Advanced Hormone-Sensitive Breast Cancer: Overcoming Resistance

Presented by Ingrid A. Mayer, MD, MSCI

Abstract

Novel strategies to overcome resistance to endocrine therapy are on the horizon, especially PI3K inhibitors, CDK 4/6 inhibitors, and agents targeting methylation. However, many, if not most, patients with progressive estrogen receptor–positive breast cancer will continue to show response to multiples lines of endocrine therapy alone. Which patient subsets will be candidates for the emerging agents is still unclear, but in the future, subtype of the tumor, mutational status, and treatment goals will be part of the equation. Always, it will be necessary to individualize treatment. (J Natl Compr Canc Netw 2015;13:655–657)

Endocrine therapies remain the standard of care for the treatment of advanced hormone-sensitive breast cancer, but on the horizon are novel strategies that may help overcome the resistance these tumors acquire, according to Ingrid Mayer, MD, MSCI, who spoke on the topic at the NCCN 20th Annual Conference.

Dr. Mayer, Associate Professor of Medicine and Clinical Director of the Breast Cancer Program at Vanderbilt-Ingram Cancer Center, described promising targeted agents but emphasized, "just because we will have targeted drugs available, does not mean we will need to use them in all our patients."

These novel therapies will need to be individualized, based on the profile of resistance, treatment goals, and potentially the tumor mutational profile. Meanwhile, with current treatments, many patients can continue to benefit from multiple lines of endocrine therapy, with chemotherapy generally reserved for patients with visceral involvement, she said.

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Dr. Mayer has disclosed that she has served as an advertising board consultant for Novartis and Genentech, and has received research support from Novartis.

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Degree of Endocrine Resistance Guides Treatment

For some time, researchers have focused on targeting mechanisms of endocrine resistance, which appear to differ between tumors that are primarily (or de novo) resistant to endocrine therapy and those that develop resistance over time (acquired or secondary resistance).

"The concept of endocrine resistance helps us make decisions regarding the next line of treatment," she noted.

The definition of endocrine resistance in advanced breast cancer is evolving. *Primary (de novo) resistance* is defined by progressive disease within 6 months of starting treatment with endocrine therapy in the metastatic setting, or the development of metastatic recurrence during or shortly after completing adjuvant therapy. *Secondary (acquired) resistance* is defined by an initial response to endocrine therapy in the adjuvant and metastatic settings, with disease progression in the metastatic setting occurring 6 months or later.

Essentially, patients with primary resistance may need an additional agent from the start. Conversely, patients with acquired, secondary resistant disease may be sufficiently treated with endocrine agents at first- and even second-line therapy and only require additional agents at later disease progression (Figure 1).

Genetic Profile of Resistance

Genetic alterations are seldom seen in endocrine therapy-sensitive tumors but may be abundant in endocrine

Patient with ER+ MBC should be treated with endocrine therapy unless:

- **Progression of disease after 3 lines of endocrine therapy**
- **Visceral crisis**

Setting	Treatment choice	Reference
1st line, no prior ET in the adjuvant setting	Fulvestrant (500)+ aromatase inhibitor	SWOG-S0026
1st line, prior ET in the adjuvant setting > 6-12 months prior to MBC	AI or Fulvestrant (500), clinical trials with endocrine therapy (PI3K inhibitors, CDK4/6 inhibitors, etc.)	FIRST
1st line, prior ET in the adjuvant setting < 6-12 months prior to MBC	Exemestane + everolimus, tamoxifen + everolimus, Fulvestrant (500), clinical trials with endocrine therapy (PI3K inhibitors, CDK4/6 inhibitors, etc.)	BOLERO-2, TAMRAD, CONFIRM
2nd line	Exemestane + everolimus, tamoxifen + everolimus, Fulvestrant (500), clinical trials with endocrine therapy (PI3K inhibitors, CDK4/6 inhibitors, etc.)	BOLERO-2, TAMRAD, CONFIRM
3rd line	Exemestane + everolimus, tamoxifen + everolimus, clinical trials with endocrine therapy (PI3K inhibitors, CDK4/6 inhibitors, etc.)	BOLERO-2, TAMRAD
> 3rd line	Clinical trials with endocrine therapy (PI3K inhibitors, CDK4/6 inhibitors, etc.); chemotherapy	NCCN, ABC-1

Figure 1 Treatment landscape for estrogen receptor–positive metastatic breast cancer.
Abbreviations: AI, aromatase inhibitor; ET, endocrine therapy, MBC, metastatic breast cancer.

therapy–resistant tumors. In de novo resistance, loss of estrogen receptors (ER) or loss of amplification of co-receptors and co-amplifiers, as well as activation of the cyclin D pathway, are common mechanisms of resistance. For patients with acquired resistance who initially show response to endocrine therapy, PI3K pathway activation is a common resistance mechanism.

Point mutations are associated with resistance to conventional endocrine therapies, and they can be detected after exposure to endocrine therapy. Several point mutations in the ligand-binding domain of ESR1 have been identified; they confer constitutive ligand-independent activation of ER transcription and ER-α expression and may mediate antiestrogen resistance.

"This is important, because novel agents can tap into some of these mutations," Dr. Mayer explained.

One of these is ARN-810, a novel selective ER-α antagonist that induces proteasomal-mediated degradation of ER-α. This drug is now in phase II trials, and may be found to be active in tumors with the *ESR1* mutation, whereas conventional endocrine therapies are not.[1]

PI3K Pathway Inhibitors

Several inhibitors are currently in development for growth factor receptor and intracellular targets. In selected patients, these drugs would be adjuncts to endocrine therapy.

Mutations within the PI3K/mTOR pathway are seen in more than one-third of ER-positive tumors. In early-stage breast cancer, these mutations confer a good prognosis, but the opposite seems to be true in the metastatic setting after exposure to endocrine therapy. In this setting, the pathway activation conferred by *PIK3CA* mutations may behave as a mechanism of antiestrogen resistance. Therefore, PI3K pathway inhibitors may have more relevance for patients with acquired endocrine therapy resistance, Dr. Mayer indicated.

BOLERO-2 is a phase III clinical trial that showed progression-free survival benefit for the addition of the mTOR inhibitor everolimus to exemestane in patients with disease refractory to aromatase inhibitors.[2] Interestingly, this benefit was seen regardless of *PIK3CA* mutation status. FDA approval was granted on the basis of this study, but it is worth noting that no overall survival advantage was seen. However, everolimus remains an option in second- or third-line endocrine treatment of ER-positive metastatic breast cancer.

"Agents blocking PI3K, either pan or selective PI3K inhibitors, are currently in phase III clinical trials and have so far shown an acceptable toxicity profile," Dr. Mayer noted. Other agents targeting this pathway are the TORC1/TORC2 inhibitors, dual PI3K/mTOR inhibitors, and AKT inhibitors, but these agents are not so far in development due to some toxicity concerns.

Preclinically, the pan-PI3K inhibitor buparlisib combined with fulvestrant has shown robust tumor suppressive activity. Clinically, it has also shown some preliminary activity in combination with letrozole, with an acceptable toxicity profile, in a somewhat heavily pretreated patient population.[3] "We saw that a subset clearly had a dramatic benefit in combination with endocrine therapy, regardless of *PIK3CA* mutation presence" she said. Data are now awaited from the phase III BELLE-2 and BELLE-3 trials.

The pan-PI3K inhibitor pictilisib[4] appears to show less benefit in a recent phase II trial, but it is worth noting that only a small proportion of patients had hyperglycemia, an on-target effect for this class of drugs. However, the alpha-specific PI3K inhibitor BYL719 and the beta-sparing PI3K inhibitor GDC0032 appear promising in patients with *PIK3CA* mutations.[5]

"The jury is still out on whether PI3K inhibitors will be useful in advanced ER-positive breast cancer," Dr. Mayer commented. At present, she said, "The combination of endocrine therapy with PI3K pathway inhibitors may further benefit ER-positive, *PIK3CA*-mutant breast cancers, particularly, and not exclusively, those at advanced stage."

Targeting CDK 4/5-Cyclin D1-E2F and Methylation

Cyclin-dependent kinases (CDKs) are key regulators of the cell cycle, and numerous inhibitors are currently in development. One of these, the CDK 4/6 inhibitor palbociclib, recently showed promising results in the phase II PALOMA-1/TRIO-18 trial.[6] Added to letrozole, palbociclib reduced the risk of disease progression by 51% ($P<.0004$), leading to an accelerated FDA approval. The phase III PALOMA-2 is seeking to confirm the benefit, while PALOMA-3 will evaluate palbociclib in second-line therapy in combination with fulvestrant.

"Palbociclib is an appropriate option to consider in combination with endocrine therapy, particularly for patients appearing to have primary endocrine resistance," Dr. Mayer suggested. It is worth noting that, because of its side effect profile (neutropenia, gastrointestinal toxicity), palbociclib may not be the best choice for all patients.

Finally, targeting methylation through inhibition of histone deacetylase could reverse resistance by opening up the DNA structure and enabling the transcription of ER. In the phase II ENCORE 301 study, entinostat plus exemestane as second-line treatment reduced deaths by 41% ($P=.036$).[7] This "outside the box strategy" is being further explored and appears promising. An ECOG-ACRIN phase III trial is now ongoing, Dr. Mayer indicated.

Meanwhile, she emphasized that not all patients with ER-positive disease that progresses after first-line treatment will be candidates for these novel approaches because of drug toxicity. "We can be thankful for these drugs. They are great options, but not all patients will need them," she said. Honoring treatment goals (survival improvement, palliation of symptoms, and maintenance of quality of life) takes precedence at an individual level.

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