

# NCCN Guidelines Updates: Breast Cancer

Presented by Melinda L. Telli, MD; William J. Gradishar, MD; and John H. Ward, MD

## ABSTRACT

Advances in molecular testing have ushered in the new era of precision medicine. The 2018 publication of the TAILORx trial helped refine the use of genetic expression assays, specifically the 21-gene recurrence score, in assigning patients to endocrine therapy alone or with chemotherapy. The NCCN Guidelines for Breast Cancer explore the clinical applications of this study. The algorithm for managing the axilla in early breast cancer has been further refined, based on the presence or absence of clinical evidence of lymph node involvement. Ovarian suppression has been validated as the optimal approach in higher risk premenopausal women, based on updated analysis of the SOFT and TEXT pivotal trials. In the metastatic setting, the NCCN Guidelines further reinforce the benefit of the CDK4/6 inhibitors, extending the “preferred” recommendation to all the available agents in metastatic disease. Options in triple-negative breast cancer now include, for the first time, an immunotherapeutic agent.

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### Greater Emphasis on Multigene Testing, Ovarian Suppression

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer now emphasize ovarian suppression in premenopausal women, as described by Melinda L. Telli, MD; the benefits to be gained from novel agents in the metastatic setting, as presented by William J. Gradishar, MD; and the benefit of multigene testing, as discussed by John H. Ward, MD.

Dr. Telli, Associate Professor of Medicine (Oncology), Stanford University School of Medicine, summarized the key changes in an interview with *JNCCN*. “We have emphasized the importance of ovarian suppression added to endocrine therapy in premenopausal women, based on longer follow-up of the SOFT and TEXT trials. We have also tried to address questions related to the 5 currently available gene expression assays,” she said. “The panel continues to specifically endorse the 21-gene recurrence score in node-negative disease, based on the phase III TAILORx trial, and we have updated the ‘gray area’ of patients with recurrence scores (RS) of 26 to 30.”

Dr. Gradishar, Professor of Breast Oncology and Medicine, and Chief of Hematology and Medical Oncology, Feinberg School of Medicine, Northwestern University, and Chair of the NCCN Breast Cancer Panel, summed up the main change in the guidelines for the metastatic setting as the addition of another inhibitor of poly (ADP-ribose) polymerase (PARP) to the recommendations and, importantly, the first inclusion of an immunotherapeutic agent in breast cancer. Dr. Ward, Professor of Medicine, University of Utah School of Medicine, and an oncologist at the Huntsman Cancer Institute, discussed the available assays.

### Multigene Testing in Breast Cancer

“Multigene panels help us personalize systemic adjuvant therapy choices,” Dr. Ward said. “The available assays have strong prognostic capability, and more data on this are coming.”

Among the available assays are the 21-gene panel (Oncotype Dx), the 70-gene panel (MammaPrint), the 50-gene panel (PAM 50), the 12-gene panel (EndoPredict), and the Breast Cancer Index (BCI). Although these are all “excellent assays,” he said, the 21-gene assay is preferred for patients with hormone receptor (HR)–positive, node-negative disease, as it is predictive of chemotherapy benefit. “Given the widespread use of adjuvant therapy, predictive factors are probably of greater importance in early breast cancer,” Dr. Ward explained.

For patients with HR-positive, node-negative, HER2-negative disease and tumors >0.5 cm, the NCCN Guidelines state as a category 1 recommendation that clinicians should “strongly consider the 21-gene assay.” The assay predicts the benefit of chemotherapy when added to tamoxifen as adjuvant therapy, regardless of menopausal status.

Dr. Telli added, “We have committed to the 21-gene assay for [patients with] node-negative disease, where there is a high level of evidence of *predictive* value. But we have taken the stance that there are multiple gene expression assays that give *prognostic* information, and clinicians can order any one of them for patients with 1 to 3 positive nodes.”

### Validation by TAILORx

Validation of the 21-gene assay emerged in 2018 with the results of the TAILORx trial.<sup>1</sup> This pivotal phase III trial

evaluated the value of adding chemotherapy to endocrine therapy in 6,722 women with HR-positive/HER2-negative, node-negative disease and intermediate risk for recurrence. The study found that endocrine therapy, with or without chemotherapy, had similar efficacy in patients with RS between 11 and 25. The invasive disease-free survival rate at 9 years was 83.3% for endocrine therapy alone versus 84.3% with the addition of chemotherapy (hazard ratio, 1.08;  $P=.26$ ). Distant recurrence rates were also similar, as were overall survival rates.

Dr. Ward added that some benefit for chemotherapy, however, was shown for women aged  $\leq 50$  years in an exploratory analysis. This was especially true for women with RS scores between 21 and 25, in whom endocrine therapy alone showed a 9-year invasive disease-free survival rate of 79.2%, increasing to 85.5% with the addition of chemotherapy ( $P=.03$ ). The conclusion was that most women with early-stage HER2-negative, HR-positive, node-negative breast cancer can safely forego chemotherapy.

TAILORx also validated the low rate of recurrence in patients with RS  $< 18$ , and the benefit from chemotherapy in those with RS  $\geq 31$ . The absolute benefit from chemotherapy, if any, in patients with limited nodal involvement and RS  $\leq 25$  awaits the SWOG 1007 (RxPonder) trial results.

Dr. Ward emphasized that all assays complement, and do not replace, the TNM classification and biomarker information, and that clinicians should order only 1 test for a specific patient. Also, in contemplating ordering tests, they should determine whether the treatment recommendation will be affected by the test result and whether, if chemotherapy appears useful, the patient will accept it.

### Treatment of HR-Positive, HER2-Negative, Early-Stage Disease

Trials from several years ago established the benefit of ovarian function suppression with tamoxifen and, even more so, exemestane in premenopausal women with early-stage breast cancer. The findings recently became more pronounced with the SOFT and TEXT trial joint analysis, which determined 8-year outcomes.<sup>2</sup> The addition of ovarian suppression to tamoxifen in SOFT resulted in significantly higher rates of both disease-free and overall survival (hazard ratio, 0.76 and 0.67, respectively) than tamoxifen alone. In TEXT, ovarian suppression plus exemestane yielded even greater freedom from recurrence than was seen with the addition of tamoxifen (86.8% vs 82.8%; hazard ratio, 0.77;  $P<.001$ ), the latest analysis revealed.

“In the NCCN Guidelines, we are now placing more emphasis on adding ovarian function to tamoxifen or exemestane in premenopausal patients, based on the

subsequent analysis showing an improvement in both disease-free and overall survival in SOFT,” Dr. Telli said.

### Value of Extended Endocrine Therapy Still Unclear

For postmenopausal HR-positive breast cancer, the most common option, among many, is upfront aromatase inhibitor therapy for 5 years. High-level evidence exists to extend therapy for 5 additional years in select patients, but overall, the reduction in distant recurrence is in the range of 1% to 1.5%. This comes at the cost of greater toxicity with longer treatment.

“We need to follow these patients longer, and certainly it’s possible that greater benefits will emerge with time, but at this point in time, extended endocrine therapy is not a strategy that can be recommended for most patients, and the guidelines clearly state that this remains an area of uncertainty,” Dr. Telli said.

### Updates in Axillary Management

The NCCN Guidelines for Breast Cancer include some updates regarding axillary management of early-stage breast cancer. For patients with operable disease who will undergo surgery as primary treatment, the recommendation is to stratify them according to the presence or absence of clinically positive lymph nodes at diagnosis.

“If you believe the patient is clinically node-positive, it is recommended that you attempt a biopsy of any suspicious lymph nodes to document this prior to proceeding to surgery,” Dr. Telli said. Patients with positive needle biopsy results for whom upfront surgery is planned have several options. The patient can proceed with an axillary lymph node dissection (ALND) or, if she meets all the ACOSOG Z0011 trial criteria<sup>3</sup> and also has low tumor burden, she can be considered for sentinel lymph node biopsy.

The Z0011 criteria are a T1 or T2 tumor, planned breast-conserving surgery and whole-breast radiation, and no preoperative therapy. A low tumor burden is defined as lymph nodes that are only radiologically detected with involvement of only 1 or 2 nodes.

For patients who are clinically node-negative upfront, the standard strategy is to proceed with sentinel lymph node biopsy first, and then, for those with 1 or 2 positive sentinel nodes, assess for Z0011 criteria to determine whether completion ALND is indicated.

“The ACOSOG Z0011 clinical trial did provide important randomized data stating that for patients with 1 to 2 positive sentinel lymph nodes who are getting breast conservation with whole-breast radiation, a full ALND could be avoided. The NCCN Guidelines continue to endorse those criteria,” she said.

In patients undergoing preoperative therapy first, the considerations are different. Imaging of the axilla and upfront biopsy of any clinically or radiographically suspicious lymph nodes is recommended. Patients with negative nodes can proceed to sentinel lymph node biopsy. Those with clinically positive nodes after preoperative therapy should undergo ALND. If nodes are clinically negative after preoperative therapy, sentinel node biopsy rather than ALND can be considered in select cases.

“Historically, our approach has often been to do an axillary lymph node dissection in patients with positive nodes prior to preoperative therapy, but we are starting to move in a different direction. For patients who are clinically node-negative after preoperative therapy, one can consider sentinel node biopsy,” Dr. Telli advised.

### Treatment of HER2-Negative Advanced Breast Cancer

With more molecular targets being identified and exploited, and immunotherapies becoming available, there will need to be greater refinement in defining patient subsets most likely to benefit from specific therapies. “We will need to consider the notion of precision medicine, based on the pathways that are dominant in a specific patient,” Dr. Gradishar said.

To this end, 2 new drugs were added to the NCCN Guidelines for advanced breast cancer: talazoparib for patients with *BRCA1/2* mutations and atezolizumab for those with triple-negative breast cancer expressing PD-L1. Dr. Gradishar described the use of these new drugs, and reinforced the recommendation of incorporating inhibitors of cyclin-D kinase 4/6 (CDK4/6) and PARP inhibitors in appropriate patients.

### Advanced HR-Positive Disease

For HR-positive disease, recommendations in the NCCN Guidelines have recently evolved from “a list of monotherapy options” to the concept of “partnering endocrine therapy with targeted therapies,” Dr. Gradishar added.

The BOLERO-1 trial triggered this evolution, showing a progression-free survival benefit for adding the mTOR inhibitor everolimus to endocrine therapy.<sup>4</sup> More recently, the focus has shifted to evaluating the contribution of the CDK4/6 inhibitors: currently, palbociclib, ribociclib, and abemaciclib. Positive findings from pivotal trials led to the recommendation that CDK4/6 inhibitors be added to endocrine therapy, either as a first- or second-line therapy. Abemaciclib can also be used as monotherapy.

“We have innumerable options for patients with metastatic estrogen receptor (ER)-positive, HER2-negative disease. As a general approach, we try to exhaust our endocrine therapies before going on to chemotherapy,”

he said. “The general takeaway from the trials is that these agents may make a difference in the clinical course of patients.”

Although some differences in toxicity profiles and administration schedule are true for the separate drugs, he said, “One thing that has been consistently found across the registration trials is a uniform effect on improving progression-free survival. The panel has therefore rephrased our recommendation more broadly to eliminate specifying an individual agent.”

The improvements in outcomes are seen in both postmenopausal women and premenopausal women rendered postmenopausal by ovarian suppression. Although they add benefit in both the first- and second-line settings, total progression-free survival is extended most when they are used as first-line treatment,<sup>4</sup> Dr. Gradishar added.

Differences in overall survival have not been established, but based on the “rather profound” benefit in progression-free survival, this is expected to emerge with longer follow-up, he predicted.

### Beyond CDK4/6 Inhibitors

Endocrine resistance inevitably develops and patients experience disease progression on CDK4/6 inhibitors. Should they be switched to another agent in the class? Should they receive a subsequent endocrine agent? These are questions currently being evaluated in clinical trials.

A retrospective study reported at the 2018 San Antonio Breast Cancer Symposium showed that for patients experiencing disease progression on CDK4/6 inhibitors, time to treatment failure was significantly extended with exemestane plus everolimus.<sup>5</sup> Such findings suggest that “you don’t use up all the advantages of endocrine therapy by combining it with the CDK4/6 inhibitor” and that “these patients can benefit from other inhibitors,” Dr. Gradishar said.

### Oral Selective ER Downregulators

Currently, fulvestrant is the only selective ER downregulator approved by the FDA, but there are limitations to its utility in the clinic and therefore its efficacy. A number of oral selective ER downregulators are in development, however, including RAD-1901 (phase III), LSZ102 (phase I), GDC-9545 (phase I), and SAR439859 (phase I). These drugs are eliciting responses in approximately 30% of heavily pretreated patients. “There is a hope that some of these agents will become available in the near term,” he said.

### Novel Targets

“A lot of the current focus is on how to target specific pathways,” Dr. Gradishar continued. In luminal A

breast cancer, the most frequently altered pathway is PIK3CA/mTOR/AKT. The mTOR inhibitor everolimus is available for this target, but attention has now turned to the development of PI3K and AKT inhibitors.

The phase III SOLAR-1 trial evaluated alpelisib, an alpha-specific PI3K inhibitor, in combination with fulvestrant in women with advanced HR-positive/HER2-negative breast cancer that had progressed on endocrine therapy.<sup>6</sup> In patients with *PIK3CA* mutations, this treatment led to a 7.4-month difference in progression-free survival. Patients with nonmutated tumors derived no benefit. A subsequent analysis showed that circulating tumor DNA assays were equal to tissue sampling for identifying mutations.<sup>7</sup> Alpelisib is expected to be approved soon, at which time it will be added to the guidelines, Dr. Gradishar said.

### Triple-Negative Metastatic Breast Cancer

Until recently, the NCCN Guidelines recommended numerous lines of chemotherapy for advanced triple-negative breast cancer. This changed with the emergence of the PARP inhibitors and checkpoint inhibitors.

For patients with *BRCA1/2* mutations, the PARP inhibitors show clear benefit, as do the older platinum agents. Olaparib became FDA-approved based on a 42% reduction in risk of progression versus treatment by physician's choice ( $P=.0009$ ) in the OLYMPIAD trial.<sup>8</sup> Talazoparib was more recently approved based on the results of EMBRACA, which found a 46% reduction in risk ( $P<.0001$ ).<sup>9</sup> Both drugs yielded a 3-month improvement in progression-free survival versus chemotherapy.

The NCCN now lists talazoparib as a preferred option, along with olaparib, for patients with HER2-negative disease and germline *BRCA1/2* mutations.

The optimal sequencing of the PARP inhibitors is still undetermined.

### Immunotherapy in Advanced Breast Cancer

Breast cancer is not a highly immunogenic tumor; however, the recent IMpassion130 study showed the benefit of the PD-L1 antibody atezolizumab in the triple-negative subtype.<sup>10</sup> Hints of efficacy with checkpoint inhibitors have also been seen in other subtypes, especially in the first-line setting. Therefore, studies are evaluating anti-PD-1/PD-L1 agents in these patients as well.

In IMpassion130, patients with triple-negative breast cancer were randomized to receive albumen-bound (nab) paclitaxel alone or with atezolizumab in the first-line setting. Among PD-L1-positive patients, progression-free survival improved from 5.0 months in the control arm to 7.5 months with atezolizumab (hazard ratio, 0.62;  $P<.0001$ ) and overall survival increased from 15.5 to 25.0 months (hazard ratio, 0.45;  $P$ , not reported). According to Dr. Gradishar, “the era of immunotherapy for breast cancer has arrived.”

**Disclosures:** Dr. Telli has disclosed that she has served as a scientific advisor for Aduro, Celgene Corporation, Genentech, Immunomedics, Merck & Co, and Pfizer. Dr. Gradishar has disclosed that he has served as a scientific advisor for AstraZeneca, MacroGenics, Roche, and Seattle Genetics. Dr. Ward has disclosed that he has no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.

**Correspondence:** Melinda L. Telli, MD, Stanford Cancer Institute, 875 Blake Wilbur Drive, MC 5820, Stanford, CA 94305-5826. Email: mtelli@stanford.edu; William J. Gradishar, MD, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, 676 North St. Clair Street, Suite 850, Chicago IL 60611. Email: w-gradishar@northwestern.edu; and John H. Ward, MD, Huntsman Cancer Institute at the University of Utah, 2000 Circle of Hope, Salt Lake City, UT 84132. Email: john.ward@hci.utah.edu

### References

- Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med* 2018;379:111–121.
- Francis PA, Pagani O, Fleming GF, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med* 2018;379:122–137.
- Giuliano AE, Ballman K, McColl L, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: long-term follow-up from the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 randomized trial. *Ann Surg* 2016;264:413–420.
- Hurvitz SA, Andre F, Jiang Z, et al. Combination of everolimus with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer (BOLERO-1): a phase 3, randomised, double-blind, multicentre trial. *Lancet Oncol* 2015;16:816–829.
- Girdhar KV, Choong GM, Leon-Ferre RA, et al. Clinical management of metastatic breast cancer after CDK4/6 inhibitors: a retrospective single-institution study [abstract]. Presented at the 2018 San Antonio Breast Cancer Symposium, December 4–8, 2018; San Antonio, Texas. Abstract P6-18-09.
- André F, Ciruelos EM, Rubovszky G, et al. Alpelisib + fulvestrant for advanced breast cancer: results of the phase 3 SOLAR-1 trial. Presented at the 2018 ESMO Congress, October 19–23, 2018; Munich, Germany.
- Juric D, Ciruelos EM, Rubovszky G, et al. Alpelisib + fulvestrant for advanced breast cancer: phase 3 SOLAR-1 trial results [abstract]. Presented at the 2018 San Antonio Breast Cancer Symposium, December 4–8, 2018; San Antonio, Texas. Abstract GS3-08.
- Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med* 2017;377:523–533.
- Litton JK, Rugo HS, Ettl J, et al. A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy in patients with advanced breast cancer and a germline *BRCA* mutation [abstract]. Presented at the 2017 San Antonio Breast Cancer Symposium, December 5–9, 2017; San Antonio, Texas. Abstract GS6-07.
- Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med* 2018;379:2108–2121.