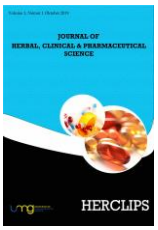

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Pembrolizumab as A Therapy for Triple-Negative Breast Cancer : Systematic Review

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Abstrak

Kanker payudara merupakan jenis kanker yang banyak terjadi di Indonesia. Salah satu jenis kanker payudara, Triple-negative breast cancer (TNBC), merupakan salah satu tipe yang memiliki fitur klinis patologis yang agresif, prognosis yang lemah, dan tingkat kematian yang tinggi dibandingkan jenis kanker payudara lainnya. Pembrolizumab merupakan sebuah imunoterapi yang baru-baru ini disetujui oleh FDA sebagai terapi untuk TNBC. Review ini bertujuan untuk menilai Pembrolizumab sebagai terapi TNBC fase awal dan metastasis. Pencarian jurnal RCT dilakukan dari Pubmed dan Science Direct hingga tanggal 1 Februari 2023 dengan kata kunci Pembrolizumab AND triple-negative breast cancer dan luaran yang dinilai meliputi respon patologis lengkap, Event Free Survival (EFS), progression-free survival, dan overall survival. Penulis mendapatkan 5 jurnal yang akan dinilai berdasarkan luaran yang telah ditentukan. Pembrolizumab sebagai terapi neoadjuvant ditambahkan dengan kemoterapi memberikan hasil yang lebih tinggi dalam hal respon klinis patologis lengkap dibandingkan dengan placebo dan kemoterapi.

***Kata kunci** : Pathological complete response ; Pembrolizumab ; Survival ; Triple-negative breast cancer*

Abstract

Breast cancer is one of the most incident cancer in Indonesia. The type of breast cancer, Triple-negative breast cancer (TNBC), is a type of cancer that have aggressive clinicopathologic features, a poorer prognosis, and high death rates compared with other types of breast cancer. Pembrolizumab is an immunotherapy recently approved by FDA as therapy for TNBC. This review aimed to assess Pembrolizumab as therapy for TNBC in early and metastatic phases. RCT journals were searched from Pubmed and Science Direct until 1 February 2023 with the keyword Pembrolizumab AND triple-negative breast cancer, comparator factor used of chemotherapy, and the outcomes included pathological complete response, Event Free Survival (EFS), progression-free survival, and overall survival. The authors include 5 studies to assess outcomes. Pembrolizumab as neoadjuvant treatment plus chemotherapy gave a higher pathological complete response than placebo plus chemotherapy.

***Keywords:** Pathological complete response , Pembrolizumab, Survival , Triple-negative breast cancer.*

1. INTRODUCTION

Breast cancer is the most common malignancy in women, accounts for about 30% of female cancers, and has a mortality-to-incidence ratio of 15% (Siegel, R.L *et al.,* 2020). Based on Globocan data in 2020, the prevalence of breast cancer in Indonesia comes to 68.858 cases from 396.914 total cases of cancer with mortality cases of about 22.430, making breast cancer the first place in new cases of cancer in Indonesia (Globocan, 2020). Head of Prevention and Control of Non-Communicable Diseases, Elvida Sariwati said seventy percent of breast cancer is identified as metastatic level (Kemenkes, 2023).

Clinically, breast cancer can be divided into three major based on hormone receptors, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status : luminal ER-positive and PR-positive, HER2-positive, and triple-negative breast cancer (TNBC) (Loibl. S. *et al.,* 2021). Triple-negative breast cancer (TNBC) comes of shortage expression on ER, PR, and HER2 (Anders C.K. *et al.,* 2022). TNBC is aggressive by clinicopathologic features compared with other types of breast cancer (e.g., larger tumor size, higher grade tumors, a poorer prognosis, earlier recurrence, and high death rates) (Tolaney S.M. *et al.,* 2021) (Li C.H. *et al.,* 2019) (Dent. R. *et al.,* 2009). Especially in patients with stages II and III, the risk of recurrence and death is higher than in the previous stage (Schmid P. *et al.,* 2022). Regardless of initial responses, the rate of distant recurrence with significant worse 3-year survival probabilities post-neoadjuvant treatment from TNBC patients is higher compared to others (Yu K.D. *et al.,*2013).

Treatment for TNBC was limited and the usage of chemotherapy with gemcitabine, taxanes, and platinum-based as a standard treatment for metastatic TNBC (mTNBC) faces a significant clinical problem by resistance (Huang M. *et al.,* 2022) (Nelly G. *et al.,* 2021) (Furlanetto J. *et al.,* 2020) (Ji X. *et al.,* 2019). Recently, immunological approaches used as agents that can target and kill cancer cells by utilizing abnormalities in the immune system (Borrie S.C. *et al.,* 2017). The use of PD-1 or the ligand (PD-L1) as immune checkpoint components which act as supresor for the response of antitumor mediated by T cells, start to be developed for optional treatment in TNBC. Their use in combination with standard regiment chemotherapy also known to enhance efficacy (Heimes A.S. *et al.,*2021) (Emens L.A. *et al.,*2015). Approximately 40% of TNBC tumors express programmed death ligand 1 (ligand of PD-1) (Tolaney S.M. *et al.,* 2021). It can be based on the development of PD-L1 targeted treatment for breast cancer with a pembrolizumab agent.

Pembrolizumab is a monoclonal antibody, binding PD-1 receptor and blocking the interaction with its ligands, PD-L1 and PD-L2. Blocking this PD-1 activity can decrease tumor growth since the binding will activation T-cell–mediated immune responses against tumor cells (Lisa A. *et al.,* 2015). This review aimed to assess pembrolizumab as a new drug approved by FDA in therapy for triple-negative breast cancer for early and metastatic phases. The clinical points that use include pathological complete response, Event

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Free Survival (EFS), progression-free survival, and overall survival.

2. METHOD

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines. The clinical trials were searched from Pubmed and Science Direct until 1 February 2023 with the keyword Pembrolizumab AND triple-negative breast cancer. The journal must be Randomized Control Trials. Then the author assessed the journals with some criteria ; the population must be Triple-Negative Breast Cancer patients, intervention with pembrolizumab, and the outcomes included pathological complete response, Event Free Survival (EFS), progression-free survival, and overall survival. The data extraction included authors, year, characteristics of the study (trial registration, study design, follow-up duration), the baseline of participants, interventions use and comparator, and observed outcomes.

A total of 6142 articles were obtained from Pubmed and Science Direct with the keywords “Pembrolizumab” and “Breast Cancer”, to specify the population of breast cancer patients, the author narrow the keywords to “Pembrolizumab” and “Triple-negative breast cancer”. As results, 411 articles were obtained from Pubmed (46 articles) and Science Direct (365 articles). 20 articles from Pubmed and 100 articles from Science Direct were excluded during not triple-negative breast cancer type trials. 5 articles from Pubmed and 176 articles from Science Direct were excluded during not using Pembrolizumab as an intervention. 15 articles from Pubmed and 86 articles from Science Direct were excluded during not using the randomized control trials method. 1 article from Pubmed was excluded during not open access. 3 articles were excluded during duplication.

The article that includes will be appraised with CASP (Critical Appraisal Skills Programme) RCT Standard Checklist with 11 questions to help the RCT articles make sense of a randomised controlled trial (RCT). Risk of bias assessed with Cochrane ROB2.

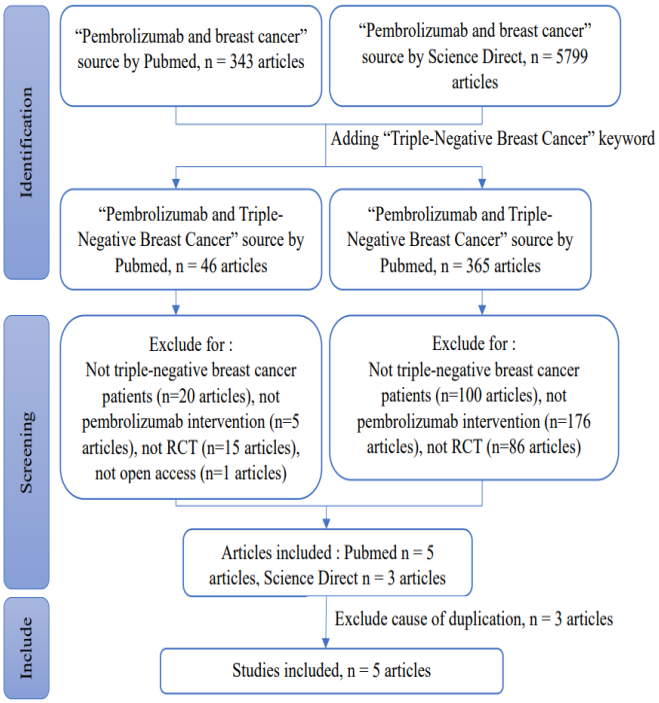

Figure 1. Flow Diagram of Literature Research.

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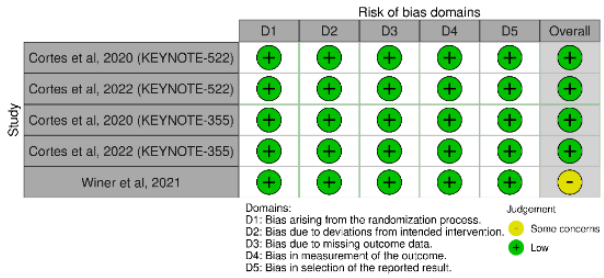

Figure 2. Result of Risk Bias Assessment by Cochrane ROB 2

3. RESULTS

As result, 5 articles were used to review, 2 trials for study in early triple-negative breast cancer, and 3 trials for study in metastatic triple-negative breast cancer. From Cochrane Assessing Risk of Bias tools, 4 study have a low risk of bias and 1 study have some concerns. The study from Winer et al (KEYNOTE-119), gave some considerations. The KEYNOTE-119 trial is an open-label trial where the sponsor, investigators, and participants were aware of the treatments administered. The participants for this trial had previously been treated with anticancer therapy.

Trials of Pembrolizumab in triple-negative breast cancer patients were given as a neoadjuvant therapy phase, adjuvant phase, and as a single intervention. Pembrolizumab as a neoadjuvant therapy phase, consisting of 2 treatments. First neoadjuvant treatment, given by 4 cycles of 200 mg pembrolizumab intravena plus carboplatin (dose based on area under the concentration-time curve of 5 mg/ml/minute once in 3 weeks or 1.5 mg/ml/minute once weekly in the first 12 weeks). Second neoadjuvant treatment, given by 4 cycles of pembrolizumab or placebo and epirubicin (90 mg/m2) or doxorubicin (60 mg/m2) plus cyclophosphamide (600 mg/m2 once in 3 weeks in the subsequent 12 weeks). Patients will receive radiation therapy as indicated a placebo or pembrolizumab once in 3 weeks for up to 9 cycles in adjuvant therapy phase (Schmid P. *et al.*, 2020).

3.1. Pathological complete response

An assay for a pathological complete response was done after patients completed neoadjuvant therapy of pembrolizumab. The pathological complete response is also known as pathological stages (post-neoadjuvant, shortened yp), consisting of ypT0/Tis ypN0, ypT0 ypN0, and ypT0/Tis. From Schmid et al. 2020, in early TNBC patients, a group that was given pembrolizumab 200 mg every 3 weeks as neoadjuvant therapy combined with paclitaxel and carboplatin have a higher pathological complete response than in the placebo-chemotherapy group (64.8% (95% confident interval [CI], 59.9-69.5) ; 51.2% (95% confident interval [CI], 44.1-58.3)), the estimated treatment difference, 13.6 percentage points (95% CI, 5.4-21.8; P<0.001) (Schmid P. *et al.*, 2020)..

3.2. Survival

EFS is defined as the time date of disease progression from randomization precluded recurrence in distant or local, definitive surgery, the incidence of death or emerging second primary cancer, whichever occurred first. Schmid et al. 2022, follow up on the disease status and survival every 3 months for the first 2 years after randomization, then every 6 months for years 3 through 5, and annually thereafter. Pembrolizumab-chemotherapy group gave 84.5% (95% CI, 81.7 to 86.9) in estimated event-free survival at 36 months. This result was higher than in the placebo-chemotherapy group which was 76.8% (95% CI, 72.2 to 80.7) in early triple-

negative breast cancer patients (Schmid P. *et al.,* 2022)..

In metastatic TNBC, the second interim analysis was 25.9 months and 26.3 months (pembrolizumab-chemotherapy group vs placebo-chemotherapy group) from the KEYNOTE-355 trial show 9.7 months in pembrolizumab-chemotherapy group and 5.6 months in placebo-chemotherapy as the progression-free survival outcome in patients with a combined positive score (CPS) ≥10 (hazard ratio [HR], 0.65, 95% CI, 0.49 – 0.86; one side p = 0.0012). In patients with CPS ≥1, the progression-free survival was 7.6 months in the pembrolizumab-chemotherapy group and 5.6 months in the placebo-chemotherapy group (HR, 0.74, 0.61 ‑ 0.90; one-sided, p = 0.0014 [not significant]) (Cortes J. *et al.,* 2020).

KEYNOTE-355 trials subsequently follow up the overall survival at 44.1 months after randomization. In pembrolizumab-chemotherapy group the overall survival analysis was 23.0 months meanwhile in placebo-chemotherapy group was 16.1 months from patients with CPS 10 (HR for death, 0.73; 95% CI 0.55-0.95; two-sided p = 0.0185), then in patients with CPS 1, pembrolizumab-chemotherapy was 17.6 months and 16.0 months in the placebo-chemotherapy group from patients with CPS 1 (HR, 0.86; 95% CI, 0.72-1.04; two-sided p = 0.1125 [not significant]) (Cortes J. *et al.,* 2022).

Different from another study, in KEYNOTE-119, in patients with mTNBC who were previously treated, pembrolizumab has no significant difference in improving survival than another chemotherapy agent. In pembrolizumab group patients with a PD-L1 CPS ≥10 the median overall survival was 12.7 months (95% CI, 9.9-16.3) and 11.6 months (95% CI, 8.3-13.7) for the chemotherapy group (HR 0.78 [95% CI 0.57-1.06]; log-rank p=0.057). Median overall survival in pembrolizumab group patients with a PD-L1 CPS ≥1 was 10.7 months (95% CI, 9.3-12.5) and 10.2 months (95% CI, 7.9 – 12 .6) for the chemotherapy group (HR 0.86 [95% CI 0.69-1.06]; log-rank p=0.73). In the overall populations, the median overall survival in pembrolizumab group patients was 9.9 months (95% CI, 8.3-11.4) and 10.8 months (95% CI, 9.1-12.6) for the chemotherapy group (HR 0.97 [95% CI 0.8 –1.15]) (Winer E.P. *et al.*, 2021)

Pembrolizumab, a type of humanized recombinant monoclonal IgG4 κ-isotype antibody to the PD-1, as a checkpoint inhibitor in the immunotherapy of cancer. PD-1 is a vital checkpoint molecule that can be modulating and down-regulating T-cell responses. Inhibition in PD receptors located on the surface of activated T cells prevents their binding to the PD receptor which activates a pathway that terminates the activation and proliferation of T cells, so without the PD-1 receptor engagement, the T cells responses will keep activated (National Institute of Diabetes and Digestive and Kidney Diseases, 2023).

In November 2020, FDA approve the pembrolizumab and in July 2021 they approvel in regular, determined by FDA-approved test using Dako 22C3 PD-L1 immunohistochemistry assay, pembrolizumab used in combination with chemotherapy for treatment of locally recurrent inoperable or mTNBC that express PD-L1 (CPS ≥ 10) as a monoclonal antibody (Huang M. *et al.,* 2022). This approval was based on the

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KEYNOTE-355 trial, where pembrolizumab-chemotherapy compared with placebo-chemotherapy has significant improvement in progression-free survival and longer overall survival among patients with metastatic TNBC with CPS ≥10 (Cortes J. *et al.*, 2020). Previously, Adams et al, on phase II KEYNOTE 086 of cohort B study observe the use of monotherapy pembrolizumab in mTNBC with no prior systemic anticancer therapy and PD-L1 CPS ≥1, given that pembrolizumab alone gave a handled safety profile and for patients with PD-L1 positive mTNBC, it show a durable antitumor activity with 2.1 months in median progression-free survival (95% CI 2.0 – 2.2) and 18.0 months in median overall survival (95% CI 12.9 – 23.0) (Adams S. *et al.*, 2019). While on phase II KEYNOTE 086 of cohort A study, using single pembrolizumab for patients who were previously treated by anthracycline and taxane in any disease setting mTNBC, gave us that Pembrolizumab also has a handle safety profile and a durable antitumor activity. It shows 2.0 months in median progression-free survival (95% CI, 1.9-2,0), and the 6 months rate was 14.9% while median overall survival was 9.0 months (95% CI, 7.6 -11.2) and the 6 months rate was 69.1% (Schmid P. *et al.*, 2020).

Unlike another study, the KEYNOTE-119 compares pembrolizumab with other chemotherapy agents like capecitabine, eribulin, gemcitabine, or vinorelbine for second or third-line treatment in mTNBC. Patients with a history of mTNBC treated with one or two treatments, who had received a taxane or an anthracycline in all settings (neoadjuvant, adjuvant, or metastatic) were enrolled. The overall survival from pembrolizumab compared with chemotherapy in the primary analysis populations (including patients with PD-L1 positive tumors with CPS ≥1 or a CPS ≥10), and the result show not significant improvement in the pembrolizumab monotherapy group. Pembrolizumab also did not give a significant improvement in objective response rate, progression-free survival, also in disease control rate compared with chemotherapy in all patients, but the improved pembrolizumab treatment effect with increasing tumor PD-L1 expression was maintained across these efficacy endpoints (Winer E.P. *et al.*, 2021).

In the early stage of TNBC, additional pembrolizumab to neoadjuvant chemotherapy gave a pathological complete response higher in the pembrolizumab plus neoadjuvant chemotherapy group than the placebo plus neoadjuvant chemotherapy group. Further, the KEYNOTE-522 trial shows adjuvant pembrolizumab after surgery following neoadjuvant pembrolizumab and chemotherapy resulting in longer event-free survival than neoadjuvant chemotherapy alone, significant (Schmid P. *et al.*, 2022). Multicohort KEYNOTE – 173 study enrolled 60 patients who evaluate the safety of chemotherapy and pembrolizumab in neoadjuvant treatment and preliminary antitumor activity, in high-risk, early-stage, non-mTNBC. After 12 months of observation, the overall survival rates and event-free survival were around 80% - 100% across cohorts (100% for 4 cohorts). Higher pCR rates were significantly associated with high of pretreatment PD-L1 CPS, pretreatment, and on-treatment sTILs, (P=0.0059, 0.0127, and 0.0085). The combination of pembrolizumab with

neoadjuvant chemotherapy in early-stage TNBC or in high risk patients showed promising antitumor activity and manageable toxicity. In an analysis of exploration, show a positive correlation in pCR rate with antitumor PD-L1 expression and sTIL levels (Schmid P. *et al.*, 2020).

A multicenter, prospective, single-arm, phase II trial (NeoIm-munoboost, AGO-B - 041) that investigates the response of nab-paclitaxel-containing neoadjuvant chemotherapy in combination with pembrolizumab for early TNBC patients was conducted. Neoadjuvant pembrolizumab with nab-paclitaxel followed by epirubicin/cyclophosphamide showed a pCR rate of 66% (95% CI, 51.2%-78.8%) (Fasching P.A. *et al.*, 2023).

The limitation of this study is the lack of trials that can be used as a review. Basically, 2 trials in early triple-negative breast cancer that we use is a continuation of the previous trial. The KEYNOTE-522 trial consists of 2 articles that conducted trials in 2020 and 2022. Same as KEYNOTE-355, the trial consists of 2 sections, the trial that conducted in 2020 and 2022. So basically, we cannot compare the KEYNOTE-522 and the KEY-NOTE-355 because they have different stage of triple-negative breast cancer. Another trial needs to be conducted in every stage of TNBC (early and metastatic stage) so they have comparison group to compare with the previous trial.

Table 1. Results of Every Study

Authors	Outcomes	Results	
		Pembrolizumab group	Placebo group
Schmid et al, 2020	Pathological complete response	64.8% (95% CI, 59.9 to 69.5)	51.2% (95% CI, 44.1 to 58.3)
Schmid et al, 2022	Event-free survival	84.5% (95% CI, 81.7 to 86.9)	76.8% (95% CI, 72.2 to 80.7)
Cortes et al, 2020	Progression-free survival	9.7 months (CPS ≥10) 7.6 months (CPS ≥1)	5.6 months (CPS ≥10) 5.6 months (CPS ≥1)
Cortes et al, 2022	Overall survival	23.0 months (CPS ≥10) 17.6 months (CPS ≥1)	16.1 months (CPS ≥10) 16.0 months (CPS ≥1)
Winer et al, 2021	Overall survival	12.7 months (95% CI 9.9 to 16.3) (CPS ≥10) 10.7 months (9.3 to 12.5) (CPS ≥1)	11.6 months (95% CI 8.3 to 13.7) (CPS ≥10) 10.2 months (7.9 to 12.6) (CPS ≥1)

5. CONCLUSION

Among patients with early TNBC, neoadjuvant treatment with pembrolizumab plus chemotherapy gave higher pathological complete response than placebo plus chemotherapy. Followed by adjuvant therapy after surgery, Pembrolizumab also showed a significant difference in longer event-free survival than in the placebo group. Consistently, Pembrolizumab in

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mTNBC whose tumors expressed PD-L1 with CPS ≥10 showed significant clinical improvement in progression-free survival compared with the placebo group. Adding pembrolizumab to chemotherapy also longer overall survival than chemotherapy alone, significantly.

6. FUNDING

This research received no external funding.

7. CONFLICT OF INTEREST

The authors declare no conflict of interest.

8. AUTHORS' CONTRIBUTIONS

This systematic review conducted by Natasya and review by Aguslina and Fauna. The data was sort by Natasya and Fauna. The manuscript was writed by Natasya and Aguslina.

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