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A Decade of AGO QS-Mamma: Adherence to the Recommendations of the AGO Breast Committee for Diagnosis and Treatment in EBC in Routine Therapy in Germany

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Keywords
Early breast cancer · Biomarker · Guideline adherence · Precision medicine · Quality assurance

Abstract
Introduction: The cure for early breast cancer (EBC) is increasing over the last decades due to the improvement of diagnosis and therapy. Individualization of cancer treatment in EBC requires constant optimization by implementing current guidelines. The AGO (working group gynecologic oncology) QS-Mamma initiative, a quality assurance program (QS) of the AGO Breast Committee, was introduced to provide insight in guideline adherence in real-world practice in Germany. We evaluated 10 years of QS-Mamma data to identify gaps and trends implementing those guidelines. ***Methods:*** QS-Mamma is a retrospective sample survey providing a representative overview of the treatment landscape of breast cancer in Germany. The last six cohorts were analyzed over a period of 10 years. Across all cohorts, an average of 264 centers documented a total of n = 4,577 patients with EBC. ***Results:*** Testing for BRCA mutations in triple-negative patients increased significantly. Breast conserving surgery has been standard of care since the start of data collection; choice of surgical procedure depends primarily on tumor size and nodal status according to the patient's preference, if possible. Axillary intervention has shifted toward SLNE or targeted axillary procedures in patients with negative preoperative nodal staging. Neoadjuvant systemic therapy in operable EBC is established. Anthracycline administration in the adjuvant setting decreases. We noted an uptake on using platinum-containing CTx in TNBC, corresponding to AGO recommendations. Dual HER2 blockade is established in HER2-positive EBC with increased risk of relapse. Changes in guidelines are reflected in real-world data. ***Conclusion:*** Guideline adherence in breast cancer care is high and new treatments and diagnostic options are implemented promptly. Finally, escalation and de-escalation of treatment depend on individual tumor characteristics resulting in the individual risk of recurrence. Guidelines should be flanked by real-world evidence to ensure and survey their impact.

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Introduction

Treatment of EBC is developing toward personalized precision medicine taking the individual risk of recurrence as the basis of treatment recommendation [1]. De-escalation and possible escalation of therapy are therefore closely linked and depend on these risk factors, resulting in the best treatment opportunities and evidence-based individualized treatment options. Consequently, the therapeutic landscape is changing, becoming more diverse and dependent on an increasing number of factors over time.

The biennial quality assurance initiative for the treatment of breast cancer in Germany (QS-Mamma) of the AGO Breast Committee provides a well-founded picture of everyday therapeutic practice in the treatment of early and metastatic breast cancer. Our retrospective collection of real-world data from everyday treatment in German facilities provides information on the implementation and impact of guidelines, treatment shifts, and new therapeutic options. Thus, the development of breast cancer therapy toward personalized precision medicine can be tracked and accompanied – identifying existing gaps.

The data collected will be compared to the AGO Breast Committee guidelines for the diagnosis and treatment of EBC for the corresponding time frame [2]. The rationale of this survey is to examine whether treatment and paradigm shifts that can be recognized in the real-world data correspond to guideline recommendations. It is assumed that the guideline recommendations of the AGO Commission on Breast Cancer are well accepted and implemented despite, or perhaps because of, their annual update.

Methods

QS-Mamma is a retrospective sample survey providing a representative overview of the treatment landscape for all German centers treating breast cancer. The last six cohorts were analyzed, spanning over a period of 10 years. The representative sample size is guaranteed by a care structure analysis (phase 1) performed prior to each cohort. For this purpose, all facilities in Germany that potentially treat patients with breast cancer are contacted by surface mail (mean value across the cohorts, n = 1,815 centers or departments). The average response rate across all cohorts was 26% (n = 472). An average of 35,129 surgical breast procedures per year were reported. In reference to the new cases estimated by the Robert Koch Institute (RKI) [3], this corresponds to a coverage rate of 51%. Considering this high coverage rate, the data are highly valid and representative. Target numbers for patient documentation (phase 2) are based on this care structure data. Participating centers are divided into clusters according to key care parameters (specialty, type of institution, region) and assigned a corresponding number of patients to be documented.

Thus, the real care situation is mapped proportionally and representatively in the sample. This methodology has been successfully applied and published in all cohorts of the QS-Mamma [4] and comparable studies of the AGO [5, 6] as well as the working group of medical oncology (AIO) and the working group on supportive measures in Oncology (AGSMO) [7–10] in the German Cancer Society (DKG). The sample size in EBC was set at approximately 1% of the annual incidence specified by the RKI to ensure valid and reliable analytical results. The survey focuses on patients with increased risk or high treatment pressure to evaluate the current treatment trends for this subset. Inclusion criteria are current treatment line, surgery, and initial diagnosis within the past 6 months: current treatment with chemotherapy (CTx), targeted therapy (TT), immune checkpoint inhibitors, and any combination of those options. Patients receiving solely endocrine therapy (ETx) or osteoprotection are not included in this analysis.

The collected variables include patient characteristics, diagnostic parameters, information on surgery and axillary intervention, as well as the drug-based tumor therapy administered. All data were collected completely anonymously. To avoid selection bias, patients were documented randomly and retrospectively from a predetermined cut-off date (point prevalence). This ensures that the treatment data are based on the current line of treatment. Statistical analysis was performed with R 4.0. The Mann-Whitney-U-Test was used to analyze changes over time between the cohorts if the independent variable was binominally distributed. If the distribution was multinominal, a correlation test was calculated using Spearman's Rho or Kruskal-Wallis test. To address the problem of inflation of type I errors through multiple testing, the p values were adjusted using the Benjamini and Hochberg method to correct for the false discovery rate [11]. Significance level was set at p = 0.05. Where applicable, the STROBE guidelines for cohort studies were followed [12].

Results

Across all cohorts, an average of n = 264 centers documented a total of n = 4,577 patients with EBC; the distribution by molecular subtype is displayed in Figure 1. The documenting centers were distributed across the various types of institutions and specialties treating breast cancer as illustrated in Figure 1. In terms of new cases as documented by the DKG [13], this results in an average coverage rate of 1.37% across the cohorts. The age distribution increases slightly across the cohorts (median:

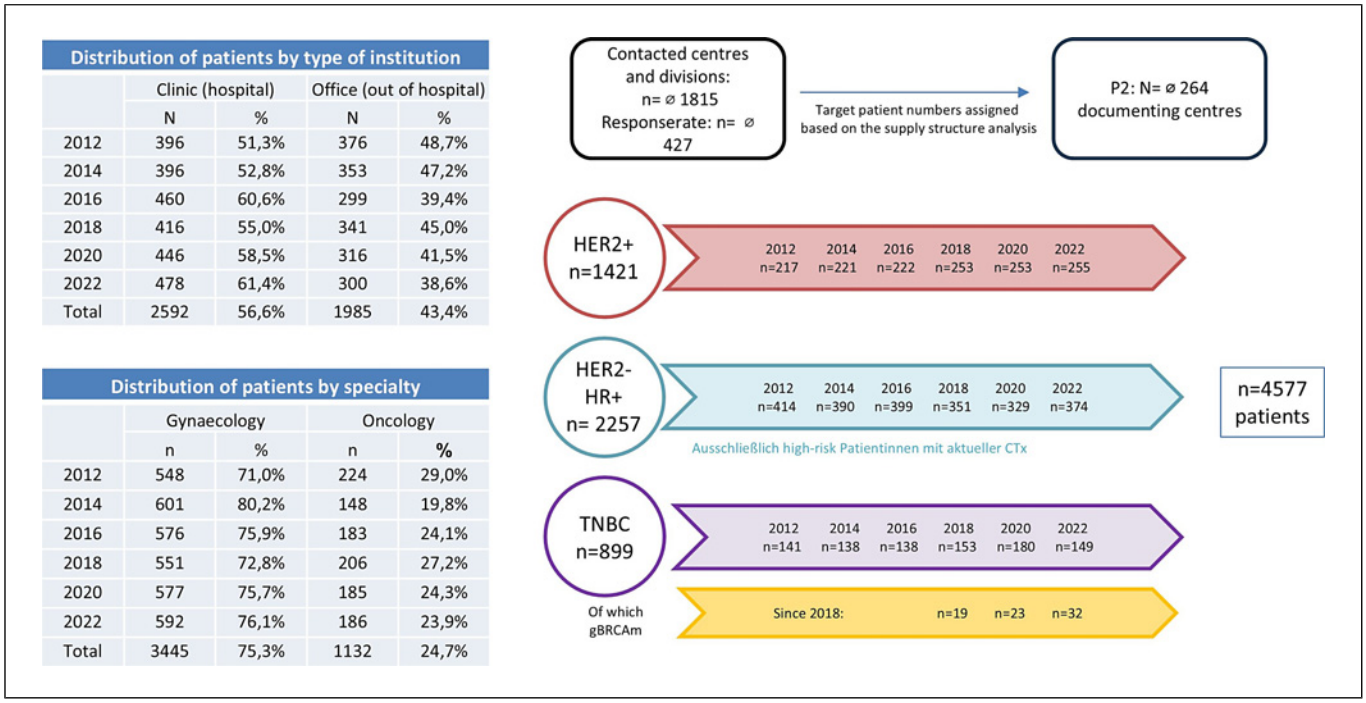

Fig. 1. Inclusion and patient collective, n = 4,577 patients over 6 cohorts.

from 55 in 2012 to 57 in 2022, $p = 0.01$), particularly the share of over 80-year-olds (Fig. 2). The number of patients with secondary carcinoma (from 2% in 2012 to 4.6% in 2022, $p = 0.001$) and patients with a BMI >35 also increased. The share of patients with a Karnofsky-Index >90 increases from 49.6% (2012) to 60.4% (2022) ($p < 0.001$). Identification and documentation of key tumor characteristics has increased over time. For both T and N as well as for UICC stage and grading, the numbers of undocumented or undetermined items decreased to almost 0 (Fig. 2). The proportion of undetermined Ki-67 proliferation dropped from 4.1% in 2014 (first surveyed) to 1.5% in 2022. Testing for BRCA mutations in triple-negative patients increased from 30.2% at the start of the survey in 2016 to 57% in 2022. Primary rationale for testing patients aged 60 and above is the incidence of familial breast cancer ($p < 0.001$). Significant reasons for testing outside the TNBC collective are age and the presence of familial breast cancer ($p < 0.001$). PDL-1 testing is not established in EBC, though a slight increase from 0.7% to 13.4% over the last three cohorts can be observed in TNBC. Other diagnostic tests (PI3K, NTRK, TILs) also do not yet play a decisive role in everyday clinical treatment of EBC. The proportion of multi-gen assays (MGAs) in HER2−/HR+ breast cancer increased from 9.3% in 2014 to 23.8% in 2022. In the relevant segment of patients with N0 or N1, the share of MGAs is 27.8% in 2022.

Breast conserving surgery (BCS) has been the standard of care since the beginning of data collection; mastectomy (MXM) was 23.7% across all cohorts since 2012. The choice of surgical procedure depends primarily on tumor size (BCS 85.3% at T1 vs. 35% at T3 and T4) and nodal status (Fig. 3). MXM was performed in 13.8% of patients with small node negative tumors (T1, N0). BCS was performed in 13.2% of patients presenting with larger tumors (T3 or T4, N3). Relative contraindications for BCS are advanced stage at presentation or very young age, familial breast cancer, very low or very high BMI, and the presence of a BRCA mutation. There is no clear influence of neoadjuvant systemic therapy (NAST) on the type of surgery. Axillary intervention was performed in n = 1,196 patients. We note an increase in sentinel lymph node excision (SLNE) in patients who underwent BCS (Fig. 4). The proportion of patients treated with both SLNE and axillary lymph node dissection (ALND) decreases over time and approaches zero in the BCS segment. ALND is mainly used in patients who have undergone MXM and has been used in around 40% of patients over the years, with a slight increase.

Concerning management of the axilla according to the preoperative nodal status, the prevalence of SLNE is confirmed for patients without nodal involvement (Fig. 4). For patients with positive nodes clinically (cN1), there was a tendency toward SLNE until 2018, which has since reversed. If ALND was performed, the number of lymph nodes removed has decreased since 2012 (<10 nodules from 30.9% in 2012 to 38.5% in 2022).

NAST is established, most notably in the subgroup of HER2+ and TNBC breast cancer. The AGO Breast

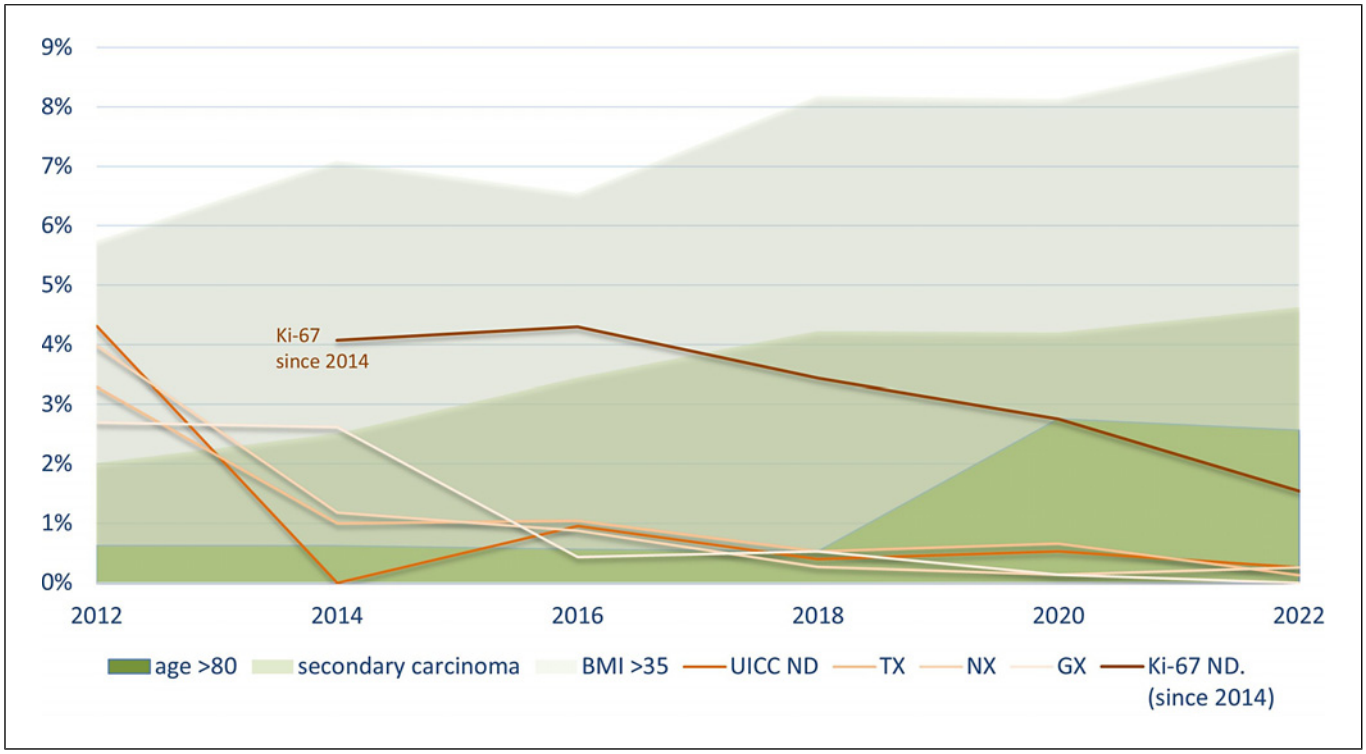

Fig. 2. Key diagnostic parameters, n = 4,577 patients over 6 cohorts.

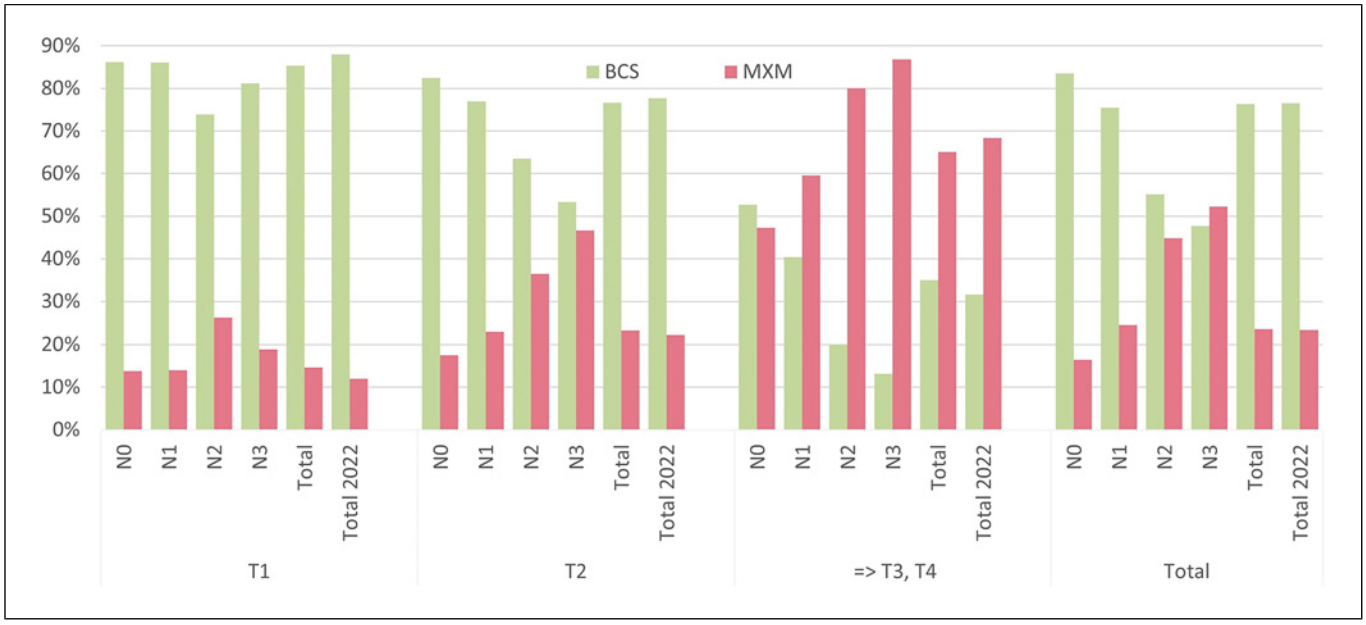

Fig. 3. Operated patients with specification of T and N, n = 3,353.

Committee reviewed their guidelines regarding the neoadjuvant use of platin-based schedules in the TNBC setting in 2016 and anthracycline (AC)-free CTx regimens in the HER2+ setting in 2021. QS-Mamma data demonstrate that AC administration is decreasing, especially in the adjuvant setting (Fig. 5). This decline is particularly prevalent in the HER2+ segment. For HER2−/HR+ and TNBC patients, AC remains an important treatment component, especially in the neoadjuvant setting (97% HER2−/HR+, 91.2% TNBC, 2022). Administration of taxanes is also established in adjuvant therapy. Platinum-containing CTx in TNBC has risen

Fig. 4. Distribution of patients with axillary intervention, type of surgery, and nodal status at presentation, n = 3,282.

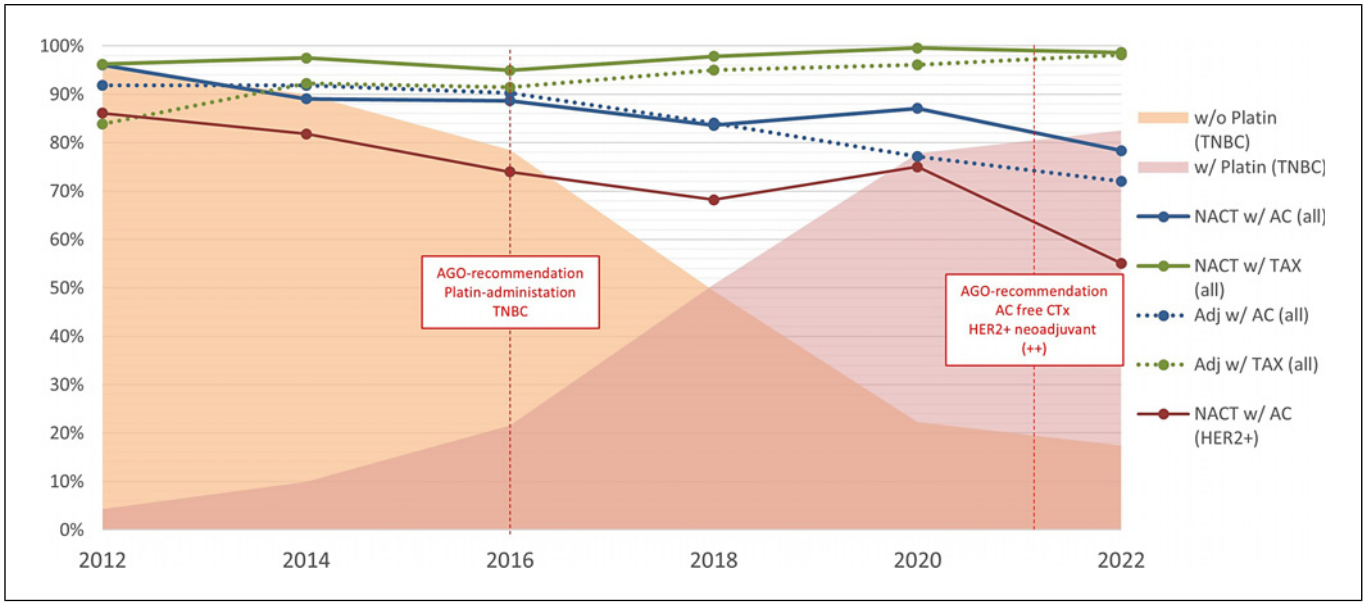

Fig. 5. Patients with CTx over time (2012–2022), n = 4,554.

continuously since 2012 to 83% in 2022 (Fig. 5). In the neoadjuvant segment, this proportion has increased up to 87.2%. In the HER2+ segment, platinum administration peaks up to 30.7% in the neoadjuvant setting in 2022 but not in HER2−/HR+ EBC.

The additional use of pertuzumab (PER) in HER2+ EBC has increased rapidly since its approval in the neoadjuvant setting and has been established since 2016. In the adjuvant setting, the proportion of PER increases from 2016 to 2018 and then gradually decreases again

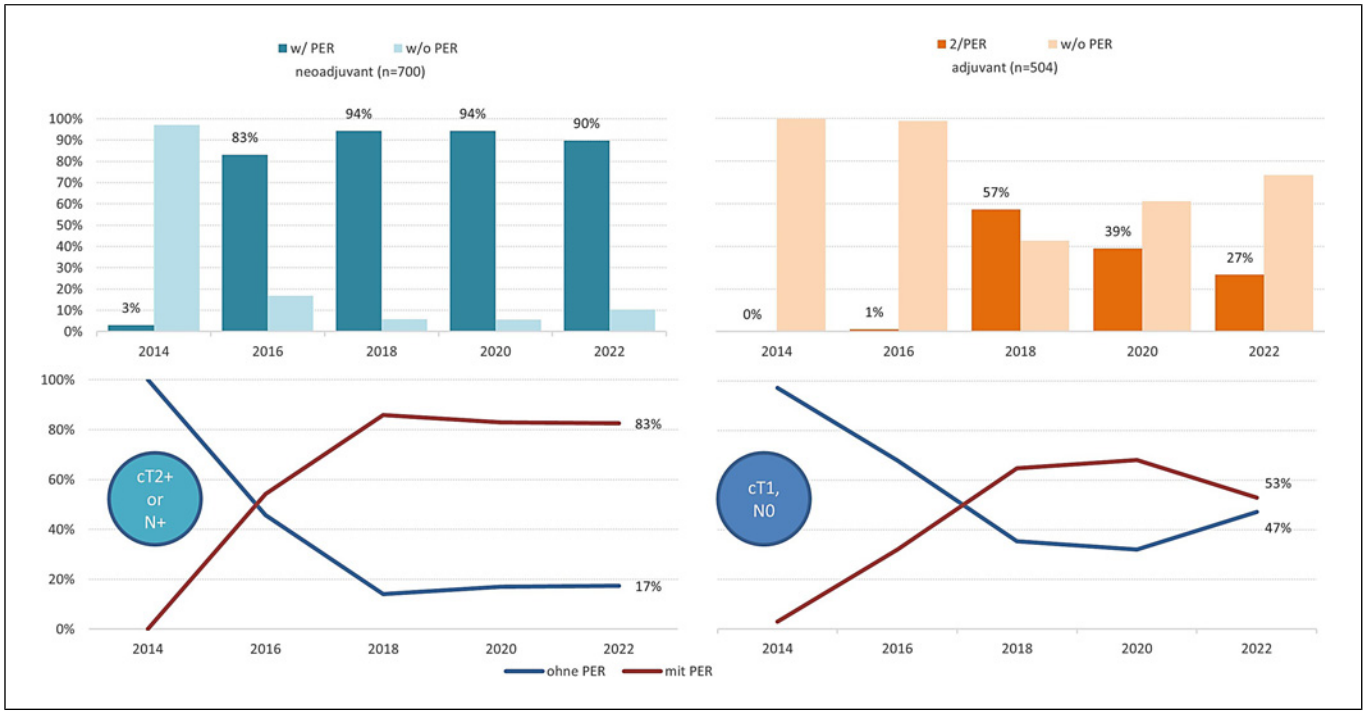

Fig. 6. Treatment in patients with HER2+ EBC, use of trastuzumab +/− PER, n = 1,204.

(Fig. 6). For patients presenting with cT2+ or N+ EBC, a significant increase in PER administration was noted in accordance with the growing evidence from the APHINITY trial [14]. Likewise, and in contrast to this, proportion of patients with cT1, N0 EBC receiving dual HER2 blockade increased from 2014 to 2020 (68.1%); but due to the more robust data from the APT trial, we observed a decline to 52.8% in 2022 in accordance to the AGO treatment recommendation [15]. There are not yet reliable data available on the use of pembrolizumab in eTNBC nor for abemaciclib in HER2−/HR+ patients. Due to our inclusion criteria, ETx in this patient population mostly comprises planned ETx after CTx. In the population of pre- and perimenopausal patients, the proportion of pure tamoxifen administration has been decreasing since 2014 (93%) to 50% in 2022. Complementarily, the proportion of aromatase inhibitors (AIs) use increases both alone and in combination with tamoxifen. In the postmenopausal subgroup, the use of AI has become increasingly prevalent since 2016, reaching 78% alone and 94% overall in 2022.

Discussion

The QS-Mamma data provide a representative insight into the treatment landscape for EBC in Germany. This is of great value for the review and adherence of the annual update of evidence-based guidelines of the AGO Breast Committee: the data analyzed here is a cross-section of the treatment landscape that is not limited to certified breast cancer centers and/or patients treated in clinical trials. Noncertified breast cancer centers were also included in this analysis to reflect actual day-to-day clinical practice. Since guideline recommendations apply to the entire treatment landscape, insight into the day-to-day treatment of EBC is indispensable for ensuring a high quality of care.

The determination and documentation of key diagnostic and prognostic markers and tumor characteristics has reached almost 100% over the last decade. From the decision on NAST to the exact sequence of TT, clinical decisions are dependent on treatment-related key parameters such as molecular subtype, TNM, and Ki-67. These factors are tested and used for therapy decision-making, routinely. The completeness of this information across all specialties and types of institution is a basic prerequisite for the implementation of evidence-based treatment, which allows increasingly individualized treatment decisions based on guidelines.

The uptake of testing for BRCA germline mutation, with a focus on TNBC in recent years, is an important indicator for the adherence to the guidelines. This is not only a "biomarker" for the application of PARP inhibitors (PARPis) but also an important indicator for non-affected family members to initiate counseling and/or genetic testing or to start specific diagnostic procedures in specialized centers for familiar breast and/or ovarian cancer supported by the German Cancer Help (DKH). Since patients over the age of 60 can also benefit from

BRCA testing and BRCAm-based therapy with PARPi, cost coverage and prospective benefit of BRCA germline mutation testing must be clarified. The approval of olaparib in EBC further emphasizes the need for comprehensive BRCAm testing for all patients who are eligible for olaparib therapy. Patients in the HER2−/HR+ subsegment with an increased risk of recurrence should therefore also be routinely counseled and tested for a germline BRCA mutation in the future [16]. The wider use of MGAs in the HER2−/HR+ subsegment with N0 – N1 EBC demonstrates that these tests are being used in line with the guidelines [2]. The use of MGAs in the HER2−/HR+ subgroup is an important functional test to avoid unnecessary toxicity by avoiding CTx if not needed. In terms of increasing individualization of the treatment decision, an even higher use of prognostic tests would therefore be desirable [17, 18].

In local therapy, increasing de-escalation (BCS, SLNE, fewer LN in ALND) can be observed as standard therapy. Guideline recommendations are implemented promptly here: the adoption of BCS as the standard has been enforced, SLNE has been implemented quickly and across the board, and the change in the AGO recommendation on SLNE for N+ (from neutral mention in 2016 to no mention in 2018 [2]) can be tracked promptly in everyday clinical practice. Currently, the implementation of TAD is not yet evident in the available QS-Mamma data but presumably will be in further analysis.

AGO recommendations on CTx were implemented promptly. Platinum-based CTx in TNBC has been established since 2012, and we have seen good guideline adherence to the AGO recommendation on platinum administration since 2016 [2].

AC-free CTx in neoadjuvant HER2-positive breast cancer has been recommended by the AGO as an equivalent treatment option since 2021 (++, indicating that this investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restriction and should be performed) and is preferred to treatment with AC in the 2022 guideline recommendations [2]. This development can also be observed as a timely shift from 2020 to 2022 (Fig. 5). In clinical practice, toxicity and the patient's resilience likely play a decisive role here. The follow-up of the TRAIN-2 study suggests that the survival data for both treatment strategies are on par. This means that the choice of CTx can be individualized based on equally ranked treatment options [19, 20].

Neoadjuvant dual HER2 blockade has been established since authorization in 2016. It should be noted that the conditions and modalities of the guideline recommendation have changed over the years. While dual blockade was still recommended in 2016 with (+) as a lower priority than TRS with CTx (++), the two treatment options were already categorized equally in 2018 and from 2021 onward, there was a specific recommendation to favor dual blockade in patients with high-risk of recurrence (cT2–4 and/or cN+). Thus, this has overruled the recommendation of TRS + combination CTx for low-risk patients with T1 and cN0, reducing toxicity by offering an AC-free CTx in EBC. This rapid and timely change in recommendations due to change of evidence shows the importance of a "living guideline" offering annual updates. The collected real-world data demonstrate that the switch from T2 and/or N+, which has been specified in the treatment algorithms of the AGO Breast Committee since 2021, has implemented a rapid treatment change including a new standard of care. There appears to be a trend toward the guideline-compliant use of dual HER2 blockade. Still, the share of patients with cT1N0 tumors receiving dual blockade as part of a neoadjuvant treatment strategy remained over 50% in 2022. This may indicate overtreatment not only regarding PER but also regarding the chosen CTx setting. In adjuvant treatment, the proportion of PER decreased since 2018, which suggests that adjuvant dual blockade has been accepted as overtreatment or that patients with high-risk disease have been treated in a neoadjuvant setting. This confirms that guideline recommendations should be flanked by real-world evidence to identify gaps in implementation but also to be able to review and challenge the guideline if necessary.

Although the available real-life data include only patients with an increased risk of relapse who were currently receiving CTx, immune checkpoint inhibitors, or TT, we also have some important information on ETx in EBC (data not shown) demonstrating the incorporation of the existing evidence to favor a sequential therapy of tamoxifen followed by an AI for the duration of 5 years, generally avoiding overtreatment with 5 years of AIs [2]. The data from a decade of QS-Mamma are a reliable indicator to demonstrate the adherence to clinical guidelines.

Conclusion

This analysis shows that diagnosis and treatment of early breast cancer in Germany has improved substantially due to an impressive adherence to the guidelines of the Breast Committee for Diagnosis and Treatment over the last decade. We have identified several indicators for this finding, such as the rapid incorporation of sentinel lymph node biopsy to abandon the classical ALND and, further down the road, implement targeted lymph node dissection in node negative disease. Due to new therapy options, HER2-positive EBC has been transformed from an

aggressive subtype into a more curable disease, optimizing the use of neoadjuvant systemic therapy if indicated in tumors larger than 2 cm in size and/or node positive tumors. On the other hand, the adherence to these guidelines implements a de-escalation in the use of ACs and dual blockade with trastuzumab and PER in node negative HER2 overexpressing EBC with tumors being smaller than 2 cm. We are pleased to note that, based on these recommendations, the utilization of MGAs is improving, reducing unnecessary CTx in endocrine-responsive ER+ EBC if the individual risk of recurrence demonstrates that CTx over ETx alone is not indicated. In triple-negative EBC, new treatment options including new drugs are likewise optimizing the outcome. We alluded to the fact that the use of checkpoint inhibitors is increasing along with the label. Likewise, the implementation of BRCA1/2 testing in TNBC is increasing, optimizing the option for PARPi use if indicated. Thus, recent treatment strategies based on the individual risk of recurrence including patient's preferences are key for de-escalation strategies optimizing patient's outcome.

Our analysis demonstrates that there is room for improvement in the use of genetic testing, e.g., in endocrine responsive disease, to identify new treatment options for the patients and their unaffected family members. In the future, the utilization of genetic testing and functional biomarker tests should be increased according to the recommendations of the AGO Breast Committee.

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Statement of Ethics

An opinion has been obtained from the Ethics Committee of Hessen, Frankfurt/Main, Germany, in accordance with the guidelines and recommendations for ensuring Good Epidemiological Practice (GEP). Due to the nature of the study, no additional opinions from Ethics Committees were required. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent from participants was not required in accordance with local/national guidelines.

Conflict of Interest Statement

Christian Jackisch: honoraria from AstraZeneca, Novartis, Roche, Pfizer, Lilly, Gilead, Seagen, and Exact Sciences; travel funds by AstraZeneca, Novartis, Roche, Pfizer, Lilly, Gilead, Seagen, and Exact Sciences; and member of the AGO Breast Cancer Treatment Task Force. Wolfgang Janni: grants, consulting fees, honoraria, and travel funds from AstraZeneca, Cellgene, Chugai, DaiichiSankyo, Eisai, Exact Sciences, GSK, Janssen, Lilly, Menarini, MSD, Novartis, Sanofi-Aventis, Roche, Pfizer, Seagen, Gilead, Inivata, and Guardant Health and speaker of AGO Commission Mamma. Volkmar Müller: honoraria from AstraZeneca, Daiichi-Sankyo, Eisai, Pfizer, MSD, Medac, Novartis, Roche, Seagen, Onkowissen, high5 Oncology, Lilly, Medscape, Gilead, Pierre Fabre, and iMED Institut; consulting fees: Roche, Pierre Fabre, PINK, ClinSol, Novartis, MSD, Daiichi-Sankyo, Eisai, Lilly, Seagen, Gilead, and Stemline; travel funds: AstraZeneca, Roche, Pfizer, Daiichi Sankyo, and Gilead; and institutional research support: Novartis, Roche, Seagen, Genentech, and AstraZeneca. Jalid Sehouli: grants from Roche, MSD, GSK, Tesaro, AstraZeneca, MSD, Eisai, Merck, and Novocure; consulting fees from Immunogen, Incyte, GSK, AstraZeneca, Clovis, Novocure, MSD Eisai, and Merck; honoraria from Immunogen, Incyte, GSK, AstraZeneca, Clovis, Novocure, Bristol Myers Squibb, Eisai, and Novartis; travel support from GSK, AstraZeneca, Roche, Novocure, Immunogen, Incyte, MSD, and Eisei; advisory board for Immunogen, Incyte, GSK, AstraZeneca, Clovis, Novocure, Bristol Myers Squibb, MSD, Merck, Bayer, and PharmaMar; and leadership roles for ENGAGE, ESGO, ASCO, ESGO, GCIG, Deutsche Stiftung Eierstockkrebs, and AGO. Athanasios Argyriadis does not declare any conflicts of interest. Andreas Jaeger, Patrik Lindenmaier, and Sabine Predehl all work for MMF Research GmbH. The institute received research funds from AstraZeneca, GSK, Merck Healthcare, MSD, Janssen-Cilag, Pharmacosmos, Roche, Takeda, Stemline, Daiichi Sankyo, Pfizer, Stiftung Endometrioseforschung, and AGO study group.

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Author Contributions

All authors contributed to the study conception and design. A.J., P.L., and S.P. performed material preparation, data collection, and analysis. C.J., A.J., and A.A. conceived initial draft and idea. P.L. wrote the first draft. All authors commented on previous versions of the manuscript and provided passages of this final version. All authors read and approved the final manuscript. C.J. is principal investigator of all cohorts of this study. V.M. and W.J. as speakers of the AGO are initiators of the study.

Data Availability Statement

The funding sources had no access to the data and were not involved in data analysis or writing of the manuscript. Authors confirm that they have full control over all primary data and agree to allow the journal to review their data if requested.

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