

Update Breast Cancer 2020 Part 1 – Early Breast Cancer: Consolidation of Knowledge About Known Therapies

Update Mammakarzinom 2020 Teil 1 – frühes Mammakarzinom: Konsolidierung des Wissens über bekannte Therapien



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Key words

early breast cancer, prevention, therapy, prognosis, immune therapy, digital medicine

Schlüsselwörter

frühes Mammakarzinom, Prävention, Therapie, Prognose, Immuntherapie, digitale Medizin

received 27. 1. 2020

revised 3. 2. 2020


accepted 3. 2. 2020

Bibliography

DOI <https://doi.org/10.1055/a-1111-2431>
 Geburtsh Frauenheilk 2020; 80: 277–287 © Georg Thieme Verlag KG Stuttgart · New York | ISSN 0016-5751

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 Deutsche Version unter:
<https://doi.org/10.1055/a-1111-2431>

ABSTRACT

This review is intended to present the latest developments in the prevention and treatment of early breast cancer. The risk of breast cancer can be increasingly better characterised with large epidemiological studies on genetic and non-genetic risk factors. Through new analyses, the evidence for high-penetrance genes as well as for low-penetrance genes was able to be improved. New data on denosumab and atezolizumab are available in the neoadjuvant situation as is a pooled appraisal

of numerous studies on capecitabine in the curative situation. There is also an update to the overall survival data of pertuzumab in the adjuvant situation with a longer follow-up observation period. Finally, digital medicine is steadily finding its way into science. A recently conducted study on automated breast cancer detection using artificial intelligence establishes the basis for a future review in clinical studies.

ZUSAMMENFASSUNG

In dieser Übersichtsarbeit werden die neuesten Entwicklungen in der Prävention und in der Behandlung des frühen Mammakarzinoms dargestellt. Mit großen epidemiologischen Studien zu genetischen und nicht genetischen Risikofaktoren

wird das Brustkrebsrisiko immer besser beschreibbar. Durch neue Analysen konnte sowohl die Evidenz für hoch-penetrante Gene als auch für niedrig-penetrante Gene verbessert werden. Neue Daten zu Denosumab und Atezolizumab liegen in der Neoadjuvanz vor, genauso wie eine gepoolte Auswertung zahlreicher Studien zu Capecitabin in der kurativen Situation. Ebenso gibt es eine Aktualisierung der Gesamtüberlebensdaten von Pertuzumab in der Adjuvanz mit einer längeren Nachbeobachtungszeit. Letztendlich hält die digitale Medizin stetigen Einzug in die Wissenschaft. Eine kürzlich durchgeführte Studie zur automatisierten Brustkrebserkennung mittels künstlicher Intelligenz schafft die Grundlagen für eine künftige Überprüfung in klinischen Studien.

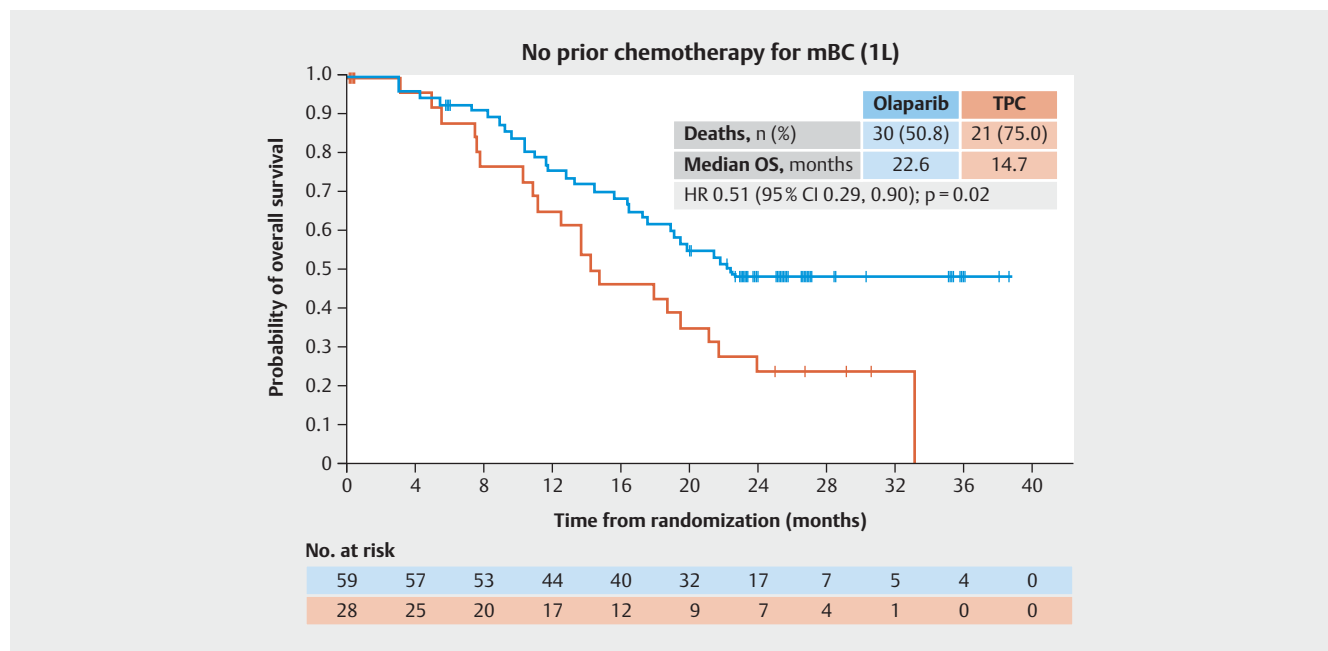
Introduction

In the areas of prevention, diagnosis and treatment of early breast cancer, continuous advancements have been made in recent years. The improvement in the prediction of disease risk, the exact assessment of the prognosis and new therapies in the neoadjuvant and adjuvant situations such as immunotherapies or antibody drug conjugates have been able to steadily contribute to an improvement in treatment. This review intends to present the current developments in view of the latest publications and conferences, such as the San Antonio Breast Cancer Symposium.

Prevention

Genetic testing for high-penetrance and moderate-penetrance risk genes

Genetic testing of germ line mutations has become a part of routine care in patients with an indication for genetic testing [1–5]. The two genes which are the most clinically relevant are *Breast Cancer (BRCA) 1* and *BRCA2* [6]. They are not only the two genes which have the greatest evidence in predictive genetic diagnostics; for patients with advanced human epidermal growth factor receptor (HER) 2-negative breast cancer and a germ line mutation in *BRCA1* or *BRCA2*, therapy with the poly-(ADP-ribose) polymerase (PARP) inhibitors olaparib and talazoparib has been approved by the European Medicines Agency (EMA) and the U.S. Food and



► **Fig. 1** Overall survival for patients in the OlympiAD study without previous therapies (printed under the Creative Commons Attribution Non-Commercial License from [10]).

Drug Administration (FDA). In the corresponding studies, an improvement in progression-free survival (PFS) was demonstrated [7–9]. In the final analysis, in an unplanned subgroup analysis of patients without pretreatment in the metastatic situation, an advantage for overall survival was demonstrated (► Fig. 1) [10]. For this reason, all patients who have a clinical indication for therapy with a PARP inhibitor should be tested for a mutation in the *BRCA1* or *BRCA2* genes. In the therapy prediction of other therapies, it was able to be shown that *BRCA1/2* mutations generally predict the response to chemotherapy and to therapy with chemotherapy containing platinum in the metastatic situation [11–14].

The benefit for genes which have been discussed to date as moderate-penetrance risk genes is still unclear. A selection of these genes according to function and *BRCA1/2* status is provided in ► Table 1. The information about the disease risk comes from large case-control studies [15, 16] which had classified *PALB2* with a similarly high risk as *BRCA1* and *BRCA2*, while other genes in the case of mutations remained far below this risk.

Low-penetrance risk genes

To date, risk variants in more than 150 genomic regions have been identified [17–30]. Some of these were also associated with the risk of specific subtypes of breast cancer [19, 26, 31–34]. An analysis has now been performed on nearly 110 000 breast cancer patients and nearly 89 000 controls which attempted to identify additional risk variants in these gene regions and to perform a functional characterisation [17]. In this analysis, 205 additional risk variants were identified which could explain another 6% of the familial breast cancer risk (increase from 17.6 to 23.6%) [17]. For the genes involved, it was also indicated which genes were associated more with a hormone-receptor-positive or hormone-receptor-negative phenotype or a phenotype independent of hormone receptor status (► Table 2).

An attempt was made to calculate the benefit in clinical practice via risk models which summarise the known low-penetrance risk genes in so-called polygenic risk models [35, 36]. Through a combination with additional factors such as mammographic density, a further improvement in risk determination can be achieved [37–40]. By means of these polygenic risk scores, the 10% of women with the highest polygenic risk scores who have an approx. 20% lifetime risk of developing breast cancer were able to be identified [35].

The Neoadjuvant Situation

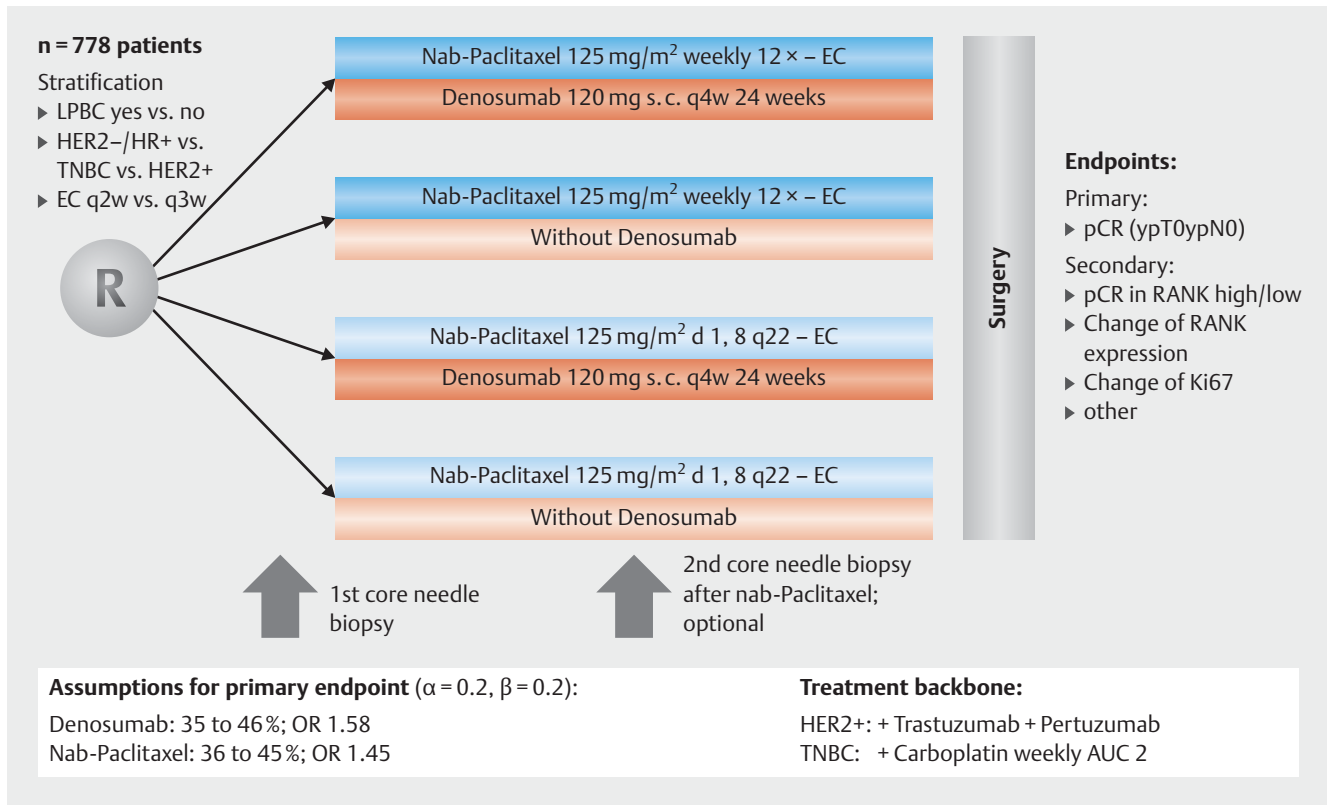
Denosumab and other data on nab-paclitaxel in the neoadjuvant situation

Since the rate of pathological complete remissions (pCR) following neoadjuvant chemotherapy (NACT) is significantly associated with survival [41–43], different strategies for increasing this are evaluated. Nab-paclitaxel, in contrast to paclitaxel, leads to an increase in pCR, which ultimately also leads to an improvement in disease-free survival [44, 45]. However the optimal dose of nab-paclitaxel is unknown and various regimens are used in clinical practice. Thus in the GeparX study (► Fig. 2), 12 weeks of nab-paclitaxel administered weekly (125 mg/m²) were compared with

► **Table 1** Genes which were either established or discussed as risk genes for breast cancer.

Gene name	<i>BRCA1/2</i>	Other homologous recombination genes	Other DNA repair genes	Other risk genes	Established breast cancer risk gene
<i>APC</i>				X	
<i>ATM</i>		X			X
<i>BARD1</i>		X			X
<i>BLM</i>			X		
<i>BRCA1</i>	X				X
<i>BRCA2</i>	X				X
<i>BRIP1</i>			X		
<i>CDH1</i>				X	X
<i>CDKN2A</i>				X	
<i>CHEK2</i>			X		X
<i>EPCAM</i>				X	
<i>ERCC2</i>			X		
<i>ERCC3</i>			X		
<i>FANCC</i>		X			
<i>FANCM</i>			X		
<i>KRAS</i>				X	
<i>MEN1</i>				X	
<i>MLH1</i>			X		
<i>MRE11A</i>			X		
<i>MSH2</i>			X		
<i>MSH6</i>			X		
<i>MUTYH</i>			X		
<i>NBN</i>			X		
<i>NF1</i>				X	X
<i>PALB2</i>		X			X
<i>PMS2</i>			X		
<i>PPM1D</i>				X	
<i>PRSS1</i>				X	
<i>PTEN</i>				X	X
<i>RAD50</i>			X		
<i>RAD51C</i>		X			X
<i>RAD51D</i>		X			X
<i>RECQL</i>			X		
<i>RINT1</i>			X		
<i>SLX4</i>		X			
<i>TP53</i>				X	X
<i>XRCC2</i>		X			

12 weeks of nab-paclitaxel (125 mg/m² d1 and d8, q3w), each followed by 4 cycles of epirubicine and cyclophosphamide (90/600 mg/m²) [46]. Triple-negative patients received weekly carboplatin (AUC2) in parallel to therapy containing taxane and patients with positive HER2 received a biosimilar of trastuzumab (ABP



► **Fig. 2** Design of the GeparX study. GeparX is a multicentre, prospective, 2 × 2 randomised, open phase IIb study to compare a neoadjuvant chemotherapy with and without denosumab in patients with untreated breast cancer.

► **Table 2** Genes in which variants are known which lead to an increase in the risk of breast cancer (according to [17]).

Genes with variants with an increase in risk for ER-positive breast cancer	Genes with variants with an increase in risk for ER-negative and ER-positive breast cancer	Genes with variants with an increase in risk for ER-negative breast cancer
<p>ABHD8, ADCY9, ALK, ANKLE1, ARMT1, ATM, BRCA2, C11orf65, CASP8, CASZ1, CCDC12, CCDC170, CCNE1, CFLAR, CREBBP, ESR1, FTO, INHBB, IRX3, KDELC2, LRRN2, MDM4, MRPL34, MSI1, NBEAL2, NIF3L1, OSR1, PEX14, PIK3C2B, PPIL3, PPP1CB, PPP1R15B, RPLP0, TNFSF10, TRMT61B, TRPS1, ZCCHC24</p>	<p>ADCY3, AKAP9, ATAD2, ATF7IP, ATP13A1, ATXN7, BMI1, BORCS8, CCDC40, CCDC91, CD151, CDYL2, CLPTM1L, COMMD3, CRLF1, CUX1, DAND5, DNMT3A, DUSP4, DYNLRB2, EBF1, ELL, EP300, EPS8L2, EWSR1, EXO1, FBXO32, FKBP8, GATA3, GATAD2A, GATD1, GCDH, GDF15, HOOK2, HRAS, ISYNA1, JUNB, KCNN4, KRIT1, KXD1, L3MBTL3, LPAR2, MAST1, MAU2, MEF2B, MRPS18C, MRTFA, NDUFA13, NTN4, PAX9, PBX4, PIAS3, PIDD1, PLAUR, PRDX2, PSMD6, PTHLH, RCCD1, RFXANK, RIN3, RSNB1, SLC25A17, SLC25A21, SMG9, SOX13, SUGP1, TCF7L2, TERT, THOC7, TLR1, TNNI1, TRIM27, UBA52, WDYHV1, WNT7B, ZMIZ1</p>	<p>AFF4, AP5B1, ARHGEF38, ARDDC3, CBX6, CCND1, CDKAL1, CFL1, CHEK2, CMSS1, DYNC1I2, EFNA1, FAM189B, FGFR2, FILIP1L, FOXI1, GBA, GRHL2, HSPA4, IGFBP5, KAT5, KCTD1, KLF4, KLHDC7A, LRRC41, MAFF, MAP3K1, MAST2, MTX1, MUC1, MYC, MYEOV, NOL7, NPTXR, NRIP1, NUDT17, OVOL1, PDZK1, PIK3R3, PLA2G6, POLR3GL, POMGNT1, RANBP9, RNASEH2C, RNF115, SETBP1, SLC50A1, SUN2, TBC1D23, TBX3, TET2, TGFBR2, THBS3, TMEM184B, TOX3, TRIM46, XBP1, ZBTB38, ZCCHC10, ZFP36L1</p>

980). In a 2 × 2-arm study design, the extent to which denosumab (120 mg subcutaneous [s.c.], q28d) improves the pCR rate was additionally investigated (► **Fig. 1**). Denosumab is an anti-RANK-ligand antibody used for the treatment of bone metastases and for osteoprotection or osteoporosis therapy and which has also been shown – including through clinical data – to have a potential

role in the prevention of distant metastases [47]. While denosumab had no effect on the pCR rate (41.0 vs. 42.8%, $p = 5.82$), this was able to be significantly increased through the weekly use of nab-paclitaxel (required level of significance: $\alpha = 0.1$) (44.9 vs. 39.0%, $p = 0.062$). The effect of weekly nab-paclitaxel was seen primarily in triple-negative patients (60.4 vs. 50.0%, $p = 0.056$).

As expected, the more intensive taxane treatment also led to more adverse effects (31.5 vs. 24.4% of the patients had at least one adverse effect classified as serious). It is thus necessary to wait to determine the extent to which the more intensive nab-paclitaxel treatment carries over to disease-free survival. Nonetheless, these data support the presumption that in the case of neoadjuvant use of nab-paclitaxel in triple-negative breast cancer (TNBC), a dose of 125 mg/m² should be continuously applied weekly. In addition, it must be investigated whether the use of denosumab has a long-term benefit independent of the pCR, since RANK ligands have potential effects on disseminated micro-metastases.

Pembrolizumab and atezolizumab in the neoadjuvant situation

Another therapeutic principle for increasing the pCR rate in the case of TNBC was already presented at the annual meeting of the European Society for Medical Oncology (ESMO) in 2019: in the Keynote-522 study, the addition of the PD-1 checkpoint inhibitor pembrolizumab (8 × 200 mg, q3w) to NACT consisting of carboplatin (4 × AUC5, q3w) and paclitaxel weekly (12 × 80 mg/m²) followed by epirubicin/cyclophosphamide (4 × 90/600 mg/m², q3w) or doxorubicin/cyclophosphamide (4 × 60/600 mg/m², q3w) led to a significant improvement in the pCR rate from 51.2 to 64.8% (p = 0.00055) [48]. Following the NACT, the treatment was continued with pembrolizumab or placebo for 1 year. In this initial interim evaluation, a clear trend in the direction of an improvement in disease-free survival was already observed after 18 months, with overall good tolerance. The pCR rates with regard to various subgroups were then shown [49]. In particular, patients with large tumours (Δ-pCR in stage III approx. 25%) and lymph node involvement (Δ-pCR: 21%) benefited from pembrolizumab. The effect was independent of the PD-L1 expression, measured with the 22C3 pharmDX assay [49]. The use of pembrolizumab in early TNBC is therefore a promising therapeutic option, particularly in the case of a high tumour load.

The NeoTrip study investigated a PD-L1 checkpoint inhibitor (4 × atezolizumab 1200 mg, q3w) in combination with another NACT (4 × carboplatin, AUC2 and nab-paclitaxel 125 mg/m², d1 and d8, q3w) in the case of a TNBC [50]. Through the additional administration of atezolizumab, a significant improvement in progression-free survival and overall survival in patients with TNBC could be demonstrated in the case of PD-L1 expression on tumour-infiltrating immune cells measured with the Ventana SP142 assay [48]. In the NeoTrip study, the pCR rate was not significantly improved by atezolizumab either in the overall collective or in PD-L1-positive patients (43.5 vs. 40.8%) [50]. It must now be investigated in additional studies whether the negative result, in comparison to the results of the Keynote-522 study, was due to the use of another checkpoint inhibitor or whether, if applicable, the chemotherapy backbone led to a change in the tumour immunogenicity.

Locoregional Therapies

Surgery still necessary after neoadjuvant assessment

Modern drugs and therapeutic regimens have led to a gratifyingly high rate of pCR through NACT and antibody therapies. The assessment of the response rate can significantly influence the further locoregional and systemic approach. On the one hand, a de-escalation in the case of pCR could result (abstention from surgery and/or radiation therapy) or an escalation in the case of non-pCR (post-neoadjuvant therapy). It appears crucial whether a pCR can be predicted with the highest possible accuracy and thus low false-negative rate (FNR = incorrectly clinically assumed pCR which is pathologically a non-pCR). To overcome the limitations of imaging methods, minimally invasive biopsies (vacuum biopsy [VAB], core needle biopsy [CNB]) to predict pCR are investigated in several working groups.

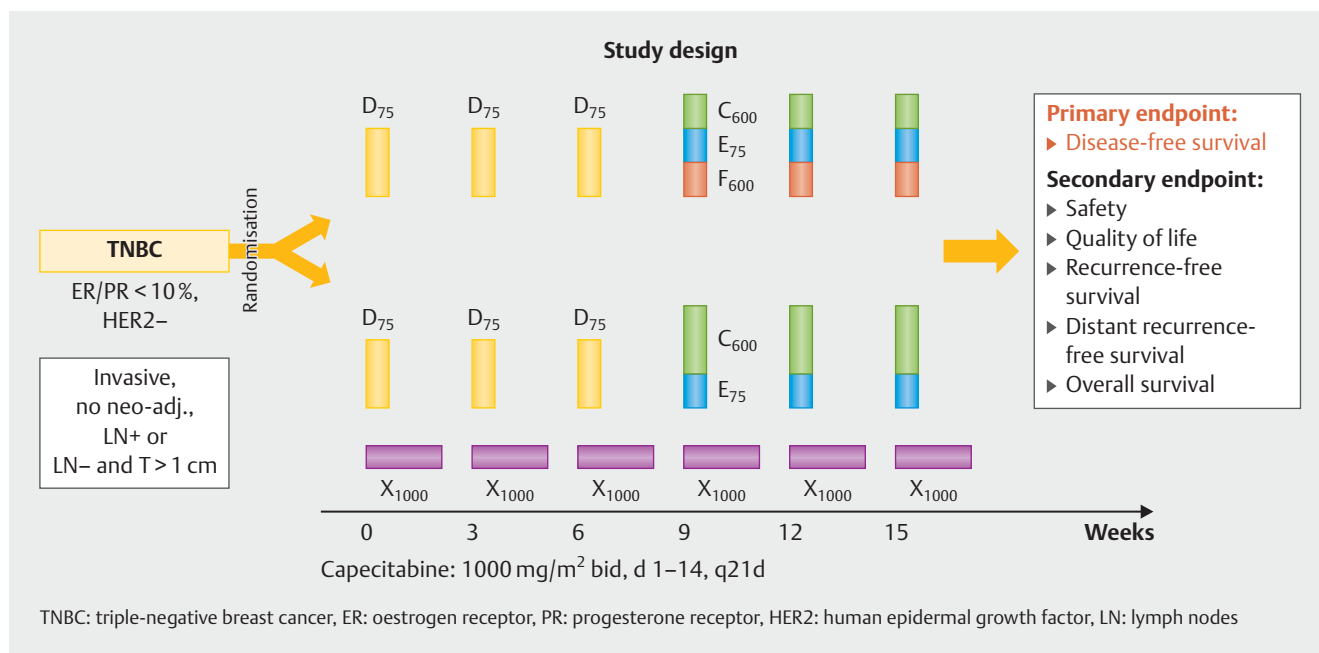
Heil et al. performed exclusively VAB in 398 patients in Germany treated neoadjuvantly and described an FNR of 17.8% [51]. These results were confirmed by Tasoulis et al. (n = 166, FNR of 18.7%) [52], whereby the working group used a VAB in 86% and a CNB in 14%. Große et al. used a mammography-guided VAB and had an FNR of 19% (n = 117). However, the detailed analysis of the false-negative cases in the case of Heil et al. shows on the one hand only minimal residual tumour load (ypTis, tumour cellularity < 10%, etc.) and a series of technical explanatory approaches with regard to the VAB itself [51].

The FNR is higher when CNB is used. Vrancken-Peeters et al. achieved an FNR of 37% [53] (n = 167) and Basik et al. achieved an FNR of 50% (n = 98) [54].

Conclusion: The VAB achieves a higher volume than the CNB and because of this, it has a lower FNR, that is, fewer residual vital tumour cells are overlooked. Nonetheless, in nearly one out of every five patients with clinically presumed complete remission, incorrect conclusions were drawn and thus a worse therapy and prognosis would result in the case of de-escalation. Multifactorial algorithms may further decrease the FNR.

Partial breast irradiation

In recent years, partial breast irradiation, particularly in the case of low-risk patients, has taken its place in international guidelines [55]. Despite these recommendations and the results of larger studies [56–58], there is still much hesitation with regard to the implementation, among other things because of the brief 5-year follow-up period in all studies. Consequently, the presentation of the 10-year follow-up (FU) of the APBI-IMRT-Florence study at the end of 2019 [59] is of great importance: it is a study in which 520 patients over age 40 with tumours less than 25 mm following breast-conserving surgery with a clear margin of more than 5 mm were randomised 1 : 1 for whole-breast irradiation (25 × 2 Gy and 5 × 2 Gy boost) or an accelerated partial breast irradiation (5 × 6 Gy) with intensity-modulated radiation therapy (IMRT). There were no significant differences with regard to locoregional recurrences, distant recurrences, breast-cancer-specific and overall survival. However, there were clinically relevant and statistically highly significant differences in the adverse effects – in particular skin toxicity – in favour of partial breast irradiation. The authors



► **Fig. 3** Design of the cbcsg010 study (Comparative Study on Two Post-operative Adjuvant Chemotherapy Regimens for Treating Triple-negative Breast Cancer, NCT01642771). [rerif]

concluded that partial breast irradiation should be accepted at the latest with this study as an equivalent standard in low-risk patients.

The Adjuvant Situation

The role of capecitabine in the adjuvant situation

The questionable efficacy of therapy of fluoropyrimidines in addition to neo-/adjuvant therapy concepts was the subject of numerous studies in recent years. In a current meta-analysis, the partially contrary results of the studies should be evaluated in a pooled manner in this area [60]. A total of 15 457 patients from a total of 12 randomised prospective studies in which capecitabine was used were included (GeparQuattro, ICE, FinXX, USON 01062, NSABP B-40, CreateX, CIBOMA/2004-01, GeparTRIO, GAIN, ICE II, CALGB 49907, GEICAM/2003-10). Capecitabine was used in these studies largely as an additive, randomised versus placebo, to systemic therapies containing anthracycline and taxane (7 studies) and in fewer studies as a replacement for other cytostatic active substances (5 studies). The primary endpoint of the meta-analysis was DFS (disease-free survival), secondary endpoint was OS and the correlation between toxicity and efficacy. In an average follow-up observation period of 79 months, an advantageous effect was seen from the addition of capecitabine to conventional therapies as compared to replacement by capecitabine (hazard ratio [HR]: 0.88 vs. 1.03). A similar picture was seen in the case of the secondary endpoint of overall survival: Through the addition of capecitabine, a higher OS was able to be achieved (HR: 0.83) versus the administration “instead of” a cytostatic (HR: 0.95). The greatest efficacy was seen with regard to DFS in the analysis of

the biological subtypes in patients with TNBC and the additional administration of capecitabine (HR: 0.81). The CREATE-X (post NAC X vs. nil), USON-01062 study (AC-D vs. AC-DX) and FINXX (D-CEF vs. DX-CEX) in particular were crucial for the positive effects in the meta-analysis, whereby the CREATE-X study demonstrated by far the greatest advantage in post-neoadjuvant application in TNBC patients in all analyses. This also corresponds to the current guideline recommendations; capecitabine should be used exclusively for TNBC post-neoadjuvantly in the case of non-pCR. Moreover, the meta-analysis did not demonstrate any significant correlation between capecitabine-specific toxicities and the efficacy.

In a new Chinese phase 3 study (cbcsg010 study) the adjuvant use of capecitabine in TNBC was tested through addition and concomitant replacement (► **Fig. 3**) [61]. In the traditional FEC-DOC regimen, 5-FU was replaced by capecitabine, while capecitabine was added to docetaxel at a dosage of 2×1000 mg/m². This corresponds to the administration of a total of 6 cycles of capecitabine. Even through no difference in overall survival could be demonstrated, there was still nonetheless a difference in the primary endpoint (disease-free survival) which was statistically significant, with an HR of 0.66 (confidence interval [CI]: 0.44–0.99). Clinically this regimen should not have any consequence after a rate of febrile neutropenia of 16% was determined in both arms, although about 40% of the patients had a dose reduction.

Another adjuvant study (POTENT study) was also performed with a 5-FU analogue, in this case with S-1 [62]. S-1 is a combination of tegafur, gimeracil and oteracil in a molar ratio of 1:0.4:1 which is administered twice daily in a regimen with 2 weeks on/1 week off. The study included only hormone-receptor-positive, intermediate- to high-risk, Japanese patients and used S-1 for a

period of one year in combination with endocrine therapy selected as standard. Surprisingly, this is thus a study which (in contrast to all recommendations) combined an endocrine therapy in parallel with a chemotherapy. The result with regard to the primary endpoint, invasive DFS, is positive with an HR of 0.63 (95% CI: 0.49–0.81) in favour of the combination with S-1 [62]. This is even more surprising since tamoxifen and S-1 antagonise each other in the cell culture. In summary, the leading data on the use of fluoropyrimidines have been recorded in Asian collectives. Asians demonstrate special pharmacogenomic features which entail increased efficacy of 5-FU analogues. We should thus be careful in general to overestimate these data and to still strictly adhere to the indication in the case of Caucasians and discuss this with the patient in detail.

Pertuzumab in the adjuvant situation – additional analyses from the APHINITY study

The APHINITY study demonstrated a statistically significant, although rather moderate advantage for disease-free survival of the entire cohort of patients with early, HER2-overexpressing breast cancer who were treated comparatively adjuvantly with trastuzumab or additionally with pertuzumab for 12 months [63]. From November 2011 to August 2013, 4805 patients were randomised 1:1, 2400 patients received pertuzumab in addition to the adjuvant therapy with trastuzumab and 2405 received a placebo. The primary analysis was published in December 2016 after a median follow-up observation period of 45.4 months. The disease-free 3-year survival in the ITT population was 94.1% in the pertuzumab group and 93.2% in the placebo group (HR 0.81, 95% CI 0.66 to 1.00; $p = 0.045$) [63]. In the group of hormone-receptor-negative patients, the HR was 0.76 [63]. This led to an approval for the combination of pertuzumab and trastuzumab in the adjuvant at-risk population.

The interim analyses after 74.1 months FU have now been published [64]. After a median of 74 months, this did not reveal any difference in overall survival between the two treatment groups (HR 0.85, 95% CI 0.67–1.07; $p = 0.171$) [64]. In the ITT population, the invasive, disease-free survival was now 90.6% after 6 years for trastuzumab and pertuzumab versus 87.8% for trastuzumab. In the node-negative group, there was no difference (IDFS 95.0 vs. 94.9%) between the two groups (the minor differences in the IDFS in favour of pertuzumab were independent of hormone-receptor status after 6 years (HR-negative IDFS 89.5 vs. 87%, Δ 2.5%, 95% CI -0.7 – 5.6 and HR-positive IDFS 91.2 vs. 88.2%, Δ 3%, 95% CI 0.8 – 5.2) and not more pronounced as in the previous analysis in the hormone-receptor-negative arm. No additional toxicity problems were reported. The next planned survival analysis is planned in 2½ years. Thus there is an indication in adjuvant therapy for double blockade with pertuzumab and trastuzumab primarily for the node-positive patients with HER2-positive disease. After the introduction of trastuzumab in the adjuvant situation [65–67], smaller but nonetheless significant steps for a curative therapeutic approach in the adjuvant situation can now be achieved through the supplementation with pertuzumab. This now yields two treatment options for the patients treated neoadjuvantly with pertuzumab and trastuzumab. For the group of women with complete remission following neoadjuvant therapy,

the double blockade can be continued for a total of 1 year, analogous to the APHINITY study, however trastuzumab alone is also an option in this situation, since there are no data which compared both of these therapeutic options following pCR after dual blockade. For the patient with a lack of complete remission – proven by the KATHERINE study [68] – treatment with T-DM1 in the adjuvant situation is available.

Endocrine therapy in the adjuvant situation

The introduction and implementation of adjuvant antihormone therapy is one of the most successful measures for reducing the mortality of breast cancer. In a recently presented analysis of pooled data in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), more than 82000 hormone-receptor-positive breast cancer patients with T1- or T2 tumours who had received 5 years of adjuvant endocrine therapy in randomised studies were analysed [69]. It was impressively shown that the prognosis of patients has significantly improved since 2000. In the node-positive patient group who were initially diagnosed in 2000 or later, the risk of developing a distant metastasis in years 5–9 after diagnosis was reduced by 25% in comparison to patients whose disease was diagnosed before 2000 (relative risk [RR] 0.75, 95% CI: 0.69–0.82) [69]. A similar reduction in the proportional risk for distant metastases was able to be demonstrated for the node-negative patients [69]. The analysis showed that an improvement in the prognosis of hormone-receptor-positive breast cancer patients can be achieved with the differentiated use of adjuvant therapies [69].

The data from the 10-year analysis of the NSBAP-B42 study also show that the nature and duration of the adjuvant endocrine therapy also plays a role [70]. In the study, around 4000 patients received the aromatase inhibitor letrozole or placebo for another 5 years following 5 years of adjuvant endocrine therapy consisting of tamoxifen and/or aromatase inhibitors. The 10-year overall survival, at 86.1 and 85.5%, did not demonstrate any differences in the two groups, however in the letrozole group, there was a significant improvement in the DFS by 4% (HR 0.84, 95% CI: 0.74–0.96) due to the expanded adjuvant therapy. Letrozole did not lead to a statistically significant increase in bone fractures due to osteoporosis or arterial thromboembolic events. The results once again show that the expanded endocrine therapy can also be considered with aromatase inhibitors for certain patient groups after a corresponding assessment of the risks and benefits [70].

CDK4/6 inhibitors and endocrine therapy in the neoadjuvant situation vs. chemotherapy

The CORALLEEN study yielded initial insights into the comparison of chemotherapy in the adjuvant situation in breast cancer with regard to the CDK4/6 inhibitors [71]. In the phase 2 study, 106 postmenopausal hormone-receptor-positive luminal B (identified according to the PAM50 test) patients were randomised and received therapy with letrozole + ribociclib vs. 4 cycles of AC chemotherapy and then subsequently underwent surgery. The endocrine combination therapy achieved a comparable response at the time of the surgery, measured by means of the percentage with ROR low risk score, however with significantly lower toxicities. The results for the chemotherapy-free combination are promising for future neoadjuvant concepts.

Other active adjuvant studies on CDK4/6 inhibitors and endocrine therapy in Germany

After the studies on palbociclib (Pallas [72]) and abemaciclib (MonarchE [73]) had already completed recruitment, the recruitment for the adjuvant study with ribociclib and endocrine therapy (Natalee study [74]) began in Germany in January 2020 and this is anticipated to remain open until the end of the year for the inclusion of patients.

Digital Medicine in Breast Cancer

Automated diagnostic measures in pathology and radiology

The automated identification of tumours with microsatellite instability (MSI) through machine learning algorithms [75] and the validation of automated breast cancer detection during screening [76, 77] are two prominent examples for machine learning applications which could be of significance for breast cancer patients.

Artificial intelligence was investigated in a recently published work on mammography screening [78] which has also been greatly acclaimed in the media [79, 80]. In this study with a total of more than 130 000 women, a system which was trained with artificial intelligence was compared with 6 radiologists and was able to achieve better accuracy overall than each of the human appraisers. The AUC of the artificial intelligence was 0.74 while that of the human appraisers was between 0.58 and 0.68. It is concluded that these systems would thus be ready to be tested prospectively in clinical studies with regard to their accuracy and efficiency [78].

Outlook

It is noteworthy that the data on certain substances such as capecitabine or the data on adjuvant antihormone therapy enable a stable analysis of important clinical questions in large pooled investigations. In view of the digitisation of medicine, such options are sure to increase in the future. While the data on some issues have consolidated, some promising new studies in the adjuvant situation with palbociclib (recruitment completed), abemaciclib (recruitment completed) and ribociclib (recruitment open) have currently been started and these will be reported on in medium-term future, where applicable.

Acknowledgements

This work was developed in part as a result of support from Hexal and Riemser, as well as the PRAEGNANT network which is supported by Pfizer, Hexal, Celgene, Daiichi Sankyo, Merrimack, Eisai, AstraZeneca and Novartis. None of the companies played a role in the drafting of this manuscript. The authors alone are responsible for the content of the manuscript.

Conflict of Interest

A.D.H. received speaker and consultancy honoraria from AstraZeneca, Genomic Health, Roche, Novartis, Celgene, Lilly, MSD, Eisai, Teva, Tesaro, Daiichi Sankyo, Hexal and Pfizer. **F.O.** received speaker and consultancy honoraria from Amgen, AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, Chugai, Celgene, Cellex, Eisai, Gilead, Hexal, Ipsen, Janssen-Cilag, Merck, MSD, Novartis, Novo Nordisk, Riemser, Roche, Servier, Shire, Tesaro, Teva. **H.-C.K.** received honoraria from Carl Zeiss meditec, Teva, Theraclion, Novartis, Amgen, AstraZeneca, Pfizer, Janssen-Cilag, GSK, LIV Pharma, Roche, Genomic Health, Theramex, ClinSol and onkowsissen.de, travel support from Carl Zeiss meditec, Novartis, Amgen, AstraZeneca, Pfizer LIV Pharma, Genomic Health, Tesaro and Daiichi Sankyo and owns stock from Theraclion and Phaon Scientific. **P.A.F.** received honoraria from Novartis, Pfizer, Roche, Amgen, Celgene, Daiichi Sankyo, AstraZeneca, Merck-Sharp & Dohme, Eisai, Puma and Teva. His institution conducts research with funding from Novartis and Biontech. **H.T.** received honoraria from Novartis, Roche, Celgene, Teva, Pfizer and travel support from Roche, Celgene and Pfizer. **J.E.** received honoraria from AstraZeneca, Roche, Celgene, Novartis, Lilly, Pfizer, Pierre Fabre, Teva and travel support from Celgene, Pfizer, Teva and Pierre Fabre. **M.P.L.** has participated on advisory boards for AstraZeneca, Lilly, MSD, Novartis, Pfizer, Eisai, Genomic Health and Roche and has received honoraria for lectures and medical education activities from MSD, Lilly, Roche, Novartis, Pfizer, Genomic Health, AstraZeneca, medac, onkowsissen.de, ClinSol and Eisai. **V.M.** received speaker honoraria from Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Eisai, Pfizer, Novartis, Roche, Teva, Janssen-Cilag and consultancy honoraria from Genomic Health, Hexal, Roche, Pierre Fabre, Amgen, Novartis, MSD, Daiichi Sankyo and Eisai, Lilly, Tesaro and Nektar. **E.B.** received honoraria from Novartis, Hexal and onkowsissen.de for consulting, clinical research management or medical education 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 promedicis 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, Lilly, Amgen and Roche and received honoraria for lectures from Roche, AstraZeneca, MSD, Novartis and Pfizer. **A.W.** participated on advisory boards for Novartis, Lilly, Amgen, Pfizer, Roche, Tesaro, Eisai, Celgene, Teva, Hexal, AstraZeneca, Sirtex, MSD and received honoraria for lectures from Novartis, Pfizer, Aurikamed, Roche, Amgen, Eisai, Lilly, AstraZeneca, Genomic Health, ClinSol, onkowsissen.de. **D.L.** received honoraria from Amgen, AstraZeneca, Celgene, ClinSol, Lilly, L'Oréal, MSD, Novartis, onkowsissen.de, Pfizer, Tesaro, Teva. **T.N.F.** has participated on advisory boards for Amgen, Daiichi Sankyo, Novartis, Pfizer, and Roche and has received honoraria for lectures from Amgen, Celgene, Daiichi Sankyo, Roche, Novartis and Pfizer. **M.T.** has participated on advisory boards for AstraZeneca, Lilly, MSD, Novartis, Pfizer, Genomic Health and Roche and has received honoraria for lectures from MSD, Lilly, Roche, Novartis, Pfizer, Genomic Health, and AstraZeneca. **M.W.** has participated on advisory boards for AstraZeneca, Lilly, MSD, Novartis, Pfizer and Roche. **J.H.** reports receiving speakers bureau honoraria from Celgene, Novartis, and Roche, and is a consultant/advisory board member for Amgen, Celgene, Novartis and Roche.

References

- [1] Ditsch N, Untch M, Thill M et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2019. *Breast Care (Basel)* 2019; 14: 224–245
- [2] Thill M, Jackisch C, Janni W et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Locally Advanced and Metastatic Breast Cancer: Update 2019. *Breast Care (Basel)* 2019; 14: 247–255

- [3] Welslau M, Hartkopf AD, Muller V et al. Update Breast Cancer 2019 Part 5 – Diagnostic and Therapeutic Challenges of New, Personalised Therapies in Patients with Advanced Breast Cancer. *Geburtsh Frauenheilk* 2019; 79: 1090–1099
- [4] Schutz F, Fasching PA, Welslau M et al. Update Breast Cancer 2019 Part 4 – Diagnostic and Therapeutic Challenges of New, Personalised Therapies for Patients with Early Breast Cancer. *Geburtsh Frauenheilk* 2019; 79: 1079–1089
- [5] Kolberg HC, Schneeweiss A, Fehm TN et al. Update Breast Cancer 2019 Part 3 – Current Developments in Early Breast Cancer: Review and Critical Assessment by an International Expert Panel. *Geburtsh Frauenheilk* 2019; 79: 470–482
- [6] Wunderle M, Olmes G, Nabieva N et al. Risk, Prediction and Prevention of Hereditary Breast Cancer – Large-Scale Genomic Studies in Times of Big and Smart Data. *Geburtsh Frauenheilk* 2018; 78: 481–492
- [7] Turner NC, Telli ML, Rugo HS et al. A Phase II Study of Talazoparib after Platinum or Cytotoxic Nonplatinum Regimens in Patients with Advanced Breast Cancer and Germline BRCA1/2 Mutations (ABRAZO). *Clin Cancer Res* 2019; 25: 2717–2724
- [8] Robson M, Im S-A, Senkus E et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N Engl J Med* 2017; 377: 523–533
- [9] Litton JK, Rugo HS, Ettl J et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. *N Engl J Med* 2018; 379: 753–763
- [10] Robson ME, Tung N, Conte P et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol* 2019; 30: 558–566
- [11] Fasching PA, Loibl S, Hu C et al. BRCA1/2 Mutations and Bevacizumab in the Neoadjuvant Treatment of Breast Cancer: Response and Prognosis Results in Patients With Triple-Negative Breast Cancer From the GeparQuinto Study. *J Clin Oncol* 2018; 36: 2281–2287
- [12] Hahnen E, Lederer B, Hauke J et al. Germline Mutation Status, Pathological Complete Response, and Disease-Free Survival in Triple-Negative Breast Cancer: Secondary Analysis of the GeparSixto Randomized Clinical Trial. *JAMA Oncol* 2017; 3: 1378–1385
- [13] Loibl S, Weber KE, Timms KM et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response – final results from GeparSixto. *Ann Oncol* 2018. doi:10.1093/annonc/mdy460
- [14] Wunderle M, Gass P, Haberle L et al. BRCA mutations and their influence on pathological complete response and prognosis in a clinical cohort of neoadjuvantly treated breast cancer patients. *Breast Cancer Res Treat* 2018; 171: 85–94
- [15] Shimelis H, LaDuca H, Hu C et al. Triple-Negative Breast Cancer Risk Genes Identified by Multigene Hereditary Cancer Panel Testing. *J Natl Cancer Inst* 2018. doi:10.1093/jnci/djy106
- [16] Couch FJ, Shimelis H, Hu C et al. Associations Between Cancer Predisposition Testing Panel Genes and Breast Cancer. *JAMA Oncol* 2017; 3: 1190–1196
- [17] Fachal L, Aschard H, Beesley J et al. Fine-mapping of 150 breast cancer risk regions identifies 191 likely target genes. *Nat Genet* 2020. doi:10.1038/s41588-019-0537-1
- [18] Wu L, Shi W, Long J et al. A transcriptome-wide association study of 229,000 women identifies new candidate susceptibility genes for breast cancer. *Nat Genet* 2018. doi:10.1038/s41588-018-0132-x
- [19] Milne RL, Kuchenbaecker KB, Michailidou K et al. Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer. *Nat Genet* 2017; 49: 1767–1778
- [20] Michailidou K, Lindstrom S, Dennis J et al. Association analysis identifies 65 new breast cancer risk loci. *Nature* 2017; 551: 92–94
- [21] Day FR, Thompson DJ, Helgason H et al. Genomic analyses identify hundreds of variants associated with age at menarche and support a role for puberty timing in cancer risk. *Nat Genet* 2017; 49: 834–841
- [22] Michailidou K, Beesley J, Lindstrom S et al. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. *Nat Genet* 2015; 47: 373–380
- [23] 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
- [24] Pharoah PD, Tsai YY, Ramus SJ et al. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. *Nat Genet* 2013; 45: 362–370, 370e1–370e2
- [25] Michailidou K, Hall P, Gonzalez-Neira A et al. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nat Genet* 2013; 45: 353–361, 361e1–361e2
- [26] Garcia-Closas M, Couch FJ, Lindstrom S et al. Genome-wide association studies identify four ER negative-specific breast cancer risk loci. *Nat Genet* 2013; 45: 392–398, 398e1–398e2
- [27] Bojesen SE, Pooley KA, Johnatty SE et al. Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. *Nat Genet* 2013; 45: 371–384, 384e1–384e2
- [28] Ghoussaini M, Fletcher O, Michailidou K et al. Genome-wide association analysis identifies three new breast cancer susceptibility loci. *Nat Genet* 2012; 44: 312–318
- [29] Haiman CA, Chen GK, Vachon CM et al. A common variant at the TERT-CLPTM1L locus is associated with estrogen receptor-negative breast cancer. *Nat Genet* 2011; 43: 1210–1214
- [30] Antoniou AC, Wang X, Fredericksen ZS et al. A locus on 19p13 modifies risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population. *Nat Genet* 2010; 42: 885–892
- [31] Ghoussaini M, French JD, Michailidou K et al. Evidence that the 5p12 Variant rs10941679 Confers Susceptibility to Estrogen-Receptor-Positive Breast Cancer through FGF10 and MRPS30 Regulation. *Am J Hum Genet* 2016; 99: 903–911
- [32] Couch FJ, Kuchenbaecker KB, Michailidou K et al. Identification of four novel susceptibility loci for oestrogen receptor negative breast cancer. *Nat Commun* 2016; 7: 11375
- [33] Purrington KS, Slager S, Eccles D et al. Genome-wide association study identifies 25 known breast cancer susceptibility loci as risk factors for triple-negative breast cancer. *Carcinogenesis* 2014; 35: 1012–1019
- [34] Stevens KN, Fredericksen Z, Vachon CM et al. 19p13.1 is a triple-negative-specific breast cancer susceptibility locus. *Cancer Res* 2012; 72: 1795–1803
- [35] Mavaddat N, Michailidou K, Dennis J et al. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. *Am J Hum Genet* 2018. doi:10.1016/j.ajhg.2018.11.002
- [36] Mavaddat N, Pharoah PD, Michailidou K et al. Prediction of breast cancer risk based on profiling with common genetic variants. *J Natl Cancer Inst* 2015; 107: pii: djv036
- [37] Vachon CM, Scott CG, Tamimi RM et al. Joint association of mammographic density adjusted for age and body mass index and polygenic risk score with breast cancer risk. *Breast Cancer Res* 2019; 21: 68
- [38] Vachon CM, Pankratz VS, Scott CG et al. The contributions of breast density and common genetic variation to breast cancer risk. *J Natl Cancer Inst* 2015; 107: pii: dju397
- [39] Rudolph A, Fasching PA, Behrens S et al. A comprehensive evaluation of interaction between genetic variants and use of menopausal hormone therapy on mammographic density. *Breast Cancer Res* 2015; 17: 110
- [40] Vachon CM, Scott CG, Fasching PA et al. Common breast cancer susceptibility variants in LSP1 and RAD51L1 are associated with mammographic density measures that predict breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2012; 21: 1156–1166

- [41] von Minckwitz G, Untch M, Blohmer 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
- [42] Cortazar P, Geyer CE jr. Pathological complete response in neoadjuvant treatment of breast cancer. *Ann Surg Oncol* 2015; 22: 1441–1446
- [43] Fasching PA, Heusinger K, Haerberle L et al. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. *BMC Cancer* 2011; 11: 486
- [44] Untch M, Jackisch C, Schneeweiss A et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): a randomised, phase 3 trial. *Lancet Oncol* 2016; 17: 345–356
- [45] Untch M, Jackisch C, Schneeweiss A et al. NAB-Paclitaxel Improves Disease-Free Survival in Early Breast Cancer: GBG 69-GeparSepto. *J Clin Oncol* 2019; 37: 2226–2234
- [46] Blohmer J, Link T, Kümmel S et al. Investigating denosumab as an add-on treatment to neoadjuvant chemotherapy and two different nab-paclitaxel schedules in a 2x2 design in primary breast cancer – First results of the GeparX study. *San Antonio Breast Cancer Symposium 2019; 2019: GS3-01*
- [47] Gnant M, Pfeiler G, Steger GG et al. Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSG-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019; 20: 339–351
- [48] Schmid P, Adams S, Rugo HS et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med* 2018; 379: 2108–2121
- [49] Schmid P, Park YH, Ferreira M et al. KEYNOTE-522 study of neoadjuvant pembrolizumab + chemotherapy vs. placebo + chemotherapy, followed by adjuvant pembrolizumab vs. placebo for early triple-negative breast cancer: pathologic complete response in key subgroups and by treatment exposure, residual cancer burden, and breast-conserving surgery. *San Antonio Breast Cancer Symposium 2019; 2019: GS3-03*
- [50] Gianni L, Huang C-S, Egle D et al. Pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple negative, early high-risk and locally advanced breast cancer. *NeoTRIPaDL1 Michelangelo randomized study. San Antonio Breast Cancer Symposium 2019; 2019: GS3-04*
- [51] Heil J, Pfob A, Sinn H et al. Diagnosing residual disease and pathologic complete response after neoadjuvant chemotherapy in breast cancer patients by image-guided vacuum-assisted breast biopsy: results of a prospective multicenter trial. *San Antonio Breast Cancer Symposium 2019; 2019: GS5-03*
- [52] Tasoulis M, Lee H, Yang W et al. Accuracy of post-neoadjuvant chemotherapy image-guided breast biopsy to predict the presence of residual cancer: A multi-institutional pooled analysis. *San Antonio Breast Cancer Symposium 2019; 2019: GS5-04*
- [53] Vrancken Peeters MTFD, van Loevezijn A, van der Noordaa MEM et al. Toward omitting breast surgery in patients with a pathologic complete response after neoadjuvant systemic treatment: interim analysis of the MICRA trial (Minimally Invasive Complete Response Assessment). *San Antonio Breast Cancer Symposium 2019; 2019: GS5-06*
- [54] Basik M, Cecchini RS, De Los Santos JF et al. Primary analysis of NRG-BR005, a phase II trial assessing accuracy of tumor bed biopsies in predicting pathologic complete response (pCR) in patients with clinical/radiological complete response after neoadjuvant chemotherapy (NCT) to explore the feasibility of breast-conserving treatment without surgery. *San Antonio Breast Cancer Symposium 2019; 2019: GS5-05*
- [55] Correa C, Harris EE, Leonardi MC et al. Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement. *Pract Radiat Oncol* 2017; 7: 73–79
- [56] Veronesi U, Orecchia R, Maisonneuve P et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* 2013; 14: 1269–1277
- [57] Strnad V, Ott OJ, Hildebrandt G et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet* 2016; 387: 229–238
- [58] Vaidya JS, Wenz F, Bulsara M et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014; 383: 603–613
- [59] Meattini I, Saieva C, Lucidi S et al. Accelerated partial breast or whole breast irradiation after breast conservation surgery for patients with early breast cancer: 10-year follow up results of the APBI IMRT Florence randomized phase 3 trial. *San Antonio Breast Cancer Symposium 2019; 2019: GS4-06*
- [60] van Mackelenberg M, Seither F, Möbus V et al. Effects of capecitabine as part of neo-/adjuvant chemotherapy. A meta-analysis of individual patient data from 12 randomized trials including 15,457 patients. *San Antonio Breast Cancer Symposium 2019; 2019: S1-07*
- [61] Li J, Yu K, Pang D et al. Adjuvant capecitabine in combination with docetaxel and cyclophosphamide plus epirubicin for triple-negative breast cancer (cbcsg010): An open-label, randomised, multicentre, phase 3 trial. *San Antonio Breast Cancer Symposium 2019; 2019: GS1-08*
- [62] Toi M, Imoto S, Ishida T et al. Addition of S-1 to endocrine therapy in the post-operative adjuvant treatment of hormone receptor-positive and human epidermal growth factor receptor 2-negative primary breast cancer: A multicenter, open-label, phase 3 randomized trial (POTENT trial). *San Antonio Breast Cancer Symposium 2019; 2019: GS1-09*
- [63] von Minckwitz G, Procter M, de Azambuja E et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med* 2017; 377: 122–131
- [64] Piccart M, Procter M, Fumagalli D et al. Interim overall survival analysis of APHINITY (BIG 4–11): A randomized multicenter, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab versus chemotherapy plus trastuzumab plus placebo as adjuvant therapy in patients with operable HER2-positive early breast cancer. *San Antonio Breast Cancer Symposium 2019; 2019: GS1-04*
- [65] Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005; 353: 1659–1672
- [66] Romond EH, Perez EA, Bryant J et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; 353: 1673–1684
- [67] Slamon D, Eiermann W, Robert N et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011; 365: 1273–1283
- [68] von Minckwitz G, Huang CS, Mano MS et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med* 2018. doi:10.1056/NEJMoa1814017
- [69] Pan H, Braybrooke J, Gray R et al. Improvements in long-term outcome for women with estrogen receptor positive (ER+) early stage breast cancer treated with 5 years of endocrine therapy: Analyses of 82,598 women in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) database. *San Antonio Breast Cancer Symposium 2019; 2019: GS2-04*
- [70] Mamounas EP, Bandos H, Lembersky BC et al. Ten-year results from NRG Oncology/NSABP B-42: A randomized, double-blinded, placebo-controlled clinical trial of extended adjuvant endocrine therapy with letrozole (L) in postmenopausal women with hormone-receptor+ breast cancer (BC) who have completed previous adjuvant therapy with an aromatase inhibitor (AI). *San Antonio Breast Cancer Symposium 2019; 2019: GS4-01*

- [71] Gavilá J, Saura C, Pascual T et al. Primary results of SOLTI-1402/COR-ALLEN phase 2 trial of neoadjuvant ribociclib plus letrozole versus chemotherapy in PAM50 Luminal B early breast cancer: An open-label, multicenter, two-arm, randomized study. *San Antonio Breast Cancer Symposium* 2019; 2019: GS2-06
- [72] clinicaltrials.gov. NCT02513394. PALbociclib CoLaborative Adjuvant Study: A Randomized Phase III Trial of Palbociclib With Standard Adjuvant Endocrine Therapy Versus Standard Adjuvant Endocrine Therapy Alone for Hormone Receptor Positive (HR+)/Human Epidermal Growth Factor Receptor 2 (HER2)-Negative Early Breast Cancer (PALLAS). NIH US National Library of Medicine 2015. Online: <https://clinicaltrials.gov/ct2/show/NCT02513394>; last access: 17.11.2018
- [73] clinicaltrials.gov. NCT03155997. Endocrine Therapy With or Without Abemaciclib (LY2835219) Following Surgery in Participants With Breast Cancer (monarchE). NIH US National Library of Medicine 2017. Online: <https://clinicaltrials.gov/ct2/show/NCT03155997>; last access: 17.11.2018
- [74] Slamon DJ, Fasching PA, Patel R et al. NATALEE: Phase III study of ribociclib (RIBO) + endocrine therapy (ET) as adjuvant treatment in hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) early breast cancer (EBC). *J Clin Oncol* 2019; 37: TPS597-TPS597
- [75] Luchini C, Bibeau F, Ligtenberg MJL et al. ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. *Ann Oncol* 2019. doi:10.1093/annonc/mdz116
- [76] Pisano ED. AI shows promise for breast cancer screening. *Nature* 2020; 577: 35-36
- [77] Ellmann S, Wenkel E, Dietzel M et al. Implementation of machine learning into clinical breast MRI: Potential for objective and accurate decision-making in suspicious breast masses. *PLoS One* 2020. doi:10.1371/journal.pone.0228446
- [78] McKinney SM, Sieniek M, Godbole V et al. International evaluation of an AI system for breast cancer screening. *Nature* 2020; 577: 89-94
- [79] Künstliche Intelligenz erkennt Tumore besser als Mediziner. *BILD* 2020. Online: <https://www.bild.de/ratgeber/2020/ratgeber/brustkrebs-frueherkennung-kuenstliche-intelligenz-erkennt-tumore-67043612.bild.html>; last access: 10.01.2020
- [80] Grady D. A.I. Is Learning to Read Mammograms. *The New York Times* 2020. Online: <https://www.nytimes.com/2020/01/01/health/breast-cancer-mammogram-artificial-intelligence.html>; last access: 01.01.2020