Highlights of the NCCN 23rd Annual Conference

© JNCCN—Journal of the National Comprehensive Cancer Network | Volume 16   Number 5.5 | May 2018

605

Abstract

The emergence of CDK4/6 inhibitors has changed the treatment algorithm for advanced/metastatic estrogen receptor–positive breast cancer. In pivotal trials of palbociclib, ribociclib, and abemaciclib, doubling in progression-free survival has been seen. All 3 agents in this class are now included in the NCCN Guidelines for Breast Cancer, and clinicians should be incorporating these agents into their treatment algorithms. The other important issue in this breast cancer setting is extended duration of endocrine therapy. Most of the benefit is modest and toxicity is an issue; therefore, extended-duration endocrine therapy should be highly individualized. For triple-negative disease, platinum agents and PARP inhibitors are helping some patients, but immunotherapies and other novel classes of drugs now in development hold the promise of even better outcomes. In HER2-positive early-stage disease, dual HER2 blockade is of modest benefit, and extended treatment with neratinib may be a good option for some high-risk patients.

Panel Refines Important Breast Cancer Recommendations

In the absence of substantive changes to the NCCN Guidelines for Breast Cancer this year, members of the NCCN panel discussed refinements to the recommendations, described the use of recently approved treatments, and highlighted agents in development that should answer some unmet needs.

Sharon H. Giordano, MD, MPH, Professor of Breast Medical Oncology and the Hubert L. and Olive Stringer Distinguished Professor in Cancer Research, The University of Texas MD Anderson Cancer Center, Houston, Texas; Anthony D. Elias, MD, University of Colorado Cancer Center, Aurora, Colorado; and William J. Gradishar, MD, Feinberg School of Medicine at Northwestern University, Chicago, Illinois.

Dr. Giordano and Dr. Gradishar have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors. Dr. Elias has disclosed that he holds equity interest and/or stock options in Abbott Laboratories, AbbVie, Inc., Agilent, Alexion Pharmaceuticals, Inc., Allergan PLC, Amgen Inc., BioMarin, Bristol-Myers Squibb Company, Celgene Corporation, Eli Lilly and Company, Gilead Sciences, Inc., Incyte Corporation, Merck & Co., Inc., Pfizer Inc., and TESARO, Inc.

Correspondence: Sharon H. Giordano, MD, MPH, The University of Texas MD Anderson Cancer Center, 1400 Pressler Street, Unite 1444, Houston, TX 77030. Email: sgiordan@mdanderson.org; Anthony D. Elias, MD, Department of Medicine, University of Colorado Cancer Center, ACP5310; F724, 1665 Aurora Court, Aurora, CO 80045. Email: anthony.elias@ucdenver.edu; and William J. Gradishar, MD, Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, 676 North St. Clair Street, Suite 850, Chicago, IL 60611. Email: w-gradishar@northwestern.edu

New Adjuvant Therapy Options for Patients With HER2-Positive Cancer

Two new adjuvant treatment options for patients with HER2-positive disease are in the 2018 NCCN Guidelines. The APHINITY trial of 4,805 patients added to the body of data for dual HER2 inhibition by showing a positive—albeit small—benefit for adding pertuzumab to trastuzumab and chemotherapy. The absolute benefit in preventing invasive disease was 0.9% at 3 years and 1.7% at 4 years (hazard ratio [HR], 0.81; P=.045), with slightly more benefit shown in the hormone receptor–negative and node-positive subsets.1 Based on the results of this trial, the FDA granted approval for adjuvant pertuzumab.
Also for patients with HER2-positive disease, neratinib was approved based on results of the Exte- 
NET trial that included 2,840 women. Patients who 
received neratinib after completing 1 year of trastu- 
zumab had an absolute benefit of 2.3% in invasive 
disease-free survival (DFS). The drug seemed to be 
of more value in the hormone receptor–positive ver- 
sus –negative subset.

The main adverse event with neratinib is diar- 
rhea, which was seen in 95% of patients, including 
40% with grade 3 toxicity. When patients follow a 
protocol for preventing and managing diarrhea, this 
side effect can be greatly diminished, Dr. Giordano 
indicated.

“You can consider extended anti-HER2 treat- 
ment with neratinib in HER2-positive, hormone 
receptor–positive patients you deem at high risk for 
recurrence, although it’s kind of difficult for this drug 
to find its place since most patients at high risk will 
have received dual targeted therapy with trastuzum- 
ab and pertuzumab,” she said.

Small HER2-Positive Tumors

No single standard treatment exists for patients with 
small, node-negative, HER2-positive breast cancers, 
but there is evidence that chemotherapy might be 
useful in some. Tolaney et al conducted a study of 
adjuvant paclitaxel (given weekly for 12 weeks with 
trastuzumab) plus trastuzumab monotherapy (for 9 
months) in 406 patients with tumors ≤3 cm. The re- 
currence-free survival rate for these stage T1, node- 
negative tumors was 99.2% at 3 years, 98.1% at 5 
years, and 97.5% at 7 years in an update presented at 
the 2017 ASCO Annual Meeting.

New Developments in TNBC

Dr. Elias updated attendees on new developments 
in TNBC, for which there is only one approved tar- 
geted agent—the oral poly(adenosine diphosphate- 
ribose) polymerase (PARP) inhibitor olaparib. With 
only chemotherapy as an approved treatment op- 
tion, “There is clearly an unmet need for targeted 
therapies in triple-negative disease,” he said.

For metastatic disease, Dr. Elias made the follow- 
ing key points:
• First-line chemotherapy should be with a taxane 
or anthracycline if not previously used (in the 
neoadjuvant or adjuvant setting). Weekly pacli- 
taxel is generally the preferred taxane.
• Sequential single agents are preferred unless 
there is visceral crisis. Combinations yield high-
er response rates but do not improve overall sur-
vival.
• Eribulin and capecitabine and platins are likely 
more effective than gemcitabine and vinorel-
bine, but line of therapy may be more predictive 
of response.
• Chemotherapy resistance develops quickly, 
and third and fourth lines of therapy offer little 
benefit.

Platins, PARP Inhibitors

Platinum agents and PARP inhibitors are effective 
drugs in patients with BRCA mutations, which oc- 
cur in approximately 30% of TNBC cases. In the 
neoadjuvant setting, single-agent cisplatin resulted 
in a 61% pathologic complete response rate in pa-
tients with BRCA mutations, including those with 
TNBC. In the metastatic setting, the TNT trial pro- 
vided no evidence of greater benefit with carboplatin 
compared with docetaxel in unselected patients with 
advanced TNBC, but the BRCA-mutated subset had 
a doubling in response and longer progression-free 
survival (PFS).

In a phase III trial of patients with metastatic disease, 
olaparib monotherapy doubled the response rate and improved median PFS from 4.2 to 7.0 months compared with standard therapy 
(HR, 0.58; P < .001). Similar data now exist for ta-
lazoparib.

Olaparib is approved for previously treated 
metastatic breast cancer with germline BRCA muta-
tions, but not for patients with somatic mutations or 
low expression of BRCA. “We don’t yet know about 
efficacy in somatic mutations, but we do know the 
germline tumors benefit,” he said.

“The question now is whether we should test ev-
everyone with metastatic breast cancer, since the assays 
are relatively cheap and olaparib is an active thera-
peutic agent. No survival advantage, however, has 
been documented,” Dr. Elias said.

Immune Checkpoint Inhibitors in TNBC

TNBC appears to be a fairly good target for immuno-
therapies, an approach that has been studied in both 
heavily pretreated and treatment-naïve patients. Re- 
sponse rates have ranged from 5% to 19% in refrac-
tory patients, but are higher in treatment-naïve pa-
tients. In studies of pembrolizumab and atezolizumab as first-line agents, responses were seen in 23% and 26%, respectively. In the atezolizumab study, duration of response was 8 to 26 months.

As neoadjuvant therapy, the addition of pembrolizumab “markedly improved” pathologic complete response rates in the TNBC and estrogen receptor (ER)–positive cohorts of the I-SPY trial. In patients with TNBC, the probability of pathologic complete response increased to 60% versus 20% with chemotherapy alone.

A number of immunotherapeutic strategies are being pursued in TNBC, including use as single agents (versus chemotherapy) and in combination with various treatments, some new and some traditional, including chemotherapy, radiotherapy, adenosine antagonists, and inhibitors of PARP, IDO, MEK, HDAC, and CTLA4. Immunologic agents are being evaluated in the adjuvant and neoadjuvant settings, including for their benefit in eradicating residual disease postoperatively.

**Promising Novel Approaches**

Many novel strategies are also being pursued for TNBC, including antibody–drug conjugates and androgen receptor antagonists. Antibody–drug conjugates in development target LIV-1 (a transmembrane zinc transporter expressed in almost 90% of TNBC), GPNMB (a gene expressed in aggressive breast cancers), Trop-2 (a cell-surface glycoprotein expressed on >90% of TNBC), and more.

A phase I trial of 35 patients with TNBC showed a response rate of 37% with SGN-LIV1A. Glembatumumab vedotin has also shown significant activity in metastatic breast cancer, including in a phase II study of 42 patients in which median PFS was 17.9 weeks for TNBC and 18.0 weeks for GPNMB-positive tumors. In a subsequent study involving 124 heavily pretreated patients, an unplanned analysis by subgroup showed the response rate to be 18% with glembatumumab versus 0% with physician’s choice in patients with TNBC and 40% and 0%, respectively, in those with GPNMB-positive cancer.

One antibody–drug conjugate that has already received breakthrough designation by the FDA is sacituzumab govitecan, which targets Trop-2. Sacituzumab govitecan has led to responses in at least 30% of heavily pretreated patients. Finally, agents targeting the androgen receptor, which is expressed by approximately half of patients with TNBC, look promising. In a phase II study of enzalutamide in 118 patients with androgen receptor–expressing disease who had been pretreated, responses were seen in 6%, with 42% experiencing clinical benefit at 24 weeks.

**Hormone-Sensitive Advanced Breast Cancer**

The NCCN Guidelines reflect some new standards for ER-positive breast cancer, primarily incorporating 3 inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6). In addition, there is continued discussion about the optimal duration of endocrine therapy. These topics were discussed by Dr. Gradishar.

Summing up the key revisions, Dr. Gradishar said, “We now have 3 CDK4/6 inhibitors in the guidelines—last year, there were only 2—and we now have premenopausal data for their use. We’ve also added fulvestrant as endocrine therapy, reflecting the results of the FALCON trial. We have further addressed the extended duration of adjuvant endocrine therapy, with every permutation of it. Mostly, we state that endocrine therapy beyond 5 years can be considered, but it’s not an absolute.”

**CDK4/6 Inhibitors Are Game-Changers**

Optimizing the treatment of ER-positive breast cancer depends on overcoming resistance to endocrine agents. This tall effort has met with some success, with the availability of CDK4/6 inhibitors. “If you reflect what’s gone on over the past couple of years, it’s really been the era of the CDK4/6 inhibitors,” Dr. Gradishar noted.

Three CDK4/6 inhibitors are approved in the metastatic setting for hormone receptor–positive/HER2-negative disease, with these indications:

- Palbociclib: in combination with an aromatase inhibitor (AI) as initial therapy in postmenopausal women, and in combination with fulvestrant in patients with metastatic disease who progress on endocrine therapy.
- Ribociclib: in combination with an AI as initial therapy in postmenopausal women.
- Abemaciclib: for women and men as monotherapy in the setting of disease progression after endocrine therapy and prior chemotherapy, and as initial therapy in combination with an AI as initial endocrine therapy for postmenopausal women.
“So you see it reflected in the guidelines that you have a number of different options among the 3 CDK4/6 inhibitors, with category 1 level evidence. Choosing which one, or in what setting to use them, is really based on the results of the clinical trials,” he said.

The pivotal trial groups—PALOMA for palbociclib, MONALEESA for ribociclib, and MONARCH for abemaciclib—have “fairly striking consistency… favoring combinations over monotherapy with an AI alone,” Dr. Gradishar noted. “To a large extent the results [Kaplan-Meier curves] are fairly superimposable…in most cases showing a doubling in PFS.”

Unfortunately, it has not been possible to identify subsets who will not benefit from the addition of CDK4/6 inhibitors, as reported from an analysis of MONARCH 3 (Figure 1). “Benefit was seen in all subsets, but what was interesting was that the worse the prognosis, based on clinical features, the bigger the gain from the addition of the CDK4/6 inhibitor,” he noted. “This may suggest there is a group who are particularly likely to benefit.”

Data are available backing the use of this class in premenopausal patients as well, based on findings from the global MONALEESA-7 trial of almost 700 premenopausal or perimenopausal women rendered postmenopausal.17 Patients had received no prior endocrine therapy for metastatic disease; by physician’s choice they received an AI (mostly) or tamoxifen, plus ribociclib or placebo. Similar to studies in postmenopausal patients, ribociclib led to a doubling in PFS, which was 13.0 months with placebo versus 23.8 months with ribociclib (HR, 0.553; P=.0000000983). Choice of the endocrine agent did not influence outcomes.

Although their efficacy appears the same, the 3 agents do have some differences in schedule of administration and toxicity profile (Figure 2).

**Fulvestrant Finds a Place in the Guidelines**
Enhancing endocrine therapy may be possible, even without adding a CDK4/6 inhibitor, Dr. Gradishar said. Fairly recent data come from the first-line FALCON trial of anastrozole versus fulvestrant at 500 mg monthly.18 PFS was significantly longer in the fulvestrant group (HR, 0.79; P=.0486), with a median PFS of 16.6 versus 13.8 months for anastrozole. In the absence of visceral disease, the difference was more striking, with an absolute benefit of at least 8 months, he added.

“The findings suggest that giving fulvestrant at 500 mg a month with a loading dose as well, may actually enhance PFS over anastrozole alone,” he commented. “So there are a number of different options that one could consider in the absence of a CDK4/6 or mTOR inhibitor [everolimus].”

**A Role for Extended Therapy?**
The NCCN Guidelines for Breast Cancer indicate that women who are postmenopausal at diagnosis can consider extending endocrine therapy for an additional 5 years. “For instance, one could consider extending tamoxifen to 10 years, or you can sequence tamoxifen with an AI. You could start with an AI, and then decide that you’re going to continue that beyond 5 years,” Dr. Gradishar explained.

The data to support longer duration of treatment rely largely on a pivotal paper published in 2017 by Pan et al.19 They performed a meta-analysis on 88 trials involving 62,923 women with ER-positive breast cancer who were disease-free after 5 years of endocrine therapy, and found that breast cancer recurrences continued to occur steadily throughout the study period, from 5 to 20 years. The risk of distant recurrence was strongly correlated with the original TN status.

“After 5 years, regardless of whether the patient was node-negative or -positive, even in the best-prognosis patients, there was an increased risk for recurrence out to 20 years,” Dr. Gradishar noted. Risk for distant recurrence at 20 years was 22% for patients who were node-negative, 32% for patients provided a larger sample size, and had more detailed analyses of patient outcomes.

**Figure 1.** Subset analysis of MONARCH 3 (placebo vs abemaciclib).
Abbreviations: HR, hazard ratio; NR, not reached; PFS, progression-free survival.

with 1 to 3 positive nodes, and 52% for patients with 4 to 9 positive nodes. “This begs the question of whether continued therapy beyond that 5 years might be prudent for some patients,” he said.

In almost 10 large studies examining the benefit of extended-duration endocrine therapy, the reduction in DFS risk has varied widely, and overall survival has not been affected. Altogether these studies are “sort of a mixed bag,” Dr. Gradishar acknowledged, “but perhaps an incremental improvement in outcome does occur with longer durations of therapy.”

Several recent data sets (all first reported in 2016) either clarify the issue or confuse it a bit. The IDEAL trial did not come does occur with longer durations of therapy.”

“From a statistical standpoint, there probably is an incremental improvement, but it really is in the prevention of contralateral breast cancer. And with the cost of the side effects that come with longer durations of an AI.”

NSABP B-42 also examined longer duration of an AI and found very modest benefit, primarily seen in the breast cancer–free interval (HR, 0.71; P = .003).21 The DATA trial found some improvement in DFS (HR, 0.79; P = .007),22 but the IDEAL trial did not (HR, 0.96; P = .07; P = .59),23 and neither showed a survival difference. The ABCSG-16 trial with 3,484 patients also showed no difference in DFS but did show much more toxicity with extended therapy.24

“What you do see, with time, is that with longer durations of therapy you are also buying more of the side effects—more osteoporotic fractures and an incremental increase in the risk of thrombotic events,” he added.

“Would I say that these data suggest that no patient should receive longer durations of therapy? No, but it really emphasizes the need to individualize,” Dr. Gradishar concluded. “We have to be cognizant, as well, of what comes with longer durations. You have to get a patient out to 5 years before you could even consider longer treatment, and she has to be absent the significant musculoskeletal complaints, and the concerns about osteoporosis, changes in lipid profile, and possibly hypertension. Decisions about duration must be individualized.”

---

### References

6. Tutt A, Ellis P, Kilburn L, et al. The TNT trial: a randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA 1/2 breast cancer (CRUK/07/012) [abstract]. Cancer Res 2015;75(Suppl):Abstract S3-01.


17. Tripathy D, Sohn J, Im SA, et al. First-line ribociclib or placebo combined with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: results from the randomized phase III MONALEESA-7 trial [abstract]. Presented at the 2017 San Antonio Breast Cancer Symposium; December 5–9, 2017; San Antonio, Texas. Abstract GS2-05.


