analyzing survival outcomes (PFS, OS, etc.), we used hazard ratios (HRs). When analyzing dichotomous variables (PFSR, OSR, complete response [CR], AEs, etc.), we used risk ratios (RRs). Heterogeneity was evaluated by the $I^2$ statistic and $\chi^2$ test. A random-effects model was used when heterogeneity was significant ($I^2 < 50\%$ or $p > 0.1$); otherwise, a fixed-effects model was used. Publication bias was evaluated through visual inspection of the funnel plots. A $P < 0.05$ was identified as statistically significant. All analyses were performed using Review Manager 5.3 and SPSS 18.0.

RESULTS

Search Results

Nine RCTs involving 4,501 patients (2,645 patients in the ICI+chemotherapy group and 1,856 patients in the chemotherapy group) were included (9–16, 18) (Figure 1). Two studies (14, 16) were conducted in Europe, one (18) was conducted in the USA, and the other five studies were global studies (9–13). The essential information of the included studies is summarized in
Table 1. According to the Jadad scale (Table S3) and CRBT (Figure S1), all eight RCTs were of high quality. According to the GRADE system, the evidence grades of all the results were medium-high.

**Antitumor Efficacy**

The ICI+chemotherapy group achieved better OS than the chemotherapy group (HR: 0.86, [0.74–0.99], p = 0.04; Figure 2). At all points in time, the overall survival rate (OSR) tended to favor the ICI+chemotherapy group (OSR-6 m, RR: 1.17, [1.13–1.21], p < 0.00001; OSR-12 m, RR: 1.08, [1.00–1.17], p = 0.05; OSR-18 m, RR: 1.11, [0.99–1.24], p = 0.07; OSR-24 m, RR: 1.12, [0.97–1.30], p = 0.13; OSR-30 m, RR: 1.20, [1.00–1.44], p = 0.04; OSR-36 m, RR: 1.33, [1.06–1.67], p = 0.01, Figure S2).

With prolonged survival time, ICI+chemotherapy had an increasing advantage for OS (Figures 3A, B).

The ICI+chemotherapy group achieved better PFS than the chemotherapy group (HR: 0.78, [0.70–0.86], p < 0.00001;...
### TABLE 1 | Characteristics of the included randomized controlled trials.

| Study          | Period          | Groups                  | Patients (n) | Median age (year) | Stage | Treatment                                                                 | Follow-up duration, mo | Design |
|----------------|-----------------|-------------------------|--------------|-------------------|-------|--------------------------------------------------------------------------|------------------------|--------|
| 2021 Miles et al. (15) | IMpassion131 Phase III 2017.08–2019.09 | ICIs +Chemotherapy | 431          | 54                | Stage IV | Atezolizumab, 840mg (d1, 15) + Paclitaxel, 90 mg/m² (d1, 8, 15), q4w until PD | 8.8                    | RCT    |
|                |                 | Chemotherapy            | 220          | 53                | 101    | Paclitaxel, 90 mg/m² (d1, 8, 15), q4w until PD                           |                        |        |
| 2021 Bachelot et al. (16) | SAFIR02-BREAST IMMUNO Phase II 2016.01–2019.09 | ICIs +Chemotherapy | 47           | 56                | Stage IV | Durvalumab, 10 mg/kg, q2w +Chemotherapy (doctor’s choice), until PD        | 19.7                   | RCT    |
|                |                 | Chemotherapy            | 35           | 56.5              | 8      | Chemotherapy (doctor’s choice), until PD                                 |                        |        |
| 2020 Schmid et al. (9) | KEYNOTE-522 Phase III 2017.03–2018.09 | ICIs +Chemotherapy | 784          | 49                | Stage II-III | Pembrolizumab, 200 mg, q3w +Paclitaxel, 80 mg/m², q1w +carboplatin³, for 12w (first neoadjuvant treatment); followed by Pembrolizumab, 200 mg, q3w+Doxorubicin, 60 mg/m², q3w (or Epirubicin, 90 mg/m², q3w) +cyclophosphamide, 600 mg/m², q3w, for 12w (second neoadjuvant treatment). After definitive surgery, pembrolizumab, 200 mg, q3w for up to 9 cycles. | 15.5                   | RCT    |
|                |                 | Chemotherapy            | 390          | 48                | 317    | Placebo, q3w+Paclitaxel, 80 mg/m², q1w+carboplatin³, for 12w (first neoadjuvant treatment); followed by Placebo, q3w+Doxorubicin, 60 mg/m², q3w (or Epirubicin, 90 mg/m², q3w) +cyclophosphamide, 600 mg/m², q3w, for 12w (second neoadjuvant treatment); after definitive surgery, placebo, q3w for up to 9 cycles. |                        |        |
| 2020 Schmid et al. (10) | IMpassion130 Phase III 2015.06–2017.05 | ICIs +Chemotherapy | 451          | 55                | Stage IV | Atezolizumab, 840 mg (d1, 15) +Nab-paclitaxel, 100 mg/m² (d1, 8, 15), q4w until PD | 18.5                   | RCT    |
|                |                 | Chemotherapy            | 451          | 56                | 184    | Nab-paclitaxel, 100 mg/m² (d1, 8, 15), q4w until PD                       |                        |        |
| 2020 Mittendorf et al. (11) | IMpassion031 Phase III 2017.07–2019.09 | ICIs +Chemotherapy | 165          | 51                | Stage II-III | Atezolizumab,840 mg, q2w +Nab-paclitaxel, 125 mg/m², qw, for 12 weeks, followed by Atezolizumab,840 mg, q2w +Doxorubicin, 60 mg/m²+Cyclophosphamide, 600 mg/m², q2w for 8w; after surgery, aezolizumab,1,200 mg, q3w for 11 cycles Nab-paclitaxel, 125 mg/m², qw, for 12 weeks, followed by Doxorubicin, 60 mg/m²+Cyclophosphamide, 600 mg/m², q2w for 8w; after surgery, subsequently monitored for 1 year | 20.6                   | RCT    |
|                |                 | Chemotherapy            | 168          | 51                | 76     |                                                                            |                        |        |
| 2020 Cortes et al. (12) | KEYNOTE-355 Phase III 2017.01–2018.06 | ICIs +Chemotherapy | 566          | 53                | Stage IV | Pembrolizumab, 200 mg q3w+Nab-paclitaxel, 100 mg/m², d1, 8, 15, q4w or Paclitaxel, 90 mg/m², d1, 8, 15, q4w or | 25.9                   | RCT    |

(Continued)
At all points in time, the progression-free survival rate (PFSR) significantly favored the ICIs+Chemotherapy group (PFSR-6 m, RR: 1.09, [0.78–1.52], p = 0.10; PFSR-12 m, RR: 1.26, [0.84–1.88], p = 0.27; PFSR-18 m, RR: 1.26, [0.90–1.75], p = 0.18; PFSR-24 m, RR: 1.35, [0.95–1.91], p = 0.10; PFSR-30 m, RR: 0.205, [1.46–2.86], p < 0.0001, Figure S3). With prolonged survival time, ICI+chemotherapy had an increasing advantage for PFS (Figures 3C, D).

In the subgroup analysis, the favorable tendency of OS did not show significant changes according to age, ECOG performance status, number of metastatic sites, PD-L1 status, neoadjuvant therapy, lymph node-only disease, bone metastases, liver metastases, lung metastases, or previous chemotherapy (chemotherapy, taxane, or anthracycline). The addition of ICIs might have the opposite effect in the subgroups by race (Asian), baseline disease status (locally advanced), and brain metastases (yes) (Table 2).

The CR of the ICI+chemotherapy group was higher than that of the chemotherapy group (584/1,106 vs. 341/825, RR: 1.38, [1.01–1.89], p = 0.04; Figure 4).

Toxicity

In summary, ICI+chemotherapy treatment was related to more Grade 3–5 AEs, treatment-related Grade 3–5 AEs, serious AEs, treatment-related serious AEs, and AEs leading to treatment discontinuation. Total AEs, treatment-related AEs, death, treatment-related death, and AEs leading to dose reduction/dose interruption were comparable between the two groups (Table 3).

For total AEs, increases in aspartate aminotransferase (AST) levels, vomiting, cough, rash, pyrexia, pruritus, infusion reaction,
FIGURE 2 | Forest plots of OS and PFS associated with ICIs+Chemotherapy versus Chemotherapy.

FIGURE 3 | Comparisons of OSR (6–36 months, A, B), and PFSR (6–30 months, C, D) associated with ICIs+Chemotherapy versus Chemotherapy according to survival time.
hypothyroidism, nail disorders, hypokalemia, hyperthyroidism, pneumonitis, hepatitis, and adrenal insufficiencies were related to the ICI+chemotherapy group. Total AEs greater than 10% are summarized in Table 4.

For Grade 3–5 AEs, more cases of diarrhea, severe skin reactions, pneumonitis, hepatitis, and adrenal insufficiencies were related to the ICI+chemotherapy group. Grade 3–5 AEs greater than 1% are summarized in Table 5.

**Sensitivity Analysis**

In the analysis of complete response, PFSR, and AEs, the \( I^2 \) statistic was >50%, which suggests significant heterogeneity. By

| Subgroups | Included studies | Total | ICI+Chemotherapy | Chemotherapy | HR (95% CI) |
|-----------|-----------------|-------|-----------------|--------------|-------------|
| All patients | 5 | 2,056 | 651 | 1,138 | 566 | 918 | 0.79 (0.63, 0.99) |
| **Age** | | | | | | | |
| 18–40 years | 1 | 114 | 44 | 63 | 37 | 51 | 0.81 (0.62, 1.25) |
| 41–64 years | 1 | 569 | 158 | 284 | 170 | 285 | 0.88 (0.71, 1.10) |
| >65 years | 1 | 219 | 53 | 104 | 72 | 115 | 0.78 (0.55, 1.12) |
| **Race** | | | | | | | |
| White | 1 | 609 | 180 | 308 | 198 | 301 | 0.80 (0.66, 0.98) |
| Asian | 1 | 161 | 39 | 85 | 34 | 76 | 1.17 (0.74, 1.87) |
| Black or African-American | 1 | 58 | 14 | 26 | 21 | 32 | 0.75 (0.38, 1.49) |
| **ECOG performance status** | | | | | | | |
| 0 | 1 | 526 | 127 | 256 | 145 | 270 | 0.85 (0.67, 1.06) |
| 1 | 1 | 372 | 127 | 193 | 132 | 179 | 0.85 (0.66, 1.08) |
| **Baseline disease status** | | | | | | | |
| Locally advanced | 1 | 88 | 21 | 46 | 13 | 42 | 1.53 (0.76, 3.06) |
| Metastatic | 1 | 812 | 234 | 404 | 266 | 408 | 0.82 (0.90, 0.98) |
| **Number of metastatic sites** | | | | | | | |
| 0-3 | 1 | 673 | 172 | 332 | 194 | 341 | 0.83 (0.68, 1.02) |
| 4+ | 1 | 226 | 83 | 118 | 83 | 108 | 0.90 (0.66, 1.22) |
| **PD-L1 status** | | | | | | | |
| PD-L1 positive | 4 | 717 | 206 | 407 | 181 | 310 | 0.79 (0.63, 0.99) |
| PD-L1 negative | 2 | 562 | 175 | 283 | 179 | 279 | 0.56 (0.23, 1.38) |
| **Neoadjuvant therapy** | | | | | | | |
| Yes | 1 | 88 | 25 | 44 | 27 | 44 | 0.87 (0.48, 1.58) |
| No | 4 | 1,968 | 626 | 1,092 | 539 | 874 | 0.86 (0.74, 0.99) |
| **Homologous recombination deficiency (HRD)** | | | | | | | |
| Low HRD | 1 | 21 | 3 | 10 | 9 | 19 | 0.27 (0.07, 1.10) |
| High HRD | 1 | 31 | 9 | 19 | 9 | 12 | 0.71 (0.26, 1.89) |
| **Brain metastases** | | | | | | | |
| Yes | 1 | 61 | 22 | 30 | 19 | 31 | 1.34 (0.72, 2.48) |
| No | 1 | 841 | 233 | 421 | 260 | 420 | 0.83 (0.70, 1.00) |
| **Bone metastases** | | | | | | | |
| Yes | 1 | 286 | 92 | 145 | 103 | 141 | 0.80 (0.61, 1.07) |
| No | 1 | 616 | 163 | 308 | 178 | 310 | 0.88 (0.71, 1.09) |
| **Liver metastases** | | | | | | | |
| Yes | 1 | 244 | 88 | 126 | 95 | 118 | 0.77 (0.58, 1.03) |
| No | 1 | 658 | 167 | 325 | 184 | 333 | 0.88 (0.72, 1.09) |
| **Lung metastases** | | | | | | | |
| Yes | 1 | 469 | 138 | 227 | 153 | 242 | 0.94 (0.74, 1.18) |
| No | 1 | 433 | 117 | 224 | 126 | 209 | 0.80 (0.62, 1.02) |
| **Lymph node-only disease** | | | | | | | |
| Yes | 1 | 56 | 12 | 33 | 11 | 23 | 0.74 (0.32, 1.67) |
| No | 1 | 843 | 243 | 417 | 266 | 426 | 0.68 (0.74, 1.05) |
| **Previous neoadjuvant or adjuvant chemotherapy** | | | | | | | |
| Yes | 1 | 570 | 160 | 284 | 166 | 286 | 0.92 (0.74, 1.15) |
| No | 1 | 332 | 95 | 167 | 113 | 165 | 0.75 (0.57, 0.99) |
| **Previous taxane treatment** | | | | | | | |
| Yes | 1 | 461 | 138 | 231 | 136 | 230 | 0.95 (0.75, 1.20) |
| No | 1 | 441 | 117 | 220 | 143 | 221 | 0.76 (0.59, 0.97) |
| **Previous anthracycline treatment** | | | | | | | |
| Yes | 1 | 485 | 143 | 243 | 144 | 242 | 1.00 (0.79, 1.26) |
| No | 1 | 417 | 112 | 208 | 135 | 209 | 0.71 (0.55, 0.92) |

PD-L1+, programmed death ligand 1 positive; ICIs, immune checkpoint inhibitors; HR, hazard ratio; CI, confidence interval; OS, overall survival; HRD, homologous recombination deficiency; ECOG, Eastern Cooperative Oncology Group.
removing each study, the sensitivity analysis suggested that the results were stable and reliable (Figure S4).

**Publication Bias**

No significant publication bias was found based on the funnel plots of survival (Figure S5A) and safety (Figure S5B).

**DISCUSSION**

Due to the lack of targets for therapeutic intervention, the treatment of TNBC is challenging (23). Whether immunotherapy can improve the curative effect when added to original standard chemotherapy treatment is still controversial (7, 8). This meta-analysis first compared ICI+chemotherapy with chemotherapy for TNBC treatment. The results suggest that ICI+chemotherapy treatment showed better efficacy in OS, PFS, and complete response. With the prolongation of survival, the survival advantage of ICI+chemotherapy increased compared with that of chemotherapy. In the toxicity analysis, more Grade 3–5 AEs and serious AEs were found in the ICI+chemotherapy group.

Better survival rates were the main benefit for the ICI+Chemotherapy group. With the prolongation of survival, the advantage of OS and PFS in the ICI+Chemotherapy group increased compared with the chemotherapy group. Similar results were confirmed by three large sample RCTs (KEYNOTE-522, IMpassion130 and KEYNOTE-355) (9, 10, 12). The I-SPY2 study and KEYNOTE-522 study suggested that significantly higher rates of CR were achieved in the ICI+Chemotherapy groups (9, 13). Two reasons may explain the benefit of ICI+Chemotherapy: (1) ICIs kill tumor cells by activating tumor immunity, which is different from chemotherapy and plays a synergistic role, especially in PD-L1-positive TNBC (9, 24). The antitumor effect may be more significant in early breast cancer than metastatic disease, because the tumor immune microenvironment is more robust (25); and (2) higher CR rates (584/1,106 vs. 341/825, RR: 1.38, [1.01–1.89]) were found in the ICIs+Chemotherapy groups, which is very important for the long-term survival of breast cancer patients after surgery (11, 13). Cortazar et al.'s pooled analysis also confirmed the strong association of PCR (no tumor in either breast or the lymph nodes) after neoadjuvant

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**TABLE 3 | Summary of adverse events.**

| Adverse events | Studies involved | ICIs+Chemotherapy Event/total | Chemotherapy Event/total | Risk ratio | 95% CI | I² (%) | P |
|----------------|-----------------|------------------------------|--------------------------|-----------|-------|--------|---|
| Total adverse events | 7               | 2462/2488 95.95%             | 1550/1589 97.55%         | 1.01      | 0.99-1.03 | 85      | 0.41 |
| Treatment-related adverse events | 5               | 1951/2013 96.92%             | 1255/1325 94.72%         | 1.02      | 0.98-1.06 | 88      | 0.43 |
| Grade 3-5 adverse events | 6               | 1697/2444 69.43%             | 901/1545 58.32%          | 1.14      | 1.03-1.25 | 69      | 0.0006 |
| Treatment-related grade 3-5 adverse events | 6               | 1295/2057 62.96%             | 724/1369 52.89%          | 1.09      | 1.03-1.16 | 45      | 0.002 |
| Serious adverse events | 2               | 155/616 25.16%               | 111/619 17.93%           | 1.40      | 1.13-1.74 | 19      | 0.002 |
| Treatment-related serious adverse events | 4               | 128/751 17.04%               | 88/740 11.89%            | 1.44      | 1.13-1.85 | 30      | 0.003 |
| Adverse event leading to treatment discontinuation | 4               | 123/751 16.38%               | 76/740 10.27%            | 1.61      | 1.24-2.10 | 46      | 0.0004 |
| Adverse event leading to dose reduction/dose interruption | 1               | 194/451 43.02%               | 173/451 38.36%           | 1.12      | 0.96-1.31 | –       | 0.16 |
| Death | 3               | 7/863 1.06%                  | 4/654 0.61%              | 1.76      | 0.52-5.97 | 0       | 0.37 |
| Treatment-related death | 1               | 2/451 0.44%                  | 1/451 0.22%              | 2.00      | 0.18-21.98 | –       | 0.57 |

ICIs, immune checkpoint inhibitors; CI, confidence interval.
| Adverse events                                                                 | Studies involved | ICIs+Chemotherapy | Chemotherapy | Total incidence | Risk ratio | 95% CI     | (2) (%) | P      |
|--------------------------------------------------------------------------------|-----------------|-------------------|--------------|----------------|------------|------------|---------|--------|
| Alopecia                                                                       | 5               | 1123/2054         | 771/1376     | 56.03%         | 55.22%     | 1.03       | 0.97-1.09| 0.33   |
| Nausea                                                                         | 6               | 1138/2123         | 825/1557     | 52.99%         | 53.26%     | 1.04       | 0.98-1.10| 0.23   |
| Infection                                                                      | 1               | 50/88             | 39/66        | 45.35%         | 51.15%     | 1.25       | 0.93-1.68| 0.13   |
| Anemia                                                                         | 6               | 1004/2123         | 640/1557     | 41.10%         | 44.67%     | 1.05       | 0.98-1.13| 0.18   |
| Fatigue                                                                        | 6               | 882/2123          | 709/1557     | 45.54%         | 43.23%     | 1.04       | 0.97-1.12| 0.30   |
| Hyperglycaemia                                                                 | 1               | 32/88             | 37/86        | 43.02%         | 39.66%     | 0.85       | 0.58-1.22| 0.33   |
| Leucopenia                                                                     | 2               | 101/253           | 96/254       | 37.80%         | 38.86%     | 1.04       | 0.91-1.19| 0.61   |
| Neutropenia                                                                    | 5               | 823/2054          | 484/1436     | 35.17%         | 38.12%     | 1.07       | 0.98-1.17| 0.12   |
| Mucositis                                                                      | 1               | 32/88             | 33/86        | 38.37%         | 37.36%     | 0.95       | 0.64-1.39| 0.78   |
| Diarrhea                                                                       | 5               | 510/1557          | 422/1276     | 33.07%         | 32.90%     | 1.07       | 0.88-1.29| 0.67   |
| Peripheral sensory neuropathy                                                  |                 | 4                 | 214/773      | 31.18%         | 31.46%     | 1.12       | 0.99-1.28| 0.30   |
| Nausea                                                                         | 6               | 25/88             | 24/86        | 27.91%         | 28.16%     | 1.02       | 0.93-1.12| 0.94   |
| Vomiting                                                                       | 1               | 24/88             | 22/86        | 25.13%         | 26.44%     | 1.07       | 0.65-1.75| 0.80   |
| Hyperglycaemia                                                                 | 1               | 32/88             | 37/86        | 43.02%         | 39.66%     | 0.85       | 0.58-1.22| 0.37   |
| Leucopenia                                                                     | 2               | 101/253           | 96/254       | 37.80%         | 38.86%     | 1.04       | 0.91-1.19| 0.61   |
| Neutropenia                                                                    | 5               | 823/2054          | 484/1436     | 35.17%         | 38.12%     | 1.07       | 0.98-1.17| 0.12   |
| Mucositis                                                                      | 1               | 32/88             | 33/86        | 38.37%         | 37.36%     | 0.95       | 0.64-1.39| 0.78   |
| Diarrhea                                                                       | 5               | 510/1557          | 422/1276     | 33.07%         | 32.90%     | 1.07       | 0.88-1.29| 0.67   |
| Peripheral sensory neuropathy                                                  |                 | 4                 | 214/773      | 31.18%         | 31.46%     | 1.12       | 0.99-1.28| 0.30   |

ICIs, immune checkpoint inhibitors; CI, confidence interval.
TABLE 5 | Grade 3–5 adverse events an incidence of more than 1% according to combination of two groups.

| Adverse events                        | Studies involved | ICIs+Chemotherapy | Chemotherapy | Total incidence | Risk ratio | 95% CI | I² (%) | P      |
|---------------------------------------|------------------|-------------------|--------------|----------------|------------|--------|--------|--------|
|                                       | Event/total %     | Event/total %     |              |                |            |        |        |        |
| Neutropenia                           | 5                | 547/2,054 (26.84%)| 319/1,376 (23.18%)| 25.26%         | 1.02       | 0.91–1.15 | 0.69   |
| Leukopenia                            | 2                | 44/253 (17.39%)   | 38/254 (14.96%)  | 16.17%         | 1.14       | 0.79–1.66 | 0.48   |
| Decreased neutrophil count            | 5                | 287/2,035 (14.10%)| 181/1,471 (12.51%)| 13.43%         | 0.90       | 0.76–1.06 | 0.20   |
| Anemia                                | 6                | 269/2,123 (12.82%)| 136/1,557 (8.73%)  | 10.98%         | 1.17       | 0.96–1.42 | 0.11   |
| Febrile neutropenia                   | 3                | 28/322 (8.70%)    | 30/435 (6.90%)   | 7.66%          | 1.28       | 0.77–2.12 | 0.34   |
| Infection                             | 1                | 5/88 (5.68%)      | 4/86 (4.65%)     | 5.17%          | 1.22       | 0.34–4.40 | 0.76   |
| Elevated alanine aminotransferase level| 5                | 96/2,054 (4.67%)  | 44/1,376 (3.20%)  | 4.08%          | 1.39       | 0.97–1.99 | 0.08   |
| Bone pain                             | 1                | 4/88 (4.55%)      | 2/86 (2.33%)     | 3.45%          | 1.95       | 0.37–10.39 | 0.43   |
| Fatigue                               | 6                | 76/2,123 (3.58%)  | 43/1,557 (2.76%)  | 3.23%          | 1.26       | 0.94–1.97 | 0.11   |
| Hypertension                          | 2                | 14/616 (2.27%)    | 23/619 (3.72%)   | 3.00%          | 0.62       | 0.32–1.18 | 0.14   |
| Peripheral sensory neuropathy         | 4                | 24/773 (3.10%)    | 24/866 (2.71%)   | 2.89%          | 1.07       | 0.62–1.87 | 0.80   |
| Aspartate aminotransferase increased  | 2                | 10/253 (3.96%)    | 3/254 (1.18%)    | 2.56%          | 3.03       | 0.91–10.04 | 0.07   |
| Peripheral neuropathy                 | 5                | 46/1,557 (2.96%)  | 25/1,276 (1.96%)  | 2.51%          | 1.58       | 0.98–2.56 | 26.06  |
| Nail discoloration                    | 2                | 8/253 (3.16%)     | 4/254 (1.57%)    | 2.37%          | 1.86       | 0.61–5.71 | 26.28  |
| Hand-foot-syndrome                    | 1                | 1/88 (1.14%)      | 3/86 (3.49%)     | 2.30%          | 0.33       | 0.03–0.30 | 0.33   |
| Nausea                                | 6                | 46/2,123 (2.17%)  | 31/1,557 (1.99%)  | 2.09%          | 0.96       | 0.33–2.73 | 67.93  |
| Diarrhea                              | 5                | 37/1,557 (2.36%)  | 19/1,276 (1.49%)  | 1.98%          | 1.76       | 1.01–3.04 | 7.04   |
| Asthenia                              | 3                | 31/1,400 (2.21%)  | 15/1,009 (1.49%)  | 1.91%          | 1.26       | 0.67–2.35 | 0.47   |
| Hypokalemia                           | 1                | 11/451 (2.44%)    | 4/451 (0.89%)    | 1.66%          | 2.75       | 0.88–8.57 | 0.08   |
| Infusion reaction                     | 3                | 21/1,037 (2.03%)  | 5/644 (0.78%)    | 1.55%          | 2.26       | 0.84–6.06 | 0.11   |
| Vomiting                              | 5                | 26/1,557 (1.67%)  | 13/1,276 (1.02%)  | 1.38%          | 1.38       | 0.72–2.67 | 0.34   |
| Severe skin reaction                  | 5                | 45/2,320 (1.93%)  | 2/1,428 (0.14%)   | 1.25%          | 8.50       | 2.54–28.46 | 0.0005 |
| Fever without neutropenia            | 1                | 1/88 (1.14%)      | 1/86 (1.16%)     | 1.15%          | 0.98       | 0.06–15.38 | 0.99   |
| Injury-poisoning and procedure        | 1                | 1/88 (1.14%)      | 1/86 (1.16%)     | 1.15%          | 0.98       | 0.06–15.38 | 0.99   |
| Anorexia                              | 1                | 1/88 (1.14%)      | 1/86 (1.16%)     | 1.15%          | 0.98       | 0.06–15.38 | 0.99   |
| Mucositis                             | 1                | 2/88 (2.27%)      | 0/86 (0.00%)     | 1.15%          | 4.89       | 0.24–100  | 0.30   |

ICIs, immune checkpoint inhibitors; CI, confidence interval.

chemotherapy with an improved long-term benefit with respect to OS and DFS, especially in patients with TNBC (26). However, subgroup analysis suggested that addition of ICIs might not have a better effect in Asian patients, patients with locally advanced disease, or patients with brain metastases. Therefore, we suggested that ICIs+Chemotherapy is better than chemotherapy alone with longer survival, especially for patients with PD-L1-positive TNBC.

Higher rate of AEs, especially Grade 3–5/serious AEs, is the main restrictive factor to add immunotherapy to chemotherapy (9, 10). Twenty-one Grade 3–5 AEs greater >2% were reported in the ICIs+Chemotherapy group (neutropenia, leukopenia, decreased neutrophil count, anemia, febrile neutropenia, infection, elevated alanine aminotransferase [ALT] levels, bone pain, increased AST levels, fatigue, nail discoloration, peripheral sensory neuropathy, peripheral neuropathy, hypokalemia, diarrhea, mucositis, hypertension, severe skin reactions, asthenia, nausea, and infusion reactions) compared with twelve in the chemotherapy group (neutropenia, leukopenia, decreased neutrophil count, anemia, febrile neutropenia, infection, hypertension, hand-foot-syndrome, elevated ALT levels, fatigue, peripheral sensory neuropathy, and bone pain). The frequency of AEs was similar as previously reported by Schmid et al. in the updated report of the IMpassion130 trial (23). Hypothyroidism, hyperthyroidism, pneumonitis, hepatitis, and adrenal insufficiency were five AEs of special interest, which were all significantly increased after the addition of ICIs (27). High levels of AEs leading to treatment discontinuation was found in the ICIs+Chemotherapy group (16.38% vs. 10.27%), which might decrease antitumor efficacy (10). In the subgroup analysis according to the organs, the addition of ICIs might have a greater impact on the gastrointestinal system, hepatobiliary system, respiratory system, and the thyroid. Therefore, we suggested that although ICIs+Chemotherapy has better survival efficacy, the increase in serious complications deserves attention to improve the lifelong treatment of patients during survival.

However, this meta-analysis had some limitations described as follows: (1) The treatments used in the ICIs+Chemotherapy group and chemotherapy group were different between the groups, which might also increase heterogeneity. (2) Four out of the eight included studies (9, 11, 13, 14) focused on neoadjuvant therapy for early breast cancers, and the other 4/8 studies (10, 12, 16, 18) focused on medical therapy for metastatic breast cancers, and the combined analysis might increase heterogeneity. (3) Only RCTs published in English were included, which might introduce language bias; and (4) significant heterogeneity was found in some analyses (CR, PFSR, etc.), which might decrease the credibility of these results.
ICIs+Chemotherapy appears to be better than chemotherapy alone for TNBC with better OS and PFS. With the prolonged survival time, ICIs+Chemotherapy had an increased advantage for survival. However, the high rates of Grade 3–5/serious AEs, especially immunotherapy-related AEs, need to be taken seriously. However, due to the limitations described above, the results must be confirmed by more large-sample and high-quality RCTs.

**REFERENCES**

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin (2021) 71(1):7–33. doi: 10.3322/caac.21564
2. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, et al. Breast Cancer Statistics, 2019. CA Cancer J Clin (2019) 69(6):438–51. doi: 10.3322/caac.21583
3. Lobli S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast Cancer. Lancet (2021) 397(10286):1750–69. doi: 10.1016/S0140-6736(20)32381-3
4. Howlader N, Forjaz G, Mooradian MJ, Meza R, Kong CY, Cronin KA, et al. The Effect of Advances in Lung-Cancer Treatment on Population Mortality. N Engl J Med (2020) 383(7):640–9. doi: 10.1056/NEJMoa1916623
5. Yang JD, Heimbach JK. New Advances in the Diagnosis and Management of Hepatocellular Carcinoma. BMJ (2020) 371:m3544. doi: 10.1136/bmj.m3544
6. Janijigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-Line Nivolumab Plus Chemotherapy Versus Chemotherapy Alone for Advanced Gastric, Gastro-Oesophageal Junction, and Oesophageal Adenocarcinoma (CheckMate 649): A Randomised, Open-Label, Phase 3 Trial. Lancet (2021) 398(10294):27–40. doi: 10.1016/S0140-6736(21)00797-2
7. Gradishar WJ, Moran MS, Abraham J, Alt R, Agnese D, Allison KH, et al. NCCN Guidelines Insights: Breast Cancer, Version 4.2021. J Natl Compr Canc Netw (2021) 19(5):484–93. doi: 10.6004/jnccn.2021.0023
8. Denduluri N, Somerfield MR, Chavez-MacGregor M, Comander AH, Dayao Z, Eisen A, et al. Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Guideline Update. J Clin Oncol (2021) 39(6):685–93. doi: 10.1200/JCO.20.02510
9. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med (2020) 382(9):810–21. doi: 10.1056/NEJMoa1910549
10. Schmid P, Adams S, Rugo HS, Schneeweiss 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. doi: 10.1056/NEJMoa1809615

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.795650/full#supplementary-material

**AUTHOR CONTRIBUTIONS**

JH had full access to all of the data in the manuscript and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the article and approved the submitted version. Concept and design: All authors. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: QJ, JD, MH, and NL. Critical revision of the manuscript for important intellectual content: QJ, JH, and WZ. Statistical analysis: QJ, JH, and WZ. Supervision: QJ and JH.

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**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.
11. Mittendorf EA, Zhang H, Barrios CH, Saji S, Hae Jung K, 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 (I Mpasion031): A Randomised, Double-Blind, Phase 3 Trial. *Lancet* (2020) 396(10257):1090–100. doi: 10.1016/S0140-6736(20)31953-X

12. Cortes J, Cescon DW, Rugo HS, Nowecki Z, Im S-A, Yusof M, et al. Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple-Negative Breast Cancer (KEYNOTE-355): A Randomised, Placebo-Controlled, Double-Blind, Phase 3 Clinical Trial. *Lancet* (2020) 396(10265):1817–28. doi: 10.1016/S0140-6736(20)32531-9

13. Nanda R, Liu MC, Yau C, Shatsky R, Pusztai L, Wallace A, et al. Effect of Pembrolizumab Plus Neoadjuvant Chemotherapy on Pathologic Complete Response in Women With Early-Stage Breast Cancer: An Analysis of the Ongoing Phase 2 Adaptively Randomized I-SPY2 Trial. *JAMA Oncol* (2020) 6(5):676–84. doi: 10.1001/jamaoncol.2019.6650

14. Loibl S, Untch M, Burchardi N, Huober J, Sinn BV, Blohmer J-U, et al. A Randomised 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. doi: 10.1093/annonc/mdz158

15. Miles D, Gilgore J, André F, Cameron D, Schneeweiss A, Barrios C, et al. Primary Results From IMpassion131, a Double-Blind, Placebo-Controlled, Randomised Phase III Trial of First-Line Paltaxel With or Without Atezolizumab for Unrespectably Locally Advanced/Metastatic Triple-Negative Breast Cancer. *Ann Oncol* (2021) 32(8):994–1004. doi: 10.1016/j.annonc.2021.05.801

16. Bachetot T, Filleron T, Bieche I, Arnedos M, Campone M, Dalenc F, et al. Durvalumab Compared to Maintenance Chemotherapy in Metastatic Breast Cancer: The Randomized Phase II SAFIR02-BREAST IMMUNO Trial. *Nat Med* (2021) 27(2):250–5. doi: 10.1038/s41591-020-01189-2

17. Brufsky A, Kim SB, Zvirbule Z, Eniu A, Mebis J, Sohn JH, et al. A Phase II Randomised Trial of Cobimetinib Plus Chemotherapy, With or Without Atezolizumab, as First-Line Treatment for Patients With Locally Advanced or Metastatic Triple-Negative Breast Cancer (COLET): Primary Analysis. *Ann Oncol* (2021) 32(5):652–60. doi: 10.1016/annonc.2021.01.065

18. Tolaney SM, Barroso-Sousa R, Keenan T, Li T, Trippa L, Vaz-Luís I, et al. Effect of Erbulin With or Without Pembrolizumab on Progression-Free Survival for Patients With Hormone Receptor-Positive, ERBB2-Negative Metastatic Breast Cancer: A Randomized Clinical Trial. *JAMA Oncol* (2020) 6(10):1598–605. doi: 10.1001/jamaoncol.2020.3524

19. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015: Elaboration and Explanation. *BMJ* (2015) 350:g7647. doi: 10.1136/bmj.g7647

20. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. **GRADE Guidelines: A New Series of Articles in the Journal of Clinical Epidemiology.** *J Clin Epidemiol* (2011) 64(4):380–2. doi: 10.1016/j.jclinepi.2010.09.011

21. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? *Control Clin Trials* (1996) 17(1):1–12. doi: 10.1016/0197-2456(95)00134-4

22. Higgins JP, Altman DG, Gotzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration’s Tool for Assessing Risk of Bias in Randomised Trials. *BMJ* (2011) 343:d5928. doi: 10.1136/bmj.d5928

23. Franzoi MA, Romano E, Piccart M. Immunotherapy for Early Breast Cancer: Too Soon, Too Superficial, or Just Right? *Ann Oncol* (2021) 32(3):532–36. doi: 10.1016/annonc.2020.11.022

24. Li S, Liu M, Do MH, Chou C, Stamatiades EG, Nixon BG, et al. Cancer Immunotherapy via Targeted TGF-Beta Signalling Blockade in T(H) Cells. *Nature* (2020) 587(7832):121–5. doi: 10.1038/s41586-020-2850-3

25. Hutchinson KE, Yost SE, Chang C-W, Johnson RM, Carr AR, McAdam PR, et al. Comprehensive Profiling of Poor-Risk Paired Primary and Recurrent Triple-Negative Breast Cancers Reveals Immune Phenotype Shifts. *Clin Cancer Res* (2020) 26(3):657–68. doi: 10.1158/1078-0432.CCR-19-1773

26. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological Complete Response and Long-Term Clinical Benefit in Breast Cancer: The CTNeoBC Pooled Analysis. *Lancet* (2014) 384(9938):164–72. doi: 10.1016/S0140-6736(13)62422-8

27. Schmid P, Rugo HS, Adams S, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab Plus Nab-Paclitaxel as First-Line Treatment for Unrespectable, Locally Advanced or Metastatic Triple-Negative Breast Cancer (IMpassion130): Updated Efficacy Results From a Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. *Lancet Oncol* (2020) 21(1):44–59. doi: 10.1016/S1470-2045(19)30689-8

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