Breast cancer

Nadia Harbeck, Michael Gnant

Lancet 2017; 389: 1134–50
Published Online November 16, 2016 http://dx.doi.org/10.1016/S0140-6736(16)31891-8

Breast Center, Department of Gynecology and Obstetrics, Comprehensive Cancer Center of the Ludwig-Maximilians-University, Munich, Germany (Prof N Harbeck MD); **and Department of Surgery and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria** (Prof M Gnant MD)

Correspondence to: Prof Nadia Harbeck, Breast Center, University of Munich, 81377 Munich, Germany **nadia.harbeck@med.uni-muenchen.de**

Breast cancer is one of the three most common cancers worldwide. Early breast cancer is considered potentially curable. Therapy has progressed substantially over the past years with a reduction in therapy intensity, both for locoregional and systemic therapy; avoiding overtreatment but also undertreatment has become a major focus. Therapy concepts follow a curative intent and need to be decided in a multidisciplinary setting, taking molecular subtype and locoregional tumour load into account. Primary conventional surgery is not the optimal choice for all patients any more. In triple-negative and HER2-positive early breast cancer, neoadjuvant therapy has become a commonly used option. Depending on clinical tumour subtype, therapeutic backbones include endocrine therapy, anti-HER2 targeting, and chemotherapy. In metastatic breast cancer, therapy goals are prolongation of survival and maintaining quality of life. Advances in endocrine therapies and combinations, as well as targeting of HER2, and the promise of newer targeted therapies make the prospect of long-term disease control in metastatic breast cancer an increasing reality.

Breast cancer: epidemiology

Breast cancer is the most common malignancy in women, and one of the three most common cancers worldwide, along with lung and colon cancer. In 2012, almost 1·7 million people were diagnosed worldwide and about half a million people died from this disease.[1,2] One in eight to ten women will get breast cancer during their lifetime. Mortality from breast cancer in North America and the European Union (EU) has decreased, and this decrease is mostly attributable to early detection and efficient systemic therapies. In 2016, mortality from breast cancer in the EU is expected to drop by 8%.[3] Nevertheless, breast cancer is still the most common cause of death from cancer in less developed countries and second to lung cancer in more developed countries. In South America, Africa, and Asia, the incidence of breast cancer is increasing—most probably because of lifestyle changes and initiated screening programmes. Mortality from breast cancer in these regions is also still increasing, partly because of a lack of access to state-of-the-art diagnosis and therapy.[2]

Early breast cancer: treatment concepts and biology

Early breast cancer without detectable distant metastases is a potentially curable disease. After diagnosis, therapy concepts need to be decided in a multidisciplinary team meeting (tumour board). Primary surgery and removal of the tumour might not be the best option for every patient even though this could be the patient's initial logical request. Yet, for certain biological tumour subtypes such as triple-negative breast cancer or HER2-positive disease, primary systemic therapy could be better suited, on the basis of the multidisciplinary team meeting recommendation and shared decision making with the patient.

Before finalising the therapeutic concept, clinical examination and thorough breast imaging (mammography, breast ultrasound) need to be completed. Diagnosis of malignancy is usually verified by core biopsy. Breast MRI needs to be restricted to specific situations, such as hereditary breast cancers, dense tissue and lobular histology, and suspected multicentric disease.[4] A large meta-analysis[5] (two randomised trials and seven comparative cohorts, 3112 patients) suggested an unfavourable harm–benefit ratio for routine use of preoperative MRI with an increased initial proportion of women with initial mastectomy (16·4% for preoperative MRI *vs* 8·1% for no preoperative MRI; odds ratio [OR] 2·22; p<0·001) and no reduction in the proportion of women who had a re-excision after initial breast conservation (11·6% for preoperative MRI *vs* 11·4% for no preoperative MRI; OR 1·02; p=0·87).

Staging and search for metastases is only needed in symptomatic patients or in those at high risk for relapse. The prevalence of metastasis in asymptomatic patients is high in large tumours (diameter >5 cm [15%]) or in patients with extensive nodal disease (>three involved lymph nodes [4%]).[6] Routine staging examinations consist of chest radiograph, abdominal ultrasound, and bone scan. Yet, CT scans might be better suited for patients who are at high risk or symptomatic because of their high sensitivity.

Search strategy and selection criteria

We searched MEDLINE between June 16, 2015, and June 19, 2016 with no language restrictions. We used the search terms "breast cancer" in combination with specific terms covering the different steps of diagnosis and treatment as appropriate. We largely selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are also cited to provide readers with more details and more references than this Seminar was able to. We also added research from the 2015 and 2016 ASCO conferences, and from ESMO 2015 and 2016, as well as the 2014 and 2015 San Antonio Breast Cancer Symposia that have not yet been published as full papers. Our reference list was modified based on comments from the peer reviewers.

Since the groundbreaking work of Perou, Sørlie, and colleagues[7,8] at the beginning of this millennium, breast cancer is considered to consist of at least four different clinically relevant molecular subtypes: luminal A, luminal B, HER2-enriched, and basal like. Yet, scientifically, up to ten different molecular subtypes have been identified using gene copy number and expression analyses.[9]

In formalin-fixed paraffin-embedded tumour samples, the four original subtypes can either be directly determined with a multigene assay such as Prosigna (NanoString Technologies) or Blueprint (Agendia) or indirectly reconstructed with immunohistochemically determined steroid hormone receptor (oestrogen receptor [ER], progesterone receptor [PgR]) and HER2 status, as well as tumour proliferation measured by Ki67 as follows: luminal A-like subtype (ER or PgR positive, or both, HER2 negative, low proliferation); luminal B-like subtype (ER or PgR positive, or both, HER2 negative, high proliferation); HER2 subtype, non-luminal (HER2 positive and ER and PgR negative) or luminal (HER2 positive and ER or PgR positive, or both); basal-like subtype (HER2 negative and ER and PgR negative; triple-negative breast cancer). In accordance with the St Gallen consensus, systemic therapy for early breast cancer could be guided by these molecular subtypes (figure 1).[11,12]

In daily clinical practice, the difficulty is distinguishing between luminal A and luminal B tumours on the basis of proliferation assessed by local non-standardised Ki67 values. Values of 10% or less are generally considered low risk, and values between 20% and 29% are considered as a minimum criterion for high proliferation.[12] Yet, because of the lack of a prospectively validated cutoff, intermediate Ki67 values between 10% and about 30% should not be used as the sole criterion for indicating adjuvant chemotherapy in luminal B tumours. International standardisation for Ki67 is still missing and the measured interlaboratory variability is rather high.[13] Thus, internationally developed standards[14] urgently need to be implemented on a local level.

The final multidisciplinary management plan in early breast cancer is based on molecular subtype, locoregional tumour load, and patients' wishes.

Early breast cancer: local therapy

Surgery

Breast conservation is established as the intended surgical standard of care for most clinical situations in breast cancer.[15] Developments in surgical techniques (oncoplastic procedures)[16] and multidisciplinary approaches (primary systemic therapy), as well as increased treatment of patients in dedicated and certified breast units, have improved women's access to this organ-saving surgical approach.[17]

While the overarching principle of achieving clear margins remains the surgical standard of care, a decade-long surgical debate appears to have come to an end—the issue of margin details. The evidence since 2012 speaks for "no ink on tumour" as the state-of-the-art strategy,[18,19] rather than surgical fighting for millimetres of clearance—this strategy has an enormous implication for both diagnostic and therapeutic strategies. For example, re-excisions after breast-conserving surgery should virtually disappear unless grossly involved margins are present after primary surgery, maybe even more so after newly emerged surgical techniques such as cavity shaving.[20] The continuing controversy about intraoperative frozen section is less a scientific one, since it is clear that intraoperative margin assessment further improves surgical results[21] and reduces the occurrence of re-excision, but rather a discussion about health-care resources and their availability.[22]

Breast conservation is nowadays technically feasible in many clinical situations that had earlier led to primary mastectomy because of advances in oncoplastic surgical techniques[23] and the increased success of neoadjuvant tumour-shrinking drug therapies. Yet, a concerning development is the increase in voluntary mastectomy, including voluntary contralateral (prophylactic) breast amputation, observed particularly in the USA.[24] Although it is certainly correct to eventually accept patient's choice, physicians have a clear ethical responsibility to impartially and completely inform patients about the options and consequences, including the fact that fear is not a good indication for mutilating surgery. Clear evidence exists that contralateral mastectomy does neither lower mortality nor improve survival.[25,26]

Neoadjuvant systemic treatment has emerged as a standard of care for treatment situations in which primary breast conservation is not possible because of tumour size or the association of the tumour and breast size,[27] provided that the patient has a chemotherapy indication at all. Both

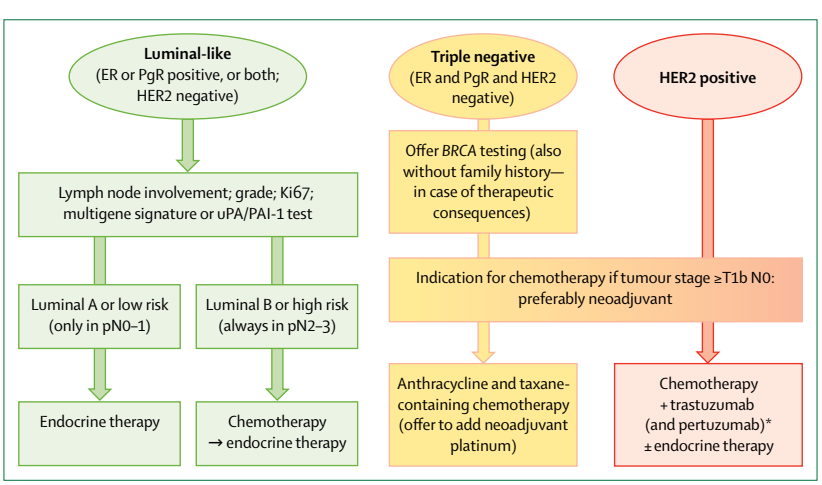

Figure 1: **Principles of systemic therapy in early breast cancer**
Summary of general treatment strategies, updated after the publication of Harbeck and colleagues, 2010.[10] For an individual patient, therapy decisions can differ since tumour and disease characteristics and patients' preferences are key elements in deciding the individual treatment strategy. ER=oestrogen receptor. PgR=progesterone receptor. *Dual HER2 blockade only registered for neoadjuvant setting. Endocrine therapy always indicated if ER or PgR positive, or both.

cytotoxic chemotherapy and endocrine therapy are used, and targeted therapy is used depending on the tumour biology.[28] For HER2-positive disease and triple-negative breast cancer, pathological complete response is high (60% or more),[29] and correlated with long-term outcome,[30] which is less clear for luminal breast cancer. Even in subtypes that allow a pathological complete response in more than 50% of patients, surgery to remove the remaining tumour or verify pathological complete response remains necessary, even though this option might be questioned by future clinical research. With a high pathological complete response occurrence and proven long-term benefit, particularly in the HER2-positive subtype, surgical issues might become less relevant in determination of the optimum primary treatment approach. Some clinicians might even advocate primary systemic therapy (chemotherapy plus anti-HER2 treatment) for all HER2-positive tumours, almost irrespective of tumour size (most experts suggest 1 cm as a reasonable limit). Yet, overtreatment for simple local tumour reduction needs to be avoided and neoadjuvant systemic therapy should only be given if the same therapy was indicated in the adjuvant setting. Nevertheless, neoadjuvant treatment offers a situation in which new drugs can be explored, even though reliable surrogate parameters for long-term outcomes are not always available.[31]

Surgery after neoadjuvant chemotherapy has dramatically changed. From the rule of excising the original tumour bed that had initially weakened the effect of neoadjuvant therapies on the prevalence of breast conservation, the development has gone to no ink on tumour after primary systemic treatment as well.[32] However, not all tumours shrink concentrically, and after neoadjuvant endocrine therapy the assessment of margins can be particularly challenging.[33] Definitely, clear margins must be achieved in this surgical situation as well. Mastectomies after pathological complete response, as reported in earlier trials,[29,34] should be avoided whenever possible. Since 2014, margin assessment after neoadjuvant systemic therapy has been standardised, which should allow for better cross-trial comparison in the future.[35,36]

The value of preoperative MRI remains controversial. Although high-quality MRI in a multidisciplinary setting can clearly improve surgical planning, the concern remains that the lack of specificity in detecting multicentric lesions could lead to unnecessarily increased mastectomy rates.[37,38] Thus, reason and common sense should be applied: although a truly multicentric tumour needs to be diagnosed properly before surgical planning (biopsy), a mastectomy indication solely based on an MRI is a mistake.

Over the past two decades, axillary surgery has substantially changed. Although level I/II lymph node dissection used to be the standard approach, the sentinel node procedure is now the state-of-the-art approach, saving patients with negative nodes from the unnecessary and avoidable side-effects of axillary surgery.[39,40] A variety of methods to reliably detect the sentinel node have been established and used in clinical practice.[39,41,42] The issue of axillary surgery after neoadjuvant systemic treatment remains controversial: pretreatment sentinel node biopsy appears to be an option; post-treatment sentinel node surgery is less reliable.[43] The differentiation regarding better or worse response of the disease and its respective implications on surgical strategies remains unclear.[44] It definitely makes a difference for further surgical (and radiotherapy) management, irrespective of whether the lymph nodes are affected before any therapy or not, and efforts are being made to clarify this differential impact on management by imaging and histology before the start of neoadjuvant therapy.[45–47]

Moreover, the need for completion axillary dissection in patients with a limited number of positive sentinel nodes remains a huge controversy: the pivotal ACOSOG Z0011 trial[41] described no outcome difference between dissection of axillary lymph node or no dissection, but severe criticism of some aspects of the methods of this trial and a few other trials was voiced. Although reports that axillary lymph node dissection can be safely omitted after a positive-sentinel node are accumulating,[48] it appears wise to remain cautious on this issue until reliable long-term (10 years or more) data and exact description of radiotherapy approaches[49] in all studies have been reported.

Radiotherapy

Another option of handling a positive-sentinel node could be axillary radiotherapy: the AMAROS trial[50] established this technique as a non-inferior option versus axillary lymph node dissection. However, several concerns about the methods have to be raised—the inadequate prevalence of level III dissections and wound infections in the surgery group might have affected the shoulder mobility data—and suggest caution when interpreting the results.

With respect to radiotherapy approaches to breast cancer, there are conflicting developments to note: less-invasive radiotherapy strategies have been established, such as partial breast irradiation[51,52] or hypofractionated radiotherapy[53] that decrease patient burden.[54] Intraoperative radiotherapy has been used as boost[55] or stand-alone radiation therapy,[56] both again aiming to reduce side-effects and logistical efforts for patients. Trials aiming to omit radiotherapy after breast conservation altogether in low-risk situations have not yielded convincing results. Yet, in the scientific community, a belief remains that such a population exists and could be identified in the future.[57] Although a small numerical benefit might exist in terms of local control, also for older patients (eg, older than 70 years), this difference is highly unlikely to translate into any relevant differences in longer-term survival.[58–60]

Based on recent pivotal trials, current clinical practice tends to extend radiotherapy fields to the axilla, and

supraclavicular and parasternal radiation fields.[61] The EORTC trial[62] suggested a 5-year overall survival benefit at borderline statistical significance (82·3% in the nodal-irradiation group *vs* 80·7% in the control group [hazard ratio for death with nodal irradiation, 0·87; 95% CI 0·76–1·00; p=0·06]). The MA-20 trial[63] reported that among women with node-positive or high-risk node-negative breast cancer, the addition of regional nodal irradiation to whole-breast irradiation did not improve overall survival but reduced the recurrence of breast cancer. In a meta-analysis[64] and investigation of these two trials[62,63] and the French trial, both overall and metastasis-free survival benefits were significant,[65] and the approach of extended radiotherapy approaches appeared to gain momentum.[64]

Nodal irradiation is increasingly advocated because of omission of axillary surgery even in cases of positive or suspicious nodes. Yet, many experienced clinicians remain concerned that we might partially be giving up the advantages we have gained for our patients by limiting surgical aggressiveness in breast and axilla by implementing more aggressive radiotherapy strategies, which ultimately could even lead to increased long-term toxicity.[66] However, modern radiation-field planning will almost certainly improve the previous occurrence of cardiac toxicity.[67]

The issue of radiotherapy for patients with one to three involved lymph nodes remains controversial, with only part of the studies indicating an overall survival benefit.[68] However, modern radiotherapy has resolved some previously discussed issues, such as the boost (dose).[69]

Early breast cancer: systemic therapy

Indication for systemic therapy

The most frequent tumour biology is HER2-negative luminal tumours (around 70%) in which the indication for neoadjuvant or adjuvant chemotherapy depends on further criteria such as proliferation, tumour grade, or lymph node involvement. Since only a few breast cancer centres routinely determine molecular subtype by a multigene assay, immunohistochemistry is mostly used to distinguish luminal A biology from luminal B. Yet, in tumours that are hormone-receptor positive with an intermediate Ki67 between 10% and 30%, this distinction cannot be made easily. Thus, other criteria for assessing risk of recurrence and response to chemotherapy are needed.

In general, patients with an estimated relapse risk of more than 10% over the course of 10 years are viewed as potential candidates for neoadjuvant or adjuvant chemotherapy. In intermediate-risk patients (pN0–1) with luminal tumours, several multigene assays (eg, Endopredict [Myriad Genetics],[70] MammaPrint [Agendia],[71] Oncotype DX [Genomic Health],[72] Prosigna[73]) have been validated for risk assessment and a few have been validated for prediction of chemotherapy response (table 1). Most of these assays give information not only about risk of early recurrence (first 5 years), but also about risk of late recurrence (>5 years). Prospective trial results for test validation only exist for Onkotype DX and MammaPrint. For Oncotype DX, the TAILORx Trial for pN0[74] and the WSG PlanB Trial for pN0–1[75] prospectively confirmed its prognostic effect. For MammaPrint, the MINDACT trial[76] showed that patient outcome is not compromised if adjuvant chemotherapy is omitted in clinically high-risk and genomically low-risk early breast cancer. All other multigene assays have only been retrospectively validated. Prospective outcome data are still missing from the randomised comparisons of the large international trials that used Onkotype DX for risk group assessment (ie, TAILORx [pN0], RxPONDER [pN1]).

The protein-based ELISA assay for uPA/PAI-1 (Femtelle [American Diagnostica/Sekisui]) has also been validated at the highest level of evidence for its prognostic and predictive effect by a prospective clinical trial[77] and a European Organisation for Research and Treatment of Cancer-pooled analysis.[78] By contrast with multigene assays, this test requires fresh-frozen tumour tissue; but if the logistics can be implemented, it can be an alternative option for risk assessment because of its low overall costs.[79] Last, but not least, prognosis can also be estimated on the basis of prognostication tools driven by clinical data, such as the PREDICT algorithm.[80]

Endocrine therapy

In all luminal—ie, hormone-receptor-positive (ER or PgR positive, or both)—early breast cancer, adjuvant endocrine therapy over the course of 5–10 years is considered standard. Current guidelines consider any ER or PgR staining (ie, ≥1%) as being positive; endocrine sensitivity is directly correlated to the degree of hormone receptor positivity.[81]

In premenopausal patients, 20 mg tamoxifen per day is the standard endocrine therapy. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis[81] showed that 5 years of tamoxifen treatment reduced the recurrence not just in the first 4 years (risk ratio [RR] 0·53; p<0·0001), but also in years 5–9 (RR 0·68; p<0·0001) in patients with ER-positive disease. This effect was independent of PgR status, age, nodal status, and chemotherapy use. Breast cancer mortality was reduced by about a third throughout the first 15 years of follow-up.[82]

In premenopausal patients at a high risk for relapse (ie, after chemotherapy or age ≤35 years), the addition of ovarian suppression drugs (gonadotropin-releasing hormone agonist [GnRH]) to tamoxifen or even administering GnRH together with an aromatase inhibitor might enhance efficacy, according to the SOFT and TEXT trial[82,83] results. So far, the data from SOFT and TEXT[82,83] only show superior disease-free survival for GnRH with tamoxifen or GnRH with aromatase inhibitor, but no overall survival advantage. As the final analysis of ABCSG trial 12[84] showed a significantly higher mortality in premenopausal patients after 3 years of GnRH with aromatase inhibitor versus GnRH with tamoxifen (hazard

	Oncotype DX	Endopredict	Mammaprint	Prosigna
Manufacturer	Genomic Health	Sividon (distribution by Myriad)	Agendia	NanoString Technologies
Assay	21 gene recurrence score	11 gene assay	70 gene assay	50 gene assay (PAM 50, ROR score)
Tissue	FFPE	FFPE	FFPE (technical validation of original fresh-frozen tissue assay)	FFPE
Method	Quantitative RT-PCR	Quantitative RT-PCR	RNA microarray	nCounter Technology
Laboratory	Centralised (USA)	Decentralised	Centralised (Netherlands)	Decentralised
Registration or accreditation	Clinical Laboratory Improvement Amendment, College of American Pathologists	CE-Mark	FDA (In Vitro Diagnostic Multivariate Index Assay)	FDA (510k), CE-Mark
Determination of molecular subtype	No	No	Yes (using Blueprint)	Yes (not reported in USA)
Prognostic information (outcome)	Yes	Yes	Yes	Yes
Risk groups	Low, intermediate, high	Low *vs* high	Low *vs* high	Low, intermediate, high
Predictive information (response to adjuvant chemotherapy)	Yes	No data so far	Yes	No data so far
Evidence-based test indication	pN0-1, ER-positive, endocrine therapy	pN0-1, ER-positive, HER2-negative, endocrine therapy	pN0-1	pN0-1, ER-positive, HER2-negative, endocrine therapy, postmenopausal
Retrospective clinical validation*	NSABP B14 and B20; TransATAC; ECOG 9127; SWOG 8814	ABCSG 6 and 8; TransATAC	Multicentre	ABCSG 8; TransATAC; MA.21
Prospective clinical trials	WSG-Plan B (3198 patients); WSG ADAPT (around 5000 patients); TAILORx (pN0; 10 253 patients); RxPONDER (pN1; around 9000 patients)	TUM (DI unicentre study, 167 patients)	MINDACT (BIG; WSG for Germany; 6693 patients); WSG PRIME (DI study; 34 centres; 452 patients)	Several European DI studies: WSG (11 centres, 200 patients); GEICAM; French multicentre study

FFPE=formalin-fixed, paraffin-embedded. FDA=Food and Drug Administration. ER=oestrogen receptor. DI=decision impact. *Cohort for translational research only, a subgroup of total study collective.

Table 1: **Commonly used multigene assays for risk assessment in early breast cancer**

ratio [HR] 1·63; 95% CI 1·05–1·45; p=0·030), the indication for GnRH with aromatase inhibitor and the respective side-effect profiles need to be carefully discussed with premenopausal patients.

In postmenopausal patients, tamoxifen and aromatase inhibitors are both valid therapeutic options, either as monotherapy for 5 years or in sequence. In the sequence setting, aromatase inhibitors significantly reduce recurrences by about 30%, but not mortality, compared with tamoxifen. In the upfront setting, 5 years of treatment with aromatase inhibitors significantly reduces breast cancer mortality by about 15% compared with 5 years of tamoxifen treatment.[85] In postmenopausal patients at a high risk for relapse[86] or with a lobular histology,[87] upfront aromatase inhibitor therapy is preferred. In all other patients, choice and sequence need to be decided on an individual basis, since both options have distinct side-effect patterns: in the EBCTCG meta-analysis,[85] fewer endometrial cancers were reported with aromatase inhibitor than with tamoxifen (10-year incidence of 0·4% for aromatase inhibitor *vs* 1·2% for tamoxifen), but more bone fractures occurred (5-year risk of 8·2% for aromatase inhibitor *vs* 5·5% for tamoxifen). Non-breast-cancer mortality was similar between aromatase inhibitor and tamoxifen.

So far, trial data have supported use of aromatase inhibitors for a total of 5 years, either in the upfront[86] or in the extended adjuvant therapy setting.[88] The results of the Australian LATER trial[89] showed that late introduction of letrozole in women after 4 years or more of adjuvant endocrine therapy for more than 1 year before study entry significantly reduced late invasive events of breast cancer. The results of the MA17.R trial[90] showed that after 5 years of tamoxifen, prolongation of extended adjuvant therapy with letrozole from 5 years to 10 years in total is beneficial in postmenopausal patients regarding disease-free survival (5-year disease-free survival of 95% for letrozole treatment for 10 years *vs* 91% for letrozole treatment for 5 years; HR 0·66; p=0·01) and particularly regarding prevention of contralateral disease (0·21% annual incidence after letrozole treatment *vs* 0·49% after placebo; p=0·007). Overall survival did not differ significantly between the two study arms. The ATLAS trial[91] showed that continuation of tamoxifen for another 5 years, up to 10 years in total, significantly reduced breast cancer recurrence and mortality. The trialists

concluded that 10 years of tamoxifen almost halves breast cancer mortality during the second decade after diagnosis compared with 5 years of tamoxifen. However, this conclusion remains controversial since longer tamoxifen therapy was also associated with increased side-effects, and some earlier studies[92,93] did not report better outcomes with longer duration of tamoxifen therapy.

When prolonging adjuvant endocrine therapy beyond 5 years, potential risks and benefits need to be carefully balanced.[94] Multigene assays are able to also assess long-term relapse risk and could therefore be helpful for decisions on duration of adjuvant endocrine therapy.[95]

If chemotherapy is also indicated, adjuvant endocrine therapy should be given consecutively,[96] even though other data exist that show no difference in efficacy either way.[97]

Chemotherapy

In early breast cancer, preoperative chemotherapy is equally effective as postoperative chemotherapy regarding disease-free survival and overall survival.[98] However, neoadjuvant chemotherapy should only be performed if the patient has an indication for adjuvant chemotherapy. Here, locoregional tumour load, molecular subtype, and risk of relapse need to be considered as "low absolute risk implies low absolute benefit".[99] Although high nodal involvement is associated with high relapse risk, the issue of micrometastases in sentinel lymph nodes appears to be settled—they have little, if any, effect on outcome and can be ignored in clinical decision making.[100,101]

Next to the advantage of better operability after neoadjuvant chemotherapy, this concept is particularly recommended in patients with triple-negative breast cancer and HER2-positive disease. These subtypes have a good correlation of pathological complete response with patient outcome.[30] This association might help to inform patients about their prognosis after surgery. Moreover, international clinical trials are now available for patients without pathological complete response. In the neoadjuvant setting, all chemotherapy should be administered before surgery to maintain dose intensity; sandwich chemotherapy thus needs to be avoided outside of clinical trials.

Adjuvant chemotherapy should be started within the first few weeks after surgery as each additional week after 3–4 weeks could impair outcome.[102] However, not all studies give such a narrow time window. In 2016, a population-based analysis showed that delays beyond 91 days between surgery and start of adjuvant chemotherapy are associated with an impaired outcome, particularly in triple-negative breast cancer.[103]

The current chemotherapy standards in early breast cancer are anthracylines and taxanes, given as a combination or in sequence over a period of 18–24 weeks (table 2). Generally, recommended regimens do not differ between neoadjuvant and adjuvant settings. The EBCTCG meta-analysis[99] suggested that anthracycline-containing and taxane-containing chemotherapy reduced 10-year breast cancer mortality by about a third. An anthracycline and taxane sequence is as effective as their combination.[104,105] Four times anthracycline followed by four times docetaxel is equally effective as the combination of the same drugs (six times TAC [docetaxel, doxorubicin, and cyclophosphamide]) but has a different toxicity pattern.[106] TAC requires granulocyte-colony-stimulating factor support because of its high rate of febrile neutropenia. After four cycles of anthracyclines, weekly paclitaxel and three-weekly docetaxel are the preferred taxane regimens.[107] The addition of 5-fluorouracil to an EC (epirubicin and cyclophosphamide)-paclitaxel sequence does not seem to improve efficacy or patient outcome.[108] Similarly, the addition of other drugs such as capecitabine[109] or gemcitabine[105] to an anthracycline-taxane regimen was not successful in phase 3 trials. Most probably, additional drugs require dose modifications for the standard drugs that then affect efficacy.

The anthracycline-free combination of four times docetaxel and cyclosphosphamide (TC) is superior to four times anthracycline and cyclophosphamide (AC) regarding disease-free survival (81% for TC *vs* 75% for AC; HR 0·74;

	Drugs	Dose	Interval	Remarks
Four times epirubicin (E; or doxorubicin [A]) + cyclophosphamide (C)—12 times paclitaxel (P; or four times docetaxel [T])	E (or A) + C, P or T	90 mg/m² E (or 60 mg/m² A) and 600 mg/m² C, 80 mg/m² P (or 100 mg/m² T)	EC (or AC) every 21 or every 14 days, P weekly (T every 21 days)	Dose dense every 14 days; requires primary GCSF prophylaxis
Six times docetaxel (T), doxorubicin (A), cyclophosphamide (C)	TAC	75 mg/m² T, 50 mg/m² A, 500 mg/m² C	Every 21 days	Requires primary GCSF prophylaxis
Four or six times docetaxel (T) and cyclophosphamide (C)	TC	75 mg/m² T and 600 mg/m² C	Every 21 days	Anthracycline-free
Epirubicin (E), paclitaxel (T), cyclophosphamide (C)	ETC	150 mg/m² E, 225 mg/m² T, and 2000 mg/m² C	Each 3 times, every 14 days	Dose dense requires primary GCSF prophylaxis
Carboplatin	Added to P weekly	AUC=5 or 6, AUC=2	AUC 5 or 6 every 21 days; AUC 2 weekly	Optional in triple-negative breast cancer

GCSF=granulocyte-colony stimulating factor. AUC=area under curve.

Table 2: **Commonly used evidence-based chemotherapy regimens for patients with early breast cancer**

95% CI 0·56–0·98; p=0·033) and overall survival (87% for TC *vs* 82% for anthracycline; HR 0·69; 0·50–0·97; p=0·032).[110] In an early prespecified interim pooled analysis for futility of the US ABC trials,[111] statistical non-inferiority could not be shown for six cycles of TC versus anthracycline followed by paclitacel or docetaxel (4242 patients; HR 1·202; 0·97–1·49). A small but significant difference (2·5%) in invasive disease-free survival existed, favouring the standard anthracycline-taxane sequence but no difference in overall survival. Thus, four to six cycles of TC are not a standard for all patients, but are an effective chemotherapy option if anthracyclines need to be avoided.

Results of several trials in node-positive high-risk disease have shown that dose-dense chemotherapy improves outcome in early breast cancer compared with standard interval chemotherapy. In the GIM trial (2091 patients, node-positive),[108] dose-dense (every 14 days) administration of an anthracycline-taxane sequence (FEC-paclitaxel or EC-paclitaxel) significantly improved 5-year disease-free survival compared with standard administration every 21 days (81% for treatment every 14 days *vs* 76% for treatment every 21 days; HR 0·77; 0·65–0·92; p=0·004) and overall survival (94% for treatment every 14 days *vs* 89% for treatment every 21 days; 0·65, 0·51–0·84; p=0·001). In patients with more than four involved lymph nodes, dose-dense and dose-intensified epirubicin, paclitaxel, and cyclophosphamide (IDD-ETC) led to a significant reduction in relapse (28%, p<0·001) and mortality (24%, p=0·0285), but also to more haematological and non-haematological toxicities than EC-paclitaxel treatment every 21 days.[112] Similar superiority of dose-dense EC-paclitaxel every 14 days versus every 21 days was seen in the CALGB 9741 trial.[104] In the MA21 trial,[113] dose-dense and dose-intensified EC followed by paclitaxel weekly was superior to standard three-weekly AC-paclitaxel but equivalent to CEF (cyclophosphamide, epirubicin, and 5-fluorouracil; 60 mg epirubicin per m² given on days 1 and 8).

Data from chemotherapy trials exist for patients with early breast cancer up to about age 70 years; however, biological age is more important than chronological age when indicating chemotherapy in elderly patients. Standard chemotherapies are preferred for fit older patients.[114] Dose and schedule can be tailored according to the special requirements of an elderly patient, as stated by the International Society of Geriatric Oncology (SIOG).[115]

For patients with triple-negative breast cancer, standard regimens containing anthracycline and taxane should be used, preferably as neoadjuvant therapy. Since 2014, trials have indicated that adding platinum to a neoadjuvant anthracycline-taxane combination or sequence improves pathological complete response.[116–118] Additionally, the GeparSixto trial[119] showed a disease-free survival advantage after adding carboplatin weekly (area under the curve 1·5) to an anthracycline-taxane combination. Yet, the addition of carboplatin every 3 weeks to a four times dose dense AC (every 2 weeks)-weekly paclitaxel sequence improved pathological complete response but not patient outcome in CALGB 40603.[120] While preclinical data and data from the TNT trial of metastatic breast cancer[121] suggest that the benefit of platinum could be greatest in *BRCA1/2* mutation carriers, exploratory analyses from GeparSixto[122] suggest that the platinum benefit is also present in patients with wildtype *BRCA*.

In summary, since platinum adds toxicity and conflicting data exist regarding a pathological complete response[123] and a potential survival benefit[118] (table 3), the addition of platinum to standard chemotherapy should be carefully discussed with all patients with triple-negative breast cancer. *BRCA1/2* mutations are present in more than 10% of unselected patients with triple-negative breast cancer with significantly higher mutation rates in patients younger than 40 years.[124]

Management of HER2-positive disease

Adding trastuzumab to an anthracycline-taxane sequence and then continuing the antibody therapy for up to 1 year substantially improves overall survival (HR 0·63, 0·54–0·73; p<0·001);[125] concurrent administration of trastuzumab with the taxane seems more effective.[126] The role of anthracyclines in HER2-positive disease remains controversial. Docetaxel, carboplatin, and trastuzumab (TCH) is an anthracycline-free alternative to the anthracycline-taxane sequence. With TCH, cardiac toxicity is significantly less, but efficacy is also lower than with the anthracycline-taxane sequence plus trastuzumab (5-year disease-free survival of 81% for TCH *vs* 84% for anthracycline-taxane sequence plus trastuzumab).[127] This outcome was confirmed by the long-term (10 year) data,[128] and TCH thus constitutes a valid option for HER2-positive disease, particularly for patients with cardiac comorbidities.

Standard duration of trastuzumab therapy in patients with early breast cancer remains at 1 year total. The results of the HERA trial[129] showed that 2 years of trastuzumab did not improve efficacy compared with 1 year of tratsuzumab. The PHARE[130] and a HORG[131] trials did not show non-inferiority of treatment for 6 months versus 12 months.

The therapy benefit of adjuvant trastuzumab is independent of tumour size.[132] Nevertheless, overtreatment of low-risk patients is a relevant clinical issue, and not all patients with HER2-positive tumours need combination chemotherapy (or neoadjuvant therapy with dual antibody blockade). In node-negative patients with tumour diameters up to 3 cm, 12 times weekly paclitaxel plus trastuzumab rendered an excellent 3-year invasive disease-free survival of 98·7% (95% CI 97·6–99·8) and could thus be considered an option for this low-risk collective group. Only 12 of 406 patients had invasive disease events at 3 years: two distant metastasis, four locoregional recurrence, four contralateral breast cancer, and two non-breast cancer deaths.[133] For HER2-positive luminal early

	Number of patients	Tumour biology	Therapy arms	pCR rates (platinum *vs* standard)	Significance
Japanese phase 2 trial 2; Ando et al, 2014[116]	75 with triple-negative breast cancer	Immunohistochemistry: ER, PgR, and HER2	Four times carboplatin AUC=5 every 21 days + 80 mg/m² paclitaxel weekly—four times CEF (500 mg/m² cyclophosphamide, 100 mg/m² epirubicin, 500 mg/m² 5-fluorouracil) *vs* P-CEF	61·2% *vs* 26·3% (pCR breast)	p=0·003 (subgroup analysis)
Geparsixto; von Minckwitz et al, 2014[117]	315 with triple-negative breast cancer	ER and PgR <1%; HER2-negative	80 mg/m² paclitaxel + 20 mg/m² non-pegylated liposomal doxorubicin ± carboplatin AUC=2 (later 1·5) weekly	53·2% *vs* 36·9% (ypT0 ypN0)	p=0·005 (planned subgroup analysis)
CALGB 40603 (Alliance); Sikov et al, 2015[118]	443	ER and PgR ≤10%; HER2-negative	80 mg/m² paclitaxel weekly—four times doxorubicin and cyclophosphamide every 2 weeks ± carboplatin AUC=6 every 3 weeks (± 10 mg/kg bevacizumab every 2 weeks)	60% *vs* 44% (pCR breast)	p=0·0018
GEICAM 2006/03; Alba et al, 2012[123]	94	Basal-like (immunohistochemistry): ER-negative, PgR-negative, HER2-negative, and cytokeratin 5/6-positive or EGFR-positive	Four times epirubicin, then four times docetaxel every 3 weeks ± carboplatin AUC=6 every 3 weeks	30% *vs* 35% (pCR breast)	p=0·61 (not significant)

pCR=pathological complete response. ER=oestrogen receptor. PgR=progesterone receptor. AUC=area under curve. P-CEF=paclitaxel followed by cyclophosphamide, epirubicin, and 5-fluorouracil.

***Table 3*: Evidence from phase 2 trials for platinum-based chemotherapy in neoadjuvant therapy of triple-negative early breast cancer**

breast cancer, no data exist for an endocrine therapy-trastuzumab combination without systemic chemotherapy.

Since pathological complete response is correlated with patient outcome in HER2-positive disease, particularly in HER2-positive, hormone-receptor-negative disease,[30,134] neoadjuvant therapy has become a preferred option for these patients. Response at surgery allows counselling about the expected individual outcome. Results from the KATHERINE trial (NCT01772472), which randomised patients without pathological complete response to standard trastuzumab versus trastuzumab emtansine (TDM-1) for the completion of anti-HER2 therapy for 1 year, are still pending. Moreover, in some countries dual blockade with pertuzumab and trastuzumab together with chemotherapy is already available—but only in the neoadjuvant setting. When using an anthracycline-taxane sequence in the neoadjuvant setting, adding trastuzumab to the anthracycline does not improve pathological complete response [135] and is thus optional.

Dual anti-HER2 blockade has been explored in the neoadjuvant setting with vertical HER2 blockade (trastuzumab and lapatinib) and dual antibody-based (horizontal) HER2 blockade (trastuzumab and pertuzumab). The neoadjuvant results regarding the dual vertical blockade are controversial: it did not result in significantly better pathological complete response than trastzumab alone in NSABP B-41[136] and CALGB 40601.[137] Yet, it had a significant pathological complete response advantage in NeoALTTO,[29] which did not translate into a significant survival advantage. Similarly, the ALTTO trial,[138] which used standard adjuvant chemotherapy, did not see a survival advantage when comparing the sequential or combined use of trastuzumab and lapatinib versus trastuzumab alone in the adjuvant setting. Thus, vertical HER2 blockade has no clinical role in patients with early breast cancer.

By contrast, the combination of the two anti-HER2—antibodies trastuzumab and pertuzumab (with a docetaxel backbone)—did receive conditional approval by the US Food and Drug Administration (FDA; and subsequent European Medicines Agency [EMA] approval) for the neoadjuvant setting and thus constitutes an important therapy option for HER2-positive early breast cancer. The approval was based on the results from NeoSphere:[34] pathological complete response in the breast was 45·8% after four cycles of docetaxel plus dual blockade (trastuzumab and pertuzumab) every 21 days versus 29·0% with docetaxel plus trastuzumab alone (p=0·0141). The approval was certainly influenced by the totality of the data with the survival advantage in the metastatic setting (CLEOPATRA)[139] and a fully recruited phase 3 adjuvant trial (APHINITY; NCT01358877). No data for adjuvant use of the dual antibody blockade will exist until the results of the APHINITY trial become available.

Bone-stabilising drugs

In early breast cancer, bisphosphonates were initially used to prevent or treat the side-effects of adjuvant endocrine treatments (particularly aromatase inhibitor) on bone.[140] Current guidelines call for risk assessment at

the beginning of adjuvant therapy and bisphosphonate treatment, if appropriate.[141,142] This recommendation is based on several trials that showed the usefulness of adjuvant bisphosphonates for prevention and therapy of treatment-induced bone loss, in both premenopausal[143] and postmenopausal women.[144,145]

Yet, adjuvant bisphosphonates do not only prevent bone loss, but might also prevent bone and even other metastases. Whether their anticancer effect is more cytotoxic or reflects indirect effects on the bone marrow environment remains controversial.[146] The results of several large clinical trials have shown outcome benefits for oral and intravenous adjuvant bisphosphonates.[147] The beneficial effect appears to be confined to postmenopausal patients,[148,149] or to premenopausal patients receiving adjuvant ovarian suppression.[150] Preclinical data also suggest that menopausal status could be important in determining the efficacy of adjuvant antiresorptive treatment.[151]

The controversy about adjuvant bisphosphonates appeared to have been finally settled by a large EBCTCG meta-analysis,[152] which showed that adjuvant bisphosphonates reduced the prevalence of breast cancer recurrence in bone, and improved breast cancer survival, with clear evidence for a benefit only in postmenopausal women. How this finding will be implemented into clinical practice, and whether bisphosphonates could be substituted by the anti-RANK-ligand antibody denosumab, after results were published regarding a reduction of fracture risk under concomitant aromatase inhibitor therapy[153] and a disease-free survival improvement,[154] remains to be determined.

Early breast cancer: special situations

Evidence is scarce on special situations in early breast cancer, such as age extremes or patients who are pregnant. Generally, therapy of young and elderly patients with breast cancer should not deviate from standard management unless individualisation is required because of comorbidities and personal situations.

For young patients (<40 years), who represent less than 7% of all patients in high-income countries, a biannual international consensus conference (breast cancer in young women [BCY]) establishes the international standards.[155] Particularly, family planning and fertility preservation[156] are issues in these patients that need to be addressed before therapy concepts are finalised. Moreover, genetic testing needs to be considered in young patients (<35 years) even without a family history.[4] If young women present with breast cancer in pregnancy, the pregnancy can be continued until term from an oncological point of view. Stage-adjusted prognosis is similar in women who are or are not pregnant, and thus, therapy should be as close to the guidelines as possible.[157] Surgery, including radioisotope-based sentinel lymph node biopsy, and chemotherapy (second and third trimesters only), can be administered during pregnancy; radiotherapy, endocrine, and antibody therapy need to be postponed until after delivery. Multidisciplinary management, including obstetrics and perinatal medicine specialists, is key to a successful outcome for mother and child.

Patients older than 70 years constitute almost a third of all patients with breast cancer in European countries.[158] Since individual comorbidities and overall life expectancy can differ substantially, special management recommendations are available by SIOG and EUSOMA.[159]

Genetic testing for *BRCA1* and *BRCA2* should be offered to all patients meeting the respective national guideline criteria, such as those with strong family history, triple-negative breast cancer, or patients younger than 35 years.[4] Regarding chances for cure, treatment of *BRCA1/2*-mutation carriers does not need to differ from that of patients with sporadic breast cancer: locoregional therapy can be performed as indicated by the individual tumour load. Yet, patients need to be counselled about their individual risk for contralateral disease[160] since patient preferences about prophylactic mastectomies need to be discussed before finalising the locoregional therapy concept. This process helps to avoid potentially unnecessary procedures, such as adjuvant radiotherapy after breast-conserving therapy, that might then affect cosmesis of immediate reconstructive surgery after secondary mastectomy, for example. Moreover, ongoing clinical trials in early breast cancer with PARP inhibitors suggest *BRCA* testing as early as possible during the course of disease in patients at risk.

Metastatic breast cancer: therapy concepts

In contrast with early breast cancer, metastatic breast cancer is considered incurable with currently available therapies. Based on data from 1996, long-term survivors do exist but are very rare—ie, less than 5%.[161] Whether and how this percentage will change with current therapies that have shown an overall survival advantage is still unknown.

Nowadays, patients with metastatic breast cancer differ substantially from patients 10–20 years ago and are much more difficult to treat because they have usually received very potent adjuvant therapies. Consequently, results from therapy trials started several years ago might not be completely transferable to current patients. Nevertheless, trials published since 2012,[139,162] particularly in HER2-positive disease, have shown not just prolongation of progression-free survival, but also overall survival. These results indicate that the concept of metastatic breast cancer as a chronic disease controlled by sequential therapies over a long period is realistic, at least for certain subgroups.

Next to prolongation of survival, therapeutic goals in metastatic breast cancer are maintenance of quality of life and palliation of symptoms. Therapy concepts are usually more individualised in metastatic breast cancer than in early breast cancer, since patients differ regarding

preferences, pretreatments, and residual side-effects from previous therapies. Tumour biology is important together with duration of response to previous therapies and tumour burden with associated symptoms (figure 2). Therapy concepts need to be decided by a multidisciplinary team right from the beginning.

The biannual Advanced Breast Cancer Conference (ABC) in Lisbon, Portugal, provides evidence-based international and multidisciplinary consensus guidelines for diagnosis and treatment of metastatic breast cancer. Generally, systemic therapy is the first therapeutic choice in metastatic breast cancer and locoregional therapy (eg, surgery, radiotherapy) can be added in specific situations (eg, primary metastatic disease, symptomatic bone, or brain metastases).[164]

If clinically feasible, biopsy of the first metastatic site is recommended to verify breast cancer histology and determine again the tumour biology (ER, PgR, and HER2).[164] Histology might differ between primary tumour and metastasis because of tumour heterogeneity or merely because of problems with the methods. Numerous retrospective reports exist of discordance rates as high as 30–40%. In prospective series, these rates seem somewhat lower and lead to treatment changes in about 15%. Because of potential heterogeneity even between metastases, gain of a therapeutic target is important for choice of therapy. In case of loss of target, methodological problems need to be addressed first before omitting targeted therapy.

Bone-modifying drugs, such as bisphosphonates or denosumab, are standard as maintenance therapy from first bone metastasis until intolerable toxic effects. Schedules differ from the setting of early breast cancer. Although denosumab was shown to be more effective than bisphosphonates in preventing skeletal-related events,[165] a survival advantage has not been reported.

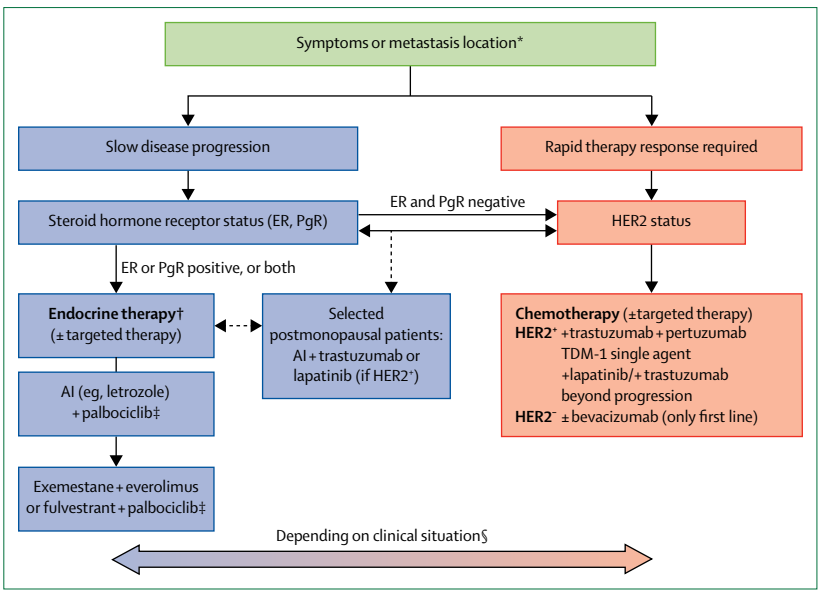

Figure 2: **Principles of systemic therapy in metastatic breast cancer**
Previous treatments and patients' preferences are key elements in deciding the individual therapeutic steps. Figure updated after the publication of Bossung and Harbeck, 2010.[163] Treatment decisions can thus differ for an individual patient. In patients with HR-positive HER2-negative tumours, endocrine therapy should be the first option unless there is life-threatening disease. Chemotherapy is always an additional therapy option depending on the course of disease. ER=oestrogen receptor. PgR=progesterone receptor. AI=aromatase inhibitor. TDM-1=trastuzumab emtansine. *If bone metastases: + bisphosphonates or denosumab. †Always combine with ovarian suppression or ablation in premenopausal patients. ‡So far, only one line of palbociclib therapy is evidence-based. §Only applicable if ER or PgR positive, or both.

Endocrine-responsive metastatic breast cancer

International guidelines recommend endocrine therapy as the first therapeutic choice in patients with HER2-negative luminal metastatic breast cancer unless visceral crisis or another life-threatening situation requires chemotherapy.[164] Endocrine therapy is usually feasible if symptoms allow a wait of about 3–4 months until best response. Endocrine drugs for metastatic breast cancer include tamoxifen, aromatase inhibitors, fulvestrant, and progestins. These drugs are ideally given sequentially, each until progression or intolerable toxic effects. Aromatase inhibitors were the preferred first-line therapy in postmenopausal women; however, the phase 2 FIRST study[166] suggested an overall survival benefit of fulvestrant 500 mg versus anastrozole 1 mg in this setting. Results of the confirmatory phase 3 FALCON study (NCT01602380) showed a progression-free survival advantage (but not an overall survival advantage) for fulvestrant 500 mg versus anastrozole 1 mg in the first-line setting.[167] For premenopausal patients, ovarian suppression is recommended with all endocrine options, even with tamoxifen.[168]

Prolongation of progression-free survival has been shown by adding targeted therapies to endocrine therapy. The m-TOR inhibitor everolimus substantially improved progression-free survival by 4·6 months (HR 0·45; 0·38–0·54; p<0·0001) but not overall survival (median 31 months for exemestane plus everolimus *vs* 26·6 months for non-steroidal aromatase inhibitor only; HR 0·89; 0·73–1·1; p=0·14) in postmenopausal patients after failure of a non-steroidal aromatase inhibitor.[169] The cyclin-dependant kinase 4/6 (CDK 4/6) inhibitor palbociclib together with letrozole also improved median progression-free survival in postmenopausal patients without previous systemic treatment for metastatic breast cancer (20·2 months [95% CI 13·8–27·5] for palbociclib and letrozole *vs* 10·2 months [95% CI 5·7–12·6 months] for letrozole alone; HR 0·488; 0·319–0·748; p=0·0004).[170] On the basis of the PALOMA 1 phase 2 data,[170] palbociclib received fast-track approval in the USA, while in Europe, approval was announced on Nov 10, 2016. The phase 3 PALOMA 2 trial[171] confirmed this progression-free survival advantage: median progression-free survival was 24·8 months for letrozol and palbociclib versus 14·5 months for letrozole alone (HR 0·58; 0·46–0·72; p<0·0001). After progression from, or relapse after, previous endocrine therapy, PALOMA 3[172] showed efficacy of palbociclib together with fulvestrant: median

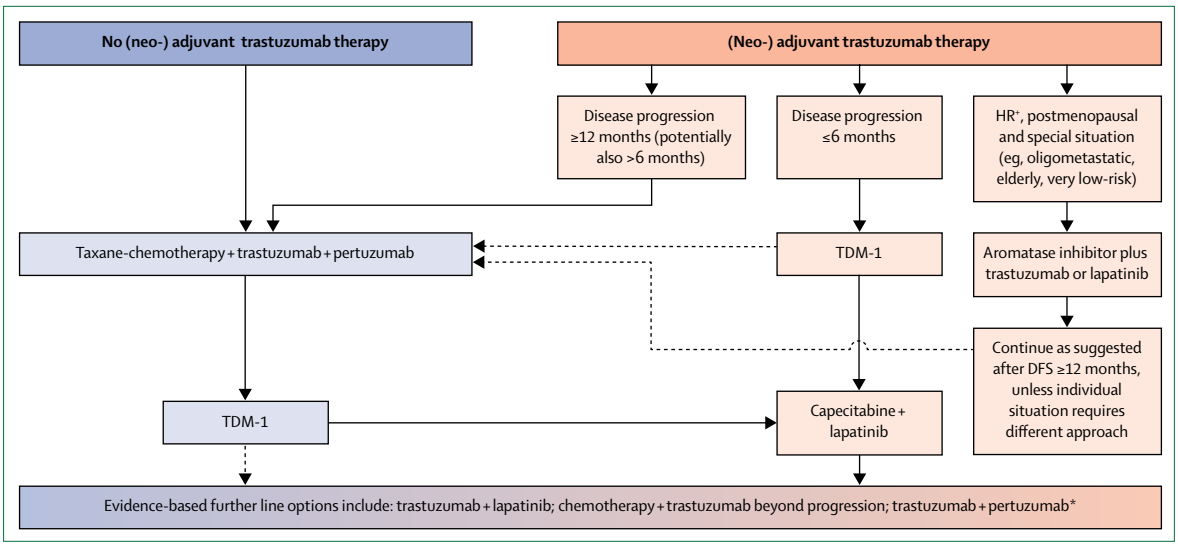

Figure 3: **Evidence-based sequence of systemic therapy in HER2-positive metastatic breast cancer**
Please note, the currently available evidence does not cover all situations because of individual differences in pretreatment. Thus, extrapolations from available evidence were applied when needed. Solid lines represent evidence-based and dotted lines are reasonable options without evidence. HR+= hormone-receptor positive (ER or PGR positive, or both). TDM-1=trastuzumab emtansine. DFS=disease-free survival. *If no previous pertuzumab.

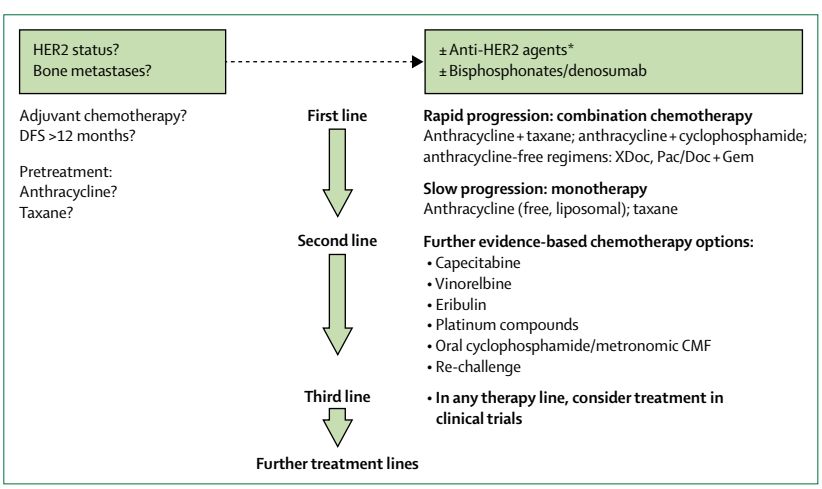

Figure 4: **Chemotherapy for metastatic breast cancer**
DFS=disease-free survival. XDoc= capecitabine and docetaxel. Pac=paclitaxel. Doc=docetaxel. Gem=gemcitabine. CMF=cyclophosphamide, methotrexate, and 5-fluorouracil. *Approved targeted drugs for addition to chemotherapy: trastuzumab, pertuzumab, or lapatinib for HER2-positive tumours; bevacizumab (first-line therapy) for HER2-negative tumours.

progression-free survival was 9·2 months (95% CI 7·5 to not estimable) for palbociclib and fulvestrant versus 3·8 months (95% CI 3·5–5·5) for fulvestrant alone (HR 0·42; 95% CI 0·32–0·56; p<0·001). Premenopausal patients received additional goserelin; the effect size of palbociclib was similar in premenopausal and postmenopausal patients.[172] An overall survival advantage versus standard therapy has not been reported for any CDK 4/6 inhibitor. For the PALOMA studies, final overall survival analyses are still pending. Ribociclib and abemaciclib are two additional CDK 4/6 inhibitors that are being assessed in clinical trials. Data from the ribociclib first-line registration trial (MONALEESA 2; NCT01958021) showed a substantial progression-free survival benefit for letrozole plus ribociclib versus letrozole alone.[173]

Given the promising evidence, endocrine therapy plus a targeted drug is most probably going to be the future for treatment of patients with luminal metastatic breast cancer. Unfortunately, beside ER and PgR, biomarkers for patient selection are still missing. Moreover, unless a survival advantage can be shown for the new therapeutic approaches, endocrine monotherapy is still a valid option, particularly in slowly progressing disease with good response to previous endocrine therapy.

Management of HER2-positive metastatic breast cancer

Anti-HER2 therapy is recommended as early as possible in patients with HER2-positive metastatic breast cancer. Even though efficacy of trastuzumab or lapatinib together with endocrine therapy (aromatase inhibitor) was shown in several phase 2–3 trials for postmenopausal patients[174] and led to registration of these combinations, combination with chemotherapy is currently recommended in early lines of therapy because of the overall survival advantage.

Based on the pivotal data,[175] trastuzumab plus taxane chemotherapy has been the first-line standard for at least a decade. The results of the CLEOPATRA trial[139] showed an unprecedented median overall survival advantage of 15·7 months, favouring docetaxel plus trastuzumab and pertuzumab in first-line treatment of HER2-positive disease. Median overall survival with dual blockade was 56·5 months (95% CI 49·3 to not reached) versus 40·8 months (95% CI 35·8–48·3) with standard (HR 0·68; 95% CI 0·56–0·84; p<0·001).[139] This combination has

therefore become the new first-line standard (figure 3). The results from the MARIANNE trial[176] showed that TDM-1 (with pertuzumab) is non-inferior but not superior to first-line taxane plus trastuzumab. The toxicity profile favoured the TDM-1 groups. Pertuzumab did not add to the efficacy of TDM-1 in the overall study population.

In second-line treatment, after treatment with taxane and trastuzumab or with rapid progression after adjuvant trastuzumab (≤6 months), TDM-1 was more effective than lapatinib and capecitabine in the phase 3 EMILIA trial:[162] median overall survival crossed the stopping boundary for efficacy at the second interim analysis (30·9 months TDM-1 for *vs* 25·1 months for lapatinib and capecitabine; HR 0·68; 95% CI 0·55–0·85; p<0·001). Consequently, TDM-1 has become the second-line standard.

Evidence-based further-line therapy options in patients with HER2-positive metastatic breast cancer include lapatinib and capecitabine,[177] lapatinib and trastuzumab,[178] chemotherapy and trastuzumab beyond progression,[179] or trastuzumab and pertuzumab.[180] Sequencing of anti-HER2 therapies in metastatic breast cancer for an individual patient will depend on the evidence (figure 3), but also on approval and reimbursement in the respective therapy setting.

Chemotherapy for metastatic breast cancer

Chemotherapy is always indicated in triple-negative breast cancer after endocrine options have been exhausted in luminal disease or if rapid response is needed in life-threating situations or in patients who are highly symptomatic. Unless patient symptoms require a combination chemotherapy, sequential mono-chemotherapies are recommended, as combination chemotherapy does not prolong survival.[181] Mono-chemotherapy can be given until progression or intolerable toxic effects, whereas because of toxicity, combination chemotherapy is usually given until best response.

Several substances are evidence based (figure 4). No optimal sequence is known and choice of individual regimens and drugs depends on patient preferences regarding schedule and side-effect pattern, as well as previous therapies and residual toxic effects. If not already given in the adjuvant setting, patients with metastatic breast cancer should receive anthracyclines and taxanes. After a good initial response and a long disease-free interval (>12 months), rechallenge with anthracyclines and taxanes is feasible. For free anthracyclines, however, cumulative dose limits need to be considered to avoid cardiotoxic effects.

The anti-VEGF antibody bevacizumab improves progression-free survival (median progression-free survival of 9·2 months for bevacizumab *vs* 6·7 months for placebo or no bevacizumab; HR 0·64; 95% CI 0·57–0·71; meta-analysis, 2447 patients) but not overall survival when given together with first-line chemotherapy such as paclitaxel or capecitabine.[182] It is approved by EMA but not by FDA, and thus constitutes a therapy option only in individual countries.

Future perspectives for metastatic breast cancer

Next-generation sequencing and mutation analysis have transformed management of other solid tumours, but not yet those of patients with metastatic breast cancer. So far, the only clinically relevant biomarkers and validated therapeutic targets in metastatic breast cancer are ER, PgR, and HER2. Nevertheless, metastatic breast cancer is heterogeneous and several clinically potentially relevant mutations have been identified. Yet, personalised approaches are currently only available for a few patients.[183] Ongoing trials and initiatives such as AURORA[184] (Breast International Group) or PRAEGNANT[185] provide valuable opportunities to assess the value of molecular characterisation of metastatic breast cancer and subsequent molecular-targeted therapy. Moreover, participation in clinical trials with new targeted therapies might benefit patients by adding effective additional therapy steps in the treatment sequence for metastatic breast cancer and should therefore always be considered.

Contributors

All authors did the literature search, wrote the manuscript, and approved the final manuscript.

Declaration of interests

NH reports personal fees from Agendia, Amgen, AstraZeneca, Celgene, Genomic Health, NanoString Technologies, Novartis, Pfizer, Roche, and Sandoz, outside the submitted work. MG reports grants and personal fees from AstraZeneca, Novartis, Pfizer, and Roche, and personal fees from Celgene, GlaxoSmithKline, and Accelsior, outside the submitted work.

References

1 Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136:** E359–86.

2 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65:** 87–108.

3 Malvezzi M, Carioli G, Bertuccio P, et al. European cancer mortality predictions for the year 2016 with focus on leukemias. *Ann Oncol* 2016; **27:** 725–31.

4 AGO Breast Commission Recommendations. Diagnosis and therapy of primary and metastatic breast cancer, 2016. http://www.ago-online.de/en/guidelines-mamma/ (accessed June 19, 2016).

5 Houssami N, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: meta-analysis of surgical outcomes. *Ann Surg* 2013; **257:** 249–55.

6 Gerber B, Seitz E, Müller H, et al. Perioperative screening for metastatic disease is not indicated in patients with primary breast cancer and no clinical signs of tumor spread. *Breast Cancer Res Treat* 2003; **82:** 29–37.

7 Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature* 2000; **406:** 747–52.

8 Sørlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci USA* 2001; **98:** 10869–74.

9 Curtis C, Shah SP, Chin SF, et al, for the METABRIC Group. The genomic and transcriptomic architecture of 2000 breast tumours reveals novel subgroups. *Nature* 2012; **486:** 346–52.

10 Harbeck N, Salem M, Nitz U, Gluz O, Liedtke C. Personalized treatment of early-stage breast cancer: present concepts and future directions. *Cancer Treat Rev* 2010; **36:** 584–94.

11 Goldhirsch A, Winer EP, Coates AS, et al, for the Panel members. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol* 2013; **24:** 2206–23.

12 Coates AS, Winer EP, Goldhirsch A, et al, for the Panel Members. Tailoring therapies-improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol* 2015; **26:** 1533–46.

13 Polley MY, Leung SC, McShane LM, et al, for the International Ki67 in Breast Cancer Working Group of the Breast International Group and North American Breast Cancer Group. An international Ki67 reproducibility study. *J Natl Cancer Inst* 2013; **105:** 1897–906.

14 Dowsett M, Sestak I, Lopez-Knowles E, et al. Comparison of PAM50 risk of recurrence score with oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. *J Clin Oncol* 2013; **31:** 2783–90.

15 McLaughlin SA. Surgical management of the breast: breast conservation therapy and mastectomy. *Surg Clin North Am* 2013; **93:** 411–28.

16 Mansfield L, Agrawal A, Cutress RI. Oncoplastic breast conserving surgery. *Gland Surg* 2013; **2:** 158–62.

17 Kiderlen M, Ponti A, Tomatis M, et al. Variations in compliance to quality indicators by age for 41 871 breast cancer patients across Europe: a European Society of Breast Cancer Specialists database analysis. *Eur J Cancer* 2015; **51:** 1221–30.

18 Morrow M, Harris, JR, Schnitt SJ. Surgical margins in lumpectomy for breast cancer—bigger is not better. *N Engl J Med* 2012; **367:** 79–82.

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

20 Chagpar AB, Killelea BK, Tsangaris TN, et al. A randomized, controlled trial of cavity shave margins in breast cancer. *N Engl J Med* 2015; **373:** 503–10.

21 Tan MP, Sitoh NY, Sim AS. The value of intraoperative frozen section analysis for margin status in breast conservation surgery in a nontertiary institution. *Int J Breast Cancer* 2014; **2014:** 715404.

22 Boughey JC, Hieken TJ, Jakub JW, et al. Impact of analysis of frozen-section margin on reoperation rates in women undergoing lumpectomy for breast cancer: evaluation of the National Surgical Quality Improvement Program data. *Surgery* 2014; **156:** 190–97.

23 Haloua MH, Krekel NM, Winters HA, et al. A systematic review of oncoplastic breast-conserving surgery: current weaknesses and future prospects. *Ann Surg* 2013; **257:** 609–20.

24 Yao K, Winchester DJ, Czechura T, et al. Contralateral prophylactic mastectomy and survival: report from the National Cancer Data Base, 1998–2002. *Breast Cancer Res Treat* 2013; **142:** 465–76.

25 Kurian AW, Lichtensztajn DY, Keegan TH, et al. Use of and mortality after bilateral mastectomy compared with other surgical treatments for breast cancer in California, 1998–2011. *JAMA* 2014; **312:** 902–14.

26 Jatoi I. Postmastectomy radiotherapy in patients with breast cancer. *Lancet* 2014; **384:** 1844–45.

27 Schmidt M. Chemotherapy in early breast cancer: when, how and which one? *Breast Care (Basel)* 2014; **9:** 154–60.

28 Teshome M, Hunt KK. Neoadjuvant therapy in the treatment of breast cancer. *Surg Oncol Clin N Am* 2014; **23:** 505–23.

29 de Azambuja E, Holmes AP, Piccart-Gebhart M, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. *Lancet Oncol* 2014; **15:** 1137–46.

30 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:** 164–72.

31 DeMichele A, Yee D, Berry DA, et al. The neoadjuvant model is still the future for drug development in breast cancer. *Clin Cancer Res* 2016; **22:** 269.

32 Kümmel S, Holtschmidt J, Loibl S. Surgical treatment of primary breast cancer in the neoadjuvant setting. *Br J Surg* 2014; **101:** 912–24.

33 Buchholz TA, Mittendorf EA, Hunt KK. Surgical considerations after neoadjuvant chemotherapy: breast conservation therapy. *J Natl Cancer Inst Monogr* 2015; **2015:** 11–14.

34 Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; **13:** 25–32.

35 Bossuyt V, Provenzano E, Symmans WF, et al. Recommendations for standardized pathological characterization of residual disease for neoadjuvant clinical trials of breast cancer by the BIG-NABCG collaboration. *Ann Oncol* 2015; **26:** 1280–91.

36 Buchholz TA, Somerfield MR, Griggs JJ, et al. Margins for breast-conserving surgery with whole-breast irradiation in stage I and II invasive breast cancer: American Society of Clinical Oncology endorsement of the Society of Surgical Oncology/American Society for Radiation Oncology consensus guideline. *J Clin Oncol* 2014; **32:** 1502–06.

37 Sung JS, Li J, Da Costa G, et al. Preoperative breast MRI for early-stage breast cancer: effect on surgical and long-term outcomes. *AJR Am J Roentgenol* 2014; **202:** 1376–82.

38 Gonzalez V, Sandelin K, Karlsson A, et al. Preoperative MRI of the breast (POMB) influences primary treatment in breast cancer: a prospective, randomized, multicenter study. *World J Surg* 2014; **38:** 1685–93.

39 Krag DN, Julian TB, Harlow SP, et al. NSABP-32: phase III, randomized trial comparing axillary resection with sentinal lymph node dissection: a description of the trial. *Ann Surg Oncol* 2004; **11:** 208S–10.

40 Reimer T, Hartmann S, Stachs A, Gerber B. Local treatment of the axilla in early breast cancer: concepts from the national surgical adjuvant breast and bowel project B-04 to the planned intergroup sentinel mamma trial. *Breast Care (Basel)* 2014; **9:** 87–95.

41 Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* 2011; **305:** 589.

42 Ahmed M, Purushotham AD, Horgan K, Klaase JM, Douek M. Meta-analysis of superficial versus deep injection of radioactive tracer and blue dye for lymphatic mapping and detection of sentinel lymph nodes in breast cancer. *Br J Surg* 2015; **102:** 169–81.

43 Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol* 2013; **14:** 609–18.

44 King TA, Morrow M. Surgical issues in patients with breast cancer receiving neoadjuvant chemotherapy. *Nat Rev Clin Oncol* 2015; **12:** 335–43.

45 Boughey JC, Ballman KV, Hunt KK, et al. Axillary ultrasound after neoadjuvant chemotherapy and its impact on sentinel lymph node surgery: results from the American College of Surgeons Oncology Group Z1071 Trial (Alliance). *J Clin Oncol* 2015; **33:** 3386–93.

46 Haffty BG, McCall LM, Ballman KV, et al. Patterns of local-regional management following neoadjuvant chemotherapy in breast cancer: results from ACOSOG Z1071 (Alliance). *Int J Radiat Oncol Biol Phys* 2016; **94:** 493–502.

47 Boughey JC, Ballman KV, Le-Petross HT, et al. Identification and resection of clipped node decreases the false-negative rate of sentinel lymph node surgery in patients presenting with node-positive breast cancer (T0-T4, N1-N2) who receive neoadjuvant chemotherapy: results from ACOSOG Z1071 (Alliance). *Ann Surg* 2016; **263:** 802–07.

48 Dengel LT, Van Zee KJ, King TA, et al. Axillary dissection can be avoided in the majority of clinically node-negative patients undergoing breast-conserving therapy. *Ann Surg Oncol* 2014; **21:** 22–27.

49 Jagsi R, Chadha M, Moni J, et al. Radiation field design in the ACOSOG Z0011 (Alliance) Trial. *J Clin Oncol* 2014; **32:** 3600–06.

50 Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981–22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014; **15:** 1303–10.

51 Barry M, Ho A, Morrow M. The evolving role of partial breast irradiation in early-stage breast cancer. *Ann Surg Oncol* 2013; **20:** 2534–40.

52 Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010; **362:** 513–20.

53 Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013; **14:** 1086–94.

54 Marta GN, Macedo CR, Carvalho Hde A, Hanna SA, da Silva JL, Riera R. Accelerated partial irradiation for breast cancer: systematic review and meta-analysis of 8653 women in eight randomized trials. *Radiother Oncol* 2015; **114:** 42–49.

55 Sedlmayer F, Reitsamer R, Fussl C, et al. Boost IORT in breast cancer: body of evidence. *Int J Breast Cancer* 2014; **2014:** 472516.

56 Maluta S, Dall'Oglio S, Goer DA, Marciai N. Intraoperative electron radiotherapy (IOERT) as an alternative to standard whole breast irradiation: only for low-risk subgroups? *Breast Care (Basel)* 2014; **9:** 102–06.

57 van de Water W, Bastiaannet E, Scholten AN, et al. Breast-conserving surgery with or without radiotherapy in older breast patients with early stage breast cancer: a systematic review and meta-analysis. *Ann Surg Oncol* 2014; **21:** 786–94.

58 Poetter R, Gnant M, Kwasny W, et al, for the ABCSG. Lumpectomy plus tamoxifen or anastrozole with or without whole breast irradiation in women with favourable early breast cancer. *Int J Radiat Oncol* 2007; **68:** 334–40.

59 Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol* 2013; **31:** 2382–87.

60 Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM, for the PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol* 2015; **16:** 266–73.

61 Poortmans P, Struikmans S, Collette S. Lymph node radiotherapy improves survival in breast cancer: 10 year results of the EORTC Radiation Oncology and Breast Cancer Groups phase III trial 22922/10925. In: Valentini V, Zips D, Fiorino C, eds. ESTRO congress report. Vienna: ESTRO, 2014: 6.

62 Poortmans PM, Collette S, Kirkove C, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med* 2015; **373:** 317–27.

63 Whelan TJ, Olivotto IA, Parulekar WR, et al. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med* 2015; **373:** 307–16.

64 Budach W, Bölke E, Kammers K, Gerber PA, Nestle-Krämling C, Matuschek C. Adjuvant radiation therapy of regional nodes in breast cancer—a meta-analysis of randomized trials—an update. *Radiat Oncol* 2015; **10:** 258.

65 Yarnold JR. What is the value of internal mammary chain RT and how can we deliver it safely? Proceedings of the Thirty-Seventh Annual CTRC-AACR San Antonio Breast Cancer Symposium; San Antonio, TX; Dec 9–13, 2014; ES4–3.

66 Brown LC, Mutter RW, Halyard MY. Benefits, risks, and safety of external beam radiation therapy for breast cancer. *Int J Womens Health* 2015; **7:** 449–58.

67 Yeboa DN, Evans SB. Contemporary breast radiotherapy and cardiac toxicity. *Semin Radiat Oncol* 2016; **26:** 71–78.

68 Nordenskjöld AE, Fohlin H, Albertsson P, et al, for the Swedish Western and Southeastern Breast Cancer Groups. No clear effect of postoperative radiotherapy on survival of breast cancer patients with one to three positive nodes: a population-based study. *Ann Oncol* 2015; **26:** 1149–54.

69 Franco P, Cante D, Sciacero P, Girelli G, La Porta MR, Ricardi U. Tumor bed boost integration during whole breast radiotherapy: a review of the current evidence. *Breast Care (Basel)* 2015; **10:** 44–49.

70 Filipits M, Rudas M, Jakesz R, et al, for the EP Investigators. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. *Clin Cancer Res* 2011; **17:** 6012–20.

71 van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med* 2002; **347:** 1999–2009.

72 Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004; **351:** 2817–26.

73 Dowsett M, Nielsen TO, A'Hern R, et al, for the International Ki-67 in Breast Cancer Working Group. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. *J Natl Cancer Inst* 2011; **103:** 1656–64.

74 Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med* 2015; **373:** 2005–14.

75 Gluz O, Nitz U, Christgen M, et al. West German Study Group Phase III PlanB Trial: first prospective outcome data for the 21-gene recurrence score assay and concordance of prognostic markers by central and local pathology assessment. *J Clin Oncol* 2016; **34:** 2341–49.

76 Piccart M, Rutgers E, van't Veer L, on behalf of TRANSBIG consortium and MINDACT investigators. Primary analysis of the EORTC 10041/ BIG 3–04 MINDACT study: a prospective, randomized study evaluating the clinical utility of the 70-gene signature (MammaPrint) combined with common clinical-pathological criteria for selection of patients for adjuvant chemotherapy in breast cancer with 0 to 3 positive nodes. AACR Annual Meeting; New Orleans, LA; April 18, 2016; CT039.

77 Harbeck N, Schmitt M, Meisner C, et al, for the Chemo-N 0 Study Group. Ten-year analysis of the prospective multicentre Chemo-N0 trial validates American Society of Clinical Oncology (ASCO)-recommended biomarkers uPA and PAI-1 for therapy decision making in node-negative breast cancer patients. *Eur J Cancer* 2013; **49:** 1825–35.

78 Look MP, van Putten WL, Duffy MJ, et al. Pooled analysis of prognostic impact of urokinase-type plasminogen activator and its inhibitor PAI-1 in 8377 breast cancer patients. *J Natl Cancer Inst* 2002; **94:** 116–28.

79 Jacobs VR, Kates RE, Kantelhardt E, et al. Health economic impact of risk group selection according to ASCO-recommended biomarkers uPA/PAI-1 in node-negative primary breast cancer. *Breast Cancer Res Treat* 2013; **138:** 839–50.

80 Wishart GC, Rakha E, Green A, et al. Inclusion of KI67 significantly improves performance of the PREDICT prognostication and prediction model for early breast cancer. *BMC Cancer* 2014; **14:** 908.

81 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011; **378:** 771–84.

82 Pagani O, Regan MM, Walley BA, et al, for the TEXT and SOFT Investigators; International Breast Cancer Study Group. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2014; **371:** 107–18.

83 Francis PA, Regan MM, Fleming GF, et al, for the SOFT Investigators; International Breast Cancer Study Group. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2015; **372:** 436–46.

84 Gnant M, Mlineritsch B, Stoeger H, et al, for the Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria. Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12. *Ann Oncol* 2015; **26:** 313–20.

85 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet* 2015; **386:** 1341–52.

86 Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol* 2010; **28:** 509–18.

87 Metzger O, Giobbie-Hurder A, Mallon E, et al, for the BIG 1–98 Collaborative Group, International Breast Cancer Study Group. Relative effectiveness of letrozole compared with tamoxifen for patients with lobular carcinoma in the BIG 1–98 Trial. Thirty-Fifth Annual CTRC-AACR San Antonio Breast Cancer Symposium; San Antonio, TX; Dec 4–8, 2012: S1–1.

88 Jin H, Tu D, Zhao N, Shepherd LE, Goss PE. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. *J Clin Oncol* 2012; **30:** 718–21.

89 Zdenkowski N, Green M, Boyle FM, et al, for the Australia and New Zealand Breast Cancer Trials Group. Final analysis of a randomized comparison of letrozole (Let) vs observation (Obs) as late reintroduction of adjuvant endocrine therapy (AET) for postmenopausal women with hormone receptor positive (HR+) breast cancer (BC) after completion of prior AET: ANZBCTG 0501 (LATER). *J Clin Oncol* 2015; **33** (suppl): 514 (abstr).

90 Goss PE, Ingle JN, Pritchard KI, et al. A randomized trial (MA.17R) of extending adjuvant letrozole for 5 years after completing an initial 5 years of aromatase inhibitor therapy alone or preceded by tamoxifen in postmenopausal women with early-stage breast cancer. *J Clin Oncol* 2016; **34** (suppl): LBA1 (abstr).

91 Davies C, Pan H, Godwin J, et al, for the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013; **381:** 805–16.

92 Land SR, Walcott FL, Liu Q, Wickerham DL, Costantino JP, Ganz PA. Symptoms and QOL as predictors of chemoprevention adherence in NRG Oncology/NSABP Trial P-1. *J Natl Cancer Inst* 2015; **108:** djv365.

93 Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998; **90:** 1371–88.

94 Blok EJ, Derks MG, van der Hoeven JJ, van de Velde CJ, Kroep JR. Extended adjuvant endocrine therapy in hormone-receptor positive early breast cancer: current and future evidence. *Cancer Treat Rev* 2015; **41:** 271–76.

95 Knauer M, Filipits M, Dubsky P. Late recurrences in early breast cancer: for whom and how long is endocrine therapy beneficial? *Breast Care (Basel)* 2014; **9:** 97–100.

96 Albain KS, Barlow WE, Ravdin PM, et al, for the Breast Cancer Intergroup of North America. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial. *Lancet* 2009; **374:** 2055–63.

97 Del Mastro L, Dozin B, Aitini E, et al, for the GONO-MIG Group. Timing of adjuvant chemotherapy and tamoxifen in women with breast cancer: findings from two consecutive trials of Gruppo Oncologico Nord-Ovest-Mammella Intergruppo (GONO-MIG) Group. *Ann Oncol* 2008; **19:** 299–307.

98 Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol* 2008; **26:** 778–85.

99 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. *Lancet* 2012; **379:** 432–44.

100 Weaver DL, Ashikaga T, Krag DN, et al. Effect of occult metastases on survival in node-negative breast cancer. *N Engl J Med* 2011; **364:** 412–21.

101 Galimberti V, Cole BF, Zurrida S, et al, for the International Breast Cancer Study Group Trial 23–01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial. *Lancet Oncol* 2013; **14:** 297–305.

102 Downing A, Twelves C, Forman D, Lawrence G, Gilthorpe MS. Time to begin adjuvant chemotherapy and survival in breast cancer patients: a retrospective observational study using latent class analysis. *Breast J* 2014; **20:** 29–36.

103 Chavez-MacGregor M, Clarke CA, Lichtensztajn DY, Giordano SH. Delayed initiation of adjuvant chemotherapy among patients with breast cancer. *JAMA Oncol* 2016; **2:** 322–29.

104 Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 2003; **21:** 1431–39.

105 Swain SM, Tang G, Geyer CE Jr, et al. Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. *J Clin Oncol* 2013; **31:** 3197–204.

106 Eiermann W, Pienkowski T, Crown J, et al. Phase III study of doxorubicin/cyclophosphamide with concomitant versus sequential docetaxel as adjuvant treatment in patients with human epidermal growth factor receptor 2-normal, node-positive breast cancer: BCIRG-005 trial. *J Clin Oncol* 2011; **29:** 3877–84.

107 Sparano JA, Zhao F, Martino S, et al. Long-term follow-up of the E1199 phase iii trial evaluating the role of taxane and schedule in operable breast cancer. *J Clin Oncol* 2015; **33:** 2353–60.

108 Del Mastro L, De Placido S, Bruzzi P, et al, for the Gruppo Italiano Mammella (GIM) investigators. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2×2 factorial, randomised phase 3 trial. *Lancet* 2015; **385:** 1863–72.

109 Joensuu H, Kellokumpu-Lehtinen PL, 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:** 11–18.

110 Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. *J Clin Oncol* 2009; **27:** 1177–83.

111 Blum JL, Flynn PJ, Yothers G, et al. Interim joint analysis of the ABC (anthracyclines in early breast cancer) phase III trials (USOR 06–090, NSABP B-46I/USOR 07132, NSABP B-49 NRG Oncology) comparing docetaxel + cyclophosphamide (TC) v anthracycline/taxane-based chemotherapy regimens (TaxAC) in women with high-risk, HER2-negative breast cancer. *J Clin Oncol* 2016; **34** (suppl): 1000 (abstr).

112 Moebus V, Jackisch C, Lueck HJ, et al. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. *J Clin Oncol* 2010; **28:** 2874–80.

113 Burnell M, Levine MN, Chapman JA, et al. Cyclophosphamide, epirubicin, and fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by paclitaxel versus doxorubicin and cyclophosphamide followed by paclitaxel in node-positive or high-risk node-negative breast cancer. *J Clin Oncol* 2010; **28:** 77–82.

114 Muss HB, Berry DA, Cirrincione CT, et al, for the CALGB Investigators. Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med* 2009; **360:** 2055–65.

115 Biganzoli L, Aapro M, Loibl S, Wildiers H, Brain E. Taxanes in the treatment of breast cancer: have we better defined their role in older patients? A position paper from a SIOG Task Force. *Cancer Treat Rev* 2016; **43:** 19–26.

116 Ando M, Yamauchi H, Aogi K, et al. Randomized phase II study of weekly paclitaxel with and without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA breast cancer without HER2 overexpression. *Breast Cancer Res Treat* 2014; **145:** 401–09.

117 von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol* 2014; **15:** 747–56.

118 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:** 13–21.

119 von Minckwitz G, Loibl S, Schneeweiss A, et al. Early survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto). Thirty-Eighth Annual CTRC-AACR San Antonio Breast Cancer Symposium; San Antonio, TX; Dec 8–12, 2015; S2–04.

120 Sikov WM, Berry DA, Perou CM, et al. Event-free and overall survival following neoadjuvant weekly paclitaxel and dose-dense AC +/- carboplatin and/or bevacizumab in triple-negative breast cancer: Outcomes from CALGB 40603 (Alliance). Thirty-Eighth Annual CTRC-AACR San Antonio Breast Cancer Symposium; San Antonio, TX; Dec 8–12, 2015; S2–05.

121 Tutt A, Ellis P, Kilburn L, et al. The TNT trial: a randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012). Thirty-Seventh Annual CRTC-AACR San Antonio Breast Cancer Symposium; Antonio, TX; Dec 9–13, 2014; S3–01.

122 von Minckwitz G, Hahnen E, Fasching PA, et al, for the GBG and AGO-B Study Groups. Pathological complete response (pCR) rates after carboplatin-containing neoadjuvant chemotherapy in patients with germline *BRCA* (g*BRCA*) mutation and triple-negative breast cancer (TNBC): results from GeparSixto. *J Clin Oncol* 2014; **32** (suppl): 1005 (abstr).

123 Alba E, Chacon JI, Lluch A, et al. A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from the GEICAM/2006–03, multicenter study. *Breast Cancer Res Treat* 2012; **136:** 487–93.

124 Couch FJ, Hart SN, Sharma P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. *J Clin Oncol* 2015; **33:** 304–11.

125 Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol* 2014; **32:** 3744–52.

126 Perez EA, Suman VJ, Davidson NE, et al. Sequential versus concurrent trastuzumab in adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2011; **29:** 4491–97.

127 Slamon D, Eiermann W, Robert N, et al, for the Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011; **365:** 1273–83.

128 Slamon DJ, Eiermann W, Robert NJ, et al, for the BCIRG-006 Investigators. Ten year follow-up of BCIRG-006 comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC→T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer. *Cancer Res* 2016; **76** (suppl 4): S5–04.

129 Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, for the Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *Lancet* 2013; **382:** 1021–28.

130 Pivot X, Romieu G, Debled M, et al, for the PHARE trial investigators. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol* 2013; **14:** 741–48.

131 Mavroudis D, Saloustros E, Malamos N, et al, for the Breast Cancer Investigators of the Hellenic Oncology Research Group (HORG), Athens, Greece. Six versus 12 months of adjuvant trastuzumab in combination with dose-dense chemotherapy for women with HER2-positive breast cancer: a multicenter randomized study by the Hellenic Oncology Research Group (HORG). *Ann Oncol* 2015; **26:** 1333–40.

132 O'Sullivan CC, Bradbury I, Campbell C, et al. Efficacy of adjuvant trastuzumab for patients with human epidermal growth factor receptor 2-positive early breast cancer and tumors ≤2 cm: a meta-analysis of the randomized trastuzumab trials. *J Clin Oncol* 2015; **33:** 2600–08.

133 Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med* 2015; **372:** 134–41.

134 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:** 1796–804.

135 Buzdar AU, Suman VJ, Meric-Bernstam F, et al, for the American College of Surgeons Oncology Group investigators. Fluorouracil, epirubicin, and cyclophosphamide (FEC-75) followed by paclitaxel plus trastuzumab versus paclitaxel plus trastuzumab followed by FEC-75 plus trastuzumab as neoadjuvant treatment for patients with HER2-positive breast cancer (Z1041): a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; **14:** 1317–25.

136 Robidoux A, Tang G, Rastogi P, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013; **14:** 1183–92.

137 Carey LA, Berry DA, Cirrincione CT, et al. Molecular heterogeneity and response to neoadjuvant human epidermal growth factor receptor 2 targeting in CALGB 40601, a randomized phase III trial of paclitaxel plus trastuzumab with or without lapatinib. *J Clin Oncol* 2016; **34:** 542–49.

138 Piccart-Gebhart M, Holmes E, et al. Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. *J Clin Oncol* 2016; **34:** 1034–42.

139 Swain SM, Baselga J, Kim SB, et al, for the CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015; **372:** 724–34.

140 Gnant M. Role of bisphosphonates in postmenopausal women with breast cancer. *Cancer Treat Rev* 2014; **40:** 476–84.

141 Coleman R, Body JJ, Aapro M, et al. Bone health in cancer patient: ESMO clinical practice guidelines. *Ann Oncol* 2014; **25** (suppl 3)**:** 124–37.

142 Hadji P, Aapro MS, Body JJ, et al. Management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer: practical guidance for prevention and treatment. *Ann Oncol* 2011; **22:** 2546–55.

143 Gnant M, Mlineritsch B, Stoeger H, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. *Lancet Oncol* 2008; **9:** 840–49.

144 Coleman R, de Boer R, Eidtmann H, et al. Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-fast study): final 60-month results. *Ann Oncol* 2013; **24:** 398–405.

145 Paterson AH, Anderson SJ, Lembersky BC, et al. Oral clodronate for adjuvant treatment of operable breast cancer (National Surgical Adjuvant Breast and Bowel Project protocol B-34): a multicentre, placebo-controlled, randomised trial. *Lancet Oncol* 2012; **13:** 734–42.

146 Gnant M, Clezardin P. Direct and indirect anticancer activity of bisphosphonates: a brief review of published literature. *Cancer Treat Rev* 2012; **38:** 407–15.

147 Coleman R, Gnant M, Morgan G, Clezardin P. Effects of bone-targeted agents on cancer progression and mortality. *JNCI* 2012; **104:** 1059–67.

148 Coleman RE, Marshall H, Cameron D, et al, for the AZURE Investigators. Breast-cancer adjuvant therapy with zoledronic acid. *N Engl J Med* 2011; **365:** 1396–405.

149 von Minckwitz G, Möbus V, Schneeweiss A, et al. German adjuvant intergroup node-positive study: a phase III trial to compare oral ibandronate versus observation in patients with high-risk early breast cancer. *J Clin Oncol* 2013; **31:** 3531–39.

150 Gnant M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009; **360:** 679–91.

151 Ottewell, PD, Wang N, Brown HK, et al. Zoledronic acid has differential antitumor activity in the pre- and postmenopausal bone microenvironment in vivo. *Clin Cancer Res* 2014; **20:** 2922–32.

152 Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Coleman R, Powles T, Paterson A, et al. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet* 2015; **386:** 1353–61.

153 Gnant M, Pfeiler G, Dubsky PC, et al, for the Austrian Breast and Colorectal Cancer Study Group. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2015; **386:** 433–43.

154 Gnant M, Pfeiler G, Dubsky PC, et al, for the Austrian Breast and Colorectal Cancer Study Group. The impact of adjuvant denosumab on disease-free survival: Results from 3425 postmenopausal patients of the ABCSG-18 trial. Thirty-Eighth Annual CTRC-AACR San Antonio Breast Cancer Symposium; San Antonio, TX; Dec 8–12, 2015; S2–02.

155 Partridge AH, Pagani O, Abulkhair O, et al. First international consensus guidelines for breast cancer in young women (BCY1). *Breast* 2014; **23:** 209–20.

156 Peccatori FA, Pup LD, Salvagno F, et al. Fertility preservation methods in breast cancer. *Breast Care (Basel)* 2012; **7:** 197–202.

157 Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. *Lancet Oncol* 2012; **13:** 887–96.

158 Ring A, Reed M, Leonard R, et al. The treatment of early breast cancer in women over the age of 70. *Br J Cancer* 2011; **105:** 189–193.

159 Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012; **13:** e148–60.

160 Graeser MK, Engel C, Rhiem K, et al. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. *J Clin Oncol* 2009; **27:** 5887–92.

161 Greenberg PA, Hortobagyi GN, Smith TL, Ziegler LD, Frye DK, Buzdar AU. Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *J Clin Oncol* 1996; **14:** 2197–205.

162 Verma S, Miles D, Gianni L, et al, for the EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012; **367:** 1783–91.

163 Bossung V, Harbeck N. Angiogenesis inhibitors in the management of breast cancer. *Curr Opin Obstet Gynecol* 2010; **22:** 79–86.

164 Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Breast* 2014; **23:** 489–502.

165 Wang X, Yang KH, Wanyan P, Tian JH. Comparison of the efficacy and safety of denosumab versus bisphosphonates in breast cancer and bone metastases treatment: a meta-analysis of randomized controlled trials. *Oncol Lett* 2014; **7:** 1997–2002.

166 Ellis MJ, Llombart-Cussac A, Feltl D, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: overall survival analysis from the phase II FIRST study. *J Clin Oncol* 2015; **33:** 3781–87.

167 Ellis MJ, Bondarenko I, Trishkina E, et al. FALCON: a phase III randomised trial of fulvestrant 500 mg vs. anastrozole for hormone receptor-positive advanced breast cancer. *Ann Oncol* 2016; **27** (suppl 6): v552–587.

168 Klijn JG, Blamey RW, Boccardo F, et al; for the Combined Hormone Agents Trialists' Group and the European Organization for Research and Treatment of Cancer. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001; **19:** 343–53.

169 Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2†. *Ann Oncol* 2014; **25:** 2357–62.

170 Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol* 2015; **16:** 25–35.

171 Finn RS, Martin M, Rugo HS, et al. PALOMA-2: primary results from a phase III trial of palbociclib (P) with letrozole (L) compared with letrozole alone in postmenopausal women with ER+/HER2– advanced breast cancer (ABC). *J Clin Oncol* 2016; **34** (suppl): 507 (abstr).

172 Turner NC, Ro J, André F, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2015; **373:** 209–19.

173 Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for hr-positive, advanced breast cancer. *N Engl J Med* 2016; **375:** 1738–48.

174 Huober J, Fasching PA, Barsoum M, et al. Higher efficacy of letrozole in combination with trastuzumab compared to letrozole monotherapy as first-line treatment in patients with HER2-positive, hormone-receptor-positive metastatic breast cancer—results of the eLEcTRA trial. *Breast* 2012; **21:** 27–33.

175 Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; **344:** 783–92.

176 Ellis PA, Barrios C, Eiermann W, et al. Phase III, randomized study of trastuzumab emtansine (T-DM1) ± pertuzumab (P) vs trastuzumab + taxane (HT) for first-line treatment of HER2-positive MBC: Primary results from the MARIANNE study. *J Clin Oncol* 2015; **33** (suppl): 507 (abstr).

177 Cameron D, Casey M, Oliva C, Newstat B, Imwalle B, Geyer CE. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. *Oncologist* 2010; **15:** 924–34.

178 Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. *J Clin Oncol* 2012; **30:** 2585–92.

179 von Minckwitz G, Schwedler K, Schmidt M, et al; GBG 26/BIG 03–05 study group and participating investigators. Trastuzumab beyond progression: overall survival analysis of the GBG 26/BIG 3–05 phase III study in HER2-positive breast cancer. *Eur J Cancer* 2011; **47:** 2273–81.

180 Cortés J, Fumoleau P, Bianchi GV, et al. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol* 2012; **30:** 1594–600.

181 Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). *J Clin Oncol* 2003; **21:** 588–92.

182 Miles DW, Diéras V, Cortés J, Duenne AA, Yi J, O'Shaughnessy J. First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients. *Ann Oncol* 2013; **24:** 2773–80.

183 André F, Bachelot T, Commo F, et al. Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER). *Lancet Oncol* 2014; **15:** 267–74.

184 Zardavas D, Maetens M, Irrthum A, et al. The AURORA initiative for metastatic breast cancer. *Br J Cancer* 2014; **111:** 1881–87.

185 Fasching PA, Brucker SY, Fehm TN, et al. Biomarkers in patients with metastatic breast cancer and the PRAEGNANT Study Network. *Geburtshilfe Frauenheilkd* 2015; **75:** 41–50.