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- Liquid Biopsy in Breast Cancer Care
- Is Pregnancy Safe after Early Breast Cancer?
- Antibody–Drug Conjugates & HER2-Negative Disease
- ASCO Meeting Recap

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FROM the Editor

It is my great pleasure to serve as editor for this issue of *Breast Cancer Update*. The rapid pace of advances in breast cancer research today makes it imperative for us to carefully consider how to incorporate new findings into the day-to-day care of patients. This is particularly true in the application of novel technologies and paradigms, as well as in areas of controversy.

In the past decade, antibody–drug conjugates (ADCs) have revolutionized how we treat advanced breast cancer. In this issue, Dr. Rita Nanda presents a comprehensive overview of the science and clinical data that have led to FDA approvals and the increasing use of these life-saving drugs in patients with HER2-negative disease. She also highlights important unanswered questions, including those that are being addressed in ongoing or planned clinical trials.

Drs. Stefania Morganti and Heather Parsons deliver a master class on the evolving role of so-called liquid biopsies in breast cancer, with a focus on circulating tumor DNA (ctDNA). They deftly describe not only the current and potential benefits of this technology in both early and metastatic breast cancer patients but also its limitations and how we might approach them.

Finally, in Two Views, two expert teams address the longstanding controversy of whether all patients should be supported to get pregnant after breast cancer in light of recent findings from the POSITIVE trial. Drs. Luca Arecco and Matteo Lambertini are enthusiastic to support patients in pursuing pregnancy, with an emphasis on shared decision making with patients. By contrast, Drs. Jasmine Sukumar and Mariana Chavez Mac Gregor emphasize more cautious optimism about this life-affirming survivorship issue for our young patients as we all eagerly await longer-term follow-up.

We hope the topics covered in this issue help you better care for breast cancer patients and survivors in the ever-changing world of breast cancer management.

Ann H. Partridge, MD, MPH, Editor

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Topic Update

ctDNA Liquid Biopsies in Breast Cancer: Using the Right Test, for the Right Patient, at the Right Time

Stefania Morganti, MD, and Heather A. Parsons, MD, MPH

Liquid biopsies are powerful tests used across tumor types, including breast tumors. However, "liquid biopsy" refers to various technologies with different aims at different stages of clinical validation. Some applications are ready to be implemented in clinical practice; others are still being assessed for their clinical utility. We offer an overview of the terminology and the research on the various available tests for patients with breast cancer.

Clarification of Terms

Terms such as circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and minimal (or molecular) residual disease (MRD) are often used interchangeably to refer to liquid biopsy. According to the National Cancer Institute *Dictionary of Cancer Terms*, liquid biopsy is "a laboratory test done on a sample of blood, urine, or other body fluid to look for cancer cells from a tumor or small pieces of DNA, RNA, or other molecules released by tumor cells into a person's body fluids." The definition reflects the complexity of liquid biopsy tests.

First, all body fluids are potential liquid biopsy sources; the term is not exclusively for a blood assay. Second, different technologies are designed to detect different "traces" of tumor, such as DNA (ctDNA), RNA (ctRNA), CTCs, extracellular vesicles, and others. ctDNA, specifically, is the fraction of cell-free DNA that is released by tumor cells following cell death or by active secretion; the ctDNA level thus depends on both tumor burden and tumor shedding. Most of the current "liquid biopsy" assays are ctDNA tests. Third, various sequencing and computational approaches can serve distinct purposes, such as to identify genomic alterations for treatment selection, to detect very low levels of ctDNA for MRD identification, or to infer tumor gene expression in characterizing tumor phenotype and associated behavior. Each of these approaches has different strengths and weaknesses. Appropriate use of a particular assay will depend on the pertinent clinical or research question.

Application to Metastatic Breast Cancer

ctDNA-guided treatment selection — detecting genomic alterations that predict response to specific therapies — has proven to be clinically useful in metastatic breast cancer (MBC). In the plasmaMATCH study, ctDNA assays identified 98% of mutations detected by coincident tissue biopsies (*Lancet Oncol* 2020; 21:1296). ctDNA is, thus, a reliable, noninvasive method of identifying actionable variants for approved targeted therapies as well as genomic alterations targeted by investigational drugs in clinical trials.

Analogously, ctDNA can detect emergent genomic variants that are known to cause treatment resistance. Ongoing research is exploring whether intervening upon molecular changes, often a harbinger of clinical progression, or "molecular progression,"

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may improve outcomes. In the phase 2 PADA-1 trial, switching to palbociclib-fulvestrant before overt progression improved progression-free survival (PFS) in patients with emergent *ESR1* mutations (*ESR1*m) who were receiving first-line treatment (*Lancet Oncol* 2022; 23:1367). A similar strategy is under investigation in the phase 3 SERENA-6 trial, in which patients with stable disease on a first-line cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor plus an aromatase inhibitor (AI) but who have emergent *ESR1*m, are being randomized to either continuing the same therapy or switching the AI to an oral selective estrogen-receptor modulator. However, the primary endpoint of SERENA-6 and of PADA-1 is PFS, not overall survival. It's questionable whether a PFS benefit alone is enough to establish the clinical benefit of real-time ctDNA assessment in this setting. A feasible, more clinically informative end point would be PFS2 (the time from study registration to second objective disease progression or death from any cause). This approach could clarify whether switching therapy earlier based on molecular progression has a clinical benefit or does not actually improve outcomes. A proven PFS2 or survival benefit would support real-time ctDNA assessment in patients with MBC.

Promise in Early-Stage Breast Cancer

ctDNA fraction is significantly lower in early-stage breast cancer than in advanced disease, requiring highly sensitive assays to assess MRD. The most sensitive approaches developed to date are so-called "tumor-informed" or "bespoke" assays, which rely on sequencing of tumor tissue to identify tumor-specific genomic alterations tracked via patient-specific tests. Those techniques allow for ctDNA detection down to 10^{-3} to 10^{-6} mutant molecules per wild-type DNA, depending on the sequencing approach and the number/type of variants tracked.

Several studies have shown that MRD at baseline is prognostic and that it correlates with risk for recurrence and with survival (e.g., *JAMA Oncol* 2019; 5:1473). Furthermore, MRD monitoring in the adjuvant setting can anticipate clinical recurrence for up to about 3 years (*J Clin Oncol* 2022; 40:2408). MRD clearance during neoadjuvant therapy is also prognostic, with better outcomes in patients who clear ctDNA over the course of therapy compared with patients who remain MRD-positive at surgery (*Cancer Cell* 2023; 41:1091).

Although tumor-informed assays are powerful risk-stratification tools with proven analytic and clinical validity, the clinical utility of MRD monitoring is still unknown. Before these assays can be used in clinical practice, research must determine whether MRD assessment improves patient outcomes.

Next Steps in Proving MRD's Clinical Utility

Despite years of biomarker research, tumor stage and subtype still guide treatment algorithms. Without tools that predict individual response and risk for relapse, many patients are over- or undertreated. MRD-guided treatment could be paradigm-changing; if proven, it could move the current approach, dependent on probabilistic risk models, to a paradigm of tailored treatment of quantifiable residual disease.

MIGHT CURING MRD CHANGE THE COURSE OF DISEASE? A first wave of clinical trials is assessing how treatment escalation affects outcomes for MRD-positive patients, but many questions remain. Some trials use MRD clearance in patients who are MRD-positive at study entry as an end point. In breast cancer, it is still unclear how MRD clearance in the adjuvant setting relates to meaningful clinical outcomes such as (distant) disease-free survival and overall survival. If MRD clearance is a meaningful surrogate, it could allow for substantially smaller, faster clinical trials. In addition, the relationship between MRD-positive status in the adjuvant setting and scan-detectable metastatic disease is unclear; progress will depend on greater clarification and increasingly effective therapy to eradicate MRD. If MRD-positive patients already have macroscopic metastatic disease, these tests may be much less useful than initially hoped. As a cautionary tale, in the c-TRAK TN study of patients with high-risk triple-negative breast cancer (TNBC) and residual disease, 71.9% of patients who became MRD-positive during follow-up were shown to have metastatic disease (*Ann Oncol* 2023; 34:200). However, this study was done in an extraordinarily high-risk patient group using a first-generation, less-sensitive MRD assay. Additional studies will evaluate more-sensitive assays.

CAN SYSTEMIC THERAPY USE BE REDUCED IN MRD-NEGATIVE PATIENTS? Patients with MRD-negative status may be candidates for clinical trials of less intensive treatment regimens. In stage II

colon cancer, for example, ctDNA-guided management spared the use of chemotherapy in about 15% of patients without compromising clinical outcomes (*N Engl J Med* 2022; 386:2261). In this context, a better understanding of ctDNA dynamics in breast cancer, together with deployment of highly sensitive assays, is crucial for avoiding undertreatment after false-negative test results. The impressive sensitivity identified by most retrospective studies of breast cancer has, so far, depended on serial testing (the sensitivity of a single timepoint for recurrence must be high to avoid inappropriate undertreatment). In the neoadjuvant setting, where substantial treatment escalation has been observed, particularly in TNBC, the best timepoint for intervening upon MRD-negative results must be identified. Neoadjuvant, MRD-guided treatment tailoring could be powerful if proven to be effective. In the I-SPY2 study, which retrospectively investigated the association between MRD clearance and clinical outcomes, early clearance appeared to better correlate with event-free survival, although prediction of pathologic complete response was low (*Cancer Cell* 2023; 41:1091). Additional studies with highly sensitive assays are needed to validate the predictive role of MRD clearance for treatment deescalation in MRD-negative patients.

Overall, ctDNA assays are powerful tools for targeted treatment selection in MBC, but evidence supporting ctDNA assessment for disease monitoring and treatment tailoring in early breast cancer is still lacking. Demonstrating clinical utility is crucial before using a biomarker in clinical practice to avoid possible harm to patients and overuse of resources. The potential to change treatment paradigms is high, but clinical trials must prove that MRD implementation can improve patients' outcomes.

Topic Update

Antibody–Drug Conjugates for HER2-Negative Advanced Breast Cancer

Rita Nanda, MD

Antibody–drug conjugates (ADCs) are molecules that consist of an antibody targeting a specific antigen conjugated to a toxic payload. Newer-generation ADCs are characterized by high drug-to-antibody ratios and payloads with "bystander effects," features that further enhance the therapeutic index by delivering highly potent chemotherapy directly into the tumor. The bystander effect refers to the toxic payload's ability to kill neighboring tumor cells that may not even express the antigen being targeted. It was initially believed that the ADC molecule had to be internalized by a tumor cell for the payload to be released, but emerging evidence suggests that for some ADCs, binding to the antigen is sufficient to enable the drug's release (*Br J Cancer* 2017; 117:1736). ADCs have been available for managing human epidermal growth factor receptor 2 (HER2)–positive breast cancer for several years, but they were only recently extended to encompass HER2-negative disease.

Two ADCs currently approved for HER2-negative disease, sacituzumab govitecan (SG) and trastuzumab deruxtecan (T-DXd), have different antigen targets (the trophoblast cell-surface antigen 2 [Trop-2] and HER2, respectively) but payloads from the same cytotoxic class (topoisomerase I inhibitors). All patients with HER2-negative advanced breast cancer are candidates for Trop-2-targeting ADCs, but at present only patients with HER2-low disease are candidates for HER2-targeting ADCs. Although the subset of patients with advanced HER2-low disease are fortunate to be candidates for both Trop-2 and HER2-targeting agents, data on optimal sequencing of these agents are not yet available.

Targeting Trop-2

Trop-2 is a glycoprotein that spans the epithelial membrane surface and plays a role in cell self-renewal, proliferation, and transformation. Trop-2 is expressed by several malignancies, including breast cancer (*Exp Mol Pathol* 2013; 94:73). SG is a Trop-2-targeting antibody linked to SN-38, the active metabolite of irinotecan. SG was granted accelerated approval in April 2020, based on remarkable efficacy in a phase 1/2 single-arm trial in heavily pretreated patients with advanced triple-negative breast cancer (TNBC). The confirmatory phase 3 ASCENT trial randomized patients with advanced TNBC who had received at least two prior treatments to either SG or treatment-of-physician's-choice (TPC) chemotherapy with capecitabine, eribulin, gemcitabine, or vinorelbine (*N Engl J Med* 2021; 384:1529). SG met both the primary end point of a significant advantage over TPC in progression-free survival (PFS; 5.6 vs. 1.7 months, $P<0.001$) and a key secondary end point of an overall survival (OS) advantage (12.1 vs. 6.7 months, respectively; $P<0.001$). On the basis of the ASCENT findings, SG received full FDA approval for second-line and later treatment of advanced TNBC in April 2021. In correlative studies, SG was superior to TPC regardless of Trop-2 expression levels, making testing for Trop-2 expression unnecessary.

A phase 1/2 study showing efficacy in heavily pretreated hormone receptor (HR)–positive breast cancer (*Ann Oncol* 2020; 31:1709) led to the TROPiCS-02 phase 3 randomized trial of SG versus TPC in patients who had received two to four prior lines of chemotherapy for advanced-stage disease (*J Clin Oncol* 2023; 41 [Suppl 16]:1003). SG had significant advantages over TPC in PFS (5.5 vs. 4.0 months; $P=0.0001$)

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and OS (14.5 vs. 11.2 months; *P*=0.0133). Given these findings, SG was approved for advanced HR-positive breast cancer in February 2023; patients benefited more from SG than TPC regardless of tumor Trop-2 expression levels, again negating the need for Trop-2 expression testing. Ongoing trials are evaluating SG for TNBC in frontline metastatic disease, with or without immunotherapy (NCT05382286, NCT05382299), and in the adjuvant setting (NCT05633654, NCT04595565); SG is poised to displace traditional chemotherapy in earlier lines of therapy, although we await data to support its use.

Another Trop-2-targeting ADC currently in late-phase development is datopotamab deruxtecan (dato-DXd). Dato-DXd consists of a humanized anti–Trop-2 IgG1 (immunoglobulin G1) monoclonal antibody conjugated to a potent topoisomerase I inhibitor. Results from the phase 1 TROPION-PanTumor01 study have shown a response rate of 32% and a disease-control rate of 80% among 44 evaluable pretreated patients with advanced HER2-negative breast cancer, including 32% previously treated with a topoisomerase I inhibitor-based ADC (*Cancer Res* 2023; 83 [Suppl 5]:P6-10-03). Responses were observed in some of the participants previously treated with SG, suggesting a role for using Trop-2-targeting ADCs with different payloads in sequence. Randomized phase 3 trials of dato-DXd versus TPC are ongoing for both advanced (NCT05374512, NCT05104866) and early-stage (NCT05629585) disease.

HER2-Targeted Antibody–Drug Conjugates for HER2-Low Advanced Breast Cancer

HER2-directed ADCs were first developed for treating HER2-positive breast cancer. With the development of next-generation ADCs that have potent bystander effects, researchers undertook investigation of such agents for tumors with low levels of HER2 expression, defined as HER2 1+ or 2+ on immunohistochemical analysis in the absence of *HER2* gene amplification. HER2-low expression varies by HR status: About two-thirds of HR-positive and one-third of HR-negative disease is HER2-low (*NPJ Breast Cancer* 2021; 7:1).

T-DXd is an ADC with an anti-HER2 antibody conjugated via a cleavable linker to a novel topoisomerase I inhibitor. A phase 1b study of 54 heavily pretreated patients with advanced HER2-low breast cancer documented a response rate of 37% with a median duration of response of 10.4 months (*J Clin Oncol* 2020; 38:1887). This proof-of-concept study led to the randomized phase 3 DESTINY-Breast04 trial (*N Engl J Med* 2022; 387:9), which enrolled patients with HER2-low breast cancer who had received one to two prior lines of chemotherapy for advanced disease; patients were randomized to T-DXd or TPC (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel). Ninety percent of the participants had HR-positive disease, and 10% had HR-negative disease. In the HR-positive cohort, T-DXd was associated with significant advantages over TPC in PFS (10.1 vs. 5.4 months; *P*<0.001) and OS (23.9 vs. 17.5 months; *P*=0.003). An exploratory analysis in the HR-negative cohort showed similar improvements in PFS and OS, and regulatory approval for T-DXd included both HR-positive and HR-negative, HER2-low advanced breast cancer.

Sequencing Antibody–Drug Conjugates and the Future

SG and T-DXd are both therapeutic options for HER2-low breast cancer. Because the trials that led to their regulatory approval enrolled participants contemporaneously, no randomized comparison of the efficacy of these agents in sequence is yet available. A 35-patient, single-center, retrospective study reported efficacy of ADCs used in sequence (*J Clin Oncol* 2023; 41 [Suppl 16]:1022), both when the same antigen (Trop-2) was targeted by different payloads *and* when the same payload (deruxtecan) was used with different antibody targets (Trop-2 and HER2). Given that both SG and T-DXd are associated with significant survival advantages compared with TPC, it is reasonable to use these agents in sequence as we await data that further inform these decisions. Given that DESTINY-Breast04 primarily enrolled patients with HR-positive, HER2-low disease who were not as heavily pretreated as those in TROPiCS-02, available data support using T-DXd prior to SG in these patients. Conversely, in the case of HR-negative, HER2-low disease, data are more robust for administering SG prior to T-DXd for patients who are candidates for both agents, given that ASCENT enrolled more than 530 patients with TNBC, compared with the exploratory cohort of 58 patients with HR-positive, HER2-low breast cancer in DESTINY-Breast04.

Randomized studies are underway to evaluate the efficacy of ADCs in sequence, including the TRADE-DXd trial, led by Garrido-Castro and colleagues, which

will evaluate the efficacy of T-DXd after dato-DXd (and vice versa) in HER2-low advanced breast cancer (personal communication). Efficacy with dato-DXd has been observed in patients who had previously progressed on SG; other studies evaluating SG and dato-DXd in sequence will also be warranted if dato-DXd gains regulatory approval as expected. Numerous other ADCs are in various phases of development; some, such as patritumab deruxtecan (anti-HER3 ADC) and ladiratuzumab vedotin (anti-LIV1a ADC with the potent mitotic inhibitor monomethyl auristatin E payload), are already showing efficacy in patients with breast cancer. While the past decade has focused on investigating immunotherapy for breast cancer, the future will focus on studies of novel ADCs that are poised to displace traditional cytotoxic chemotherapy agents.

Two Views

Interpreting the POSITIVE Trial: Is Pregnancy after Early-Stage Breast Cancer Safe?

Many young patients diagnosed with early-stage breast cancer are interested in having a future pregnancy. However, not only do most of these patients need chemotherapy, which can threaten fertility, but the majority also need endocrine therapy, which is standardly recommended for 5–10 years, during which time a pregnancy is contraindicated.

We designed the POSITIVE trial to address this clinical dilemma by prospectively enrolling women with previous hormone receptor-positive early breast cancer who wished to temporarily interrupt adjuvant endocrine therapy to attempt pregnancy. The early results were promising, living up to the trial's name, suggesting that pregnancy appears safe and feasible (*N Engl J Med* 2023; 388:1645). However, concerns remain regarding the safety of this strategy, and oncologists have varying opinions regarding the findings and applicability to patient care. In the following essays, experts offer differing views on how to consider the results of this trial.

– Ann H. Partridge, MD, MPH, Editor
Dr. Partridge was the lead author of the POSITIVE trial.

POSITIVE: Temporary Discontinuation of Endocrine Therapy to Achieve Pregnancy for Young Patients with HR-Positive Early Breast Cancer

Luca Arecco, MD, and Matteo Lambertini, MD, PhD

INTRODUCTION

Thanks to the constant improvement in breast cancer outcomes, survivorship has become an increasingly important part of patients' treatment paths (*Ann Oncol* 2022; 33:1119). Specifically for young women, their interest in having a pregnancy following completion of anticancer treatments should always be considered in their counseling before starting any therapy (*Ann Oncol* 2020; 31:1664).

In recent years, increasingly robust data have shown that pregnancy following anticancer treatments is safe in breast cancer survivors, even in patients with a prior history of hormone receptor (HR)–positive disease (*J Clin Oncol* 2021; 39:3293; *Human Reprod* 2023; 38

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[Suppl 1]:dead093.331). However, to date, few data have been available to counsel women who do not want to wait or cannot wait for the completion of adjuvant endocrine therapy to attempt conception.

This is the main reason why the first results of the POSITIVE trial are of paramount importance in the counseling and management of young women with HR-positive breast cancer receiving adjuvant endocrine therapy who have a strong pregnancy desire (*N Engl J Med* 2023; 388:1645). Albeit based on a short follow-up, the findings of the POSITIVE study are reassuring: After completing 18 to 30 months of adjuvant endocrine therapy, its temporary interruption for a maximum of 24 months does not seem to worsen the prognosis of young women with HR-positive disease at low or intermediate risk of recurrence.

"The POSITIVE trial provides the first prospective evidence to help physicians in counseling premenopausal patients with HR-positive breast cancer who want to temporarily interrupt adjuvant endocrine therapy to try to become pregnant."
— Luca Arecco, MD, and Matteo Lambertini, MD, PhD

PATIENT SAFETY RESULTS

The POSITIVE trial is the first study to prospectively evaluate the safety of a temporary interruption of adjuvant endocrine therapy to attempt pregnancy. Investigators enrolled 518 premenopausal women aged ≤42 years with HR-positive early breast cancer and a strong pregnancy desire who had completed at least 18 months and no more than 30 months of adjuvant endocrine treatment. As per protocol, patients could discontinue treatment for up to 24 months to become pregnant, deliver, and breastfeed, and then resume therapy until the total planned duration of adjuvant treatment was completed.

The 3-year incidence of breast cancer events was 8.9% in the POSITIVE trial, nearly identical to the 9.2% rate of breast cancer events observed in the external control cohort of premenopausal women who were randomized in the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) and would have fulfilled the inclusion criteria of the POSITIVE study (*N Engl J Med* 2018; 379:122). Similarly, the 3-year incidence of distant recurrences in the treatment-interruption group and the control cohort were comparable at 4.5% and 5.8%, respectively.

Therefore, as shown by these first results, despite the relatively short follow-up of the study (median of 41 months), the temporary interruption of adjuvant endocrine therapy to try to achieve a pregnancy may be considered safe and feasible, particularly for those patients who are highly motivated and have biological and disease characteristics overlapping with those of the majority of women enrolled in the POSITIVE study (*Nat Rev Clin Oncol* 2023 July 6; [e-pub]; DOI:10.1038/s41571-023-00797-4). Indeed, in interpreting these results, it should be considered that 93% of included patients had stage I or II breast cancer, with 66% having node-negative disease and only 5% having more than four positive axillary nodes. In addition, almost half of the patients (42%) received a selective estrogen-receptor modulator (SERM) alone, generally indicating a relatively low risk of recurrence at diagnosis, while only 16% of patients received ovarian function suppression plus an aromatase inhibitor (AI) as adjuvant endocrine treatment.

PREGNANCY OUTCOMES

The safety of this approach has also been shown in terms of pregnancy outcomes and newborns. Out of the 497 patients with reproductive data available, approximately three out of four (74%) women became pregnant, with an even higher pregnancy rate among women younger than 35 years (86%). This pregnancy rate in motivated patients is much higher than ever reported among

breast cancer survivors and appears to be higher than the rate expected in healthy women of a similar age (*Fertil Steril* 2014; 101:633). Of the 368 patients who had a pregnancy, 86% had at least one previous live birth. The rate of pregnancy complication was 11%, while 2% of the 365 offspring had birth defects; both rates are in line with those expected in the general population (*Circulation* 2023; 147:1014). It should be noted that almost half of the patients (43%) included in the POSITIVE trial underwent assisted reproductive technology (ART) techniques to achieve a pregnancy. This high percentage of ART use might have been related to the short time window that was allowed in the trial for conception; however, more data are needed to properly interpret these findings.

The POSITIVE approach with a 24-month window for getting pregnant seems to be safe; importantly, this interval includes a 3-month wash-out from adjuvant endocrine therapy and time for having a pregnancy, delivery, and breastfeeding (as desired and feasible) before subsequent resumption of adjuvant endocrine therapy. Of the patients enrolled in the study who temporarily interrupted endocrine treatment, only 15% had not resumed adjuvant therapy at the time of database lock for the first analysis, a rate that is slightly lower than the discontinuation rates reported in other adjuvant endocrine trials (*N Engl J Med* 2018; 379:122).

PRACTICAL CONSIDERATIONS

The POSITIVE trial provides the first prospective evidence to help physicians in counseling premenopausal patients with HR-positive breast cancer who want to temporarily interrupt adjuvant endocrine therapy to try to become pregnant instead of waiting 5 to 10 years. The short median follow-up to date precludes drawing definitive conclusions, and more mature results are awaited, especially given the stable risk of breast cancer recurrence even beyond 10 years from diagnosis in this patient population (*EClinicalMedicine* 2023; 59:101931). However, the current evidence supports its safety for both the mother and the baby, particularly in the setting of low/intermediate risk of breast cancer recurrence (*Nat Rev Clin Oncol* 2023 Jul 6; [e-pub]; DOI:10.1038/s41571-023-00797-4).

When counseling patients on adjuvant endocrine therapy interruption for pregnancy, the POSITIVE trial approach should be considered: completion of at least 18 months of adjuvant endocrine therapy, followed by a wash-out period of 3 months before attempting to become pregnant, and resumption of adjuvant endocrine therapy after pregnancy, or a maximum of 24 months in those unable to conceive during this time. Despite not being mandatory or encouraged in the POSITIVE trial, a total-body restaging procedure may be considered prior to or during the wash-out period to avoid the diagnosis of disease recurrence during pregnancy. It is important to note that higher-risk patients were not well represented in the POSITIVE trial and that counseling regarding future fertility and pregnancy should be tailored to the individual's preferences and values with acknowledgement of the underlying risk of disease recurrence.

POSITIVE: Pregnancy after Breast Cancer Should Be Supported for Many, but Not All

Jasmine S. Sukumar, MD, and Mariana Chavez Mac Gregor MD, MSC, FASCO

Many women face a unique challenge of meeting family planning goals following a breast cancer diagnosis. The POSITIVE trial is the first prospective study evaluating outcomes associated with temporary interruption of endocrine therapy (ET) to attempt pregnancy in hormone receptor (HR)–positive breast cancer. Outcomes of interest included recurrence and maternal and reproductive safety. The trial addresses a clinically relevant question. However, this is a complex topic, and several factors impact the decision of whether and when to attempt pregnancy after a breast cancer diagnosis and whether patients should interrupt ET to achieve this goal. Based on the existing data, we believe these decisions need to be individualized. ET interruption to

attempt pregnancy should be supported for *many, but not all*, breast cancer survivors.

LONGER FOLLOW-UP NEEDED

POSITIVE provides a safety signal with no compromise in breast cancer events, but these data are still immature, particularly when considering the natural history of HR-positive disease, where recurrences are not uncommon even decades after the initial diagnosis (*N Engl J Med* 2017; 377:1836). The median follow-up in POSITIVE is only 3.4 years (*N Engl J Med* 2023; 388:1645), and long-term results are imperative. Patients in the study will be followed for 10 years; analyzing breast cancer-related events at subsequent time intervals will better inform standard practice. As of now, the data are still too immature to confidently support ET interruption as a safe and acceptable approach in *all* breast cancer survivors desiring to conceive.

CAUTION IN HIGH-RISK DISEASE

A "healthy mother effect" cannot be excluded based on the nature of the study. This refers to the potential for healthier women to be more likely to participate and carry a term pregnancy, thereby introducing bias. Most patients in the study had low-risk disease, including 64% with tumors ≤2 cm and 66% without node involvement. Moreover, POSITIVE included women who were strongly motivated to become pregnant, resulting in a cohort less representative of the general population.

The results of POSITIVE should not be extrapolated to patients with very high-risk disease. Certain clinicopathologic features were uncommon, such as tumor size >5 cm (n=21; 4.1%) and >3 positive axillary lymph nodes (n=23; 4.5%). Given that breast cancer outcomes are associated in part with anatomical stage, with cumulative risk of distant recurrence as high as 50% at 20 years in the highest-risk clinicopathologic categories (*N Engl J Med* 2017; 377:1836), we advise caution in selecting patients and only consider ET interruption in those who are well represented by the trial population. In POSITIVE, the 3-year incidence of breast cancer events was 19% among patients with >3 positive lymph nodes and 21% for those with tumor size >5 cm. As we interpret these results, we must not forget that young age is independently a poor prognostic factor in luminal breast cancer. Moreover, the substantial reduction in risk of relapse and improvement in survival gained from adjuvant ET are well established (*Lancet* 2011; 378:771; *J Clin Oncol* 2023; 41:1376). Therefore, we recommend completing the standard 5- to 10-year course of ET whenever possible in patients with high-risk disease prior to pregnancy attempt.

TARGETED ADJUVANT THERAPY IN THE CONTEXT OF POSITIVE

POSITIVE completed accrual prior to the widespread use of targeted adjuvant therapies. Many high-risk patients are now candidates to receive novel drugs in combination with ET to improve disease-free survival. This includes 1 year of the poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitor olaparib among those with *BRCA* germline pathogenic variants (*N Engl J Med* 2021; 384:2394) or 2 years of the cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor abemaciclib (*J Clin Oncol* 2020; 38:3987). Additionally, 3 years of ribociclib may soon be an option for many patients (*J Clin Oncol* 2023; 41 [Suppl 17]:LBA500). In the context of the established clinical benefit of these newer agents, we recommend their completion prior to embarking on reproductive plans. Specifically, in patients who are at the 18- to 30-month mark of ET but have not yet completed targeted therapy, we advise finishing the recommended course prior to attempting pregnancy.

COMPLETION OF ENDOCRINE THERAPY IS CRITICAL

POSITIVE endorsed a strong recommendation to resume ET after completion of pregnancy and breastfeeding, or after a maximum 24 months of temporary interruption. However, 15% of patients expected to resume ET had not done so 48 months after drug interruption. While this percentage is similar in other trials, in real-world practice, the rate will likely be higher. Up to 60% of women do not complete the planned duration

of ET due to early discontinuation or nonadherence, and this is unfortunately associated with worse outcomes (*J Clin Oncol* 2010; 28:4120; *Breast Cancer Res Treat* 2011; 126:529). Furthermore, younger age is associated with a greater risk of treatment discontinuation (*J Clin Oncol* 2010; 28:4120). We strongly recommend that patients considering ET interruption for pregnancy have an open dialogue with their oncologist to mutually agree upon a maximal time to hold therapy, and we advocate for providers to counsel patients about the utmost importance of treatment resumption and completion.

REMAINING KNOWLEDGE GAPS

While the results of POSITIVE are favorable, many areas of uncertainty remain. For one, the population was not representative of older premenopausal women. Only 23% were 40 years or older, but this age group has even less time to successfully conceive. This biologic factor should be considered in determining the optimal timing and practicality of pregnancy. Moreover, data cannot be fully extrapolated to other breast cancer subtypes. The safety of future conception and the appropriate surveillance time before pregnancy in HR-negative disease is poorly described, although limited observational data do not suggest a detrimental effect (*J Natl Cancer Inst* 2018; 110:426). Lastly, a limitation of any single-arm study is the potential for confounding. While the external-control cohort matched patients across prognostic factors, imbalances will invariably remain that could have impacted the results.

SHARED DECISION MAKING IS KEY

One size does not fit all, and shared decision making is crucial to guiding our conversations. We need to improve patient support by informing them about fertility preservation techniques and addressing concerns as early as possible. Decisions must be tailored in the context of existing data, consideration of an individual's recurrence risk, ovarian reserve, comorbidities, and understanding one's personal preferences and psychosocial needs. We must continue to advance the field through refining fertility risk assessment, decision aids, and implementation tools. Alternative pathways to parenthood, such as surrogacy or adoption, may also be a suitable approach to explore for some.

In summary, informed, bidirectional discussions are key to considering a safe, effective, and personalized oncofertility plan in selected breast cancer survivors desiring pregnancy. POSITIVE is a well-conducted, international collaboration addressing a challenging question in a prospective manner. However, ET interruption should not be recommended to all, and it is imperative that patients and physicians engage in careful conversations regarding the risks, benefits, uncertainties, and alternatives.

NEJM Research Summary

Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer

Kunkler IH et al. **DOI: 10.1056/NEJMoa2207586**

CLINICAL PROBLEM

For low-risk older patients with smaller, hormone receptor (HR)–positive breast tumors, the omission of radiotherapy after breast-conserving surgery is controversial, with only limited long-term level 1 evidence available to guide treatment decisions.

CLINICAL TRIAL

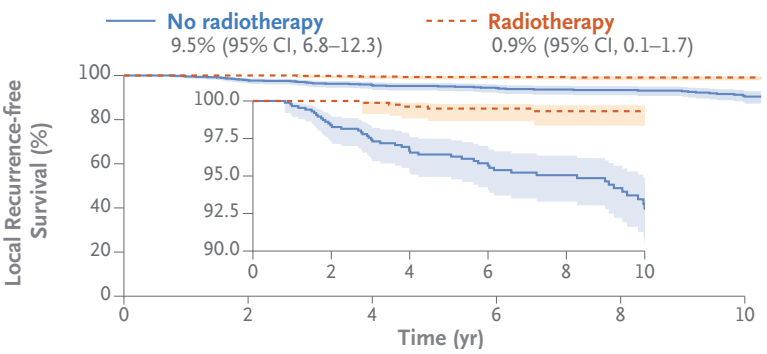
Design: An international, phase 3, randomized, controlled trial evaluated the effect of the omission of radiotherapy on the incidence of breast cancer recurrence among older women who had undergone breast-conserving surgery for early, low-risk breast tumors.

Intervention: 1326 patients ≥65 years of age with HR-positive, node-negative, smaller primary tumors (T1 or T2, up to 3 cm in largest dimension) treated with breast-conserving surgery with clear margins and adjuvant or neoadjuvant endocrine therapy were assigned to receive whole-breast irradiation (40 to 50 Gy over 3 to 5 weeks) or no irradiation. The primary end point was local breast cancer recurrence. Regional recurrence, breast cancer–specific survival, distant recurrence as the first event, and overall survival were also assessed.

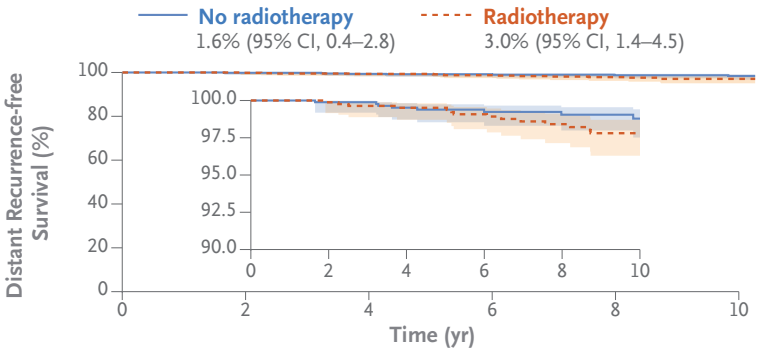
RESULTS

Efficacy: After 10 years of follow-up, the incidence of local breast cancer

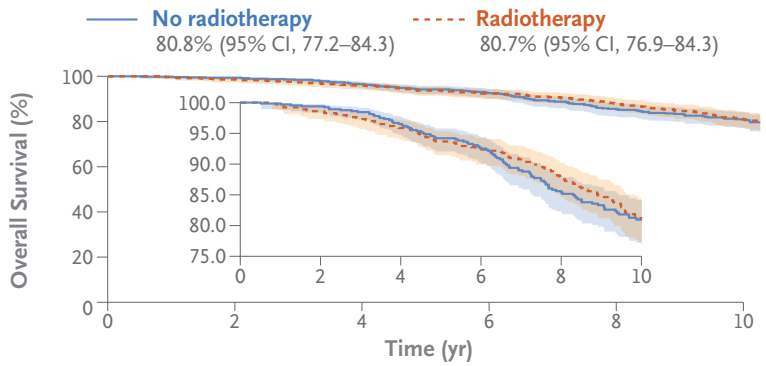
Cumulative Incidence of Local Recurrence at 10 Yr



Cumulative Incidence of Distant Recurrence as First Event at 10 Yr



Overall Survival at 10 Yr



recurrence was significantly lower in the radiotherapy group than in the no-radiotherapy group. However, the incidence of distant recurrence as the first event and overall survival, two secondary end points, was similar in the two groups.

LIMITATIONS AND REMAINING QUESTIONS

- The trial did not include assessment of the toxic effects of radiation.
- The researchers did not collect data on coexisting conditions or assess adherence to endocrine therapy prospectively.

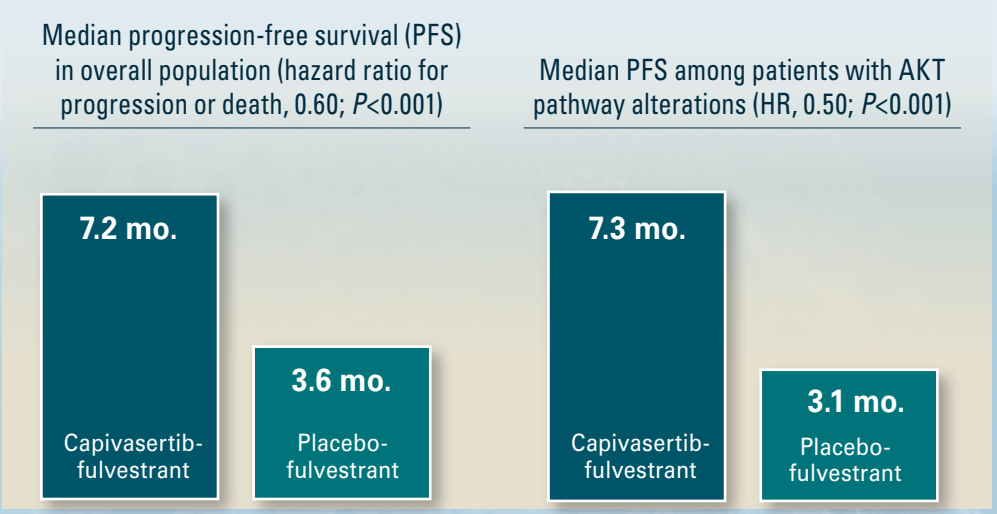
CONCLUSIONS

Among older patients with low-risk, HR-positive, smaller breast tumors treated with breast-conserving surgery and endocrine therapy, omission of radiotherapy was associated with an increased incidence of local recurrence but did not affect distant recurrence or overall survival.

Visual Summary

Capivasertib for Advanced ER+/HER2– Breast Cancer

Roughly 700 patients with ER-positive/HER2-negative metastatic breast cancer who had relapse or progression following treatment with an aromatase inhibitor with or without a CDK4/6 inhibitor were randomized to fulvestrant (500 mg intramuscularly every 14 days for three injections and every 28 days thereafter) plus either the AKT inhibitor capivasertib (400 mg orally twice daily for 4 days each week) or matching placebo.



Comment

Capivasertib may offer yet another partner for endocrine therapy following treatment with a CDK4/6 inhibitor. As of this writing, the FDA is considering capivasertib for approval in this setting. Alpelisib combined with fulvestrant is available for treating patients with *PIK3CA* mutations; however, capivasertib appears to have a better toxicity profile than alpelisib and is effective even in patients without a mutation in the AKT pathway.

William J. Gradishar, MD, reviewing Turner NC et al. *N Engl J Med* 2023 Jun 1

Dr. Gradishar is Professor of Medicine in the Feinberg School of Medicine at Northwestern University and a member of the Robert H. Lurie Comprehensive Cancer Center. He serves as Director of Maggie Daley Center for Women's Cancer Care at Northwestern University and Northwestern Memorial Hospital. **Disclosures:** He reports consultant or advisory board roles with Lilly, AstraZeneca, and Gilead; grant or research support from the Breast Cancer Research Foundation; editorial board roles with *Clinical Breast Cancer, Oncology, Annals of Surgery*, and *Breast Cancer Research and Treatment*; and leadership positions with the National Comprehensive Cancer Network (Chair, Breast Cancer Panel) and the American Board of Internal Medicine (Medical Oncology Board).

Meeting Report

ASCO 2023 Meeting Report — Breast Cancer

Highlights of the latest research

The 2023 American Society of Clinical Oncology (ASCO) annual meeting, held June 2 to 6 in Chicago, highlighted important advances in treatment across a broad spectrum of malignancies. Here, *NEJM Journal Watch Oncology and Hematology* Editor-in-Chief **Dr. William Gradishar** reviews key trials in breast cancer.

Adjuvant Ribociclib in Early-Stage ER+/HER2– Breast Cancer

Researchers presented long-awaited disease-free survival results from a planned interim analysis of the NATALEE trial, which evaluated adjuvant therapy with the CDK4/6 inhibitor ribociclib in patients with high-risk ER+/HER2– early-stage breast cancer (abstract LBA500). This large, industry-funded, phase 3 trial randomized a broader population of patients than either the PALLAS (palbociclib) or monarchE (abemaciclib) adjuvant trials; in addition to patients with anatomical stage IIB and III disease, NATALEE also included those with stage IIA disease (node negative with grade 2 and evidence of high-risk features such as Ki-67 ≥20% or high genomic risk based on a molecular assay or with grade 3).

In the trial, 5101 patients were randomized to receive a nonsteroidal aromatase inhibitor (AI) for 5 years with or without ribociclib (400 mg/day; 3 weeks on/1 week off) for 3 years; male and premenopausal patients also received goserelin. In trials of ribociclib in metastatic breast cancer, 600 mg/day is the standard dose, but efficacy was found to be similar with 400 mg and tolerability was improved.

The treatment groups were well balanced with respect to menopausal status and exposure to prior adjuvant endocrine therapy and chemotherapy. At the time of the report, 57% of patients had completed ≥2 years of ribociclib therapy and 20% had completed 3 years. The absolute 3-year invasive disease-free survival (iDFS) benefit with ribociclib plus AI compared with AI alone was 3.3% (90.4% vs. 87.1%; P=0.0014), representing a 25% relative risk reduction. All subgroups seemed to benefit. The absolute 3-year distant DFS benefit with ribociclib was 2.2% (90.8% vs. 88.6%; P=0017). Overall survival was immature. No new safety signals were identified, and the incidence of QT prolongation was lower than reported with the higher dose of ribociclib in other trials.

COMMENT

Although most patients had not yet completed all therapy or even all 3 years of ribociclib at the time of this analysis, there is clearly a reduction in recurrence risk with adjuvant ribociclib. Longer follow-up will be needed to identify which subgroups benefit from the addition of ribociclib.

Comparing First- and Second-Line Use of a CDK4/6 Inhibitor in ER+/HER2– Metastatic Breast Cancer

Since researchers first reported the benefit of combining endocrine therapy with a CDK4/6 inhibitor in the first- or second-line setting in patients with endocrine-sensitive, metastatic breast cancer, no patient group has been identified for which the addition of a CDK4/6 inhibitor does not improve progression-free survival (PFS) compared with endocrine therapy alone. To address this, the Dutch phase 3 SONIA trial randomized 1050 patients with ER+/HER2– metastatic breast cancer to receive a nonsteroidal

aromatase inhibitor (AI) with or without a CDK4/6 inhibitor (abstract LAB1000). At the time of disease progression, patients who received a CDK4/6 inhibitor started fulvestrant, while those who received a nonsteroidal AI alone started fulvestrant and a CDK4/6 inhibitor. Patients were ineligible for the trial if they had received prior therapy for metastatic disease, although neoadjuvant or adjuvant therapy was permitted.

PFS on first-line therapy was superior in patients who had received a CDK4/6 inhibitor compared with those who had received an AI alone (median 24.7 vs. 16.1 months; hazard ratio, 0.59; *P*=0.0001). However, PFS on second-line therapy — the primary outcome — did not differ between patients who received a CDK4/6 inhibitor in the first line and those who received a CDK4/6 inhibitor in the second line (31.0 and 26.8 months; HR, 0.87; *P*=0.10). There was no difference in overall survival (OS) or quality of life between the two treatment arms. Median duration on the CDK4/6 inhibitor was 24.6 months in the first-line group compared with 8.1 months in the second-line group. Grade 3/4 toxicity was more common with first-line than second-line therapy.

COMMENT

Delaying use of a CDK4/6 inhibitor to the second-line setting did not affect OS, PFS, or quality of life; however, patients who received a CDK4/6 inhibitor in the first-line setting were able to stay on first-line therapy for 16.5 months longer. Most patients in the trial received palbociclib, and this choice raises the possibility that a more effective CDK4/6 inhibitor could have generated different results. There is always some attrition between first-line and second-line therapy, so most U.S. oncologists will likely continue to use CDK4/6 inhibitors in the first line. Being able to stay on a given therapy longer is also encouraging for patients psychologically, although it is associated with increased drug costs and toxicity.

"A fixed-dose schedule of capecitabine in patients with metastatic breast cancer achieves the same therapeutic effect as the FDA-approved dose and schedule, but with far less toxicity. This is a win for patients."
— William Gradishar, MD

Using PET/CT to Identify Patients Who Can Avoid Chemotherapy

Much attention has been focused on de-escalating therapy in both the early- and late-stage setting in an effort to more precisely craft treatment for individual patients and avoid unnecessary toxicity. The industry-sponsored, phase 2 PHERGain trial assessed the opportunity of chemotherapy de-escalation with a response-adapted strategy in patients with HER2+ stage I–IIIa breast cancer who were eligible for neoadjuvant therapy (abstract LBA506).

After undergoing baseline ^{18}F-FDG PET/CT imaging, patients were randomized to receive two cycles of docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP; group A) or trastuzumab and pertuzumab alone (group B). After the two cycles, PET/CT was repeated. In group A, treatment was continued for another 4 to 6 cycles, followed by surgery. In group B, patients judged by PET/CT to have a metabolic response continued treatment for another 4 to 6 cycles, followed by surgery, whereas those who did not achieve a metabolic response were switched to TCHP for 4 to 6 cycles, followed by surgery. The primary end points were pathologic complete response (pCR) in group B patients with a PET/CT response and 3-year invasive disease-free survival (iDFS) in group B patients who underwent surgery.

Of the 285 patients in group B, 79.6% had a PET/CT response, and of those, 37.9% had a pCR. The 3-year iDFS was 95.4% overall and

98.8% among patients who had both a PET/CT response and a pCR.

COMMENT

Although longer follow-up is required, these results suggest that a metabolic biomarker (^{18}F-FDG PET/CT) may identify a group of HER2+ patients who can avoid chemotherapy and still have an exceptionally good prognosis.

Patritumab-Deruxtecan Activity in Metastatic Breast Cancer across a Range of HER3 Expression Levels

HER3-DXd is an antibody-drug conjugate made up of patritumab, a human anti-HER3 IgG1 monoclonal antibody, linked covalently to deruxtecan, a topoisomerase inhibitor. A prior phase 1/2 study demonstrated HER3-DXd activity in patients with heavily pretreated metastatic breast cancer, regardless of breast cancer subtype and HER2 expression (*J Clin Oncol*; 40:16 suppl 1002).

Now, in an industry-funded, phase 2 trial, researchers evaluated HER3-DXd in patients with HER2– locally advanced or metastatic breast cancer who had hormone receptor-positive (HR+) disease and had received endocrine therapy, a CDK4/6 inhibitor, and two or fewer lines of chemotherapy, or had HR– disease and had received one to three lines of chemotherapy (abstract 1004). Patients were treated with HER3-DXd every 3 weeks (5.6 mg/kg IV). The primary end point was objective response rate (ORR) and progression-free survival (PFS) at 6 months.

Of the 61 patients, median age was 59, 77% were white, 90% had received chemotherapy in the metastatic setting, and 8% had received sacituzumab govitecan. Approximately 50% of tumors were ER+/PR+, and baseline HER3 expression was >75% in 64% of tumors. The ORR was 35% and was not higher in high- versus low-HER3-expressing tumors. The duration of response was at least 6 months in 48% of patients who responded. Most adverse events were grade 1 and 2, most commonly nausea, fatigue, and diarrhea.

COMMENT

Patritumab deruxtecan appeared to have activity across breast cancer subtypes regardless of HER3 expression, although there were few patients with HER3 expression <25% in the trial. Assessing whether this agent will work in HER3 low-expressing tumors as seen with trastuzumab deruxtecan will help us to understand if target expression is important.

Comparing Fixed-Dose to Standard-Dose Capecitabine in Metastatic Breast Cancer

Capecitabine is one of the most widely used chemotherapy drugs for treatment of advanced breast cancer. It is also one of the few oral chemotherapy drugs available with a reasonable toxicity profile, yet many patients experience debilitating or prohibitive side effects, such as hand-foot syndrome and diarrhea. Long ago, the FDA-approved standard dose of 1250 mg/m^2 twice daily, 2 weeks on/1 week off, was modified for routine use to 1000 mg/m^2 twice daily, 2 weeks on/1 week off. Many physicians also adopted a 1 week on/1 week off schedule for patients not tolerating the standard schedule. The efficacy and tolerability of these two schedules had not previously been directly compared.

The phase 2 X-7/7 trial randomized patients with metastatic breast cancer to fixed-dose capecitabine (1500 mg twice daily, 1 week on/1 week off) or to the FDA-approved or standard dose capecitabine (1250 mg/m^2 twice daily, 2 weeks on/1 week off; (abstract 1007). The trial was pragmatic, as it allowed any number of prior endocrine or chemotherapy treatments in the metastatic disease setting. Of 153 patients enrolled, 78% had ER+ disease, and only a few had HER2+ disease (requiring concurrent trastuzumab).

Progression-free survival was the same in both treatment arms at 3 months (the primary outcome) and at 12, 24, and 36 months. Overall survival also did not differ between arms. Grade 2 to 4 adverse events, including diarrhea,

oral mucositis, and hand-foot syndrome, were significantly less frequent with the fixed-dose regimen (49% vs. 23%).

COMMENT

Although this study did not report a novel therapy, the findings are critically important for clinicians in day-to-day practice. A fixed-dose schedule of capecitabine in patients with metastatic breast cancer achieves the same therapeutic effect as the FDA-approved dose and schedule, but with far less toxicity. This is a win for patients.

Dr. Gradishar is Professor of Medicine in the Feinberg School of Medicine at Northwestern University and a member of the Robert H. Lurie Comprehensive Cancer Center. He serves as Director of Maggie Daley Center for Women's Cancer Care at Northwestern University and Northwestern Memorial Hospital. **Disclosures:** He reports consultant or advisory board roles with Lilly, AstraZeneca, and Gilead; grant or research support from the Breast Cancer Research Foundation; editorial board roles with *Clinical Breast Cancer, Oncology, Annals of Surgery,* and *Breast Cancer Research and Treatment*; and leadership positions with the National Comprehensive Cancer Network (Chair, Breast Cancer Panel) and the American Board of Internal Medicine (Medical Oncology Board).

NEJM Journal Watch Summary

How Common Is Breast Cancer Overdiagnosis with Screening Mammography in Older Women?

Potentially overdiagnosed breast cancer accounted for about half of screen-detected breast cancers in women 75 or older.

Cancer overdiagnosis refers to cancers detected by screening that never would have caused clinically apparent disease had the screening not occurred. For women older than 70 — who might be weighing the benefits and risks of continuing breast cancer screening — there are limited data on risk of overdiagnosis with mammography.

In this U.S. study, researchers identified 54,000 women (age, ≥70) who had negative screening mammograms in 2002. The cumulative incidence of breast cancer through 2017 was compared in those who had another screening mammogram during the subsequent 3 years and those who did not.

Potential cancer overdiagnosis (the difference in cumulative breast cancer incidence between the screened and unscreened cohorts) was common in all age groups:

- Ages 70–74: 1.9 cases per 100 patients (6.1 vs. 4.2)
- Ages 75–84: 2.3 cases per 100 patients (4.9 vs. 2.6)
- Age ≥85: 1.5 cases per 100 patients (2.8 vs. 1.3)

Potentially overdiagnosed cancers accounted for 31%, 47%, and 54% of cancers in those three age groups, respectively. Importantly, screening was not associated with statistically significantly lower breast cancer mortality or incidence of regional or distant breast cancers.

Comment

Discussions on benefits and harms of screening mammography are becoming more complex amid advances in breast cancer treatments, genetic testing, and screening technologies, along with changing guidelines. Communicating cancer overdiagnosis risk is challenging but important to ensure that patients make truly informed decisions on whether continued screening is best for them.

Marie Claire O'Dwyer, MB BCh BAO, MPH

Dr. O'Dwyer is a principal residency faculty member at the University of Michigan Medical School and serves as the Director of Resident Scholarship for the Family Medicine Residency. She has nothing to disclose.

Richman IB et al. Estimating breast cancer overdiagnosis after screening mammography among older women in the United States. **Ann Intern Med** 2023 Aug 8; [e-pub]. (https://doi.org/10.7326/M23-0133)

NEJM Journal Watch Summary

Gynecologic Surgery and Breast Cancer Risk

Risk for breast cancer varied depending on type of surgery and hormone replacement therapy in a large study of women with sisters who had breast cancer.

Women with a first-degree relative with breast cancer have twice the risk of developing breast cancer, on average, compared with other women. To assess the impact of gynecologic surgery on breast cancer risk in such women, researchers analyzed data from the Sister Study, a nationwide, prospective cohort of roughly 50,000 women aged 35 to 74 years with a biological sister with breast cancer and no breast cancer themselves at enrollment. Participants were enrolled from 2003 to 2009; more than 90% were active through 2019.

At baseline, participants reported history of gynecologic surgery (none; hysterectomy only; bilateral oophorectomy, with or without hysterectomy) as well as age and reason for procedure. Subsequent questionnaires every 2 to 3 years captured interim gynecologic surgeries. Use of hormone replacement therapy was also captured. The primary outcome was self-reported noninvasive or invasive breast cancer, which was confirmed by examination of medical records.

At baseline, 13.8% of participants reported hysterectomy only and 18.1% reported bilateral oophorectomy, with or without hysterectomy. During a median follow-up of 11.4 years, 3948 cases of breast cancer were diagnosed. Compared with no surgery, bilateral oophorectomy was inversely associated with breast cancer (hazard ratio, 0.91) whereas hysterectomy alone was positively associated (HR, 1.12). Compared with no surgery and no hormone therapy, bilateral oophorectomy combined with estrogen-only therapy was inversely associated with breast cancer (HR, 0.83) whereas hysterectomy combined with estrogen plus progestin therapy was positively associated (HR, 1.25).

Comment

Gynecologic surgery has been thought to decrease the risk for breast cancer, but some studies provide conflicting results. This well-done study shows that the type of surgery performed as well as the composition of hormone replacement therapy, if given, can influence the subsequent risk of breast cancer. As many prior observational studies have suggested, bilateral oophorectomy significantly reduces estrogen levels and, by extension, breast cancer risk, regardless of estrogen supplementation. Patients undergoing hysterectomy alone with combined estrogen/progestin replacement have an elevated risk for breast cancer.

William J. Gradishar, MD

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Lovett SM et al. Hysterectomy, bilateral oophorectomy, and breast cancer risk in a racially diverse prospective cohort study. **J Natl Cancer Inst** 2023 June; 115:662. (https://doi.org/10.1093/jnci/djad038)

NEJM Journal Watch Summary

Breast Density Change Over Time and Risk for Breast Cancer

The rate of change in breast density differed between women who developed breast cancer and those who did not.

Breast density is an established risk factor for the development of breast cancer, but changes in breast density over time and their correlation with risk is less clear due to limited investigation. Now, in a nested, case-control, cohort study, investigators examined changes in breast density using a sample from the Joanne Knight Breast Health Cohort of 10,481 women who were cancer-free at entry and were observed from 2008 to 2020 with screening mammograms every 1 to 2 years.

The study sample included 289 pathology-confirmed breast cancer cases and 658 controls matched for age and year of enrollment, with a total of 8710 mammograms. Most women were white (81%), 15% were Black. Most women in both the case and control groups were postmenopausal and parous. When the mean volumetric density of the two breasts was analyzed, breast density at study entry was significantly higher in cases than controls but the rate of change (decrease) in breast density over time did not differ between cases and controls. However, when density change in each breast was analyzed separately, the rate of density change over time in breasts that developed cancer was significantly slower than the rate of change in breasts of controls.

Comment

The rate of decrease in density of the breast was significantly slower in women who developed breast cancer than in those who did not. These findings suggest that the dynamic change in breast density over time could serve as a tool to provide better insight into individual risk. For women whose breast density is not changing in any meaningful way, more emphasis may be placed on risk-reduction strategies, either standard or investigational. This study was conducted in a mostly white population and study of a more diverse population would validate whether these findings are widely applicable.

William J. Gradishar, MD

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Jiang S et al. Longitudinal analysis of change in mammographic density in each breast and its association with breast cancer risk. **JAMA Oncol** 2023 Jun 1; 9:808. (https://doi.org/10.1001/jamaoncol.2023.0434)

NEJM Journal Watch Summary

Cognitive Impairment in Patients with Early-Stage Breast Cancer

Impairment was greater in patients than controls, but declines in some cognitive domains abated over time.

Cancer-related cognitive impairment has long been described in association with breast cancer therapy, and patients often express feeling "less sharp and more forgetful" than before the breast cancer diagnosis. Investigators in France report neurocognitive findings for 276 patients with stage I–III breast cancer who were evaluated before treatment and 1 and 2 years after the diagnosis of breast cancer. A group of 135 age-matched healthy controls underwent the same evaluations.

A battery of neuropsychological tests were used to assess five cognitive domains, including episodic memory, working memory, information processing speed, attention, and executive function. Participants also self-reported cognitive difficulties and were evaluated for anxiety, depression, and fatigue.

Most patients underwent at least one neuropsychological assessment after baseline, and 85% underwent cognitive assessment after surgery. Mean patient age was 54 years. Sixty-two percent of patients received chemotherapy, mostly an anthracycline and taxane in the adjuvant setting. Median follow-up was 24 months.

Cognitive impairment was present in 33% of patients at year 1 and 29% at 2, compared with 11% and 10%, respectively, of controls. Similarly, cognitive difficulties were reported by significantly more patients than controls at years 1 and 2. Executive function decreased significantly in patients compared with controls at year 1 but not at year 2. Compared with patients not taking chemotherapy, those receiving chemotherapy reported more cognitive difficulties and cognitive fatigue at year 1 but not at year 2. Factors associated with cognitive difficulties included use of psychotropic medications, cognitive fatigue, and anxiety.

Comment

This report reaffirms that cognitive dysfunction is common in patients with breast cancer, particularly in those receiving chemotherapy. An important observation was that a significant fraction of patients had impairment in these domains prior to initiation of any therapy. In addition, the decline in executive function and increase in self-reported cognitive difficulties among patients subsided over the course of follow-up.

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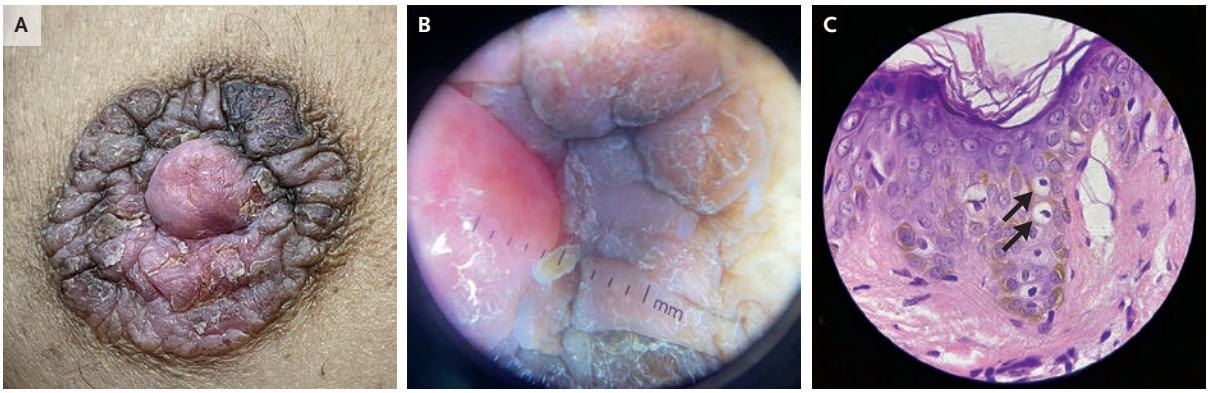
Lange M et al. Cognitive change in breast cancer patients up to 2 years after diagnosis. **J Natl Cancer Inst** 2023 Mar; 115:322. (https://doi.org/10.1093/jnci/djac240)

Images in Clinical Medicine

Paget's Disease of the Breast



A 44-year-old woman presented to the dermatology clinic with a 1-year history of an itchy skin lesion on the right nipple and intermittent nipple discharge. On physical examination, there was a well-demarcated, dark-pink plaque over the entire nipple–areola complex on the right side. The lesion had a raised, irregular margin, as well as overlying crusting and excoriation (Panel A). Dermoscopy of the lesion showed superficial furrows and scaling (Panel B). There was no palpable breast mass or axillary lymphadenopathy. A punch biopsy of the lesion revealed malignant, intraepithelial adenocarcinoma cells — also known as Paget cells (Panel C, arrows; hematoxylin and eosin staining). A diagnosis of Paget's disease of the breast was made. Paget's disease of the breast is an uncommon manifestation of breast cancer that develops in the skin of the nipple. It is usually associated with underlying ductal carcinoma in situ or invasive ductal carcinoma. Diagnosis may be challenging because the lesion often resembles benign conditions, such as eczema. Magnetic resonance imaging of the right breast showed ductal carcinoma in situ in the areola. Treatment with nipple–areola resection and wide local excision followed by radiotherapy was completed. At 1 year of follow-up, there was no evidence of recurrence.

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