Chapter 2
Molecular Diagnosis and Targeting Therapy for Breast Cancer

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Abstract Breast cancer (BC) is a representative cancer for which molecular targeting therapy is most popular, because systemic therapy is selected according to tumor biological subtypes, luminal A, luminal B, HER2-enriched, and basal-like; those are decided by gene expression pattern or estrogen receptor (ER), HER2, and tumor proliferation measured by Ki67 expression in immunohistochemistry. Approximately 70–80% of BC is ER positive. Adjuvant therapy is selected according to the guideline based on the large-scale randomized control trials. Selective estrogen receptor modulators (SERM), like tamoxifen or toremifene, and gonadotropin-releasing hormone agonist (GnRH) are used in combination or alone for premenopausal metastatic BC (MBC) and in adjuvant setting. Aromatase inhibitor (AI) targeting the enzyme aromatase is recommended for postmenopausal BC in adjuvant and MBC both in pre- and postmenopausal.

A multigene assay predicts the prognosis of luminal-type BC and selects the candidates for chemotherapy (CT). Selective ER downregulator (SERD), fulvestrant, is used for MBC. Overexpression of the human epidermal growth factor 2 (HER2) worsens the prognosis of BC, but the monoclonal antibody, trastuzumab, has drastically improved the prognosis of HER2-overexpressing BC. Anti-HER2 blockade (trastuzumab/lapatinib or trastuzumab/pertuzumab) is associated with chemotherapy (CT), or Trastuzumab-Emtansine (T-DM1) can be used for trastuzumab-resistant MBC. mTOR inhibitor everolimus or cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with AI can be used for ER-positive MBC.

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New therapeutic approach like apoptosis induction, inhibition of anti-apoptosis, cell cycle progression, and signal transduction are now under developing.

Keywords Breast cancer • Molecular targeting therapy • ER • PgR • Human epidermal growth factor 2 (HER2) • VEGF • Cyclin-dependent kinase 4/6 inhibitor

Breast cancer (BC) is the most common cancer worldwide, being also the leading cause of cancer death among women [1]. It is also the most common cancer in female with increasing morbidity year after year in Japan, and the most common affected generation is 40th (http://ganjoho.jp/reg_stat/statistics/stat/annual.html). The number of the patients is increasing in the world, but the mortality from BC in North America and the European Union (EU) has decreased from the end of twentieth century. In 2016, mortality from BC in the EU is expected to drop by 8% [2]. Increased survival is due to the drastic success in early diagnosis by screening and breakthrough of the treatment, with targeting the molecules. The first epoch-making target of BC is estrogen receptor (ER) and the next is CerbB2.

2.1 Surgical Anti-hormonal Treatment

BC has the longest history of treatment among all cancers [3].

In 1896, George Thomas Beatson published a paper entitled "On Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a New Method of Treatment," with detailed treatment of three patients with advanced breast cancer through bilateral oophorectomy. Oophorectomy became the standard treatment for advanced BC over the following years. He is considered the father of anti-hormonal treatment of BC [4]. Oophorectomy and bilateral adrenalectomy have been introduced in treatment for advanced BC for long time [5].

2.2 Estrogen Receptor (ER) and Anti-Estrogen Receptor Targeting Therapy

ER, binding sites for 17β-estradiol, was found in rat uterus, and it was also recognized existing in BC tissue [6]. Drugs targeting for ER have been developed and became the major arms for BC. The first drug targeting ER is tamoxifen, a selective estrogen receptor modulator (SERM). Gonadotropin-releasing hormone (GnRH) agonist and aromatase inhibitor (AI) have been developed and became the gold standard therapeutic agents after several large-scale randomized controlled clinical trials (RCT).

2.3 Human Epidermal Growth Factor Receptor 2 (HER2) and Targeting Therapy

HER2/neu or ErbB-2 is a member of the epidermal growth factor receptor (EGFR) family, along with HER1 (EGFR), HER3, and HER4 [7]. These receptors, functioning as homo- or heterodimers, activate multiple cellular pathways, such as the p44/42 mitogen-activated protein kinase (MAPK) and the phosphatidylinositol-3-kinase (PI3K) pathways, and stimulate cell growth, survival, and differentiation [8, 9]. Unlike other members of the family, HER2 is not activated by a specific ligand and is always in an active conformational state, ready to interact with other ligand-activated EGF receptors [10], particularly HER3 [11]. Overexpression of the membrane HER2 in BC cells is known as a major negative prognostic factor [12]. Overexpression occurs in 20–25% of cases and is detected either as gene amplification (fluorescence in situ hybridization: FISH) or as protein expression with immunohistochemistry (IHC) [13]. The anti-HER2 humanized monoclonal antibody, trastuzumab (Herceptin®), has been introduced in 1998, and a tyrosine kinase inhibitor of EGFR and HER2, lapatinib (Tykerb®), in 2007; they showed significant improvement in the outcome of patients with HER2-overexpressing BC.

2.4 Subtype of BC as a Decision Making for Targeting Treatment

Since the groundbreaking works at the beginning of this millennium [14, 15], BC is considered to consist of at least four different clinically relevant molecular subtypes: luminal A, luminal B, HER2-enriched, and basal-like. Yet, scientifically, up to ten different molecular subtypes have been identified using gene copy number and expression analyses [16]. The four original subtypes can either be directly determined with a multigene assay such as Prosigna (NanoString Technologies) or BluePrint (Agendia) or indirectly reconstructed with immunohistochemistry (IHC) with formalin-fixed paraffin-embedded tumor tissue [17]. Subtypes according to ER, progesterone receptor (PgR), and HER2, as well as tumor proliferation measured by Ki67 status are as follows: luminal A-like (ER or PgR positive, or both, HER2 negative, low proliferation), luminal B-like (ER or PgR positive, or both, HER2 negative, high proliferation), HER2, non-luminal (HER2 positive and ER and PgR negative) or luminal (HER2 positive and ER or PgR positive, or both), and basal-like (HER2 negative and ER and PgR negative; triple-negative breast cancer) (Table 2.1) [18].

In accordance with the St Gallen consensus, systemic therapy for early BC is guided by these molecular subtypes (Fig. 2.1) [19, 20].

Table 2.1 Molecular Subtypes of Breast Cancer

a. Luminal A: ER positive, HER2 negative, Ki-67 protein low, and PR high
b. Luminal B: ER positive, HER2 negative, and either Ki-67 protein high or PR low [23]
c. Basal-like breast cancer: typically lacks expression of the molecular targets that confer responsiveness to highly effective targeted therapies such as tamoxifen and aromatase inhibitors (AIs) or trastuzumab (HER2 amplification) [24]
d. Triple-negative breast cancer (TNBC): ER-, PR-, and HER2-negative tumors [24]. Most BRCA1 breast cancers are basal-like TNBC. Triple negative also includes some special histological types such as (typical) medullary and adenoid cystic carcinoma with low risks of distant recurrence [25]
e. HER2+: ERBB2+ has amplified HER2/neu. HER-2/neu status can be analyzed by fluorescence in situ hybridization (FISH) assays. HER2-positive cancer is diagnosed in 10–20% of breast cancer patients. This cancer is particularly aggressive and more likely to spread rapidly than other types of breast cancer [17]
f. Claudin low: a more recently described class; often triple negative, but distinct in that there is low expression of cell–cell junction proteins including E-cadherin. Infiltration with lymphocytes is common

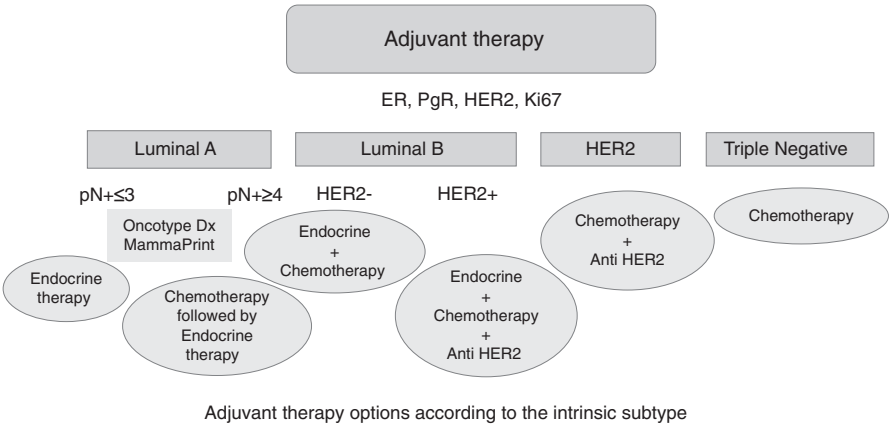

Fig. 2.1 In patients with luminal tumors, several multigene assays like MammaPrint and Oncotype DX assess long-term relapse risk, duration of adjuvant ET, and adoption of CT

In daily clinical practice, the difficulty is distinguishing between luminal A and luminal B on the basis of proliferation assessed by non-standardized Ki67 values. Values of 10% or less are generally considered low risk, and values between 20% and 29% are considered as a minimum criterion for high proliferation. Yet, because of the lack of a prospectively validated study for cutoff value, intermediate values between 10% and about 30% should not be used as the sole criterion for indicating adjuvant chemotherapy. International standardization for Ki67 is still missing, and the measured inter laboratory variability is rather high [21].

2.5 Adjuvant Therapy According to Subtype of BC

2.5.1 Endocrine Therapy (ET)

In all luminal—i.e., hormone receptor (HR) positive (ER or PgR positive or both)—early BC, adjuvant endocrine therapy over the course of 5–10 years is considered standard. Current guidelines consider any ER or PgR staining (i.e., ≥1%) as being positive; endocrine sensitivity is directly correlated to the degree of HR positivity [22]. In premenopausal patients, 20 mg tamoxifen per day is the standard endocrine therapy. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis showed that 5 years of tamoxifen treatment reduced the recurrence not just in the first 4 years in patients with ER-positive disease. This effect was independent of PgR status, age, nodal status, and chemotherapy use. BC mortality was reduced by about a third throughout the first 15 years of follow-up [23].

2.6 Chemotherapy (CT)

The benefit of CT is more pronounced in ER-negative BC. CT is recommended in the majority of TNBC, in HER2-positive BC, and in high-risk luminal tumors. The current CT standards in early BC are anthracyclines and taxanes, given as a combination or in sequence over a period of 18–24 weeks. Generally, recommended regimens do not differ between neoadjuvant and adjuvant settings. The EBCTCG meta-analysis suggested that anthracycline and taxane-containing CT reduced 10-year BC mortality by about one-third [24]. Anthracycline and taxane sequence is as effective as their combination [25]. Four times anthracycline followed by four times docetaxel is equally effective as the combination of the same drugs (six times TAC [docetaxel, doxorubicin, and cyclophosphamide]) but has a different toxicity pattern [26]. A population-based analysis showed that delays beyond 91 days between surgery and start of adjuvant CT are associated with an impaired outcome, particularly in triple-negative breast cancer [27].

For patients with triple-negative BC, standard regimens containing anthracycline and taxane should be used, preferably as neoadjuvant therapy. Trials have indicated that adding platinum to a neoadjuvant anthracycline-taxane combination or sequence improves pathological complete response (pCR) [28].

2.7 Multigene Assay for ER+ HER2-BC

In patients with luminal tumors, several multigene assays assess long-term relapse risk, duration of adjuvant ET, and adopt of CT. EndoPredict [Myriad Genetics] [29], MammaPrint [Agendia] [30], Oncotype DX [Genomic Health] [31], and Prosigna [32] have been validated for risk assessment and prediction of CT response. Most of these assays give information not only about risk of early recurrence (first 5 years) but also about risk of late recurrence (>5 years). Prospective trial results for test validation only exist for Oncotype DX and MammaPrint. For Oncotype DX, the TAILORx trial for pN0 [33] and the WSG PlanB trial for pN0–1 prospectively confirmed its prognostic effect [34]. MammaPrint showed that patient outcome is not compromised if adjuvant CT is omitted in clinically high-risk and genomically low-risk early BC. All other multigene assays have been retrospectively validated. Prospective outcome data are still missing from the randomized comparisons of the large international trials that used Oncotype DX for risk group assessment (i.e., TAILORx [pN0], RxPONDER [pN1]). The protein-based ELISA assay for uPA/PAI-1 (Femtelle [American Diagnostica/Sekisui Diagnostics]) has also been validated at the highest level of evidence for its prognostic and predictive effect by a prospective clinical trial [35] and European Organisation for Research and Treatment of Cancer pooled analysis [36]. By contrast with multigene assays, this test requires fresh-frozen tumor tissue; it can be an alternative option for risk assessment because of its low overall costs [37].

2.8 Targeting Agents for ER

2.8.1 Selective Estrogen Receptor Modulator (SERM)

Tamoxifen (TAM), ICI 46,474, and orphan drug have been described as antifertility agent in rats, and its modest activity has been investigated looking for a therapeutic application for MBC. Initial clinical studies demonstrated that it was safe and effective for the treatment of MBC in postmenopausal women [38–40]. Targeting study for aromatase enzyme was started also in 1977.

2.8.2 Gonadotropin-Releasing Hormone (GnRH) Agonist

The hormone secretions of the ovary are controlled by the secretions from the pituitary, which in turn is controlled by the hypothalamus through its own secretions. With the elucidation of the last-mentioned secretions in the form of the structure of gonadotropin-releasing hormone (GnRH) by Guillemin and Schally in 1967, it became possible to synthesize thousands of different analogues of the primary

decapeptide, GnRH [41]. Leuprorelin and goserelin and the other synthetic models were made and tested for clinical use [42]. They were introduced in prostate and BC treatment. Those agonists induce reversible hypogonadism (decrease the level of LH) by achieving through receptor downregulation by internalization of receptors.

2.9 Aromatase Inhibitor

Aromatase is the enzyme which synthesizes estrogen from androgen. Aromatase inhibitor (AI) inhibits aromatization and decreases estrogen level. AI has been also proposed as the drug for female infertility by its ovarian stimulation. There are two types of AIs approved to treat BC. Irreversible steroidal inhibitors, such as exemestane (Aromasin®), form a permanent and deactivating bond with the aromatase enzyme. Nonsteroidal inhibitors, such as anastrozole (Arimidex®) and letrozole (Femara®), inhibit the synthesis of estrogen via reversible competition for the aromatase [43].

In postmenopausal BC patients, TAM and AI are both valid therapeutic options, as each monotherapy for 5 years. Sequential AIs followed by 2–3 years TAM also significantly reduce recurrences by 30%, but not mortality, compared with TAM. 5 years of AI significantly reduce BC mortality by 15% compared with 5 years of TAM treatment [44]. In postmenopausal patients, upfront AI therapy is preferred [45].

SOFT and TEXT trial results showed additional treatment of GnRH to TAM or even administering GnRH together with an AI enhances efficacy in premenopausal patients with a high-risk recurrence (i.e., after chemotherapy or age $\leq$ 35 years) [46, 47].

2.10 Selective ER Downregulator (SERD)

The SERD fulvestrant, selective ER downregulator, blocks ERα dimerization and promotes ERα protein degradation, resulting in the inhibition of ERα function. It has a steroidal structure and high affinity with the cellular membrane and matrix, as well as high chemical stability, resulting in long-lasting effects [48].

2.11 Anti-HER2 Therapy

Two drugs are currently approved for HER2-positive BC: trastuzumab (Herceptin®), introduced in 1998, and lapatinib (Tykerb®), in 2007.

The introduction of the anti-HER2 humanized monoclonal antibody, "trastuzumab," was associated with a significant improvement in the outcome of patients with HER2-overexpressing BC. Clinical studies have shown that, in the HER2-positive BC, the addition of trastuzumab to chemotherapy (CT) significantly improves both recurrence-free survival (RFS) and overall survival (OS) in the adjuvant setting [49, 50].

It also increases the rate of pathologic complete response (pCR) in the primary systemic therapy (PST) setting for HER2-positive BC [51] and also improves OS in the metastatic setting [52]. HER2 positive was decided as >30% in IHC or FISH/CEP17 ratio > 2.2 according to American Society of Clinical Oncology/College of American Pathologists clinical practice guideline [53]. Trastuzumab should not be administered routinely concomitantly with anthracyclines because of its cardiotoxicity [54]. Combination with taxanes is safe and has been demonstrated to be more effective than sequential treatment. Trastuzumab may also be safely combined with radiotherapy (RT) and endocrine therapy (ET) [55]. Anti-HER2 therapy is recommended as early as possible in patients with HER2-positive MBC. Even though efficacy of trastuzumab or lapatinib together with AI was shown in several phase 2–3 trials for postmenopausal patients [56] and led to registration of these combinations, combination with chemotherapy is currently recommended in early lines of therapy because of the overall survival advantage. In the neoadjuvant setting, dual anti-HER2 blockade associated with CT (trastuzumab/lapatinib or trastuzumab/pertuzumab) has led to improvements in the outcomes when compared with CT associated with one anti-HER2 agent [57]. However, long-term outcomes are not known, and such a treatment cannot be recommended outside of clinical trials.

Trastuzumab still leads the market but with biosimilar and new-generation agents now on the horizon. Pertuzumab plus trastuzumab plus docetaxel regimen now is a first-line therapy for patients with HER2-positive MBC [58]. Dual HER-2 blockade has been shown to be more effective than single blockade in the metastatic setting. FDA approved the first antibody–drug conjugate for the treatment of HER2-positive metastatic BC, T-DM1 (Kadcyla®) on February 2013. T-DM1 is trastuzumab-maytansinoid (microtubule-depolymerizing agents) conjugates through a non-reducible linker showed greater activity compared with nonconjugated trastuzumab while maintaining selectivity for HER2-overexpressing tumor cells. It offers improved efficacy and pharmacokinetics and reduced toxicity [59].

2.12 Cross Talk of ER and HER2

In vitro and in vivo models suggested the existence of a cross talk between the two downstream pathways. Estrogens act via a nuclear/genomic and a nonnuclear/non-genomic activity. Nonnuclear ER interacts directly or indirectly (e.g., via G proteins) with HER 2/HER1–4 dimers activating their downstream kinase

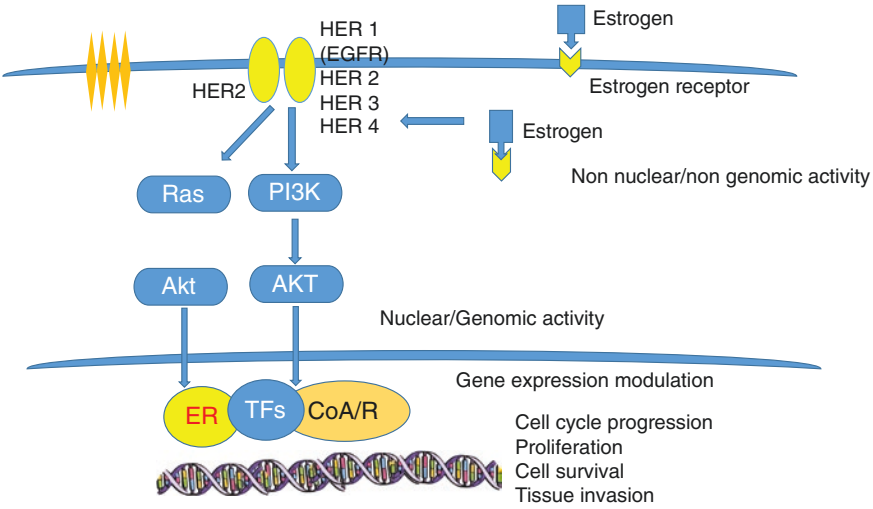

Fig. 2.2 Cross talk of ER and HER2 estrogens act via a nuclear and nonnuclear activity. Nonnuclear ER interacts directly or indirectly (via G proteins) with HER 2/HER1–4 dimers activating their downstream kinase pathways (Ras-MAPK and PI3K-Akt pathways), which in turn phosphorylate ER and other transcription factors (TFs) and coactivators/corepressors (CoA/R), modulating gene expression. HER2 signaling pathways also reduce ER expression at both mRNA and protein levels. ER also promotes HER2, other tyrosine kinase receptors (TKR), and TKR ligands' gene expression. This bidirectional cross talk leads to cancer cell cycle progression, proliferation, survival, and invasiveness [60]

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2.13 Anti-Vascular Endothelial Growth Factor Targeting Agents

Anti-vascular endothelial growth factor (VEGF) antibody bevacizumab (Avastin®) is a specific drug for HER2-negative metastatic BC. Bevacizumab improved PFS 9.2 vs. 6.7 months but not overall survival when given together with first-line chemotherapy such as paclitaxel or capecitabine [61]. Bevacizumab (Avastin®) was approved by the European Committee for Medicinal Products for Human Use (CHMP) but not by FDA and thus constitutes a therapy option only in individual countries.

2.14 New Molecular Targeting Agents

2.14.1 Phosphatidylinositol 3-Kinase/Mammalian Target of Rapamycin (PI3K/mTOR) Pathway

Phosphatidylinositol 3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway is commonly dysregulated in BC [62]. mTOR inhibitor has demonstrated antitumor activity in a variety of cancer types, including ER positive [63]. mTOR inhibitor, everolimus can be used for postmenopausal patients after failure of AI treatment [64]. Afinitor® (everolimus) is the only FDA-approved inhibitor of mTOR to be used in combination with exemestane to treat postmenopausal women with advanced HR+, HER2-BC from 2012.

PI3K pathway activation occurs frequently in TNBC and confers susceptibility to mTOR inhibitors [65]. Gonzalez-Angulo et al. investigated the addition of everolimus to paclitaxel in the neoadjuvant setting for the treatment of TNBC and showed that downregulation of mTOR was achieved after 48 h [66].

2.15 Cyclin-Dependent Kinase (CDK) Targeting Agents

CDK targeting treatment has been emerging in the last few years. The cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor palbociclib (Ibrance®) together with letrozole also improved median PFS in postmenopausal patients without previous systemic treatment for MBC [67]. Palbociclib received approval in the USA and Europe from November 2016. PALOMA 3 study also showed efficacy of palbociclib together with fulvestrant for fulvestrant alone in progressive disease and the relapse cases after previous endocrine therapy. The efficacy of palbociclib was similar in premenopausal patients received additional goserelin and postmenopausal patients [68]. An OS advantage versus standard therapy has not been reported for any CDK 4/6 inhibitor. For the PALOMA studies, final OS analyses are still pending. Ribociclib and abemaciclib are two additional CDK 4/6 inhibitors that are being assessed in clinical trials. Data from the ribociclib first-line registration trial (MONALEESA 2; NCT01958021) showed a substantial progression-free survival benefit for letrozole plus ribociclib versus letrozole alone [69]. On the same aspect, abemaciclib, a potent inhibitor of CDK4/6, is under investigation by Lilly Inc.

The aforementioned protein, enzyme, and molecular targeting agents are listed on Table 2.2. New therapeutic approach for apoptosis induction, inhibition of antiapoptosis, cell cycle progression, and signal transduction are now under developing.

Table 2.2 List of currently approved targeted drug by FDA for breast cancer

Agents	Target molecules or protein	Indications
SERM		
Tamoxifen	ER	Premenopausal and postmenopausal
Toremifene	ER	
GnRH agonist		
Goserelin		Premenopausal
Leuprorelin		Premenopausal
Aromatase inhibitor		
Anastrozole (Arimidex®)	Aromatase	Postmenopausal
Letrozole (Femara®)	Aromatase	Postmenopausal
Exemestane (Aromasin®)	Aromatase	Postmenopausal
Trastuzumab (Herceptin®)	HER2 (ERBB2/neu)	(HER2+) cancer
Pertuzumab (Perjeta®)	HER2 (ERBB2/neu)	(HER2+)
Ado-trastuzumab emtansine (Kadcyla®)	HER2 (ERBB2/neu)	(HER2+)
Lapatinib (Tykerb®)	HER2 (ERBB2/neu), EGFR (HER1/ERBB1) (HER2+)	
Bevacizumab (Avastin®)	VEGF ligand	
Everolimus (Afinitor®)	mTOR	(HR+, HER2-)
Palbociclib (Ibrance®)	CDK4, CDK6	(ER+, HER2-)

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