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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

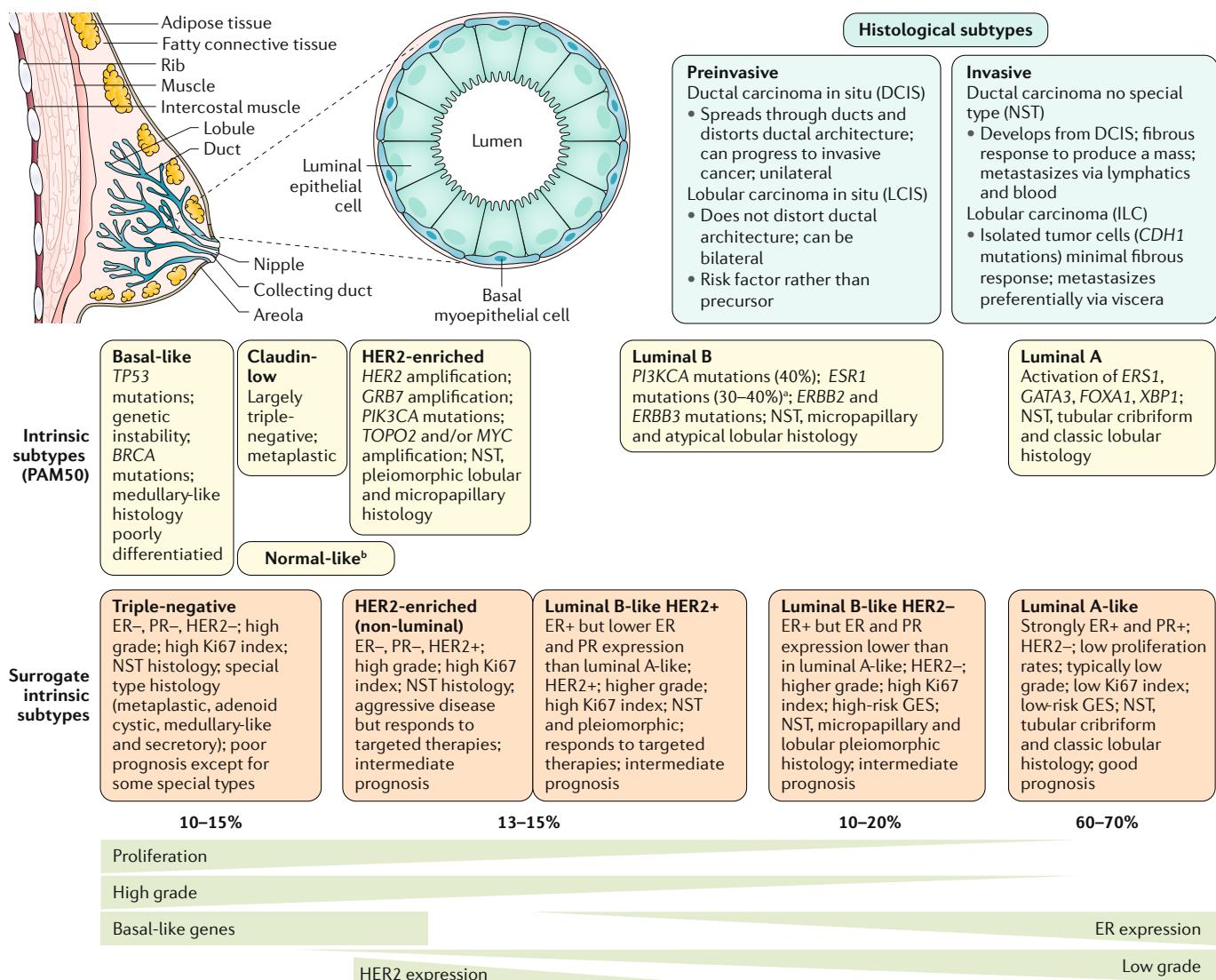


Fig. 1 | Breast cancer. All breast cancers arise in the terminal duct lobular units (the functional unit of the breast) of the collecting duct. The histological and molecular characteristics have important implications for therapy, and several classifications on the basis of molecular and histological 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)^{32,31}. 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 contraindication 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 years⁵. 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
BRCA1 hereditary breast cancer syndrome, and BRCA1 breast and ovarian breast cancer syndrome	BRCA1; 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
BRCA2 hereditary breast cancer syndrome, and BRCA2 breast and ovarian breast cancer syndrome	BRCA2; 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	TP53; mutations: no hot spots; BRCA2, Fanconi genes, MMR 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
PALB2	PALB2 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
CHEK2	CHEK2 mutations (CHEK2*1100delC more frequent than 470C>T or I157Thr missense variants); cell cycle checkpoint kinase, DNA repair, activated BRCA1 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 CHEK2*1100delC mutation carriers
Ataxia telangiectasia	ATM; mutations: no hot spots; homozygotes more affected than heterozygotes; protein kinase DNA damage response through p53, BRCA1 and CHECK2 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	PTEN; 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 CDH1; 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	STK11; 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	NF1 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

^a, 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}. ^bLynch 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

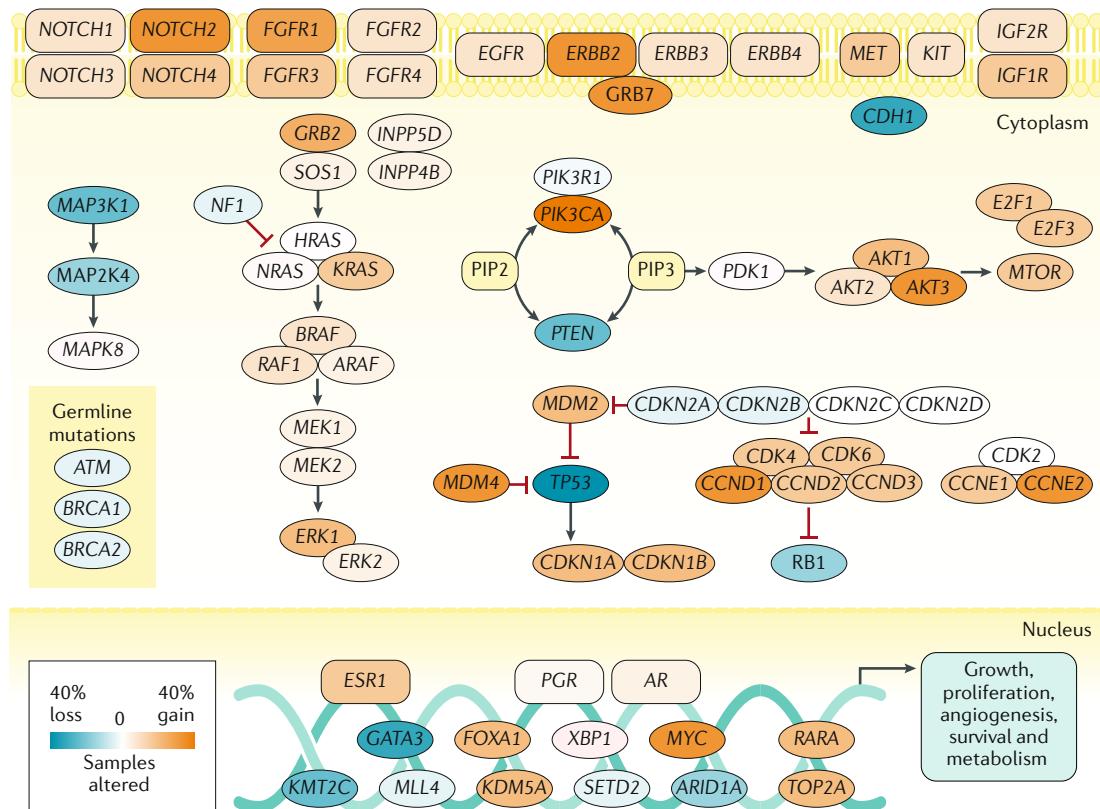


Fig. 2 | Molecular mutations in breast cancer. The Cancer Genome Atlas data on breast tumour DNA copy number and somatic mutations were used to identify the frequency of each genetic alteration across 792 patients with breast cancer (all subtypes)³²². Each gene is shaded according to the overall frequency 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

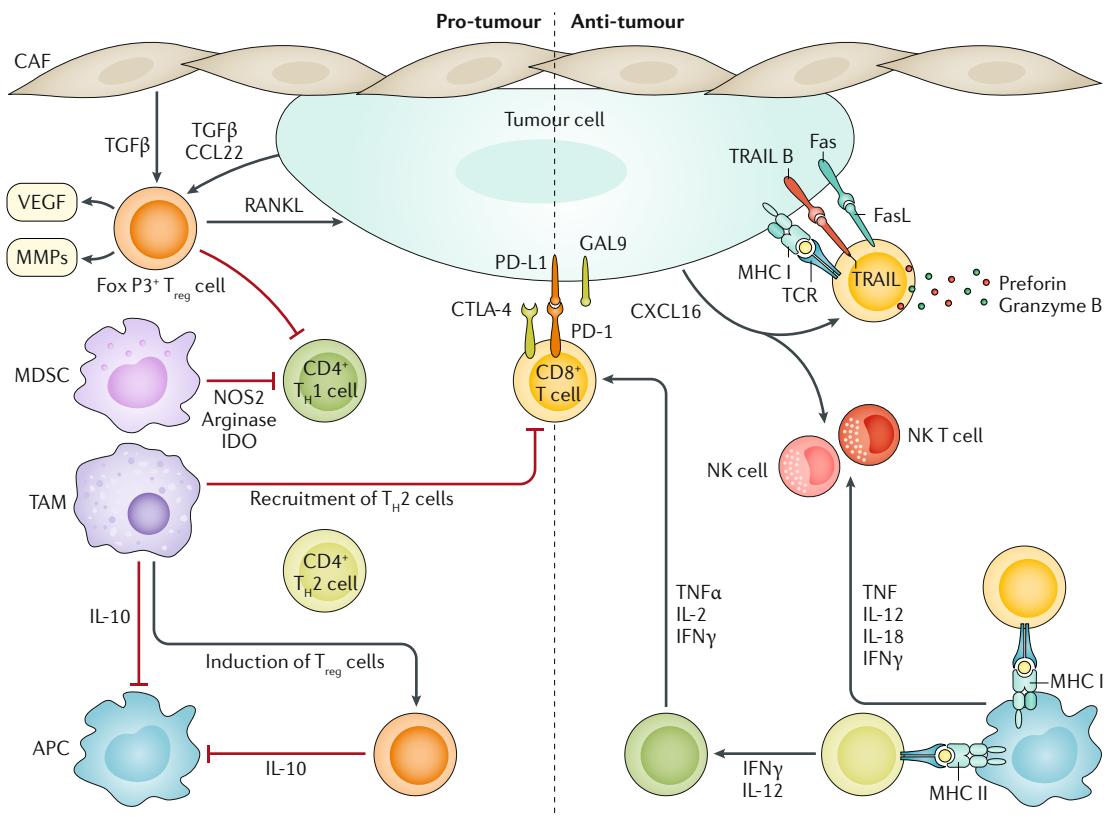


Fig. 3 | Immune crosstalk in breast cancer. The immune reaction to breast cancer is initiated by the neoantigens expressed by tumour cells, encoded by altered genes and presented by antigen-presenting cells (APCs) on major histocompatibility complex class I (MHC I) or MHC II molecules. Neoantigen presentation 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 REF⁷⁵, 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.

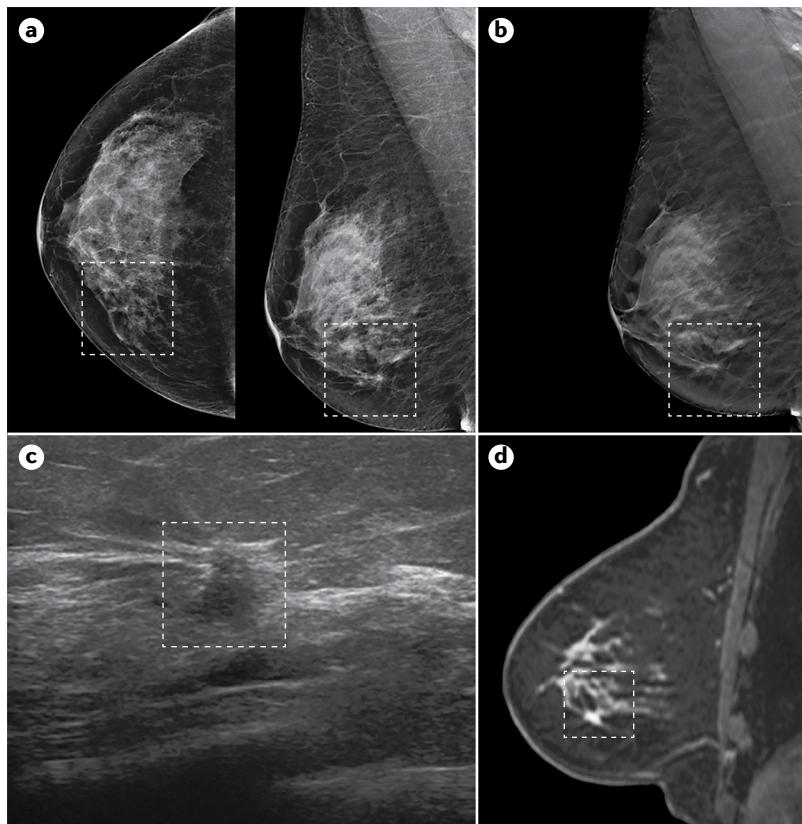


Fig. 4 | Breast cancer imaging. A postmenopausal woman 53 years of age with no family history and no clinical findings underwent routine breast screening with mammography, which detected a lesion in the right breast (panel **a**, cranio-caudal view (left) and mediolateral oblique view (right)). The images 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.

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 healthcare 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

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
- Peritumoural 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 ≥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

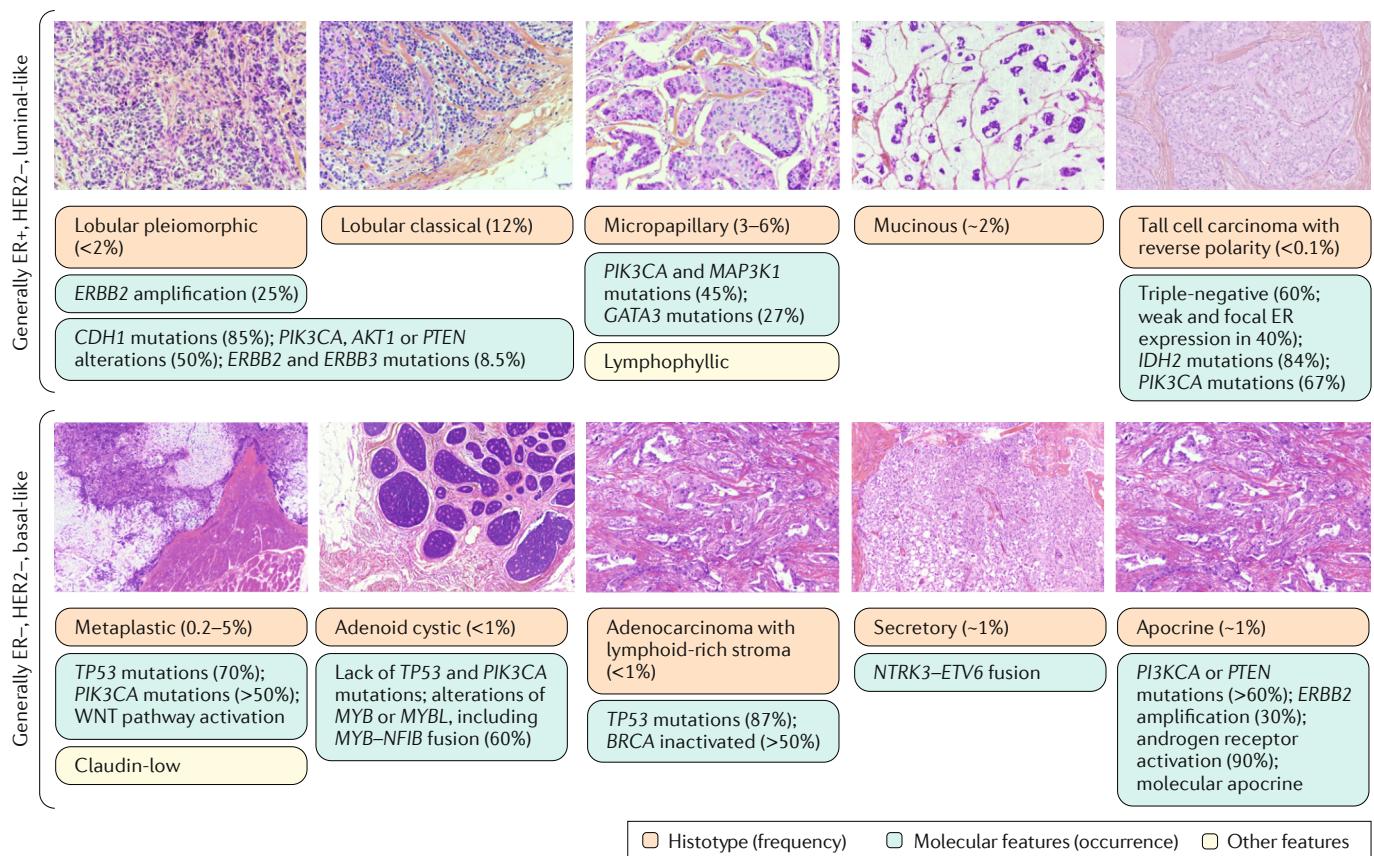


Fig. 5 | Breast cancer histological types and molecular alterations. The WHO classification recognizes different subtypes of invasive breast cancer, some of which are shown here, that harbour specific molecular alterations¹⁰⁷. For example, lobular carcinomas and their precursors (lobular neoplasia) harbour 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-NFIB³²⁷. 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 Bergonié, 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 ≥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 ≥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	<p>Absence of international consensus for scoring and threshold</p> <p>Prognostic value in ER-positive, HER2-negative tumours (primary tumours and post-neoadjuvant tumour residues)</p> <p>Absence of prognostic value in HER2-positive disease or TNBC</p> <p>Predictive of response to neoadjuvant endocrine therapy^a</p> <p>Predictive of response to neoadjuvant chemotherapy</p> <p>If elevated, chemotherapy is often prescribed in ER-positive, HER2-negative tumours</p> <p>Part of the IHC definition of luminal tumours whereby when Ki67 is low, luminal A tumour likely and when Ki67 high, luminal B tumour likely</p>	I I I I Expert opinion Expert opinion Expert opinion
Intrinsic subtypes	Gene expression profile, N-Counter technology	<p>Prognostic</p> <p>Predictive; different responses to neoadjuvant chemotherapy and anti-HER2 therapy according to subtype</p>	II and III 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 ²⁰
PD-L1	IHC; positive if expression in immune cells ≥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.

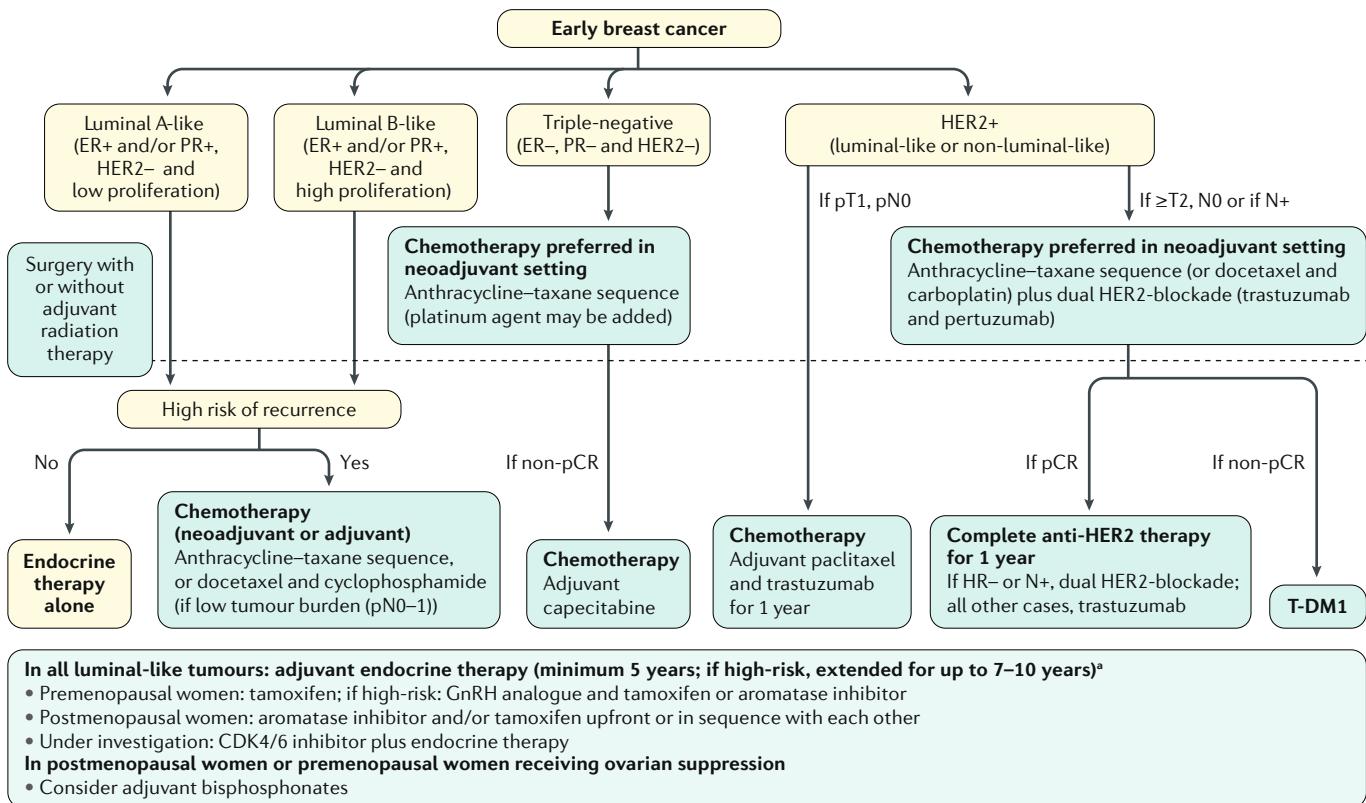


Fig. 6 | Algorithm for early breast cancer. Management of early breast cancer is based on tumour burden and subtype. All patients with oestrogen receptor (ER)-positive disease receive adjuvant endocrine therapy after surgery. If patients are at high risk of recurrence (for example, owing to high-risk 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

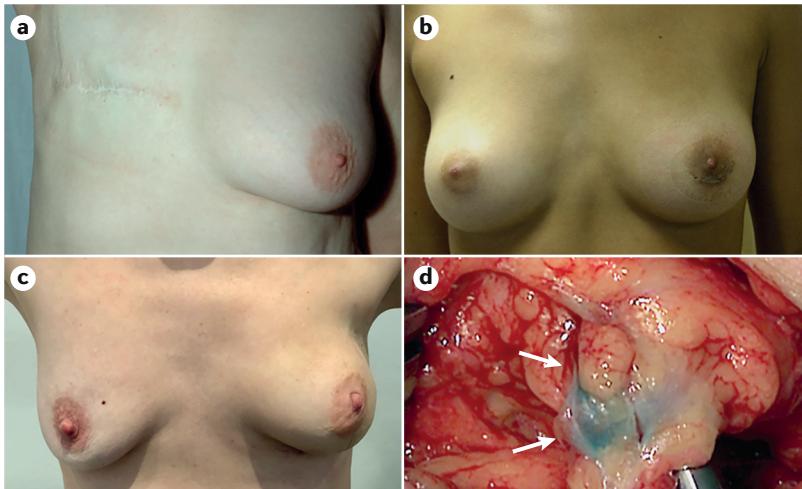


Fig. 7 | Breast-conserving surgery. Current surgical standards of care for breast-conserving surgery not only preserve the organ but also maintain the patient's self-image, femininity and integrity compared with mastectomy (panel **a**; post mastectomy, 8 weeks after surgery). Selection factors for breast-conserving 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 down-staging. 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.

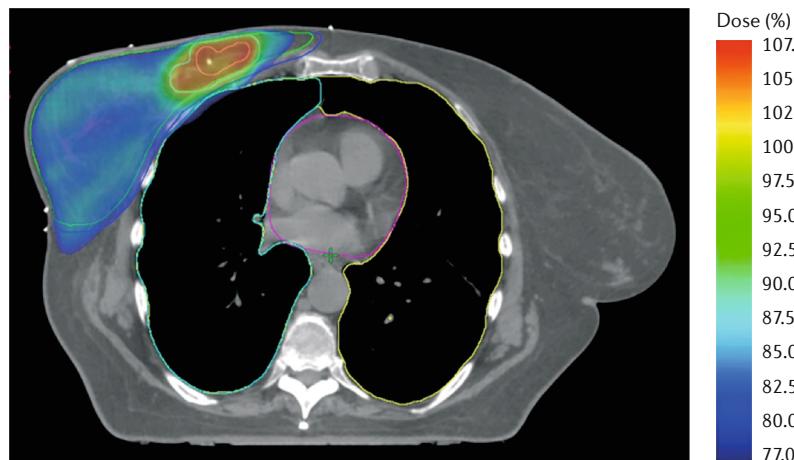


Fig. 8 | Radiation therapy for breast cancer. The schematic illustrates the volumetric intensity-modulated dose distribution at the level of the original tumour location, including a simultaneous integrated boost dose for a patient with early-stage disease who had a medially located primary tumour bed 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 oestradial 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

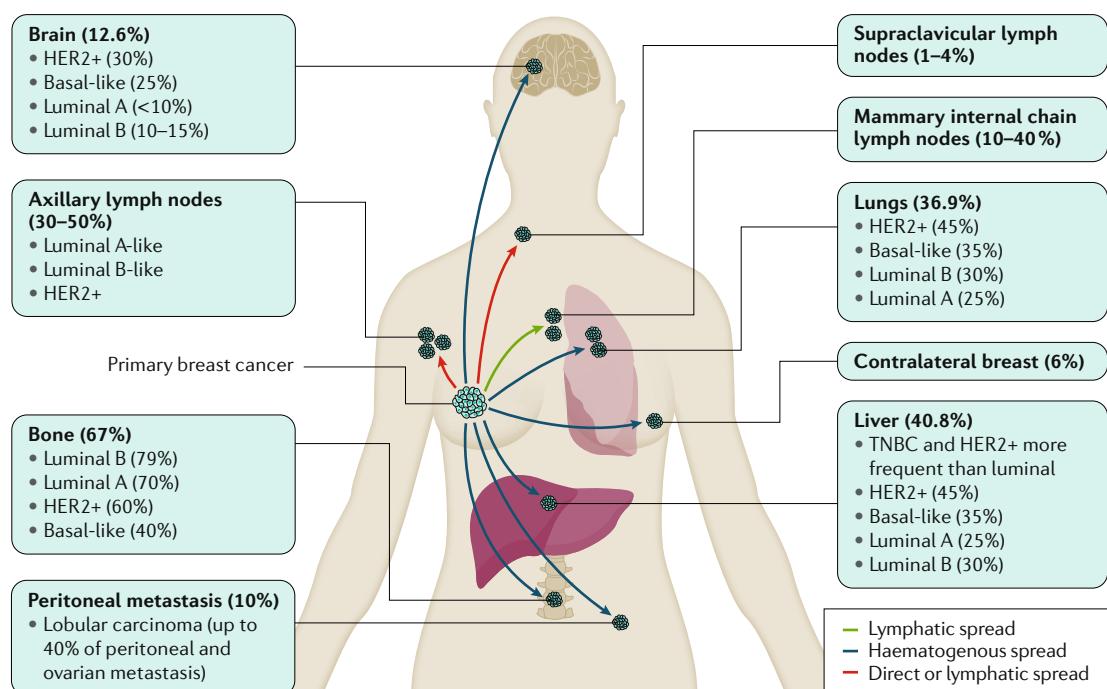


Fig. 9 | Common metastatic sites in breast cancer. The most frequent nodal site is the axillary lymph nodes and the frequency of involvement depends on the size of the tumour. 10–40% of breast cancers have metastasis in the internal mammary chain, influenced by the topography of the tumour in the breast (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

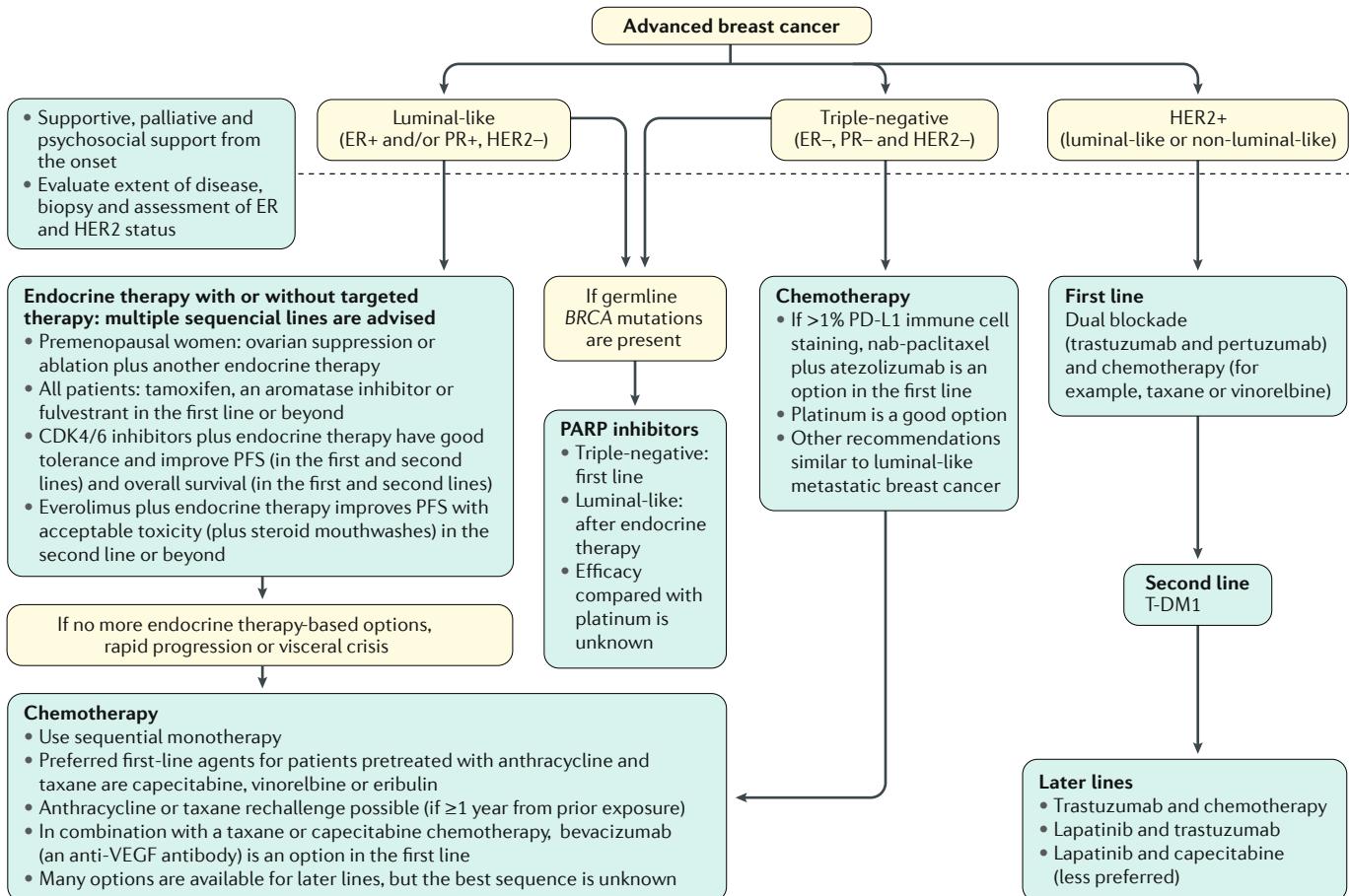


Fig. 10 | Algorithm for advanced breast cancer. Management of advanced breast cancer with distant metastases should be according to subtype as well as disease characteristics and patient preferences. Supportive, palliative and psychosocial support are crucial from the time of diagnosis. Biopsy of a metastatic 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 ≤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*, *IGFIR*, *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 toxicity²⁹⁰.

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

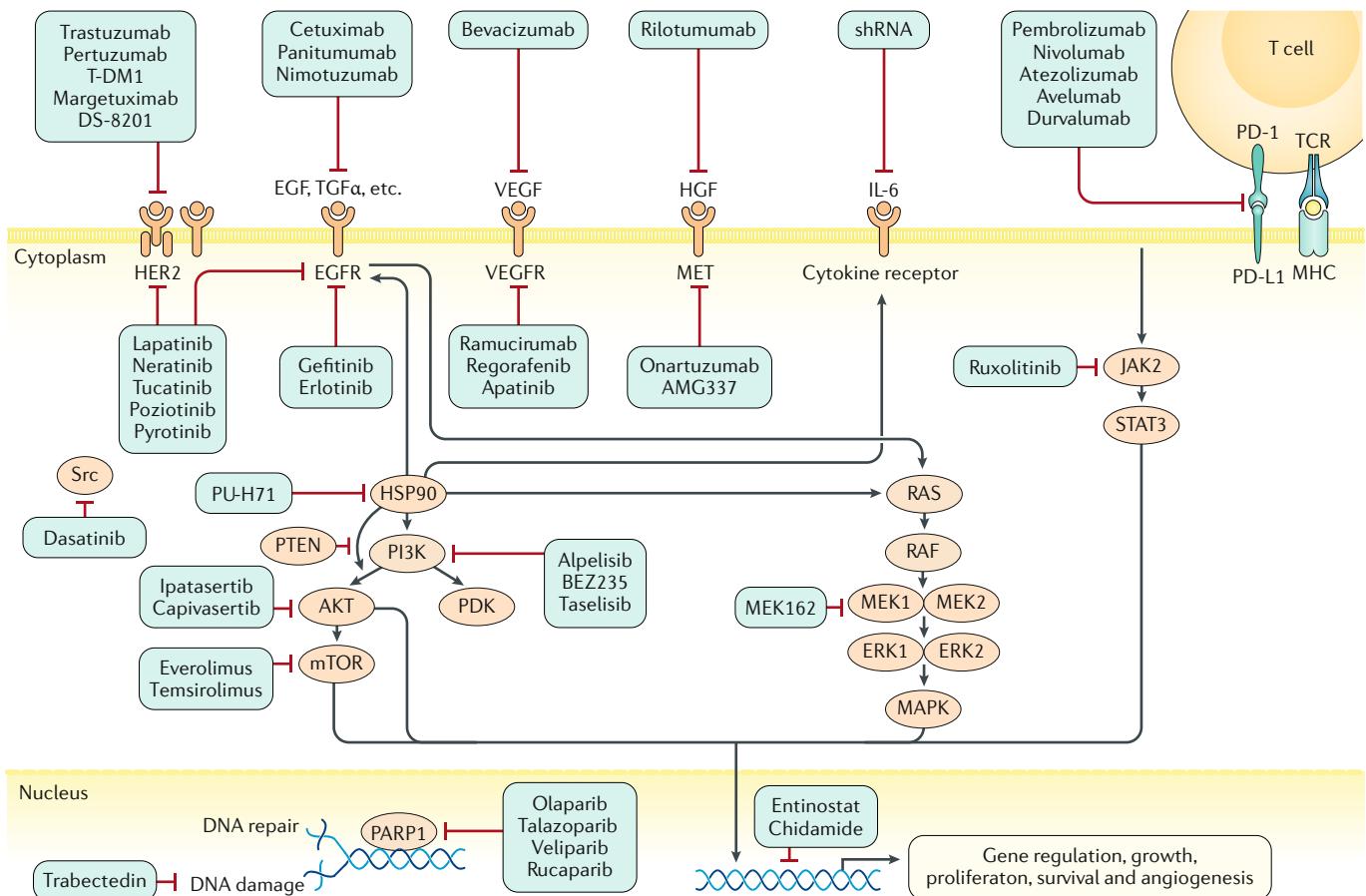


Fig. 11 | Emerging targetable pathways in breast cancer. Different membrane receptor inhibitors have shown activity in breast cancer, including monoclonal antibodies against human epidermal growth factor receptor 2 (HER2), such as trastuzumab, margetuximab and pertuzumab; antibody–drug conjugates, such 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 monochemotherapy^{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 ≥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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- Perou, C. M. et al. Molecular portraits of human breast tumours. *Nature* **406**, 747–752 (2000).
- Cardoso, F. et al. European Breast Cancer Conference manifesto on breast centres/units. *Eur. J. Cancer* **72**, 244–250 (2017).
- Bray, F. et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **68**, 394–424 (2018).
- Bray, F. et al. Cancer Incidence in Five Continents: inclusion criteria, highlights from Volume X and the global status of cancer registration. *Int. J. Cancer* **137**, 2060–2071 (2015).
- Mariotto, A. B., Etzioni, R., Hurlbert, M., Penberthy, L. & Mayer, M. Estimation of the number of women living with metastatic breast cancer in the United States. *Cancer Epidemiol. Biomark. Prev.* **26**, 809–815 (2017).
- Ren, J.-X., Gong, Y., Ling, H., Hu, X. & Shao, Z.-M. Racial/ethnic differences in the outcomes of patients with metastatic breast cancer: contributions of demographic, socioeconomic, tumor and metastatic characteristics. *Breast Cancer Res. Treat.* **173**, 225–237 (2019).
- Torre, L. A., Siegel, R. L., Ward, E. M. & Jemal, A. Global cancer incidence and mortality rates and trends — an update. *Cancer Epidemiol. Biomark. Prev.* **25**, 16–27 (2016).
- Ginsburg, O. et al. The global burden of women's cancers: a grand challenge in global health. *Lancet* **389**, 847–860 (2017).
- Allemani, C. et al. Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet* **385**, 977–1010 (2015).
- Winters, S., Martin, C., Murphy, D. & Shokar, N. K. Breast cancer epidemiology, prevention, and screening. *Prog. Mol. Biol. Transl. Sci.* **151**, 1–32 (2017).
- Hossain, M. S., Ferdous, S. & Karim-Kos, H. E. Breast cancer in South Asia: a Bangladeshi perspective. *Cancer Epidemiol.* **38**, 465–470 (2014).
- Leong, S. P. L. et al. Is breast cancer the same disease in Asian and western countries? *World J. Surg.* **34**, 2308–2324 (2010).
- Bhoo Pathy, N. et al. Breast cancer in a multi-ethnic Asian setting: results from the Singapore–Malaysia hospital-based breast cancer registry. *Breast* **20**, S75–S80 (2011).
- Raina, V. et al. Clinical features and prognostic factors of early breast cancer at a major cancer center in North India. *Indian J. Cancer* **42**, 40 (2005).
- Agarwal, G., Pradeep, P. V., Aggarwal, V., Yip, C.-H. & Cheung, P. S. Y. Spectrum of breast cancer in Asian women. *World J. Surg.* **31**, 1031–1040 (2007).
- Li, C. I., Malone, K. E. & Daling, J. R. Differences in breast cancer hormone receptor status and histology by race and ethnicity among women 50 years of age and older. *Cancer Epidemiol. Biomark. Prev.* **11**, 601–607 (2002).
- Wong, F. Y., Tham, W. Y., Nei, W. L., Lim, C. & Miao, H. Age exerts a continuous effect in the outcomes of Asian breast cancer patients treated with breast-conserving therapy. *Cancer Commun.* **38**, 39 (2018).
- Kohler, B. A. et al. Annual report to the nation on the status of cancer, 1975–2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. *J. Natl Cancer Inst.* **107**, <https://doi.org/10.1093/jnci/djv048> (2015).
- DeSantis, C. E. et al. Breast cancer statistics, 2015: Convergence of incidence rates between black and white women. *Breast Cancer Statistics, 2015. CA Cancer J. Clin.* **66**, 31–42 (2016).
- DeSantis, C. E., Ma, J., Goding Sauer, A., Newman, L. A. & Jemal, A. Breast cancer statistics, 2017, racial disparity in mortality by state: Breast Cancer Statistics, 2017. *CA Cancer J. Clin.* **67**, 439–448 (2017).
- Shiovitz, S. & Korde, L. A. Genetics of breast cancer: a topic in evolution. *Ann. Oncol.* **26**, 1291–1299 (2015).
- Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58 209 women with breast cancer and 101 986 women without the disease. *Lancet* **358**, 1389–1399 (2001).
- Brewer, H. R., Jones, M. E., Schoemaker, M. J., Ashworth, A. & Swerdlow, A. J. Family history and risk of breast cancer: an analysis accounting for family structure. *Breast Cancer Res. Treat.* **165**, 193–200 (2017).
- Huen, M. S. Y., Sy, S. M. H. & Chen, J. BRCA1 and its toolbox for the maintenance of genome integrity. *Nat. Rev. Mol. Cell Biol.* **11**, 138–148 (2010).
- Kuchenbaecker, K. B. et al. Risks of breast, ovarian, and contralateral breast cancer for *BRCA1* and *BRCA2* mutation carriers. *JAMA* **317**, 2402 (2017).
- Balmaga, J., Diez, O., Rubio, I. T. & Cardoso, F. On behalf of the ESMO Guidelines Working Group. BRCA in breast cancer: ESMO clinical practice guidelines. *Ann. Oncol.* **22**, vi31–vi34 (2011).
- Paluch-Shimon, S. et al. Prevention and screening in *BRCA* mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. *Ann. Oncol.* **27**, v103–v110 (2016).
- Daly, M. B. et al. Genetic/familial high-risk assessment: breast and ovarian, version 2.2015. *J. Natl Compr. Cancer Netw.* **14**, 153–162 (2016).
- Forbes, C., Fayter, D., de Kock, S. & Quek, R. G. W. A systematic review of international guidelines and recommendations for the genetic screening, diagnosis, GENETIC COUNSELING and treatment of *BRCA*-mutated breast cancer. *Cancer Manag. Res.* **2019**, 2321–2337 (2019).
- Robson, M. et al. Olaparib for metastatic breast cancer in patients with a germline *BRCA* mutation. *N. Engl. J. Med.* **377**, 523–533 (2017).
- Litton, J. K. et al. Talazoparib in patients with advanced breast cancer and a germline *BRCA* mutation. *N. Engl. J. Med.* **379**, 753–763 (2018).
- FDA. FDA approves olaparib germline *BRCA*-mutated metastatic breast cancer. *Fda.gov* <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-germline-brca-mutated-metastatic-breast-cancer> (2018).
- FDA. FDA approves talazoparib for g*BRCA* HER2-negative locally advanced or metastatic breast cancer. *Fda.gov* <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-talazoparib-gbrcam-her2-negative-locally-advanced-or-metastatic-breast-cancer> (2018).
- Pasche, B. Recent advances in breast cancer genetics. *Cancer Treat. Res.* **141**, 1–10 (2008).
- Cobain, E. F., Milliron, K. J. & Merajver, S. D. Updates on breast cancer genetics: clinical implications of detecting syndromes of inherited increased susceptibility to breast cancer. *Semin. Oncol.* **43**, 528–535 (2016).
- Crawford, B. et al. Multi-gene panel testing for hereditary cancer predisposition in unsolved high-risk breast and ovarian cancer patients. *Breast Cancer Res. Treat.* **163**, 383–390 (2017).
- Taylor, A. et al. Consensus for genes to be included on cancer panel tests offered by UK genetics services: guidelines of the UK Cancer Genetics Group. *J. Med. Genet.* **55**, 372–377 (2018).
- Althuis, M. D., Dozier, J. M., Anderson, W. F., Devesa, S. S. & Brinton, L. A. Global trends in breast cancer incidence and mortality 1973–1997. *Int. J. Epidemiol.* **34**, 405–412 (2005).
- Colditz, G. A., Sellers, T. A. & Trapido, E. Epidemiology — identifying the causes and preventability of cancer? *Nat. Rev. Cancer* **6**, 75–83 (2006).
- Britt, K., Ashworth, A. & Smalley, M. Pregnancy and the risk of breast cancer. *Endocr. Relat. Cancer* **14**, 907–933 (2007).

41. Siwko, S. K. et al. Evidence that an early pregnancy causes a persistent decrease in the number of functional mammary epithelial stem cells — implications for pregnancy-induced protection against breast cancer. *Stem Cells* **26**, 3205–3209 (2008).
42. Hilakivi-Clarke, L., de Assis, S. & Warri, A. Exposures to synthetic estrogens at different times during the life, and their effect on breast cancer risk. *J. Mammary Gland. Biol. Neoplasia* **18**, 25–42 (2013).
43. Danaei, G., Vander Hoorn, S., Lopez, A. D., Murray, C. J. & Ezzati, M. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. *Lancet* **366**, 1784–1793 (2005).
44. Chen, W. Y., Rosner, B., Hankinson, S. E., Colditz, G. A. & Willett, W. C. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. *JAMA* **306**, 1884 (2011).
45. Singletary, K. W. & Gapstur, S. M. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. *JAMA* **286**, 2143 (2001).
46. Smith-Warner, S. A. et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA* **279**, 535 (1998).
47. Bandera, E. V., Maskarinec, G., Romieu, I. & John, E. M. Racial and ethnic disparities in the impact of obesity on breast cancer risk and survival: a global perspective. *Adv. Nutr.* **6**, 803–819 (2015).
48. Picon-Ruiz, M., Morata-Tarifa, C., Valle-Goffin, J. J., Friedman, E. R. & Slingerland, J. M. Obesity and adverse breast cancer risk and outcome: mechanistic insights and strategies for intervention: breast cancer, inflammation, and obesity. *CA Cancer J. Clin.* **67**, 378–397 (2017).
49. Shieh, Y. et al. Body mass index, mammographic density, and breast cancer risk by estrogen receptor subtype. *Breast Cancer Res.* **21**, 48 (2019).
50. Suzuki, Y., Tsunoda, H., Kimura, T. & Yamauchi, H. BMI change and abdominal circumference are risk factors for breast cancer, even in Asian women. *Breast Cancer Res. Treat.* **166**, 919–925 (2017).
51. Del Pup, L., Codacci-Pisanelli, G. & Peccatori, F. Breast cancer risk of hormonal contraception: counselling considering new evidence. *Crit. Rev. Oncol. Hematol.* **137**, 123–130 (2019).
52. Busund, M. et al. Progestin-only and combined oral contraceptives and receptor-defined premenopausal breast cancer risk: the Norwegian Women and Cancer Study. *Int. J. Cancer* **142**, 2293–2302 (2018).
53. Mørch, L. S. et al. Contemporary hormonal contraception and the risk of breast cancer. *N. Engl. J. Med.* **377**, 2228–2239 (2017).
54. Ganz, P. A. et al. Supportive care after curative treatment for breast cancer (survivorship care): resource allocations in low- and middle-income countries. A Breast Health Global Initiative 2013 consensus statement. *Breast* **22**, 606–615 (2013).
55. Burris, J. L., Armes, K. & Sterba, K. R. A closer look at unmet needs at the end of primary treatment for breast cancer: a longitudinal pilot study. *Behav. Med.* **41**, 69–76 (2015).
56. Coughlin, S. S., Yoo, W., Whitehead, M. S. & Smith, S. A. Advancing breast cancer survivorship among African-American women. *Breast Cancer Res. Treat.* **153**, 253–261 (2015).
57. Bodai, B. Breast cancer survivorship: a comprehensive review of long-term medical issues and lifestyle recommendations. *Perm. J.* **19**, 48–79 (2015).
58. Ho, P. J., Gernaat, S. A. M., Hartman, M. & Verkooijen, H. M. Health-related quality of life in Asian patients with breast cancer: a systematic review. *BMJ Open* **8**, e020512 (2018).
59. Miyashita, M. et al. Unmet information needs and quality of life in young breast cancer survivors in Japan. *Cancer Nurs.* **38**, E1–E11 (2015).
60. Bombonati, A. & Sgroi, D. C. The molecular pathology of breast cancer progression. *J. Pathol.* **223**, 307–317 (2011).
61. Ellis, M. J. et al. Whole-genome analysis informs breast cancer response to aromatase inhibition. *Nature* **486**, 353–360 (2012).
62. Lopez-Garcia, M. A., Geyer, F. C., Lacroix-Triki, M., Marchiò, C. & Reis-Filho, J. S. Breast cancer precursors revisited: molecular features and progression pathways: molecular evolution of breast cancer. *Histopathology* **57**, 171–192 (2010).
63. Nik-Zainal, S. et al. Landscape of somatic mutations in 560 breast cancer whole-genome sequences. *Nature* **534**, 47–54 (2016).
64. Yates, L. R. & Desmedt, C. Translational genomics: practical applications of the genomic revolution in breast cancer. *Clin. Cancer Res.* **23**, 2630–2639 (2017).
65. Heitzer, E., Haque, I. S., Roberts, C. E. S. & Speicher, M. R. Current and future perspectives of liquid biopsies in genomics-driven oncology. *Nat. Rev. Genet.* **20**, 71–88 (2019).
66. Ediriweera, M. K., Tennekoole, K. H. & Samarakoon, S. R. Emerging role of histone deacetylase inhibitors as anti-breast-cancer agents. *Drug Discov. Today* **24**, 685–702 (2019).
67. Munster, P. N. et al. A phase II study of the histone deacetylase inhibitor vorinostat combined with tamoxifen for the treatment of patients with hormone therapy-resistant breast cancer. *Br. J. Cancer* **104**, 1828–1835 (2011).
68. Zhou, Y., Wang, Y., Zhang, K., Zhu, J. & Ning, Z. Reverse effect of chidamide on endocrine resistance in estrogen receptor-positive breast cancer. *J. Shenzhen Univ. Sci. Eng.* **35**, 359 (2018).
69. Jiang, Z. et al. Phase III trial of chidamide, a subtype-selective histone deacetylase (HDAC) inhibitor, in combination with exemestane in patients with hormone receptor-positive advanced breast cancer [abstract]. *Ann. Oncol.* **29**, 2830_PR (2018).
70. Williams, C. & Lin, C.-Y. Oestrogen receptors in breast cancer: basic mechanisms and clinical implications. *Eccancermedicalscience* **7**, 370 (2013).
71. Levin, E. R. & Pietras, R. J. Estrogen receptors outside the nucleus in breast cancer. *Breast Cancer Res. Treat.* **108**, 351–361 (2008).
72. Santen, R. J. Clinical review: effect of endocrine therapies on bone in breast cancer patients. *J. Clin. Endocrinol. Metab.* **96**, 308–319 (2011).
73. Ruffell, B. et al. Leukocyte composition of human breast cancer. *Proc. Natl. Acad. Sci. USA* **109**, 2796–2801 (2012).
74. Solinas, C., Carbognin, L., De Silva, P., Criscitiello, C. & Lambertini, M. Tumor-infiltrating lymphocytes in breast cancer according to tumor subtype: current state of the art. *Breast* **35**, 142–150 (2017).
75. Nagarajan, D. & McArdle, S. Immune landscape of breast cancers. *Biomedicines* **6**, 20 (2018).
76. Savas, P. et al. Clinical relevance of host immunity in breast cancer: from TILs to the clinic. *Nat. Rev. Clin. Oncol.* **13**, 228–241 (2016).
77. Dieci, M. V. et al. Update on tumor-infiltrating lymphocytes (TILs) in breast cancer, including recommendations to assess TILs in residual disease after neoadjuvant therapy and in carcinoma in situ: a report of the International Immuno-Oncology Biomarker Working Group on Breast Cancer. *Semin. Cancer Biol.* **52**, 16–25 (2018).
78. Boudreau, A., van't Veer, L. J. & Bissell, M. J. An 'elite hacker': breast tumors exploit the normal microenvironment program to instruct their progression and biological diversity. *Cell Adhes. Migr.* **6**, 236–248 (2012).
79. Smyth, M. J., Dunn, G. P. & Schreiber, R. D. Cancer immunosurveillance and immunoediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity. *Adv. Immunol.* **90**, 1–50 (2006).
80. Schreiber, R. D., Old, L. J. & Smyth, M. J. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science* **331**, 1565–1570 (2011).
81. Buonomo, O. C. et al. New insights into the metastatic behavior after breast cancer surgery, according to well-established clinicopathological variables and molecular subtypes. *PLOS ONE* **12**, e0184680 (2017).
82. Gobbini, E. et al. Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort. *Eur. J. Cancer* **96**, 17–24 (2018).
83. Santé Publique France. Breast cancer [French]. *Santepubliquefrance.fr* <https://www.santepubliquefrance.fr/maladies-et-traumatismes/cancers/cancer-du-sein> (2019).
84. Zhang, K. et al. Clinical value of circulating ESR1 mutations for patients with metastatic breast cancer: a meta-analysis. *Cancer Manag. Res.* **10**, 2573–2580 (2018).
85. Yates, L. R. et al. Genomic evolution of breast cancer metastasis and relapse. *Cancer Cell* **32**, 169–184.e7 (2017).
86. Gingras, I., Salgado, R. & Ignatiadis, M. Liquid biopsy: will it be the 'magic tool' for monitoring response of solid tumors to anticancer therapies? *Curr. Opin. Oncol.* **27**, 560–567 (2015).
87. Aurilio, G. et al. A meta-analysis of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 discordance between primary breast cancer and metastases. *Eur. J. Cancer* **50**, 277–289 (2014).
88. Independent, U. K. Panel on breast cancer screening. The benefits and harms of breast cancer screening: an independent review. *Lancet* **380**, 1778–1786 (2012).
89. Nelson, H. D. et al. Effectiveness of breast cancer screening: systematic review and meta-analysis to update the 2009 U.S. Preventive Services Task Force recommendation. *Ann. Intern. Med.* **164**, 244–255 (2016).
90. Lauby-Secretan, B. et al. Breast-cancer screening — viewpoint of the IARC Working Group. *N. Engl. J. Med.* **372**, 2353–2358 (2015).
91. Houssami, N. Overdiagnosis of breast cancer in population screening: does it make breast screening worthless? *Cancer Biol. Med.* **14**, 1–8 (2017).
92. Suhrke, P. et al. Effect of mammography screening on surgical treatment for breast cancer in Norway: comparative analysis of cancer registry data. *BMJ* **343**, d4692–d4692 (2011).
93. Stang, A., Kääb-Sanyal, V., Hense, H.-W., Becker, N. & Kuss, O. Effect of mammography screening on surgical treatment for breast cancer: a nationwide analysis of hospitalization rates in Germany 2005–2009. *Eur. J. Epidemiol.* **28**, 689–696 (2013).
94. IARC Handbooks of Cancer Prevention. Breast Cancer Screening (Volume 15). *Iarc.fr* <http://publications.iarc.fr/Book-And-Report-Series/Iarc-Handbooks-Of-Cancer-Prevention/Breast-Cancer-Screening-2016> (2016).
95. Nelson, H. D. et al. Harms of breast cancer screening: systematic review to update the 2009 U.S. Preventive Services Task Force recommendation. *Ann. Intern. Med.* **164**, 256–267 (2016).
96. Carter, J. L., Coletti, R. J. & Harris, R. P. Quantifying and monitoring overdiagnosis in cancer screening: a systematic review of methods. *BMJ* **350**, g7773 (2015).
97. Saslow, D. et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J. Clin.* **57**, 75–89 (2007).
98. Phi, X.-A. et al. Magnetic resonance imaging improves breast screening sensitivity in BRCA mutation carriers age ≥ 50 years: evidence from an individual patient data meta-analysis. *J. Clin. Oncol.* **33**, 349–356 (2015).
99. Sardanelli, F. et al. Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. *Eur. J. Cancer* **46**, 1296–1316 (2010).
100. Melnikow, J. et al. Supplemental screening for breast cancer in women with dense breasts: a systematic review for the U.S. preventive services task force. *Ann. Intern. Med.* **164**, 268–278 (2016).
101. Houssami, N. & Lee, C. I. The impact of legislation mandating breast density notification — review of the evidence. *Breast* **42**, 102–112 (2018).
102. Marinovich, M. L., Hunter, K. E., Macaskill, P. & Houssami, N. Breast cancer screening using tomosynthesis or mammography: a meta-analysis of cancer detection and recall. *J. Natl. Cancer Inst.* **110**, 942–949 (2018).
103. Irwig, L., Macaskill, P. & Houssami, N. Evidence relevant to the investigation of breast symptoms: the triple test. *Breast* **11**, 215–220 (2002).
104. Houssami, N., Ciatto, S., Turner, R. M., Cody, H. S. & Macaskill, P. Preoperative ultrasound-guided biopsy of axillary nodes in invasive breast cancer: meta-analysis of its accuracy and utility in staging the axilla. *Ann. Surg.* **254**, 243–251 (2011).
105. Morrow, M., Waters, J. & Morris, E. MRI for breast cancer screening, diagnosis, and treatment. *Lancet* **378**, 1804–1811 (2011).
106. Sirigley, J. R. et al. Standardized synoptic cancer pathology reporting: a population-based approach. *J. Surg. Oncol.* **99**, 517–524 (2009).
107. World Health Organisation. *WHO Classification of Tumours of the Breast, Fourth Edition*. (World Health Organization, 2012).
108. Elston, C. W. & Ellis, I. O. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology* **19**, 403–410 (1991).
109. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. *Nccn.org* https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (2018).
110. Curigliano, G. et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. *Ann. Oncol.* **28**, 1700–1712 (2017).

111. Senkus, E. et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **24** (Suppl. 6), vi7–vi23 (2013).
112. Hammond, M. E. H. et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J. Clin. Oncol.* **28**, 2784–2795 (2010).
113. Wolff, A. C. et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. *J. Clin. Oncol.* **36**, 2105–2122 (2018).
114. Dowsett, M. et al. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. *J. Natl Cancer Inst.* **103**, 1656–1664 (2011).
115. Rakha, E. A. et al. The prognostic significance of lymphovascular invasion in invasive breast carcinoma. *Cancer* **118**, 3670–3680 (2012).
116. Barrio, A. V. & Morrow, M. Appropriate margin for lumpectomy excision of invasive breast cancer. *Chin. Clin. Oncol.* **5**, 35–35 (2016).
117. Chung, A. et al. Impact of consensus guidelines by the Society of Surgical Oncology and the American Society for Radiation Oncology on margins for breast-conserving surgery in stages I and II invasive breast cancer. *Ann. Surg. Oncol.* **22**, 422–427 (2015).
118. Schulman, A. M. et al. Reexcision surgery for breast cancer: an analysis of the American Society of Breast Surgeons (ASBrS) MasterySM database following the SSO-ASTRO “no ink on tumor” guidelines. *Ann. Surg. Oncol.* **24**, 52–58 (2017).
119. Morrow, M. et al. Society of Surgical Oncology–American Society for Radiation Oncology–American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. *Pract. Radiat. Oncol.* **6**, 287–295 (2016).
120. Morrow, M. et al. Society of Surgical Oncology–American Society for Radiation Oncology–American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. *J. Clin. Oncol.* **34**, 4040–4046 (2016).
121. Moran, M. S. et al. Society of Surgical Oncology–American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **88**, 553–564 (2014).
122. Amin, M. B. et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more ‘personalized’ approach to cancer staging. *CA Cancer J. Clin.* **67**, 93–99 (2017).
123. Tao, L. et al. Breast cancer mortality in older and younger breast cancer patients in California. *Cancer Epidemiol. Biomark. Prev.* **28**, 303–310 (2018).
124. Salgado, R. et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. *Ann. Oncol.* **26**, 259–271 (2015).
125. Green, A. R. et al. Nottingham Prognostic Index Plus: validation of a clinical decision making tool in breast cancer in an independent series. *J. Pathol. Clin. Res.* **2**, 32–40 (2016).
126. Candido dos Reis, F. J. et al. An updated PREDICT breast cancer prognostication and treatment benefit prediction model with independent validation. *Breast Cancer Res.* **19**, 58 (2017).
127. Phung, M. T., Tin Tin, S. & Elwood, J. M. Prognostic models for breast cancer: a systematic review. *BMC Cancer* **19**, 230 (2019).
128. Senkus, E. et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **26** (Suppl. 5), v8–v30 (2015).
129. Cortazar, P. et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* **384**, 164–172 (2014).
130. Cardoso, F. et al. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. *N. Engl. J. Med.* **375**, 717–729 (2016).
131. Sparano, J. A. et al. Prospective validation of a 21-gene expression assay in breast cancer. *N. Engl. J. Med.* **373**, 2005–2014 (2015).
132. Sparano, J. A. et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N. Engl. J. Med.* **379**, 111–121 (2018).
133. Harris, L. N. et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline. *J. Clin. Oncol.* **34**, 1134–1150 (2016).
134. Krop, I. et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. *J. Clin. Oncol.* **35**, 2838–2847 (2017).
135. Nitz, U. et al. West German Study PlanB trial: adjuvant four cycles of epirubicin and cyclophosphamide plus docetaxel versus six cycles of docetaxel and cyclophosphamide in HER2-negative early breast cancer. *J. Clin. Oncol.* **37**, 799–808 (2019).
136. Sestak, I. Risk stratification in early breast cancer in premenopausal and postmenopausal women: integrating genomic assays with clinicopathological features. *Curr. Opin. Oncol.* **1**, 29–34 (2018).
137. McLaughlin, S. A. Surgical management of the breast: breast conservation therapy and mastectomy. *Surg. Clin. North Am.* **93**, 411–428 (2013).
138. Margenthaler, J. A. & Ollila, D. W. Breast conservation therapy versus mastectomy: shared decision-making strategies and overcoming decision-making conflicts in your patients. *Ann. Surg. Oncol.* **23**, 3133–3137 (2016).
139. Buchholz, T. A., Mittendorf, E. A. & Hunt, K. K. Surgical considerations after neoadjuvant chemotherapy: breast conservation therapy. *J. Natl Cancer Inst. Monogr.* **2015**, 11–14 (2015).
140. Houssami, N., Macaskill, P., Luke Marinovich, M. & Morrow, M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. *Ann. Surg. Oncol.* **21**, 717–730 (2014).
141. Morrow, M., Harris, J. R. & Schnitt, S. J. Surgical margins in lumpectomy for breast cancer — bigger is not better. *N. Engl. J. Med.* **367**, 79–82 (2012). This commentary and the meta-analysis by Houssami et al. (2014) settled the decade-long discussions about surgical resection margins and are, therefore, landmark contributions.
142. Tan, M. P., Sitoh, N. Y. & Sim, A. S. The value of intraoperative frozen section analysis for margin status in breast conservation surgery in a nontertiary institution. *Int. J. Breast Cancer* <https://doi.org/10.1155/2014/715404> (2014).
143. Boughey, J. C. et al. Impact of analysis of frozen-section margin on reoperation rates in women undergoing lumpectomy for breast cancer: evaluation of the National Surgical Quality Improvement Program data. *Surgery* **156**, 190–197 (2014).
144. Haloua, M. H. et al. A systematic review of oncoplastic breast-conserving surgery: current weaknesses and future prospects. *Ann. Surg.* **257**, 609–620 (2013).
145. Benelli, L. A new periareolar mammoplasty: the ‘round block’ technique. *Aesthetic Plast. Surg.* **14**, 93–100 (1990).
146. Clough, K. B., Kaufman, G. J., Nos, C., Buccimazza, I. & Sarfati, I. M. Improving breast cancer surgery: a classification and quadrant per quadrant atlas for oncoplastic surgery. *Ann. Surg. Oncol.* **17**, 1375–1391 (2010).
147. Yao, K., Winchester, D. J., Czechura, T. & Huo, D. Contralateral prophylactic mastectomy and survival: report from the national cancer data base, 1998–2002. *Breast Cancer Res. Treat.* **142**, 465–476 (2013).
148. Vila, J., Gandini, S. & Gentilini, O. Overall survival according to type of surgery in young (<40 years) early breast cancer patients: a systematic meta-analysis comparing breast-conserving surgery versus mastectomy. *Breast* **24**, 175–181 (2015).
149. Lucci, A. et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group trial Z0011. *J. Clin. Oncol.* **25**, 3657–3663 (2007).
150. Krag, D. N. et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol.* **11**, 927–933 (2010). This large clinical trial confirms that there is no overall survival difference between sentinel lymph node biopsy and axillary lymph node dissection.
151. Veronesi, U. et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N. Engl. J. Med.* **349**, 546–553 (2003).
152. Giuliano, A. E. et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: long-term follow-up from the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 randomized trial. *Ann. Surg.* **264**, 413–420 (2016).
153. Balic, M., Thomassen, C., Würstlein, R., Gnant, M. & Harbeck, N. St. Gallen/Vienna 2019: a brief summary of the consensus discussion on the optimal primary breast cancer treatment. *Breast Care* **14**, 1–8 (2019).
154. Kaidar-Person, O., Meattini, I. & Poortmans, P. M. P. Between uncertainties and overtreatment. *Int. J. Radiat. Oncol.* **104**, 15–16 (2019).
155. Kuehn, T. et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol.* **14**, 609–618 (2013).
156. King, T. A. & Morrow, M. Surgical issues in patients with breast cancer receiving neoadjuvant chemotherapy. *Nat. Rev. Clin. Oncol.* **12**, 335–343 (2015).
157. Giuliano, A. E. et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* **305**, 569–575 (2011). This meta-analysis underlines that the contribution of radiation therapy should always be the standard approach for breast-conserving therapy.
158. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* **378**, 1707–1716 (2011). This meta-analysis helps us to better identify those patients who would benefit most from radiation therapy after mastectomy.
159. EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 81 35 women in 22 randomised trials. *Lancet* **383**, 2127–2135 (2014). This meta-analysis helps us to better identify those patients who would benefit most from radiation therapy after mastectomy.
160. Jatoi, I., Benson, J. R. & Kunkler, I. Hypothesis: can the abscopal effect explain the impact of adjuvant radiotherapy on breast cancer mortality? *NPJ Breast Cancer* **4**, 8 (2018).
161. Bartelink, H. et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol.* **16**, 47–56 (2015).
162. Poortmans, P. M. Postmastectomy radiation in breast cancer with one to three involved lymph nodes: ending the debate. *Lancet* **383**, 2104–2106 (2014).
163. Poortmans, P. M. et al. Internal mammary and medial supraclavicular irradiation in breast cancer. *N. Engl. J. Med.* **373**, 317–327 (2015).
164. Whelan, T. J. et al. Regional nodal irradiation in early-stage breast cancer. *N. Engl. J. Med.* **373**, 307–316 (2015).
165. Thorsen, L. B. J. et al. DBCG-IMN: a population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. *J. Clin. Oncol.* **34**, 314–320 (2016).
166. Curigliano, G. et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. *Ann. Oncol.* **29**, 2153–2153 (2018).
167. Olai, C. & Hurvitz, S. A. The debate over post-mastectomy radiotherapy should continue: breast cancer. *Nat. Rev. Clin. Oncol.* **12**, 567–568 (2015).
168. Recht, A. et al. Postmastectomy radiotherapy: an American Society of Radiation Oncology, and Society of Surgical Oncology focused guideline update. *Ann. Surg. Oncol.* **24**, 38–51 (2017).
169. Dodwell, D. et al. Abstract GS4-02: regional lymph node irradiation in early stage breast cancer: an EBCTCG meta-analysis of 13,000 women in 14 trials. in *General Session Abstracts GS4-02-GS4-02* <https://doi.org/10.1158/1538-7445.SACBS18-GS4-02> (American Association for Cancer Research, 2019).
170. Kunkler, I. H., Canney, P., van Tienhoven, G. & Russell, N. S. MRC/EORTC (BIG 2-04) SUPREMO Trial Management Group. Elucidating the role of chest wall irradiation in ‘intermediate-risk’ breast cancer: The MRC/EORTC SUPREMO trial. *Clin. Oncol.* **R. Coll. Radiol.** **20**, 31–34 (2008).
171. Poortmans, P., Aznar, M. & Bartelink, H. Quality indicators for breast cancer: revisiting historical evidence in the context of technology changes. *Semin. Radiat. Oncol.* **22**, 29–39 (2012).
172. Osman, S. O. S., Hol, S., Poortmans, P. M. & Essers, M. Volumetric modulated arc therapy and breath-hold in

- image-guided locoregional left-sided breast irradiation. *Radiat. Oncol.* **112**, 17–22 (2014).
173. Essers, M., Poortmans, P. M., Verschueren, K., Hol, S. & Cobben, D. C. P. Should breathing adapted radiotherapy also be applied for right-sided breast irradiation? *Acta Oncol.* **55**, 460–465 (2016).
174. Poortmans, P. M. P., Arenas, M. & Livi, L. Over-irradiation. *Breast* **31**, 295–302 (2017).
175. Blamey, R. W. et al. Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial. *Eur. J. Cancer* **49**, 2294–2302 (2013).
176. McGuire, S. E. et al. Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve a pathologic complete response to neoadjuvant chemotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* **68**, 1004–1009 (2007).
177. Mamounas, E. P. et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of national surgical adjuvant breast and bowel project B-18 and B-27. *J. Clin. Oncol.* **30**, 3960–3966 (2012).
178. Krug, D. et al. Individualization of post-mastectomy radiotherapy and regional nodal irradiation based on treatment response after neoadjuvant chemotherapy for breast cancer: a systematic review. *Strahlenther. Onkol.* **194**, 607–618 (2018).
179. Amoroso, V. et al. International Expert Consensus on Primary Systemic Therapy in the Management of Early Breast Cancer: Highlights of the Fifth Symposium on Primary Systemic Therapy in the Management of Operable Breast Cancer, Cremona, Italy (2013). *J. Natl Cancer Inst. Monogr.* **2015**, 90–96 (2015).
180. Offersen, B. V. et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer, version 1.1. *Radiat. Oncol.* **118**, 205–208 (2016).
181. Haviland, J. S. et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol.* **14**, 1086–1094 (2013).
182. Whelan, T. J. et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N. Engl. J. Med.* **362**, 513–520 (2010).
183. Wang, S.-L. et al. Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial. *Lancet Oncol.* **20**, 352–360 (2019).
184. Brouwers, P. J. A. M. et al. Predictors for poor cosmetic outcome in patients with early stage breast cancer treated with breast conserving therapy: results of the Young Boost trial. *Radiat. Oncol.* **128**, 434–441 (2018).
185. Polgár, C. et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the groupe européen de curithérapie-european society for therapeutic radiology and oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). *Radiat. Oncol.* **94**, 264–273 (2010).
186. Correa, C. et al. Accelerated partial breast irradiation: executive summary for the update of an ASTRO Evidence-Based. *Consensus Statement. Pract. Radiat. Oncol.* **7**, 73–79 (2017).
187. Miranda, F. A. et al. Accelerated partial breast irradiation: current status with a focus on clinical practice. *Breast J.* <https://doi.org/10.1111/tbj.13164> (2018).
188. Marta, G. N. et al. Effectiveness of different accelerated partial breast irradiation techniques for the treatment of breast cancer patients: systematic review using indirect comparisons of randomized clinical trials. *Rep. Pract. Oncol. Radiother.* **24**, 165–174 (2019).
189. Veronesi, U. et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol.* **14**, 1269–1277 (2013).
190. Vaidya, J. S. et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* **383**, 603–613 (2014).
191. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* **378**, 771–784 (2011).
192. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomized trials. *Lancet* **379**, 432–444 (2012).
- This meta-analysis demonstrates the benefits of adjuvant chemotherapy in early breast cancer.**
193. Rastogi, P. et al. Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. *J. Clin. Oncol.* **26**, 778–785 (2008).
194. Francis, P. A. et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N. Engl. J. Med.* **379**, 122–137 (2018).
195. Gnant, M. et al. Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozole plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12. *Ann. Oncol.* **26**, 513–520 (2015).
196. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet* **386**, 1341–1352 (2015).
- This meta-analysis demonstrates the benefit of the two individual options for adjuvant endocrine therapy in postmenopausal patients with early breast cancer.**
197. Pan, H. et al. 20-Year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. *N. Engl. J. Med.* **377**, 1836–1846 (2017).
198. Gray, R. et al. Increasing the dose density of adjuvant chemotherapy by shortening intervals between courses or by sequential drug administration significantly reduces both disease recurrence and breast cancer mortality: an EBCTCG meta-analysis of 21,000 women in 16 randomised trials [abstract]. *SABCS GS1-GS01* (2018).
199. Finn, R. S. et al. Palbociclib and letrozole in advanced breast cancer. *N. Engl. J. Med.* **375**, 1925–1936 (2016).
200. Hortobagyi, G. N. et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N. Engl. J. Med.* **375**, 1738–1748 (2016).
201. Goetz, M. P. et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J. Clin. Oncol.* **35**, 3638–3646 (2017).
202. Mackey, J. R. et al. Long-term outcomes after adjuvant treatment of sequential versus combination docetaxel with doxorubicin and cyclophosphamide in node-positive breast cancer: BCIRG-005 randomized trial. *Ann. Oncol.* **27**, 1041–1047 (2016).
203. Del Mastro, L. et al. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2x2 factorial, randomised phase 3 trial. *Lancet* **385**, 1863–1872 (2015).
204. Blum, J. L. et al. Anthracyclines in early breast cancer: the ABC Trials-USOR 06-090, NSABP B-46/I-USOR 07132, and NSABP B-49 (NRG Oncology). *J. Clin. Oncol.* **35**, 2647–2655 (2017).
205. Gray, R. et al. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. *Lancet* **393**, 1440–1452 (2019).
206. Gianni, L. et al. 5-Year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol.* **17**, 791–800 (2016).
207. von Minckwitz, G. et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N. Engl. J. Med.* **380**, 617–628 (2018).
208. von Minckwitz, G. et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N. Engl. J. Med.* **377**, 122–131 (2017).
209. Martin, M. et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* **18**, 1688–1700 (2017).
210. Tolanay, S. M. et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N. Engl. J. Med.* **372**, 134–141 (2015).
211. Tolanay, S. M. et al. Seven-year (yr) follow-up of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC). *J. Clin. Oncol.* **35**, 511–511 (2017).
212. Earl, H. M. et al. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. *Lancet* **393**, 2599–2612 (2019).
213. Pivot, X. et al. Either 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol.* **14**, 741–748 (2013).
214. Joensuu, H. et al. Effect of adjuvant trastuzumab for a duration of 9 weeks vs 1 year with concomitant chemotherapy for early human epidermal growth factor receptor 2-positive breast cancer: the SOLD randomized clinical trial. *JAMA Oncol.* **4**, 1199 (2018).
215. Piccart-Gebhart, M. J. et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N. Engl. J. Med.* **353**, 1659–1672 (2005).
216. Goldhirsch, A. et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *Lancet* **382**, 1021–1028 (2013).
217. Hahnemann, E. et al. Germine mutation status, pathological complete response, and disease-free survival in triple-negative breast cancer: secondary analysis of the GeparSixto randomized clinical trial. *JAMA Oncol.* **3**, 1378–1385 (2017).
218. Sikov, W. M. et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). *J. Clin. Oncol.* **33**, 13–21 (2015).
219. Masuda, N. et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N. Engl. J. Med.* **376**, 2147–2159 (2017).
220. Gnant, M. et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* **386**, 433–443 (2015).
221. Gnant, M. et al. Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSG-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* **20**, 339–351 (2019).
222. Coleman, R. E. et al. Adjuvant denosumab in early breast cancer: first results from the international multicenter randomized phase III placebo controlled D-CARE study [abstract]. *J. Clin. Oncol.* **36** (Suppl.), a501 (2018).
223. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet* **386**, 1353–1361 (2015).
224. Coleman, R. E. et al. Benefits and risks of adjuvant treatment with zoledronic acid in stage II/III breast cancer. 10 years follow-up of the AZURE randomized clinical trial (BIG 01/04). *J. Bone Oncol.* **13**, 123–135 (2018).
225. Cardoso, F. et al. 4th ESO–ESMO international consensus guidelines for advanced breast cancer (ABC 4)†. *Ann. Oncol.* **29**, 1634–1657 (2018).
226. Golse, N. & Adam, R. Liver metastases from breast cancer: what role for surgery? Indications and results. *Clin. Breast Cancer* **17**, 256–265 (2017).
227. Xie, Y. et al. Surgery of the primary tumor improves survival in women with stage IV breast cancer in southwest China: a retrospective analysis. *Medicine* **96**, e7048 (2017).
228. Shien, T. & Doihara, H. Resection of the primary tumor in stage IV breast cancer. *World J. Clin. Oncol.* **5**, 82–85 (2014).
229. Badwe, R. et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. *Lancet Oncol.* **16**, 1380–1388 (2015).
230. Soran, A., Ozbas, S., Kelsey, S. F. & Gulluoglu, B. M. Randomized trial comparing locoregional resection of primary tumor with no surgery in stage IV breast cancer at the presentation (Protocol MF07-01): a study of Turkish Federation of the National Societies for Breast Diseases. *Breast* **15**, 399–403 (2009).
231. Fitzal, F. et al. Impact of breast surgery in primary metastasized breast cancer: outcomes of the prospective randomized phase III ABCSG-28 POSITIVE Trial. *Ann. Surg.* <https://doi.org/10.1097/SLA.0000000000002771> (2018).
232. Barinoff, J. et al. Primary metastatic breast cancer in the era of targeted therapy — prognostic impact and the role of breast tumour surgery. *Eur. J. Cancer* **83**, 116–124 (2017).

233. Shien, T. et al. A randomized controlled trial comparing primary tumor resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (JCOG1017 PRIM-BC). *J. Clin. Oncol.* **35**, TPS588–TPS588 (2017).
234. Cameron, D. Removing the primary tumour in metastatic breast cancer. *Lancet Oncol.* **16**, 1284–1285 (2015).
235. Dare, A. J. et al. Surgical Services for Cancer Care. In: *Cancer: Disease Control Priorities, Third Edition* (Volume 3) (eds. Gelband, H., Jha, P., Sankaranarayanan, R. & Horton, S.) (The International Bank for Reconstruction and Development/The World Bank, 2015).
236. Phillips, C., Jeffree, R. & Khasraw, M. Management of breast cancer brain metastases: a practical review. *Breast* **31**, 90–98 (2017).
237. Thavarajah, N. et al. Continued success in providing timely palliative radiation therapy at the rapid response radiotherapy program: a review of 2008–2012. *Curr. Oncol.* **20**, e206–e211 (2013).
238. Chow, E. et al. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. *Lancet Oncol.* **15**, 164–171 (2014).
239. Sologuren, I., Rodriguez-Gallego, C. & Lara, P. C. Immune effects of high dose radiation treatment: implications of ionizing radiation on the development of bystander and abscopal effects. *Transl. Cancer Res.* **3**, 18–31–31 (2014).
240. Morgan, S. C. & Parker, C. C. Local treatment of metastatic cancer — killing the seed or disturbing the soil? *Nat. Rev. Clin. Oncol.* **8**, 504–506 (2011).
241. Morgan, S., Caudrelier, J.-M. & Clemons, M. Radiotherapy to the primary tumor is associated with improved survival in stage IV breast cancer [abstract]. SABCs P4, 16–06 (2012).
242. Bernier, J. Immuno-oncology: allying forces of radio- and immuno-therapy to enhance cancer cell killing. *Crit. Rev. Oncol. Hematol.* **108**, 97–108 (2016).
243. Fietz, T. et al. Palliative systemic therapy and overall survival of 1,395 patients with advanced breast cancer — rResults from the prospective German TMK cohort study. *Breast* **34**, 122–130 (2017).
244. Rugo, H. S. et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology guideline. *J. Clin. Oncol.* **34**, 3069–3103 (2016).
245. Turner, N. C. et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N. Engl. J. Med.* **379**, 1926–1936 (2018).
246. Miles, D. W. et al. First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients. *Ann. Oncol.* **24**, 2773–2780 (2013).
247. Giordano, S. H. et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. *J. Clin. Oncol.* **32**, 2078–2099 (2014).
248. Partridge, A. H. et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology clinical practice guideline. *J. Clin. Oncol.* **32**, 3307–3329 (2014).
249. Schmid, P. et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N. Engl. J. Med.* **379**, 2108–2121 (2018).
250. Marinovich, M. L. et al. Early prediction of pathologic response to neoadjuvant therapy in breast cancer: systematic review of the accuracy of MRI. *Breast* **21**, 669–677 (2012).
251. Avril, S. et al. ¹⁸F-FDG PET/CT for monitoring of treatment response in breast cancer. *J. Nucl. Med.* **57**, 34S–39SS (2016).
252. Marinovich, M. L. et al. Meta-analysis of magnetic resonance imaging in detecting residual breast cancer after neoadjuvant therapy. *J. Natl. Cancer Inst.* **105**, 321–333 (2013).
253. Marinovich, M. L. et al. Agreement between MRI and pathologic breast tumor size after neoadjuvant chemotherapy, and comparison with alternative tests: individual patient data meta-analysis. *BMC Cancer* **15**, 662 (2015).
254. Humbert, O. et al. Role of positron emission tomography for the monitoring of response to therapy in breast cancer. *Oncologist* **20**, 94–104 (2015).
255. Pennant, M. et al. A systematic review of positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) for the diagnosis of breast cancer recurrence. *Health Technol. Assess.* **14**, 1–103 (2010).
256. Shachar, S. S. Assessing treatment response in metastatic breast cancer. *Am. J. Hematol. Oncol.* **12**, (2016).
257. Lee, C. I. et al. Comparative effectiveness of imaging modalities to determine metastatic breast cancer treatment response. *Breast* **24**, 3–11 (2015).
258. Pagani, O. et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N. Engl. J. Med.* **371**, 107–118 (2014).
259. Francis, P., Regan, M. & Fleming, G. Adjuvant ovarian suppression in premenopausal breast cancer. *N. Engl. J. Med.* **372**, 1672–1673 (2015).
260. Mao, J. J. et al. Electroacupuncture versus gabapentin for hot flashes among breast cancer survivors: a randomized placebo-controlled trial. *J. Clin. Oncol.* **33**, 3615–3620 (2015).
261. Elkins, G. et al. Randomized trial of a hypnosis intervention for treatment of hot flashes among breast cancer survivors. *J. Clin. Oncol.* **26**, 5022–5026 (2008).
262. Loprinzi, C. L. et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet* **356**, 2059–2063 (2000).
263. Niravath, P. Aromatase inhibitor-induced arthralgia: a review. *Ann. Oncol.* **24**, 1443–1449 (2013).
264. Barton, D. L. et al. Impact of vaginal dehydroepiandrosterone (DHEA) on vaginal symptoms in female cancer survivors: Trial N10C1 (Alliance). *J. Clin. Oncol.* **32**, 9507–9507 (2014).
265. Razvi, Y. et al. ASCO, NCCN, MASCC/ESMO: a comparison of antiemetic guidelines for the treatment of chemotherapy-induced nausea and vomiting in adult patients. *Support. Care Cancer* **27**, 87–95 (2019).
266. Gulati, G. et al. Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA): a 2x2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. *Eur. Heart J.* **37**, 1671–1680 (2016).
267. Smith, E. M. L. et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *JAMA* **309**, 1359–1367 (2013).
268. Hershman, D. L. et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J. Clin. Oncol.* **32**, 1941–1967 (2014).
269. Hanai, A. et al. Effects of cryotherapy on objective and subjective symptoms of paclitaxel-induced neuropathy: prospective self-controlled trial. *J. Natl. Cancer Inst.* **110**, 141–148 (2018).
270. Kadakia, K. C., Rozell, S. A., Butala, A. A. & Loprinzi, C. L. Supportive cryotherapy: a review from head to toe. *J. Pain Symptom Manage.* **47**, 1100–1115 (2014).
271. Hou, S., Huh, B., Kim, H. K., Kim, K.-H. & Abdi, S. Treatment of chemotherapy-induced peripheral neuropathy: systematic review and recommendations. *Pain Physician* **21**, 571–592 (2018).
272. Ahmed, R. L., Schmitz, K. H., Prizment, A. E. & Folsom, A. R. Risk factors for lymphedema in breast cancer survivors, the Iowa Women's Health Study. *Breast Cancer Res. Treat.* **130**, 981–991 (2011).
273. Gillespie, T. C., Sayegh, H. E., Brunelle, C. L., Daniell, K. M. & Taghian, A. G. Breast cancer-related lymphedema: risk factors, precautionary measures, and treatments. *Gland. Surg.* **7**, 379–403 (2018).
274. Runowicz, C. D. et al. American Cancer Society®/American Society of Clinical Oncology breast cancer survivorship care guideline. *J. Clin. Oncol.* **34**, 611–635 (2016).
275. Velikova, G. et al. Quality of life after postmastectomy radiotherapy in patients with intermediate-risk breast cancer (SUPREMO): 2-year follow-up results of a randomised controlled trial. *Lancet Oncol.* **19**, 1516–1529 (2018).
276. Hofmann, D. et al. WSG ADAPT — adjuvant dynamic marker-adjusted personalized therapy trial optimizing risk assessment and therapy response prediction in early breast cancer: study protocol for a prospective, multi-center, controlled, non-blinded, randomized, investigator initiated phase II/III trial. *Trials* **14**, 261 (2013).
277. Robertson, J. F. R., Dowsett, M. & Bliss, J. M. Peri-operative aromatase inhibitor treatment in determining or predicting long-term outcome in early breast cancer — the POETIC Trial (CRUK/07/015) [abstract]. SABCs GS1-03 (2017).
278. Ellis, M. J. et al. Ki67 Proliferation index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: results from the American College of Surgeons Oncology Group Z1031 trial (Alliance). *J. Clin. Oncol.* **35**, 1061–1069 (2017).
279. Hölzle, D. et al. Improved systemic treatment for early breast cancer improves cure rates, modifies metastatic pattern and shortens post-metastatic survival: 35-year results from the munich cancer registry. *J. Cancer Res. Clin. Oncol.* **143**, 1701–1712 (2017).
280. Hölzle, D. et al. Survival of de novo stage IV breast cancer patients over three decades. *J. Cancer Res. Clin. Oncol.* **143**, 509–519 (2017).
281. Angus, L. et al. The genomic landscape of 501 metastatic breast cancer patients [abstract]. SABCs GS1-07 (2018).
282. Desmedt, C. et al. Unraveling lobular breast cancer progression and endocrine resistance mechanisms through genomic and immune characterization of matched primary and metastatic samples [abstract]. SABCs GS1-06 (2018).
283. Baselga, J. et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* **18**, 904–916 (2017).
284. André, F. et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N. Engl. J. Med.* **380**, 1929–1940 (2019).
285. Baselga, J. et al. Phase III study of taselisib (GDC-0032) + fulvestrant (FULV) v FULV in patients (pts) with estrogen receptor (ER)-positive, PIK3CA-mutant (MUT), locally advanced or metastatic breast cancer (MBC): primary analysis from SANDPIPER. *J. Clin. Oncol.* **36**, LBA1006–LBA1006 (2018).
286. Kim, S.-B. et al. Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol.* **18**, 1360–1372 (2017).
287. Schmid, P. et al. AZD5363 plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (PAKT): a randomised, double-blind, placebo-controlled, phase II trial. *J. Clin. Oncol.* **36** (15 Suppl.), 1007 (2018).
288. Jones, R. H. et al. Capivasertib (AZD5363) plus fulvestrant versus placebo plus fulvestrant after relapse or progression on an aromatase inhibitor in metastatic ER-positive breast cancer (FAKITION): a randomized, double-blind, placebo-controlled, phase II trial [abstract]. *J. Clin. Oncol.* **37** (no. 15_suppl), 1005–1005 (2019).
289. Yardley, D. A. et al. Randomized phase II, double-blind, placebo-controlled study of exemestane with or without entinostat in postmenopausal women with locally recurrent or metastatic estrogen receptor-positive breast cancer progressing on treatment with a nonsteroidal aromatase inhibitor. *J. Clin. Oncol.* **31**, 2128–2135 (2013).
290. Ogita, Y. et al. DS-8201a, a novel HER2-targeting ADC with a novel DNA Topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. *Clin. Cancer Res.* **22**, 5097–5108 (2016).
291. Tamura, K. et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: a dose-expansion, phase 1 study. *Lancet Oncol.* **20**, 816–826 (2019).
292. Burris III, H. A., Giaccone, G. & Im, S. A. Updated findings of a first-in-human phase 1 study of margetuximab, an Fc-optimized chimeric monoclonal antibody, in patients with HER2-positive advanced solid tumors [abstract]. *Am. Soc. Clin. Oncol. Meet.* **33** (no. 15_suppl), A523 (2015).
293. Rugo, H. S. et al. SOPHIA primary analysis: a phase 3 (P3) study of margetuximab (M) + chemotherapy (C) versus trastuzumab (T) + C in patients (pts) with HER2+ metastatic (met) breast cancer (MBC) after prior anti-HER2 therapies (Tx) [abstract]. *J. Clin. Oncol.* **37** (Suppl.), Abstr 1000 (2019).
294. Hyman, D. M., Piha-Paul, S. & Rodon, J. Neratinib in HER2- or HER3-mutant solid tumors: SUMMIT, a global, multi-histology, open-label, phase 2 'basket' study [abstract]. *Am. Assoc. Cancer Res. Meet.* CT001 (2017).
295. Saura, C. et al. Neratinib + capecitabine versus lapatinib + capecitabine in patients with HER2+ metastatic breast cancer previously treated with ≥2 HER2-directed

- regimens: findings from the multinational, randomized, phase III NALA trial [abstract]. *J. Clin. Oncol.* **37** (Suppl.), Abstract 1002 (2019).
296. Gucalp, A. et al. Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic breast cancer. *Clin. Cancer Res.* **19**, 5505–5512 (2013).
297. Cortes, J., Crown, J. & Awada, A. Overall survival (OS) from the phase 2 study of enzalutamide (ENZA), an androgen receptor (AR) signaling inhibitor, in AR+ advanced triple-negative breast cancer (aTNBC) [abstract]. *Eur. Cancer Congr.* **51** (Suppl. 3), 1802 (2015).
298. Gelmon, K. A. et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol.* **12**, 852–861 (2011).
299. Nanda, R. et al. Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib KEYNOTE-012 Study. *J. Clin. Oncol.* **34**, 2460–2467 (2016).
300. Schmid, P., Cruz, C. & Braiteh, F. S. Atezolizumab in metastatic triple-negative breast cancer: long-term clinical outcomes and biomarker analyses [abstract]. *Am. Assoc. Cancer Res.* **77**, A2986 (2017).
301. André, F. et al. Alpelisib (ALP) + fulvestrant (FUL) for advanced breast cancer (ABC): results of the phase 3 SOLAR-1 trial [abstract]. *ESMO LBA3 PR* (2018).
302. Hyman, D. M. et al. HER kinase inhibition in patients with HER2- and HER3-mutant cancers. *Nature* **554**, 189–194 (2018).
303. Hartley, R. L., Stone, J. P. & Temple-Oberle, C. Breast cancer in transgender patients: a systematic review. Part 1: male to female. *Eur. J. Surg. Oncol.* **44**, 1455–1462 (2018).
304. Cardoso, F. et al. Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. *Ann. Oncol.* **29**, 405–417 (2017).
305. Di Oto, E. et al. X chromosome gain is related to increased androgen receptor expression in male breast cancer. *Virchows Arch.* **473**, 155–163 (2018).
306. Severson, T. M. & Zwart, W. A review of estrogen receptor/androgen receptor genomics in male breast cancer. *Endocr. Relat. Cancer* **24**, R27–R34 (2017).
307. Deb, S. et al. PIK3CA mutations are frequently observed in BRCA1 but not BRCA2-associated male breast cancer. *Breast Cancer Res.* **15**, R69 (2013).
308. Gucalp, A. et al. Male breast cancer: a disease distinct from female breast cancer. *Breast Cancer Res. Treat.* **173**, 37–48 (2019).
309. Korde, L. A. et al. Multidisciplinary meeting on male breast cancer: summary and research recommendations. *J. Clin. Oncol.* **28**, 2114–2122 (2010).
310. Cardoso, F. et al. Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **30**, 1194–1220 (2019).
311. Bareche, Y. et al. Unravelling triple-negative breast cancer molecular heterogeneity using an integrative multiomic analysis. *Ann. Oncol.* **29**, 895–902 (2018).
312. Lehmann, B. D. & Pietropol, J. A. Clinical implications of molecular heterogeneity in triple negative breast cancer. *Breast* **24**, S36–S40 (2015).
313. Lehmann, B. D. et al. Refinement of triple-negative breast cancer molecular subtypes: implications for neoadjuvant chemotherapy selection. *PLOS ONE* **11**, e0157368 (2016).
314. Burstein, M. D. et al. Comprehensive genomic analysis identifies novel subtypes and targets of triple-negative breast cancer. *Clin. Cancer Res.* **21**, 1688–1698 (2015).
315. Siu, A. L. & on behalf of the U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. *Ann. Intern. Med.* **164**, 279 (2016).
316. Klarenbach, S. et al. Recommendations on screening for breast cancer in women aged 40–74 years who are not at increased risk for breast cancer. *Can. Med. Assoc. J.* **190**, E1441–E1451 (2018).
317. Oeffinger, K. C. et al. Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. *JAMA* **314**, 1599 (2015).
318. European Commission Initiative on Breast Cancer. Recommendations from European Breast Guidelines Europa.eu <https://ecibc.jrc.ec.europa.eu/recommendations/list/Professional> (2019).
319. Dawood, S. et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. *Ann. Oncol.* **22**, 515–523 (2011).
320. Cserni, G., Charafe-Jauffret, E. & van Diest, P. J. Inflammatory breast cancer: the pathologists' perspective. *Eur. J. Surg. Oncol.* **44**, 1128–1134 (2018).
321. Cheang, M. C. U. et al. Defining breast cancer intrinsic subtypes by quantitative receptor expression. *Oncologist* **20**, 474–482 (2015).
322. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature* **490**, 61–70 (2012).
- This research establishes the contemporary method of classifying breast cancer into clinically relevant molecular subtypes.**
323. Hoadley, K. A., Andre, F., Ellis, M. J. & Perou, C. M. Breast cancer intrinsic subtypes (Poster). *Nat. Rev. Clin. Oncol.* https://www.nature.com/documents/nrclinonc_posters_breastcancer.pdf (2014).
324. Desmedt, C. et al. Genomic characterization of primary invasive lobular breast cancer. *J. Clin. Oncol.* **34**, 1872–1881 (2016).
325. Ciriello, G. et al. Comprehensive molecular portraits of invasive lobular breast cancer. *Cell* **163**, 506–519 (2015).
326. Vasudev, P. & Onuma, K. Secretory breast carcinoma: unique, triple-negative carcinoma with a favorable prognosis and characteristic molecular expression. *Arch. Pathol. Lab. Med.* **135**, 1606–1610 (2011).
327. Martelotto, L. G. et al. Genomic landscape of adenoid cystic carcinoma of the breast. *J. Pathol.* **237**, 179–189 (2015).
328. Goss, P. E. et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. *N. Engl. J. Med.* **375**, 209–219 (2016).
329. Liang, M. et al. Association between CHEK2*1100delC and breast cancer: a systematic review and meta-analysis. *Mol. Diagn. Ther.* **22**, 397–407 (2018).
330. Wang, X. et al. Breast cancer risk and germline genomic profiling of women with neurofibromatosis type 1 who developed breast cancer. *Genes. Chromosomes Cancer* **57**, 19–27 (2018).
331. McCart Reed, A. E. et al. Phenotypic and molecular dissection of metaplastic breast cancer and the prognostic implications: prognostic features of metaplastic breast cancer. *J. Pathol.* **247**, 214–227 (2019).
332. Wendt, C. & Margolin, S. Identifying breast cancer susceptibility genes — a review of the genetic background in familial breast cancer. *Acta Oncol.* **58**, 135–146 (2019).
333. Couch, F. J. et al. Associations between cancer predisposition testing panel genes and breast cancer. *JAMA Oncol.* **3**, 1190 (2017).
334. Nguyen, J. et al. EORTC QLQ-BR23 and FACT-B for the assessment of quality of life in patients with breast cancer: a literature review. *J. Comp. Eff. Res.* **4**, 157–166 (2015).
335. McLachlan, S. A., Devins, G. M. & Goodwin, P. J. Factor analysis of the psychosocial items of the EORTC QLQ-C30 in metastatic breast cancer patients participating in a psychosocial intervention study. *Qual. Life Res.* **8**, 311–317 (1999).
336. Bjelic-Radisic, V. et al. An international update of the EORTC questionnaire for assessing quality of life in breast cancer patients (EORTC QLQ-BC23) — EORTC QLQ-BR45. *Ann. Oncol.* **29**, viii58–viii86 (2018).
337. Ganz, P. A., Kwan, L., Stanton, A. L., Bower, J. E. & Belin, T. R. Physical and psychosocial recovery in the year after primary treatment of breast cancer. *J. Clin. Oncol.* **29**, 1101–1109 (2011).
338. Revicki, D. A. et al. Predicting EuroQol (EQ-5D) scores from the patient-reported outcomes measurement information system (PROMIS) global items and domain item banks in a United States sample. *Qual. Life Res.* **18**, 783–791 (2009).
339. Hays, R. D., Bjorner, J. B., Revicki, D. A., Spritzer, K. L. & Celli, D. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. *Qual. Life Res.* **18**, 873–880 (2009).
340. Bevans, M., Ross, A. & Celli, D. Patient-reported outcomes measurement information system (PROMIS): efficient, standardized tools to measure self-reported health and quality of life. *Nurs. Outlook* **62**, 339–345 (2014).

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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, Odonto, Pfizer, Roche, Sandoz/Hexal and Seattle Genetics. F.P.-L. declares personal financial interests in Abbvie, Agendia, Astrazeneca, BMS, Genomic Health, Janssen, Lilly, Merck, 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, Daichi-Sankyo, Erytech Pharma, Merus, Polyphor, Roche and Seattle Genetics; has received research funding from Ariad, Astrazeneca, Baxalta, Bayer, Eisai, Guardian 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, Macrogenics, 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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