Breastcancer

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BREAST CANCER

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Abstract|Breastcanceristhemostfrequentmalignancyinwomenworldwideandiscurable in~70–80%ofpatientswithearly-stage,non-metastaticdisease.Advancedbreastcancer withdistantorganmetastasesisconsideredincurablewithcurrentlyavailabletherapies. Onthemolecularlevel,breastcancerisaheterogeneousdisease;molecularfeaturesinclude activationofhumanepidermalgrowthfactorreceptor2(HER2,encodedby*ERBB2*),activation ofhormonereceptors(oestrogenreceptorandprogesteronereceptor)and/or*BRCA*mutations. Treatmentstrategiesdifferaccordingtomolecularsubtype.Managementofbreastcanceris multidisciplinary;itincludeslocoregional(surgeryandradiationtherapy)andsystemictherapy approaches.Systemictherapiesincludeendocrinetherapyforhormonereceptor-positive disease,chemotherapy,anti-HER2therapyforHER2-positivedisease,bonestabilizingagents, poly(ADP-ribose)polymeraseinhibitorsfor*BRCA*mutationcarriersand,quiterecently, immunotherapy.Futuretherapeuticconceptsinbreastcanceraimatindividualizationof therapyaswellasattreatmentde-escalationandescalationbasedontumourbiologyand earlytherapyresponse.Nexttofurthertreatmentinnovations,equalworldwideaccessto therapeuticadvancesremainstheglobalchallengeinbreastcancercareforthefuture.

Breastcanceristhemostfrequentmalignancyinwomen 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 principleof modern-day treatments, some features such as the impact of locoregional tumour burden or metastatic patterns are shared and influence therapy. Early breast cancer—thatis,cancerthatiscontainedinthebreastor that has only spread to the axillary lymph nodes — is considered curable. Improvements in multimodal therapyhaveledtoincreasingchancesforcurein~70–80% ofpatients.Bycontrast,advanced(metastatic)diseaseis not considered curable using currently available therapeutic options. However, advanced breast cancer is a treatable disease, for which the main goals of therapy aretoprolongsurvivalandcontrolsymptomswithlow treatment-associated toxicity to maintain or improve quality of life (that is, improved quality-adjusted life expectancy).

Thetwomajorpillarsofbreastcancermanagementare locoregionaltreatmentandsystemictherapy;thehistological and molecular characteristics of breast cancer largelyinfluencetreatmentdecisions.Themolecular alterations that drive breast carcinogenesis are many, and several classifications have been developed to group tumours accordingly. The intrinsic classification of Perou and Sorlie[1], reported in 2000, distinguished foursubtypesofbreastcancer:luminalAandluminalB (expressingtheoestrogenreceptor(ER)),basal-likeand human epidermal growth factor receptor 2 (HER2)-enriched (without ER expression). This classification shiftedclinicalmanagementofbreastcancerfrombeing basedontumourburdentobiology-centredapproaches. Currently, clinical practice typically uses a surrogate classificationoffivesubtypesonthebasisofhistological andmolecularcharacteristics(FIG.1).Tumoursexpressing ER and/or progesterone receptor (PR) are consideredhormonereceptor-positivebreastcancers,whereas tumoursthatdonotexpressER,PRorHER2aretriple-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 accordingtohigh-qualityguidelines.Establishmentofspecialized breastcancercentresisamajorpriorityworldwide,and is supported by the European Parliament[2].

Asbreastcancerisaglobalproblem,majoremphasisneedstobeputondiminishingworldwidedisparitiesinaccesstodiagnosis,multimodaltreatmentand 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 died[3]. 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 (REF.[4]); 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 alone[5]. 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 subtypes[6].

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 later stage and is, accordingly, associated with poorer survival[9] — 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 Africa[10] and developing Asian countries[11], 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 countries[15]. The biology of the tumour also varies by ethnicity, which has implications for the difference in mortality[17]. 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 survival[18]. 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 patternism multifactorial and involves genetic predisposition, lifestyle and other environmental factors.

Genetic predisposition

Approximately 10% of breast cancers are inherited and associated with a family history[21], 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 developed[23].

Mutations in two high-penetrance tumour suppressor genes, *BRCA1* (17q21) and *BRCA2* (13q13), whose proteins are involved in DNA repair through homologous repair[24], 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%, respectively[25]; the relative risk of breast cancer in men (BOX1) 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 study[28]. Germline *BRCA* testing will now be performed as a companion diagnostic in patients with metastatic breast cancer[29] 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

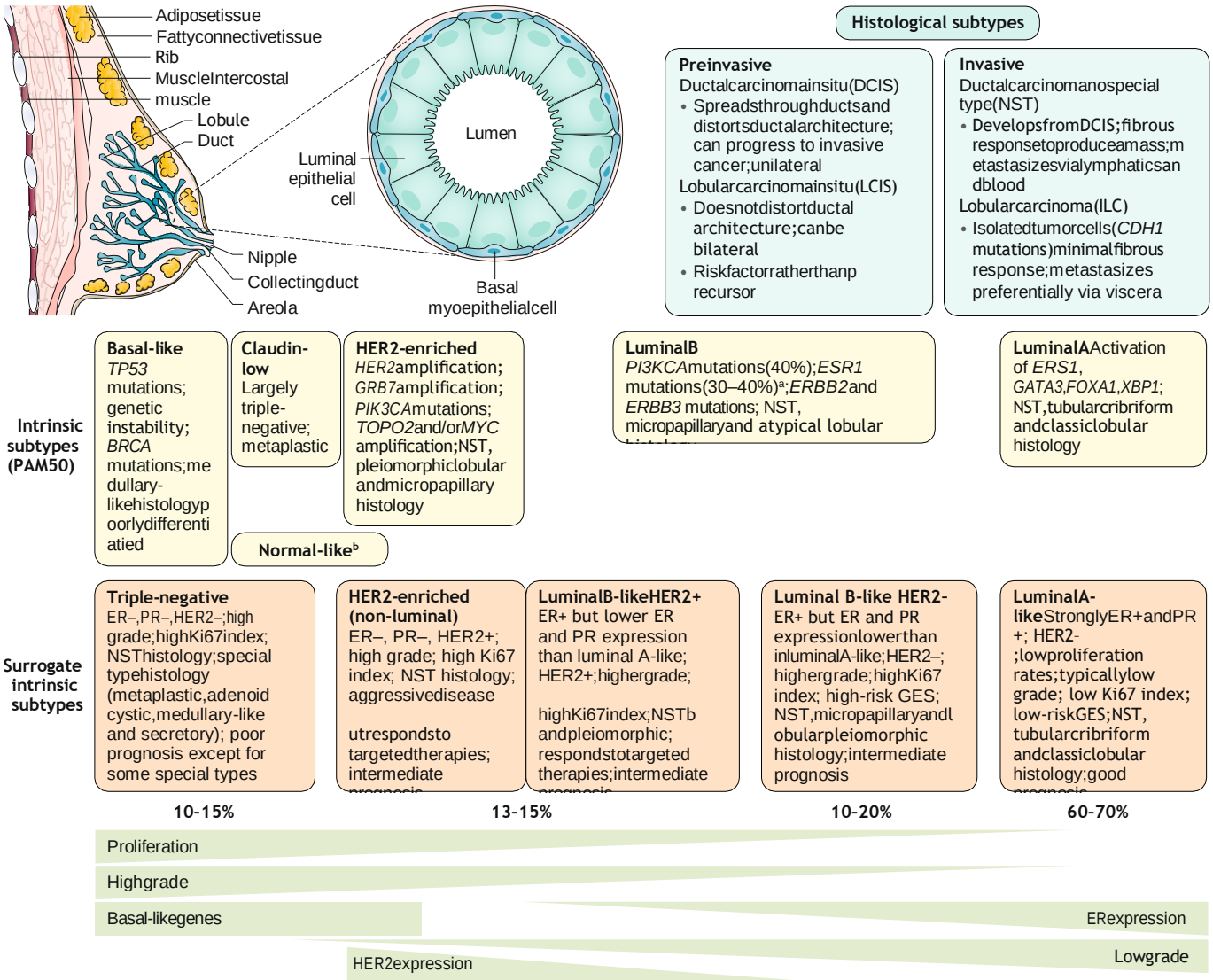

Fig. 1 | **Breast cancer.** All breast cancers arise in the terminal duct lobular units (the functional unit of the breast) of the collecting duct. The histological and molecular characteristics have important implications for therapy, and several classifications on the basis of molecular and histological 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 pre-invasive counterparts are ductal carcinoma in situ and lobular carcinoma in situ (or lobular neoplasia), respectively. The intrinsic subtypes of Perou and Sorlie[1] are based on a 50-gene expression signature (PAM50)[32,1]. 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. [b]Artefact; expression of normal breast components due to low tumour cellularity.

Box1|**Breastcancerinmen**

Themalebreastisarudimentaryorganthatislimitedtoductsintheretro-aerolararea, expressing oestrogen receptor (ER), progesterone receptor (PR) and androgen receptor (AR).Benignandmalignantlesionspresentingasretro-aerolarlumpscanoccur, althoughmalebreastcancerisrare:<1%ofallbreastcancersoccurinmenand<0.5% ofdeathsinmencanbeattributedtobreastcancer.Thelifetimeriskforbreastcancerin menis1in833comparedwith1in10forawoman.Ofaffectedmen,20%haveafirst-degreefamilyhistoryofcancer;4–14%ofcasesinmalesareattributedtogermline *BRCA2*mutationsandthereisa60–76%chanceofa*BRCA2*mutationinfamilieswithat leastoneaffectedmale.Klinefeltersyndromeengendersarelativeriskof30–50for malebreastcancer(owingtoelevatedcirculatingoestrogens);5%ofmenwithbreast cancershavethissyndrome.Otherriskfactorsforbreastcancerdevelopmentinmen includeelevatedoestrogens(imbalanceofoestrogenandtestosterone),livercirrhosis, prostatecancer,age,obesityandsmoking.Inindividualswhoundergomale-to-femalegenderreassignment,hormonalstimulationmaypromotebreastcancer development[303].Clinically,menwithbreastcancerpresentatolderage(60–70years) andwithhigherstagethanwomenwithbreastcancer.Invasiveductalcarcinoma (FIG.1)isthemostfrequentsubtype,whereasinvasivelobularcarcinomaisextremely rarecomparedwithfemalebreastcancer;papillarycarcinomaisthesecondmost frequenthistologicaltype.Intermsoftheintrinsicsubtypes(FIG. 1),>90%ofmale breastcancersareluminalAorluminalB;humanepidermalgrowthfactorreceptor2 (HER2)-positiveandtriple-negativebreastcancerareextremelyrareinmen[304].ARis oftenoverexpressedinmalebreastcancer[305,306].Expressionpathwaysofluminalgenes arealsopredominant;activationoffibroblastgrowthfactorreceptor2(FGFR2)and phosphatidylinositol3-kinase(PI3KCA)pathwaysarepotentialtherapeutictargetsto beexploredinthefuture[307].Prognosisissimilartostage-matchedwomenwithbreast cancer,althoughoverallsurvivalisworsebecausemalepatientswithbreastcancerare oftenolder,havemorecomorbiditiesandhavelowerlifeexpectancy[304,308].Treatments arelargelyextrapolatedfromfemalebreastcancer,duetoapaucityofavailabledata. Asthevastmajorityofbreastcancersinmenareluminalcancers,themostimportant therapyisendocrinetherapy[308,309].Intheadjuvantsetting,tamoxifen(whichbindsto andinhibitstheER)isthestandardofcareandaromataseinhibitorsshouldnotbeused alone(asthesareassociatedwithworsesurvival).Incasesofabsolutecontra-indicationfortamoxifenuse,acombinationofanaromataseinhibitorandaluteinizing hormone-releasinghormoneagonistcanbeconsidered,althoughthisapproachis associated with higher toxicity[308–310]. Recommendations for adjuvant chemotherapy andradiationtherapyaresimilartothoseinwomenwithluminalearlybreastcancer, asarerecommendationsformanagementofadvancedbreastcancer[308–310].

early pregnancy and high levels of oestrogen during pregnancyreducebreastcancerrisk.Theproposedmechanismsincludealteredsensitivityofthemammarygland tolaterhormonalexposures[40];reductioninthenumber of stem or progenitor cells and, consequently, elimination of targets for malignant transformation[41]; and changesingeneexpressionpatternsresultinginreduced proliferationandincreaseddifferentiation[42].Otherrisk factorsforbreastcancerincludeearlymenarche,lackof breastfeedingandlate-onsetmenopause.

Ithasbeenestimatedthat~20%ofbreastcancers worldwidecanbeattributedtomodifiableriskfactors, including obesity, physical inactivity and alcohol use, offeringthepotentialforreductioninthediseaseburden bypromotinga healthy lifestyle[43]. For example, each 10g (~1drink)ofalcoholconsumeddailybyanadultwoman willleadtoa7–10%increaseinbreastcancerrisk;this association is observed in both premenopausal and postmenopausal women[44–46]. Furthermore, the influenceofcentralobesityonbreastcancerriskandsurvival hasbeenstudied;currentevidencesuggestsastronger adverseeffectofobesityonbreastcancerriskandsurvivalinwomenofAsianancestrythaninnon-Hispanic white women in the United States and Europe[47]. For AfricanAmericanandnon-whiteHispanicwomen,the strengthoftheassociationsseemstobecomparablewith that of non-Hispanic white women, particularly when accountingforsubtypeandmenopausalstatus[48].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 UnitedStateshaveelevatedBMIandbreastdensityand may benefit from lifestyle modifications involving weight lossandexercise[49].However,thisbenefitisnotlimitedto premenopausalwomen,especiallywhentheAsianbreast cancerpopulationisbeingstudied.Forexample,itwas notedthatpostmenopausalAsianwomenwhoseBMI increased≥5.0weresignificantlymorelikelytodevelop breastcancerthanthosewithastableBMI(definedasa change in BMI of ±2.5). Additionally, postmenopausal womenwith abdominal circumference ≥90cm were significantly more likely to develop breast cancer than those with abdominal circumference <70 cm[50]. Among postmenopausalwomenwithBMI≥20,thosewithhigh (≥6.5)glycatedhaemoglobin(HbA1c)weremorelikelyto developbreastcancerthanthosewithlow(<5.5)HbA1c. Thus, breast cancer incidence, obesity and increased BMI areassociatedinpostmenopausalAsianwomen[50].

The possibility that the use of hormonal contraceptives may increase the risk of breast cancer has been raised for many years[51]. Two recent papers showed a statistically significant increase in breast cancer with use of hormonal contraception, even contemporary lose-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

In2018,anestimated6.8millionwomenworldwide survivedbreastcancerafterbeingdiagnosedwithinthe previous5years[3].Unfortunately,andbecausemostcancerregistriesonlyrecordtheincidenceandmortality butnotthedateofrelapse,itisunknownhowmanyof these6.8millionwomenarelivingwithmetastaticdis- ease and how many are cancer-free survivors. Meeting thelong-termmedicalandpsychosocialneedsofsurvivorsinlow-andmiddle-incomecountriesisparticularlydifficultduetolimitedresources—theseissuesare attractingglobalattention[54].Theemergentissuesinclude butarenotlimitedtocommonadverseeffectsoverlong periods after cancer treatment, loss of strength, sexualdysfunction,bonehealth,andphysicalandmental healthconcerns[55–59].

Mechanisms/pathophysiology

Theexactmechanismbywhichbreastcancerisinitiated is unknown; however, much effort has been made to molecularlycharacterizebreastcanceranddelineateits formationandprogression.Atthecelloforiginlevel,the clonalevolutionmodel(inwhichmutationsaccumulate, epigeneticchangesintumourcellsoccurandthe‘fittest’ cellssurvive)andthecancerstemcellmodel(inwhich only the precursor cancer cells initiate and sustain progression)arebothimplicated,andfurthercomplicatedby thefactthatcancerstemcellsmayalsoevolveinaclonal fashion[60].Atthemorphologicallevel,thereisacontinuum

oflesionsandgeneticmodificationsfromnormalglands to cancer (FIG. 1). At the molecular level, there is evidence showingthatbreastcancerevolvesalongtwodivergent 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.

Thefirstpathway—thelow-grade-likepathway — is characterized by gain of 1q, loss 16q, infrequent amplificationof17q12andageneexpressionsignature (GES) with a majority of genes associated with the ER phenotype, diploid or near diploid karyotypes and low tumourgrade.TheluminalAgroupandtosomeextent 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 proliferation[61]. Tumours composed of intermediate to high grade, including HER2-positive tumours and TNBC, fall into thispathway[62].

Table1|**Themostfrequentinheritedbreastcancersyndromes**

Syndromeorkeygene[a]	Mutationcharacteristics	Penetrance	Prevalence	Breastcancertypes
*BRCA1*hereditarybreast cancersyndrome,and *BRCA1*breastandovarian breastcancersyndrome	*BRCA1*;mutations:nohotspots; tumoursuppressor;DNArepair ofdouble-strandedDNAbreaks	Cumulativeriskof breastcanceratage 70yearsof65%;very highpenetrance	• Autosomaldominant, 3in1,000 • Rare • Averagerelativerisk 11.4	• Adenocarcinoma NST • Medullary-like • Metaplasic • Triple-negative • 80%basal-like • Femaleandmale
*BRCA2*hereditarybreast cancersyndrome,and *BRCA2*breastandovarian breastcancersyndrome	*BRCA2*;mutations:nohotspots; tumoursuppressor;DNArepair ofdouble-strandedDNAbreaks	Cumulativeriskofbreast canceratage70yearsof 45%;highpenetrance	• Autosomaldominant, 7in1,000 • Rare • Averagerelativerisk 11.7	• Adenocarcinoma • Nodistinctphenotype • Femaleandmale
LiFraumenisyndrome andLiFraumeni-like syndrome	*TP53*;mutations:nohotspots; *BRCA2*,Fanconigenes,*MMR*also mutated;tumoursuppressor, cellcyclecontrol,DNArepair, apoptosisandDNAreplication	Cumulativeriskof breastcanceratage 60yearsof50%;very highpenetrance	• Autosomaldominant, 1in20,000–1in5,000 • Veryrare • Averagerelativerisk 10.5	• Phyllodestumours • Adenocarcinoma NST • 80%HER2+female
PALB2	*PALB2*monoallelicgermline mutations;ifbiallelic:Fanconi anaemia;DNArepairof double-strandedDNAbreaks	Cumulativeriskofbreast cancerinone'slifetime of33–58%;moderateto highpenetrance	• Autosomaldominant • Averagerelativerisk5.3	• Adenocarcinoma NST • Nodistinctclass • Pancreas,ovary
CHEK2	*CHECK2*mutations (*CHEK2*1100delC*morefrequent than470C>TorI157Thrmissense variants);cellcyclecheckpoint kinase,DNArepair,activated BRCA1andp53	Cumulativeriskofbreastca ncerinone'slifetimeof 20–30%;moderatetolow penetrance	• Autosomaldominant • Averagerelativerisk2.26for womenand3.13formen • Higherincasesoffamily history • Missensevariantsconfer lowerrisk[329]	• Adenocarcinoma NST • ERpositivityvaries accordingtothetype ofmutations • Femaleandmale • Colorectalcancerrisk in*CHEK2*1100delC* mutationcarriers
Ataxiatelangiectasia	*ATM*;mutations:nohotspots; homozygotesmoreaffectedthan heterozygotes;proteinkinase DNAdamageresponsethrough p53,BRCA1andCHECK2 pathways	Cumulativeriskofbreast cancerinone'slifetime of20%;lowtomoderate penetrance	• Autosomalrecessive, 1–2.5in100,000 • Common • Averagerelativerisk2.8	• Adenocarcinoma NST • Nodistinctclass
Cowdensyndrome	*PTEN*;germlinemutations, variantsandepimutations; tumoursuppressor,PIK3CA pathway	Cumulativeriskof breastcancerinone's lifetimeof85%;veryhigh penetrance	• Autosomaldominant, 1in250,000 • Averagerelativeriskof25% • Veryrare	• Adenocarcinoma NST • Nodistinctclass • Femaleandmale • Benignbreastlesions
Hereditarydiffusegastric cancersyndrome	Germline*CDH1*;mutations: nohotspots;cellinvasion suppressorandcell–celladhesion	Cumulativeriskofbreastca ncerinone'slifetimeof42–60%;highpenetrance	• Autosomaldominant, <0.1in100,000 • Averagerelativeriskof6.6	• Invasivelobular carcinoma • Female
Peutz–Jeghersyndrome	*STK11*;mutations:nohotspots; tumoursuppressorgene,cell-cycleregulationandapoptosis	Cumulativeriskofbreastca nceratage60yearsof 32–54%;highpenetrance	• Autosomaldominant • Insufficientdatatodetermine averagerelativerisk	• Adenocarcinoma NST • Nodistinctclass
Neurofibromatosis	*NF1*germlinemutations; tumoursuppressorandnegative regulationoftheRASsignalling pathway	Cumulativeriskofbreast cancerinone'slifetime of17%;lowtomoderate penetrance[330]	• Autosomaldominant, 1–5in10,000 • Averagerelativeriskof2.6	• Adenocarcinoma NST • Higherprevalence ofmetaplastic carcinoma[331] • Femaleandmale

+,positive;ER,oestrogenreceptor;HER2,humanepidermalgrowthfactorreceptor2;NST,nospecialtype(alsoknownasinvasiveductalcarcinoma).Datafrom REFS[34–36,332,333].[a]Lynchsyndromemayalsobeassociatedwithanincreasedfrequencyofbreastcancer,butthelinkisnotclear.

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 cancers[63] (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 reactivated (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 rare[64], 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 vary[65].

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 targetable[66]. For example, in luminal-like breast cancer cell lines, inhibition of histone deacetylase with specific inhibitors such as vorinostat[67] or chidamide[68] 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 cancers showed the superiority of a treatment combining chidamide with endocrine therapy (namely, the aromatase inhibitor exemestane) to exemestane alone[69].

Hormone receptors. The major risk factors for sporadic breast cancer are linked to hormone exposure. Oestrogens 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

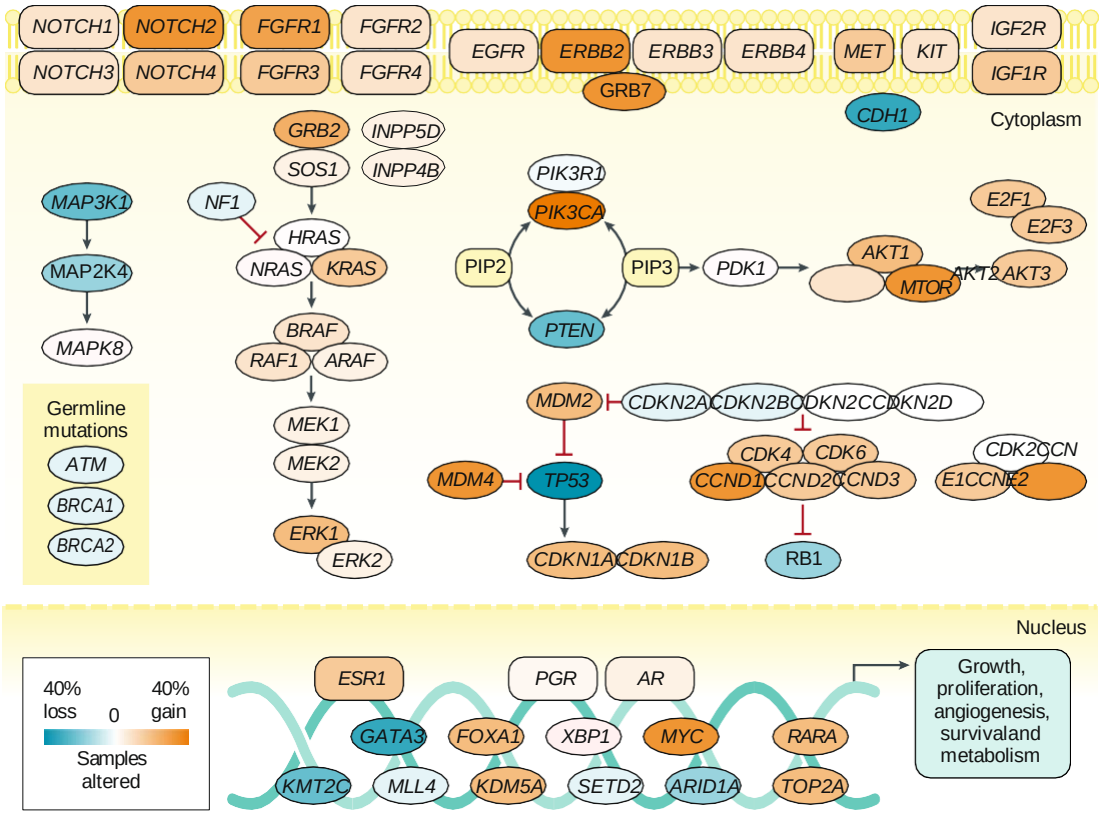

Fig. 2 | **Molecular mutations in breast cancer.** The Cancer Genome Atlas data on breast tumour DNA copy number and somatic mutations were used to identify the frequency of each genetic alteration across 792 patients with breast cancer (all subtypes)[322]. Each gene is shaded according to the overall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

Box2|Triple-negativebreastcancermolecularclassification

Geneexpressionassayshaveidentifiedsixdifferenttriple-negativebreastcancer (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)andluminalandrogenreceptor(LAR).BL1hasahigh*TP53*mutationrate(92%), alterationsingenesinvolvedinDNArepairmechanisms(suchas*BRCA1*,*BRCA2*,*TP53* and*RB1*)andacell-cyclegenesignature[311].BL2hascell-cyclegenesignatures, overexpressionofgrowthfactorsignallinggenesandoverexpressionofmyoepithelial differentiationgenes.MandMSLsubtypesareenrichedforgenesencodingregulators ofcellmotility,invasionandmesenchymaldifferentiation,buttheMSLsubtypeis uniquelyenrichedforthegenesthatencoderegulatorsofepithelial–mesenchymal transitionandstemness.TheClaudin-lowsubtypefromtheintrinsicclassification (FIG. 1)ismostlycomposedoftheMandMSLsubtypes[312].MSLalsosharesnumerous genesinvolvedintheregulationofimmuneresponsewiththeIMsubtype.Finally,LAR ischaracterizedbyahighermutationalburdenwithoverexpressionofgenescodingfor mammaryluminaldifferentiation,overexpressionoftheregulatorsoftheandrogen receptor(AR)signallingpathwayandincreasedmutationsin*PI3KCA*(55%),*AKT1*(13%) and*CDH1*(13%)genes[311].Thisclassificationhasbeenrefinedintofourgroups:BL1 (immunoactivated),BL2(immunosuppressed),M(includingmostoftheMSL)and LAR[313],withimplicationsforresponsetoneoadjuvantchemotherapy.CombiningRNA andDNAprofilinganalyses,asimilarclassificationofTNBChasbeenreported (Burstein'sclassification),dividedintofourdistinctsubtypes.Thesesubtypesare LAR, mesenchymal(MES),basal-likeimmunosuppressed(BLIS)andbasal-likeimmune-activated(BLIA)[314].Eachsubtypehasspecifictherapeutictargets(forexample,theLAR subtypecanbetargetedviatheARandthecellsurfaceproteinmucin)anddifferent prognosis(forexample,theBLIAsubtypeisassociatedwithbetterprognosisthanBLIS). Despitethesemultipleefforts,thereisnoestablisheddiagnosticassayyetforthe 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 eachcycle,adefectiverepairprocesscanoccur,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 supportcancerdevelopment.Whenactivatedbyligand binding,theERcanmodulategeneexpressionbyinteracting with oestrogen response elements located in the promoterregionofspecificgenes.Extracellularsignals can also stimulate the expression and activation of the ER in the absence of oestrogen[70]. Furthermore, the ER can also interact directly with proteins, such as growth factor receptors, to enhance gene expression related to cell proliferation and survival[71]. Thus, drugs blocking the effects of oestrogen on the mammary gland, suchas tamoxifen, or drugs that block the production of oestrogen,suchasaromataseinhibitors,havemajorroles in the treatment of hormone-sensitive breast cancer.As oestrogen interacts with bone, aromatase inhibi-tors can also cause osteoporosis (as menopause does). Bycontrast,tamoxifenhasoestrogen-likeeffectsonthe bone, thereby preventing osteoporosis[72].

HER2.*ERBB2*isamplifiedin13–15%ofbreastcancers, causinganactivationoftheHER2pathway.HER2is,with epidermal growth factor receptor (HER1), HER3 and HER4,amemberofthehumanepidermalgrowthfactor family.Theseproteinscompriseanextracellularligand-binding domain, a transmembrane domain and a tyrosine kinase intracellular catalytic domain. HER2 activationoccursthroughdimerizationafterligandbinding, althoughnoligandspecificforHER2hasbeenidentified.HER2signallingactivatesproliferation,cellsurvival, metastasisandadhesionthroughdifferentpathwayssuch astheRASpathwayandthephosphoinositide3-kinase (PI3K)–protein kinase B (AKT)–mitogen-activated protein kinase (MAPK) pathway. Targeting HER2 has proven to be effective in HER2-positive breast cancersthataredefinedbyproteinoverexpressionorgene amplification(seebelow,Management).

Immuneinvolvement

Breast cancer develops in a complex microenvironment comprising several benign cell types and the extracellularmatrix(whichprovidesmechanicalsupport for the tumour and enables cellular interaction in a paracrine fashion). The most abundant cell type iscancer-associatedfibroblasts,butthebreastcancer microenvironmentalsocontainscellsofleukocyteline-age(includinglymphocytes,macrophagesandmyeloid-derivedstromalcells),mostofwhichareinvolvedinthe immuneresponse(FIG.3)[73].Immunogenicityofbreast cancervariesbetweenthemolecularsubtypes,being highestinTNBCandHER2-positivetumoursandlower in luminal A and luminal B subtypes[74,75]. Moreover, the response to neoadjuvant treatment and the prognosisofbreastcancerarepositivelyinfluencedbythe amount of tumour-infiltrating lymphocytes, which reflectstheintensityoftheimmuneresponsewithinthe tumourbed[76,77].

The immune microenvironment influences the developmentandprogressionofbreastcanceraccordingtoimmunesurveillanceandimmuneeditingprinciples.Intheearlyphaseofcarcinogenesis,theimmune microenvironmentexertsmostlyanti-tumouraction,via thecytokinemilieuderivedfromactivated$CD8^+$and $CD4^+$Tcells.Bycontrast,onceatumourbecomesinvasive,themicroenvironmentcellcomposition,including cancer-associated fibroblasts and cytokine content, are tumour-promoting,'hacked'bybreastcancercells[78–80].

Tumourbiologyandmetastaticdisease

Theintrinsicclassification(FIG.1)influencestheprofile (timing,sites)ofmetastaticdisease.LuminalAtumours tend to relapse late (after 5 years of first presentation) and have a tropism for bone and lymph nodes (as do luminalB,HER2-negativetumours).TNBCsareprone to early recurrences (within 2–3 years of first presentation) and tend to form visceral (lung) and brain metastases.Sincetheeraofanti-HER2targetedtherapy, HER2-positivebreastcancersshowbetterprognosis,but they escape therapy through brain metastasis[81].

Breastcancersthatarediagnosedasmetastaticatfirst presentation(denovo)accountfor25–28%ofmetastatic breastcancers[5,82].Theirproportionvarieswiththeageat diagnosisfrom5.1%forwomen<40yearsofageupto 34.3% if aged >75 years (data from France[83]). The true numberofmetastaticbreastcancersxyearsafterinitial presentation,atsitesand/ororgansoutsidethelocalinitialbreasttumourareaandregionalnodes(including infra-clavicular and supra-clavicular ipsilateral lymph nodes), depends on several factors including age, presence of mass screening,quality of initiallocal treatment

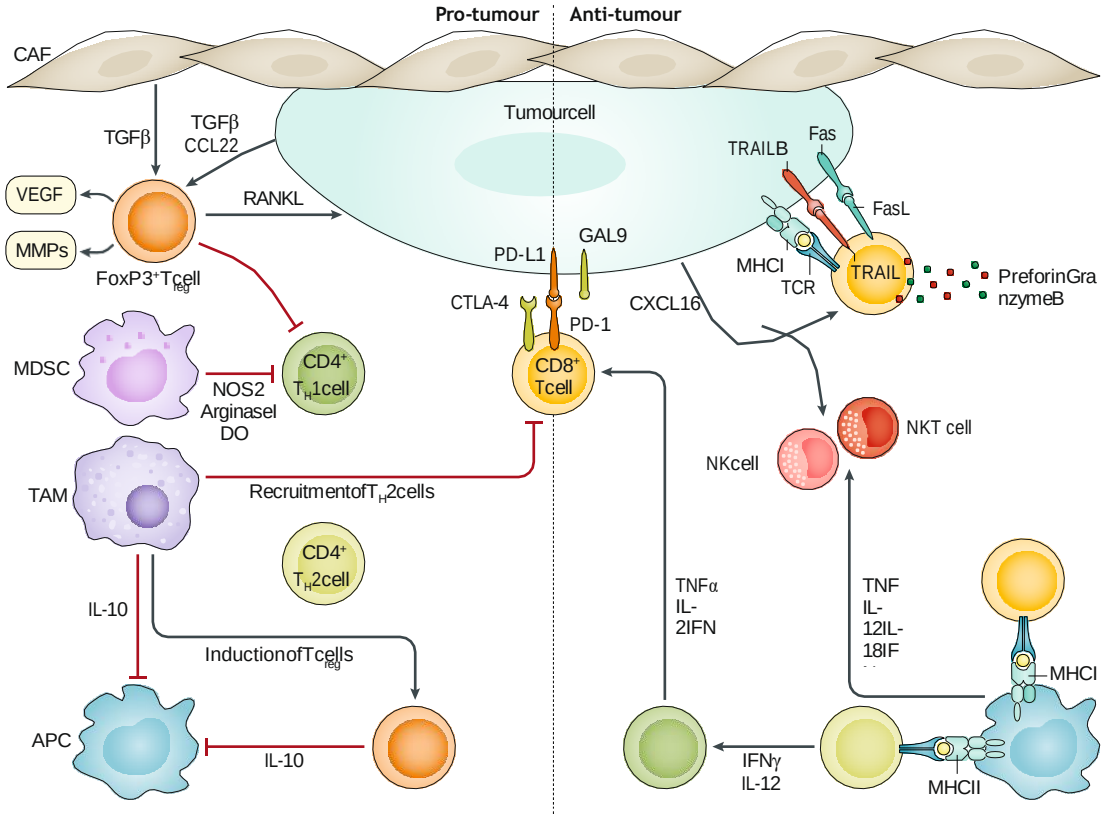

Fig.3|**Immunecrosstalkinbreastcancer.** Theimmunereactiontobreastcancerisinitiatedbytheneoantigens expressedbytumourcells,encodedbyalteredgenesandpresentedbyantigen-presentingcells(APCs)onmajor histocompatibilitycomplexclassI(MHCI)orMHCIImolecules.Neoantigenpresentationresultsinactivationof$CD8^+$(cytotoxic) and$CD4^+$(helper)Tcells.$CD8^+$Tcellsarethemaineffectorcelloftheanti-tumourimmuneresponse;their activation(principallythroughtheTcellreceptor(TCR))resultsinreleaseofthecytolyticmoleculesperforinandgranzymeB, whichdirectlyinducetumourcelllysis.Theanti-tumouractionof$CD8^+$Tcellsisamplifiedbycytokinessecretedfrom $CD4^+$Tcells,namelyIFNγ,IL-2andtumournecrosisfactor(TNF).Activated$CD8^+$TcellsalsoupregulateexpressionofFas ligand(FasL)andTNF-relatedapoptosis-inducingligand(TRAIL;alsoknownasTNFSF10)ontheirmembrane,whichinduce apoptoticpathwaystokilltumourcells.Cancercellselicitaninnateimmuneresponse,comprisingnaturalkiller(NK)and NKTcellsthatarecapableofdirecttumourcellkilling.Malignantcellscansuppresstheimmuneresponsebyexpressing immunecheckpointregulators(forexample,cytotoxicTlymphocyte-associatedprotein4(CTLA-4)andprogrammedcell death1ligand1(PD-L1)),whichareupregulatedbyeffectorTcellsasaconsequenceofchronicexposuretotumour antigens(Tcellexhaustion).Thereducedanti-tumourimmuneresponsebyupregulatedimmunecheckpointmolecules establishesapro-tumourmicroenvironment,whichisfurtherenrichedbyrecruitmentofimmunosuppressivecells, Tregulatory(T_{reg})cellsandmyeloid-derivedstromalcells(MDSCs).T_{reg}cells,whichinhibitactivationof$CD4^+$and$CD8^+$Tcells,areinducedbytumour-associatedmacrophages(TAMs)andbytumour-secretedandcancer-associatedfibroblast (CAF)-secretedfactors,suchastransforminggrowthfactor-β(TGFβ).Inaddition,TAMsandT_{reg}cellsinhibitAPCsviaIL-10 secretion,inducingatolerogenicstateofAPCs.MDSCsarerecruitedtothetumourbedbytumour-secretedfactors, inhibittraffickingofTcellstothetumourbedandinhibiteffectorTcellactivationbyupregulating2,3-indoleamine-dioxygenase(IDO)andarginaseexpression,enzymesinvolvedintheTcellnutrientdepletion.Thesecretomeofthe pro-tumourmicroenvironment,containingfactorsthatstimulateangiogenesisandinvasion(suchasvascular-endothelial growthfactor(VEGF)andmatrixmetalloproteinases(MMPs))alsocontributetotumourimmuneescapeandpropagation.CCL22, CC-chemokineligand22;CXCL16,CXC-chemokineligand16;NOS,nitricoxidesynthase;PD-1,programmedcell death1;RANKL,receptoractivatorofnuclearfactor-κB(RANK)ligand;$T_H1$cell,type1Thelpercell.AdaptedfromREF.[75], CC-BY-4.0https://creativecommons.org/licenses/by/4.0/.

andaccesstodrugsandinnovations(suchasprecision radiation therapy for brain metastases or access to clinical trials)[5,82].Inwesterncountries,theproportionofpatients who experience metastatic recurrence is probably 20–30%.Recurrenceanddisease-freesurvival(DFS)are measuredafterthecompletionoftheinitialtreatment.

Tumour features that lead to metastasis in breast cancer are not well known. Additionally, although someresearchersareattemptingtofindinterventions topreventmetastaticrecurrence(suchasaspirinand metformin),theresultsareasyetmostlyinconclusive.

Tumourmolecularevolution

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), resultingin subclonal diversification and discrepancies between

thebiologyofbreastcancersatdifferentmetastaticsites within an individual patient. Such alterations occurlate, and some alterations are subsequent to treatment pressure; for example, *ESR1* mutations can arise after aromatase inhibitor treatment (which targets oestrogensynthesis)whereasothersmightbe'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 phenomenondoesnotseemtoinfluencesensitivitytofulvestrant (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 polyclonalevolutionarypathwaysfromtheprimarytumour, showing different genetic and epigenetic evolution. This processishighlycomplexandstillpoorlyunderstood[85]. Liquid biopsy with an evaluation of circulating tumour DNA profiles can reflect the clonal heterogeneity, but this approach may lack sensitivity[86].

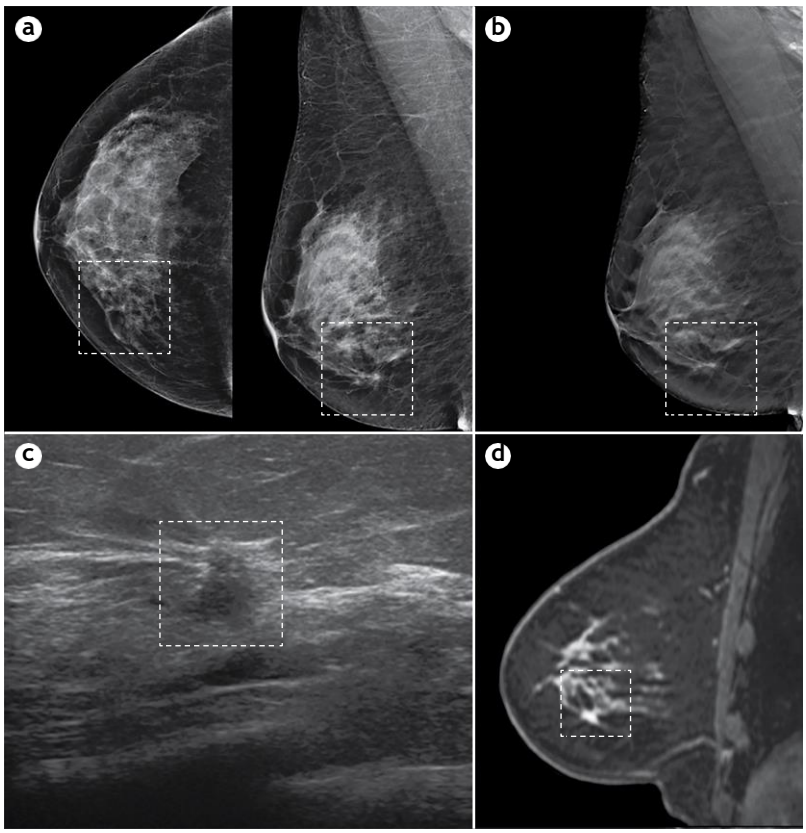

Fig.4|**Breastcancerimaging.** Apostmenopausalwoman53yearsofagewithnofamily historyandnoclinicalfindingsunderwentroutinebreastscreeningwithmammography, whichdetectedalesionintherightbreast(panel**a**,cranio-caudalview(left)and mediolateralobliqueview(right)).Theimageswerealsoacquiredwithdigitalbreast tomosynthesis,whichshowedasmallspiculatedlesioninthelowerinnerquadrant (panel**b**,mediolateralobliqueview).Thelesionwasinvestigatedwithultrasonography (panel**c**),andbiopsyconfirmedaninvasiveductalcarcinomaonhistology.MRIshowed theenhancingspiculatedmass(panel**d**).Thetumourisindicatedwithinthedashedlines ineachpanel.

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-negativemetastaseswhereasonly5%ofHER2-negative primarytumoursgenerateHER2-positivemetastases)[87], which affects treatment strategies.

Diagnosis,screeningandprevention

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. Populationscreeningforbreastcancerusingmammography 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 invitedtoscreening[88].Efficacyofmammographyscreening is age-dependent and is most evident in women 50–69 years of age, with weaker evidence of benefit in those outside this range[89]. Observational studies conducted in real-world screening practice provide similar evidenceonthebenefitofmammographyscreening torandomizedcontrolledtrials,althoughestimates 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 examplelowermastectomyrates.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,intheUnitedStates,UnitedKingdom,Europeand Australia),althoughtheorganizationofscreeningservicesanduptake(participation)bywomenvaryconsiderably between countries[94]. Southeast Asian countries implemented mammography screening later than Europeancountriesandseveral Asiancountrieshave onlypartialscreeningprogrammes[94].Nationswithlimitedresources(forexample,sub-SaharanAfricanand east African countries), where women often present with more-advanced cancers, have not implemented mammographyscreeningandthisreflectsthegenerally 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 mammographyscreeningisfalse-positiverecall,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,isinherentlyandmethodologicallychallenging

toquantify,andisthemostseriousharmfromscreening becauseitwouldlikelyleadtoovertreatment[88,90,91,95,96].

Womenathigherriskofbreastcancerthantheaverage (population) risk owing to predisposing genetic mutations(TABLE1) aregenerallyadvisedtohaverisk-tailored screening, which may include more frequent screening and/or use of technologies other than mammography. Adding MRI to mammography increases screening sensitivityinwomenwith*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, theInternationalAgencyforResearchonCancerreports that this has not been shown to improve mortality end points[90]. Use of adjunct imaging, such as ultrasonography, MRI and digital breast tomosynthesis (near-3D mammography), to screen women with high breast tissuedensity[100,101](heterogeneouslyormarkedlydense breasts), in which there is a large amount of glandular tissue on the mammogram, increases breast cancer detection[100]buthasnotbeenevaluatedformortalityoutcomes[90].Emergingtechnologiessuchastomosynthesis, contrast-enhancedmammographyandgammaimaging show enhanced cancer detection rates in observational studies when added to mammography, but the body of evidenceisrobustonlyfortomosynthesis[102],makingthis themostlikelycandidateforfuturebreastcancerscreening.Atpresent,thereisnoconvincingevidencethatthese new technologies enhance the screening benefit above that achieved with mammography alone[90]. Breast self-examinationhasnotbeenshowntoreducebreastcancer mortality,ortodetectintervalcancersbetweenscreening examinations[90].

Box3|**Recommendationsonpopulationscreening**

Populationmammographyscreeningrecommendations(forwomenwithaveragerisk[a]) differbetweencountriesandagencies,reflectingpersistentnon-consensusonthe magnitudeofbenefit(mortalityreduction)andharms(inparticular,theextentof overdiagnosis),andhowtheseoutcomesbalanceoutoverallandinspecificagegroups. Thisisexemplifiedinselectedrecommendations:

- TheUSPreventiveServicesTaskForcerecommendsscreeningevery2yearsfor womenaged50–74years,andemphasizesindividualizeddecisionsforthoseaged 40–49yearsthattakeaccountofthewoman'svalues[315]
- Canadianguidelinessupportshareddecisions,donotrecommendscreeningfor womenaged40–49yearsandrecommendscreeningevery2–3yearsforwomenaged 50–69years[316]
- TheAmericanCancerSocietyrecommendsannualscreeningforwomenaged 40–54years,andatransitionto2-yearlyscreeningforthoseaged≥55years(withthe opportunitytocontinueannualscreening)[317]
- The International Agency for Research on Cancer reports that there is sufficient evidencethatscreeningconfersbenefitinwomenaged50–74years(butlimited evidenceinthe40–49yearsagegroup)andthatthereissufficientevidencethat mammographydetectsbreastcancersthatwouldneverhavebeendiagnosedorwouldn everhavecausedharmifwomenhadnotbeenscreened(overdiagnosis)[90]
- Europeanrecommendationsspecifymammographythroughorganizedscreening programmesevery2–3yearsinwomenaged45–74years(andsuggestagainst annualscreening)[318]

[a]Womenataveragerisk donothaveapre-existingbreastcancerorapreviousdiagnosisofahigh-riskbreastlesion(suchasatypicalductalhyperplasia),anddonotharboura

Diagnosticwork-up

Women experiencing breast symptoms or breast changes,suchasalump,localizedpain,nipplesymptoms or skin changes, require appropriate diagnostic evaluation,asdowomenwhoarerecalledforfurther testingbecauseofpositivescreeningmammography. Diagnosingbreastcancerisbasedonatripletestcomprisingclinicalexamination,imaging(usuallymammography and/or ultrasonography) and needle biopsy[103]. Assessmententailsperformingtheappropriateelements of the triple test, factoring in the patients' characteristicsandpresentation,andshouldbeperformedbefore beginning treatment. Appropriate assessment helps to accurately discriminate between those who have breast cancerandthosewhohavebenignconditions(suchas fibroadenoma) or normal breast changes and can be reassured or safely managed with follow-up, obviating the need for surgical intervention.

Ultrasonographyisalmostuniversallyusedtoassess localizedsymptoms,asaninitialimagingmodalityin young women, to identify and characterize screen-detectedabnormalitiesand,preferentially,forimaging-guided percutaneous biopsy. Breast ultrasonography may also be used to characterize and biopsy axillary lymphnodesinwomensuspectedofhavingbreastcancer[104].ImagingevaluationalsoincludesMRIforspecific clinicalindications,suchasinwomenforwhomconventional imaging tests have been equivocal, inconclusiveordiscordant,forevaluatingwomenwithbreast implants and for evaluating women with axillary nodal metastasesbutnodetectable(occult)breasttumour[99,105]. PreoperativeMRIisalsoselectivelyusedforstaging newly diagnosed disease, but this is a debated practice given the limited evidence on whether it enhances a patient'sclinicaloutcomes[105].However,MRIisadvised forpreoperativeassessmentofnewlydiagnosedinvasive lobularcancers[99].

Pathologicalreporting

The use of a standardized synoptic pathology report withachecklistishighlyrecommended[106].Foraninva- sive carcinoma, the pathology report should provide detailsonthetumourhistotype(accordingtotheWHO classification), histological grade, hormone receptor and HER2status,tumoursizeandlymphnodeinvolvement; atsurgery,thesurgicalspecimenisusedtoprovideinformationonperitumoralvascularinvasionandsurgical marginstatus(BOX4).Thesedataareindispensablefor 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 histotypesandtheirsubclassifiers)[107](FIG.5).Breastcancer of 'no special type' is a carcinoma that does not fit intoaspecifichistotype.Someofthespecialtypes(such as tubular, cribriform and mucinous) — if at least 90% pure(thatis,nomixedhistologyor<10%ofanother

Box 4 | The pathology report for breast cancer

- Histological type according to the current WHO classification[107]
- Histological grade according to the Elston-and Ellis-modified Scarff–Bloom–Richardson system[108]
- Peritumoral vascular or lymphatic emboli[a]
- Hormone receptor status (oestrogen receptor (ER) and progesterone receptor)
- Human epidermal growth factor receptor 2 (HER2) status
- Excision margins (mm)[a]
- Tumour size, single or multiple tumours
- Ductal carcinoma in situ component type, grade and percentage
- Lymph node status
- Pathological stage according to the Union for International Cancer Control TNM system[122]
- Ki67 score according to the international group guidelines[b]

[a]Information obtained at surgical resection. [b]Particularly relevant for ER-positive HER2-negative

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 system[108] 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 tissues 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 approaches[113]. 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 recommended[114]. 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 recurrences[115]. 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 surgery[116]. 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 nodal 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

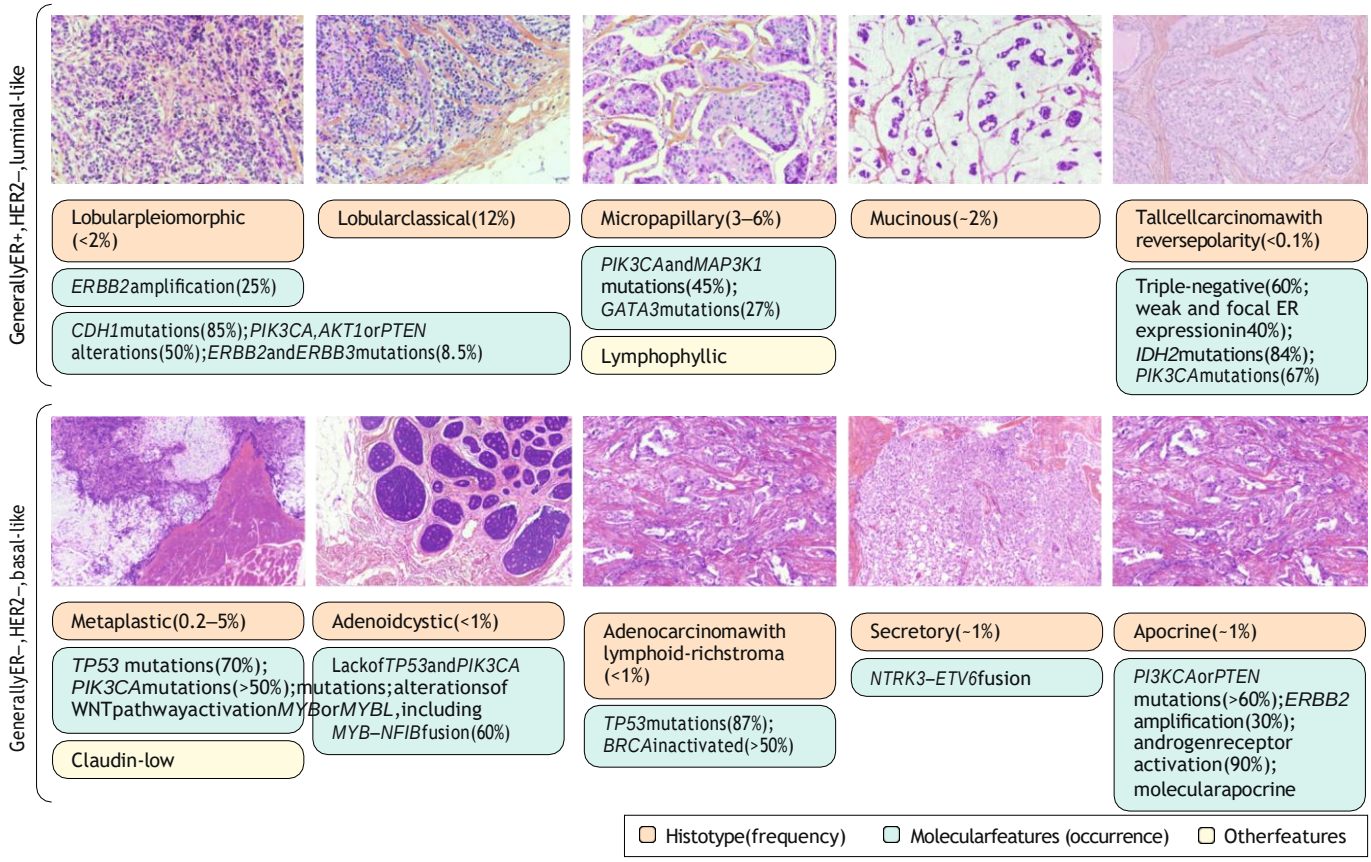

Fig. 5 | **Breast cancer histological types and molecular alterations.** The WHO classification recognizes different subtypes of invasive breast cancer, some of which are shown here, that harbour specific molecular alterations[107]. For example, lobular carcinomas and their precursors (lobular neoplasia) 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 adenoidcystic carcinoma is characterized by t(6;9) and the fusion gene *MYB–NFIB*[327]. Understanding these features may help in the design of tailored therapeutics for particular histological subtypes[324]. ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2. Image of tall cell carcinoma with reverse polarity courtesy of G. MacGrogan, Institut Bergognié, France.

breast carcinoma is the TNM system published by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC). This system provides information about the extent of cancer at the primary site (tumour or T), at the regional lymph nodes (nodes or N) and spread to distant metastatic sites (metastases or M). Tumour size is assessed microscopically by measuring the largest diameter. In the case of multicentric tumours[122], the largest tumour focus is the reference for T assessment (no additions 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 patients[123]. 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 prognosis[124]. As HER2-positive breast cancers and TNBCs are usually treated with chemotherapy with or without targeted therapy (see below,

Management), tumour-infiltrating lymphocytes alsorepresentpredictivebiomarkersfortreatmentrespons e. For the purpose of prognostication and treatmentdecision-making, several scoring systems have beendeveloped, such as Adjuvant! Online, the Nottingham Prognostic Index[125]and PREDICT[126]. These validated algorithms render good general estimates of patientprognosis and can aid in discussing therapy optionswith patients. However, they do not accurately reflect all specific patient subgroups or tumour biology sub-types[127]andcannotbeusedasthesolecriterionfor treatmentdecisionsinindividualpatients.Thesurrogate intrinsic subtypes are the most important criteria fortreatmentdecisions(FIG.1).Foursubtypesofbreastcancer are clinically valuable and imply distinct treatment approaches[110,128].LuminalA-liketumoursusuallypresent withlow-riskfeaturessuchaslowgrade,highexpression ofERandPR,lowproliferationandalow-riskGES.By contrast,theluminal-B-likegroupexpressesERbutnot (ortoalesserextent)PR,anddisplayshighgradeorhigh proliferationandhigh-riskGESs.TNBCandnon-luminal types show aggressive features such as high grade, no expressionofER,PRandHER2,andhighproliferation. HER2-positive tumours more frequently display G2 or G3features,loworabsentexpressionofERandPR,and mediumtohighproliferation.Theclaudin-lowintrinsic transcriptomicgrouphasnosurrogatebiomarkerandis consequentlynotcurrentlyusedinclinicalpractice.

Management

In early breast cancer without metastases, women with tumours that are deemed operable undergo surgery. However,mostwomenalsoneedsomeformofsystemic therapy. Systemic therapy can be given before surgery (neoadjuvant)inwomenwithlargetumoursforwhom reducingthetumourburdenispreferredorifinforma-tionofpathologicalcompleteresponse(pCR),whichis anabsenceofcancercellsinthesurgicalspecimenafter treatment, to pre-surgical treatment has prognostic value (suchasinHER2-positivediseaseorTNBC[129]).Moreover, systemictherapycanbegivenaftersurgery(adjuvant)if thesurgicalresultorbiomarkersindicateincreasedrisk ofrecurrence.Forsystemictherapies,manybiomarkers havebeenvalidatedfortherapeuticdecision-making (TABLE2).AllpatientswithER-positiveand/orPR-positive breastcancer,independentofHER2status,shouldreceive endocrinetherapytoblocktheERactivity.

Themainquestioninluminal(hormone-receptor-positive, HER2-negative) early breast cancer is which patientsneedchemotherapy(neoadjuvantoradjuvant) inadditiontoendocrinetherapy.Inpatientswithluminal Adiseaseandwithlowtumourburden,chemotherapy shouldbeomitted.Ingeneral,therecommendationfor chemotherapy in ER-positive, HER2-negative tumours maybeinfluencedbyproliferation(Ki67expression) and—ifavailable—theresultsofaGES.

Aswellasthetraditionalimmunohistochemicalmarkers, 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 MammaPrint[130]and OncotypeDx[131,132]issupportedbylevelofevidenceIaandtheir 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 (consideredhavingahigh-clinicalriskofrelapseaccording to traditional criteria) who have a low genomic risk score can safely forgo neoadjuvant or adjuvant chemotherapy. However, the use MammaPrint and OncotypeDxinpatientswith1–3positivelymphnodes 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)canbeperformedde-centrallyondedicated instruments. These assays have level of evidence IbforprognosisinpatientswithER-positive,HER2-negativebreastcancertreatedwithendocrinetherapy[136]; thelowerevidencelevelisattributedtoretrospective validation only. Indeed, the results generated from retrospective analysis of trials in which patients had only beentreatedwithendocrinetherapyneedtobeinterpreted with caution when applied to patients at high clinicalriskwhowouldnormallyrequirechemotherapy. Inadditiontoearlyrelapserisk,theseassaysalsopredictlaterecurrences,informationthatmaybeusedto indicate extended adjuvant endocrine therapy. Finally, GESshavenoroleintreatmentdecision-makingincases of very low clinico-pathological risk (such as patients withpT1a–b,pN0,G1andhighERdisease)orifclinico-pathological factors all point into the same direction (thatis,towardslow-riskortowardshigh-riskdisease).

Earlybreastcancer

Locoregional therapy in early breast cancer regardless ofmolecularsubtypecomprisessurgerytoremove the tumour and to either stage the axillary tumour burdenorexcisetheaffectedaxillarylymphnodes.

Box5|Inflammatorybreastcancer

Inflammatorybreastcancerisarareandaggressive-stage(stageT4d)phenotypeof breastcancerencompassing~3%ofnewlydiagnosedbreasttumourscharacterized byasubstantialinvolvementofdermallymphaticsofthebreastskin.Thediagnosisis clinicalwithrapidevolutionofdenovoerythema(rednessoftheskin),'peaud'orange' (dimpledtexture)and/orwarmswollenbreastinvolvingatleastone-thirdofthebreast skinwithorwithoutaclinicalbreastmass[319].Patientsshouldundergoskinbiopsyto identifydermallymphaticembolithatarefoundin<75%ofcasesandtumourbiopsies incaseofidentifiablemass[319].Thiscancertypehastobedifferentiatedfromsecondary inflammatorybreastcancer(thatis,thedevelopmentofinflammatoryskinchangesthat mimicprimaryinflammatorybreastcancereitherinabreastthatalreadyhadcanceror onthechestwallafteramastectomyfornon-inflammatorybreastcancer)andfrom locallyadvancedbreastcancer(thatis,breastcancerthathasextendedtothechest wall(stageT4a),thathasulceration,ipsilateralsatelliteskinnodulesorskinoedema (includingpeaud'orange;stageT4b)orboth(stageT4c)).Inflammatorybreastcanceris associatedwithhighbodymassindex,youngerageatdiagnosis,highertumourgrade andoestrogenreceptor-negativeand/orhumanepidermalgrowthfactorreceptor2-positivestatus,andismorefrequentinnorthAfricanorAfrican-Americanwomen[320].

Postoperativeradiationtherapyand/orsystemicther- apies (which may comprise endocrine therapy, chemotherapy,targetedtherapyandbone-modifyingagents) areusuallygivendependingontheinitialtumourbur- den and molecular expression pattern of the tumour. Tumourdown-sizingwithsystemictherapiespriorto surgeryisalsoencouragedforlargetumoursprovided thatthesamesystemictherapywouldalsobeindicated after surgery. FIGURE 6summarizes the therapeutic strategies for early breast cancer.

Surgery. Surgeryoftheprimarytumourremainsacornerstoneofcurativebreastcancertreatment.Overthepast decades,breastconservationhasbecometheprimary surgicalgoal[137],substitutingmastectomy,whichwas thehistoricalstandard(FIG.7).Resectionoftheprimary breasttumouriseitherthefirststepoftreatmentorsecond,afterinitialsystemictherapydependingontumour size,tumourtobreastsizerelationship,tumourbiology, comorbiditiesandpatientchoice[138].Afterneoadjuvant systemictherapy,thesurgicalextentshouldbeoriented

Table2|**Biomarkers validatedfor therapy decision-making**

Biomarker	Methodandthreshold	Use	LOE
ER	IHC;positiveif≥1%	• EssentialforthecharacterizationoftheIHCluminalgroup • Poorprognosticmarkerifnegative • Predictive markerforendocrinetreatment • Mandatoryforendocrinetreatmentprescription	I
PR	IHC;positiveif≥1%	• Ifnegative,tumourclassifiedasIHCluminalB • Strongpoorprognosticmarkerifnegative • Predictive markerforendocrinetreatment	I
HER2	• IHC;positiveif>10%complete membranestaining(3+) • Single-probeISH;positiveifHER2 ≥6copies • Dual-probeISH;positiveifHER2 andCEP17≥2andHER2≥4copies, orHER2andCEP17<2andHER2 ≥6copies	• EssentialtocharacterizeHER2-enriched(ER-negative)diseaseand luminalB,HER2-positive • Prognosticmarker • Predictivemarkerforanti-HER2treatment • Mandatoryforanti-HER2therapy	I(IHC) andI(ISH)
Ki67	IHC;nofinalconsensusoncut-off valuebutvalues<10%areconsidered lowand>30%areconsideredhigh[a]	Absenceofinternationalconsensusforscoringandthreshold	I
		PrognosticvalueinER-positive,HER2-negativetumours(primary tumoursandpost-neoadjuvanttumourresidues)	I
		AbsenceofprognosticvalueinHER2-positivediseaseorTNBC	I
		Predictiveofresponsetoneoadjuvantendocrinetherapy[a]	I
		Predictiveofresponsetoneoadjuvantchemotherapy	Expert opinion
		Ifelevated,chemotherapyisoftenprescribedinER-positive, HER2-negativetumours	Expert opinion
		PartoftheIHCdefinitionofluminaltumourswherebywhenKi67islow, luminalAtumourlikelyandwhenKi67high,luminalBtumourlikely	Expert opinion
Intrinsicsubtypes	Geneexpressionprofile,N-Counter technology	Prognostic	IIandIII
		Predictive;differentresponsestoneoadjuvantchemotherapyand anti-HER2therapyaccordingtosubtype	I
First-generation signatures(MammaPrint andOncotypeDx)	Geneexpressionprofile,RT-PCR	• PrognosticforER-positive,HER2-negativetumours(with0–3 involvedlymphnodes) • Chemotherapyisindicatedifhighriskorhighscore	Ia
Second-generation signatures(Prosigna andEndopredict)	N-Countertechnology,RT-PCR	• PrognosticforER-positive,HER2-negativetumours(with0–3 involvedlymphnodes),includeTsizeandNstatusintheirfinalscore • Chemotherapyisindicatedifhighriskorhighscore	Ib
*PIK3CA*mutations	MutationsdetectedbyPCRorNGS inexons9or20fromcancerbiopsy specimenorliquidbiopsies	PredictivemarkerforspecificPI3KCAinhibitors(suchasalpelisib) inluminalAandluminalBmetastaticbreastcancer	Ia[284]
Germline*BRCA* mutation	NGSonbloodlymphocytesoron tumourcells	• PredictivemarkerforPARPinhibitorsinmetastaticbreastcancer (evidence-basedforHER2-negativedisease) • Germlinemutationsimplyfamilycounselling • Predictiveimpactofsomaticmutationsisunderevaluation	Ia[30]
PD-L1	IHC;positiveifexpressioninimmune cells≥1%intumourspecimens (metastaticorprimary)	Predictiveforimmunotherapywithatezolizumabcombinedwith nab-paclitaxelinTNBC	Ia[249]

CEP17,chromosomeenumerationprobe17;ER,oestrogenreceptor;HER2,humanepidermalgrowthfactorreceptor2;IHC,immunohistochemistry;ISH,insitu 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,progesteronereceptor;RT-PCR,PCRwithreversetranscription;T,tumour;TNBC,triple-negativebreastcancer.DatafromREFS[111,128,225].[a]Accordingtothe InternationalKi67WorkingGroupGuidelines[114].

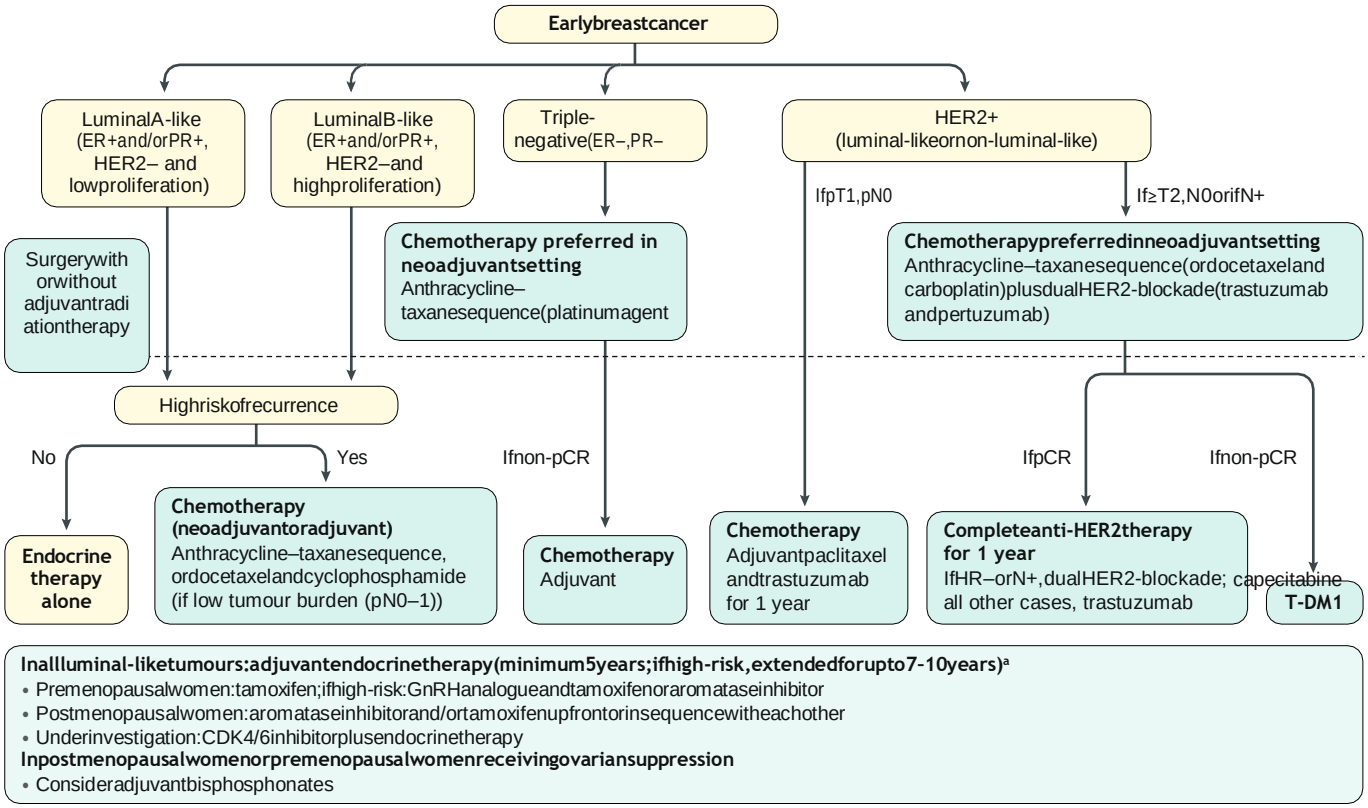

Fig.6|**Algorithmforearlybreastcancer.** Managementofearlybreastcancerisbasedontumourburdenandsubtype. Allpatientswithoestrogenreceptor(ER)-positivediseasereceiveadjuvantendocrinetherapyaftersurgery.Ifpatientsare athighriskofrecurrence(forexample,owingtohigh-riskgeneexpressionsignatureresultswith0–3involvedlymphnodes, involvementof≥4lymphnodesora>10%riskofbreastcancer-specificmortalityat10years)[130],chemotherapyneedsto berecommendedaswell.Intriple-negativeandhumanepidermalgrowthfactorreceptor2(HER2)-positiveearlybreast cancer,neoadjuvantsubtype-specificsystemictherapyisstandard,followedbysurgery.Inthecasethatpathological completeresponse(pCR)isnotachieved,systemictherapycanbeescalated.Bisphosphonatesareanadditionaladjuvant therapyoptionforallpostmenopausalpatientsandpremenopausalpatientsreceivingovariansuppression;theyalso conservebonedensity.Ifindicated,radiationtherapycanbeadministeredaftersurgery.Themanagementalgorithmtakes evidence-basedregisteredtherapyoptionsintoaccount.Availabilityandreimbursementofindividualdiagnosticor therapeuticoptionsmaydifferregionallyandrequireadjustmentsofthetreatmentconceptsoutlinedhere.−,negative; +,positive;GnRH,gonadotropin-releasinghormone;HR,hormonereceptor;p,pathological;PR,progesteronereceptor; N,nodestatus;T,tumourgrade;T-DM1,ado-trastuzumabemtansine.[a]Onestudyshowedabenefitwith15yearsofadjuvant endocrinetherapy[328].

atthe‘new’tumourborders[139].Recently,thediscussion 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 strategy[121]. Frozen sections, in whichthemarginsoftheresectedspecimenareassessed duringthesurgicalprocedure,canassistthesurgeonto optimize the resection extent[142], but are not available everywhere due to resource limitations[143].

Indeed, breast-conserving surgery has been made possiblebythewidespreaduseofneoadjuvantsystemic therapytodownsizetumoursandthedevelopmentof advancedoncoplastictechniques[144],suchasthe‘round-block’procedure[145](avolumedisplacementtechnique forreconstruction)ortheV-mammoplasty[146](inwhich aV-shapedwedgeiscutaroundthetumouruptothe pointofthenippleandthebreastis‘closed’together). However,anincreasingrateofso-calledprophylactic mastectomies(inwhich‘healthy’breastsareremovedfor preventionbecauseoffearofthedisease)isundermining this success; in general, prophylactic mastectomy does not improve overall survival[147]in patients without *BRCA*germlinemutations.Indeed,inyoungwomen <40yearsofage,breast-conservingsurgerypluswhole-breast radiation therapy renders equivalent overall survival compared with mastectomy[148]. If mastectomy is oncologically required, breast reconstruction can be offered as an immediate or delayed procedure depending on the oncological situation and patient preference. Reconstructivetechniquescompriseimplantsurgeryas well as autologous tissue breast reconstruction.

As axillary dissection results in considerable morbidity(despiteeffectivelyachievinglocoregionalcontrol)[149], efforts to de-escalate nodal assessment have been successfullyimplementedinseveralpivotalclinicaltrials[150]. 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,numbnessoraxillaryweb

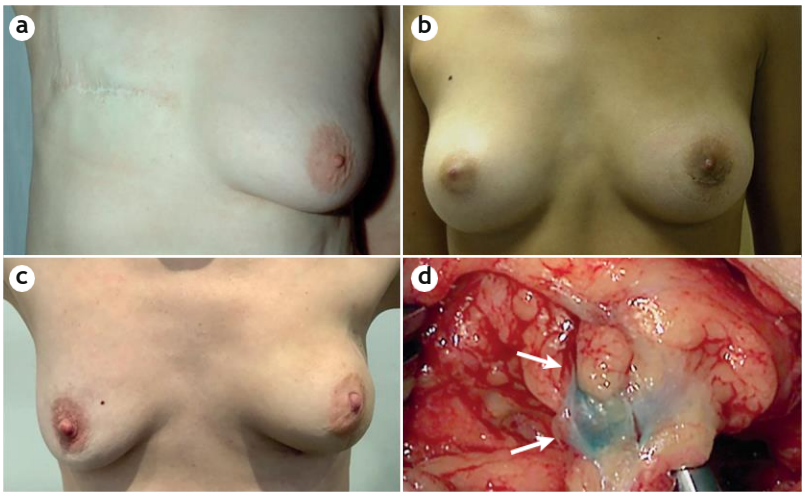

Fig.7|**Breast-conservingsurgery.** Currentsurgicalstandardsofcareforbreast-conservingsurgerynotonlypreservetheorganbutalsomaintainthepatient'sself-image, femininityandintegritycomparedwithmastectomy(panel**a**;postmastectomy,8weeks aftersurgery).Selectionfactorsforbreast-conservingsurgeryincludetumourtobreast sizerelationship,numberoftumours,tumourbiologyandthepatient'spreference(after adequateinformation).Evencomplexsurgicalsituationscanbemanagedwithsatisfying aestheticresults(panel**b**;breast-conservingsurgeryforcancerofthe leftbreast,6weeks aftersurgery)withmodernoncoplastictechniques.Incasesinwhichmastectomyis inevitable(forexample,insufficientdownstagingafterneoadjuvantsystemictherapy), theprocedureshouldbe(intermsofsurgicaltechnique)undertakenwiththeoptionof subsequentreconstructiveproceduresinmind;thatis,unnecessary'invasiveness'(affecting themuscle,bloodvesselsandskin)shouldbeavoidedwheneveroncologicallysafeclearmargi nscanbeachieved.Insituationsinwhichnipple-sparingmastectomy(panel**c**;nipple-sparingmastectomyoftheleftbreastwithimmediatetransversemusculocutaneousgracilis flapreconstruction,8weeksaftersurgerywithcorrectionoftherightsidestillpending)and orskin-sparingmastectomyareindicated(forexample,extensiveductalcarcinomainsituor risk-reducingsurgeryinwomenwithgermline*BRCA*mutations),completecounselling aboutallavailablestrategies(autologousoralloplastic,immediateordelayed,modified radicalversussskin-sparingversusnipple-sparingmastectomy)shouldbeprovidedtothe patient.**d**|Anothereffortoreducethepotentialharmsofbreastcancersurgeryincludes substitutingaxillarynodedissection(removal)withsentinelnodebiopsy.Inthistechnique, adyeisinjectedintraoperatively(and/oraradioactivetracerpre-operatively)toidentifythe sentinelnode(arrows)sothatitcanbeidentifiedandremoved.

syndrome (whereby rope-like soft-tissue density can develop in the axilla after dissection)[151] and is associated with excellent long-term locoregional relapse rates[152]. 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 involvement[153].

In the context of neoadjuvant therapy, sentinel node biopsy is performed after the systemic therapy to enable the patient to benefit from locoregional tumour downstaging. Whether 'escalation' of radiation therapy 'compensates' for less invasive axillary surgery is less clear and may at least partly erase the benefits of the surgical de-escalation[154]. Currently, the indications for sentinel node biopsy include situations after neoadjuvant systemic therapy[155], but other surgical issues remain under discussion in this special context[156]. 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 effect[160]. The proportional reduction of locoregional recurrences with radiation therapy following surgery is, for most indications, ~75%, with a dose–effect relationship for local control[161]. 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 therapy[162]. 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 (>5cm)[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 nodes[169]. Thus, as we await the outcome of the MRC/EORTC (BIG 2–04) SUPREMO phase III trial[170] (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 survival[174]. 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 combined[175]. 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 exam- ining 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.

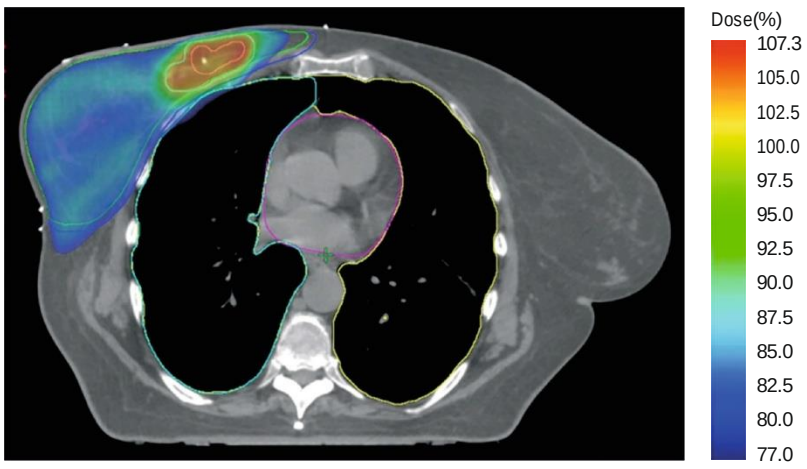

Fig.8|**Radiation therapy for breast cancer.** The schematic illustrates the volumetric intensity-modulated dose distribution at the level of the original tumour location, including a simultaneous integrated boost dose for a patient with early-stage disease who had a medially located primary tumour bed 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 as single intraoper- ative 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 electrons[189] or low-energy photons[190] (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 trial[193]. 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 trials[194]. A GnRH analogue plus an aromatase inhibitor also improves

recurrence-free survival compared with tamoxifen alone orcomparedwithtamoxifenplusaGnRHanalogue, butattheexpenseofhighertoxicity;however,regard- ing overall survival, tamoxifen plus a GnRH analogue seemsmorebeneficial[194,195].Inpostmenopausalwomen withluminalearlybreastcancer,tamoxifenandanaro- mataseinhibitorarestandardeitherasmonotherapies (upfront)orinsequence.Anaromataseinhibitorsshould be included in adjuvant endocrine therapy to reduce recurrenceratescomparedwithtamoxifen(albeitwith only minor impact on overall survival). Compared withtamoxifen,5yearsofanaromataseinhibitorreduces breastcancermortalityby~15%(relativebenefit)[196]. Thedefinitechoiceofagentdependsontherelapserisk, tolerability,bonehealthandpatientpreference.

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 burden[197]. Extended adjuvant endocrine therapy for up to 10 years, or even 15 years, imparts favourable patient outcomes[198]. Nevertheless, the deci- sionforsuchanapproachneedstotakerelapseriskand tolerability into account; extended adjuvant endocrine therapy is particularly beneficial for patients at high risk for relapse (that is, those with node-positive dis- ease). Several randomized phase III trials have shown CDK4/6inhibitors(whichblockcellcycling)tobeactive and they have become the preferred treatment optionin combination with endocrine therapy in hormone receptor-positive, HER2-negative metastatic breast cancer[199–201]. Currently, four large international adju- vant trials are evaluating addition of a CDK4/6 inhib- itor 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)arestillrecruiting.

InluminalHER2-negativeearlybreastcancer,the recommendationforchemotherapyinadditiontoendo- crinetherapydependsontheindividualriskofrecur- rence.Ingeneral,iftheriskofrecurrenceisestimatedto be>10%over10years,chemotherapyisrecommended. Standardchemotherapyregimensincludeananthracy- clineandataxanegivenpreferentiallyinsequencewith care to avoid excessive toxicity[202]. 5-Fluorouracil does notincreaseefficacyofananthracyclineandcyclophos- phamidebackboneinearlybreastcancer[203].Inpatients withintermediateclinicalrisk,docetaxelpluscyclo- phosphamide is not inferior to a standard sequential anthracycline–taxane regimen[135]. However, in patients with high clinical risk (that is, >3 involved lymph nodes),ananthracycline–taxaneregimenseemstobe superior[204].Dose-denseadministrationofchemother- apy(inwhichtherateofdelivery,ratherthantheoverall dose, is increased) significantly improves 10-year breast cancer-relatedmortalityindependentofERstatusand tumourburdenwithoutanydetectableadverseeffects on non-breast-cancer-related mortality[205]. Adding drugs, suchascapecitabine,gemcitabineorbevacizumab,toan anthracycline–taxanechemotherapydoesnotimprove outcomes in early breast cancer.

InHER2-positiveearlybreastcancer(thatis,luminal- likeandnon-luminal-likeHER2-positiveearlybreast cancer),neoadjuvantchemotherapytogetherwithanti- HER2therapyhasbecomethestandardofcare(atleast intumours≥cT2,cN0andallcN+).Thisapproachispre- ferred as achievement of pCR is correlated with improved outcome(DFSandoverallsurvival)[129]andadjuvantther- apyselectionmaybeinfluencedbypCRstatus.Intheneo- adjuvantsetting,dualHER2-blockadewithtrastuzumab andpertuzumabtogetherwithchemotherapyimproves ratesofpCRandis,therefore,consideredstandard[206]. Based on data from the adjuvant setting, chemotherapy inHER2-positiveearlybreastcancermayconsistofeither ananthracycline–taxanesequenceoracombinationof docetaxel and carboplatin together with anti-HER2 therapy(for1year).TheKATHERINEtrialdemon- stratedforthefirsttimethatpCRstatuscanbeusedto escalatepostoperativeanti-HER2therapy:switching fromtrastuzumab(ananti-HER2antibody)toT-DM1 (a trastuzumab–emtansine conjugate that combines HER2-blockadewithacytotoxicagent)inthecaseofnon- pCRsignificantlyandsubstantiallyimproveoutcomes (HR0.5forinvasiveDFS;95%CI0.39–0.64,*P*<0.001)[207] andwillnowbethenewstandardforpatientswith non-pCR.

In the adjuvant setting, dual HER2-blockade with trastuzumab and pertuzumab also improves DFS compared with trastuzumab alone. After short- termfollow-up, absolute 3-year survival differences are small and patients with node-positive or hormone receptor- negativetumourseemtobenefitmost[208].Inpatientswho hadalreadyreceived1yearoftrastuzumab,anadditional 1 year of neratinib (versus placebo) improved invasive DFS with the effect being most pronounced in in hor- monereceptor-positive,HER2-positivedisease(HR0.73; 95%CI0.57–0.92,*P*=0.0083)[209].However,theadditional valueofneratinibinthecontextofadjuvantdualblock- adeorpost-neoadjuvantT-DM1isnotclear.Inpatients with a low tumour burden, de-escalation seems possi- ble;adjuvantadministrationofpaclitaxeland1year of trastuzumab is correlated with excellent outcomesin patients with pN0 HER2-positive tumours ≤3cm in size[210,211].Sofar,1-yeartotaldurationofanti-HER2ther- apy remains the standard for all patients as the data on shorterdurationarestillcontroversial;thePERSEPHONE trial[212]demonstratednon-inferiorityof6monthsof trastuzumabcomparedwith12monthsforpatients receivinganthracycline–taxane,whereasothersstudies, suchasPHARE[213]andSOLD[214],havefailedtoprovethis non- inferiority. Longer than 1 year of duration is nomoreeffective,asdemonstratedbytheHERAtrial[215,216].

InTNBC,chemotherapyisstandardandtypicallycon- tainsananthracyclineandataxane,althoughdocetaxel and cyclophosphamide are as effective[135]— at least in TNBCwithlimiteddiseaseburden—andmaybeused if anthracyclines need to be avoided. As with HER2- positiveearlybreastcancer,chemotherapyispreferentially administeredintheneoadjuvantsetting.Achievementof a pCR is correlated with improved outcome (DFS and overallsurvival)[129];aplatinumcompoundincreasespCR ratesindependentof*BRCA*status[217].Addingaplatinum compoundalsoincreasestoxicity(mostlyhaematologi- cal),whichmayimpairadequatetaxanedoseintensity.

Whether adding platinum also improves outcome in addition to pCR is still under debate as 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 CREATE xtrial; additional adjuvant capecitabine improved DFS and overall survival, with the survival benefit being most pronounced in TNBC[219].

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 inhibitors[220], its use may also improve DFS in selected postmenopausal patients[221] but not in a more general breast cancer population as demonstrated by the negative phase IIID-CARE trial[222]. 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 therapy[223]. In premenopausal women receiving ovarian suppression, zoledronic acid also improved DFS in the ABCSG-12 trial[195], but there is no clear advantage for premenopausal women in other trials such as AZURE[224] as well as in the EBCTCG meta-analysis[223].

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 years[225]. 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

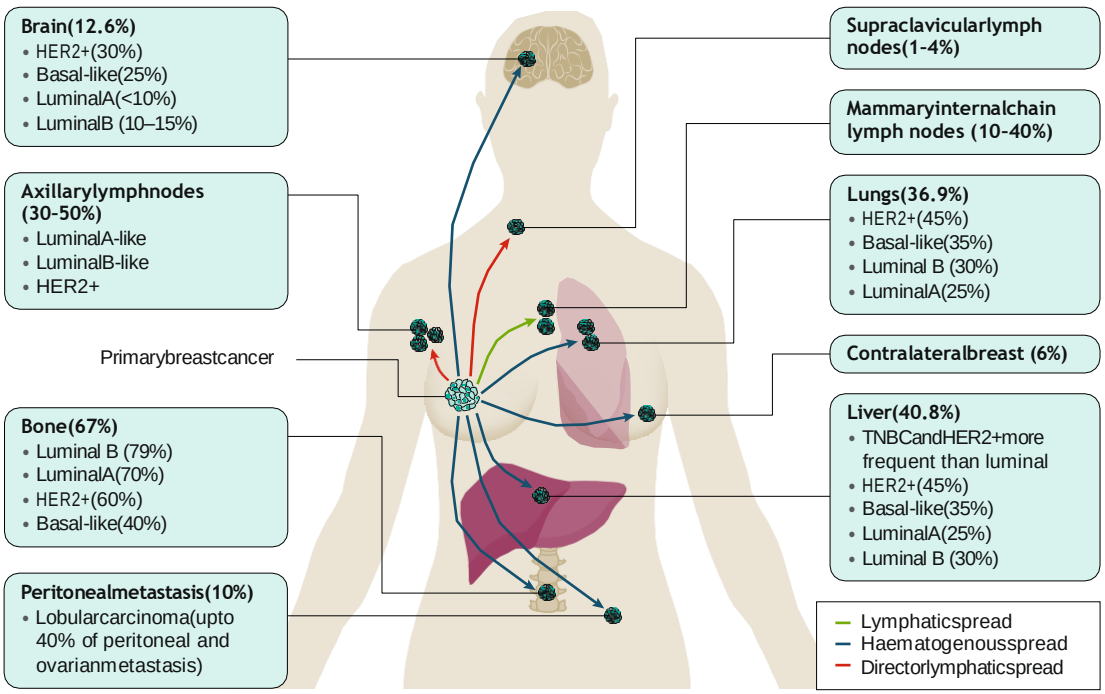

Fig.9|**Commonmetastaticsitesinbreastcancer.** Themostfrequentnodalsiteistheaxillarylymphnodesandthe frequencyofinvolvementdependsonthesizeofthetumour.10–40%ofbreastcancershavemetastasisintheinternal mammarychain,influencedbythetopographyofthetumourinthebreast(innerquadrantversusouterquadrantandthe size).Controversyaboundswithregardtothevalueofstagingandtreatmentofthesenodes,forexample,whetherornot theyneedtobedealtwithsurgicallyorbyradiationtherapy.Breastcancerhonestodistantmetastaticsitesdifferentially accordingtothemolecularsubtypeaccordingtodatafromtheUSSurveillance,Epidemiology,andEndResultsProgram (SEER)database(datafrom2010to2014,295,213patientswithinvasivebreastcancer).Locoregionallymphaticspreadis lessfrequentintriple-negativebreastcancer(TNBC)thaninothersubtypes.Theoppositeistrueforbrainmetastases, whicharemorefrequentinTNBCthanluminaltumours.Additionally,metastaticdiseaseoccursatdifferenttimepointsin thenaturalhistory;forexample,luminalAcancerstypicallyshowlatemetastaticoccurrence(5–10yearsafterdiagnosis) andlongsurvivalispossible.Bycontrast,basal-likesubtypesusuallymetastasizewithin2years,andlongsurvivaldurations areuncommon.Thepercentageofmetastasesfoundatthatsitearesshowninparentheses.+,positive;HER2,human epidermalgrowthfactorreceptor2.BasedondatafromREF.[81].

reduce the risk of dying due to distant metastasis[162]. 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 disease[226]. 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 environments[235].

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 trial[238]. 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 cells[239]. 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 immunotherapy[242]. Most breast cancer types are non-inflamed, immune 'cold' tumours that are likely unresponsive to immunotherapy. Thus, the microenvironment 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 setting[243]. 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 tumour[225]. Multigene panels have not yet been proven useful in the metastatic setting in clinical trials and are only research tools[225]. 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 imaging[225].

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 PALOMA3 phase III trial suggest that the PFS benefit may be maintained as an overall survival benefit, but this finding was not statistically significant[245]. 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

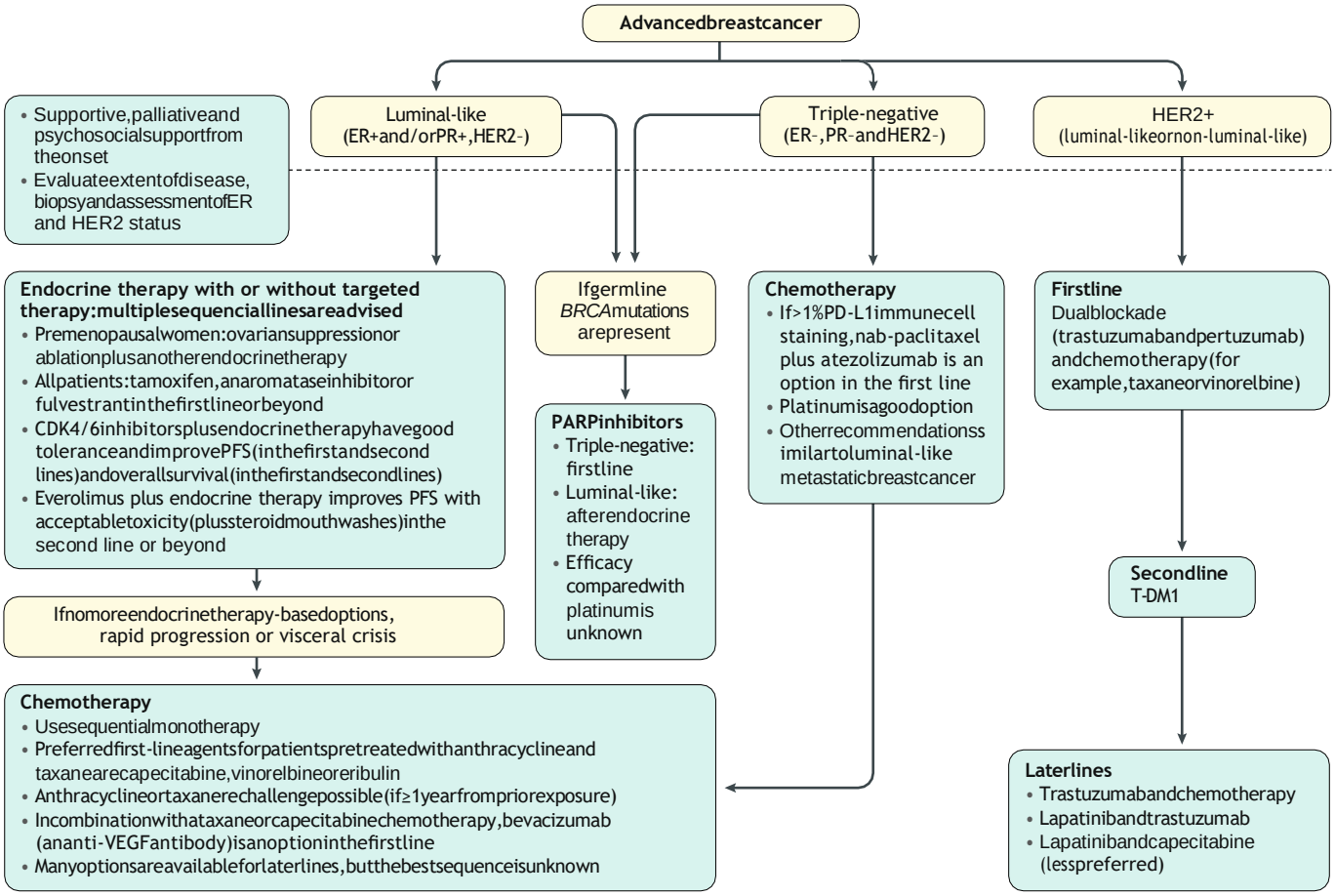

Fig.10|**Algorithmforadvancedbreastcancer.** Managementofadvancedbreastcancerwithdistantmetastasesshouldbeaccordingtosubtypeaswellasdiseasecharacteristicsandpatientpreferences.Supportive,palliativeandpsychosocial supportarecrucialfromthetimeofdiagnosis.Biopsyofametastaticsiteandassessmentofoestrogenreceptor(ER), progesteronereceptor(PR)andhumanepidermalgrowthfactorreceptor2(HER2)status,atleastonceinthemetastatic setting,arealsonecessary.Endocrinetherapy,withorwithouttargetedtherapy,isthemainstayforluminal-likedisease, and—unlesslife-threatening—severallinesaretobeusedbeforecommencingchemotherapy.Whenchemotherapyis used,sequentialmonotherapyisadvised.Fortriple-negativedisease,chemotherapyisthemaintreatment,withno specificrecommendationsexceptthatplatinumisoneofthepreferredoptions.Triple-negativetumourswithimmune cellsexpressingprogrammeddeath-ligand1(PD-L1)maybecandidatesforfirst-lineimmunotherapy.ForHER2-positive disease,itiscrucialtocontinueblockingtheHER2pathway,withasequenceofanti-HER2agentsandchemotherapy; combinationsofendocrinetherapywithanti-HER2therapycanalsobeusedinER-positive,HER2-positivedisease, preferentiallyasmaintenancetherapy.Forwomenharbouringermline*BRCA*mutations,poly(ADP-ribose)polymerase (PARP)inhibitorsareanadditionaltherapyoption.Themanagementalgorithmtakesevidence-basedregisteredtherapy optionsintoaccount.Availabilityandreimbursementofindividualdiagnosticortherapeuticoptionsmaydifferregionally andrequireadjustmentsofthetreatmentconceptsoutlinedhere.−,negative;+,positive;PFS,progression-freesurvival; T-DM1,ado-trastuzumabemtansine;VEGF,vascularendothelialgrowthfactor.

recommended;combinationchemotherapyshouldbe reserved for situations of visceral crisis or rapidly progressivedisease[225].Thepreferredfirst-lineagentsfor patientspreviouslytreatedwithadjuvantanthracyclines andtaxanesarecapecitabine,vinorelbineoreribulin. Anthracycline and/or taxane rechallenge therapy may alsobeanoptioninpatientswithatreatment-freeinterval of≥1year.Incombinationwithtaxaneorcapecita- bine chemotherapy, bevacizumab (an antibody against vascularendothelialgrowthfactor)isafirst-lineoption thatimprovesPFSbutnotoverallsurvival;itisregistered inEuropebutnottheUnitedStates[246].Forlaterlinesof therapy,manyavailableoptionsareavailableandthe decisionshouldbeindividualizedconsidering different toxicity profiles, previous exposure, patient preferences, country availability and costs[225]. The duration of each regimen and the number of cycles should also be individualized,andchemotherapyshouldbecontinueduntil diseaseprogressionorunacceptabletoxicity.Again,the optimal sequence is unknown.

ForHER2-positiveadvancedbreastcancer(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 pertuzumabpluschemotherapy(usuallydocetaxel,paclitaxel,nab-paclitaxel,vinorelbineorcapecitabine)[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 used[225]. 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 used[225], 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 awaited[249].

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 chemotherapy[252] and improves measurement of tumour size compared with ultrasonography, mammography and clinical examination[253]. 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 cancer[254].

In the metastatic setting, imaging of the chest (CT or X-ray), abdomen (CT or ultrasonography) and bone (usually radionuclide bone scan) is recommended[225] for pretreatment staging, although PET or PET–CT may be used selectively for staging or restaging[255]. 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 testing[256]. 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 outcomes[257]. 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 modalities[257]. 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 imaging[257]. 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 throughall 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 evidence[263]. 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 understudy[264].

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 regimens[265]. 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 function[266]. 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 valuable[91]. 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	• 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	• 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	• 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	• Copyright held by EuroQol • Permissions details at https://euroqol.org/
Patient-Reported Outcomes Measurement Information System[339,340]	PROMIS-10	10	7 days	• 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.

diagnosisandareprovidedwithadequatesupportive and palliative care services.

Earlybreastcancer

Inearlybreastcancer,cancer-specificmortalityhasbeen substantiallyreducedbymodernmultimodaltherapy concepts.Treatmentde-escalationandescalationare currentlybeingevaluated—inbothlocoregionaland systemic therapies. However, evidence-based adaptation of current standards is required to ensure that patientsarenotundertreatedwhileattemptingtoavoid overtreatment. De-escalation of radiation therapy trials areattemptingtodefinepopulationswithluminal Aearlybreastcanceratlowrisk,forwhomradiation therapy after breast-conserving surgery may not be needed. Surgical de-escalation trials are examining the roleofsentinelnodebiopsyincN0disease,provided thatstandardpostoperativetherapyisbeingadministered. The neoadjuvant setting in early breast cancer offersanidealmodelforinvivoresponsetestingand stratifyingthepostoperativeapproachaccordingtopCR. Forexample,patientswithpCRmaybeableto de-escalate postoperative adjuvant therapy whereas patientswithnon-pCRarecandidatesforfurtherapyescalation.Withregardstolocoregionaltherapy, theroleofsurgeryincasesofclinicalcompleteresponse (thatis,whetheritcanbecompletelyomitted)andthe roleofpostoperativeradiationtherapyinpatientswho converted from node-positive to node-negative disease with neoadjuvant systemic therapy (for example, the aforementioned NSABP-B51/RTOG1304 trial) arebeinginvestigated.Inluminalearlybreastcancer, short-termendocinetherapybeforesurgeryandassessmentoftheproliferationresponse(forexample,Ki67 ≤10%) in the surgical specimen — as a surrogate for endocinetherapyresponsiveness—mayhelptoadapt adjuvant therapy concepts[276–278].

In the adjuvant setting, decreasing unnecessary toxicities from overtreatment without compromising outcomewillalsobeachallengefortheyearstocome. However,thedownsideofthesuccessinadjuvanttherapies is the substantial alteration in metastatic disease, withless-favourablemetastasispatternsandshorterpostmetastasissurvival[279],whichincreasesthechallengefor managementofadvancedbreastcancer.Epidemiological datasuggestthatcontemporaryadjuvantsystemictherapiesexertevolutionarypressuresonthetumours[279]given changes in metastatic patterns and decreased survival timesthathavenotbeenobservedindenovometastatic breast cancer[280]. These epidemiological findings parallel those of whole-genome sequencing studies, which showthatmetastaticbreastcancershavesimilargenetic patterns to primary breast cancer with subtype-specific enrichment of selected driver mutations in the metastaticlesions[281].Ininvasivelobularcancers,matched-pair analysis of primary tumours and their corresponding metastasesalsorevealedacquisitionofseveralgenomic alterations(suchasmutationsin*CDH1*, *ESR1*,*ARID1A*, *ERBB2*,*GATA3*, *IGF1R*,*MAP3K1*and*PIK3CA*)atafrequency of 5–11% in metastatic disease that could be associatedwithdiseaseprogressionanddevelopmentof endocrine resistance[282].Someofthesealterations,such as*ESR1*or*PIK3CA*,arealreadybecomingrelevantfor choosing specific targeted therapies.

Advancedbreastcancer

Upcomingdrugsandpathways. Recentpreclinicalstudieshaverevealedvarioustargetablepathwaysthatmay optimize available therapies or overcome resistance to availabledrugs(FIG.11).Forexample,thePI3K–AKT–mTOR signalling pathway is the subject of intense researchinbreastcancer.Pan-PI3Kinhibitorsprovedto betootoxicandtheirdevelopmentwasreplacedbyPI3K isoform-specific inhibitors such as alpelisib and taselisib[283]. Alpelisib, an α-specific PI3K inhibitor, has been approved by the FDA on the basis of the longest PFS improvementofthisclassofagentssofar(~5monthsof benefitinPFS,HR0.65;95%CI0.50–0.85)inhormone-resistantER-positive,HER2-negative*PIK3CA*-mutated advanced breast cancer when combined with fulvestrant, with moderate toxicity[284]. Taselisib, a β-sparing PI3Kinhibitor,moderatelyimprovesPFSininthesame population when combined with fulvestrant in patients withwild-typeandwith*PI3K*-mutanttumoursbutwith clinicallyrelevanttoxicities[285].Recently,tworandomized phaseIIstudieshaveshownthatAKTinhibitorscanbe active in patients with TNBC. When the AKT pathway was active, both ipatasertib[286]and capivasertib[287]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 involvedinchromatinremodellingandepigeneticregulation,havebecomeaveryinterestingfieldofresearch. 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)isunderway[289].AnotherphaseIIItrial withtheoralsubtype-selectivehistonedeacetylaseinhibitorchidamidehasalreadyshowninterestingresultswith moderatetoxicity[69].

In HER2-positive metastatic breast cancer, new antibody–drug conjugates and monoclonal antibodies arebeingtestedinphaseII/IIItrials.DS-8201,anew anti-HER2antibody-drugconjugatedtoatopoisomeraseIinhibitor,hasshownpotentactivityinvitroand in vivo[290], and seems to be effective in patients with HER2-positive breast cancer who were previously treated withT-DM1(REF.[291])aswellasinpatientswithadvanced breastcancerwithlowHER2expression.Margetuximab, ananti-HER2Fc-optimizedmonoclonalantibody,has shown preliminary activity in heavily trastuzumab-pretreated patients in a phase I trial[292]. The phase III SOPHIA trial showed a significant but modest PFS improvementformargetuximabversustrastuzumaband a chemotherapy backbone in both arms[293]. New HER2-targeted tyrosine kinase inhibitors such as tucatinib (particularlyincasesofbrainmetastases)andneratinib (particularly in cases of HER2-negative, HER2-mutant andHER2-positivebreastcancer[294])arealsobeingdeveloped.ThephaseIIINALAtrialshowedsignificantly improvedPFSbutsubstantialgastrointestinaltoxicityfor

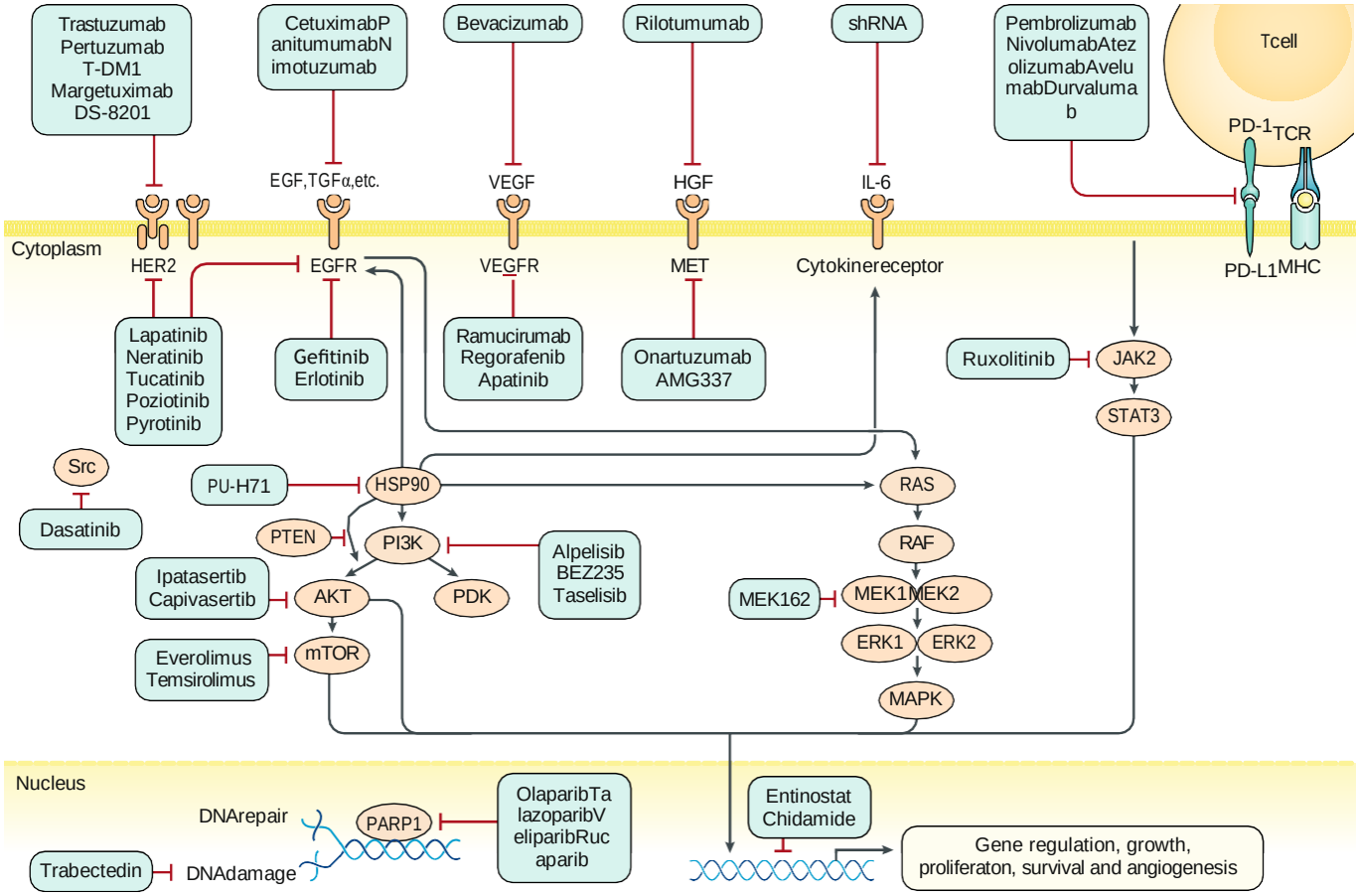

Fig. 11 | **Emergingtargetablepathwaysinbreastcancer.** Differentmembranereceptorinhibitorshaveshownactivity inbreastcancer,includingmonoclonalantibodiesagainsthumanepidermalgrowthfactorreceptor2(HER2),suchas trastuzumab,margetuximabandpertuzumab;antibody–drugconjugates,suchasado-trastuzumabemtansine(T-DM1); immunotherapythatblocksprogrammedcelldeath1(PD-1)and/orprogrammedcelldeath1ligand1(PD-L1),suchas atezolizumabandpembrolizumab;ordrugsthattargetangiogenesis(suchasthemonoclonalantibodybevacizumab, whichtargetsvascularendothelialgrowthfactor(VEGF)).Tyrosinekinaseinhibitors,suchaslapatinib,neratinibor tucatinib,amongothers,haveshownactivityinbreastcancersthatoverexpressHER2.Thesedrugscanblockthe activationofdifferentsignallingpathwayssuchastheRAS–RAF–mitogen-activatedproteinkinase(MAPK)pathwayorthephosphoinositide3-kinase(PI3K)–proteinkinaseB(AKT)–mechanistictargetofrapamycin(mTOR)pathway,whichcanalso beblockedwithsmallmoleculessuchaseverolimusordifferentPI3Kinhibitors;thecrosstalkbetweenthesepathwaysis anareaofactiveresearch.Additionally,differentpoly(ADP-ribose)polymerase(PARP)inhibitorsinpatientswithgermline *BRCA*mutation-associatedbreastcancerhavedemonstratedgoodactivity.Theroleoftheseagentsinpatientswith somaticmutationsisnotknown.EGF,epidermalgrowthfactor;EGFR,epidermalgrowthfactorreceptor;HGF,hepatocyte growthfactor;MET,hepatocytegrowthfactorreceptor;MHC,majorhistocompatibilitycomplex;shRNA,shorthairpin RNA;TCR,Tcellreceptor;TGF,transforminggrowthfactor;VEGFR,vascularendothelialgrowthfactorreceptor.

neratinibversuslapatinibinacapecitabinecombinationinwomenwithpretreatedHER2-postitiveadvanced breastcancer[295].

Due to the heterogeneity and the absence of clear drivers,theachievementsinTNBCremainfarbehind other subtypes. The luminal androgen receptor subtype(BOX2) sharesfeatureswithclassicluminal-like hormone receptor-positive tumours; anti-androgens havebeenshownactiveinthispatientpopulation[296,297]. Additionally,inthosepatientswithTNBCand*BRCA* germline mutations, two phase III trials have now demonstrated better efficacy and better tolerability andqualityoflifeforPARPinhibitorscomparedwith monochemotherapy[30,31],buildingonearlierpreliminary findings[298].

Finally,althoughfarbehindinclinicaldevelopment compared with other tumour types, immunotherapy has shown promise with immune checkpoint inhibitors suchaspembrolizumab[299]oratezolizumab[300].Forexample,asmentioned,afirstphaseIIItrialshowedaslightly improved PFS and preliminary evidence that atezolizumab combined with nab-paclitaxel may provide an overallsurvivalbenefitcomparedwiththetaxanealone intumourswith≥1%PD-L1immunecellstaining[249]. Some of the biomarker assessment-based new drugs havealreadybeenapproved,suchasPD-L1immunohistochemistryinTNBCforimmunotherapy[249],*BRCA* germlinemutationsforPARPinhibitors[30,31]and*PIK3CA* mutationsforPIK3inhibitors[301],whereasforothersthere is evidence but no specific approval, such as assessing

HER2 mutations for neratinib[302] 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 endpoints to evaluate therapies in the advanced setting are debated. Research should determine optimal composite endpoints 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 imag-ing and new applications of nanotechnology. Knowing the driving pathway at every given moment will ena- ble 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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