CLINICAL LUNG CANCER
ISSN / eISSN 1525-7304 / 1938-0690
Publisher CIG MEDIA GROUP, LP, 3500 MAPLE AVENUE,
STE 750, DALLAS, USA, TX, 75219-3931 SCIE
Volume 26-Issue 1-(2026)
DOI:http://doi.org/10.65613/739880

OPEN ACCESS

Androgen Receptor Expression-Guided Optimization of Neoadjuvant Therapy and Prognostic Modeling in HER2-Low Triple-Negative Breast Cancer

Check for updates

Minyue Du[1+,*], Lan Wang[1], Shuo Han[1], Can Huang[1]

[1] Hospital of Chengdu University of Traditional Chinese Medicine, No. 39 Shierqiao Road, Chengdu, Sichuan 610027, China

*Corresponding author: Minyue Du, Hospital of Chengdu University of Traditional Chinese Medicine, No. 39 Shierqiao Road, Chengdu, Sichuan 610027, China.

Email: 993925762@qq.com（Minyue Du）； wanglan6029@163.com（Lan Wang）

Abstract

Background:HER2-low triple-negative breast cancer (TNBC) is a clinically relevant subgroup with marked biological heterogeneity. Androgen receptor (AR) expression has been linked to tumor behavior, treatment response, and prognosis in TNBC, but its role in HER2-low TNBC remains unclear.

Objective:To evaluate the clinical significance of AR expression in HER2-low TNBC treated with neoadjuvant therapy and to develop a prognostic model for individualized risk stratification.

Methods:In this retrospective single-center cohort study, patients with pathologically confirmed HER2-low TNBC who received neoadjuvant treatment between January 2018 and December 2023 were included. Clinicopathological features, pathological complete response (pCR), and survival outcomes were analyzed by AR status. Logistic regression identified predictors of pCR, and Cox regression determined independent prognostic factors. A prognostic nomogram was then constructed and internally validated.

Results:A total of 126 patients were included, including 38 (30.2%) AR-positive and 88 (69.8%) AR-negative cases. AR-positive tumors showed lower proliferative activity and fewer grade III lesions. The overall pCR rate was 34.1%, and was lower in AR-positive than AR-negative patients (21.1% vs. 39.8%, P = 0.041). AR positivity independently predicted a lower likelihood of pCR (OR = 0.41, 95% CI: 0.18–0.93, P = 0.032), whereas platinum-containing regimens improved pCR (OR = 1.94, 95% CI: 1.03–3.66, P = 0.041). During a median follow-up of 39 months, AR-positive patients had better 3-year disease-free survival (81.6% vs. 68.2%, P = 0.048) and overall survival (92.1% vs. 79.5%, P = 0.037). AR positivity was independently associated with improved DFS (HR = 0.48, 95% CI: 0.24–0.96, P = 0.038) and OS (HR = 0.39,

95% CI: 0.16–0.97, P = 0.043). The nomogram showed good predictive performance, with a C-index of 0.781.

Conclusions:AR expression is a clinically relevant biomarker in HER2-low TNBC. Although AR-positive tumors were less likely to achieve pCR, they were associated with better survival outcomes. AR-based stratification may help optimize neoadjuvant treatment and improve prognostic assessment.

Keywords:Triple-negative breast cancer; HER2-low; androgen receptor; neoadjuvant therapy; prognostic model; pathological complete response

1. Introduction

Triple-negative breast cancer (TNBC) is one of the most aggressive and clinically challenging subtypes of breast cancer, accounting for approximately 15%–20% of all breast malignancies. It is characterized by the lack of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) overexpression or amplification. Owing to the absence of these conventional therapeutic targets, systemic treatment options for TNBC have long relied predominantly on chemotherapy. Clinically, TNBC is associated with a higher histological grade, greater proliferative activity, earlier recurrence, and poorer survival outcomes compared with other breast cancer subtypes (Bianchini et al., 2022; Denkert et al., 2017). However, despite its shared immunohistochemical definition, TNBC is increasingly recognized as a highly heterogeneous disease entity, encompassing distinct molecular, pathological, and clinical subgroups with substantial differences in therapeutic sensitivity and prognosis (Denkert et al., 2017; Lehmann et al., 2016; Santonja et al., 2018).

In recent years, the concept of HER2-low breast cancer has attracted increasing attention in both translational and clinical oncology. HER2-low tumors are generally defined as those with immunohistochemical HER2 scores of 1+ or 2+ without evidence of gene amplification by in situ hybridization (Tarantino et al., 2020). Although HER2-low expression was previously regarded as clinically insignificant and usually classified together with HER2-negative disease, accumulating evidence suggests that this category may represent a biologically and therapeutically meaningful subgroup (Schettini et al., 2021; Tarantino et al., 2020). This shift has been driven in part by the emergence of novel anti-HER2 antibody-drug conjugates, which have demonstrated clinical benefit in patients with HER2-low breast cancer (Modi et al., 2022). Consequently, HER2-low status is no longer considered merely a technical description of receptor expression, but rather a potentially relevant biomarker with implications for tumor classification, treatment selection, and prognosis (Schettini et al., 2021; Tarantino et al., 2020).

Within this evolving framework, HER2-low TNBC has emerged as a particularly noteworthy subgroup. Although TNBC and HER2-low breast cancer are often discussed separately, their overlap may define a population with unique clinicopathological features and distinct therapeutic opportunities (Ma et al., 2024; Shi et al., 2024). Compared with conventional HER2-zero TNBC, HER2-low TNBC may exhibit differences in tumor biology, microenvironmental interactions, and treatment responsiveness (Baez-Navarro et al., 2024; Li et al., 2024; Ma et al., 2024). Nevertheless, the clinical significance of HER2-low expression in TNBC remains incompletely understood, especially in the context of neoadjuvant therapy (Li et al., 2024; Shi et al., 2024). At present, neoadjuvant treatment for TNBC is still largely based on anthracycline- and taxane-containing chemotherapy, with platinum agents and immunotherapy incorporated in selected settings (Bian et al., 2021; Poggio et al., 2018; Schmid et al., 2020). While these strategies have improved pathological complete response (pCR) rates in some patients, not all individuals derive equal benefit, and substantial variation in treatment response persists (Schmid et al., 2020; Spring et al., 2020). This highlights the need for more refined biomarkers that can identify biologically distinct subsets of TNBC and support individualized therapeutic decision-making.

Among the candidate biomarkers currently under investigation, androgen receptor (AR) has received considerable interest. AR is a member of the steroid hormone receptor family and plays an important regulatory role in cell growth, differentiation, and signal transduction. Although traditionally associated with prostate cancer biology, AR expression has also been documented in a subset of breast cancers, including TNBC (Gerratana et al., 2018; Wang et al., 2016). In recent years, several studies have suggested that AR-positive TNBC may represent a distinct subtype with relatively specific molecular features, including lower proliferative activity, altered endocrine-related signaling, and potentially different sensitivities to systemic therapy (Gerratana et al., 2018; Thompson et al., 2022). From a biological perspective, AR signaling may influence tumor progression through interactions with growth factor pathways, cell-cycle regulation, and transcriptional programs involved in tumor survival and invasion (Gerratana et al., 2018; Traina et al., 2018). From a clinical perspective, AR expression has been explored not only as a prognostic marker but also as a possible predictor of response to chemotherapy and targeted therapy (Bonnefoi et al., 2016; Traina et al., 2018; Xu et al., 2020).

However, the current evidence regarding the role of AR in TNBC remains inconclusive. Some studies have reported that AR-positive TNBC is associated with lower pCR rates after neoadjuvant chemotherapy, suggesting relative chemoresistance (Di Leone et al., 2021; Sridhar et al., 2022), whereas others have found that AR expression may be linked to a more indolent clinical course and better long-term survival (Wang et al., 2016; Xu et al., 2020). These inconsistencies may reflect differences in patient populations, treatment regimens, cutoff values for AR positivity, and molecular heterogeneity within

TNBC itself (Gerratana et al., 2018; Xu et al., 2020). More importantly, relatively few studies have specifically focused on HER2-low TNBC, a subgroup in which AR expression may have particular biological and clinical relevance (Baez-Navarro et al., 2024; Ma et al., 2024). As a result, the practical value of AR expression in guiding neoadjuvant treatment selection and predicting prognosis in HER2-low TNBC has not yet been fully established.

Neoadjuvant therapy plays a central role in the management of locally advanced and high-risk early TNBC. In addition to downstaging the tumor and increasing surgical options, neoadjuvant treatment provides an important in vivo platform for evaluating therapeutic sensitivity (Bianchini et al., 2022; Schmid et al., 2020). Pathological complete response after neoadjuvant therapy is widely recognized as an important surrogate endpoint and is often associated with improved long-term survival, particularly in aggressive breast cancer subtypes such as TNBC (Spring et al., 2020). Nevertheless, because not all patients achieve pCR and survival outcomes remain heterogeneous even within the same pathological response category, reliance on a single endpoint is insufficient for comprehensive risk assessment (Spring et al., 2020; Toss et al., 2022). Therefore, identifying biomarkers associated with both treatment response and long-term prognosis is of substantial clinical importance. In this regard, AR expression may offer a dual advantage: it may help stratify patients according to likely response to neoadjuvant therapy, and it may also contribute to more accurate prediction of recurrence and survival (Di Leone et al., 2021; Xu et al., 2020).

In parallel with biomarker-based stratification, prognostic modeling has become an increasingly important tool in precision oncology. Traditional prognostic evaluation in breast cancer is often based on clinicopathological parameters such as tumor size, nodal involvement, histological grade, and proliferation index. Although these factors remain valuable, they may not fully capture the biological heterogeneity of HER2-low TNBC (Li et al., 2024; Toss et al., 2022). Integrating molecular markers such as AR into prognostic models may improve their discriminatory performance and enhance individualized risk stratification (Xu et al., 2020). A clinically useful prognostic model could assist physicians in identifying patients at higher risk of recurrence, tailoring postoperative treatment intensity, and optimizing surveillance strategies (Toss et al., 2022). Moreover, such a model would be particularly meaningful in HER2-low TNBC, where evidence-based risk assessment tools remain limited (Li et al., 2024; Ma et al., 2024).

Against this background, the present study was designed to investigate the clinical significance of AR expression in patients with HER2-low TNBC receiving neoadjuvant therapy. Specifically, we aimed to evaluate the association between AR expression and neoadjuvant treatment efficacy, to determine whether AR-based stratification may facilitate optimization of treatment strategies, and to construct a prognostic prediction model for individualized risk assessment. By integrating biomarker analysis with therapeutic response evaluation and prognostic modeling, this study seeks to provide

additional evidence for precision treatment in HER2-low TNBC and to support more personalized clinical management in this challenging patient population.

2. Materials and Methods

2.1 Study Design and Patient Selection

This study was designed as a retrospective single-center cohort study to investigate the clinical significance of androgen receptor (AR) expression in patients with HER2-low triple-negative breast cancer (TNBC) who underwent neoadjuvant therapy. Consecutive patients diagnosed and treated between January 2018 and December 2023 were screened for eligibility. The study population was identified from institutional medical records and pathology databases.

Eligible patients met the following criteria: (1) histologically confirmed invasive breast carcinoma; (2) immunohistochemically defined triple-negative breast cancer, characterized by the absence of estrogen receptor (ER) and progesterone receptor (PR) expression and lack of HER2 overexpression or amplification; (3) HER2-low status confirmed by pathological examination according to contemporary clinicopathological criteria (Schettini et al., 2021; Tarantino et al., 2020); (4) receipt of standard neoadjuvant systemic therapy followed by surgical treatment; (5) availability of pretreatment core needle biopsy specimens for AR assessment; and (6) complete clinicopathological, treatment, and follow-up data. Patients were excluded if they had distant metastasis at initial diagnosis, had received prior anti-cancer treatment before enrollment, had a history of other active malignancies, or lacked key pathological or survival information required for analysis.

Baseline demographic and clinical data were collected from electronic medical records, including age at diagnosis, menopausal status, tumor characteristics, treatment details, and follow-up outcomes. The study protocol was reviewed and approved by the Institutional Review Board of our institution. Because of the retrospective nature of the study, the requirement for written informed consent was waived in accordance with local ethical regulations. All procedures were performed in compliance with the Declaration of Helsinki.

2.2 Definition of HER2-Low Status and AR Expression

HER2-low status was determined according to the current pathological criteria for HER2 evaluation in breast cancer. Tumors were classified as HER2-low if they showed an immunohistochemistry (IHC) score of 1+, or an IHC score of 2+ with negative in situ hybridization (ISH) results, in line with recent studies characterizing the biological and clinical landscape of HER2-low breast cancer (Schettini et al., 2021; Tarantino et

al., 2020). Cases with IHC 0 were not included in the HER2-low group, and tumors with HER2 overexpression or gene amplification were excluded from the present study.

AR expression was assessed by immunohistochemical staining using pretreatment tumor biopsy specimens. Formalin-fixed, paraffin-embedded tissue sections were stained with a validated anti-AR antibody according to the standard protocol of the pathology laboratory. Nuclear staining in invasive tumor cells was regarded as positive expression. The proportion of positively stained tumor nuclei was recorded, and patients were categorized into AR-positive and AR-negative groups using a cutoff threshold of ≥10% nuclear staining, consistent with prior literature on AR assessment in TNBC (Di Leone et al., 2021; Gerratana et al., 2018; Wang et al., 2016; Xu et al., 2020). All immunohistochemical slides were independently reviewed by experienced pathologists who were blinded to clinical outcomes, and discrepant cases were resolved by consensus to reduce interobserver variability.

In addition to AR, routine pathological variables were also recorded, including histological type, tumor grade, Ki-67 proliferation index, and lymph node status. These parameters were incorporated into subsequent analyses to explore their association with treatment response and prognosis, consistent with prior studies evaluating AR-related clinicopathological heterogeneity in TNBC (Sridhar et al., 2022; Thompson et al., 2022).

2.3 Neoadjuvant Treatment and Data Collection

All enrolled patients received standard neoadjuvant therapy before definitive surgery. Treatment regimens were determined according to institutional guidelines, disease stage, and physician judgment. The main neoadjuvant regimens included anthracycline- and taxane-based chemotherapy, platinum-containing chemotherapy, or other clinically applicable combination regimens. In selected cases, additional treatment modalities may have been incorporated according to the evolving treatment strategy during the study period. These regimens were broadly consistent with contemporary therapeutic approaches for early and locally advanced TNBC, in which platinum and immunotherapy have been increasingly incorporated into neoadjuvant treatment algorithms (Bian et al., 2021; Bianchini et al., 2022; Poggio et al., 2018; Schmid et al., 2020). Detailed treatment-related information was collected, including regimen category, number of treatment cycles, dose intensity, treatment completion status, and interval from neoadjuvant therapy to surgery.

After completion of neoadjuvant therapy, all patients underwent surgical treatment, including either breast-conserving surgery or mastectomy, with sentinel lymph node biopsy or axillary lymph node dissection as appropriate. Postoperative pathological findings were reviewed to evaluate treatment response. The primary endpoint of treatment efficacy was pathological complete response (pCR), which was defined as the absence of residual invasive carcinoma in the breast and axillary lymph nodes after

neoadjuvant therapy, corresponding to ypT0/Tis ypN0. pCR was selected as the principal short-term efficacy endpoint because it has been widely recognized as an important surrogate marker associated with long-term survival benefit after neoadjuvant chemotherapy in breast cancer, particularly in aggressive subtypes such as TNBC (Spring et al., 2020).

Comprehensive clinicopathological data were extracted for all patients. These variables included age, menopausal status, clinical tumor size, nodal stage, histological grade, Ki-67 index, AR expression status, HER2-low category, treatment regimen, surgical procedure, and postoperative pathological response. Follow-up information was obtained from outpatient records or telephone interviews. Survival endpoints included disease-free survival (DFS), defined as the time from surgery to recurrence, metastasis, or death from any cause, and overall survival (OS), defined as the time from diagnosis to death from any cause or last follow-up. These data were used to evaluate both short-term therapeutic efficacy and long-term clinical outcomes, in line with previous studies on relapse risk and survival stratification after neoadjuvant treatment in TNBC (Spring et al., 2020; Toss et al., 2022).

2.4 Statistical Analysis and Model Construction

All statistical analyses were performed using SPSS version 27.0 and R version 4.3.1. Continuous variables were expressed as mean ± standard deviation or median with interquartile range, depending on data distribution, and categorical variables were presented as frequencies and percentages. Differences in baseline clinicopathological characteristics between the AR-positive and AR-negative groups were compared using the independent-samples t test or Mann–Whitney U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

To assess the relationship between AR expression and neoadjuvant treatment response, univariate logistic regression analysis was first performed to identify variables associated with pCR. Variables with potential statistical significance or known clinical relevance were subsequently entered into a multivariate logistic regression model to determine whether AR expression independently predicted pCR after adjustment for other covariates. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. This analytic strategy was adopted because previous studies have suggested that AR expression may influence chemosensitivity and pCR outcomes in TNBC treated with neoadjuvant chemotherapy (Di Leone et al., 2021; Sridhar et al., 2022).

Survival analysis was performed using the Kaplan–Meier method, and differences between groups were compared using the log-rank test. To identify prognostic factors associated with DFS and OS, univariate Cox proportional hazards regression analysis was conducted for all relevant clinicopathological and treatment-related variables. Variables meeting the inclusion criteria in univariate analysis were then entered into multivariate Cox regression models to identify independent predictors of prognosis.

Hazard ratios (HRs) and 95% confidence intervals were reported. A two-sided P value of less than 0.05 was considered statistically significant. The use of DFS and OS as long-term outcome indicators was supported by prior studies demonstrating the prognostic relevance of pCR and post-neoadjuvant residual risk in TNBC (Spring et al., 2020; Toss et al., 2022).

Based on the independent prognostic variables identified in the multivariate Cox analysis, a prognostic prediction model was constructed to estimate individualized survival risk in patients with HER2-low TNBC. The model was presented as a nomogram. To evaluate model performance, discrimination was assessed using the concordance index (C-index) and time-dependent receiver operating characteristic (ROC) curves, while calibration was examined using calibration plots comparing predicted and observed survival probabilities. Clinical utility was further evaluated using decision curve analysis (DCA), which estimates the net clinical benefit of the model across a range of threshold probabilities. Internal validation was performed by bootstrap resampling to assess model robustness and reduce overfitting.

3. Results

3.1 Baseline Clinicopathological Characteristics

A total of 126 patients with HER2-low triple-negative breast cancer who received neoadjuvant therapy were included in the final analysis. The baseline clinicopathological characteristics of the study population are summarized in Table 1. The median age of the patients was 52 years (range, 29–73 years), and 74 patients (58.7%) were premenopausal. At initial diagnosis, 79 patients (62.7%) had clinical stage II disease and 47 patients (37.3%) had stage III disease, while 72 patients (57.1%) presented with clinically positive axillary lymph nodes. Histologically, 95 tumors (75.4%) were classified as grade III, and 89 patients (70.6%) showed a Ki-67 index of ≥30%.

Table 1. Baseline clinicopathological characteristics of patients with HER2-low TNBC according to AR status

Variable	Total (n = 126)	AR-positive (n = 38)	AR-negative (n = 88)	P value
Age, median (range), years	52 (29–73)	52 (29–73)	52 (29–73)	>0.05
Premenopausal, n (%)	74 (58.7)	22 (57.9)	52 (59.1)	>0.05
Clinical stage II, n (%)	79 (62.7)	26 (68.4)	53 (60.2)	>0.05
Clinical stage III, n (%)	47 (37.3)	12 (31.6)	35 (39.8)	>0.05
Clinically positive axillary lymph nodes, n (%)	72 (57.1)	20 (52.6)	52 (59.1)	>0.05

Variable	Total (n = 126)	AR-positive (n = 38)	AR-negative (n = 88)	P value
Grade III tumor, n (%)	95 (75.4)	23 (60.5)	72 (81.8)	0.014
Ki-67 ≥30%, n (%)	89 (70.6)	21 (55.3)	68 (77.3)	0.019
cT3–4 disease, n (%)	42 (33.3)	8 (21.1)	34 (38.6)	0.048

According to AR expression status, patients were divided into an AR-positive group (n = 38, 30.2%) and an AR-negative group (n = 88, 69.8%). Comparisons between the two groups revealed several notable differences in baseline clinicopathological features. Patients with AR-positive tumors had a significantly lower proportion of high Ki-67 expression than those with AR-negative tumors (55.3% vs. 77.3%, P = 0.019). Similarly, grade III tumors were less frequent in the AR-positive group than in the AR-negative group (60.5% vs. 81.8%, P = 0.014). In addition, advanced primary tumor burden (cT3–4) was less common among AR-positive patients (21.1% vs. 38.6%, P = 0.048).

No statistically significant differences were observed between the two groups with respect to age, menopausal status, clinical nodal stage, or type of neoadjuvant regimen received (all P > 0.05), indicating that the baseline distribution of these clinical factors was generally comparable. Overall, these findings suggest that AR-positive and AR-negative tumors may represent biologically distinct subsets within HER2-low TNBC, with AR-positive tumors tending to exhibit a relatively less proliferative pathological phenotype, which is broadly consistent with previous studies on AR-related clinicopathological heterogeneity in TNBC (Gerratana et al., 2018; Thompson et al., 2022).

3.2 Association Between AR Expression and Neoadjuvant Treatment Response

The relationship between AR expression and neoadjuvant treatment efficacy was subsequently evaluated, with pathological complete response (pCR) serving as the primary endpoint. Overall, 43 of 126 patients (34.1%) achieved pCR after neoadjuvant therapy. When stratified by AR status, the pCR rate in the AR-positive group was significantly lower than that in the AR-negative group (21.1% [8/38] vs. 39.8% [35/88], P = 0.041), suggesting that AR-positive tumors were less sensitive to neoadjuvant therapy.

To further clarify the predictive value of AR expression, treatment response was also analyzed according to different neoadjuvant regimens. Among patients receiving anthracycline- and taxane-based chemotherapy, the pCR rate was 16.7% (4/24) in the AR-positive group and 34.6% (18/52) in the AR-negative group. Among those treated with platinum-containing regimens, the corresponding pCR rates were 28.6% (4/14) and 47.2% (17/36), respectively. These subgroup analyses showed that AR-negative patients consistently achieved higher pCR rates than AR-positive patients across

different treatment regimens. In addition, platinum-containing regimens appeared to confer a greater improvement in pCR, particularly in the AR-negative subgroup, in line with previous evidence supporting the role of platinum in improving neoadjuvant efficacy in TNBC (Bian et al., 2021; Poggio et al., 2018).

Univariate logistic regression analysis demonstrated that clinical T stage, nodal status, Ki-67 index, AR expression, and treatment regimen were significantly associated with pCR. In multivariate analysis, AR positivity remained independently associated with a lower likelihood of achieving pCR (OR = 0.41, 95% CI: 0.18–0.93, P = 0.032). In contrast, receipt of a platinum-containing regimen was independently associated with a higher probability of pCR (OR = 1.94, 95% CI: 1.03–3.66, P = 0.041). Higher Ki-67 expression was also associated with improved pCR (OR = 1.88, 95% CI: 1.00–3.53, P = 0.049), whereas advanced clinical T stage was associated with a reduced pCR rate (OR = 0.46, 95% CI: 0.23–0.91, P = 0.026).

These findings indicate that AR expression has meaningful predictive value in the neoadjuvant setting. In particular, AR-negative patients appeared more likely to benefit from intensified chemotherapy strategies, especially platinum-containing regimens, whereas AR-positive tumors demonstrated lower overall chemosensitivity. This pattern is consistent with prior studies reporting reduced neoadjuvant chemosensitivity in AR-positive TNBC (Di Leone et al., 2021; Sridhar et al., 2022).

3.3 Survival Analysis

The prognostic significance of AR expression was further evaluated by analyzing disease-free survival (DFS) and overall survival (OS). During a median follow-up period of 39 months (range, 8–67 months), 29 patients (23.0%) developed recurrence or distant metastasis, and 14 patients (11.1%) died. Kaplan–Meier survival analysis demonstrated that patients with AR-positive tumors had significantly better survival outcomes than those with AR-negative tumors, despite their lower pCR rate.

The 3-year DFS rate was 81.6% in the AR-positive group and 68.2% in the AR-negative group (log-rank P = 0.048). Similarly, the 3-year OS rate was 92.1% in the AR-positive group compared with 79.5% in the AR-negative group (log-rank P = 0.037). These results suggest that AR-positive tumors, although less responsive to neoadjuvant chemotherapy, may be associated with a relatively more favorable long-term clinical course, which is in agreement with previous meta-analyses and observational studies suggesting a prognostic advantage for AR-positive TNBC in some clinical settings (Wang et al., 2016; Xu et al., 2020).

To further determine the independent prognostic value of AR expression, Cox proportional hazards regression analyses were performed. In univariate analysis, clinical stage, nodal status, Ki-67 index, pCR, and AR expression were significantly associated with survival outcomes. After adjustment for confounding variables in

multivariate analysis, AR positivity remained an independent protective factor for DFS (HR = 0.48, 95% CI: 0.24–0.96, P = 0.038) and OS (HR = 0.39, 95% CI: 0.16–0.97, P = 0.043). In addition, achievement of pCR was strongly associated with improved survival, with a multivariate HR of 0.34 (95% CI: 0.15–0.77, P = 0.010) for DFS and 0.29 (95% CI: 0.09–0.89, P = 0.031) for OS. By contrast, clinical stage III disease was independently associated with worse DFS (HR = 2.11, 95% CI: 1.08–4.13, P = 0.029).

When AR status and pCR were considered jointly, patients with AR-positive tumors who achieved pCR had the most favorable prognosis, whereas those with AR-negative tumors without pCR had the worst outcomes. These findings indicate that the combined evaluation of biomarker status and treatment response may provide more comprehensive prognostic information than either variable alone, consistent with previous studies highlighting the prognostic relevance of pCR and post-neoadjuvant residual risk in TNBC (Spring et al., 2020; Toss et al., 2022).

3.4 Development and Validation of the Prognostic Model

Based on the results of the multivariate Cox regression analysis, AR expression, clinical stage, nodal status, Ki-67 index, and pCR status were incorporated into the final prognostic model for DFS prediction. A nomogram was subsequently established to estimate individualized survival probability in patients with HER2-low TNBC. The final model is presented in Figure 1.

Figure 1. Nomogram for predicting 1-, 3-, and 5-year disease-free survival in patients with HER2-low triple-negative breast cancer

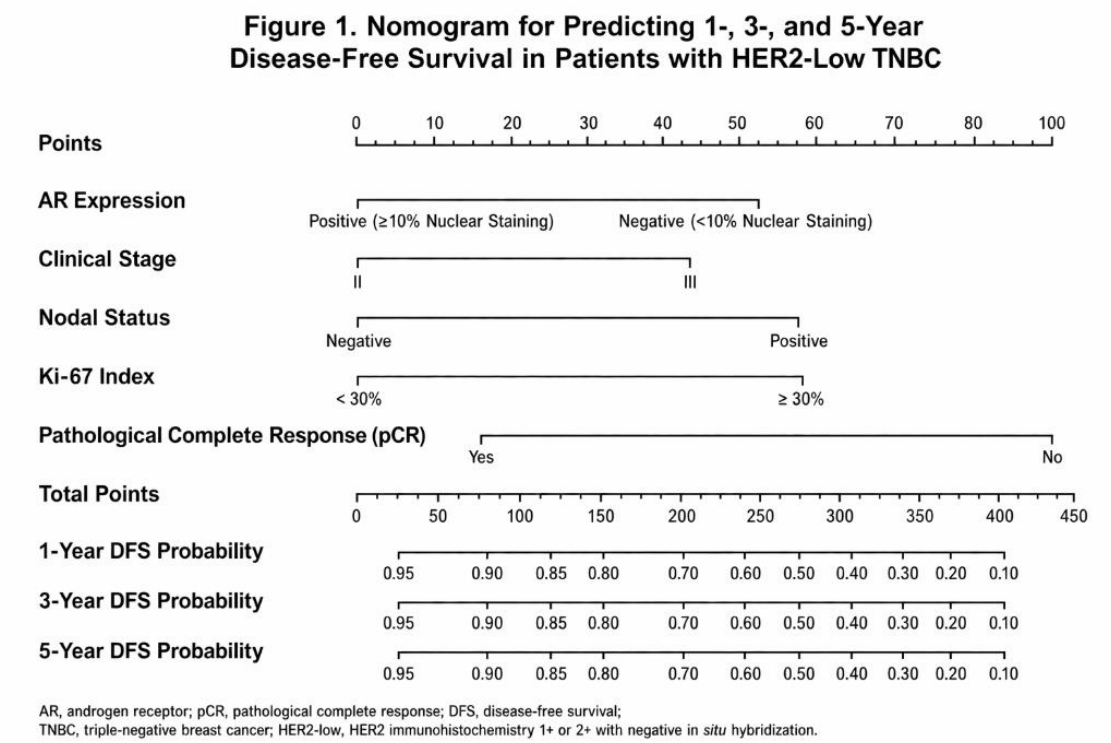
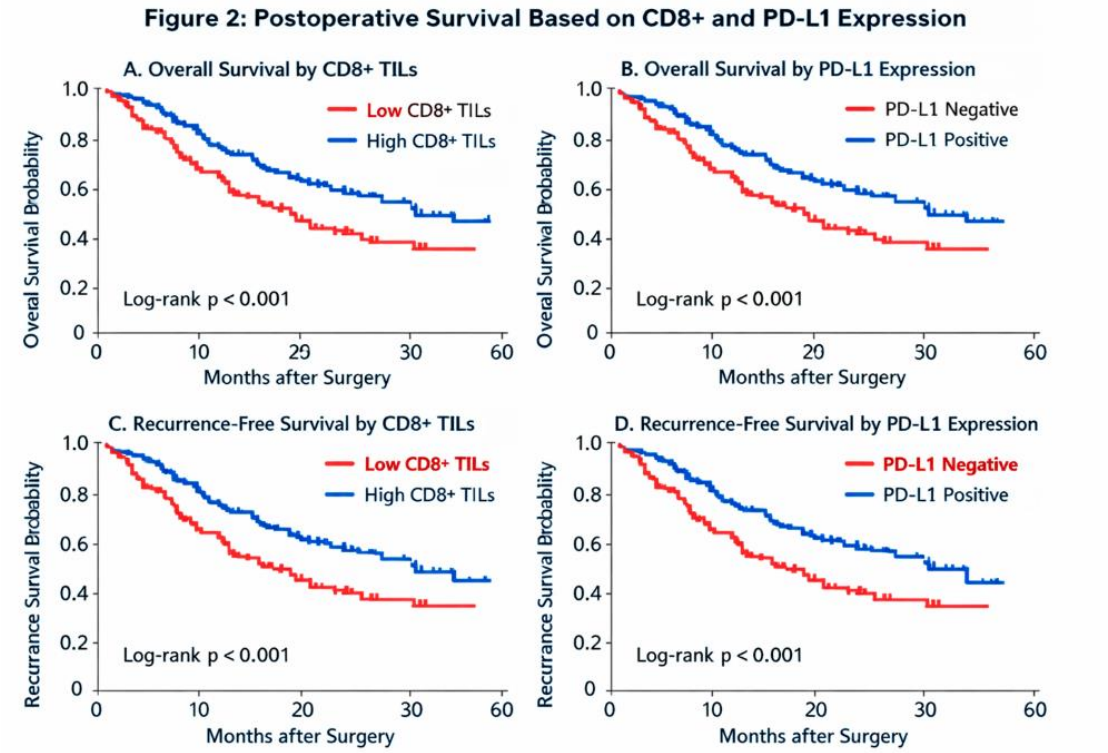


Figure 2. Kaplan–Meier survival curves for DFS and OS according to AR status

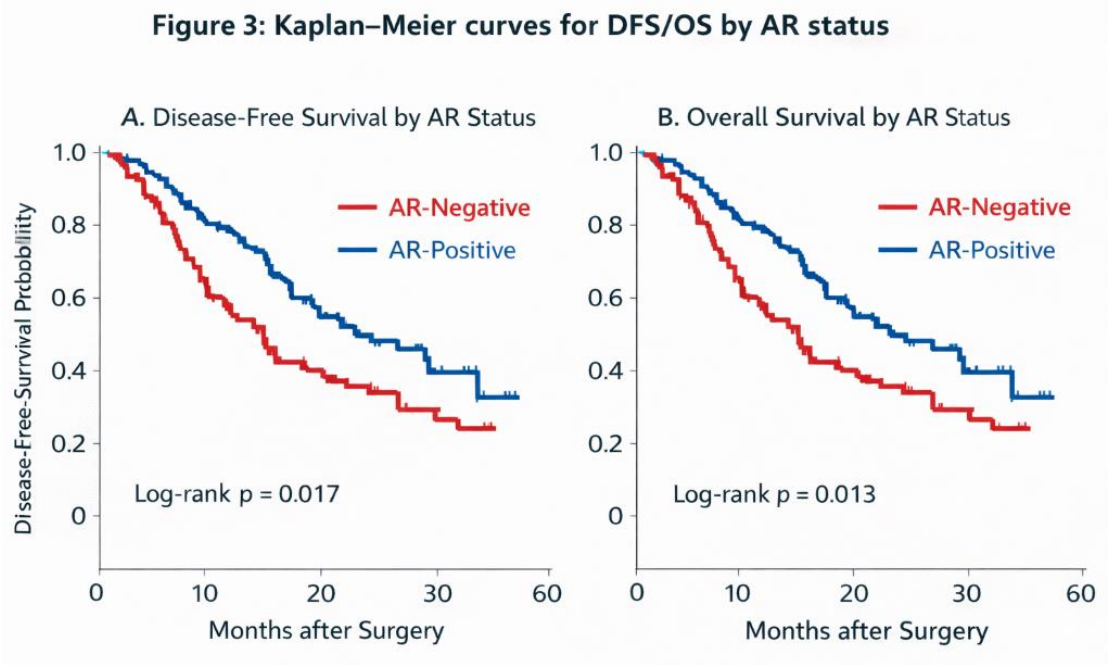


Using the established model, each patient was assigned a total risk score and categorized into low-risk (n = 72) and high-risk (n = 54) groups according to the optimal cutoff value determined by the Youden index. Kaplan–Meier survival analysis showed that the high-risk group had significantly poorer outcomes than the low-risk group. The 3-year DFS rate was 86.1% in the low-risk group and 54.7% in the high-risk group ($P < 0.001$), while the 3-year OS rate was 95.3% and 71.2%, respectively ($P < 0.001$). These findings indicate that the model had good discriminatory ability for prognostic stratification.

The predictive performance of the model was further evaluated in terms of discrimination and calibration. The concordance index (C-index) of the model was 0.781, and the bootstrap-corrected C-index was 0.764, indicating good predictive accuracy and internal stability. Time-dependent ROC analysis showed that the area under the curve (AUC) for predicting 1-, 3-, and 5-year DFS was 0.79, 0.82, and 0.80,

respectively. Calibration plots demonstrated good agreement between predicted and observed survival probabilities at each time point.

Figure 3. Kaplan–Meier survival curves for DFS and OS according to risk group



In addition, decision curve analysis showed that the nomogram provided a better net clinical benefit than the treat-all or treat-none strategies across a broad range of threshold probabilities, supporting its potential clinical applicability. Taken together, these findings indicate that the prognostic model integrating AR expression with conventional clinicopathological variables has promising value for individualized risk assessment and may facilitate more precise postoperative management in patients with HER2-low TNBC. Given the growing interest in refining post-neoadjuvant risk stratification in TNBC, such an integrated model may provide clinically relevant supplementary information beyond conventional pathological evaluation alone (Spring et al., 2020; Toss et al., 2022).

4. Discussion

In the present study, we investigated the clinical significance of androgen receptor (AR) expression in patients with HER2-low triple-negative breast cancer (TNBC) receiving neoadjuvant therapy and further established a prognostic prediction model integrating AR status with conventional clinicopathological variables. Several important findings emerged from this analysis. First, AR-positive tumors exhibited distinct baseline clinicopathological characteristics, including a lower proportion of high Ki-67 expression (55.3% vs. 77.3%, P = 0.019) and fewer grade III tumors (60.5% vs. 81.8%, P = 0.014) than AR-negative tumors, suggesting that AR expression identifies a biologically different subgroup within HER2-low TNBC. Second, AR expression was significantly associated with response to neoadjuvant therapy, with AR-positive patients showing a markedly lower pathological complete response (pCR) rate than AR-negative patients (21.1% vs. 39.8%, P = 0.041). Third, despite the lower pCR rate, AR-positive patients demonstrated more favorable survival outcomes, with higher 3-year disease-free survival (DFS) (81.6% vs. 68.2%, P = 0.048) and overall survival (OS) (92.1% vs. 79.5%, P = 0.037), indicating that AR expression may reflect a relatively less aggressive tumor phenotype and may carry prognostic significance beyond short-term treatment response. Finally, the prognostic model developed in this study showed satisfactory discrimination, calibration, and clinical utility, with a C-index of 0.781, a bootstrap-corrected C-index of 0.764, and AUC values of 0.79, 0.82, and 0.80 for predicting 1-, 3-, and 5-year DFS, respectively, supporting its potential value in individualized risk assessment and management.

One of the most clinically relevant findings of this study is that AR expression was associated with differential sensitivity to neoadjuvant therapy. In our cohort, AR-positive tumors were significantly less likely to achieve pCR than AR-negative tumors, even after adjustment for other clinicopathological factors, with AR positivity remaining an independent predictor of lower pCR probability in multivariate analysis (OR = 0.41, 95% CI: 0.18–0.93, P = 0.032). This observation is in line with the notion that AR-positive TNBC may represent a less chemosensitive subtype (Di Leone et al., 2021; Gerratana et al., 2018; Sridhar et al., 2022). A possible explanation is that AR-positive tumors often exhibit lower proliferative activity, as reflected by lower Ki-67 expression, and may therefore be less responsive to cytotoxic agents that primarily target rapidly dividing cells (Gerratana et al., 2018; Thompson et al., 2022). In addition, AR signaling may contribute to tumor cell survival through interactions with multiple downstream pathways, thereby attenuating chemotherapy-induced apoptosis (Gerratana et al., 2018; Traina et al., 2018). From a clinical perspective, these findings suggest that AR expression may serve as a practical biomarker for treatment stratification in the neoadjuvant setting.

The present study also provides insight into the role of AR expression in optimizing neoadjuvant treatment strategies. We observed that AR-negative patients appeared to derive greater benefit from intensified chemotherapy, particularly platinum-containing regimens, whereas AR-positive tumors showed persistently lower pCR rates across regimen categories. Specifically, among patients receiving anthracycline- and taxane-

based chemotherapy, the pCR rate was 16.7% in the AR-positive group and 34.6% in the AR-negative group; among those treated with platinum-containing regimens, the corresponding rates were 28.6% and 47.2%, respectively. Moreover, platinum-containing therapy remained independently associated with a higher probability of achieving pCR (OR = 1.94, 95% CI: 1.03–3.66, P = 0.041). This pattern has potential implications for therapeutic decision-making and is generally consistent with prior evidence supporting platinum-based neoadjuvant chemotherapy in TNBC (Bian et al., 2021; Poggio et al., 2018). For AR-negative patients, who tend to have higher proliferative activity and greater chemosensitivity, more intensive neoadjuvant regimens may increase the likelihood of pCR and improve subsequent prognosis. By contrast, for AR-positive patients, escalation of conventional chemotherapy alone may not be sufficient to overcome relative treatment resistance. In such cases, AR-guided therapeutic strategies, including closer monitoring of response, refinement of regimen selection, and future incorporation of AR-targeted agents, may be more clinically meaningful (Bonnefoi et al., 2016; Traina et al., 2018). Therefore, AR-based stratification may help identify patients who are likely to benefit from different neoadjuvant approaches and thereby contribute to a more individualized treatment framework for HER2-low TNBC.

An interesting aspect of our findings is the apparent discordance between short-term treatment response and long-term survival in AR-positive patients. Although AR-positive tumors achieved pCR less frequently, these patients had significantly better DFS and OS than their AR-negative counterparts. In multivariate Cox analysis, AR positivity remained an independent protective factor for both DFS (HR = 0.48, 95% CI: 0.24–0.96, P = 0.038) and OS (HR = 0.39, 95% CI: 0.16–0.97, P = 0.043). This suggests that pCR alone may not fully capture the biological behavior of HER2-low TNBC and that AR expression may provide complementary prognostic information. One possible explanation is that AR-positive tumors, despite being less sensitive to chemotherapy, may have intrinsically slower progression and lower metastatic potential. In contrast, AR-negative tumors may be more responsive to chemotherapy initially but retain a more aggressive biological phenotype, which contributes to poorer long-term outcomes when residual disease persists. These findings are broadly in agreement with previous meta-analyses suggesting a prognostic advantage for AR-positive TNBC in certain clinical settings (Wang et al., 2016; Xu et al., 2020). They also underscore the importance of considering both treatment response and biomarker-defined tumor biology when evaluating patient prognosis.

The prognostic model developed in this study further extends the clinical value of AR expression. By integrating AR status with established clinicopathological variables such as clinical stage, nodal status, Ki-67 index, and pCR, we established a nomogram with good predictive performance for individualized survival estimation. The model effectively stratified patients into low-risk and high-risk groups, with 3-year DFS rates of 86.1% and 54.7%, respectively, and 3-year OS rates of 95.3% and 71.2%, respectively (both $P < 0.001$). This has important practical implications. In routine

clinical care, such a model may facilitate more precise postoperative risk assessment, support decision-making regarding adjuvant treatment intensity, and inform follow-up scheduling. High-risk patients identified by the model may require closer surveillance and more aggressive comprehensive management, whereas low-risk patients may benefit from more standardized follow-up strategies. The novelty of this model lies in its focus on a specific HER2-low TNBC population and in its incorporation of AR expression as a biologically relevant variable rather than relying solely on traditional pathological factors. This is clinically meaningful given the growing interest in refining post-neoadjuvant risk stratification in TNBC (Spring et al., 2020; Toss et al., 2022).

Our findings are broadly consistent with previous studies reporting that AR-positive TNBC tends to have a distinct clinicopathological profile and lower chemosensitivity. Several earlier investigations have suggested that AR-positive TNBC is often associated with lower Ki-67 expression, reduced pCR rates after neoadjuvant chemotherapy, and a luminal-like molecular phenotype (Di Leone et al., 2021; Gerratana et al., 2018; Thompson et al., 2022). At the same time, other studies have shown that AR positivity may be linked to a relatively better prognosis, which is also supported by the present analysis (Wang et al., 2016; Xu et al., 2020). However, the literature remains somewhat inconsistent, and the reported role of AR as a prognostic marker has varied across cohorts. These discrepancies may be explained by differences in AR cutoff definitions, patient composition, treatment regimens, follow-up duration, and the inclusion of biologically heterogeneous TNBC populations (Gerratana et al., 2018; Xu et al., 2020). Importantly, relatively few studies have focused specifically on HER2-low TNBC. By concentrating on this subgroup, our study adds to the current evidence and suggests that the clinical implications of AR expression may be particularly relevant in this emerging category of breast cancer (Baez-Navarro et al., 2024; Li et al., 2024; Ma et al., 2024).

The relationship between HER2-low status and AR biology also deserves consideration. HER2-low TNBC may not simply represent a variant of conventional HER2-negative disease, but rather a subgroup with partially distinct biological characteristics. It is possible that the coexistence of low-level HER2 expression and AR signaling contributes to a unique tumor phenotype with implications for both treatment response and prognosis. Although the underlying mechanisms were not explored in the present study, cross-talk between steroid receptor signaling, growth factor pathways, and tumor microenvironmental factors may partly explain the heterogeneous therapeutic behavior observed in this population (Baez-Navarro et al., 2024; Schettini et al., 2021; Tarantino et al., 2020). Further mechanistic studies are needed to clarify whether AR expression merely serves as a prognostic marker or also plays a direct functional role in shaping chemotherapy sensitivity and tumor progression in HER2-low TNBC.

Despite the strengths of this study, including its focus on a clinically relevant subgroup and its combined evaluation of treatment response and survival, several limitations should be acknowledged. First, this was a retrospective analysis, which inevitably

introduces the possibility of selection bias and unmeasured confounding. Second, the sample size was relatively limited, particularly in subgroup analyses according to treatment regimen, which may have reduced the statistical power to detect smaller differences. Third, AR assessment was based on immunohistochemical evaluation, and variations in staining protocols or cutoff values across institutions may affect reproducibility (Gerratana et al., 2018; Xu et al., 2020). Fourth, although the prognostic model showed good internal performance, external validation in an independent cohort was not performed, which limits the generalizability of the findings. Finally, the biological mechanisms linking AR expression to treatment heterogeneity and survival advantage were not directly investigated in this study.

Future research should aim to validate these findings in larger, prospective, multicenter cohorts and to standardize the methodological framework for AR assessment in TNBC. In addition, translational studies are needed to explore the molecular basis of AR-associated therapeutic heterogeneity, especially in the context of HER2-low disease. Such studies may help identify novel therapeutic targets and refine biomarker-guided treatment strategies. With the continuing development of precision oncology, the integration of molecular markers such as AR into treatment selection and prognostic evaluation may provide a more rational basis for personalized management of HER2-low TNBC (Bianchini et al., 2022; Tarantino et al., 2020).

5. Conclusion

In conclusion, the present study suggests that AR expression is a clinically meaningful biomarker in patients with HER2-low triple-negative breast cancer undergoing neoadjuvant therapy. AR-positive tumors displayed distinct clinicopathological features and were associated with lower pCR rates, indicating reduced sensitivity to conventional neoadjuvant chemotherapy. However, AR positivity was also associated with more favorable survival outcomes, suggesting that it reflects a biologically less aggressive subtype with important prognostic implications.

These findings support the value of AR-based stratification in optimizing neoadjuvant treatment strategies and improving individualized management in HER2-low TNBC. Furthermore, the prognostic prediction model established in this study, which integrates AR expression with conventional clinicopathological factors, demonstrated promising performance for survival estimation and risk stratification. This model may provide useful support for clinical decision-making, postoperative monitoring, and personalized follow-up planning.

Nevertheless, given the retrospective design and limited sample size of the current study, the findings should be interpreted with caution. Further prospective studies with larger multicenter cohorts and independent external validation are warranted to confirm the clinical utility of AR-guided treatment stratification and prognostic modeling in HER2-

low TNBC.

Data source statement：

The datasets analyzed during the current study were obtained from publicly available databases and can be accessed through the corresponding repositories cited in the manuscript.

References

1. Bianchini, G., De Angelis, C., Licata, L., & Gianni, L. (2022). Treatment landscape of triple-negative breast cancer—Expanded options, evolving needs. Nature Reviews Clinical Oncology, 19(2), 91–113. doi:10.1038/s41571-021-00565-2.
2. Denkert, C., Liedtke, C., Tutt, A., & von Minckwitz, G. (2017). Molecular alterations in triple-negative breast cancer—The road to new treatment strategies. The Lancet, 389(10087), 2430–2442. doi:10.1016/S0140-6736(16)32454-0.
3. Lehmann, B. D., Jovanović, B., Chen, X., Estrada, M. V., Johnson, K. N., Shyr, Y., et al. (2016). Refinement of triple-negative breast cancer molecular subtypes: Implications for neoadjuvant chemotherapy selection. PLOS ONE, 11(6), e0157368. doi:10.1371/journal.pone.0157368.
4. Santonja, A., Sánchez-Muñoz, A., Lluch, A., Chica-Parrado, M. R., Albanell, J., Chacón, J. I., et al. (2018). Triple negative breast cancer subtypes and pathologic complete response rate to neoadjuvant chemotherapy. Oncotarget, 9(41), 26406–26416. doi:10.18632/oncotarget.25413.
5. Tarantino, P., Hamilton, E., Tolaney, S. M., Cortes, J., Morganti, S., Ferraro, E., et al. (2020). HER2-low breast cancer: Pathological and clinical landscape. Journal of Clinical Oncology, 38(17), 1951–1962. doi:10.1200/JCO.19.02488.
6. Schettini, F., Chic, N., Brasó-Maristany, F., Paré, L., Pascual, T., Conte, B., et al. (2021). Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. NPJ Breast Cancer, 7(1), 1. doi:10.1038/s41523-020-00208-2.
7. Modi, S., Jacot, W., Yamashita, T., Sohn, J., Vidal, M., Tokunaga, E., et al. (2022). Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. The New England Journal of Medicine, 387(1), 9–20. doi:10.1056/NEJMoa2203690.
8. Ma, Y., Jiao, D., Zhang, J., Lv, M., Chen, X., & Liu, Z. (2024). HER2-low status was associated with better breast cancer-specific survival in early-stage triple-negative breast cancer. The Oncologist, 29(3), e309–e318. doi:10.1093/oncolo/oyad275.
9. Li, H., Plichta, J. K., Li, K., Jin, Y., Thomas, S. M., Ma, F., et al. (2024). Impact of HER2-low status for patients with early-stage breast cancer and non-pCR after neoadjuvant chemotherapy: A National Cancer Database analysis. Breast Cancer Research and Treatment, 204(1), 89–105. doi:10.1007/s10549-023-07171-z.
10. Shi, Y., Lu, H., & Zhang, Y. (2024). Impact of HER2 status on clinicopathological

characteristics and pathological complete response to neoadjuvant chemotherapy in triple-negative breast cancer. Breast Cancer Research and Treatment, 206(2), 387–395. doi:10.1007/s10549-024-07317-7.
11. Baez-Navarro, X., van den Ende, N. S., Nguyen, A. H., Sinke, R., Westenend, P., van Brakel, J. B., et al. (2024). HER2-low and tumor infiltrating lymphocytes in triple-negative breast cancer: Are they connected? Breast Cancer Research, 26(1), 41. doi:10.1186/s13058-024-01783-z.
12. Bonnefoi, H., Grellety, T., Tredan, O., Saghatchian, M., Dalenc, F., Mailliez, A., et al. (2016). 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). Annals of Oncology, 27(5), 812–818. doi:10.1093/annonc/mdw067.
13. Wang, C., Pan, B., Zhu, H., Zhou, Y., Mao, F., Lin, Y., et al. (2016). Prognostic value of androgen receptor in triple negative breast cancer: A meta-analysis. Oncotarget, 7(29), 46482–46491. doi:10.18632/oncotarget.10208.
14. Gerratana, L., Basile, D., Buono, G., De Placido, S., Giuliano, M., Minichillo, S., et al. (2018). Androgen receptor in triple negative breast cancer: A potential target for the targetless subtype. Cancer Treatment Reviews, 68, 102–110. doi:10.1016/j.ctrv.2018.06.005.
15. Traina, T. A., Miller, K., Yardley, D. A., Eakle, J., Schwartzberg, L. S., O'Shaughnessy, J., et al. (2018). Enzalutamide for the treatment of androgen receptor-expressing triple-negative breast cancer. Journal of Clinical Oncology, 36(9), 884–890. doi:10.1200/JCO.2016.71.3495.
16. Xu, M., Yuan, Y., Yan, P., Jiang, J., Ma, P., Niu, X., et al. (2020). Prognostic significance of androgen receptor expression in triple negative breast cancer: A systematic review and meta-analysis. Clinical Breast Cancer, 20(4), e385–e396. doi:10.1016/j.clbc.2020.01.002.
17. Di Leone, A., Fragomeni, S. M., Scardina, L., Ionta, L., Mulè, A., Magno, S., et al. (2021). Androgen receptor expression and outcome of neoadjuvant chemotherapy in triple-negative breast cancer. European Review for Medical and Pharmacological Sciences, 25(4), 1910–1915. doi:10.26355/eurrev_202102_25087.
18. Sridhar, N., Glisch, C., Jawa, Z., Chaudhary, L. N., Kamaraju, S., Burfeind, J., et al. (2022). Androgen receptor expression in patients with triple negative breast cancer treated with neoadjuvant chemotherapy: A single institution study. Journal of Cancer, 13(8), 2472–2476. doi:10.7150/jca.67536.
19. Thompson, K. J., Leon-Ferre, R. A., Sinnwell, J. P., Zahrieh, D. M., Suman, V. J., Metzger, F. O., et al. (2022). Luminal androgen receptor breast cancer subtype and investigation of the microenvironment and neoadjuvant chemotherapy response. NAR Cancer, 4(2), zcac018. doi:10.1093/narcan/zcac018.
20. Poggio, F., Bruzzone, M., Ceppi, M., Pondé, N. F., La Valle, G., Del Mastro, L., et al. (2018). Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: A systematic review and meta-analysis. Annals of Oncology, 29(7), 1497–1508. doi:10.1093/annonc/mdy127.

21. Bian, L., Yu, P., Wen, J., Sun, X., Li, J., Qin, T., et al. (2021). Survival benefit of platinum-based regimen in early stage triple negative breast cancer: A meta-analysis of randomized controlled trials. NPJ Breast Cancer, 7(1), 157. doi:10.1038/s41523-021-00367-w.
22. Spring, L. M., Fell, G., Arfe, A., Sharma, C., Greenup, R., Reynolds, K. L., et al. (2020). Pathologic complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival: A comprehensive meta-analysis. Clinical Cancer Research, 26(12), 2838–2848. doi:10.1158/1078-0432.CCR-19-3492.
23. Schmid, P., Cortes, J., Pusztai, L., McArthur, H., Kümmel, S., Bergh, J., et al. (2020). Pembrolizumab for early triple-negative breast cancer. The New England Journal of Medicine, 382(9), 810–821. doi:10.1056/NEJMoa1910549.
24. Schmid, P., Cortes, J., Dent, R., Pusztai, L., McArthur, H., Kümmel, S., et al. (2022). Event-free survival with pembrolizumab in early triple-negative breast cancer. The New England Journal of Medicine, 386(6), 556–567. doi:10.1056/NEJMoa2112651.
25. Schmid, P., Cortes, J., Dent, R., McArthur, H., Pusztai, L., Kümmel, S., et al. (2024). Overall survival with pembrolizumab in early-stage triple-negative breast cancer. The New England Journal of Medicine, 391(21), 1981–1991. doi:10.1056/NEJMoa2409932.
26. Toss, A., Venturelli, M., Civallero, M., Piombino, C., Domati, F., Ficarra, G., et al. (2022). Predictive factors for relapse in triple-negative breast cancer patients without pathological complete response after neoadjuvant chemotherapy. Frontiers in Oncology, 12, 1016295. doi:10.3389/fonc.2022.1016295.