Update Breast Cancer 2018 (Part 1) – Primary Breast Cancer and Biomarkers

Update Mammakarzinom 2018 (Teil 1) – primäres Mammakarzinom und Biomarker

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Key words
breast cancer, treatment/therapy, local recurrence, trials, prognostic factors, predictive factors

Schlüsselwörter
Mammakarzinom, Behandlung, Lokalrezidiv, Studien, Prognosefaktoren, Prädiktivfaktoren

received 19.1.2018
revised 24.1.2018
accepted 24.1.2018

Bibliography
DOI https://doi.org/10.1055/s-0044-101613
Geburtsh Frauenheilk 2018; 78: 237–245 © Georg Thieme Verlag KG Stuttgart · New York | ISSN 0016-5751

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Deutsche Version unter:
https://doi.org/10.1055/s-0044-101613

ABSTRACT
This summary provides an overview of how new therapies or new aspects of established therapies relate to the latest findings. Neoadjuvant therapy, local therapy, new aspects of systemic therapy, and prognostic and predictive factors are presented. In the neoadjuvant setting, the association between pathological complete response (pCR) and prognosis is still of interest as is the identification of new molecular predictors.
for new therapies such as CDK4/6 inhibitors. As regards surgical treatment, the target is still to reduce the aggressiveness of surgery. To achieve this, a better understanding particularly of ductal carcinoma in situ is required. With regard to systemic therapy, more data on the best combinations and therapy sequences for existing therapies is available. Finally, the use of prognostic and predictive factors may help to avoid overtreatment and ensure that patients only receive therapies which have been shown to be effective for their specific condition and have fewer side effects.

**ZUSAMMENFASSUNG**

In dieser Übersichtsarbeit wird dargestellt, wie neue Therapien oder neue Aspekte etablierter Therapien in Zusammenhang mit neuesten, aktuellen Erkenntnissen stehen. Neoadjuvant ist nach wie vor der Zusammenhang zwischen pCR und Prognose von Interesse, ebenso wie neue molekulare Prädiktoren für neue Therapien wie CDK4/6-Inhibitoren zu identifizieren. Bei der operativen Behandlung wird weiter nach einer Reduktion der Aggressivität gestrebt. Insbesondere das duktales Carcinoma in situ muss dafür noch besser verstanden werden. Bei den Systemtherapien wächst die Dauerlage zum Verständnis der besten Kombinationen und Therapieabläufe für bestehende Therapieverfahren. Letztendlich muss mithilfe von Prognose- und Prädiktivfaktoren vermieden werden, dass Übertherapien stattfinden und nur die Patientin spezifische Therapien erhält, welche bei dieser individuellen Patientin eine nachgewiesene Wirksamkeit mit wenig Nebenwirkungen haben.

**Introduction**

In recent decades a number of major medical advances have improved the treatment of primary breast cancer [1 – 3]. Particularly the attempts to create targeted therapies for molecular subgroups appear to be very promising; the goal is to be as effective as possible while keeping side effects to a minimum and only treating patients who will actually benefit from a specific therapy. A few studies carried out in an adjuvant setting and which included tens of thousands of patients were unable to show a prognostic benefit, indicating that there is still a long way to go. A better understanding of prognostic and predictive factors would be useful to plan new intelligent studies.

The basic treatment approaches for primary breast cancer and the prognostic and predictive factors based on recently published studies and on data presented at recent conferences (including the San Antonio Breast Cancer Symposium 2017) are discussed in more detail below.

**Neoadjuvant Therapy of Primary Breast Cancer**

Neoadjuvant therapy has become the standard therapy to treat early breast cancer in certain patient groups [4], although numerous issues are still being investigated in ongoing studies, including the issue of predictive markers [5, 6], the choice of the right chemotherapy, and the integration of biological therapies [2, 7]. A recently published meta-analysis which compared patients who received neoadjuvant therapy with patients who received adjuvant therapy was able to show that overall survival did not differ between groups and that neoadjuvant therapy offered results equal to those for adjuvant therapy. However patients who underwent neoadjuvant therapy based on historic criteria appear to have a higher risk of local recurrence if they undergo breast-conserving therapy (BCT) [8], although it is not clear whether these findings are transferable to patients treated in accordance with the most recent criteria.

**Predictive factors for anti-HER2 therapy in the neoadjuvant setting**

In a recent analysis of the NeoALTTO trial which reported that the pathological complete response (pCR) rate almost doubled following the addition of lapatinib to trastuzumab, the question of predicting the pCR and event-free survival (EFS) based on CNAs (copy number alterations) was investigated. The results were not surprising as it is the reason why HER2 expression has a higher impact on pCR than its amplification. The higher genomic instability of hormone receptor-positive tumors predicts the higher pCR rate. No specific gene or gene region was identified which would allow EFS to be predicted [9]. New findings on the association between pCR and invasive event-free survival (iDFS) are also available from another study, the CALBG 40601 trial, which looked at a combination of lapatinib and trastuzumab in the neoadjuvant setting. Although the addition of lapatinib only had a marginal impact on pCR, the study found a significant benefit with regard to iDFS. Patients classified as luminal A had the most favorable prognosis. Immune activation as measured by an RNA signature was found to be an independent predictive factor for both pCR and iDFS [10].

**Association between pCR and prognosis**

An analysis of the I-SPY2 platform trial which investigated the association between pCR and EFS and distant disease-free survival (DDFS) has provided an important data on prediction in the neo-adjuvant setting, a topic which has been the subject of ongoing debates since the publication of two landmark articles [11, 12]. The analysis showed a significant association between pCR and the survival variables EFS and DDFS, which was present irrespective of the biological subtype or type of therapy. These data once again confirm that the decision by regulatory authorities in both the USA and Europe to take pCR as the endpoint for the expedited approval of new drugs was and is the right one [13]. This was also convincingly confirmed by a recently published analysis from the GeparSepto trial, which showed that the significant pCR benefit resulting from the substitution of weekly paclitaxel by weekly
nab-paclitaxel (which had already been reported in 2016) has now also translated into a significant survival benefit [14].

**CDK4/6 inhibitors in the neoadjuvant setting**

The neoadjuvant NeoMONARCH trial [15, 16] investigated a chemotherapy-free combination of the CDK4/6 inhibitor abemaciclib and the aromatase inhibitor anastrozole compared to either abemaciclib alone or anastrozole alone. The primary endpoint was a drop in Ki-67 as the parameter for proliferation activity after 14 days of therapy, with values determined by repeat punch biopsy. Both the abemaciclib combined with anastrozole and abemaciclib alone resulted in a stronger drop in Ki-67 compared to anastrozole alone. This was also found to be correlated with clinical response after 16 weeks, indicating that the combination of an aromatase inhibitor and a CDK4/6 inhibitor could be a promising option for neoadjuvant endocrine therapy. The most common side effect of abemaciclib was diarrhea with an incidence of 61.4%, although only 4.9% of cases had grade 3 diarrhea [17].

**Loco-regional Therapy of Primary Breast Cancer**

**More precise assessment of the role of resection margins**

In breast-conserving surgery (BCT), complete removal of the tumor is the precondition for a low risk of local recurrence. But the question about the optimal resection margin is controversial and still debated. Both the current S3-guideline and the guideline of the American Society of Oncology (ASCO) consider resection to be sufficient if no tumor tissue is verifiable on the inked edge on the surface of the specimen (“no ink on tumor”) [18]. This view is primarily based on a meta-analysis from 2014 which included a total of 33 individual studies [19]. A more recent meta-analysis [20], which included a total of 38 individual studies and data from more than 55,000 patients, confirmed that the rate of local recurrence depends on the resection status (R0, i.e. “no ink on tumor”: 3.8% vs. R1: 10.3%). However, compared to the findings of the previous meta-analysis, the rate of local recurrence appears to decrease as the margin increases: while the rate of local recurrence was 7.2% for resection margins of 0–2 mm, the rate of recurrence was only 3.6% for margins of 2–5 mm and 3.2% for margins >5 mm. Based on the limited validity of retrospective meta-analyses more prospective studies will be needed to answer the question about the optimum resection margin in the context of the respective tumor biology, modern preoperative diagnostic procedures, and adjuvant systemic therapy.

**Further decrease in aggressive axillary surgery probable**

Since the results of the ASOG Z0011 trial, it is generally accepted that pT1c/pT2/cN0 patients who undergo breast-conserving surgery followed by radiotherapy should not undergo secondary axillary lymph node dissection (ALNE), even if a maximum of two sentinel lymph nodes are affected [21]. The IBCSG 23-01 trial, a prospective randomized study, investigated whether it was feasible to dispense with subsequent ALNE in patients with micro-metastasis (≥2 mm) in one or more sentinel lymph nodes [22]. After a median follow-up of 9.8 years, no difference was found with regard to disease-free or overall survival. The findings of the IBCSG 23-01 trial therefore confirm the results of the Z0011 study and the oncological safety of de-escalating axillary lymph node surgery.

**Identification of DCIS patients for anti-hormone therapy**

Estrogen is one of the mediators of tumor growth and metastasis. Anti-estrogen therapy, for example with letrozole, is known to stop tumor growth in invasive carcinoma [23]. But such data are not available for patients with ductal carcinoma in situ (DCIS), although the question of whether patients with DCIS should receive anti-hormone therapy and if so, which patients with DCIS should receive it, is currently being discussed. A recent single-arm phase-II trial (CALGB 40903) investigated outcomes after a 6-month therapy with letrozole in a preoperative setting in 55 patients with estrogen receptor-positive (>1% positive cells in immunohistochemistry) DCIS [24]. The aim of the study was to identify those subgroups who would benefit most from systemic anti-hormone therapy. The selected dependent variable was a lesion with a diameter of between 1 and 7 cm, measurable with MRI. After 3 months of therapy, the average tumor volume as measured with MRI had decreased by 33% (37% volume reduction after 6 months). Moreover, over the course of the treatment the expression of estrogen and progesterone receptors and concentrations of the proliferation marker Ki-67 in the tumor were also lower. The study shows that monitoring these biomarkers would offer an ideal basis for identifying patients who would respond to therapy.

**New Aspects of Systemic Therapy for Primary Breast Cancer**

In addition to developing new therapies and carrying out large therapeutic trials, new aspects of existing therapies are increasingly being investigated as they could help to optimize established therapy regimens, either through introducing prognostic or predictive factors, simplifying therapy regimens, or avoiding side effects.

**Changes in Ki-67 concentrations as a predictive marker in anti-hormone therapy**

The preliminary findings of the CALGB 40903 DCIS trial were already available for invasive breast cancer [25, 26]. The fact that treatment with aromatase inhibitors reduces Ki-67 levels after 2 weeks in certain patients begs the question whether the reduction measured after two weeks represents a predictive marker for the efficacy of the anti-hormone therapy. This question was investigated in the POETIC trial [27]. The trial randomized 4480 patients. One group received two weeks’ treatment with an aromatase inhibitor prior to surgery, the other group did not receive preoperative therapy. Patients in both groups underwent biopsy two weeks before surgery to compare Ki-67 concentrations in the punch biopsy and at surgery. The study confirmed that the aro-
Matase inhibitor down-regulated the expression of Ki-67 [27]. The recurrence rate of patients in whom anti-hormone therapy was unable to down-regulate the expression of Ki-67 was approximately 20%. Given the magnitude of this figure it remains to be seen whether this form of testing is likely to prevail against multi-gene testing.

GnRH confirmed as ovarian protector during chemotherapy

As more and more patients with a good prognosis are identified, interest is increasingly focusing on the side effects of treatment. One of these side effects is the toxicity associated with chemotherapy and its impact on the ovaries of young women who want to have children. One strategy to minimize side effects consists of administering GnRH analogues simultaneously with chemotherapy. This administration is believed to protect the ovaries during chemotherapy. The data of 873 patients from 5 prospective randomized studies were included in a meta-analysis. The meta-analysis showed that the rate of chemotherapy-induced premature ovarian insufficiency was significantly lower in patients who were treated with GnRH analogues compared with women who did not receive GnRH analogues (14.1 vs. 30.9%). The pregnancy rate in the GnRH-treated group was also significantly higher (10.3 vs. 5.5%) [28]. The investigated prognostic parameters showed no differences between the two groups, indicating that oncological safety did not appear to be compromised by the additional administration of GnRH analogues.

In view of these findings, predictors that show which women have a particularly high risk of chemotherapy-induced premature ovarian insufficiency could be useful when deciding whether to administer additional treatment with a GnRH analogue. Potential predictors currently being discussed include anti-Müllerian hormone (AMH) [29] or genetic germline cell variants associated with age at menarche and menopause [30–33].

Increasing the dose density in adjuvant chemotherapy reduces the rate of recurrence and mortality

An EBCTCG meta-analysis of 21 000 patients from 16 randomized studies investigated the effect of increasing the dose density in adjuvant chemotherapy [34]. Irrespective of whether the dose density was increased by shortening the intervals between courses or by the simultaneous administration of anthracyclines and taxanes, an increased dose density significantly reduced the rate of recurrence and mortality.

Treatment of Primary Hormone Receptor-positive HER2-negative Breast Cancer

Ovarian suppression and aromatase inhibitors optimal for premenopausal patients?

The optimal anti-endocrine treatment for patients with primary breast cancer is still debated. The question here was whether treatment with an aromatase inhibitor and ovarian function suppression (OFS) is adequate to treat premenopausal, hormone receptor-positive patients or whether they should receive tamoxifen. The first analysis of the SOFT and TEXT trials (▶ Fig. 1) showed that breast cancer patients in all subgroups did not benefit from OFS [35]. After a follow-up of 8 years a more recent analysis was published. After the long observation period, a benefit of OFS in terms of recurrence-free survival and overall survival was demonstrated for premenopausal patients compared with patients who did not have OFS. In absolute terms, overall survival improved by 1.9% in the general patient population and by 4.2% in the group of patients who had a high risk of recurrence and received therapy with tamoxifen and OFS [36]. These data could be clinically relevant insofar as OFS could be offered to patients with a high risk of recurrence. In recent years, these patients were in-
creasingly less likely to undergo OFS because of the inconsistent data and because no improvement in overall survival had been reported. The analysis with the longer follow-up was also able to confirm that treatment with an aromatase inhibitor combined with OFS resulted in a better prognosis than treatment with tamoxifen combined with OFS. The absolute improvement in recurrence-free survival was 4% [36]. Even greater effects were reported for the group of very young women and for the group treated with chemotherapy. However, this still did not translate into a benefit in terms of overall survival. Patients who undergo OFS require careful monitoring with regard to side effects. After one year, 19% of patients who had OFS terminated the treatment compared with 6% of patients who did not undergo OFS [36].

Is extended therapy with an aromatase inhibitor for 2 years after 5 years of anti-hormone therapy sufficient?

When treating postmenopausal patients with primary hormone receptor-positive breast cancer, studies were able to show that treatment with an aromatase inhibitor following 5 years of therapy with tamoxifen led to an improvement in recurrence-free survival [37]. The optimal duration of this so-called extended anti-hormone therapy is still a matter of debate [38], particularly as the published data are inconsistent [38–42]. An Austrian study on this issue was recently published (▶ Fig. 2) [43]. The ABCSG-16 trial randomized 3494 postmenopausal patients with primary hormone receptor-positive breast cancer who had already undergone 5 years’ treatment with tamoxifen or a sequence of tamoxifen and an aromatase inhibitor or an up-front aromatase inhibitor either into a therapy arm to receive an aromatase inhibitor for 2 years or a therapy arm to receive an aromatase inhibitor for 5 years. No differences were found between the two groups with regard to recurrence-free survival, overall survival, time to second primary cancer or time to contralateral breast cancer [43]. However, the rate of bone fractures was significantly higher in the group of patients who received an aromatase inhibitor for an additional 5 years (6 vs. 4%) [43]. These data support the suggestion that 2 years of extended therapy following 5 years of endocrine treatment should be sufficient to have an impact on prognosis. As the data remains inconsistent, a meta-analysis would be useful.

Treatment of Primary HER2-positive Breast Cancer

Duration of trastuzumab therapy – nothing has changed

The treatment of HER2-positive patients with early breast cancer includes the administration of trastuzumab over a total period of 12 months. The HERA trial showed that patients derived no additional benefit from extending the administration of trastuzumab to 24 months [44]. However, the duration of treatment has not been determined empirically. This therefore begged the question whether shorter treatment times might not be just as effective as the standard treatment time. The French PHARE trial carried out a non-inferiority study into the adjuvant administration of trastuzumab for a period of only 6 months compared to the standard therapy of 12 months but failed to show that 6 months’ treatment was non-inferior [45]. However there were indications that the benefit of a 12-month treatment was largely limited to those patients who received trastuzumab sequentially with chemotherapy. The explanation for this could be that a synergy effect is created by the parallel administration of trastuzumab and taxanes [46]. The SOLE study [47] therefore set out to investigate whether, after receiving a short trastuzumab therapy of nine weeks in parallel to chemotherapy with docetaxel (3 cycles of 80 or 100 mg/m² every three weeks), it would be possible to then dispense with further trastuzumab therapy. All patients additionally received anthracycline-based therapy with F600/E75/C600 and adjuvant radiotherapy and/or adjuvant endocrine therapy for at least 5 years, depending on the indication. A total of 2176 patients were included in the study. After a mean follow-up of 5 years, the primary endpoint (non-inferiority of 9 weeks treatment with trastuzumab with
regard to disease-free survival) was not achieved (after 5 years, 90.5% of patients who received trastuzumab for 12 months were disease-free compared to only 88.0% of patients who received trastuzumab for 9 weeks; HR: 1.39; 90% CI: 1.12–1.72). Treatment with trastuzumab over a total of 12 months therefore remains the standard approach. Interesting, the subgroup analysis again appeared to show a synergy effect with regard to taxane-based chemotherapy: patients who received docetaxel at a dose of just 80 mg/m² benefited most from the 12 month treatment. Further prospective studies are therefore required to investigate the optimal doses for taxane-based treatment when combined with HER2-targeted therapy.

**Biosimilars of trastuzumab – the data is getting stronger**

Now that the patent has expired, several biosimilars of trastuzumab are available for HER2-targeted therapies [2]. The molecular structure of these substances is not entirely identical to that of the original active agent. This means that, in contrast to classic generic drugs, more expensive approval procedures are required before these products will be generally available. A biosimilar should not show any significant clinical difference in terms of quality, efficacy and safety compared to the original active ingredient. In a randomized double-blinded study, the biosimilar ABP-980 was compared with the original trastuzumab to treat patients with early, non-metastatic, HER2-positive breast cancer. The study consisted of a neoadjuvant phase (4 cycles combined with paclitaxel) and an adjuvant phase (continuation of the HER2-targeted therapy for up to one year). The data for the neoadjuvant phase were already presented at the 2017 ESMO conference; no differences were found with regard to efficacy (pCR rate) and safety [48]. The safety data for the adjuvant phase was presented at the 2017 San Antonio Breast Cancer Symposium [49]. Once again, no significant differences were found compared to trastuzumab; cardiac toxicity in particular (the incidence of decreased left ventricular ejection fraction was 1–3%) was similar for all therapy arms of the study. It is expected that biosimilars will play an increasingly important role in clinical practice in future. However it is not currently clear which preparations will reach the market, because some pharmaceutical companies are currently involved in patent infringement proceedings against one another [50].

**Circulating tumor cells as prognostic markers in long-term follow-up**

One prognostic factor that has already been described in the literature is based on the detection of circulating tumor cells (CTCs) in blood prior to adjuvant or neoadjuvant therapy using the CellSearch® CTC test [56–58]. Assessing the risk of recurrence several years after primary therapy is clinically relevant as the findings can be used to guide decision-making on whether adjuvant endocrine therapy should continue after more than 5 years have passed. The results of a recently published study are important in this context [59]. The blood of 546 patients from a clinical study into adjuvant chemotherapy (E5103) was examined once for CTCs. The median time between inclusion in the study and blood collection was 5.2 years. At least one CTC was detected in 4.9% of patients. In a multivariate analysis adjusted for clinical risk factors, patients in whom CTCs were detected had an 18.3 times higher risk of recurrence. These results underscore the biological relevance of CTCs even in the non-metastatic setting, although the findings were not compared with results obtained using classic tumor markers. The findings support the results of the SUCCESS A trial [60] which reported that determination of CTCs 2 years after the primary diagnosis offered prognostic information for the course of disease after 2 years.

**Germline mutations as prognostic and predictive markers**

Increasing attention is also being paid to germline mutations of patients with breast cancer. A prognostic or predictive significance has been established for some genetic variants [61–69]. There is relatively detailed data on the prognostic importance of BRCA1 and BRCA2 mutations for certain groups of patients. The recently published POSH study followed up almost 3000 patients with primary breast cancer who developed breast cancer before the age of 40 years and tested them for BRCA1 and BRCA2 mutations [70]. This study found no difference in survival between groups. These data could have implications for clinical procedures in terms of the surgical treatment of these patients, as the diagnosis would provide enough time to counsel affected women about prophylactic surgery of the contralateral side [71]. A PARP inhibitor has already been approved specifically to treat patients with a BRCA1 or BRCA2 mutation [72]. The PRAEGNANT network in Germany has recently reported on the mutation frequency of BRCA1 and BRCA2 and other panel genes and estimated the relevance of these findings for therapy under “real world” conditions [73]. The germline DNA of 1462 patients with metastatic breast cancer was investigated. A germline mutation in one of the panel genes was identified in 8.4% of cases. The most common mutations were found in genes in the BRCA2, CHEK2, BRCA1, PALB2 and ATM regions. The highest rate of mutations was found in patients with triple-negative and luminal B-like tumors. Patients with mutations had a poorer prognosis compared to the overall patient cohort.
Conclusion

The data presented here offers a good summary of current developments and shows that more and more new therapies are being developed to treat special subgroups and are combined with the use of biomarkers. The second part of this update [74] will provide a summary of recent developments in metastatic breast cancer, supportive therapy, quality of life and prevention.

Acknowledgements

This work was partly the result of funding received from Riemser and the PRAEGNANT study network, neither of which had any involvement in compiling this manuscript. The authors alone are responsible for the contents of this paper.

Conflict of Interest

F.-A. T. received honoraria from AstraZeneca, Genomic Health and Novartis. A.D.H. received honoraria from AstraZeneca, Genomic Health, Roche, Novartis, Celgene and Pfizer. N. N. received consultancy honoraria from Janssen-Cilag and travel support from Novartis. F.O. received speaker and consultancy honoraria from Amgen, Celgene, TEVA, AstraZeneca, Novartis, Roche, and MSD. H.-C. K. received honoraria from Carl Zeiss meditec, TEVA, Thermalcion, Novartis, AstraZeneca, Pfizer, Janssen-Cilag, GSK, LIV Pharma, Roche and Genomic Health. P.H. received honoraria, unrestricted educational grants and research funding from Amgen, AstraZeneca, Eli Lilly, MSD, Novartis, Pfizer and Roche. P.A.F. received honoraria from Roche, Pfizer, Novartis and Celgene. His institution conducts research for Novartis. H.T. received honoraria from Novartis, Roche, Celgene, TEVA, Pfizer and travel support from Roche, Celgene and Pfizer. J. E. received honoraria from Roche, Celgene, Novartis, Pfizer, Pierre Fabre, TEVA and travel support from Celgene, Pfizer, TEVA and Pierre Fabre. M. P. L. has participated on advisory boards for AstraZeneca, MSD, Novartis, Pfizer, Genomic Health and Roche and has received honoraria for lectures from Lilly, Roche, Novartis, Pfizer, Genomic Health, AstraZeneca, medac and Eisai. M. W. received speaker honoraria from AstraZeneca, Celgene and Novartis. V. M. received speaker honoraria from Amgen, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, Pfizer, Pierre-Fabre, Novartis, Roche, Teva, Janssen-Cilag and consultancy honoraria from Genomic Health, Roche, Pierre Fabre, Amgen, Daiichi-Sankyo and Eisai. E. B. received honoraria from Novartis, Riemsir and Hexal for consulting and clinical research management activities. A. S. received honoraria from Roche, Celgene, AstraZeneca, Novartis, Pfizer, Zuckschwerdt Verlag GmbH, Georg Thieme Verlag, Aurikamed GmbH, MCI Deutschland GmbH, bsh medical communications GmbH and promedics GmbH. W. J. received honoraria and research grants from Novartis, Roche, Pfizer, Lilly, AstraZeneca, Chugai, Sanofi, Daiichi, Tesaro. F. S. participated on advisory boards for Novartis, Amgen and Roche and received honoraria for lectures from Roche, Novartis and Pfizer.

References

[1] Kolberg HC, Luftner D, Lux MP et al. Breast cancer 2012 – new aspects. Geburtsh Frauenheilk 2012; 72: 602–615
[2] Lux MP, Janni W, Hartkopf AD et al. Update breast cancer 2017 – implementation of novel therapies. Geburtsh Frauenheilk 2017; 77: 1281–1290
[3] Maas N, Schutz F, Fasching PA et al. Breast cancer update 2014 – focus on the patient and the tumour. Geburtsh Frauenheilk 2015; 75: 170–182
[4] Kolberg HC. Editorial: Primary systemic therapy for breast cancer. Rev Recent Clin Trials 2017; 12: 66
[5] Fasching PA, Heusinger K, Haebeler L et al. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. BMC Cancer 2011; 11: 486
[6] Fuji T, Kogawa T, Dong W et al. Revisiting the definition of estrogen receptor positivity in HER2-negative primary breast cancer. Ann Oncol 2017; 28: 2420–2428
[7] Untch M, Huober J, Jackisch C et al. Initial treatment of patients with primary breast cancer: evidence, controversies, consensus: spectrum of opinion of German specialists at the 15th International St. Gallen Breast Cancer Conference (Vienna 2017). Geburtsh Frauenheilk 2017; 77: 633–644
[8] Early Breast Cancer Trials’ Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol 2018; 19: 27–39
[9] Sotiriou C, Rothé f, Maetens M et al. Copy number aberration analysis to predict response to neoadjuvant anti-HER2 therapy: results from the NeoALTO phase III trial [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. Cancer Res 2018; 78: Abstr. GS1-04
[10] Kroop IE, Hillman D, Polley MY et al. Invasive disease-free survival and gene expression signatures in CALGB (Alliance) 40601, a randomized phase III neoadjuvant trial of dual HER2-targeting with lapatinib added to chemotherapy plus trastuzumab [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. Cancer Res 2018; 78: Abstr. GS3-02
[11] Cortazar P, Geyer CE Jr. Pathological complete response in neoadjuvant treatment of breast cancer. Ann Surg Oncol 2015; 22: 1441–1446
[12] von Minckwitz G, Untch M, Blohmmer JU et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30: 1796–1804
[13] Yee D, DeMichelle A, Isaacs C et al. Pathological complete response predicts event-free and distant disease-free survival in the I-SPY2 TRIAL [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. Cancer Res 2018; 78: Abstr. GS5-03
[14] Schneweiss A, Jackisch C, Schmatloch S et al. Survival analysis of the prospectively randomized phase III CepaSepto trial comparing neoadjuvant chemotherapy with weekly nab-paclitaxel with solvent-based paclitaxel followed by anthracycline-cyclophosphamide for patients with early breast cancer – GBC69 [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. Cancer Res 2018; 78: Abstr. GS3-05
[15] Fasching PA, Abad MF, Garcia-Saenz JA et al. Biological and clinical effects of abemaciclib in a phase 2 neoadjuvant study for postmenopausal patients with HR+/HER2+ breast cancer. Oncol Res Treat 2017; 40: 225–226
[16] Guameri V, Fasching PA, Abad MF et al. Biological and clinical effects of abemaciclib in a phase 2 neoadjuvant study for postmenopausal patients with HR+/HER2– breast cancer. Oncol Res Treat 2017; 40: 225–226
[17] Martin M, Hurvitz SA, Chan D et al. Final results of NeoMONARCH: a phase 2 neoadjuvant study of abemaciclib in postmenopausal women with hormone receptor positive (HR+), HER2 negative breast cancer (BC) [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. Cancer Res 2018; 78: Abstr. PDS-01
[18] Buchholz TA, Somerfield MR, Griggs JJ et al. Margins for breast-conserving surgery with whole-breast irradiation in stage I and II invasive breast cancer: American Society of Clinical Oncology endorsement of the Society of Surgical Oncology/American Society for Radiation Oncology consensus guideline. J Clin Oncol 2014; 32: 1502–1506

[19] Houssami N, Macaskill P, Marinovich ML et al. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol 2014; 21: 717–730

[20] Shah C, Verma V, Sayles H et al. Appropriate margins for breast conserving surgery in patients with early stage breast cancer: a meta-analysis [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. Cancer Res 2018; 78: Abstr. GS5-01

[21] Giuliano AE, Hunt KK, Ballman KV et al. Axillary dissection vs. no axillary dissection surgery with whole-breast irradiation in stage I and II invasive breast cancer: American Society of Clinical Oncology endorsement of the Society of Surgical Oncology/American Society for Radiation Oncology consensus guideline. J Clin Oncol 2014; 32: 1502

[22] Robertson JFR, Dowsett M, Bliss JM et al. Peri-operative aromatase inhibition: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined TEXT and SOFT trials [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. Cancer Res 2018; 78: Abstr. GS5-02

[23] Perry JR, Hsu YH, Chasman DI et al. DNA mismatch repair gene MSH6 implicated in determining age at natural menopause. Hum Mol Genet 2014; 23: 2490–2497

[24] Francis PA, Regan MM, Fleming GF. Adjuvant ovarian suppression in premenopausal breast cancer, N Engl J Med 2015; 372: 1673

[25] Francis PA, Pagani O, Regan MM et al. Randomized comparison of adjuvant aromatase inhibitor exemestane (E) plus ovarian function suppression (OFS) vs. tamoxifen (T) plus OFS in premenopausal women with hormone receptor positive (HR+) early breast cancer (BC): update of the combined TEXT and SOFT trials [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. Cancer Res 2018; 78: Abstr. GS5-04

[26] Francis PA, Muss HB, Ingle JN et al. Extended adjuvant endocrine therapy in breast cancer: current status and future directions. Clin Breast Cancer 2008; 8: 411–417

[27] Goss PE, Ingle JN, Pritchard KI et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med 2016; 375: 209–219

[28] Goss PE, Harnes TA, Seruga B et al. Toxicity of extended adjuvant aromatase inhibitors in early breast cancer: a systematic review and meta-analysis. J Natl Cancer Inst 2018. doi:10.1093/jnci/djy134

[29] Song F, Zhang J, Li S et al. ER-positive breast cancer patients with more than three positive nodes or grade 3 tumors are at high risk of late recurrence after 5-year adjuvant endocrine therapy. Onco Targets Ther 2017; 10: 4859–4867

[30] Colleoni M, Luo W, Karlsson P et al. Extended adjuvant intermittent letrozole versus continuous letrozole in postmenopausal women with breast cancer (SOLE): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2018; 19: 127–138

[31] Cameron D, Piccart-Gebhart MJ, Gelber RD et al. 11 years of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HER2ceptin Adjuvant (HERA) trial. Lancet 2017; 389: 1195–1205

[32] Day FR, Ruth KS, Thompson DJ et al. Large-scale genomic analyses link reproductive aging to hypothalamic signaling, breast cancer susceptibility and BRCA1-mediated DNA repair. Nat Genet 2015; 47: 1294–1303

[33] Perrucci JR, Day F, Elks CE et al. Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche. Nature 2014; 514: 92–97

[34] Gray R, Bradley R, Braybrooke J et al. Increasing the dose density of adjuvant chemotherapy by shortening intervals between courses or by sequential drug administration significantly reduces both disease recurrence and breast cancer mortality: an EBCTCG meta-analysis of 21,000 women in 16 randomised trials of 60 weeks duration. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. Cancer Res 2018; 78: Abstr. GS5-01

[35] Francis PA, Regan MM, Fleming GF. Adjuvant ovarian suppression in premenopausal breast cancer, N Engl J Med 2015; 372: 1673

[36] Francis PA, Pagani O, Regan MM et al. Randomized comparison of adjuvant aromatase inhibitor exemestane (E) plus ovarian function suppression (OFS) vs. tamoxifen (T) plus OFS in premenopausal women with hormone receptor positive (HR+) early breast cancer (BC): update of the combined TEXT and SOFT trials [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. Cancer Res 2018; 78: Abstr. GS5-04

[37] Goss PE, Muss HB, Ingle JN et al. Extended adjuvant endocrine therapy in breast cancer: current status and future directions. Clin Breast Cancer 2008; 8: 411–417

[38] Goss PE, Pritchard KI, Ingle JN, et al. Extended aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med 2016; 375: 209–219

[39] Guldas B, Barnes TA, Seruga B et al. Toxicity of extended adjuvant aromatase inhibitors in early breast cancer: a systematic review and meta-analysis. J Natl Cancer Inst 2018. doi:10.1093/jnci/djy134

[40] Song F, Zhang J, Li S et al. ER-positive breast cancer patients with more than three positive nodes or grade 3 tumors are at high risk of late recurrence after 5-year adjuvant endocrine therapy. Onco Targets Ther 2017; 10: 4859–4867

[41] Colleoni M, Luo W, Karlsson P et al. Extended adjuvant intermittent letrozole versus continuous letrozole in postmenopausal women with breast cancer (SOLE): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2018; 19: 127–138

[42] Blok Ej, Koepp J, Meershoek-Klein Kranenburg E et al. Optimal duration of extended adjuvant endocrine therapy for early breast cancer: results of the IDEAL trial (BOOG 2006-05). J Natl Cancer Inst 2018. doi:10.1093/jnci/djx134

[43] van der Velden W, van der Lans EEJ, van der Ploeg AL et al. Prospective randomised, multi-center, phase III trial of additional versus standard 5 years of Anastrozole after initial 5 years of adjuvant endocrine therapy – results from 3,484 postmenopausal women in the ABCSG-16 trial [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. Cancer Res 2018; 78: Abstr. GS5-01

[44] Cameron D, Piccart-Gebhart MJ, Gelber RD et al. 11 years’ follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HER2ceptin Adjuvant (HERA) trial. Lancet 2017; 389: 1195–1205

[45] Pivovarova L, Romieu G, Debled M et al. Months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. Lancet Oncol 2013; 14: 741–748

[46] Perez EA, Suman VJ, Davidson NE et al. Sequential versus concurrent trastuzumab in adjuvant chemotherapy for breast cancer. J Clin Oncol 2011; 29: 4491–4497

[47] Joenje H, Fraser J, Wildiers H et al. A randomized phase III study of adjuvant trastuzumab for a duration of 9 weeks versus 1 year, combined with adjuvant taxane-anthracycline chemotherapy, for early HER2-positive breast cancer (the SOLD study) [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. Cancer Res 2018; 78: Abstr. GS5-04
[48] von Minckwitz G, Pononarova O, Morales S et al. Efficacy and safety of biosimilar ABP 980 compared with trastuzumab in HER2 positive early breast cancer. Ann Oncol 2017; 28 (Suppl. 5): v43–v67, Abstr. 151PD

[49] Kolberg HC, Demetriou GS, Zhang N et al. Safety results from a randomized, double-blind, phase 3 study of ABP 980 compared with trastuzumab in patients with breast cancer [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. Cancer Res 2018; 78: Abstr. PD3-10

[50] Yasielko C. Roche sues Pfizer to bar biosimilar of cancer drug Herceptin. Bloomberg Technology 2017. Online: https://www.bloomberg.com/news/articles/2017-11-20/roche-sues-pfizer-to-block-biosimilar-of-cancer-drug-herceptin; last access: 16.01.2018

[51] Fasching PA, Brucker SY, Fehm TN et al. Biomarkers in patients with metastatic breast cancer and the PRAEGNANT Study Network. Geburtsh Frauenheilk 2015; 75: 41–50

[52] Schmidt M, Fasching PA, Beckmann MW et al. Biomarkers in breast cancer – an update. Geburtsh Frauenheilk 2012; 72: 819–832

[53] Sparano JA, Gray RJ, Makower DF et al. Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med 2015; 373: 2005–2014

[54] Cardoso F, van’t Veer LJ, Bogaerts J et al. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 2016; 375: 717–729

[55] Polasik A, Tzschachel M, Schochter F et al. Circulating tumour cells, circulating tumour DNA and circulating MicroRNA in metastatic breast carcinoma – what is the role of liquid biopsy in breast cancer? Geburtsh Frauenheilk 2017; 77: 1291–1298

[56] Riethdorf S, Muller V, Loibl S et al. Prognostic impact of circulating tumor cells for breast cancer patients treated in the neoadjuvant “Geparquattro” trial. Clin Cancer Res 2017; 23: 5384–5393

[57] Janni WJ, Rack B, Terstappen LW et al. Pooled analysis of the prognostic relevance of circulating tumor cells in primary breast cancer. Clin Cancer Res 2016; 22: 2583–2593

[58] Rack B, Schindlbeck C, Juckstock J et al. Circulating tumor cells predict survival in early average-to-high risk breast cancer patients. J Natl Cancer Inst 2014. doi:10.1093/jnci/dju066

[59] Sparano JA, O’Neill A, Alpaugh K et al. Circulating tumor cells (CTCs) five years after diagnosis are prognostic for late recurrence in operable stage II–III breast cancer [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. Cancer Res 2018; 78: Abstr. GS6-03

[60] Janni W, Rack B, Fasching P et al. Persistence of circulating tumor cells in high risk early breast cancer patients during follow-up care suggests poor prognosis – results from the adjuvant SUCCESS A trial. Cancer Res 2016; 76; Abstr. S2-03

[61] Hein A, Rack B, Li L et al. Genetic breast cancer susceptibility variants and prognosis in the prospectively randomized SUCCESS A study. Geburtsh Frauenheilk 2017; 77: 651–659

[62] Fasching PA, Haberle L, Rack B et al. Clinical validation of genetic variants associated with in vitro chemotherapy-related lymphoblastoid cell toxicity. Oncotarget 2017; 8: 78133–78143

[63] Hein A, Lambrechts D, von Minckwitz G et al. Genetic variants in VEGF pathway genes in neoadjuvant breast cancer patients receiving bevacizumab: results from the randomized phase III GeparQuinto study. Int J Cancer 2015; 137: 2981–2988

[64] Guo Q, Schmidt MK, Kraft P et al. Identification of novel genetic markers of breast cancer survivor. J Natl Cancer Inst 2015; 107: pii: djv081. doi:10.1093/jnci/djv081

[65] Hein A, Bayer CM, Schrauder MG et al. Polymorphisms in the RANK/RANKL genes and their effect on bone specific prognosis in breast cancer patients. Biomed Res Int 2014; 2014: 842452

[66] Fasching PA, Pharoah PD, Cox A et al. The role of genetic breast cancer susceptibility variants as prognostic factors. Hum Mol Genet 2012; 21: 3926–3939

[67] Fasching PA, Loehberg CR, Strissel PL et al. Single nucleotide polymorphisms of the aromatase gene (CYP19A1), HER2/neu status, and prognosis in breast cancer patients. Breast Cancer Res Treat 2008; 112: 89–98

[68] Fagerholm R, Schmidt MK, Khan S et al. The SNP rs6500843 in 16p13.3 is associated with survival specifically among chemotherapy-treated breast cancer patients. Oncotarget 2015; 6: 7390–7407

[69] Weissher M, Nordestgaard BG, Pharoah P et al. CHEK2*1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. J Clin Oncol 2012; 30: 4308–4316

[70] Copson ER, Maishman TC, Tapper WJ et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. Lancet Oncol 2018. doi:10.1016/S1470-2045(17)30891-4

[71] Fasching PA. Breast cancer in young women: do BRCA1 or BRCA2 mutations matter? Lancet Oncol 2018. doi:10.1016/S1470-2045(18)30008-1

[72] United States Food and Drug Administration (FDA). FDA approves first treatment for breast cancer with a certain inherited genetic mutation. 2018. Online: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm592347.htm; last access: 16.01.2018

[73] Fasching PA, Hu C, Hart SN et al. Cancer predisposition genes in metastatic breast cancer – association with metastatic pattern, prognosis, patient and tumor characteristics [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. Cancer Res 2018; 78: Abstr. PD1-02

[74] Schneeweiss A, Lux MP, Janni W et al. Update breast cancer 2018 (part 2) – advanced breast cancer, quality of life and prevention. Geburtsh Frauenheilk 2018; 78: 246–259