

Efficacy and Safety of Androgen Receptor Pathway-Targeted Therapies in AR-Positive Triple-Negative Breast Cancer: A Systematic Review and Meta-Analysis

Qiang Liu

Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University

Zhiyu Wu

wuzhy239@mail2.sysu.edu.cn

Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University

Zhijing Liang

Peking University Third Hospital

Research Article

Keywords: Androgen receptor, Triple-negative breast cancer, AR pathway-targeted therapy, Single-arm proportional meta-analysis, Clinical benefit rate

Posted Date: October 20th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10998076/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background:

Androgen receptor (AR)-positive triple-negative breast cancer (TNBC) represents a distinct molecular subtype driven by androgen signaling. However, existing clinical evidence is largely limited to small, early-phase single-arm trials with inconsistent endpoint definitions. This systematic review and meta-analysis evaluates the clinical activity and safety profile of AR pathway-targeted therapies in patients with AR-positive TNBC.

Methods:

PubMed, Embase, Web of Science, the Cochrane Library, and ClinicalTrials.gov were systematically searched from database inception through February 2026. Quantitative synthesis focused on patients with advanced or metastatic disease, using a random-effects generalized linear mixed model to pool objective response rates (ORR) and clinical benefit rates (CBR) at standardized timepoints (16 weeks and 6 months). Neoadjuvant studies were evaluated qualitatively.

Results:

Eleven studies met inclusion criteria (10 in advanced/metastatic settings, 1 neoadjuvant). Across nine advanced-disease studies (296 patients), the pooled ORR was 5.4% (95% CI: 3.3%–8.6%; $I^2 = 0.0\%$). Standardized CBR was 30.7% (95% CI: 24.3%–37.9%) at 16 weeks (176 patients across 5 studies) and 19.6% (95% CI: 11.2%–32.1%) at 6 months (56 patients across 2 studies). In the neoadjuvant setting, 16.7% of patients achieved a pathological complete response. Safety outcomes were synthesized narratively due to varied reporting definitions.

Conclusion:

AR pathway-targeted therapies demonstrate limited direct tumor shrinkage but achieve durable disease control in nearly one-third of patients at standardized intervals. Given the reliance on small single-arm trials with varying AR positivity cutoffs, these findings represent signals of clinical activity rather than direct proof of superiority over standard treatments.

1. Introduction

Breast cancer remains one of the most prevalent malignancies among women globally. Accounting for approximately 11.6% of all new global cancer cases in 2022, its overall disease burden continues to be substantial (Bray et al., 2024). Triple-negative breast cancer (TNBC), defined by the lack of estrogen receptor, progesterone receptor, and HER2 expression, comprises roughly 12% to 17% of all breast cancer cases. Although recent years have witnessed an expanding therapeutic armamentarium, including immunotherapies, poly(ADP-ribose) polymerase (PARP) inhibitors, and antibody-drug conjugates (ADCs), TNBC exhibits profound molecular and clinical heterogeneity. Consequently, there remains an urgent, unmet clinical need for more precise biomarkers and actionable therapeutic targets in patients with advanced or metastatic disease (Bianchini et al., 2022).

Transcriptomic analysis has stratified TNBC into several molecular subtypes with unique biological features, among which the luminal androgen receptor (LAR) subtype is uniquely driven by AR-associated transcriptional networks (Lehmann et al., 2016, 2011). LAR tumors typically display luminal-like gene expression profiles alongside relatively low proliferation indices, resulting in lower pathological complete response rates to neoadjuvant chemotherapy than those observed in basal-like counterparts (Lehmann et al., 2016; Ravaoli et al., 2022; Thompson et al., 2022). Compared to other breast cancer subtypes, TNBC often has a relatively low frequency of AR expression; only 12% of TNBC patients express AR (Castellano et al., 2013; Gonzalez-Angulo et al., 2009; Gucalp et al., 2013; Loibl et al., 2011; Park et al., 2011; Peters et al., 2009, 2012; Tsutsumi, 2012). Prior studies have employed heterogeneous nuclear staining thresholds, ranging from $> 0\%$ and $\geq 1\%$ to $\geq 10\%$, thereby confounding patient selection criteria and limiting cross-study comparability (Barton et al., 2015; You et al., 2022).

Grounded in this biological rationale, various AR pathway-targeted strategies have entered clinical evaluation. These include direct AR antagonists, CYP17/androgen synthesis inhibitors, selective androgen receptor modulators (SARMs), and combination regimens incorporating immune checkpoint inhibitors, CDK4/6 inhibitors, or chemotherapy. Early clinical trials investigating bicalutamide, abiraterone, and enzalutamide demonstrated modest objective responses accompanied by durable disease stabilization (Bonnet et al., 2016; Gucalp et al., 2013; Traina et al., 2018). Subsequently, studies evaluating enobosarm plus pembrolizumab, neoadjuvant enzalutamide combined with paclitaxel, and the START trial have further expanded the exploration of combination platforms and biomarker-guided patient

enrichment(Bonnefoi, 2025; Jiang et al., 2022; Lim et al., 2024; Yuan et al., 2021). Nevertheless, the existing evidence base is limited by small sample sizes and a predominance of single-arm designs. Crucially, reported clinical benefit rates (CBR) have been evaluated across inconsistent timepoints (e.g., 8 weeks, 16 weeks, 24 weeks, or 6 months); directly pooling these disparate endpoints into a generic "overall CBR" or "disease control rate (DCR)" introduces significant clinical ambiguity.

To address these knowledge gaps, this systematic review and meta-analysis aims to evaluate the clinical efficacy and safety of AR pathway-targeted therapies in patients with AR-positive TNBC. Specifically, we sought to derive precise pooled estimates for objective response rate (ORR) and timepoint-standardized CBR in advanced or metastatic settings, while conducting exploratory analyses to dissect the influence of therapeutic regimens, AR positivity cutoffs, and evidence sources.

2. Materials and Methods

2.1. Reporting Guidelines and Protocol Registration

This meta-analysis was designed and reported in accordance with the PRISMA 2020 guidelines(Page et al., 2021), and the protocol was registered with PROSPERO (CRD420261469091). As this study is a meta-analysis of previously published, publicly available data, individual patient-level data were not accessed, and no primary data collection was performed. Accordingly, ethical committee approval and individual informed consent were not required.

2.2. Search Strategy

A comprehensive, systematic search was conducted across PubMed, Embase, Web of Science, the Cochrane Library (including CENTRAL) and ClinicalTrials.gov from database inception through February 2026. The search string integrated three primary concept domains: triple-negative breast cancer (TNBC), androgen receptor (AR), and specific AR pathway-targeted agents (including bicalutamide, enzalutamide, abiraterone, darolutamide, proxalutamide, seviteronel, orteronel, and enobosarm). Reference lists of included studies and relevant review articles were manually screened to identify additional eligible citations. Furthermore, conference proceedings from the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and San Antonio Breast Cancer Symposium (SABCS) were systematically evaluated; conference abstracts were included only if endpoint definitions, event numbers, and exact denominators were explicitly obtainable. The full search strategy for PubMed Embase, Web of Science, the Cochrane Library and ClinicalTrials.gov is detailed in Appendix 1.

2.3. Eligibility Criteria

Studies that met the following inclusion criteria were eligible for inclusion in this meta-analysis: Population (P): Patients confirmed TNBC classified as AR-positive according to criteria specified in studies. Primary quantitative syntheses were restricted to advanced, recurrent, unresectable, or metastatic disease. Cohorts consisting predominantly ($\geq 90\%$) of TNBC, or studies with extractable TNBC subgroup data, were eligible. Early-stage or neoadjuvant cohorts were evaluated separately and excluded from advanced-disease pooled syntheses. Intervention (I): AR pathway-targeted therapies, encompassing direct AR antagonists, CYP17/androgen synthesis inhibitors, selective AR modulators (SARMs), and combination incorporating immune checkpoint inhibitors, CDK4/6 inhibitors, or chemotherapy. Comparator (C): Comparator groups were not required for single-arm proportional meta-analyses. For randomized or comparative studies, data from the AR-targeted intervention arm were extracted for proportional pooling, while control arm data were retained and reported separately to preserve randomization integrity. Outcomes (O): The primary efficacy outcome was objective response rate (ORR), defined as the proportion of patients achieving complete response (CR) or partial response (PR) according to RECIST criteria. The primary clinical benefit endpoint was 16-week clinical benefit rate (CBR₁₆; defined as the proportion of patients achieving CR + PR + stable disease (SD) durable to 16 weeks); 6-month CBR (CBR_{6m}) was pooled separately. Other endpoints, 24-week CBR, 8-week disease control rate (DCR), timepoint-undefined DCR, 6-month progression-free survival (PFS) rate, neoadjuvant pathological complete response (pCR), and pCR combined with Residual Cancer Burden class I (pCR + RCB-I), were reported separately. PFS and OS were synthesized narratively owing to the reliance on median estimates with incomplete confidence intervals. Safety outcomes were categorized into treatment-related adverse events (trAEs), treatment-related grade ≥ 3 AEs, and serious adverse events (SAEs). Study Design (S): Prospective phase I/II single-arm trials, non-comparative randomized phase II trials, extractable experimental arms from randomized controlled trials (RCTs), and eligible conference abstracts reporting precise event counts.

The following studies were excluded: 1)Non-original publications, basic science or animal studies, duplicate reports, case reports or editorials; 2) mixed-population cohorts lacking dedicated data for AR-positive TNBC, studies missing event counts or denominators, and studies with outcome definitions incompatible with our pre-specified endpoints; 3) non-English publications.

2.4. Data Extraction and quality assessment

Two researchers independently extracted the necessary information and appraised the quality of the included studies. They extracted author, publication year, country/region, design, clinical setting, enrolled and evaluable sample sizes, age, prior lines of systemic therapy, AR antibody clone and positivity threshold, therapeutic regimen, efficacy outcome definitions and timepoints, event/denominator counts, as well as clinical and safety outcomes such as ORR, DCR, OS, PFS, and grade 3 or higher AEs or serious adverse events (SAEs).

Single-arm studies were critically appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series (Munn et al., 2020), with items rated as "Yes", "No", "Unclear", or "Not Applicable" (avoiding arbitrary composite score summation). For the randomized START trial, risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool across five standard domains (Sterne et al., 2019). Unreported details in conference abstracts were categorized as "Unclear" rather than defaulted to low risk.

2.5. Statistical Analysis

All statistical analyses were executed in STATA 15.1 software (StataCorp LP, College Station, TX, USA) and R 4.4.1 using the meta (version 8.2-1) and metafor packages. Single-arm proportional data were pooled using a binomial-normal random-effects generalized linear mixed model (GLMM) with a logit link function. Study-level 95% confidence intervals (CIs) were derived using the Clopper-Pearson exact method. No continuity correction was applied to studies with zero events. A random-effects model was pre-specified for all pooled analyses and was not altered based on statistical heterogeneity testing.

Statistical heterogeneity was quantified using τ^2 , I^2 , and the Cochran's Q test. In accordance with contemporary evidence-synthesis guidelines, I^2 was interpreted in the context of study number, effect magnitude, and clinical heterogeneity, rather than relying on rigid mechanical thresholds. Where at least three studies contributed to a synthesis, 95% prediction intervals (PIs) were calculated.

Exploratory subgroup analyses were performed according to treatment strategy (monotherapy vs. combination therapy), AR positivity threshold ($\geq 10\%$ vs. lower/mixed thresholds), and publication format (full-text articles vs. conference abstracts). Sensitivity analyses were conducted by restricting the synthesis to TNBC cohorts, full-text publications, monotherapy regimens, studies with evaluable sample sizes ≥ 10 . Because fewer than 10 studies contributed to each meta-analyzed outcome, quantitative publication bias assessments (funnel plots, Egger's test, and trim-and-fill analysis) were omitted. PFS, OS, and heterogeneous safety endpoints were synthesized narratively.

3. Results

3.1. Study Selection

Initially, 224 studies were retrieved from PubMed (n = 106), Embase (n = 27), Web of Science (n = 24), and the Cochrane Library (n = 27) and ClinicalTrials.gov (n = 40). After removing duplicates, 142 unique records were screened. Based on title and abstract screening, 16 articles were retained for full-text evaluation. Following detailed full-text review, 5 articles were excluded due to missing data or data unavailability. Ultimately, 10 studies met the eligibility criteria and the randomized START trial were separately reported. The detailed study selection flowchart is illustrated in the PRISMA flow diagram (Fig. 1).

3.2. Baseline Characteristics

The 11 included reports were published between 2013 and 2025, comprising 10 studies in the advanced or metastatic setting and 1 in the neoadjuvant setting. Seven studies were published as full-text peer-reviewed articles, whereas four were available only as conference abstracts. Among the 10 advanced-setting studies, seven evaluated monotherapy or endocrine-like regimens, and three evaluated combination strategies with immunotherapy or CDK4/6 inhibitors. The 11 included studies comprised a total of 326 patients. Regarding biomarker criteria, eight studies employed an androgen receptor (AR) nuclear staining cutoff of $\geq 10\%$ (or $> 10\%$), two utilized $\geq 1\%$, and one applied variable thresholds across different trial phases. (Bonnefoi, 2025; Bonnefoi et al., 2016; Gucaip, 2020, 2017; Gucaip et al., 2013; Jiang et al., 2022; Knight-Shefner, 2025; Lim et al., 2024; Traina et al., 2018; Yardley et al., 2021; Yuan et al., 2021) Study designs, treatment regimens, and outcome definitions are detailed in Table 1.

Table 1
Baseline characteristics of the studies included in the meta-analysis.

Study	Study Design	Study Design	Sample Size	Age	Previous lines of treatment	Therapeutic Intervention	AR Cut-off & Antibody Clone	Primary Endpoints
Gucalp et al. (2013)	Phase II single-arm; Advanced/metastatic	International multicenter	28/26	66 (41–83)	Median 1 line (0–8)	Bicalutamide 150 mg daily	> 10% nuclear staining; AR441	CBR at 6 months
Bonnefoi et al. (2016)	Phase II single-arm; Advanced/metastatic	France	34/30	62.5 (39–86)	Median 2.5 lines (0–9)	Abiraterone 1000 mg daily plus prednisone 5 mg twice daily	>=10% nuclear staining	CBR at 6 months
Traina et al. (2018)	Phase II single-arm; Advanced/metastatic	International multicenter	118/78	57 (32–85)	Median 1 line (0–7)	Enzalutamide 160 mg daily	> 0% for enrollment; >=10% for evaluable subgroup; SP107	CBR at 16 weeks
Yuan et al. (2021)	Phase II single-arm; Advanced/metastatic	USA	18/16	64 (36–81)	At least 1 line; 44% had at least 2	Enobosarm 18 mg daily plus pembrolizumab 200 mg every 3 weeks	>=10% and 1 + IHC; SP107	ORR and CBR at 16 weeks
Jiang et al. (2022)	Phase Ib open-label dose expansion; Advanced/metastatic	China multicenter	45/13	54 (34–79)	Median 3 lines (1–13)	Proxalutamide 200 or 300 mg daily	>=1% nuclear staining	DCR at 8 and 16 weeks
Lim et al. (2024)	Phase II single-arm; Neoadjuvant	USA	24/24	57.5 (39–74)	Neoadjuvant AC before study treatment	Enzalutamide 120 mg daily plus weekly paclitaxel 80 mg/m ²	>=10% AR IHC	pCR and pCR plus RCB-I
Bonnefoi et al. (2025)	Non-comparative randomized phase II; Advanced/metastatic	France and Belgium	61/58	60 (56–70)	No more than 1 prior chemotherapy line	Darolutamide 600 mg twice daily	>=10% nuclear staining; SP107	CBR at 16 weeks
Yardley et al. (2021)	Phase II single-arm; Advanced/metastatic	USA	26/26	57 (33–92)	1–3 chemotherapy regimens for metastatic disease	Orteronel 300 mg twice daily	>=10% central IHC	ORR and DCR
Gucalp et al. (2017)	Phase II stage 1 single-arm; Advanced/metastatic	Multicenter	16/6	Not reported	60% had at least 2 prior lines for advanced disease	Seviteronel 450 mg daily	>=10% central IHC	CBR at 16 weeks
Gucalp et al. (2020)	Phase I/II single-arm; Advanced/metastatic	USA	33/31	67 (42–79)	Median 3 lines (0–9)	Bicalutamide 150 mg daily plus palbociclib 125 mg days 1–21	>=1%; AR441 then SP107	6-month PFS
Knight-Shefner et al. (2025)	Phase I/II single-arm; Advanced/metastatic	USA	21/18	56 (37–75)	No more than 3 prior systemic therapy lines	Bicalutamide 150 mg daily plus ribociclib 600 mg days 1–21	> 0% in phase I and >= 10% in phase II	CBR at 16 weeks

AR, androgen receptor; BC, breast cancer; CBR, clinical benefit rate; DCR, disease control rate; ER, estrogen receptor; IHC, immunohistochemistry; LAR, luminal androgen receptor; MBC, metastatic breast cancer; NR, not reported; ORR, objective response rate; pCR, pathological complete response; PFS, progression-free survival; PgR, progesterone receptor; RCB, residual cancer burden; TNBC, triple-negative breast cancer.

3.3. Risk of Bias

Across the 10 non-randomized studies, a total of 100 Joanna Briggs Institute (JBI) items were appraised, yielding 71 "Yes" ratings, 29 "Unclear" ratings, and zero "No" ratings. All studies adequately described inclusion criteria and primary outcomes; however, consecutive patient enrollment was not explicitly confirmed in any report. Among full-text publications, 52 of 60 items (86.7%) were rated as "Yes", compared with only 19 of 40 items (47.5%) in conference abstracts, where uncertainties primarily pertained to consecutive/complete sampling, details of diagnostic and statistical methods, and clinical setting descriptions. For the randomized START trial, Cochrane RoB 2 assessment demonstrated a low risk of bias in randomization, outcome measurement, and selective reporting; however, concerns regarding its open-label design, per-protocol analysis, and minor missing efficacy data resulted in an overall judgment of "some concerns" (Fig. 2).

3.4. Objective Response Rate (ORR)

The ORR synthesis included 9 studies comprising 296 evaluable patients, among whom 16 achieved a complete response (CR) or partial response (PR). Using a random-effects generalized linear mixed model (GLMM), the pooled ORR was 5.4% (95% CI: 3.3%–8.6%), with $\tau^2=0.000$, $I^2=0.0\%$, and a Cochran's Q-statistic of 6.78 (df = 8, P = 0.561). The 95% prediction interval (PI) ranged from 3.1% to 9.4% (Fig. 3).

In exploratory subgroup analyses, the pooled ORR was 5.2% (95% CI: 3.0%–8.9%) for monotherapy and 6.2% (95% CI: 2.3%–15.3%) for combination regimens. Studies applying an AR cutoff of $\geq 10\%$ yielded a pooled ORR of 6.0%, compared with 3.2% in those using lower or mixed thresholds. Given the limited number of studies per subgroup and clinical variations in treatment regimens, these subgroup findings should be interpreted cautiously as hypothesis-generating (Supplementary Figure S1). Sensitivity analyses restricted to strict TNBC cohorts, full-text publications, monotherapy regimens, or excluding the START trial consistently yielded pooled ORRs between 5.2% and 5.9%. Leave-one-out sensitivity analyses yielded pooled ORR estimates ranging from 4.6% to 5.9% (Supplementary Figures S2, S4).

3.5. Benefit Rates

Five studies including 176 patients contributed to the 16-week clinical benefit rate (CBR_{16}) analysis, with 54 patients achieving CR, PR, or stable disease (SD) sustained for at least 16 weeks. The pooled (CBR_{16}) was 30.7% (95% CI: 24.3%–37.9%), with $\tau^2=0.000$, $I^2=0.0\%$, Cochran's Q = 0.65 (df = 4, P = 0.957), and a 95% prediction interval of 21.9%–41.1% (Fig. 4A).

The 6-month clinical benefit rate (CBR_{6m}) analysis included 2 studies with 56 patients, among whom 11 experienced clinical benefit; the pooled (CBR_{6m}) was 19.6% (95% CI: 11.2%–32.1%), with $\tau^2=0.000$, $I^2=0.0\%$, and Cochran's Q = 0.005 (df = 1, P = 0.942) (Fig. 4B).

Subgroup analyses for (CBR_{16}) demonstrated a pooled rate of 31.7% in the monotherapy subgroup and 26.5% in the combination subgroup; full-text publications and conference abstracts yielded pooled rates of 30.9% and 29.2%, respectively. Sensitivity analyses restricted to full-text publications, studies with evaluable sample sizes $n < 10$, monotherapy regimens, and excluding the START trial showed consistent estimates ranging from 30.6% to 31.7%. Leave-one-out sensitivity analyses yielded pooled rates between 28.6% and 31.4% (Supplementary Figures S3, S4). While supporting the stability of the primary findings, these analyses remain exploratory.

3.6. Clinical Efficacy and Survival Outcomes

Disease control outcomes evaluated at non-standardized timepoints were not pooled with CBR_{16} or CBR_{6m} . Specifically, Traina et al. reported a 24-week CBR (CBR_{24}) of 22/78; Jiang et al. reported an 8-week disease control rate (DCR_8) of 5/13 in TNBC subgroup; Yardley et al. reported a timepoint-undefined DCR of 4/26; and Gucaip et al. reported a 6-month PFS rate of 11/33. In the randomized START trial, the darolutamide arm demonstrated a CBR_{16} of 17/58 and an ORR of 3/58, whereas the capecitabine arm showed 19/32 and 4/32, respectively; given its non-comparative randomized phase II design, no superiority inferences were drawn. In the neoadjuvant trial by Lim et al., the pathological complete response (pCR) rate was 4/24, and the rate of pCR combined with Residual Cancer Burden class I (pCR + RCB-I) was 10/24 (Table 2).

Table 2
Other clinical active outcomes that were not combined

Study	Endpoints	Outcome ratio	Data processing
Traina et al. (2018)	CBR at 24 weeks	22/78 (28.2%)	Different time points, separate reports
Jiang et al. (2022)	DCR at 8 weeks	5/13 (38.5%)	Different definition, separate reports
Yardley et al. (2021)	DCR, duration not specified	4/26 (15.4%)	Duration not defined, separate reports
Gucalp et al. (2020)	6-month PFS	11/33 (33.3%)	Different definition, separate reports
Lim et al. (2024)	pCR; pCR + RCB-I	4/24 (16.7%); 10/24 (41.7%)	Neoadjuvant chemotherapy, separate reports
Bonnefoi et al. (2025)	Capecitabine comparator: CBR; ORR	19/32 (59.4%); 4/32 (12.5%)	Retain the comparison arms information, separate reports

CBR, clinical benefit rate; DCR, disease control rate; ORR, objective response rate; pCR, pathological complete response; RCB, residual cancer burden.

Across six advanced-setting studies, median progression-free survival (PFS) predominantly ranged from 1.9 to 3.3 months, while four studies reported median overall survival (OS) ranging from 10.2 to 25.5 months. Quantitative pooling for survival endpoints was precluded due to the reliance on median estimates with incomplete confidence intervals, lack of comparative control arms, and absence of hazard ratios (HRs).

3.7. AEs

Substantial reporting heterogeneity was observed for safety endpoints: some studies reported treatment-related adverse events (TRAEs), whereas others presented all-cause AEs or TRAEs. Furthermore, grade ≥ 3 AEs and serious adverse events (SAEs) were not used interchangeably, and studies presenting itemized specific AEs created potential double-counting of individual patients. Consequently, pooled overall incidence rates for all-grade or grade ≥ 3 AEs were not generated; instead, original denominators and definitions were retained on a study-by-study basis (Table 3).

Table 3
Meta-analysis of adverse events.

AE	Study	(I ² ,p)	Rate, 95%CI
Fatigue	10	43.5%, p = 0.07	0.32 (0.25, 0.39)
Hot flushes	4	29.7%, p = 0.23	0.15 (0.10, 0.22)
Elevatedamino transferases	3	61.7%, p = 0.07	0.09 (0.03, 0.25)
Nausea	6	27.3%, p = 0.23	0.27 (0.21, 0.33)
Appetite loss	4	88.1%, p < 0.01	0.42 (0.11, 0.81)
Diarrhea	3	76.9%, p = 0.01	0.11 (0.03, 0.34)
Anemia	2	0%, p = 0.87	0.05 (0.02, 0.14)
Leukopenia	4	92%, p < 0.01	0.45 (0.09, 0.86)
Neutropenia	4	91.2%, p < 0.01	0.40 (0.08, 0.84)
Serious adverse events	4	20.1%, p = 0.29	0.09 (0.05, 0.16)
Lymphocyte reduction	2	84.1%, p = 0.01	0.35 (0.10, 0.73)
Thrombocytopenia	2	81%, p = 0.02	0.21 (0.05, 0.61)
Febrile neutropenia	2	94.3%, p < 0.01	0.30 (0.00, 0.98)
Grade 3–4 AEs	11	82.1%, p < 0.01	0.23 (0.12, 0.39)

Overall, single-agent AR pathway-targeted therapies were predominantly characterized by fatigue, nausea, hot flashes, and elevated transaminases. Conversely, combination platforms incorporating CDK4/6 inhibitors exhibited higher frequencies of leukopenia and neutropenia. Given the marked variations in regimen composition, causality attribution criteria, and evaluable safety denominators, the

available evidence does not support a definitive conclusion that overall severe toxicity associated with AR pathway-targeted therapy remains below any specific fixed threshold.

4. Discussion

The pooled findings from this systematic review and meta-analysis demonstrate a clinical response pattern which characterized by a low ORR coexisting with a substantial CBR among patients with AR-positive TNBC receiving AR pathway-targeted therapies. The pooled quantitative synthesis revealed a modest overall ORR of only 5.4%, whereas the 16-week clinical benefit rate (CBR₁₆) reached 30.7%, with the 6-month CBR (CBR_{6m}) maintaining a level of 19.6%. This paradoxical clinical phenomenon directly mirrors the distinct indolent biology inherent to the luminal androgen receptor (LAR) molecular subtype of TNBC. As a ligand-dependent nuclear transcription factor, activated AR translocates to the nucleus upon androgen binding to drive the transcription of target genes regulating cell cycle progression. The primary pharmacological mechanism of direct AR antagonists (e.g., bicalutamide, enzalutamide, darolutamide, and proxalutamide) and androgen synthesis inhibitors (e.g., abiraterone) evaluated in this study lies in the competitive inhibition of ligand binding. By suppressing the downstream Cyclin D/CDK4/6/Rb signaling axis, these agents induce G₁ phase cell cycle arrest and impede transition into the S phase. Consequently, their clinical activity predominantly manifests as effective tumor growth containment and durable stable disease (SD), rather than rapid tumor shrinkage (complete response [CR] or partial response [PR]) driven by mass apoptosis (Ma et al., 2025). Conventional ORR metrics, which rely strictly on volumetric tumor regression, thus suffer from intrinsic limitations when capturing the efficacy of cytostatic endocrine-based interventions.

A granular interpretation of these discordant findings requires a deep dive into the complex biological heterogeneity of TNBC. LAR tumors characteristically exhibit luminal-like differentiation with expression of luminal lineage genes, accompanied by relatively low Ki-67 and lower histological grades, culminating in a clinically sluggish, biologically indolent trajectory (Syrniti et al., 2025). Most studies have shown that AR expression is associated with favorable characteristics such as improved recurrence-free survival, overall survival, response to endocrine therapy and chemotherapy, older age at diagnosis, lower tumor grade, lower Ki67 positivity, smaller tumor volume, and less necrosis. (Honma et al., 2012; Ntziifa et al., 2021; Park et al., 2011; Ricciardi et al., 2015; Söiland et al., 2008) In contrast to highly proliferative basal-like subtypes that display pronounced acute sensitivity to neoadjuvant chemotherapy (high pathological complete response [pCR] rates) but suffer early lethal relapses if pCR is not achieved (Harrell et al., 2012), LAR TNBC tumors exhibit marked intrinsic resistance to conventional cytotoxic neoadjuvant regimens, with pCR rates typically ranging between 10% and 21% (Santonja et al., 2018). Paradoxically, this very proliferative indolence aligns synergistically with long-term, low-toxicity AR pathway-targeted therapy. In patients whose tumors are genuinely driven by androgen signaling, AR blockade may convert advanced TNBC into a chronic, manageable disease state akin to hormone receptor-positive luminal breast cancer, thereby conferring sustained disease control.

Nevertheless, the principal bottleneck hindering the successful clinical translation of AR-targeted regimens remains the lack of standardized AR diagnostic criteria and the marked heterogeneity in defining positivity cutoffs. Across the clinical trials included in this meta-analysis, immunohistochemical (IHC) cutoffs for AR positivity varied widely from $\geq 10\%$ to $\geq 1\%$. While permissive staining thresholds aim to broaden the eligible patient population, they inevitably introduce a substantial proportion of non-LAR tumors (such as basal-like or immunomodulatory subtypes) that display weak, non-functional AR staining. The oncogenic drivers in these tumors are independent of the AR transcriptional network, rendering AR pathway blockade therapeutically ineffective.

Robust translational evidence supporting this paradigm shift was provided by the recent randomized phase II START trial (UCBG 3–06) published in *The Lancet Oncology*. Although the overall trial failed to meet its primary efficacy endpoint for darolutamide in IHC-defined ($\geq 10\%$) advanced TNBC, post-hoc transcriptomic stratification demonstrated that in patients classified as molecular apocrine-high (MA-high, reflecting genuine high-level "ARness" pathway activation), the 16-week CBR reached 57%, compared with merely 16% in the MA-low subgroup. These findings align with the TBCRC 032 trial evaluating taselisib plus enzalutamide, where patients with Lehmann-defined LAR subtype TNBC achieved significantly superior CBR₁₆ (75.0% vs. 12.5%) and median progression-free survival (4.6 vs. 2.0 months) compared with non-LAR subtypes, whereas raw IHC staining percentages showed no correlation with clinical response (Lehmann et al., 2011). Taken together, relying solely on IHC protein positivity introduces an unacceptably high false-positive rate. Future companion diagnostics must transition from simple "AR expression percentage" to multidimensional precision molecular assessment frameworks, incorporating transcriptomic signature profiling, splice variant (e.g., AR-SVs) detection, and circulating tumor cell-derived multigene AR activity signatures, to accurately identify true "ARness" dependence.

Beyond the imperative for refined biomarker selection, heterogeneity in therapeutic trial designs exerted a substantial influence on pooled efficacy outcomes. While single-agent AR blockade exhibits durable disease control in a subset of highly androgen-dependent tumors, the rapid activation of compensatory bypass pathways, such as transcriptional activation of the PI3K/AKT/mTOR axis and bypass of cell cycle checkpoints, frequently leads to secondary resistance and attenuated late-phase benefit. To overcome these limitations, clinical development

has increasingly pivoted toward rational combination platforms (Ghidini et al., 2026). Given the high frequency of PI3K pathway alterations (approximately 40%–65%) across TNBC and specifically within the LAR subtype, dual inhibition with the AR antagonist enzalutamide and the PI3K inhibitor taselisib in TBCRC 032 achieved a pooled CBR₁₆ of 35.7% while effectively suppressing reactive feedback activation (Lehmann et al., 2020). Furthermore, leveraging the dependency of LAR cell cycle machinery on an intact Rb pathway, the TBCRC-BRE15-024 trial explored bicalutamide combined with the CDK4/6 inhibitor trilaciclib, achieving a disease control rate (CBR₁₆) of 50% at the recommended phase II dose (Hu et al., 2021). Similarly, Yuan et al. evaluated the selective androgen receptor modulator (SARM) enobosarm combined with pembrolizumab to remodel the immunosuppressive tumor microenvironment and enhance immune responsiveness [27]. Thus, therapeutic heterogeneity and the biological necessity of combination platforms to intercept bypass resistance constitute the core mechanisms underlying the clinical variability observed in this meta-analysis.

Finally, the clinical utility of AR-targeted therapies demonstrated herein must be contextualized within several intrinsic methodological limitations. The primary evidence base comprised predominantly early-phase, single-arm, non-randomized trials with modest sample sizes (evaluable populations ranging between 6 and 78 patients), precluding direct comparative superiority inferences and introducing potential selection and publication biases. Although statistical heterogeneity metrics (I^2) were estimated at 0.0%, this should not be overinterpreted as true clinical homogeneity, as it primarily reflects limited statistical power due to small study numbers and sample sizes. Moreover, due to inconsistent safety reporting definitions across trials, quantitative pooling of adverse events was omitted, limiting precision in defining the absolute toxicity profile.

In the contemporary treatment landscape where frontline chemo-immunotherapy (KEYNOTE-355) and second-line antibody-drug conjugates (ADCs, such as sacituzumab govitecan and trastuzumab deruxtecan) yield overwhelming survival benefits, AR-targeted therapy perhaps unsuitable as a first-line cytoreductive option for patients requiring rapid tumor shrinkage to relieve high tumor burden or achieve surgical conversion. Nevertheless, owing to the safety profile of single-agent AR inhibitors and the convenience of oral administration, this strategy occupies a unique clinical niche. AR pathway-targeted therapy may be positioned as a maintenance option for patients with non-visceral crisis, LAR subtype advanced disease, or as a late-line, quality-of-life-preserving palliative strategy for elderly or patients with poor performance status who are unable to tolerate conventional cytotoxic chemotherapy.

5. Conclusion

Our systematic review and meta-analysis demonstrates that AR-targeted blockade has significantly improved clinical outcomes, acquired resistance driven by AR alterations, parallel pathways, and lineage plasticity remains a primary challenge. Overcoming these bottlenecks requires shifting from sequential monotherapies toward biomarker-guided combination strategies. Standardizing AR testing protocols and validating predictive biomarkers in prospective trials remain critical to refining risk stratification and guiding personalized treatment plans in precision oncology.

6. Critical View

This meta-analysis delivers a systematic quantitative synthesis evaluating androgen receptor (AR)-targeted therapies in AR-positive triple-negative breast cancer (AR+ TNBC). Encompassing 11 clinical trials (N = 326) across advanced, metastatic, and neoadjuvant settings, including AR antagonists, CYP17 inhibitors, and selective AR modulators (SARMs). By evaluating both conventional tumor shrinkage metrics (RECIST-defined ORR) and time-standardized endpoints (16-week and 6-month CBR), this review offers exhaustive coverage of the current clinical evidence landscape.

Unlike prior qualitative reviews or isolated single-arm trial reports, this study resolves a long-standing "clinical paradox" in subtype-specific TNBC management. While conventional literature mistakenly classified AR-targeted agents as inactive based on low objective response rates, our pooled analysis demonstrates robust disease stabilization (16-week CBR = 30.7%). This distinction highlights that AR pathway inhibition functions through cell-cycle arrest rather than acute apoptosis, aligning directly with the indolent nature of the Luminal AR (LAR) subtype.

We propose two critical shifts for future clinical development in AR+ TNBC. Firstly, regarding patient selection, standard immunohistochemistry (IHC ≥ 10%) is insufficient for precise stratification, requiring clinical eligibility to evolve toward transcriptomic "ARness" signatures that isolate true pathway-driven tumors. Secondly, from a therapeutic standpoint, single-agent AR blockade inherently hits a cytostatic ceiling, meaning future trial designs must emphasize rational combinations, such as dual AR inhibition paired with CDK4/6 or PI3K/mTOR pathway blockers, to bypass secondary resistance. Ultimately, by establishing CBR as the benchmark endpoint for endocrine-like therapies in TNBC, this review may redefine how targeted efficacy should be evaluated in AR+ TNBC.

Abbreviations

AR, Androgen Receptor;

BC, Breast cancer;

ER, Estrogen Receptor;

PR, Progesterone Receptor;

HER2, Human epidermal growth factor receptor;

AR, Androgen Receptor;

LAR, Luminal Androgen Receptor;

TNBC, Triple-negative breast cancer;

ER, Estrogen Receptor;

PR, Progesterone Receptor;

HER2, Human epidermal growth factor receptor;

LAR, Luminal Androgen Receptor;

TNBC, Triple-negative breast cancer;

ORR, Objective Response Rate;

CBR, Clinical Benefit Rate;

CBR₁₆, 16-week Clinical Benefit Rate;

CBR_{6m}, 6-month Clinical Benefit Rate;

RECIST, Response Evaluation Criteria in Solid Tumors;

ADC, Antibody-Drug Conjugate;

AE, Adverse Event;

ASCO, American Society of Clinical Oncology;

CDK4/6, Cyclin-Dependent Kinase 4/6;

CENTRAL, Cochrane Central Register of Controlled Trials;

CI, Confidence Interval;

CYP17, Cytochrome P450 17;

ESMO, European Society for Medical Oncology;

GLMM, Generalized Linear Mixed Model;

HR, Hazard Ratio;

IHC, Immunohistochemistry;

I², Heterogeneity Statistic;

JB, Joanna Briggs Institute;

MA, Molecular Apocrine;

mTOR, mammalian Target of Rapamycin;

PARP, Poly(ADP-ribose) Polymerase;

PI, Prediction Interval;

PI3K, Phosphoinositide 3-Kinase;

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses;

RCT, Randomized Controlled Trial;

Rb, Retinoblastoma Protein;

RoB 2, Risk of Bias 2;

SABCS, San Antonio Breast Cancer Symposium;

SAE, Serious Adverse Event;

SARM, Selective Androgen Receptor Modulator;

SD, Stable Disease;

TBCRC, Translational Breast Cancer Research Consortium;

TRAE, Treatment-Related Adverse Event;

τ^2 , au-squared

Declarations

CRedit authorship contribution statement

WZ: literature search, data curation, analysis and interpretation preparation of manuscript.

LZ: data curation, preparation of manuscript.

LQ: concept and design, overall supervision, editing of the final manuscript.

All authors read and approved the final version of the manuscript.

Ethics and consent

Not applicable.

Conflict of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics and consent

Not applicable.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Funding

This study was supported by the Noncommunicable Chronic Diseases-National Science and Technology Major Project (Grant No. 2025ZD0552502). The funder had no role in study design, data collection, systematic synthesis, data analysis, interpretation of data, writing

of the manuscript, or the decision to submit the paper for publication.

Author Contribution

WZ: literature search, data curation, analysis and interpretation preparation of manuscript. LZ: data curation, preparation of manuscript. LQ: concept and design, overall supervision, editing of the final manuscript. All authors read and approved the final version of the manuscript.

Acknowledgement

The authors gratefully acknowledge the financial support provided by the Noncommunicable Chronic Diseases-National Science and Technology Major Project (Grant No. 2025ZD0552502). The authors also express their sincere appreciation to all members and staff of the Breast Tumor Center, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University for their invaluable support throughout the study.

Data availability statement

The original contributions presented in the study include the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

References

1. Barton VN, D'Amato NC, Gordon MA, Christenson JL, Elias A, Richer JK. Androgen Receptor Biology in Triple Negative Breast Cancer: a Case for Classification as AR + or Quadruple Negative Disease. *Horm Cancer*. 2015;6:206–13. <https://doi.org/10.1007/s12672-015-0232-3>.
2. Bianchini G, De Angelis C, Licata L, Gianni L. Treatment landscape of triple-negative breast cancer - expanded options, evolving needs. *Nat Rev Clin Oncol*. 2022;19:91–113. <https://doi.org/10.1038/s41571-021-00565-2>.
3. Bonnefoi. 2025. Darolutamide or capecitabine in triple-negative, androgen receptor-positive, advanced breast cancer (UCBG 3–06 START): a multicentre, non-comparative, randomised, phase 2 trial - PubMed [WWW Document]. URL <https://pubmed.ncbi.nlm.nih.gov/39978376/> (accessed 3.25.26).
4. Bonnefoi H, Grellety T, Tredan O, Saghatchian M, Dalenc F, Mailliez A, L'Haridon T, Cottu P, Abadie-Lacourtoisie S, You B, Mousseau M, Dauba J, Del Piano F, Desmoulins I, Coussy F, Madranges N, Grenier J, Bidard FC, Proudhon C, MacGrogan G, Orsini C, Pulido M, Gonçalves A. A phase II trial of abiraterone acetate plus prednisone in patients with triple-negative androgen receptor positive locally advanced or metastatic breast cancer (UCBG 12 – 1). *Ann Oncol*. 2016;27:812–8. <https://doi.org/10.1093/annonc/mdw067>.
5. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74:229–63. <https://doi.org/10.3322/caac.21834>.
6. Castellano I, Chiusa L, Vandone AM, Beatrice S, Goia M, Donadio M, Arisio R, Muscarà F, Durando A, Viale G, Cassoni P, Sapino A. A simple and reproducible prognostic index in luminal ER-positive breast cancers. *Ann Oncol*. 2013;24:2292–7. <https://doi.org/10.1093/annonc/mdt183>.
7. Ghidini A, Bukovec R, Roncari L, Garassino I, Cribiù FM, Petrelli F. The role of androgen receptor and antiandrogen therapy in breast cancer: a scoping review. *Curr Oncol*. 2026;33:41. <https://doi.org/10.3390/curroncol33010041>.
8. Gonzalez-Angulo AM, Stemke-Hale K, Palla SL, Carey M, Agarwal R, Meric-Berstam F, Traina TA, Hudis C, Hortobagyi GN, Gerald WL, Mills GB, Hennessy BT. Androgen receptor levels and association with PIK3CA mutations and prognosis in breast cancer. *Clin Cancer Res*. 2009;15:2472–8. <https://doi.org/10.1158/1078-0432.CCR-08-1763>.
9. Gucalp. 2020. https://ascopubs.org/doi/10.1200/JCO.2020.38.15_suppl.1017 (accessed 3.26.26).
10. Gucalp. 2017. Phase (Ph) 2 stage 1 clinical activity of seviteronel, a selective CYP17-lyase and androgen receptor (AR) inhibitor, in women with advanced AR+ triple-negative breast cancer (TNBC) or estrogen receptor (ER) + BC: CLARITY-01. *Journal of Clinical Oncology*.
11. Gucalp A, Tolaney S, Isakoff SJ, Ingle JN, Liu MC, Carey LA, Blackwell K, Rugo H, Nabell L, Forero A, Stearns V, Doane AS, Danso M, Moynahan ME, Momen LF, Gonzalez JM, Akhtar A, Giri DD, Patil S, Feigin KN, Hudis CA, Traina TA. Translational Breast Cancer Research Consortium (TBCRC 011), 2013. Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic Breast Cancer. *Clin Cancer Res* 19, 5505–12. <https://doi.org/10.1158/1078-0432.CCR-12-3327>

12. Harrell JC, Prat A, Parker JS, Fan C, He X, Carey L, Anders C, Ewend M, Perou CM. Genomic analysis identifies unique signatures predictive of brain, lung, and liver relapse. *Breast Cancer Res Treat.* 2012;132:523–35. <https://doi.org/10.1007/s10549-011-1619-7>.
13. Honma N, Horii R, Iwase T, Saji S, Younes M, Ito Y, Akiyama F. Clinical importance of androgen receptor in breast cancer patients treated with adjuvant tamoxifen monotherapy. *Breast Cancer.* 2012. <https://doi.org/10.1007/s12282-012-0337-2>.
14. Hu Y, Gao J, Wang M, Li M. Potential Prospect of CDK4/6 Inhibitors in Triple-Negative Breast Cancer. *Cancer Manag Res.* 2021;13:5223–37. <https://doi.org/10.2147/CMAR.S310649>.
15. Jiang H, Ouyang Q, Yin Y, Tong Z, Shen K, Yuan Z, Geng C, Liu Y, Song G, Ran R, Li W, Qu Q, Wang M, Meng L, Tong Y, Li H. Proxalutamide in patients with AR-positive metastatic breast cancer: Results from an open-label multicentre phase Ib study and biomarker analysis. *Eur J Cancer.* 2022;176:1–12. <https://doi.org/10.1016/j.ejca.2022.08.025>.
16. Knight-Shefner. 2025. A phase I/II, single arm, non-randomized study of ribociclib, a CDK 4/6 inhibitor, in combination with bicalutamide, an androgen receptor inhibitor, in advanced AR-positive triple-negative breast cancer: A Big Ten Cancer Research Consortium Study [WWW Document]. URL <https://www.abstractsonline.com/pp8/#!/21392/presentation/1786> (accessed 4.7.26).
17. Lehmann BD, Abramson VG, Sanders ME, Mayer EL, Haddad TC, Nanda R, Van Poznak C, Storniolo AM, Nangia JR, Gonzalez-Ericsson PI, Sanchez V, Johnson KN, Abramson RG, Chen S-C, Shyr Y, Arteaga CL, Wolff AC, Pietenpol JA. Translational Breast Cancer Research Consortium, 2020. TBCRC 032 IB/II Multicenter Study: Molecular Insights to AR Antagonist and PI3K Inhibitor Efficacy in Patients with AR+ Metastatic Triple-Negative Breast Cancer. *Clin Cancer Res* 26, 2111–2123. <https://doi.org/10.1158/1078-0432.CCR-19-2170>
18. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, Pietenpol JA. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest.* 2011;121:2750–67. <https://doi.org/10.1172/JCI45014>.
19. Lehmann BD, Jovanović B, Chen X, Estrada MV, Johnson KN, Shyr Y, Moses HL, Sanders ME, Pietenpol JA. Refinement of triple-negative breast cancer molecular subtypes: implications for neoadjuvant chemotherapy selection. *PLoS ONE.* 2016;11:e0157368. <https://doi.org/10.1371/journal.pone.0157368>.
20. Lim B, Seth S, Yam C, Huo L, Fujii T, Lee J, Bassett R, Nasser S, Ravenberg L, White J, Clayborn A, Guerra G, Litton JK, Damodaran S, Layman R, Valero V, Tripathy D, Lewis M, Dobrolecki LE, Lei J, Candelaria R, Arun B, Rauch G, Zhao L, Zhang J, Ding Q, Symmans WF, Chang JT, Thompson AM, Moulder SL, Ueno NT. Phase 2 study of neoadjuvant enzalutamide and paclitaxel for luminal androgen receptor-enriched TNBC: trial results and insights into ARness. *Cell Rep. Med.* 2024;5:101595. <https://doi.org/10.1016/j.xcrm.2024.101595>.
21. Loibl S, Müller BM, von Minckwitz G, Schwabe M, Roller M, Darb-Esfahani S, Ataseven B, du Bois A, Fissler-Eckhoff A, Gerber B, Kulmer U, Alles J-U, Mehta K, Denkert C. Androgen receptor expression in primary breast cancer and its predictive and prognostic value in patients treated with neoadjuvant chemotherapy. *Breast Cancer Res Treat.* 2011;130:477–87. <https://doi.org/10.1007/s10549-011-1715-8>.
22. Ma L, Xu H, Wang C, Hu Y, Ren Q, Yu S. Advances of androgen receptor in triple-negative breast cancer: from molecular mechanisms to clinical applications. *Discov Oncol.* 2025;16:1677. <https://doi.org/10.1007/s12672-025-03431-0>.
23. Munn Z, Barker TH, Moola S, Tufanaru C, Stern C, McArthur A, Stephenson M, Aromataris E. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. *JBI Evid Synth.* 2020;18:2127–33. <https://doi.org/10.11124/JBISIR-D-19-00099>.
24. Ntzifa A, Strati A, Koliou G-A, Zagouri F, Pectasides D, Pentheroudakis G, Christodoulou C, Gogas H, Magkou C, Petraki C, Kosmidis P, Aravantinos G, Kotoula V, Fountzilas G, Lianidou E. Androgen Receptor and PIM1 Expression in Tumor Tissue of Patients With Triple-negative Breast Cancer. *Cancer Genomics Proteom.* 2021;18:147–56. <https://doi.org/10.21873/cgp.20249>.
25. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71. <https://doi.org/10.1136/bmj.n71>.
26. Park S, Koo JS, Kim MS, Park HS, Lee JS, Lee JS, Kim SI, Park BW, Lee KS. Androgen receptor expression is significantly associated with better outcomes in estrogen receptor-positive breast cancers. *Ann Oncol.* 2011;22:1755–62. <https://doi.org/10.1093/annonc/mdq678>.
27. Peters AA, Buchanan G, Ricciardelli C, Bianco-Miotto T, Centenera MM, Harris JM, Jindal S, Segara D, Jia L, Moore NL, Henshall SM, Birrell SN, Coetzee GA, Sutherland RL, Butler LM, Tilley WD. Androgen receptor inhibits estrogen receptor-alpha activity and is prognostic in breast cancer. *Cancer Res.* 2009;69:6131–40. <https://doi.org/10.1158/0008-5472.CAN-09-0452>.
28. Peters KM, Edwards SL, Nair SS, French JD, Bailey PJ, Salkield K, Stein S, Wagner S, Francis GD, Clark SJ, Brown MA. Androgen receptor expression predicts breast cancer survival: the role of genetic and epigenetic events. *BMC Cancer.* 2012;12:132. <https://doi.org/10.1186/1471-2407-12-132>.
29. Ravaioli S, Maltoni R, Pasculli B, Parrella P, Giudetti AM, Vergara D, Tumedei MM, Pirini F, Bravaccini S. Androgen receptor in breast cancer: The 5W questions. *Front Endocrinol (Lausanne).* 2022;13:977331. <https://doi.org/10.3389/fendo.2022.977331>.

30. Ricciardi GRR, Adamo B, Ieni A, Licata L, Cardia R, Ferraro G, Franchina T, Tuccari G, Adamo V. Androgen Receptor (AR), E-Cadherin, and Ki-67 as Emerging Targets and Novel Prognostic Markers in Triple-Negative Breast Cancer (TNBC) Patients. *PLoS ONE*. 2015;10:e0128368. <https://doi.org/10.1371/journal.pone.0128368>.
31. Santonja A, Sánchez-Muñoz A, Lluch A, Chica-Parrado MR, Albanell J, Chacón JI, Antolín S, Jerez JM, de la Haba J, de Luque V, Fernández-De Sousa CE, Vicioso L, Plata Y, Ramírez-Tortosa CL, Álvarez M, Llácer C, Zarcos-Pedrinaci I, Carrasco E, Caballero R, Martín M, Alba E. Triple negative breast cancer subtypes and pathologic complete response rate to neoadjuvant chemotherapy. *Oncotarget*. 2018;9:26406–16. <https://doi.org/10.18632/oncotarget.25413>.
32. Søiland H, Kørner H, Skaland I, Janssen EAM, Gudlaugsson E, Varhaug JE, Baak JPA, Søreide JA. Prognostic relevance of androgen receptor detection in operable breast cancer. *J Surg Oncol*. 2008;98:551–8. <https://doi.org/10.1002/jso.21156>.
33. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. <https://doi.org/10.1136/bmj.l4898>.
34. Syrnioti A, Timotheadou E, Papadopoulos V, Syrnioti G, Koletsis T. Dissecting the non-immune tumor microenvironment in triple-negative breast cancer: molecular subtype-specific patterns and prognostic implications. *Int J Mol Sci*. 2025;26:11211. <https://doi.org/10.3390/ijms262211211>.
35. Thompson KJ, Leon-Ferre RA, Sinnwell JP, Zahrieh DM, Suman VJ, Metzger FO, Asad S, Stover DG, Carey L, Sikov WM, Ingle JN, Liu MC, Carter JM, Klee EW, Weinshilboum RM, Boughey JC, Wang L, Couch FJ, Goetz MP, Kalari KR. Luminal androgen receptor breast cancer subtype and investigation of the microenvironment and neoadjuvant chemotherapy response. *NAR Cancer*. 2022;4:zcac018. <https://doi.org/10.1093/narcan/zcac018>.
36. Traina TA, Miller K, Yardley DA, Eakle J, Schwartzberg LS, O'Shaughnessy J, Gradishar W, Schmid P, Winer E, Kelly C, Nanda R, Gucalp A, Awada A, Garcia-Estevez L, Trudeau ME, Steinberg J, Uppal H, Tudor IC, Peterson A, Cortes J. Enzalutamide for the Treatment of Androgen Receptor-Expressing Triple-Negative Breast Cancer. *J Clin Oncol*. 2018;36:884–90. <https://doi.org/10.1200/JCO.2016.71.3495>.
37. Tsutsumi Y. Apocrine carcinoma as triple-negative breast cancer: novel definition of apocrine-type carcinoma as estrogen/progesterone receptor-negative and androgen receptor-positive invasive ductal carcinoma. *Jpn J Clin Oncol*. 2012;42:375–86. <https://doi.org/10.1093/jjco/hys034>.
38. Yardley DA, Young RR, Adelson KB, Silber AL, Kommor MD, Najera JE, Daniel DB, Peacock NW, Shastry M, Hainsworth JD, Burris HA, III. Abstract PS11-29: A phase 2 study evaluating orteronel, an inhibitor of androgen biosynthesis, in patients with androgen receptor (AR)-expressing metastatic triple-negative breast cancer (TNBC). *Cancer Res*. 2021;81:PS11–29. <https://doi.org/10.1158/1538-7445.SABCS20-PS11-29>.
39. You C-P, Leung M-H, Tsang W-C, Khoo U-S, Tsoi H. Androgen Receptor as an Emerging Feasible Biomarker for Breast Cancer. *Biomolecules*. 2022;12:72. <https://doi.org/10.3390/biom12010072>.
40. Yuan Y, Lee JS, Yost SE, Frankel PH, Ruel C, Egelston CA, Guo W, Gillece JD, Folkerts M, Reining L, Highlander SK, Robinson K, Padam S, Martinez N, Tang A, Schmolze D, Waisman J, Sedrak M, Lee PP, Mortimer J. 2021. A phase II clinical trial of pembrolizumab and enobosarm in patients with androgen receptor-positive metastatic triple-negative breast cancer. *Oncologist* 26, 99–e217. <https://doi.org/10.1002/onco.13583>

Figures

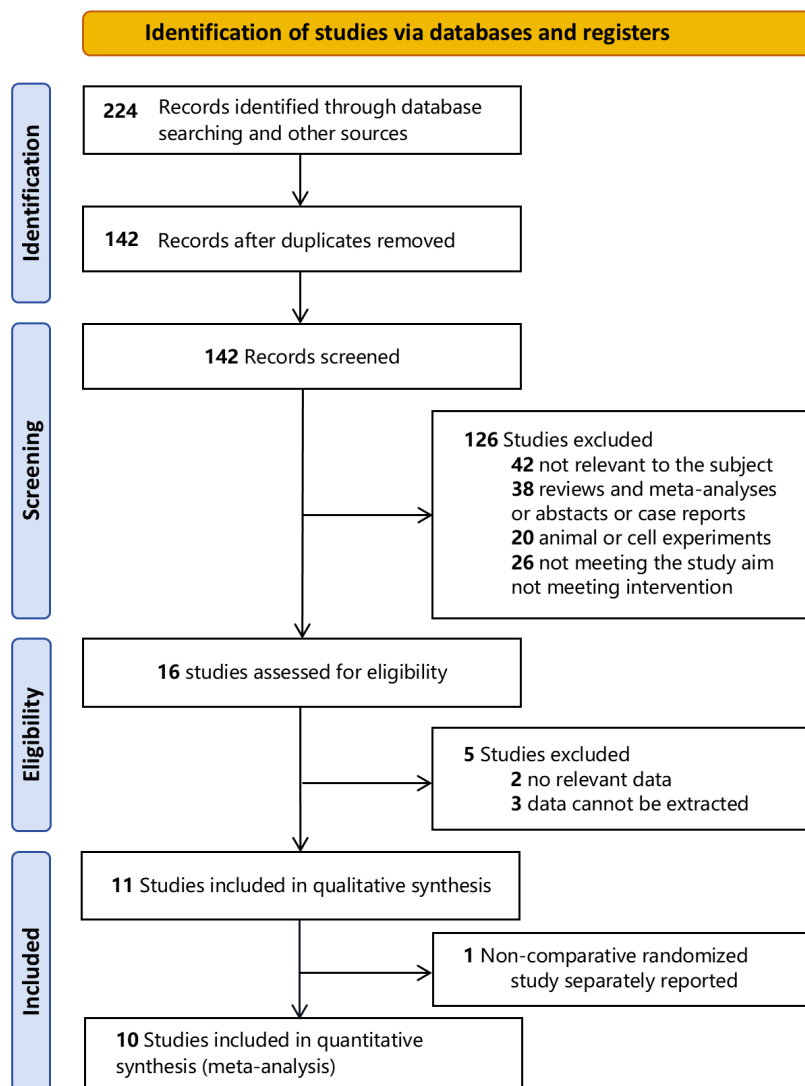


Figure 1

PRISMA flow diagram illustrating the study selection process.

A. JBI Critical Appraisal Checklist for Case Series

Gucalp et al. (2013)	+	+	+	?	+	+	+	+	+	+
Bonnefoi et al. (2016)	+	+	+	?	+	+	+	+	+	+
Traina et al. (2018)	+	+	+	?	+	+	+	+	+	+
Yuan et al. (2021)	+	+	+	?	+	+	+	+	+	+
Jiang et al. (2022)	+	+	+	?	+	?	?	+	+	+
Lim et al. (2024)	+	+	+	?	+	+	+	+	+	+
Yardley et al. (2021)	+	+	?	?	?	+	+	+	?	?
Gucalp et al. (2017)	+	+	?	?	?	?	+	+	?	?
Gucalp et al. (2020)	+	+	?	?	?	+	+	+	?	?
Knight-Shefner et al. (2025)	+	?	?	?	?	+	+	+	+	?
	Q1 Inclusion	Q2 Reliable measure	Q3 Valid identification	Q4 Consecutive	Q5 Complete	Q6 Demographics	Q7 Clinical data	Q8 Outcomes	Q9 Sites	Q10 Analysis

Unclear Yes

B. Cochrane RoB 2 assessment for the START trial

D1 randomization; D2 deviations; D3 missing data; D4 outcome measurement; D5 selective reporting

Bonnefoi et al. (2025)	+	!	!	+	+	!
	D1	D2	D3	D4	D5	Overall

Low risk Some concerns

Figure 2

Evaluation of bias risk in the included studies. A: JBI case series evaluation; B: START study Cochrane RoB 2 evaluation.

Objective response rate

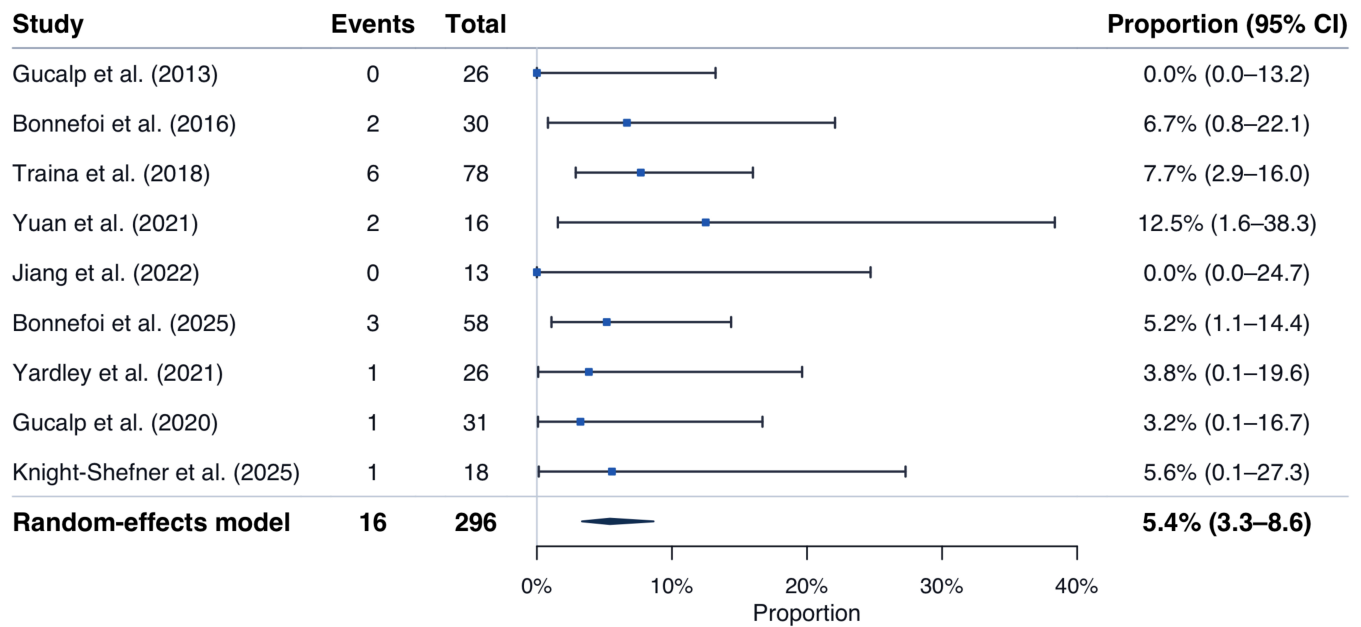
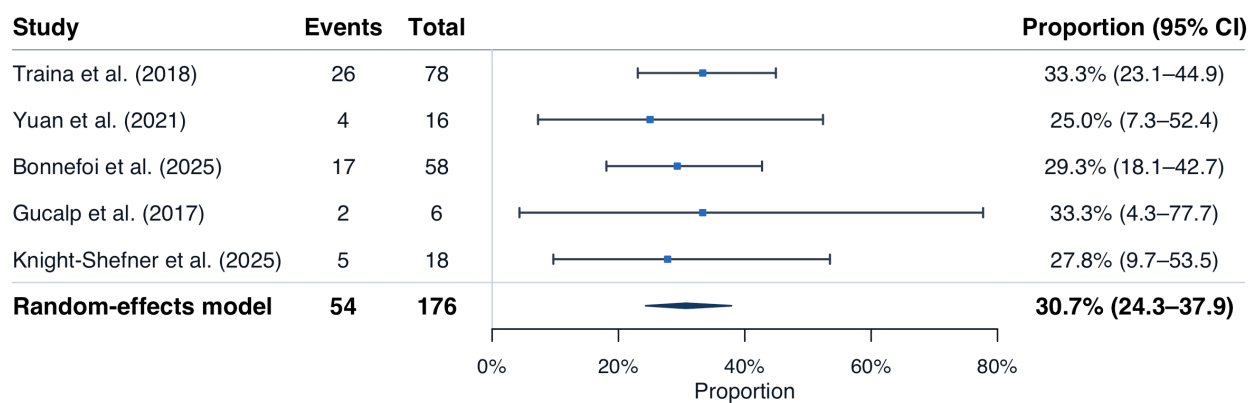


Figure 3

Objective response rate of AR pathway-targeted therapy in advanced or metastatic AR-positive triple-negative breast cancer.

A. Clinical benefit rate at 16 weeks



B. Clinical benefit rate at 6 months

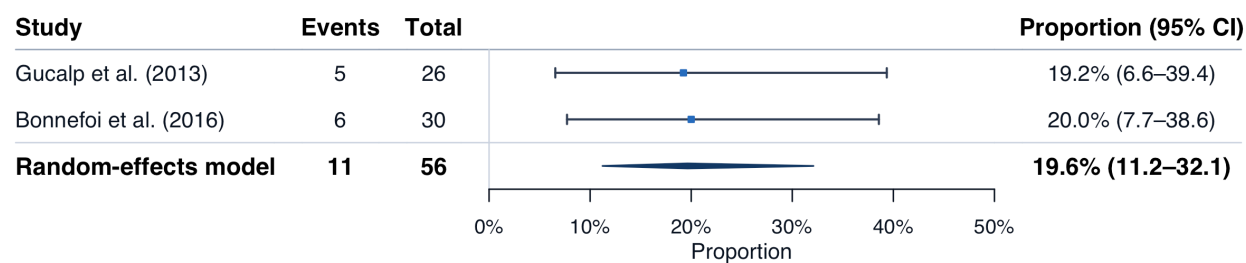


Figure 4

Time-point standardized clinical benefit rates. A: 16-week CBR; B: 6-month CBR.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [graphicalabstract.pptx](#)
- [FigureS1.jpg](#)

- [FigureS2.jpg](#)
- [FigureS3.jpg](#)
- [FigureS4.jpg](#)