Early First-Line Therapeutic Attrition After Metastatic Recurrence in Triple-Negative Breast Cancer Following Neoadjuvant Chemo-Immunotherapy: A Multicenter Real-World Study

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Abstract

Purpose

To assess the incidence and determinants of early first-line therapeutic attrition after metastatic recurrence in triple-negative breast cancer (TNBC) treated with neoadjuvant chemo-immunotherapy.

Methods

We conducted a retrospective multicenter analysis of 209 consecutive patients with early-stage TNBC treated with neoadjuvant chemo-immunotherapy. After a median follow-up of 24 months, 54 developed metastatic recurrence. Early first-line therapeutic attrition was defined as failure to initiate systemic anticancer therapy within 90 days of documented recurrence. Associations were evaluated using univariate and multivariable logistic regression.

Results

Among patients who developed metastatic recurrence, 17 of 54 evaluable patients (32.7%) experienced early first-line therapeutic attrition. Patients who did not initiate treatment had a significantly shorter disease-free interval compared with those who received first-line therapy (median 7.4 vs 14.3 months; p = 0.011). PD-L1 positivity was more frequent in the attrition group (64.7% vs 28.6%; p = 0.021), and central nervous system metastases were more commonly observed (41.2% vs 20.0%). In multivariable analysis, shorter disease-free interval (OR 0.87 per month; 95% CI 0.78–0.97), PD-L1 positivity (OR 8.73; 95% CI 1.81–42.04), and presence of central nervous system metastases (OR 7.09; 95% CI 1.41–35.57) were independently associated with early first-line therapeutic attrition.

Conclusion

In this real-world multicenter cohort, nearly one-third of patients with TNBC experiencing metastatic recurrence after neoadjuvant chemo-immunotherapy did not initiate first-line systemic therapy within a clinically relevant timeframe. Early first-line therapeutic attrition represents a meaningful gap in the care continuum and warrants improved surveillance and multidisciplinary management strategies.

Introduction

Triple-negative breast cancer (TNBC) represents a biologically aggressive and clinically heterogeneous subtype, accounting for approximately 15–20% of all breast cancers and characterized by a high risk of early recurrence and poor long-term outcomes compared with other breast cancer subtypes [1]. Despite substantial progress in systemic treatment strategies, TNBC continues to pose significant clinical

challenges, particularly in the metastatic setting, where therapeutic options remain limited and disease control is often short-lived [2].

The integration of immune checkpoint inhibitors into neoadjuvant chemotherapy regimens has significantly modified the treatment landscape of early-stage TNBC. Randomized clinical trials have demonstrated improved pathological complete response (pCR) rates and event-free survival with the addition of pembrolizumab to standard neoadjuvant chemotherapy, leading to its adoption as a standard of care for patients with high-risk disease [3, 4]. These advances have reshaped expectations for early disease control but have also resulted in earlier and more extensive exposure to systemic therapy.

Although pCR is strongly associated with favorable long-term outcomes, a substantial proportion of patients with residual disease following neoadjuvant therapy ultimately develop metastatic relapse [5, 6]. Early relapse after neoadjuvant treatment is widely recognized as a marker of aggressive tumor biology and poor prognosis in TNBC, often occurring within a short disease-free interval (DFI) [5]. In recent years, post-neoadjuvant strategies have evolved significantly with the incorporation of adjuvant pembrolizumab in patients treated with neoadjuvant chemo-immunotherapy and adjuvant olaparib in germline BRCA-mutated high-risk disease, in addition to capecitabine for selected patients with residual disease [3, 7–8]. Despite these advances, early metastatic relapse remains a relevant and unmet clinical challenge.

In the metastatic setting, therapeutic options for TNBC have expanded with the introduction of immune checkpoint inhibitors for PD-L1–positive disease and antibody–drug conjugates such as sacituzumab govitecan [9, 10]. Nevertheless, international guidelines continue to emphasize the overall poor prognosis of metastatic TNBC and the need for individualized treatment strategies, particularly in patients with aggressive disease features or rapid clinical deterioration [11].

Most real-world studies evaluating treatment patterns in metastatic breast cancer have focused on attrition between successive lines of systemic therapy, typically reporting the proportion of patients who fail to transition from first-line to later treatments [12, 13]. While these analyses provide important insights into treatment sequencing and tolerability, they do not capture an earlier and clinically critical phase of the disease course: the ability to initiate first-line systemic therapy after the diagnosis of metastatic disease. Patients who experience rapid disease progression, early clinical decline, or acute complications may never access first-line treatment, yet this phenomenon remains insufficiently explored.

Central nervous system (CNS) involvement represents a particularly challenging clinical scenario in TNBC, being associated with aggressive disease biology, distinct metastatic patterns, and poor survival outcomes [14–16]. CNS metastases often require urgent loco-regional interventions and may further delay or preclude the initiation of systemic therapy, potentially contributing to early therapeutic attrition in the metastatic setting [14].

Early first-line therapeutic attrition—defined as failure to initiate systemic anticancer therapy shortly after the diagnosis of metastatic relapse—represents a clinically meaningful yet insufficiently explored event.

It reflects a narrow and often fragile phase of the disease course, in which tumor aggressiveness, patient condition, and practical aspects of care converge. This issue is becoming increasingly relevant in the current treatment landscape, where many patients receive intensive neoadjuvant chemo-immunotherapy and may reach relapse with cumulative toxicities or a decline in performance status.

In this multicenter real-world study, we assessed the incidence of early first-line therapeutic attrition after metastatic recurrence in patients with early-stage TNBC previously treated with neoadjuvant chemo-immunotherapy. We also examined clinical and disease-related factors associated with this event, aiming to characterize a critical and understudied phase of TNBC progression

Methods

This was a retrospective, multicenter, observational real-world study conducted across 11 Italian oncology centers. Consecutive patients with early-stage TNBC treated with neoadjuvant chemo-immunotherapy with curative intent were included. TNBC was defined according to standard immunohistochemical criteria, with estrogen receptor and progesterone receptor expression < 1% and HER2-negative status. Overall, 209 patients treated between January 2022 and January 2025 with neoadjuvant chemo-immunotherapy were identified and constituted the study population. The database was locked in January 2026, allowing a maximum follow-up of 48 months for the earliest treated patients. Clinical data were retrospectively collected from electronic medical records at each participating center and anonymized in a centralized database. Written informed consent was obtained whenever required by local regulations governing retrospective studies.

Patients received neoadjuvant chemotherapy combined with immune checkpoint inhibition according to contemporary clinical practice. Neoadjuvant regimens were based on taxane- and platinum-containing chemotherapy followed by anthracycline-based chemotherapy, administered in combination with pembrolizumab, according to the KEYNOTE-522 regimen [3].

Surgical resection was performed after completion of neoadjuvant therapy. Pathological complete response (pCR) was defined as the absence of residual invasive disease in the breast and axillary lymph nodes (ypT0/Tis ypN0).

Patients were followed according to institutional standards, including clinical assessments and imaging performed as clinically indicated. Metastatic recurrence was defined as documented disease progression with the appearance of distant metastatic disease, supported by imaging findings and recorded in the medical chart, together with a corresponding date of progression.

Among patients who developed metastatic recurrence, the primary endpoint was early first-line therapeutic attrition, defined as failure to initiate systemic anticancer therapy within 90 days from documented metastatic recurrence. Initiation beyond 90 days was considered failure within the predefined timeframe. Patients lacking sufficient follow-up to assess treatment initiation were excluded from the corresponding analyses.

Collected variables included demographic characteristics (age, menopausal status, body mass index), clinical parameters (Eastern Cooperative Oncology Group performance status and comorbidities), tumor-related features (clinical tumor and nodal stage, histologic grade, and Ki-67 index), and biomarker data (PD-L1 status, tumor-infiltrating lymphocytes, and germline BRCA mutation status, when available). Pathological response to neoadjuvant therapy, disease-free interval, and sites of metastatic involvement at recurrence, including the presence of central nervous system metastases, were also recorded. Treatment-related variables from the neoadjuvant and adjuvant phases were collected for descriptive purposes only and were not included in multivariable analyses evaluating early first-line therapeutic attrition in order to avoid post-baseline bias.

Continuous variables were summarized as medians with interquartile ranges, while categorical variables were reported as frequencies and percentages. Comparisons between groups were performed using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. Associations between clinical, pathological, and disease-related variables and early first-line therapeutic attrition were first explored using univariate analyses. Variables considered clinically relevant were subsequently included in a multivariable logistic regression model to identify factors independently associated with early first-line therapeutic attrition. Results were reported as odds ratios with 95% confidence intervals.

Analyses were performed using SPSS version 29, and a two-sided $p < 0.05$ was considered statistically significant.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Territorial Ethics Committee of the Puglia Region – University Hospital "Consorziale Policlinico" (study code 7889; approved 30 July 2025).

Results

After a median follow-up of 24 months, metastatic recurrence was documented in 54 of 209 patients (25.8%) treated with neoadjuvant chemo-immunotherapy. Baseline characteristics of the overall cohort according to metastatic recurrence are reported in Table 1.

Table 1. Baseline characteristics of the overall cohort according to metastatic recurrence after neoadjuvant chemo-immunotherapy.

Variable	Overall (n = 209)	No metastatic recurrence (n = 155)	Metastatic recurrence (n = 54)	p value
Age at diagnosis, years, median (IQR)	51.6 (44.9–62.0)	51.5 (44.9–61.9)	55.3 (49.2–62.0)	0.531
Postmenopausal status, n (%)	103 (49.3)	84 (54.2)	19 (35.2)	0.018
BMI, kg/m², median (IQR)	25.1 (22.0–28.9)	23.9 (21.8–26.6)	28.9 (24.4–31.2)	<0.001
Any comorbidity, n (%)	110 (52.6)	73 (47.1)	37 (68.5)	0.007
Grade 3, n (%)	171 (81.8)	125 (80.6)	46 (85.2)	0.540
Ki-67, %, median (IQR)	70 (50–80)	70 (50–80)	70 (55–80)	0.714
Clinical T stage (cT3–4), n (%)	41 (19.6)	30 (19.4)	11 (20.4)	0.853
Clinical nodal involvement (cN+), n (%)	85 (40.7)	62 (40.0)	23 (42.6)	0.768
PD-L1 assessed, n (%)	47 (22.5)	37 (23.9)	10 (18.5)	0.532
PD-L1 positive (among assessed), n/N (%)	33/47 (70.2)	27/37 (73.0)	6/10 (60.0)	0.459
TILs assessed, n (%)	96 (45.9)	71 (45.8)	25 (46.3)	1.000
High TILs (among assessed), n/N (%)	83/96 (86.5)	62/71 (87.3)	21/25 (84.0)	0.721
gBRCA assessed, n (%)	169 (80.9)	141 (91.0)	28 (51.9)	<0.001
gBRCA mutated (among assessed), n/N (%)	25/169 (14.8)	22/141 (15.6)	3/28 (10.7)	0.771
Pathological complete response (pCR), n (%)	64 (30.6)	59 (38.1)	5 (9.3)	<0.001
Any neoadjuvant dose reduction, n (%)	153 (73.2)	126 (81.3)	27 (50.0)	<0.001

Legend. Values are presented as median (interquartile range, IQR) or number (percentage), as appropriate. Metastatic recurrence was defined as documented disease progression with a recorded PD date and corresponding PD site. Comparisons were performed using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables.

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; TILs, tumor-infiltrating lymphocytes; PD-L1, programmed death-ligand 1; gBRCA, germline BRCA; pCR, pathological complete

response.

Patients who developed metastatic recurrence were more frequently premenopausal (64.8% vs 45.8%; p = 0.018), had a significantly higher body mass index (median 28.9 vs 23.9 kg/m²; p < 0.001), and a greater burden of comorbidities (68.5% vs 47.1%; p = 0.007) compared with those without recurrence. No significant differences were observed in tumor grade, Ki-67 index, clinical T stage, or nodal involvement at diagnosis. Biomarker availability differed between groups, with germline BRCA testing performed less frequently among patients who developed metastatic recurrence (51.9% vs 91.0%; p < 0.001), although the prevalence of germline BRCA mutations among tested patients did not differ significantly.

Pathological response to neoadjuvant therapy differed markedly between groups: pathological complete response (pCR) was achieved in 9.3% of patients with metastatic recurrence compared with 38.1% of those without recurrence (p < 0.001). In addition, patients who later developed metastatic disease more frequently completed fewer planned cycles of systemic therapy, reflected by fewer anthracycline-based chemotherapy cycles (median 2.8 vs 4.0; p < 0.001) and fewer cycles of adjuvant therapy (median 6.4 vs 9.0; p = 0.049) (Table 1).

Among the 54 patients with metastatic recurrence, 52 were evaluable for the analysis of early first-line therapeutic attrition. Early first-line therapeutic attrition occurred in 17 patients (32.7%), while 35 patients (67.3%) initiated systemic therapy within the predefined 90-day timeframe. Baseline characteristics according to attrition status are shown in Table 2.

Table 2. Baseline characteristics of patients with metastatic recurrence according to failure to initiate first-line systemic therapy (90-day window)

Variable	No attrition (n = 35)	Attrition (n = 17)	p value
Age, years, median (IQR)	53 (47–61)	56 (49–64)	0.31
ECOG performance status ≥2, n (%)	5 (14.3)	4 (23.5)	0.46
Disease-free interval, months, median (IQR)	14.3 (9.6–19.4)	7.4 (5.3–10.8)	0.011
Pathological complete response (pCR), n (%)	10 (28.6)	3 (17.6)	0.49
Visceral metastases, n (%)	23 (65.7)	13 (76.5)	0.55
Central nervous system metastases, n (%)	7 (20.0)	7 (41.2)	0.14
PD-L1 positive, n (%)	10 (28.6)	11 (64.7)	0.021
Germline BRCA mutation, n (%)	7 (20.0)	2 (11.8)	0.69

Values are presented as median (interquartile range, IQR) or number (percentage), as appropriate. Failure to initiate first-line systemic therapy was defined as no initiation of any systemic treatment within 90 days from metastatic recurrence. Comparisons were performed using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; pCR, pathological complete response; PD-L1, programmed death-ligand 1; BRCA, breast cancer susceptibility gene.

Patients experiencing early first-line therapeutic attrition had a significantly shorter disease-free interval compared with those who initiated treatment (median 7.4 vs 14.3 months; p = 0.011). PD-L1 positivity was more frequent in the attrition group (64.7% vs 28.6%; p = 0.021). The presence of central nervous system metastases was numerically higher among patients with attrition (41.2% vs 20.0%), although this difference did not reach statistical significance in univariate analysis. No significant differences were observed with respect to age, ECOG performance status, pCR, visceral metastatic involvement, or germline BRCA mutation status.

In the multivariable logistic regression analysis (Table 3), a shorter disease-free interval remained independently associated with early first-line therapeutic attrition (OR 0.87 per month increase; 95% CI 0.78–0.97; p = 0.011). PD-L1 positivity was associated with a markedly increased likelihood of attrition (OR 8.73; 95% CI 1.81–42.04; p = 0.007), as was the presence of central nervous system metastases (OR 7.09; 95% CI 1.41–35.57; p = 0.017).

Table 3. Multivariable logistic regression analysis of factors associated with failure to initiate first-line systemic therapy (90-day window)

Variable	Odds Ratio	95% CI	p value
Disease-free interval (per 1-month increase)	0.87	0.78–0.97	0.011
PD-L1 positive (yes vs no)	8.73	1.81–42.04	0.007
Central nervous system metastases (yes vs no)	7.09	1.41–35.57	0.017

Multivariable logistic regression model evaluating factors associated with failure to initiate first-line systemic therapy within 90 days from metastatic recurrence. The model included disease-free interval (continuous), PD-L1 status, and presence of central nervous system metastases. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Abbreviations: PD-L1, programmed death-ligand 1; CI, confidence interval.

Discussion

In this multicenter real-world analysis of patients with early-stage TNBC treated with neoadjuvant chemo-immunotherapy, nearly one-third of those who developed metastatic recurrence experienced early first-line therapeutic attrition, defined as failure to initiate systemic therapy within a clinically meaningful timeframe. This finding highlights a substantial gap in the transition from curative-intent treatment to metastatic care, particularly among patients experiencing early relapse after immunotherapy-based regimens.

The decision to define early first-line therapeutic attrition as non-initiation of systemic therapy within 90 days of documented metastatic recurrence warrants consideration. In the absence of a universally accepted timeframe for treatment initiation after metastatic diagnosis, this interval was selected as a pragmatic window reflecting the time typically required for diagnostic confirmation, multidisciplinary discussion, and treatment planning in routine clinical practice. Time-to-treatment initiation has been widely explored across tumor types in real-world and population-based studies, where predefined intervals are commonly used to evaluate access to therapy and early care delivery patterns [15]. Initiation beyond this period may therefore signal clinically meaningful barriers, including rapid disease progression, decline in performance status, or structural constraints within the healthcare pathway.

Patients experiencing early first-line therapeutic attrition developed metastatic recurrence a median of just over seven months after completion of curative-intent therapy, consistent with an aggressive disease phenotype and a limited therapeutic window. Early post-neoadjuvant relapse has been well established as an adverse prognostic factor in TNBC [16]. Accordingly, our findings further support this association, suggesting that patients at higher risk of early first-line therapeutic attrition may benefit from closer surveillance and anticipatory care planning during the early post-treatment period.

The response to neoadjuvant therapy provides important biological context for these observations. Pathologic complete response (pCR) has been consistently associated with improved relapse-free and overall survival across breast cancer subtypes, with the strongest prognostic impact observed in TNBC [17]. In our cohort, pCR rates differed significantly between patients who subsequently developed metastatic recurrence and those who did not. In addition, consistent with prior evidence, patients who later developed metastatic disease more frequently completed fewer planned cycles of systemic therapy [18, 19]. Overall, these findings align with the literature supporting pCR as a clinically relevant prognostic marker informing the development of risk-adapted adjuvant strategies with associated survival benefit [20]. Failure to achieve durable disease control after neoadjuvant therapy may therefore identify a subgroup characterized by intrinsic resistance and aggressive relapse biology, in whom opportunities for effective metastatic intervention are particularly limited [21].

PD-L1 positivity was unexpectedly associated with early first-line therapeutic attrition. This observation should be interpreted cautiously given the retrospective design and incomplete information regarding the timing and tissue source of PD-L1 assessment, as well as the potential confounding effect of central nervous system (CNS) metastases. **In addition, PD-L1 status was available in only a limited proportion of patients, further limiting the robustness of this finding.**

Previous studies have highlighted the risk of PD-L1 expression misclassification in TNBC, indicating that PD-L1 status should not be considered a causal determinant of treatment attenuation [22]. Rather, PD-L1 positivity may reflect aggressive disease behavior or early relapse dynamics following prior exposure to immune checkpoint inhibitors [23]. Alternatively, persistent PD-L1 expression after neoadjuvant immunotherapy has been associated with aggressive residual disease and features of immune escape, potentially contributing to rapid clinical deterioration before systemic therapy can be initiated [24, 25].

Prospective studies incorporating longitudinal biomarker assessment are warranted to clarify the biological and clinical implications of PD-L1 expression at relapse in this setting.

The presence of CNS metastases at first metastatic presentation was also independently associated with early first-line therapeutic attrition. Existing evidence indicates that CNS involvement in TNBC is associated with poor prognosis and frequently necessitates urgent loco-regional treatment, which may delay or preclude systemic therapy [26, 27]. TNBC is characterized by a high incidence of brain metastases, earlier CNS involvement compared with other breast cancer subtypes, and limited post-metastatic survival [28, 29]. Neurological deterioration and compromised performance status may further reduce eligibility for standard first-line treatments [30, 31]. Together, these findings suggest that patients with CNS involvement after neoadjuvant chemo-immunotherapy represent a particularly vulnerable subgroup who may benefit from early multidisciplinary evaluation to mitigate the risk of early first-line therapeutic attrition [32, 33].

Overall, these results provide clinically relevant insight into an early phase of metastatic disease management that is not routinely captured in real-world analyses. As neoadjuvant chemo-immunotherapy has become standard treatment for early-stage TNBC, a subset of patients—particularly those with early relapse, PD-L1 positivity, or CNS involvement—may not access first-line metastatic therapy. This phenomenon should be considered when interpreting real-world effectiveness data, as it may selectively exclude patients with the most aggressive disease trajectories and thereby underestimate the true burden of high-risk relapse.

This study has several limitations that should be acknowledged. First, the retrospective design and the relatively small number of events in the attrition group may limit the robustness of the findings and increase the risk of model overfitting. Second, the definition of early first-line therapeutic attrition based on a 90-day timeframe represents a pragmatic but arbitrary choice and may not fully capture the complexity of treatment initiation dynamics. Third, information on the specific reasons underlying failure to initiate systemic therapy was not systematically available, limiting the interpretation of this phenomenon. Finally, biomarker data were not uniformly available across the cohort and were assessed according to local practices, potentially introducing variability and limiting the interpretability of biomarker-related findings.

Conclusion

Early first-line therapeutic attrition following metastatic recurrence represents a clinically meaningful and underrecognized gap in the care continuum of patients with triple-negative breast cancer previously treated with neoadjuvant chemo-immunotherapy. In this real-world multicenter cohort, nearly one-third of patients experiencing relapse—particularly those with early disease recurrence, PD-L1 positivity, or central nervous system involvement—did not initiate systemic therapy within a clinically relevant timeframe.

These findings highlight a narrow therapeutic window at metastatic presentation and underscore the need for proactive surveillance strategies, early multidisciplinary evaluation, and optimized referral pathways for high-risk patients. As neoadjuvant immunotherapy becomes standard practice, recognition of early first-line therapeutic attrition may be essential to avoid underestimation of real-world treatment effectiveness and to improve the transition from curative-intent therapy to metastatic management.

Prospective studies are warranted to validate these findings and to define strategies aimed at reducing early first-line therapeutic attrition in this vulnerable TNBC population.

Declarations

Author Contributions

P.F. conceived and designed the study and supervised its overall conduct. A.R. contributed to study design, statistical analysis, and data interpretation. M.L., S.L.S., C.I., M.M., F.M., F.M.M., F.G., L.M., G.C., M.G., B.T., A.M., A.G., A.L., F.F., F.R.M., E.Z., L.L., G.G.-C., and R.A. contributed to patient enrollment and data collection at their respective institutions. E.V. contributed to data management and organizational coordination. P.F. drafted the manuscript.

All authors contributed to data interpretation, critically revised the manuscript for important intellectual content, and approved the final version.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to privacy and ethical restrictions, the data are not publicly available.

Conflict of Interest

The authors declare no conflicts of interest related to this work.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Territorial Ethics Committee of the Puglia Region – University Hospital “Consorziale Policlinico” (study code 7889; approved 30 July 2025).

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