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- Two Views on Anthracyclines in Early Breast Cancer
- Screening for Recurrence in Early-Stage Breast Cancer?
- Axillary Evaluation in Early-Stage Invasive Disease
- Implications of DESTINY-Breast06

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TABLE of Contents

FROM the Editor

In this issue of *Breast Cancer Update*, we are pleased to share provocative articles detailing emerging issues in breast oncology. The scope of the issue is broad, ranging from evolving data to inform the optimal tailored management of the axilla in early-stage disease to surveillance in survivorship to systemic therapy for metastatic breast cancer. A unifying theme is presentation of the latest data to highlight practice-changing findings and illuminate areas of controversy and unanswered questions.

Drs. Mitchell J. Elliott and David W. Cescon summarize current guidelines that recommend against surveillance testing for metastatic disease in asymptomatic survivors of early-stage disease. Yet, they discuss hopefully how this may change in the future with the development of blood-based biomarkers such as circulating tumor DNA (ctDNA) to identify molecular residual disease (MRD), thereby detecting micrometastatic disease that might be eradicated with therapeutic intervention and improve patient outcomes.

The evolving value of trastuzumab deruxtecan (T-DXd) in hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–low metastatic breast cancer from the DESTINY-Breast06 trial is presented by Dr. Tess A. O'Meara. She helps to clarify when first-line T-DXd may be optimal and when this impactful antibody–drug conjugate is best saved for later-line treatment.

Then, Dr. Alastair M. Thompson details the complexities of axillary management in early-stage breast cancer, incorporating recent studies into a proposed framework for approaching axillary surgery. With appropriate clinical evaluation, many patients undergoing surgery first for low-risk disease can safely forego lymph node sampling or undergo sentinel node biopsy only. When neoadjuvant therapy is required, emerging data suggest that the extent axillary surgery should be driven by the response to neoadjuvant systemic therapy and potentially tumor subtype.

Finally, two teams discuss the ongoing debate on the value of anthracyclines in the treatment of individuals with early-stage breast cancer. Drs. Guilherme Nader Marta and Martine J. Piccart extol the long-standing, robust track record for anthracyclines improving disease outcomes and the limitations of data to support foregoing the drug class in chemotherapy treatment. Dr. Virginia F. Borges focuses on comparative studies suggesting little absolute difference in outcomes, particularly in HER2-positive and estrogen receptor (ER)–positive disease, and espouses the use of anthracycline-free regimens for many patients now to reduce toxicity.

Ann H. Partridge, MD, MPH, Editor

Dr. Partridge is Vice Chair of Medical Oncology at Dana-Farber Cancer Institute and Professor of Medicine at Harvard Medical School. She reports research support from Novartis; external grant support from Susan G. Komen, the Breast Cancer Research Foundation (BCRF), National Cancer Institute, Patient-Centered Outcomes Research Institute (PCORI), and American Cancer Society; and royalties from UpToDate.

Topic Update

Surveillance for Metastatic Recurrence in Early Breast Cancer: Where Are We Now?

Mitchell J. Elliott, MD, AAHIVS, and David W. Cescon, MD, PhD

Most metastatic breast cancer develops as a recurrence of previously treated early breast cancer. Substantial advances in the delivery of systemic therapy with curative intent, including use of chemo, targeted, and endocrine agents — as well as improved methods for risk stratification — have contributed to better outcomes for early breast cancer. Still, many patients experience lethal metastatic disease recurrence months, years, or decades following such treatment. While current standards employ a reactive approach to identifying distant recurrence, there is hope that modern therapies and new minimally invasive diagnostic techniques may shift this paradigm. In this Topic Update, we summarize the current guideline recommendations for imaging and laboratory surveillance following curative intent therapy. We also highlight the latest data for the use of circulating tumor DNA (ctDNA) assays to detect breast cancer recurrence.

Current Recommendations for the Surveillance of Metastatic Disease

No major international guideline recommends routine radiographic or blood-based biomarker surveillance for metastatic breast cancer recurrence after the completion of curative intent therapy (*J Clin Oncol* 2013; 31:961; *Ann Oncol* 2024; 35:159). However, these guidelines are based on data generated several decades ago, when many of today's most effective interventions were unavailable and breast cancer biologic subtypes were not yet described. To move forward, we need to evaluate modern diagnostic methods paired with effective therapeutics in high-quality studies to establish the clinical utility of surveillance in diverse patient populations with varying disease biology and clinical risk. In this regard, the results of a large randomized trial launched in 2013 evaluating intensive imaging and tumor marker surveillance in high-risk patients are awaited (*Cancer Res* 2019; 79:OT2-01-05). Also, looking beyond imaging-based diagnostics, in theory, breast cancer recurrence may be diagnosed at the molecular level.

Molecular Residual Disease and Metastatic Disease Recurrence

Advancements in high-sensitivity nucleic acid detection have facilitated the development of blood-based liquid biopsy assays capable of identifying tumor-derived DNA at very low concentrations in the bloodstream (*Nat Cancer* 2020; 1:276). In contrast to serial radiographic imaging, which formed the basis for previous surveillance studies and identifies established and typically incurable metastatic disease, ctDNA can be detected in some patients who are clinically and radiographically disease-free before subsequent relapse. This identification of "molecular residual disease" (MRD) introduces a new possibility for using systemic therapy to eradicate micrometastatic disease in a manner similar to traditional adjuvant therapy. Unlike current adjuvant treatments, MRD-directed interventions may specifically target individuals at imminent risk of

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recurrence, rather than broadly administering systemic therapy based on estimated risk. Additionally, the presence of a measurable MRD marker could serve as a surrogate for treatment efficacy, providing opportunities to monitor and tailor therapeutic interventions.

Several retrospective analyses have demonstrated that it is possible to identify ctDNA prior to clinical recurrence (*Cancer Cell* 2023; 41:1091; *Clin Cancer Res* 2019; 25:4255; *J Clin Oncol* 2022; 40:2408). However, a lack of concurrent imaging limits the ability to definitively ascertain true MRD — that is, ctDNA detection in the absence of radiographically identifiable metastatic disease. The assay sensitivity required to optimally identify true MRD and support effective interventions is uncertain. In general, for a surveillance and MRD intervention use case, it is desirable to achieve the highest possible sensitivity while retaining near-perfect specificity, using an assay that can be efficiently and repeatedly deployed. Over the last decade, the sensitivity of ctDNA assays has increased by several orders of magnitude as approaches have moved from identifying common cancer-driver mutations to assessing large numbers of tumor-informed alterations or cancer-associated methylation patterns.

"The possibility of using ctDNA to reduce treatment intensity is appealing, especially given the extensive use of adjuvant therapy that delivers, on average, small absolute benefits."
— Mitchell J. Elliott, MD, AAHIVS, and David W. Cescon, MD, PhD

Establishing Clinical Utility: Treatment Escalation

While retrospective studies have been essential in determining the clinical validity of ctDNA detection, prospective trials evaluating patient outcomes are necessary to evaluate its clinical utility. Several trials have assessed serial liquid biopsy surveillance in high-risk patient populations who received treatment with curative intent. In the c-TRAK TN clinical trial, patients with triple-negative breast cancer were followed with serial ctDNA surveillance (*Ann Oncol* 2023; 34:200). Unfortunately, most patients (23/32; 72%) with ctDNA detected had radiographically apparent metastatic disease on reflex imaging. Five ctDNA-positive participants received pembrolizumab; none had clearance of ctDNA, and all had subsequent disease recurrence. This study was the first to highlight the important limitation of ctDNA positivity corresponding to asymptomatic but radiographically detectable metastatic disease, a scenario in which pharmacologic interventions are unlikely to yield cure. While a secondary comparative analysis demonstrated an improvement in the lead time between ctDNA detection and clinical recurrence with a more-sensitive assay (RaDaR, NeoGenomics Laboratories Inc.), the magnitude of improvement was modest (*Clin Cancer Res* 2024; 30:895).

In the phase 3 ZEST trial, a similar patient population (with triple-negative or germline *BRCA*-related HER2-negative breast cancers) underwent ctDNA surveillance with the Signatera assay (Natera Inc.). Patients with ctDNA detected who were free of radiographically detectable metastatic disease were randomized to niraparib or placebo. Unfortunately, this trial faced similar challenges to c-TRAK TN; the rate of detectable metastatic disease in participants who had identifiable ctDNA was "much higher than expected," and the trial was closed because of challenges with patient accrual (GSK Q1 2023 results announcement; www.gsk.com/media/10013/q1-2023-results-announcement.pdf). The detailed results of this screening effort and outcomes of participants who were randomized are highly anticipated.

Additional trials in other receptor subtypes are underway, including DARE (NCT04567420) in which participants are undergoing ctDNA surveillance with Signatera. Interim results presented at the 2023 San Antonio Breast Cancer Symposium demonstrated ctDNA positivity in a small proportion of screened participants (37/542, 6.8%) and total tests (3.3%). Of these 37 patients with ctDNA detected, 22 had molecular relapse without radiographically apparent metastatic disease while 10 (27%) had radiographically overt metastases. This trial is ongoing, and no efficacy results have been reported.

Establishing Clinical Utility: Treatment Deescalation

The possibility of using ctDNA to reduce treatment intensity is appealing, especially given the extensive use of adjuvant therapy that delivers, on average, small absolute benefits. However, no trials have yet evaluated the impact of reducing standard systemic therapy based on undetectable ctDNA. Across reported studies of various ctDNA assays, many patients who ultimately experience disease recurrence have initially undetectable ctDNA, highlighting either limitations in assay sensitivity or the biology of ctDNA shedding, which currently pose barriers to such applications. Therefore, deviating from standard therapy based on an absence of ctDNA should not be considered in routine clinical care, and any studies evaluating such a strategy must be carefully designed. More data are required in this setting to establish feasibility and clinical utility.

Moving Forward

Advances in diagnostics and effective breast cancer therapeutics call for a reevaluation of posttreatment surveillance for metastatic recurrence. While ctDNA tests designed to detect MRD are commercially available, there are still considerable knowledge gaps about how to interpret and manage the results. The current focus should be on establishing clinical utility through prospective studies paired with targeted interventions, prioritizing meaningful improvements in patient outcomes before broad clinical adoption.

Topic Update

T-DXd in HR-Positive Metastatic Breast Cancer: Clinical Implications of DESTINY-Breast06

Tess A. O'Meara, MD, MHS

In 2019, the U.S. Food and Drug Administration (FDA) approved trastuzumab deruxtecan (T-DXd) for use in patients with human epidermal growth factor receptor 2 (HER2)–positive, unresectable or metastatic breast cancer (MBC) who had received two or more lines of prior anti-HER2 therapies. Since then, the benefits of T-DXd have been proven in earlier lines of treatment and for patients whose tumors have lower HER2 expression, culminating in the recent presentation of DESTINY-Breast06 (DB-06) at the American Society of Clinical Oncology (ASCO) 2024 annual conference (*J Clin Oncol* 2024; 42:LBA1000). This study demonstrated the efficacy of T-DXd for the treatment of hormone receptor (HR)–positive, HER2-low or HER2-ultralow MBC in patients whose disease had progressed on endocrine therapy (ET) but who had not received chemotherapy in the metastatic setting. These results have left clinicians with the pressing questions: Can all patients with HR-positive MBC now be considered candidates for T-DXd, irrespective of HER2 status, and in what line should this medication be used?

Breaking Ground in HER2-Low Disease: DB-04 and DAISY

Two important trials set the stage for DB-06 by demonstrating that T-DXd could be effective in breast cancers with lower HER2 expression. In the first such trial, DESTINY-Breast04 (DB-04), researchers compared T-DXd with treatment of physician's choice (TPC) among 557 patients with HER2-low MBC who had received one or two prior lines of chemotherapy. Low expression of HER2 was defined by an immunohistochemical (IHC) score of 1+ (faint, incomplete membrane staining in >10% of tumor cells) or by an IHC score of 2+ (weak-to-moderate staining in >10% of tumor cells) with negative results on in situ hybridization (ISH). The study's primary end point was progression-free survival (PFS) in patients with HR-positive disease, but the study did include a small exploratory subgroup of patients with triple-negative breast cancer (TNBC).

In the HR-positive cohort of DB-04, median PFS was significantly longer with T-DXd than with TPC (10.1 vs. 5.4 months), as was overall survival (OS; 23.9 vs. 17.5 months; *N Engl J Med* 2022; 387:9). Interestingly, median PFS with T-DXd was similar regardless of the degree of HER2 expression — 10.3 months in HR-positive patients with HER2 1+ disease and 10.1 months in those with HER2 2+/ISH-negative disease. In a subgroup analysis of the 58 patients with TNBC, both median PFS and OS were significantly longer with T-DXd than with TPC (PFS, 8.5 vs. 2.9 months; OS 18.2 vs. 8.3 months; *ESMO Open* 2023; 8:6).

These results led to FDA approval of T-DXd in HER2-low MBC after one line of prior chemotherapy in the metastatic setting or after recurrence within 6 months of adjuvant chemotherapy. However, because the degree of HER2 staining in this trial was not associated with clinical outcomes, the question remained whether T-DXd would benefit those with even lower levels of HER2 expression. Enter the results of DAISY, a multicenter, open-label, phase 2 trial designed to study the efficacy of T-DXd in both HR-positive and HR-negative MBC, irrespective of HER2 status, after at least one line of prior chemotherapy (*Nat Med* 2023; 29:2110).

The DAISY study population consisted of a relatively small cohort of 177 patients with MBC resistant to both ET and CDK4/6 inhibition, and the primary end point was the confirmed objective response rate

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(ORR) by investigator assessment. Patients were divided into three groups according to level of HER2 expression: HER2-overexpressing (IHC 3+), HER2-low (IHC 2+ or 1+), and HER2-nonexpressing (IHC 0). Confirmed ORRs across the groups were 70.6%, 37.5%, and 29.7%, respectively. Median PFS was 11.1 months, 6.7 months, and 4.2 months, respectively. Notably, only 71.5% of the study population was HR-positive and 53% had received ≥5 lines of therapy in the metastatic setting.

Approximately half of the HER2 0 cohort in DAISY had some HER2 staining detected upon pathology review, raising the question of whether the benefit in this group was driven by tumors with greater-than-null HER2 expression and not true HER2-null cases. It is mechanistically feasible that T-DXd could be efficacious in true HER2-null cases, either through off-target effects of antibody–drug conjugates (ADC) or activation of anti-tumor immunity. Only about 0.1% of an injected dose of an ADC, such as T-DXd, is estimated to be delivered to the targeted cancer cell population; most of the drug is catabolized by off-target cells. The mechanisms of these off-target effects include deconjugation of free chemotherapy payload from the target antibody in circulation, nonspecific endocytosis of intact ADC into cells, and off-target receptor-mediated uptake of ADCs into cells via the Fc gamma receptor (*Cancers [Basel]* 2023; 15:713; *Am Soc Clin Oncol Educ Book* 2024; 44:e431766). In addition, it has been shown that T-DXd internalization into tumor-resident myeloid cells via Fc receptor binding, as well as activation of the stimulator of interferon genes (STING) pathway by the chemotherapy payload (DXd), stimulates strong tumor-specific adaptive immunity that may drive much of the medication's efficacy (*Cancer Res* 2024; 84:2377 and *Nat Commun* 2024; 15:5842). Nevertheless, preclinical studies have suggested that T-DXd is not effective against cancer cell lines that do not express HER2, implying that there may be a lower limit of HER2 expression under which T-DXd is not efficacious (*Clin Cancer Res* 2016; 22:5097).

Defining the Lower Limits: DB-06

Pushing this question into the clinical setting, DB-06 researchers identified a new patient subset with "HER2-ultralow" disease, defined as faint, incomplete membrane staining in 1% to 10% of tumor cells (currently classified as HER2 0 on clinical pathology reports). This group is estimated to comprise 20% to 25% of all HR-positive, HER2-negative MBC cases, whereas true HER2-null cases are thought to comprise 10% to 20% (Figure).

For DB-06, researchers enrolled patients with HER2-low or -ultralow, HR-positive MBC who had no prior lines of chemotherapy in the metastatic setting (*J Clin Oncol* 2024; 42:LBA1000). Approximately 90% of participants had received prior CDK4/6 inhibition, and approximately 85% had received ≥2 lines of prior ET. HER2 status was determined by a central laboratory for eligibility; 713 patients were classified as having HER2-low tumors and 153 as HER2-ultralow. In the HER2-low cohort, median PFS was found to be significantly longer with T-DXd than with TPC (13.2 vs. 8.1 months). Importantly, a similar benefit was seen in the HER2-ultralow cohort (13.2 vs. 8.3 months), but this did not reach statistical significance (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.50–1.21), most likely due to a lack of power. In the HER2-low cohort, the confirmed ORR was 56.5% with T-DXd versus 32.2% for TPC; in the HER2-ultralow cohort, it was 61.8% versus 26.3%. Although the OS data are not yet mature, there is currently no significant OS benefit with T-DXd compared with TPC in either cohort. The survival data will be affected by high rates of crossover to T-DXd after treatment discontinuation in the TPC group; the rate was approximately 20% at the time of this analysis.

Notably, unlike the DB-04 trial, where the median PFS benefit of T-DXd over TPC was similar between HER2 2+/ISH-negative and HER2 1+ tumors, the DB-06 trial demonstrated a greater median PFS benefit of T-DXd in the HER2+/ISH-negative group (HR, 0.43) than in the HER2 1+ group (HR, 0.74; Figure). This difference may be attributable to the fact that central HER2 testing in DB-06 was performed on metastatic samples only, whereas testing in DB-04 was performed on either primary or metastatic tissue.

Where Do We Go from Here?

Given the impressive benefits seen with T-DXd relative to TPC in median PFS and ORR in DB-06, an approval for first-line use in patients with endocrine-refractory, HR-positive, HER2-low MBC is anticipated. Wider use of this agent in clinical practice,

(continued on page 9)

FIGURE. T-DXd in HR-positive, HER2-low and -ultralow MBC: Staining and Trial Outcomes

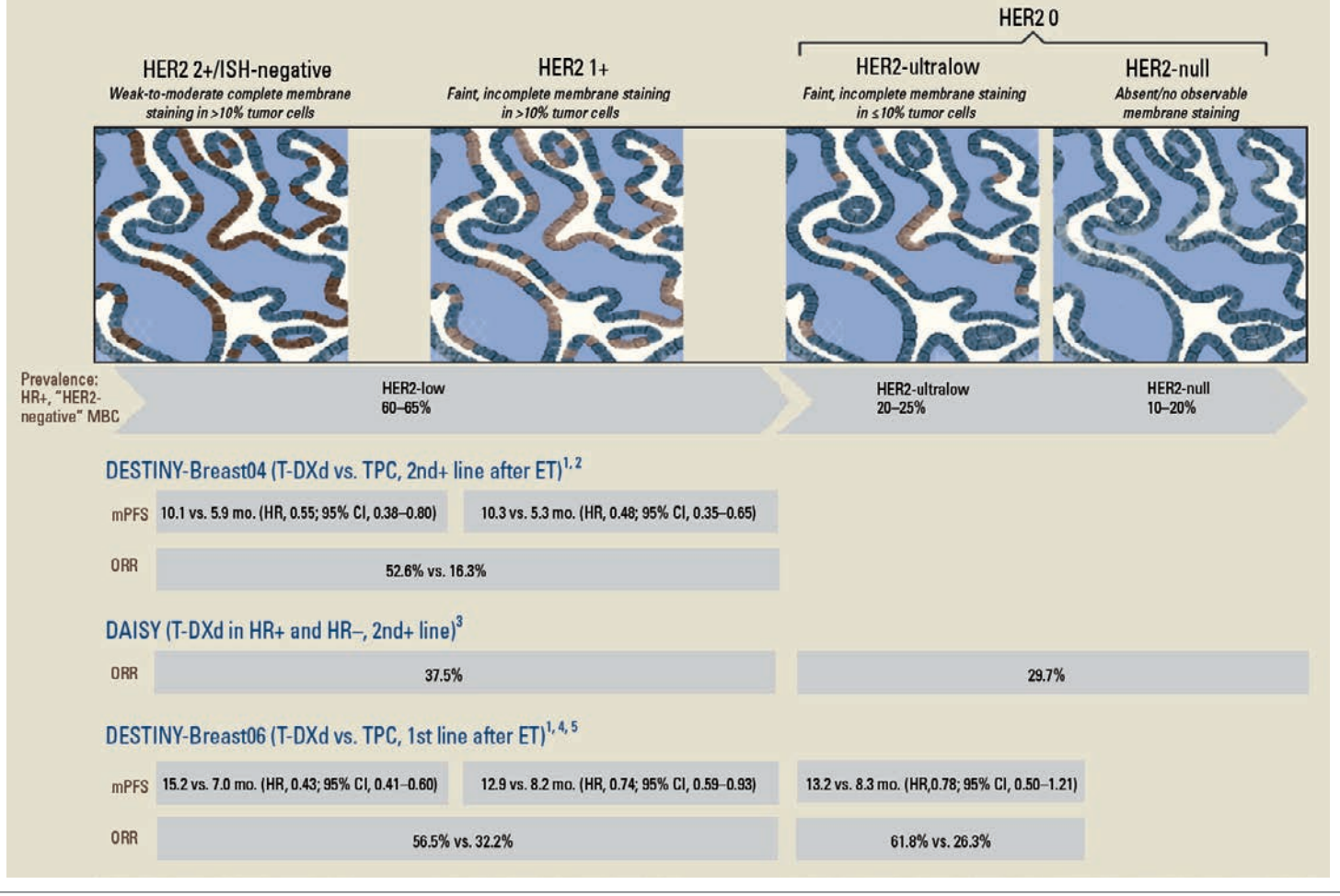

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FIGURE. T-DXd in HR-positive, HER2-low and -ultralow MBC: Staining and Trial Outcomes (continued)

HER2 — human epidermal growth factor receptor 2; HR — hormone receptor; ET — endocrine therapy; ISH — in situ hybridization; MBC — metastatic breast cancer; T-DXd — trastuzumab deruxtecan; TPC — treatment of physician's choice

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(continued from page 7)

including for patients with HER2-ultralow disease, will require consideration of individual patient conditions as well as new tools to more finely classify HER2 expression.

CLINICAL CONSIDERATIONS

As with any medication, the potential benefits of T-DXd must be weighed against potential risks. In DB-06, T-DXd was associated with significantly more toxicity than TPC, which included capecitabine in approximately 60% of patients, nab-paclitaxel in 24%, and paclitaxel in 16% (*J Clin Oncol* 2024; 42:LBA1000). Grade ≥3 drug-related adverse events occurred in 40.6% of patients taking T-DXd compared with 31.4% of those taking TPC; 11.3% and 0.2%, respectively, were diagnosed with interstitial lung disease (ILD) or pneumonitis. Three of the ILD cases in the T-DXd group were fatal.

Capecitabine, in particular, as a first-line regimen may be preferred by many patients given it is administered orally, causes little alopecia, is generally well tolerated, and can yield durable long-term disease control for some.

Lastly, the appropriateness of T-DXd for a given patient may depend on the pattern of metastases. Approximately 85% of patients in DB-06 had visceral metastases at baseline, with only 3% of patients having bone-only disease, according to the 2024 ASCO presentation. In patients with visceral metastases, impending visceral crisis, short duration of ET benefit, or bulky or symptomatic metastases, the high ORR associated with T-DXd makes it a desirable first-line option. In patients with bone-only or low-volume MBC who have previously experienced long duration of benefit from ET, other first-line options such as capecitabine may still be preferable. Use of T-DXd may be reserved for a later line in these patients, particularly if the OS data continue to show no significant difference on longer-term follow-up, which would imply no survival benefit with earlier- versus later-line use of T-DXd.

IDENTIFICATION OF PATIENTS WITH HER2-ULTRALOW DISEASE

If T-DXd receives FDA approval for the relatively small patient population with HR-positive, HER2-ultralow MBC, there will be a need to accurately identify these patients in clinic. As of this writing,

the ASCO–College of American Pathologists expert panel does not have guidelines for measuring or reporting HER2-ultralow expression, and interpathologist concordance is poor even for HER2-low reporting (*J Clin Oncol* 2023; 41:3867; *JAMA Oncol* 2022; 8:607).

There are several new assays in development to refine HER2 categorization. For example:

- Reveal Genomics' HER2DX assay uses gene expression signatures to report tumor HER2 expression levels, long-term relapse risk, and probability of therapy response (*eBioMedicine* 2022; 75:103801).
- Yale Cancer Center is developing quantitative immunofluorescence assays that maximize the sensitivity of HER2 expression detection in the lowest ranges (*Lab Invest* 2022; 102:1101).
- An image analysis–based, quantitative continuous score is under development at AstraZeneca that addresses the spatial distribution of HER2-expressing cells (*Sci Rep* 2024; 14:12129).
- Theralink's reverse phase protein array (RPPA) assay showed that approximately 40% of HR-positive, HER2-null breast cancers had modest-to-moderate HER2 expression (*Can Res* 2023; 83:HER2-17).

Until such diagnostic assays are clinically deployed, the question remains whether all patients with HR-positive MBC should be eligible for T-DXd, given the small percentage of true HER2-null cases and the ambiguity of T-DXd efficacy in HER2-null tumors. The DESTINY-Breast15 trial will address this question by investigating T-DXd in HER2-null versus HER2 0 MBC.

Conclusion

In the short time since the FDA approved T-DXd as second-line treatment for HER2-low MBC, DB-06 and DAISY have demonstrated strong evidence for T-DXd activity and clinical benefit in cases with even lower levels of HER2 expression. Whether T-DXd has clinical benefit in HER2-null cases requires further investigation and more refined measurement of HER2 expression.

Given the substantial ORR and median PFS benefit seen with T-DXd as first-line therapy for HR-positive, HER2-low MBC in DB-06, T-DXd is a preferred first-line option following ET and CDK4/6 inhibition for patients with high-volume visceral metastases, impending visceral crisis, rapid progression or recurrence on ET, or symptomatic metastatic disease. For patients with bone-only or low-volume metastases who have had a long duration of response to ET, other agents with more favorable toxicity profiles are likely still suitable in the first line, depending on patient preference.

Topic Update

A Lot, a Little, or Nothing at All: Axillary Surgery for Early Invasive Breast Cancer

Alastair M. Thompson, BSc (Hons), MBChB, MD, FRCSEd(Gen), FACS

Axillary management in early breast cancer has evolved during the past 20 years, with one of the most notable changes being the continued deescalation of axillary surgery. In patients with node-negative disease, the standard of care has shifted from axillary lymph node dissection (ALND) to less-extensive surgical procedures or in some cases to no axillary surgery at all. Several trials are ongoing to evaluate whether axillary surgery can be de-escalated even further in certain populations and what the best approach might be.

As clinicians await these results, we need a framework for how best to advise patients. Decision-making in this area is complicated by the growing number of options for axillary surgery, the lack of universal agreement among professional groups and across health care systems, and the complexities of breast cancer and its treatment (including sequencing of surgery before or after drug therapy).

Background

The rationale for axillary surgery has historically been twofold: first, to assess metastatic nodal involvement to guide systemic and adjuvant radiation therapy, and second, to improve disease control. Current options for axillary surgery include ALND, sentinel lymph node biopsy (SLNB), and targeted axillary dissection (TAD), a relatively new procedure that involves removing the sentinel nodes plus any nodes that were initially found to be positive. In a meta-analysis of individual patient-level data from clinical trials that compared more-extensive versus less-extensive axillary surgery in early breast cancer, researchers found that more-extensive surgery halved the rate of axillary recurrences (from approximately 1% at baseline) but had no effect on mortality and doubled the rate of lymphedema (to approximately 20%; Abstract GS02-05, 2023 San Antonio Breast Cancer Symposium). These data support the overall trend toward de-escalation of axillary surgery and increasingly individualized approaches to early breast cancer management.

Decisions around axillary surgery for individuals with early breast cancer depend on many factors, including age, initial nodal status, other tumor characteristics (such as tumor size and receptor positivity), and plans for upfront surgery versus neoadjuvant chemotherapy (NAC).

Axillary Management in Patients Undergoing Surgery First

For patients undergoing upfront surgery for small, clinically node-negative cancers, regardless of tumor subtype, SLNB has replaced ALND as standard of care. These patients usually will indeed be node-negative on SLNB, but if tumor is detected in one or two nodes, then regional nodal radiation therapy provides comparable control to that of ALND with fewer adverse effects (*J Clin Oncol* 2023; 41:2159). ALND may be considered in patients who have substantial axillary-disease burden (multiple node involvement, extranodal extension of axillary-node metastasis), but this is rare. For the vast majority of sentinel node–negative patients, ALND can be safely omitted with no effect on recurrence-free survival; this has been shown to be true with both mastectomy and breast-conserving surgery (*N Engl J Med* 2024; 390:1163).

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Some patients also may be able to safely forego SLNB. The most obvious group is clinically node-negative patients ≥70 years of age with small estrogen receptor (ER)–positive, human epidermal growth factor 2 (HER2)–negative invasive breast cancer. Multiple studies have shown that SLNB has no effect on locoregional recurrence or breast cancer–specific mortality in this group. Thus, the Choosing Wisely guidelines recommend against routine use of SLNB in this population (*Surgery* 2023; 174:413).

Whether axillary surgery can be safely omitted in younger patients has been more controversial and is the subject of much research. Data from the SOUND trial provide the best evidence to date (*JAMA Oncol* 2023; 9:1557). In this study, women of any age with a small breast cancer, a negative preoperative axillary ultrasound, and a plan to undergo breast-conserving treatment were randomized to either SLNB or observation; 81% were ≥50 years of age (median, 60 years), 78% had ductal cancer, 50% were T1c, and 93% were ER-positive. In the SLNB group, 14% had positive nodes, including 9% with macrometastases and 0.6% with >3 positive nodes. After a median follow-up of 5.7 years, axillary recurrence was rare in both groups (0.7% with observation and 0.4% with SLNB), with no significant differences in locoregional recurrence (1.6% vs. 1.7%) or 5-year distant disease–free survival (98% vs. 97.7%).

These results suggest that extending the Choosing Wisely guideline to patients >50 years old with T1, ER-positive, axillary ultrasound–negative cancer could avoid the morbidity of axillary surgery without clinical detriment. Other trials from around the world — NAUTILUS, BOOG 2013-08, INSEMA, SOAPET — seek to replicate these reassuring data.

The younger age extension could be expanded to 50 years or restricted to perimenopausal or postmenopausal women. Node staging will likely remain useful in premenopausal patients (where diagnostic assays guide chemotherapy omission in node-negative but not node-positive women), in patients with HER2-positive cancer (guiding adjuvant anti-HER2 therapy), and in patients with triple-negative breast cancer (who are underrepresented in current trials).

Axillary Management after Neoadjuvant Chemotherapy

For patients with early breast cancer who are initially found to have one or more positive lymph node and who subsequently undergo NAC (including anti-HER2 therapy where appropriate), ALND has been the standard of care. However, 40% of patients who initially have one positive node will have no nodal disease remaining after NAC, raising the question

TABLE. A Proposed Framework for Approaching Axillary Surgery in Early Breast Cancer Based on Plans for Upfront Surgery vs. Neoadjuvant Chemotherapy and on Tumor Characteristics

	Upfront Surgery			Neoadjuvant Chemotherapy (NAC)		
Tumor Characteristics	ER+, T1 N0	ER+, T2/T3 N0	HER2+/ TNBC, T1 N0	ER+, N1 prior to NAC	HER2+/ TNBC, N1 prior to NAC	ER+/HER2+/ TNBC, N2 prior to NAC
Recommendation for Axillary Surgery	Depends on age: • ≥50 years: No axillary surgery • <50 years: SLNB	SLNB	SLNB	Depends on response to NAC: • If good: SLNB or TAD • If poor: ALND	Depends on response to NAC: • If good: SLNB or TAD • If poor: ALND	ALND

ALND — axillary lymph node dissection; ER+ — estrogen receptor–positive; HER2+ — human epidermal growth factor 2–positive; SLNB — sentinel lymph node biopsy; TAD — targeted axillary dissection; TNBC — triple-negative breast cancer
Tumor size: T1, <2 cm; T2, 2–5 cm; T3, >5 cm
Nodal status: N0, no axillary nodes involved; N1, 1–3 nodes involved; N2, ≥4 nodes involved

of whether ALND can be avoided in this population as well.

More than a decade ago, attempts were made to replace ALND with SLNB among patients who had node-positive disease before NAC, but the false-negative rate associated with SLNB was found to be >10%, which was unacceptably high (*JAMA* 2013; 310:1455). More recently, researchers have found promising results with TAD (*J Clin Oncol* 2016; 34:1072); in a multicenter study, it was associated with a false-negative rate of 3.5% and a negative predictive value of 92.8% (*JAMA Surg* 2022; 157:991). This approach requires colleagues in imaging, pathology, and surgery to work well together to target and remove selected nodes, ideally with a low (~2%) false-negative rate. An intraoperatively detectable marker can be placed in the biopsied node at the time of initial diagnosis rather than performing a repeat procedure before surgery. If the multidisciplinary work for TAD is too challenging, another option is to retrieve a minimum of three sentinel nodes using a dual blue dye/technetium–labelled colloid or equivalent superparamagnetic iron oxide (*Ann Surg Oncol* 2016; 23:1508 and *JAMA Oncol* 2024; 10:793).

Historically, patients with an initially positive axillary node have gone on to ALND after NAC and then received regional radiation therapy, even if there was no residual nodal disease in the ALND. However, this practice is likely to change: the B-51/RTOG 1304 trial demonstrated that if the nodes are cleared of tumor post-NAC, then subsequent radiation therapy may not be necessary (*Cancer Res* 2024; 84:GS02). In addition, results are eagerly awaited from the Alliance 11202 trial, which is evaluating the need for ALND after a positive SLNB post-NAC (if regional nodal radiotherapy is planned).

Conclusion

Debate continues regarding the extent of de-escalation of axillary surgery that ensures safety and minimizes unnecessary surgical risks in early breast cancer. In the meantime, clinicians and patients need a framework for how best to make decisions around axillary surgery (Table). For patients undergoing upfront surgery, "a little" axillary surgery (SLNB) or "none at all" (omission of axillary surgery for selected patients) is now the standard. For those who have undergone NAC, we should perform "less" axillary surgery (TAD or 3-node sentinel node biopsy) in those who may have no residual cancer in nodes and reserve "a lot" (ALND) for those with a poor response in the axilla or initially N2 disease.

Two Views

Anthracyclines and Treatment of Early-Stage Breast Cancer

For decades, anthracyclines have played an important role in treating early-stage breast cancer. But whether this class of drugs should continue to be recommended in early disease given that other available therapies are less toxic is a matter of some debate. Incorporating data from recent trials, two groups of experts present their views on whether anthracyclines should remain in treatment protocols and for which patients.

A Long-Lasting Mainstay of Breast Cancer Treatment

Guilherme Nader Marta, MD, and Martine J. Piccart, MD, PhD

Anthracyclines have been a cornerstone in the treatment of early-stage breast cancer for the past several decades and remain an essential component of such treatment. The argument for omitting these agents from therapeutic regimens is largely based on the assumption that similar outcomes can be achieved with the use of less toxic agents. However, the efficacy of anthracycline-containing regimens is supported by a robust body of evidence and new mechanisms of action, and synergistic interactions continue to be unveiled. Furthermore, there have been significant advances in patient selection and in the prevention and management of adverse effects related to anthracyclines, allowing for safer administration. Finally, anthracyclines are an affordable treatment option, and any alternative would have to be both equally effective and equally accessible.

UNEQUIVOCAL EFFICACY

One of the most compelling demonstrations of anthracycline efficacy comes from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of individual patient-level data from 18,103 women across 15 trials. In that study, the 10-year cumulative rate of breast cancer recurrence was significantly lower with taxane-based regimens that included an anthracycline than those that did not (rate ratio, 0.86). Importantly, this benefit of anthracyclines was observed regardless of estrogen-receptor expression and nodal status (*Lancet* 2023; 401:1277).

HER2-Negative Breast Cancer

Anthracyclines are a standard treatment option for estrogen receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer. Although several trials have been designed to demonstrate the noninferiority of non-anthracycline regimens to anthracycline-containing regimens in this setting, they have generally failed to do so. In three such adjuvant trials (referred to as the ABC trials), researchers

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evaluated the efficacy of six cycles of docetaxel with cyclophosphamide relative to doxorubicin-containing regimens. In the final joint analysis, the hazard ratio for invasive disease–free survival was 1.14, but the upper boundary of the 80% confidence interval (1.04 to 1.25) did not exclude the prespecified inferiority threshold; thus, noninferiority was not demonstrated (*J Clin Oncol* 2024; 42:1344).

Determining which patients will benefit most from anthracyclines is critical. Until recently, predictive biomarkers of response have never achieved sufficient accuracy to be incorporated into clinical practice. Emerging data suggest that patients classified as having Luminal B-Type tumors and MammaPrint (MP) High 2 risk appear to derive significant benefit from anthracyclines, whereas those classified as MP High 1 achieve similar outcomes from regimens with or without anthracyclines (*J Clin Oncol* 2024; 42[S16]: abstract 511). If further validated, the MP assay could support clinical decisions in this setting and improve patient selection.

HER2-Positive Breast Cancer

No trials have been specifically designed and powered to establish the noninferiority of anthracycline-free regimens in HER2-positive breast cancer. For instance, the BCIRG-006 study demonstrated the benefit of adding trastuzumab to adjuvant chemotherapy but was not powered to detect equivalence between the two trastuzumab-containing arms (*N Engl J Med* 2011; 365:1273). Similarly, the TRAIN-2 trial was designed to demonstrate that an anthracycline-containing regimen would improve the rates of pathologic complete response compared with a non-anthracycline regimen (*Lancet Oncol* 2018; 19:1630), but it was not powered to evaluate noninferiority. Although the outcomes between different arms of superiority trials may appear numerically comparable, caution should be exercised when claiming equivalence from studies not designed for this purpose.

SYNERGISTIC ACTIVITY BETWEEN ANTHRACYCLINES AND TARGETED THERAPIES

A growing body of evidence suggests that the presence of anthracyclines may enhance the efficacy of certain targeted therapies. Several targeted therapies incorporated into breast cancer management have been tested in trials that included an anthracycline-containing chemotherapy backbone. Widely used drugs that have shown significant benefits and were tested primarily in patients treated with anthracyclines include pembrolizumab for triple-negative breast cancer (*N Engl J Med* 2020; 382:810), dual HER2 blockade and adjuvant trastuzumab emtansine for HER2-positive disease (*J Clin Oncol* 2021; 39:1448, *N Engl J Med* 2019; 380:617), and adjuvant olaparib for patients with germline *BRCA* mutations (*N Engl J Med* 2021; 384:2394).

Interestingly, recent research has shed light on the immunogenic activity of anthracyclines in the tumor microenvironment. Doxorubicin has been shown to induce immunogenic cell death, an anticancer effect that may be enhanced when the drug is combined with an immune checkpoint inhibitor. Doxorubicin upregulates immune-related genes and pathways, creating a more favorable tumor microenvironment for programmed cell death protein 1 (PD-1) blockade (*Nat Med* 2019; 25:920).

Taken together, these data suggest that the activity of targeted therapies may be partially dependent on their interaction with anthracyclines, thus raising the question of whether the benefit of targeted therapies observed in pivotal studies would have been sustained if anthracycline-free backbones had been used.

MITIGATING LONG-TERM TOXICITIES

The main concerns associated with anthracycline use are related to the risk of cardiotoxicity and myeloproliferative malignancies. However, in the EBCTCG meta-analysis, the risk of death without recurrence, including from cardiovascular disease or other primary cancers, was not increased with anthracycline-based regimens (*Lancet* 2023; 401:1277). Although there was an increase in the incidence of acute myeloid leukemia, with one additional case per 700 women treated with anthracyclines, the overall incidence of non-breast primary cancers was similar between patients taking anthracyclines and those taking non-anthracycline regimens. In aggregate, these data suggest that the benefits of

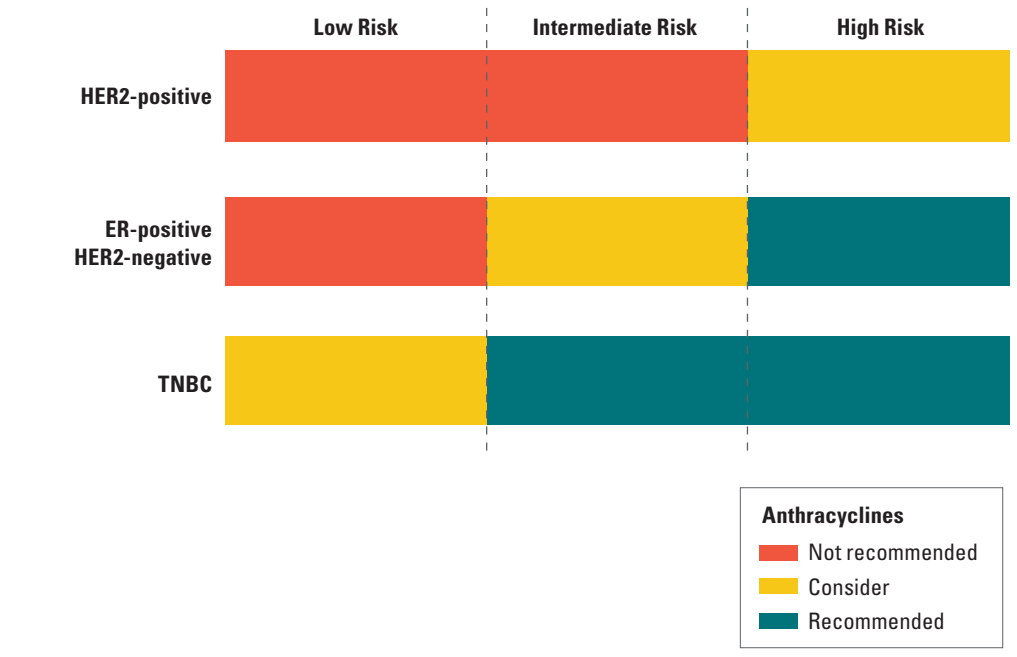
anthracyclines outweigh the risks. Furthermore, the risk of cardiotoxicity can be effectively mitigated through careful patient selection, early detection of cardiac damage, and prompt treatment of such damage. Significant developments in these three areas have been achieved in recent years, allowing for safer use of these agents.

- Patients being considered for anthracycline-based therapy should be screened for cardiotoxicity risk factors, including age, smoking history, obesity, comorbidities (i.e., diabetes, hypertension, dyslipidemia), use of other cardiotoxic agents, and prior chest radiotherapy (*Ann Oncol* 2020; 31:171). Patients with multiple cardiac risk factors may require anthracycline-free regimens.
- Close monitoring and early detection of cardiac damage allows for timely intervention, which has been associated with favorable long-term cardiovascular outcomes in the vast majority of patients (*Circulation* 2015; 131:1981).
- The combination of novel cardiac imaging modalities, echocardiographic parameters, and circulating biomarkers (e.g., troponin I, natriuretic peptides, cardiomyocyte cell-free DNA, and circulating microRNAs) may allow for early identification of cardiomyocyte damage, even before the onset of left ventricular dysfunction.
- When available, multidisciplinary cardio-oncology evaluation may support the development of personalized, risk-adapted monitoring and management protocols for cardiotoxicity, including the initiation of cardioprotective therapies (e.g., angiotensin-converting–enzyme inhibitors and beta-blockers) before the start of chemotherapy or at the first signs of dysfunction.

EFFECTIVE AND AFFORDABLE TREATMENT OPTIONS

Improvements in patient outcomes have historically been achieved through the administration of increasingly efficacious drug combinations.

FIGURE 1. Anthracycline Recommendations in Early Breast Cancer According to Breast Cancer Type and Risk of Recurrence



ER — estrogen receptor; HER2 — human epidermal growth factor receptor 2; TNBC — triple-negative breast cancer

In the case of early breast cancer, several of the newer drugs have led to remarkable improvements in the chances of cure, but many of the regimens have not demonstrated noninferiority to anthracycline-based regimens, and the toxicity concerns with anthracyclines can be overcome as outlined above. Furthermore, these newer agents are not accessible to a significant proportion of patients diagnosed with breast cancer worldwide. Anthracyclines remain a major, affordable component of early breast cancer therapy in developing countries, and their omission should not be supported in the absence of equally effective and widely available alternative therapies.

Although good evidence is required to implement an effective therapy, even more compelling data are needed to abandon one. Until robust evidence establishes the safety of omitting anthracyclines from the treatment of high-risk early-stage breast cancer, these agents should remain a part of treatment protocols for carefully selected patients (Figure 1). This decision should be based on a comprehensive assessment of individual risks and benefits, which must be communicated and discussed with the patient.

Tailoring Treatment to Avoid Toxicities

Virginia F. Borges, MD, MMSc

Anthracyclines have been a backbone of early breast cancer (EBC) treatment since doxorubicin was first approved in the early 1970s. However, they are associated with significant toxicity and do not benefit all patients equally. Although these medications still play an important role for some patients, an increasing body of data supports omitting them from treatment in many cases. Non-anthracycline regimens are efficacious with fewer adverse effects, and we are increasingly able to select which patients will benefit most from these treatments.

EFFICACY OF NON-ANTHRACYCLINE REGIMENS

The efficacy of non-anthracycline regimens was first demonstrated in 2006, when a U.S. Oncology Research Trial demonstrated the superiority of four cycles of docetaxel and cyclophosphamide (TC) compared with four cycles of doxorubicin and cyclophosphamide (AC) when administered every 3 weeks. These results persisted at 7 years of follow-up, and four cycles of TC became an established regimen for EBC (*J Clin Oncol* 2006; 24:5381; *J Clin Oncol* 2009; 27:1177). TC also became the non-anthracycline regimen of choice to compare with anthracycline-based regimens in multiple studies.

Fast forward to 2023, when the EBCTCG released updated results from their meta-analysis. Although anthracycline-containing regimens were found to be associated with significant reductions in both recurrence and mortality at 10 years' postdiagnosis compared with anthracycline-omitting, taxane-based regimens, the absolute reductions were small (2.6% for recurrence and 1.6% for mortality). Furthermore, these differences were significant only for regimens in which the anthracycline and taxane were administered concurrently; if the medications were given sequentially, as is often the case in clinical practice, the statistical significance was lost (*Lancet* 2023; 401:1277). More recently, researchers released updated results from a preplanned combined analysis of the ABC trials in which 4,181 patients with high-risk EBC received six cycles of either TC or a regimen containing an anthracycline, a taxane, and cyclophosphamide, given concurrently or sequentially. In this updated analysis, while the non-anthracycline regimens failed to demonstrate noninferiority for invasive disease outcomes, there was no difference in overall survival at approximately 7 years of follow-up (*J Clin Oncol* 2024; 42:1344).

In subgroup analyses of these various trials, the benefits of anthracycline were found to be proportionally similar across all patient groups but reached significance only in certain groups. In the EBCCTG meta-analysis, anthracyclines had significant benefits in:

- Patients who were ≤54 years of age, but not those ≥55
- Those with high-grade tumors, but not low- to medium-grade tumors

- Those with estrogen receptor (ER)–negative tumors but not ER-positive tumors, whether lymph nodes were involved or not (*Lancet* 2023; 401:1277)

In subgroup analyses of the ABC trials, the benefits of anthracycline regimens were seen in patients with ER-negative tumors and in patients with ER-positive tumors who had ≥4 nodes involved (*J Clin Oncol* 2017; 35:2647).

Finally, researchers recently analyzed SEER data from patients ≥66 years of age with triple-negative breast cancer (TNBC). Among those with node-negative TNBC, cancer-specific survival and overall survival were significantly better with taxane-based chemotherapy than with anthracycline-containing regimens (*Breast Can Res Treat* 2022; 191:389). Among those with node-positive TNBC, there was a trend toward improved cancer-specific and overall survival with anthracycline regimens compared with taxane-based regimens in patients with 4+ nodal involvement, and the two types of regimens appeared similar in the overall population (*Eur J Cancer* 2023; 185:69).

In sum, these data point to our being at an inflection point in the longstanding use of anthracyclines for EBC. We now have an opportunity for thoughtful strategy employing shared decision making and personalized medicine moving forward.

"In sum, these data point to our being at an inflection point in the longstanding use of anthracyclines for EBC."
— Virginia F. Borges, MD, MMSc

ADVERSE EFFECTS OF ANTHRACYCLINES

The main reason to consider omitting anthracyclines from treatment regimens is their life-threatening and life-altering toxicities, particularly in people who are not deriving significant benefit from their use. The main negative consequences are increased cardiotoxicity, secondary leukemia and myelodysplastic syndromes (SL/MDS), infertility and early menopause, cognitive dysfunction, and cancer-related fatigue.

The cardiotoxicity of anthracyclines is a cumulative dose-dependent risk, and the mainstay of avoidance is dose caps that are employed before the risk increases beyond 3% (*US Pharm* 2014; 39:HS2; *Cancer* 2023; 97:2869). The risk for cardiotoxicity is influenced by the presence of defined comorbidities, race/ethnicity, social determinants of health, and genetic susceptibility factors (Figure 2), many of which we cannot yet gauge well as synergistic or additive features for accurate personalized risk determination (*Biomedicines* 2023; 11:2286; *Circulation* 2021; 144:A13090).

Treatment-related secondary SL/MDS is a less common adverse effect (10-year incidence, 0.5%), carries high mortality, and arises most commonly within 1 to 10 years posttreatment; it is most often of myeloid lineage with uncommon presentations as lymphoid lineage disease. The degree of risk is related to the combination of anthracyclines with cyclophosphamide and is cumulative, with an identifiable dose threshold above which the risk rapidly increases. In a database study of more than 90,000 patients age ≥65 years, those who received anthracycline-containing regimens were significantly more likely to develop acute myeloid leukemia and MDS than those who received no chemotherapy (hazard ratios, 1.7 and 2.18, respectively). No increase in risk was seen in patients who received TC or other taxane-based regimens without an anthracycline (*Cancer* 2018; 124:899).

The best way to avoid these toxicities is to limit the use of anthracyclines to those patients who are most likely to benefit from them and are at the lowest risk for adverse outcomes (or in whom we can counteract the toxicities). Achieving that goal is a work in progress. An alternative is to not give anthracyclines at all, which would require highly effective alternatives with improved

long-term safety and tolerability — also a work in progress.

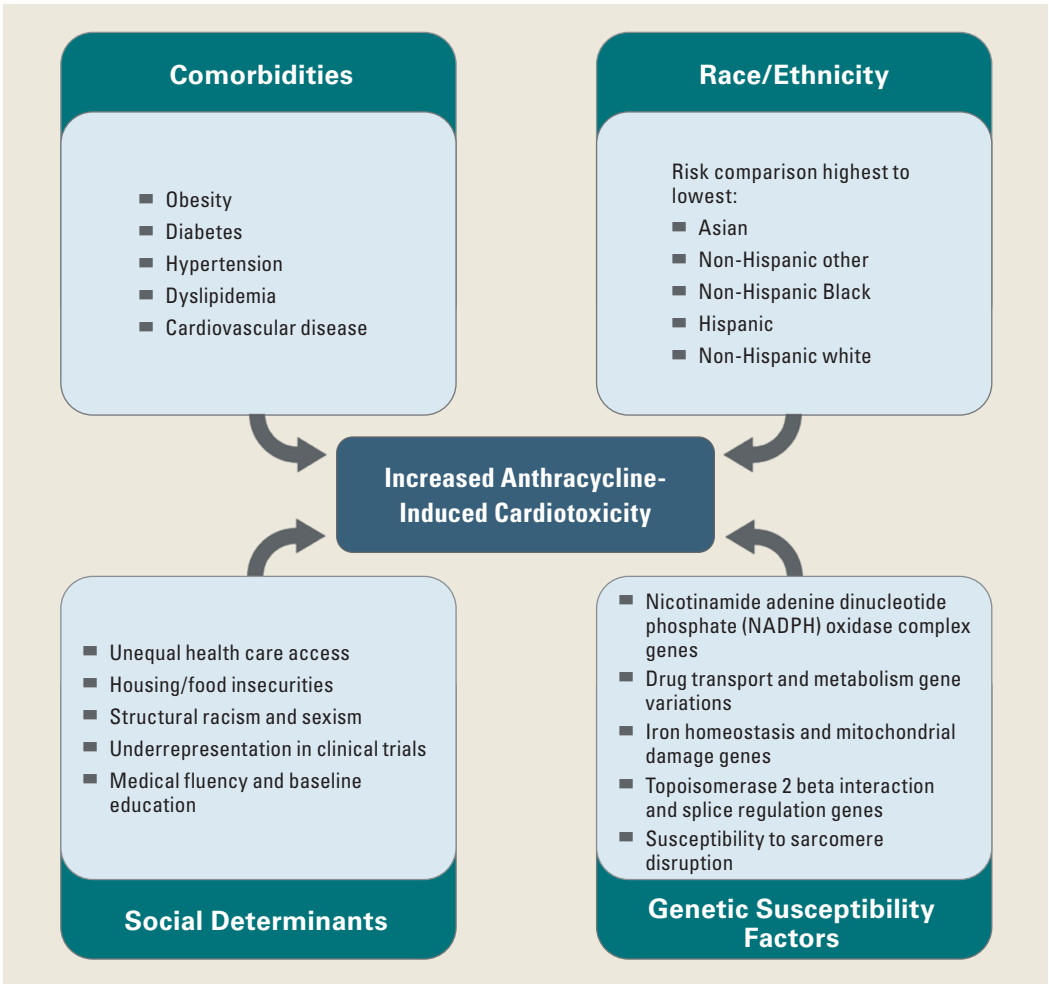
WHEN CAN WE OMIT ANTHRACYCLINES?

Where are we today with understanding when avoiding anthracyclines is the preferred choice? Breast cancer is now identified by biologic subsets that make a large difference in our treatment choices. Prior studies or meta-analyses of "all-comers" are no longer the only data to consider, and subset-specific advances define today's best regimens, with the value of anthracyclines being very much subset-dependent.

ER-Positive, HER2-Negative Breast Cancer

In women with ER-positive, HER2-negative breast cancer, three clinical trials (MINDACT, TAILORx, and RxPONDER) have demonstrated the utility of genomic assays in determining which women (among those with tumors <5 cm and <4 positive nodes) will most likely benefit from chemotherapy and which can reasonably avoid it. However, these trials were not sufficiently powered to offer regimen-specific information for the patients expected to benefit from chemotherapy (*Lancet Oncol* 2021; 22:476; *N Engl J Med* 2018; 379:111; *N Engl J Med* 2021; 385:2336).

FIGURE 2. Host Factors Influencing Frequency of Anthracycline-Induced Cardiotoxicity



Other studies are now evaluating whether genomic assays can be used to inform choice of regimen.

In a recent analysis of data from the FLEX registry cohort, researchers compared outcomes with TC versus anthracycline-based regimens among 614 people with EBC who had undergone testing with the 70-gene genomic assay MammaPrint (MP). Among the people with MP High Risk 1 category, Luminal type tumors, there was no difference in 3-year disease-free survival with TC compared with anthracycline regimens, whereas survival was significantly better for MP High Risk 2 patients with the inclusion of an anthracycline (*J Clin Oncol* 2024; 42(S16):abstract 511). This provocative finding at short-term follow-up suggests that genomic assays could eventually have a regimen-defining role.

In the meantime, we have the results of the EBCTCG and ABC trials to determine when anthracyclines are warranted and when their risks outweigh their benefits. In patients with ≥4 nodes involved, the benefit to anthracyclines remains notable. In lower-risk groups, it is a personalized decision based on clinical factors and risk factors as best as we can currently apply them.

HER2-Positive Breast Cancer

For our HER2-positive patients, we have more robust data to support the omission of anthracyclines. Docetaxel, carboplatin, and trastuzumab (TCH) is a scientifically designed regimen, and the 10-year results of the BCIRG-006 study showed no statistical difference in disease-free or overall survival for this regimen compared with anthracycline and cyclophosphamide (AC) followed by TH (*Cancer Res* 2016; 76:S5-04), including node-positive patients even with high nodal involvement. Although the study was not powered to detect a difference between the two trastuzumab-containing arms, the persistence of similar survival at 10 years offers confidence in TCH's outcomes. In terms of safety, the anthracycline-based regimen was associated with a higher frequency of serious congestive heart failure (Grade 3/4; 21 vs. 4 cases), sustained loss of cardiac ejection fraction over 10% (200 vs. 97 people) and secondary leukemia (7 vs. 0 cases).

Neoadjuvant trials TRYPHAENA and TRAIN-2 demonstrated that taxane-based, anthracycline-omitting regimens with dual HER2 blockade including trastuzumab and pertuzumab (HP) were equal or better at inducing a pathologic complete response (pCR) and led to similar survival outcomes compared with anthracycline regimens containing epirubicin followed by sequential taxane-HP cycles (*Eur J Cancer* 2018; 89:27, *JAMA Oncol* 2021; 7:978). Subsequently, the West German Study Group–ADAPT HER2+/HR– trial and the DAPHNE trial both studied a de-escalated paclitaxel-HP regimen in the neoadjuvant setting, demonstrating pCR rates of 90.5% and 56.7%, respectively (*Ann Oncol* 2017; 28:2768, *NPJ Breast Cancer* 2022; 8:63). These data provided the evidence to support the CompassHER2-pCR clinical trial, which has recently closed to accrual and is poised to confirm the option to de-escalate neoadjuvant treatment. The safety of this de-escalation is supported by our enhanced understanding of the prognostic strength of achieving a pCR and the ability to regain better outcomes for those patients who do not obtain a pCR using adjuvant therapy as seen in the KATHERINE trial (*N Engl J Med* 2019; 380:617). In summary, there is a large body of evidence to support the avoidance of anthracyclines for HER2-positive EBC. Current National Comprehensive Cancer Network guidelines have adopted these data and removed anthracycline-based regimens from the list of preferred options for patients with HER2-positive breast cancer.

Triple-Negative Breast Cancer

In TNBC, early-stage, smaller tumors and node-negative cases do not appear to derive sufficient benefit from anthracyclines, compared with TC, to warrant the added risks. Until alternative options are found, patients with stage II and III TNBC who are fit for anthracycline-based chemotherapy are best treated with the combined anthracycline chemotherapy–immunotherapy regimen used in the KEYNOTE-522 trial (*N Engl J Med* 2020; 382:810).

FUTURE DIRECTIONS

For all EBC subtypes we now have adaptive clinical trials, such as the I-SPY 2.2 study, which employ the "best in class" of novel drugs such as immunotherapy or antibody–drug conjugates, as initial neoadjuvant therapy. In this trial, genomic data are used to help define best treatment choices, and a pCR is estimated after each block of therapy so that participants can be sent to surgery at "just the right" moment, allowing them to avoid additional chemotherapy, immunotherapy, or anthracyclines if their tumor is adequately responding (*Global Forum* 2021 Jul). This trial is a move toward tailoring the treatment of EBC, including TNBC, to the individual patient. Such studies put us further down the path to ensuring we use anthracyclines only when needed and otherwise can safely avoid their toxicities.

NEJM Research Summary

Ribociclib plus Endocrine Therapy in Early Breast Cancer

Slamon D et al. **DOI: 10.1056/NEJMoa2305488**

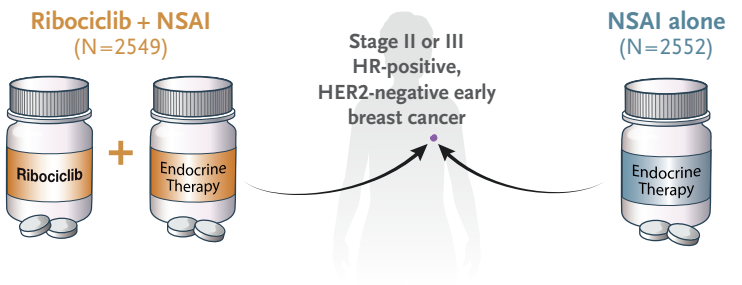
CLINICAL PROBLEM

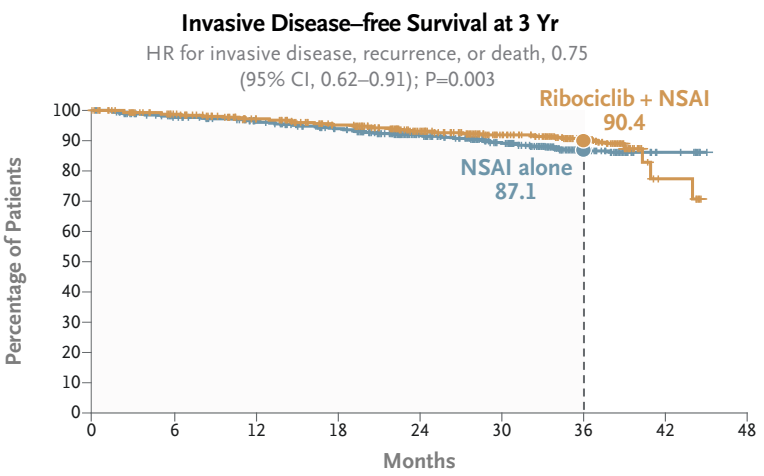
Hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer is the most common subtype of breast cancer, with the majority of cases diagnosed early and treated with curative intent. Adjuvant endocrine therapy improves outcomes in these patients; however, the disease can recur up to 20 years after diagnosis. Ribociclib is a cyclin-dependent kinase 4 and 6 inhibitor with an established benefit in advanced breast cancer. Whether this benefit extends to early breast cancer is unclear.

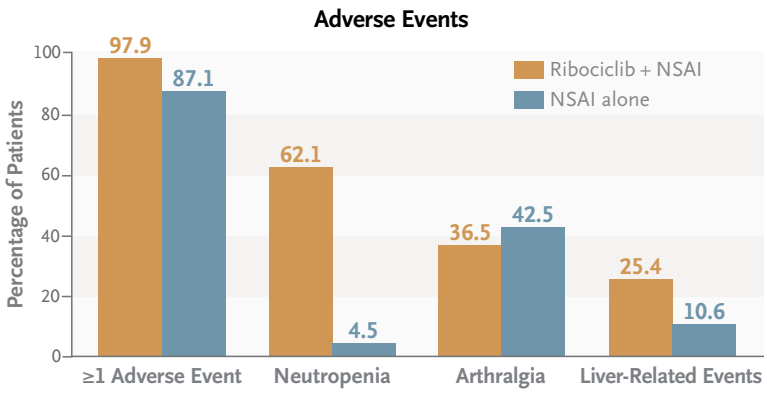
CLINICAL TRIAL

Design: A phase 3, international, open-label, randomized trial is examining the efficacy and safety of adjuvant ribociclib plus endocrine therapy (a nonsteroidal aromatase inhibitor [NSAI]) as compared with an NSAI alone in patients with stage II or III HR-positive, HER2-negative early breast cancer.

Intervention: 5101 patients were assigned to receive either ribociclib (400 mg per day for 3 weeks, followed by 1 week off, for 3 years) plus an NSAI (letrozole [2.5 mg per day] or anastrozole [1 mg per day] for ≥5 years) or an NSAI alone. The primary end point was survival free from invasive disease.







RESULTS

Efficacy: At 3 years, invasive disease–free survival was significantly higher with the addition of ribociclib to an NSAI than with an NSAI alone.

Safety: Treatment with ribociclib plus an NSAI was not associated with any new safety signals. The most common adverse events of any grade were neutropenia, arthralgia, and liver-related events.

LIMITATIONS AND REMAINING QUESTIONS

- Additional follow-up regarding the long-term efficacy of ribociclib in this population is needed.
- Patients were younger than the median age at diagnosis in the United States, and Black patients were underrepresented.

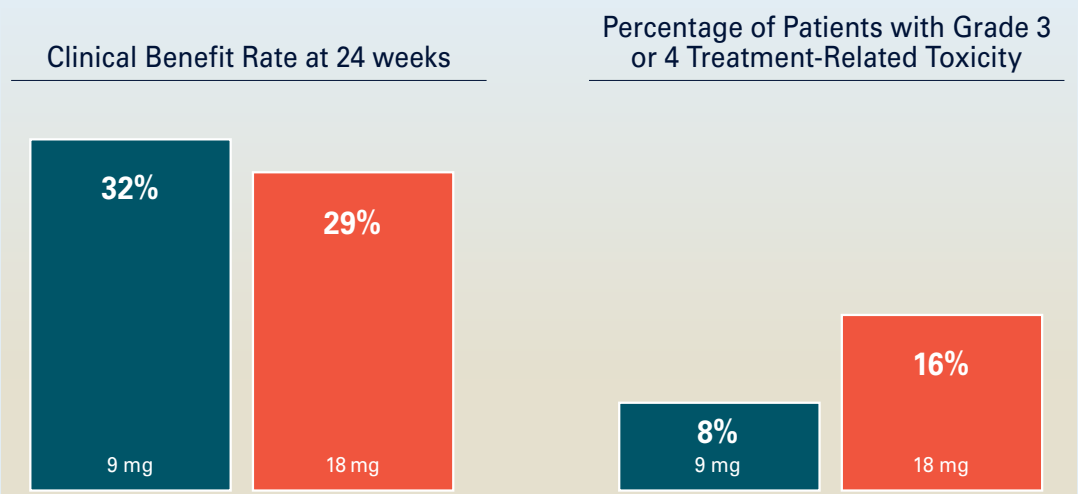
CONCLUSIONS

Among patients with stage II or III HR-positive, HER2-negative early breast cancer, the addition of ribociclib to adjuvant endocrine therapy significantly improved 3-year invasive disease–free survival.

Visual Summary

Targeting the Androgen Receptor in Breast Cancer

In a multinational, randomized, open-label, phase 2 trial, researchers assessed the effects of the selective androgen receptor modulator (SARM) enobosarm at two dose levels (9 mg or 18 mg daily) in 136 postmenopausal patients with estrogen receptor (ER)–positive and androgen receptor (AR)–positive metastatic breast cancer.



Comment

Although the small sample size, open-label design, and lack of a control arm limit drawing conclusions from this study, it shows that enobosarm has antitumor activity in patients with heavily pretreated, ER-positive metastatic breast cancer and is well tolerated. Further development of enobosarm and other SARMs is warranted.

William J. Gradishar, MD, reviewing Palmieri C et al. *Lancet Oncol* 2024 Mar

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Guideline Watch

USPSTF Releases New Breast Cancer Screening Guidelines

The Task Force now recommends biennial screening for average-risk women who are 40 to 74.

SPONSORING ORGANIZATION

U.S. Preventive Services Task Force (USPSTF)

BACKGROUND

Screening mammography lowers breast cancer–related mortality, but incidence of invasive breast cancer is increasing among women in their 40s. Compared with white women, Black women are more likely to develop aggressive cancers at younger ages and are at higher risk for breast cancer–related mortality. In 2016, the USPSTF recommended biennial mammograms for middle-aged women (age range, 50–74; grade B) with individualized decision making for those who were 40 to 49 (grade C; *Ann Intern Med* 2016; 164:279). Now, the Task Force has updated this guideline.

KEY RECOMMENDATIONS

These recommendations apply to all people assigned female at birth and at average risk for breast cancer.

- The USPSTF recommends biennial screening mammograms for women who are 40 to 74 (grade B) and concludes with moderate certainty that such screening has net benefit in preventing breast cancer–related mortality.
- In women who are 75 or older, evidence is insufficient to recommend for or against screening.
- For women with dense breasts, the Task Force found inadequate evidence to make a recommendation on benefits and harms of supplemental screening with ultrasound or magnetic resonance imaging after negative mammography.

WHAT'S NEW

For women in their 40s, the USPSTF previously recommended shared decision making about screening but stopped short of formally recommending it; now, they recommend screening all women in this age group. A decision analysis estimates this change will avert 1.3 additional breast cancer–related deaths per 1000 women screened biennially during a lifetime of screening — at the expense of an approximately 60% increase in false-positive results.

Comment

Expert groups disagree about optimal ages, intervals, and modalities for breast cancer screening. For example, the American Cancer Society strongly recommends screening starting at age 45 (initially annually) and makes a "qualified" (weaker) recommendation to start at age 40. Guidelines differ for several reasons.

Few rigorous studies have been designed to compare screening strategies, so most of the Task Force recommendations are based on modeling studies rather than direct evidence. Equally importantly, medical organizations (and individuals) differ in how they weigh harms and benefits of different approaches. For example, computer models suggest that screening biennially instead of annually could lead to a 50%

(continued on page 26)

(continued from page 25)

decrease in false positives but a slight increase in breast cancer–related mortality. This tradeoff will seem reasonable to some but unacceptable to others. In several ongoing trials, researchers are comparing standard one-size-fits-all screening schedules and individualized risk-based schedules; those results might help address some areas of uncertainty.

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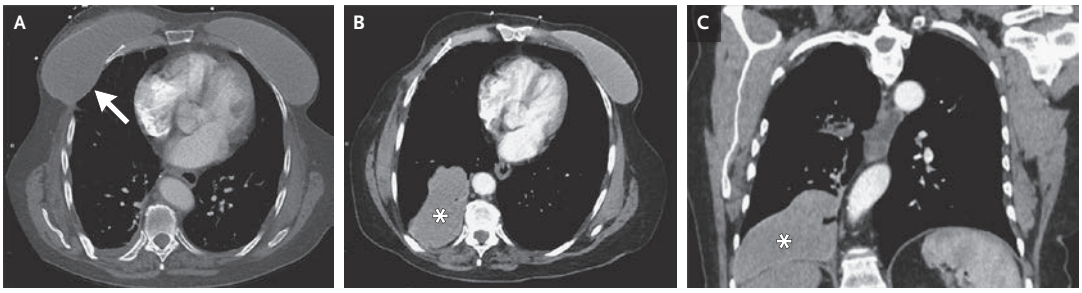
Trentham-Dietz A et al. Collaborative modeling to compare different breast cancer screening strategies: A decision analysis for the US Preventive Services Task Force. **JAMA** 2024 Apr 30; [e-pub]. (https://doi.org/10.1001/jama.2023.24766)

Images in Clinical Medicine

Intrathoracic Migration of a Breast Implant



A 73-year-old woman had sudden displacement of her right breast implant during pulmonary-function testing for evaluation of a 1-year history of cough. She had a history of breast cancer, for which a double mastectomy with breast reconstruction had been performed 23 years earlier, followed by the insertion of silicone breast implants 12 years later. She also had a history of non–small-cell lung cancer, for which a superior segmentectomy of the right lower lung had been performed by means of open thoracotomy 3 years before presentation. On physical examination after the pulmonary-function test, the breast implant was not palpable on the right side. A computed tomographic (CT) scan of the chest that had been obtained 1 month earlier was reviewed. The scan was notable for focal herniation of the breast implant on the right side (Panel A, arrow). Repeat CT of the chest showed displacement of the breast implant on the right side into the lower pleural space (Panels B [axial view] and C [coronal view], asterisk). A diagnosis of intrathoracic migration of the breast implant was made. During a subsequent right thoracotomy, the breast implant was removed, and a chest-wall defect was reconstructed. The left breast implant was also later removed. She recovered well, and her cough, which was attributed to lung herniation through the chest-well defect, abated.

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