Editorial Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.4829375610-293

Systemic Therapy After Curative Local Treatment for Isolated Locoregional Recurrence in Triple-Negative Breast Cancer: Evidence Gaps and a Practical Clinical Framework

Veli Çakıcı*[a]

[a]*Department of Internal Medicine, Division of Medical Oncology, Çanakkale Onsekiz Mart University Faculty of Medicine Hospital, Çanakkale, Turkey*

Triple-negative breast cancer (TNBC) represents one of the most challenging breast cancer subtypes in clinical decision-making following isolated locoregional recurrence (LRR) due to its aggressive biological characteristics and early propensity for systemic dissemination. Achieving locoregional control with curative intent through surgery, radiotherapy, or both does not necessarily imply that the disease has been biologically controlled in the context of TNBC. Rather, isolated LRR can often be interpreted as a clinical manifestation of underlying micrometastatic disease. Nevertheless, optimal systemic treatment strategies following curative local therapy—particularly in the TNBC population—remain insufficiently defined, even in contemporary clinical guidelines. In this article, I aim to address this TNBC-specific evidence gap in light of the existing literature and to propose a clinically applicable approach grounded in biological rationale.

The strongest prospective evidence directly evaluating the value of systemic therapy after isolated LRR is derived from the randomized CALOR trial. In its final analysis, adjuvant chemotherapy significantly improved disease-free survival in patients with completely resected isolated LRR who had estrogen receptor (ER)-negative disease, whereas no comparable benefit was observed in the ER-positive subgroup.[1] Given the substantial biological and clinical overlap between the ER-negative phenotype and TNBC, these findings strongly support adjuvant chemotherapy as a core component of treatment following locoregional recurrence in TNBC. Although the lack of standardized chemotherapy regimens in the CALOR trial represents a limitation, the results indicate that adjuvant chemotherapy in this setting represents a clinically well-supported strategy rather than merely an optional consideration.

However, the CALOR trial does not resolve the most critical question faced in daily practice: which chemotherapy regimen is appropriate for which patient? In routine clinical care, this decision is guided by prior exposure to anthracyclines and taxanes, the interval to recurrence, pathologic risk factors, and treatment tolerance. In particular, patients who experience early recurrence after intensive anthracycline-based and taxane-based therapy raise concerns regarding cross-resistance, prompting consideration of agents with alternative mechanisms of action.[1,2] Nevertheless, prospective validation of this approach in the TNBC LRR population remains limited. In this context, evidence derived from other high-risk clinical scenarios in early-stage TNBC may serve as an indirect but informative guide.

The CREATE-X trial demonstrated that adjuvant capecitabine significantly improved survival outcomes in patients with human epidermal growth factor receptor 2 (HER2)-negative breast cancer who had residual invasive disease after neoadjuvant chemotherapy, with the benefit being most pronounced in the TNBC subgroup. In contrast, the GEICAM/2003-11_CIBOMA/2004-01 trial, which evaluated routine use of capecitabine following standard neoadjuvant or adjuvant chemotherapy in early-stage TNBC, yielded negative results with respect to its primary end point.[3] This divergence suggests that capecitabine is not a universal adjuvant

***Address for correspondence:**
Veli Çakıcı,
Department of Internal Medicine, Division of Medical Oncology, Çanakkale Onsekiz Mart University, Faculty of Medicine Hospital, Çanakkale, Türkiye
E-mail: cakiciveli@gmail.com

strategy in TNBC but rather one that gains relevance in biologically high-risk settings, such as the presence of residual disease.[4] Accordingly, in selected patients with TNBC who develop isolated locoregional recurrence after curative local therapy, who have not previously received capecitabine, and who exhibit early recurrence or aggressive tumor features, capecitabine may be considered a reasonable therapeutic option. Beyond this, anthracyclines (e.g., doxorubicin or epirubicin), taxanes (e.g., paclitaxel or docetaxel), and platinum-based agents (e.g., carboplatin or cisplatin) may be biologically plausible choices; however, there is no comparable level of direct randomized evidence supporting their adjuvant use specifically after isolated LRR. Thus, the relative prominence of capecitabine in this context reflects not its proven superiority over other cytotoxic agents but rather the persistent evidence gap surrounding alternative chemotherapy options.

In patients with TNBC who harbor germline *BRCA1/2* mutations, the systemic treatment approach is supported by a more robust evidence base. The OlympiA trial demonstrated that 1 year of adjuvant olaparib significantly improved invasive disease-free survival and distant disease-free survival in patients with high-risk HER2-negative early breast cancer, with subsequent analyses confirming a benefit in overall survival.[5] These data suggest that, following curative local treatment for isolated locoregional recurrence in *BRCA*-mutated TNBC—particularly in patients without prior exposure to poly(ADP-ribose) polymerase (PARP) inhibitors—olaparib represents a strong, evidence-based systemic treatment option. Nevertheless, the absence of prospective data defining the optimal sequencing of olaparib relative to chemotherapy or capecitabine necessitates individualized treatment decisions based on clinical risk profiles and prior therapeutic exposure.

Immunotherapy has gained clinical relevance in early-stage TNBC primarily through neoadjuvant-based strategies. In the KEYNOTE-522 trial, the addition of pembrolizumab to neoadjuvant chemotherapy, followed by continuation of therapy after surgery, resulted in a significant improvement in event-free survival, with more recent analyses demonstrating an overall survival benefit.[6] However, these favorable outcomes do not imply that immunotherapy will confer a similar benefit when administered solely as an adjuvant approach after surgery. Indeed, in the ALEXANDRA/IMpassion030 trial, the addition of atezolizumab to standard adjuvant chemotherapy following surgery did not yield a clinically meaningful benefit.[7] Collectively, these findings indicate that adjuvant immunotherapy cannot be routinely recommended after curative local treatment for isolated LRR in TNBC based on current evidence. Accordingly, immunotherapy in this clinical setting should preferably be limited to clinical trials or—when trials are unavailable—considered only in carefully selected patients using an individualized approach.

Looking forward, the concept of minimal residual disease (MRD) and circulating tumor DNA (ctDNA)-based approaches may contribute to a more rational management of this clearly defined clinical gray zone. Recent systematic reviews and meta-analyses have consistently demonstrated that ctDNA positivity in early breast cancer is associated with a significantly increased risk of recurrence and mortality.[8,9] This biological signal offers substantial potential to identify patients with TNBC who harbor persistent systemic risk following curative local treatment for isolated locoregional recurrence.[9,10] However, ctDNA-guided treatment strategies have not yet been prospectively validated, and further studies are required before such approaches can be integrated into routine clinical practice. Taken together, these concepts are summarized in a descriptive clinical reasoning framework (Figure 1) integrating biological risk, prior treatment exposure, evidence-informed systemic options, and emerging MRD-guided strategies.

In conclusion, systemic treatment strategies following curative local therapy for isolated locoregional recurrence in TNBC continue to be shaped largely by indirect evidence despite a clear clinical need. Available data indicate that adjuvant chemotherapy represents an indispensable backbone in ER-negative or TNBC disease; that capecitabine gains relevance only in biologically high-risk, selected patients; and that olaparib offers a strong, evidence-based option in *BRCA*-mutated cases. In contrast, decisions regarding immunotherapy must carefully account for the distinction between perioperative success and the consistent lack of benefit observed with purely adjuvant strategies. In this context, biomarker-driven prospective studies—particularly those incorporating ctDNA or MRD—represent the most critical and currently unmet need for defining which patients should receive systemic therapy, when it should be administered, and on what biological basis. In the absence of such data, treatment decisions following isolated locoregional recurrence will inevitably continue to rely heavily on clinical judgment.

In conclusion, systemic treatment strategies following curative local therapy for isolated locoregional recurrence in TNBC continue to be shaped largely by indirect evidence despite a clear clinical need. Available data indicate that adjuvant

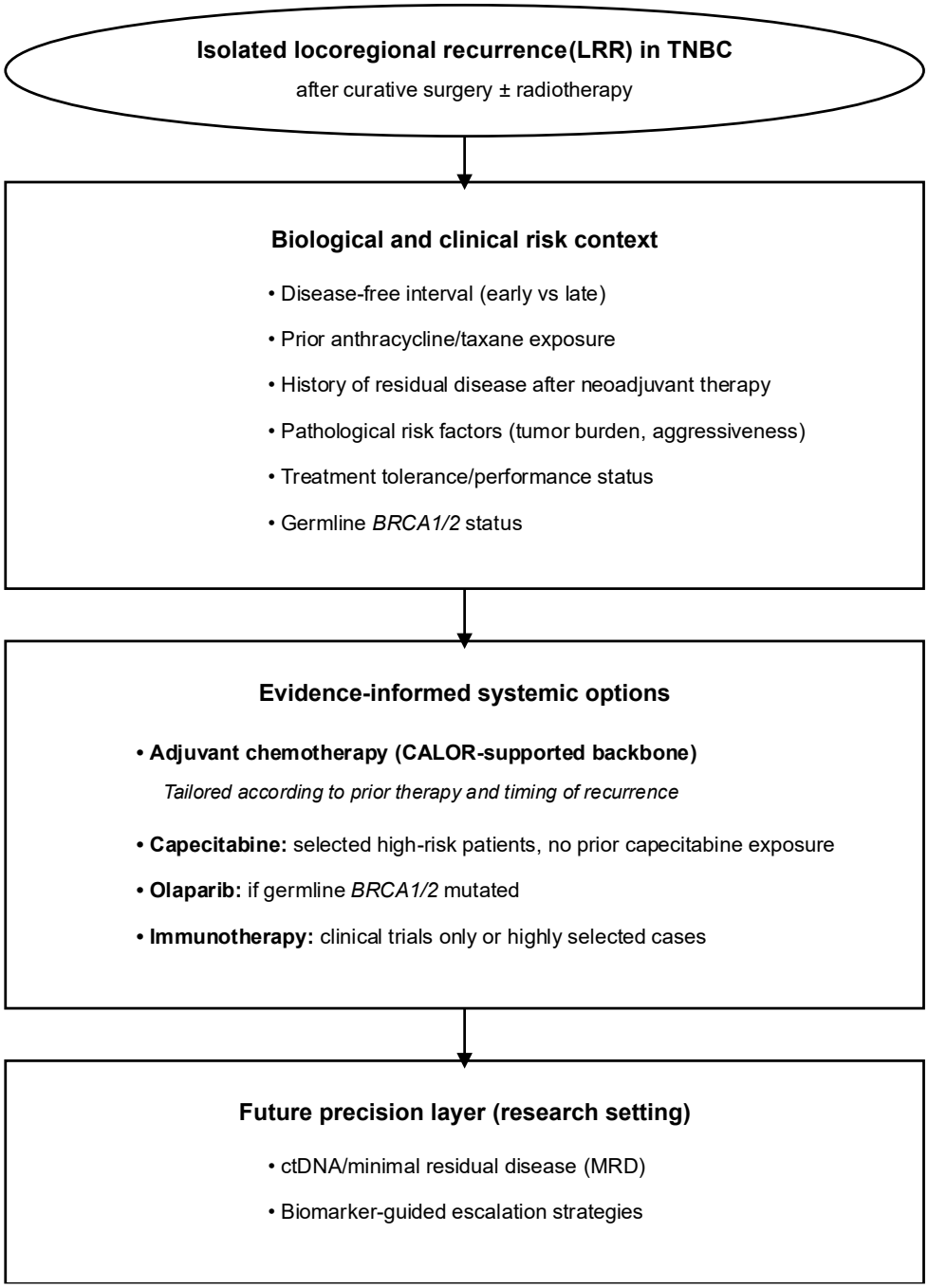

Figure 1. Conceptual Clinical Reasoning Framework for Systemic Therapy After Curative Local Treatment of Isolated Locoregional Recurrence in Triple-Negative Breast Cancer

chemotherapy represents an indispensable backbone in ER-negative or TNBC disease; that capecitabine gains relevance only in biologically high-risk, selected patients; and that olaparib offers a strong, evidence-based option in *BRCA*-mutated cases. In contrast, decisions regarding immunotherapy must carefully account for the distinction between perioperative success and the consistent lack of benefit observed with purely adjuvant strategies. In this context, biomarker-driven prospective studies—particularly those incorporating ctDNA or MRD—represent the most critical and currently unmet need for defining which patients should receive systemic therapy, when it should be administered, and on what biological basis. In the absence of such data, treatment decisions following isolated locoregional recurrence will inevitably continue to rely heavily on clinical judgment.

CONFLICT OF INTEREST

The author declares no conflict of interest related to this work.

ETHICAL CONSIDERATIONS

This article is a literature-based perspective and does not include any new patient data. Therefore, ethical committee approval was not required.

FUNDING

This study received no external funding.

AI DISCLOSURE

Generative artificial intelligence was used to assist with language editing and drafting. The final content was reviewed by the author, who takes full responsibility for the accuracy and integrity of the manuscript.

REFERENCES

1. Wapnir IL, Price KN, Anderson SJ, et al. Efficacy of Chemotherapy for ER-Negative and ER-Positive Isolated Locoregional Recurrence of Breast Cancer: Final Analysis of the CALOR Trial. *J Clin Oncol.* Apr 10 2018;36(11):1073-1079. doi:10.1200/JCO.2017.76.5719.
2. Ferrari P, Scatena C, Ghilli M, Bargagna I, Lorenzini G, Nicolini A. Molecular Mechanisms, Biomarkers and Emerging Therapies for Chemotherapy Resistant TNBC. *Int J Mol Sci.* Jan 31 2022;23(3). doi:10.3390/ijms23031665.
3. Lluch A, Barrios CH, Torrecillas L, et al. Phase III Trial of Adjuvant Capecitabine After Standard Neo-/Adjuvant Chemotherapy in Patients With Early Triple-Negative Breast Cancer (GEICAM/2003-11_CIBOMA/2004-01). *J Clin Oncol.* Jan 20 2020;38(3):203-213. doi:10.1200/JCO.19.00904.
4. Mayer IA, Zhao F, Arteaga CL, et al. Randomized Phase III Postoperative Trial of Platinum-Based Chemotherapy Versus Capecitabine in Patients With Residual Triple-Negative Breast Cancer Following Neoadjuvant Chemotherapy: ECOG-ACRIN EA1131. *J Clin Oncol.* Aug 10 2021;39(23):2539-2551. doi:10.1200/JCO.21.00976.
5. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. *N Engl J Med.* Jun 24 2021;384(25):2394-2405. doi:10.1056/NEJMoa2105215.
6. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. *N Engl J Med.* Feb 27 2020;382(9):810-821. doi:10.1056/NEJMoa1901917.
7. Ignatiadis M, Bailey A, McArthur H, et al. Adjuvant Atezolizumab for Early Triple-Negative Breast Cancer: The ALEXANDRA/IMpassion030 Randomized Clinical Trial. *Jama.* Jan 30 2025;333(13):1150-1160. doi:10.1001/jama.2024.26886.
8. Nader-Marta G, Monteforte M, Agostinetto E, et al. Circulating tumor DNA for predicting recurrence in patients with operable breast cancer: a systematic review and meta-analysis. *ESMO Open.* Mar 2024;9(3):102390. doi:10.1016/j.esmoop.2024.102390.
9. Zhang D, Jahanfar S, Rabinowitz JB, et al. Role of circulating tumor DNA in early-stage triple-negative breast cancer: a systematic review and meta-analysis. *Breast Cancer Res.* Mar 12 2025;27(1):38. doi: 10.1186/s13058-025-01986-y.
10. Xu J, Fang K, Li X, Han L, Sun S, Sun T. From residual risk to precision intervention: the evolving role of minimal residual disease in breast cancer management. *Cancer Biol Med.* Nov 28 2025;22(12):1493-1514. doi: 10.20892/j.issn.2095-3941.2025.0431.

How to Cite This Article

Çakıcı V. Systemic Therapy After Curative Local Treatment for Isolated Locoregional Recurrence in Triple-Negative Breast Cancer: Evidence Gaps and a Practical Clinical Framework. Arch Breast Cancer. 2026; 13(2):124-7.

Available from: https://www.archbreastcancer.com/index.php/abc/article/view/1276