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Editorial

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Breast Cancer Outcome: What Have We Achieved

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Welcome to this special issue of Breast Care titled "Breast Cancer Outcome: What Have We Achieved" (in the last 30 years), shortly summarized: the past 3 decades have reshaped our understanding and approach to this complex disease.

Early detection, prognosis, and treatment options for patients with early-stage breast cancer have improved significantly. We have seen an unprecedented progress in the development of systemic therapies, the shift from adjuvant to neoadjuvant strategies, particularly in the triple negative (TNBC) and the human epidermal growth factor receptor 2 (HER2+) subtypes, and the establishment of postneoadjuvant therapies for patients failing a pathologic complete response in these two subtypes, but also in luminal B subtype. We have integrated gene signatures into clinical decision-making and are aware of the relevance of preoperative decline of Ki-67 by antihormonal treatment in the luminal B subtype. Advances in early detection and primary prevention of hereditary breast cancer, as well as tremendous changes in the surgical and radiotherapeutic locoregional management, are also key points of our new understanding of breast cancer. The establishment of antibody treatment and antibody-drug conjugates in HER2+ breast cancer has transformed an aggressive subtype to a highly curable disease. The same is true for TNBC with the advent of immunotherapy in addition to standard treatment in the neoadjuvant setting.

Personalized medicine aims to tailor treatment to patients' individual risk. Accordingly, we have established new deescalated and escalated systemic treatment options in the different subtypes. In the luminal B subtype, the WSG-ADAPT-HR+/HER2− trial was the first to combine the 21-gene expression assay (recurrence score) and response to 3-week preoperative endocrine treatment to guide systemic therapy in early breast cancer and spare chemotherapy in pre- and postmenopausal patients with ≤3 involved lymph nodes [1]. The APT trial showed that in low-risk HER2+ breast cancer, 12 cycles with paclitaxel and trastuzumab alone resulted in an outstanding 10-year breast cancer-specific survival of 98.8% [2]. In addition, the recently presented PHERGain trial assessed the feasibility of a chemotherapy-free treatment with a dual HER2+ blockade only by using a PET scan-based judgement of early response after two cycles. This strategy identified about one third of HER2+ early breast cancer patients who may safely omit chemotherapy with significantly reduced toxicity [3]. Despite these impressive results, the omission of chemotherapy in HER2+ responders is not yet standard of care. We must wait for the results of a confirmatory phase III trial, but it is expected that targeted therapy alone will become an accepted treatment option in early HER2+ responders in the near future. Treatment de-escalation also applies to the increasingly popular use of anthracycline-free therapies [4], less radical surgery [5], and less intensive radiation therapy [6]. However, improving therapy requires not only de-escalation but also escalation in certain scenarios.

We know the results of a variety of studies, which have shown that new drugs given in addition to the previous standard of care improve the chance of cure in certain subtypes. The OlympiA trial [7] showed that regardless of hormone receptor expression, breast cancer gene (BRCA) 1/2 + and HER2− patients at increased risk had a significantly longer distant disease-free survival and overall survival when olaparib was given for 1 year after the

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completion of standard therapy [8]. The monarchE [9] trial showed that luminal B patients with ≥4 or 1–3 involved lymph nodes and additional risk factors (T3 tumor and/or G3) have a highly significant benefit of the cyclin-dependent kinase (CDK) 4/6 inhibitor abemaciclib given for 2 years in addition to standard endocrine therapy. At 4 years, the absolute difference in iDFS was 6.4%. Most importantly, the benefit increased beyond the completion of treatment. Results of the NATALEE trial were recently presented at ASCO 2023 [10]. Consistent with monarchE, the NATALEE trial also demonstrated that the addition of ribociclib to aromatase inhibitors improves outcome in early breast cancer. Ribociclib was given for 3 years with a lower dose of 400 mg. In contrast to monarchE, the NATALEE trial also recruited node-negative patients and demonstrated a longer iDFS of 3.3% for both node-positive and node-negative patients.

The monarchE and the NATALEE trial establish a new standard of care in the high-risk luminal subtype by combining endocrine therapy with CDK 4/6 inhibitors. But these results also raise several questions, especially when compared to the WSG-ADAPT-HR+/HER2− trial. 59.9% of the patients in the WSG-ADAPT trial had an endocrine response (78.1% with aromatase inhibitors vs. 41.1% with tamoxifen, $p < 0.001$), and endocrine response was strongly associated with recurrence score. In the endocrine trial without chemotherapy, 5-year iDFS and dDFS were similar for the experimental arm (RS: 12–25 with endocrine response) versus control (RS ≤11) according to nodal status (pN0 and pN1). The NATALEE trial also recruited N0 patients with an increased risk (i.e., G2 and Ki-67 ≥ 20%) without evaluating response to Ki-67 after 3-week preoperative endocrine treatment. Although ribociclib is still pending approval by the European Medicines Agency (EMA) for the treatment of early breast cancer, it does not appear reasonable to treat all patients with node-negative disease and an elevated risk with ribociclib and an aromatase inhibitor in the near future.

The new standard of care for TNBC also represents an escalation of systemic therapy. Having established carboplatin as the fourth chemotherapeutic drug to optimize pathologic complete response and survival in the neoadjuvant setting, we are now combining the four-drug regimen with the checkpoint inhibitor pembrolizumab. Event-free survival at 36 months was 84.5% in the pembrolizumab-chemotherapy group compared to 76.8% in the placebo-chemotherapy group. Most interestingly, patients with moderate residual cancer burden (RCB-II) after completion of neoadjuvant chemotherapy benefit greatly from postneoadjuvant continuation of pembrolizumab [11].

This compilation of five reviews defines the current standard of care and the path to cure. But we also recognize that our journey is far from over. For instance, a recently published trial [12] comparing digital breast tomosynthesis with digital screening mammography for early breast cancer detection showed a significantly higher detection rate with digital tomosynthesis and could become the new standard in screening. In addition, trastuzumab deruxtecan has recently been shown to improve survival compared to physician-directed chemotherapy in HER2-low metastatic breast cancer, which accounts for more than half of our breast cancer patients [13]. The minimum level of HER2− expression required for trastuzumab deruxtecan to be effective is currently being explored in clinical trials and will open up completely new strategies. These studies provide compelling evidence that both diagnosis and treatment can be significantly improved beyond established standards.

These improvements listed above should eventually lead to improved survival. In fact, Caswell-Jin and colleagues recently showed that 10-year survival without recurrence improved from 82.5% in 2000 to 87.3% in 2017 [14]. Survival after diagnosis of metastatic disease also increased, doubling from 1.48 years in 2000 to 2.80 years in 2017, with the best survival for women with ER+HER2+ cancer (4.08 years) and the worst for ER-HER2- (1.22 years). We are fortunate to live in a world where the ever-increasing knowledge of breast cancer molecular oncology is paving the way for new therapies and, ultimately, improved survival for breast cancer patients.

Conflict of Interest Statement

Volker Möbus declares no conflict of interest. Marcus Schmidt reports personal fees from AstraZeneca, BioNTech, Daiichi Sankyo, Eisai, Lilly, MSD, Novartis, Pantarhei Bioscience, Pfizer, Pierre Fabre, Roche, and Seagen. His institution has received research funding from AstraZeneca, BioNTech, Eisai, Genentech, German Breast Group, Novartis, Palleos, Pantarhei Bioscience, Pierre Fabre, and Seagen. In addition, he has a patent for EP 2390370 B1 and a patent for EP 2951317 B1 issued.

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Author Contributions

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