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Efficacy and Safety of First-line Therapy in Patients with Triple Negative Advanced Breast Cancer：A network Meta-analysis of Randomized Controlled Trials

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Citation
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REVIEW TITLE AND BASIC DETAILS

Review title
Efficacy and Safety of First-line Therapy in Patients with Triple Negative Advanced Breast Cancer：A network Meta-analysis of Randomized Controlled Trials

Condition or domain being studied
Advanced Breast Cancer; Triple-negative breast cancer; Immunotherapy; First Line Treatment

Rationale for the review
Triple-negative breast cancer (TNBC) is an aggressive subtype with limited treatment options and poor prognosis in the advanced setting . The first-line treatment landscape is evolving. Immunotherapy combined with chemotherapy, based on the KEYNOTE-355 trial, has become a standard-of-care for patients with PD-L1 positive (CPS≥10) metastatic TNBC . However, benefits are largely confined to this biomarker-selected population, and primary or acquired resistance remains a significant challenge .

Recently, novel targeted therapeutic strategies have emerged showing promise. These include, for example, oral Selective Estrogen Receptor Degraders (SERD) combined with mTOR inhibitors and PAM pathway inhibitors, which may offer new mechanisms to overcome resistance.

Currently, there is a lack of head-to-head randomized controlled trials (RCTs) directly comparing these novel regimens with each other and with established immunotherapy-chemotherapy combinations. Therefore, the relative efficacy and safety ranking of these diverse treatment options for first-line TNBC are unclear for clinicians and patients.

This systematic review will conduct a network meta-analysis (NMA) to synthesize both direct and indirect evidence from available RCTs. The aim is to quantitatively compare all relevant interventions and generate a hierarchy of their relative effectiveness (e.g., on PFS and ORR) and safety, using surface under the cumulative ranking curve (SUCRA) values. The findings will provide crucial evidence to inform clinical decision-making and guide future research priorities.

Review objectives

Primary Objective:

- To systematically compare and rank the relative efficacy and safety of all available first-line systemic treatments for advanced triple-negative breast cancer (TNBC), including immunotherapy-chemotherapy combinations, oral SERD with mTOR inhibitor regimens, PAM inhibitor-based regimens, and standard chemotherapy, through a Bayesian network meta-analysis.

Secondary Objectives:

- To generate a hierarchy of these treatments for the key efficacy endpoints of progression-free survival (PFS) and ORR, as well as for safety (incidence of grade ⩾3 adverse events), using surface under the cumulative ranking curve (SUCRA) probabilities.
- To provide quantitative estimates of the comparative effects (e.g., hazard ratios, odds ratios) for all possible pairwise comparisons between the included interventions.
- To conduct subgroup analyses, if feasible, to investigate the robustness of findings in clinically relevant subgroups, such as patients stratified by PD-L1 expression status.
- To assess the quality and consistency of the evidence contributing to the network meta-analysis.

Keywords

Advanced breast cancer; Triple negative breast cancer; First-line treatment; Network Meta-Analysis

Country

China

ELIGIBILITY CRITERIA

Population

Included

1. phase II or III clinical studies of all Triple Negative ABC undergoing first-line treatment, 2. RCTs with at least two treatment arms, 3. abstracts reported by San Antonio Breast Cancer Symposiums (SABCS), American Society of Clinical Oncology (ASCO), and European Society

for Medical Oncology (ESMO), 4. studies included at least one type of following data: PFS, objective response rate (ORR), adverse events of grade 3 or higher (⩾3 AEs).

Intervention(s) or exposure(s)

Included
Chemotherapy; Pembrolizumab

Comparator(s) or control(s)

Included
PICO tags selected: Placebo; Chemotherapy

Study design
Only randomized study types will be included.

Included
The review of clinical effectiveness will include only RCTs.

Context
1. phase II or III clinical studies of all Triple Negative ABC undergoing first-line treatment, 2. RCTs with at least two treatment arms, 3. abstracts reported by San Antonio Breast Cancer Symposiums (SABCS), American Society of Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO), 4. studies included at least one type of following data: PFS, objective response rate (ORR), adverse events of grade 3 or higher (⩾3 AEs).

TIMELINE OF THE REVIEW

Date of first submission to PROSPERO
29 October 2025

Review timeline
Start date: 29 October 2025. End date: 30 June 2026.

Date of registration in PROSPERO
29 October 2025

AVAILABILITY OF FULL PROTOCOL

Availability of full protocol
A full protocol has not been written.

SEARCHING AND SCREENING

Search for unpublished studies
Only published studies will be sought.

Main bibliographic databases that will be searched
The main databases to be searched are *CENTRAL - Cochrane Central Register of Controlled Trials*, *Embase.com* and *PubMed*.

Search language restrictions
The review will only include studies published in English.

Search date restrictions
There are no search date restrictions.

Other methods of identifying studies
Other studies will be identified by: *contacting authors or experts*, *reference list checking (backward citation searching)*, *searching conference proceedings*, *searching dissertation and thesis databases* and *searching trial or study registers*.

Link to search strategy
A full search strategy is available in the full protocol as described in the *Availability of full protocol* section

Selection process
Studies will be screened independently by at least two people (or person/machine combination) with a process to resolve differences.

Other relevant information about searching and screening
None

DATA COLLECTION PROCESS

Data extraction from published articles and reports
Data will be extracted independently by at least two people (or person/machine combination) with a process to resolve differences.

Authors will be asked to provide any required data not available in published reports.

Study datasets/IPD will be obtained from study investigators or via a data repository

Study risk of bias or quality assessment
Risk of bias will be assessed using: *Cochrane RoB-1* and *Cochrane RoB-2*

Data will be assessed independently by at least two people (or person/machine combination) with a process to resolve differences.

Additional information will be sought from study investigators if required information is unclear or unavailable in the study publications/reports.

Reporting bias assessment
We will assess the risk of reporting bias, including publication bias and selective outcome reporting, at both the study and outcome synthesis levels.

Publication Bias: For pairwise comparisons where 10 or more trials are available, we will use funnel plots to visually inspect for asymmetry.

Certainty assessment
The certainty of the evidence for each pairwise comparison within the network meta-analysis will be assessed using the GRADE approach for NMA , operationalized through the CINeMA framework.

1. Assessment Domains: We will evaluate the evidence across six domains:

◦ Within-study bias (risk of bias): Based on the Cochrane RoB 2.0 tool assessment of the individual RCTs contributing to the comparison.

◦ Reporting bias: We will use contour-enhanced funnel plots to explore the potential for small-study effects and publication bias for comparisons where a sufficient number of studies (e.g., ⩾10) are available.

◦ Indirectness: We will judge the relevance of the included populations, interventions, and outcomes to our review question (PICOS).

◦ Imprecision: We will evaluate the width of the 95% credible intervals (CrI) for the effect estimates against a pre-specified clinical decision threshold.

◦ Heterogeneity: We will assess the variability in treatment effects across studies contributing to a specific comparison.

◦ Incoherence (also known as inconsistency): We will evaluate the disagreement between direct and indirect evidence for the same comparison using node-splitting methods.

2. Judgment and Summary: For each comparison-outcome pair (e.g., Immunotherapy vs. Chemotherapy for PFS), the evidence will be initially rated as 'High' (as it originates from RCTs) and then potentially downgraded by one or more levels (to 'Moderate', 'Low', or 'Very Low') based on the assessments in the above domains. A summary of findings table for the most critical comparisons and outcomes will be created to present the final certainty ratings.

OUTCOMES TO BE ANALYSED

Main outcomes
progression free survival, overall survival, objective response rate, adverse events

Additional outcomes
progression combined with adverse events

PLANNED DATA SYNTHESIS

Strategy for data synthesis
We categorize drugs of the same type into one category. For example: Avelumab, Atezolizumab, Durvalumab, Envafolimab and Pembrolizumab categorize as PD-L1. Paclitaxel, Gemcitabine, and Carboplatin are classified as chemotherapy drugs.

CURRENT REVIEW STAGE

Stage of the review at this submission

Review stage	Started	Completed
Pilot work	✓	✓
Formal searching/study identification	✓	
Screening search results against inclusion criteria		

Review stage	Started	Completed
Data extraction or receipt of IPD		
Risk of bias/quality assessment		
Data synthesis		

Review status
The review is currently planned or ongoing.

Publication of review results
Results of the review will be published in English.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members
Mr junxiao Wang (review guarantor and contact) the second hospital of sanming. China.

No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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Funding source
Review has no specific/external funding but is supported by guarantor/review team (non-commercial) institutions.

Peer review
There has been no peer review of this planned review.

ADDITIONAL INFORMATION

Review conflict of interest
Declared individual interests are recorded under team member details.. No additional interests are recorded for this review.

Medical Subject Headings
Triple Negative Breast Neoplasms; Breast Neoplasms; Network Meta-Analysis; Progression-Free Survival; Immunotherapy

SIMILAR REVIEWS

Check for similar records already in PROSPERO

PROSPERO identified a number of existing PROSPERO records that were similar to this one (last check made on 29 October 2025). These are shown below along with the reasons given by that the review team for the reviews being different and/or proceeding.

- Assessing the efficacy and safety of first-line immunotherapy for metastatic triple-negative breast cancer : Systematic review and network meta-analysis based on RCT studies, focusing on PD-L1 expression [published 3 September 2025] [CRD420251138714]. The review was judged **not to be similar**
- Comparative Efficacy and Safety of PD-1 Inhibitor with Concurrent Chemotherapy as First-Line Treatment for Unresectable Locally Advanced, HER2-negative Gastric or Gastroesophageal Junction Cancer: A Systematic Review and Bayesian Network Meta-Analysis [published 8 June 2025] [CRD420251066976]. The review was judged **not to be similar**
- Efficacy and safety of first line treatments for patients with advanced triple negative breast cancer: a systematic review and network meta-analysis [published 20 December 2020] [CRD42020221864]. The review was acknowledged as **similar** but the authors opted to continue because *the review will be more up to date*, *the review looks at additional or different outcomes*, *the review uses improved methods*
- Efficacy and safety of platinum-based chemotherapy regimens as first-line therapy for metastatic triple-negative breast cancer: a meta-analysis of randomised controlled trials [published 5 July 2020] [CRD42020190209]. The review was judged **not to be similar**
- Efficacy and Safety Evaluation of Immunotherapy Combinations in Advanced Triple-Negative Breast Cancer: A Network Meta-Analysis [published 6 April 2025] [CRD420251007571]. The review was judged **not to be similar**

PROSPERO version history

- Version 1.0, published 29 Oct 2025

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