Endocrine Therapeutic Strategies for Patients with Hormone Receptor-positive Advanced Breast Cancer

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Endocrine treatment constitutes the therapeutic backbone for patients with oestrogen and/or progesterone receptor-positive breast cancer unless there is visceral crisis or suspected or known endocrine resistance. Whether all patients who are suitable for endocrine therapy should receive combination therapy or whether there remains a role for single-agent endocrine therapy is yet to be determined. Cancer biology (ESR1 mutational status) and disease pattern determine the choice of single-agent endocrine treatment. Possibly, patients with low disease burden, slow progression and presumed endocrine sensitivity might still be considered for single-agent endocrine therapy, whereas patients with more aggressive disease including visceral metastases might benefit from combination therapy. Improved guidance on selection and sequencing of treatments should become available once overall survival (OS) and progression-free survival (PFS) data have been reported from the ongoing trials in breast cancer, principally, FALCON (NCT01602380), PALOMA-2 (NCT01740427) and MONALEESA-2 (NCT01958021), which include different patient groups and, probably, different endocrine sensitivity.

Keywords

Hormone receptor-positive advanced breast cancer, selective oestrogen receptor modulators, aromatase inhibitors, selective oestrogen receptor degrader, endocrine resistance, endocrine sensitivity

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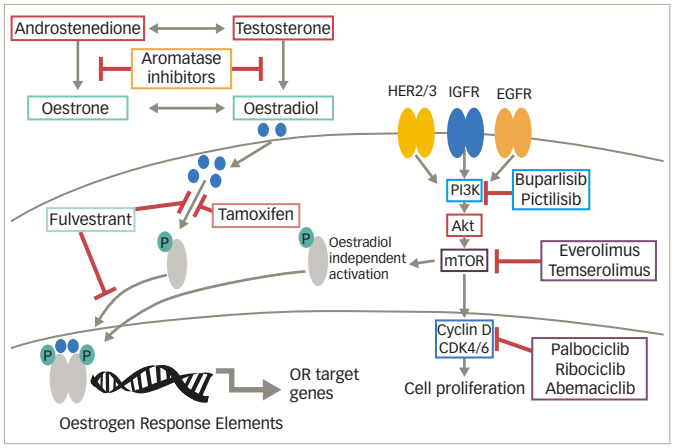
The majority (60–75%) of all breast cancers have oestrogen and/or progesterone receptors.[1] Endocrine treatment constitutes the therapeutic backbone for patients with this cancer subtype unless there is a visceral crisis or concern/proof of endocrine resistance,[2] as recommended by the third European School of Oncology (ESO)/European Society for Medical Oncology (ESMO) international consensus guidelines for Advanced Breast Cancer (ABC 3)[3] and the National Comprehensive Cancer Network (NCCN) guidelines.[4] Current endocrine therapy includes: selective oestrogen receptor modulators, aromatase inhibitors, and selective oestrogen-receptor degraders (*Table 1*), and the modes of action of these therapies are outlined in *Figure 1*. Not all patients have a response to first-line endocrine therapy (primary or de novo resistance). Such resistance occurs in approximately 40% of patients with hormone receptor (HR)-positive breast cancer, and even patients who do respond eventually exhibit acquired resistance.[5] Cytotoxic chemotherapy is also considered a first-line treatment option in patients diagnosed with HR-positive breast cancer. The decision for chemotherapy or endocrine therapy depends on a number of factors, outlined below, and there is a wide variation in the use of these treatments.[6]

Endocrine resistance

Several molecular mechanisms have been proposed to underlie endocrine resistance, including: loss of oestrogen receptor expression; altered activity of oestrogen-receptor co-regulators; deregulation of apoptosis and cell cycle signalling; hyperactive receptor tyrosine kinase; and stress/cell kinase pathways.[7] The oestrogen receptor may be activated in a ligand-independent manner via intracellular signal transduction pathways mediated either by the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway, (*Figure 1*) or the mitogen-activated protein kinase (MAPK) pathway which promotes oestrogen receptor phosphorylation and subsequently, activation.[8,9] In addition, mutations in the ESR1 gene have recently attracted attention as an important mechanism for endocrine resistance in metastatic breast cancer (MBC). These mutations occur in approximately 20–40% of patients with metastatic oestrogen receptor-positive disease who received endocrine therapies, with the higher occurrence in more advanced patients.[10] Clustered in a 'hotspot' within the ligand-binding domain (LBD) of the oestrogen receptor, these mutations lead to ligand-independent oestrogen receptor activity that promotes tumour growth, and partial resistance to endocrine therapy, and potentially enhanced metastatic capacity.[10] The purpose of this article is to provide a concise overview of endocrine therapeutic strategies for MBC, including studies with cohorts in first-line therapy, second-line and beyond.

Figure 1: Mode of action of endocrine therapies and promising targeted therapies aimed at enhancing endocrine responsiveness



Akt = protein kinase B; CDK4/6 = cyclin-dependent kinases 4/6; EGFR = epidermal growth factor receptor; HER 2/3 = human epidermal growth factor receptor 2/3; IGFR = insulin-like growth factor receptor; mTOR = mammalian target of rapamycin; PI3K = phosphatidylinositol-3-kinase; OR = oestrogen receptor.

Table 1: Key randomised clinical trials of endocrine therapy as first-line treatment in advanced breast cancer

Study arms	Study name (if applicable)	Phase	n	Overall response rate (%)	Median overall survival (months)	Reference
Anastrozole versus tamoxifen	–	–	353	21 versus 17	33 versus 32	Nabholtz et al., 2000[16]
Letrozole versus tamoxifen	–	III	907	32 versus 21*	34 versus 32	Mouridsen et al., 2001[66]
Exemestane versus tamoxifen	–	III	391	46 versus 31*	37 versus 43	Paridaens et al., 2008[67]
Fulvestrant 250 mg versus tamoxifen	–	–	578	31.6 versus 33.9	36.9 versus 38.7	Howell et al., 2004[18]
Fulvestrant 250 mg versus anastrozole	–	–	400	17.5 versus 17.5	–	Osborne et al., 2002[19]
Fulvestrant LD + anastrozole versus anastrozole	FACT	III	514	31.8 versus 33.6	37.8 versus 38.2	Bergh et al., 2012[21]
Fulvestrant LD + anastrozole versus anastrozole	SWOG study S0226	III	707	–	47.7 versus 41.3*	Mehta et al., 2012[22]
Fulvestrant 500 mg + anastrozole versus anastrozole	FIRST	II	205	36 versus 35.5	54.1 versus 48.4*	Robertson et al., 2009[68]
Fulvestrant 500 mg versus anastrozole	FALCON	III	462	46.1 versus 44.9	–	Ellis et al., 2016[28]
Letrozole + palbociclib versus letrozole	PALOMA-1	II	165	43 versus 33	–	Finn et al., 2015[35]

**Statistically significant difference; LD = loading dose.*

Endocrine therapy

Tamoxifen

Tamoxifen, first described in the treatment of advanced breast cancer in 1971,[11] is the oldest selective oestrogen receptor modulator in clinical use. In the 1990s, tamoxifen became standard first-line treatment based on randomised, controlled trials, demonstrating comparable efficacy to megestrol acetate or aminoglutethimide, but with superior tolerability. Subsequently, tamoxifen was replaced by third-generation aromatase inhibitors (letrozole, anastrozole, exemestane), which have demonstrated 3–4 months improvement in progression-free survival (PFS) in a range of randomised, controlled trials, for example, in postmenopausal women with oestrogen synthesis occurring mainly in peripheral tissues, but do not benefit in overall survival (OS) (*Table 1*).[12–16]

Fulvestrant

Fulvestrant is a selective oestrogen receptor degrader that blocks oestrogen receptor dimerisation and DNA binding, inhibiting nuclear translocation while increasing turnover of the oestrogen receptor (*Figure 1*). This leads to inhibition of oestrogen signalling via a reduction of oestrogen receptor expression and accelerated oestrogen receptor degradation.[17] A multicentre, double-blind, randomised trial, in patients with metastatic/locally advanced breast cancer comparing treatment with fulvestrant (250 mg/month) versus tamoxifen (20 mg/day) found no significant difference between fulvestrant and tamoxifen for the primary end point of time to progression (TTP).[18] Similarly, in a double-blind, randomised trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy, fulvestrant was found to be at least as effective as anastrozole, with efficacy endpoints slightly favouring fulvestrant.[19]

Initial investigation of fulvestrant in breast cancer used a dose of 250 mg, which the latest evidence suggests is suboptimal. Whereas fulvestrant 250 mg is sufficient to competitively inhibit binding of oestradiol to the oestrogen receptor, oestrogen receptor downregulation is a dose-dependent process.[20] At this dose, inhibition of oestrogen receptor transcription may occur but with incomplete oestrogen receptor degradation, i.e., so that both mechanisms of action of fulvestrant are not being utilised fully. This might explain why initial trials investigating fulvestrant at the 250 mg dose showed only comparable efficacy to anastrozole or tamoxifen.[18,19] The open-label, randomised, phase III Fulvestrant and Anastrozole Combination Therapy (FACT) trial found no clinical advantage with the combination of fulvestrant 250 mg plus anastrozole versus anastrozole alone.[21] In contrast, the Southwest Oncology Group (SWOG), in another open-label, randomised, phase III trial, reported results favouring this combination approach over anastrozole alone (*Table 2*).[22] In this study, among women who had not received prior tamoxifen therapy, the median PFS was 12.6 months with anastrozole alone versus 17.0 months with fulvestrant plus anastrozole (hazard ratio, 0.74; 95% confidence interval [CI], 0.59–0.92; p=0.006), suggesting an increased clinical benefit in patients who were endocrine therapy-naïve. A potential drug interaction has also been reported with fulvestrant plus anastrozole, resulting in a decrease in trough anastrozole concentration in patients in this study.[23]

Further supporting the effect of fulvestrant dose on efficacy, fulvestrant 500 mg/month versus 250 mg/month was compared in the Comparison of Faslodex in Recurrent or MBC (CONFIRM), a randomised, double-blind, phase III trial.[24] Fulvestrant 500 mg was associated with a 19% reduction in the risk of death and a 4.1 month difference in median OS compared with fulvestrant 250 mg (median OS 26.4 months versus 22.3 months, respectively; hazard ratio, 0.81; 95% CI, 0.69–0.96; nominal p=0.02). Fulvestrant 500 mg regimens therefore offer the possibility of

greater antitumour activity than the 250 mg regimen.[25,26] Comparison of the fulvestrant high-dose 500 mg regimen versus anastrozole in the Fulvestrant fIRst-line Study comparing endocrine Treatments (FIRST) trial showed a 34% reduction in the risk of progression in patients treated with fulvestrant (hazard ratio, 0.66; 95% CI, 0.47–0.92; p=0.01).[27]

To investigate further the potential benefits of fulvestrant 500 mg/month, and expand upon earlier data suggesting an increased clinical benefit for fulvestrant in patients who were endocrine therapy naïve,[22] the Fulvestrant and AnastrozoLe COmpared in hormonal therapy-Naïve advanced breast cancer (FALCON) first-line therapy cohort only randomised, double-blind, multicentre phase III trial was initiated.[28] In this study, there was a statistically significant 21% reduction in the risk of disease progression or death in women with HR-positive advanced breast cancer who had been treated with fulvestrant 500 mg (n=230) compared with those who had received anastrozole 1 mg/day (n=232). The median PFS was 16.6 months with fulvestrant versus 13.8 months with anastrozole (hazard ratio, 0.797; 95% CI, 0.637–0.999; p=0.0486).[29] Subgroup analysis showed improved PFS in fulvestrant-treated patients whose disease had not spread to the liver or lungs at baseline, indicating that fulvestrant would be a particularly advantageous option for patients with non-visceral disease whereas, for patients with visceral disease, outcomes were similar.

Enhancing endocrine responsiveness with combination therapies

Despite the development of resistance to endocrine therapies in some tumours, the oestrogen receptor can still remain functional and interact with growth factor signalling pathways. Using model systems of oestrogen receptor-positive breast cancers, resistance to endocrine therapy has been associated with persistent cyclin D1 expression and constitutive activation of cyclin-dependent kinase 4 and 6 (CDK4/6).[30] Furthermore, treatment with the CDK4/6 inhibitor palbociclib, found that cell lines representing luminal oestrogen receptor-positive subtypes were the most sensitive to growth inhibition.[31] Preclinical data have demonstrated growth inhibition by CDK4/6 inhibitors in HR-positive breast cancer cells.[30–32] It has also been demonstrated in vitro that breast cancer cells can escape hormone dependence due to hyperactivation of the PI3K pathway, and PI3K or mTOR inhibitors can block this effect.[33] These preclinical data provide a strong rationale for combining targeted therapies such as CDK4/6, PI3K, or mTOR inhibitors with endocrine therapy to enhance efficacy (*Figure 1*).

Cyclin-dependent kinase 4/6 inhibitors

Disordered cell cycle regulation results in uncontrolled cell proliferation and is therefore an important target for cancer therapies, with the goal of diverting tumour cells from proliferation, towards a state of non-division.[34] One important pathway in cellular proliferation involves CDK4/6, which coordinate cell cycle progression via reversible combination with cyclin D.[34] It has been demonstrated in vitro that co-targeting the CDK4/6 pathway can restore endocrine sensitivity in cancer cells,[31] potentially improving the efficacy of endocrine therapies in HR-positive breast cancer patients. Three specific CDK4/6 inhibitors, palbociclib, abemaciclib and ribociclib are currently being tested in combination with endocrine therapy in clinical trials.

Palbociclib

Palbociclib is a selective CDK4/6 inhibitor (*Figure 1*), which prevents cellular DNA synthesis by preventing downstream phosphorylation of retinoblastoma protein (Rb) and blocking cell cycle progression from the G1 to the S phase.[31] During preclinical investigation of palbociclib it was found that treatment of cell lines representing luminal oestrogen receptor-positive subtype were the most sensitive to growth inhibition, while non-luminal/basal subtypes were the most resistant.[31] These results present a strong rationale for clinical studies of palbociclib and endocrine therapy combinations in oestrogen receptor-positive breast cancer patients.[31]

In the first-line, randomised, phase II PALbociclib: Ongoing trials in the MAnagement of breast cancer (PALOMA-1) study of patients with HR-positive MBC, patients treated with palbociclib plus the aromatase inhibitor, letrozole showed significantly improved PFS (median follow-up 29.6 months [95% CI 27.9–36.0]) compared with letrozole alone (27.9 months [25.5–31.1]).[35] PALOMA-1 included postmenopausal women with advanced oestrogen receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer who had not received any systemic treatment (n=165). Median PFS in this patient subgroup was 20.2 months (13.8–27.5) for those in the palbociclib plus letrozole group and 10.2 months (95% CI, 5.7–12.6) in the letrozole monotherapy group (hazard ratio, 0.488; 95% CI, 0.319–0.748; one-sided p=0.0004). On the strength of the data from this trial, the US Food and Drug Administration granted an accelerated new drug approval, conditional upon results from PALOMA-2, a randomised, multicentre, phase III study (n=666) of palbociclib plus letrozole versus letrozole alone as first-line therapy.[36] Survival data are not yet available, however, PFS was 24.8 months (95% CI, 22.1 to not estimable) in the palbociclib plus letrozole group, versus 14.5 months (95% CI, 12.9–17.1) in the placebo plus letrozole group (hazard ratio, 0.58; 95% CI, 0.46–0.72; p<0.001). The benefit of CDK4/6 inhibition was consistent across subgroups and unaffected by the presence of ESR1 mutations.

The multicentre, double-blind, randomised phase III PALOMA-3 study (NCT01942135) (n=521) investigated the combination of fulvestrant plus palbociclib versus fulvestrant plus placebo as second-line treatment or in patients with HR-positive, HER2-negative resistant MBC.[37] Fulvestrant plus palbociclib was associated with significant and consistent improvement in PFS compared with fulvestrant plus placebo, irrespective of the degree of endocrine resistance, HR expression level, and PIK3CA mutational status.[38] Median PFS was 9.5 months (95% CI, 9.2–11.0) in the fulvestrant plus palbociclib group and 4.6 months (3.5–5.6) in the fulvestrant plus placebo group (hazard ratio, 0.46; 95% CI, 0.36–0.59; p<0.0001). Treatment with palbociclib in combination with fulvestrant was generally safe and well tolerated, with neutropaenia representing the most common adverse event. Unlike results seen with chemotherapy, in the palbociclib arm the rate of febrile neutropaenia was very low (0.9%) despite the high rate of grade 3–4 neutropaenia (65%). To manage neutropaenia in patients receiving this drug combination, it is recommended that blood counts should be monitored before the start of each new cycle as well as on day 14 of the first two cycles, with appropriate palbociclib dose delays and reductions.[39] Overall, these data show promising efficacy with fulvestrant plus palbociclib, with manageable adverse events.

Ribociclib

Ribociclib is a small molecule inhibitor of CDK4/6 that exhibits highly specific inhibitory activity against CDK4/cyclin D1 and CDK6/cyclin D3 complexes.[32] In mouse models, ribociclib has shown activity (as a single agent and in combination with letrozole and PI3K inhibitors), in breast cancers with intact oestrogen receptor and/or activating aberrations of PIK3CA/HER-2.[32] In the Mammary ONcology Assessment of LEE011's (ribociclib's) efficacy and SAfety (MONALEESA-2) phase III trial, 668 postmenopausal women with HR-positive, HER2-negative advanced breast cancer, who had not undergone any prior systemic treatment, were

Table 2: Key randomised phase III clinical trials of endocrine therapy as second-line treatment in advanced breast cancer

Study arms	Study name	n	Overall response rate (%)	Median overall survival (months)	Reference
Fulvestrant 500 mg versus Fulvestrant 250 mg	CONFIRM	736	9.1 versus 10.2	25.2 versus 22.8*	Di Leo et al., 2010[24] Di Leo et al., 2014[69]
Fulvestrant LD versus exemestane	EFECT	693	7.4 versus 6.7	–	Chia et al., 2008[70]
Fulvestrant LD + anastrozole versus fulvestrant LD versus exemestane	SoFEA	703	7.4 versus 6.9	20.2 versus 19.4	Johnston et al., 2013[71]
Everolimus + exemestane versus exemestane	BOLERO-2	724	9.5 versus 0.4*	31.0 versus 26.6	Baselga et al., 2012[50]
Fulvestrant 500 mg + palbociclib versus fulvestrant 500 mg	PALOMA-3	521	10.47 versus 6.3	–**	Turner et al., 2015[72]
Fulvestrant 500 mg + buparlisib versus fulvestrant 500 mg	BELLE-2	1,147	18.4 versus 3.5	–**	Baselga et al., 2015[56]
Fulvestrant 500 mg + abemaciclib versus fulvestrant 500 mg	MONARCH2	669	48.1 versus 21.3	–**	Sledge et al., 2017[43]

**Statistically significant difference; **Statistically significant difference in PFS, however, OS data is not yet available. LD = loading dose; OS = overall survival; PFS = progression-free survival.*

randomised to ribociclib plus letrozole, or letrozole plus placebo.[40] There was a 44% improvement in PFS in those who had received ribociclib plus letrozole, compared with those who had received letrozole alone (hazard ratio, 0.556; p=0.00000329). At data cut-off, the median PFS was 14.7 months in the letrozole arm, but was not reached in the ribociclib plus letrozole arm. The observed benefit of CDK4/6 inhibition was consistent across subgroups. Neutropaenia was the most commonly observed adverse event, however it was reversible with dose modifications. It is estimated that results from the MONALEESA-3 trial of ribociclib in combination with fulvestrant will be available in August 2019.[41]

Abemaciclib

Abemaciclib is potent inhibitor of Rb phosphorylation and has been found to inhibit tumour growth in mouse models.[42] This compound has been investigated in combination with endocrine therapy, in two clinical trials. MONARCH2 (NCT02107703), a study in women with HR-positive, HER2-negative advanced breast cancer, compared PFS among patients receiving the CDK4/6 inhibitor, abemaciclib plus fulvestrant versus fulvestrant alone as second-line treatment or in patients with resistant disease. Abemaciclib plus fulvestrant significantly extended PFS compared with fulvestrant alone (median, 16.4 versus 9.3 months; hazard ratio, 0.553; 95% CI, 0.449 to 0.681; p<0.001).[43] Unlike CDK4/6 inhibitors palbociclib and ribociclib, the most common adverse event in the abemaciclib arm was diarrhoea (86.4%), followed by neutropaenia (46.0%), nausea (45.1%) and fatigue (39.9%).

MONARCH3 (NCT02246621) is a randomised, double-blind, placebo-controlled, phase III study investigating anastrozole or letrozole plus abemaciclib, or placebo in postmenopausal women with HR-positive, HER2-negative locoregionally recurrent or MBC with no prior systemic therapy. An interim analysis showed that the combination of abemaciclib and endocrine therapy significantly prolonged PFS (hazard ratio, 0.543; p=0.000021).[44] Rates of diarrhoea and neutropaenia in the abemaciclib arm were 81.3% and 41.3%, respectively.

Mammalian target of rapamycin and phosphoinositide 3 kinase inhibition

The PI3K/Akt/mTOR pathway is a prototypic survival pathway that is constitutively activated in many types of cancer (*Figure 1*).[45] Increased activation of the PI3K/Akt/mTOR pathway is a common mechanism of resistance to endocrine therapy,[46,47] and therefore inactivation of this pathway presents an exciting potential target for increasing endocrine therapy responsiveness.

Mammalian target of rapamycin inhibitors

Temsirolimus is a specific inhibitor of mTOR (*Figure 1*), which in preclinical studies was shown to inhibit the proliferation of oestrogen-dependent breast cancer cell lines.[48] In HORIZON (NCT00083993; n=1,112), a phase III randomised, placebo-controlled study combining temsirolimus with letrozole as first-line therapy, there was no improvement in PFS in patients with aromatase inhibitor-naive advanced breast cancer.[49] Treatment-emergent adverse events were observed more frequently in the temsirolimus plus letrozole arm in comparison with letrozole only. It should be noted that some benefit was seen in exploratory analyses of the HORIZON trial, where patients aged ≤65 years receiving letrozole plus temsirolimus showed improved PFS over those receiving letrozole/placebo, 9.0 versus 5.6 months, respectively (hazard ratio, 0.75; 95% CI, 0.60–0.93; p=0.009).

Everolimus, another specific inhibitor of mTOR (*Figure 1*), in combination with the aromatase inhibitor exemestane has been shown to improve outcomes in patients with MBC resistant to hormone therapies.[50] In the BOLERO-2 (NCT00863655) phase III, randomised trial comparing everolimus and exemestane, versus exemestane and placebo (n=724) (*Table 2*), median PFS was significantly longer in patients receiving everolimus plus exemestane versus exemestane (4.6-months prolongation; p<0.0001).[51] However, there was no significant improvement in the secondary endpoint of OS.[52] Common adverse events included stomatitis, anaemia, dyspnoea and hyperglycaemia were typically of mild or moderate severity, and generally manageable with dose reduction and interruption. Exploratory analysis from BOLERO-2 suggests that the efficacy of everolimus is largely independent of the most commonly altered genes or genetic pathways in HR-positive, HER2-negative breast cancer.[53] The positive results from BOLERO-2 contrast with those reported for HORIZON and this may, in part, be a reflection of the different patient populations, in particular, of the proportion of patients with secondary resistance.

BOLERO-4 (NCT01698918) is the first trial to evaluate the efficacy and safety of first-line everolimus plus letrozole in postmenopausal women with oestrogen receptor-positive, HER2-negative metastatic or locally advanced breast cancer.[54] The median PFS was not yet reached at data cut-off, which was 2 months after the last patient's first visit. Estimated PFS rates (95% CI) were 83.6% (77.3–88.2%) and 71.4% (64.0–77.5%) at 6 and 12 months, respectively. The most common adverse events were stomatitis (67.8%), weight loss (42.6%) and diarrhoea (36.1%). Based on these results, everolimus combined with letrozole appears to provide

Table 3: Key upcoming phase III clinical trials combining alpha-selective phosphatidylinositol 3-kinase inhibitors with endocrine therapies

Study arms	Study population	Study name (ClinicalTrials.gov identifier)
Taselisib + fulvestrant versus placebo + fulvestrant	Patients with advanced or metastatic breast cancer who have disease recurrence or progression during or after aromatase inhibitor therapy	SANDPIPER (NCT02340221)
Alpelisib + fulvestrant versus fulvestrant + placebo	Men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer, who received prior treatment with an aromatase Inhibitor either as (neo)-adjuvant or for advanced disease	SOLAR-1 (NCT02437318)

HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.

clinical benefit in HR-positive, HER2-negative advanced breast cancer in the first-line setting. However, optimisation of treatment exposure must be balanced with the adequate management of adverse events. As such, careful monitoring with appropriate dose reductions and interruptions is recommended.

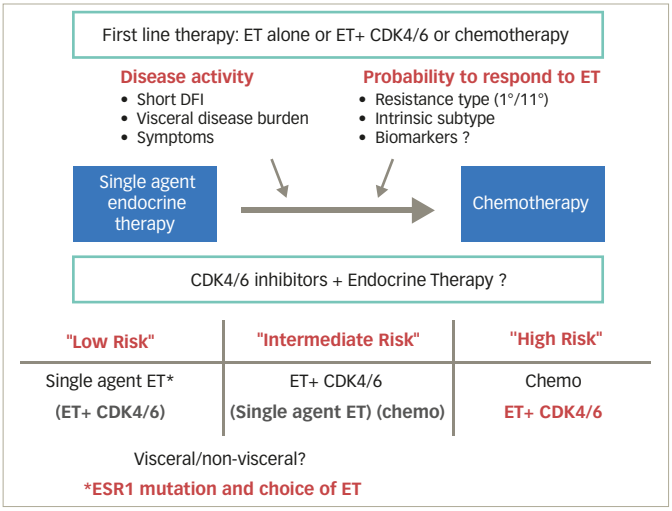
Phosphoinositide 3 kinase inhibitors

PI3K CA mutations are frequently found in breast cancer.[47] Results with pan PI3K inhibitors are largely disappointing, showing modest improvement at best and substantial toxicity. The phase II FERGI (NCT01437566) study found that the addition of the PI3K inhibitor pictilisib to fulvestrant did not significantly improve PFS. However, toxicity issues limited pictilisib dosing, thereby potentially limiting its efficacy.[55] BELLE-2 (NCT01610284) (n=1,147) was a randomised, phase III clinical trial designed to assess the efficacy of the PI3K inhibitor, buparlisib, plus fulvestrant in breast cancer patients whose tumours no longer respond to aromatase inhibitors.[56] A modest benefit in terms of PFS was observed, with a median PFS of 6.9 months with the combination versus 5.0 months with fulvestrant alone (hazard ratio, 0.78; p<0.001). The safety profile of the combination was characterised by transaminitis, hyperglycaemia, rash and mood disorders, in particular, depression (26.2% of patients with buparlisib plus fulvestrant versus 8.9% with fulvestrant alone).

Patients progressing after mTOR inhibition may still receive benefit from re-targeting the same pathway, although only in those with PIK3CA mutation. In BELLE-3 (NCT01633060), patients had HR-positive, HER2-negative, aromatase inhibitor-treated, locally advanced or MBC that had either progressed on or after treatment with everolimus. In total, 432 patients were randomly assigned (2:1) to receive daily buparlisib plus fulvestrant or placebo plus fulvestrant.[57] Median PFS for patients in the buparlisib arm was 3.9 months compared with 1.8 months for those in the placebo arm (p<0.001). Among patients with PIK3CA mutations, PFS was 4.7 months for those in the buparlisib arm compared with 1.4 months for the placebo arm (p<0.001).

In summary, PI3K/mTOR pathway inhibition has shown substantial benefit in resistant disease, especially with mTOR inhibitors; it may be that these agents are best used in acquired resistance (as in BOLERO-2), whereas in sensitive disease (e.g. HORIZON) the benefit is less clear. Future development is focusing on alpha-selective (beta-sparing) inhibitors. Since side-effects are often mediated through beta effects, the hope is for better tolerability, allowing improved targeting and higher efficacy. Further results from phase III programmes are expected in 2018 and 2019 (*Table 3*).

Figure 2. Suggested treatment algorithm



ET = endocrine therapy; CDK = cyclin-dependent kinase; DFI = disease-free interval.

Clinical decisions for treatment strategy

Where clinicians previously only had the options for chemotherapy with single-agent endocrine therapies, multiple strategies are now available. It is to be determined whether all patients suitable for endocrine therapy should receive combination therapy or whether there remains a role for single-agent endocrine therapy. Single-agent endocrine therapy shows consistent activity with PFS of 12–14 months for aromatase inhibitors and 16 months for fulvestrant 500 mg, establishing fulvestrant 500 mg as the most effective single-agent endocrine therapy. The CDK4/6 combinations seem to lead to substantially better PFS than aromatase inhibitors. However, currently no advantage has been shown on OS, and combination strategies increase the risk of side effects and are also more expensive. Even if first-line trials had shown benefit in terms of OS, it would not answer the question as to whether similar effects can be achieved with cross-over. CDK4/6 inhibitors show comparable overall benefits relative to aromatase inhibitors and fulvestrant 500 mg in second-line therapy. Therefore, it is reasonable to still consider single-agent endocrine therapy for some patients, ideally those at low risk with low activity and presumed sensitivity (*Figure 2*). This choice depends on a range of factors, such as: the type of adjuvant treatment received, length of disease-free interval, organ function, disease extent at recurrence, pre/postmenopausal status, adverse effect profile of therapy, and tumour biology (i.e., HR-receptor expression, HER2 expression levels, and mutational status). Unfortunately, there is a great deal of heterogeneity in HR-positive MBC and so there is a critical need for the development of predictive biomarkers to allow improved guidance in treatment choice.

When recommending appropriate endocrine therapy, fulvestrant's efficacy must be weighed against its intramuscular administration, which necessitates more frequent visits. Particular benefit with fulvestrant has been seen in those with non-visceral disease and ESR1 mutation status. Impressive response rates have been reported with CDK4/6 combinations, with objective response rates in excess of 40%. This is in the range of chemotherapy response rates in phase III trials with endocrine receptor-positive disease. Combination strategies might therefore allow more patients to benefit from endocrine therapy rather than chemotherapy initially, even those patients with higher risk disease.

Guidance on selection and sequencing of treatments should be re-examined following the availability of survival data, both OS and PFS, from the ongoing FALCON, PALOMA-2 and MONALEESA-2 trials. These three trials included different patient groups, with presumably different endocrine sensitivity. However, the efficacy of anastrozole appears consistent across the trials, a finding that has not yet been explained. In phase III trials, the response rates observed with CDK4/6 inhibitor combination have been similar to that for chemotherapy. Based on current available data, recent guidelines from the American Society for Clinical Oncology (ASCO) made the following key recommendations for endocrine therapy in HR-positive MBC:[39]

- Patients with tumours and any level of HR expression should be offered hormonal therapy.
- Therapy recommendations should take into account the type of adjuvant treatment, disease-free interval, and extent of disease at the time of recurrence. If recurrence occurs >12 months following prior therapy, a specific endocrine therapy may be reused.
- With the exception of patients with life-threatening disease, or those on adjuvant endocrine therapy who experience rapid visceral recurrence, endocrine therapy should be recommended as the initial treatment option.
- Treatment should be continued until disease progression occurs.
- Combined use of endocrine therapy and chemotherapy is not recommended.
- All patients, including those receiving first-line treatment should be encouraged to consider enrolling in clinical trials.

The choice of single-agent endocrine therapy can be influenced by biology (ESR1 mutational status) and disease pattern (e.g. non-visceral versus visceral). In light of the assumed impact of ESR1 mutations on the outcome of patients in response to endocrine therapy, detecting ESR1 mutations is likely to be of interest to individualise treatment of MBC.[5] ESR1-status does not appear to determine response to selective oestrogen receptor downregulators.[58,59] However, preclinical studies revealed relative resistance of the mutations to tamoxifen and fulvestrant but effective inhibition with high doses.[60–64] Retrospective analyses of ESR1 mutations in baseline plasma circulating tumour DNA from completed clinical trials suggest that these mutations are prognostic and predictive of resistance to aromatase inhibitors in metastatic disease. However, we need prospective studies to confirm these results and to determine the best treatment combinations for patients with ESR1 mutations. Clinical development of novel agents to overcome resistance engendered by ESR1 mutations is also needed. Higher doses of fulvestrant appear to improve outcomes for patients with these mutations.[59]

Concluding remarks

Patients with low disease burden, slow progression and presumed endocrine sensitivity might still be considered for single-agent endocrine therapy, whereas patients with more aggressive disease e.g. visceral metastases, could benefit from combination therapy. There is an apparent improvement in efficacy of fulvestrant in the patient group with non-visceral versus visceral disease in the FALCON trial (*Figure 2*), and similar observations were reported in the FIRST[65] and CONFIRM[24] trials. Current guidelines still recommend the use of endocrine therapy for visceral patients not in visceral crisis, however.[2,4] Overall, there is some evidence in support of a more tailored approach, although the 'one-size fits-all' tactic cannot be dismissed at present. ❑

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