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# Targeted Therapies in Breast Cancer: New Approaches and Old Challenges

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Within the last years, we have experienced tremendous progress in therapeutic approaches for breast cancer. Many of these improvements were based on better insights into tumor biology leading to the development of new therapeutics or to a more sophisticated use of existing therapies. Breast cancer is the prototype of a concept where therapy is based on predictive markers. Therapy involving the estrogen receptor was the first 'targeted therapy' of cancer long before this term was used in oncology. As early as in the 19th century, publications described the observation that some breast cancers grow faster within certain phases of the menstrual cycle and that ovarectomy is able to induce tumor regression in premenopausal women [1]. However, it took more than 100 years before the estrogen receptor as mediator of estrogen action was discovered and estrogen receptor measurements were established in clinical routine [2]. With this breakthrough in oncology, 2 aspects became evident that are still a challenge in most therapeutic settings: First, standardization and quality assurance of tests. The determination of estrogen receptor content in tumors was not always reproducible. Many efforts were undertaken to standardize the radioligand-based assays that were being used for many years to determine estrogen receptor status. In Europe, the EORTC receptor and biomarker group organized ring experiments and pioneered the important aspect of quality assurance for the testing of biologic markers [3]. Interestingly, the way to similar procedures in HER2 testing was not straightforward since several reports found high rates of discordances and false-positive results in early clinical trials [4]. The second lesson to be learned from the use of estrogen receptor measurements as predictive marker in breast cancer is the insight that therapies often do not work even if the 'target' is really there. This challenge of therapy resistance is much more complex than standardization of tests. For estrogen receptor-mediated signaling, a crosstalk between nuclear steroid receptors and growth factor receptors was discovered more than 20 years ago [5]. However, it took many years to develop therapeutic approaches interacting with growth factor signaling pathways that lead to estrogen receptor activation. Currently, we are experiencing relevant progress in endocrine therapy through approaches interacting with these signaling pathways, and several compounds will become available for clinical use within the next years. However, despite the fact that several compounds which target mTOR, PI3K, or CDK4/6 are approved or undergoing clinical development, no useful predictive marker has been established for response prediction so far.

In the field of HER2-postive breast cancer, the great progress is encouraging and has led to clinically relevant improvements in patient outcome. Nevertheless, a similar problem with lacking clinically useful predictive markers is evident in HER2-positive breast cancer. Several treatment options are now available, but there are no predictors allowing the selection between these different therapies.

Finally, the most challenging subgroup of patients are those without an evident 'target' for established therapeutic approaches: those with triple-negative tumors. Here, we have experienced frustratingly few improvements for many years with some patients being almost completely resistant to existing therapies. However, in the last 2 years it has emerged that there may be some light at the end of the tunnel. We have seen reports about remarkable efficacy of platinum compounds, especially in those patients with BRCA 1 or 2 mutations [6]. Also, the development of PARP inhibitors is moving forward after a long pause caused by disappointing results of a phase III trial [7]. In addition, compounds modifying the immune escape of tumor cells show promising results and might open a new perspective in breast cancer treatment [8].

In summary, we have achieved great improvements for our patients within the last years, and many new treatment options are available or undergoing clinical development. Nevertheless, we have to keep in mind that continuous effort to improve our knowledge about tumor biology in order to improve treatment selection

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is needed. In this issue of Breast Care, experts summarize the current status of targeted breast cancer therapy and discuss the perspectives as well as the challenges that must be faced in order to improve patient outcome.

## Disclosure Statement

The authors declare no conflict of interest.

## References


1 Beatson C: On treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment with illustrative cases. Lancet 1896;2:104–107.
2 Jensen EV: Estrogen receptors in hormone-dependent breast cancers. Cancer Res 1975;35:3362–3364.
3 Nagaraj G, Ma C: Revisiting the estrogen receptor pathway and its role in endocrine therapy for postmenopausal women with estrogen receptor-positive metastatic breast cancer. Breast Cancer Res Treat 2015; 150:231–242.
4 McCullough AE, Dell'orto P, Reinholz MM, Gelber RD, Dueck AC, Russo L, Jenkins RB, Andrighetto S, Chen B, Jackisch C, Untch M, Perez EA, Piccart-Gebhart MJ, Viale G: Central pathology laboratory review of HER2 and ER in early breast cancer: an ALTTO trial (BIG 2-06/NCCTG N063D (Alliance)) ring study. Breast Cancer Res Treat 2014;143:485–492.
5 Schiff R, Massarweh SA, Shou J, Bharwani L, Arpino G, Rimawi M, Osborne CK: Advanced concepts in estrogen receptor biology and breast cancer endocrine resistance: implicated role of growth factor signaling and estrogen receptor coregulators. Cancer Chemother Pharmacol 2005;56(suppl 1):10–20.
6 Carey L: Old drugs, new tricks for triple-negative breast cancer. Lancet Oncol 2015;16:357–359.
7 Lord CJ, Tutt AN, Ashworth A: Synthetic lethality and cancer therapy: lessons learned from the development of PARP inhibitors. Annu Rev Med 2015;66:455–470.
8 Ernst B, Anderson KS: Immunotherapy for the treatment of breast cancer. Curr Oncol Rep 2015;17:5.