Breast cancer

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Lancet 2021; 397: 1750–69

Published Online
April 1, 2021
https://doi.org/10.1016/S0140-6736(20)32381-3

This online publication has been corrected. The corrected version first appeared at thelancet.com on May 6, 2021

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Breast cancer is still the most common cancer worldwide. But the way breast cancer is viewed has changed drastically since its molecular hallmarks were extensively characterised, now including immunohistochemical markers (eg, ER, PR, HER2 [ERBB2], and proliferation marker protein Ki-67 [MKI67]), genomic markers (eg, *BRCA1*, *BRCA2*, and *PIK3CA*), and immunomarkers (eg, tumour-infiltrating lymphocytes and PD-L1). New biomarker combinations are the basis for increasingly complex diagnostic algorithms. Neoadjuvant combination therapy, often including targeted agents, is a standard of care (especially in HER2-positive and triple-negative breast cancer), and the basis for de-escalation of surgery in the breast and axilla and for risk-adapted post-neoadjuvant strategies. Radiotherapy remains an important cornerstone of breast cancer therapy, but de-escalation schemes have become the standard of care. ER-positive tumours are treated with 5–10 years of endocrine therapy and chemotherapy, based on an individual risk assessment. For metastatic breast cancer, standard therapy options include targeted approaches such as CDK4 and CDK6 inhibitors, PI3K inhibitors, PARP inhibitors, and anti-PD-L1 immunotherapy, depending on tumour type and molecular profile. This range of treatment options reflects the complexity of breast cancer therapy today.

Epidemiology and risk factors

Worldwide, breast cancer accounts for about 30% of female cancers, and has a mortality-to-incidence ratio of 15%.[1] Worldwide incidence varies between 27 in 100 000 (Africa and east Asia) and 97 in 100 000 (North America), reflecting the association between breast cancer incidence and the degree of economic development and associated social and lifestyle factors.[2] In contrast, death rates continue to decline, but not everywhere. Declines in breast cancer mortality could be further accelerated by expanding access to high-quality prevention, early detection, and treatment services to all women, not neglecting the vast differences in access to these services.[3,4]

About 10% of all cases of breast cancer are related to genetic predisposition or family history, with variances by country and ethnicity. The most common germline mutations associated with breast cancer are in the *BRCA1* and *BRCA2* genes, with an average cumulative lifetime risk of about 70%.[5,6]

Search strategy and selection criteria

Data for this Seminar were identified by searches of MEDLINE, PubMed, German Association of the Scientific Medical Societies Guideline Register/Clinical Practice Guidelines, and references from relevant articles between Jan 1, 2016, and Dec 31, 2020, using the search term "breast cancer" in combination with specific terms covering the different steps of diagnosis and treatment as appropriate. We mostly selected literature published in the past 5 years, but did not exclude older publications that are commonly referenced and highly regarded. We have arbitrarily chosen clinical studies with the highest level of evidence or the highest number of most recent meta-analysis and review articles. Abstracts and reports from meetings that have not yet been published as full papers were also cited to provide readers with up-to-date literature. Only articles published in English and human studies were included.

Next-generation sequencing in breast cancer is based on gene panels, which include, in addition to *BRCA* genes, *PALB2*, *ATM*, *CHEK2*, *RAD51C*, *BARD1*, and *TP53*, among others. The partner and localiser of BRCA2 (PALB2) is a protein that promotes the localisation and stability of BRCA2.[7] Mono-allelic *PALB2* germline mutations lead to a 53% increased risk of breast, 2–3% increased risk of pancreatic, and 5% increased risk of ovarian cancer.[8,9,10] Several genetic syndromes (eg, Lynch syndrome) are associated with an increased risk of breast cancer, although such syndromes have a low to moderate penetrance and are rare in the general population.[11] National guidelines for genetic testing guide the therapeutic procedure after personal and family history taking, risk assessment, and genetic counselling.[12]

A high proportion of breast cancer cases might be attributed to pregnancy-associated factors, hormonal therapy, lifestyle factors (ie, obesity, physical inactivity, alcohol intake, low-fibre diet, and smoking), and other risk factors (panel 1).[13] In high-income countries, more than a third of cases of breast cancer seem to be preventable through lifestyle changes.[13] There is a long debate on whether oral hormonal contraceptives increase the risk of breast cancer; the absolute risk is small and not associated with an increased risk of mortality.[14] Menopausal hormone therapy, on the other hand, has been more clearly shown to increase the risk of breast cancer in women.[15]

Screening

Eight randomised clinical trials have shown that screening mammography reduces breast cancer mortality by at least 20%.[16] Conventional screening mammography detects 2–8 cancers per 1000 mammograms, which is increased by 1·6 cancers per 1000 mammograms with the use of digital breast tomosynthesis.[17] Ultrasonography screening, particularly in women with dense breasts, detects an additional 4·4 cancers per 1000 screening examinations, but the positive predictive value of ultrasonography is only 3–8%.[18] MRI screening is

highly sensitive in the detection of cancer, and showed a sensitivity of 90–93%, compared with 48–63% for mammography and ultrasound combined, in prospective trials of asymptomatic women at high risk of breast cancer.[19,20] The use of MRI screening in some countries has been limited to women at greatly elevated risk of breast cancer (eg, mutation carriers). New screening techniques, such as abbreviated MRI or contrast-enhanced spectral mammography, might be promising options to replace conventional MRI.[21,22]

Women with a germline *BRCA1* or *BRCA2* mutation can reduce their risk by undergoing bilateral mastectomy and salpingo-oophorectomy. Medical prevention with tamoxifen (IBIS-I and NSABP-P1 trials), raloxifene (STAR trial), or an aromatase inhibitor (IBIS-II) has been shown to reduce the risk of breast cancer development, but not mortality.[23–26] Low-dose tamoxifen (5 mg) seems to reduce the risk of ipsilateral and contralateral recurrences in patients with an intraepithelial neoplasia.[27]

Biology and molecular pathology

Breast cancer is very heterogeneous, and clinically divided into three main subtypes by hormone receptor (ER and PR) and HER2 (ERBB2) status: luminal ER-positive and PR-positive, which is further subdivided into luminal A and B; HER2-positive; and triple-negative breast cancer (TNBC).[28] Standardised diagnostic evaluation of hormone receptors (ER and PR) and HER2 based on international guidelines is essential for the determination of these subtypes.[29,30] Histochemical staining for the proliferation marker protein Ki-67 (MKI67) can be used to differentiate between luminal A-like and B-like breast cancers without gene expression profiling.[31]

The most common histological tumour type is invasive ductal carcinoma (also called no special type), followed by invasive lobular breast cancer, which is characterised by epithelial cadherin (CDH1) mutations and a dissociated growth pattern. Tumour-infiltrating lymphocytes in the tumour and stroma have been identified and showed prognostic and predictive value for response to chemotherapy, mainly in TNBC and HER2-positive breast cancer.[32,33] PD-L1 assessment in TNBC is recommended in metastatic breast cancer because it predicts response to checkpoint inhibitors, but the same correlation could not be demonstrated in early breast cancer. Tumour-infiltrating lymphocytes, as well as PD-L1, can be assessed following international standards.[34,35] Somatic *PIK3CA* mutations predict response to PI3K inhibitors in ER-positive, HER2-negative metastatic breast cancer.[36] In early HER2-positive breast cancer, *PIK3CA* mutations predict pathological complete response, but are not yet of clinical relevance.[37] The *ESR1* acquired mutation is induced by therapeutic pressure in 20–30% of metastatic ER-positive breast cancer, but is infrequent (less than 1% of cases) in early ER-positive breast cancer.[38]

About 15–20% of all TNBC cases are associated with germline mutations in *BRCA1* or *BRCA2*. High-risk, HER2-negative, hormone receptor-positive breast cancer is associated with germline mutations in *BRCA1* or *BRCA2* in about 10–15% of cases.[39] *PALB2* mutations are prevalent in about 0·6–3·9% of familial breast cancers.[39] *BRCA1*-associated breast cancers, which are mostly of triple-negative phenotype (70%–85%), differ from *BRCA2*-associated and *PALB2*-associated breast cancers in their distribution into ER and HER2 clinical subgroups, which is similar to that of sporadic cancers.[40] Assessing germline *BRCA* mutations in metastatic breast cancer identifies patients (with TNBC or HER2-negative, hormone receptor-positive breast cancer) who might benefit from poly(ADP-ribose) polymerase (PARP) inhibitor therapy.[41] In TNBC and high-risk luminal breast cancer, germline *BRCA* mutations predict the pathological complete response rate to neoadjuvant chemotherapy.[39] Germline *BRCA* mutations can confer a survival benefit, but this seems to be true only in TNBC.[42] Guidelines for germline *BRCA* mutation testing in early breast cancer have been developed by a variety of organisations. Most guidelines recommend testing all patients with TNBC younger than 50 years, regardless of family history,[12] but the predictive aspect (for therapeutic decisions) needs to be differentiated from the hereditary aspect (for management of prevention).

Panel 1: **Risk factors for breast cancer**

- Older age
- Genetic mutations (eg, *BRCA1*, *BRCA2*, *PALB2*, *RAD51*, etc)
- Family history of cancer, especially breast, ovarian, pancreatic, and prostate
- Personal history of breast lesions
  - Non-proliferative lesions
  - Proliferative lesions without atypia
  - High-risk lesions (ie, atypical ductal hyperplasia and lobular intraepithelial neoplasia)
  - Breast cancer (ductal carcinoma in situ, invasive breast cancer)
- High breast density
- History of irradiation to the chest
- Type II diabetes
- High total lifetime number of menstrual cycles
- Late pregnancy factors
- Low number of births or no pregnancy
- Advanced age at first full-term delivery
- Short or no breastfeeding
- Obesity
- Diet content (eg, high fat and low fibre)
- Alcohol intake
- Smoking
- Exposure to steroid hormones
  - Hormonal therapy for climacteric symptoms
  - Recent oral contraceptives
- Low physical activity

Panel 2: Open questions and their current status in breast cancer diagnosis and therapy controversies

Molecular classification

How can we distinguish between luminal A and luminal B type tumours?

Status: resolved. Proliferation marker protein Ki-67, as well as gene expression profiling, can be used to identify low-risk tumours.

Limitation: all methods are clinically valid for prediction of low-risk status, but the concordance between methods is low.

What is the best treatment for tumours with low (1–10%) ER expression?

Status: not resolved. The biology of these tumours is similar to that of triple-negative breast cancer (TNBC), but patients are not eligible for TNBC trials and therapy options.

How do we address differences in ER, PR, and HER2 (ERBB2) expression between primary tumours and residual disease?

Status: not resolved. In general, follow the initial diagnosis. However, the level of evidence is low.

How do we identify patients with TNBC that are eligible for immunotherapy?

Status: partly resolved. In the metastatic setting, PD-L1 is a biomarker of eligibility for checkpoint inhibitor therapy. In the neoadjuvant setting, however, PD-L1 expression is not a valid biomarker to select for checkpoint inhibitor therapy.

Treatment of early breast cancer

How to best identify patients with luminal, node-negative breast cancer for chemotherapy?

Status: partly resolved. Currently, a combination of clinicopathological markers and genomic assays is recommended to identify patients at high risk of breast cancer relapse.

Which patients with TNBC benefit from carboplatin?

Status: partly resolved. Pathological complete response can be increased with carboplatin-based therapy, but no conclusive data on long-term outcomes are yet available.

Do all patients without pathological complete response need capecitabine as post-neoadjuvant therapy in TNBC?

Status: partly resolved. A preplanned subgroup analysis of a phase 3 trial (NCT00130533) showed that capecitabine increases disease-free survival and overall survival in non-basal patients. This effect might be overestimated, considering the data from a pooled analysis of 12 randomised trials.

How long should endocrine therapy be given?

Status: resolved. Based on risk, endocrine therapy for longer than 5 years can be recommended for individual patients.

What patients can be safely offered de-escalated HER2-positive therapy?

Status: partly resolved. Patients at low risk of breast cancer relapse can be treated with less chemotherapy and trastuzumab instead of standard therapy.

Can patients undergo sentinel node biopsy after neoadjuvant chemotherapy?

Status: partly resolved. In principle, yes, but the pre-neoadjuvant chemotherapy status needs to be considered.

Can we use extreme hypofractionation (eg, radiotherapy in 1 week) in more patient subgroups?

Status: partly resolved. The FAST-Forward trial (ISRCTN19906132) reported that 26 Gy in five fractions over 1 week results in non-inferior local recurrence rates and normal tissue effects for breast and chest wall radiotherapy. Long-term follow-up evaluating late effects of locoregional radiotherapy is ongoing.

Treatment of metastatic breast cancer

What is the best treatment sequence in hormone receptor-positive, HER2-negative metastatic breast cancer?

Status: unresolved. There are no clear data on the optimal therapeutic sequence for these patients.

Does chemotherapy have a role in patients with hormone receptor-positive, HER2-negative breast cancer?

Status: partly resolved. Targeted agents seem to have pushed chemotherapy to third-line treatment strategies, but monochemotherapy can be less toxic than targeted agents plus endocrine therapy. Direct comparisons are scarce.

Do patients with primary metastatic breast cancer benefit from surgery?

Status: partly resolved. Not yet conclusively answered, but there are no data suggesting the opposite (harm from surgery).

How do we address differences in ER, PR, and HER2 status between primary tumour and metastases?

Status: partly resolved. Not yet conclusively answered. The general recommendation is to follow the most recent histological or immunophenotypic findings, although the level of evidence is low.

Diagnosis and therapy: current controversies and scientific discussions

There are still controversies around every aspect of breast cancer diagnosis and care. For example, it has been shown that tumours with low-hormone receptor expression are biologically similar to TNBC. The American Society of Clinical Oncology and the College of American Pathologists have recently defined low-ER tumours as tumours with ER expression between 1% and 10%, without changing treatment recommendations,[43] so that treating low-hormone receptor breast cancer as TNBC would be the logical consequence. This is one of several examples of controversy around treatment individualisation, especially for HER2-positive disease, but also for TNBC (panel 2). Normally, de-escalation refers to optimisation of treatment. Although breast cancer screening has been widely adopted in many high-income countries, it is unclear to what extent this has led to an

overdiagnosis of non-invasive breast lesions (ie, ductal carcinoma in situ), which are associated with a high risk of developing invasive breast cancer, but have a minimal risk of breast cancer mortality. How effective screening is in terms of lowering breast cancer mortality is still debated, considering that the increased rate of detection of ductal carcinoma in situ has not been accompanied by a parallel decrease in invasive cancer incidence or breast cancer mortality. The increased rate of diagnosis of smaller invasive breast cancers has led to the discussion of whether local therapy and systemic treatment need to be de-escalated to avoid harm. The increasing rates of pathological complete response with modern systemic therapy have led to trials investigating the accuracy of determining pathological complete response non-surgically, in preparation for studies examining the safety of eliminating surgery altogether. In the absence of clear data indicating the safety of de-escalation, the tendency is still to overtreat some patients to avoid their undertreatment.

Early breast cancer: neoadjuvant treatment concept

Neoadjuvant therapy (mainly chemotherapy with targeted agents) has been widely accepted as a standard of care, especially in HER2-positive breast cancer and TNBC, even when the disease is operable. The general concept is to use the same systemic therapy as would be given postoperatively before surgery, followed by surgery and irradiation and further post-neoadjuvant systemic therapy, if required. Primary endocrine therapy is used in ER-positive breast cancer when primary surgery is contraindicated due to comorbidities, or in patients with endocrine-responsive tumours desiring downstaging to breast conservation. The observation that patients achieving a pathological complete response have significantly better disease-free survival and overall survival than patients with residual disease[44] has led to studies examining the use of additional systemic therapy in patients without pathological complete response. In the CREATE-X trial, adjuvant capecitabine improved disease-free survival and overall survival after neoadjuvant anthracycline and taxanes-based chemotherapy in patients with HER2-negative breast cancer.[45] Extrapolation of these results to clinical practice is controversial because only patients with TNBC benefited from this approach, and none of the patients in the trial received carboplatin as part of the neoadjuvant regimen. In addition, patients with TNBC who do not reach pathological complete response are generally considered to be chemoresistant, and capecitabine is unlikely to rescue these patients.[46] Nevertheless, most national and international guidelines recommend that capecitabine is at least considered for these patients. The KATHERINE trial showed that switching from antibody-based anti-HER2 neoadjuvant therapy to trastuzumab emtansine (an antibody–drug conjugate) after surgery in patients without pathological complete response improved invasive disease-free survival (from 77%, with trastuzumab, to 88%, with trastuzumab emtansine).[47] These results are very homogeneous and independent of the extent of residual disease and ER status.

Although primary surgery is highly effective, the widespread use of neoadjuvant therapy in early-stage breast cancer allows further de-escalation of surgery in the breast and axilla, converting approximately 40% of patients with HER2-positive breast cancer and TNBC initially requiring mastectomy to breast-conserving surgery candidates.[48,49] The use of breast-conserving surgery post-neoadjuvant therapy has been limited by the inability to reliably distinguish between viable and non-viable tumour on post-neoadjuvant therapy imaging, and by the inappropriate belief that pathological complete response and excision of the entire initial tumour volume are both required for breast-conserving surgery in patients with larger tumours.[50] The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of ten randomised trials (1983–2002) of neoadjuvant therapy versus adjuvant therapy showed a 3·2% (95% CI 0·6–5·8%; p=0·01) increase in locoregional recurrence in patients having breast-conserving surgery post-neoadjuvant therapy, compared with those having the planned surgery first, which raised some concerns. However, locoregional recurrence was no more frequent in those requiring neoadjuvant therapy to downstage to breast-conserving surgery than in those who were candidates for breast-conserving surgery at presentation. Many of the studies in the meta-analysis did not require negative resection margins, and some of them required no surgery to the breast at all, suggesting that these findings probably reflect incomplete familiarity with post-neoadjuvant therapy imaging and surgery during that time, and highlighting the importance of multidisciplinary teamwork.[51,52]

The use of neoadjuvant chemotherapy reduces nodal positivity among clinically node-negative (cN0) and cN-positive patients. In patients with cN0 status before the start of neoadjuvant therapy, sentinel lymph node identification rates (94–96%), false-negative rates (6–7%), and nodal recurrence rates (<1·5%) mirror those seen in patients who undergo primary surgery.[53–56] High rates of nodal pathological complete response in patients with cN-positive status receiving neoadjuvant therapy[57,58] led to four prospective multicentre trials evaluating sentinel lymph node biopsy accuracy in this setting (table 1).[55–59] False-negative rates were largely determined by the number of sentinel lymph nodes retrieved. In a meta-analysis including 1921 patients with biopsy-proven nodal metastases, the sentinel lymph node identification rate was 90% with a 14% false-negative rate, which fell to 4% with removal of three or more sentinel lymph nodes.[60] In a single-institution study, three or more negative sentinel lymph nodes were retrieved and axillary lymph node dissection was avoided in 237 (42%) of 573 patients who became cN0 after neoadjuvant therapy.[61] Another approach to decrease false negative rates of

	GANEA 2[55] (n=307)	SN FNAC[57] (n=153)	ACOSOG Z1071[58] (n=689)	SENTINA[59] (n=592)
Clinical stage	pN1	cT0–3 N1/2	cT0–4 N1/2	cN1/2
SLN identification rate	80%	88%	93%	80%
Overall SLN false-negative rate	12%	13%	13%	14%
False-negative rate by number of SLNs				
1 SLN	19%	18%	32%	24%
2 SLNs	8%	5%	21%	19%
≥3 SLNs	NR	NR	9%	5%

SLN=sentinel lymph node. NR=not reported.

Table 1: **SLN biopsy in clinically node-positive patients receiving neoadjuvant chemotherapy (results of prospective trials)**

	IBCSG 23–01[75] (n=934)	ACOSOG Z0011[76] (n=891)	AMAROS[77] (n=1425*)	OTOASOR[78] (n=2016)
Breast surgery	BCS or mastectomy (9%)	BCS	BCS or mastectomy (17%)	BCS or mastectomy (16%)
Experimental group	SLN biopsy only	SLN biopsy only	SLN biopsy plus nodal radiotherapy	SLN biopsy plus nodal radiotherapy
% patients with <3 involved SLNs	100%	97%	96%	Not stated, mean 1·2 (range 1–4)
Additional positive nodes in ALND group	13%	27%	33%	39%
10 year nodal recurrence rate	2%	1%	2%	2%†

BCS=breast-conserving surgery. SLN=sentinel lymph node. ALND=axillary lymph node dissection. *With tumour-positive sentinel lymph node biopsy. †8 year rate (OTOASOR had sufficient power for the planned statistical analysis after 8 years of follow-up and rates were estimated at 8 years).

Table 2: **Trials on SLN biopsy without axillary node dissection in node-positive patients undergoing initial surgery**

sentinel lymph node biopsy after primary systemic treatment is targeted axillary dissection.[62] Rates of nodal recurrence after sentinel lymph node biopsy alone in patients presenting initially as cN-positive are not yet available. Micrometastases or macrometastases in the sentinel lymph node after neoadjuvant therapy and initial presentation with T4 or N2/3 disease are often considered to be indications for axillary lymph node dissection after neoadjuvant therapy.[57,63]

Because there is no definite information available about the initial pT-pN stage, the indications for chest wall radiotherapy after mastectomy and for regional radiotherapy after mastectomy and breast-conserving surgery following neoadjuvant therapy needed to be reviewed. Both the initial clinical stage and the final stage after neoadjuvant therapy should be considered together with other risk factors, including age, tumour biology, and further adjuvant treatment options, including endocrine and targeted treatments.[64–67] A review showed that post-mastectomy radiotherapy reduces locoregional recurrence rates from 24·4% to 3·2% in patients with ypN0 (no lymph node metastases present after neoadjuvant therapy) status and from 56·3% to 10·8% in patients with ypN+ (lymph node metastases present after neoadjuvant therapy) after neoadjuvant therapy.[67] Ongoing research concerning the relative contributions of pre-neoadjuvant therapy and post-neoadjuvant therapy stage to locoregional recurrence will inform about the indications for chest wall and lymph node irradiation and for the integration of radiotherapy as part of the preoperative treatment paradigm.[68]

Early breast cancer: locoregional therapy

Options for the treatment of early-stage breast cancer include breast-conserving surgery and mastectomy with or without immediate reconstruction. Absolute contraindications to breast-conserving surgery are uncommon, but include inability to obtain negative margins and contraindications to radiotherapy. Multicentric cancer, previously thought to necessitate mastectomy, can be safely managed with breast-conserving surgery if two or more lumpectomies can be done with satisfactory cosmetic outcomes.[69] The widespread use of systemic therapy contributed to the reduction of locoregional recurrence.[70] Rates of locoregional recurrence after breast-conserving surgery followed by radiotherapy are approximately 2–3% at 10 years for ER-positive and HER2-positive tumours and 5% for TNBC, and do not differ significantly from those seen after mastectomy.[71,72] The practice of re-excision after lumpectomy has declined with the adoption of the so-called no ink on tumour approach as the standard for a negative margin.[73,74]

Axillary lymph node dissection is no longer the initial approach to nodal metastases for most patients. Four prospective randomised trials have shown no significant differences in locoregional recurrence or survival in patients with cN0 status with metastases in one to two sentinel lymph nodes treated with sentinel lymph node biopsy alone,[75,76] or with sentinel lymph node biopsy plus radiotherapy (table 2).[77,78] The application of these findings to a consecutive cohort of 793 patients with positive sentinel lymph nodes having breast-conserving surgery avoided axillary lymph node dissection in 85% of patients.[79] When postmastectomy radiotherapy is indicated based on metastases in one to two sentinel lymph nodes, axillary lymph node dissection can be avoided as well, as shown by the AMAROS trial.[80]

Postoperative radiotherapy to eradicate clinically occult tumour deposits in the breast, chest wall, and regional lymphatic drainage system is offered to most women after either breast-conserving surgery or mastectomy in the presence of risk factors. In a meta-analysis by the EBCTCG, which included 8135 women from 22 randomised trials, postmastectomy radiotherapy for patients with involved axillary lymph nodes reduced the 10 year first recurrence rate by 10·6%, leading to an 8·1% reduction in breast cancer mortality after 20 years.[81] The benefit was independent of the number of involved lymph nodes or the administration of systemic therapy, and was larger after partial or no axillary lymph node

dissection and smaller in case of regional radiotherapy without coverage of the chest wall. The EBCTCG meta-analysis of the effect of radiotherapy after breast-conserving surgery involving individual patient data of 10 801 women from 17 randomised trials showed reductions in 10 year recurrences rates of 15·4% in patients with negative nodes and 21·2% in patients with positive nodes, and reductions in 15-year overall mortality rates of 3·3% (patients with negative nodes) and 8·5% (patients with positive nodes).[82]

The indications for lymph node radiotherapy increased following these two EBCTCG meta-analyses[81,82] and a third meta-analysis[83] of regional lymph node irradiation involving 13 500 women in 14 trials. Furthermore, especially in patients at high risk, the decreasing frequency of axillary surgery is compensated by an increasing use of nodal radiotherapy, while avoidance of both surgery and radiotherapy is possible in patients with limited nodal involvement and no high-risk features.[80,84]

De-escalation of radiotherapy in patients at low risk, involving combinations of decreased number of sessions, size of target volumes, or both, and lower doses and shorter treatment duration, includes anatomy-based target volume contouring, hypofractionation, decreased use of a tumour bed boost dose, and (accelerated) partial breast irradiation.[85–88]

A major shift from the conventional field-based radiotherapy setup towards an anatomically-defined, target volume-based treatment planning and delivery greatly facilitates proper delivery of the prescribed dose to the target volumes, while respecting the dose and volume defined constraints for normal tissues.[70,79,89] The extent to which this will decrease late normal-tissue toxicity is yet to be defined, although early evaluations are encouraging.[90–92]

Moderate hypofractionation (40–42·5 Gy in 15–16 sessions over 3 weeks) was shown to be non-inferior in terms of outcome and cosmetic result, compared with 50 Gy over 5 weeks, and consequently became the preferred scheme for most if not all patients.[71,93] Subsequent research demonstrated that a 1 week radiotherapy schedule to the breast or the chest wall, delivering 26 Gy in five sessions of 5·2 Gy, is non-inferior to the 3 week schedule for local tumour control, and is as safe in terms of normal tissue effects up to 5 years.[94] Ongoing, long-term follow-up and a nodal substudy will show the influence of the ultrafast 1 week hypofractionation schedule on late cardiovascular toxicity.[95]

The sharp decrease in local recurrence rates has also led to the development of partial breast radiotherapy, which decreases the treatment burden by reducing both the treatment duration and the treated volumes. Several techniques are available and can be grouped into brachytherapy, intra-operative radiotherapy, and external beam radiotherapy.[96–99] The two basic principles behind partial breast radiotherapy include proper selection of patients with low-risk breast cancer, and the ability to deliver an adequate tumouricidal dose to the target volume.[100,101] If these two principles are respected, outcomes will not be inferior to whole breast radiotherapy, independently of the used technique.[102]

All these developments lower the burden of radiotherapy for patients with breast cancer and improve the integration of (shorter courses of) radiotherapy into the overall multidisciplinary workflow (table 3).

Current challenges include the integration and optimisation of radiotherapy with breast reconstruction,

	Trial methodology	Patient eligibility (accrual target)	Primary endpoint	Radiation therapy technique
PAPBI-2 (NCT02913729): preoperative radiation therapy	Phase 3 randomised trial comparing preoperative *vs* postoperative accelerated partial breast irradiation	Patients at low risk aged >50 years (500 patients)	Cosmetic outcome, assessed by digital photographs, and patient and specialist questionnaires	Partial breast IMRT (28·5 Gy in five fractions over 1 week)
DBCG RT Recon (NCT03730922): breast reconstruction and PMRT	Phase 3 randomised trial comparing a delayed-immediate breast reconstruction with a delayed breast reconstruction	Women who are offered a mastectomy, are candidates for PMRT, and wish breast reconstruction (590 patients)	The occurrence of any complication deeming surgical intervention necessary within 1 year after the final reconstruction	Target volume delineation according to the ESTRO-ACROP guidelines; any technique achieving the objectives and constraints is allowed
NSABP 51 (NCT01872975): axillary management after primary systemic therapy	Phase 3 randomised trial evaluating regional lymph node irradiation in case of ypN0 (assessed by SLNB or ALND)	Patients with cT1–3N1M0 breast cancer who received primary systemic therapy (1636 patients)	Invasive breast cancer recurrence-free interval	Standard locoregional radiation therapy
Alliance 11202 (NCT01901094): axillary management after primary systemic therapy	Phase 3 randomised trial comparing ALND with regional lymph node irradiation *vs* regional lymph node irradiation only in case of ypN+ (assessed by SLNB)	Patients with cT1–3N1M0 breast cancer who received primary systemic therapy (1660 patients)	Invasive breast cancer recurrence-free interval	Standard locoregional radiation therapy

IMRT=intensity-modulated radiotherapy. DBCG=Danish Breast Cancer Group. PMRT=postmastectomy radiotherapy. ESTRO=European Society for Radiotherapy and Oncology. ACROP=Advisory Committee for Radiation Oncology Practice. SLNB=sentinel lymph node biopsy. ALND=axillary lymph node dissection.

Table 3: **Summary of a short selection of ongoing clinical trials involving radiation therapy**

identifying patients in whom radiotherapy can be omitted without jeopardising outcomes including quality of life, and selective treatment escalation in patients at high risk, especially in case of resistance to neoadjuvant therapy.[31,103–105] The ultimate aim is to achieve individualised, risk-adapted radiotherapy, combining a variety of biomarkers with novel applications of artificial intelligence.[106–108]

Early breast cancer: systemic therapy

Endocrine therapy

Endocrine therapy for 5–10 years is the standard treatment for women with ER-positive early breast cancer. For postmenopausal women, options include tamoxifen or a steroidal (exemestane) or non-steroidal (letrozole or anastrozole) aromatase inhibitor. Front-line therapy with an aromatase inhibitor results in a significant absolute risk reduction of recurrence at 10 years of 3·6% and in an increase in overall survival of 2·1% compared with tamoxifen. The sequential approach of aromatase inhibitor after 2–5 years of tamoxifen results in a smaller benefit than the aromatase inhibitor upfront therapy, but it still results in significant risk reduction for breast cancer recurrence of 2·0% and death of 1·5% compared with tamoxifen alone.[109,110] Aromatase inhibitor therapy has been shown to provide greater benefit in patients with advanced stage (II–III), high-grade, HER2-positive, or highly proliferative disease. Despite little supporting data, aromatase inhibitors are also the preferred option for lobular cancers based on the results of the BIG 1-98 trial.[111] The standard duration of endocrine therapy with aromatase inhibitors is 5 years, especially for stage I disease.[112] The role of adjuvant therapy extended for up to 10 years has been investigated in several trials and data suggest that continuation of endocrine therapy reduces the risk of recurrence in patients at high risk (node-positive, high genomic score).[113–117] Patients with ER-positive disease remain at risk of recurrence even after 10 years, and the decision to extend adjuvant therapy needs to take into account and balance potential benefits against toxicity and impaired quality of life.[118]

Patients in the premenopause with hormone receptor-positive, HER2-negative, lymph node-positive breast cancer benefit from combined endocrine therapy and chemotherapy. Recent data from the phase 3 RxPONDER trial (NCT01272037) showed that the addition of chemotherapy to endocrine therapy improved 5 year invasive disease-free survival and overall survival in premenopausal women that were also of low biological risk by multigene testing.[119]

In premenopausal women with ER-positive early breast cancer, based on the SOFT and TEXT trials, ovarian function suppression in combination with an aromatase inhibitor or tamoxifen reduces the recurrence rate when compared with tamoxifen alone, and is therefore recommended in all women with an indication for chemotherapy.[113,120] Ovarian function suppression plus an aromatase inhibitor is recommended for patients younger than 35 years.[121] Patients without an indication for adjuvant chemotherapy, which implies a lower risk of recurrence, can be treated with tamoxifen alone. Quality of life deteriorates when ovarian function suppression is used, even more so when an aromatase inhibitor is added instead of tamoxifen, mainly because of an increase in vasomotor symptoms (which resolve after the end of therapy).[122] Patients who are prescribed adjuvant tamoxifen after chemotherapy and remain premenopausal, or resume ovarian function after a temporary chemotherapy-induced ovarian failure, benefit from the addition of ovarian function suppression to tamoxifen, as shown by the ASTRRA trial.[123]

Starting ovarian function suppression 2 weeks before the first chemotherapy dose should be advised for preservation of ovarian function in women between 35 and 40 years and is independent of the ER status of the tumour.[124] Pregnancy after breast cancer is not contraindicated, since there are no data showing an adverse outcome.[125] Tamoxifen needs to be stopped at least 2–3 months before conception. It is recommended to resume endocrine therapy after delivery and lactation, and to complete at least 5 years of therapy. The optimal timing of pregnancy after a breast cancer diagnosis and treatment is an area of uncertainty, and is based on the individual risk and age of the patient. The PREFER study (NCT02895165) and the prospective POSITIVE study (NCT02308085) are collecting important data on fertility preservation and selection of ovarian function preservation strategies; POSITIVE will also assess the feasibility and safety of endocrine therapy discontinuation to attempt pregnancy after breast cancer diagnosis and treatment.

CDK4 and CDK6 inhibitors (palbociclib, abemaciclib, and ribociclib) in addition to endocrine therapy in patients at high or very high risk are currently being evaluated in several phase 3 trials (PENELOPE-B [NCT01864746], 1 year; PALLAS [NCT02513394] and monarchE [NCT03155997], 2 years; NATALEE [NCT03701334], 3 years). All three CDK4 and CDK6 inhibitors have been shown to improve progression-free survival and overall survival in endocrine-sensitive and endocrine-resistant metastatic breast cancer.[126] The PENELOPE-B trial did not show that the addition of 1 year of palbociclib to standard adjuvant endocrine therapy improves 3 year invasive-disease free survival in patients at high risk of relapse after neoadjuvant chemotherapy (81·2% with palbociclib *vs* 77·7% with placebo).[127] In the PALLAS study, palbociclib given for 2 years did not improve the outcome (3 years invasive disease-free survival) of early breast cancer in patients at intermediate and high risk of recurrence (88·2% for palbociclib plus endocrine therapy *vs* 88·5% for endocrine therapy alone; hazard ratio [HR] 0·93 [95% CI 0·76–1·15]; p=0·51).[128] The monarchE study, in which abemaciclib was used in an exclusively high-risk breast cancer population, did show a 3·5% absolute difference in 2 year invasive disease-free survival rates after a

median follow-up of 15 months: 92·2% for abemaciclib versus 88·7% for endocrine therapy alone (HR 0·75 [95% CI 0·60–0·93]; p=0·01), which is rather short for a HER2-negative, hormone receptor-positive breast cancer population.[129]

Chemotherapy in patients with ER-positive breast cancer and TNBC

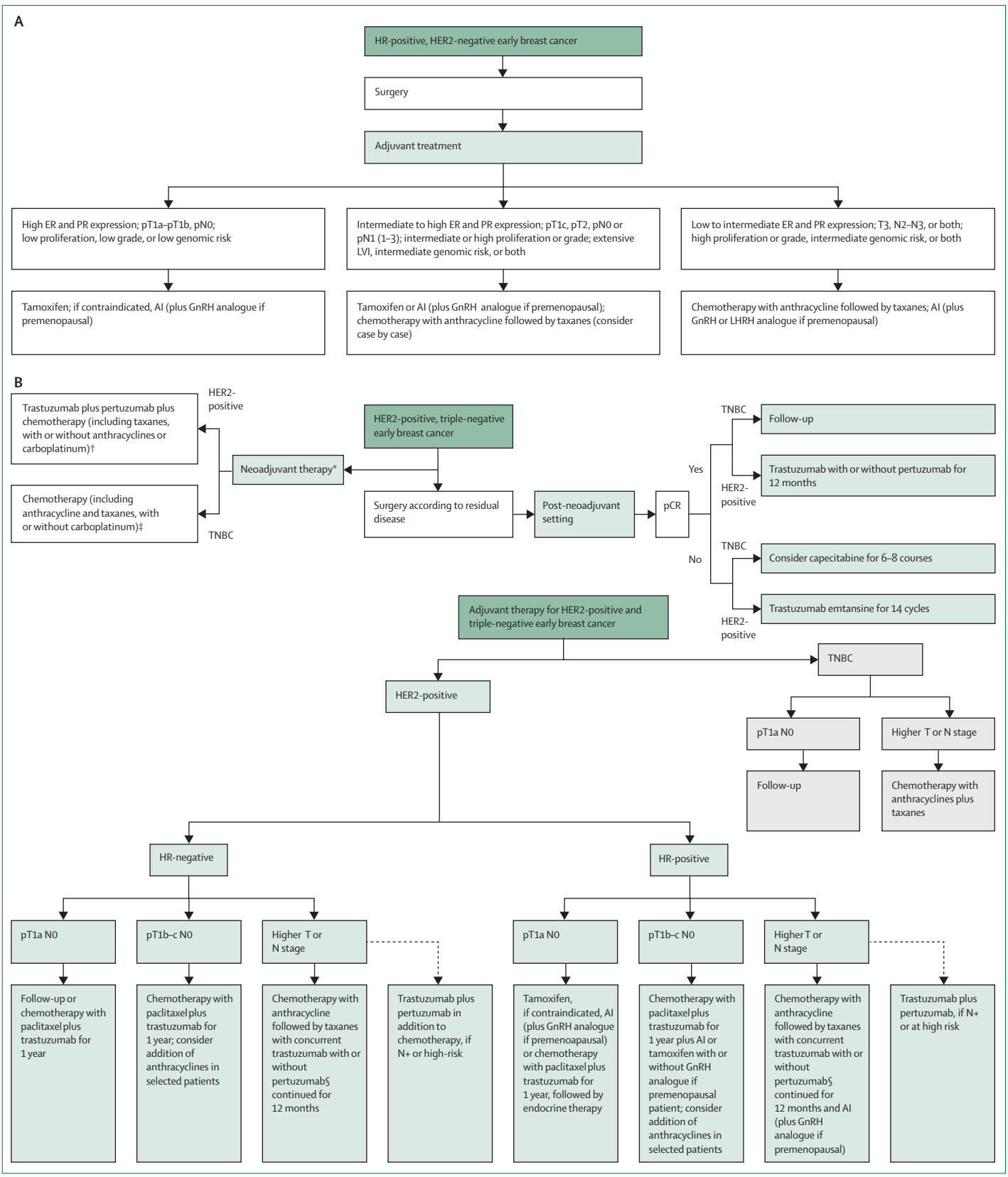
The use of chemotherapy generally reduces the risk of recurrence by about 30% in selected patients. The absolute benefit from neoadjuvant or adjuvant chemotherapy depends on the risk of recurrence.[130] When neoadjuvant or adjuvant chemotherapy is indicated, the optimal regimen consists of a taxane-based regimen with or without anthracyclines in sequence. The use of anthracyclines is often controversially debated, but it seems to be necessary in patients at high risk.[131,132] Fluorouracil as part of adjuvant chemotherapy does not seem to add benefit to an anthracycline and taxane-based therapy.[133] Dose-dense or dose-intensified chemotherapy is generally superior to conventionally dosed therapy. The relative risk reduction is independent of prognostic factors and the absolute benefit varies with the level of risk.[134] The most important clinical and pathological determinants to stratify risk and to identify candidates for additional chemotherapy are: advanced-stage disease with nodal involvement, tumour size, less endocrine-responsive disease (low expression of ER, PR, or both), high grade or high proliferative index, patient age, and lymphovascular invasion.[135] To better stratify the risk and identify patients who might derive benefit from chemotherapy, multigene assays can be used when available, especially in node-negative ER-positive, HER2-negative breast cancer to support decision making (figure 1A).[136–141] In postmenopausal patients with up to three positive nodes and low or intermediate genomic score, there is no indication to add chemotherapy, although chemotherapy is recommended for patients with a high genomic score. Regarding the use of chemotherapy in premenopausal women with no nodal involvement, a retrospective analysis questioned a potential benefit for patients with tumours harbouring an intermediate recurrence score.[142] Since no prospective data for lobular cancers are available, the same recommendations apply to these patients, although acknowledging that their chemosensitivity is much lower.[143]

In women with early TNBC, an anthracycline and taxane-based chemotherapy is the mainstay of treatment. Whether an anthracycline-free regimen is appropriate for these patients is controversial. Several clinical trials incorporating platinum salts into standard regimens have shown an associated absolute improvement in pathological complete response rates of about 15%.[144–147] The effect on long-term disease-free survival and overall survival is less convincing, due to the small size of some trials and the absence of long-term follow-up in others.[148] One adjuvant therapy study, mainly in patients with pT1 and node-negative status, showed improved disease-free survival with a carboplatin anthracycline-free combination over epirubicin, fluorouracil, and cyclophosphamide followed by docetaxel.[149] The carboplatin effect in early breast cancer seems to be independent of *BRCA* status.[150] To date, PARP inhibitors have not been shown to improve short-term or long-term outcomes in breast cancer. The only phase 3 trial of PARP inhibitors for breast cancer to date did not show an increased pathological complete response rate with the addition of veliparib (probably the PARP inhibitor with the least activity) to paclitaxel plus carboplatin followed by doxorubicin–cyclophosphamide.[147] Smaller studies using either olaparib or talazoparib have shown some promising effects. The full results of the OlympiA (NCT02032823) study, where olaparib 600 mg was given for 1 year after standard neoadjuvant or adjuvant chemotherapy in patients with germline *BRCA*-mutated, HER2-negative breast cancer, with positive preliminary findings in invasive disease-free survival in the olaparib group, are awaited (figure 1B).

Addition of the anti-PD-1 antibody pembrolizumab to neoadjuvant paclitaxel and carboplatin followed by doxorubicin–cyclophosphamide increased the pathological complete response rate by up to 64%. The effect was independent of PD-L1 status and mainly seen in node-positive breast cancer.[151] Very similar results could be observed with atezolizumab being added to nab-paclitaxel followed by doxorubicin–cyclophosphamide every 2 weeks.[152] This combination might change the primary therapy in high-risk early TNBC. In all neoadjuvant phase 3 breast cancer trials investigating a checkpoint inhibitor, including the currently recruiting GeparDouze trial (NCT03281954), patients continued taking the checkpoint inhibitor after surgery for up to 1 year. The rational for this decision is not clear, but it is in analogy to the anti-HER2 therapy in HER2-positive early breast cancer.

Management of HER2-positive early breast cancer

The addition of anti-HER2 therapy (mainly trastuzumab and pertuzumab) to chemotherapy has changed the natural history of this disease.[153] The vast majority of patients with a tumour of 2 cm or larger or nodal involvement receive neoadjuvant trastuzumab plus pertuzumab, in addition to doxorubicin–cyclophosphamide or epirubicin–cyclophosphamide followed by a taxane, or in addition to docetaxel–carboplatin, which is associated with higher toxicity. This regimen increased the pathological complete response rate to about 65–70% and led to an improvement in event-free survival and disease-free survival.[154,155] Attempts have been made to decrease either the duration of anti-HER2 therapy or to reduce the use of chemotherapy agents. None of the randomised trials using a shorter duration of trastuzumab convincingly showed that such a reduction


A
HR-positive, HER2-negative early breast cancer
Surgery
Adjuvant treatment
High ER and PR expression; pT1a–pT1b, pN0; low proliferation, low grade, or low genomic risk
Intermediate to high ER and PR expression; pT1c, pT2, pN0 or pN1 (1–3); intermediate or high proliferation or grade; extensive LVI, intermediate genomic risk, or both
Low to intermediate ER and PR expression; T3, N2–N3, or both; high proliferation or grade, intermediate genomic risk, or both
Tamoxifen; if contraindicated, AI (plus GnRH analogue if premenopausal)
Tamoxifen or AI (plus GnRH analogue if premenopausal); chemotherapy with anthracycline followed by taxanes (consider case by case)
Chemotherapy with anthracycline followed by taxanes; AI (plus GnRH or LHRH analogue if premenopausal)
B
HER2-positive, triple-negative early breast cancer
Neoadjuvant therapy*
HER2-positive
Trastuzumab plus pertuzumab plus chemotherapy (including taxanes, with or without anthracyclines or carboplatinum)†
TNBC
Chemotherapy (including anthracycline and taxanes, with or without carboplatinum)‡
Surgery according to residual disease
Post-neoadjuvant setting
pCR
Yes
TNBC
Follow-up
HER2-positive
Trastuzumab with or without pertuzumab for 12 months
No
TNBC
Consider capecitabine for 6–8 courses
HER2-positive
Trastuzumab emtansine for 14 cycles
Adjuvant therapy for HER2-positive and triple-negative early breast cancer
HER2-positive
TNBC
pT1a N0
Follow-up
Higher T or N stage
Chemotherapy with anthracyclines plus taxanes
HR-negative
HR-positive
pT1a N0
Follow-up or chemotherapy with paclitaxel plus trastuzumab for 1 year
pT1b–c N0
Chemotherapy with paclitaxel plus trastuzumab for 1 year; consider addition of anthracyclines in selected patients
Higher T or N stage
Chemotherapy with anthracycline followed by taxanes with concurrent trastuzumab with or without pertuzumab§ continued for 12 months
Trastuzumab plus pertuzumab in addition to chemotherapy, if N+ or high-risk
pT1a N0
Tamoxifen, if contraindicated, AI (plus GnRH analogue if premenoapausal) or chemotherapy with paclitaxel plus trastuzumab for 1 year, followed by endocrine therapy
pT1b–c N0
Chemotherapy with paclitaxel plus trastuzumab for 1 year plus AI or tamoxifen with or without GnRH analogue if premenopausal patient; consider addition of anthracyclines in selected patients
Higher T or N stage
Chemotherapy with anthracycline followed by taxanes with concurrent trastuzumab with or without pertuzumab§ continued for 12 months and AI (plus GnRH analogue if premenopausal)
Trastuzumab plus pertuzumab, if N+ or at high risk

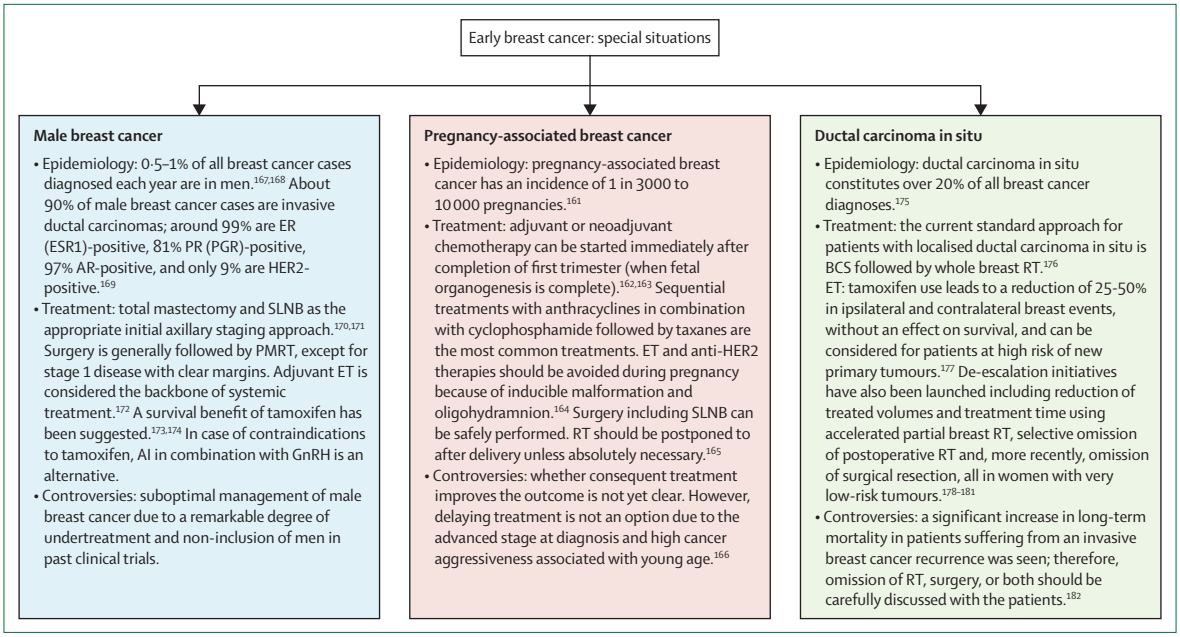


Figure 2: **Special situations in early breast cancer**
SLNB=sentinel lymph node biopsy. PMRT=postmastectomy radiotherapy. ET=endocrine therapy. AI=aromatase inhibitor. GnRH=gonadotropin-releasing hormone. RT=radiotherapy. BCS=breast-conserving surgery.

is satisfactory.[156–158] The standard duration of anti-HER2 therapy continues to be 1 year, although shorter durations can be considered in countries with low resources, to allow more women to benefit to a slightly lower extent. The non-randomised APT trial (NCT00542451) showed a 7 year disease-free survival of 93% (95% CI 90–93%) for women treated with paclitaxel for 18 weeks and trastuzumab for 1 year. This regimen has become a standard option for patients with low-risk HER2-positive breast cancer—namely, those with low tumour burden.[159] The ExteNET study demonstrated that an additional 1 year of therapy with neratinib after 1 year of trastuzumab in patients with high-risk HER2-positive, hormone receptor-positive breast cancer can improve disease-free survival (figure 1B, appendix p 1).[160]

Special situations in early breast cancer, such as pregnancy-associated breast cancer,[161–166] male breast cancer,[167–174] and ductal carcinoma in situ[175–182] are presented in figure 2.

Figure 1: **Treatment algorithm for HR-positive and HER2-negative early breast cancer (A) and HER2-positive and triple-negative early breast cancer (B)**
AI=aromatase inhibitor. GnRH=gonadotropin-releasing hormone. HR=hormone receptor. LHRH=luteinising hormone-releasing hormone. LVI=lymphovascular invasion. pCR=pathological complete response. TNBC=triple-negative breast cancer. *Preferred approach for all stage II and stage III tumours. †An anthracycline-free regimen containing paclitaxel and carboplatin can be considered, in association with trastuzumab and pertuzumab. ‡Adding carboplatin can be considered because it improves pCR rates, although it causes increased toxicity. §Shorter durations of trastuzumab can be considered in selected patients, such as in case of treatment-induced cardiotoxicity.

Metastatic breast cancer

Endocrine-responsive metastatic breast cancer

Endocrine therapy is standard of care, unless immediate response needs to be reached in patients with symptomatic breast cancer (which is an indication for chemotherapy).[183] A CDK4/6 inhibitor combined with endocrine therapy should be considered a standard of care for patients with ER-positive, HER2-negative metastatic breast cancer. In comparison with endocrine therapy, this combination results in a higher response rate, progression-free survival benefit, and substantially increases overall survival while maintaining or improving quality of life. CDK4/6 inhibitors can be combined with an aromatase inhibitor (preferentially in a setting of endocrine-sensitive disease) or with fulvestrant or possibly tamoxifen (in endocrine-resistant disease) in de-novo or recurrent metastatic breast cancer, in first, second, or further lines, and in premenopausal and postmenopausal women (figure 3A).[184,185]

See Online for appendix

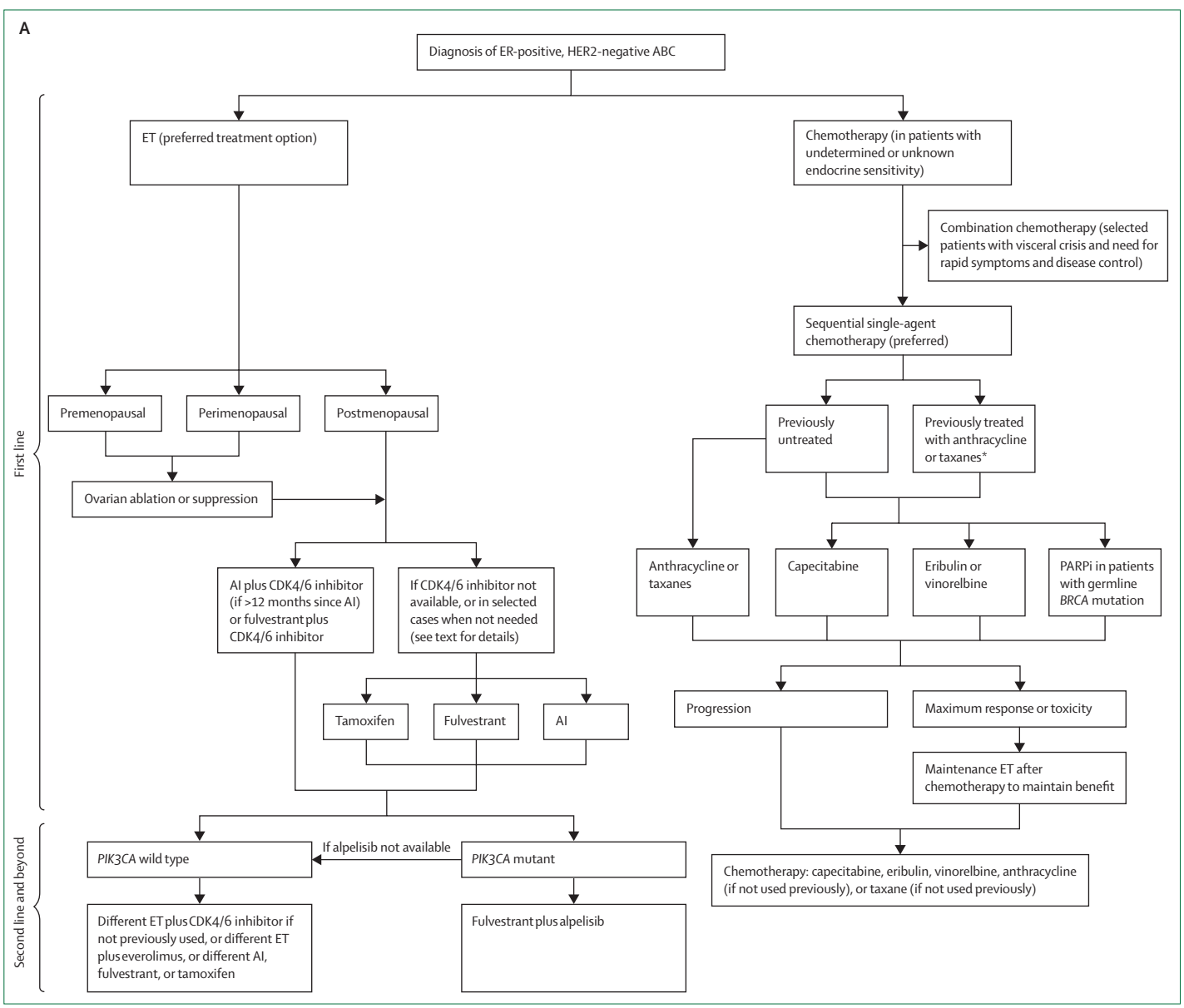
Alpelisib, the first in class α-elective PIK3 inhibitor, combined with fulvestrant is a treatment option for patients with *PIK3CA*-mutant tumours (in exons 9 or 20, detected preferably in the tumour, or alternatively in circulating tumour DNA) previously exposed to an aromatase inhibitor, showing an improvement in progression-free survival.[36,186] Another option is the addition of everolimus, an mTOR inhibitor, to exemestane, which significantly improved progression-free survival by more than two times in patients with ER-positive, HER2-negative endocrine-resistant metastatic breast cancer that recurred or progressed during or after treatment with

non-steroidal aromatase inhibitors.[187] Single-agent abemaciclib is also an option.[188]

In patients with ER-positive metastatic breast cancer harbouring a germline *BRCA1* or *BRCA2* mutation, PARP inhibitors such as olaparib or talazoparib, which have been shown to improve progression-free survival compared with monochemotherapy, should be considered.[41,189,190] The optimal sequence of PARP inhibitors and endocrine therapy with or without CDK4/6 inhibitors is unknown. Given the overall survival benefit seen with CDK4/6 inhibitors, these can be recommended before a PARP inhibitor (appendix p 2). The optimal sequence of endocrine-based therapy is uncertain because it depends on which agents were previously used (in the [neo]adjuvant or advanced settings), duration of response to those agents, burden of the disease, patients' preference, and availability.

Management of HER2-positive metastatic breast cancer

As in early HER2-positive breast cancer, anti-HER2 therapy beyond progression, in combination with either chemotherapy or endocrine therapy, improves survival. The median overall survival is currently 5 years. As a first-line therapy, dual HER2 blockade with trastuzumab plus pertuzumab in combination with chemotherapy (mainly taxanes) is recommended. Second-line therapy consists of trastuzumab emtansine, or, if this is not available, trastuzumab plus any chemotherapy agent. Trastuzumab



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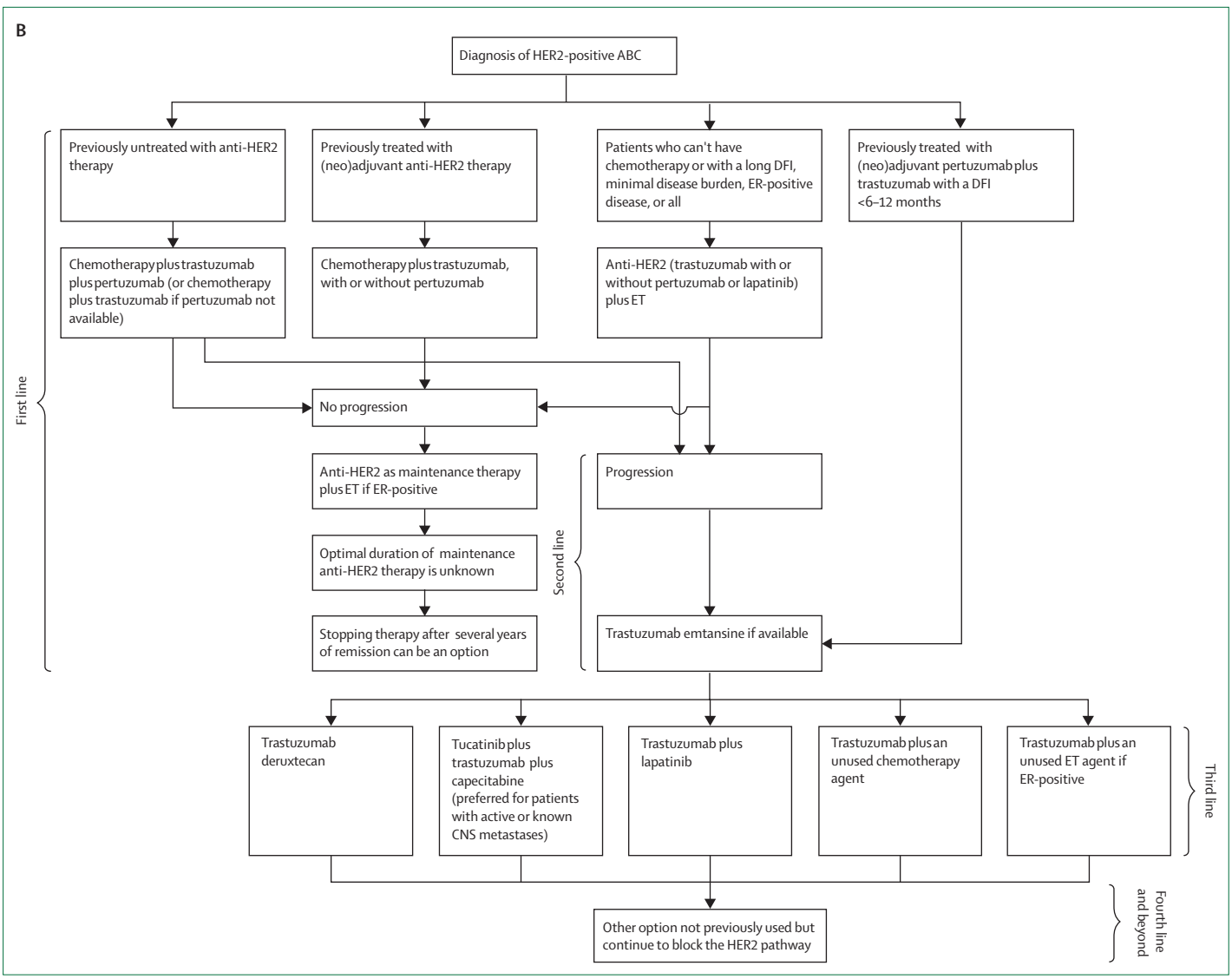

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plus lapatinib is another treatment option (plus endocrine therapy in HER-2 positive, hormone receptor-positive tumours). Neratinib, a pan-ERBB tyrosine kinase inhibitor, in combination with paclitaxel was not superior to paclitaxel plus trastuzumab as a first-line therapy, but seemed to delay the onset of brain metastases.[191] Neratinib plus capecitabine in further line was superior to lapatinib plus capecitabine.[192] Compared with a placebo, the highly selective anti-HER2 tyrosine kinase inhibitor tucatinib in addition to capecitabine and trastuzumab has resulted in significantly higher progression-free survival and overall survival in the overall population and in patients with brain metastases after pretreatment with trastuzumab, pertuzumab, and trastuzumab emtansine, as shown by the HER2CLIMB study.[193] Trastuzumab deruxtecan, an antibody–drug conjugate, has shown a high overall response rate of 61% in a phase 1/2 study.[194] The main side-effect, in addition to nausea (78% of patients; any grade), decreased neutrophil count (35% of patients), and anaemia (30% of patients; any grade) was interstitial lung disease (14% of patients).[194] Whether the drug is more effective than trastuzumab emtansine is being investigated in an ongoing trial (NCT03529110). Trastuzumab deruxtecan has also shown an overall response rate of 37% in heavily pretreated patients with HER2-low disease.[195] These new anti-HER2 drugs will expand the armamentarium for treating HER2-positive breast cancer, for which continuous anti-HER2 treatment is key (figure 3B).

Management of metastatic TNBC

Atezolizumab, an immune checkpoint inhibitor, plus nab-paclitaxel improved progression-free survival by about

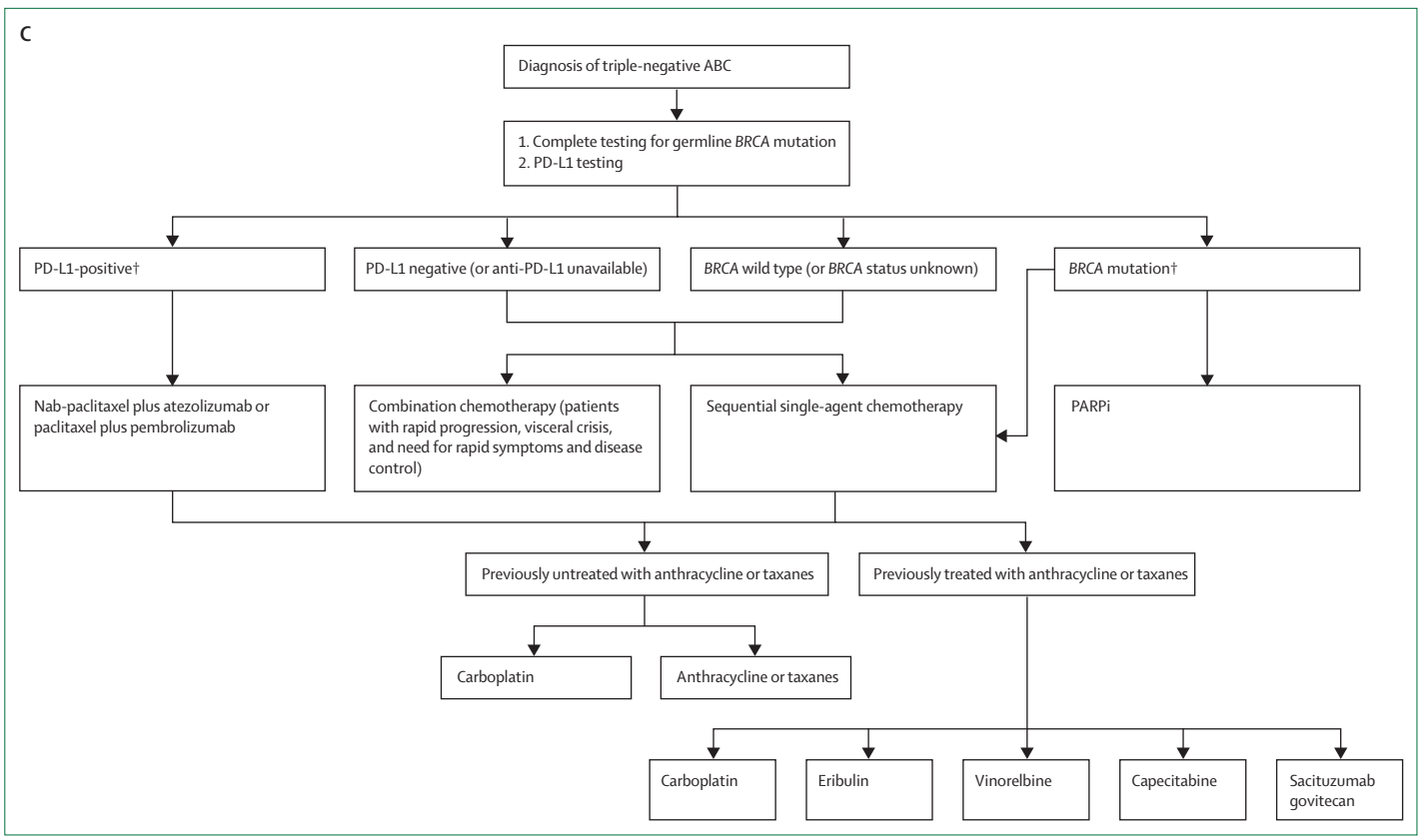

Figure 3: **Treatment algorithm for ER-positive and HER2-negative metastatic breast cancer (A), HER2-positive metastatic breast cancer (B), and triple-negative metastatic breast cancer (C)**
ABC=advanced breast cancer. AI=aromatase inhibitor. DFI=disease-free interval. ET=endocrine therapy. PARPi=poly(ADP-ribose) polymerase inhibitor. *Rechallenge with taxanes or anthracycline is possible (if cumulative dose not reached and DFI ≥12 months). †Patients with PD-L1-positive or *BRCA*-mutated breast cancer should first receive a checkpoint inhibitor with taxane, then PARPi (no data available for checkpoint inhibitors as second-line threapy).

2·5 months in TNBC expressing more than 1% PD-L1.[196] The overall survival analysis indicated no significant difference between the treatment groups, but suggests a clinically meaningful overall survival benefit (of about 10 months) with atezolizumab plus nab-paclitaxel in the PD-L1-positive population.[197] The KEYNOTE-355 study, investigating the efficacy of pembrolizumab in combination with one of three chemotherapy options (nab-paclitaxel, paclitaxel, or carboplatin–gemcitabine) reported the pembrolizumab combination to have a positive effect on progression-free survival in PD-L1-positive metastatic TNBC (figure 3C).[198] Conversely, atezolizumab in addition to paclitaxel did not show a significant progression-free survival benefit compared with paclitaxel alone.[199] Taking all the relevant data into consideration, there is still controversy about the effect size of checkpoint inhibitors in breast cancer, but checkpoint inhibitor monotherapy does not seem to be effective in breast cancer.[200]

Similarly to patients with ER-positive, HER2-negative metastatic breast cancer, single-agent PARP inhibitor (talazoparib or olaparib) is a treatment option for patients harbouring a germline *BRCA1* or *BRCA2* mutation.[189,190] The combination of veliparib with paclitaxel plus carboplatin as a first-line therapy for germline *BRCA1*-mutant or *BRCA2*-mutant metastatic TNBC was also superior to chemotherapy alone.[201] The therapeutic implications of somatic *BRCA1* or *BRCA2* mutations in breast cancer need to be further explored within a research setting, and should not be considered an indication for PARP inhibitors in clinical practice. The optimal sequence in patients with PD-L1-positive and germline *BRCA1* or *BRCA2* mutations would first be checkpoint inhibitor-based therapy and then the PARP inhibitor. In a study setting, only 7% of patients with PD-L1-positive metastatic TNBC harboured a mutation; conversely, 50% of patients with the germline *BRCA* mutant had PD-L1-positive tumours, suggesting that the PD-L1 positivity rate is independent from germline *BRCA* status.[202]

In all other patients with metastatic disease, chemotherapy remains the standard of care.

Non-systemic options for metastatic breast cancer, including local therapies

The relation between tumour burden and outcome is known for all stages of breast cancer. Therefore, radical treatments directed to at least part of the residual tumour after systemic therapy are assumed to improve outcomes.[203]

Another possible mechanism is a so-called abscopal effect beyond the irradiated volume, influencing the distribution and growth of distant tumour deposits.[204]

Although several retrospective analyses[205–207] suggested that local or locoregional surgery, radiotherapy, or both, improve overall survival, two prospective randomised trials did not show a consistent and clear benefit with surgery, which might at least in part be attributed to methodological and regional issues.[208,209] However, a multicentre retrospective cohort including 4507 patients with primary metastatic breast cancer showed that radiotherapy with or without surgery, but not surgery alone, improved overall survival after adjustment for known prognostic factors and propensity score analysis.[210] The ECOG-ACRIN 2108 trial (NCT01242800), which randomly assigned 390 patients who did not progress after 4–8 months of systemic therapy to continued systemic therapy or early local therapy (consisting of surgery to negative margins and standard of care radiotherapy), showed no improvement in progression-free survival or overall survival for local therapy at a median follow-up of 53 months. Survival worsened by 3·3 times and local progression increased by 2·5 times with local therapy in TNBC, leading the authors to conclude that local therapy should be reserved for patients with stable metastases and symptomatic progression at the primary site.[211]

Any palliative treatment should aim to deliver a good compromise between symptom relief and treatment-related burden, taking into account all other factors related to the tumour, treatment, and patient. An emerging field concerns oligometastatic disease, most often defined as up to five metastases.[212] Although early data show improved outcomes after radical metastases-directed therapy, these data are based upon a widely variable range of clinical scenarios, with different prognoses and requiring different therapeutic approaches.[213] Most patients can be treated with short courses of radiotherapy, ranging between one and five of conventional or stereotactic techniques, with palliative, radical, and even curative intentions. A special case is brain metastases, which are seen in up to a third of metastatic breast cancer patients, most commonly at 1–3 years after metastatic breast cancer diagnosis.[214]

The progresses in diagnostic procedures and systemic treatments improve the identification of metastatic breast cancer patients with a low overall disease burden, who might benefit more from optimised locoregional therapy and from metastases-directed treatments.[215] All of this should be discussed in a multidisciplinary tumour board, ideally one dedicated to metastatic disease.

Conclusion and future perspectives

Future research in breast cancer will focus not only on new drugs, but even more on the individualisation of therapy for every single tumour in every single patient. Several agents (ie, PARP inhibitors, checkpoint inhibitors, and PI3K inhibitors) approved in recent years work only in patients or tumours with a certain biomarker or mutation. The European Society for Medical Oncology has set a scale for actionability of molecular targets.[216] New drugs, such as AKT inhibitors (eg, ipatasertib, tested in the LOTUS trial,[217] or capivasertib, tested in the PAKT trial[218]) show promising results, but the IPATunity130 trial failed to confirm the phase 2 data for ipatasertib added to paclitaxel in first-line metastatic TNBC.[219] There are also antibody–drug conjugates for the treatment of TNBC and ER-positive, HER2-negative breast cancer, independently of any biomarker. Sacituzumab govitecan, which targets TROP2 (TACSTD2) has been shown to significantly improve progression-free survival and overall survival in TNBC and shows promising phase 2 results in hormone receptor-positive, HER2-negative metastatic breast cancer.[220–222] The results of the histone deacetylase inhibitor entinostat E2112 trial (NCT02115282) are awaited.[223] New endocrine agents (selective ER downregulators) are being developed to overcome or prevent endocrine resistance, which is based, for instance, on *ESR1* mutations.[224]

A general focus is de-escalation, which, as discussed, is controversial. Care is required not to jeopardise the progress made in the last 40 years. De-escalation in surgery has been a goal for many years, whereas in systemic and radiation therapy, de-escalation has only become of interest more recently. There must be a careful balance between acceptable increase in the relapse risk and potential decrease of side-effects, including financial toxicity. Discussions are ongoing, but it remains vital that all de-escalation measures are tested within clinical trials. "ASCO [American Society of Clinical Oncology] believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate."[225] We are convinced of this.

Contributors

All authors contributed actively to the manuscript and approved the final version.

Declaration of interests

SL reports grants and honorarium for lectures and advice boards paid to institution from AbbVie, Amgen, AstraZeneca, Celgene, Novartis, Pfizer, Roche, and Daiichi-Sankyo; honorarium for lectures and advice boards paid to institution from Seattle Genetics, priME/Medscape, Lilly, Samsung, Eirgenix, BMS, Puma, and MSD; personal fees from Chugai; grants from Teva, Vifor, and Immunomedics outside the submitted work; and has a patent (EP14153692.0) pending. PP reports a medical advisor role for Sordina IORT Technologies outside the submitted work. MM reports personal fees from Genomic Health outside the submitted work. CD reports personal fees from Novartis, Roche, MSD Oncology, and Daiichi Sankyo; grants from Myriad Genetics; is a cofounder and shareholder of Sividon Diagnostics/Myriad (unrelated to the submitted work); has two patents pending (EP18209672 and EP20150702464), and a patent Software pending (VMscope digital pathology). GC reports grants from Roche and Pfizer; and personal fees from Daichii Sankyo, MSD, and AstraZeneca outside the submitted work.

Acknowledgments

We thank Valentina Vladimirova for editorial assistance.

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