Luminal Breast Cancer: The Head of Janus in Breast Oncology

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About 70% of all invasive breast cancer (BC) cases are associated with expression of estrogen and/or progesterone receptors and are classified as hormone receptor-positive/HER2-negative (luminal) BC corresponding to 1.5 million diagnosed patients and about 300.000 deaths worldwide per year. Early detection, better treatment, and less use of hormone replacement therapy in the last decades led to a decrease of the BC mortality rate in the EU, but overall mortality remains on a stable level due to ageing of the population [1]. The aim of the present issue of *Breast Care* is to spotlight some novel aspects in the management of luminal BC.

Although luminal BC seems to have a better prognosis compared to non-luminal cases with a 5-year survival of 94% (vs. 76% in the HR-/HER2- and 85–90% in HER2+ BC, as an example in the US SEER database due to high-efficacy of adjuvant endocrine therapy; <https://seer.cancer.gov/statfacts/html/breast-subtypes.html>), early and in particular late recurrences in at least 20–25% of the cases remain a clinical challenge. Duration of adjuvant endocrine therapy, impact of ovarian suppression in premenopausal women, significant overtreatment by chemotherapy addition to endocrine therapy, as well as use of CDK 4/6 inhibitors in the metastatic and in the near future also in the adjuvant setting lead to huge scientific discussion.

Krauss and Stickeler [2] have reviewed current standards in the (neo-)adjuvant management of endocrine-sensitive BC as the most important issue in clinical routine affecting millions of women worldwide. Furthermore, they recapitulated current predictive markers for their response, such as Ki-67 course after short-term pre-operative endocrine therapy, as one of the most promising markers in its early efficacy estimation.

Moreover, luminal BC appears rather as a general topic for substantially biologically different cases with dramatically divergent prognosis. On the one hand, it appears to be of significant clinical importance to distinguish between lobular and non-lobular cases as a morphological phenotype of luminal BC to understand different growth and patterns, and to put novel prognostic markers such as gene signatures in the right context. Hence, the review by Erber and Harmann [3] focuses on standards in histological assessment of luminal BC and some pitfalls in the pathological workflow.

On the other hand, relapse risk stratification is of immediate clinical impact to differentiate between low-risk/low-proliferating luminal-A and high-proliferating/high-risk luminal-B cases. Unfortunately, there is no clarity about the optimal method to classify luminal BC, therefore several multigene signatures have been developed in the last years as a surrogate for such a classification. Use of such tests together with classical clinical-pathological factors such as nodal status, tumor size, and age changed clinical routine regarding the use of chemotherapy in addition to endocrine therapy after the release of first prospective trials as TAILORx [4], MINDACT [5], PlanB [6]. Puppe et al. [7] have given a summary on the use of such tools in the clinical routine. Due to various interpretations of the study results, still limited evidence, and/or conflicting results, in some groups of patients (node-positive disease, premenopausal women) this field represents a current debate like few others in oncology.

Furthermore, primary and secondary endocrine resistance in early and metastatic luminal BC remains an unsolved clinical problem. Hartkopf et al. [8] summarized current evidence on resistance mechanisms in HR+/-

HER2+ BC as well as strategies to overcome it by use of CDK 4/6, PI3-K, and mTOR inhibitors with focus on advanced disease. Some of these drugs have significantly changed the course of disease in the metastatic setting. It remains to be seen which of these strategies will be established in the adjuvant treatment of early BC within next years. Adjuvant PALLAS and Monrache trials reported conflicting results by recently presented press releases. Final data presentation is highly awaited by the community. Further studies (e.g., ADAPTcycle) currently investigate

whether some of these drugs may be a suitable substitute for chemotherapy in high-risk early BC after careful patient selection based on Ki-67 decrease after preoperative endocrine therapy and genomic signature (OncotypeDX).

Conflict of Interest Statement

Personal fees: Roche, Novartis, Pfizer, Lilly, MSD, Celgene, Nanostring, Genomic Health, Amgen.

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References

- 1 Malvezzi M, Carioli G, Bertuccio P, Boffetta P, Levi F, La Vecchia C, et al. European cancer mortality predictions for the year 2019 with focus on breast cancer. *Ann Oncol*. 2019 May; 30(5):781–7.
- 2 Krauss K, Stickeler E. Endocrine Therapy in Early Breast Cancer. *Breast Care (Basel)*. 2020; 15(4): <https://doi.org/10.1159/000509362>.
- 3 Erber R, Harman A. Histology of Luminal Breast Cancer. *Breast Care (Basel)*. 2020; 15(4): <https://doi.org/10.1159/000509025>.
- 4 Sparano JA, Gray RJ, Makower DF et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. *New England Journal of Medicine* 2018; 0: null.
- 5 Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, et al.; MINDACT Investigators. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. *N Engl J Med*. 2016 Aug;375(8):717–29.
- 6 Nitz U, Gluz O, Christgen M, Kates RE, Clemens M, Malter W, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. *Breast Cancer Res Treat*. 2017 Oct;165(3): 573–83.
- 7 Puppe J, Seifert T, Eichler C, Pilch H, Mallmann P, Malter W. Genomic Signatures in Luminal Breast Cancer. *Breast Care (Basel)*. 2020; 15(4): <https://doi.org/10.1159/000509846>.
- 8 Hartkopf AD, Grischke EM, Brucker SY. Endocrine Resistant Breast Cancer – Mechanisms and Treatment. *Breast Care (Basel)*. 2020;15(4): <https://doi.org/10.1159/000508675>.