

# Efficacy and safety profiles of programmed cell death-1/programmed cell death ligand-1 inhibitors in the treatment of triple-negative breast cancer: A comprehensive systematic review

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## Abstract

Triple-negative breast cancer (TNBC) is associated with worse prognosis, with limited treatment regimens available and higher mortality rate. Immune checkpoint inhibitors targeting programmed cell death-1 (PD-1) or programmed cell death-ligand 1 (PD-L1) showed great potentials in treating malignancies and may serve as potential therapies for TNBC. This systematic review aims to evaluate the efficacy and safety profiles of PD-1/PD-L1 inhibitors in the treatment of TNBC. Literature search was performed via PubMed, EBSCOhost, Scopus, and CENTRAL databases, selecting studies which evaluated the use of anti-PD-1/PD-L1 for TNBC from inception until February 2019. Risk of bias was assessed by the Newcastle-Ottawa Scale (NOS). Overall, 7

studies evaluating outcomes of 1395 patients with TNBC were included in this systematic review. Anti-PD-1/PD-L1 showed significant antitumor effect, proven by their promising response (objective response rate (ORR), 18.5-39.4%) and survival rates (median overall survival (OS), 9.2-21.3 months). Moreover, anti-PD-1/PD-L1 yielded better outcomes when given as first-line therapy, and overexpression of PD-L1 in tumors showed better therapeutic effects. On the other hands, safety profiles were similar across agents and generally acceptable, with grade  $\geq 3$  treatment-related adverse effects (AEs) ranging from 9.5% to 15.6% and no new AEs were experienced by TNBC patients. Most grade  $\geq 3$  AEs are immune-mediated, which are manifested as neutropenia, fatigue, peripheral neuropathy, and anemia. PD-1/PD-L1 inhibitors showed promising efficacy and tolerable AEs, and thus may benefit TNBC patients. Further studies of randomized controlled trials with larger populations are needed to better confirm the potential of these agents.

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Conflicts of interest: the authors declare no conflicts of interest.

See online Appendix 1 for additional contents.

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## Introduction

Breast cancer (BC) remains a global health concern, especially for females.<sup>1,2</sup> The Global Cancer Observatory<sup>1</sup> stated that breast cancer constitutes 6.6% of all deaths from cancer in 2018 and is the leading cause of cancer deaths in females.<sup>2</sup> Furthermore, the 5-year survival rate diminished greatly across each stage from stage 0 and I (100%), stage II and III (93% and 72%, respectively), to stage IV (22%).<sup>3</sup>

Among all breast cancer subtypes, triple-negative BC (TNBC) is associated with the highest mortality rate.<sup>4-7</sup> TNBC is mostly, but not always, included in basal-like BC subtypes<sup>4</sup> because it expresses epithelial cytokeratin 5/6/14/17, laminin, and/or epidermal growth factor receptor.<sup>8</sup> It is defined by the lack of expression of prognostic factors of BC such as estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor-2 (HER2),<sup>9-11</sup> which makes it often associated with worse prognosis since there are no commonly utilized targeting agents for this case.<sup>10</sup> There are several pathways known in the pathogenesis of TNBC, some of which include under-expression of receptors by BRCA1-related pathway and *de novo* mutations.<sup>11</sup> Although it only accounts for 10% to 20% of all BC cases, it is responsible for around 30% BC associated deaths.<sup>5</sup> Moreover, some TNBC has deregulated integrin expression which may contribute to its highly metastatic behavior.<sup>8</sup>

Due to the inexpressiveness of hormone receptors, patients with TNBC cannot benefit from trastuzumab and/or hormonal-based therapy.<sup>12</sup> That being said, surgery<sup>11,12</sup> and chemotherapy<sup>11,12</sup> are the only treatment available for TNBC, unlike other types of BC that can fully benefit from common adjuvant/neoadjuvant therapies.<sup>13</sup> There are currently several trials conducted to

develop chemotherapies for TNBC (e.g. anthracycline and taxane<sup>14</sup>, cytotoxic chemotherapy<sup>15</sup>). However, optimal chemotherapy regimens have yet to be established.<sup>16</sup> Furthermore, usage of chemotherapies have showed significant adverse events, ranging from pain,<sup>17</sup> nausea,<sup>17</sup> neurocognitive dysfunction,<sup>18</sup> cardiovascular diseases,<sup>18</sup> and often deterioration of quality life,<sup>17</sup> to ultimately death.<sup>18</sup>

Recently, researchers have extensively conducted trials about the utilization of immunotherapy for the management of TNBC. The identification of tumor-infiltrating lymphocytes (TILs) as a prognostic biomarker for TNBC has led to the study of immune-checkpoint inhibitors (ICIs). Current researches have focused on the role of programmed cell death-1 (PD-1) and its ligand (PD-L1), and also cytotoxic T-lymphocyte antigen-4 (CTLA-4), in maintaining immunosuppression in the tumor microenvironment.<sup>19</sup> PD-1 is an inhibitory immune checkpoint that limits immune effector cells' function within tissues, which is expressed on B cells, T cells, dendritic cells, NK cells, and TILs.<sup>20</sup> It interacts with PD-L1 and PD-L2 and mediate immune tolerance by attenuating T-cell function, expansion, and survival.<sup>19</sup> On the other hand, CTLA-4 diminishes signaling via CD28 receptor indirectly and thus also mediates immunosuppression. Inhibitors of those immune checkpoints yield promising activity by increasing patients' survival.<sup>21</sup> Several PD-1/PD-L1 and CTLA-4 inhibitors have been tested for TNBC, including atezolizumab, avelumab, durvalumab, ipilimumab, and tremelimumab.<sup>22</sup> This systematic review aims to integrate and assess the efficacy and safety profiles of PD-1/PD-L1 inhibitor in treating TNBC.

## Materials and methods

### Search strategy

This systematic review was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions<sup>23</sup> and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.<sup>24</sup> We retrieved relevant studies from PubMed, EBSCOhost, Scopus, and Cochrane Controlled Register of Trials (CENTRAL) databases from inception to 20 February 2019, with search terms as following: ("PD-1 antibody"[All Fields] OR "PD-L1 antibody"[All Fields] OR "avelumab"[All Fields] OR "atezolizumab"[All Fields] OR "pembrolizumab"[All Fields] OR "nivolumab"[All Fields] OR "checkpoint inhibitor"[All Fields] OR "immune checkpoint"[All Fields] OR "checkpoint blockade"[All Fields] OR "checkpoint blocker"[All Fields] OR "durvalumab"[All Fields] OR "immune blockade inhibitor"[All Fields]) AND ("triple-negative breast cancer"[All Fields] OR "triple negative breast cancer"[All Fields] OR "TNBC"[All Fields]). The search was limited to human participants and no language restrictions were applied. However, studies included in the review was restricted to English and Bahasa Indonesia, which were the only languages readable by the reviewers. Details of the literature search strategy are shown on Figure 1.

### Inclusion and exclusion criteria

The following inclusion criteria were applied: i) study design, clinical trials (either randomized or non-randomized); ii) study population, patients over 18 years old with confirmed TNBC; iii) language, English and Bahasa Indonesia; iv) comparison and intervention, PD-1 and/or PD-L1 inhibitor either as neoadjuvant or adjuvant therapy; and v) outcome parameter, overall response rate (ORR), disease control rate (DCR), duration of response (DOR),

progression-free survival (PFS), overall survival (OS), and adverse effects (AEs) grade  $\geq 3$ . Furthermore, exclusion criteria comprising of i) no extractable data (i.e. ORR, DCR, DOR, PFS, OS, or AEs grade  $\geq 3$ ) and ii) irretrievable full-text articles were also set.

### Data extraction and quality assessment

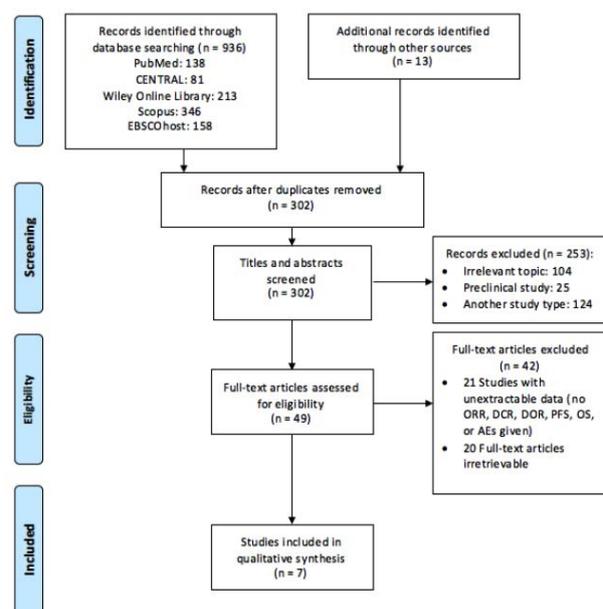
Literature screening and data extraction were performed by two independent reviewers (GL and JA), and discrepancies were resolved by the consensus of all authors. The following information was extracted from each trial: first author; publication year; study design; trial phase; subject characteristics, consisting of median age and sample size; intervention, consisting of treatment groups, target molecule, and line of therapy; duration of follow-up; ORR, defined as proportion of patients with complete (CR) or partial response (PR); DCR, defined as the percentage of patients with CR, PR, or stable disease for 24 weeks, PFS, defined as time from patient enrollment to disease progression or death; OS, defined as time from patient enrollment to death from any cause; and significant AEs (grade 3).

Two reviewers (GL and JA) independently assessed the quality of included trials, disagreements between authors were adjudicated by a third investigator (AW). Risk of bias and methodological quality assessment was performed using the Newcastle-Ottawa Scale (NOS).<sup>25</sup> Appendix 1 provides details of quality assessment of included studies.

## Results

### Study selection

The selection process for included studies in the systematic review is shown in Figure 1. The initial search yielded 949 relevant studies from PubMed, EBSCOhost, CENTRAL, and Scopus. Among them, 648 studies were deduplicated, and 253 studies were excluded after title and/or abstract screening. Furthermore, 42



**Figure 1. Diagram flow of literature search strategy for this systematic review.**

studies were excluded because 21<sup>26-46</sup> did not provide outcomes of our interest, 20<sup>47-66</sup> were irretrievable, and 1<sup>67</sup> was not in English or Bahasa Indonesia. Finally, 7 clinical trials were identified for the qualitative analysis, consisting of 6 non-randomized trials and 1 randomized trial.

### Study characteristics

The main patient characteristics of included studies are shown in Table 1. A pooled total of 1395 patients were included in our systematic review. Patient characteristics were matched for locally advanced and metastatic (stage III/IV) TNBC (ER-negative, PgR-negative, and HER2-negative). The trials were published between 2016 and 2018, and mostly were international, multicentered, and/or multi-cohort studies. All trials aimed to investigate the efficacy and safety of immune checkpoint inhibitors. In addition, two trials<sup>68,69</sup> also evaluated the clinical activity of checkpoint inhibitors.

### Efficacy

Four studies evaluated the effects of PD-L1 inhibitors, while the remaining three analyzed the effects of PD-1 inhibitors, all on TNBC type (Table 2). Outcomes extracted to assess clinical activity include ORR, DCR, DOR, PFS, and OS.

Overall, ORR ranges from 5.2–56.0 months and DCR ranges from 7.6–51.5 months. DOR ranges from 9.1–21+ months, as median DOR was not reached in several studies. Median PFS ranges from 1.4–7.2 months, whereas median OS ranges from 9.2–21.3 months.<sup>68-74</sup> In one randomized trial by Schmid *et al.*,<sup>72</sup> effects of PD-L1 inhibitor combined with nab-paclitaxel were compared to effects of nab-paclitaxel alone with placebo. Results showed a higher PFS (7.2 vs 5.5 months) and OS (21.3 vs 17.6 months) in intervention group when compared to placebo, with HR of 0.80 and 0.84 respectively.

### Safety profiles

AEs in each study were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In the included studies, AEs were described as generally manageable, acceptable, or well tolerable. Their results were consistent with known safety profiles of each agent and no new adverse effects were reported. AEs of grade  $\geq 3$  is summarized in Table 2. The rate of treatment-related AEs (TRAEs) of any grade ranges from 56.3% to 100%.<sup>68-74</sup> Grade 3 or higher AEs were experienced by 9.5%–15.6% (n=35) patients administered pembrolizumab,<sup>70,71,74</sup> 13.7% (n=23) administered avelumab,<sup>73</sup> and 12.9% (n=15) administered atezolizumab as monotherapy.<sup>69</sup> In patients treated with combination of atezolizumab plus nab-paclitaxel, grade 3 or higher AEs were found in 48.7% (n=220) patients compared to 42.2% in placebo-nab-paclitaxel group,<sup>72</sup> while in another study the rate is 73% (n=24) in atezolizumab-nab-paclitaxel group.<sup>68</sup> Treatment-related deaths were found in 1, 2, 2 and 3 patients receiving pembrolizumab,<sup>74</sup> avelumab,<sup>73</sup> atezolizumab,<sup>69</sup> and atezolizumab plus nab-paclitaxel,<sup>72</sup> respectively.

### Discussion

Plenty of studies have shown the potential of checkpoint inhibitor as a treatment candidate against cancer, and this type of immunotherapy has been approved in several cancer types, such as melanoma<sup>75</sup> and lung cancer.<sup>76</sup> Based on our systematic review, we found that checkpoint inhibitor also shows positive effects on breast cancer, especially TNBC, proven by increase in patients'

response rates and survival.

The mechanism by which immune checkpoint inhibitors function involves a unique way of modulating immune response against tumor cells. Unlike previous targeted therapy which target specific receptors on tumor cells, checkpoint inhibitors work by removing certain inhibitions which under normal conditions help to keep the immune system in check. This is based on the findings that cancer cells have certain immunosuppressive abilities which make use of normal immune regulatory mechanism.<sup>77</sup> Under normal conditions, presentation of antigens to T cells, together with co-stimulatory signals from the binding of CD28 to its ligand B7-1/2, would result in T cell activation. T cells also express protein receptor molecules, such as CTLA-4 and PD-1, which function as checkpoint molecules. Binding of CTLA-4 to B7-1/2 or PD-1 to PD-L1 would inhibit T cell activation, thus preventing T cells from turning over-reactive. However, when this regulatory mechanism is hijacked by cancer cells, it helps to shield tumor cells from the host immune response.<sup>78,79</sup>

Preclinical studies with mice aimed to examine *in vivo* activities of anti-PD-1 against TNBC have previously yielded encouraging results. Anti-PD-1 was shown to succeed in inhibiting tumor growth in humanized mice implanted with tumor xenografts.<sup>36,80,81</sup> Mice treated with anti-PD-1 had an increased level of antitumor T-cell responses and decreased activities of regulatory T cells as well as myeloid populations which may play an important role in suppressing immune response against tumor cells in host.<sup>80</sup> These pre-clinical models give valuable insights regarding the mechanism of PD-1 blockade therapy against TNBC, and provide the basis to facilitate further investigation and clinical studies.

Clinical therapy of TNBC with PD-1 inhibitor shows a promising response and survival rate. Studies by Adams<sup>71</sup> and Nanda<sup>74</sup> shows response rates of 21.4% and 18.5% respectively, and median overall survival of 18 and 11.2 months respectively. Meanwhile, treatment with PD-L1 inhibitor also exhibit favorable outcomes, with an ORR as high as 39.4% and median OS of 14.7 months in a study by Adams.<sup>68</sup> Another study by Schmid<sup>72</sup> also compared the effects of PD-L1 inhibitor combined with chemotherapy nab-paclitaxel to the effects of nab-paclitaxel with placebo, and results show a significant increase in PFS and OS of the patients. Aside from its response rate, checkpoint inhibitors also show a durable response, as expressed by median DOR which ranges from 9.1 to 21+ months, compare to low DOR in chemotherapy of TNBC patients, ranging from 4 to 12 months.<sup>82</sup> These outcomes demonstrate positive clinical antitumor activities when used as single or combination therapy, highlighting the potential of checkpoint inhibitors for the treatment of TNBC.

Effects of PD-1/PD-L1 inhibitors also differ when given as first-line therapy compared to second-line or greater treatment. Pembrolizumab, a PD-1 inhibitor, shows higher response rate and survival (ORR 21.4% and OS 18 months) when given as first-line therapy compared to when given after other systemic therapy (ORR 5.3% and OS 9 months).<sup>70,71</sup> A study by Emens<sup>69</sup> with PD-L1 inhibitor also shows similar results, with ORR of 24% and OS 17.6 months when atezolizumab was given as first line therapy, compared to ORR 6% and OS 7.3 months when administered as second-line or greater treatment.<sup>69</sup>

The positive results discussed above were comparable to the effects of PD-1/PD-L1 blockade therapy in cancer types where it had been officially approved for treatment. A meta-analysis comparing the effects of such checkpoint inhibitor over docetaxel in patients with non-small-cell lung carcinoma (NSCLC), exhibited favorable outcomes in immunotherapy arms, shown by the significant increase in OS (HR=0.71) and PFS (HR=0.86).<sup>83</sup> Similar results were shown with studies involving advanced melanoma,

where significant difference were found in PFS (HR=0.53), OS (HR=0.60), and ORR (RR=2.87), all in favor of PD-1 inhibitors.<sup>84</sup> These results demonstrated the possibility of PD-1/PD-L1 inhibitors to emerge as one of main choices of therapy for TNBC in the future, as how it had been for other cancer types.

Although clinical trials on PD-1/PD-L1 blockade show encouraging antitumor results, responses were seen better in certain subgroups of patients. This emphasize the need of certain markers to predict response to PD-1/PD-L1 blockade therapy, as well as to select proper candidates which would benefit most from the therapy. Patients with increased tumor PD-L1 expression are found to respond better to checkpoint inhibitor therapy. Pembrolizumab, when given to PD-L1 positive population, gives an ORR of 5.7% and DCR of 9.5%, higher than PD-L1 negative population with ORR 4.7% and DCR 4.7%. Another study by Nanda<sup>74</sup> shows similar results, with increasing ORR as PD-L1 expression increases (P=0.028).<sup>74</sup> Overexpression of PD-L1 in tumors help tumor cells to inhibit cytotoxic T cells, thereby allowing the cancer to evade the immune system, correlating with poorer

prognosis. However, with PD-1/PD-L1 blockade therapy, the expression of these molecules could predict a better therapeutic effect, as these pre-existing binding of PD-1/PD-L1 provide a target for the drug's blocking action.<sup>85</sup>

These results with TNBC is consistent with a meta-analysis conducted by Khunger<sup>86</sup> which studied the predictive value PD-L1 expression as biomarker in other cancer types, including NSCLC, melanoma, renal, and bladder carcinoma. Except for bladder carcinoma, PD-L1 expression was found to be predictive of favorable responses in tumors treated with PD-1/PD-L1 inhibitors in the other cancer types (OR=2.77), where its effect was largest in NSCLC (OR=3.33).<sup>86</sup> Nevertheless, studies found that the expression of PD-L1 is a dynamic process, thus sampling of tissues at one time may not accurately depict a patient's response accurately. Moreover, up until now, there is still no exact cut-off values for PD-L1 overexpression.<sup>87</sup> Thus, further studies regarding its use as a prognostic biomarker are still needed.

Checkpoint inhibitor therapy also demonstrated a lower response rate in patients with poor clinical prognostic factors.

**Table 1. Study characteristics.**

Year; Author	Study characteristics			Subject characteristics			Intervention			NOS Score	
	Study design	Phase	Aims/Purpose	Median age (years)	Sample size	Disease stage	Target molecule	Treatment groups	Line of therapy		Follow-up (months)
2018; Adams S <sup>68</sup>	Single-arm trial, multi-cohort, multicenter	Ib	To examine the safety, tolerability, and preliminary clinical activity of atezolizumab + nab-paclitaxel in mTNBC	55	33	IV	PD-L1	Atezolizumab + nab-paclitaxel	≥1L	24.4 (22.1-28.8)	8
2018; Adams S Cohort A <sup>70</sup>	Single-arm trial, open-label	II	To examine the efficacy and safety of pembrolizumab monotherapy in large cohort of patients with previously treated mTNBC regardless of PD-L1 expression	53.5	170	IV	PD-1	Pembrolizumab	≥1L	9.6 (0.1-25.7)	7
2018; Adams S Cohort B <sup>71</sup>	Single-arm trial, open-label	II	To examine the safety and efficacy of single-agent pembrolizumab in patients with previously untreated PD-L1+ mTNBC	52.5 (26-91)	84	IV	PD-1	Pembrolizumab	1L	12.3 (0.9-23.5)	7
2018; Schmid P <sup>72</sup>	Randomized, multi-cohort	III	To investigate the efficacy and safety of first line atezolizumab + nab-paclitaxel, as compared with placebo + nab-paclitaxel, in patients with locally advanced or mTNBC	Atezolizumab–nab-paclitaxel: 55 Placebo–nab-paclitaxel: 56	902	III/IV	PD-L1	Atezolizumab + nab-paclitaxel vs placebo vs nab-paclitaxel	1L	Atezolizumab–nab-paclitaxel: 13.0 Placebo–nab-paclitaxel: 12.5	9
2018; Emens LA <sup>69</sup>	Single-arm trial, multi-cohort, open-label	I	To evaluate the safety, clinical activity, and biomarkers associated with the use of single agent atezolizumab in patients with mTNBC	53	116	IV	PD-L1	Atezolizumab	≥1L	25.3 (0.4-45.6)	6
2017; Dirix LY <sup>73</sup>	Single-arm trial, open-label, international	I	To assess the activity of avelumab, a PD-L1 inhibitor, in patients with mBC	52.5 (31-80)	58	III/IV	PD-L1	Avelumab	≥1L	10.0 (6.0-15.2)	7
2016; Nanda R <sup>74</sup>	Non-randomized, multicenter	Ib	To assess the safety and antitumor activity of PD-1 inhibitor pembrolizumab in patients with advanced TNBC	50.5	32	IV	PD-1	Pembrolizumab	≥1L	10.0 (0.4-19.5)	7

NOS, Newcastle-Ottawa Scale; mTNBC, metastatic triple-negative breast cancer; mBC, metastatic breast cancer; TNBC, triple-negative breast cancer; PD-1, programmed

Table 2. Reported outcomes related to efficacy and adverse effects.

Year; Author	ORR (%) [95% CI]	DCR (%) [95% CI]	DOR (months) [95% CI]	Median PFS (months) [95% CI]	Progression-free survival (PFS)			Overall survival (PFS)				Adverse effects (Grade ≥3) Treatment related	n (%)	
					PFS6m (%)	PFS1y (%)	HR [95% CI]	Median OS (months) [95% CI]	OS6m (%)	OS1y (%)	OS2y (%)			HR [95% CI]
2018; Adams S <sup>68</sup>	39.4 [22.9-57.9]	51.5 [33.5-69.2]	9.1 [2.9-20.9]	5.5 [5.1-7.7]	45.5	-	-	14.7 [10.1-NE]	-	57.4	40.6	-	All AEs Neutropenia Thrombocytopenia Diarrhea Anemia Pneumonia Leukopenia Peripheral neuropathy Myalgia Bone pain Colitis Syncope Elevated AST Febrile neutropenia Type 1 diabetes mellitus Pneumonia mycoplasma Paronychia	24 (73) 15 (46) 3 (9) 2 (6) 2 (6) 2 (6) 2 (6) 1 (3) 1 (3) 1 (3) 1 (3) 1 (3) 1 (3) 1 (3) 1 (3) 1 (3) 1 (3)
2018; Adams S Cohort A <sup>70</sup>	5.3 [2.7-9.9]	7.6 [4.4-12.7]	-	2.0 [1.9-2.0]	14.9	8.1	-	9.0 [7.6-11.2]	69.7	39.8	-	-	Any AEs Diarrhea Fatigue Nausea	22 (13) 3 (1.8) 1 (0.6) 1 (0.6)
2018; Adams S Cohort B <sup>71</sup>	21.4 [13.9-31.4]	23.8 [15.9-34.0]	10.4 [4.9-19.2]	2.1 [2.0-2.2]	27.0	-	-	18.0 [12.9-23.0]	81.0	61.7	-	-	Any AEs Diarrhea Fatigue Anemia	8 (9.5) 1 (1.2) 1 (1.2) 1 (1.2)
2018; Schmid P <sup>72</sup>	56.0 [51.3-60.6]	-	7.4 [6.9-9.0]	7.2 [5.6-7.5]	50.1	23.7	0.62* [0.49-0.78]	21.3 [17.3-23.4]	-	60.09	42.1	0.62* [0.45-0.86]	Neutropenia Peripheral neuropathy Nausea Alopecia Pyrexia	37 (8.2) 25 (5.5) 5 (1.1) 3 (0.7) 3 (0.7)
2018; Emens LA <sup>69</sup>	24.0 [8.0-47.0]	29.0	21.0 [10.0-38.0]	1.4 [1.3-1.6]	-	-	-	17.6 [10.2-NE]	-	41.0	19.0	2.21° [1.17-4.16]	Any AEs Hyperglycemia Pneumonitis Pulmonary hypertension	46 (40) 1 (0.9) 1 (0.9) 1 (0.9)
2017; irix LY <sup>73</sup>	5.2 [1.1-14.4]	31.0	-	5.9 [5.7-6.9]	12.4	-	-	9.2 [4.3-NE]	-	37.9	-	-	Any AEs Fatigue Anemia Autoimmune hepatitis Elevated GGT Arthralgia Acute hepatic failure Dyspnea exertional Elevated AST Elevated ALT Hypoxia Hypokalemia Pneumonitis Axillary pain Pleuritic pain Non-cardiac chest pain Thrombocytopenia Cardiac arrest Hypertriglyceridemia Neutropenia Proteinuria Respiratory failure Respiratory distress Pulmonary arterial hypertension	23 (13.7) 3 (1.8) 3 (1.8) 3 (1.8) 3 (1.8) 1 (0.6) 1 (0.6)
2016; Nanda R <sup>74</sup>	18.5 [6.3-38.1]	25.9	-	1.9 [1.7-5.5]	24.4	-	-	11.2 [5.3-NE]	66.7	43.0	-	-	Anemia Aseptic meningitis Disseminated intravascular coagulation Headache Lymphopenia Pyrexia	1 (3.1) 1 (3.1) (3.1) 1 (3.1) 1 (3.1) 1 (3.1)

ORR, overall response rate; DCR, disease control rate; DOR, duration of response; PFS, progression-free survival; PFS6m, 6-months PFS rate; PFS1y, 1-year PFS rate; OS, overall survival; OS6m, 6-months OS rate; OS1y, 1-year OS rate; OS2y, 2-year OS rate; HR, hazard ratio; NE, not estimable; AEs, adverse effects; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, -glutamyl transferase; \*HR calculated between intervention arm and placebo arm; °HR calculated between 1<sup>st</sup> and 2<sup>nd</sup> line of therapy.

These include an elevated lactate dehydrogenase level which is associated with faster disease progression, presence of liver metastases, more metastatic sites, and other visceral diseases.<sup>69,70,74</sup> Alternative therapy strategies as well as combination therapy should be considered in these settings to help improve response rate to therapy.<sup>70</sup>

Safety profiles of PD-1/PD-L1 inhibitors are generally acceptable. Grade 3 or higher AEs were found in 9.5%-15.6%, 13.7%, and 12.9% patients receiving pembrolizumab, avelumab, and atezolizumab, respectively. These numbers indicated that each agent have a similar safety profile. Furthermore, our results are comparable with recent studies on other types of metastatic cancer.<sup>88-91</sup>

Some common TRAEs of pembrolizumab therapy were fatigue (18.8%-26.2%; n=63),<sup>70,71,74</sup> nausea (11.2%-13.1%; n=35),<sup>69,70,74</sup> diarrhea (11.9%; n=10),<sup>70</sup> arthralgia (18.8%; n=6),<sup>74</sup> and myalgia (18.8%; n=6).<sup>74</sup> A study on metastatic esophageal cancer reported less incidence of fatigue (10.7%; n=13) and diarrhea (4.9%), despite similar proportion of pruritus (6.6% vs 6.3%-7.1%<sup>70,71,74</sup>), rash (7.4% vs 6.0%<sup>70</sup>), and total AEs of grade 3-5 (12.4%).<sup>88</sup> Fatigue was also the most common AE in patients with advanced recurrent ovarian cancer (33.8%; n=127), followed by nausea (15.4%).<sup>91</sup> Additionally, the incidence of diarrhea (10.1%), pruritus (8.2%), and rash (7.2%) were similar;<sup>91</sup> however, less patients experienced arthralgia (5.3%)<sup>91</sup> compared to our included studies. Grade 3 or higher AEs including aseptic meningitis, headache, anemia, lymphopenia and pyrexia were in line with previous reports.<sup>92-94</sup>

The most common AEs of any grade in anti PD-L1 monotherapy were fatigue (13%-19.0%; n=47), pyrexia (16%; n=19),<sup>69</sup> infusion-related reaction (14.3%; n=24),<sup>73</sup> and nausea (11%-13.1%; n=35).<sup>69,73</sup> A study in which patients with metastatic melanoma had received avelumab reported less grade 3 AEs (7.8%; n=4)<sup>89</sup> when compared with avelumab monotherapy in patients with TNBC (13.7%; n=23).<sup>73</sup> Infusion-related reaction had higher prevalence (29.4%) and was the most AE experienced by melanoma patients, followed by fatigue (17.6%), chills (11.8%), and diarrhea (9.8%).<sup>89</sup> Atezolizumab monotherapy in patients with TNBC was assessed by Emens *et al.*<sup>69</sup> In this study, grade 3-5 AEs were present in 12.9% (n=15) patients, with frequent AEs being pyrexia (16%), fatigue (13%), nausea (11%), diarrhea (10%), asthenia (10%), and pruritus (11%). In comparison, patients with metastatic urothelial cancer who were given atezolizumab monotherapy experienced less grade 3-5 AEs (9%; n=9). Both studies had similar incidences of fatigue (18%), asthenia (14%), pruritus (13%), nausea (12%) and diarrhea (7%).<sup>90</sup>

Grade 3 or higher AEs were mostly immune-mediated (Table 2), which might manifest as organ-specific autoimmune reaction.<sup>95</sup> Dirix *et al.*<sup>73</sup> reported two treatment-related deaths, one of which was due to respiratory distress in a patient with liver, lung, and soft tissue metastases. Grade 3 or higher AEs related to respiratory system also constituted significantly in this study, including dyspnea (5.4%; n=9) and pleural effusion (5.4%; n=9). Other treatment-related adverse events were similar to known safety profiles of anti PD-L1 agents.<sup>96</sup>

Most patients receiving atezolizumab plus nab-paclitaxel combination therapy experience neutropenia (70%; n=23), fatigue (67%; n=22), alopecia (42%; n=14), diarrhea (39%; n=13), peripheral sensory neuropathy (36%; n=12), and nausea (30%; n=10).<sup>68</sup> When compared to placebo, higher frequency of nausea, pyrexia, hypothyroidism, neutropenia, and cough were found in the atezolizumab-nab-paclitaxel group, thus suggesting AEs caused by atezolizumab. The most common grade 3 or 4 AEs in both groups were neutropenia, decreased neutrophil count, peripheral neuropathy, fatigue, and anemia. Percentage of grade 3 or 4 peripheral neu-

ropathy was higher than placebo (5.5%; n=25 vs 2.7%; n=12), which is consistent with a similar study on metastatic non-squamous NSCLC.<sup>97</sup>

Considering the pharmacodynamics of PD-1/PD-L1 inhibitors, most AEs are due to immune system activation.<sup>95</sup> Therefore, immune-related AEs (irAEs) are of special interest and considered by all studies included in our review, regardless of attribution to treatment. According to a meta-analysis on other types of cancer, organ specific irAEs include hypothyroidism, pneumonitis, colitis, hepatitis and hypophysitis, with pneumonitis being the most common serious AE. Additionally, general adverse events such as fatigue, diarrhea, rash, are also the known AEs related to immune activation.<sup>95</sup> Similarly, we found hypothyroidism,<sup>70,71,73</sup> hyperthyroidism,<sup>70,71,73</sup> type 1 diabetes mellitus,<sup>70</sup> pneumonitis,<sup>68-70,72,73</sup> colitis,<sup>68,74</sup> and hepatitis<sup>72-74</sup> as irAEs, while fatigue, rash, and diarrhea are mostly grade 1 or 2.<sup>68-74</sup> These results were consistent with the previous studies on checkpoint inhibitors.<sup>95,98</sup>

Though considerable amount of studies has shown the potential of checkpoint inhibitors in treating TNBC patients, more knowledge about their synergistic effect with other therapeutic agents is needed. In fact, combinations of these agents are currently evaluated. Common examples include the combination of chemotherapeutic drugs with checkpoint inhibitors or other agents of immunotherapy. NeoPACT<sup>99</sup> is studying the effect of pembrolizumab when combined with carboplatin and docetaxel in stage I-III TNBC, while multiple combinations of chemotherapy with atezolizumab are included in the Morpheus-TNBC trial-a currently ongoing phase Ib/II trial.<sup>100</sup> Another study is evaluating the combination of olaparib, a poly (ADP-ribose) polymerase inhibitor, and durvalumab (anti-PD-L1 monoclonal antibody) in metastatic TNBC.<sup>101</sup> Chemotherapies mainly prevent cancer to grow and spread, while checkpoint inhibitors help the immune system to combat tumor cells; thus, combining these agents might work better against TNBC. Treatment of TNBC using combination of PVX-410 vaccine and pembrolizumab is currently on phase 1b.<sup>102</sup> Since both agents ameliorate immune system against cancer, such combinations might offer better efficacy; however, increased rate and severity of AEs should be anticipated.

### Study limitation

As in other studies, our systematic review also has several limitations. A major limitation is the fact that most studies included in our review are non-randomized and open-labelled. Moreover, checkpoint inhibitor is only recently tried in TNBC, thus most studies are still in phase I or II of clinical trials. A larger, randomized controlled trial with more samples is therefore needed to further confirm these results. Despite these drawbacks, we believe that the result of this review would provide useful clinical implications, serving as a basis to encourage further studies in this research area.

### Conclusions

Based on the above systematic review, we found that checkpoint inhibitor exhibits an excellent potential as a novel therapy against TNBC. Clinical trials found that checkpoint inhibitors showed good antitumor activity, demonstrated by their promising response and survival rates. Responses are seen better with increased PD-L1 expression. Adverse effects of PD-1/PD-L1 blockade therapy are generally immune-related; however, these effects are mostly tolerable, with hardly any grade 3 or above adverse effects in each study. We hope that this result could serve

as a basis for further studies regarding checkpoint inhibitor immunotherapy to uncover its potential as an effective and tolerable therapy for breast cancer, especially TNBC, thus helping to reduce its mortality rate worldwide.

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