Current trends in the treatment of HR+/HER2+ breast cancer

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Abstract

Treatment for hormone receptor-positive/human epidermal growth factor receptor 2-positive (HR+/HER2+) patients has been debated, as some tumours within this luminal HER2+ subtype behave like luminal A cancers, while others like non-luminal HER2+ breast cancers. Recent research and clinical trials have revealed a combination of hormone and targeted anti-HER2 approaches without chemotherapy provides long-term disease control for at least some HR+/HER2+ patients. Novel anti-HER2 therapies, including neratinib and ado-trastuzumab emtansine, and new agents that are effective in HR+ cancers, including the next generation of oral selective oestrogen receptor downregulators/degraders (SERDS) and CDK4/6 inhibitors such as palbociclib, are now being evaluated in combination. This review discusses current trials and results from previous studies that will provide the basis for current recommendations on how to treat newly diagnosed patients with HR+/HER2+ disease.

Lay abstract

About 10% of all breast cancer tumours are both hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) positive. It is clear that some patients with this type of breast cancer will require only hormone therapy (HT) aimed at HRs and others will require a combination of HT and drugs targeted at HER2. This review discusses current clinical trials and results from previous studies of patients with HR+/HER2+ disease.

Keywords

Breast Cancer, Hormone receptor, HER2-positive, HR+/HER2+, Triple positive breast cancer, luminal HER2, Clinical trials, Combination treatment, Emerging therapeutics

1. Introduction

Breast cancer is the most common cancer in women worldwide, with over 2 million new diagnoses in 2018 alone [1]. Patients with breast cancer are stratified and treated based on the expression status of certain receptors in their tumour. Identification of the oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) enabled the first stratification according to tumour biology. These receptors have proved to be important prognostic and predictive biomarkers in women with breast cancer. To determine the presence and amount of ER, PR and HER2 protein expressed, immunohistochemistry (IHC) is used and a pathologist assigns a score for each. For ER and PR, the percentage and intensity of staining is measured. These can be combined to create what is known as a histoscore or an Allred score; the latter score is 0 when negative and between 2 and 8 if positive [2]. These receptors are often classified as overall positive (+) or negative (-) despite there being wide variations in the level of positivity in both ER and PR. HER2 status is assessed according to the intensity of staining as 0, 1+, 2+ or 3+. HER2 tumours with scores of 0 and 1+ are considered HER2-negative, 2+ tumours are deemed equivocal and require further testing to determine positive/negative status, while 3+ is considered HER2-positive. A variety of in situ hybridisation tests, including fluorescence in-situ hybridisation (FISH), are used in 2+ HER2 cancers to assess whether there is amplification of the *HER2* gene and if so, these cancers are also classified as HER2-positive.

Hormone receptor-positive (HR+) breast cancers are those that express ER, PR or both. These tumours account for 70-80% of all breast cancers [3]. These hormone-dependent cancers can often be treated successfully with a variety of drugs that modulate the oestrogen receptor or reduce oestrogen. HER2+ breast cancers tend to be associated with a worse prognosis than HER2- breast cancers [4], although the emergence of targeted HER2 therapies such as trastuzumab and pertuzumab has improved outcomes for HER2+ disease [5,6]. There remains a group of women who recur despite these anti-HER2 therapies and whose outlook remains poor.

Among the most significant discoveries in breast cancer has been the identification of breast cancer subtypes with distinct biological characteristics that translate into differences in prognosis and response to treatments [7]. The subtypes are Luminal A, Luminal B, HER2-enriched, Basal-like and Normal-like. The presence or absence of ER, PR and HER2 largely align with these five molecular subtypes as shown in Figure 1. Stratification of breast cancers into these subgroups has been the focus of much research in recent years in the hopes of allowing each patient to be treated with therapy optimal to their specific cancer subtype. Several multigene predictive and prognostic signatures are now available commercially to aid treatment decisions, with Prosigna's Breast Cancer Prognostic Gene Signature Assay (previously known as the PAM50 test) designed specifically based on the intrinsic subtypes [8]. Studies evaluating this are underway.

The aim of this review is to explore the subgroup of patients that have cancers that are both HR and HER2 positive. Known as the luminal HER2 subgroup, cancers that are both HR+ and HER2+ have a complex interaction between the endocrine and HER2 pathways linked to these receptors. Traditionally, there are three main treatment options for this subgroup of breast tumours: (i) hormone therapy alone, (ii) targeted anti-HER2 therapy and chemotherapy combined with later hormone therapy, or (iii) primary hormone therapy followed later by targeted anti-HER2 therapy and chemotherapy. This review will focus on tumour biology and hormone, anti-HER2 and combination therapies currently available for the luminal HER2 subgroup. Recently completed clinical trials and those currently underway will be summarised.

2. Hormone and targeted therapies for invasive breast cancer

2.1. Hormone therapy

HR+ breast cancer is treated with hormone therapy, also known as endocrine therapy or anti-oestrogen therapy. The view of HR+ cancers is that they are dependent on oestrogen for their growth and survival, so targeting this hormone, its signalling and its downstream effects is an important therapeutic strategy. In premenopausal women, the main source of oestrogen is the ovaries. Therapeutic strategies include (i) stopping oestrogen production by ovarian ablation (surgically removing them via oophorectomy) or temporarily suppressing ovarian function with gonadotropin releasing hormone (GnRH) agonists (which will initiate menopause), or (ii) blocking the effect of oestrogen on the cancer with drugs that target the oestrogen receptor. Studies have shown that between 5 and 10 years of hormone therapy in HR+ breast cancers significantly improves survival. In premenopausal women, hormone therapy options are tamoxifen alone or an LHRH analogue combined with tamoxifen or an aromatase inhibitor. Tamoxifen is a selective oestrogen receptor modulator (SERM) that is a partial ER agonist, blocking the activation of oestrogen receptor by oestrogen in the breast but acting as an agonist on the ER of the

endometrium and the skeleton. Tamoxifen was first given to women with breast cancer in the early 1970s [9] and it has saved countless lives. Recent studies in premenopausal women show that compared with tamoxifen alone, a combination of LHRH or oophorectomy and tamoxifen or aromatase inhibitors produces an even greater improvement in survival, although this comes with a greater incidence of adverse events.

In postmenopausal women, most of the body's oestrogen is synthesised peripherally in the liver, fat and locally in the breast from androgen precursors released from the adrenal gland through a reaction catalysed by the enzyme aromatase. An aromatase inhibitor (AI) given to postmenopausal women thus stops the production of oestrogen. AIs currently available include the non-steroidal letrozole and anastrozole and the steroidal exemestane. Tamoxifen together with selective oestrogen receptor downregulators or degraders (SERDs), such as the ER antagonist fulvestrant are other alternative therapies in ER+ breast cancers. SERDS induce a conformational change in ER that prevents the binding of oestrogen and leads to degradation of the receptor. Fulvestrant, an injectable SERD, is currently the only SERD available and is most often used to treat recurrent or metastatic ER+/HER2- breast cancer in postmenopausal women who have recurred on prior endocrine therapy. New oral SERDS are currently being developed and tested [10–12].

2.2. HER2-targeted therapy

The emergence of anti-HER2 therapies has led to significant improvements in the prognosis and outcome for patients with HER2+ breast cancers. Trastuzumab, a recombinant humanised monoclonal antibody, targets an extracellular domain of HER2, preventing its dimerisation with other HER receptors to halt cancer growth [13,14]. Pertuzumab, another monoclonal antibody, acts on a different extracellular domain of HER2 and halts dimerisation particularly of HER2 with HER3, the most growth-promoting dimerisation of the HER family of receptors [15]. Combinations of trastuzumab and pertuzumab with chemotherapy are more effective that either drug alone with chemotherapy. Lapatinib is a dual tyrosine kinase inhibitor of both HER2 and HER1 (EGFR) that was approved by the United States Food and Drug Administration (FDA) for use in combination with the chemotherapy drug capecitabine in 2007 [16]. Lapatinib can also be given together with trastuzumab [17] and this combination provides a more complete blockade of HER signalling than either alone [18]. Neratinib, a tyrosine kinase inhibitor, is a pan-HER inhibitor, licensed and currently recommended by the UK's National Institute for Health and Care Excellence (NICE) in the technology appraisal guidance TA612 for use as extended adjuvant treatment following trastuzumab in patients with ER+/HER2+ breast cancer [19]. Trastuzumab emtansine (T-DM1), also known as ado-trastuzumab emtansine, is an antibody-drug conjugate in which trastuzumab is linked to the cytotoxic agent DM1 [20]. This was approved by the U.S. FDA in 2013 for the treatment of HER2+ metastatic breast cancer and in 2019 for patients with HER2+ early breast cancer who have residual disease following neoadjuvant trastuzumab and a taxane. In the UK, T-DM1 is recommended for the treatment of HER2+ advanced breast cancer following treatment with trastuzumab and a taxane [21]. Trastuzumab deruxtecan is an antibody drug combination comprising trastuzumab and a cytotoxic topoisomerase I inhibitor and has broader anti-tumour activity than T-DM1, including efficacy against low HER2-expressing tumours [22]. There is a series of other anti-HER2 drugs in development and in early clinical trials.

2.3. Other targeted therapies for invasive breast cancer

The emergence of CDK4/6 inhibitors in recent years has provided another treatment option [23]. These inhibitors induce cell cycle arrest, thereby stopping proliferation [24] and all three drugs currently available (palbociclib, ribociclib and abemaciclib) have been combined with endocrine therapy to treat HR+/HER2- advanced breast cancer [25]. Not as much is known about the utility of CDK inhibitors in HR+/HER2+ disease, although trials of CDK inhibitors in combination with endocrine therapies and anti-HER2 therapies are currently underway (Table 1). Targeted therapies currently available for the treatment of HR+ and/or HER2+ breast cancer, as single agents or in combination, are listed in Table 2.

3. Complications treating HR+/HER2+ breast cancer

3.1. Worse prognosis for HR+/HER2+ subgroup

The subgroup of HR+ breast cancers that also express HER2 has been shown to have a significantly worse prognosis compared to other HR+ breast tumours [26]. These HR+/HER2+ tumours account for about 10% of all breast cancers, or about half of all HER2+ tumours [27,28]. HR status in HER2+ tumours aligns with differences in response to neoadjuvant treatment, location, type of metastases and survival [29,30].

Since the approval of trastuzumab (Herceptin), patients with HER2+ breast cancer (including those that overexpress both ER (and/or PR) and HER2) have been treated with chemotherapy and anti-HER2 therapy [5]; however, recent data has suggested there may be other options. Combining hormone therapy with an anti-HER2 agent has proven beneficial to some specific patients [31,32], particularly those presenting with tumours that are HER2+ and have high ER expression. These patients have a reduced response to trastuzumab plus chemotherapy [33] but many are endocrine-sensitive, so combining trastuzumab and endocrine therapy produces a high response rate and is an attractive option. However, not all HR+/HER2+ tumours respond is the same manner. Identification of which patients require single, sequential or combination treatments is an urgent need.

3.2. Treatment resistance, tumour biology and HR/HER2 crosstalk

Treating luminal HER2 breast cancer is complex; there is not one treatment or combination of treatments that is suited to all patients with this subtype. Identifying what is biologically driving the cancer can help (i.e. oestrogen or HER signalling and their downstream effects), although pathway interaction and crosstalk can cause the cancer to change course throughout treatment (Figure 2). HR+/HER2+ tumours often respond initially to hormone therapy and/or HER2-targeted therapy but develop resistance over time [34]. One reason may be the known crosstalk between the ER and HER2 signalling pathways and the involvement of other downstream pathways, such as PI3K and MAPK [35–39]. A study of HER2+ cell lines showed an increase in ER or its downstream signalling targets following treatment with lapatinib and trastuzumab, indicating ER signalling as a survival mechanism for HER2+ cells [18]. Upregulation of ER signalling is also evident in HER2+ tumours treated with trastuzumab, pertuzumab and lapatinib. In one study, 18% of HER2+ tumours that were originally ER- were converted to ER+ following two weeks of neoadjuvant lapatinib, providing further evidence of the interconnectedness of the ER and HER pathways [40]. Another study revealed primary resistance to T-DM1 in metastatic HER2+ breast cancer was linked to there being negative *HER2* gene amplification in circulating tumour DNA and ER-positivity and/or PR-positivity by IHC [41]. Investigations into ER and HER pathway interactions are ongoing and include a study of Positron Emission Tomography with ^{18}F-

fluoroestradiol (FES-PET) imaging as a tool to detect possible reversion of ER status in patients with metastatic ER-/HER2+ breast cancer treated with trastuzumab, pertuzumab and a taxane (Clinical Trial NCT03619044).

The mechanisms by which ER+/HER2+ tumours become resistant to their original therapy remains unclear. The development of acquired resistance is complex and likely due to multiple factors rather than just one. In addition to ER and HER2 pathway crosstalk, resistance could also be caused by a loss or gain of ER overexpression resulting in reduced efficacy of hormone therapy, existing or acquired mutations in the ER gene *ESR1* [42], reactivation of HER2 [43] or acquired *HER2* mutations [44,45]. ER epigenetic changes have also been described [46]. We are now advancing to the point where the tumour's endocrine resistance profile should be assessed. For instance the timing (and measurement) of acquired *ESR1* mutations in resistant cancers may be critical to dictate future endocrine therapy [47,48]. Allouchery *et al* identified *ESR1* mutations at first relapse and at progression on metastatic treatment, but these mutations were not present early during adjuvant therapy [49]. It is also clear that a primary tumour and its recurrence(s) can differ in hormone receptor positivity and temporal heterogeneity likely plays a role in treatment resistance [45]. Assessment of ER, PR and HER2 in every breast cancer metastasis will help improve selection of the most appropriate treatment.

Other potential targets that are involved in ER/HER crosstalk have also been implicated recently. The enzyme fatty acid synthase (FASN) is known to be involved in ER/HER2 crosstalk by way of the PI3K/AKT pathway. It was successfully inhibited by the mTOR inhibitor rapamycin in ER+/HER2+ breast cancer cells and a combination of rapamycin with the FASN inhibitor cerulenin induced apoptosis and inhibited cell migration and tumorigenesis in ER+/HER2+ cells, suggesting FASN as a potentially new therapeutic target [50]. The tyrosine kinase receptor IGF1R is also involved in ER/HER2 pathway crosstalk and may also be a useful biomarker in ER+/HER2+ cancers. High expression of IGF1R is associated with shorter disease-free survival in patients in this subgroup and inhibition of both IGF1R and ER in breast cancer cell lines causes growth inhibition [51]. The addition of trastuzumab inhibited growth further, suggesting this combined targeting of pathways could be a successful approach for ER+/HER2+/IGF1R+ cancers. Other novel ideas to eliminate ER/HER pathway crosstalk and successfully block multiple pathways include the use of proteasome inhibitors [52] that have been successful in treating other types of cancer including multiple myeloma, together with standard endocrine treatments. Targeting the PI3 kinase pathways using PI3K inhibitors [53] such as alpelisib, approved by the U.S. FDA in 2019, combined with fulvestrant is one alternative. Finally, there are new anti-HER2 dendritic cell vaccines on the horizon [54].

As more research emerges regarding signalling pathway crosstalk [55] in triple positive breast cancer and how this is related to resistance to therapies [56], it is clear that for some women both ER and HER2 need to be targeted. This can be sequentially or with combined therapy, but for some a single treatment may suffice. It is critical that we are able to predict which patients require which treatment as more targeted endocrine and HER2 therapies are being developed and being trialled in combination studies.

4. Treating HR+/HER2+ breast cancer: What we've learned so far

4.1. Standard-of-care for HR+/HER2+ tumours

Historically, ER+/HER2+ breast cancer was treated with endocrine therapy combined in some patients with chemotherapy. Following the development of trastuzumab (Herceptin) in the 1990s [57], this group is now typically given chemotherapy and trastuzumab followed by endocrine therapy to reduce the risk of recurrence. Some patients with low risk HR+/HER2+ breast cancers are treated with adjuvant hormone therapy alone. However, in most cases adjuvant chemotherapy is given in combination with trastuzumab followed by endocrine therapy [58]. Clinicians take into account all factors including tumour size and node status to avoid overtreatment, as some small node-negative tumours do well with adjuvant endocrine therapy followed by trastuzumab and chemotherapy if they recur [59]. Remarkably, a recent study investigating the treatment of HR+/HER2+ metastatic breast cancer revealed that only 42% of the 6,234 patients ever received anti-HER2 therapy, despite previous studies showing survival benefits for patients treated with both hormone and anti-HER2 therapies [60]. Emerging novel drugs and combinations are being investigated in clinical trials so eventually clear treatment strategies for patients with HR+/HER2+ breast cancers should become available.

It has been suggested that HR+/HER2+ tumours should be treated as a distinct molecular subtype of breast cancer. It should also be defined further based on other characteristics to ensure that patients with these cancers receive appropriate treatment whilst also avoiding overtreating. Some tumours, particularly early-stage or smaller ones, may be driven primarily by hormone receptor(s) and thus may not need HER2-targeted treatment [61]. A recent study of patients with triple-positive breast cancer in Korea showed that treatment with trastuzumab did not improve overall survival and that many of these tumours behave clinically more like luminal A than HER2-enriched cancers [62].

4.2. HR+/HER2+ metastatic breast cancer

A number of previous clinical trials, summarised in Table 3, have been instrumental in identifying new combination treatments for patients with HR+/HER2+ tumours. The TAnDEM, EGF30008 and eLEcTRA phase III trials, all treating postmenopausal patients with metastatic breast cancer, showed positive outcomes for the combination of an aromatase inhibitor and trastuzumab or lapatinib. This included a progression-free survival (PFS) benefit and, in 15% of TAnDEM patients, no disease progression for two years. However, there was no overall survival (OS) benefit from the combined treatment [63–65].

One of the problems with studying HER2+ breast cancer is the variation in scoring across centres. Discrepancies in testing methods and reproducibility of results have been and remain a challenge [66,67]. Identifying which tumours are truly *HER2* amplified, with HER2 overexpressed, is critical to both retrospective survival studies and to the current treatment issues for this subgroup of breast cancer. A retrospective analysis of metastatic breast cancers showed some tumours that were deemed HER2-negative but were enriched for HER2 could benefit from combined lapatinib and letrozole treatment [68]. Additionally, changes to the American Society of Clinical Oncology (ASCO) treatment guidelines in 2018 reclassified some HER2+ tumours. Patients with cancers that were deemed equivocal in assessment by IHC and FISH were reclassified as HER2-negative as there has not been any proven benefit from HER2-targeted therapy in these individuals [69].

A combined hormone and anti-HER2 therapy approach clearly benefits some patients, but the challenge lies in accurately identifying the subpopulation of patients likely

to gain additional benefit from a combined treatment strategy. The addition of pertuzumab improved overall survival in HER2+ patients in the CLEOPATRA study. The combination of trastuzumab, pertuzumab and docetaxel compared to just trastuzumab and docetaxel increased both PFS and OS in patients with HER2+ metastatic breast cancer. However, no significant difference in response was related to hormone receptor status [70]. NICE now recommends the combination of trastuzumab, pertuzumab and chemotherapy for treatment of metastatic HER2+ breast cancer [71] and also suggests the same strategy as an option in the neoadjuvant setting [72].

4.3. Neoadjuvant management of HR+/HER2+ breast cancer

The best approach to managing HR+/HER2+ breast cancer in the neoadjuvant setting has been the subject of debate. Chemotherapy has been shown to be much more beneficial in ER- disease; however, some women, particularly those of advanced age, struggle with toxic side effects [73,74]. The timing of chemotherapeutic or targeted, sequential or combined treatments is also being questioned for this group, with new evidence suggesting reducing or postponing the use of chemotherapy in favour of using targeted therapies, such as letrozole or trastuzumab [75]. Targeted treatment of breast cancer in the neoadjuvant setting has been useful, particularly for women with advanced age who may not tolerate chemotherapy well. Studies have shown neoadjuvant letrozole can shrink tumour size and induce gene expression changes in HR+ breast cancers [76,77] and that the addition of trastuzumab to neoadjuvant chemotherapy can increase the pathologic complete response (pCR) in HER2+ tumours [78].

Changes in current recommendations for chemotherapy in the neoadjuvant setting could be near, as new combination regimens have shown promising results. In the neoadjuvant phase II trial NA-PHER2 that combined palbociclib, fulvestrant and two anti-HER2 drugs (trastuzumab and pertuzumab), an objective clinical response was seen in 29/30 patients, as well as a decrease in proliferation (assessed by Ki67 expression) following two weeks of treatment prior to surgery [79]. Neoadjuvant palbociclib and letrozole produces effective clinical responses and decreases expression of the genes *IL6ST* and *RBBP8*, which have been associated with proliferation, in postmenopausal ER+/HER2- patients [80]. Biomarkers of response to neoadjuvant treatment are also emerging for ER+/HER2+ tumours, including a gene expression signature of retinoblastoma loss-of-function that has the potential to identify patients who would benefit from neoadjuvant chemotherapy [81]. Other predictive markers of poor response to neoadjuvant chemotherapy and HER2-targeted therapy in ER+/HER2+ patients are increased expression of stromal colXα1 and low levels of tumour-infiltrating lymphocytes [82]. Further research is still needed to identify which tumours within the complex HR+/HER2+ subgroup of breast cancers might benefit from specific single-agent and combined treatments in the neoadjuvant settings.

5. Where we are now: current trials and emerging therapeutic strategies

5.1. Metastatic and locally advanced HR+/HER2+ breast cancer

It is clear now that HR+/HER2- and HR+/HER2+ breast cancers have different biological characteristics, mechanisms of growth and response to treatment. Even within these groups of breast cancer there are inherent differences, with some HR+/HER2+ tumours behaving more like the luminal A subtype (i.e., ER-driven cancer) and others requiring a multipronged targeted blockade of the ER, PR and HER pathways. An improved

outcome from combination treatment with anti-HER2 therapy (trastuzumab or lapatinib) and an AI is evident for some, but not all, HR+/HER2+ patients (TAnDEM, EGF3008, eLEcTRA trials). Drugs like pertuzumab have improved response for some in this subgroup but its addition is costly and may cause more adverse events (PERTAIN trial of metastatic or locally advanced HR+/HER2+ breast cancer) [83].

Fulvestrant has also proven useful in the treatment of ER+/HER2+ patients with multiple metastases who have received prior anti-HER2 therapy in combination with chemotherapy or an AI [84]. A clinical trial (NCT03289039) is currently investigating the combination treatment of neratinib and fulvestrant in ER+/HER2+ metastatic or locally advanced breast cancer [85] (Table 1). So far, 46 patients with HR+/HER2-mutant metastatic breast cancer have been treated with neratinib and fulvestrant. This combination shows positive results in patients who have been treated previously with various agents; in particular, patients who had previously received fulvestrant or CDK4/6 inhibitors responded well to the combined regimen. The rate of diarrhoea was similar to that of single-agent neratinib and was not dose-limiting and no patients discontinued treatment because of it [86].

Fulvestrant and palbociclib also show great promise when combined and both are now being tested in combination with anti-HER2 therapies in the metastatic setting (Table 1). Palbociclib has previously been tested in patients with ER+/HER2- advanced breast cancer who progressed on endocrine therapy and, together with fulvestrant, has been shown to increase PFS compared to fulvestrant alone (PALOMA3 trial) [87]. Further analysis of circulating tumour DNA from PALOMA3 trial participants revealed acquired mutations in *RB1*, *ESR1* and *PI3KCA* associated with resistance following treatment with fulvestrant [88]. Combining palbociclib with endocrine therapies other than fulvestrant may avoid these acquired mutations. A trial designed to determine the recommended dose of palbociclib in combination with letrozole and T-DM1 in patients with ER+/HER2+ metastatic breast cancer is currently recruiting patients (Clinical Trial NCT03709082) [89].

Additional CDK4/6 inhibitors including ribociclib and abemaciclib are also being tested in current clinical trials of HR+/HER2+ patients (Table 1). Particularly noteworthy is the treatment of advanced HR+/HER2+ breast cancer with abemaciclib, fulvestrant and trastuzumab in the monarcHER phase 2 trial. This combination treatment not only proved tolerable and safe but also improved PFS compared to standard-of-care trastuzumab plus chemotherapy [90]. Another recent study evaluating a triplet combination is the ALTERNATIVE phase 3 trial. This study too showed a PFS benefit from treating with a dual HER2 blockade of lapatinib and trastuzumab plus an aromatase inhibitor in the treatment of postmenopausal women with HR+/HER2+ metastatic breast cancer [91]. These triplet combinations of therapies could truly change the way HR+/HER2+ breast cancer is treated as they eliminate the need for chemotherapy and its often toxic side effects.

5.2. Neoadjuvant management of HR+/HER2+ breast cancer

In the neoadjuvant setting, it is unclear whether a combined anti-oestrogen and anti-HER2 approach offers any significant improvement to current practice. While some patients do have a positive clinical response to neoadjuvant treatment with letrozole and lapatinib (Neo-ALL-IN), a decrease in the ER Allred score after neoadjuvant treatment was linked to poor outcome [92]. In addition, depriving oestrogen with a LHRH agonist or with an AI

combined with neoadjuvant docetaxel, carboplatin, trastuzumab and pertuzumab did not statistically improve response (B-52 trial) [93] (Table 3).

5.3. Adjuvant management of HR+/HER2+ breast cancer

One of the most promising drugs for the treatment of HR+/HER2+ breast cancers is the pan-HER tyrosine kinase inhibitor neratinib. Results from the ExteNET trial showed one year of extended adjuvant neratinib following neoadjuvant and adjuvant chemotherapy and trastuzumab significantly reduced the risk of relapse in early-stage HER2+ breast cancer. Interestingly, a greater benefit from neratinib was seen in HR+/HER2+ patients compared to HR- patients [94]. Many of the HR+ patients were also receiving endocrine therapy, suggesting that supressing both pathways was required to improve invasive disease-free survival. The U.S. FDA approved neratinib (Nerlynx) for extended adjuvant treatment of early-stage, HER2+ breast cancer in 2017 and in the UK NICE now recommends neratinib for extended adjuvant treatment of HR+/HER2+ early stage breast cancer after adjuvant trastuzumab [19]. In a xenograft study, extended adjuvant therapy with neratinib plus fulvestrant maintained a prolonged complete response and blocked ER/HER2 crosstalk [95,96].

6. The need for a better understanding of the diverse biology of HR+/HER2+ and associated biomarkers

As shown by the evidence and studies summarised here, selection of the most appropriate treatment strategy for the management of a patient that has a breast tumour that is both HR+ and HER2+ poses a conundrum. The crux lies in the difficulty of determining which receptors and their associated pathways are driving the tumour cells and what is the interaction and crosstalk between them. A better understanding of the molecular diversity within the subgroup of HR+/HER2+ breast cancer is essential before we can improve its management.

There is now a need for biomarkers to predict response and recurrence. In the Neo-ALL-IN trial of patients with ER+/HER2+ breast cancer, a number of predictors were identified. These included a decrease in the ER Allred score after neoadjuvant treatment, an SUVmax (a measure of activity in PET imaging linked to cell viability and proliferation) lower than 5.5 on the baseline FES PET-CT and high baseline tumour-infiltrating lymphocytes of over 20% [92]. These may be useful as biomarkers of response for future patients. Trefoil factor 3 (TFF3) is another potential biomarker for resistance to trastuzumab, as its expression is upregulated in trastuzumab-resistant ER+/HER2+ breast cancer cells and it has been shown to activate HER family receptors [97].

IL6ST, a surrogate for endocrine therapy response [56], may also be a useful biomarker for ER+/HER2+ breast cancer. In a study presented at the 2019 San Antonio Breast Cancer Symposium, higher levels of IL6ST were associated with active ER signalling and predicted clinical response to neoadjuvant letrozole in ER+/HER2+ tumours [98]. Importantly, lower levels of IL6ST were associated with a lack of response to endocrine therapy and more active HER2 signalling. This supports the notion of a diverse underlying biology within the ER+/HER2+ population, with two subgroups with distinct gene expression profiles. These subgroups may be linked to differences in endocrine therapy responsiveness and, importantly, might be easily stratified. IL6ST could potentially select ER+/HER2+

patients who need both endocrine and HER2-targeted therapy and others who should receive endocrine therapy alone. Further work is needed both in the laboratory and within clinical trials to better characterise those potential predictive signatures within the ER+/HER2+ subgroup. ER+/HER2+ patient-derived xenografts (PDXs) have recently been characterised and could provide a useful preclinical testing ground for new drugs and combinations. Interestingly, the take rate in culture was higher for ER+/HER2+ tumours compared to ER+/HER2- PDXs, possibly indicating a greater drive for survival [99].

7. Conclusion

In summary, the HR+/HER2+ breast cancer subtype consists of a range of cancers with varying interaction between ER and HER2 receptors and pathways. Some HR+/HER2+ tumours behave more like the luminal A subtype and others are more like non-luminal HER2+ disease. The latter will likely require more intensive treatment and appears to respond better to combinations of endocrine and anti-HER2 targeted therapies. The time of giving the same treatments for all ER+/HER2+ cancers is over.

More research into the use of drugs including neratinib, T-DM1, fulvestrant, novel oral SERDS, and CDK4/6 inhibitors alone or in combination with each other or with more traditional therapies is required. Such research will hopefully provide information on the best treatment approaches for individual patients and their cancers, as it is clear not all HR+/HER2+ cancers behave the same. Results from these studies must be combined with research to characterise the complex underlying biology of HR+/HER2+ disease, in particular the intricate interactions of the ER and HER2 pathways. It is imperative that biomarkers of response, disease progression and resistance are identified in order to fully understand how the disease progresses and be able to stratify patients for first, second and third-line treatment if necessary. Additional markers linked to molecular diversity will also be required to help determine how best to treat individual patients with this breast cancer subtype. To provide a truly individualised medicine there needs to be better characterisation of each individual cancer both at diagnosis and recurrence. Markers including IL6ST will provide the advances needed to achieve this goal.

Future perspective

As HR+/HER2+ breast cancer continues to be characterised as its own subgroup of breast cancer of which there are at least two divisions (those which more closely resemble luminal A cancers and others more similar to non-luminal HER2+ tumours), we are hopeful that treatment for this subtype will become more personalised over the next 5-10 years based on the outcome of recent and currently-ongoing trials. Some patients will require combined treatment targeting both ER and HER2 signalling and others will need only endocrine treatment. We can only get better at predicting this. Prognostic and predictive biomarkers such as IL6ST will help stratify HR+/HER2+ tumours and identify which treatment plan is best for each patient. We expect additional biomarkers and molecular signatures for this subgroup to be identified soon, as well as better laboratory research models developed and new breast cancer treatments and combinations of therapies approved. Collectively, this will improve personalised care and outcome for this set of patients.

Executive summary

Hormone and targeted therapies for invasive breast cancer

- Here we review hormone, HER2-targeted and other breast cancer treatments currently available.

Hormone therapy

- Hormone receptor positive (HR+) cancers are dependent on oestrogen for their growth and survival, so targeting this hormone, its signalling and its downstream effects with hormone therapy is an important therapeutic strategy.
- Tamoxifen, aromatase inhibitors and fulvestrant are hormone (also known as endocrine or anti-oestrogen) therapies currently available for the treatment of HR+ disease.

HER2-targeted therapy

- HER2-targeted therapies have significantly improved the prognosis and outcome for patients with HER2+ breast cancer.
- Monoclonal antibodies trastuzumab and pertuzumab, tyrosine kinase inhibitors lapatinib and neratinib and antibody-drug conjugates trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan are HER2-targeted therapies currently available.

Other targeted therapies for invasive breast cancer

- CDK4/6 inhibitors induce cell cycle arrest, thereby stopping proliferation.
- Palbociclib, ribociclib and abemaciclib are CDK4/6 inhibitors currently available for the treatment of HR+/HER2- breast cancer; not as much is known about the utility of CDK inhibitors in HR+/HER2+ disease.

Complications of the HR+/HER2+ subgroup

- HR+/HER2+ tumours account for about 10% of all breast cancers, or about half of all HER2+ tumours and have been shown to have a significantly worse prognosis compared to other HR+ breast tumours.
- Combining hormone therapy with an anti-HER2 agent has proven beneficial to some but not all HR+/HER2+ patients.

Treating HR+/HER2+ breast cancer: What we've learned so far

- Here we outline how patients with HR+/HER2+ tumours have been treated historically and that these tumours should be treated as a distinct molecular subtype of breast cancer.
- Previous clinical trials evaluating combined hormone and HER2-targeted therapies in the neoadjuvant and adjuvant setting are discussed.

Where we are now: current trials and emerging therapeutic strategies

- Some HR+/HER2+ tumours behave more like the luminal A subtype (i.e., ER-driven cancer) and others require a multipronged targeted blockade of the ER, PR and HER pathways.
- Clinical trials with HR+/HER2+ patients currently underway are discussed; neratinib, fulvestrant, palbociclib and T-DM1 show great promise alone and in various combinations.

Treatment resistance and HR/HER2 crosstalk

- HR+/HER2+ tumours often respond initially to hormone therapy and/or HER2-targeted therapy but develop resistance over time.
- The reason why some HR+/HER2+ cancers fail to respond to combined therapy or become resistant to it remains unclear but evidence of ER and HER pathway crosstalk, mutations in *ESR1* and *HER2*, lower *HER2* FISH ratio and activation of other downstream pathways are likely to play a role.

The need for a better understanding of the diverse biology of HR+/HER2+ and associated biomarkers

- Further investigation into the biology of HR+/HER2+ breast cancer is necessary in order to have a clearer picture of how these tumours operate.
- Validated prognostic and predictive biomarkers are required to identify the patients who will need combined endocrine/HER2 therapy and those who will need only endocrine treatment.

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Table 1 Current clinical trials treating HR+/HER2+ breast cancer. (Oestrogen receptor, ER; Hormone receptor, HR; Aromatase inhibitor, AI; Human epidermal growth factor receptor, HER; ado-trastuzumab emtansine, T-DM1; Epidermal growth factor receptor, EGFR).

Trial	Phase	Recruitment	Cohort size	Menopausal status	Cancer stage	Breast cancer type	Treatment group (s)
AI in combination with lapatinib, trastuzumab or both (ALTERNATIVE) (Clinical Trial NCT01160211)	III	2011-2020	355	Post	Metastatic	HR+/HER2+ breast cancer	Lapatinib with trastuzumab and an AI v. trastuzumab and an AI v. lapatinib and an AI [100]. Recently published results show PFS benefit in the lapatinib with trastuzumab and an AI group compared to trastuzumab plus AI group [91].
Palbociclib and Trastuzumab With Endocrine Therapy in HER2+ Metastatic Breast Cancer (PATRICIA) (Clinical Trial NCT02448420)	II	2015-ongoing	232 (estimated enrolment)	Both	Locally Advanced or Metastatic	HR+/HER2+ breast cancer	Palbociclib, trastuzumab and endocrine therapy v. T-DM1 or chemotherapy in combination with trastuzumab (physician's choice) who previously received at least 1 anti-HER2 regimen [101].
Ribociclib (Lee011) In Combination With Trastuzumab Or T-DM1 (Clinical Trial NCT02657343)	1b/II	2016-ongoing	26	Both	Metastatic or advanced	HER2+ breast cancer, some of which are also ER+	Ribociclib and T-DM1 v. ribociclib and trastuzumab v. ribociclib, trastuzumab and fulvestrant [102].
Abemaciclib (LY2835219) in HR+/HER2+ Breast Cancer (monarcHER) (Clinical Trial NCT02675231)	II	2016-ongoing	237	Post	Locally Advanced or Metastatic	HR+/HER2+ breast cancer	Abemaciclib with trastuzumab with or without fulvestrant or chemotherapy [90]. Recently published results show abemaciclib, fulvestrant and trastuzumab combination treatment not only proved tolerable and safe but also improved PFS compared to standard-of-care trastuzumab plus chemotherapy [103].

Hemay022 in Combination with Exemestane (Clinical Trial NCT03308201)	I	2017-ongoing	48 (estimated enrolment)	Post	Metastatic or advanced	ER+/HER2+ breast cancer	EGFR inhibitor Hemay022 with exemestane [104].
Neratinib with Fulvestrant in HER2+/ER+ Metastatic Breast Cancer (Clinical Trial NCT03289039)	II	2017-ongoing	152 (estimated enrolment)	Both	Locally advanced Metastatic	ER+/HER2+ breast cancer	Neratinib with fulvestrant or neratinib alone [65].
Palbociclib to Treat Metastatic Breast Cancer (PATINA) (Clinical Trial NCT02947685)	III	2017-ongoing	496 (estimated enrolment)	Both	Metastatic	ER+/HER2+ breast cancer	Anti-HER2 therapy (trastuzumab/pertuzumab) with endocrine therapy (letrozole, anastrozole, exemestane or fulvestrant) with or without palbociclib [105].
Palbociclib in ER+/HER2+ metastatic breast cancer (Clinical Trial NCT03709082)	I/II	2018-ongoing	4 (estimated enrolment)	Post	Metastatic	ER+/HER2+ breast cancer	Palbociclib, letrozole and T-DM1 [106].
TOUCH (Clinical Trial NCT03644186)	II	2019-ongoing	144 (estimated enrolment)	Post	Early breast cancer	Elderly patients with HR+/HER2+ breast cancer	Neoadjuvant palbociclib with both hormonal therapy and anti-HER2 therapy v. treatment with paclitaxel and anti-HER2 therapy (standard of care) [107].

Table 2 Targeted treatments available, alone or in combination, for the treatment of HR+ and/or HER2+ breast cancer. (Oestrogen receptor, ER; Hormone receptor, HR; Aromatase inhibitor, AI; Selective oestrogen receptor downregulator/degrader, SERD; Human epidermal growth factor receptor, HER; Epidermal growth factor receptor, EGFR).

Drug	Commercial Brand Name(s)	Type of drug	Target	For which patients
Tamoxifen	Nolvadex, Tamosin, Emblon, Tamofen	ER modulator	ER	HR+ (premenopausal)
Letrozole	Femara	AI	Aromatase	HR+ (postmenopausal)
Anastrozole	Arimidex	AI	Aromatase	HR+ (postmenopausal)
Exemestane	Aromasin	AI	Aromatase	HR+ (postmenopausal)
Fulvestrant	Fasodex	SERD	ER	Metastatic ER+/HER2- (postmenopausal who have recurred on endocrine therapy)
Trastuzumab	Herceptin	Monoclonal antibody	Extracellular domain of HER2	HER2+
Pertuzumab	Perjeta	Monoclonal antibody	Extracellular domain of HER2 (different one than trastuzumab)	HER2+
Lapatinib	Tyverb, Tykerb	Tyrosine kinase inhibitor	HER1 (EGFR) & HER2	HER2+
Neratinib	Nerlynx	Tyrosine kinase inhibitor	HER1, HER2, and HER4	Extended adjuvant treatment following trastuzumab in HER2+ (including ER+/HER2+) patients
Trastuzumab emtansine (T-DM1)	Kadcyla	Antibody-drug conjugate	HER2	HER2+ breast cancer that has recurred
Trastuzumab deruxtecan	Enhertu	Antibody-drug conjugate	HER2	Metastatic HER2+ breast cancer patients who have received two or more prior anti-HER2 therapies in the metastatic setting
Palbociclib	Ibrance	CDK4/6 inhibitor	CDK4/6	HR+/HER2- breast cancer
Ribociclib	Kisqali	CDK4/6 inhibitor	CDK4/6	HR+/HER2- breast cancer
Abemaciclib	Verzenio, Verzenios	CDK4/6 inhibitor	CDK4/6	Locally advanced or metastatic HR+/HER2- breast cancer patients who previously received endocrine therapy

Table 3 Previous clinical trials treating HR+/HER2+ breast cancer. (Oestrogen receptor, ER; Hormone receptor, HR; Progression-free survival, PFS; Human epidermal growth factor receptor, HER; Pathological complete response, pCR; Aromatase inhibitor, AI).

Trial	Phase	Recruitment	Cohort size	Menopausal status	Cancer stage	Breast cancer type	Treatment groups	Results (HR+/HER2+ tumours)
Herceptin Adjuvant Trial (HERA)	III	2001-2005	5099	Post	Early-stage	HER2+ breast cancer	Trastuzumab or no trastuzumab for 1 or 2 years, following adjuvant chemotherapy	Patients with ER+/HER2+ breast cancers but with a low HER2 FISH ratio or higher *ESR1* levels receive less benefit from adjuvant trastuzumab after chemotherapy[108][109][110][111].
TAnDEM (Clinical Trial NCT00022672)	III	2001-2004	207	Post	Metastatic	HR+/HER2+ breast cancer previously treated with tamoxifen	Anastrozole alone or with trastuzumab but no chemotherapy	There was a significant improvement in PFS for the group that received anastrozole plus trastuzumab in combination [63].
EGF30008 (Clinical Trial NCT00073528)	III	2003-2006	219	Post	Metastatic	HR+ breast cancer	Lapatinib combined with letrozole or letrozole with placebo for first-line therapy	In HR+/HER2+ cancers, the combination of lapatinib and letrozole showed an increase in PFS compared to those who received letrozole with placebo [112][113].
Efficacy and Safety of Letrozole combined with Trastuzumab (eLEcTRA)	III	2003-2007	57	Post	Metastatic	HR+/HER2+ breast cancer	Trastuzumab with letrozole or letrozole alone as first-line treatment	Better outcomes, including time to progression and clinical benefit, were seen in those treated with the combined trastuzumab plus letrozole treatment [64].

ExteNET (Clinical Trial NCT00878709)	III	2009-2011	2840	Post	Stage I-III	HER2+ breast cancer previously received neoadjuvant and adjuvant trastuzumab	Neratinib	12 months treatment with neratinib significantly improved 2-year invasive disease-free survival; the benefit from neratinib was greater in HR+ patients [93][114].
Neo-ALL-IN (Clinical Trial NCT01275859)	II	2010-2012	24	Post	Stage II–III	ER+/HER2+ breast cancer	Neoadjuvant letrozole and lapatinib for 18-21 weeks before surgery	Overall clinical response rates were 62.5% however no pCR was achieved [92][115].
PERTAIN (Clinical Trial NCT01491737)	II	2012-2014	258	Post	Metastatic or locally advanced	HR+/HER2+ breast cancer patients who had not received prior therapy, with the exception of endocrine	Trastuzumab and an AI or trastuzumab, an AI and pertuzumab. Some also received chemotherapy	Greater PFS in the pertuzumab+trastuzumab+AI group but also more serious adverse events in the pertuzumab+trastuzumab+AI group [83][116].
PAMELA (Clinical Trial NCT01973660)	II	2013-2015	151	Both	Stage I–IIIA	HER2+ breast cancer	Lapatinib combined with trastuzumab (and letrozole or tamoxifen if HR+)	41% of patients with the HER2-enriched subtype and 10% of patients with non-HER2 enriched subtypes achieved pCR at the time of surgery. Patients with the HER2-enriched subtype may benefit the most from dual HER2 blockade [117][118].

NSABP B-52 trial	III	2014-2016	315	Both	Locally advanced (but not metastasised)	HR+/HER2+ breast cancer	A luteinizing hormone-releasing hormone agent or AI with docetaxel, carboplatin, trastuzumab, and pertuzumab neoadjuvant therapy	Depriving oestrogen along with docetaxel, carboplatin, trastuzumab, and pertuzumab treatment in the neoadjuvant setting improved pCR however this was not statistically significant [93].
NA-PHER2 trial (Clinical Trial NCT02530424)	II	2015-2016	102	Both	Early (> 1.5 cm) or locally advanced untreated breast cancer	ER+/HER2+ breast cancer	Neoadjuvant treatment with trastuzumab, pertuzumab, palbociclib and fulvestrant	A clinical objective response was achieved for 29/30 patients, as well as a decrease in proliferation (assessed through Ki67 expression) following two weeks of treatment and at the time of surgery [79][119].

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Figure 1. Molecular subtypes of breast cancer and key receptor/biomarker expression. Oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and proliferation marker Ki67 expression status in Perou's five molecular subtypes.

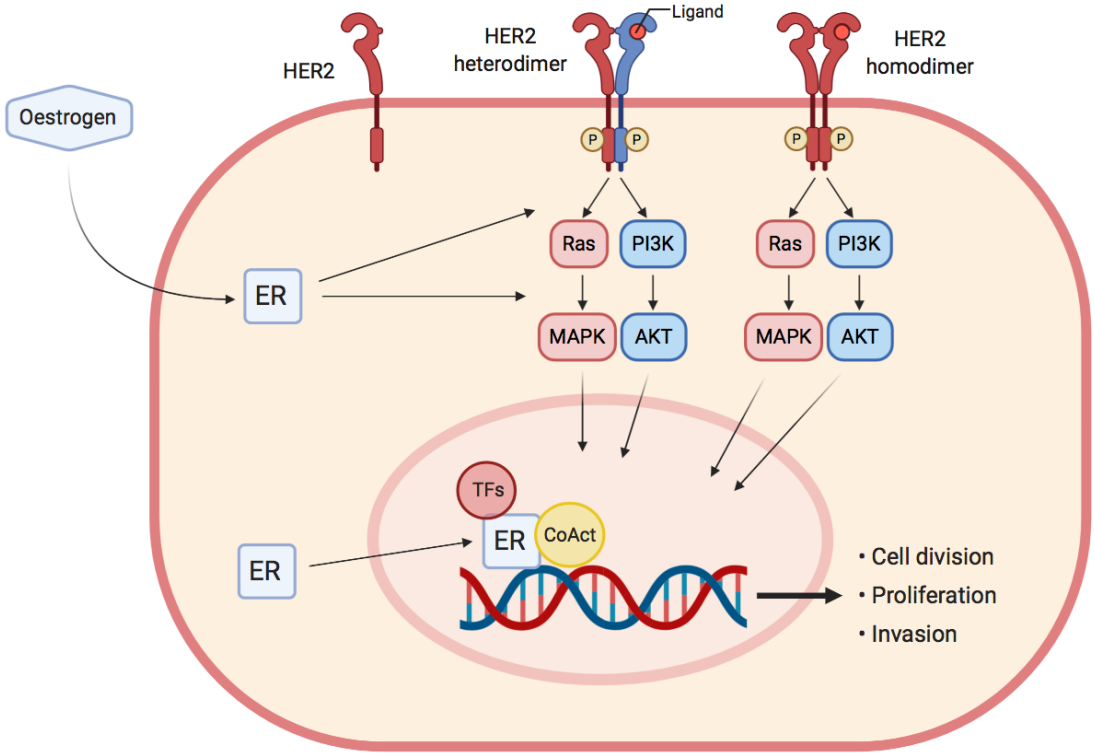
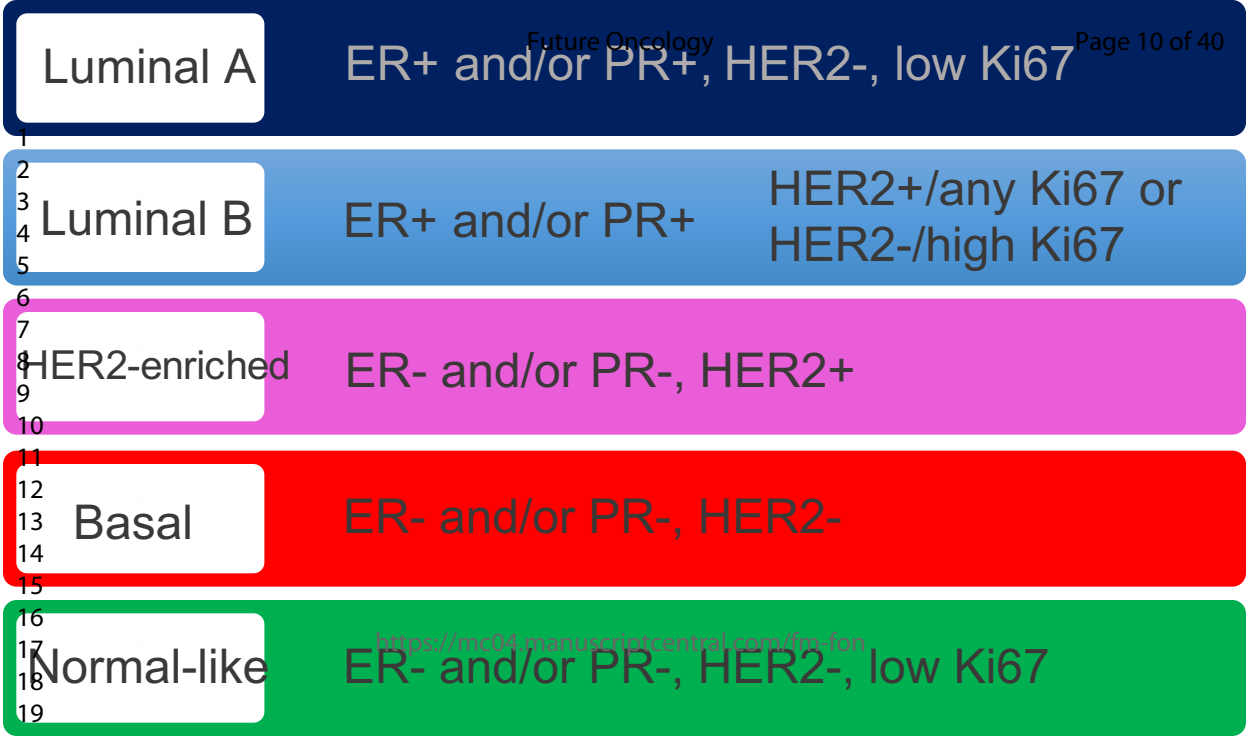
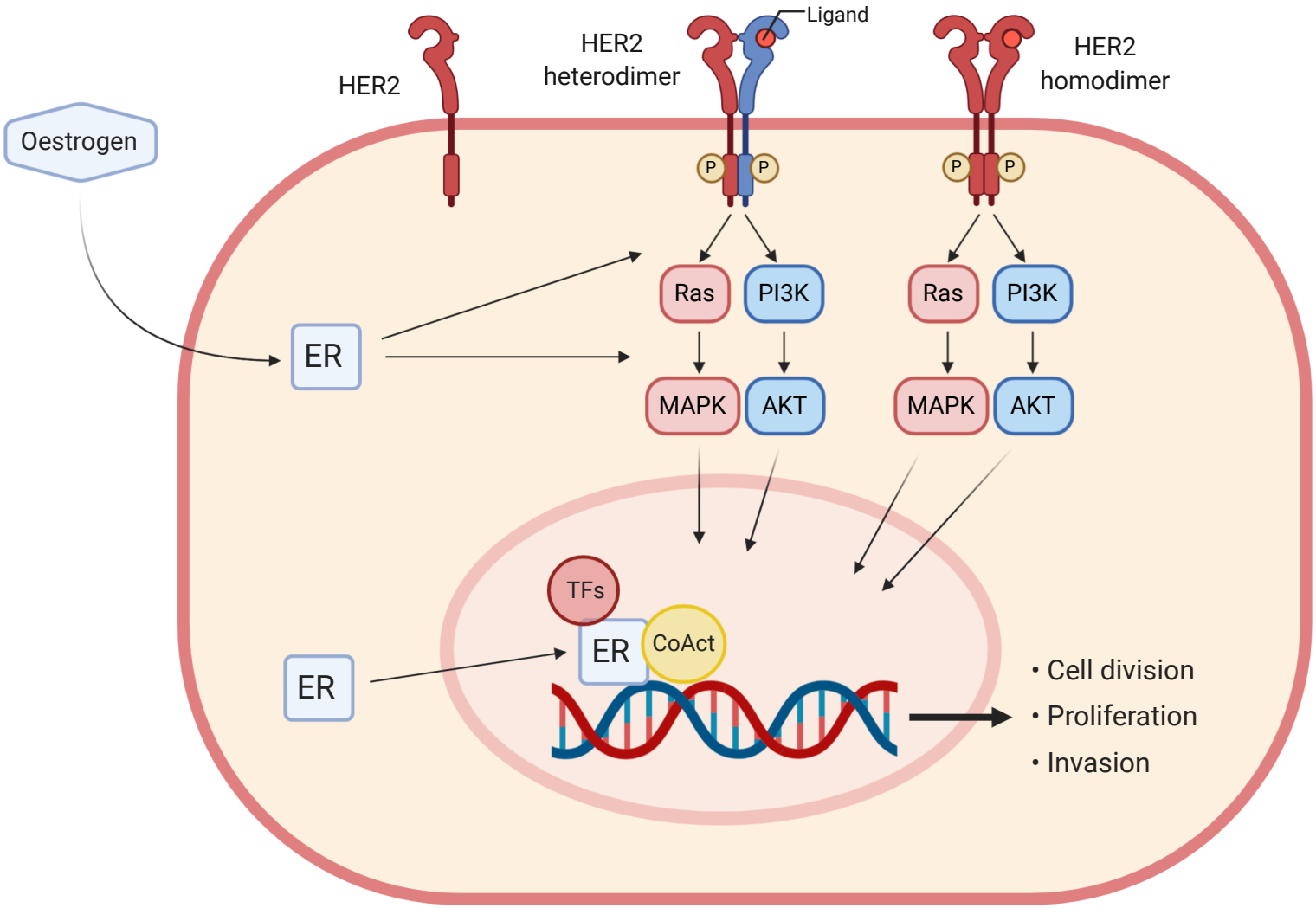


Figure 2. Crosstalk between the oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) signalling. In the presence of oestrogen, ER, which resides in both the cytoplasm and nucleus of a breast epithelial cell, can activate HER dimers and their downstream pathways (MAPK and AKT). In addition to the effects of these pathways, this signalling can also lead to modulation of active nuclear ER, which interacts with other transcription factors (TFs) and co-activators (CoAct) to regulate the expression of genes regulating processes essential to cell survival and cancer progression.




HER2
HER2
heterodimer
Ligand
HER2
homodimer
Oestrogen
P
P
P
P
Ras
PI3K
Ras
PI3K
ER
MAPK
AKT
MAPK
AKT
TFs
ER
CoAct
ER
• Cell division
• Proliferation
• Invasion