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[Intervention Protocol]

Immune checkpoint inhibitors and chemotherapy versus chemotherapy for early triple-negative breast cancer

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the efficacy and safety of PD-1 inhibitors or PD-L1 inhibitors plus chemotherapy compared with chemotherapy for people with early triple-negative breast cancer.

BACKGROUND

Description of the condition

Breast cancer is the most common type of cancer and the leading cause of cancer deaths in women worldwide (Sung 2021). In 2020, there were approximately 2.3 million new cases of breast cancer and 683,100 deaths (Sung 2021). Newly diagnosed breast cancers should be tested for oestrogen (ER) and progesterone (PR) receptor expression and for overexpression of human epidermal growth factor receptor 2 (HER2). This information is critical for therapeutic and prognostic purposes. Breast cancer can be characterised into different subtypes according to whether or not they express ER, PR, and HER2 (O'Brien 2010; Parise 2009). Triple-negative breast cancer (TNBC) is defined by the lack of expression of the ER, PR, and HER2 on cancer cells (Mittendorf 2020). Approximately 12% to 17% of breast cancers are TNBC, and early-stage TNBC accounts for 10% to 20% of new diagnoses of early breast cancer (Foulkes 2010). TNBC tends to behave more aggressively than other types of breast cancer and is associated with higher mortality and a higher likelihood of recurrence (Hudis 2011).

In general, people with early-stage breast cancer undergo primary surgery (lumpectomy or mastectomy) of the breast and regional nodes with or without radiation therapy (RT). However, some people with early-stage invasive breast cancer (particularly those with TNBC) may be treated with preoperative (or neoadjuvant) therapy first, followed by surgery. Chemotherapy remains the standard of care for primary TNBC (Loibl 2019).

Most international guidelines recommend sequential use of a taxane and anthracycline plus cyclophosphamide as the optimal chemotherapy regimen for early TNBC (Cardoso 2019; NCCN 2020). Multiagent chemotherapy regimens have shown benefits in improving disease-specific and overall survival outcomes when provided as neoadjuvant or adjuvant (postoperative) therapy for early TNBC (Budd 2015; Burstein 2019; Gianni 2018; Untch 2016). However, the five-year metastasis-free survival rate is about 70%, and about 30% to 40% of people will develop metastatic disease (Budd 2015; Masuda 2017; Sharma 2017). Recently, immune checkpoint inhibitors have been used to treat early-stage TNBC and have been shown to improve pathological complete response and event-free survival (Mittendorf 2020; Schmid 2020; Schmid 2022).

Description of the intervention

Immune checkpoints are molecules that modulate the immune response in peripheral tissues and are activated to prevent tissue damage (Pardoll 2012). The programmed cell death ligand 1 or 2 (PD-L1, PD-L2) and programmed cell death protein 1 (PD-1) are immune checkpoint proteins found on cells that help keep this immune response in check. When the PD-L1 binds to PD-1, this partnership sends a signal that inhibits immune cells from killing their partner cell (Collin 2016; Okazaki 2001; Topalian 2013; Walankiewicz 2018). This is one mechanism by which cancer cells can evade the immune response. Immune checkpoint inhibitors work by blocking the binding of these two proteins and reactivating the immune response.

Many immune checkpoint inhibitors have been used to prolong survival in lung cancer (Chae 2018), Hodgkin's lymphoma (Ansell 2015), melanomas (Zaretsky 2016), and renal cell carcinoma (Motzer 2015). Immune checkpoint inhibitors have been shown to have antitumour activity and a range of low-grade toxic effects in people with metastatic TNBC (Adams 2019a; Adams 2019b; Nanda 2016). Some types of immune checkpoint inhibitors include pembrolizumab, nivolumab, durvalumab, and atezolizumab. Recently, the combination of PD-1 or PD-L1 inhibitors and chemotherapy has been used for treating early-stage TNBC. A double-blind, randomised, phase 3 trial reported that pembrolizumab plus neoadjuvant chemotherapy resulted in a significantly higher percentage of pathological complete responses (64.8% versus 51.2%) than placebo plus neoadjuvant chemotherapy (Schmid 2020). Another randomised controlled trial showed that early-stage TNBC treated with atezolizumab plus chemotherapy had higher pathological complete responses but higher treatment-related serious adverse events compared with placebo plus chemotherapy (Mittendorf 2020).

How the intervention might work

PD-1 protein is expressed on various cells such as NK cells, B cells, dendritic cells, antigen-presenting cells, activated CD4+ T cells and CD8+ T cells, and monocytes (Dinesh 2010; Walankiewicz 2018). The function of PD-1 is to inhibit the activation of T cells and B cells, which is a normal mechanism of the immune system. However, the tumour microenvironment will induce the T cells to highly express PD-1 molecules, and the tumour cells will highly express PD-1 ligands (PD-L1 and PD-L2). This leads to the continuous activation of the PD-1 pathway in the tumour microenvironment where T cell function is inhibited and T cells are unable to kill tumour cells.

PD-1 inhibitors can block this pathway and partially restore the function of T cells so that these cells can continue to kill tumour cells (Gaynor 2022; Pilipow 2021). In addition, PD-L1 inhibitors can block the interaction of immune checkpoint proteins and play a similar role to PD-1 inhibitors. PD-1 inhibitors and PD-L1 inhibitors have similar mechanisms: they can block the binding of PD-1 and PD-L1, upregulate the growth and proliferation of T cells, enhance T cells' recognition of tumour cells, and activate T cell attack and killing functions to achieve antitumour effects (Gaynor 2022). Furthermore, chemotherapy increases the release of tumour-specific antigens on cancer cells, and immune checkpoint inhibitors can subsequently enhance the immune response against cancer cells (Farkona 2016). In summary, chemotherapy may work synergistically with immune checkpoint inhibitors (Galluzzi 2015; Spigel 2013).

Why it is important to do this review

Early TNBC is associated with an increased risk of recurrence compared to other breast cancers. Achieving a pathological complete response after neoadjuvant chemotherapy is strongly associated with improved survival outcomes, whilst the presence of residual disease (i.e. a high residual cancer burden score) is significantly associated with worse event-free survival (Yau 2022).

Recently, immune checkpoint inhibitors plus chemotherapy have shown potential to improve pathological complete response or event-free survival in people with early-stage TNBC. However, it is unclear whether the combination of immune-targeted therapy and chemotherapy regimen leads to higher efficacy at the cost of increased toxicity, and whether treatment effects vary across different subgroups of patients (e.g. PD-L1-positive population or -negative population) and types of agents (e.g. nivolumab,

pembrolizumab, durvalumab). It is therefore important to conduct a systematic review to summarise all of the evidence on the effects of immune checkpoint inhibitors (PD-1 inhibitors or PD-L1 inhibitors) plus chemotherapy for early TNBC and report toxicities, quality of life, and treatment benefits, which will benefit physicians and people with early TNBC.

OBJECTIVES

To assess the efficacy and safety of PD-1 inhibitors or PD-L1 inhibitors plus chemotherapy compared with chemotherapy for people with early triple-negative breast cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We will include parallel, cross-over, cluster-, or quasi-, phase II or III randomised controlled trials (RCTs) with or without blinding. To limit publication bias, we will also incorporate unpublished online data if sufficient data are provided for analysis and possible bias assessment.

Types of participants

Women or men aged 18 years or older and histologically confirmed triple-negative breast cancer in all foci (by central assessment of negative HER2, oestrogen receptor, and progesterone receptor status according to American Society of Clinical Oncology/College of American Pathologists guidelines). We will include people with potentially curable breast cancer (stages 1 to 3). We will include trials where bilateral or multifocal primary tumours and inflammatory breast cancers are eligible for enrolment.

We will exclude studies where people receive treatment for recurrent breast cancer.

Types of interventions

Interventions: PD-1 inhibitors (such as nivolumab, pembrolizumab/lambrolizumab, pidilizumab, or tislelizumab) or PD-L1 inhibitors (such as atezolizumab, avelumab, or durvalumab) plus chemotherapy. Given that our review focuses on PD-1 inhibitors and PD-L1 inhibitors, we will exclude interventions of CTLA-4 inhibitors plus chemotherapy or PD-1 inhibitors/PD-L1 inhibitors plus CTLA-4 inhibitors plus chemotherapy.

Comparator: chemotherapy or chemotherapy plus placebo. We will not limit the chemotherapy regimen.

We will include the following pair-wise comparisons:

- PD-1 inhibitors or PD-L1 inhibitors plus chemotherapy versus chemotherapy;
- PD-1 inhibitors or PD-L1 inhibitors plus chemotherapy versus chemotherapy plus placebo.

Types of outcome measures

Primary outcomes

- Pathological complete response: defined as no invasive and no non-invasive tumour residuals in the breast and in axillary lymph nodes.
- Disease-free survival (DFS): time from randomisation to disease recurrence, progression, or death from any cause.

Secondary outcomes

- Overall survival (OS): time from randomisation to death from any cause.
- Health-related quality of life (HRQoL), measured by a validated scale.
- Overall rates of any adverse events and serious adverse events (SAEs): severity level assessed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) (NCI-CTCAE 2010), including the percentage of treatment-related deaths, as well as (if separate data are available) immune-related adverse events (irAEs).

Search methods for identification of studies

Electronic searches

We will search the following databases:

- The Cochrane Breast Cancer Group's (CBCG's) Specialised Register. Details of the search strategies used by the Group for the identification of studies and the procedure used to code references are outlined in the Group's module. Trials with the key words 'immunotherapy', 'immune checkpoint inhibitors', 'PD-1 Inhibitor', 'PD-L1 Inhibitor', 'Programmed Cell Death Protein 1 Inhibitor', 'Programmed Death-Ligand 1 Inhibitor', 'nivolumab', 'pembrolizumab', 'lambrolizumab', 'pidilizumab', 'tislelizumab', 'atezolizumab', 'avelumab', 'durvalumab', 'cemiplimab', 'dostarlimab', 'spartalizumab' and 'toripalimab' will be extracted and considered for inclusion in the review.
- The Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, latest issue). See Appendix 1.
- MEDLINE (via OvidSP) from 2005 (immune checkpoint inhibitors were not available - even in clinical trials - before 2005) to present. See Appendix 2.
- Embase (via OvidSP) from 2005 to present. See Appendix 3.
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/Default.aspx) for all prospectively registered and ongoing trials. See Appendix 4.
- ClinicalTrials.gov (clinicaltrials.gov/). See Appendix 5.

We will not apply any restrictions on language.

Searching other resources

Bibliographic searching: we will screen the reference lists of identified relevant trials or reviews. We will obtain a copy of the full article for each reference reporting a potentially eligible trial. Where this is not possible, we will attempt to contact authors to provide additional information.

Conference proceedings: we will search the Embase database available via OvidSP for the conference proceedings of:

- American Association of Cancer Research (AACR); and
- European Society of Medical Oncology (ESMO).

Data collection and analysis

Selection of studies

Two review authors (YG, ML) will independently screen the titles and abstracts of all references identified by the search strategy. The same two review authors will further evaluate the full text of each record deemed potentially eligible to determine study eligibility. Any disagreements will be resolved by consensus or adjudication from a third review author.

We will record the selection process in the PRISMA flow diagram. In addition, we will list the reasons for excluding key full-text articles in the 'Characteristics of excluded studies' table. We will apply no language restrictions.

Data extraction and management

Two review authors (YG, ML) will independently extract data from each eligible trial. Any discrepancies will be resolved by consensus or adjudication from another review author (JHT). When we encounter multiple publications for the same trial, we will choose the first publication reporting the primary endpoint in this review as a study identifier (study ID).

We will extract the following data.

- Study details: study design, randomisation protocol, number of study centres, location, study setting, date of study, duration of study, duration of follow-up period.
- Characteristics of participants: inclusion and exclusion criteria, sample size (total and by arm), age, sex, stage, severity of condition, diagnostic criteria, smoking status, comorbidities, previous treatments, histology, PD-L1 expression.
- Characteristics of interventions: detail of interventions, e.g. choice and dosing schedule of immune checkpoint inhibitors and chemotherapies.
- Outcomes: primary and secondary outcomes with definitions and time points.
- Results: number of participants allocated to each group, the total number analysed for each outcome, summary data for each group, and whether analyses have been performed by intention-to-treat (ITT) or per-protocol methods.
- Miscellaneous: funding source.

If we identify cross-over RCTs, we will use the data reported before the cross-over (if reported separately). If we identify cluster-RCTs, we will use the data from such studies after adjusting the design effect. We will calculate the design effect by 1 + (M − 1) ICC, where M is the average cluster size and ICC is the intracluster correlation coefficient (Higgins 2021).

Assessment of risk of bias in included studies

Two review authors (YG, ML) will independently assess risk of bias of the included studies using the Cochrane risk of bias tool (Higgins 2011). Any disagreements will be resolved by discussion with a third review author (JHT). We will assess, at the outcome level, the risk of bias for the blinding of outcome assessment domain. Overall, we will assess the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other potential bias.

We will assign a rating of low, high, or unclear risk of bias for each risk of bias domain for each included study. We will report the results in a risk of bias graph and risk of bias summary. When interpreting treatment effects and meta-analyses, we will take into account the risk of bias for the studies that contribute to that outcome.

Measures of treatment effect

We will analyse time-to-event outcomes (DFS and OS) using the hazard ratio (HR) and corresponding 95% confidence intervals (CIs). We will extract HR and associated variances directly from the trial publications. If these are not reported, we will attempt to estimate the log (HR) and its standard error indirectly using the methods described by Parmar 1998 and Tierney 2007.

We will express dichotomous outcomes (pathological complete response, overall rates of any adverse events and serious adverse events) using risk ratio (RR) and corresponding 95% CIs.

We will express continuous outcomes (HRQoL) using mean differences (MD) (if trials measured outcomes on the same scale) or standardised mean differences (SMD) (if trials measured outcomes on different scales) with 95% CIs.

For the purposes of data extraction, we will give preference to data derived from ITT analysis than to per-protocol analysis.

Unit of analysis issues

For studies comparing two or more intervention groups and the same control group, we will halve the control group to allow a comparison with each of the two intervention groups. Similarly, for studies comparing one intervention group to two or more control groups, we will divide the intervention group as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Dealing with missing data

When possible, we will contact the authors of the included trials by email to obtain missing data. For trials in which we are unable to retrieve missing data, we will perform sensitivity analyses by excluding trials assessed as having a high risk of attrition bias.

Assessment of heterogeneity

We will assess heterogeneity using the Chi^2 test and the I^2 statistic (Cochran 1954; Higgins 2003). For the I^2 statistic, a value of 25% to 50% may represent mild heterogeneity, 50% to 75% moderate heterogeneity, and 75% considerable heterogeneity (Higgins 2021). If we identify heterogeneity between trials, we will explore possible sources through subgroup analyses and sensitivity analyses. If there is clinical heterogeneity, we will not conduct meta-analyses but will provide a narrative description of the results of each study as outlined in Chapter 12 of the *Cochrane Handbook* (McKenzie 2019). Otherwise, we will use the random-effects model to perform meta-analyses.

Assessment of reporting biases

If at least 10 studies are included in a meta-analysis, we will explore investigating reporting by using funnel plot asymmetry (Higgins 2021). Where possible, we will compare eligible trials and corresponding protocols to assess outcome reporting bias.

Data synthesis

We will perform meta-analyses with data based on ITT analysis when possible. We will synthesise adjuvant and neoadjuvant studies separately. We will use the random-effects model for meta-analyses.

- For dichotomous outcomes, we will estimate pooled RRs and 95% CIs using the DerSimonian and Laird random method (DerSimonian 1986). For eligible trials with zero events in only a single arm, we will use the continuity correction method; for eligible trials with zero events in double arms, we will estimate risk differences (RDs).
- For continuous outcomes, we will estimate pooled MD or SMD and 95% CIs using the inverse-variance method.
- For time-to-event data, we will pool HRs using the inverse-variance method.

We will perform meta-analyses using Review Manager Web (RevMan Web 2022), following the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

If outcomes data cannot be synthesised using meta-analyses, we will apply the Synthesis Without Meta-analysis (SWiM) approach as outlined in Chapter 12 of the *Cochrane Handbook* (McKenzie 2019). We will perform a narrative synthesis of results and present findings in tables. We will present the outcomes and results, organised by intervention categories according to the major types or aims of the identified interventions, or both.

Subgroup analysis and investigation of heterogeneity

If sufficient data are available, we will consider the following factors for subgroup analyses.

- PD-1 inhibitors or PD-L1 inhibitors.
- PD-L1 status: positive versus negative.
- Age < 65 or ≥ 65.
- Eastern Cooperative Oncology Group (ECOG) score 0 or 1.
- Duration of intervention.

Sensitivity analysis

If adequate data are available, we will perform sensitivity analyses to assess the robustness of the results. We will conduct sensitivity analyses by excluding studies:

- at high risk of bias (i.e. at high risk for at least one risk of bias domain);
- with unpublished data;
- with missing data;
- where there are different definitions of DFS across studies;
- with cross-over, cluster-RCT, or quasi-RCT design.

Summary of findings and assessment of the certainty of the evidence

Two review authors (YG, ML) will rate the certainty of the evidence for outcomes using the five GRADE considerations (risk of bias, inconsistency, imprecision, indirectness, and publication bias). We will rate the overall certainty of evidence as high, moderate, low, or very low.

We will include the following outcomes:

- pathological complete response;
- disease-free survival;
- overall survival;
- health-related quality of life;
- overall rates of adverse events.

We will use GRADEpro GDT software to develop the summary of findings tables (GRADEpro GDT).

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APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Breast Neoplasms] explode all trees
#2 triple negative breast near neoplasm*
#3 triple negative breast near carcinoma*
#4 triple negative breast near cancer*
#5 triple negative breast near tumour*
#6 triple negative breast near tumor*
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Immunotherapy] explode all trees
#9 MeSH descriptor: [Immune Checkpoint Inhibitors] explode all trees
#10 immunotherap*
#11 immune checkpoint inhibitor*
#12 PD-1 Inhibitor* or Programmed Cell Death Protein 1 Inhibitor*
#13 PD-L1 Inhibitor* or Programmed Death-Ligand 1 Inhibitor*
#14 MeSH descriptor: [Nivolumab] explode all trees
#15 nivolumab or pembrolizumab or lambrolizumab or pidilizumab or tislelizumab or atezolizumab or avelumab or durvalumab or cemiplimab or dostarlimab or spartalizumab or toripalimab
#16 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17 MeSH descriptor: [Antineoplastic Agents] explode all trees
#18 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees
#19 MeSH descriptor: [Antineoplastic Agents, Immunological] explode all trees
#20 MeSH descriptor: [Neoadjuvant Therapy] explode all trees
#21 MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees
#22 chemoimmunotherap*
#23 #17 or #18 or #19 or #20 or #21 or #22
#24 #16 and #23
#25 #7 and #24 in Trials

Appendix 2. MEDLINE (via OvidSP) search strategy

#	Searches
1	exp Breast Neoplasms/
2	exp Triple Negative Breast Neoplasms/

(Continued)

3	Triple Negative Breast cancer$.tw.
4	Triple Negative Breast neoplasm$.tw.
5	Triple Negative Breast carcinoma$.tw.
6	Triple Negative Breast tumo?r$.tw.
7	or/1-6
8	exp Immunotherapy/
9	immunotherap*.tw.
10	exp Immune Checkpoint Inhibitors/
11	immune checkpoint inhibitor*.tw.
12	PD-1 Inhibitor*.mp.
13	PD-L1 Inhibitor*.mp.
14	Programmed Cell Death Protein 1 Inhibitor*.mp.
15	Programmed Death-Ligand 1 Inhibitor*.mp.
16	exp Nivolumab/
17	(nivolumab or Opdivo or MDX-1106 or MDX 1106 or ONO 4538 or ONO-4538).mp.
18	(pembrolizumab or MK-3475 or lambrolizumab or Keytruda or MK 3475 or Sch 900475 or SCH-900475).mp.
19	(pidilizumab or CT011 or CT-011).mp.
20	(tislelizumab or BGB-A317 or BGB A317).mp.
21	(atezolizumab or Tecentriq or MPDL 3280A or MPDL-3280A or MPDL3280A or RG 7446 or RG-7446).mp.
22	(avelumab or Bavencio or MSB-0010682 or MSB0010682 or MSB0010718C).mp.
23	(durvalumab or Imfinzi or MEDI 4736 or MEDI4736).mp.
24	(cemiplimab or REGN 2810 or REGN-2810 or REGN2810 or Libtayo).mp.
25	(dostarlimab or TSR-042 or "TSR 042" or WBP-285 or WBP 285 or Jemperli).mp.
26	(Spartalizumab or PDR001 or PDR-001 or NVP-LZV184 or NVP LZV184).mp.
27	(Toripalimab or JS001 or TAB001).mp.
28	or/8-27
29	chemoimmunotherap*.tw.

(Continued)

30	exp Antineoplastic Combined Chemotherapy Protocols/
31	exp Neoadjuvant Therapy/
32	exp Antineoplastic Agents/
33	exp Chemotherapy, Adjuvant/
34	exp Antineoplastic Agents, Immunological/
35	or/29-34
36	28 and 35
37	7 and 36
38	animals/ not humans/
39	37 not 38
40	randomized controlled trial.pt.
41	controlled clinical trial.pt.
42	randomized.ab.
43	placebo.ab.
44	Clinical Trials as Topic/
45	randomly.ab.
46	trial.ti.
47	(crossover or cross-over).tw.
48	Pragmatic Clinical Trials as Topic/
49	pragmatic clinical trial.pt.
50	or/40-49
51	39 and 50
52	limit 51 to yr="2005 -Current"

Appendix 3. Embase (via OvidSP) search strategy

#	Searches
1	exp breast cancer/

(Continued)

2	exp triple negative breast cancer/
3	Triple Negative Breast cancer$.tw.
4	Triple Negative Breast neoplasm$.tw.
5	Triple Negative Breast carcinoma$.tw.
6	Triple Negative Breast tumo?r$.tw.
7	or/1-6
8	exp immunotherapy/
9	exp cancer immunotherapy/
10	immunotherap*.tw.
11	exp immune checkpoint inhibitor/
12	immune checkpoint inhibitor*.tw.
13	PD-1 Inhibitor*.mp.
14	PD-L1 Inhibitor*.mp.
15	Programmed Cell Death Protein 1 Inhibitor*.mp.
16	Programmed Death-Ligand 1 Inhibitor*.mp.
17	exp nivolumab/
18	(nivolumab or Opdivo or MDX-1106 or MDX 1106 or ONO 4538 or ONO-4538).mp.
19	exp pembrolizumab/
20	(pembrolizumab or MK-3475 or lambrolizumab or Keytruda or MK 3475 or Sch 900475 or SCH-900475).mp.
21	exp pidilizumab/
22	(pidilizumab or CT011 or CT-011).mp.
23	exp tislelizumab/
24	(tislelizumab or BGB-A317 or BGB A317).mp.
25	exp atezolizumab/
26	(atezolizumab or Tecentriq or MPDL 3280A or MPDL-3280A or MPDL3280A or RG 7446 or RG-7446).mp.
27	exp avelumab/
28	(avelumab or Bavencio or MSB-0010682 or MSB0010682 or MSB0010718C).mp.

(Continued)

29	exp durvalumab/
30	(durvalumab or Imfinzi or MEDI 4736 or MEDI4736).mp.
31	exp cemiplimab/
32	(cemiplimab or REGN 2810 or REGN-2810 or REGN2810 or Libtayo).mp.
33	exp dostarlimab/
34	(dostarlimab or TSR-042 or "TSR 042" or WBP-285 or WBP 285 or Jemperli).mp.
35	exp spartalizumab/
36	(Spartalizumab or PDR001 or PDR-001 or NVP-LZV184 or NVP LZV184).mp.
37	exp toripalimab/
38	(Toripalimab or JS001 or TAB001).mp.
39	or/8-38
40	exp antineoplastic agent/
41	exp neoadjuvant therapy/
42	exp adjuvant chemotherapy/
43	exp immunological antineoplastic agent/
44	chemoimmunotherap*.tw.
45	or/40-44
46	39 and 45
47	7 and 46
48	Randomized controlled trial/
49	Controlled clinical study/
50	Random$.ti,ab.
51	randomization/
52	intermethod comparison/
53	placebo.ti,ab.
54	(compare or compared or comparison).ti.
55	(open adj label).ti,ab.
56	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

(Continued)

57	double blind procedure/
58	parallel group$1.ti,ab.
59	(crossover or cross over).ti,ab.
60	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
61	(assigned or allocated).ti,ab.
62	(controlled adj7 (study or design or trial)).ti,ab.
63	(volunteer or volunteers).ti,ab.
64	trial.ti.
65	or/48-64
66	47 and 65
67	limit 66 to (human and embase and yr="2005 -Current")
68	remove duplicates from 67

Appendix 4. WHO ICTRP search strategy

Basic searches:

1. Triple negative breast cancer AND immune checkpoint inhibitor*

2. Triple negative breast cancer AND immunotherap*

Advanced searches:

1. Condition:triple negative breast cancer OR triple negative breast neoplasm

Intervention: immune checkpoint inhibitor*

Recruitment status: All

2. Condition: triple negative breast cancer OR triple negative breast neoplasm

Intervention: immunotherap*

Recruitment status:All

3. Condition: triple negative breast cancer OR triple negative breast neoplasm

Intervention: PD-1 inhibitor* OR PD-L1 inhibitor* OR Programmed Cell Death Protein 1 inhibitor* OR Programmed Death-Ligand 1 inhibitor* OR nivolumab OR pembrolizumab OR lambrolizumab OR pidilizumab OR tislelizumab OR atezolizumab OR avelumab OR durvalumab OR cemiplimab OR dostarlimab OR Spartalizumab OR Toripalimab

Recruitment status: All

4. Condition: triple negative breast cancer OR triple negative breast neoplasm

Intervention: Opdivo OR MDX-1106 OR ONO-4538 OR MK-3475 OR Keytruda OR SCH-900475 OR CT-011 OR BGB-A317 OR MPDL-3280A OR RG-7446 OR Bavencio OR MSB-0010682 OR MSB0010718C OR Imfinzi OR MEDI4736 OR REGN-2810 OR Libtayo OR TSR-042 OR WBP-285 OR Jemperli OR PDR-001 OR NVP-LZV184 OR JS001 OR TAB001

Recruitment status: All

Appendix 5. ClinicalTrials.gov search strategy

Basic searches:

1. Condition or disease: Triple negative breast cancer

Other terms: immune checkpoint inhibitor OR immune checkpoint inhibitors

2. Condition or disease: Triple negative breast cancer

Other terms: immunotherapy OR immunotherapies

Advanced searches:

1. Condition or disease: Triple negative breast cancer OR triple negative breast neoplasm

Intervention/treatment: PD-1 inhibitor OR PD-1 inhibitors OR PD-L1 inhibitor OR PD-L1 inhibitors OR Programmed Cell Death Protein 1 inhibitor OR Programmed Cell Death Protein 1 inhibitors OR Programmed Death-Ligand 1 inhibitor OR Programmed Death-Ligand 1 inhibitors

Study type: All studies

2. Condition or disease: Triple negative breast cancer OR triple negative breast neoplasm

Intervention/treatment: nivolumab OR pembrolizumab OR lambrolizumab OR pidilizumab OR tislelizumab OR atezolizumab OR avelumab OR durvalumab OR cemiplimab OR dostarlimab OR Spartalizumab OR Toripalimab

Study type: All studies

3. Condition or disease: Triple negative breast cancer OR triple negative breast neoplasm

Intervention/treatment: Opdivo OR MDX-1106 OR ONO-4538 OR MK-3475 OR Keytruda OR SCH-900475 OR CT-011 OR BGB-A317 OR MPDL-3280A OR RG-7446 OR Bavencio OR MSB-0010682 OR MSB0010718C

Study type: All studies

4. Condition or disease: Triple negative breast cancer OR triple negative breast neoplasm

Intervention/treatment: Imfinzi OR MEDI4736 OR REGN-2810 OR Libtayo OR TSR-042 OR WBP-285 OR Jemperli OR PDR-001 OR NVP-LZV184 OR JS001 OR TAB001

Study type: All studies

CONTRIBUTIONS OF AUTHORS

YG and JHT designed and drafted the protocol. All authors reviewed and approved the final version of the protocol.

For the review:
Study selection: YG, ML, LL
Extract data from studies: YG, ML, LL
Enter data into RevMan: YG, ML
Carry out the analysis: YG, LL, JZ
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Disagreement resolution: JHT
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YG: none known
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LL: none known
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