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Breast cancer

Nadia Harbeck^{1*}, Frédérique Penault-Llorca², Javier Cortes^{3,4}, Michael Gnant⁵, Nehmat Houssami⁶, Philip Poortmans^{7,8}, Kathryn Ruddy⁹, Janice Tsang¹⁰ and Fatima Cardoso¹¹

Abstract | Breast cancer is the most frequent malignancy in women worldwide and is curable in ~70–80% of patients with early-stage, non-metastatic disease. Advanced breast cancer with distant organ metastases is considered incurable with currently available therapies. On the molecular level, breast cancer is a heterogeneous disease; molecular features include activation of human epidermal growth factor receptor 2 (HER2, encoded by *ERBB2*), activation of hormone receptors (oestrogen receptor and progesterone receptor) and/or *BRCA* mutations. Treatment strategies differ according to molecular subtype. Management of breast cancer is multidisciplinary; it includes locoregional (surgery and radiation therapy) and systemic therapy approaches. Systemic therapies include endocrine therapy for hormone receptor-positive disease, chemotherapy, anti-HER2 therapy for HER2-positive disease, bone stabilizing agents, poly(ADP-ribose) polymerase inhibitors for *BRCA* mutation carriers and, quite recently, immunotherapy. Future therapeutic concepts in breast cancer aim at individualization of therapy as well as at treatment de-escalation and escalation based on tumour biology and early therapy response. Next to further treatment innovations, equal worldwide access to therapeutic advances remains the global challenge in breast cancer care for the future.

Breast cancer is the most frequent malignancy in women and is a heterogeneous disease on the molecular level. Over the past 10–15 years, treatment concepts have evolved to take this heterogeneity into account, with emphasis being placed on more biologically-directed therapies and treatment de-escalation to reduce the adverse effects of treatment. Despite the inherent molecular heterogeneity, which is a driving principle of modern-day treatments, some features such as the impact of locoregional tumour burden or metastatic patterns are shared and influence therapy. Early breast cancer — that is, cancer that is contained in the breast or that has only spread to the axillary lymph nodes — is considered curable. Improvements in multimodal therapy have led to increasing chances for cure in ~70–80% of patients. By contrast, advanced (metastatic) disease is not considered curable using currently available therapeutic options. However, advanced breast cancer is a treatable disease, for which the main goals of therapy are to prolong survival and control symptoms with low treatment-associated toxicity to maintain or improve quality of life (that is, improved quality-adjusted life expectancy).

The two major pillars of breast cancer management are locoregional treatment and systemic therapy; the histological and molecular characteristics of breast cancer largely influence treatment decisions. The molecular

alterations that drive breast carcinogenesis are many, and several classifications have been developed to group tumours accordingly. The intrinsic classification of Perou and Sorlie¹, reported in 2000, distinguished four subtypes of breast cancer: luminal A and luminal B (expressing the oestrogen receptor (ER)), basal-like and human epidermal growth factor receptor 2 (HER2)-enriched (without ER expression). This classification shifted clinical management of breast cancer from being based on tumour burden to biology-centred approaches. Currently, clinical practice typically uses a surrogate classification of five subtypes on the basis of histological and molecular characteristics (FIG. 1). Tumours expressing ER and/or progesterone receptor (PR) are considered hormone receptor-positive breast cancers, whereas tumours that do not express ER, PR or HER2 are triple-negative breast cancer (TNBC). Importantly, treatment by a specialized multidisciplinary team improves survival and quality of life for patients with early and metastatic breast cancer, as does treatment according to high-quality guidelines. Establishment of specialized breast cancer centres is a major priority worldwide, and is supported by the European Parliament².

As breast cancer is a global problem, major emphasis needs to be put on diminishing worldwide disparities in access to diagnosis, multimodal treatment and novel drugs. In this Primer, we provide state-of-the-art

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information on the biology, diagnosis and treatment of early and metastatic breast cancer, emphasizing the necessity for multidisciplinary management of this heterogeneous disease.

Epidemiology

Demographics, incidence and mortality

In 2018, an estimated 2.1 million women were newly diagnosed with breast cancer, approximately one new case diagnosed every 18 seconds; additionally, 626,679 women with breast cancer died³. The global incidence of breast cancer has been rising with annual increases of 3.1%, beginning with 641,000 cases in 1980 and increasing to >1.6 million in 2010 (REF⁴); this trend is likely to continue. Indeed, the global cancer burden in women is increasing in countries regardless of income level, owing to population growth and an ageing population. The female population accounts for 49.5% of the global population, and they form a larger proportion of the population >60 years of age. Furthermore, the epidemiology of advanced breast cancer is a research priority as, in most countries, the number of patients with advanced disease is unknown; cancer registries mostly track diagnosis and deaths but not relapses. One study estimated that, in 2017, ~160,000 patients live with advanced-stage breast cancer in the United States alone⁵. The death rates also vary among subtypes of breast cancer with HER2-positive disease associated with a higher death rate, followed by the TNBC, luminal A and luminal B subtypes⁶.

Incidence varies worldwide, with higher incidence in high-income regions (92 per 100,000 in North America) than in lower income regions (27 per 100,000 in middle Africa and eastern Asia)^{7,8}. These patterns reflect both the risk factors and the availability and utility of mammography (and, therefore, detected breast cancers); the highest breast cancer incidence is in North America, Australia, New Zealand and northern and western Europe. Furthermore, in high-income countries, breast cancer is often diagnosed at an early stage and the prognosis is usually good. However, in low- and middle-income countries, breast cancer is often diagnosed at a later stage and is, accordingly, associated with poorer survival⁹ — a fact that is reflected in the mortality statistics. Breast cancer mortality is usually higher in

many low- and middle-income countries, such as those in sub-Saharan Africa¹⁰ and developing Asian countries¹¹, despite their lower incidence, due to delayed presentation, late stage at diagnosis and limited access to treatment. Several studies have also shown that breast cancer presents earlier in Asian women (typically 40–50 years of age) than in their western counterparts (typically 60–70 years of age)^{12–17}. In addition, patients in developing countries who are diagnosed with breast cancer are ~10 years younger than those in developed countries. The proportion of young patients (<35 years of age) varies from ~10% in developed countries to up to 25% in developing Asian countries¹⁵. The biology of the tumour also varies by ethnicity, which has implications for the difference in mortality¹⁷. For example, African and African-American women had the highest rates of TNBC compared with any other ethnic group. They also had higher rates of metastatic disease, and the highest rates of poorly differentiated or undifferentiated grade among all subtypes, all of which are associated with lower survival¹⁸. Additionally, metastatic breast cancer represents 9% of diagnoses among non-Hispanic black women compared with 5–6% of diagnoses in other ethnic groups. Regarding the survival gains in patients with advanced disease during the years 1975–2013, the 5-year cause-specific survival of non-Hispanic white women was higher than that of other ethnic groups, particularly non-Hispanic black women (19–37% compared with 16–26%)^{19,20}. This pattern is multifactorial and involves genetic predisposition, lifestyle and other environmental factors.

Genetic predisposition

Approximately 10% of breast cancers are inherited and associated with a family history²¹, although this varies frequently by ethnicity and across countries in the context of early-onset, bilateral and/or TNBC. Individuals with a first-degree relative who had breast cancer have an elevated relative risk (RR) of 3 of early-onset breast cancer (before 35 years of age)²². However, a family history of breast cancer is associated with an ‘erratic’ individual risk of breast cancer composed of different variables, including the size of the family and environmental factors. To determine the family’s risk, models such as the family history score have been developed²³.

Mutations in two high-penetrance tumour suppressor genes, *BRCA1* (17q21) and *BRCA2* (13q13), whose proteins are involved in DNA repair through homologous repair²⁴, show an autosomal-dominant inheritance pattern (loss of function > missense). *BRCA1* and *BRCA2* mutations are associated with an average cumulative risk of developing breast cancer by the age of 80 years of 72% and 69%, respectively²⁵; the relative risk of breast cancer in men (BOX 1) harbouring *BRCA2* mutations is 6%^{26,27}. More than 2,000 *BRCA* gene alterations have been described (mutations and large rearrangements), but only few have been found repeatedly in unrelated families, for example, founder mutations in Ashkenazi Jewish families (*BRCA1* 185delAG or *BRCA2* 6174delT) or Icelandic families (*BRCA2* 999del5). The prevalence of *BRCA1* and *BRCA2* mutations varies between ethnic groups, being lower in the Asian group (0.5%) and higher

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in the Ashkenazi group (10.2%) in a US nationwide study²⁸. Germline *BRCA* testing will now be performed as a companion diagnostic in patients with metastatic breast cancer²⁹ given the availability of poly(ADP-ribose) polymerase (PARP) inhibitors, which prolong progression-free survival (PFS) and improve quality of life^{30,31}, as a targeted therapy for *BRCA* mutation carriers in HER2-negative metastatic breast cancer^{32,33}.

Several syndromes related to germline mutations of genes involved in DNA repair and maintaining genomic integrity have been shown to be linked to, to a lesser degree, the inherited breast cancer risk (TABLE 1). Next-generation sequencing has enabled panels of genes to be

screened — beyond *BRCA1* and *BRCA2* — to determine the inherited breast cancer risk^{34–36}, and include *ATM*, *CHEK2*, *PALB2*, *PTEN*, *STK11* and *TP53* (REF.³⁷).

Lifestyle and other environmental factors

Breast cancer epidemiology pattern differences across countries are further compounded by cultural factors, lifestyle factors and national awareness campaigns. The increase in breast cancer incidence between 1980 and the late 1990s is likely due to changes in reproductive factors, with advanced maternal age for first pregnancy, and an increase in awareness and mammography screening^{38,39}. Several explanations have been offered as to why

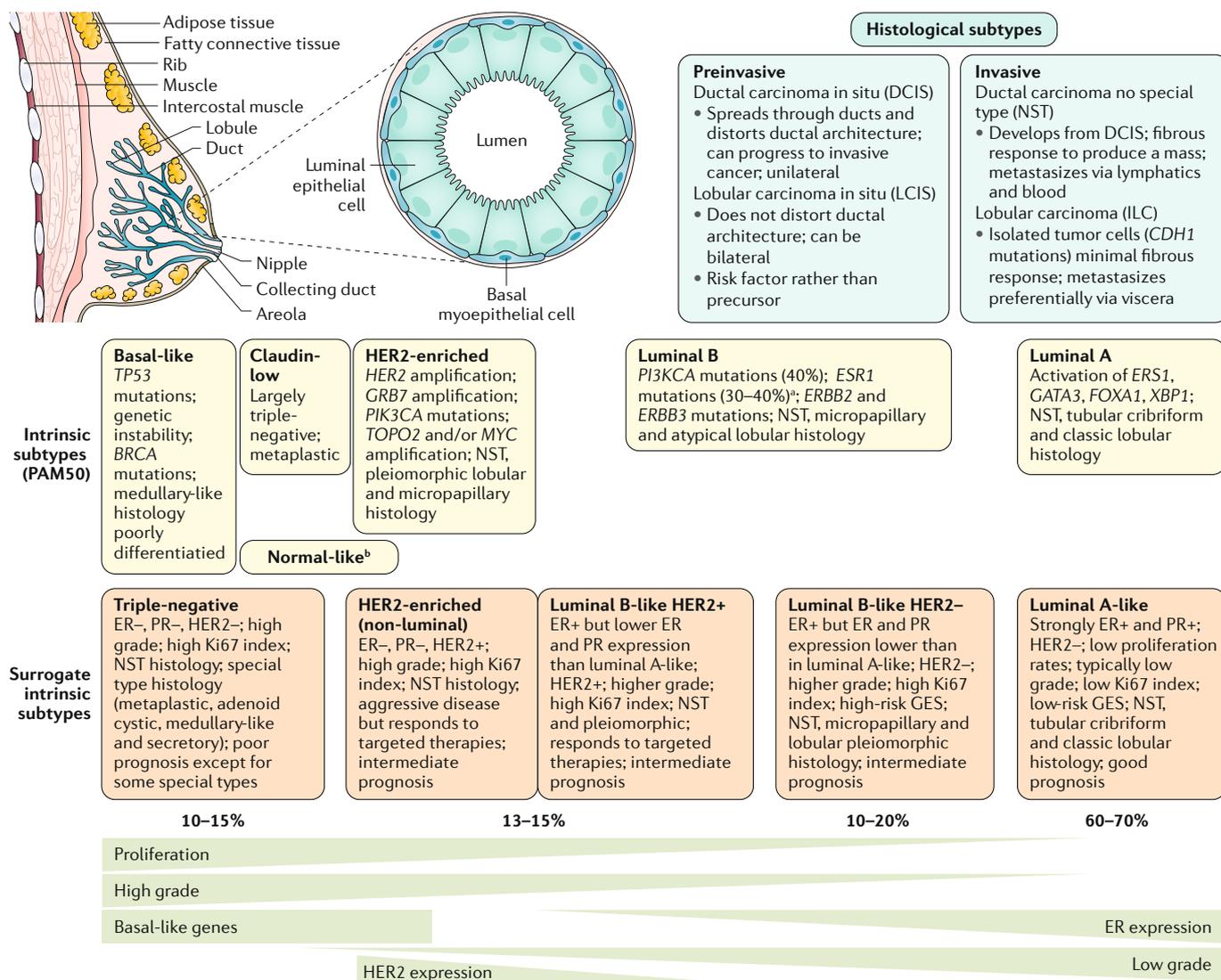


Fig. 1 | Breast cancer. All breast cancers arise in the terminal duct lobular units (the functional unit of the breast) of the collecting duct. The histological and molecular characteristics have important implications for therapy, and several classifications on the basis of molecular and histological characteristics have been developed. The histological subtypes described here (top right) are the most frequent subtypes of breast cancer; ductal carcinoma (now referred to as ‘no special type’ (NST)) and lobular carcinoma are the invasive lesions; their preinvasive counterparts are ductal carcinoma in situ and lobular carcinoma in situ (or lobular neoplasia), respectively. The intrinsic subtypes of Perou and Sorlie¹ are based on a 50-gene expression signature (PAM50)³²¹. The surrogate

intrinsic subtypes are typically used clinically and are based on histology and immunohistochemistry expression of key proteins: oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and the proliferation marker Ki67. Tumours expressing ER and/or PR are termed ‘hormone receptor-positive’; tumours not expressing ER, PR and HER2 are called ‘triple-negative’. The relative placement of the boxes align with the characteristics (for example, proliferation and grade) in green. –, negative; +, positive. GES, gene expression signature. ^a*ESR1* mutations induced by aromatase inhibitor targeted therapy. ^bArtefact; expression of normal breast components due to low tumour cellularity.

Box 1 | Breast cancer in men

The male breast is a rudimentary organ that is limited to ducts in the retro-aerolar area, expressing oestrogen receptor (ER), progesterone receptor (PR) and androgen receptor (AR). Benign and malignant lesions presenting as retro-aerolar lumps can occur, although male breast cancer is rare: <1% of all breast cancers occur in men and <0.5% of deaths in men can be attributed to breast cancer. The lifetime risk for breast cancer in men is 1 in 833 compared with 1 in 10 for a woman. Of affected men, 20% have a first-degree family history of cancer; 4–14% of cases in males are attributed to germline *BRCA2* mutations and there is a 60–76% chance of a *BRCA2* mutation in families with at least one affected male. Klinefelter syndrome engenders a relative risk of 30–50 for male breast cancer (owing to elevated circulating oestrogens); 5% of men with breast cancers have this syndrome. Other risk factors for breast cancer development in men include elevated oestrogens (imbalance of oestrogen and testosterone), liver cirrhosis, prostate cancer, age, obesity and smoking. In individuals who undergo male-to-female gender reassignment, hormonal stimulation may promote breast cancer development³⁰³. Clinically, men with breast cancer present at older age (60–70 years) and with higher stage than women with breast cancer. Invasive ductal carcinoma (FIG. 1) is the most frequent subtype, whereas invasive lobular carcinoma is extremely rare compared with female breast cancer; papillary carcinoma is the second most frequent histological type. In terms of the intrinsic subtypes (FIG. 1), >90% of male breast cancers are luminal A or luminal B; human epidermal growth factor receptor 2 (HER2)-positive and triple-negative breast cancer are extremely rare in men³⁰⁴. AR is often overexpressed in male breast cancer^{305,306}. Expression pathways of luminal genes are also predominant; activation of fibroblast growth factor receptor 2 (FGFR2) and phosphatidylinositol 3-kinase (PI3KCA) pathways are potential therapeutic targets to be explored in the future³⁰⁷. Prognosis is similar to stage-matched women with breast cancer, although overall survival is worse because male patients with breast cancer are often older, have more comorbidities and have lower life expectancy^{304,308}. Treatments are largely extrapolated from female breast cancer, due to a paucity of available data. As the vast majority of breast cancers in men are luminal cancers, the most important therapy is endocrine therapy^{308,309}. In the adjuvant setting, tamoxifen (which binds to and inhibits the ER) is the standard of care and aromatase inhibitors should not be used alone (as these are associated with worse survival). In cases of absolute contra-indication for tamoxifen use, a combination of an aromatase inhibitor and a luteinizing hormone-releasing hormone agonist can be considered, although this approach is associated with higher toxicity^{308–310}. Recommendations for adjuvant chemotherapy and radiation therapy are similar to those in women with luminal early breast cancer, as are recommendations for management of advanced breast cancer^{308–310}.

early pregnancy and high levels of oestrogen during pregnancy reduce breast cancer risk. The proposed mechanisms include altered sensitivity of the mammary gland to later hormonal exposures⁴⁰; reduction in the number of stem or progenitor cells and, consequently, elimination of targets for malignant transformation⁴¹; and changes in gene expression patterns resulting in reduced proliferation and increased differentiation⁴². Other risk factors for breast cancer include early menarche, lack of breast feeding and late-onset menopause.

It has been estimated that ~20% of breast cancers worldwide can be attributed to modifiable risk factors, including obesity, physical inactivity and alcohol use, offering the potential for reduction in the disease burden by promoting a healthy lifestyle⁴³. For example, each 10 g (~1 drink) of alcohol consumed daily by an adult woman will lead to a 7–10% increase in breast cancer risk; this association is observed in both premenopausal and postmenopausal women^{44–46}. Furthermore, the influence of central obesity on breast cancer risk and survival has been studied; current evidence suggests a stronger adverse effect of obesity on breast cancer risk and survival in women of Asian ancestry than in non-Hispanic white women in the United States and Europe⁴⁷. For African American and non-white Hispanic women, the

strength of the associations seems to be comparable with that of non-Hispanic white women, particularly when accounting for subtype and menopausal status⁴⁸. Central obesity seems to have a stronger influence on breast cancer risk in African-American women than general adiposity as measured by body mass index (BMI)⁴⁷.

Currently, 18% of premenopausal women in the United States have elevated BMI and breast density and may benefit from lifestyle modifications involving weight loss and exercise⁴⁹. However, this benefit is not limited to premenopausal women, especially when the Asian breast cancer population is being studied. For example, it was noted that postmenopausal Asian women whose BMI increased ≥ 5.0 were significantly more likely to develop breast cancer than those with a stable BMI (defined as a change in BMI of ± 2.5). Additionally, postmenopausal women with abdominal circumference ≥ 90 cm were significantly more likely to develop breast cancer than those with abdominal circumference < 70 cm⁵⁰. Among postmenopausal women with BMI ≥ 20 , those with high (≥ 6.5) glycated haemoglobin (HbA1c) were more likely to develop breast cancer than those with low (< 5.5) HbA1c. Thus, breast cancer incidence, obesity and increased BMI are associated in postmenopausal Asian women⁵⁰.

The possibility that the use of hormonal contraceptives may increase the risk of breast cancer has been raised for many years⁵¹. Two recent papers showed a statistically significant increase in breast cancer with use of hormonal contraception, even contemporary low-dose formulations^{52,53}. Thus, counselling may be needed to encourage women of child-bearing age to adopt lifestyle habits that may reduce the cancer risk.

Survivors

In 2018, an estimated 6.8 million women worldwide survived breast cancer after being diagnosed within the previous 5 years³. Unfortunately, and because most cancer registries only record the incidence and mortality but not the date of relapse, it is unknown how many of these 6.8 million women are living with metastatic disease and how many are cancer-free survivors. Meeting the long-term medical and psychosocial needs of survivors in low- and middle-income countries is particularly difficult due to limited resources — these issues are attracting global attention⁵⁴. The emergent issues include but are not limited to common adverse effects over long periods after cancer treatment, loss of strength, sexual dysfunction, bone health, and physical and mental health concerns^{55–59}.

Mechanisms/pathophysiology

The exact mechanism by which breast cancer is initiated is unknown; however, much effort has been made to molecularly characterize breast cancer and delineate its formation and progression. At the cell of origin level, the clonal evolution model (in which mutations accumulate, epigenetic changes in tumour cells occur and the 'fittest' cells survive) and the cancer stem cell model (in which only the precursor cancer cells initiate and sustain progression) are both implicated, and further complicated by the fact that cancer stem cells may also evolve in a clonal fashion⁶⁰. At the morphological level, there is a continuum

of lesions and genetic modifications from normal glands to cancer (FIG. 1). At the molecular level, there is evidence showing that breast cancer evolves along two divergent molecular pathways of progression, mainly related to ER expression, and tumour grade and proliferation (described in the intrinsic classification). Furthermore, the identification of breast cancer susceptibility genes has shed the light on some aspects of the pathogenesis of both sporadic and inherited breast cancer.

The first pathway —the low-grade-like pathway — is characterized by gain of 1q, loss 16q, infrequent amplification of 17q12 and a gene expression signature

(GES) with a majority of genes associated with the ER phenotype, diploid or near diploid karyotypes and low tumour grade. The luminal A group and to some extent the luminal B group fall into this pathway. The second pathway — the high-grade-like pathway — is characterized by loss of 13q, gain of chromosomal region 11q13, amplification of 17q12 (containing *ERBB2*, encoding HER2) and an expression signature of genes involved in the cell cycle and cellular proliferation⁶¹. Tumours composed of intermediate to high grade, including HER2-positive tumours and TNBC, fall into this pathway⁶².

Table 1 | The most frequent inherited breast cancer syndromes

Syndrome or key gene ^a	Mutation characteristics	Penetrance	Prevalence	Breast cancer types
<i>BRCA1</i> hereditary breast cancer syndrome, and <i>BRCA1</i> breast and ovarian breast cancer syndrome	<i>BRCA1</i> ; mutations: no hot spots; tumour suppressor; DNA repair of double-stranded DNA breaks	Cumulative risk of breast cancer at age 70 years of 65%; very high penetrance	<ul style="list-style-type: none"> Autosomal dominant, 3 in 1,000 Rare Average relative risk 11.4 	<ul style="list-style-type: none"> Adenocarcinoma NST Medullary-like Metaplastic Triple-negative 80% basal-like Female and male
<i>BRCA2</i> hereditary breast cancer syndrome, and <i>BRCA2</i> breast and ovarian breast cancer syndrome	<i>BRCA2</i> ; mutations: no hot spots; tumour suppressor; DNA repair of double-stranded DNA breaks	Cumulative risk of breast cancer at age 70 years of 45%; high penetrance	<ul style="list-style-type: none"> Autosomal dominant, 7 in 1,000 Rare Average relative risk 11.7 	<ul style="list-style-type: none"> Adenocarcinoma No distinct phenotype Female and male
Li Fraumeni syndrome and Li Fraumeni-like syndrome	<i>TP53</i> ; mutations: no hot spots; <i>BRCA2</i> , Fanconi genes, <i>MMR</i> also mutated; tumour suppressor, cell cycle control, DNA repair, apoptosis and DNA replication	Cumulative risk of breast cancer at age 60 years of 50%; very high penetrance	<ul style="list-style-type: none"> Autosomal dominant, 1 in 20,000–1 in 5,000 Very rare Average relative risk 10.5 	<ul style="list-style-type: none"> Phyllodes tumours Adenocarcinoma NST 80% HER2+ female
<i>PALB2</i>	<i>PALB2</i> monoallelic germline mutations; if biallelic: Fanconi anaemia; DNA repair of double-stranded DNA breaks	Cumulative risk of breast cancer in one's lifetime of 33–58%; moderate to high penetrance	<ul style="list-style-type: none"> Autosomal dominant Average relative risk 5.3 	<ul style="list-style-type: none"> Adenocarcinoma NST No distinct class Pancreas, ovary
<i>CHEK2</i>	<i>CHEK2</i> mutations (<i>CHEK2</i> *1100delC more frequent than 470C>T or I157Thr missense variants); cell cycle checkpoint kinase, DNA repair, activated <i>BRCA1</i> and p53	Cumulative risk of breast cancer in one's lifetime of 20–30%; moderate to low penetrance	<ul style="list-style-type: none"> Autosomal dominant Average relative risk 2.26 for women and 3.13 for men Higher in cases of family history Missense variants confer lower risk³²⁹ 	<ul style="list-style-type: none"> Adenocarcinoma NST ER positivity varies according to the type of mutations Female and male Colorectal cancer risk in <i>CHEK2</i>*1100delC mutation carriers
Ataxia telangiectasia	<i>ATM</i> ; mutations: no hot spots; homozygotes more affected than heterozygotes; protein kinase DNA damage response through p53, <i>BRCA1</i> and <i>CHEK2</i> pathways	Cumulative risk of breast cancer in one's lifetime of 20%; low to moderate penetrance	<ul style="list-style-type: none"> Autosomal recessive, 1–2.5 in 100,000 Common Average relative risk 2.8 	<ul style="list-style-type: none"> Adenocarcinoma NST No distinct class
Cowden syndrome	<i>PTEN</i> ; germline mutations, variants and epimutations; tumour suppressor, PIK3CA pathway	Cumulative risk of breast cancer in one's lifetime of 85%; very high penetrance	<ul style="list-style-type: none"> Autosomal dominant, 1 in 250,000 Average relative risk of 25% Very rare 	<ul style="list-style-type: none"> Adenocarcinoma NST No distinct class Female and male Benign breast lesions
Hereditary diffuse gastric cancer syndrome	Germline <i>CDH1</i> ; mutations: no hot spots; cell invasion suppressor and cell–cell adhesion	Cumulative risk of breast cancer in one's lifetime of 42–60%; high penetrance	<ul style="list-style-type: none"> Autosomal dominant, <0.1 in 100,000 Average relative risk of 6.6 	<ul style="list-style-type: none"> Invasive lobular carcinoma Female
Peutz–Jegher syndrome	<i>STK11</i> ; mutations: no hot spots; tumour suppressor gene, cell-cycle regulation and apoptosis	Cumulative risk of breast cancer at age 60 years of 32–54%; high penetrance	<ul style="list-style-type: none"> Autosomal dominant Insufficient data to determine average relative risk 	<ul style="list-style-type: none"> Adenocarcinoma NST No distinct class
Neurofibromatosis	<i>NF1</i> germline mutations; tumour suppressor and negative regulation of the RAS signalling pathway	Cumulative risk of breast cancer in one's lifetime of 17%; low to moderate penetrance ³³⁰	<ul style="list-style-type: none"> Autosomal dominant, 1–5 in 10,000 Average relative risk of 2.6 	<ul style="list-style-type: none"> Adenocarcinoma NST Higher prevalence of metaplastic carcinoma³³¹ Female and male

+, positive; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; NST, no special type (also known as invasive ductal carcinoma). Data from REFS^{34–36,332,333}. ^aLynch syndrome may also be associated with an increased frequency of breast cancer, but the link is not clear.

Molecular alterations

The most frequently mutated and/or amplified genes in the tumour cells are *TP53* (41% of tumours), *PIK3CA* (30%), *MYC* (20%), *PTEN* (16%), *CCND1* (16%), *ERBB2* (13%), *FGFR1* (11%) and *GATA3* (10%), as reported in a series of early breast cancers⁶³ (FIG. 2). These genes encode cell-cycle modulators that are either repressed (for example, p53) or activated (for example, cyclin D1), sustaining proliferation and/or inhibiting apoptosis, inhibiting oncogenic pathways that are activated (*MYC*, *HER2* and *FGFR1*) or inhibiting elements that are no longer repressed (*PTEN*). The majority of the mutations affecting 100 putative breast cancer drivers are extremely rare⁶⁴, therefore, most breast cancers are caused by multiple, low-penetrant mutations that act cumulatively. Luminal A tumours have a high prevalence of *PIK3CA* mutations (49%), whereas a high prevalence of *TP53* mutations is a hallmark of basal-like tumours (84%). For TNBC, different molecular drivers underline its subtypes (BOX 2). At the metastatic stage, specific predictive alterations, such as *PIK3CA* mutations, can be easily detected non-invasively in the plasma in circulating tumour DNA rather than on tumour biopsy; nevertheless, depending on the technology used, the level of sensitivity may vary⁶⁵.

Epigenetic alterations are involved in breast carcinogenesis and progression. In breast cancer, genes can be

either globally hypomethylated (leading to gene activation, upregulation of oncogenes and chromosomal instability) or, less frequently, focally (locus-specific) hypermethylated (leading to gene repression and genetic instability due to the silencing of DNA repair genes). Other epigenetic mechanisms involve histone tail modifications by DNA methylation, inducing chromatin structure changes to silence gene expression and nucleosomal remodelling. These changes are reversible, enzyme-mediated and potentially targetable⁶⁶. For example, in luminal-like breast cancer cell lines, inhibition of histone deacetylase with specific inhibitors such as vorinostat⁶⁷ or chidamide⁶⁸ can reverse resistance to endocrine therapy via inhibition of the resistance pathway driven by epidermal growth factor receptor signalling. Recently, a phase III trial in metastatic luminal breast cancer showed the superiority of a treatment combining chidamide with endocrine therapy (namely, the aromatase inhibitor exemestane) to exemestane alone⁶⁹.

Hormone receptors. The major risk factors for sporadic breast cancer are linked to hormone exposure. Oestrogen is clearly a promoter of breast cancer, through its binding of the ER located in the nucleus (encoded by *ESR1*), which is a ligand-activated transcription factor. Hormones stimulate breast development during puberty, menstrual cycles and pregnancy (the only period when

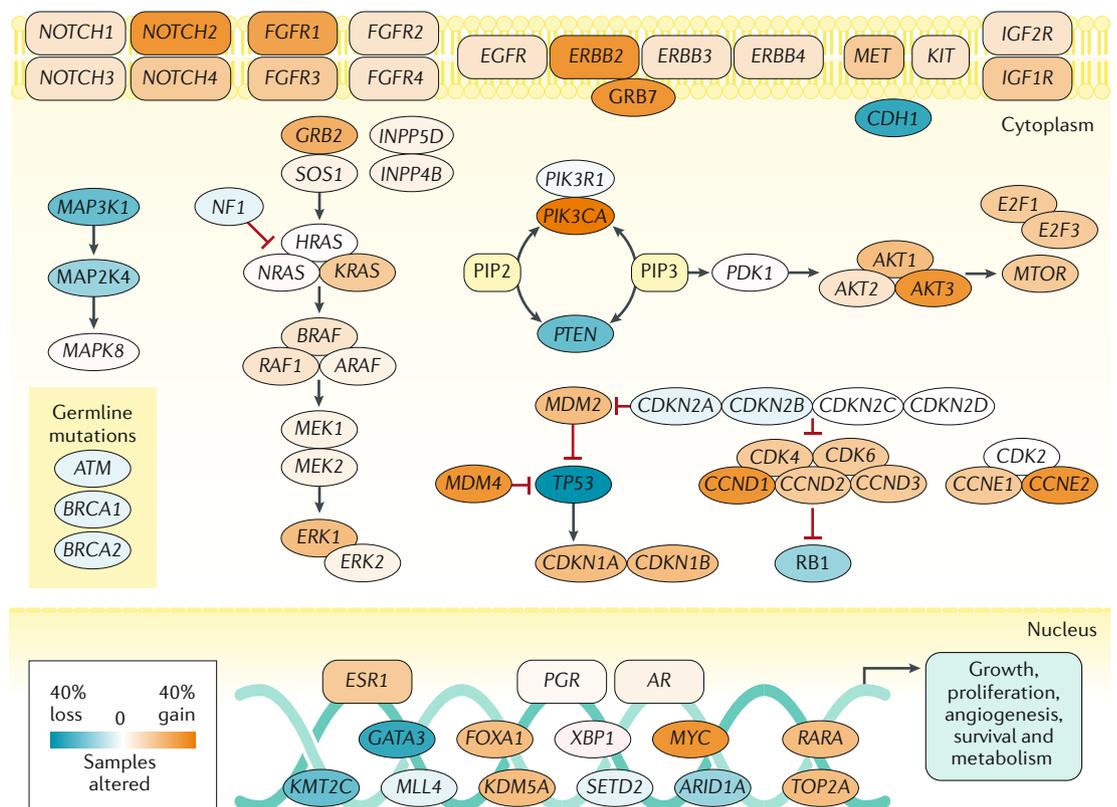


Fig. 2 | **Molecular mutations in breast cancer.** The Cancer Genome Atlas data on breast tumour DNA copy number and somatic mutations were used to identify the frequency of each genetic alteration across 792 patients with breast cancer (all subtypes)³²². Each gene is shaded according to the overall frequency of alteration. Orange indicates a high level of amplification and/or likely gain-of-function mutations; blue represents homozygous deletions and/or likely loss-of-function mutations. Figure adapted from REF.³²³, Springer Nature Limited.

Box 2 | Triple-negative breast cancer molecular classification

Gene expression assays have identified six different triple-negative breast cancer (TNBC) molecular subtypes (Lehman's classification). These are basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal-like (M), mesenchymal/stem-like (MSL), immunomodulatory (IM) and luminal androgen receptor (LAR). BL1 has a high *TP53* mutation rate (92%), alterations in genes involved in DNA repair mechanisms (such as *BRCA1*, *BRCA2*, *TP53* and *RB1*) and a cell-cycle gene signature³¹¹. BL2 has cell-cycle gene signatures, overexpression of growth factor signalling genes and overexpression of myoepithelial differentiation genes. M and MSL subtypes are enriched for genes encoding regulators of cell motility, invasion and mesenchymal differentiation, but the MSL subtype is uniquely enriched for the genes that encode regulators of epithelial–mesenchymal transition and stemness. The Claudin-low subtype from the intrinsic classification (FIG. 1) is mostly composed of the M and MSL subtypes³¹². MSL also shares numerous genes involved in the regulation of immune response with the IM subtype. Finally, LAR is characterized by a higher mutational burden with overexpression of genes coding for mammary luminal differentiation, overexpression of the regulators of the androgen receptor (AR) signalling pathway and increased mutations in *PI3KCA* (55%), *AKT1* (13%) and *CDH1* (13%) genes³¹¹. This classification has been refined into four groups: BL1 (immunoactivated), BL2 (immunosuppressed), M (including most of the MSL) and LAR³¹³, with implications for response to neoadjuvant chemotherapy. Combining RNA and DNA profiling analyses, a similar classification of TNBC has been reported (Burstein's classification), divided into four distinct subtypes. These subtypes are LAR, mesenchymal (MES), basal-like immunosuppressed (BLIS) and basal-like immune-activated (BLIA)³¹⁴. Each subtype has specific therapeutic targets (for example, the LAR subtype can be targeted via the AR and the cell surface protein mucin) and different prognosis (for example, the BLIA subtype is associated with better prognosis than BLIS). Despite these multiple efforts, there is no established diagnostic assay yet for the classification of TNBC in routine practice.

the organ is functional). During the menstrual cycles, an imbalance between oestrogen and progesterone enhances cell proliferation and may cause DNA damage accumulation. With the repetition of the process at each cycle, a defective repair process can occur, leading to mutations in pre-malignant, and then in malignant, cells. At this stage, oestrogen stimulates the growth of these cells and the proliferation of stromal cells that support cancer development. When activated by ligand binding, the ER can modulate gene expression by interacting with oestrogen response elements located in the promoter region of specific genes. Extracellular signals can also stimulate the expression and activation of the ER in the absence of oestrogen⁷⁰. Furthermore, the ER can also interact directly with proteins, such as growth factor receptors, to enhance gene expression related to cell proliferation and survival⁷¹. Thus, drugs blocking the effects of oestrogen on the mammary gland, such as tamoxifen, or drugs that block the production of oestrogen, such as aromatase inhibitors, have major roles in the treatment of hormone-sensitive breast cancer. As oestrogen interacts with bone, aromatase inhibitors can also cause osteoporosis (as menopause does). By contrast, tamoxifen has oestrogen-like effects on the bone, thereby preventing osteoporosis⁷².

HER2. *ERBB2* is amplified in 13–15% of breast cancers, causing an activation of the HER2 pathway. HER2 is, with epidermal growth factor receptor (HER1), HER3 and HER4, a member of the human epidermal growth factor family. These proteins comprise an extracellular ligand-binding domain, a transmembrane domain and a tyrosine kinase intracellular catalytic domain. HER2 activation occurs through dimerization after ligand binding,

although no ligand specific for HER2 has been identified. HER2 signalling activates proliferation, cell survival, metastasis and adhesion through different pathways such as the RAS pathway and the phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT)–mitogen-activated protein kinase (MAPK) pathway. Targeting HER2 has proven to be effective in HER2-positive breast cancers that are defined by protein overexpression or gene amplification (see below, Management).

Immune involvement

Breast cancer develops in a complex microenvironment comprising several benign cell types and the extracellular matrix (which provides mechanical support for the tumour and enables cellular interaction in a paracrine fashion). The most abundant cell type is cancer-associated fibroblasts, but the breast cancer microenvironment also contains cells of leukocyte lineage (including lymphocytes, macrophages and myeloid-derived stromal cells), most of which are involved in the immune response (FIG. 3)⁷³. Immunogenicity of breast cancer varies between the molecular subtypes, being highest in TNBC and HER2-positive tumours and lower in luminal A and luminal B subtypes^{74,75}. Moreover, the response to neoadjuvant treatment and the prognosis of breast cancer are positively influenced by the amount of tumour-infiltrating lymphocytes, which reflects the intensity of the immune response within the tumour bed^{76,77}.

The immune microenvironment influences the development and progression of breast cancer according to immune surveillance and immune editing principles. In the early phase of carcinogenesis, the immune microenvironment exerts mostly anti-tumour action, via the cytokine milieu derived from activated CD8⁺ and CD4⁺ T cells. By contrast, once a tumour becomes invasive, the microenvironment cell composition, including cancer-associated fibroblasts and cytokine content, are tumour-promoting, 'hacked' by breast cancer cells^{78–80}.

Tumour biology and metastatic disease

The intrinsic classification (FIG. 1) influences the profile (timing, sites) of metastatic disease. Luminal A tumours tend to relapse late (after 5 years of first presentation) and have a tropism for bone and lymph nodes (as do luminal B, HER2-negative tumours). TNBCs are prone to early recurrences (within 2–3 years of first presentation) and tend to form visceral (lung) and brain metastases. Since the era of anti-HER2 targeted therapy, HER2-positive breast cancers show better prognosis, but they escape therapy through brain metastasis⁸¹.

Breast cancers that are diagnosed as metastatic at first presentation (de novo) account for 25–28% of metastatic breast cancers^{5,82}. Their proportion varies with the age at diagnosis from 5.1% for women <40 years of age up to 34.3% if aged >75 years (data from France⁸³). The true number of metastatic breast cancers *x* years after initial presentation, at sites and/or organs outside the local initial breast tumour area and regional nodes (including infra-clavicular and supra-clavicular ipsilateral lymph nodes), depends on several factors including age, presence of mass screening, quality of initial local treatment

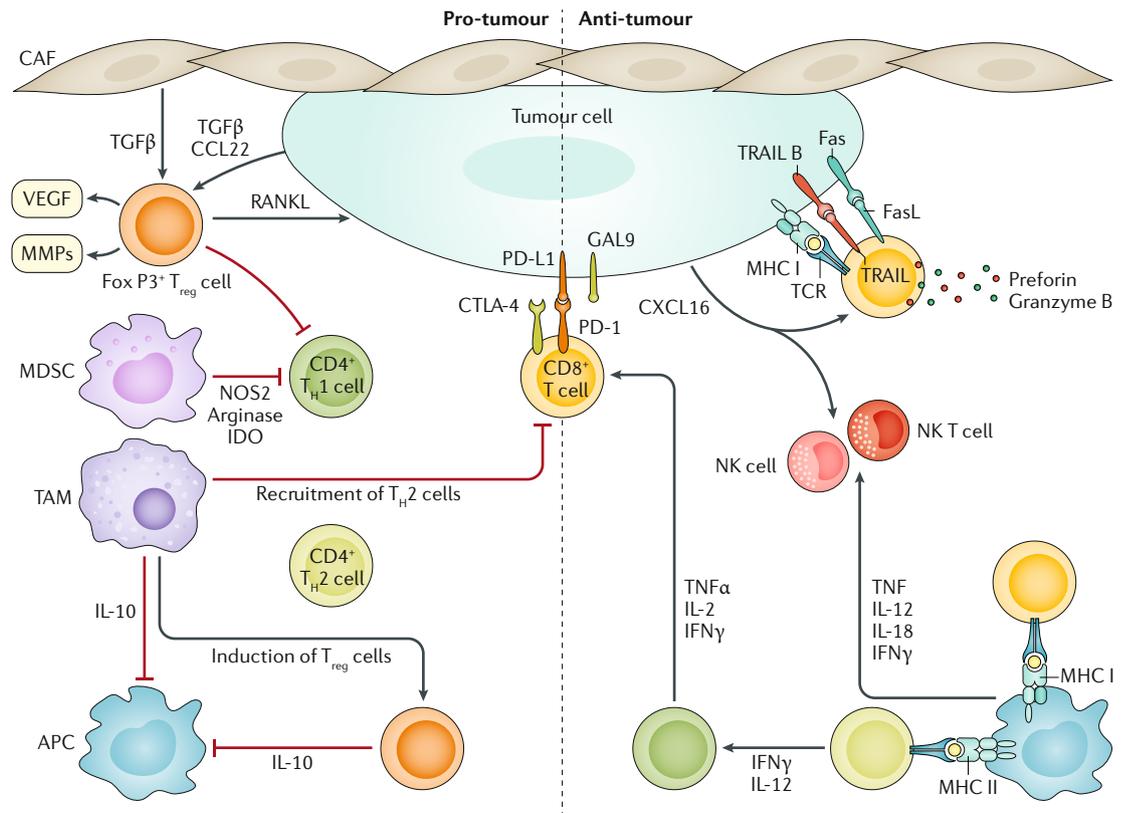


Fig. 3 | Immune crosstalk in breast cancer. The immune reaction to breast cancer is initiated by the neoantigens expressed by tumour cells, encoded by altered genes and presented by antigen-presenting cells (APCs) on major histocompatibility complex class I (MHC I) or MHC II molecules. Neoantigen presentation results in activation of CD8⁺ (cytotoxic) and CD4⁺ (helper) T cells. CD8⁺ T cells are the main effector cell of the anti-tumour immune response; their activation (principally through the T cell receptor (TCR)) results in release of the cytolytic molecules perforin and granzyme B, which directly induce tumour cell lysis. The anti-tumour action of CD8⁺ T cells is amplified by cytokines secreted from CD4⁺ T cells, namely IFN γ , IL-2 and tumour necrosis factor (TNF). Activated CD8⁺ T cells also upregulate expression of Fas ligand (FasL) and TNF-related apoptosis-inducing ligand (TRAIL; also known as TNFSF10) on their membrane, which induce apoptotic pathways to kill tumour cells. Cancer cells elicit an innate immune response, comprising natural killer (NK) and NK T cells that are capable of direct tumour cell killing. Malignant cells can suppress the immune response by expressing immune checkpoint regulators (for example, cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 ligand 1 (PD-L1)), which are upregulated by effector T cells as a consequence of chronic exposure to tumour antigens (T cell exhaustion). The reduced anti-tumour immune response by upregulated immune checkpoint molecules establishes a pro-tumour microenvironment, which is further enriched by recruitment of immunosuppressive cells, T regulatory (T_{reg}) cells and myeloid-derived stromal cells (MDSCs). T_{reg} cells, which inhibit activation of CD4⁺ and CD8⁺ T cells, are induced by tumour-associated macrophages (TAMs) and by tumour-secreted and cancer-associated fibroblast (CAF)-secreted factors, such as transforming growth factor- β (TGF β). In addition, TAMs and T_{reg} cells inhibit APCs via IL-10 secretion, inducing a tolerogenic state of APCs. MDSCs are recruited to the tumour bed by tumour-secreted factors, inhibit trafficking of T cells to the tumour bed and inhibit effector T cell activation by upregulating 2,3-indoleamine-dioxygenase (IDO) and arginase expression, enzymes involved in the T cell nutrient depletion. The secretome of the pro-tumour microenvironment, containing factors that stimulate angiogenesis and invasion (such as vascular-endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs)) also contribute to tumour immune escape and propagation. CCL22, CC-chemokine ligand 22; CXCL16, CXC-chemokine ligand 16; NOS, nitric oxide synthase; PD-1, programmed cell death 1; RANKL, receptor activator of nuclear factor- κ B (RANK) ligand; T_H1 cell, type 1 T helper cell. Adapted from REF.⁷⁵, CC-BY-4.0 <https://creativecommons.org/licenses/by/4.0/>.

and access to drugs and innovations (such as precision radiation therapy for brain metastases or access to clinical trials)^{5,82}. In western countries, the proportion of patients who experience metastatic recurrence is probably 20–30%. Recurrence and disease-free survival (DFS) are measured after the completion of the initial treatment.

Tumour features that lead to metastasis in breast cancer are not well known. Additionally, although some researchers are attempting to find interventions

to prevent metastatic recurrence (such as aspirin and metformin), the results are as yet mostly inconclusive.

Tumour molecular evolution

The majority (~80%) of the driver alterations of the primary breast cancer are conserved in the metastatic sites. However, different metastatic sites may harbour 'private' mutations (including new drivers), resulting in subclonal diversification and discrepancies between

the biology of breast cancers at different metastatic sites within an individual patient. Such alterations occur late, and some alterations are subsequent to treatment pressure; for example, *ESR1* mutations can arise after aromatase inhibitor treatment (which targets oestrogen synthesis) whereas others might be ‘true’ metastatic precursors. Indeed, mutations of *ESR1* that affect the ligand-binding domain are detected in the metastatic tissue or the plasma in 23–40% of women with breast cancer who progress after prior successful aromatase inhibitor treatment. This acquired resistance phenomenon does not seem to influence sensitivity to fulvestrant (a selective ER degrader) but does affect sensitivity to aromatase inhibitors and is dependent on the type of mutation observed (for example, D538G mutation is worse than Y537S)⁸⁴. During metastatic development, the different deposits exhibit linear, parallel or polyclonal evolutionary pathways from the primary tumour, showing different genetic and epigenetic evolution. This process is highly complex and still poorly understood⁸⁵. Liquid biopsy with an evaluation of circulating tumour DNA profiles can reflect the clonal heterogeneity, but this approach may lack sensitivity⁸⁶.

Subclonal diversification may explain the discrepancies observed between primary breast cancers and metastatic breast cancer for the expression of ER (~20% discordance), PR (~33% discordance) and HER2 (~8% discordance). These molecular targets are more frequently lost than newly acquired (for instance, 13% of HER2-positive primary tumours generate HER2-negative metastases whereas only 5% of HER2-negative primary tumours generate HER2-positive metastases)⁸⁷, which affects treatment strategies.

Diagnosis, screening and prevention

Screening

Population screening aims at finding early disease for which there is effective treatment, using a test that is non-invasive, accurate and acceptable to end-users. Population screening for breast cancer using mammography is a secondary prevention strategy aimed at detecting the disease at an early stage to enable effective treatment. Collectively, mammography (low-dose X-ray imaging of the breasts; FIG. 4) randomized controlled trials have provided high-level evidence that population screening significantly reduces mortality from breast cancer by a relative risk of 20% for those invited to screening⁸⁸. Efficacy of mammography screening is age-dependent and is most evident in women 50–69 years of age, with weaker evidence of benefit in those outside this range⁸⁹. Observational studies conducted in real-world screening practice provide similar evidence on the benefit of mammography screening to randomized controlled trials, although estimates of effect are heterogeneous^{90,91}. Given that screening improves early detection of breast cancer, an expected benefit is a reduction in more intensive treatment, for example lower mastectomy rates. However, population-level studies have shown conflicting reports regarding the effect of screening on treatment^{92,93}.

Mammography screening has been implemented in the majority of developed health systems (for example, in the United States, United Kingdom, Europe and Australia), although the organization of screening services and uptake (participation) by women vary considerably between countries⁹⁴. Southeast Asian countries implemented mammography screening later than European countries and several Asian countries have only partial screening programmes⁹⁴. Nations with limited resources (for example, sub-Saharan African and east African countries), where women often present with more-advanced cancers, have not implemented mammography screening and this reflects the generally limited health services infrastructure.

Debate is ongoing regarding whether the harms associated with mammography screening outweigh its potential benefit in reducing breast cancer deaths, with different recommendations on population screening by various agencies (BOX 3). The most frequent harm from mammography screening is false-positive recall, which varies according to screening intensity and the health-care setting^{91,95}. Overdiagnosis, an epidemiologically-proven ‘excess’ of screen-detected breast cancer that would not have emerged clinically in the individual’s lifetime, is inherently and methodologically challenging

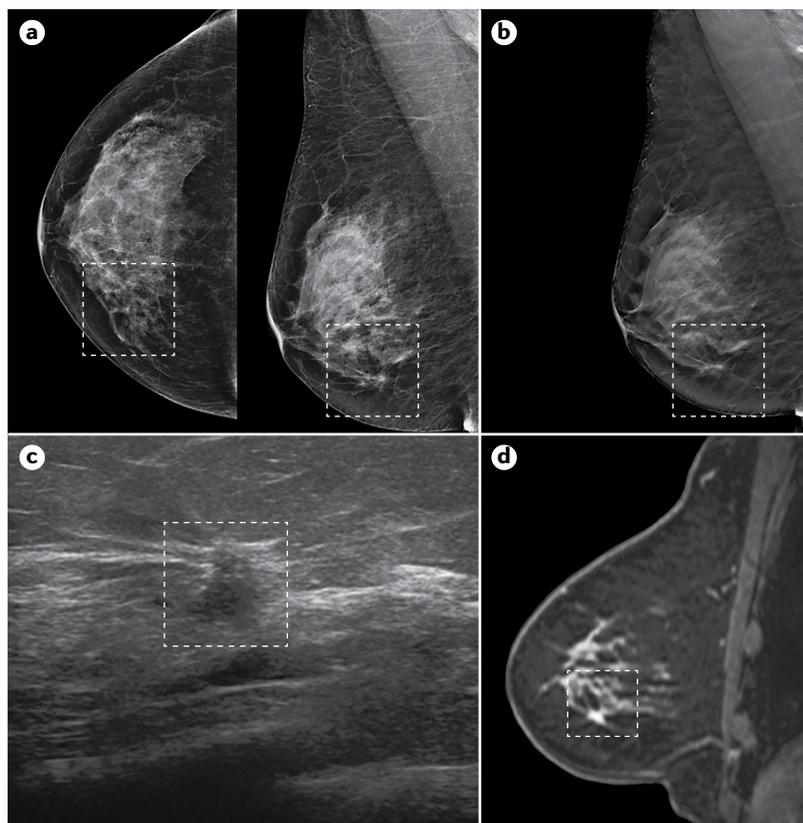


Fig. 4 | Breast cancer imaging. A postmenopausal woman 53 years of age with no family history and no clinical findings underwent routine breast screening with mammography, which detected a lesion in the right breast (panel a, cranio-caudal view (left) and mediolateral oblique view (right)). The images were also acquired with digital breast tomosynthesis, which showed a small spiculated lesion in the lower inner quadrant (panel b, mediolateral oblique view). The lesion was investigated with ultrasonography (panel c), and biopsy confirmed an invasive ductal carcinoma on histology. MRI showed the enhancing spiculated mass (panel d). The tumour is indicated within the dashed lines in each panel.

to quantify, and is the most serious harm from screening because it would likely lead to overtreatment^{88,90,91,95,96}.

Women at higher risk of breast cancer than the average (population) risk owing to predisposing genetic mutations (TABLE 1) are generally advised to have risk-tailored screening, which may include more frequent screening and/or use of technologies other than mammography. Adding MRI to mammography increases screening sensitivity in women with *BRCA1* and/or *BRCA2* mutations and is the recommended screening approach for *BRCA* mutation carriers and women at substantially increased lifetime risk of breast cancer^{97–99}. However, the International Agency for Research on Cancer reports that this has not been shown to improve mortality end points⁹⁰. Use of adjunct imaging, such as ultrasonography, MRI and digital breast tomosynthesis (near-3D mammography), to screen women with high breast tissue density^{100,101} (heterogeneously or markedly dense breasts), in which there is a large amount of glandular tissue on the mammogram, increases breast cancer detection¹⁰⁰ but has not been evaluated for mortality outcomes⁹⁰. Emerging technologies such as tomosynthesis, contrast-enhanced mammography and gamma imaging show enhanced cancer detection rates in observational studies when added to mammography, but the body of evidence is robust only for tomosynthesis¹⁰², making this the most likely candidate for future breast cancer screening. At present, there is no convincing evidence that these new technologies enhance the screening benefit above that achieved with mammography alone⁹⁰. Breast self-examination has not been shown to reduce breast cancer mortality, or to detect interval cancers between screening examinations⁹⁰.

Box 3 | Recommendations on population screening

Population mammography screening recommendations (for women with average risk^a) differ between countries and agencies, reflecting persistent non-consensus on the magnitude of benefit (mortality reduction) and harms (in particular, the extent of overdiagnosis), and how these outcomes balance out overall and in specific age groups. This is exemplified in selected recommendations:

- The US Preventive Services Task Force recommends screening every 2 years for women aged 50–74 years, and emphasizes individualized decisions for those aged 40–49 years that take account of the woman's values³¹⁵
- Canadian guidelines support shared decisions, do not recommend screening for women aged 40–49 years and recommend screening every 2–3 years for women aged 50–69 years³¹⁶
- The American Cancer Society recommends annual screening for women aged 40–54 years, and a transition to 2-yearly screening for those aged ≥55 years (with the opportunity to continue annual screening)³¹⁷
- The International Agency for Research on Cancer reports that there is sufficient evidence that screening confers benefit in women aged 50–74 years (but limited evidence in the 40–49 years age group) and that there is sufficient evidence that mammography detects breast cancers that would never have been diagnosed or would never have caused harm if women had not been screened (overdiagnosis)⁹⁰
- European recommendations specify mammography through organized screening programmes every 2–3 years in women aged 45–74 years (and suggest against annual screening)³¹⁸

^aWomen at average risk do not have a pre-existing breast cancer or a previous diagnosis of a high-risk breast lesion (such as atypical ductal hyperplasia), and do not harbour a risk-enhancing genetic mutation (such as *BRCA1* or *BRCA2* mutations or other familial breast cancer syndromes).

Diagnostic work-up

Women experiencing breast symptoms or breast changes, such as a lump, localized pain, nipple symptoms or skin changes, require appropriate diagnostic evaluation, as do women who are recalled for further testing because of positive screening mammography. Diagnosing breast cancer is based on a triple test comprising clinical examination, imaging (usually mammography and/or ultrasonography) and needle biopsy¹⁰³. Assessment entails performing the appropriate elements of the triple test, factoring in the patients' characteristics and presentation, and should be performed before beginning treatment. Appropriate assessment helps to accurately discriminate between those who have breast cancer and those who have benign conditions (such as fibroadenoma) or normal breast changes and can be reassured or safely managed with follow-up, obviating the need for surgical intervention.

Ultrasonography is almost universally used to assess localized symptoms, as an initial imaging modality in young women, to identify and characterize screen-detected abnormalities and, preferentially, for imaging-guided percutaneous biopsy. Breast ultrasonography may also be used to characterize and biopsy axillary lymph nodes in women suspected of having breast cancer¹⁰⁴. Imaging evaluation also includes MRI for specific clinical indications, such as in women for whom conventional imaging tests have been equivocal, inconclusive or discordant, for evaluating women with breast implants and for evaluating women with axillary nodal metastases but no detectable (occult) breast tumour^{99,105}. Preoperative MRI is also selectively used for staging newly diagnosed disease, but this is a debated practice given the limited evidence on whether it enhances a patient's clinical outcomes¹⁰⁵. However, MRI is advised for preoperative assessment of newly diagnosed invasive lobular cancers⁹⁹.

Pathological reporting

The use of a standardized synoptic pathology report with a checklist is highly recommended¹⁰⁶. For an invasive carcinoma, the pathology report should provide details on the tumour histotype (according to the WHO classification), histological grade, hormone receptor and HER2 status, tumour size and lymph node involvement; at surgery, the surgical specimen is used to provide information on peritumoral vascular invasion and surgical margin status (BOX 4). These data are indispensable for optimal patient management.

Histotype WHO classification. According to the latest edition of the WHO classification, breast carcinomas are divided into 19 different major subtypes, including invasive carcinomas of no special type (70–75%; also known as not otherwise specified (formerly ductal carcinoma)), lobular carcinomas (10–14%) and the other carcinomas of special type (including 17 different rare histotypes and their subclassifiers)¹⁰⁷ (FIG. 5). Breast cancer of 'no special type' is a carcinoma that does not fit into a specific histotype. Some of the special types (such as tubular, cribriform and mucinous) — if at least 90% pure (that is, no mixed histology or <10% of another

Box 4 | The pathology report for breast cancer

- Histological type according to the current WHO classification¹⁰⁷
- Histological grade according to the Elston- and Ellis-modified Scarff–Bloom–Richardson system¹⁰⁸
- Peritumoral vascular or lymphatic emboli^a
- Hormone receptor status (oestrogen receptor (ER) and progesterone receptor)
- Human epidermal growth factor receptor 2 (HER2) status
- Excision margins (mm)^a
- Tumour size, single or multiple tumours
- Ductal carcinoma in situ component type, grade and percentage
- Lymph node status
- Pathological stage according to the Union for International Cancer Control TNM system¹²²
- Ki67 score according to the international group guidelines^b

^aInformation obtained at surgical resection. ^bParticularly relevant for ER-positive, HER2-negative breast cancers.

subtype) — have a very good prognosis. On the other hand, some other special types (such as pleiomorphic lobular carcinoma, high-grade metaplastic carcinoma and micropapillary carcinoma) are associated with the poorest clinical outcome. Another special case is inflammatory breast cancer, a rare and aggressive form characterized by malignant cells blocking the lymph vessels in the skin of the breast (BOX 5).

Histological grade. Assessment of histological grade is made according to the Elston- and Ellis-modified Scarff–Bloom–Richardson system¹⁰⁸ and is based on three tumour features: the proportion of cancer cells that are in tubule formation, anisokaryosis (the variation of nuclear size and shape between the cells) and the number of mitoses (cell divisions). Each feature is scored with a three-tier system, and the final grade (G1, G2 or G3) is determined by adding the individual scores. Tumour grade reflects the potential aggressiveness of the breast cancer and is a strong prognostic factor.

Theranostic biomarkers. Determination of the ER, PR and HER2 status is mandatory for all patients with invasive breast cancer. These markers are recognized by international guidelines^{109–111} as predictive factors indispensable for invasive breast cancer therapy decision-making. At diagnosis, they are routinely tested by immunohistochemistry on the formalin-fixed paraffin-embedded tissue samples obtained from pre-surgical core biopsies.

Any nuclear staining (irrespective of the signal intensity) in >1% of invasive tumour cells is considered hormone receptor-positive (ER and/or PR) by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP)¹¹². Some countries, such as France, do not endorse these guidelines and consider 10% a more relevant cut-off value for hormone-sensitivity determination. According to ASCO and CAP, the HER2 status can be positive, negative or equivocal as assessed by one or two technical approaches¹¹³. Immunohistochemistry, fluorescent in situ hybridization or chromogenic in situ hybridization is currently

recommended in routine practice; because of its availability and cost-effectiveness, immunohistochemistry is the preferred choice for HER2 status evaluation worldwide. HER2-positive status is characterized by a strong complete immunohistochemical membrane staining or by an amplification of *ERBB2* detected by an in situ hybridization method (chromogenic in situ hybridization or fluorescent in situ hybridization) in $\geq 10\%$ of invasive tumour cells. Repeat testing of the surgical specimen may be considered if results seem discordant with other histopathological findings.

Ki67 is widely used to determine proliferation and predicts chemosensitivity. However, Ki67 is relevant only for ER-positive, HER2-negative breast cancers. As HER2-positive breast cancers and TNBCs (with some exceptions) require chemotherapy, Ki67 does not bring any benefit to therapy decision-making in these subtypes. Furthermore, Ki67 determination is neither standardized nor generally recommended¹¹⁴. The most widely used cut-off value is 20% stained nuclei in invasive tumour cells; a fraction of <15% stained nuclei, whatever the intensity, is considered low proliferation, and >30% considered high proliferation.

Finally, given that TNBC does not express ER, PR or HER2, treatment decision-making is more difficult. However, genetic expression studies have identified subtypes of TNBC (BOX 2), which may have prognostic and therapeutic implications although their clinical utility remains to be assessed.

Vascular invasion and surgical margins. Histology, grade, ER, PR and HER2 are routinely assessed on the pre-surgical biopsy specimens. Tumour type and grade are systematically reassessed on the surgical specimen, as are the predictive biomarkers if they are discrepant with the histopathological features.

Peri-tumoural vascular invasion is highly correlated with lymph node metastases and local recurrences¹¹⁵. A positive tumour margin when the tumour is excised (that is, cancer cells extending past the edge) — noted as a 0-mm margin, or ‘ink on tumour’ — confers a significant impact on local recurrence after conservation surgery¹¹⁶. The adequacy of a no ink on tumour margin in invasive breast cancer is endorsed by most guidelines and the margin for ductal carcinoma in situ is 2 mm with no abnormal cells around the specimen^{117–121}. The report should specify the status of the margins: free or containing malignant cells, the distance to the closest margin and its nature (in situ or invasive). Non-free surgical margins necessitate further surgical intervention.

Lymph node status and pathological stage. The pathologist evaluates lymph node specimens either from a sentinel lymph node biopsy procedure or from a complete axillary dissection. A sentinel lymph node biopsy is accurate to assess axillary node status in clinical node-negative (that is, not palpable and not visible on imaging) disease, and avoids unnecessary axillary clearance with its associated morbidity (such as lymphoedema). In the biopsy procedure, the entire node must be extensively examined by serial sectioning to maximize its predictive value. The most widely used system for staging

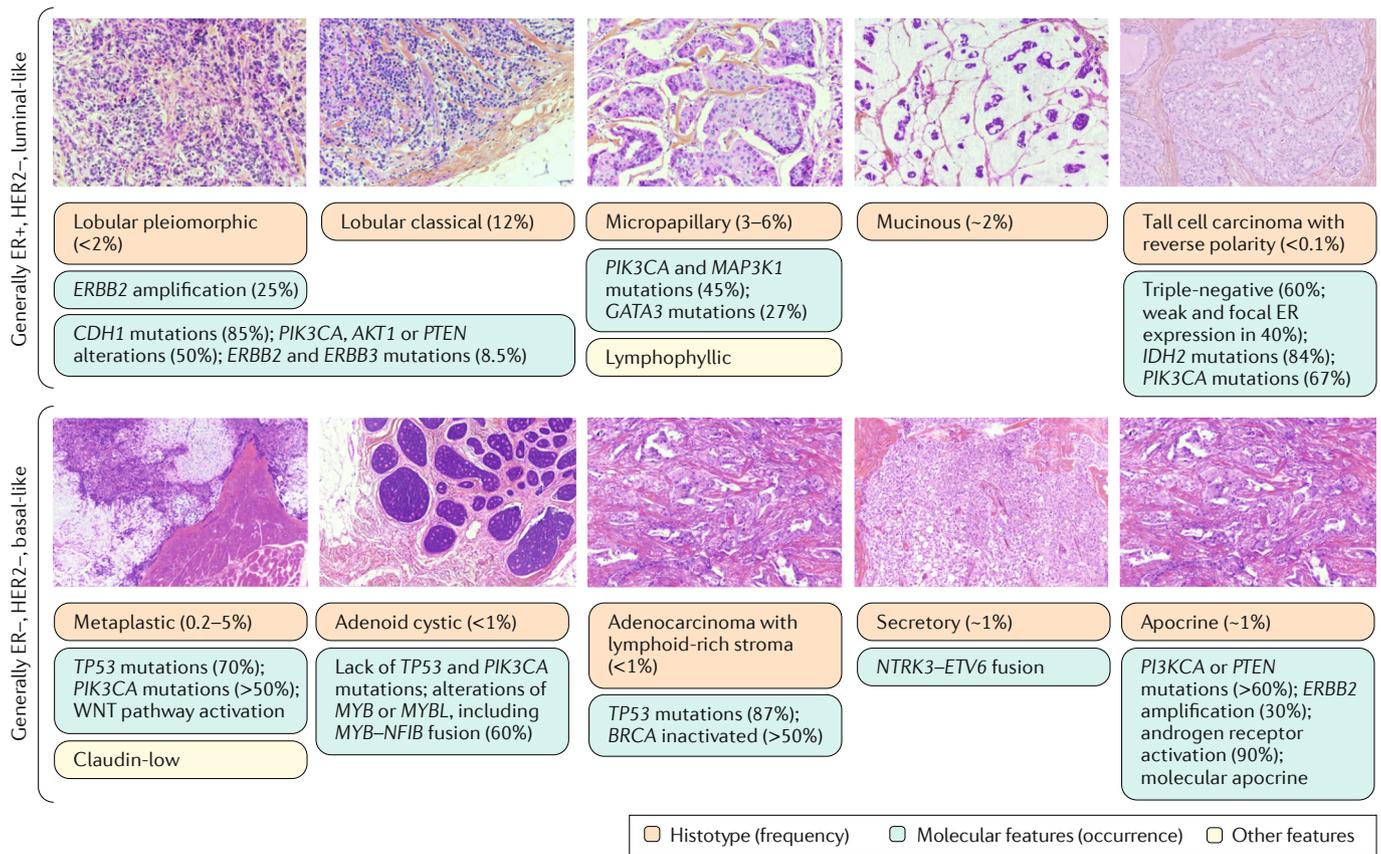


Fig. 5 | Breast cancer histological types and molecular alterations. The WHO classification recognizes different subtypes of invasive breast cancer, some of which are shown here, that harbour specific molecular alterations¹⁰⁷. For example, lobular carcinomas and their precursors (lobular neoplasia) harbour *CDH1* mutations leading to the pathognomonic loss of E-Cadherin expression by immunohistochemistry (85% of cases)^{324,325}. They also harbour *PIK3CA*, *PTEN*, *AKT1*, *ERBB2* and *ERBB3* mutations and copy number gains in *ESR1*. Secretory carcinomas harbour a specific translocation t(12;15) leading to a fusion gene *NTRK3-ETV6* (REF.³²⁶), whereas the adenoid cystic carcinoma is characterized by t(6;9) and the fusion gene *MYB-NFIB*³²⁷. Understanding these features may help in the design of tailored therapeutics for particular histological subtypes³²⁴. ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2. Image of tall cell carcinoma with reverse polarity courtesy of G. MacGrogan, Institut Bergognié, France.

breast carcinoma is the TNM system published by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC). This system provides information about the extent of cancer at the primary site (tumour or T), at the regional lymph nodes (nodes or N) and spread to distant metastatic sites (metastases or M). Tumour size is assessed microscopically by measuring the largest diameter. In the case of multicentric tumours¹²², the largest tumour focus is the reference for T assessment (no addition is allowed). Special techniques for classification are not required and comparable information can, therefore, be collected over time and in different locations. T, N and M are combined to create five stages (stages 0–IV) that summarize information about the extent of regional disease (tumour size, skin or chest-wall invasion and nodal involvement) and metastasis to distant sites. Alongside clinical (c) and pathological (p) assessment, prefixes can also be used in the pathology report to indicate prior systemic therapy (y) or locoregional recurrence (r). Metastases are usually detected by imaging and then may be verified by biopsy. For individual patients, this information is important for

making decisions concerning the control of local disease, as well as to determine the value of systemic therapy.

Prognosis

Classic prognostic factors include age, stage, tumour grade, tumour type and lymphovascular status. Breast cancer before 35 years of age is rare (<5% of patients), potentially more aggressive and more frequently associated with hereditary breast cancer. Geriatric patients with breast cancer (>75 years of age) experience 17% higher disease-specific mortality than younger patients¹²³. With the extent of mammography screening, the stage at diagnosis has decreased and, concomitantly, the natural history of breast cancer has changed; prognostication, therefore, relies on tumour biology (histological type, grade, lymphovascular invasion and theranostic marker status). For ER-negative, HER2-negative breast cancers and for HER2-positive breast cancers, the presence of tumour-infiltrating lymphocytes is associated with good prognosis¹²⁴. As HER2-positive breast cancers and TNBCs are usually treated with chemotherapy with or without targeted therapy (see below,

Management), tumour-infiltrating lymphocytes also represent predictive biomarkers for treatment response.

For the purpose of prognostication and treatment decision-making, several scoring systems have been developed, such as *Adjuvant! Online*, the Nottingham Prognostic Index¹²⁵ and PREDICT¹²⁶. These validated algorithms render good general estimates of patient prognosis and can aid in discussing therapy options with patients. However, they do not accurately reflect all specific patient subgroups or tumour biology subtypes¹²⁷ and cannot be used as the sole criterion for treatment decisions in individual patients. The surrogate intrinsic subtypes are the most important criteria for treatment decisions (FIG. 1). Four subtypes of breast cancer are clinically valuable and imply distinct treatment approaches^{110,128}. Luminal A-like tumours usually present with low-risk features such as low grade, high expression of ER and PR, low proliferation and a low-risk GES. By contrast, the luminal-B-like group expresses ER but not (or to a lesser extent) PR, and displays high grade or high proliferation and high-risk GESs. TNBC and non-luminal types show aggressive features such as high grade, no expression of ER, PR and HER2, and high proliferation. HER2-positive tumours more frequently display G2 or G3 features, low or absent expression of ER and PR, and medium to high proliferation. The claudin-low intrinsic transcriptomic group has no surrogate biomarker and is consequently not currently used in clinical practice.

Management

In early breast cancer without metastases, women with tumours that are deemed operable undergo surgery. However, most women also need some form of systemic therapy. Systemic therapy can be given before surgery (neoadjuvant) in women with large tumours for whom reducing the tumour burden is preferred or if information of pathological complete response (pCR), which is an absence of cancer cells in the surgical specimen after treatment, to pre-surgical treatment has prognostic value (such as in HER2-positive disease or TNBC¹²⁹). Moreover, systemic therapy can be given after surgery (adjuvant) if the surgical result or biomarkers indicate increased risk of recurrence. For systemic therapies, many biomarkers

have been validated for therapeutic decision-making (TABLE 2). All patients with ER-positive and/or PR-positive breast cancer, independent of HER2 status, should receive endocrine therapy to block the ER activity.

The main question in luminal (hormone-receptor-positive, HER2-negative) early breast cancer is which patients need chemotherapy (neoadjuvant or adjuvant) in addition to endocrine therapy. In patients with luminal A disease and with low tumour burden, chemotherapy should be omitted. In general, the recommendation for chemotherapy in ER-positive, HER2-negative tumours may be influenced by proliferation (Ki67 expression) and — if available — the results of a GES.

As well as the traditional immunohistochemical markers, GES panels are used in many western countries, if available and/or reimbursed, for chemotherapy decisions in ER-positive, HER2-negative early breast cancer. Currently, several GES assays are available. First-generation signatures (OncotypeDx and MammaPrint) are performed in centralized (company-owned) laboratories. In tumours with 0–3 involved lymph nodes classified as low risk by a GES, adding chemotherapy to endocrine therapy can be avoided, whereas high-risk patients should receive chemotherapy. Currently, the prognostic value of MammaPrint¹³⁰ and OncotypeDx^{131,132} is supported by level of evidence Ia and their use is recommended by several guidelines^{110,128,133,134}. Consensus opinion is that patients with ER-positive, HER2-negative node-negative early breast cancer (considered having a high-clinical risk of relapse according to traditional criteria) who have a low genomic risk score can safely forgo neoadjuvant or adjuvant chemotherapy. However, the use MammaPrint and OncotypeDx in patients with 1–3 positive lymph nodes is still controversial as only few prospective trials have so far been reported^{130,135}; the results of RxPONDER (ClinicalTrials.gov NCT01272037) are awaited.

Second-generation GES assays (Prosigna and Endopredict) can be performed de-centrally on dedicated instruments. These assays have level of evidence Ib for prognosis in patients with ER-positive, HER2-negative breast cancer treated with endocrine therapy¹³⁶; the lower evidence level is attributed to retrospective validation only. Indeed, the results generated from retrospective analysis of trials in which patients had only been treated with endocrine therapy need to be interpreted with caution when applied to patients at high clinical risk who would normally require chemotherapy. In addition to early relapse risk, these assays also predict late recurrences, information that may be used to indicate extended adjuvant endocrine therapy. Finally, GESs have no role in treatment decision-making in cases of very low clinico-pathological risk (such as patients with pT1a–b, pN0, G1 and high ER disease) or if clinico-pathological factors all point into the same direction (that is, towards low-risk or towards high-risk disease).

Early breast cancer

Locoregional therapy in early breast cancer regardless of molecular subtype comprises surgery to remove the tumour and to either stage the axillary tumour burden or excise the affected axillary lymph nodes.

Box 5 | Inflammatory breast cancer

Inflammatory breast cancer is a rare and aggressive-stage (stage T4d) phenotype of breast cancer encompassing ~3% of newly diagnosed breast tumours characterized by a substantial involvement of dermal lymphatics of the breast skin. The diagnosis is clinical with rapid evolution of *de novo* erythema (redness of the skin), 'peau d'orange' (dimpled texture) and/or warm swollen breast involving at least one-third of the breast skin with or without a clinical breast mass³¹⁹. Patients should undergo skin biopsy to identify dermal lymphatic emboli that are found in <75% of cases and tumour biopsies in case of identifiable mass³¹⁹. This cancer type has to be differentiated from secondary inflammatory breast cancer (that is, the development of inflammatory skin changes that mimic primary inflammatory breast cancer either in a breast that already had cancer or on the chest wall after a mastectomy for non-inflammatory breast cancer) and from locally advanced breast cancer (that is, breast cancer that has extended to the chest wall (stage T4a), that has ulceration, ipsilateral satellite skin nodules or skin oedema (including peau d'orange; stage T4b) or both (stage T4c)). Inflammatory breast cancer is associated with high body mass index, younger age at diagnosis, higher tumour grade and oestrogen receptor-negative and/or human epidermal growth factor receptor 2-positive status, and is more frequent in north African or African-American women³²⁰.

Postoperative radiation therapy and/or systemic therapies (which may comprise endocrine therapy, chemotherapy, targeted therapy and bone-modifying agents) are usually given depending on the initial tumour burden and molecular expression pattern of the tumour. Tumour down-sizing with systemic therapies prior to surgery is also encouraged for large tumours provided that the same systemic therapy would also be indicated after surgery. FIGURE 6 summarizes the therapeutic strategies for early breast cancer.

Surgery. Surgery of the primary tumour remains a cornerstone of curative breast cancer treatment. Over the past decades, breast conservation has become the primary surgical goal¹³⁷, substituting mastectomy, which was the historical standard (FIG. 7). Resection of the primary breast tumour is either the first step of treatment or second, after initial systemic therapy depending on tumour size, tumour to breast size relationship, tumour biology, comorbidities and patient choice¹³⁸. After neoadjuvant systemic therapy, the surgical extent should be oriented

Table 2 | Biomarkers validated for therapy decision-making

Biomarker	Method and threshold	Use	LOE
ER	IHC; positive if $\geq 1\%$	<ul style="list-style-type: none"> Essential for the characterization of the IHC luminal group Poor prognostic marker if negative Predictive marker for endocrine treatment Mandatory for endocrine treatment prescription 	I
PR	IHC; positive if $\geq 1\%$	<ul style="list-style-type: none"> If negative, tumour classified as IHC luminal B Strong poor prognostic marker if negative Predictive marker for endocrine treatment 	I
HER2	<ul style="list-style-type: none"> IHC; positive if $>10\%$ complete membrane staining (3+) Single-probe ISH; positive if HER2 ≥ 6 copies Dual-probe ISH; positive if HER2 and CEP17 ≥ 2 and HER2 ≥ 4 copies, or HER2 and CEP17 < 2 and HER2 ≥ 6 copies 	<ul style="list-style-type: none"> Essential to characterize HER2-enriched (ER-negative) disease and luminal B, HER2-positive Prognostic marker Predictive marker for anti-HER2 treatment Mandatory for anti-HER2 therapy 	I (IHC) and I (ISH)
Ki67	IHC; no final consensus on cut-off value but values $<10\%$ are considered low and $>30\%$ are considered high ^a	Absence of international consensus for scoring and threshold	I
		Prognostic value in ER-positive, HER2-negative tumours (primary tumours and post-neoadjuvant tumour residues)	I
		Absence of prognostic value in HER2-positive disease or TNBC	I
		Predictive of response to neoadjuvant endocrine therapy ^a	I
		Predictive of response to neoadjuvant chemotherapy	Expert opinion
		If elevated, chemotherapy is often prescribed in ER-positive, HER2-negative tumours	Expert opinion
Intrinsic subtypes	Gene expression profile, N-Counter technology	Prognostic	II and III
		Predictive; different responses to neoadjuvant chemotherapy and anti-HER2 therapy according to subtype	I
First-generation signatures (MammaPrint and OncotypeDx)	Gene expression profile, RT-PCR	<ul style="list-style-type: none"> Prognostic for ER-positive, HER2-negative tumours (with 0–3 involved lymph nodes) Chemotherapy is indicated if high risk or high score 	Ia
Second-generation signatures (Prosigna and Endopredict)	N-Counter technology, RT-PCR	<ul style="list-style-type: none"> Prognostic for ER-positive, HER2-negative tumours (with 0–3 involved lymph nodes), include T size and N status in their final score Chemotherapy is indicated if high risk or high score 	Ib
PIK3CA mutations	Mutations detected by PCR or NGS in exons 9 or 20 from cancer biopsy specimen or liquid biopsies	Predictive marker for specific PI3KCA inhibitors (such as alpelisib) in luminal A and luminal B metastatic breast cancer	Ia ²⁸⁴
Germline BRCA mutation	NGS on blood lymphocytes or on tumour cells	<ul style="list-style-type: none"> Predictive marker for PARP inhibitors in metastatic breast cancer (evidence-based for HER2-negative disease) Germline mutations imply family counselling Predictive impact of somatic mutations is under evaluation 	Ia ³⁰
PD-L1	IHC; positive if expression in immune cells $\geq 1\%$ in tumour specimens (metastatic or primary)	Predictive for immunotherapy with atezolizumab combined with nab-paclitaxel in TNBC	Ia ²⁴⁹

CEP17, chromosome enumeration probe 17; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; LOE, level of evidence; N, node; NGS, next-generation sequencing; PARP, poly(ADP-ribose) polymerase; PD-L1, programmed cell death 1 ligand 1; PR, progesterone receptor; RT-PCR, PCR with reverse transcription; T, tumour; TNBC, triple-negative breast cancer. Data from REFS^{111,128,225}. ^aAccording to the International Ki67 Working Group Guidelines¹¹⁴.

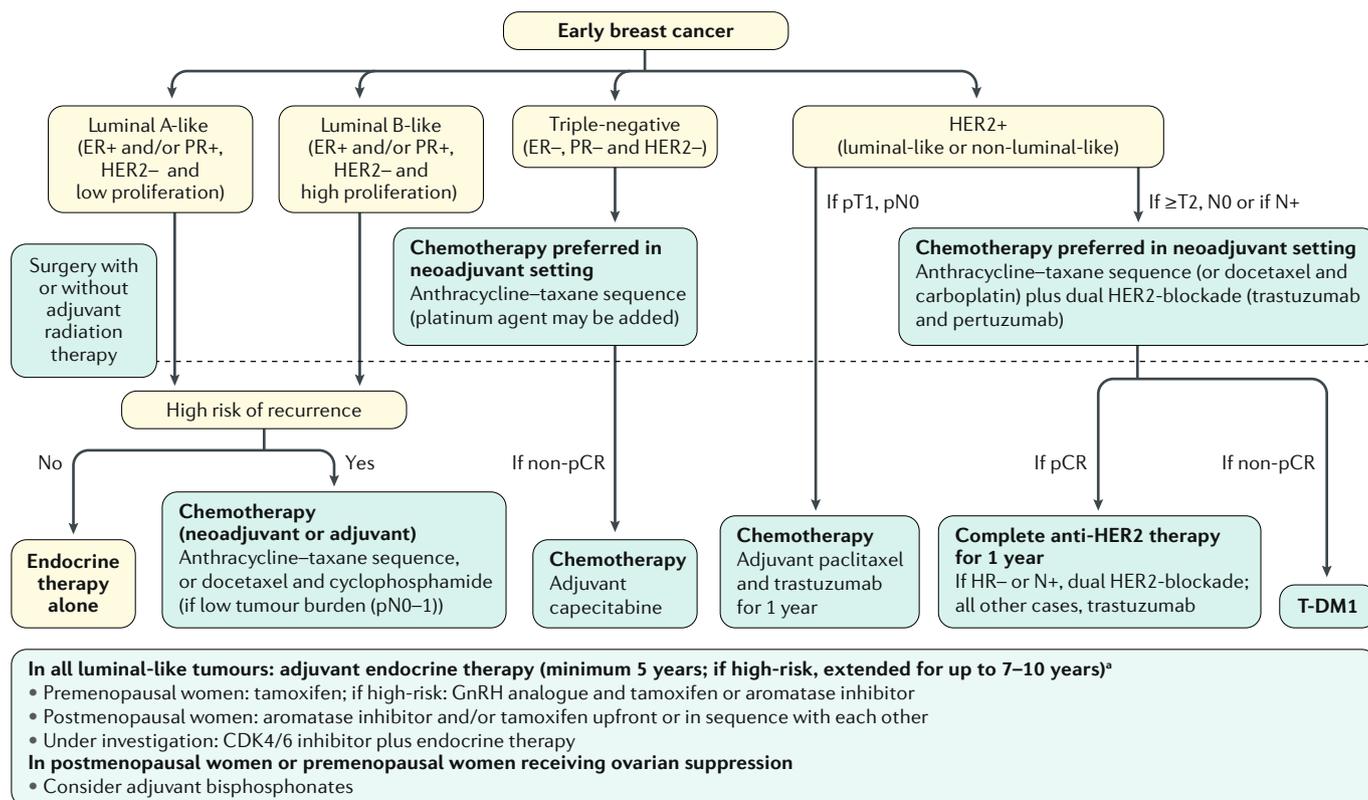


Fig. 6 | Algorithm for early breast cancer. Management of early breast cancer is based on tumour burden and subtype. All patients with oestrogen receptor (ER)-positive disease receive adjuvant endocrine therapy after surgery. If patients are at high risk of recurrence (for example, owing to high-risk gene expression signature results with 0–3 involved lymph nodes, involvement of ≥ 4 lymph nodes or a $>10\%$ risk of breast cancer-specific mortality at 10 years)¹³⁰, chemotherapy needs to be recommended as well. In triple-negative and human epidermal growth factor receptor 2 (HER2)-positive early breast cancer, neoadjuvant subtype-specific systemic therapy is standard, followed by surgery. In the case that pathological complete response (pCR) is not achieved, systemic therapy can be escalated. Bisphosphonates are an additional adjuvant therapy option for all postmenopausal patients and premenopausal patients receiving ovarian suppression; they also conserve bone density. If indicated, radiation therapy can be administered after surgery. The management algorithm takes evidence-based registered therapy options into account. Availability and reimbursement of individual diagnostic or therapeutic options may differ regionally and require adjustments of the treatment concepts outlined here. –, negative; +, positive; GnRH, gonadotropin-releasing hormone; HR, hormone receptor; p, pathological; PR, progesterone receptor; N, node status; T, tumour grade; T-DM1, ado-trastuzumab emtansine. ^aOne study showed a benefit with 15 years of adjuvant endocrine therapy³²⁸.

at the 'new' tumour borders¹³⁹. Recently, the discussion about the optimal margin width has come to a close with a global consensus^{140,141} that no ink on tumour is the appropriate surgical strategy¹²¹. Frozen sections, in which the margins of the resected specimen are assessed during the surgical procedure, can assist the surgeon to optimize the resection extent¹⁴², but are not available everywhere due to resource limitations¹⁴³.

Indeed, breast-conserving surgery has been made possible by the widespread use of neoadjuvant systemic therapy to downsize tumours and the development of advanced oncoplastic techniques¹⁴⁴, such as the 'round-block' procedure¹⁴⁵ (a volume displacement technique for reconstruction) or the V-mammoplasty¹⁴⁶ (in which a V-shaped wedge is cut around the tumour up to the point of the nipple and the breast is 'closed' together). However, an increasing rate of so-called prophylactic mastectomies (in which 'healthy' breasts are removed for prevention because of fear of the disease) is undermining

this success; in general, prophylactic mastectomy does not improve overall survival¹⁴⁷ in patients without *BRCA* germline mutations. Indeed, in young women <40 years of age, breast-conserving surgery plus whole-breast radiation therapy renders equivalent overall survival compared with mastectomy¹⁴⁸. If mastectomy is oncologically required, breast reconstruction can be offered as an immediate or delayed procedure depending on the oncological situation and patient preference. Reconstructive techniques comprise implant surgery as well as autologous tissue breast reconstruction.

As axillary dissection results in considerable morbidity (despite effectively achieving locoregional control)¹⁴⁹, efforts to de-escalate nodal assessment have been successfully implemented in several pivotal clinical trials¹⁵⁰. Sentinel node biopsy, in which at least one sentinel lymph node is identified and removed (FIG. 7), is associated with no or almost no risk of arm lymphoedema, shoulder mobility restrictions, numbness or axillary web

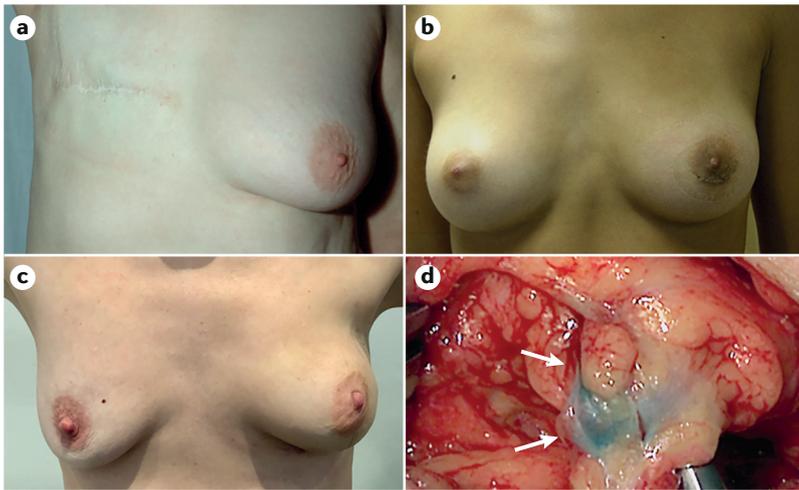


Fig. 7 | Breast-conserving surgery. Current surgical standards of care for breast-conserving surgery not only preserve the organ but also maintain the patient's self-image, femininity and integrity compared with mastectomy (panel **a**; post mastectomy, 8 weeks after surgery). Selection factors for breast-conserving surgery include tumour to breast size relationship, number of tumours, tumour biology and the patient's preference (after adequate information). Even complex surgical situations can be managed with satisfying aesthetic results (panel **b**; breast-conserving surgery for cancer of the left breast, 6 weeks after surgery) with modern oncoplastic techniques. In cases in which mastectomy is inevitable (for example, insufficient downstaging after neoadjuvant systemic therapy), the procedure should be (in terms of surgical technique) undertaken with the option of subsequent reconstructive procedures in mind; that is, unnecessary 'invasiveness' (affecting the muscle, blood vessels and skin) should be avoided whenever oncologically safe clear margins can be achieved. In situations in which nipple-sparing mastectomy (panel **c**; nipple-sparing mastectomy of the left breast with immediate transverse musculocutaneous gracilis flap reconstruction, 8 weeks after surgery with correction of the right side still pending) and or skin-sparing mastectomy are indicated (for example, extensive ductal carcinoma in situ or risk-reducing surgery in women with germline *BRCA* mutations), complete counselling about all available strategies (autologous or alloplastic, immediate or delayed, modified radical versus skin-sparing versus nipple-sparing mastectomy) should be provided to the patient. **d** | Another effort to reduce the potential harms of breast cancer surgery includes substituting axillary node dissection (removal) with sentinel node biopsy. In this technique, a dye is injected intraoperatively (and/or a radioactive tracer pre-operatively) to identify the sentinel node (arrows) so that it can be identified and removed.

syndrome (whereby rope-like soft-tissue density can develop in the axilla after dissection)¹⁵¹ and is associated with excellent long-term locoregional relapse rates¹⁵². A multitude of clinical research questions about technology, detection strategies and tracers, procedural splitting in the context of neoadjuvant systemic therapy and others are currently being intensely discussed, but overall they all convey the benefit of surgical de-escalation to patients without gross nodal disease involvement¹⁵³.

In the context of neoadjuvant therapy, sentinel node biopsy is performed after the systemic therapy to enable the patient to benefit from locoregional tumour downstaging. Whether 'escalation' of radiation therapy 'compensates' for less invasive axillary surgery is less clear and may at least partly erase the benefits of the surgical de-escalation¹⁵⁴. Currently, the indications for sentinel node biopsy include situations after neoadjuvant systemic therapy¹⁵⁵, but other surgical issues remain under discussion in this special context¹⁵⁶. More recently, it has been suggested that not all patients with limited sentinel node metastasis require further axillary dissection^{145,157}.

Radiation therapy. Postoperative radiation therapy improves disease-free and overall survival for patients with early breast cancer with lymph node involvement and/or in the framework of breast-conserving therapy, either by the elimination of residual tumour cells^{158,159} and/or by the induction of an abscopal effect¹⁶⁰. The proportional reduction of locoregional recurrences with radiation therapy following surgery is, for most indications, ~75%, with a dose-effect relationship for local control¹⁶¹. However, the benefits in terms of any recurrences, including distant metastases, show a complex interaction with the risk factors of the primary tumour and the effectiveness of the adjuvant systemic therapy¹⁶². On the basis of risk factors for the development of distant metastases, primary or adjuvant systemic treatment, including endocrine therapy, chemotherapy and targeted treatments, can be prescribed. These treatments interact in a positive way with the benefits of locoregional treatments such as radiation therapy: for patients with high-risk disease, effective systemic treatments will decrease the risk of distant metastases, thereby increasing the importance of optimizing locoregional treatments to obtain definitive cancer cure.

Modern regional lymph node radiation therapy improves disease outcome without increasing non-breast-cancer-related mortality^{158,159,163–165}. Generally, patients with large tumours (>5 cm)¹⁶⁶ with extensive lymph node involvement (>3 axillary nodes), or in the presence of other unfavourable risk factors, receive lymph node radiation therapy; however, no consensus has been reached on the use of lymph node radiation therapy in lower-risk patients, including those with 1–3 involved axillary lymph nodes^{162,167,168}. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of clinical trials evaluating regional lymph node radiation therapy, as presented at the San Antonio Breast Cancer Symposium in December 2018, showed a statistically significant benefit for breast cancer-related and overall mortality that was greatest in patients with ≥4 involved axillary lymph nodes¹⁶⁹. Thus, as we await the outcome of the MRC/EORTC (BIG 2–04) SUPREMO phase III trial¹⁷⁰ (which is assessing the value of chest wall irradiation in intermediate-risk patients with breast cancer) and further optimize the technical aspects of radiation therapy^{171–173}, we must explain the option of postmastectomy irradiation to patients with less advanced disease as well. Additionally, several studies have shown that completion of axillary surgery after a sentinel node biopsy confirmed nodal involvement does not improve outcome in women with early breast cancer compared with axillary nodal irradiation; instead, regional nodal radiation therapy can improve outcomes in selected patients and is increasingly being used instead of axillary surgery^{163–165,174}.

For patients with low-risk features — based on tumour size, grade, nodal involvement, age and molecular profile — radiation therapy after local excision offers, for the same relative risk reduction, lower absolute benefits. This is especially the case if local treatments are followed by adjuvant endocrine treatment, further reducing the absolute benefits in terms of local control and overall survival¹⁷⁴. However, trials that included a

treatment arm that omitted both radiation and endocrine therapy demonstrated that long-term recurrence rates without any postoperative treatment were too high and that both radiation and endocrine therapy reduced local recurrence rates to a similar extent, with an additive effect if both treatments were combined¹⁷⁵. Although these trials only reported outcomes in terms of disease recurrence and survival, without an evaluation of the quality of life, and the benefit derived from adjuvant endocrine therapy for these patients is very low, the findings reignited the debate concerning (the omission of) treatment in low-risk patients.

Patients who receive primary systemic therapy (typically those with locoregionally advanced disease but increasingly those with early-stage breast cancer) pose a clinical challenge for the indications and prescription of radiation therapy. On the basis of results from retrospective evaluation of prospective clinical trials^{176–178}, current international clinical guidelines^{166,179} recommend that radiation therapy should be given based on the risk factors present at initial diagnosis, taking into account the response to primary systemic therapy. Until the results from prospective trials examining the role of radiation therapy in these patients, including ALLIANCE A011202 (NCT01901094) and NSABP B-51/RTOG1304 (NCT01872975), become available, it is recommended that a radiation oncologist is involved in treatment planning before initiation of primary systemic therapy. This approach will not only optimize target volume selection and dose prescription, but will also facilitate the making of CT scans dedicated for radiation therapy for later image co-registration, which is of utmost importance to deliver precision radiation therapy following remission on imaging and subsequent surgery.

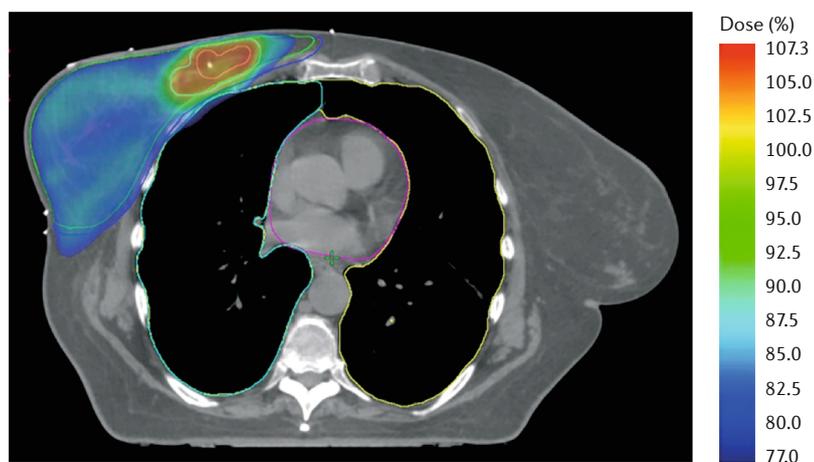


Fig. 8 | Radiation therapy for breast cancer. The schematic illustrates the volumetric intensity-modulated dose distribution at the level of the original tumour location, including a simultaneous integrated boost dose for a patient with early-stage disease who had a medially located primary tumour bed in the right breast. The blue colour wash represents a 50-Gy-equivalent dose, prescribed to the entire breast; the red colour wash represents the 10–16-Gy-equivalent dose to the high-risk zone at the primary tumour bed. The white dot in the middle of the colour wash represents the surgical clip left behind to guide the identification of the original tumour location. This treatment typically causes mild and temporary skin reactions and possibly leads to late development of fibrosis at the primary tumour site that received the boost dose.

Decreasing the burden of radiation therapy can be achieved by several means, starting with the strict adaptation of volume-based radiation therapy techniques using anatomically defined contouring guidelines to improve the dose coverage of the risk-bearing tissues while simultaneously decreasing the size of the irradiated volumes^{174,180}. This approach facilitates a broad adaptation of hypofractionated radiation therapy that shortens the duration of a radiation therapy series from typically 5 weeks to ~3 weeks using fewer but slightly higher-dosed fractions combined with a reduced numerical but radiobiologically-equivalent dose^{181–183}. Another approach to shorten the duration of the radiation therapy series, to lower the risks of developing fibrosis and to reduce unfavourable cosmetic outcomes is applying more restrictive indications for boost dose delivery to the primary tumour bed after breast-conserving therapy^{174,184}. Finally, (accelerated) partial breast irradiation is now an accepted treatment for selected patients with low-risk features for local recurrence that not only reduces the irradiated volume but can also shorten the radiation therapy series to 1–2 weeks or even a single intraoperative dose delivery during the surgical procedure^{185,186}. However, a careful evaluation and interpretation^{187,188} of the literature is necessary to select the most appropriate radiation therapy strategy from the wide range of treatment techniques available, including intraoperative techniques using electrons¹⁸⁹ or low-energy photons¹⁹⁰ (which has an insufficient reported follow-up duration of 27 months). With all these optimizations of all aspects of radiation therapy in breast cancer, the adverse effects can be reduced without compromising outcome (FIG. 8).

Systemic therapy. Systemic therapies for early breast cancer are highly effective, and adjuvant endocrine therapy and adjuvant chemotherapy are able to decrease breast cancer mortality by approximately one-third independent of each other^{191,192}. However, the individual indication depends on the molecular subtype, tumour burden and absolute risk of recurrence. Chemotherapy can be given before (neoadjuvant) or after (adjuvant) surgery with equivalent effects on outcomes, as first demonstrated by the NSABP-B18 trial¹⁹³. Neoadjuvant application is preferred if reduction of tumour size is warranted for optimal surgical results or to assess the response of the tumour *in vivo*. In certain subtypes (HER2-positive breast cancers and TNBCs), neoadjuvant administration has become the standard of care as the pCR is correlated with patient outcome and adjuvant therapy choice may differ based on the pCR status.

In luminal early breast cancer (that is, all ER-positive and/or PR-positive tumours), adjuvant endocrine therapy is standard for at least 5 years after surgery. In premenopausal patients, tamoxifen (which binds to and inhibits ER) is standard; in high-risk premenopausal patients who also received adjuvant chemotherapy, adding ovarian suppression with a gonadotropin-releasing hormone (GnRH) analogue (which inhibits oestradiol production) to tamoxifen improves DFS and overall survival compared with tamoxifen alone, as demonstrated by the joint analysis of the SOFT and TEXT trials¹⁹⁴. A GnRH analogue plus an aromatase inhibitor also improves

recurrence-free survival compared with tamoxifen alone or compared with tamoxifen plus a GnRH analogue, but at the expense of higher toxicity; however, regarding overall survival, tamoxifen plus a GnRH analogue seems more beneficial^{194,195}. In postmenopausal women with luminal early breast cancer, tamoxifen and an aromatase inhibitor are standard either as monotherapies (upfront) or in sequence. An aromatase inhibitor should be included in adjuvant endocrine therapy to reduce recurrence rates compared with tamoxifen (albeit with only minor impact on overall survival). Compared with tamoxifen, 5 years of an aromatase inhibitor reduces breast cancer mortality by ~15% (relative benefit)¹⁹⁶. The definite choice of agent depends on the relapse risk, tolerability, bone health and patient preference.

After 5 years of endocrine therapy, recurrences still occur in patients with luminal early breast cancer over at least 20 years, at a rate strongly dependent on the initial tumour burden¹⁹⁷. Extended adjuvant endocrine therapy for up to 10 years, or even 15 years, imparts favourable patient outcomes¹⁹⁸. Nevertheless, the decision for such an approach needs to take relapse risk and tolerability into account; extended adjuvant endocrine therapy is particularly beneficial for patients at high risk for relapse (that is, those with node-positive disease). Several randomized phase III trials have shown CDK4/6 inhibitors (which block cell cycling) to be active and they have become the preferred treatment option in combination with endocrine therapy in hormone receptor-positive, HER2-negative metastatic breast cancer^{199–201}. Currently, four large international adjuvant trials are evaluating addition of a CDK4/6 inhibitor to endocrine therapy for 2–3 years in patients with intermediate to high-risk luminal HER2-negative early breast cancer. PALLAS (NCT02513394) and monarchE (NCT03155997) have already completed recruitment; NATALEE (NCT03701334) and ADAPTcycle (EudraCT 2018-003749-40) are still recruiting.

In luminal HER2-negative early breast cancer, the recommendation for chemotherapy in addition to endocrine therapy depends on the individual risk of recurrence. In general, if the risk of recurrence is estimated to be >10% over 10 years, chemotherapy is recommended. Standard chemotherapy regimens include an anthracycline and a taxane given preferentially in sequence with care to avoid excessive toxicity²⁰². 5-Fluorouracil does not increase efficacy of an anthracycline and cyclophosphamide backbone in early breast cancer²⁰³. In patients with intermediate clinical risk, docetaxel plus cyclophosphamide is not inferior to a standard sequential anthracycline–taxane regimen¹³⁵. However, in patients with high clinical risk (that is, >3 involved lymph nodes), an anthracycline–taxane regimen seems to be superior²⁰⁴. Dose-dense administration of chemotherapy (in which the rate of delivery, rather than the overall dose, is increased) significantly improves 10-year breast cancer-related mortality independent of ER status and tumour burden without any detectable adverse effects on non-breast-cancer-related mortality²⁰⁵. Adding drugs, such as capecitabine, gemcitabine or bevacizumab, to an anthracycline–taxane chemotherapy does not improve outcomes in early breast cancer.

In HER2-positive early breast cancer (that is, luminal-like and non-luminal-like HER2-positive early breast cancer), neoadjuvant chemotherapy together with anti-HER2 therapy has become the standard of care (at least in tumours \geq cT2, cN0 and all cN+). This approach is preferred as achievement of pCR is correlated with improved outcome (DFS and overall survival)¹²⁹ and adjuvant therapy selection may be influenced by pCR status. In the neoadjuvant setting, dual HER2-blockade with trastuzumab and pertuzumab together with chemotherapy improves rates of pCR and is, therefore, considered standard²⁰⁶. Based on data from the adjuvant setting, chemotherapy in HER2-positive early breast cancer may consist of either an anthracycline–taxane sequence or a combination of docetaxel and carboplatin together with anti-HER2 therapy (for 1 year). The KATHERINE trial demonstrated for the first time that pCR status can be used to escalate postoperative anti-HER2 therapy: switching from trastuzumab (an anti-HER2 antibody) to T-DM1 (a trastuzumab–emtansine conjugate that combines HER2-blockade with a cytotoxic agent) in the case of non-pCR significantly and substantially improved outcomes (HR 0.5 for invasive DFS; 95% CI 0.39–0.64, $P < 0.001$)²⁰⁷ and will now be the new standard for patients with non-pCR. In the adjuvant setting, dual HER2-blockade with trastuzumab and pertuzumab also improves DFS compared with trastuzumab alone. After short-term follow-up, absolute 3-year survival differences are small and patients with node-positive or hormone receptor-negative tumours seem to benefit most²⁰⁸. In patients who had already received 1 year of trastuzumab, an additional 1 year of neratinib (versus placebo) improved invasive DFS with the effect being most pronounced in hormone receptor-positive, HER2-positive disease (HR 0.73; 95% CI 0.57–0.92, $P = 0.0083$)²⁰⁹. However, the additional value of neratinib in the context of adjuvant dual blockade or post-neoadjuvant T-DM1 is not clear. In patients with a low tumour burden, de-escalation seems possible; adjuvant administration of paclitaxel and 1 year of trastuzumab is correlated with excellent outcomes in patients with pN0 HER2-positive tumours \leq 3 cm in size^{210,211}. So far, 1-year total duration of anti-HER2 therapy remains the standard for all patients as the data on shorter duration are still controversial; the PERSEPHONE trial²¹² demonstrated non-inferiority of 6 months of trastuzumab compared with 12 months for patients receiving anthracycline–taxane, whereas others studies, such as PHARE²¹³ and SOLD²¹⁴, have failed to prove this non-inferiority. Longer than 1 year of duration is no more effective, as demonstrated by the HERA trial^{215,216}.

In TNBC, chemotherapy is standard and typically contains an anthracycline and a taxane, although docetaxel and cyclophosphamide are as effective¹³⁵ — at least in TNBC with limited disease burden — and may be used if anthracyclines need to be avoided. As with HER2-positive early breast cancer, chemotherapy is preferentially administered in the neoadjuvant setting. Achievement of a pCR is correlated with improved outcome (DFS and overall survival)¹²⁹; a platinum compound increases pCR rates independent of *BRCA* status²¹⁷. Adding a platinum compound also increases toxicity (mostly haematological), which may impair adequate taxane dose intensity.

Whether adding platinum also improves outcome in addition to pCR is still under debate as a DFS advantage was shown in the GeparSixto trial but not in the CALGB 40603 trial^{217,218}. In the case of non-pCR, treatment escalation with additional adjuvant chemotherapy is feasible in HER2-negative early breast cancer, as demonstrated by the CREATEx trial; additional adjuvant capecitabine improved DFS and overall survival, with the survival benefit being most pronounced in TNBC²¹⁹.

Finally, bone-modifying agents such as bisphosphonates or the RANK-L antibody denosumab not only improve bone mineral density and decrease treatment-related bone loss but may also improve patient outcomes. However, the data on denosumab in early breast cancer are controversial. Although it is effective in lowering fracture rates in postmenopausal patients receiving adjuvant aromatase inhibitors²²⁰, its use may also improve DFS in selected postmenopausal patients²²¹ but not in a more general breast cancer population as demonstrated by the negative phase III D-CARE trial²²². By contrast, an EBCTCG meta-analysis ($n > 18,000$) showed that adjuvant bisphosphonates improve DFS, distant DFS and breast cancer mortality (HR 0.82; 95% CI 0.73–0.93, $P = 0.002$) in postmenopausal patients independent of

tumour biology or type of bisphosphonate therapy²²³. In premenopausal women receiving ovarian suppression, zoledronic acid also improved DFS in the ABCSG-12 trial¹⁹⁵, but there is no clear advantage for premenopausal women in other trials such as AZURE²²⁴ as well as in the EBCTCG meta-analysis²²³.

Advanced breast cancer

Advanced breast cancer comprises inoperable locally advanced breast cancer, which has not spread to distant organs, and metastatic (stage IV) breast cancer; common sites of spread are bone, the lungs and the liver (FIG. 9)²²⁵. Currently, it is a treatable but virtually incurable disease, with metastases being the cause of death in almost all patients, and a median overall survival of 2–3 years²²⁵. Patients with metastatic breast cancer receive treatments that aim to relieve their symptoms and to prolong quality-adjusted life expectancy. Generally, local treatments are not the mainstay of advanced breast cancer treatment but are very useful in some situations, such as brain and bone metastases. Multidisciplinary evaluation of the complex interaction between the contributions of systemic and locoregional treatments to the final outcome (such as survival and toxicity) will ultimately

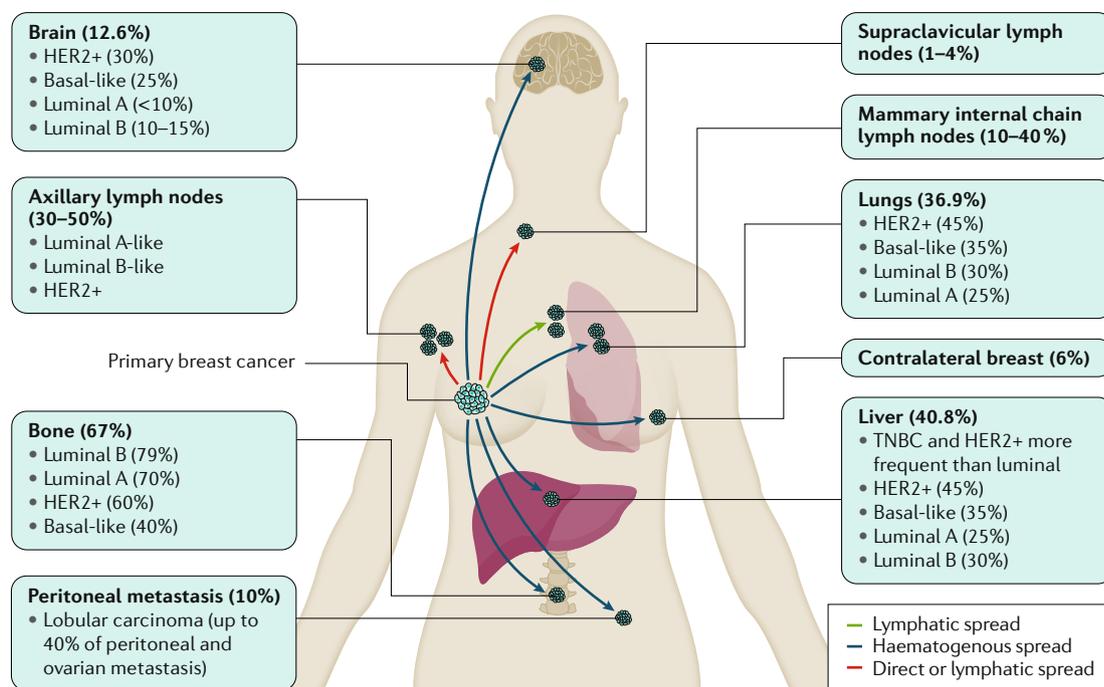


Fig. 9 | Common metastatic sites in breast cancer. The most frequent nodal site is the axillary lymph nodes and the frequency of involvement depends on the size of the tumour. 10–40% of breast cancers have metastasis in the internal mammary chain, influenced by the topography of the tumour in the breast (inner quadrant versus outer quadrant and the size). Controversy abounds with regard to the value of staging and treatment of these nodes, for example, whether or not they need to be dealt with surgically or by radiation therapy. Breast cancer hones to distant metastatic sites differentially according to the molecular subtype according to data from the US Surveillance, Epidemiology, and End Results Program (SEER) database (data from 2010 to 2014, 295,213 patients with invasive breast cancer). Locoregional lymphatic spread is less frequent in triple-negative breast cancer (TNBC) than in other subtypes. The opposite is true for brain metastases, which are more frequent in TNBC than luminal tumours. Additionally, metastatic disease occurs at different time points in the natural history; for example, luminal A cancers typically show late metastatic occurrence (5–10 years after diagnosis) and long survival is possible. By contrast, basal-like subtypes usually metastasize within 2 years, and long survival durations are uncommon. The percentage of metastases found at that site are shown in parentheses. +, positive; HER2, human epidermal growth factor receptor 2. Based on data from REF.⁸¹.

reduce the risk of dying due to distant metastasis¹⁶². De novo metastatic disease (which presents as metastatic at initial diagnosis) and recurrent metastatic disease (which presents after initial diagnosis and treatment of early breast cancer) are somewhat different biologically and some differences exist in management. Recurrent disease is more aggressive and more resistant to therapy, whereas de novo metastatic disease poses the problem of how to treat the primary tumour.

Surgery. In patients with metastatic breast cancer, resection of metastases remains controversial, but may be an option for selected patients based on the pattern and metachronicity of the disease²²⁶. Although resection of the primary tumour in de novo stage IV breast cancer has long been controversial based on retrospective series that had suggested some benefit^{227,228}, three contemporary prospective trials did not demonstrate any benefit^{229–231}. Still, these findings may not be true for every individual patient in the era of increasingly effective systemic therapies^{232,233} and, in general, surgery of the primary tumour is not recommended although it may be discussed on a case-by-case basis for patients with excellent responses to systemic therapy and a low burden of distant disease^{225,234}. Palliative surgery is also of important value in individual situations of locally advanced breast cancer to achieve adequate locoregional control, as well as a frequent treatment tool in resource-limited environments²³⁵.

Radiation therapy. Radiation therapy, which has a crucial role in alleviating symptoms from bone, brain and soft tissue metastases, among others, should be prescribed in a multidisciplinary and individualized approach with dose and fractionation schedules depending on the severity of the lesions and the remaining life expectancy^{236,237}. For most patients with bone metastases, a single dose of 8 Gy is sufficient, as demonstrated in a large prospective randomized trial²³⁸. This approach provides sufficient tumour volume reduction for restoration of the invaded or compressed surrounding normal structures.

The paradigm of not treating the primary tumour is increasingly being challenged, particularly in cases of only a limited number of metastases (currently set at 5). Radiation therapy might also induce a systemic immune response, which may act on neighbouring (bystander effect) or distantly located (abscopal effect) non-irradiated tumour cells²³⁹. A population-based US Surveillance, Epidemiology, and End Results Program (SEER) study (median follow-up 98 months, $n = 3,529$) showed that the 768 patients who received radiation therapy to the primary tumour demonstrated improved overall survival (HR 0.80, $P < 0.001$); even after adjusting for prognostic factors, the benefit of radiation therapy remained significant (HR 0.86, $P = 0.011$)^{240,241}.

This potentially important use of radiation therapy in metastatic disease has spurred new research in the field of immunotherapy²⁴². Most breast cancer types are non-inflamed, immune ‘cold’ tumours that are likely unresponsive to immunotherapy. Thus, the micro-environment needs to be primed to stimulate the

immune response, which can be achieved with radiation therapy, among others. This could be of future interest for all patients with high-risk disease.

Systemic therapies. Given the rapidly evolving nature of systemic therapies and regimens in this setting, here we focus on approved therapies. As in the early setting, systemic therapy is guided by biology (FIG. 10); the relative distribution of subtypes in the metastatic setting is similar to that in the early setting²⁴³. Biopsy and assessment of receptor status (ER and HER2 in particular; PR is less relevant in the metastatic setting) at least once during the course of advanced breast cancer, preferentially at first metastasis, can verify histology and assess potential changes in tumour biology from the primary tumour²²⁵. Multigene panels have not yet been proven useful in the metastatic setting in clinical trials and are only research tools²²⁵. Circulating tumour markers (of which cancer antigen 15–3 (CA 15–3) is the most important protein marker produced by breast cancer cells) alone should not initiate a change in therapy, and progression must be confirmed by imaging²²⁵.

For all luminal-like metastatic breast cancers, several lines of endocrine-based therapy should be used until no response is obtained (endocrine resistance), unless there is rapid progression or visceral crisis (severe organ dysfunction) emerges^{225,244}. For premenopausal patients, ovarian suppression or ablation is required, in addition to another endocrine therapy agent (tamoxifen, an aromatase inhibitor or fulvestrant (a selective ER degrader))^{225,244}. For postmenopausal patients, first-line endocrine therapy can be an aromatase inhibitor, fulvestrant or tamoxifen, depending on the adjuvant endocrine therapy received and the duration of DFS^{225,244}.

When aiming at delaying or overcoming endocrine resistance, CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) and mechanistic target of rapamycin (mTOR) inhibitors (everolimus) have been studied and approved. Everolimus improves PFS by ± 5 months but not overall survival. CDK4/6 inhibitors substantially improve PFS (± 10 months in the first line and ± 5 months in the second line). Results from the PALOMA 3 phase III trial suggest that the PFS benefit may be maintained as an overall survival benefit, but this finding was not statistically significant²⁴⁵. The MONALEESA-7 study in premenopausal patients showed a significant prolongation of overall survival for first-line use of a CDK4/6 (ribociclib) in combination with ovarian suppression and an aromatase inhibitor or tamoxifen compared with endocrine therapy alone (HR 0.71; 95% CI, 0.54–0.95, $P = 0.00973$). At 42 months, 70% of patients were still alive in the ribociclib group compared with only 46% in the control group. In view of additional cardiac toxicity with tamoxifen, ribociclib is only approved with an aromatase inhibitor (plus GnRH) in this setting.

Even though the MONALEESA-7 data now suggest a survival advantage in the first-line setting for CDK4/6 inhibitor therapy, the optimal sequence of therapies in metastatic disease is still unknown. When chemotherapy is needed (for example, once endocrine therapy options have been exhausted or if no response is obtained with them), sequential use of monochemotherapy is

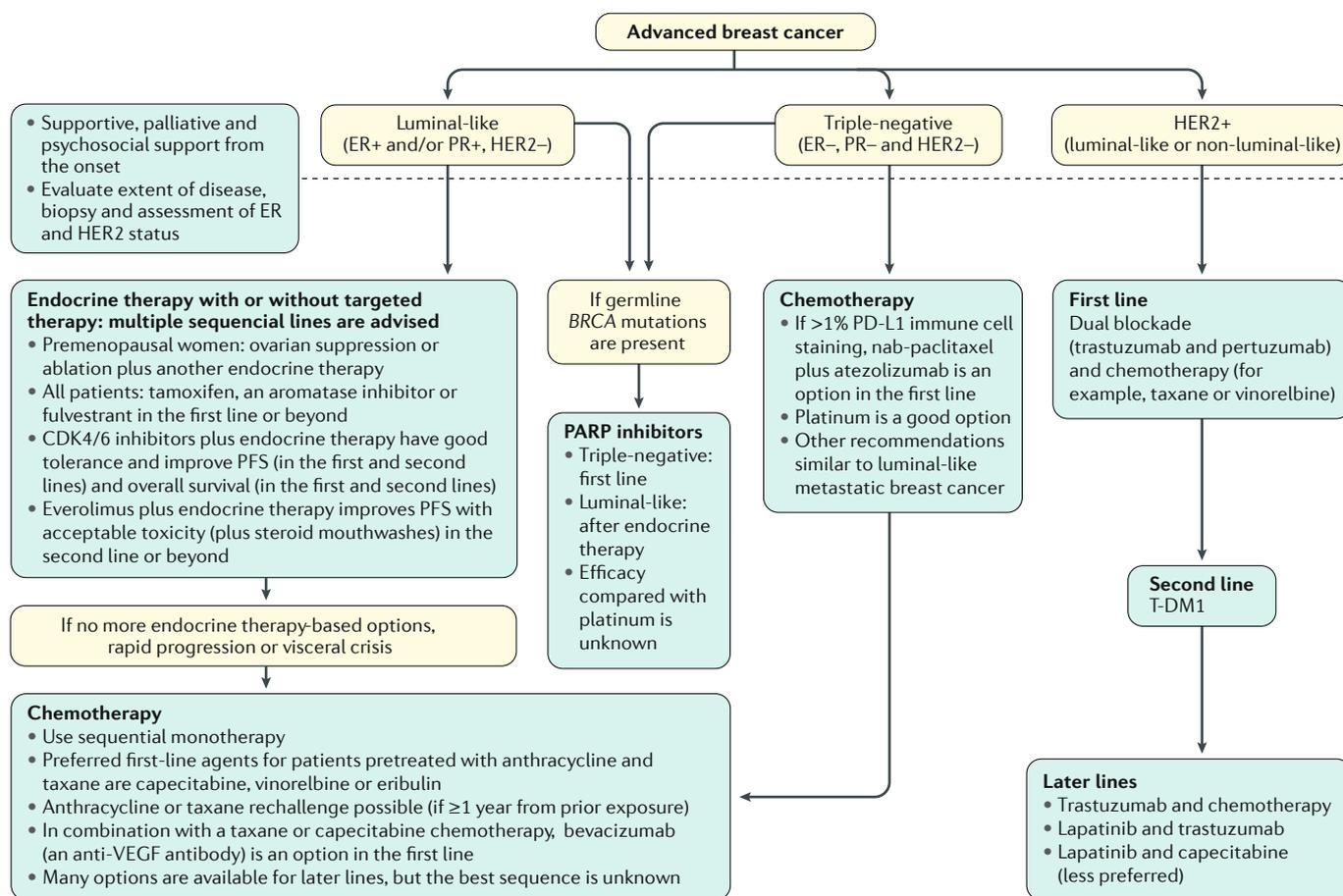


Fig. 10 | Algorithm for advanced breast cancer. Management of advanced breast cancer with distant metastases should be according to subtype as well as disease characteristics and patient preferences. Supportive, palliative and psychosocial support are crucial from the time of diagnosis. Biopsy of a metastatic site and assessment of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status, at least once in the metastatic setting, are also necessary. Endocrine therapy, with or without targeted therapy, is the mainstay for luminal-like disease, and — unless life-threatening — several lines are to be used before commencing chemotherapy. When chemotherapy is used, sequential monotherapy is advised. For triple-negative disease, chemotherapy is the main treatment, with no specific recommendations except that platinum is one of the preferred options. Triple-negative tumours with immune cells expressing programmed death-ligand 1 (PD-L1) may be candidates for first-line immunotherapy. For HER2-positive disease, it is crucial to continue blocking the HER2 pathway, with a sequence of anti-HER2 agents and chemotherapy; combinations of endocrine therapy with anti-HER2 therapy can also be used in ER-positive, HER2-positive disease, preferentially as maintenance therapy. For women harbouring germline *BRCA* mutations, poly(ADP-ribose) polymerase (PARP) inhibitors are an additional therapy option. The management algorithm takes evidence-based registered therapy options into account. Availability and reimbursement of individual diagnostic or therapeutic options may differ regionally and require adjustments of the treatment concepts outlined here. –, negative; +, positive; PFS, progression-free survival; T-DM1, ado-trastuzumab emtansine; VEGF, vascular endothelial growth factor.

recommended; combination chemotherapy should be reserved for situations of visceral crisis or rapidly progressive disease²²⁵. The preferred first-line agents for patients previously treated with adjuvant anthracyclines and taxanes are capecitabine, vinorelbine or eribulin. Anthracycline and/or taxane rechallenge therapy may also be an option in patients with a treatment-free interval of ≥ 1 year. In combination with taxane or capecitabine chemotherapy, bevacizumab (an antibody against vascular endothelial growth factor) is a first-line option that improves PFS but not overall survival; it is registered in Europe but not the United States²⁴⁶. For later lines of therapy, many available options are available and the decision should be individualized considering different

toxicity profiles, previous exposure, patient preferences, country availability and costs²²⁵. The duration of each regimen and the number of cycles should also be individualized, and chemotherapy should be continued until disease progression or unacceptable toxicity. Again, the optimal sequence is unknown.

For HER2-positive advanced breast cancer (including ER-positive and ER-negative, HER2-positive disease), anti-HER2 agents should be started early and continued beyond progression^{225,247}. In patients previously untreated with trastuzumab, the preferred first-line option is dual HER2-blockade with trastuzumab and pertuzumab plus chemotherapy (usually docetaxel, paclitaxel, nab-paclitaxel, vinorelbine or capecitabine)^{225,247}.

In patients previously exposed to adjuvant trastuzumab (or those in countries without access to pertuzumab), this regimen or trastuzumab plus chemotherapy (usually vinorelbine or a taxane) can be used²²⁵. Second-line options include T-DM1, trastuzumab plus another chemotherapy agent (usually capecitabine, vinorelbine or taxane (if not used previously), but also eribulin, liposomal anthracyclines, platinum, gemcitabine or metronomic cyclophosphamide with methotrexate), or trastuzumab plus lapatinib (a tyrosine kinase inhibitor that interrupts the HER2 and epidermal growth factor receptor pathways)^{225,247}. Combinations of trastuzumab plus chemotherapy are superior to lapatinib plus chemotherapy. Sequential monochemotherapy should be used²²⁵, although the optimal sequence of all available options is unknown. For HER2-positive, ER-positive disease, combinations of endocrine therapy and anti-HER2 agents are possible both as initial treatment and as maintenance treatment^{225,247}.

For TNBC, there are no different or specific chemotherapy recommendations for patients without *BRCA* mutations^{225,248}. For *BRCA*-associated advanced TNBC, a platinum agent is the preferred option. In these patients and in those with *BRCA*-mutated luminal advanced breast cancer, recent data have shown improved PFS and improved quality of life with a PARP inhibitor (olaparib or talazoparib) compared with monochemotherapy^{30,31}. In TNBC with >1% programmed cell death 1 ligand 1 (PD-L1) immune cell staining, nab-paclitaxel plus atezolizumab has shown significantly superior PFS compared with nab-paclitaxel alone in the first-line setting; although a numerical overall survival advantage (7–10 months) seems evident in the PD-L1 immune cell-staining subgroup, final data on overall survival are still awaited²⁴⁹.

Monitoring treatment response

In early breast cancer, imaging during neoadjuvant chemotherapy may be used to guide tailored treatment to improve rates of pCR and breast conservation in both early responders and non-responders. Clinical examination and ultrasonography have been used in clinical trials to monitor tumour size before and during neoadjuvant chemotherapy to inform a change in therapy during the regimen. Metabolic and functional imaging (PET, dynamic contrast-enhanced MRI or diffusion-weighted MRI) potentially enable earlier assessment of response, but response criteria for these tests are not yet standardized^{250,251}. After neoadjuvant chemotherapy, imaging can identify pCR and assist in surgical planning. MRI accurately detects pCR after neoadjuvant chemotherapy²⁵² and improves measurement of tumour size compared with ultrasonography, mammography and clinical examination²⁵³. Studies also show that PET performed after 1–2 cycles of neoadjuvant chemotherapy can also predict treatment response in patients with large operable and locally advanced breast cancer²⁵⁴.

In the metastatic setting, imaging of the chest (CT or X-ray), abdomen (CT or ultrasonography) and bone (usually radionuclide bone scan) is recommended²²⁵ for pretreatment staging, although PET or PET-CT may be

used selectively for staging or restaging²⁵⁵. Additional organ-specific imaging in patients with metastatic breast cancer is reserved for symptom evaluation, and for response monitoring when it complements clinical evaluation and appropriate laboratory testing²⁵⁶. However, there is a paucity of good-quality evidence on the comparative effectiveness of imaging tests, and a lack of data on optimal timing and frequency of monitoring and the effect that imaging monitoring has on patient outcomes²⁵⁷. With these limitations in mind, either conventional imaging (CT, bone scan or MRI depending on the site of metastases) or PET-CT may be used for response monitoring; PET-CT has been reported to have equivalent or better accuracy in detecting treatment response compared with each of the conventional imaging modalities²⁵⁷. PET-CT provides functional information on tumour metabolism and, therefore, can potentially identify response at earlier time points during treatment than the relatively delayed gross morphological changes defined by conventional imaging²⁵⁷. However, in many countries, the use of PET-CT is more expensive than other imaging modalities.

Quality of life

Treatment individualization is crucial and should consider patient-related and tumour-related factors. The assessment of patient-reported outcomes related to toxicities and quality of life is increasingly recognized as an important component of oncology research to inform individualized clinical decision-making. Frank discussion of the goals of treatment, using accessible language, is fundamental — as is appropriate psychosocial, supportive and palliative care, from the initial diagnosis and through all stages of treatment. All patients should be discussed and managed by a multidisciplinary team.

Many breast cancer treatments cause substantial toxicities that can impair quality of life. Although most existing data on symptom management and quality of life come from postmenopausal patients with early-stage breast cancer, studying and managing adverse effects is particularly important in patients with metastatic disease, who generally continue to take a given systemic therapy until progression or excessive toxicity requires a change. Impact on quality of life is a critical consideration when weighing the risks and benefits of any breast cancer therapy, but especially for palliative therapies. Indeed, the adverse effects of systemic therapies are numerous for most patients. Endocrine therapy frequently causes hot flashes, with tamoxifen and ovarian suppression-based regimens known to be particularly powerful hot-flash inducers^{258,259}. Management strategies for hot flashes include medications (such as serotonin-norepinephrine reuptake inhibitor venlafaxine and GABA analogue gabapentin) and mind-body techniques (such as hypnosis and acupuncture)^{260–262}. Aromatase inhibitors often produce arthralgias (joint pain), which are commonly treated with NSAIDs and exercise, but these strategies are not supported by strong evidence²⁶³. Aromatase inhibitors also cause vaginal dryness and dyspareunia, for which vaginal moisturizers and lubricants have been the traditional mainstays of management in patients with hormone-sensitive tumours, but novel

treatments such as vaginal dehydroepiandrosterone are under study²⁶⁴.

Chemotherapy causes both acute toxicities (such as nausea and fatigue) and chronic toxicities (such as infertility, cardiotoxicity, neuropathy and cognitive dysfunction). Cancer-related fatigue and cognitive dysfunction are difficult to treat, but nausea is now well-managed in most patients using multi-agent anti-emetic regimens²⁶⁵. With regard to cardiotoxicity, the PRADA study showed that carvedilol (a non-selective adrenergic receptor used to treat heart failure and hypertension) may protect against asymptomatic anthracycline-induced reductions in ejection fraction, which could translate into later improvements in quality of life related to cardiac function²⁶⁶. In addition, the serotonin and norepinephrine reuptake inhibitor duloxetine has been definitively proven to treat (albeit with modest benefit) chemotherapy-induced peripheral neuropathy^{267,268}, and ongoing research is assessing methods for prevention of chemotherapy-induced peripheral neuropathy (including tactile stimulation, cryotherapy and acupuncture)^{269–271}. With the development of new targeted therapies for breast cancer (see below, Outlook), it will be important to study their effects on quality of life, and to develop management strategies for their associated symptoms (for example, steroid mouthwashes for stomatitis from everolimus).

Local therapies can also impair quality of life. Reduced use of full axillary dissection has limited the incidence and severity of lymphoedema in breast cancer survivors, but some patients are still affected. Risk of lymphoedema is increased by obesity, more extensive axillary surgery, use of radiation therapy and, possibly, chemotherapy^{272,273}. Dermatitis and pneumonitis are other quality-of-life-limiting radiation toxicities, and both surgery and radiation therapy can produce acute fatigue, chronic pain and cosmetic concerns^{274,275}.

In addition to impacting the symptom burden, breast cancer treatments can burden patients financially and psychosocially. Lost employment and cost of care can be economically challenging, and dealing with a potentially fatal diagnosis (including relying on friends and family to help with, for example, transportation and home responsibilities) can be emotionally challenging. Clinical trials must take into account the effect of new drugs and treatment strategies on quality of life by collecting patient-reported outcomes using validated instruments (TABLE 3). In addition, more research is needed to identify effective supportive interventions both during and after active treatment.

Outlook

The impressive increase in knowledge in the field of molecular biology and immunology has helped to elucidate the molecular characteristics of cancer and is the basis for a plethora of upcoming drugs. However, although important improvements have been achieved in recent years in terms of metastatic breast cancer outcomes, more and better treatments are needed. Research that provides biological insights into overdiagnosis as a result of breast cancer screening or that mitigates its consequences through modified therapeutic approaches would also be valuable⁹¹. Nevertheless, one of the global challenges we face is the limited access to diagnosis and affordable and effective treatment that leads to disparities in cancer survival between countries. As one of the most common cancers, breast cancer is a bustling research field. Here, we summarize some of the emerging findings that are likely to have the most impact on patients. However, we emphasize that the most pressing global challenge in the breast cancer field is to ensure that all patients have access to high-quality standard diagnosis (imaging and pathology) and treatment (surgery, radiation and systemic therapy), avoid late

Table 3 | Validated measures of quality of life in breast cancer

Instrument	Abbreviation	Number of items ^a	Recall period ^b	Notes
Functional Assessment of Cancer Therapy — Breast ³³⁴	FACT-B	37	7 days	<ul style="list-style-type: none"> • Copyright owned by David Cella • Permission details at http://www.facit.org/FACITOrg
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire — Core 30 and Breast Cancer Module ^{334,335}	EORTC QLQ-C30 and BR23	53	1 week	<ul style="list-style-type: none"> • QLQ-C30 (30 items) can be used without the breast cancer-specific BR23 (23 items), but not vice versa • BR23 has been recently updated to BR45 (REF.³³⁶) • Free • Permission details at https://qol.eortc.org/modules/
Short Form Health Survey-36 ³³⁷	SF-36	36	4 weeks	<ul style="list-style-type: none"> • Free, no need to obtain permission for use • Available at http://www.rand.org/health/surveys_tools/mos/36-item-short-form.html
EuroQol 5-Dimensions ³³⁸	EQ-5D	5	Today	<ul style="list-style-type: none"> • Copyright held by EuroQol • Permissions details at https://euroqol.org/
Patient-Reported Outcomes Measurement Information System ^{339,340}	PROMIS-10	10	7 days	<ul style="list-style-type: none"> • Free, no need to obtain permission for use • Available at http://www.healthmeasures.net/explore-measurement-systems/promis

^a'Items' refers to the questions a patient is asked to respond to as part of the survey. ^b'Recall period' refers to the time period over which a patient is asked to reflect when answering a question.

diagnosis and are provided with adequate supportive and palliative care services.

Early breast cancer

In early breast cancer, cancer-specific mortality has been substantially reduced by modern multimodal therapy concepts. Treatment de-escalation and escalation are currently being evaluated — in both locoregional and systemic therapies. However, evidence-based adaptation of current standards is required to ensure that patients are not undertreated while attempting to avoid overtreatment. De-escalation of radiation therapy trials are attempting to define populations with luminal A early breast cancer at low risk, for whom radiation therapy after breast-conserving surgery may not be needed. Surgical de-escalation trials are examining the role of sentinel node biopsy in cN0 disease, provided that standard postoperative therapy is being administered. The neoadjuvant setting in early breast cancer offers an ideal model for *in vivo* response testing and stratifying the postoperative approach according to pCR. For example, patients with pCR may be able to de-escalate postoperative adjuvant therapy whereas patients with non-pCR are candidates for further therapy escalation. With regards to locoregional therapy, the role of surgery in cases of clinical complete response (that is, whether it can be completely omitted) and the role of postoperative radiation therapy in patients who converted from node-positive to node-negative disease with neoadjuvant systemic therapy (for example, the aforementioned NSABP-B51/RTOG1304 trial) are being investigated. In luminal early breast cancer, short-term endocrine therapy before surgery and assessment of the proliferation response (for example, Ki67 $\leq 10\%$) in the surgical specimen — as a surrogate for endocrine therapy responsiveness — may help to adapt adjuvant therapy concepts^{276–278}.

In the adjuvant setting, decreasing unnecessary toxicities from overtreatment without compromising outcome will also be a challenge for the years to come. However, the downside of the success in adjuvant therapies is the substantial alteration in metastatic disease, with less-favourable metastasis patterns and shorter post-metastasis survival²⁷⁹, which increases the challenge for management of advanced breast cancer. Epidemiological data suggest that contemporary adjuvant systemic therapies exert evolutionary pressures on the tumours²⁷⁹ given changes in metastatic patterns and decreased survival times that have not been observed in *de novo* metastatic breast cancer²⁸⁰. These epidemiological findings parallel those of whole-genome sequencing studies, which show that metastatic breast cancers have similar genetic patterns to primary breast cancer with subtype-specific enrichment of selected driver mutations in the metastatic lesions²⁸¹. In invasive lobular cancers, matched-pair analysis of primary tumours and their corresponding metastases also revealed acquisition of several genomic alterations (such as mutations in *CDH1*, *ESR1*, *ARID1A*, *ERBB2*, *GATA3*, *IGF1R*, *MAP3K1* and *PIK3CA*) at a frequency of 5–11% in metastatic disease that could be associated with disease progression and development of endocrine resistance²⁸². Some of these alterations, such

as *ESR1* or *PIK3CA*, are already becoming relevant for choosing specific targeted therapies.

Advanced breast cancer

Upcoming drugs and pathways. Recent preclinical studies have revealed various targetable pathways that may optimize available therapies or overcome resistance to available drugs (FIG. 11). For example, the PI3K–AKT–mTOR signalling pathway is the subject of intense research in breast cancer. Pan-PI3K inhibitors proved to be too toxic and their development was replaced by PI3K isoform-specific inhibitors such as alpelisib and taselisib²⁸³. Alpelisib, an α -specific PI3K inhibitor, has been approved by the FDA on the basis of the longest PFS improvement of this class of agents so far (~5 months of benefit in PFS, HR 0.65; 95% CI 0.50–0.85) in hormone-resistant ER-positive, HER2-negative *PIK3CA*-mutated advanced breast cancer when combined with fulvestrant, with moderate toxicity²⁸⁴. Taselisib, a β -sparing PI3K inhibitor, moderately improves PFS in the same population when combined with fulvestrant in patients with wild-type and with *PI3K*-mutant tumours but with clinically relevant toxicities²⁸⁵. Recently, two randomized phase II studies have shown that AKT inhibitors can be active in patients with TNBC. When the AKT pathway was active, both ipatasertib²⁸⁶ and capivasertib²⁸⁷ improved the activity of paclitaxel. In the phase II FAKTION trial (NCT01992952)²⁸⁸, capivasertib was also active in combination with fulvestrant in luminal-like metastatic breast cancer.

Drugs that inhibit histone deacetylases, which are involved in chromatin remodelling and epigenetic regulation, have become a very interesting field of research. Indeed, a randomized phase III trial of entinostat in combination with endocrine therapy in patients with ER-positive, HER2-negative advanced breast cancer based on the activity and toxicity profile exhibited (NCT02115282) is underway²⁸⁹. Another phase III trial with the oral subtype-selective histone deacetylase inhibitor chidamide has already shown interesting results with moderate toxicity⁶⁹.

In HER2-positive metastatic breast cancer, new antibody–drug conjugates and monoclonal antibodies are being tested in phase II/III trials. DS-8201, a new anti-HER2 antibody–drug conjugated to a topoisomerase I inhibitor, has shown potent activity *in vitro* and *in vivo*²⁹⁰, and seems to be effective in patients with HER2-positive breast cancer who were previously treated with T-DM1 (REF.²⁹¹) as well as in patients with advanced breast cancer with low HER2 expression. Margetuximab, an anti-HER2 Fc-optimized monoclonal antibody, has shown preliminary activity in heavily trastuzumab-pretreated patients in a phase I trial²⁹². The phase III SOPHIA trial showed a significant but modest PFS improvement for margetuximab versus trastuzumab and a chemotherapy backbone in both arms²⁹³. New HER2-targeted tyrosine kinase inhibitors such as tucatinib (particularly in cases of brain metastases) and neratinib (particularly in cases of HER2-negative, HER2-mutant and HER2-positive breast cancer²⁹⁴) are also being developed. The phase III NALA trial showed significantly improved PFS but substantial gastrointestinal toxicity for

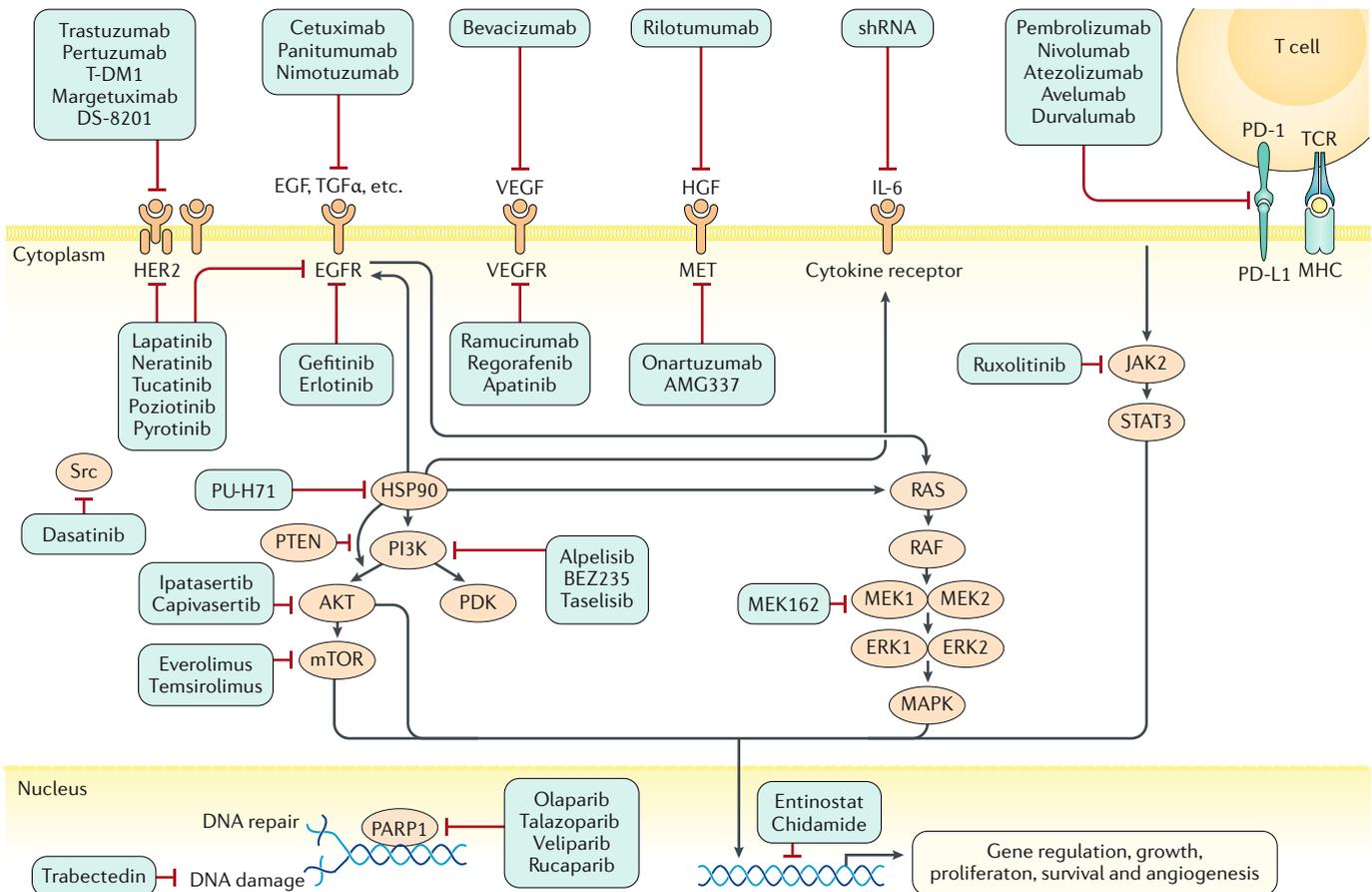


Fig. 11 | Emerging targetable pathways in breast cancer. Different membrane receptor inhibitors have shown activity in breast cancer, including monoclonal antibodies against human epidermal growth factor receptor 2 (HER2), such as trastuzumab, margetuximab and pertuzumab; antibody–drug conjugates, such as ado-trastuzumab emtansine (T-DM1); immunotherapy that blocks programmed cell death 1 (PD-1) and/or programmed cell death 1 ligand 1 (PD-L1), such as atezolizumab and pembrolizumab; or drugs that target angiogenesis (such as the monoclonal antibody bevacizumab, which targets vascular endothelial growth factor (VEGF)). Tyrosine kinase inhibitors, such as lapatinib, neratinib or tucatinib, among others, have shown activity in breast cancers that overexpress HER2. These drugs can block the activation of different signalling pathways such as the RAS–RAF–mitogen-activated protein kinase (MAPK) pathway or the phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT)–mechanistic target of rapamycin (mTOR) pathway, which can also be blocked with small molecules such as everolimus or different PI3K inhibitors; the crosstalk between these pathways is an area of active research. Additionally, different poly(ADP-ribose) polymerase (PARP) inhibitors in patients with germline *BRCA* mutation-associated breast cancer have demonstrated good activity. The role of these agents in patients with somatic mutations is not known. EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; MET, hepatocyte growth factor receptor; MHC, major histocompatibility complex; shRNA, short hairpin RNA; TCR, T cell receptor; TGF, transforming growth factor; VEGFR, vascular endothelial growth factor receptor.

neratinib versus lapatinib in a capecitabine combination in women with pretreated HER2-positive advanced breast cancer²⁹⁵.

Due to the heterogeneity and the absence of clear drivers, the achievements in TNBC remain far behind other subtypes. The luminal androgen receptor subtype (BOX 2) shares features with classic luminal-like hormone receptor-positive tumours; anti-androgens have been shown active in this patient population^{296,297}. Additionally, in those patients with TNBC and *BRCA* germline mutations, two phase III trials have now demonstrated better efficacy and better tolerability and quality of life for PARP inhibitors compared with monotherapy^{30,31}, building on earlier preliminary findings²⁹⁸.

Finally, although far behind in clinical development compared with other tumour types, immunotherapy has shown promise with immune checkpoint inhibitors such as pembrolizumab²⁹⁹ or atezolizumab³⁰⁰. For example, as mentioned, a first phase III trial showed a slightly improved PFS and preliminary evidence that atezolizumab combined with nab-paclitaxel may provide an overall survival benefit compared with the taxane alone in tumours with $\geq 1\%$ PD-L1 immune cell staining²⁴⁹. Some of the biomarker assessment-based new drugs have already been approved, such as PD-L1 immunohistochemistry in TNBC for immunotherapy²⁴⁹, *BRCA* germline mutations for PARP inhibitors^{30,31} and *PIK3CA* mutations for PI3K inhibitors³⁰¹, whereas for others there is evidence but no specific approval, such as assessing

HER2 mutations for neratinib³⁰² or *ESR1* mutation screening for resistance to aromatase inhibitors. Many of these assessments need further data to validate their clinical utility and technical standardization

Conclusions

The best end points to evaluate therapies in the advanced setting are debated. Research should determine optimal composite end points and incorporate patient-reported outcome measures. Dedicated quality-of-life tools to evaluate metastatic disease are urgently needed.

Additionally, the mechanisms underlying tumour resistance and how to overcome it are main topics of ongoing research. As therapies induce alterations of tumour biology, ongoing evaluation of disease status and active pathways is necessary throughout the cancer journey. Serial biopsies are very difficult to implement, and hope lies with liquid biopsies, functional imaging and new applications of nanotechnology. Knowing the driving pathway at every given moment will enable the correct determination of the optimal sequence of therapies, which currently is largely unknown for all advanced breast cancer subtypes. New techniques such as next-generation sequencing will continue to

provide deeper knowledge of the biology of advanced disease but are not yet in play for individualized treatments. Furthermore, understanding the metastatic tropism of each tumour may enable future preventive measures. New targets (FIG. 11) and more efficient and/or less toxic therapies are needed to achieve the aim of personalized/precision medicine.

Apart from scientific advances, a deeper understanding of the needs of patients with advanced breast cancer and intense lobbying for their rights is crucial. In this regard, the **ABC Global Alliance** was created and is actively fighting for, among others, better survival and quality of life, accurate information, access to multidisciplinary and high-quality care, early access to supportive and palliative measures, financial support and ability to maintain or return to work. The ABC Charter, which is a comprehensive needs assessment of the field of advanced breast cancer, clearly highlights that much work is still needed and that intense collaboration between all stakeholders involved is crucial to improve the length and quality of life of all patients and perhaps one day be able to reach a cure for advanced breast cancer.

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Competing interests

N. Harbeck reports honoraria for lectures and/or consulting from Agendia, Amgen, AstraZeneca, Celgene, Daiichi-Sankyo, Genomic Health, Lilly, MSD, Novartis, Odonate, Pfizer, Roche, Sandoz/Hexal and Seattle Genetics. F.P.-L. declares personal financial interests in Abbvie, Agendia, AstraZeneca, BMS, Genomic Health, Janssen, Lilly, Merck Lifa, MSD, Myriad, Nanostring, Novartis, Pfizer and Roche; institutional financial interests in AstraZeneca, BMS, Genomic Health, MSD, Myriad, Nanostring and Roche; and congress invitations from Abbvie, AstraZeneca, BMS, MSD and Roche. J.C. has received honoraria from Celgene, Chugai, Eisai, Novartis, Pfizer, Roche and Samsung; has served as a consultant for AstraZeneca, Biothera, Celgene, Daiichi Sankyo, Erytech Pharma, Merus, Polyphor, Roche and Seattle Genetics; has received research funding from Ariad, AstraZeneca, Baxalta GMBH, Bayer, Eisai, Guardant Health, Merck Sharp & Dohme, Pfizer, Puma and Roche; and has stocks in MedSIR. M.G. reports honoraria from Amgen, AstraZeneca, Celgene, Eli Lilly, Medison, Nanostring Technologies, Novartis and Roche; advisory fees from Accelsoir; research funding from AstraZeneca, Novartis, Pfizer and Roche; and travel expenses from Amgen, AstraZeneca, Celgene, Eli Lilly, Ipsen, Medison, Novartis and Pfizer. K.R. declares previous ownership of Merck and Pfizer stock (October 2016–February 2018). J.T. reports honoraria and consultancy or advisory roles for AstraZeneca, Astellas, De Novo, Eisai, Foundation Medicine, Nanostring, Novartis, Pfizer and Roche. F.C. declares consultancy roles for Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, Genentech, GE Oncology, GlaxoSmithKline, Macrognics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, prIME Oncology, Roche, Sanofi, Seattle Genetics and Teva. The remaining authors declare no competing interests.

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