Original Article

The efficacy and safety of PD-1/PD-L1 inhibitors in breast cancer: a systematic review and meta-analysis

Bo-Ya Xiao[1], Guo-He Lin[2], Yan-Xia Zhao[3], Bi-Cheng Wang[3]

[1]Shanghai Eastern Hepatobiliary Surgery Hospital, Shanghai, China; [2]Department of Oncology, the Second Affiliated Hospital of Anhui Medical University, Hefei, China; [3]Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Contributions: (I) Conception and design: BC Wang, YX Zhao; (II) Administrative support: Union Hospital, Tongji Medical College, Huazhong University of Science and Technology; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: BC Wang, GH Lin; (V) Data analysis and interpretation: BC Wang, BY Xiao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Bi-Cheng Wang, MD. Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan, China. Email: bcsnowell@163.com; Yan-Xia Zhao, MD. Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan, China. Email: sophia7781@126.com.

Background: Immune checkpoint inhibition has been increasingly used in breast cancer therapy. Understanding the benefit and risk of programmed cell death 1 (*PD-1*) and programmed cell death ligand 1 (*PD-L1*) inhibitors is critical for clinical practice. This study aims to determine the objective response, disease control and adverse events of breast cancer patients treated with *PD-1/PD-L1* inhibitors.

Methods: PubMed, Cochrane Library, Web of Science and EMBASE databases were searched up to Aug 1, 2019. Both nonrandomized and randomized studies were included. Pooled objective response rate (ORR), disease control rate (DCR) and adverse events were pooled analyzed.

Results: A total of nine clinical studies were identified. Triple-negative breast cancer (TNBC) showed the highest estimates of ORR [overall population: 49.7%, 95% confidence interval (CI): 33.9–65.5%; *PD-L1* positive population: 55.8%, 95% CI: 42.9–68.8%] and DCR (overall population: 67.5%, 95% CI: 38.6–96.4%; *PD-L1* positive population: 83.4%, 95% CI: 72.2–94.5%) post-anti-*PD-L1* plus nab-paclitaxel treatment. With respect to grade ≥3 treatment related adverse events, the pooled estimates ranged from 12.0% to 50.9% for anti-*PD-1/PD-L1* monotherapy. The pooled estimates percentages of grade ≥3 treatment related adverse events in TNBC patients treated with anti-*PD-L1* plus nab-paclitaxel were 59.6% (95% CI: 36.1–83.0).

Conclusions: We presented the aggregate estimates of ORR, DCR, and treatment related adverse events for breast cancer patients receiving anti-*PD-1/PD-L1* treatment. However, these results were largely derived from single-arm studies, and randomized studies with head-to-head comparison of *PD-1/PD-L1* inhibitors and chemotherapy are lacking. Additionally, the incidence of varying treatment related adverse events should be also carefully monitored.

Keywords: Programmed cell death ligand 1 (*PD-L1*) inhibitor; programmed cell death 1 (*PD-1*) inhibitor; objective response rate (ORR); disease control rate (DCR); breast cancer

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Introduction

Despite 5-year overall survival rate of breast cancer was 90%, approximately 30% breast cancer patients with an early-stage diagnosis eventually progressed to advanced metastatic disease, and about 6% of patients were metastatic disease at diagnosis (1). Treatments of advanced breast cancer include chemotherapy, endocrine-based therapeutic strategies, HER2-related regimens, *CDK4/6* inhibitors and

Poly (ADP-ribose) polymerase (*PARP*) inhibitors (2). The two most important targets for breast cancer are HER2 and *CDK4/6*. For HER2 positive breast cancer, trastuzumab greatly improves survival outcomes (3). *CDK4/6* inhibitors, including palbociclib, ribociclib, and abemaciclib, combined with endocrine therapies could be suggested as the core treatment modality in patients with hormone receptor positive advanced breast cancer (4,5). Additionally, three PARP inhibitors, olaparib, rucaparib, and niraparib, have received approval for advanced cancers with breast cancer type 1/2 susceptibility protein (*BRCA1/2*) mutations, but the efficacy in breast cancer patients remains controversial (6-8). For triple-negative breast cancer (TNBC) lacking the expression of estrogen (*ER*), progesterone receptor (*PR*), and HER-2, cytotoxic chemotherapy is the standard treatment. However, the treatment is limited by considerable toxicity and short duration of response (9-11).

Given the suboptimal outcomes with traditional chemotherapy, new targeted therapeutic regimens for breast cancer are urgently needed. Fortunately, immune checkpoint inhibitors, including programmed cell death 1 (*PD-1*) and programmed cell death ligand 1 (*PD-L1*) inhibitors, have revolutionized cancer therapy (12,13). To date, the US Food and Drug Administration has approved three *PD-1* inhibitors (pembrolizumab, nivolumab and cemiplimab) and three *PD-L1* inhibitors (atezolizumab, durvalumab and avelumab). Blocking the *PD-1/PD-L1* pathway with monoclonal antibodies might be one means of restoring immune surveillance and T cell-mediated antitumor immunity (13). Substantial researches showed that *PD-L1* was expressed in multiple solid tumors and might be a predictor of response to *PD-1/PD-L1* axis inhibition (14-16). Approximately half of breast cancers expressed *PD-L1*, with expression generally higher in TNBC (17-22). Moreover, it was reported that, in patients with TNBC, *PD-1* occurred mainly on tumor-infiltrating immune cells (19,23). Thus, both the *PD-1* and *PD-L1* inhibitors might be useful therapeutic regimens for breast cancer.

To date, many single-arm clinical trials have reported the benefits and toxicities of *PD-1/PD-L1* inhibitors for breast cancer without control therapies. Most of the trials found that *PD-1/PD-L1* inhibitors provided durable clinical benefit and were well tolerated with or without combined treatment, whereas two recent meta-analyses emphasized that immune checkpoint inhibitors related adverse events warranted consideration (24,25). Amounts of clinical trials are ongoing to detect the benefit and risk of *PD-1/PD-L1* inhibitors in breast cancer. Pooled analyses of the published results of anti-*PD-1/PD-L1* therapies could provide useful information for these ongoing and future explorations in breast cancer. Therefore, in this study, we aim to summarize the antitumor activity and safety of the *PD-1/PD-L1* inhibitors in published clinical studies of breast cancer. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/tcr-19-3020).

Methods

Search strategy and study selection

Trials identification followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline (PRISMA) (26).

The search was done in PubMed, Cochrane Library, Web of Science, and EMBASE databases using the terms "nivolumab or pembrolizumab or cemiplimab or atezolizumab or durvalumab or avelumab or PD-1 inhibitor or PD-L1 inhibitor", "breast cancer or breast neoplasm or breast carcinoma or breast tumor", and "trial or clinical trial or randomized clinical trial or randomized controlled trial". We also manually searched the references of relevant published trials and review articles for further eligible studies. The search was completed on Aug 1, 2019.

Studies eligible for inclusion met all of the following criteria: (I) phase I to IV trials in patients with breast cancer, (II) participants were treated with a single agent *PD-1/PD-L1* inhibitor or with a combination therapy including a *PD-1/PD-L1* inhibitor, (III) inclusion of antitumor activity and safety data, (IV) trials were published in English. Conference abstracts were excluded due to the absence of adverse events data and the increase of heterogeneity. This is because the conference reports are intended to show the positive results rather than negative results. For multiple publications that were identified reporting on the same trial population, the one with the most complete publication data was selected. *PD-L1* positive (+) breast cancer was defined as ≥1% tumor cells, lymphocytes, and macrophages. BW and GL reviewed the articles independently. Any discrepancies regarding the literature search, study selection, and data extraction of an article were resolved by discussion.

Data extraction

Detailed reviews of full-text articles were performed by two authors (BW and GL) independently. The first author's

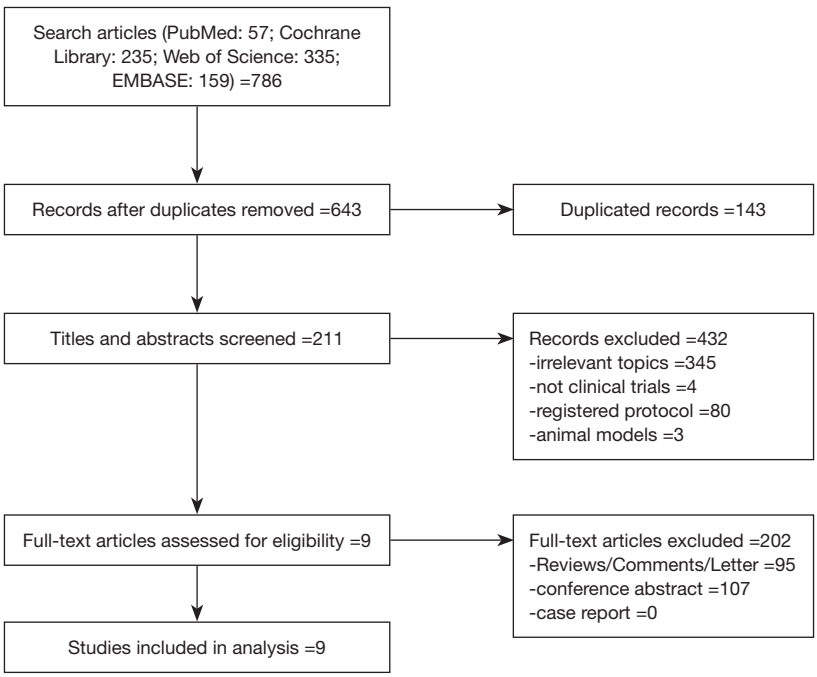

Figure 1 Flow diagram of the analysis.

name, publication year, trial name, study design, number of patients, number of TNBC patients, *PD-L1* status, phase, cancer type, *PD-1* and *PD-L1* inhibitor used, and dosing schedule were obtained from each included study. Objective response rate (ORR), disease control rate (DCR), median overall survival (OS), median progression-free survival (PFS), median time to response, median duration of response, and safety data reporting in the publication were collected.

Statistical analysis

All analyses were done using STATA statistical software (version 14.0) and P<0.05 was considered statistically significant. Random-effects models were applied for all pooled effect sizes due to the absence of corresponding single-arm trials. As mean rates could not be smaller than 0, some 95% confidence intervals (CIs) below 0 were considered as 0. Statistical heterogeneity between studies was tested by the Cochran Q chi-square test and I^2 statistic percentages, and P<0.10 indicated apparent heterogeneity. I^2<50% was defined as low heterogeneity, otherwise was high heterogeneity. Subgroup analyses were performed according to the drug types for ORR, DCR, any-grade and grade ≥3 treatment related adverse events. Egger's test was used to evaluate latent publication bias for small-study effects.

Results

Eligible studies and characteristics

Literature search and review of reference lists identified 786 relevant publications. After screening and eligibility assessment, we included in the systematic review a total of 9 clinical trials involving 1,137 breast cancer patients, comprising one randomized controlled trial (27) and eight single-arm trials (28-35) (*Figure 1*). The *PD-1* and *PD-L1* inhibitors used included pembrolizumab (n=5), nivolumab (n=0), cemiplimab (n=0), atezolizumab (n=3), avelumab (n=1), and durvalumab (n=0). Six studies involved the treatment of triple-negative breast cancer (TNBC), two studies included non-TNBC, and one study had both TNBC and non-TNBC arms. The treatment strategy included atezolizumab plus nab-paclitaxel (n=2), pembrolizumab plus trastuzumab (n=1), atezolizumab (n=1), avelumab (n=1), and pembrolizumab (n=4). The primary characteristics of the nine eligible studies were presented in *Table 1*.

PFS and OS

Table 2 displayed the main survival outcomes in the selected

Table 1 Characteristics of the selected studies in the analysis

Study [year]	Trial	Phase	Patients	TNBC patients	PD-L1+ patients	Age, mean [range]	Race	Drug	Dose	Clinical setting	Combined with	Line of therapy
Peter Schmid [2018]	IMpassion130	III	451	451 (100%)	185 (41.02%)	55 [20–82]	White, Asian, Black, Native American, Hawaiian or other Pacific Islander, Multiple and Unknown	Atezolizumab	800 mg	d1 and d15, q4w, iv, minimum 1 cycle	Nab-paclitaxel, 100 mg/m^2, d1, 8, 15, q4w, 6 cycles or more	1 line
Sylvia Adams [2018]	GP28328	Ib	33	33 (100%)	12 (36.36%)	55 [32–84]	White, Black or African American, Asian, Mutiple, Other	Atezolizumab	800 mg	d1 and d15, q2w, iv, minimum 4 cycles	Nab-paclitaxel, 125 mg/m^2, d1, 8, 15, q4w, minimum 4 cycles	1+ line
Luc Y. Dirix [2017]	JAVELIN	Ib	168	58 (34.52%)	85 (50.60%)	55 [31–81]	White, Black or African American, Asian, Other	Avelumab	10 mg/kg	d1, q2w, iv, minimum 1 cycle	Single-agent	2+ line
Leisha A. Emens [2018]	PCD4989g	I	116	116 (100%)	91 (78.45%)	53 [29–82]	Not mentioned	Atezolizumab	15 or 20 mg/kg, or at a 1,200-mg flat dose	d1, q3w, iv, minimum 1 cycle	Single-agent	1+ line
Rita Nanda [2016]	KEYNOTE-012	Ib	32	32 (100%)	32 (100%)	50.5 [29–72]	White, Black or African American	Pembrolizumab	10 mg/kg	d1, q2w, iv, minimum 1 cycle	Single-agent	1+ line
Sylvia Adams [2018]	KEYNOTE-086 cohort A	II	170	170 (100%)	105 (61.76%)	53.5 [28–85]	NR	Pembrolizumab	200 mg	d1, q3w, iv, minimum 1 cycle, up to 2 years	Single-agent	2+ line
Sylvia Adams [2018]	KEYNOTE-086 cohort B	II	84	84 (100%)	84 (100%)	52.5 [26–91]	NR	Pembrolizumab	200 mg	d1, q3w, iv, minimum 1 cycle, up to 2 years	Single-agent	1 line
Sherene Loi [2019]	PANACEA	Ib-II	58	0 (0%)	46 (79.31%)	NR	NR	Pembrolizumab	Phase Ib: 2 mg/kg or 10 mg/kg; Phase II: 200 mg	d1, q3w, iv, minimum 1 cycle, up to 2 years	Trastuzumab, 6 mg/kg	1+ line
Hope S. Rugo [2018]	KEYNOTE-028	Ib	25	0	25 (100%)	53 [36–79]	White, Asian, Black or African American, and not specified	Pembrolizumab	10 mg/kg	d1, q2w, iv, minimum 1 cycle, up to 2 years	Single-agent	1+ line

TNBC, triple-negative breast cancer; PD-L1, programmed death-ligand 1; NR, not reported.

studies. In IMpassion130 trial, previously untreated metastatic TNBC patients received nab-paclitaxel plus atezolizumab or placebo. The median PFS was 7.2 months in the atezolizumab group, as compared with 5.5 months in the placebo group. The median OS was 21.3 months in the atezolizumab group and 17.6 months in the placebo group. In *PD-L1*+ patients treated with atezolizumab plus nab-paclitaxel, the median PFS and OS were, respectively, 7.5 and 25 months. Recurrent or metastatic TNBC patients in GP28328 trial were similarly treated with atezolizumab plus nab-paclitaxel. But the median PFS and OS were decreased to 5.5 and 14.7 months. In *PD-L1*+ population, the median PFS and OS were decreased to 6.9 and 21.9 months. The differences between the two studies might be attributed to the lines of prior systemic chemotherapy, as patients in GP28328 had received several lines of previous chemotherapy.

However, in PCD4989g trial, TNBC patients treated with atezolizumab monotherapy had a median PFS of 1.4 months and a median OS of 8.9 months. Ninety-one (79.1%) of 115 participants were *PD-L1*+ breast cancer. In this cohort, the median OS prolonged 1.2 months but not PFS. Avelumab showed a similar efficacy on breast cancer including TNBC and non-TNBC. Nevertheless, the median OS was 6.5 months in *PD-L1*+ patients.

The median PFS of pembrolizumab treated *PD-L1*+ TNBC patients ranged from 1.9 to 2.1 months, while the median OS ranged from 8.8 to 18 months. Additionally, patients with *PD-L1*+ non-TNBC showed a median PFS of 1.8 months and a median OS of 8.6 months after the pembrolizumab treatment. When *PD-L1*+ non-TNBC patients were administrated with pembrolizumab plus trastuzumab, the median PFS was 2.7 months, with an unreached median OS.

ORR

The ORR data were available from nine trials including 1,130 patients in overall population and 660 patients in *PD-L1*+ population (*Table 3*). *Figure 2* and *Figure 3* showed the pooled ORRs for overall population and *PD-L1*+ population respectively. In TNBC patients received anti-*PD-L1* plus nab-paclitaxel therapy, the pooled ORR was 49.7% (95% CI: 33.9–65.5%) in overall population, and 55.8% (95% CI: 42.9–68.6%) in *PD-L1*+ population. The ORR of anti-*PD-L1* monotherapy in TNBC was 9.6% (95% CI: 4.2–15.0%) in overall population and 12.1% (95% CI: 5.4–18.8%) in *PD-L1*+ population. In the anti-*PD-L1* treatment for breast cancer containing both TNBC and non-TNBC, the ORRs of overall and *PD-L1*+ cohort were 3.0% (95% CI: −0.4–5.6%) and 2.4% (95% CI: −0.9–5.7%). The pooled ORR for *PD-L1*+ TNBC patients administrated with a *PD-1* inhibitor was 14.4% (95% CI: 2.5–26.3). *PD-L1*+ non-TNBC patients received anti-*PD-1* therapy had an ORR with 12.0% (−0.7–24.7%). When non-TNBC patients were treated with anti-*PD-1* plus trastuzumab regimen, the ORRs were 12.1% (95% CI: 3.7–20.5%) in overall population and 15.2% (95% CI: 4.8–25.6%) in *PD-L1*+ population.

DCR

A total of 1,130 patients from nine studies were analyzed in the pooled DCR of overall population, and 575 patients from eight studies were analyzed in the pooled DCR of *PD-L1*+ population (*Table 4*). *Figure 4* and *Figure 5* showed the pooled DCRs for overall population and *PD-L1*+ population respectively. The pooled DCRs of overall population and *PD-L1*+ population for anti-*PD-L1* + nab-paclitaxel treated TNBC patients were 67.5% (95% CI: 38.6–96.4%) and 83.4% (95% CI: 72.2–94.5%). In the overall group, the pooled DCR of anti-*PD-L1* therapy for TNBC was 13.0% (95% CI: 6.9–19.1%) versus 28.0% (95% CI: 21.2–34.8%) in TNBC + non-TNBC subgroup. In the group of *PD-L1*+ patients, the pooled DCR of anti-*PD-L1* therapy for TNBC was 15.4% (95% CI: 8.0–22.8%). Anti-*PD-1* therapy had a pooled DCR with 18.4% (95% CI: 6.8–30.1%) for *PD-L1*+ TNBC cohort. *PD-L1*+ non-TNBC patients had a DCR of 20% (95% CI: 4.3–35.7%) in anti-*PD-1* treatment versus 23.9% (95% CI: 11.6–36.2%) in anti-*PD-1* plus trastuzumab treatment. When overall non-TNBC patients were treated with anti-*PD-1* plus trastuzumab, the DCR was 19.0% (8.9–29.1%).

Treatment related adverse events

Of 1,080 breast cancer patients from eight trials, 901 (83.43%) developed at least 1 treatment related adverse event of any grade, and 394 (34.62%) of 1,138 from nine trials developed at least 1 grade ≥3 treatment related adverse event (*Table 5*).

The incidences of any-grade and grade ≥3 treatment related adverse events in *PD-1* inhibition plus nab-paclitaxel treated TNBC were 99.3% (95% CI: 98.6–100.1%) and 59.6% (95% CI: 36.1–83.0%). In anti-*PD-L1* monotherapy, the incidence of any-grade treatment related adverse events

Table 2 Summary of outcomes in the studies

Trial	Median follow-up (months)	Median TTR (months)	Median DOR (months)	Median PFS (months)	Median OS (months)	PD-L1+Median TTR (months)	PD-L1+Median DOR (months)	PD-L1+Median PFS (months)	PD-L1+Median OS (months)
IMpassion130	12.9	NR	7.4 (95% CI, 6.9–9.0)	7.2 (95% CI, 5.6–7.5)	21.3 (95% CI, 17.3–23.4)	NR	8.5 (95% CI, 7.3–9.7)	7.5 (95% CI, 6.7–9.2)	25 (95% CI, 22.6–not estimable)
GP28328	24.4 (95% CI, 22.1–28.8)	NR	9.1 (95% CI, 2.0–20.9)	5.5 (95% CI, 5.1–7.7)	14.7 (95% CI, 10.1–not estimable)	NR	9.1 (95% CI, 2.9–16.2)	6.9 (95% CI, 5.2–11.0)	21.9 (95% CI, 13.1–not estimable)
JAVELIN	10 (range, 6.0–15.2)	2.7 (range, 1.3–4.1)	Not estimable (95% CI, 6.7–not estimable)	1.4 (95% CI, 1.4–1.4)	8.1 (95% CI, 6.4–not estimable)	NR	NR	1.4 months (95% CI, 1.3–1.4)	6.5 (95% CI, 3.7–9.2)
PCD4989g	25.3 (range, 0.4–45.6)	NR	21 (range, 3 to ≥38)	1.4 (95% CI, 1.3–1.6)	8.9 (95% CI, 7.0–12.6)	NR	NR	1.4 (95% CI, 1.3–1.9)	10.1 (95% CI, 7.0–13.8)
KEYNOTE-012	10.0 (range, 0.4–19.5)	4.2 (range, 1.7–7.6)	Not estimable (95% CI, 3.5 to ≥11.0)	1.9 (95% CI, 1.7–5.5)	11.2 (95% CI, 5.3–not estimable)	4.2 (range, 1.7–7.6)	Not estimable (95% CI, 3.5 to ≥11.0)	1.9 months (95% CI, 1.7–5.5)	11.2 (95% CI, 5.3–not estimable)
KEYNOTE-086 cohort A	9.6 (range, 0.1–25.7)	3.9 (range, 1.9–8.1)	Not estimable (95% CI, ≥1.2 to ≥21.5)	2.0 (95% CI, 1.9–2.0)	9.0 (95% CI, 7.7–11.2)	3.1 (range, 1.9–6.2)	Not estimable (95% CI, 6.3 to ≥21.5)	2.0 (95% CI, 1.9–2.1)	8.8 (95% CI, 7.1–11.2)
KEYNOTE-086 cohort B	12.3 (range, 0.9–23.5)	2.0 (range, 1.7–6.2)	10.4 (95% CI, 4.2 to ≥19.2)	2.1 (95% CI, 2.0–2.2)	18.0 (95% CI, 12.9–23.0)	2.0 (range, 1.7–6.2)	10.4 (95% CI, 4.2 to ≥19.2)	2.1 (95% CI, 2.0–2.2)	18.0 (95% CI, 12.9–23.0)
PANACEA	Phase Ib: 25.7 (IQR, 25.6–25.8); phase II: 13.6 (IQR, 11.6–18.4)	NR	NR	NR	NR	2.7 (95% CI, 2.6–4.0)	3.5 (95% CI, 2.7–not estimable)	2.7 (95% CI, 2.6–4.0)	Not estimable (95% CI, 13.1–not estimable)
KEYNOTE-028	9.7 (range, 0.7-31.8)	1.7 (range, 1.7–1.9)	12.0 (range, 7.4–15.9)	1.8 (95% CI, 1.4–2.0)	8.6 (95% CI, 7.3–11.6)	1.7 (range, 1.7–1.9)	12.0 (range, 7.4–15.9)	1.8 (95% CI, 1.4–2.0)	8.6 (95% CI, 7.3–11.6)

TTR, time to response; DOR, duration of response; PFS, progression-free survival; OS, overall survival; 95% CI, 95% confidence interval; NR, not reported.

Table 3 Pooled ORR in breast cancer patients.

Study	Overall			PD-L1 positive		
	n	MR	95% CI	n	MR	95% CI
TNBC/anti-PD-L1 + nab-paclitaxel						
IMpassion130	450	0.560	0.514–0.606	185	0.589	0.518–0.660
GP28328	33	0.394	0.227–0.561	12	0.417	0.138–0.696
Sub-total	483	0.497	0.339–0.655	197	0.558	0.429–0.688
TNBC + non-TNBC/Anti-PD-L1						
JAVELIN	168	0.030	0.004–0.056	85	0.024	–0.009–0.057
TNBC/anti-PD-L1						
PCD4989g	115	0.096	0.042–0.150	91	0.121	0.054–0.188
TNBC/anti-PD-1						
KEYNOTE-012	27	0.185	0.039–0.331	27	0.185	0.039–0.331
KEYNOTE-086 cohort A	170	0.053	0.019–0.087	105	0.057	0.013–0.101
KEYNOTE-086 cohort B	84	0.214	0.126–0.302	84	0.214	0.126–0.302
Sub-total	281	0.142	0.018–0.266	216	0.144	0.025–0.263
Non-TNBC/Anti-PD-1 + trastuzumab						
PANACEA	58	0.121	0.037–0.205	46	0.152	0.048–0.256
Non-TNBC/anti-PD-1						
KEYNOTE-028	25	0.120	–0.007–0.247	25	0.120	–0.007–0.247

ORR, objective response rate; TNBC, triple-negative breast cancer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; n, number of patients; MR, mean rate; CI, confidence interval.

was 98.3% (95% CI: 95.9–100.6%) in TNBC versus 68.5% (95% CI: 61.4–75.5%) in breast cancer containing TNBC and non-TNBC. The incidences of any-grade and grade ≥3 treatment related adverse events in TNBC patients received anti-*PD-1* therapy were 60.9% (95% CI: 55.2–66.5%) and 12.0% (95% CI: 8.2–15.7%). In addition, the incidence of grade ≥3 treatment related adverse events in non-TNBC were 16.0% (95% CI: 1.6–30.4%) in anti-*PD-1* monotherapy versus 50.0% (95% CI: 37.1–62.9%) in anti-*PD-1* plus trastuzumab therapy.

As shown in *Table 6* and *Table 7*, we focused on treatment related adverse events that were reported by at least three studies. Using the criteria, the most common any-grade treatment related adverse events were fatigue (29.2%, 95% CI: 15.8–42.6%), nausea (20.2%, 95% CI: 9.7–30.7%), neutropenia (19.4%, 95% CI: 7.5–31.3%), and diarrhea (16.8%, 95% CI: 8.7–25.0%) (*Table 6*). The most common grade ≥3 treatment related adverse events were neutropenia (6.0%, 95% CI: 1.0–10.9%), anemia (2.3%, 95% CI: 1.3–3.2%), diarrhea (1.4%, 95% CI: 0.6–2.3%), and dyspnea (1.0%, 95% CI: –0.3–2.3%) (*Table 7*).

Heterogeneity and publication bias

Even a random-effects model was applied for all pooled data analysis and subgroup analyses were conducted, heterogeneity was high owing to the eligible studied in our analysis were almost phase I and II trials. Additionally, publication bias was not observed in the results of Egger's test based on the analysis of ORR (overall: P=0.393>0.05; *PD-L1*+: P=0.191>0.05) and DCR (overall: P=0.466>0.05; *PD-L1*+: P=0.973>0.05).

Discussion

This study quantitatively integrated the results of published clinical trials and was conducted to estimate the antitumor activity and safety of *PD-1/PD-L1* inhibitors in patients

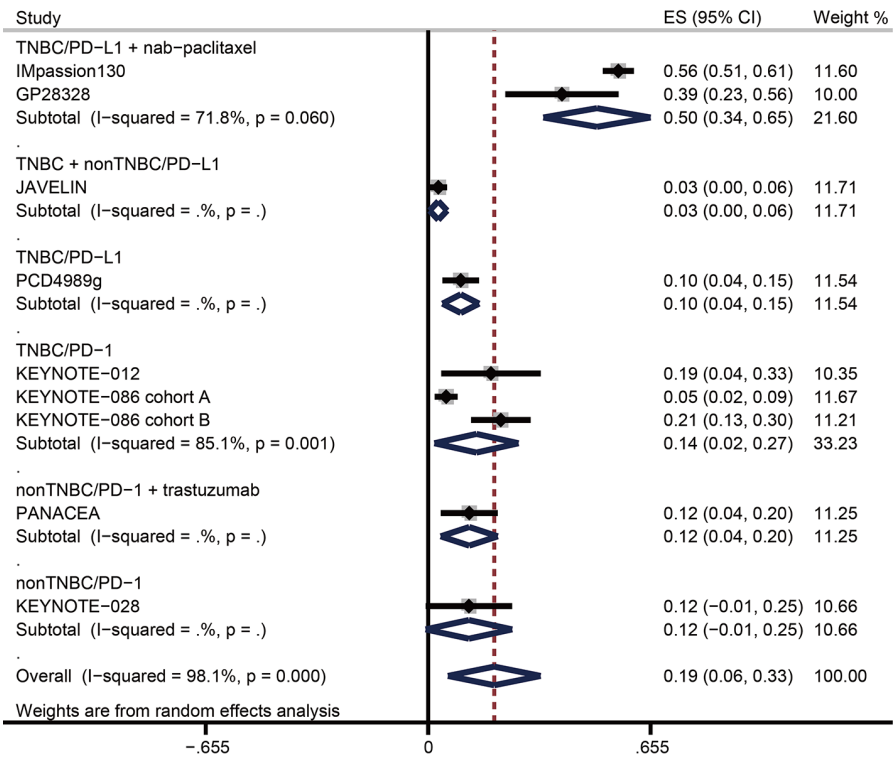

Figure 2 The estimates of objective response in overall population.

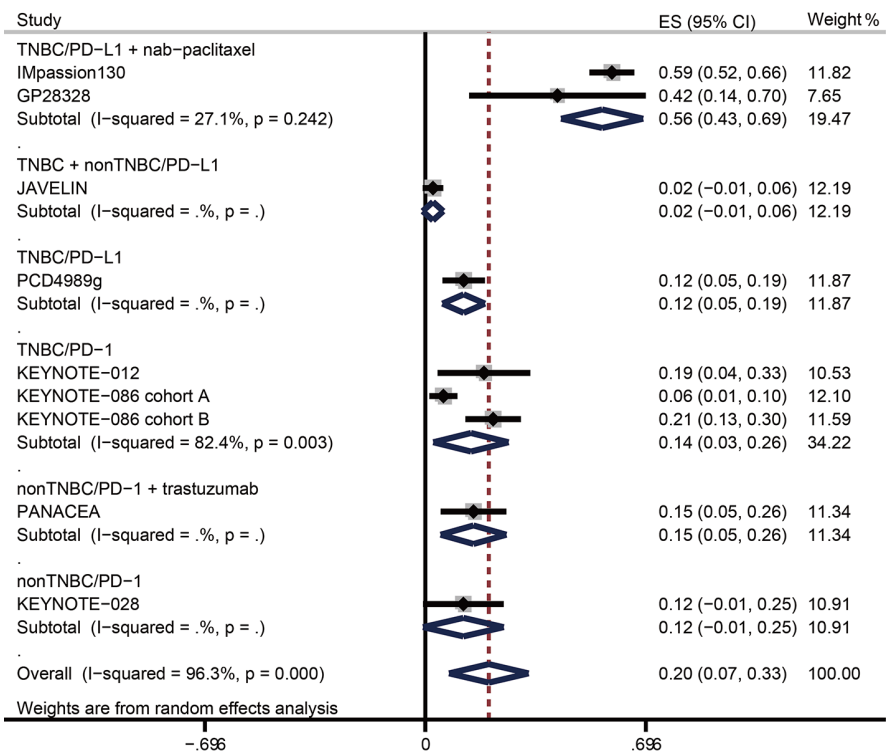

Figure 3 The estimates of objective response in PD-L1 positive population.

Table 4 Pooled DCR in breast cancer patients

Study	Overall			PD-L1 positive		
	n	MR	95% CI	n	MR	95% CI
TNBC/Anti-PD-L1 + nab-paclitaxel						
IMpassion130	450	0.811	0.775–0.847	185	0.795	0.737–0.853
GP28328	33	0.515	0.344–0.686	12	0.917	0.761–1.073
Sub-total	483	0.675	0.386–0.964	197	0.834	0.722–0.945
TNBC + non-TNBC/anti-PD-L1						
JAVELIN	168	0.280	0.212–0.348	–	–	–
TNBC/anti-PD-L1						
PCD4989g	115	0.130	0.069–0.191	91	0.154	0.080–0.228
TNBC/anti-PD-1						
KEYNOTE-012	27	0.259	0.094–0.424	27	0.259	0.094–0.424
KEYNOTE-086 cohort A	170	0.076	0.036–0.116	105	0.095	0.039–0.151
KEYNOTE-086 cohort B	84	0.238	0.147–0.329	84	0.238	0.147–0.329
Sub-total	281	0.179	0.044–0.313	216	0.184	0.068–0.301
Non-TNBC/anti-PD-1 + trastuzumab						
PANACEA	58	0.190	0.089–0.291	46	0.239	0.116–0.362
Non-TNBC/an-PD-1						
KEYNOTE-028	25	0.200	0.043–0.357	25	0.200	0.043–0.357

DCR, disease control rate; TNBC, triple-negative breast cancer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; n, number of patients; MR, mean rate; CI, confidence interval.

with breast cancer.

In *PD-L1* positive breast cancer patients treated with *PD-L1* inhibitors (atezolizumab and avelumab), the pooled ORRs ranged from 2.4% in JAVELIN to 58.9% in IMpassion130. The difference mainly caused by two reasons: first, patients in IMpassion130 were previously untreated, whereas patients in JAVELIN had received prior lines of cytotoxic therapy; second, atezolizumab was used in IMpassion130, and avelumab was used in JAVELIN. In the phase Ib trial GP28328, although patients were also received previous systemic cytotoxic regimens, the ORR was 41.7% in *PD-L1*+ population. Additionally, when patients were treated with single atezolizumab agent, the ORR of *PD-L1* positive patients was 12.1% in PCD4989g study. Studies of combination treatment that might increase the probability of antitumor activity were warranted, and promising treatment benefit in TNBC had been reported for a treatment regimen of pembrolizumab in combination with eribulin mesylate and of atezolizumab administered in combination with taxane chemotherapy in preliminary studies (36,37). In our analysis, patients in both IMpassion130 and GP28328 had received atezolizumab plus nab-paclitaxel therapy and the rates of progressive disease were sharply decreased (15.3% in IMpassion130 and 18.2% in GP28328). Based on the presence of TILs in tumor tissues, TNBC were immunogenic and higher percentages of TILs were relevant to response to *PD-1/PD-L1* inhibitors (30,38). In addition, cytotoxic drugs might enhance the efficacy of immunotherapy via increasing the expression of *PD-L1* (39). Thus, we supposed that atezolizumab combined with nab-paclitaxel could be an option of front-line therapeutic paradigm for advanced or metastatic breast cancer. Moreover, *PD-L1* positive breast cancer patients might have higher responses when receiving anti-*PD-L1* therapy plus cytotoxic treatment.

Recently, there are several ongoing clinical trials in studying the combination therapy of a *PD-1/PD-L1* inhibitor and chemotherapy. IMpassion031 is comparing

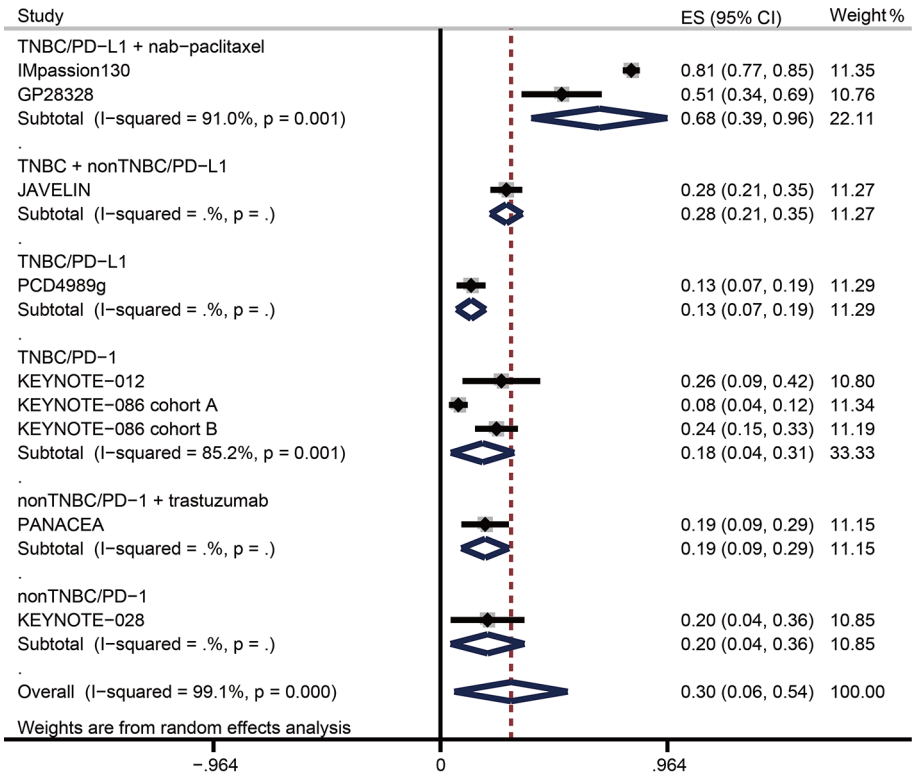

Figure 4 The estimates of disease control in overall population.

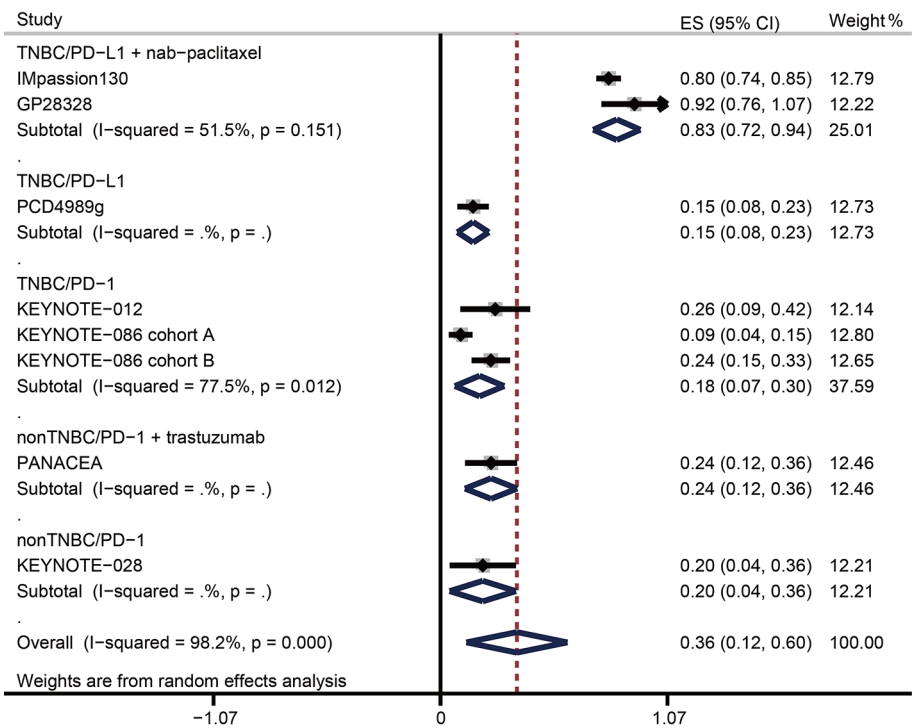

Figure 5 The estimates of disease control in PD-L1 positive population.

Table 5 Pooled treatment related adverse events in breast cancer

Study	Any-grade			Grade ≥3		
	n	MR	95% CI	n	MR	95% CI
TNBC/anti-PD-L1 + nab-paclitaxel						
IMpassion130	452	0.993	0.986–1.001	452	0.487	0.441–0.533
GP28328	–	–	–	33	0.727	0.575–0.879
Sub-total	–	–	–	485	0.596	0.361–0.830
TNBC + non-TNBC/anti-PD-L1						
JAVELIN	168	0.685	0.614–0.755	168	0.137	0.085–0.189
TNBC/anti-PD-L1						
PCD4989g	116	0.983	0.959–1.006	116	0.509	0.418–0.600
TNBC/anti-PD-1						
KEYNOTE-012	32	0.563	0.391–0.734	32	0.156	0.030–0.282
KEYNOTE-086 cohort A	170	0.606	0.532–0.679	170	0.129	0.079–0.180
KEYNOTE-086 cohort B	84	0.631	0.528–0.734	84	0.095	0.032–0.158
Sub-total	286	0.609	0.552–0.665	286	0.120	0.082–0.157
Non-TNBC/anti-PD-1 + trastuzumab						
PANACEA	–	–	–	58	0.500	0.371–0.629
Non-TNBC/an-PD-1						
KEYNOTE-028	25	0.640	0.452–0.828	25	0.160	0.016–0.304

TNBC, triple-negative breast cancer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; n, number of patients; MR, mean rate; CI, confidence interval.

neoadjuvant atezolizumab *vs* placebo in combination with anthracycline/nab-paclitaxel-based chemotherapy in early TNBC (40). IMpassion132 is evaluating atezolizumab with first-line chemotherapy [capecitabine (mandatory in platinum-pretreated patients) or gemcitabine/carboplatin] for inoperable locally advanced/metastatic TNBC (41). Moreover, KEYNOTE-355 is a global phase III study of pembrolizumab + chemotherapy (pembrolizumab + nab-paclitaxel, pembrolizumab +paclitaxel, pembrolizumab +gemcitabine/carboplatin) *vs.* placebo + chemotherapy in patients with previously untreated, locally recurrent, inoperable TNBC (42). KEYNOTE-522 is a phase III study of pembrolizumab + chemotherapy *vs.* placebo + chemotherapy as neoadjuvant treatment, followed by pembrolizumab *vs.* placebo as adjuvant treatment in patients with TNBC (43). Additionally, we noticed that the median time to response in KEYNOTE-028 was 1.7 months (range, 1.9–1.9 months). However, in KEYNOTE-012, the median time to response was 17.9 weeks (range, 7.3–32.4 weeks). Both the trails were taken single agent without combination with chemotherapy. As the progressive disease rate in KEYNOTE-012 was 48.1% and in KEYNOTE-028 was 60.0%, the long time to response might be a critical reason for the high rate of progressive disease. Taken together, the data for anti-*PD-L1* agents appeared encouraging for patients with PD-L1 positive breast cancer and showed that *PD-L1* might be a predictor of response to *PD-L1* antagonists. Further, anti-*PD-1/PD-L1* agents plus chemotherapy could achieve more efficacy than expected. Thus, in the future researches of *PD-1/PD-L1* in breast cancer, if anti-*PD-1/PD-L1* monotherapy fails to exert expected effects, combination therapeutic strategies could be another choice (44).

From the standpoint of patient counseling, several results of adverse events are important. Approximately 83.43% breast cancer patients treated with *PD-1/PD-L1* inhibitors in clinical trials experienced at least 1 treatment related adverse event of any grade, and 34.62% breast cancer patients had at

Table 6 Subgroup analysis of any grade treatment related adverse events in breast cancer.

Toxicities	n	MR	95% CI
Fatigue	1,138	0.292	0.158–0.426
Nausea	1,138	0.202	0.097–0.307
Neutropenia	769	0.194	0.075–0.313
Diarrhea	1,113	0.168	0.087–0.250
Dyspnea	678	0.135	0.022–0.247
Anemia	911	0.134	0.038–0.229
Headache	658	0.130	0.022–0.238
Rash	797	0.108	0.042–0.173
Arthralgia	1,054	0.105	0.057–0.153
Vomiting	710	0.104	0.030–0.178
Pruritus	909	0.098	0.061–0.135
Hypothyroidism	990	0.079	0.040–0.118
Infusion-related reaction	422	0.050	–0.002–0.102
ALT increased	404	0.042	0.014–0.070
AST increased	407	0.035	0.017–0.053
Hyperthyroidism	422	0.032	–0.004–0.068
Pneumonia	513	0.028	0.014–0.042

ALT, alanine aminotransferase; AST, aspartate aminotransferase; n, number of patients; MR, mean rate; CI, confidence interval.

Table 7 Subgroup analysis of grade ≥3 treatment related adverse events in breast cancer

Toxicities	n	MR	95% CI
Neutropenia	769	0.060	0.010–0.109
Anemia	943	0.023	0.013–0.032
Diarrhea	739	0.014	0.006–0.023
Dyspnea	678	0.010	–0.003–0.023
Vomiting	626	0.009	0.002–0.017
Nausea	647	0.009	0.002–0.017
Fatigue	874	0.008	0.002–0.014
AST increased	259	0.008	–0.003–0.019
ALT increased	256	0.008	–0.003–0.019
Pneumonia	429	0.007	–0.001–0.015
Arthralgia	769	0.003	–0.001–0.007

ALT, alanine aminotransferase; AST, aspartate aminotransferase; n, number of patients; MR, mean rate; CI, confidence interval.

least 1 grade ≥3 treatment related adverse event. Moreover, *PD-L1* inhibitors had a higher incidence of any-grade and grade ≥3 treatment related adverse events than *PD-1* inhibitors in TNBC (any-grade: 98.3% *vs.* 60.9%; grade ≥3: 50.9% *vs.* 12.0%). These numbers can be important to share with patients with breast cancer before they begin treatment with an anti-*PD-1/PD-L1* agent. Fatigue was the most common any-grade treatment related adverse event (29.2%), and neutropenia was the most common grade ≥3 treatment related adverse event (6.0%). Nausea, neutropenia and diarrhea are the next most common any-grade treatment related adverse events (>15%). Thus, clinical vigilance is needed for early recognition and intervention to prevent severe complications.

Limitations

This study has several limitations. First, the present analysis, including only one randomized controlled trial, was limited as the included studies were all single-arm phase I-II clinical trials. Second, published clinical trials of nivolumab, cemiplimab and durvalumab were absent. Third, since nab-paclitaxel was administrated in IMpassion 130 and GP28328 trials, hematological toxicities, such as neutropenia, might be mainly caused by chemotherapy. Despite the limitations, this analysis is a meaningful study of the estimates of the antitumor activity and safety of *PD-1/PD-L1* antagonists.

In conclusion, we found that *PD-1* and *PD-L1* inhibitors appeared to be effective for treating advanced breast cancer, and anti-*PD-L1* plus systemic chemotherapy might be a front- or first-line treatment option for patients with *PD-L1* positive advanced TNBC. Meanwhile, careful monitoring of the adverse events of anti-*PD-1/PD-L1* agents should be needed. More randomized clinical studies are warranted to confirm our findings.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/tcr-19-3020.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-19-3020). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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