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Heterogeneity of Residual Disease After Neoadjuvant Systemic Therapy in Breast Cancer
A Review

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IMPORTANCE Over the past 2 decades, systemic therapy for early-stage breast cancer has gradually moved from the adjuvant to the neoadjuvant setting. Administration of systemic therapy before surgery leads to potential improvements in surgical outcomes and allows for the assessment of the pathologic response to treatment. For patients with residual disease (RD), 3 adjuvant strategies have been shown to improve outcomes: (1) adjuvant trastuzumab emtansine for *ERBB2*-positive disease, (2) adjuvant capecitabine for triple-negative disease, and (3) adjuvant olaparib for patients with germline *BRCA* variants. Furthermore, studies are testing novel drugs in the postneoadjuvant setting. Given the potential to tailor adjuvant therapy based on the response to preoperative systemic therapy, recognizing the complexities of response to neoadjuvant therapy and moving beyond the binary paradigm of RD vs experiencing a pathologic complete response is becoming increasingly necessary.

OBSERVATIONS Novel antibody-drug conjugates, anti-*ERBB2* tyrosine kinase inhibitors, and immune checkpoint inhibitors are being evaluated as additional rescue options in phase 3 trials for patients with RD after neoadjuvant treatment. Concomitantly, the prognostic role of RD has been refined by the introduction of the residual cancer burden. In addition, the genomic landscape of RD has been found to be associated with long-term prognosis, as has the immune background of the disease evaluated via the presence of tumor-infiltrating lymphocytes. Lastly, the dynamics of circulating tumor DNA may allow for further improvement in prognostication by understanding which patients harbor detectable minimal RD.

CONCLUSIONS AND RELEVANCE Escalating adjuvant treatment has led to meaningful survival improvements among patients with breast cancer and RD after neoadjuvant therapy. Uncovering the anatomic and biological intricacies of RD will allow for increased precision in postneoadjuvant treatments, moving beyond the binary paradigm of RD vs pathologic complete response, toward more tailored rescue strategies in the adjuvant setting.

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Recognizing that the administration of adjuvant chemotherapy can significantly reduce the risk of breast cancer recurrence has ignited great advancements in the treatment of this disease.[1] In the past 50 years, chemotherapy regimens have been fine-tuned, biologic treatments have been developed, and identification of breast cancer subtypes, genomic signatures, and other prognostic factors have allowed for the refined use of systemic therapy.[2] Notably, a major change that has occurred in the field has been the movement from the adjuvant use of chemotherapy to neoadjuvant administration. Indeed, most patients with *ERBB2*-positive (formerly *HER2*-positive) and triple-negative breast cancer (TNBC) are currently treated with neoadjuvant systemic therapy before surgery.[3] While the pendulum had swung away from neoadjuvant systemic therapy for hormone receptor (HR)–positive disease with the use of multigene assays identifying even node-positive patients who would not benefit from chemotherapy, preoperative systemic therapy in high-risk HR-positive disease may experience a resurgence given the promising data with neoadjuvant chemoimmunotherapy in two phase 3 trials.[4-6]

The neoadjuvant administration of systemic therapy has several advantages compared to the adjuvant administration, including downstaging the disease allowing for less extensive surgery, obtaining an in vivo assessment of treatment sensitivity, and providing more refined information about a patient's prognosis. Patients with residual disease (RD) at surgery after neoadjuvant systemic therapy have worse long-term prognosis than those experiencing a pathologic complete response (pCR).[7] However, recent insights into the complexity of RD have enabled further refinement of this binary concept and the analysis of different degrees of RD associated with distinct prognoses within each breast cancer subtype. In this Review, we discuss ongoing efforts and future perspectives in the tailoring of treatment according to the complexity of RD after neoadjuvant therapy.

Observations

Current Standard of Treatment of RD

A large meta-analysis published in 2014 from 12 clinical trials of neoadjuvant treatment for breast cancer found that patients who experience pCR at surgery after neoadjuvant systemic therapy have improved long-term event-free survival (EFS) and overall survival (OS) compared to those with RD.[7] Response at surgery and long-term outcomes are associated with disease subtype, with the largest effect size observed in patients with TNBC and *ERBB2*-positive breast cancer, although statistical and clinical significance was also reached among patients with HR-positive/*ERBB2*-negative disease.[7] Moreover, such associations were found at the patient level but were weaker at the trial level.[8]

Based on the observation of worse outcomes for patients with RD at surgery, prospective trials were developed to escalate adjuvant treatment in this population, ultimately shaping current clinical practice. The phase 3 CREATE-X trial demonstrated that adding 6 to 8 cycles of adjuvant capecitabine can improve OS among patients with TNBC with RD after neoadjuvant therapy.[9] Similarly, the phase 3 KATHERINE trial showed that escalating adjuvant treatment with trastuzumab emtansine (T-DM1) can improve invasive disease-free survival and OS compared with adjuvant trastuzumab among patients with *ERBB2*-positive breast cancer and RD after neoadjuvant therapy.[10,11] More recently, the phase 3 Olympia trial demonstrated that adjuvant olaparib can improve OS among patients with a germline *BRCA* variant and RD after neoadjuvant therapy, with a beneficial effect observed among patients with TNBC and high-risk HR-positive breast cancer.[12] All these strategies have allowed for improvements in long-term prognoses for patients with RD at surgery and may have partly overcome the adverse prognostic effect associated with this biomarker, particularly for TNBC and *ERBB2*-positive tumors. However, not all trials succeeded at improving outcomes for patients with RD at surgery, such as the randomized phase 3 EA1131 trial (adjuvant platinum vs capecitabine), the randomized phase 2 BRE09-146 trial (adjuvant cisplatin with or without rucaparib), and the randomized phase 2 BRE12-158 trial (personalized vs standard adjuvant treatment), which all did not improve outcomes for patients with TNBC and RD after neoadjuvant treatment. Moreover, a relevant recurrence rate was still observed even in trials achieving significant results despite adjuvant treatment escalation, suggesting the need for further research to optimize patient outcomes.[13-15]

Ongoing Trials of Treatment Escalation for Patients With RD at Surgery

A rapid expansion in the arsenal of effective anticancer drugs is creating new opportunities for postneoadjuvant treatment escalation (**Table**).[16-39] The anti-*ERBB2* antibody-drug conjugate (ADC) trastuzumab deruxtecan has been found to improve OS compared with T-DM1 in the metastatic setting and is now being compared to T-DM1 for the postneoadjuvant treatment of patients with *ERBB2*-positive RD (DESTINY-Breast05 trial).[16,40] The anti-Trop2 ADC sacituzumab govitecan has achieved improvements in OS in both metastatic HR-positive and TNBC, and is now being tested as an escalation therapy in the postneoadjuvant setting for patients with *ERBB2*-negative RD after neoadjuvant therapy (OptimICE-RD trial and SASCIA trial).[25,26,41,42] Two additional Trop2-targeted ADCs, datopotamab deruxtecan and sacituzumab tirumotecan, have been shown to be superior to traditional chemotherapy in the metastatic setting.[43] They are now being tested in the postneoadjuvant setting in the TROPION-Breast03 phase 3 trial and in the MK-2870-012 phase 3 trial, respectively.[24]

Beyond ADCs, other drugs that could improve outcomes in the postneoadjuvant setting include the *ERBB2* tyrosine kinase inhibitor tucatinib (in combination with T-DM1) and the immune checkpoint inhibitor pembrolizumab. These are being tested in the postneoadjuvant CompassHER2-RD and SWOG1418 phase 3 trials, respectively, after demonstrating improved outcomes in the metastatic setting.[18,31,44,45] Additional immune checkpoint inhibitors being tested in the postneoadjuvant setting include the programmed death-ligand 1 (PD-L1) inhibitors avelumab (A-Brave phase 3 trial) and atezolizumab (Astefania phase 3 trial).[17,32]

All the above-mentioned agents hold promise in improving outcomes for patients with RD after neoadjuvant therapy. Simultaneously, however, these escalation strategies may result in an increase in toxic effects experienced by patients. Both trastuzumab deruxtecan and datopotamab deruxtecan have been associated with the risk of life-threatening interstitial lung disease and preliminary safety results from SASCIA have shown an increase in severe toxic effects with sacituzumab govitecan.[25,43,46-48] Adjuvant immunotherapy has been associated with potentially permanent and life-threatening immune-related adverse effects; when combined with T-DM1, tucatinib has been associated with high (>50%) rates of nausea, diarrhea, and fatigue.[49,50] Thus, optimizing the selection of patients for these highly effective but also potentially toxic escalation strategies is imperative. Recent insights on the intricacies of RD after neoadjuvant therapy may help in achieving this goal.

Analyzing the Heterogeneity of RD

Moving beyond the binary concept of RD and pCR requires the analysis of multiple factors pertaining to the anatomic extent of RD as well as the biological characteristics and immunologic background of the residual tumor. The integration of these features with additional relevant prognostic factors such as minimal RD (MRD) may lead to improvement in treatment tailoring by modulating treatment intensity according to the predicted risk of recurrence (**Figure**).

Residual Cancer Burden

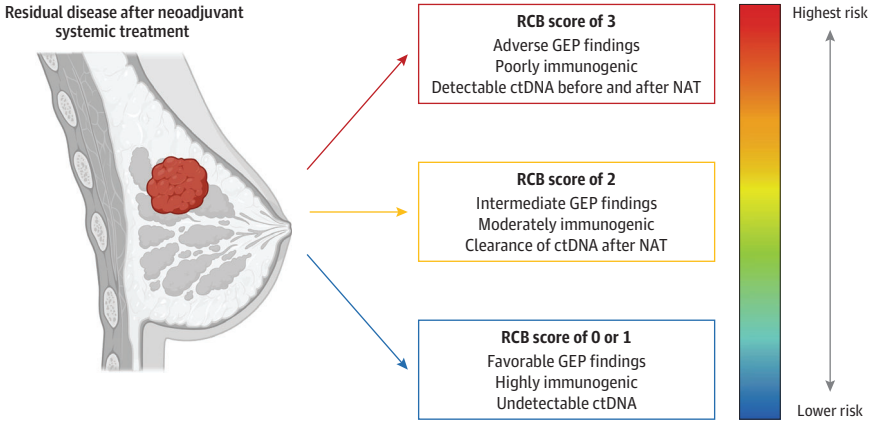
RD represents a heterogeneous entity, which includes differing extents of residual invasive tumors that can be found at surgery. On one end of the spectrum, only microscopic invasive cancer can be found on pathologic examination of the surgical specimen; on the other end, however, tumors can progress during neoadjuvant therapy, resulting in extensive invasive disease at surgery. To account for this heterogeneity in RD extent, more granular scores have been developed in the past few decades. For instance, the Miller/Payne 5-tiered grading system was developed in 2003 to account for different degrees of tumor cellularity found at surgery and was found to be significantly and independently associated with outcomes among patients with RD at surgery.[51] The residual cancer burden (RCB) was subsequently introduced in 2007 as a more comprehensive assessment of risk that also took into account the primary tumor dimensions and nodal burden.[52] More specifically, the RCB is derived by the integration of 4 parameters of RD: the diameter of

Table. Ongoing Trials of Treatment Escalation for Patients With Breast Cancer and Residual Disease After Neoadjuvant Treatment

Clinical trial/phase	Population	Drug regimen
***ERBB2*-positive disease**		
DESTINY-Breast05/phase 3 trial[16]	Patients with *ERBB2*-positive breast cancer with residual invasive disease following completion of ≥6 cycles of neoadjuvant therapy including taxanes and *ERBB2* blockade	Trastuzumab deruxtecan for 14 cycles (vs trastuzumab emtansine)
Astefania/phase 3 trial[17]	Patients with *ERBB2*-positive breast cancer with residual invasive disease following completion of ≥9 wk of neoadjuvant therapy including taxanes and *ERBB2* blockade	Trastuzumab emtansine with or without atezolizumab for 14 cycles
CompassHER2 RD/phase 3 trial[18]	Patients with *ERBB2*-positive breast cancer with residual invasive disease following completion of neoadjuvant therapy including taxanes and *ERBB2* blockade	Trastuzumab emtansine with or without tucatinib for 14 cycles
KAN-HER2/phase 2 trial[19]	Patients with *ERBB2*-positive breast cancer with detected molecular residual disease following standard neoadjuvant therapy	Trastuzumab emtansine and neratinib for 1 y
ATP/phase 3 trial[20]	Patients with *ERBB2*-positive breast cancer with residual invasive disease following completion of neoadjuvant therapy including chemotherapy and *ERBB2* blockade	Pyrotinib vs placebo for 1 y
NCT04973319/phase 3 trial[21]	Patients with *ERBB2*-positive breast cancer with residual invasive disease following completion of neoadjuvant therapy including trastuzumab and pertuzumab	Pyrotinib for 1 y
NCT04197687/phase 2 trial[22]	Patients with *ERBB2*-positive breast cancer with detected molecular residual disease following standard neoadjuvant therapy	TPIV100 and sargramostim
NCT03384914/phase 2 trial[23]	Patients with *ERBB2*-positive breast cancer with residual invasive disease following completion of neoadjuvant therapy including chemotherapy and *ERBB2* blockade	DC1 vaccine or WOKVAC vaccine in addition to standard-of-care adjuvant treatment
***ERBB2*-negative disease**		
TROPION-Breast03/phase 3 trial[24]	Patients with triple-negative breast cancer with residual invasive disease following ≥6 cycles of neoadjuvant therapy containing an anthracycline and/or a taxane with or without platinum chemotherapy, with or without pembrolizumab	Datopotamab deruxtecan with or without durvalumab for 8 cycles (vs treatment of physician's choice)
SASCIA/phase 3 trial[25]	Patients with *ERBB2*-negative breast cancer with residual invasive disease following neoadjuvant taxane-based chemotherapy for ≥16 wk	Sacituzumab govitecan for 8 cycles (vs standard-of-care chemotherapy)
OptimICE-RD/ASCENT-05/phase 3 trial[26]	Patients with triple-negative breast cancer with residual invasive disease following standard neoadjuvant therapy	Sacituzumab govitecan and pembrolizumab for 8 cycles (vs treatment of physician's choice)
MK-2870-012/phase 3 trial[27]	Patients with triple-negative breast cancer with residual invasive disease following the neoadjuvant KEYNOTE-522 regimen (chemotherapy plus pembrolizumab)	Sacituzumab tirumotecan and pembrolizumab (vs pembrolizumab or pembrolizumab plus capecitabine)
ZEST/phase 3 trial[28]	Patients with *ERBB2*-negative breast cancer with residual invasive disease following standard neoadjuvant therapy	Niraparib (vs placebo)
ASPRIA/phase 2 trial[29]	Patients with triple-negative breast cancer with residual invasive disease and detectable ctDNA following standard neoadjuvant therapy	Sacituzumab govitecan and atezolizumab for 6 cycles
COGNITION-GUIDE/phase 2 trial[30]	Patients with breast cancer with residual invasive disease following standard neoadjuvant therapy (any *ERBB2* and ER status)	Molecularly targeted adjuvant treatment
SWOG1418/BR006/phase 3 trial[31]	Patients with triple-negative breast cancer with residual invasive disease following standard neoadjuvant therapy	Pembrolizumab for 1 y (vs observation)
A-BRAVE stratum B/phase 3 trial[32]	Patients with triple-negative breast cancer with residual invasive disease following neoadjuvant chemotherapy including ≥3 courses of an anthracycline agent and 3 courses of a taxane agent	Avelumab for 1 y (vs observation)
APOLLO/phase 2 trial[33]	Patients with stage II or III triple-negative breast cancer with residual disease and detectable ctDNA following standard neoadjuvant chemotherapy	Addition of tislelizumab to capecitabine
NCT03872388/phase 2 trial[34]	Patients with stage IIB or III triple-negative breast cancer with RCB-2 or RCB-3 following standard neoadjuvant chemotherapy	Atorvastatin
PHOENIX/phase 2 trial[35]	Patients with triple-negative breast cancer with radiographically measurable tumor mass following ≥6 cycles of neoadjuvant chemotherapy	Perioperative ceralasertib, olaparib and/or durvalumab
BreastImmune03/phase 2 trial[36]	Patients with triple-negative breast cancer with RCB-2 or RCB-3 following standard neoadjuvant chemotherapy containing anthracyclines and taxanes	Nivolumab plus ipilimumab (vs capecitabine) in addition to radiation treatment
NCT04437160/phase 2 trial[37]	Patients with triple-negative breast cancer with residual invasive disease following standard neoadjuvant chemotherapy	Anthracycline-based chemotherapy (vs observation)
NCT04297267/phase 2 trial[38]	Patients with triple-negative breast cancer with residual invasive disease following standard neoadjuvant chemotherapy	Gemcitabine plus cisplatin
RSBNAT/phase 2 trial[39]	Patients with ER-positive breast cancer with residual invasive disease following standard neoadjuvant chemotherapy including anthracyclines and taxanes	Stratified according to multiple genetic testing-based recurrence risk level: cohort A (high risk) received capecitabine and cohort B (low risk) received no capecitabine

Abbreviations: ctDNA, circulating tumor DNA; ER, estrogen receptor; *ERBB2*, human epidermal growth factor receptor 2 (formerly *HER2*); RD, residual disease.

Figure. Analysis of Characteristics of Residual Disease in 3 Risk Categories



All characteristics should be contextualized according to the disease subtype (ie, hormone receptor–positive/*ERBB2*-negative, *ERBB2*-positive, triple-negative), which retains prognostic value across risk categories. ctDNA indicates circulating tumor DNA; *ERBB2*, human epidermal growth factor receptor 2 (formerly *HER2*); GEP, gene expression profiling; NAT, neoadjuvant treatment; and RCB, residual cancer burden. Created with BioRender.com.

the primary tumor bed in the resection specimen; the proportion of the primary tumor bed that contains invasive carcinoma; the number of metastatic axillary lymph nodes; and the diameter of the largest axillary metastatic deposit. After integration, these parameters are converted into a continuous score, with pCR being the equivalent of RCB-0, and RCB-1, RCB-2, and RCB-3 representing increasing extents of RD at surgery.[52] A pooled analysis of more than 5000 patients with breast cancer receiving neoadjuvant therapy with available RCB scores demonstrated the added value of RCB in informing prognoses for all breast cancer subtypes, with a hazard ratio per unit increase in RCB score of 1.86 for distant relapse-free survival.[53] The difference in prognosis by RCB groups has led to the recent recommendation by the NeoSTEEP (Standardized Definitions for Efficacy End Points in Neoadjuvant Breast Cancer Clinical Trials) working group to routinely implement RCB as a secondary end point in neoadjuvant breast cancer trials, a measure that is expected to facilitate future assessment of the utility of this biomarker.[54]

The strength of the association between the RCB score and survival outcomes differs across breast cancer subtypes. Indeed, the most dramatic differences are observed among patients with TNBC, both in the pooled analysis and in recent clinical trials.[53] For instance, in the KEYNOTE-522 trial, which established neoadjuvant chemotherapy plus immunotherapy as the current standard treatment for stage II to III TNBC, patients with an RCB-1 score after chemoimmunotherapy had a 3-year EFS of 83.8%, compared with only 26.2% for patients with an RCB-3 score.[55] These entities, commonly grouped within the broad definition of RD, are unquestionably different in prognostic terms, warranting their analysis in pathologic reports. Notably, the KEYNOTE-522 trial also suggested that similar degrees of RD can be associated with different long-term prognoses depending on the type of treatment received by the patient. This is true both for pCR and the degree of RCB.[55] Indeed, among patients experiencing pCR in the trial, 5-year EFS was 92.2% among those receiving neoadjuvant chemoimmunotherapy, compared with 88.2% among those receiving chemotherapy alone (hazard ratio, 0.65 [95% CI, 0.39-1.08]).[56] This finding may be of particular relevance for the more common HR-positive subtype, based on findings from the phase 3 KEYNOTE-756 and Checkmate 7FL trials, both of which demonstrated a nearly doubled pCR rate with the addition of PD-1 inhibition (pembrolizumab and nivolumab, respectively) to neoadjuvant chemotherapy among patients with high-risk, HR-positive breast cancer.[5,6] Given the current absence of survival data, the results from the latter trials do not yet support a change in clinical practice, which should only be considered if the pCR improvements translate into meaningful EFS improvements with longer follow-up.

Beyond the type of treatment, the anatomic extent of disease at diagnosis also impacts the risk of recurrence, including among patients who experience a pCR. In a large retrospective cohort of 2066 patients with breast cancer experiencing pCR after neoadjuvant treatment, patients with positive lymph node involvement at diagnosis had double the risk of recurrence compared with patients with node-negative disease.[57]

Moving beyond the duality of pCR/RD to embrace the variable degrees of RCB represents only the first of several steps warranted to achieve precision in the prognostication of patients after neoadjuvant therapy. To better refine the prognosis of patients with RD, we also need to consider the biological characteristics of the tumor, its immune microenvironment, and the presence or absence of detectable MRD, among other features.

Biological Background

Improved understanding of a tumor's underlying biological characteristics may allow us to better understand the response to neoadjuvant therapy as well as the prognosis beyond the RCB score, which reflects the anatomic extent of RD. As an example, although the presence of RD at surgery can represent a signal of treatment resistance, it can also be related to tumor indolence. This is particularly true for HR-positive/*ERBB2*-negative tumors, for which both pCR and RCB provide less prognostic information compared to other breast cancer subtypes.[7] In this setting, adverse findings on gene expression profiling (ie, higher OncotypeDX recurrence scores) have been associated with a higher likelihood of pCR with neoadjuvant therapy, despite concomitantly representing a marker of worse long-term prognosis.[58] Those with a lower OncotypeDX recurrence score have tumors that are more indolent, and not sensitive to chemotherapy, thus not necessarily warranting an escalation of postneoadjuvant chemotherapy. One promising strategy developed to screen for indolent HR-positive tumors is exposing patients to a short course of endocrine treatment, with a comparison of baseline and postendo-

crine therapy Ki67 levels. Multiple studies have demonstrated an excellent long-term prognosis for tumors with significant Ki67 suppression with endocrine therapy, regardless of the anatomic extent of pathologic response at surgery.[59,60]

Analogous to HR-positive/*ERBB2*-negative tumors, during the development of the HER2DX gene expression profiling signature, Prat et al[61] noted how higher expression of luminal-related genes predicts a lower likelihood of pCR among *ERBB2*-positive tumors, with the same variable also being associated with improved long-term prognosis. On the contrary, expression of proliferation-related genes predicts a higher likelihood of pCR but also denotes a worse long-term prognosis.[61] This is consistent with what was observed in the biomarker analysis of the KATHERINE phase 3 trial, where the prediction analysis of microarray (PAM50) gene profiling on RD from patients with *ERBB2*-positive breast cancer highlighted a poor prognosis for patients with basal-like RD, compared with higher survival rates for patients having luminal A or B RD.[62] Analogous results were observed in patients with TNBC in the ECOG-ACRIN Cancer Research Group EA1131 phase 3 trial, where PAM50 profiling of the RD demonstrated worse prognoses among patients with basal vs nonbasal intrinsic subtype.[13] Analyzing and validating these biological variables could help to refine prognostication among patients with RD, informing the required intensity for postneoadjuvant treatment strategies.

Importantly, evidence suggests that the prognostic value of RD can be also impacted by the racial background of the patient. In a large population-based study (N = 103 605) evaluating the impact of race on the benefit of neoadjuvant treatment for breast cancer, Black patients with RD after neoadjuvant treatment were found to have a higher mortality risk compared to White patients across breast cancer subtypes.[63]

Immunologic Background

The immunologic background of a tumor can also significantly impact disease outcomes. For TNBC and *ERBB2*-positive breast cancer, the presence of tumor-infiltrating lymphocytes (TILs), the expression of immune checkpoint molecules (eg, PD-L1), and the expression of immune signatures have an established association with a higher likelihood of experiencing a pCR and better long-term outcomes. Importantly, the same association with improved outcomes has been observed when characterizing the immunogenicity of RD. Among 375 patients with TNBC and RD after neoadjuvant therapy, Luen et al[64] found that higher TIL levels correlated with improved recurrence-free survival and OS and that TILs added significant prognostic value to multivariate models including RCB class. The greatest magnitude of positive effect was observed in cases with RCB-2, with 3-year recurrence-free survival being 83% for patients with high (>20%) TILs and 57% for patients with low (≤20%) TILs. Similarly, Blaye et al[65] found that higher expression of immune-related pathways was associated with better prognosis among 115 patients with TNBC and RD after neoadjuvant therapy. Overall, mounting evidence highlights how the immunogenicity of the residual tumor tissue can modulate the prognostic effect of RCB, ultimately refining prognostication for TNBC and possibly *ERBB2*-positive tumors. Fewer data are available for HR-positive/*ERBB2*-negative tumors.

MRD

One additional determinant of prognosis among patients with RD after neoadjuvant therapy is the presence or absence of MRD detected via circulating tumor DNA (ctDNA). The detection of MRD at any time point is associated with a higher risk of recurrence and death across breast cancer subtypes,[66] and it has been found to add prognostic information to pCR and RCB. In a cohort of 193 patients with TNBC RD enrolled in the BRE12-158 randomized phase 2 trial, Schneider et al[15] reported a nearly 2-fold increase in the risk of recurrence for patients with ctDNA detected after surgery. Magbanua et al[67] reported that, in a cohort of 295 patients with *ERBB2*-negative breast cancer treated within the I-SPY2 trial, those in RCB-2 or RCB-3 groups after neoadjuvant therapy could have their prognosis significantly refined by the presence of detectable ctDNA immediately before surgery. In that cohort, the presence of ctDNA increased the risk of recurrence greater than 5-fold among patients with HR-positive disease (hazard ratio, 5.89 [95% CI, 2.68-12.98]) and by more than 3-fold among patients with TNBC with RD (hazard ratio, 3.79 [95% CI, 1.87-7.68]). Notably, despite being clearly prognostic among patients with RD, ctDNA detection still harbors complexities that warrant fine-tuning before implementation in clinical practice, with the most relevant one being the wide differences in sensitivity of the assays.[68] In this setting, strategies are being pursued to optimize sensitivity through the tracking of large numbers of individualized tumor genetic variants and the development of priming agents that transiently reduce the clearance of ctDNA, improving the sensitivity of detection for small tumors.[69-71] These strategies may hopefully reduce the risk of false negative MRD findings, enabling better prognostication and potentially improving treatment tailoring.

Conclusions

In the past decade, multiple biomarkers have been shown to significantly refine the prognostic information provided by the pathologic response among patients with breast cancer receiving neoadjuvant therapy. Taken together, the data are strong enough to support the routine evaluation and reporting of parameters such as RCB and TILs, both of which have standardized reporting criteria available. For variables that require more complex analysis, such as gene signatures and ctDNA, clinical validation may be warranted before routine implementation, but assessment in clinical trials should be encouraged. Thinking forward, the assessment and reporting of the prognostic variables described herein will likely produce data for training machine learning algorithms, which could inform both prognosis and optimal adjuvant therapy regimens. In the future, the vast amount of data collected on RCB, TILs, gene expression data, ctDNA, and additional relevant biomarkers may inform the development of machine learning–based tools that leverage all the relevant variables to provide a multidimensional assessment of prognosis.[72] Although these advancements will not happen immediately, the data that we collect now will lay the necessary groundwork to enable this advancement. Collection of these additional biomarkers is a necessary next step to move beyond the simplistic threshold of pCR vs RD and toward more tailored treatment approaches for patients with breast cancer following neoadjuvant systemic therapy.

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REFERENCES

1. Bonadonna G, Brusamolino E, Valagussa P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med*. 1976;294(8):405-410. doi:10.1056/NEJM197602192940801

2. Agostinetto E, Gligorov J, Piccart M. Systemic therapy for early-stage breast cancer: learning from the past to build the future. *Nat Rev Clin Oncol*. 2022;19(12):763-774. doi:10.1038/s41571-022-00687-1

3. Miglietta F, Dieci MV, Griguolo G, Guarneri V. Neoadjuvant approach as a platform for treatment personalization: focus on HER2-positive and triple-negative breast cancer. *Cancer Treat Rev*. 2021;98:102222. doi:10.1016/j.ctrv.2021.102222

4. Garufi G, Carbognin L, Arcanà C, et al. Tailoring neoadjuvant treatment of HR-positive/HER2-negative breast cancers: which role for gene expression assays. *Cancer Treat Rev*. 2022;110:102454. doi:10.1016/j.ctrv.2022.102454

5. Loi S, Curigliano G, Salgado RF, et al. LBA20 a randomized, double-blind trial of nivolumab (NIVO) vs placebo (PBO) with neoadjuvant chemotherapy (NACT) followed by adjuvant endocrine therapy (ET) ± NIVO in patients (pts) with high-risk, ER+ HER2− primary breast cancer (BC). *Ann Oncol*. 2023;34:S1259-S1260. doi:10.1016/j.annonc.2023.10.010

6. Cardoso F, McArthur HL, Schmid P, et al. LBA21 KEYNOTE-756: phase III study of neoadjuvant pembrolizumab (pembro) or placebo (pbo) + chemotherapy (chemo), followed by adjuvant pembro or pbo + endocrine therapy (ET) for early-stage high-risk ER+/HER2− breast cancer. *Ann Oncol*. 2023;34:S1260-S1261. doi:10.1016/j.annonc.2023.10.011

7. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384(9938):164-172. doi:10.1016/S0140-6736(13)62422-8

8. Squifflet P, Saad ED, Loibl S, et al; CTNeoBC Project. Re-evaluation of pathologic complete response as a surrogate for event-free and overall survival in human epidermal growth factor receptor 2-positive, early breast cancer treated with neoadjuvant therapy including anti-human epidermal growth factor receptor 2 therapy. *J Clin Oncol*. 2023;41(16):2988-2997. doi:10.1200/JCO.22.02363

9. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med*. 2017;376(22):2147-2159. doi:10.1056/NEJMoa1612645

10. von Minckwitz G, Huang CS, Mano MS, et al; KATHERINE Investigators. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med*. 2019;380(7):617-628. doi:10.1056/NEJMoa1814017

11. Loibl S, Mano MS, Untch M, Huang CS, Mamounas EP. GS03-12 phase III study of adjuvant ado-trastuzumab emtansine vs trastuzumab for residual invasive HER2-positive early breast cancer after neoadjuvant chemotherapy and HER2-targeted therapy: KATHERINE final IDFS and updated OS analysis. *Cancer Res*. 2024;84(9)(suppl):GS03-GS12. doi:10.1158/1538-7445.SABCS23-GS03-12

12. Geyer CE Jr, Garber JE, Gelber RD, et al; OlympiA Clinical Trial Steering Committee and Investigators. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. *Ann Oncol*. 2022;33(12):1250-1268. doi:10.1016/j.annonc.2022.09.159

13. 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*. 2021;39(23):2539-2551. doi:10.1200/JCO.21.00976

14. Kalra M, Tong Y, Jones DR, et al. Cisplatin +/− rucaparib after preoperative chemotherapy in patients with triple-negative or BRCA mutated breast cancer. *NPJ Breast Cancer*. 2021;7(1):29. doi:10.1038/s41523-021-00240-w

15. Schneider BP, Jiang G, Ballinger TJ, et al. BRE12-158: A postneoadjuvant, randomized phase II trial of personalized therapy versus treatment of physician's choice for patients with residual triple-negative breast cancer. *J Clin Oncol*. 2022;40(4):345-355. doi:10.1200/JCO.21.01657

16. DESTINY-Breast05. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04622319

17. Astefania. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04873362

18. CompassHER2 RD. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04457596

19. KAN-HER2. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05388149

20. ATP. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04254263

21. Trastuzumab combined with pertuzumab for adjuvant treatment of breast cancer after neoadjuvant therapy. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04973319

22. TPIV100 and sargramostim for the treatment of *HER2* positive, stage 2-3 breast cancer in patients with residual disease after chemotherapy and surgery. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04197687

23. Vaccine to Prevent recurrence in patients with HER-2 positive breast cancer. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03384914

24. TROPION-Breast03. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05629585

25. SASCIA. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04595565

26. OptimICE-RD/ASCENT-05. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05633654

27. MK-2870-012. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06393374

28. ZEST. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04915755

29. ASPRIA. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04434040

30. COGNITION-GUIDE. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05332561

31. SWOG1418. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT02954874

32. A-Brave. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT02926196

33. APOLLO. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04501523

34. Atorvastatin in treating patients with stage IIb-III triple negative breast cancer who did not achieve a pathologic complete response after receiving neoadjuvant chemotherapy. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03872388

35. PHOENIX. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03740893

36. BreastImmune03. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03818685

37. Adjuvant chemotherapy for triple negative breast cancer patients with residual disease after neoadjuvant chemotherapy. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04437160

38. A study to evaluate gemcitabine plus cisplatin in the treatment of TNBC patients following neoadjuvant chemotherapy (nonpCR GP). ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04297267

39. RSBNAT. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03638648

40. Hurvitz SA, Hegg R, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. *Lancet*. 2023;401(10371):105-117. doi:10.1016/S0140-6736(22)02420-5

41. Rugo HS, Bardia A, Marmé F, et al. LBA76 overall survival (OS) results from the phase III TROPiCS-02 study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with HR+/HER2− metastatic breast cancer (mBC). *Ann Oncol*. 2022;33:S1386. doi:10.1016/j.annonc.2022.08.012

42. Bardia A, Hurvitz SA, Tolaney SM, et al; ASCENT Clinical Trial Investigators. Sacituzumab govitecan in metastatic triple-negative breast

cancer. *N Engl J Med*. 2021;384(16):1529-1541. doi:10.1056/NEJMoa2028485

43. Bardia A, Jhaveri K, Im SA, et al. LBA11 datopotamab deruxtecan (Dato-DXd) vs chemotherapy in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2−) breast cancer (BC): primary results from the randomised phase III TROPION-Breast01 trial. *Ann Oncol*. 2023;34: S1264-S1265. doi:10.1016/j.annonc.2023.10.015

44. Curigliano G, Mueller V, Borges V, et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis. *Ann Oncol*. 2022;33(3):321-329. doi:10.1016/j.annonc.2021.12.005

45. Cortes J, Rugo HS, Cescon DW, et al; KEYNOTE-355 Investigators. Pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. *N Engl J Med*. 2022;387(3):217-226. doi:10.1056/NEJMoa2202809

46. Tarantino P, Modi S, Tolaney SM, et al. Interstitial lung disease induced by anti-*ERBB2* antibody-drug conjugates: a review. *JAMA Oncol*. 2021;7(12):1873-1881. doi:10.1001/jamaoncol.2021.3595

47. Spira A, Lisberg A, Sands J, et al. OA03.03 datopotamab deruxtecan (Dato-DXd; DS-1062), a TROP2 ADC, in patients with advanced NSCLC: updated results of TROPION-PanTumor01 phase 1 study. *J Thorac Oncol*. 2021;16(3):S106-S107. doi:10.1016/j.jtho.2021.01.280

48. Marmé F, Hanusch C, Furlanetto J, Morris P, Link T, Denkert C. 580 Safety interim analysis (SIA) of the phase III postneoadjuvant SASCIA study evaluating sacituzumab govitecan (SG) in patients with primary HER2-negative breast cancer (BC) at high relapse risk after neoadjuvant treatment. *Ann Oncol*. 2022;33(3):S148-S149. doi:10.1016/j.annonc.2022.03.074

49. Schmid P, Cortes J, Pusztai L, et al; KEYNOTE-522 Investigators. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med*. 2020;382(9):810-821. doi:10.1056/NEJMoa1910549

50. Borges VF, Ferrario C, Aucoin N, et al. Tucatinib combined with ado-trastuzumab emtansine in advanced *ERBB2*/HER2-positive metastatic breast cancer: a phase 1b clinical trial. *JAMA Oncol*. 2018;4 (9):1214-1220. doi:10.1001/jamaoncol.2018.1812

51. Ogston KN, Miller ID, Payne S, et al. A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival. *Breast*. 2003; 12(5):320-327. doi:10.1016/S0960-9776(03)00106-1

52. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol*. 2007;25(28):4414-4422. doi:10.1200/JCO.2007.10.6823

53. Yau C, Osdoit M, van der Noordaa M, et al; I-SPY 2 Trial Consortium. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. *Lancet Oncol*. 2022;23(1):149-160. doi:10.1016/S1470-2045(21)00589-1

54. Litton JK, Regan MM, Pusztai L, et al. Standardized definitions for efficacy end points in neoadjuvant breast cancer clinical trials: NeoSTEEP. *J Clin Oncol*. 2023;41(27):4433-4442. doi:10.1200/JCO.23.00435

55. Pusztai L, Denkert C, O'Shaughnessy J, et al. Event-free survival by residual cancer burden after neoadjuvant pembrolizumab + chemotherapy versus placebo + chemotherapy for early TNBC: exploratory analysis from KEYNOTE-522. *J Clin Oncol*. 2022;40(16)(suppl):503. doi:10.1200/JCO.2022.40.16_suppl.503

56. Schmid P, Cortés J, Dent RA, et al. LBA18 pembrolizumab or placebo plus chemotherapy followed by pembrolizumab or placebo for early-stage TNBC: updated EFS results from the phase III KEYNOTE-522 study. *Ann Oncol*. 2023;34: S1257. doi:10.1016/j.annonc.2023.10.008

57. Huober J, van Mackelenbergh M, Schneeweiss A, et al. Identifying breast cancer patients at risk of relapse despite pathological complete response after neoadjuvant therapy. *NPJ Breast Cancer*. 2023;9(1):23. doi:10.1038/s41523-023-00525-2

58. Freeman JQ, Shubeck S, Howard FM, Chen N, Nanda R, Huo D. Evaluation of multigene assays as predictors for response to neoadjuvant chemotherapy in early-stage breast cancer patients. *NPJ Breast Cancer*. 2023;9(1):33. doi:10.1038/s41523-023-00536-z

59. Nitz UA, Gluz O, Kümmel S, et al. Endocrine therapy response and 21-gene expression assay for therapy guidance in HR+/HER2− early breast cancer. *J Clin Oncol*. 2022;40(23):2557-2567. doi:10.1200/JCO.21.02759

60. Ellis MJ, Suman VJ, Hoog J, et al. Ki67 proliferation index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: results from the American College of Surgeons Oncology Group Z1031 Trial (Alliance). *J Clin Oncol*. 2017;35(10): 1061-1069. doi:10.1200/JCO.2016.69.4406

61. Prat A, Guarneri V, Pascual T, et al. Development and validation of the new HER2DX assay for predicting pathological response and survival outcome in early-stage HER2-positive breast cancer. *EBioMedicine*. 2022;75:103801. doi:10.1016/j.ebiom.2021.103801

62. Denkert C, Lambertini C, Fasching PA, et al. Biomarker data from the phase III KATHERINE study of adjuvant T-DM1 versus trastuzumab for residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer. *Clin Cancer Res*. 2023;29(8):1569-1581. doi:10.1158/1078-0432.CCR-22-1989

63. Roy AM, Patel A, Catalfamo K, et al. Racial and ethnic disparity in preoperative chemosensitivity and survival in patients with early-stage breast cancer. *JAMA Netw Open*. 2023;6(11):e2344517-e2344517. doi:10.1001/jamanetworkopen.2023.44517

64. Luen SJ, Salgado R, Dieci MV, et al. Prognostic implications of residual disease tumor-infiltrating lymphocytes and residual cancer burden in triple-negative breast cancer patients after neoadjuvant chemotherapy. *Ann Oncol*. 2019;30 (2):236-242. doi:10.1093/annonc/mdy547

65. Blaye C, Darbo É, Debled M, et al. An immunological signature to predict outcome in patients with triple-negative breast cancer with residual disease after neoadjuvant chemotherapy. *ESMO Open*. 2022;7(4):100502. doi:10.1016/j.esmoop.2022.100502

66. Papakonstantinou A, Gonzalez NS, Pimentel I, et al. Prognostic value of ctDNA detection in patients with early breast cancer undergoing neoadjuvant therapy: a systematic review and meta-analysis. *Cancer Treat Rev*. 2022;104:102362. doi:10.1016/j.ctrv.2022.102362

67. Magbanua MJM, Brown Swigart L, Ahmed Z, et al. Clinical significance and biology of circulating tumor DNA in high-risk early-stage HER2-negative breast cancer receiving neoadjuvant chemotherapy. *Cancer Cell*. 2023;41(6):1091-1102.e4. doi:10.1016/j.ccell.2023.04.008

68. Pantel K, Alix-Panabières C. Liquid biopsy and minimal residual disease—latest advances and implications for cure. *Nat Rev Clin Oncol*. 2019;16 (7):409-424. doi:10.1038/s41571-019-0187-3

69. Parsons HA, Rhoades J, Reed SC, et al. Sensitive detection of minimal residual disease in patients treated for early-stage breast cancer. *Clin Cancer Res*. 2020;26(11):2556-2564. doi:10.1158/1078-0432.CCR-19-3005

70. Gydush G, Nguyen E, Bae JH, et al. Massively parallel enrichment of low-frequency alleles enables duplex sequencing at low depth. *Nat Biomed Eng*. 2022;6(3):257-266. doi:10.1038/s41551-022-00855-9

71. Martin-Alonso C, Tabrizi S, Xiong K, et al. Priming agents transiently reduce the clearance of cell-free DNA to improve liquid biopsies. *Science*. 2024;383(6680):eadf2341. doi:10.1126/science.adf2341

72. Sammut SJ, Crispin-Ortuzar M, Chin SF, et al. Multi-omic machine learning predictor of breast cancer therapy response. *Nature*. 2022;601(7894): 623-629. doi:10.1038/s41586-021-04278-5