

Breast Cancer Update



from NEJM Group

- Bone-Modifying Agents: Where Do We Stand?
- Two Views on the RxPONDER Trial
- How Low Can We Go?: Trastuzumab Deruxtecan
- ASCO Meeting Coverage



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FROM the Editor

It is a joy to serve as Editor for this issue of *Breast Cancer Update* at a time of such rapid breast cancer treatment advances that include the emergence of multiple antibody–drug conjugates, true personalized medicine with risk stratification assays for early hormone receptor–positive breast cancer, as well as improved supportive care agents.

I am honored to be joined in this issue by esteemed colleagues from across the globe. The breast oncology community in some ways is a victim of our own successes. With each question we answer, it seems many more nuanced questions arise. This issue explores the personalized medicine debate in early hormone receptor–positive breast cancer around whether the benefit of chemotherapy in RxPONDER for premenopausal women is due to the cytotoxic effect

itself or the result of ovarian suppression from chemotherapy. Drs. Megan Tesch and Ann Partridge make the case for ovarian suppression as the main driver for chemotherapy benefit, while Drs. Sibylle Loibl and Jenny Furlanetto argue that there is substantial benefit from cytotoxicity itself. In the absence of randomized data, these two views are ever present in our conversations and counsel to young women having to make decisions regarding chemotherapy in their individual treatment course.

In 2022, the first therapy for human epidermal growth factor receptor 2 (HER2)–low breast cancer was approved, leading to a shift not only in our classification of breast tumors but also in how we think of the expression level needed to target cell surface proteins. Dr. Hope Rugo explores trastuzumab deruxtecan, how HER2-low cancers are identified, and, finally, “how low we can go” in terms of target expression with the novel antibody–drug conjugates today and in the future.

Finally, Drs. Michael Gnant and Stephanie Kacerovsky-Strobl give us a state-of-the-science for bone-modifying agents, exploring their benefit for bone health, fracture prevention, and, ultimately, chance of cure.

Erika Hamilton, MD, Editor

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Two Views

Explaining the Benefit of Adjuvant Chemotherapy in Premenopausal Women in the RxPONDER Trial: Ovarian Suppression vs. Cytotoxicity

RxPONDER was a trial designed to evaluate whether women with node-positive breast cancer and recurrence scores between 0 and 25 benefited from the addition of chemotherapy to standard endocrine therapy. Patients were stratified by recurrence score (0–13 vs. 14–25), menopausal status, and type of axillary surgery. One third of the patients enrolled were premenopausal. The results showed a significant interaction of menopausal status and chemotherapy effect, with premenopausal women receiving a significant benefit of chemotherapy and their postmenopausal counterparts receiving no chemotherapy benefit (*N Engl J Med* 2021; 385:2336). This result has raised the question of whether the significantly greater 5-year invasive disease-free survival among premenopausal women receiving chemotherapy plus endocrine therapy (94%) compared with endocrine therapy (89%) was due to benefits from the cytotoxics themselves or from cessation of menses associated with chemotherapy administration — i.e., an ovarian suppression effect. If the benefit in premenopausal patients really comes from cessation of menses and postmenopausal status, this could alternatively be accomplished with ovarian suppression agents such as leuprolide or goserelin and potentially spare these young women the additional toxicities associated with chemotherapy.

In the essays that follow, experts offer two differing views on this question.

— Erika Hamilton, MD, Editor

RxPONDER: It Was Predominantly Ovarian Suppression

Megan E. Tesch, MD, and Ann H. Partridge, MD, MPH

Beyond the already extensive list of potential adverse effects from chemotherapy, premenopausal patients with breast cancer are at risk for additional

toxicities related to their age, including premature menopause and infertility, which can have detrimental health and quality of life impacts. As such, the identification of young women with early-stage breast cancer who can be safely spared adjuvant chemotherapy is crucial.

While advances have been made through risk-stratification by genomic signatures in hormone receptor (HR)-positive breast cancer, progress has been slower in premenopausal patients compared with their postmenopausal counterparts, given the age-dependent chemotherapy benefits observed in RxPONDER and other recent gene-expression, profile-driven adjuvant chemotherapy trials (Table). However, the late emergence of a survival benefit among chemotherapy-treated patients in these trials conflicts with prior findings indicating that chemotherapy provides much greater proportional reductions in early (i.e., within the first 5 years of diagnosis) versus later breast cancer recurrence rates (*Lancet* 2005; 365:1687). Other contradictory findings are from the prospective Young Women's Breast Cancer Study, which showed that distant relapse-free survival at 6 years did not differ by receipt of chemotherapy among node-negative patients aged ≤40 years with recurrence score (RS) 11–25 (*J Clin Oncol* 2020; 38:725). Coupled with the fact that less than 20% of premenopausal women on oral endocrine therapy (ET) in RxPONDER, TAILORx, and MINDACT received ovarian function suppression (OFS), we are left with several important questions: Does most of the efficacy of chemotherapy in this population stem from its ovarian suppressive effects as opposed to direct cytotoxicity?

And, more importantly, can chemotherapy be avoided in selected patients, in favor of optimizing endocrine treatment with OFS and oral ET?

THE PROGNOSTIC IMPACT OF CHEMOTHERAPY-RELATED AMENORRHEA

Standard adjuvant chemotherapy regimens for breast cancer are gonadotoxic and cause temporary or permanent loss of menses (chemotherapy-related amenorrhea [CRA]) in many young women. However, CRA is also a well-established predictor of improved disease-free survival (DFS) and overall survival (OS) in premenopausal patients with HR-positive breast cancer (*J Clin Oncol* 2006; 24:5769; *Menopause* 2015; 22:1091). This positive prognostic association of CRA was shown among premenopausal women in the RxPONDER trial: Those assigned to chemotherapy who were amenorrheic during the first 24 months of follow-up had numerically improved invasive DFS compared with those with ongoing periods (hazard ratio, 0.82; 95% CI: 0.43–1.55), although analyses were limited by small sample sizes (*N Engl J Med* 2021; 385:2336).

The higher incidence of CRA observed in older versus younger premenopausal women (*J Clin Oncol* 2006; 24:5769) likely explains why, in a subgroup analysis of TAILORx, a chemotherapy benefit was only seen in patients aged 41–50 years but not those aged ≤ 40 years, the group least likely to experience CRA (*N Engl J Med* 2019; 380:2395). These findings collectively suggest that some, if not all, of the survival advantage premenopausal women derive from chemotherapy is attributable to CRA, which means a similar benefit might be achieved in selected patients using OFS and oral ET alone.

COMPARING CHEMOTHERAPY WITH OVARIAN FUNCTION SUPPRESSION

The SOFT and TEXT trials demonstrated absolute improvements in distant recurrence of at least 4% with the addition of OFS to either tamoxifen or aromatase inhibitors in high-risk patients (*J Clin Oncol* 2020; 38:1293). This result is similar to the 3% absolute improvement in 5-year distant relapse-free survival that was observed with chemotherapy in RxPONDER trial

Table. Key Characteristics of Gene Expression Profile–Driven Adjuvant Chemotherapy Trials

Trial	TAILORx	RxPONDER	MINDACT
Gene expression assay	Oncotype DX (21-gene RS)	Oncotype DX (21-gene RS)	MammaPrint (70-gene signature)
Primary endpoint	iDFS	iDFS	dMFS
Primary patient population	HR-positive/HER2-negative/node-negative, with RS 11–25 (n=6711)	HR-positive/HER2-negative/1–3 positive nodes, with RS ≤ 25 (n=5018)	HR-positive/HER2-positive, with high clinical/low genomic risk (n=1551)
Premenopausal patients (%)	34%	33%	35% (aged ≤ 50 years)
Premenopausal patients on endocrine therapy receiving OFS (%)	13%	13%	18%
Subgroup analyses of primary endpoint by menopausal status within primary patient population	Reduction in 9-year iDFS with endocrine only vs. chemoendocrine therapy in premenopausal group (hazard ratio: 1.36, 95% CI: 1.06–1.75), but not in postmenopausal group (hazard ratio: 0.99, 95% CI: 0.84–1.17)	Improvement in 5-year iDFS with chemoendocrine vs. endocrine-only therapy in premenopausal group (absolute difference: 4.9%, hazard ratio: 0.60, 95% CI: 0.43–0.83), but not in postmenopausal group (absolute difference: –0.6%, hazard ratio: 1.02, 95% CI: 0.82–1.26)	Improvement in 8-year dMFS with chemotherapy vs. no chemotherapy in aged ≤ 50 years group (absolute difference: 5.0%, hazard ratio: 0.54, 95% CI: 0.30–0.98), but not in aged > 50 years group (absolute difference: 0.2%, hazard ratio: 0.82, 95% CI: 0.55–1.24)
Citation	<i>N Engl J Med</i> 2018; 379:111	<i>N Engl J Med</i> 2021; 385:2336	<i>Lancet Oncol</i> 2021; 22:476

RS — recurrence score; iDFS — invasive disease-free survival; dMFS — distant metastasis-free survival; HR — hormone receptor; HER2 — human epidermal growth factor receptor 2; OFS — ovarian function suppression; CI — confidence interval

participants who were premenopausal (*N Engl J Med* 2021; 385:2336). Although variably limited by lack of concomitant oral ET and/or anti-HER2 (human epidermal growth factor receptor 2) therapy, short follow-up durations, and underpowered sample sizes, older phase 3 trials and a meta-analysis have previously demonstrated that gonadotropin-releasing hormone analog (GnRHa) treatment is as effective as adjuvant chemotherapy at reducing the rate of recurrence and death after recurrence in premenopausal patients with HR-positive breast cancer (*Lancet* 2007; 369:1711). Unsurprisingly, survival benefits with the addition of GnRHa to chemotherapy were seen only in patients aged ≤ 40 years, in whom, as aforementioned, chemotherapy is less likely to induce CRA. Prospective randomized clinical trials, including NRG Oncology's planned BR009 study, will be instrumental in elucidating once and for all the true benefit of chemotherapy, or lack thereof, for premenopausal patients with low- or intermediate-genomic risk early-stage breast cancer in the setting of optimal ET including OFS.

PRACTICAL CONSIDERATIONS

While adjuvant chemotherapy has shown clear benefits in premenopausal patients with high genomic risk and can undoubtedly be safely omitted in low clinical/genomic-risk patients, available data support an individualized approach to intermediate-risk patients, with consideration of other clinicopathologic risk factors and careful weighing of the risks and benefits of adjuvant chemotherapy, particularly when maximal ET is planned. Avoidance of chemotherapy is highly desirable in this younger population, who are often motivated to preserve future fertility and who face decades of risk for long-term and late effects of chemotherapy, including permanent neuropathy, cardiotoxicity, cognitive problems, and secondary cancers. However, if the decision is made to forego chemotherapy, the importance of adherence to ET cannot be understated, and diligent efforts to mitigate the anticipated increased menopausal side effects associated with OFS are essential. In addition, regular estradiol monitoring (e.g., every 6 months) to ensure

adequate suppression is advisable while patients are receiving GnRHa, especially if on concurrent aromatase inhibitors or if there are concerns about suboptimal OFS, such as breakthrough vaginal bleeding.

In summary, while we await the results of BR009 to confirm the suspicions that have been brought forth by trials like RxPONDER — i.e., that chemotherapy benefits are predominantly from OFS induction in premenopausal patients — shared decision making with selected patients is warranted regarding the uncertain benefit of chemotherapy when enhanced ET strategies are used and, given the uncertainty, whether the estimated benefit is sufficient to justify the risks of chemotherapy.

RxPONDER: Cytotoxicity Played an Important Role

Sibylle Loibl, MD, and Jenny Furlanetto, MD

The RxPONDER trial is not the only trial demonstrating a chemotherapy benefit for all premenopausal women regardless of the biological risk assessment by a genomic test. In an updated 8-year analysis, the MINDACT trial showed a significant chemotherapy effect in the low-genomic risk group among premenopausal women (*Lancet Oncol* 2021; 22:476; *J Clin Oncol* 2020; 38:506). As this trial occurred in the era prior to the SOFT and TEXT trials, the administration of luteinizing hormone-releasing hormone analog (LHRHa) was low (21.3% overall; 16.2% in the no-chemotherapy group and 26.4% in the chemotherapy group), but this does not imply that the whole chemotherapy effect is due to gonadotoxicity. Further evidence for our position is summarized below.

BREAST CANCER IN YOUNG WOMEN

Several studies demonstrate that in hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer, premenopausal patients have a worse prognosis than postmenopausal patients, especially the very young women compared with older women (*Clinical Cancer Res* 2012; 18:1341;

Cancer Res 2019; 79 [Suppl 4]:P1-17-07). This implies a different biology of breast cancer in young women. Clinically, age shows a strong inverse correlation with response to neoadjuvant chemotherapy, especially in patients with HR-positive/HER2-negative breast cancer. Standard gene expression assays do not seem to capture this age-related biological difference and, therefore, these tests fail to select young women who do not benefit from chemotherapy. More recent gene analysis shows that the tumors in younger women do express immune genes to a higher extent compared with older women, which makes the tumors more chemosensitive. They also exhibit lower expression of ER-associated genes, which could lead to less endocrine sensitivity (Pusztai, personal communication).

OVARIAN FUNCTION SUPPRESSION (OFS) AND THE EFFECT OF CHEMOTHERAPY BEYOND OFS

The addition of OFS to tamoxifen or aromatase inhibitors (AIs) is very effective in treating breast cancer in premenopausal women, as shown by the SOFT and TEXT studies (*N Engl J Med* 2018; 379:122). The majority of women in SOFT and TEXT received chemotherapy (a surrogate for high risk), and among these women, adding OFS to tamoxifen versus tamoxifen alone resulted in a significantly improved 8-year disease-free survival (DFS) of 76.7% versus 71.4%. This shows that an LHRHa added to chemotherapy enhances effect. This would not be the case if the effect of chemotherapy were driven only by OFS. Moreover, the meta-analyses by the Early Breast Cancer Trialists' Collaborative Group support chemotherapy regardless of endocrine therapy (ET) and menopausal status, showing a relative chemotherapy effect of about 20% to 30% (*Lancet* 2012; 379:432). If the chemotherapy effect were confined to OFS, then chemotherapy would not work at all in postmenopausal women. Additionally, the best chemotherapy regimens used today are not the most effective inducers of OFS, which indicates an effect of chemotherapy beyond OFS and the necessity to combine both treatment modalities to improve the outcome of young patients. Taxanes reduce the risk of breast cancer-related death in patients with HR-positive

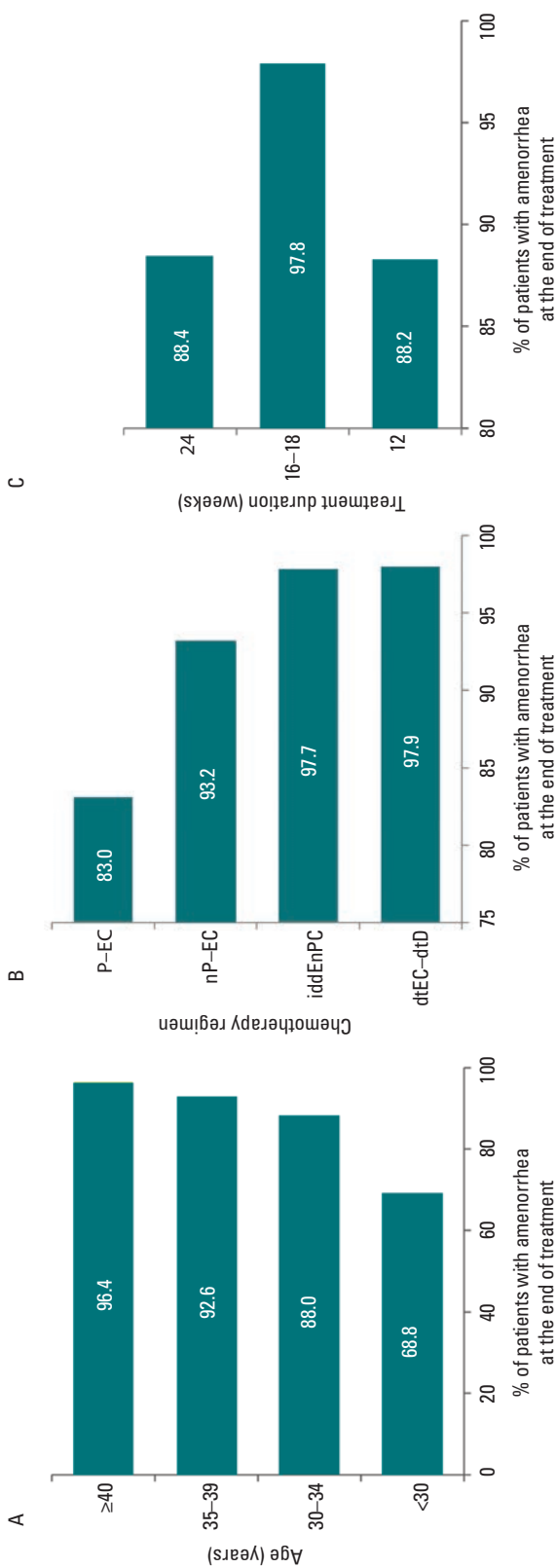
breast cancer, both in young patients as well as in patients older than 55 years (*Lancet* 2012; 379:432). Anthracycline- and taxane-containing chemotherapy regimens are more effective than the cyclophosphamide, methotrexate, 5-fluorouracil (CMF) regimen. Dose-dense chemotherapy is even more effective in reducing the risk of recurrence than standard chemotherapy, independent of age and HR status (*Lancet* 2019; 393:1440). There is an age-dependent effect of chemotherapy versus no chemotherapy in patients with HR-positive breast cancer, with patients younger than 40 years benefiting most from the use of polychemotherapy (a 45% reduction in recurrence risk), supporting the effect of chemotherapy on top of ET.

CHEMOTHERAPY-INDUCED AMENORRHEA

Chemotherapy can induce amenorrhea, which is considered a surrogate for chemotherapy-induced OFS. Women with chemotherapy-induced amenorrhea have a better outcome than those without (*N Engl J Med* 2010; 363:2268). Cyclophosphamide regimens, especially the CMF regimen, have the highest rate of amenorrhea, mainly affecting women between 40 and 50 years. The dose of cyclophosphamide in the docetaxel, cyclophosphamide (TC) regimen, which was predominantly used in RxPONDER, is lower than in the CMF regimen but similar to modern chemotherapy regimens. In RxPONDER, the chemotherapy effect was seen in all premenopausal women. As shown from the above-reported data, OFS is temporary, as is the endocrine effect of chemotherapy, especially in women below the age of 40 years, who tend to regain menses and should therefore receive an LHRHa in addition.

OFS, while important, does not explain the whole chemotherapy effect in young premenopausal patients with early breast cancer. The International Breast Cancer Study Group Trial VIII demonstrated that CMF and LHRHa have similar efficacies but the combination of the two is significantly better (*J Natl Cancer Inst* 2003; 95:1833) in patients younger than 40 with HR-positive breast cancer. In another study, women who received chemotherapy and regained

Figure: Influence of Age (A), Chemotherapy Regimen (B), and Treatment Duration (C) on Amenorrhea After Treatment



P — paclitaxel; E — epirubicin; C — cyclophosphamide; nP — nab-paclitaxel; idd — intense dose-dense; dt — dose-tailored; D — docetaxel
Adapted from Furlanetto J et al. Chemotherapy-induced ovarian failure in young women with early breast cancer: Prospective analysis of four randomised neoadjuvant/adjuvant breast cancer trials.
Eur J Cancer 2021; 152:193.

menstruation after OFS had a significantly better DFS when an LHRHa was added to tamoxifen after regaining menstruation (*J Clin Oncol* 2020; 38: 434). Younger patient age and less-intense and shorter chemotherapy treatment increase the likelihood that a woman will regain menstruation (*Eur J Cancer* 2021; 151:190; Figure).

EFFECTIVENESS AND ADHERENCE TO OFS

The use of an LHRHa does not completely suppress ovarian function. In very young women, OFS with an LHRHa occurs in about 80%, leaving 20% without adequate OFS. This was shown in the SOFT trial; even after 6 months of treatment, up to 20% of patients did not have a complete shutdown of ovarian function as defined by the serum level of estradiol (*J Clin Oncol* 2016; 34:1584). The toxicity rate of 5 years of LHRHa-containing ET is not negligible and should not be underestimated, compared with 4 to 6 months of chemotherapy. Compliance with LHRHa therapy in young women is lower than in adjuvant chemotherapy, compromising the effectiveness of adjuvant therapy. If the LHRHa is discontinued early, the only treatment possible is tamoxifen, which is not adequate ET in high-risk, premenopausal women.

CONCLUSION

Young age is a surrogate for a high biological risk in women with HR-positive/HER2-negative breast cancer. Premenopausal women with node-positive, HR-positive/HER2-negative breast cancer benefit from the use of chemotherapy even when a genomic risk score indicates a low biological risk. Chemotherapy in young women has two components: (1) direct cytotoxic effect and (2) indirect endocrine effect on ovarian function. Both effects are important. Adding an LHRHa to oral ET should be mandatory in all premenopausal women with intermediate- and

high-risk early breast cancer. The effect seen in RxPONDER is not a pure endocrine effect. We need to acknowledge that chemotherapy still has a role in our efforts to cure breast cancer patients.

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Topic Update

How Low Can We Go? Trastuzumab Deruxtecan for Metastatic Breast Cancer

Hope S. Rugo, MD, FASCO

Antibody–drug conjugates (ADCs) are a novel way to deliver a cytotoxic payload directly to the tumor cell, thereby having the potential to both reduce toxicity and increase efficacy by concentrated delivery of chemotherapy. The development of ADCs has been based on an antibody backbone directed to a receptor highly expressed on the tumor cell, with minimal expression on normal tissues. Recent data demonstrate that newer ADCs may be less dependent on high receptor expression, showing remarkable efficacy even in the presence of very low cell surface antigen. This intriguing result has already changed our approach to the treatment of metastatic breast cancer (MBC), as we step into a new therapeutic approach for cytotoxic therapy.

What Are Antibody–Drug Conjugates, and How Do They Work?

ADCs consist of an antigen-specific monoclonal antibody linked to a highly potent cytotoxic agent, or payload. The antibody must be able to bind to a receptor expressed on the tumor cell to enable endocytosis of the receptor plus ADC complex, delivering the agent intracellularly, and the antibody itself may also contribute to antitumor immune activity. The linker must remain stable in the circulation but then release the cytotoxic agent by enzymatic degradation following endocytosis of the ADC complex. The payload itself is also critical and must be highly toxic at very low concentrations. Newer ADCs have membrane-permeable payloads, allowing toxin to leak out of its target, killing nearby tumor cells. This “bystander effect” is, at least in part, the hypothesized basis for the efficacy of trastuzumab deruxtecan (T-DXd) in human epidermal growth factor receptor 2 (HER2)–low disease. An additional factor partially impacting efficacy and drug delivery is the drug-to-antibody ratio (DAR), defined as the number of cytotoxic molecules per antibody.

Identifying HER2-Low Disease: Definitions and Challenges

Identifying HER2-positive breast cancer is of critical therapeutic importance to determine optimal therapy. HER2-low, of only recent therapeutic importance, is defined using immunohistochemistry as HER2 1+ or 2+ membrane staining without *HER2* gene amplification (*J Clin Oncol* 2020; 38:1951).

Is there really an entity of HER2-low disease biologically? It appears that low expression of HER2 (compared with no expression by immunohistochemistry) is more commonly seen in hormone receptor (HR)-positive versus HR-negative/HER2-negative disease (triple-negative breast cancer, or TNBC), and in luminal versus basal-like subtypes, suggesting that this is simply a companion rather than its own biologic entity (*NPJ Breast Cancer* 2021; 7:1). *ERBB2* transcript abundance is relatively higher in HR-positive disease compared with TNBC disease, and this difference is seen within HER2-low subsets. Indeed, low expression of HER2 does not appear to have prognostic significance over and above established biologic subtypes, and expression may change with progression of disease (*Eur J Cancer* 2022; 163:35; *Lancet Oncol* 2021; 22:1151; *Ann Oncol* 2021; 32 [Suppl 2]:S31). Testing for the HER2 receptor was designed to detect HER2-positive disease, and separate out HER2-negative tumors, rather than to differentiate the degree of receptor positivity. There appears to be greater discordance between pathologists in differentiating HER2 zero from 1+ (defined as incomplete and faint membrane staining in at least 10% of cells), compared with 2+ using the American Society of Clinical Oncology/College of American Pathology guidelines (*JAMA Oncol* 2022; 8:607). In addition, significant heterogeneity in HER2 receptor expression across tumor sites and even within a single tumor sample is a further confounding variable.

Trastuzumab Deruxtecan in HER2-Low Disease

T-DXd is a novel ADC comprised of a trastuzumab biosimilar; a tumor protease–cleavable plasma-stable linker; and deruxtecan, a membrane-permeable topoisomerase I inhibitor with a DAR of 8:1 and remarkable efficacy in breast, gastric, and lung cancers. In HER2-positive MBC, T-DXd markedly improved progression-free survival (PFS) compared with the ADC trastuzumab emtansine. Based on preclinical data and the bystander effect, in a phase 1 study, 54 patients with heavily pretreated HER2-low MBC (47 with HR-positive disease) received T-DXd, establishing the 5.4 mg/kg dose given intravenously every 3 weeks, and resulting in an overall response rate of 37% and a PFS of 11.1 months (*J Clin Oncol* 2020; 38:1887). These exciting data led to the phase 3 DESTINY-Breast04 trial, which demonstrated dramatic efficacy with T-DXd compared with treatment of physician's choice (TPC) in patients who had received a median of one line of chemotherapy for metastatic HER2-low disease, improving both PFS (10.1 vs. 5.4 months) and overall survival (OS; 23.9 vs. 17.5 months) in those with HR-positive disease (*N Engl J Med* 2022; 387:9). Although the primary endpoint was PFS in HR-positive disease, in the 58 patients with TNBC, PFS and OS were also improved, leading to regulatory approval in both subgroups.

Understanding Toxicity

Although ADCs are reasonably well tolerated, toxicities occur that appear to be related to both the payload and delivery of the ADC, with possible variations based on receptor expression on nontumor cells. In DESTINY-Breast04, the most common toxicity from T-DXd was nausea (73%), primarily low grade, with less frequent cytopenias and alopecia (38%). The unique toxicity of interstitial lung disease (ILD) or pneumonitis, seen in 12.1% of patients in DESTINY-Breast04 (with grade 5 toxicity in three patients [0.8%]), is poorly understood, although historically it has been associated with multiple anticancer agents. For T-DXd, it is clear that early identification and aggressive management has significantly reduced severity and risk of death (*ESMO Open* 2022; 7:100553). Several factors that increase ILD risk have been uncovered, including drug dose (*ESMO Open* 2022; 7:100554).

Next Steps

T-DXd is now a standard of care as second-line chemotherapy for HER2-low MBC. Next steps include further target definition and expression requirements for efficacy. A large ongoing phase 3 study, DESTINY-Breast06 (NCT04494425), is evaluating T-DXd compared with TPC in patients with HR-positive, chemotherapy-naïve MBC including both HER2-low and HER2-ultralow disease, with ultralow defined as any staining over zero but less than 1+. The efficacy of T-DXd in HER2-zero disease requires further investigation.

Other HER2 ADCs have been or are being tested in HER2-low disease, as well as other subsets of MBC. For example, the TROP2 ADC sacituzumab govitecan, which carries a different topoisomerase payload, has demonstrated improved PFS and OS in patients with heavily pretreated TNBC and HR-positive/HER2-negative disease (*N Engl J Med* 2021; 384:1529; *J Clin Oncol* 2022 Aug 26 [e-pub]; *Ann Oncol* 2022 [Suppl 7]:Abstract LBA76). In addition, a new TROP2 ADC, datopotamab deruxtecan, has shown significant efficacy in metastatic TNBC (*Cancer Res* 2022; 82 [Suppl 4]:Abstract GS1-05) and is now being studied in phase 3 trials in both TNBC and HR-positive disease. New studies are testing these highly effective ADCs in combination with immunotherapy based on preclinical data suggesting potential enhanced immune response and in earlier lines of treatment with early encouraging data. Our new challenge is to understand sequencing of ADCs: Is efficacy driven by antibody targeting or the toxin?

Clearly, new-generation ADCs represent a major step forward in cytotoxic therapy. T-DXd has changed not only our treatment options, but also our entire approach — and this is just the beginning.

Hope Rugo, MD, FASCO

Dr. Rugo is Professor of Medicine, Director of Breast Oncology and Clinical Trials Education, and Medical Director of Infusion Services at the University of California San Francisco Helen Diller Family Comprehensive Cancer Center.



DISCLOSURES

Hope Rugo, MD, FASCO, reports external grant support from Pfizer, Merck, Ayala, Novartis, Lilly, Roche, MacroGenics, Sermonix, Astellas, Boehringer Ingelheim, Polyphor, AstraZeneca, and Gilead; and honoraria from Puma Biotechnology, Samsung Bioepis, Chugai, Blueprint Medicines, and Napo Pharmaceuticals.

Topic Update

Adjuvant Bone-Modifying Agents: Where Do We Stand?

Michael Gnant, MD, FACS, FEBS, and Stephanie Kacerovsky-Strobl, MD

Bone physiology and breast cancer are connected in several ways. First, the “hormonal” background physiology affects both, including some interesting (yet partly unexplained) findings: While one would expect that, in general, lower estrogen levels might lead to lower breast cancer incidence and more osteoporosis, the contrary is true; breast cancer patients — even at baseline — are more likely to also suffer from osteoporosis than women without breast cancer (*Arch Osteoporos* 2021; 16:98). Furthermore, estrogen receptor (ER)–positive breast cancer demonstrates a strong bone tropism in metastasis — and the bone marrow microenvironment affects function (and fate) of dormant micrometastases (*Dev Cell* 2021; 8:1100). Finally, and most importantly from a clinical standpoint, endocrine therapy — which is the cornerstone of drug treatment in luminal (the most common form of) breast cancer — can have a negative impact on bone health, leading to treatment-induced bone loss and fractures (*Lancet Diabetes Endocrinol* 2018; 11:901). Fortunately, bone-targeted agents such as bisphosphonates and denosumab can counteract these side effects, protect patients’ bone health, and even improve outcomes in early breast cancer (*Am Soc Clin Oncol Educ Book* 2017; 37:116).

Bone Physiology

For the breast cancer caregiver, it is important to understand how the disease and its treatments affect bone health. Modern endocrine therapies lower circulating estradiol, which activates osteoclasts in bone, leading to increased bone resorption and reduced bone formation. Bone-targeted therapies inhibit osteoclast function, and thus can restore the balance in bone physiology, which helps to improve bone health and reduce detrimental clinical side effects including fractures (*J Bone Oncol* 2017; 7:1). The anticancer activity of antiresorptive agents was initially believed to be a direct antineoplastic effect but is now understood as an indirect effect of these agents on the bone (marrow) microenvironment (*Semin Oncol* 2010; 37:S53). In addition to inhibiting

osteoclasts, both bisphosphonates and denosumab can promote the immobilization of dormant cancer (stem) cells in the endosteal niche of bone marrow (*Cancer Treat Rev* 2012; 38:407).

Bisphosphonates

Already decades ago, several trials investigated the adjuvant effects of the early oral bisphosphonate clodronate. In a pivotal trial, 302 patients were selected for the presence of disseminated tumor cells in their bone marrow and randomized to receive oral clodronate or not. The results demonstrated significant improvements in disease-free and overall survival with clodronate use (*N Engl J Med* 1998; 339:357). Also, the Royal Marsden trial of 2 years’ use of clodronate versus placebo yielded significant outcome improvements (*J Clin Oncol* 2002; 15:3219). Trials with the more-potent intravenous aminobisphosphonate zoledronic acid confirmed these results (ABCSG-12, Z/ZO-FAST), but there were also controversial findings in other clinical trials (*Cancer Treat Rev* 2014; 40:476). The totality of the evidence eventually showed that the metastasis-preventing effect of bisphosphonates is confined to postmenopausal women (and to premenopausal women therapeutically rendered postmenopausal by ovarian function suppression). Once more, this suggests that menopausal (i.e., estrogen) effects on the bone microenvironment exert a pivotal impact on the benefit of antiresorptive agents (*Clin Cancer Res* 2014; 20:2922). In a huge patient-level meta-analysis of all adjuvant bisphosphonate trials, the Early Breast Cancer Trialists’ Collaborative Group finally confirmed the benefit of adjuvant bisphosphonates for (naturally or therapeutically induced) postmenopausal breast cancer patients with respect to overall breast cancer recurrence (first-event rate ratio, 0.86), distant recurrence at any site (first-event RR, 0.82), bone recurrence (first-event RR, 0.72), and breast cancer–specific mortality (first-event RR, 0.82) (*Lancet* 2015; 386:1353).

Denosumab

Denosumab is a humanized monoclonal antibody that targets the receptor activator of nuclear factor- κ B (RANK) ligand (RANKL) with very high affinity and specificity to the soluble and cell membrane-bound forms of human RANKL. The RANK/RANKL system is an important signaling mediator for bone resorption and has also been shown to influence biologic processes beyond the skeletal system, including the immune system (*Gerontology* 2015; 61:534). Like bisphosphonates, denosumab is also a standard of care in the treatment of patients with solid tumors who have developed bone metastasis.

In the Austrian Breast Cancer Study Group-18 (ABCSG-18) trial, we evaluated the effect of 60 mg denosumab administered subcutaneously twice yearly versus placebo in aromatase inhibitor (AI)-treated, postmenopausal, early hormone receptor-positive breast cancer patients (*Lancet* 2015; 386:433). With respect to fracture prevention, the results were dramatic: The 6-monthly antibody treatment virtually cut their incidence in half, suggesting that all postmenopausal breast cancer patients on AI treatment should have this intervention in order to protect their bone. This conclusion was particularly supported by the minor side effects observed at this low “bone-protecting” dose of denosumab. Notably, there was not a single reported episode of osteonecrosis of the jaw (ONJ), which can occur from higher-dose treatment for advanced disease (*Lancet* 2015; 386:433).

At the 2022 American Society of Clinical Oncology annual meeting, we presented the final long-term outcome results of this adjuvant denosumab trial (*J Clin Oncol* 2022; 40(Suppl):507). At 8 years of median follow-up, disease-free survival, bone metastasis-free survival, and overall survival were all improved by 20% to 25%, which results in absolute outcome benefits between 3.5% and 5% at 9 and 11 years of follow-up, respectively. These benefits are preserved long term, more than 5 years after the randomized treatment has ended. This contradicts the

early negative results from another large clinical trial, D-CARE (*Lancet Oncol* 2020; 21:60).

As occurs sometimes with therapeutic interventions that are controversially discussed over many years, there might still be “believers” and “nonbelievers” with respect to adjuvant bone-targeted treatment. From a patient’s perspective, however, bisphosphonates and denosumab are well-studied, effective, highly tolerable, and affordable agents that will not only improve bone health and prevent fractures (which is particularly relevant in an aging breast cancer population) but will also improve long-term outcomes for postmenopausal patients. Thus, every breast cancer patient should be informed about this therapeutic option.

Michael Gnant, MD, FACS, FEBS

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Stephanie Kacarovsky-Strobl, MD

Dr. Kacarovsky-Strobl is a board-certified surgeon specializing in breast cancer. She leads the Breast Health Center at St. Francis Hospital in Vienna, Austria.



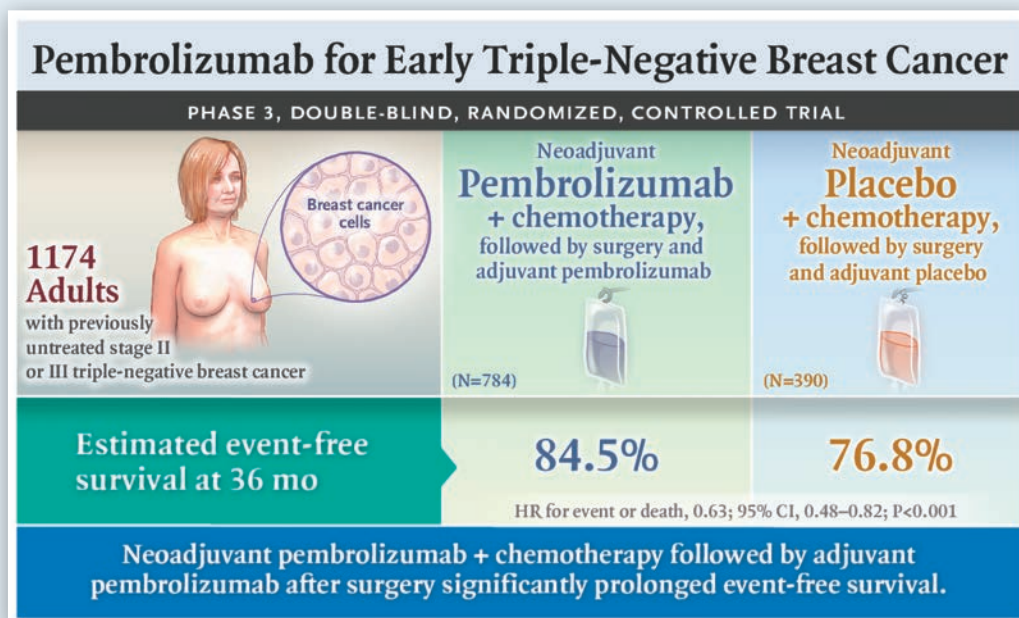
DISCLOSURES

Michael Gnant, MD, FACS, FEBS, reports fees/compensation from Daiichi Sankyo, Eli Lilly, Veracyte, Novartis, Pierre Fabre, MSD.

Stephanie Kacarovsky-Strobl, MD, reports no disclosures.

NEJM Visual Abstract

Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer



Background

The addition of pembrolizumab to neoadjuvant chemotherapy led to a significantly higher percentage of patients with early triple-negative breast cancer having a pathological complete response (defined as no invasive cancer in the breast and negative nodes) at definitive surgery in an earlier analysis of this phase 3 trial of neoadjuvant and adjuvant therapy. The primary results regarding event-free survival in this trial have not been reported.

Conclusions

In patients with early triple-negative breast cancer, neoadjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab after surgery, resulted in significantly longer event-free survival than neoadjuvant chemotherapy alone. (Funded by Merck Sharp and Dohme, a subsidiary of Merck; KEYNOTE-522 ClinicalTrials.gov number, NCT03036488.)

Peter Schmid, MD, PhD, et al.

February 10, 2022; *N Engl J Med* 2022; 386:556
www.nejm.org/doi/full/10.1056/NEJMoa2112651

NEJM Research Summary

Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer

Hortobagyi GN et al. DOI: 10.1056/NEJMoa2114663

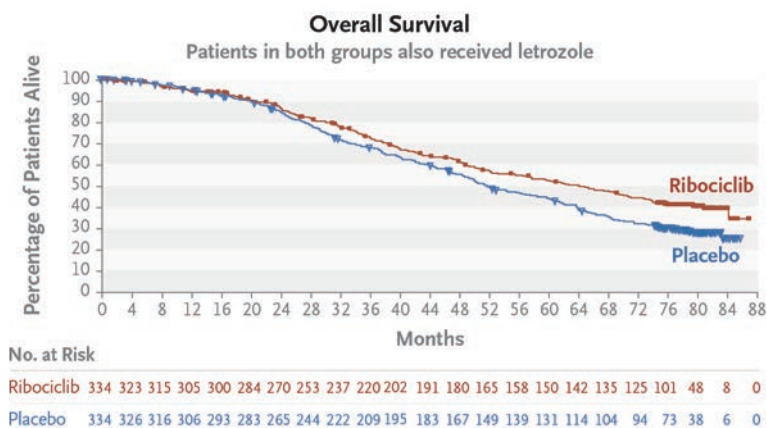
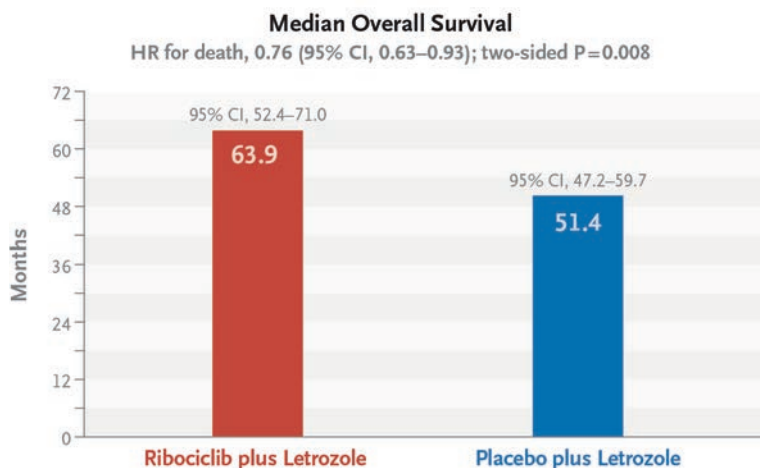
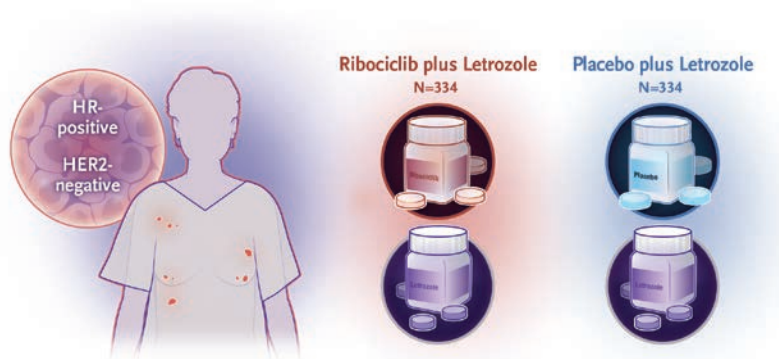
CLINICAL PROBLEM

A preliminary analysis showed that the cyclin-dependent kinase inhibitor ribociclib was associated with prolonged progression-free survival among women with advanced breast cancer, but whether the drug affected overall survival in the trial was not known.

CLINICAL TRIAL

Design: This is the final analysis of a phase 3, randomized, controlled trial that assessed the efficacy and safety of ribociclib in combination with letrozole among postmenopausal women with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative recurrent or metastatic breast cancer who had not received previous systemic therapy for advanced disease. A hierarchical testing strategy was used for analyses of progression-free and overall survival to ensure the validity of the findings.

Intervention: 668 patients were randomly assigned to receive either ribociclib (600 mg daily in cycles of 21 days of treatment followed by 7 days of no treatment) or placebo, with both groups receiving daily letrozole (2.5 mg). The primary end point of this analysis was overall survival, a key secondary end point of the trial.



RESULTS

Efficacy: At a median follow-up of 6.6 years, the median overall survival was significantly longer with ribociclib plus letrozole than with placebo plus letrozole (63.9 months vs. 51.4 months); the survival benefit was consistent across most subgroups.

Safety: This trial identified no new safety signals. Neutropenia was the most common grade 3 or 4 adverse event in the ribociclib group.

LIMITATIONS AND REMAINING QUESTIONS

- The small number of patients in some subgroups led to wide confidence intervals.
- Black patients were underrepresented; only 2.5% of the trial population was Black.

CONCLUSIONS

Among postmenopausal patients with HR-positive, HER2-negative advanced breast cancer, median overall survival was more than 1 year longer with first-line ribociclib than with placebo.

Meeting Report

ASCO 2022 Meeting Report — Breast Cancer

Key trials in breast cancer management

The 2022 American Society of Clinical Oncology (ASCO) annual meeting, held in Chicago June 3–7, highlighted important advances in cancer research. Here, *NEJM Journal Watch Oncology and Hematology* Editor-in-Chief Dr. William Gradishar focuses on key trials in breast cancer. Meeting abstracts can be viewed in the ASCO meeting library (<https://jwat.ch/3RtZ30A>).

Trastuzumab Deruxtecan in HER2-Low Advanced Breast Cancer

By far the most impactful presentation at ASCO 2022 was DESTINY-Breast04, reported by Modi and colleagues (abstract LBA3). Previously, the decision to use HER2-targeted therapy in either the early or late stage was based on a binary decision: HER2-positive or HER2-negative. HER2-positive status was defined as immunohistochemistry (IHC)2+ if fluorescent in situ hybridization (FISH)-positive or IHC3+ (with or without ISH testing). Although nuances to test interpretation have been defined by the ASCO-CAP guidelines, the essential decision was straightforward for most patients. Any case that fell outside of these parameters was not considered an appropriate candidate for HER2-directed therapy.

Now, results from the industry-sponsored, randomized, phase 3 DESTINY-Breast04 trial will allow clinicians to broaden the population of patients who are candidates for HER-directed therapy with the antibody–drug conjugate trastuzumab deruxtecan (T-DXd).

Patients with HER2-low (IHC1+, or IHC2+ and ISH negative) metastatic breast cancer refractory to endocrine therapy and 1 or 2 lines of prior chemotherapy for advanced disease were randomized 2:1 to T-DXd or physician's choice of treatment (gemcitabine, capecitabine, eribulin, paclitaxel, or nab-paclitaxel). Of 557 patients, approximately 90% were ER-positive and of these, two thirds received a prior CDK4/6 inhibitor.

The primary endpoint, progression-free survival, was a median of 9.9 months in the T-DXd arm versus 5.1 months in the physician's choice arm ($P<0.0001$). Results were similar in the subset of patients with ER-positive disease. A statistically significant improvement in overall survival was also seen in patients receiving T-DXd (median, 23.4 vs. 16.8 months; $P=0.001$). Although the subset of patients with HER2-low/ER-negative disease was small, similar trends in progression-free survival and overall survival were observed. The objective response rate was also three times higher in patients receiving T-DXd. No new safety signals were identified, and the rate of drug-induced interstitial lung disease remained low in those receiving T-DXd.

This trial will change the way advanced breast cancer is treated. The population in this study would typically receive single-agent chemotherapy, but identifying patients defined as HER2-low opens another option with superior efficacy: T-DXd. National Comprehensive Cancer Network guidelines have already been updated to reflect T-DXd as an appropriate option for patients who would have met the entry criteria to DESTINY-Breast04.

For more on this trial, see "How Low Can We Go? Trastuzumab Deruxtecan for Metastatic Breast Cancer" on page 11.

Switching CDK4/6 Inhibitors in Metastatic ER+/HER2– Breast Cancer

The question of whether sequential use of CDK4/6 inhibitors confers clinical benefit in metastatic ER-positive/HER2-negative breast cancer has been debated and the approach occasionally tried in clinical practice, but trials addressing this clinical issue have been lacking. The first trial to explore this question, the randomized, phase 2, industry-sponsored MAINTAIN trial, was reported by Kalinsky and colleagues (abstract LBA1004).

Patients with ER-positive/HER-negative metastatic disease who received ≤ 1 line of chemotherapy for advanced disease and had disease progression on endocrine therapy and any CDK4/6 inhibitor were randomized to receive ribociclib or placebo and to switch their endocrine therapy (from fulvestrant to exemestane, from any other agent to fulvestrant). The primary endpoint was progression-free survival.

Of 119 patients, 86% had received prior palbociclib and the median duration of prior CDK4/6 exposure was approximately 16 months. Only 9% of patients had received chemotherapy for metastatic disease. Progression-free survival was significantly improved from a median of 2.76 months without ribociclib to 5.29 months with it. The fraction of patients without disease progression at 6 and 12 months was also greater for those receiving ribociclib. An exploratory analysis of progression-free survival in fulvestrant recipients and exemestane recipients showed the addition of ribociclib improved progression-free survival with either agent. In another exploratory analysis, the benefit of adding ribociclib appeared to be limited to patients

with *ESR1* wild-type disease, whereas there was no benefit in those with *ESR1* mutations.

This is the first trial showing a potential clinical benefit to switching to a different CDK4/6 inhibitor after disease progression on another CDK4/6 inhibitor. The fact that the endocrine therapy was also changed at disease progression brings another variable into these results. Several other trials are addressing this issue and results will likely be reported in the next year.

Omitting Radiotherapy after Breast-Conserving Surgery in Patients with Low-Risk for Recurrence

Just as it has become a priority to identify patients in whom systemic adjuvant therapy can be de-escalated without compromising outcome, similar efforts have been undertaken for local therapy. Whelan and colleagues reported findings from LUMINA, a prospective, multicenter, single-arm trial evaluating omission of radiation therapy after breast conserving therapy for low-risk, T1N0 breast cancers (abstract LBA501).

Using a combination of clinical and pathological factors and molecularly defined intrinsic subtypes, investigators identified a group of patients with a particularly low risk of local recurrence (age ≥ 55 and disease characterized as T1N0, nuclear grade 1–2, and luminal A subtype, defined as ER $\geq 1\%$, PR $> 20\%$, HER2-negative, and Ki67 $\leq 13.25\%$). Patients with multifocal or multicentric disease, extensive ductal carcinoma in situ, or lymphatic-vascular invasion were excluded. All patients were to receive adjuvant endocrine therapy and were not offered radiotherapy. The primary endpoint was local recurrence, either noninvasive or invasive.

Of 505 patients, mean age was 67 years, approximately half had tumors 1.1–2.0 cm in size, and two thirds had grade 1 tumors. Adjuvant endocrine therapy consisted



of tamoxifen in 41% and an aromatase inhibitor in 59%. At 5 years a total of 10 local recurrence events occurred, for a 5-year recurrence rate of 2.3%. This low rate was below the boundary of 5% set at the outset of the study.

The investigators estimated that in North America alone, 30,000 to 40,000 women meeting this study's criteria could safely avoid adjuvant radiation therapy.

William J. Gradishar, MD

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 reports consultant or advisory board roles with Genentech/Roche, AstraZeneca, MacroGenics, Segen, and Merck; 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

Underrecognition of Symptoms Caused by Breast Radiation Therapy

Radiation oncologists underrecognized common symptoms of acute toxicity in more than half of patients, and more often in Black patients than white patients.

Clinicians will readily acknowledge that limited time with patients in a busy clinic often does not allow for a complete survey of all symptoms that may be affecting a given patient. This is true in all subspecialties caring for patients with breast cancer. The current analysis comparing patient-reported outcomes (PROs) with radiation oncologists' assessments of common symptoms of breast radiotherapy (pain, pruritis, edema, and fatigue) brings this issue to the fore.

Nearly 10,000 patients from across radiation oncology 29 practices were included, of whom 17% were Black and 80% were white. More than 50% of patients experienced acute toxicity related to radiation therapy that went underrecognized by physicians. Factors independently associated with underreporting included younger patient age (< 50 years vs. 60–69 years: odds ratio, 1.35; 50–59 years vs. 60–69 years: OR, 1.19), patient race (Black vs. white: OR, 1.56; “other” race and ethnicity vs. white: OR, 1.52), conventional radiation fractionation (OR, 1.26), male

physician (OR, 1.54), and receipt of 2-field radiotherapy without supraclavicular field (OR, 0.80).

Comment

These results add to previous evidence of discordance between PROs and physician assessments of toxicities. Another important and troubling finding is that adverse side effects experienced by Black patients and patients of other underrepresented racial and ethnic groups were more often underreported or minimized by clinicians compared with those of white patients. Previous studies suggest that physicians may be less willing to prescribe pain medications to Black patients and may have more difficulty recognizing skin toxicity due to radiation therapy in Black patients (*J Pain* 2009; 10:1187). Although the current data speak to side effects experienced during radiation therapy, their broader implication is that unconscious bias, or at a minimum lack of awareness, may result in disparities in care for certain populations of patients

William J. Gradishar, MD

Please see page 20 for Dr. Gradishar's bio and disclosures he's reporting.

Jagsi R et al. Identifying patients whose symptoms are underrecognized during treatment with breast radiotherapy. *JAMA Oncol* 2022 Apr 21; 8:887. (<https://doi.org/10.1001/jamaoncol.2022.0114>)

Preserving Ovarian Function in Women with Breast Cancer

Treatment with a gonadotropin-releasing hormone analog reduced the risk of premature ovarian insufficiency.

In an effort to preserve fertility in women with breast cancer without compromising efforts to reduce the risk of disease recurrence, many strategies have been employed, including the use of gonadotropin-releasing hormone analogs (GnRHa) to make the ovaries quiescent during adjuvant chemotherapy. Two prior studies, POEMS and PROMIS-GIM6, demonstrated that GnRHa administered during adjuvant chemotherapy had a protective effect on ovarian function and reduced the risk of early menopause induced by chemotherapy; however, the sample sizes were modest. Furthermore, prior studies used traditional markers of ovarian function, such as menstrual history, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and inhibin B, which have proven to be unstable over time and not particularly sensitive.

Now, investigators in China report a trial in which 330 premenopausal women with stage I to III breast cancer were randomized to receive adjuvant chemotherapy with or without a GnRHa (either goserelin or leuprorelin administered monthly). GnRHa treatment was started 1 to 2 weeks prior to chemotherapy initiation and continued until 4 weeks after completion of chemotherapy. Although a variety of adjuvant chemotherapy regimens were allowed, all patients received cyclophosphamide, an alkylating agent with potent gonadotoxic properties. Anti-Müllerian hormone (AMH), a more sensitive biomarker of

ovarian reserve was utilized to evaluate the protective effect of a GnRHa co-administered during adjuvant chemotherapy. The primary outcome was the rate of chemotherapy-induced premature ovarian insufficiency (POI; defined as an AMH level <0.5 ng/mL) 12 months after completion of chemotherapy.

At 6 months after chemotherapy, POI was present in 17.1% of the GnRHa group and 28.4% of the control group. At 12 months, the rate of POI was 10.3% in the GnRHa group and 44.5% in the control group, a significant difference ($P<0.001$). AMH resumption at 12 months — meaning that an originally normal AMH value dropped to <0.5 ng/mL with receipt of chemotherapy but later recovered to >0.5 ng/mL — occurred in 15 of 25 patients in the GnRHa group and 6 of 44 in the control group ($P<0.001$). There was no difference in overall survival between the groups, but among women younger than 35 years, those in the GnRHa group had longer tumor-free survival than controls.

Comment

This trial demonstrates that GnRHa can increase the probability of preserving ovarian function and that AMH levels may be more sensitive than traditional markers of ovarian reserve.

William J. Gradishar, MD

Please see page 20 for Dr. Gradishar's bio and disclosures he's reporting.

Zong X et al. Effects of gonadotropin-releasing hormone analogs on ovarian function against chemotherapy-induced gonadotoxic effects in premenopausal women with breast cancer in China: A randomized clinical trial. *JAMA Oncol* 2022 Feb 1; 8:252. (<https://doi.org/10.1001/jamaoncol.2021.6214>)

NEJM Journal Watch Summary

Medicaid, the ACA, and Breast Cancer Survival

Survival improved for patients with metastatic breast cancer in states that expanded Medicaid coverage, and the disparity between white and other racial/ethnic groups decreased.

Healthcare as a human right has been championed by many for generations, yet significant inequities still exist among vulnerable populations in the U.S. Disparities in accessing care or receiving optimal care have been documented in cardiovascular health, cancer care, and diabetes management, as examples. Suboptimal healthcare outcomes, including overall survival (OS), are experienced more often in certain racial, ethnic, and socioeconomic groups.

These investigators assessed whether mortality disparities improved for patients with de novo metastatic breast cancer in states that expanded Medicaid coverage under the Affordable Care Act (ACA). Using data from the National Cancer Database, they evaluated survival outcomes in 19 states before and after expansion, comparing white and other racial/ethnic populations.

The analysis included 5077 patients aged 40 to 64 with a diagnosis in the 4-year pre-expansion period and 4245 in the 3-year postexpansion period. The white group comprised 6777 patients (73%) and the other racial/ethnic group comprised 2545 (27.3%) patients, including 5.4% Hispanic (any race), 16.3% non-Hispanic Black, and 5.7% non-Hispanic other (American Indian or Alaska Native, Asian or Pacific Islander, unknown).

Overall survival was significantly higher among white patients than those of other racial/ethnic identities in the preexpansion period (64% vs. 56%) but did not differ significantly between groups in the postexpansion period (71.0% and 71.8%). Overall, 2-year mortality declined from 32.2% pre-expansion to 26.0% postexpansion. The adjusted 2-year mortality decreased from 40.6% to 36.3% among white patients and from 45.6% to 35.8% among other racial/ethnic groups. Among patients in the lowest income quartile, other racial/ethnic groups had an increased risk of death compared with white patients in the preexpansion period but lower risk in the postexpansion period.

Comment

Although this study does not prove causality between greater Medicaid coverage and improved outcomes, it does suggest a compelling association. Policies and programs that allow for greater access to timely cancer care can improve outcomes across many historically disadvantaged populations.

William J. Gradishar, MD

Please see page 20 for Dr. Gradishar's bio and disclosures he's reporting.

Malinowski C et al. Association of Medicaid expansion with mortality disparity by race and ethnicity among patients with de novo stage IV breast cancer. **JAMA Oncol** 2022 Apr 7; 8:863. (<https://doi.org/10.1001/jamaoncol.2022.0159>)

Images in Clinical Medicine

Carcinoma en Cuirasse



24

A 65-year-old man presented to the dermatology clinic with a 7-month history of painless skin thickening over the left side of his chest and on his left arm. On physical examination, the skin on the left side of the chest and on the left nipple was sclerotic. Multiple erythematous nodules were observed on the left arm, axilla, and posterior trunk, and lymphedema in the left arm and left axillary lymphadenopathy were present. A skin-biopsy specimen from the chest showed metastatic carcinoma that was strongly suggestive of a primary breast cancer, without expression of hormone receptors or human epidermal growth factor receptor 2. The patient's skin findings were attributed to carcinoma en cuirasse, a rare form of cutaneous breast cancer metastasis that results in extensive fibrosis of the skin and subcutaneous tissues of the chest wall. The name derives from the resemblance of the condition to a breastplate of armor. The patient was referred to the oncology clinic, and combined positron-emission tomography and computed tomography revealed diffuse ^{18}F -fluorodeoxyglucose-avid stranding in the subcutaneous soft tissue of the left chest wall, as well as involvement of the left axillary lymph nodes and bones. Palliative chemotherapy was administered.

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December 30, 2021; *N Engl J Med* 2021; 381:2562
www.nejm.org/doi/full/10.1056/NEJMimc2111669