INPLASY

Different targeted therapies combined with adjuvant chemotherapy on clinical remission, survival and safety in patients with triple-negative breast cancer (TNBC): a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 September 2025 and was last updated on 23 September 2025.

INTRODUCTION

Review question / Objective To systematically review the efficacy of chemotherapy combined with targeted therapy in the handling of advanced triple-negative breast cancer(TNBC).

Condition being studied Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer characterized by the absence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) amplification. TNBC accounts for approximately 15–20% of all breast cancers and is more prevalent among younger women and certain ethnic groups, such as African American women. The lack of these receptor targets limits the effectiveness of conventional hormonal therapies and HER2-targeted treatments, making chemotherapy the current standard systemic option.

Clinically, TNBC is associated with rapid progression, a higher rate of metastasis, and poorer overall prognosis compared to other breast cancer subtypes. The median survival for patients with advanced or metastatic TNBC remains dismal, often less than two years, despite aggressive treatment. Recurrence typically occurs within the first three to five years after diagnosis, and therapeutic resistance is a common challenge.

Given these limitations, there is growing interest in integrating targeted therapies with chemotherapy to improve treatment outcomes. Targeted therapies aim to disrupt specific molecular pathways involved in tumor growth and survival, such as angiogenesis (via VEGF inhibitors), DNA damage repair (PARP inhibitors), and immune checkpoint signaling. The rationale for combining these agents with chemotherapy is to enhance cytotoxic efficacy, prolong progression-free survival, and improve overall survival while minimizing toxicity.

The clinical evidence regarding this combined approach remains evolving. Several trials have investigated the addition of targeted agents to standard chemotherapy regimens in TNBC, with variable outcomes. While some studies suggest improved response rates and survival benefits, concerns about heterogeneity, limited sample sizes, and potential publication bias remain. As such, a systematic review and meta-analysis is needed to comprehensively evaluate the efficacy and safety of chemotherapy combined with targeted therapy in patients with advanced TNBC.

METHODS

Participant or population The population of interest in this review will be adult patients diagnosed with advanced or metastatic triple-negative breast cancer (TNBC). Participants are defined as individuals with histologically or cytologically confirmed breast cancer that is negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression.

Eligible participants include both female and male patients, although TNBC predominantly affects women. There will be no restrictions on ethnicity, geographic location, or menopausal status. Patients may have received prior systemic treatments, such as chemotherapy, but those included must have been enrolled in clinical controlled studies directly comparing chemotherapy combined with targeted therapy versus chemotherapy alone.

The review will focus on studies involving individuals with advanced, recurrent, or metastatic disease, as these populations face limited therapeutic options and poorer prognoses. Patients with early-stage TNBC will not be included, as the treatment strategies and outcomes differ significantly in that setting.

Intervention The intervention of interest in this review is chemotherapy combined with targeted therapy for the treatment of advanced or metastatic triple-negative breast cancer (TNBC).

Chemotherapy: Standard cytotoxic chemotherapy agents commonly used in TNBC management, such as anthracyclines, taxanes, platinum-based agents, or other recognized regimens for advanced disease.

Targeted therapy: Agents designed to interfere with specific molecular pathways involved in tumor growth, proliferation, and survival. These may include, but are not limited to:

PARP inhibitors (e.g., olaparib, talazoparib) targeting DNA damage repair pathways, particularly in patients with BRCA1/2 mutations.

Anti-angiogenic agents (e.g., bevacizumab) targeting vascular endothelial growth factor (VEGF) to inhibit tumor angiogenesis.

Other investigational targeted therapies, such as EGFR inhibitors, PI3K/AKT/mTOR inhibitors, or immune checkpoint inhibitors if used in combination with chemotherapy in controlled studies.

The intervention group will consist of TNBC patients receiving chemotherapy plus at least one targeted agent, while the comparator group will be those treated with chemotherapy alone. The review aims to determine whether the addition of targeted therapy improves clinical outcomes such as progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and disease control rate (DCR), without significantly increasing treatment-related adverse events.

Comparator The comparative intervention for this review will be chemotherapy alone, administered according to standard treatment protocols for advanced or metastatic triple-negative breast cancer (TNBC).

This may include single-agent or combination regimens such as:

Anthracyclines (e.g., doxorubicin, epirubicin)

Taxanes (e.g., paclitaxel, docetaxel)

Platinum-based agents (e.g., cisplatin, carboplatin)

Other conventional cytotoxic agents used in clinical practice for TNBC

The comparator group provides a baseline for evaluating whether the addition of targeted therapy to chemotherapy offers measurable improvements in survival and response outcomes, while also allowing assessment of any differences in treatment-related toxicity.

Study designs to be included This review will include randomized controlled trials (RCTs) and clinical controlled studies that directly compare chemotherapy combined with targeted therapy versus chemotherapy alone in patients with

advanced or metastatic triple-negative breast cancer. Only studies with clear outcome reporting on survival, response rates, or adverse events will be considered. Case reports, reviews, and observational studies without a control group will be excluded.

Eligibility criteria Additional Inclusion and Exclusion Criteria

Inclusion criteria:

Studies published in peer-reviewed journals.

Articles available in English or Chinese.

Studies providing sufficient data for extraction of primary or secondary outcomes (e.g., overall survival, progression-free survival, response rates, or adverse events).

Full-text availability.

Exclusion criteria:

Abstracts, conference proceedings, reviews, meta-analyses, case reports, and letters without original data.

Duplicate publications of the same study; in such cases, only the most complete or recent dataset will be included.

Studies lacking a clear comparator group (chemotherapy alone).

Preclinical, animal, or in vitro studies.

Information sources A comprehensive search strategy will be employed to identify relevant studies. The following electronic databases will be systematically searched from their inception to the present:

PubMed/MEDLINE

EMBASE

ScienceDirect

Cochrane Library

Chinese medical databases (such as CNKI, Wanfang, and VIP)

In addition, clinical trial registries (e.g., ClinicalTrials.gov, WHO International Clinical Trials Registry Platform [ICTRP]) will be consulted to identify ongoing or unpublished trials.

To minimize publication bias, grey literature sources will also be screened, including conference abstracts, dissertations, and reports, provided sufficient outcome data are available. References from relevant systematic reviews and included studies will be manually checked to identify additional eligible publications.

Where necessary, authors of primary studies may be contacted to obtain missing or incomplete data.

The search strategy will not be limited by publication year but will be restricted to English and Chinese language studies. All identified records will be imported into reference management software, and duplicates will be removed prior to screening.

Main outcome(s) The primary outcomes of this review will include:

Overall Survival (OS): Time from initiation of treatment to death from any cause, reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

Progression-Free Survival (PFS): Time from initiation of treatment to documented disease progression or death, assessed by HRs with 95% CIs.

Secondary outcomes will include:

Objective Response Rate (ORR): Proportion of patients achieving complete or partial tumor response, expressed as risk ratios (RRs) or odds ratios (ORs).

Disease Control Rate (DCR): Combined proportion of patients with complete response, partial response, or stable disease.

Adverse Events (AEs): Incidence and severity of treatment-related toxicities, classified by the Common Terminology Criteria for Adverse Events (CTCAE) where reported.

Timing of outcome measurement will be based on individual study follow-up periods, with subgroup analyses performed if sufficient data are available. Outcomes will be pooled using meta-analytic methods to estimate overall effect sizes.

Quality assessment / Risk of bias analysis Quality Assessment

The methodological quality and risk of bias of the included primary studies will be independently assessed by two reviewers. Disagreements will be resolved through discussion or consultation with a third reviewer.

For randomized controlled trials (RCTs), the Cochrane Risk of Bias Tool (version 5.3) will be applied. The following domains will be evaluated:

Random sequence generation (selection bias)

Allocation concealment (selection bias)

Blinding of participants and personnel (performance bias)

Blinding of outcome assessment (detection bias)

Incomplete outcome data (attrition bias)

Selective outcome reporting (reporting bias)

Other potential sources of bias

Each domain will be rated as “low risk,” “high risk,” or “unclear risk.”

For non-randomized controlled studies, the Newcastle-Ottawa Scale (NOS) will be used, focusing on three aspects:

Selection of study groups

Comparability of cohorts

Outcome assessment and adequacy of follow-up

Studies will be graded based on the number of stars awarded, with higher scores reflecting better methodological quality.

The overall quality of evidence across outcomes will be further evaluated using the GRADE approach (Grading of Recommendations, Assessment, Development, and Evaluation), considering study limitations, consistency of results, directness of evidence, precision, and risk of publication bias.

The results of the quality assessment will be presented in both tabular and narrative form to provide transparency in how study reliability was judged.

Strategy of data synthesis Data Analysis

All statistical analyses will be performed using RevMan 5.3 software (The Cochrane Collaboration). Extracted outcome data will be pooled for meta-analysis when studies are sufficiently homogenous in design, participants, interventions, and outcome measures.

Effect Measures:

For time-to-event outcomes (overall survival [OS], progression-free survival [PFS]), results will be expressed as hazard ratios (HRs) with 95% confidence intervals (CIs).

For dichotomous outcomes (objective response rate [ORR], disease control rate [DCR], adverse events), pooled results will be presented as risk ratios (RRs) or odds ratios (ORs) with 95% CIs.

For continuous variables, weighted mean differences (WMD) with 95% CIs will be calculated.

Assessment of Heterogeneity:
Statistical heterogeneity across studies will be assessed using the Chi-squared (χ^2) test and quantified with the I^2 statistic. An I^2 0.05 will be considered low heterogeneity, and a fixed-effect model will be applied. If $I^2 \geq 50\%$ and $P < 0.05$, a random-effects model will be used. When heterogeneity remains high and cannot be explained, a narrative/descriptive synthesis will be performed.

Subgroup and Sensitivity Analyses:
Where data allow, subgroup analyses will be conducted based on:

Type of targeted therapy (e.g., PARP inhibitors, VEGF inhibitors, immune checkpoint inhibitors)

Type of chemotherapy regimen

Patient characteristics (e.g., age, treatment line, disease stage)

Sensitivity analyses will be performed by sequentially excluding studies with high risk of bias or small sample sizes to test the robustness of pooled results.

Publication Bias:
Potential publication bias will be assessed visually using funnel plots and statistically using Egger’s test ($P < 0.1$ indicating bias). Where bias is detected, the Trim and Fill method will be applied to adjust pooled estimates.

Data Presentation:

Forest plots will be generated for each pooled analysis to illustrate effect sizes and confidence intervals. All analyses will follow PRISMA guidelines to ensure transparency and reproducibility.

Subgroup analysis Where sufficient data are available, subgroup analyses will be conducted to explore potential sources of heterogeneity and to assess differential treatment effects. Planned subgroups include:

Type of targeted therapy – e.g., immune checkpoint inhibitors (atezolizumab, pembrolizumab), VEGF inhibitors (apatinib, bevacizumab), PARP inhibitors, or other targeted agents.

Chemotherapy regimen – single-agent vs. combination chemotherapy; specific agents such as capecitabine, paclitaxel, or carboplatin.

Line of treatment – first-line, second-line, or third-line/above therapy.

Disease stage and burden – early metastatic versus advanced/refractory disease.

Patient characteristics – including age (<60 vs. ≥60 years), performance status, and menopausal status where reported.

These subgroup analyses will help identify whether certain populations derive greater benefit from combination therapy and clarify treatment effects in different clinical contexts. Results will be interpreted cautiously, as subgroup comparisons may have limited statistical power.

Sensitivity analysis Sensitivity analyses will be performed to assess the robustness and reliability of the pooled results. These analyses will include:

Study Quality – Reanalyzing outcomes after excluding studies with high risk of bias or low methodological quality scores (e.g., low Newcastle–Ottawa Scale ratings).

Sample Size – Excluding small-sample studies to determine their influence on overall effect estimates.

Statistical Models – Comparing results obtained from fixed-effect versus random-effects models when heterogeneity is present.

Outcome Reporting – Excluding studies with incomplete or unclear reporting of primary outcomes (e.g., missing HRs or CIs).

Publication Bias Adjustment – Applying the Trim and Fill method to evaluate the impact of potential unpublished studies on pooled estimates.

If substantial differences are observed between the main analysis and sensitivity analyses, results will be interpreted with caution, and potential reasons for discrepancies will be discussed.

Country(ies) involved The study was conducted in China, with all authors affiliated with The First People's Hospital of Jiujiang, Jiangxi Province.

Keywords Targeted therapy; Chemotherapy; Triple-negative breast cancer; Clinical response rate; Safety Analysis.

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