META-ANALYSIS

Atezolizumab and pembrolizumab in triple-negative breast cancer: a meta-analysis

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ABSTRACT

Background: The approval of anti-PD-L1 drugs, including atezolizumab/pembrolizumab in triple-negative breast cancer (TNBC), potentially improve treatment regimens available for TNBC.

Methods: We conducted a meta-analysis to review the efficacy of atezolizumab/pembrolizumab for the treatment of TNBC in both the adjuvant and neoadjuvant settings. We calculated standardized mean difference (SMD) for the associations of progression-free survival (PFS) and overall survival (OS) and odds ratios (ORs) to estimate objective response rate (ORR) and pathological complete response (pCR), using 95% confidence intervals (CIs).

Results: Six clinical trials comprising 3612 patients were included. For adjuvant therapies, the ORR (OR = 1.26, P = 0.04) of atezolizumab/pembrolizumab plus chemotherapy was higher in the intention to treat (ITT) arms than the placebo groups in TNBC. A positive effect size was found for PFS in the ITT arms (d = 1.55, P < 0.001). The atezolizumab plus chemotherapy group had a positive effect size for OS compared to control groups (d = 0.52, P < 0.001). In the neoadjuvant setting, patients in ITT arms had higher pCR rates than the control groups (OR = 1.61, P = 0.001).

Conclusion: We collate evidence of atezolizumab/pembrolizumab as viable therapeutics among patients with TNBC with PD-L1 subgroups deriving higher benefits.

PLAIN LANGUAGE SUMMARY

Immune checkpoint inhibitors (ICI), atezolizumab and pembrolizumab, have received approval for patients with triple-negative breast cancer (TNBC) expressing PD-L1. Thus far, it has only been approved for patients with unresectable locally advanced or metastatic TNBC. With the IMPassion130 and KEYNOTE-355 trials introducing the immunotherapy era for TNBC, ongoing trials have started exploring the outcomes of the ICIs in early-stage TNBC in combination. Recently, the ICIs have demonstrated positive efficacy outcomes in neoadjuvant settings. Both the ICIs have shown a safe profile in terms of adverse events. The recent advances made by clinical trials indicate promising results for early-stage and advanced/metastatic TNBC. However, there is a need to harmonize and explore biomarkers and endpoints in the ongoing clinical trials to enhance patient treatment protocols. As TNBC is an aggressive subtype, exploring beyond the PD-L1 positive subgroup is necessary to expand the target population receiving ICIs for TNBC.

1. Introduction

Triple-negative breast cancer (TNBC) is an aggressive type of breast cancer [1]. TNBC is associated with high recurrence rates and a worse prognosis than other breast cancer subtypes. Until recently, cytotoxic chemotherapy had been the mainstay of TNBC management [2]. However, the efficacy of immunotherapy in triple-negative breast cancer remains unclear. Targeted immunotherapy is currently a viable treatment option for various cancers, including more aggressive breast cancers such as TNBC. The binding of the ligand PD-L1 to PD-1 results in the suppressed activity of the T-cell-mediated immune response against cancer cells [3]. TNBC has a higher programmed cell death ligand 1 (PD-L1) mRNA expression, which is a ligand to programmed death protein 1 (PD-1) [3]. PD-L1 expression is measured by immunohistochemistry (IHC), which reports the combined positivity score (CPS), which is the number of PD-L1 staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable cells multiplied by 100 [4]. PD-L1 is crucial for tumor immune escape with its presence establishing a potential therapeutic target by immune checkpoint inhibitors. Consequently, PD-L1 has emerged as a predictive biomarker in clinical trial settings and is the only one approved for immune checkpoints so far [5].

Pembrolizumab is a highly selective humanized monoclonal IgG-4 antibody that blocks the PD-1 receptor on the cell surface, resulting in activation of T-cell mediated immune responses against tumor cells similar to atezolizumab [6]. Atezolizumab is another highly-selective humanized IgG-1 monoclonal antibody that binds to the ligand of PD-1 known...
as PD-L1, thereby blocking its interaction with PD-1 and enhancing T-cell activity against tumor cells [6]. The United States Food and Drug Administration (U.S. FDA) has approved two immune checkpoint inhibitors for TNBC, including atezolizumab in combination with nab-paclitaxel for PD-L1+ (PD-L1 stained tumor-infiltrating immune cells of any intensity covering ≥1% of the tumor area determined by an FDA approved test) unresectable locally advanced or metastatic TNBC in March 2019 [7], and pembrolizumab in combination with chemotherapy for PD-L1+ (CPS≥10 determined by an FDA approved test) locally recurrent, unresectable, or metastatic TNBC in November 2020 [8].

The following meta-analysis synthesizes common endpoints of atezolizumab and Pembrolizumab clinical trials among patients with TNBC. Clinical trials enrolling patients with any stage of TNBC, receiving any of the two aforementioned immunotherapeutic agents, and as first-line or beyond, will be statistically interpreted to present a quantitative summary of available data. The following paper aims to comment on the efficacy of immune checkpoint inhibitors atezolizumab and pembrolizumab in adjuvant and neoadjuvant settings among patients with TNBC. While cautiousness is required, our findings are an updated guide to current practices, comprising recent literature, addressing the efficacy and safety of these agents for PD-1/PD-L1 positive, early-stage, locally advanced, and metastatic TNBC.

2. Objective
The objective is to assess the efficacy of immune checkpoint inhibitors including atezolizumab and pembrolizumab among the entire group and PD-L1 positive subgroups, measured as pathological complete response (pCR) in neoadjuvant settings, and progression-free survival (PFS), objective response rate (ORR), and overall survival (OS) in adjuvant settings.

3. Methods
Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), statement 2020, we included clinical trials in the meta-analysis that reported efficacy or safety in TNBC [9]. We reported specific outcomes for PD-L1 positive and negative subgroups. When applicable, the control group, receiving placebo, was also compared with the intention-to-treat (ITT) group. The meta-analytical findings present pertinent evidence for current TNBC care compared to controlled groups for clinical trials of immune checkpoint inhibitors (atezolizumab and pembrolizumab) approved in triple-negative breast cancer (TNBC).

3.1. Inclusion and exclusion criteria
We included the following types of studies: randomized or controlled clinical trials. All cohort studies, case-controlled studies, and case series were excluded due to the high risk of associated biases. High-quality clinical trials that compared PD-L1 positive and negative sub-groups were included. All other trials and entries that did not focus on these endpoints were excluded. We included studies of adult participants regardless of their age groups. A follow-up period was not pre-determined for inclusion due to the dearth of data. The target condition was triple-negative breast cancer with further exploration of PD-L1 expression.

3.2. Study tasks
Included trials investigated efficacy (using different markers) endpoints. These were further tabulated by all researchers in a shared spreadsheet, discussed as baseline characteristics (trial’s name, phase, design, total sample (n), treatment, target population) and outcome measures (objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) in adjuvant therapy groups; and pathological complete response (pCR) rates in neoadjuvant groups) in total and PDL1+ subgroups.

3.3. Comparator/Control
We compared outcome measures in individuals with triple-negative breast cancer to the controlled/placebo arm in clinical trials with multiple arms.

3.4. Search strategy
We used a unique, systematic search strategy to search key electronic databases, registers, and other sources per the PRISMA 2020 statement. We searched the following databases from inception (i.e. no time restriction of the starting date for the search) until 20 August 2021: PubMed, MEDLINE, Web of Science, Cochrane, Scopus, CINAHL Plus, Science Direct. The key register used was ClinicalTrials.Gov to locate and identify ongoing or completed trials and identify preliminary or published clinical trial data. Additional entries comprised records identified from websites (i.e. conference proceedings of ongoing trials. An additional journal search was conducted utilizing the following (i.e. to ensure that we did no study was omitted, a search run was conducted using Google
Scholar to locate studies fitting the inclusion criteria): Annals of Oncology, The Lancet Oncology (the Lancet was searched comprising the multitude of subsidiary journals in the Lancet network), Journal of Clinical Oncology, New England Journal of Medicine, JAMA Oncology (JAMA was searched consisting of the multitude of subsidiary journals in the JAMA network), and the BMJ. We assessed the reference lists of all screened studies (Umbrella review) to ensure that no study was omitted. We systematically searched these databases from their inception to 20 August 2021, for clinical trials of immune checkpoint inhibitors (atezolizumab and pembrolizumab) approved in triple-negative breast cancer (TNBC). The search terms used across databases are enlisted in Supplementary Table S1. There were no language restrictions.

3.5. Selection process
The titles and abstracts of identified studies, in addition to register and other source records, were independently screened by two reviewers (MA and SS) and were double-checked by a third and fourth reviewer (ZS and AS). The third and fourth reviewers (ZS and AS) undertook the secondary review of full papers, and Cohen’s Coefficient of Agreement was calculated to quantify inter-reviewer agreement.

3.6. Data analysis
Bibliographic entries from all identified database records were stored in the Endnote software (X9, Clarivate Analytics, USA). Any duplicates were removed using the Endnote deduplication tool. We found no duplicates neither removed from additional sources (i.e. websites, ClinicalTrials.Gov). We applied a quantitative analytical methodology to ascertain differences in efficacy outcomes post adjuvant and neoadjuvant treatment, with an analysis of PDL1+ subgroups conducted. For continuous variables, namely PFS and OS, the standardized mean difference (SMD), reported as Cohen’s d, with 95% confidence interval (CI), was computed using a fixed-effects model. Using the random-effects model, we presented pooled estimates, 95% CI, Odds Ratio (OR) for dichotomous data, namely ORR and pCR. Forest plots documenting OR, SMD, 95% CI are presented in Figures 2–5. The minimum requirement to assess meta-analysis findings using plots was at least two or more trials reporting the same outcome measure. While we did not generate a funnel plot to assess publication bias due to the limited number of trials (less than 10), the heterogeneity between included studies was assessed using the I² index and the χ²-based Q test. All statistical analyses were conducted using Review Manager (RevMan) 5.4.

4. Results
Figure 1 illustrates the PRISMA flowchart for this meta-analysis. The overall Kappa score computed for the inter-rater agreement was 0.92, indicating an almost perfect agreement. During the first round of screening databases and registered trials, we identified 488 records; identification of studies via other methods yielded 320 records. We retrieved five hundred ninety-two records from all sources, of which 92 were assessed for eligibility. Finally, we included six trials in the meta-analysis.

4.1. Outcomes in adjuvant therapeutic trials
4.1.1. ORR in Atezolizumab/Pembrolizumab Plus Chemotherapy vs. Placebo with PDL1+ subgroup analysis
Three of the 3-adjuvant therapeutic trials presented data of ORR upon treatment with Atezolizumab/Pembrolizumab plus chemotherapy vs. placebo. We found that patients in the treatment arm (Atezolizumab/Pembrolizumab plus chemotherapy) had higher odds of achieving an objective response rate (ORR) than the control groups in the study. The statistical significance was noteworthy (p < 0.001) with higher probabilities of increased ORR in treatment arms (OR = 1.35, 95% CI: 1.14–1.60). There was no heterogeneity between the included studies (I² = 0%) (Figure 2a). We conducted a sensitivity analysis to assess these preliminary findings. On removing IMPassion130, the trial with the highest weight (41%), the test for overall effect was significant (OR = 1.26, 95% CI: 1.01, 1.57, P = 0.04) with no heterogeneity in the included studies (I² = 0%) (Figure 2a).

Two of the 3-adjuvant trials presented subgroup data of PDL1 + patients on treatment with Atezolizumab plus chemotherapy vs. placebo. The findings were pertinent as PDL1+ patient groups also presented with higher odds of increased ORR than the control groups of the included trials. Compared to the larger ITT vs. control groups, the PDL1+ subset versus control groups had a higher chance of increased ORR (OR = 1.7, 95% CI: 1.24–2.33). The results were statistically significant (P = 0.001), with no heterogeneity among the included studies (I² = 0%) (Figure 2b).

4.1.2. PFS in Atezolizumab plus Chemotherapy vs. Placebo with PDL1+ subgroup analysis
All values of SMDs greater than zero indicated the degree to which adjuvant treatment was more efficacious than control groups. Two of the three adjuvant studies reported PFS values in the ITT vs. Control groups (Atezolizumab plus chemotherapy vs. placebo) (Figure 3a). We found a positive effect size for PFS in the ITT arms (Cohen’s d = 1.55, 95% CI = 1.40–1.70, P < 0.001). Given the diversity of included trials, high heterogeneity was noted (I² = 100%) (Figure 3a).

Two of the three adjuvant studies noted outcomes in the PDL1+ group (ITT vs. Control groups). The Atezolizumab plus chemotherapy PDL1+ subgroup had a positive effect size for PFS (Cohen’s d = 1.89, 95% CI = 1.66–2.11, P < 0.001). High heterogeneity was noted in the included studies (100%) (Figure 3b).

4.1.3. OS in Atezolizumab plus Chemotherapy vs. Placebo
Only two trials published OS trends in ITT and Control groups. The Atezolizumab plus chemotherapy group had a positive effect size with statistically significant findings as compared to the control groups (Cohen’s d = 0.52, 95% CI = 0.36–0.68, P < 0.001) (Figure 4). The I² index was 100% suggesting high heterogeneity among two of the three included studies.
4.2. The outcome in neoadjuvant trials

4.2.1. pCR Rates in Atezolizumab/Pembrolizumab Plus Chemotherapy vs. Placebo with PDL1+ subgroup analysis

Three of the three neo-adjuvant trials reported pCR rates in the ITT versus Control groups. We found that patients in the treatment arms had higher odds of achieving pCR than the control groups (OR = 1.61, 95% CI: 1.21–2.15). This indicated that neoadjuvant treatment groups were more likely to obtain increased pCR rates, ultimately leading to the absence of invasive/in situ cancer in the breast or axillary lymph nodes. Achieving pCR was a common outcome measure following neoadjuvant chemotherapy, ultimately leading to improved survival; we found statistical associations to our findings (P = 0.001) (Figure 5a).

Two of the three neo-adjuvant trials reported pCR rates of PDL1+ patients in the ITT versus Control groups. The treatment group had a higher likelihood of presenting with increased pCR rates, ultimately suggesting increased survival.

Figure 2. Forest plots for the objective response rate (ORR) in Atezolizumab/Pembrolizumab plus chemotherapy vs placebo with PDL1+ subgroup analysis. (a) The plot illustrates ORR outcomes in three adjuvant trials in the entire group, namely 1) IMpassion130, 2) IMpassion 131 [Atezolizumab plus chemotherapy and vs placebo], and 3) KN355 [Pembrolizumab + chemotherapy vs placebo]. (b) The plot illustrates ORR outcomes in the subgroup PDL1+, in two adjuvant trials, 1) IMpassion130, 2) IMpassion 131 [Atezolizumab plus chemotherapy and vs placebo].
than the control groups (OR = 1.92, 95% CI: 1.38–2.68). The results were statistically significant (P = 0.001), with no heterogeneity among the included studies (I² = 0%) (Figure 5b).

5. Discussion

To our best understanding, this is the first meta-analysis to quantify the efficacy of immune checkpoint inhibitors atezolizumab and pembrolizumab in adjuvant and neoadjuvant settings among patients with TNBC. We reported six clinical trials of pembrolizumab (KN355 and KN522) and atezolizumab (IMpassion130, IMpassion131, NeoTRIP, and IMpassion031) in our pooled meta-analysis. The trials provided atezolizumab and pembrolizumab as either first-line or beyond and adjuvant or neoadjuvant settings among patients with TNBC. Our findings demonstrate stronger comparable
efficacy among PDL1+ subgroups (IMpassion130 and IMpassion131) in adjuvant settings with either atezolizumab or pembrolizumab combined with chemotherapy. In the overall group in the adjuvant setting, IMpassion130, IMpassion131, and KN355 demonstrated positive efficacy. A similar trend was observed in the neo-adjuvant setting in PDL1+ subgroups (IMpassion031 and KN522); the overall efficacy was also positive among all the neo-adjuvant trials (IMpassion031, KN522, and Neotrip). The most common immune-mediated adverse event was hypothyroidism in 4–18% of the intention-to-treat patients across the clinical trials.

In adjuvant settings, IMpassion 130 and IMpassion131 were conducted in first-line settings, yet IMpassion131 failed to validate the improved outcomes of atezolizumab and nab-paclitaxel of IMpassion130. These findings were discussed by the US FDA in April 2021 with the advisory panel in favor of keeping approval for atezolizumab in TNBC. However, Genentech, a member of the Roche Group (SIX: RO, ROG; OTCQX: RHHBY) and manufacturer Tecentriq® (atezolizumab) in combination with chemotherapy (Abraxane®, albumin-bound paclitaxel; nab-paclitaxel), voluntarily withdrew accelerated approval for the treatment of unresectable locally advanced or metastatic TNBC following concerns of efficacy from findings from the confirmatory IMpassion131 trial. Potentially, the IMpassion131 trial [10] was negative and different from the IMpassion130 trial [11] despite having similar designs due to the use of paclitaxel rather than nab-paclitaxel was used in the earlier IMpassion130 trial, as well as the higher use of steroids and differences in patient selection.

Both atezolizumab and pembrolizumab have been observed to be well tolerated. Concerning current practices, it is pertinent to identify biomarkers when deciding the best treatment regimens for patients with TNBC [12]. During planning TNBC care, the following features that may improve efficacy in treating immune checkpoint inhibitors should be prioritized: higher PD-L1 expression [13], higher mutational load [14], and increased tumor-infiltrating lymphocyte levels (TILs) [15]. Overall, combination regimens of PD-1/L1 inhibitors have demonstrated efficacious outcomes among patients with TNBC. They have already received treatment and among treatment-naïve patients in both metastatic and early-stage TNBC. The health-related quality of life (HRQoL) was documented during the treatment and followed every four weeks during the 1-year follow-up in the IMpassion130 trial [16]. There were no comparable differences in the HRQoL between the intention-to-treat patients and the placebo group receiving atezolizumab and nab-paclitaxel as first-line for metastatic TNBC [16]. The challenge of treating metastatic TNBC remains in closely monitoring the most critical endpoint, including survival and symptom relief and quality of life, which is a primary concern in care provision and trials.

Until now, PD-L1 is the only predictive biomarker approved by the FDA based on two commercial assays, the VENTANA PD-L1 (SP142) assay and the PD-L1 IHC 22C3 pharmDX assay for selection of patients with TNBCs meeting respective criteria for atezolizumab and pembrolizumab, respectively [17]. There has been discordance for PD-L1 scoring based on different cell assays, patient specimens, and inter-personal assessment differences [18]. A key concern for immunotherapy clinical trials is the heterogeneity associated with measuring PD-L1 protein levels that vary by antibody clone, staining platform, and scoring system when assessing through IHC technology [19,20]. The assessment of PD-L1 expression in clinical trials may be challenging due to the type of tissue (fresh or archival), type of assay, expression cutoffs, and type of cells (tumor cells, immune cells, or both) considered [5]. Outside of clinical trials, the routine assessment of PD-L1 expression as a biomarker for TNBC requires validation and reproducibility to be clinically meaningful [21]. The PD-1/PD-L1 interaction is one of many pathways employed by the tumor to escape immune checkpoints. Therefore, it is essential to consider exploring additional biomarkers while also standardizing PD-L1 to provide valuable insight into patient selection and prognosis of immune checkpoint inhibitors for TNBC [22]. Clinical trials are required to focus on mechanisms of response and resistance to immunotherapy to improve outcomes for TNBC patients receiving immunotherapy.

Developing new targeted drugs in oncology requires careful designing of phase II/III trials. These trials need to be powered to assess for OS, conducted until the outcomes are mature, and carefully monitored for radiological evaluation by independent reviewers [23]. Further, the synergistic role of chemotherapy and immunotherapy cannot be undermined, as observed with the contrasting outcomes of IMpassion130 and IMpassion131. An exploration of biomarkers will allow for a better treatment protocol and selection of patients. Further studies have commenced reviewing the enhancement of efficacy in neo-adjuvant and adjuvant settings and with different combination regimens. While the outcomes of the clinical trials have been promising, considerations to homogenize PD-L1 biomarker assessment with comprehensive follow-up data are required [24].

Certain limitations ought to be addressed. Given the limitations in obtaining efficacy and safety data from ongoing trials, our findings must be used with caution. It ought to be acknowledged that a diverse racial and ethnic population was not present in all included trials, hence, limiting the applicability to all racial groups. In addition, KN355, the metastatic adjuvant Pembrolizumab, and the chemotherapy trial did not present data so far for progression-free survival or overall survival. The metastatic adjuvant Atezolizumab and chemotherapy trials, IMpassion130 and IMpassion131, published non-estimated interquartile ranges for PDL1+ subgroups for overall survival. The metastatic neoadjuvant Atezolizumab and chemotherapy trial, Neotrip, had unquantified PDL1+ subgroups to assess pCR outcomes. We could not graphically present experimental results of whole blood findings in the form of graphs that was beyond the scope of this meta-analysis. Finally, we received no response on intending to obtain additional data from the principal investigators in the included trials.

6. Conclusion

Our findings collate and synthesize better efficacy using markers including pCR in neoadjuvant settings and ORR, PFS, and OS in adjuvant settings with atezolizumab and pembrolizumab. Our analysis offers insight into the outcomes of atezolizumab or pembrolizumab with combination chemotherapy with chemotherapeutic agents. Following the approval of
immunotherapeutic drugs for metastatic TNBC combined with chemotherapy, ongoing clinical trials focus on efficacy outcomes in different subgroups of patients. More insight into the efficacy and adverse events may help determine and optimize treatment regimens for patients with TNBC.

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Declaration of interest

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**Miles and Colleagues published results for IMpassion 131 that was a phase 3 trial comparing 1L atezolizumab with paclitaxel vs placebo in treatment-naive patients with metastatic or locally advanced TNBC. The multi-center, randomized, double blind, placebo-controlled study set the rational target for atezolizumab for patients with high PD-L1 expression and is useful in the planning of subsequent clinical trials.**

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• TNBC comprises a collection of distinct disease entities based on transcriptomic, genomic, and phenotypic characterization. The systematic presentation of data in the appended paper advances knowledge about the ongoing exponential increase in interest in translational and clinical research to develop paradigms for TNBC.

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