Cancer Treatment Reviews 72 (2019) 7–14

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Anti-Tumour Treatment

Post-neoadjuvant strategies in breast cancer: From risk assessment to treatment escalation

Giacomo Pelizzari[a,b], Lorenzo Gerratana[a,b,*], Debora Basile[a,b], Valentina Fanotto[a,b], Michele Bartoletti[a,b], Alessia Liguori[c], Caterina Fontanella[d], Simon Spazzapan[a], Fabio Puglisi[a,b]

[a] Dipartimento di Oncologia Clinica, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, 33081 Aviano, Italy
[b] Department of Medicine (DAME), University of Udine, 33100 Udine, Italy
[c] Department of Human Pathology "G. Barresi", University of Messina, 98122 Messina, Italy
[d] UOC Oncologia, ULSS1 Dolomiti, Belluno Medical Hospital "San Martino", 32100 Belluno, Italy

ARTICLE INFO

Keywords:
Breast cancer
Post-neoadjuvant treatment
pCR
Residual disease

ABSTRACT

The post-neoadjuvant setting in early breast cancer represents an attractive scenario for adjuvant clinical trials, offering the opportunity to test new drugs or combinations in high-risk patients who did not achieve pathologic complete response after primary treatment. No standard therapies are routinely proposed to patients with residual disease after neoadjuvant chemotherapy and few trials have explored this setting. To date, only one randomized phase III study showed the benefit of additional capecitabine after neoadjuvant chemotherapy, and international guidelines recommend at least to consider its use, particularly for triple negative breast cancer. Therefore, the management of these patients is still a clinical challenge, with limited data supporting the use of an additional adjuvant non-cross-resistant chemotherapy. Escalation strategies are currently under evaluation, with new agents proposed as supplementary post-neoadjuvant treatment (e.g. platinum salts, capecitabine, poly ADP-ribose polymerase inhibitors, immune checkpoint inhibitors, cyclin-dependent kinase 4/6 inhibitors). Based on these premises, selection criteria are critical to identify patients who may benefit from post-neoadjuvant therapies, through the validation of prognostic and predictive biomarkers for a reliable risk assessment and estimation of benefit.

The present review summarizes the efforts in introducing new therapeutic options for patients with breast cancer and residual disease after neoadjuvant treatment, with a particular focus on the ongoing clinical trials and useful biomarkers for risk stratification.

Introduction

Neoadjuvant treatment for early breast cancer (EBC) has been historically proposed to enable breast-conserving surgery in stage II-III disease, in particular for triple negative and HER2-positive EBC, although a recently published meta-analysis suggests that this strategy could fail in reducing the mastectomy rate [1–3]. Interestingly, in the last few years, this setting has become an ideal scenario for drug development and biomarker discovery, with an *in vivo* evaluation of tumor dynamic response as early outcome [4–6]. This proved to be appealing for translational trial design, especially when considering the limits of traditional adjuvant studies, which require longer follow-ups and larger sample sizes [7].

Pathological complete response (pCR) is the most common primary endpoint in the neoadjuvant setting and it is typically associated with longer patients' survival, regardless of disease subtype or received treatments [8,9]. Considering pCR as a valuable endpoint to assess the activity of new drugs and its strong association with long-term outcomes, neoadjuvant trials have been potentiated with additional agents (e.g. platinum salts, capecitabine, poly ADP-ribose polymerase inhibitors, immune checkpoint inhibitors, cyclin-dependent kinase 4/6 inhibitors) to increase pCR rates and enhance patient's prognosis [8,10]. Moreover, a treatment escalation has been proposed in the post-neoadjuvant setting for those patients who did not achieve pCR, with new or additional agents evaluated as adjuvant therapy.

The aim of this review is to summarize the current knowledge on new therapeutic options for patients with EBC and residual disease (RD) after neoadjuvant treatment (NAT), with a particular focus on ongoing clinical trials and useful biomarkers or risk-assessment models.

* Corresponding author at: Department of Medicine (DAME), University of Udine, 33100 Udine, Italy
E-mail address: gerratana.lorenzo@spes.uniud.it (L. Gerratana).

https://doi.org/10.1016/j.ctrv.2018.10.014
Received 23 July 2018; Received in revised form 16 October 2018; Accepted 29 October 2018

pCR: definition and potential surrogacy

The American Joint Committee on Cancer (AJCC) staging system defined pCR as the complete eradication of invasive carcinoma from both breast and axillary lymph nodes, including cancer within blood or lymph vessels, with or without residual carcinoma in situ (ypT0 ypN0 or ypT0/is ypN0) [11]. The pooled analysis from Cortazar et al. found that patients who achieved pCR after NAT had a 64% death risk reduction compared to patients who had RD at the time of surgery. These data support a strong prognostic role of pCR, with an 84% (95% CI, 75%–89%) death risk reduction in triple negative breast cancer (TNBC), 92% (95% CI, 78%–97%) in HER2-positive/hormone-receptor (HR)-negative breast cancer treated with trastuzumab and 71% (95% CI, 35%–87%) in high-grade HR-positive/HER2-negative breast cancer, compared to patients without pCR [8]. Considering a potential surrogacy for long-term outcomes, incremental gains of the intermediate endpoint for different treatments (i.e. pCR) should also result in a significant extensions of survival outcomes within the same trial. Nevertheless, the analysis by Cortazar et al., by using a weighted linear regression model, failed to establish a trial-level association between increases in pCR rates and overall survival (OS) or event free survival (EFS) gains [8,12,13], with some considerations to be made. As a matter of fact, post-surgery adjuvant therapy may dissociate pCR from survival benefit, while baseline prognostic factors may limit the power to detect significant differences in survival (e.g. in a very low-risk population) [14,15].

From residual disease profiling to risk assessment

As previously showed, only a subgroup of patients with EBC achieve pCR after NAT, and often, may relapse notwithstanding the achievement of pCR. Several markers, such as residual cancer burden (RCB), tumor immune-infiltrates (TILs), genetic alterations, and composite risk scores have been proposed as predictors of recurrence after NAT, more specially in the presence of RD. Based on these premises, selection criteria are necessary to identify patients who may benefit from additional post-NAT therapies, through the validation of prognostic and predictive biomarkers for a reliable risk-assessment.

Residual cancer burden (RCB)

Several studies explored the prognostic role of RCB after NAT, defined as the primary tumor dimension, cellularity of tumor bed, and axillary nodal burden. A significant association has been observed between RCB and the risk of breast cancer recurrence (BR) (Hazard Ratio, HR: 2.50, 95% CI: 1.70–3.69, $p < .001$), regardless of BC subtype [16,17]. The RCB index identifies four different groups (RCB-0 to RCB-III), from pCR to extensive RD, with relevant contribution to prognostic stratification. These four classes are expression of a continuous spectrum of treatment response and represent a useful clue to estimate the long-term risk for patients with RD [17]. Additionally, the high reproducibility of this score makes it a practical tool for clinical practice [18].

After 5 years from surgery, patients with RCB-I (i.e. patients with minimal RD and lower risk of relapse) experienced a similar prognosis to those with pCR (RCB-0), regardless of the treatment received or the pathologic RD stage. Thus, the RCB is able to identify a subset of patients with minimal benefit from post-NAT therapies [16]. Moreover, as reported by Sheri et al., the integration of Ki-67 to RCB was significantly more precise in stratifying patient's outcome than either Ki-67 or RCB alone [19]. However, the lack of a standardized Ki-67 assessment could also cause discordance and variability of its prognostic value [20]. Based on these results, RCB represents a valuable factor for the evaluation of an additional post-NAT adjuvant treatment in patients with RD.

Composite risk scores

The prognostic value of traditional pathological staging has been widely explored both in the adjuvant and post-neoadjuvant setting [9,11]. To better stratify patients with RD after NAT, a composite risk score has been designed by integrating clinical stage (CS) and post-NAT stage (PS) with pre-treatment indicators of tumor biology such as estrogen receptor status (E) and tumor grading (G) (CPS + EG score) [21,22]. In addition, for patients treated with neoadjuvant endocrine therapy, a preoperative endocrine prognostic index (PEPI) was able to predict long-term outcomes, taking into consideration post-treatment tumor size, node status, HR status, and Ki-67 levels [23]. Notably, in the Z1031 trial, after 5.5 years of median follow-up, patients with PEPI = 0 (yN0, $yT \leqq 2$, HR+, Ki-67 $\leqq 2.7\%$) showed a very low recurrence rate without additional adjuvant chemotherapy compared to patients with PEPI > 0 (3.6% vs. 14.4%, HR: 0.27, 95% CI: 0.092–0.764, $p = .014$) [20]. Based on these results, the PEPI score may be useful to avoid chemotherapy in very low-risk patients after neoadjuvant endocrine treatment (e.g. patients with PEPI = 0). Conversely, the management of high-risk patients after neoadjuvant endocrine therapy (e.g. patients with PEPI > 0) remains an unmet clinical need, and a meager benefit was seen in terms of pCR for additional neoadjuvant chemotherapy. Therefore, alternative systemic therapies such as fulvestrant and cyclin-dependent kinase (CDK) 4/6 inhibitors represent valid options and are currently investigated both in the neoadjuvant and post-NAT setting [24,25].

In conclusion, the prognostic value of these scores is easily transferable to clinical practice and may provide robust prognostic information for patients' selection and treatment.

TILs

In the last few years, new insights have revealed the pivotal role played by immune system in cancer growth control. More specially, TILs presence (composed by T lymphocytes, 70–80%), and immune related gene-expression signatures were shown to be associated with BC prognosis [26,27]. TILs expression varies among BC subtypes and could be detected in 20% of TNBC, 16% of HER2-positive BC and 6% of HR-positive BC [28]. Their role as predictors of response to neoadjuvant chemotherapy has been well-established in several retrospective analyses, especially in HER2-positive BC and TNBC [29–34]. Interestingly, a greater involvement of T helper 1 compared to T helper 2 is associated with a favorable prognosis [35,36], and the presence of CD8 infiltrate is an independent predictive factor for pCR in HR-negative BC [37–40].

Of note, the presence of TILs in RD also plays an important role in stratifying the risk of relapse in EBC patients after neoadjuvant chemotherapy. Indeed, particularly in TNBC, recent studies indicated that high TILs in RD were independent predictors of improved survival [41,42]. On the other hand, the prognostic role of TILs in HER2-positive EBC is still controversial, with several studies suggesting that high TILs levels in RD might be associated with worse disease-free survival (DFS) (TILs > 25%, HR: 7.98, $p = .009$) [43]. Moreover, Asano et al. showed that the combined evaluation of both TILs and RCB could be more sensitive than TILs alone in estimating the risk of BC recurrence after neoadjuvant chemotherapy [44]. In conclusion, the presence of TILs before neoadjuvant chemotherapy or in RD has an established predictive and prognostic value, respectively [45].

Genetic alterations

Clinical and pathological markers routinely used in clinical practice are not able to completely describe BC biology as well as the risk of recurrence [46]. Gene expression profiling could provide relevant prognostic information for selecting patients who may need additional treatment after NAT [47,48]. In particular, recent studies pointed out a relative frequent discordance in the molecular features between pre-

treatment core biopsies and post-NAT residual samples [49]. Beitsch et al. evaluated RD through Mammaprint® and Blueprint® analysis, showing a genomic profile switching after neoadjuvant chemotherapy, which could result in a risk profile changing. Interestingly, these genomic alterations occurred in a subtype-dependent manner, with a very poor impact in luminal disease [50].

Interestingly, genetic alterations such as down-regulation of the gene encoding for DUSP4, an ERK phosphatase were identified by profiling RD and were associated with drug resistance and poor prognosis, regardless of the EBC molecular subtype [51]. To identify further driver gene mutations, Balko et al. profiled the residual tumors of 111 TNBC patients. The most common alterations detected were TP53 aberrations (89%), MCL1 (54%) and MYC (35%) amplifications, in basal-like tumors. Moreover, some genetic signatures were associated with patient outcomes, such as JAK2 and BRCA1 alterations as negative prognostic factors, and PTEN modification as a good prognostic predictor [52]. Notably, most of the identified genetic alterations would be potentially targetable in the post-neoadjuvant setting, if targeted therapy were available at least in clinical trials (e.g. loss or mutation of PTEN, amplifications of CDK4, amplifications or mutations of PIK3CA or PIK3R1, mutations of BRCA1, BRCA2, or mutations of ATM) [52].

Defining Minimal Residual Disease (MRD): Circulating Tumor Cells (CTCs) and circulating tumor DNA (ctDNA)

The deployment of liquid biopsy techniques such as CTCs enumeration and ctDNA is gaining momentum as a promising strategy to detect and monitor micrometastatic disease. CTCs have been widely validated in the metastatic setting and are primarily linked to the inherit biology of the disease, and thus have a strong prognostic relevance and are directly linked to the metastatization process [53,54].

CTCs enumeration through the CellSearch® immunomagnetic system (Menarini Silicon Biosystem), highlighted significantly homogenous results in the neoadjuvant setting and, unlike common prognostic factors, was not associated with pCR [55,56]. The Geparquattro trial explored two different CTCs cutoff points (i.e. ≥ 1 CTC/7.5 mL and ≥ 2 CTCs/7.5 mL) both before and after neoadjuvant chemotherapy. CTCs detection was independently associated with reduced DFS and OS but only at the time point before NAT, while post-NAT enumeration had no prognostic impact. Consistently with the BEVERLY-2 trial, patients experiencing a pCR without detectable CTCs had the best outcome, while a low tumor response defined both in terms of CTCs enumeration and pCR, identified a high risk subgroup for local and distant recurrence [56]. Comparable results were obtained through the AdnaTest® (QIAGEN) RT-PCR-based assay [57]. Interestingly, the IMENEO meta-analysis confirmed these findings and furthermore highlighted a significant prognostic impact of persistently high post-NAT CTCs [58]. On the other hand, slightly diverging results were observed with the Maintrack© cytology-based detection system (Genostics), where a decreased CTCs enumeration was found to be associated with pCR [59].

Unlike CTCs, ctDNA is thought to be directly correlated with tumor burden and thus, more suitable for disease monitoring. It is, furthermore, capable to provide useful information on resistance onset and new actionable mutations, enabling the optimization of both treatment options and resources [60,61]. Under this premise, shorter DFS and OS were indeed observed when ctDNA was still measurable after one cycle of neoadjuvant chemotherapy, without any association with pCR [60,62]. Consistent results were obtained by measuring post-surgical levels of ctDNA [63]. On the other hand, the NeoALTTO trial showed that certain specific mutations (e.g. PI3KCA and TP53) in HER2-positive EBC could impact negatively on pCR [64]. The utility of a longitudinal ctDNA assessment was explored by the Chemo-NEAR study [61]. Consistent results were observed in case of ctDNA persistence after NAT, but more interestingly an increase in sensitivity was obtainable through a seriate mutational tracking, with a median lead time of 7.9 months of the ctDNA technique over clinical relapse [61]. It was notably demonstrated that the targeted sequencing of ctDNA was more accurate than the primary tumor, further underlying the importance of liquid biopsy in capturing tumor heterogeneity.

Similar results were observed by analyzing epigenetic events rather than mutational ones. The detection of ctDNA hyper-methylation before and after NAT was associated with treatment response and disease recurrence [65,66].

Post-NAT adjuvant therapies

Few studies explored the benefit of additional treatments in the post-neoadjuvant setting and limited data are available, with no standard therapies routinely recommended for patients with RD after NAT, despite their worst outcome. Escalating strategies with innovative drugs in this setting (e.g. poly ADP-ribose polymerase inhibitors, immune checkpoint inhibitors, cyclin-dependent kinase 4/6 inhibitors) are now under investigation and clinical trials are ongoing.

The CREATE-X trial

The Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) trial was conceived with the aim of improving the prognosis of patients who did not achieve a pCR after NAT. This multicenter, open-label, randomized, phase 3 trial enrolled patients with stage I to IIIB HER2-negative EBC who had residual invasive disease and/or tumor-positive lymph nodes afterstandard NAT containing anthracycline, taxane, or both. All patients received standard post-surgical treatments, which comprised endocrine therapy in HR-positive disease and radiotherapy if indicated. After surgery, the capecitabine group received oral capecitabine (1250 mg/m^2, twice per day, on days 1–14) every 3 weeks for 6–8 cycles. A total of 887 patients were included in the full analysis set (443 patients in the capecitabine group and 444 in the control group). The trial was terminated early for meeting its primary endpoint: at the final analysis, the 5-year DFS improved from 67.6% to 74.1% (HR: 0.70, 95% CI 0.53–0.92, p = .01) and OS improved from 83.6% to 89.2% (HR: 0.59, 95% CI 0.39–0.90, p = .01). The most prominent hazard ratio was seen in the subgroup of 286 patients (32.2%) with TNBC (DFS: HR: 0.58, 95% CI: 0.39–0.87; OS: HR: 0.52, 95% CI: 0.30–0.90). The safety profile of capecitabine was consistent with previous findings, with hand–foot syndrome being the most frequent adverse event (AE). All capecitabine-related serious AEs resolved and were nonfatal [67]. As for the starting dose of capecitabine used in the CREATE-X trial, it corresponded to the approved upper limit in Western countries (1000–1250 mg/m^2 PO twice daily days 1–14, q21) [68,69]. However, there are known pharmacokinetic and pharmacogenomics differences in the metabolism of capecitabine and its tolerance between Asian and Western populations, and dose adjustments may be required to manage toxic effects in Caucasian patients [70]. As for safety reasons, clinicians could also consider a screening for dihydropyrimidine dehydrogenase (DPD) variants before starting treatment [71].

The post-NAT approach studied in CREATE-X is certainly attractive, since it does not affect the ability to deliver the standard anthracycline/taxane chemotherapy. Indeed, 95.3% of patients enrolled in this trial had received both. Moreover, a drug-sequence effect could also be hypothesized, since anthracyclines and taxanes are able to induce thymidine phosphorylase, an enzyme that activates capecitabine [72–74].

However, previously reported trials did not show a benefit in using adjuvant capecitabine in combination with chemotherapy, failing to meet their primary endpoints [75–79]. These studies included patients mainly from Western Countries, with different prognosis and breast cancer biology. The CREATE-X trial, on the contrary, focused on a specific population, selected for its response to neoadjuvant chemotherapy and enriched with high-risk woman who did not experience pCR [8,9,67,80].

Notably, the subgroup analysis of CREATE-X study highlighted a greater activity of post-NAT capecitabine in TNBC patients, consistently with previous otherwise negative reported studies [67]. Specifically, in a prespecified exploratory analysis of the USON 01062 trial, an OS advantage was observed in TNBC (HR: 0.62, 95% CI: 0.41–0.94) and, similarly, a subgroup analysis of the FinXX trial showed an improvement in recurrence-free survival (RFS) (HR: 0.53, p = .02) and OS (HR: 0.55, p = .03) in TNBC [75,76,78]. Additionaly, a recent meta-analysis including 8 randomized trials with adjuvant or neoadjuvant capecitabine added to standard chemotherapy failed to show a benefit on DFS (HR: 0.99, p = .93) or OS (HR: 0.90, p = .36) in EBC. A DFS improvement was seen only in the subset of patients with TNBC vs. non-TNBC (HR: 0.72 vs. 1.01, p = .02) [81]. Considering all data together, although adjuvant capecitabine seems to provide a greater benefit in TNBC, caution is needed to interpret subset analyses. In this regard, the 2017 St. Gallen Consensus Conference stressed the absence of confirmatory historical data on adjuvant capecitabine in EBC when discussing the results of the CREATE-X trial [2].

In conclusion, even if there are certain caveats on the generalizability of its results, the CREATE-X trial provides us with the option to use post-surgery capecitabine in patients with RD after NAT, especially for TNBC.

Other post-NAT clinical trials

The CREATE-X trial represents the first randomized phase III study showing the benefit of additional chemotherapy after NAT, reevaluating the role of adjuvant capecitabine in EBC [67]. A current phase II trial will provide additional evidence on the use of non-cross-resistant chemotherapy after NAT, examining the value of eribulin in high-risk patients with RD (NCT01401959). Additionally, in the ExteNET trial, patients with stage II-IIIc HER2-positive EBC or RD after NAT (25% of the whole trial population) received adjuvant neratinib for 1 year after completion of standard therapy, with a significant benefit in terms of 5-year DFS rate (90.2% vs. 87.7%, HR: 0.73, 95% CI: 0.57–0.92, p = .008), particularly for those with HR-positive BC (91.2% vs. 86.8, HR: 0.60, 95% CI: 0.43–0.83) [82]. Of note, OS data are not yet mature and 39.9% of patients treated with neratinib experienced grade 3–4 diarrhea, hence efficacy-toxicity trade-offs and loperamide prophylaxis are both recommended when considering its use [82]. Other clinical trials were conducted in this setting with modest results. A phase II study randomized patients with HER2-negative BC with RD after NAT to ixabepilone versus observation (NCT00877500). The study was suspended earlier because of relevant toxicities in the ixabepilone arm, with no significant differences in 3-year RFS and OS [83]. Additionally, the phase III NeoAdjuvant Trial Add-oN (NaTaN) study explored the role of zoledronic acid for patients with RD after NAT [84]. Accumulating data support the use of adjuvant bisphosphonates for EBC [85], but this study did not meet its primary endpoint, with no impact on DFS and OS [84].

Other trials have been proposed to further test post-NAT adjuvant treatments, also including innovative agents. Most of these studies are still ongoing and results are expected. Two randomized phase III trials are currently investigating the role of immune checkpoint inhibitors in this setting: the A-Brave trial (NCT02926196), with the anti-PD-L1 avelumab tested as adjuvant or post-NAT treatment for high-risk TNBC patients, and the SWOG S1418 trial (NCT02954874), in which TNBC patients with RD after NAT are randomized to adjuvant pembrolizumab or observation. The role of immunotherapy for BC is still under evaluation, with limited efficacy observed [86,87], but high expectation is placed over TNBC.

Platinum salts in TNBC have been evaluated both in the neoadjuvant [88] and metastatic setting [89]. Reported data suggest a benefit with their use in combination with standard neoadjuvant chemotherapy, even if long-term outcomes are still uncertain and additional toxicities were observed [90]. No evidence is available on the efficacy of post-NAT platinum-based chemotherapy for TNBC, but the ongoing ECOG-ACRIN EA1131 study (NCT02445391) will examine this issue further, with patients who did not achieve pCR randomized to adjuvant carboplatin, cisplatin or observation. Actually, taking into account the results of the CREATE-X trial, the observation arm was replaced by adjuvant capecitabine as comparator.

Additionally, poly ADP-ribose polymerase (PARP) inhibitors have been evaluated in this scenario, targeting the potential homologous recombination deficiency in TNBC. Rucaparib was tested in combination with cisplatin in a cohort of post-NAT high-risk TNBC or BRCA-mutant patients (BRE09-146 study), but no differences in 2-year DFS were observed between the combination arm versus cisplatin alone [91]. Moreover, the ongoing phase III OlympiA trial (NCT02032823) will evaluate the role of olaparib as adjuvant or post-NAT treatment for high-risk HER2-negative BRCA-mutant patients. Of note, as seen in the BRIGHTNESS trial, the addition of neoadjuvant veliparib to carboplatin and paclitaxel did not increase pCR rate in TNBC compared to platinum-based chemotherapy [92]. Nevertheless, PARP inhibitors are still under investigation in this setting, and the PARTNER study (NCT03150576) will test olaparib in addition to platinum-based neoadjuvant chemotherapy for TNBC and/or BRCA-mutant patients.

Escalating strategies have been shown to be successful also for HER2-positive BC, with the use of pertuzumab and trastuzumab both in the neo/adjuvant and metastatic setting [93,94] and neratinib as extended adjuvant therapy for high-risk HER2-positive EBC [82]. Interestingly, an ongoing phase III trial will test the efficacy of trastuzumab emtansine (T-DM1) compared to standard adjuvant trastuzumab in patients with RD after NAT (KATHERINE, NCT01772472).

Upcoming studies will also explore the post-NAT treatment of HR-positive BC, uncovering the role of CDK 4/6 inhibitors in this setting. Two twin phase III, placebo-controlled trials, the PENELOPE-B (NCT01864746) and the CLEE011G2301 (NCT03078751) are currently randomizing HR-positive/HER2-negative patients with RD after NAT to receive adjuvant palbociclib or ribociclib, respectively, in addition to standard adjuvant endocrine therapy. The results of these studies will be discussed in the light of the findings of a third trial, the PALbociclib coLlaborative Adjuvant Study (PALLAS, NCT02513394), in which palbociclib is combined with adjuvant endocrine therapy for the treatment of HR-positive EBC. Promising results have been obtained by CDK 4/6 inhibitors for HR-positive metastatic BC [95], and the above-mentioned trials will clarify if a similar benefit could be also confirmed in the adjuvant setting (Table 1).

Conclusions

The post-neoadjuvant setting represents an attractive scenery for adjuvant clinical trials, offering the opportunity to test new drugs or combinations in a population enriched with high-risk patients with RD after NAT. No standard therapies are routinely proposed for these patients and the CREATE-X trial represents the first randomized phase III study showing an OS benefit with adjuvant non-cross-resistant chemotherapy after NAT. The management of these patients is still a clinical challenge, and the CREATE-X trial provides us with an additional option that should be discussed with patients, if clinical trials are not available. With this respect, international guidelines suggest at least to consider the use of adjuvant capecitabine in this setting, especially for TNBC [67,69,96]. This may cause relevant repercussions on post-neoadjuvant clinical trials design, since conventional arms should also include adjuvant capecitabine from now on. Additionally, when considering patients with HER2-positive/HR-positive EBC and RD after NAT, an extended adjuvant treatment with neratinib may represent and additional option, but OS confirmatory data are still awaited [69,82,96].

A treatment escalation is currently explored in the post-NAT setting with new agents or combinations proposed as adjuvant treatments (e.g. platinum salts, poly ADP-ribose polymerase inhibitors, immune

Table 1
Trials in the post-neoadjuvant setting.

Completed trials

Trial	Phase	Post-NAT population	N. of patients	Post-NAT adjuvant therapy	Results
NCT00877500 [83]	II	HER2– BC with RD and RCB ≥ II	19 24	Arm A: Ixabepilone 40 mg/m^2 IV q21 × 6 cycles Arm B: Observation	No differences in 3-year RFS and OS
BRE09-146 [91]	II	TNBC or gBRCAm with RD ≥ 2 cm and RCB ≥ II or yN+	65 70	Arm A: Cisplatin 75 mg/m^2 IV q21 × 4 cycles Arm B: Rucaparib 24 mg C1, 30 mg C2-4, d1-3 q21 + cisplatin 75 mg/m^2 IV q21 × 4 cycles, then rucaparib 30 mg IV or 100 mg orally q7 × 24 cycles	No differences in 2-year DFS
NaTaN GBG36 [84]	III	BC with RD	343 350	Arm A: Zoledronic acid 4 mg IV q28 × 6 doses, then every 3 months × 8 doses, then every 6 months × 5 doses Arm B: Observation	No differences in DFS and OS
CREATE-X [67]	III	HER2– BC with RD	443 444	Arm A: Capecitabine 1250 mg/m^2 BID d1-14 q21 × 6 or 8 cycles + standard adjuvant endocrine therapy if indicated Arm B: Observation + standard adjuvant endocrine therapy if indicated	Significant differences in 5-year DFS (74.1% vs. 67.6%, HR 0.70, 95% CI 0.53–0.92, P = .01) and 5-year OS (89.2% vs. 83.6%, HR 0.58, 95% CI 0.39–0.90, P = .01)
ExteNET [82]	III	HER2+ with RD*	1420 1420	Arm A: Neratinib 240 mg × 1 year Arm B: Placebo + standard adjuvant endocrine therapy if indicated	Significant differences in 5-year IDFS (90.2% vs. 87.7%, HR 0.73, 95% CI 0.57–0.92, P = .008)§

Ongoing trials

Trial	Phase	Post-NAT population	Estimated Enrollment	Post-NAT adjuvant therapy	Primary Endpoint
SCRI BRE 186 (NCT01401959)	II	BC with RD ≥ 5 mm or yN+	127	Arm A (TNBC): Eribulin 1.4 mg/m^2 IV d1,8 q21 × 6 cycles Arm B (HR+/HER2–): Eribulin 1.4 mg/m^2 IV d1,8 q21 × 6 cycles Arm C (HER2+): Eribulin 1.4 mg/m^2 IV d1,8 q21 × 6 cycles + trastuzumab 6 mg/kg IV q21 × 1 year	2-year DFS
ECOG-ACRIN EA1131 (NCT02445391)	III	TNBC with RD ≥ 1 cm	562	Arm A: Cisplatin 75 mg/m^2 IV q21 × 4 cycles Arm B: Carboplatin 6AUC q21 × 4 cycles Arm C: Capecitabine 1000 mg/m^2 BID d1-14 q21 × 6 cycles	IDFS of patients with basal-like TNBC
A-Brave (NCT02926196)	III	TNBC with RD*	335	Arm A: Avelumab 10 mg/kg IV q14 × 1 year Arm B: Observation	DFS, DFS in PD-L1+ patients§
SWOG S1418 (NCT02954874)	III	TNBC with RD ≥ 1 cm or yN+	1000	Arm A: Pembrolizumab 200 mg IV q21 × 1 year Arm B: Observation	IDFS, Severity of fatigue measured by PROMIS, Physical function measured by PROMIS
OlympiA (NCT02032823)	III	HER2– BC with gBRCAm*	1800	Arm A: Olaparib 300 mg BID × 1 year Arm B: Placebo	IDFS§
KATHERINE (NCT01772472)	III	HER2 + BC with RD	1487	Arm A: trastuzumab 6 mg/kg IV q21 × 14 cycles Arm B: T-DM1 3.6 mg/kg IV q21 × 14 cycles	IDFS
PENELOPE-B (NCT01864746)	III	HR+/HER2– BC with RD and CPSEG ≥ 3, or 2 if ypN+	1250	Arm A: Palbociclib 125 mg d1-21 q28 × 13 cycles + standard adjuvant endocrine therapy Arm B: Placebo + standard adjuvant endocrine therapy	IDFS
CLEE011G2301 (NCT03078751)	III	HR+/HER2– BC with RD ≥ 1 cm or yN1 ≥ 2 mm*	2000	Arm A: Ribociclib 600 mg d1-21 q28 × 26 cycles + standard adjuvant endocrine therapy Arm B: Placebo + standard adjuvant endocrine therapy	IDFS using STEPP criteria§

Abbreviations: NeoAdjuvant Treatment: NAT; Triple Negative Breast Cancer: TNBC; Residual Disease: RD; Intravenously: IV; Residual Cancer Burden: RCB; Breast Cancer: BC; Reurrence-free survival: RFS; Overall Survival: OS; Disease-free Survival: DFS; Confidence Interval: CI; Peripheral Immunoscore: PIS; Area under the curve: AUC; Bis In Die: BID; Invasive Disease-free Survival: IDFS; Programmed death-ligand 1: PD-L1; Patient Reported Outcomes Measurement Information System: PROMIS; Germline BRCA1-2 mutation: gBRCAm; Trastuzumab emtansine: T-DM1; Post-treatment pathologic stage, estrogen receptor status and tumor grade score: CPSEG; Hormone Receptor: HR; Human Epidermal growth factor Receptor 2: HER2; Subpopulation Treatment Effect Pattern Plot: STEPP.

* High-risk patients who completed adjuvant treatments were also included.

§ The results/endpoints refer to the whole trial population, including patients enrolled after adjuvant treatments.

checkpoint inhibitors, cyclin-dependent kinase 4/6 inhibitors). Unfortunately, clinical algorithms for patients' selection are missing and even after the achievement of pCR many women equally relapse. Therefore, risk assessment is critical to identify patients who could benefit from additional post-surgical treatment. In this regard, CTC and ctDNA maintain an independent prognostic value regardless of pCR and may represent the novel paradigm for BC staging and monitoring, especially for low-risk patients (e.g. patients with pCR after NAT). Lastly, additional biomarkers such as RCB, TILs, and some composite risk scores have been proposed as predictors of recurrence after NAT. However, despite the prognostic impact confirmed in several studies, these markers must still be validated and integrated for their routine use in clinical practice.

Disclosures

No conflict of interest is to be declared for the handwriting of this manuscript.

- Lorenzo Gerratana has no conflict of interests to declare.
- Giacomo Pelizzari has no conflict of interests to declare.
- Debora Basile has no conflict of interests to declare.
- Valentina Fanotto has no conflict of interests to declare.
- Michele Bartoletti has no conflict of interests to declare.
- Alessia Liguori has no conflict of interests to declare.
- Caterina Fontanella has no conflict of interests to declare.
- Simon Spazzapan has no conflict of interests to declare.
- Fabio Puglisi has no conflict of interest to declare.

Funding

No funding was necessary for the writing of this paper since the work is a literature review.

References

[1] van der Hage JA, van de Velde CJ, Julien JP, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001;19(22):4224–37.
[2] Curigliano G, Burstein HJ, Winer P, E,, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. Ann Oncol 2017;28(8):1700–12.
[3] Criscitiello C, Golshan M, Barry WT, et al. Impact of neoadjuvant chemotherapy and pathological complete response on eligibility for breast-conserving surgery in patients with early breast cancer: a meta-analysis. Eur J Cancer 2018;97:1–6.
[4] Curigliano G, Gómez Pardo P, Meric-Bernstam F, et al. Ribociclib plus letrozole in early breast cancer: a presurgical, window-of-opportunity study. Breast 2016;28:191–8.
[5] Loibl S, de la Pena L, Nekljudova V, et al. Neoadjuvant buparlisib plus trastuzumab and paclitaxel for women with HER2+ primary breast cancer: a randomised, double-blind, placebo-controlled phase II trial (NeoPHOEBE). Eur J Cancer 2017;85:133–45.
[6] Gandini S, Guerrieri-Gonzaga A, Pruneri G, et al. Association of molecular subtypes with Ki-67 changes in untreated breast cancer patients undergoing pre-surgical trials. Ann Oncol 2014;25(3):618–23.
[7] Berry DA, Hudis CA. Neoadjuvant therapy in breast cancer as a basis for drug approval. JAMA Oncol 2015;1(7):875–6.
[8] Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384(9938):164–72.
[9] 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(15):1796–804.
[10] Broglio KR, Quintana M, Foster M, et al. Association of pathologic complete response to neoadjuvant therapy in HER2-positive breast cancer with long-term outcomes: a meta-analysis. JAMA Oncol 2016;2(6):751–60.
[11] AJCC. Cancer staging manual. 8th ed. Springer International Publishing; 2017. XVII, 1032 p.
[12] Korn EL, Sachs MC, McShane LM. Statistical controversies in clinical research: assessing pathologic complete response as a trial-level surrogate end point for early-stage breast cancer. Ann Oncol 2016;27(1):10–5.
[13] von Minckwitz G, Fontanella C. Comprehensive review on the surrogate endpoints of efficacy proposed or hypothesized in the scientific community today. J Natl Cancer Inst Monogr 2015;2015(51):29–31.
[14] Bossuyt V, Hatzis C. The neoadjuvant model and complete pathologic response in breast cancer: all or nothing? JAMA Oncol 2016;2(6):760–1.
[15] Hatzis C, Symmans WF, Zhang Y, et al. Relationship between complete pathologic response to neoadjuvant chemotherapy and survival in triple-negative breast cancer. Clin Cancer Res 2016;22(1):26–33.
[16] Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol Off J Am Soc Clin Oncol 2007;25:4414–22. https://doi.org/10.1200/JCO.2007.10.6823.
[17] Symmans WF, Wei C, Gould R, et al. Long-term prognostic risk after neoadjuvant chemotherapy associated with residual cancer burden and breast cancer subtype. J Clin Oncol Off J Am Soc Clin Oncol 2017;35:1049–60. https://doi.org/10.1200/JCO.2015.63.1010.
[18] Peintinger F, Sinn B, Hatzis C, et al. Reproducibility of residual cancer burden for prognostic assessment of breast cancer after neoadjuvant chemotherapy. Mod Pathol 2015;28(7):913–20. https://doi.org/10.1038/modpathol.2015.53.
[19] Sheri A, Smith IE, Johnston SR, et al. Residual proliferative cancer burden to predict long-term outcome following neoadjuvant chemotherapy. Ann Oncol Off J Eur Soc Med Oncol 2015;26:75–80. https://doi.org/10.1093/annonc/mdu508.
[20] Ellis MJ, Suman VJ, Hoog J, et al. Ki67 proliferation index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: Results from the American college of surgeons oncology group Z1031 trial (Alliance). J Clin Oncol; 35: 1061–9 [no. 10 (April 1 2017)].
[21] Mittendorf EA, Jeruss JS, Tucker SL, et al. Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. J Clin Oncol 2011;29(15):1956–62. https://doi.org/10.1200/JCO.2010.31.8469.
[22] Marmé F, Lederer B, Blohmer JU, et al. Utility of the CPS+EG staging system in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer treated with neoadjuvant chemotherapy. Eur J Cancer 2016;53:65–74. https://doi.org/10.1016/j.ejca.2015.09.022.
[23] Ellis MJ, Tao Y, Luo J, et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. J Natl Cancer Inst 2008;100(19):1380–8. https://doi.org/10.1093/jnci/djn309.
[24] Ellis MJ. Lessons in precision oncology from neoadjuvant endocrine therapy trials in ER+ breast cancer. Breast 2017;34(Suppl 1):S104–7. https://doi.org/10.1016/j.breast.2017.06.039.
[25] Suman VJ, Ellis MJ, Ma CX, et al. The ALTERNATE trial: assessing a biomarker driven strategy for the treatment of post-menopausal women with ER+/Her2- invasive breast cancer. Chin Clin Oncol 2015;4(3):34. https://doi.org/10.3978/j.issn.2304-3865.2015.09.01.
[26] Savas P, Salgado R, Denkert C, et al. Clinical relevance of host immunity in breast cancer: from TILs to the clinic. Nat Rev Clin Oncol 2016;13:228–41. https://doi.org/10.1038/nrclinonc.2015.215.
[27] Kochi M, Iwamoto T, Niikura N, et al. Tumour-infiltrating lymphocytes (TILs)-related genomic signature predicts chemotherapy response in breast cancer. Breast Cancer Res Treat 2018;167:39–47. https://doi.org/10.1007/s10549-017-4502-3.
[28] Wang Y, Waters J, Leung ML, et al. Clonal evolution in breast cancer revealed by single nucleus genome sequencing. Nature 2014;512:155–60. https://doi.org/10.1038/nature13600.
[29] Denkert C, Loibl S, Noske A, et al. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol Off J Am Soc Clin Oncol 2010;28:105–13. https://doi.org/10.1200/JCO.2009.23.7370.
[30] Denkert C, von Minckwitz G, Brase JC, et al. Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. J Clin Oncol Off J Am Soc Clin Oncol 2015;33:983–91. https://doi.org/10.1200/JCO.2014.58.1967.
[31] Salgado R, Denkert C, Campbell C, et al. Tumor-infiltrating lymphocytes and associations with pathological complete response and event-free survival in HER2-positive early-stage breast cancer treated with lapatinib and trastuzumab: a secondary analysis of the NeoALTTO trial. JAMA Oncol 2015;1:448–54. https://doi.org/10.1001/jamaoncol.2015.0830.
[32] Melichar B, Študentova H, Kalábová H, et al. Predictive and prognostic significance of tumor-infiltrating lymphocytes in patients with breast cancer treated with neoadjuvant systemic therapy. Anticancer Res 2014;34:1115–25.
[33] Ono M, Tsuda H, Shimizu C, et al. Tumor-infiltrating lymphocytes are correlated with response to neoadjuvant chemotherapy in triple-negative breast cancer. Breast Cancer Res Treat 2012;132:793–805. https://doi.org/10.1007/s10549-011-1554-7.
[34] Denkert C, von Minckwitz G, Darb-Esfahani S, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. Lancet Oncol 2018;19:40–50. https://doi.org/10.1016/S1470-2045(17)30904-X.
[35] Teschendorff AE, Gomez S, Arenas A, et al. Improved prognostic classification of breast cancer defined by antagonistic activation patterns of immune response pathway modules. BMC Cancer 2010;10:604. https://doi.org/10.1186/1471-2407-10-604.
[36] Kristensen VN, Vaske CJ, Ursini-Siegel J, et al. Integrated molecular profiles of invasive breast tumors and ductal carcinoma in situ (DCIS) reveal differential vascular and interleukin signaling. Proc Natl Acad Sci U S A 2012;109:2802–7. https://doi.org/10.1073/pnas.1108781108.
[37] Seo AN, Lee HJ, Kim EJ, et al. Tumour-infiltrating CD8+ lymphocytes as an independent predictive factor for pathological complete response to primary systemic therapy in breast cancer. Br J Cancer 2013;109:2705–13. https://doi.org/10.1038/bjc.2013.634.
[38] Mahmoud SMA, Paish EC, Powe DG, et al. Tumor-infiltrating CD8+ lymphocytes

predict clinical outcome in breast cancer. J Clin Oncol Off J Am Soc Clin Oncol 2011;29:1949–55. https://doi.org/10.1200/JCO.2010.30.5037.
[39] Liu S, Lachapelle J, Leung S, et al. CD8+ lymphocyte infiltration is an independent favorable prognostic indicator in basal-like breast cancer. Breast Cancer Res BCR 2012;14:R48. https://doi.org/10.1186/bcr3148.
[40] Ali HR, Provenzano E, Dawson S-J, et al. Association between CD8+ T-cell infiltration and breast cancer survival in 12,439 patients. Ann Oncol Off J Eur Soc Med Oncol 2014;25:1536–43. https://doi.org/10.1093/annonc/mdu191.
[41] Dieci MV, Criscitiello C, Goubar A, et al. Prognostic value of tumor-infiltrating lymphocytes on residual disease after primary chemotherapy for triple-negative breast cancer: a retrospective multicenter study. Ann Oncol Off J Eur Soc Med Oncol 2014;25:611–8. https://doi.org/10.1093/annonc/mdt556.
[42] Loi S, Dushyanthen S, Beavis PA, et al. RAS/MAPK activation is associated with reduced tumor-infiltrating lymphocytes in triple-negative breast cancer: therapeutic cooperation between MEK and PD-1/PD-L1 immune checkpoint inhibitors. Clin Cancer Res Off J Am Assoc Cancer Res 2016;22:1499–509. https://doi.org/10.1158/1078-0432.CCR-15-1125.
[43] Hamy A-S, Pierga J-Y, Sabaila A, et al. Stromal lymphocyte infiltration after neoadjuvant chemotherapy is associated with aggressive residual disease and lower disease-free survival in HER2-positive breast cancer. Ann Oncol Off J Eur Soc Med Oncol 2017;28:2233–40. https://doi.org/10.1093/annonc/mdx309.
[44] Asano Y, Kashiwagi S, Goto W, et al. Prediction of survival after neoadjuvant chemotherapy for breast cancer by evaluation of tumor-infiltrating lymphocytes and residual cancer burden. BMC Cancer 2017;17:888. https://doi.org/10.1186/s12885-017-3927-8.
[45] Dieci MV, Radosevic-Robin N, Fineberg S, et al. Update on tumor-infiltrating lymphocytes (TILs) in breast cancer, including recommendations to assess TILs in residual disease after neoadjuvant therapy and in carcinoma in situ: a report of the International Immuno-Oncology Biomarker Working Group on Breast Cancer. Semin Cancer Biol 2017. https://doi.org/10.1016/j.semcancer.2017.10.003.
[46] Prat A, Pineda E, Adamo B, et al. Clinical implications of the intrinsic molecular subtypes of breast cancer. Breast Edinb Scotl 2015;24(Suppl 2):S26–35. https://doi.org/10.1016/j.breast.2015.07.008.
[47] Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61–70. https://doi.org/10.1038/nature11412.
[48] Callari M, Cappelletti V, D'Aiuto F, et al. Subtype-specific metagene-based prediction of outcome after neoadjuvant and adjuvant treatment in breast cancer. Clin Cancer Res Off J Am Assoc Cancer Res 2016;22:337–45. https://doi.org/10.1158/1078-0432.CCR-15-0757.
[49] Xie L, Li X, Wang Q, et al. Effects of core needle biopsy and subsequent neoadjuvant chemotherapy on molecular alterations and outcome in breast cancer. OncoTargets Ther 2018;11:677–85. https://doi.org/10.2147/OTT.S145715.
[50] Beitsch P, Whitworth P, Baron P, et al. Genomic impact of neoadjuvant therapy on breast cancer: incomplete response is associated with altered diagnostic gene signatures. Ann Surg Oncol 2016;23:3317–23. https://doi.org/10.1245/s10434-016-5329-6.
[51] Balko JM, Cook RS, Vaught DB, et al. Profiling of residual breast cancers after neoadjuvant chemotherapy identifies DUSP4 deficiency as a mechanism of drug resistance. Nat Med 2012;18:1052–9. https://doi.org/10.1038/nm.2795.
[52] Balko JM, Giltnane JM, Wang K, et al. Molecular profiling of the residual disease of triple-negative breast cancers after neoadjuvant chemotherapy identifies actionable therapeutic targets. Cancer Discov 2014;4:232–45. https://doi.org/10.1158/2159-8290.CD-13-0286.
[53] Cristofanilli M, Budd GT, Ellis MJ, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N Engl J Med 2004;351:781–91.
[54] Bulfoni M, Gerratana L, Del Ben F, et al. In patients with metastatic breast cancer the identification of circulating tumor cells in epithelial-to-mesenchymal transition is associated with a poor prognosis. Breast Cancer Res 2016;18:30.
[55] Pierga J-Y, Petit T, Levy C, et al. Pathological response and circulating tumor cell count identifies treated HER2+ inflammatory breast cancer patients with excellent prognosis: BEVERLY-2 survival data. Clin Cancer Res 2015;21:1298–304.
[56] Riethdorf S, Müller 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;23:5384–93.
[57] Kasimir-Bauer S, Bittner AK, König L, et al. Does primary neoadjuvant systemic therapy eradicate minimal residual disease? Analysis of disseminated and circulating tumor cells before and after therapy. Breast Cancer Res 2016;18:20.
[58] Bidard F-C, Michiels S, Mueller V, et al. Abstract S3-01: IMENEO: International MEta-analysis of circulating tumor cell detection in early breast cancer patients treated by NEOadjuvant chemotherapy. Cancer Res 2017;77:S3-1-S3-1.
[59] Pachmann K, Camara O, Kavallaris A, et al. Monitoring the response of circulating epithelial tumor cells to adjuvant chemotherapy in breast cancer allows detection of patients at risk of early relapse. J Clin Oncol 2008;26:1208–15.
[60] Riva F, Bidard F-C, Houy A, et al. Patient-specific circulating tumor DNA detection during neoadjuvant chemotherapy in triple-negative breast cancer. Clin Chem 2017;63:691–9.
[61] Garcia-Murillas I, Schiavon G, Weigelt B, et al. Mutation tracking in circulating tumor DNA predicts relapse in early breast cancer. Sci Transl Med 2015;7.302ra133-302ra133.
[62] Chen Y-H, Hancock BA, Solzak JP, et al. Next-generation sequencing of circulating tumor DNA to predict recurrence in triple-negative breast cancer patients with residual disease after neoadjuvant chemotherapy. npj Breast Cancer 2017;3:24.
[63] Olsson E, Winter C, George A, et al. Serial monitoring of circulating tumor DNA in patients with primary breast cancer for detection of occult metastatic disease. EMBO Mol Med 2015;7:1034–47.
[64] Sotiriou C, Rothé F, Maetens M, et al. Abstract GS1-04: copy number aberration analysis to predict response to neoadjuvant anti-HER2 therapy: results from the NeoALTTO phase III trial. Cancer Res 2018;78. GS1-04-GS1-04.
[65] Sharma G, Mirza S, Parshad R, et al. DNA methylation of circulating DNA: a marker for monitoring efficacy of neoadjuvant chemotherapy in breast cancer patients. Tumor Biol 2012;33:1837–43.
[66] Takahashi H, Kagara N, Tanei T, et al. Correlation of methylated circulating tumor DNA with response to neoadjuvant chemotherapy in breast cancer patients. Clin Breast Cancer 2017;17(61–69):e3.
[67] Masuda N, Lee S-J, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med 2017;376(22):2147–59.
[68] Bajetta E, Procopio G, Celio L, et al. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. J Clin Oncol 2005;7(23):2155–61.
[69] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Breast Cancer, Version 1.2018—March 20, 2018.
[70] Midgley R, Kerr DJ. Capecitabine: have we got the dose right? Nat Rev Clin Oncol 2009;6(1):17–24.
[71] Amstutz U, Froehlich TK, Largiadèr CR. Dihydropyrimidine dehydrogenase gene as a major predictor of severe 5-fluorouracil toxicity. Pharmacogenomics 2011;12(9):1321–36.
[72] Toi M, Rahman MA, Bando H, et al. Thymidine phosphorylase (platelet-derived endothelial-cell growth factor) in cancer biology and treatment. Lancet Oncol 2005;6(3):158–66.
[73] Bonotto M, Bozza C, Di Loreto C, et al. Making capecitabine targeted therapy for breast cancer: which is the role of thymidine phosphorylase? Clin Breast Cancer 2013;13(3):167–72.
[74] Puglisi F, Andreetta C, Valent F, et al. Anthracyclines and taxanes induce the up-regulation of thymidine phosphorylase in breast cancer cells. Anticancer Drugs 2007;18(8):883–8. PubMed PMID: 17667593.
[75] Joensuu H, Kellokumpu-Lehtinen P-L, Huovinen R, et al. Adjuvant capecitabine, docetaxel, cyclophosphamide, and epirubicin for early breast cancer: final analysis of the randomized FinXX trial. J Clin Oncol 2012;30(1):11–8.
[76] Joensuu H, Kellokumpu-Lehtinen P-L, Huovinen R, et al. Adjuvant capecitabine in combination with docetaxel, epirubicin, and cyclophosphamide for early breast cancer: the randomized clinical FinXX trial. JAMA Oncol 2017;3(6):793–800.
[77] Martín M, Ruiz Simón A, Ruiz Borrego M, et al. Epirubicin plus cyclophosphamide followed by docetaxel versus epirubicin plus docetaxel followed by capecitabine as adjuvant therapy for node-positive early breast cancer: results from the GEICAM/2003-10 study. J Clin Oncol 2015;33(32):3788–95.
[78] O'Shaughnessy J, Koeppen H, Xiao Y, et al. Patients with slowly proliferative early breast cancer have low five-year recurrence rates in a phase III adjuvant trial of capecitabine. Clin Cancer Res 2015;21(19):4305–11.
[79] Kelly CM, Green MC, Broglio K, et al. Phase III trial evaluating weekly paclitaxel versus docetaxel in combination with capecitabine in operable breast cancer. J Clin Oncol 2012;30(9):930–5.
[80] Kuroi K, Toi M, Ohno S, et al. Prognostic significance of subtype and pathologic response in operable breast cancer; a pooled analysis of prospective neoadjuvant studies of JBCRG. Breast Cancer 2015;22(5):486–95.
[81] Natori A, Ethier JL, Amir E, et al. Capecitabine in early breast cancer: a meta-analysis of randomised controlled trials. Eur J Cancer 2017;77:40–7.
[82] Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2016;17:367–77.
[83] Gonzalez-Angulo AM, Lei X, Alvarez RH, et al. Phase II randomized study of ixabepilone versus observation in patients with significant residual disease after neoadjuvant systemic therapy for HER2-negative breast cancer. Clin Breast Cancer 2015;15(5):325–31.
[84] von Minckwitz G, Rezai M, Tesch H, et al. Zoledronate for patients with invasive residual disease after anthracyclines-taxane-based chemotherapy for early breast cancer – the Phase III NeoAdjuvant Trial Add-oN (NaTaN) study (GBG 36/ABCSG 29). Eur J Cancer 2016;64:12–21.
[85] Dhesy-Thind S, Fletcher GG, Blanchette PS, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a cancer care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2017;35(18):2062–81. https://doi.org/10.1200/JCO.2016.70.7257.
[86] Hu ZI, McArthur HL. Immunotherapy in breast cancer: the new frontier. Curr Breast Cancer Rep 2018;10(2):35–44.
[87] Basile D, Pelizzari G, Vitale MG, et al. Atezolizumab for the treatment of breast cancer. Expert Opin Biol Ther 2018;18(5):595–603. https://doi.org/10.1007/s12609-018-0274-y. Epub 2018 Apr 16.
[88] Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol 2015;33(1):13–21.
[89] Yardley DCR, Conte P, Cortes J, et al. Nab-paclitaxel + carboplatin or gemcitabine vs gemcitabine/carboplatin as first-line treatment for patients with triple-negative metastatic breast cancer: results from the randomized phase 2 portion of the tnAcity trial [abstract]. Proceedings of the 2016 San Antonio Breast Cancer Symposium; 2016 Dec 6-10; San Antonio, TX. Philadelphia (PA): AACR; 2016. Cancer Res 2017;77(4 Suppl):Abstract nr P5-15-03.
[90] Gerratana L, Fanotto V, Pelizzari G, et al. Do platinum salts fit all triple negative breast cancers? Cancer Treat Rev 2016;48:34–41.
[91] Miller KTY, Jones DR, Walsh T, et al. Cisplatin with or without rucaparib after preoperative chemotherapy in patients with triple negative breast cancer: final

efficacy results of Hoosier oncology group BRE09-146. J Clin Oncol 2015;33(Suppl):1082. abst.
[92] Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. Lancet Oncol 2018;19(4):497–509. https://doi.org/10.1016/S1470-2045(18)30111-6.
[93] Gerratana L, Bonotto M, Bozza C, et al. Pertuzumab and breast cancer: another piece in the anti-HER2 puzzle. Expert Opin Biol Ther 2017;17(3):365–74. https://doi.org/10.1080/14712598.2017.1282944. Epub 2017 Jan 30.
[94] 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(2):122–31. https://doi.org/10.1056/NEJMoa1703643.
[95] Kwapisz D. Cyclin-dependent kinase 4/6 inhibitors in breast cancer: palbociclib, ribociclib, and abemaciclib. Breast Cancer Res Treat 2017;166(1):41–54. https://doi.org/10.1007/s10549-017-4385-3.
[96] Denduluri N, Chavez-MacGregor M, Telli ML, et al. Selection of optimal adjuvant chemotherapy and targeted therapy for early breast cancer: ASCO clinical practice guideline focused update. J Clin Oncol 2018;36(23):2433–43. https://doi.org/10.1200/JCO.2018.78.8604.