Optimizing treatment-sequencing strategies for the management of postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: A Malaysian perspective

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Abstract: The incidence of postmenopausal, hormone receptor (HR)-positive, human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer is high in Malaysia. Despite the high incidence and other challenges in the local settings, there is an unmet need for optimal treatment strategies for the management of these patients. The current article includes a comprehensive review of the key clinical evidences on the management of postmenopausal women with HR+, HER2– or unknown HER2 status advanced breast cancer, with focus on the emerging role of fulvestrant and novel combinations of hormone and targeted therapies, in improving the survival outcomes. All the evidences have been rated based on the GRADE criteria by local Oncology experts through a consensus opinion, and treatment-sequencing strategies have been proposed for the optimal first- and second-line management of this patient population. The proposed strategies may serve as a useful guide to the clinicians for optimizing the treatment of these patients. Optimization of treatment in the local context may be further improved, by addressing the immediate challenges, related to availability/access to emerging treatments, enhancement of disease awareness and early diagnosis. Detection of driver mutations, and reliable biomarkers for predicting treatment outcomes may serve as a step ahead in the management of these patients in future.

Keywords: postmenopausal advanced breast cancer; HR-positive; HER2-negative; treatment-sequencing strategies

Introduction

According to the latest GLOBOCAN estimates, breast cancer is the second most common type of cancer and is the fifth leading cause of cancer death worldwide. The estimated number of new breast cancer cases and related deaths in Southeast Asia (SEA) was 107,500 and 43,000, respectively in 2012[1]. In Malaysia, a developing SEA nation, the current National Cancer Registry reports breast cancer as the most common type of cancer among women, accounting for about 32% of all cancer cases[2]. The latest regional Penang Cancer Registry in Malaysia also reports breast cancer to be the most common type of cancer in Penang[3]. The overall range of hormone receptor-positive (HR+) breast cancer cases in Malaysia has also been found to be high (50% – 65%). These high rates may be attributed to rapid urbanization and changes in parity and breast-feeding patterns over time[4,5]. Furthermore, while a study conducted in the Sarawak region of Malaysia detected close to 50% HR+, human epidermal growth factor receptor 2-negative (HER2–) cases, another study reported about 65% estrogen receptor (ER)-positive, 55% progesterone receptor (PR)-positive, and 74% HER2– cases in Kuala Lumpur[5,6].

In addition to the high incidence of breast cancer...
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(including HR+, HER2− cases), there are several other challenges that hinder the optimal management of breast cancer in Malaysia. Delay in presentation and consultation for breast cancer has been highlighted as one of the challenges in a recent meta-synthesis and other systematic reviews7–9.

Delay in diagnosis is another challenge in the Malaysian context. A delay in diagnosis by more than 3 and 6 months has been noted in about 73% and 46% of cases, respectively9,10. Furthermore, mammography screening remains under-utilized in Malaysia, with its use reserved only for the screening of high-risk women, mainly due to high cost and lack of expertise9,10.

Consultation and diagnosis delays in Malaysia may result in presentation at a more advanced stage9,11,12. The current Malaysian National Cancer Registry reports close to 43% cases presenting with de novo advanced breast cancer at the time of diagnosis11. Presentation at advanced breast cancer stages is associated with relatively low overall survival (OS) in Malaysia, as compared to corresponding data from the West10,12,13,14.

Another interesting finding is that there is a relatively evident variation in breast cancer survival rates among different hospital settings within Malaysia. This indicates that differences in access to optimal treatment and compliance to treatment may also be important determinants of survival15. Despite all these challenges, an accurate overall picture of optimal treatment strategies and survival outcomes for postmenopausal HR+, HER2− advanced breast cancer is still lacking in Malaysia, as most of the studies conducted in Malaysia are single-centre studies.

In the current landscape of breast cancer therapies, several neo-adjuvant and adjuvant therapies have been clinically proven to improve the response rate and disease-free survival in postmenopausal women with HR+, HER2− breast cancer15–17. The therapeutic armamentarium for the adjuvant therapy of postmenopausal HR+ breast cancer has evolved from the standard-of-care, tamoxifen, to third-generation aromatase inhibitor (AI) therapy18,19. Improved survival outcomes have been noted with adjuvant AIs, either as switch-over after prior 2 to 3 years of adjuvant tamoxifen or as upfront initial adjuvant therapy20–25. Furthermore, the benefit of sequential AI after 2 to 3 years of prior tamoxifen versus adjuvant tamoxifen alone was found to be more pronounced in patients with invasive lobular cancer versus invasive ductal cancer26. Another evolving strategy associated with a lesser risk of disease recurrence in this setting is the use of extended tamoxifen or AI therapy (for up to 10 years)27,28. However, with the upfront use of AIs in the adjuvant setting, this may result in the development of resistance in latter settings and thus, entails for new treatment strategies to address this unmet medical need.

Potential mechanisms of endocrine resistance

The latest European Society of Medical Oncology (ESMO) guidelines define primary endocrine resistance as relapse while on the first two years of adjuvant endocrine therapy, or disease progression within the first six months of first-line line endocrine therapy for metastatic breast cancer while on endocrine therapy. Secondary (acquired) endocrine resistance has been defined as relapse while on adjuvant endocrine therapy, but after the first 2 years or relapse within 12 months of completing adjuvant endocrine therapy or disease progression ≥ 6 months after initiating endocrine therapy for metastatic disease while on endocrine therapy29.

Several potential mechanisms of resistance to endocrine therapy have been elucidated, including: (1) reduction or loss of ER or overexpression of mutant ER (may be due to loss of expression or mutations in estrogen receptor 1 [ESR1], the gene coding for ER); (2) loss of PR; (3) upregulation of HER2 after endocrine therapy, due to crosstalk between ER and receptor tyrosine kinases, resulting in activation of alternate signaling and proliferation pathways; (4) compensatory activation of the phosphoinositide 3-kinase (P13K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) pathway; (5) increase in nuclear factor-kB (NFkB) signaling and inflammation; (6) hypersensitivity to residual estrogen after prolonged deprivation of estrogen by AI therapy; and (7) epithelial-mesenchymal transition (EMT) and subsequent loss of differentiation and intracellular adhesion18,30.

The emerging challenge of tumor heterogeneity

In addition to endocrine therapy resistance, another key challenge is the varied response of patients with HR+, HER2− breast cancer to endocrine therapy, due to heterogeneity in tumor biology. Single HR+ (ER+PR− or ER−PR+) HER2− tumors have been noted to have poor survival rates compared to ER+PR+HER2− tumors31. Also, ER− subtypes have been found to be at an increased risk of

DOI:10.18282/amor.v4.i1.255
Current unmet needs and objectives

Research is ongoing to address the potential challenges and to develop new treatment strategies for the management of postmenopausal patients with HR+, HER2– advanced breast cancer. With the evolving treatment landscape and emerging clinical evidence, the unmet clinical need is to develop optimal treatment-sequencing strategies for the management of these patients. These strategies would serve as a guide for clinicians in choosing the appropriate treatment, to optimize outcomes.

The objectives of the current article are to review current and new clinical evidences on the treatment of postmenopausal women with HR+, HER2– or unknown HER2 status advanced breast cancer, explore the contribution of new clinical evidence and emerging therapies in optimizing and impacting future treatment-sequencing strategies, and to develop a proposed treatment-sequencing pathway for optimal management in these patients. The article also includes opinions from experts that provide further insights on the applicability and adaptability of the proposed treatment-sequencing strategies in developing Asian countries such as Malaysia.

First-line therapy

Endocrine therapy or chemotherapy: Which is the optimal choice for initial treatment of advanced HR+, HER2– breast cancer?

Currently, several key guidelines and evidences recommend endocrine therapy as the preferred first-line treatment for the management of postmenopausal HR+ advanced breast cancer with HER2– status, even in the presence of visceral disease. Endocrine therapy offers lesser toxicity and better quality of life compared to chemotherapy in these patients. Chemotherapy may be an option only in patients with: (1) immediate life-threatening disease, (2) rapid visceral crisis, or (3) concern or proof of endocrine resistance. The currently available endocrine therapy landscape comprises selective estrogen receptor modulators (SERM), selective estrogen receptor down-regulators (SERD), and AIs, with the recent addition of targeted therapies such as CDK4/6 inhibitors and mTOR inhibitors to endocrine therapies to form novel combination treatment strategies.

Single-agent therapy

Tamoxifen

Tamoxifen was one of the earliest endocrine therapies to be considered as the standard-of-care for the first-line therapy of HR+ metastatic breast cancer prior to the introduction of AIs. Tamoxifen exhibits mixed agonistic and antagonistic activity on estrogen receptors. In breast cancer, tamoxifen acts by binding to the estrogen receptors and subsequently blocking the actions of estrogen. Nevertheless, due to its partial agonist properties, eventually resistance may develop to tamoxifen.

The efficacy of tamoxifen (20 mg/day) was compared to high-dose medroxyprogesterone acetate (MPA) (1 g/day) in patients with advanced breast cancer (ER+, PR+, or unknown status), who had not received prior endocrine therapy in either adjuvant or advanced settings. Although, MPA was associated with a significantly higher response rate versus tamoxifen (complete + partial response: 34% versus 17%, respectively, p = 0.01), there was no significant difference between the treatment arms in the time to treatment failure (TTF) (tamoxifen: 5.5 months versus MPA: 6.3 months, p = 0.48) or median survival (tamoxifen: 24 months versus MPA: 33 months, p = 0.09). Furthermore, a higher percentage of patients on MPA had more than 9 kg weight gain as compared to tamoxifen (35% versus 2%, respectively). In a separate meta-analysis evaluating tamoxifen versus toremifene, a higher incidence of vaginal bleeding was noted with toremifene compared to tamoxifen in advanced breast cancer patients. Furthermore, tamoxifen monotherapy has been found to have a better safety profile compared to combinations with targeted agents, due to the increased risk of toxicity with the latter.

Tamoxifen versus AIs

Aromatase inhibitors (AIs) represent a class of drugs that act by inhibiting the aromatase enzyme essential for the conversion of androgens to estrogen, the source for about 90% of total body estrogen after menopause. While steroidal AIs such as exemestane bind irreversibly to the enzyme and inactivate it, non-steroidal AIs (NSAIs) such as anastrozole and letrozole bind reversibly to the enzyme, both exhibiting specificity against the enzyme. Several studies have evaluated the efficacy of AIs versus tamoxifen for the first-line treatment of HR+ metastatic breast cancer.
The International Letrozole Breast Cancer group included both patients with and without prior adjuvant anti-estrogen therapy (only late-relapse patients were included in the former category). At 32 months’ follow-up, letrozole therapy when compared to tamoxifen therapy, was associated with a significantly superior time to progression (TTP) (9.4 versus 6.0 months; \( p < 0.0001 \)), TTF (9.0 versus 5.7 months; \( p < 0.0001 \)), objective response rate (ORR) (32% versus 21%; \( p = 0.0002 \)), and clinical benefit rate (CBR) (50% versus 38%; \( p = 0.0004 \)). Both the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability (TARGET) study and the North American trial included patients with and without prior adjuvant endocrine therapy (patients who received tamoxifen within 12 months prior to study entry were excluded in the former category). While the TARGET study demonstrated comparable efficacy of anastrozole versus tamoxifen (TTP: 8.2 versus 8.3 months, \( p = 0.941 \); ORR: 32.9% versus 32.6%, \( p = 0.787 \); CBR: 56.2% versus 55.5%, respectively), the North American trial revealed a significantly better TTP with anastrozole (11.1 months with anastrozole versus 5.6 months with tamoxifen; \( p = 0.005 \)). However, a retrospective subgroup analysis of the combined population of both the studies defined by receptor status revealed a significantly superior TTP with anastrozole versus tamoxifen in the subgroup of patients with HR+ and/or PR+ tumors (about 60% of the combined trial population) (TTP: 10.7 months with anastrozole versus 6.4 months with tamoxifen; \( p = 0.022 \)). Anastrozole was associated with fewer thromboembolic events and vaginal bleeding episodes compared to tamoxifen in both the studies. The study by the European Organisation for Research and Treatment of Cancer (EORTC) compared exemestane with tamoxifen and included patients with and without prior adjuvant endocrine therapy and a disease-free interval of at least 2 years after completing adjuvant therapy. The study revealed greater ORR, longer progression-free survival (PFS) and comparable tolerability with exemestane versus tamoxifen (ORR: 46% versus 31%; \( p = 0.005 \); PFS: 9.9 versus 5.8 months; \( p = 0.028 \)). A meta-analysis of 23 randomized controlled trials (\( n = 8504 \)) revealed a significant survival benefit with third-generation AIs (letrozole, exemestane, anastrozole) versus tamoxifen, with an 11% reduction in the relative hazard (\( p = 0.03 \)).

These findings formed the basis of the shift of standard-of-care from tamoxifen to AIs in the first-line setting.

Steroidal AIs versus NSAIs

In a randomized, double-blind controlled study comparing the steroidal AI, exemestane with the NSAI, anastrozole for the first-line treatment of postmenopausal Japanese women with HR+, HER2– advanced breast cancer, exemestane was found to have an efficacy and safety profile similar to anastrozole. Both the Tolerability (TARGET) study and the North American trial included both patients with and without prior adjuvant anti-estrogen therapy (patients who received tamoxifen within 12 months prior to study entry were excluded in the former category). While the TARGET study demonstrated comparable efficacy of anastrozole versus tamoxifen (TTP: 8.2 versus 8.3 months, \( p = 0.941 \); ORR: 32.9% versus 32.6%, \( p = 0.787 \); CBR: 56.2% versus 55.5%, respectively), the North American trial revealed a significantly better TTP with anastrozole (11.1 months with anastrozole versus 5.6 months with tamoxifen; \( p = 0.005 \)). However, a retrospective subgroup analysis of the combined population of both the studies defined by receptor status revealed a significantly superior TTP with anastrozole versus tamoxifen in the subgroup of patients with HR+ and/or PR+ tumors (about 60% of the combined trial population) (TTP: 10.7 months with anastrozole versus 6.4 months with tamoxifen; \( p = 0.022 \)). Anastrozole was associated with fewer thromboembolic events and vaginal bleeding episodes compared to tamoxifen in both the studies. The study by the European Organisation for Research and Treatment of Cancer (EORTC) compared exemestane with tamoxifen and included patients with and without prior adjuvant endocrine therapy and a disease-free interval of at least 2 years after completing adjuvant therapy. The study revealed greater ORR, longer progression-free survival (PFS) and comparable tolerability with exemestane versus tamoxifen (ORR: 46% versus 31%; \( p = 0.005 \); PFS: 9.9 versus 5.8 months; \( p = 0.028 \)). A meta-analysis of 23 randomized controlled trials (\( n = 8504 \)) revealed a significant survival benefit with third-generation AIs (letrozole, exemestane, anastrozole) versus tamoxifen, with an 11% reduction in the relative hazard (\( p = 0.03 \)).

Rationale for high dose fulvestrant

The Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) study compared the 500-mg dose of fulvestrant with the approved 250-mg dose for the treatment of postmenopausal women with HR+ advanced breast cancer progressing on prior endocrine therapy. The study included patients in both first-line (patients relapsing during or within 12 months after completing adjuvant therapy) and second-line (patients relapsing > 12 months after completing adjuvant therapy and progressing on first-
line endocrine therapy with an AI or anti-estrogen, and *de novo* advanced breast cancer patients progressing on first-line endocrine therapy with an AI or anti-estrogen) advanced breast cancer settings. The study revealed significantly longer PFS and OS benefits with the 500-mg versus the 250-mg dose, without any significant difference in the tolerability between the two treatment arms (PFS: 6.5 versus 5.5 months, respectively; *p* = 0.006 and OS: 26.4 versus 22.3 months, respectively; *p* = 0.02)\[63,64]. These results are in line with the findings obtained from the Neoadjuvant Endocrine Therapy for Women with Estrogen-Sensitive Tumors (NEWEST) trial, which proved the superior biological activity of high-dose fulvestrant versus the 250-mg dose in reducing the Ki67 labeling index, a marker of cell proliferating activity (−78.8% versus −47.4%, respectively; *p* < 0.0001) and in suppressing the expression of ER (−50.3% versus −13.7%, respectively; *p* < 0.0001) and PR (−80.5% versus −46.3%, respectively; *p* = 0.0018) in the neoadjuvant setting\[65]. Therefore, the dose of fulvestrant was revised from the initially approved 250 mg to 500 mg\[66].

**Fulvestrant versus NSAIs**

The phase II, Fulvestrant fIRst-line Study comparing endocrine Treatments (FIRST) study compared fulvestrant 500 mg regimen with anastrozole 1 mg/day for the first-line treatment of postmenopausal patients with HR+ advanced breast cancer. Although the primary efficacy endpoint of CBR was similar for both the treatment arms (72.5% with fulvestrant versus 67.0% with anastrozole; *p* = 0.386), fulvestrant therapy was associated with a significantly longer TTP and OS versus anastrozole (TTP: 23.4 versus 13.1 months, respectively; *p* = 0.01 and OS: 54.1 versus 48.4 months, respectively; *p* = 0.04)\[67–69]. These superior results for fulvestrant versus anastrozole were further validated in the recent phase III *Fulvestrant and Anastrozole Combination Therapy (FACT)* study, which enrolled endocrine therapy-naïve postmenopausal *de novo* advanced breast cancer patients with HR+ HER2− status. The PFS in this study was significantly longer in the fulvestrant group compared to the anastrozole group (16.6 versus 13.8 months, respectively; *p* = 0.05). The treatment effect was more enhanced in patients with non-visceral disease with a median PFS of 22.3 months (95% CI: 16.62–32.79) in the fulvestrant group versus 13.8 months (95% CI: 11.04 – 16.59) in the anastrozole group (HR was 0.59 [0.42 – 0.84]). The results from the FALCON trial suggested that fulvestrant has superior efficacy and is the preferred treatment option for patients with HR+ locally advanced or metastatic breast cancer who have not received previous endocrine therapy\[70].

**Combination therapy**

*Fulvestrant+anastrozole*

Results are conflicting in the literature with respect to the efficacy of fulvestrant plus anastrozole combination versus single-agent anastrozole in the first-line setting. While the Fulvestrant and Anastrozole Combination Therapy (FACT) study (HER2 status not reported) revealed no significant benefit with regard to OS or TTP with the combination (OS: 37.8 months with the combination versus 38.2 months with anastrozole single-agent therapy, *p* = 1.00; TTP: 10.8 versus 10.2 months, respectively, *p* = 0.91), the study by the Southwest Oncology Group (SWOG) (91% HER2− patients) revealed superior benefits with regard to both PFS and OS with the combination versus anastrozole monotherapy (PFS: 15 versus 13.5 months, respectively; *p* = 0.007 and OS: 47.7 versus 41.3 months, respectively; *p* = 0.05). In the SWOG study, the PFS benefits with combination therapy were more evident in patients with no prior adjuvant tamoxifen (17.0 months with combination versus 12.6 months with anastrozole single-agent therapy; *p* = 0.006), thus highlighting the role of previous endocrine therapy and its influence on outcomes with subsequent endocrine treatments\[71,72].

The difference in the results of the FACT and SWOG trials may be due to three factors: (1) The FACT study included fewer patients (n = 514) versus SWOG (n = 707), indicating that a larger study might have been required to detect differences between the treatment arms in the FACT study; (2) The FACT study included patients with locally recurrent disease, which may be associated with a better prognosis and fewer relapse events, than patients with metastatic disease (about 39% of SWOG study patients had metastatic disease at presentation); and (3) In the FACT study, more patients had received prior endocrine therapy in the combination group compared to the SWOG study (70% versus 40%, respectively)\[73,72]. These findings suggest that the combination therapy group in the FACT study was more likely to have endocrine resistance compared to the SWOG study.
Combination with CDK4/6 inhibitors

Cyclin-dependent kinase (CDK) inhibitors act by inhibiting the formation of cyclin D/CDK complexes, which are responsible for the phosphorylation of retinoblastoma protein, enabling and regulating the progression from the G1-phase to S-phase and to M-phase of the cell cycle, and subsequent proliferation in breast cancer[73]. Several combinations of CDK inhibitors with endocrine therapies have been evaluated in the first-line setting in clinical trials, including the combination of the CDK4/6 inhibitor, palbociclib with letrozole. In the phase 2, open-label, randomized, palbociclib ongoing trials in the management of breast cancer (PALOMA)-1 study, the combination of palbociclib with letrozole was found to significantly improve PFS in comparison to letrozole (20.2 versus 10.2 months, respectively; \( p = 0.0004 \)), for the first-line treatment of postmenopausal patients with HR+, HER2– advanced breast cancer. Grades 3–4 neutropenia was high in the combination therapy group versus the letrozole monotherapy group (54% versus 1%, respectively)[74]. Furthermore, in another randomized, double-blind, phase 3 study (PALOMA-2), the combination of palbociclib plus letrozole was associated with a significantly longer PFS compared to letrozole alone (24.8 versus 14.5 months, respectively; \( p < 0.001 \)). Grade 3 or 4 neutropenia was again higher with the combination (66.4%) compared to letrozole monotherapy (1.4%)[75].

Ribociclib and abemaciclib are the other CDK4/6 inhibitors being evaluated in clinical trials. In a phase 3, randomized, placebo-controlled trial (Study of Efficacy and Safety of LEE011 in Postmenopausal Women With Advanced Breast Cancer [MONALEESA-2]), the efficacy and safety of ribociclib were assessed in combination with letrozole for the first-line management of postmenopausal patients with HR+, HER2– advanced breast cancer. The treatment arms were ribociclib plus letrozole and letrozole plus placebo. The median follow-up was 15.3 months. The PFS rate after 18 months significantly improved in the combination therapy group (63% versus 42.2% in placebo group; \( p < 0.001 \)). The corresponding response rates were 52.7% and 37.1%, respectively (\( p < 0.001 \)). Neutropenia was again high in the combination group in this study (59.3% versus 0.9% in the placebo group)[76]. This combination has received both European Union (EU) and US Food and Drug Administration (US FDA) approval[77,78]. Based on the results presented at the ESMO 2017 conference, the median PFS with the combination was 25.3 months (95% CI: 23.0–30.3) versus 16.0 months (95% CI: 13.4–18.2) with letrozole monotherapy; \( HR = 0.568 \) (95% CI: 0.457–0.704; \( p < 0.0001 \)). About 55% of patients with measurable disease treated with the combination were reported to have at least 30% tumor reduction[77]. The Study of Nonsteroidal Aromatase Inhibitors Plus Abemaciclib (LY2835219) in Postmenopausal Women With Breast Cancer (MONARCH-3) is another ongoing randomized, double-blind, placebo-controlled, phase 3 study assessing abemaciclib in combination with anastrozole or letrozole versus NSAI monotherapy in patients with HR+, HER2–, locoregionally recurrent or metastatic breast cancer, with PFS as the primary endpoint and OS as the secondary endpoint[79]. In an interim analysis of MONARCH-3, the combination of abemaciclib and NSAI exhibited significantly prolonged PFS compared to NSAI monotherapy. The investigator-assessed median PFS with the combination was not reached compared to 14.7 months with NSAI monotherapy (hazard ratio 0.543; 95% CI: 0.409, 0.723; \( p = 0.000021 \)). Furthermore, the ORR was also significantly high with the abemaciclib–NSAI combination compared to NSAI monotherapy (59% versus 44%, respectively; \( p = 0.004 \)). The most common adverse events with the combination were diarrhoea, neutropenia, and fatigue, which were higher when compared to NSAI monotherapy[80]. Of note, early data also suggests that abemaciclib penetrates brain metastases in breast cancer patients, with the levels of the drug and its active metabolites in the cerebrospinal fluid being comparable to that noted in the serum and tumor tissue[81]. These findings may be suggestive of the possible usefulness of abemaciclib-based regimens in breast cancer patients with brain metastases. The brain penetration of palbociclib has however, been found to be restricted by P-glycoprotein and breast cancer resistance protein in experimental models[82].

On the safety front, the high rates of myelosuppression in all the studies with CDK4/6 inhibitor plus hormone therapy combinations may necessitate frequent monitoring, and dose reductions/interruptions. Thus, this suggests that patient selection is of utmost importance and that endocrine monotherapies still remain a valid option for some patients.

Combination with anti-VEGF therapy

Vascular endothelial growth factor (VEGF) is a pro-angiogenic factor and a key therapeutic target for anti-
cancer therapy. Anti-VEGF therapies may act by interfering with the VEGF ligand, VEGF receptors (VEGFR) or intracellular signaling of VEGFR. Bevacizumab, an anti-VEGF therapy, which acts by inhibiting the interaction between VEGF ligands and receptors}[83], has been studied in combination with hormone therapy for the first-line management of patients with HR+ advanced breast cancer with predominantly HER2− status. The results are conflicting, with the combination of bevacizumab and letrozole exhibiting improved PFS versus hormone monotherapy in the Cancer and Leukemia Group B (CALBG) study, and the combination of bevacizumab with letrozole/fulvestrant failing to demonstrate improvement in PFS versus letrozole or fulvestrant monotherapy in the Letrozole/Fulvestrant and Avastin (LEA) study. Furthermore, the incidence of grades 3–4 toxicities in both these studies was considerably high with the combinations, thus emphasizing the need to further define specific patient subgroups that may likely benefit from this combination treatment strategy[84,85].

Combination with mTOR inhibitors

The mammalian target of rapamycin signaling has been shown to play an important role in estrogen-induced proliferative response in breast cancer cells. Hence, a combination of hormonal agents and mTOR inhibitor has been demonstrated to hold promise in postmenopausal HR+ advanced breast cancers[86]. Studies in breast cancer cell lines have suggested a potential role for hormonal agent plus mTOR inhibitor combination in HR+ and both hormone-sensitive and resistant breast cancer[86,87].

The Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) is a phase III, double-blind, randomized, placebo-controlled trial that assessed the efficacy and safety of the combination of the mTOR inhibitor, everolimus and the steroidal AI, exemestane versus exemestane monotherapy in postmenopausal HR+, HER2− advanced breast cancer in the second-line setting. An exploratory analysis earlier in the first-line setting revealed a significant PFS benefit with the combination versus exemestane single-agents therapy (PFS by central assessment: 15.2 versus 4.2 months, respectively; HR = 0.32 [95% CI: 0.18–0.57]), but with an increased incidence of stomatitis, pneumonitis, hyperglycemia, diarrhea, and rash, among other adverse events associated with the combination[88]. Furthermore, the tamoxifen plus everolimus (TAMRAD) study revealed significant benefits in CBR and OS with the combination of tamoxifen and everolimus versus tamoxifen monotherapy (CBR: 61% versus 42%, respectively; p = 0.045 and OS was not reached with the combination versus 32.9 months with tamoxifen; p = 0.007). However, the incidence of adverse effects, including fatigue, stomatitis, rash, anorexia and diarrhea, was higher with the combination[46].

Second-line therapy

Key considerations

The essential considerations for the selection of second-line treatment include:

Endocrine therapies in combination with targeted therapies may be considered, such as the use of exemestane combined with everolimus or fulvestrant combined with palbociclib[29,35].

Sequential hormone (single agent/combination) therapy may be considered in endocrine-responsive disease without any evidence of immediately life-threatening disease or rapid progression of visceral disease[35].

The addition of a new hormonal agent to an existing drug that is no longer suppressing cancer growth is not recommended[35].

Patients who develop recurrent disease while receiving adjuvant hormone therapy or within 1 year of completing that treatment are defined as being resistant to that specific therapy, but they can respond to sequential hormone therapy[35].

In general, disease that recurs within the first 2 years of adjuvant hormone therapy is considered less responsive to hormone therapy[35].

In the case of progression of the tumor with a specific agent, other agents in that class may be considered ineffective for further treatment[35].

Resistance to first-line endocrine therapy may not preclude response to another endocrine therapy, and hence underlines the importance of the mechanism of action of the subsequent therapy. For example, in the North Central Cancer Treatment Group Trial N0032, fulvestrant exhibited antitumor activity with a response rate of 14.3% and CBR of 52.4%, in postmenopausal women progressing after treatment with a third-generation AI in both the adjuvant and metastatic settings[89]. Furthermore, the lack of estrogen agonist effects, unlike with tamoxifen, may render fulvestrant useful in the treatment of tamoxifen-resistant cancer.
tumors. The unique mechanism of action of fulvestrant, involving degradation of ER and complete abrogation of estrogen-sensitive gene transcription, allows for a lack of cross-resistance with other endocrine agents, thus making the drug a useful alternative in tumors resistant to first-line endocrine therapy.\[90,91\]

Mutations in the genes coding for the ESR1 are another emerging challenge associated with acquired endocrine resistance. Recurrent ESR1 mutations have been reported in about 20% of patients with metastatic HR+ breast cancer who received endocrine therapies, mostly AIs.\[92–95\]

Therefore, assessing these mutations in metastatic breast cancer patients may be useful in individualizing treatment options. Patients with ESR1 mutations have been found to significantly benefit from fulvestrant compared to AIs. Furthermore, patients with acquired resistance from prior AI treatment due to ESR1 mutations have been found to benefit from fulvestrant and palbociclib combination. This explains the potential role of ESR1 mutations in decision-making regarding further endocrine-based therapy in advanced breast cancer patients.\[95\]

Single-agent therapy

Tamoxifen

The administration of a higher dose of tamoxifen has been cited to be a useful approach in view of prolongation of the duration of stable disease, minimal side-effects, and good quality of life in cases of both primary and secondary failure to tamoxifen treatment.\[96\]

Furthermore, tamoxifen may be a safer second-line alternative to the emerging combination of tamoxifen with targeted agents, due to the increased risk of stomatitis, pneumonitis, and hyperglycemia with the latter, which may necessitate dose reduction and/or interruptions and careful monitoring during combination therapy.\[35,46\]

Aromatase inhibitors versus megestrol acetate

In a phase III, double-blind, randomized, parallel-group study, the steroidal AI, exemestane was compared with megestrol acetate in postmenopausal women with advanced breast cancer who experienced failure on tamoxifen in adjuvant or advanced settings. Although there was no significant difference between the two treatment arms with regard to the primary endpoint of ORR (15.0% with exemestane versus 12.4% with megestrol), median survival time was significantly longer with exemestane versus megestrol (median survival not reached versus 123.4 weeks, respectively; \(p = 0.039\)). The TTP and TTF were also significantly longer with exemestane versus megestrol (TTP: 20.3 versus 16.6 weeks, respectively; \(p = 0.037\) and TTF: 16.3 versus 15.7 weeks, respectively; \(p = 0.042\)). While both the drugs were well tolerated, weight gain was more common with megestrol.\[97\]

Fulvestrant versus AIs

The efficacy and safety of fulvestrant have been compared with AIs for the second-line treatment of HR+ breast cancer in advanced settings. The Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) was conducted to assess the value of fulvestrant versus exemestane in postmenopausal women with advanced breast cancer whose disease relapsed during prior NSAI therapy in the adjuvant or advanced settings. Both the treatments were found to be equally effective and well tolerated in this setting with the duration of clinical response and clinical benefit being higher in the fulvestrant group. The dose of fulvestrant used in this study was an initial loading dose of 500 mg on day 0 followed by a low, 250-mg dose on days 14, 28 and every 28 days thereafter.\[98\]

Additionally, there were other studies that were conducted to evaluate fulvestrant 250 mg versus anastrozole 1 mg, in which they were found to be equally effective and well-tolerated. It is pertinent to mention that low doses of fulvestrant were used in these studies.\[99–102\]

Furthermore, a higher percentage of patients in the study by Xu et al. were treated with two or more cycles of chemotherapy, thus predisposing them to a worse prognosis.\[99\]

The CONFIRM study conducted later revealed superior PFS and OS benefits with fulvestrant higher dose (500 mg) with a similar tolerability profile compared to the 250-mg dose in the second-line setting, thus establishing 500 mg as the preferred treatment dosing.\[63,64\]

Combination therapy

Combination hormone therapy

The Study of Faslodex, Exemestane and Arimidex (SoFEA) trial enrolled postmenopausal HR+ breast cancer patients who relapsed or progressed with locally advanced or metastatic disease on an NSAI (given as adjuvant for at least 12 months or as first-line treatment for at least 6 months). Eligible patients were randomized to receive
fulvestrant plus anastrozole, fulvestrant plus placebo, or exemestane. There were no clinically significant differences between the treatment arms in terms of PFS or response rate, suggesting no additional benefit with the combination hormone therapy. However, the combination therapy was found to exhibit PFS benefit in patients with positive status for both ER and PR (hazard ratio 0.85 [95% CI: 0.66–1.10]), thus highlighting a subset of patients with endocrine-responsive disease that may potentially benefit from this combination strategy. Furthermore, the effect of fulvestrant might not have been better than that of exemestane in this trial likely due to the suboptimal dose of fulvestrant used in the study (500 mg loading dose on day 1, followed by the low, 250-mg dose on days 15, 29 and every 28 days thereafter)\textsuperscript{103}.

**Combination with CDK4/6 inhibitors**

The PALOMA-3 trial compared the efficacy and safety of the combination of fulvestrant and palbociclib versus fulvestrant monotherapy in women with HR+, HER2– advanced breast cancer, with early recurrence in the adjuvant or metastatic settings, regardless of the menopausal status. Eligible postmenopausal patients were required to have disease progression during prior AI therapy (progression during or within 1 month after the end of therapy in metastatic settings, or during or within 12 months after the completion or discontinuation of adjuvant therapy). Eligible pre- or perimenopausal patients were required to have disease progression during prior endocrine therapy (during or within 1 month after the end of prior endocrine therapy in metastatic settings, or progression during or within 12 months after discontinuation of adjuvant tamoxifen), and were given goserelin at about 4 weeks prior to randomization and every 28 days thereafter throughout the duration of the study. At the final analysis (median follow-up of 8.9 months), the combination was noted to have a significantly higher median PFS compared to monotherapy with fulvestrant (9.5 versus 4.6 months, respectively; \(p < 0.0001\)). However, the rate of hematological adverse reactions was higher in the combination therapy group, suggestive of the need for frequent monitoring\textsuperscript{104,105}.

Similar studies on combinations of fulvestrant with other CDK4/6 inhibitors are also currently ongoing. The MONALEESA-3 trial is a phase III, double-blind study in postmenopausal women with HR+, HER2– advanced breast cancer who have received no or only one line of prior endocrine therapy. The study is ongoing and is comparing ribociclib plus fulvestrant combination therapy versus fulvestrant monotherapy with PFS as the primary endpoint\textsuperscript{106}. The study of Abemaciclib (LY2835219) combined with Fulvestrant in women with hormone receptor positive HER2 negative breast cancer (MONARCH-2) is a randomized, double-blind, placebo-controlled, phase III trial that compared abemaciclib plus fulvestrant combination therapy versus fulvestrant monotherapy in postmenopausal women with HR+, HER2– locally advanced or metastatic breast cancer. Eligible patients were required to have progressed while receiving neoadjuvant or adjuvant endocrine therapy, ≤12 months after adjuvant endocrine therapy, or while receiving endocrine therapy for advanced breast cancer. Of note, patients recruited in this study received no more than one prior line of endocrine therapy for metastatic disease and no prior chemotherapy for metastatic disease. The primary endpoint of the study was PFS. There was a significant extension of PFS with abemaciclib plus fulvestrant versus fulvestrant alone (median PFS: 16.4 versus 9.3 months [HR: 0.553; 95% CI: 0.449 to 0.681; \(p < 0.001\)]). The improvement in PFS with the combination was noted across all patient subgroups. The ORR in the abemaciclib group was 35.2% (95% CI: 30.8% to 39.6%) compared to 16.1% (95% CI: 11.3% to 21.0%) with fulvestrant monotherapy (\(p < 0.001\)). Diarrhea, neutropenia, nausea, and fatigue were the most common adverse events noted to a greater extent in the abemaciclib treatment arm\textsuperscript{107}.

**Combination with mTOR inhibitors**

The interim and final analysis of the phase III BOLERO-2 study in the second-line setting revealed a significantly higher PFS with exemestane plus everolimus combination therapy compared to exemestane monotherapy (interim analysis: 6.9 versus 2.8 months, respectively by investigator assessment, \(p < 0.001\) and final analysis: 7.8 versus 3.2 months, respectively by investigator review, \(p < 0.0001\)). However, there was an increased incidence of grade 3 or 4 adverse events, including stomatitis, anemia, and pneumonitis with the combination therapy\textsuperscript{108,109}. Adverse events leading to discontinuation of at least one study drug were reported in 26.3% of patients treated with the combination therapy versus 5% of patients treated with exemestane monotherapy\textsuperscript{109}. The OS analysis conducted
later did not reveal any statistically significant OS benefit with the combination therapy versus exemestane monotherapy (31.0 versus 26.6 months, respectively; \( p = 0.14 \))\textsuperscript{[10]}. Similarly, the TAMRAD study in second-line settings revealed a significantly higher CBR, TTP, and OS with everolimus plus tamoxifen combination therapy versus tamoxifen alone, but with an increased incidence of side effects\textsuperscript{[46]}. Therefore, due to the safety profile of the combination therapies, appropriate patient selection, increased awareness of the possible side effects, and careful monitoring of the patients may be needed during treatment.

A summary of the study characteristics and efficacy outcomes of the key first-line and second-line trials in postmenopausal HR+, HER2– or unknown HER2 status advanced breast cancer is available in Table 1. The quality of the trials has been rated as high quality (HQ), moderate quality (MQ), low quality (LQ), or very low quality (VLQ), based on a consensus opinion from the authors. The definitions for the quality of evidence rating are based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, and have been provided in Table 1\textsuperscript{[111]}.

### Discussion

Breast cancer is one of the most common type of cancers, both worldwide and in developing nations such as Malaysia. In addition to the increasing disease burden, the presentation of a high percentage of breast cancer cases at an advanced stage with large tumors due to delay in consultation and diagnosis, is a major concern in Malaysia. Additionally, the variation in the presentation of breast cancer cases between different hospital settings in Malaysia is another evident challenge. In private settings, most cases present at early stages, with about 15%–20% cases presenting with de novo advanced disease with metastasis in the lymph nodes and bone. This scenario may, however, be different in government settings, where patients may present at more advanced stages and with visceral disease. Therefore, the survival rates may also vary between different hospital settings in Malaysia.

Despite all these challenges, there is lack of clarity on the optimal management of postmenopausal patients

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**Table 1. Key first- and/or second-line studies for the management of postmenopausal women with HR+, HER2– or unknown HER2 status advanced breast cancer: Study characteristics\textsuperscript{a} and key endpoint outcomes**

<table>
<thead>
<tr>
<th>First author [year] [reference] [study name]</th>
<th>Treatment-line</th>
<th>Treatment arms [n]</th>
<th>HER2– status [Patients [n/%]]</th>
<th>Key endpoint outcomes</th>
<th>Evidence rating\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muss HB et al., 1994\textsuperscript{[49]} [Piedmont Oncology Association study]</td>
<td>First- or second-line</td>
<td>▪ Tamoxifen 20 mg/day orally [n = 91] ▪ Medroxyprogesterone acetate 1000 mg/day orally [n = 91]</td>
<td>NR</td>
<td>Tamoxifen/ Medroxyprogesterone acetate: Median survival: 24/33 mos; ( p = 0.09 )</td>
<td>LQ</td>
</tr>
<tr>
<td>Mauri D et al., 2006\textsuperscript{[54]}</td>
<td>First-, second- or subsequent lines</td>
<td>Meta-analysis of RCTs [n = 8504] ▪ AI [steroidal/ NSAIs] ▪ Tamoxifen or progestogens</td>
<td>NR</td>
<td>Survival benefit [11% RH reduction] with AI versus Tamoxifen [first-line] ( p = 0.03 )</td>
<td>HQ</td>
</tr>
<tr>
<td>Mouridsen H et al., 2001, 2003\textsuperscript{[56,59]} [International Letrozole Breast Cancer Group]</td>
<td>First-line</td>
<td>▪ Letrozole 2.5 mg OD [n = 453] ▪ Tamoxifen 20 mg OD [n = 454]</td>
<td>NR</td>
<td>Results at final 32 mos FU: Letrozole/ Tamoxifen: TTP = 9.4/6.0 mos; ( p &lt; 0.0001 ) OS = 34/30 mos; ( p = NS )</td>
<td>HQ</td>
</tr>
<tr>
<td>Bonneterre J et al., 2009\textsuperscript{[90,91]} [TARGET]</td>
<td>First-line</td>
<td>▪ Anastrozole 1 mg OD [n = 340] ▪ Tamoxifen 20 mg OD [n = 328]</td>
<td>NR</td>
<td>Anastrozole/ Tamoxifen: ( p = NS ) for all TTP = 8.2/8.3 mos</td>
<td>De novo: MQ</td>
</tr>
<tr>
<td>Nabholtz JM et al., 2009\textsuperscript{[92]} [the North American trial]</td>
<td>First-line</td>
<td>▪ Anastrozole 1 mg OD [n = 171] ▪ Tamoxifen 20 mg OD [n = 182]</td>
<td>NR</td>
<td>Anastrozole/ Tamoxifen: TTP = 11.1/5.6 mos; ( p = 0.005 )</td>
<td>MQ</td>
</tr>
<tr>
<td>Paridaens RJ et al., 2008\textsuperscript{[100]} [EORTC BCCG]</td>
<td>First-line</td>
<td>▪ Exemestane 25 mg OD [n = 182] ▪ Tamoxifen 20 mg OD [n = 189]</td>
<td>NR</td>
<td>Exemestane/ Tamoxifen: PFS = 9.9/5.8 mos; ( p = 0.028 )</td>
<td>HQ</td>
</tr>
</tbody>
</table>
| First author, year [reference] [study name] | Treatment-line | Treatment arms \([n=\ldots]\) | HER2–status [Patients \([n=\%]\)] | Key endpoint outcomes | Evidence rating*

| Iwata H et al., 2013 | First-line | • Exemestane 25 mg + Anastrozole placebo OD \([n=149]\) • Anastrozole 1 mg + Exemestane placebo OD \([n=149]\) | Exemestane/Anastrozole: 93.9%/93.6% | All patients: Fulvestrant/ Tamoxifen: TTP = 13.8/11.1 mos [HR:1.007] | MQ

| Howell A et al., 2004 | First-line | • Fulvestrant 250 mg IM once-monthly \([n=313]\) • Tamoxifen 20 mg OD \([n=274]\) | NR | Fulvestrant 500 mg/ Fulvestrant 250 mg: • PFS: 6.5/5.5 mos; \(p = 0.006\) • OS [final analysis]: 26.4/22.3 mos; \(p = 0.02\) | MQ

| Di Leo A et al., 2010, 2014 [CONFIRM] | First- or second-line | • Fulvestrant 500 mg IM on days 0, 14, and 28, and every 28 days thereafter \([n=362]\) • Fulvestrant 250 mg IM every 28 days \([n=374]\) | NR | Fulvestrant 500 mg/ Fulvestrant 250 mg: • PFS: 6.5/5.5 mos; \(p = 0.006\) • OS [final analysis]: 26.4/22.3 mos; \(p = 0.02\) | HQ

| Robertson JF et al., 2009, 2012; Ellis MJ et al., 2015 [FIRST] | First-line | • Fulvestrant 500 mg IM on days 0, 14, and 28, and every 28 days thereafter \([n=102]\) • Anastrozole 1 mg OD \([n=103]\) | Fulvestrant/Anastrozole \(n=48/49\) | Fulvestrant/Anastrozole: Primary analysis: TTP: 23.4/13.1 mos; \(p = 0.01\) OS analysis: OS: 54.1/48.4 mos; \(p = 0.04\) | MQ

| Robertson JF et al., 2016 [FALCON] | First-line | • Fulvestrant 500 mg IM on days 0, 14, and 28, and every 28 days thereafter \([n=230]\) • Anastrozole 1 mg OD \([n=232]\) | Fulvestrant/Anastrozole \(n=230/231\) | Fulvestrant/Anastrozole: PFS: 16.6/13.8 mos; \(p = 0.05\) | HQ

| Bergh J et al., 2012 [FACT] | First-line | • Anastrozole 1 mg OD \([n=256]\) • Anastrozole 1mg OD plus fulvestrant 500 mg IM on day 1 and 250 mg on days 15 and 29 of first cycle, and every fourth week thereafter \([n=258]\) | NR | Fulvestrant + Anastrozole/ Anastrozole: TTP: 10.8/10.2 mos; \(p = NS\) OS: 37.8/38.2 mos; \(p = NS\) | HQ

| Mehta RS et al., 2012 [SWOG 0226] | First-line | • Anastrozole 1 mg OD \([n=345]\) • Anastrozole 1mg OD plus fulvestrant 500 mg IM on day 1 and 250 mg on days 14 and 28 of first cycle, and 28 days thereafter \([n=349]\) | 90.5% | Anastrozole/ Fulvestrant + Anastrozole All patients: PFS:13.5/15 mos; \(p = 0.007\) OS: 41.3/47.7 mos; \(p = 0.05\) [significant difference in patients with no prior tamoxifen] Patients with no prior tamoxifen PFS:12.6/17 mos; \(p = 0.006\) Patients with prior tamoxifen PFS: 14.1/13.5; \(p = 0.37\) | HQ

| Finn RS et al., 2015 [PALOMA-1] | First-line | • Letrozole 2.5 mg OD \([n=81]\) • Letrozole 2.5 mg OD + Palbociclib 125 mg OD for 3 weeks followed by 1 week off \([n=84]\) | All | Letrozole + Palbociclib/ Letrozole: PFS:20.2/10.2 mos; \(p = 0.0004\) | MQ

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*Table 1. Continued*
Table 1. Continued

<table>
<thead>
<tr>
<th>First author, year [reference [study name]]</th>
<th>Treatment-line</th>
<th>Treatment arms [n]</th>
<th>HER2 – status [Patients [n= %]]</th>
<th>Key endpoint outcomes</th>
<th>Evidence rating*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finn RS et al., 2016 [PALOMA-2]</td>
<td>First-line</td>
<td>• Letrozole 2.5 mg OD [n = 222]</td>
<td>All</td>
<td>Letrozole + Palbociclib/ Letrozole: PFS: 24.8/14.5 mos; p &lt; 0.001</td>
<td>HQ</td>
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<tr>
<td></td>
<td></td>
<td>• Letrozole 2.5 mg OD + Palbociclib 125 mg OD for 3 weeks followed by 1 week off [n = 444]</td>
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<td>Hortobagyi GN et al., 2016 [MONALEESA-2]; ESMO oncology news 2017</td>
<td>First-line</td>
<td>• Letrozole 2.5 mg OD + Placebo [n = 334]</td>
<td>All</td>
<td>Letrozole + Ribociclib/ Letrozole + Placebo: PFS: 25.3/16.0 mos; p &lt; 0.0001</td>
<td>HQ</td>
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<tr>
<td></td>
<td></td>
<td>• Letrozole 2.5 mg OD + Ribociclib 600 mg per day on a 3-weeks-on, 1-week-off schedule in 28-day treatment cycles [n = 334]</td>
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<td>Goetz MP et al., 2015 [MONARCH-3]; Di Leo A et al., 2017 [Interim analysis of MONARCH-3]</td>
<td>First-line</td>
<td>• Anastrozole 1 mg or Letrozole 2.5 mg OD + Placebo [n = 165]</td>
<td>All</td>
<td>Abemaciclib + NSAI/ NSA1 + Placebo: PFS: Not reached/14.7 mos; p = 0.000021</td>
<td>HQ</td>
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<td></td>
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<td>• Anastrozole 1 mg or Letrozole 2.5 mg OD + Abemaciclib 150 mg orally every 12 hours till progression [n = 328]</td>
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<tr>
<td>Beck JT et al., 2014 [Exploratory analysis of BOLERO-2]</td>
<td>First-line</td>
<td>• Everolimus 10 mg OD + Exemestane 25 mg OD [n = 100]</td>
<td>All</td>
<td>Everolimus + Exemestane/ Exemestane: PFS: 11.5/4.1 mos PFS [according to central assessment]: 15.2/4.2 mos</td>
<td>MQ</td>
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<td></td>
<td></td>
<td>• Exemestane 25 mg OD [n = 37]</td>
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<tr>
<td>Bachelot T et al., 2012 [GINECO]</td>
<td>First- or second-line</td>
<td>• Tamoxifen 20 mg OD [n = 57]</td>
<td>Tamoxifen/ Tamoxifen + Everolimus: n = 53/53</td>
<td>Tamoxifen/ Tamoxifen + Everolimus: TTP: 4.5/8.6 mos; p = 0.002 OS: 32.9 mos/not reached, p = 0.007</td>
<td>LQ</td>
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<td></td>
<td></td>
<td>• Tamoxifen 20 mg OD + Everolimus 10 mg OD [n = 54]</td>
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<td>Kaufmann M et al., 2009 [16]</td>
<td>Second-line</td>
<td>• Exemestane 25 mg/day [n = 366]</td>
<td>NR</td>
<td>Exemestane/ Megestrol: TTP: 20.3/16.6 wks; p = 0.037 Median survival: Not reached/123.4 wks; p = 0.04</td>
<td>HQ</td>
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<td></td>
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<td>• Megestrol 40 mg four times daily [n = 403]</td>
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<td>Chia S et al., 2008 [EFECT]</td>
<td>First- or second-line</td>
<td>• Fulvestrant 500 mg IM on day 1, and 250 mg on days 14, and 28, and every 28 days thereafter [n = 351]</td>
<td>NR</td>
<td>Fulvestrant/ Exemestane: TTP: 3.7 mos in both groups</td>
<td>MQ</td>
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<tr>
<td></td>
<td></td>
<td>• Exemestane 25 mg OD [n = 342]</td>
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<tr>
<td>Xu B et al., 2011 [179]</td>
<td>First- or second-line</td>
<td>• Fulvestrant 250 mg/month [n = 121]</td>
<td>NR</td>
<td>Fulvestrant/ Anastrozole: p = NS for all TTP: 110/159 days</td>
<td>MQ</td>
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<tr>
<td></td>
<td></td>
<td>• Anastrozole 1 mg/day [n = 113]</td>
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<tr>
<td>Robertson JFR et al., 2003 [140]</td>
<td>First- or second-line</td>
<td>• Fulvestrant 250 mg/month [n = 428]</td>
<td>NR</td>
<td>Fulvestrant/ Anastrozole: p = NS for all TTP: 5.5/4.1 mos</td>
<td>MQ</td>
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<tr>
<td></td>
<td></td>
<td>• Anastrozole 1 mg OD [n = 423]</td>
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<td>Johnston SR et al., 2013 [SoFEA]</td>
<td>First- or second-line [second-line: 81%]</td>
<td>• Fulvestrant 500 mg IM on day 1 and 250 mg IM on days 15 and 29 of first cycle, and every 28 days thereafter +Anastrozole 1 mg OD [n = 243]</td>
<td>Fulvestrant + Anastrozole/ Fulvestrant/ Exemestane HER2+: N = 122/141/142 HER2 unknown: n = 104/76/90</td>
<td>Fulvestrant + Anastrozole/ Fulvestrant/ Exemestane: PFS: 4.4/4.8/3.4 mos; p = NS OS: 20.2/19.4/21.6 mos; p = NS</td>
<td>MQ</td>
</tr>
</tbody>
</table>

Note: MQ = Medium Quality; HQ = High Quality; LQ = Low Quality
Table 1. Continued

<table>
<thead>
<tr>
<th>First author, year [reference] [study name]</th>
<th>Treatment-line</th>
<th>Treatment arms [n]</th>
<th>HER2- status [Patients [n/%]]</th>
<th>Key endpoint outcomes</th>
<th>Evidence rating*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner NC et al., 2015, Cristofanilli M et al., 2016 [104,105] [PALOMA-3]</td>
<td>First-or second-line</td>
<td>Fulvestrant 500 mg IM on days 1, 15 and 29 of the first cycle, and every 28 days thereafter + Palbociclib 125 mg for 3 wks followed by 1 wk off [n = 347]</td>
<td>All</td>
<td>Fulvestrant + Palbociclib/ Placebo + Fulvestrant: Results at final analysis</td>
<td>HQ</td>
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<td></td>
<td></td>
<td>Placebo + Fulvestrant [same as Fulvestrant dose in combination] [n = 174]</td>
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<td>PFS: 9.5/4.6 mos; p &lt; 0.0001</td>
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<td>Fulvestrant [same as above] + placebo twice-daily [n = 223]</td>
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<tr>
<td>Sledge GW Jr et al., 2017 [107] [MONARCH-2]</td>
<td>First-or second-line</td>
<td>Fulvestrant 500 mg IM on days 1 and 15 of the first cycle, and every 28 days thereafter + Abemaciclib 200 mg twice-daily, during each 28-day cycle, tapered later to 150 mg [n = 446]</td>
<td>All</td>
<td>Fulvestrant + Abemaciclib/ Fulvestrant + Placebo: PFS: 16.4/9.3 mos; p &lt; 0.001</td>
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<tr>
<td></td>
<td></td>
<td>Fulvestrant [same as above] + placebo twice-daily [n = 223]</td>
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<tr>
<td>Baselga J et al., 2012, Yardley DA et al., 2013, Piccart M et al., 2014 [108-110] [BOLERO-2]</td>
<td>Second-line</td>
<td>Everolimus 10 mg OD + Exemestane 25 mg OD [n = 485]</td>
<td>All</td>
<td>Everolimus + Exemestane/ Exemestane: PFS [by investigator review]: 7.8/3.2 mos; p &lt; 0.0001 OS: 31/26.6 mos; p = NS</td>
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<tr>
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<td>Exemestane 25 mg OD [n = 239]</td>
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</table>


*Complete study/patient characteristics not shown; available upon request. *Evidence rating was done based on Experts’ consensus. The definitions for the quality of evidence rating are based on the Grading of Recommendations Assessment, Development and Evaluation [GRADE] system by Guyatt GH et al., 2008[111]. HQ: High quality: Further research is very unlikely to change our confidence in the estimate of effect; MQ: Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; LQ: Low quality: Further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; VLQ: Very low quality: Any estimate of effect is very uncertain.

with HR+, HER2− or unknown HER2 status advanced breast cancer in Malaysia. In this review, an attempt has been made to address this unmet need. Evidence-based treatment sequencing strategies for the management of postmenopausal patients with HR+, HER2− or unknown status advanced breast cancer have been proposed in Figure 1. Due to the lack of predictive biomarkers, potential factors such as type and duration of prior adjuvant endocrine therapy and disease-free interval, used by key guidelines for the selection of treatment choices, have been considered for the development of the current proposed treatment-sequencing strategies[29,35].

In the management of postmenopausal HR+, HER2− status breast cancer, endocrine therapy is the recommended adjuvant treatment of choice. However, emerging endocrine resistance and varied response of patients to endocrine therapy based on tumor heterogeneity, suggest that a ‘one-size-fits-all’ approach may no longer be applicable for further treatment in advanced settings.

This scenario thus highlights the importance of potential factors cited in previous guidelines, such as type and duration of prior adjuvant endocrine therapy and disease-free interval, in driving treatment selection and sequencing strategies for the first- and second-line management of postmenopausal women with HR+, HER2− advanced breast cancer[29,35]. In addition to these factors, treatment selection may also depend on other factors in the local context such as age, health condition of the patient, presence of comorbidities like diabetes, hypertension, stroke, joint/musculoskeletal pain, skeletal fracture or osteoporosis,

doi:10.18282/amor.v4.i1.255

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Optimizing treatment-sequencing strategies for the management of postmenopausal women...

Figure 1. Proposed treatment sequencing for postmenopausal HR+ HER2– or unknown advanced breast cancer

De novo advanced disease or no prior adjuvant endocrine therapy

Prior treatment with tamoxifen

Prior treatment with AI

<table>
<thead>
<tr>
<th>De novo advanced disease or no prior adjuvant endocrine therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed adjuvant therapy and relapsed ≤12 months or short PFS on previous treatment</td>
</tr>
<tr>
<td>• Ribociclib+letrozole (76,77,78)</td>
</tr>
<tr>
<td>• Abemaciclib+NSAI (79,80)</td>
</tr>
<tr>
<td>• Palbociclib+NSAI (74,75)</td>
</tr>
<tr>
<td>• Fulvestrant (78)</td>
</tr>
<tr>
<td>• NSAIs+fulvestrant (72)</td>
</tr>
<tr>
<td>• NSAI (48,49,50,51)</td>
</tr>
<tr>
<td>• Tamoxifen*</td>
</tr>
</tbody>
</table>

| Completed adjuvant therapy and relapsed >12 months or long PFS on previous treatment |
| • Ribociclib+letrozole (76,77,78) |
| • Abemaciclib+NSAI (79,80) |
| • Palbociclib + Letrozole (74,75) |
| • Fulvestrant (63,64) |
| • AI (Steroidal/NSAI) (55) |
| • Fulvestrant (67,68,69) |
| • NSAI+fulvestrant (72) |
| • NSAI (48,49,50,51) |
| • Tamoxifen* |

| Completed adjuvant therapy and relapsed ≤12 months or short PFS on previous treatment |
| • Fulvestrant+abemaciclib (107) |
| • Fulvestrant+palbociclib (104,105) |
| • Steroidal AI+everolimus (108,109,110) |
| • Fulvestrant (63,64) |
| • Steroidal AI* |
| • Tamoxifen* |
| • Fulvestrant+abemaciclib (107) |
| • Fulvestrant+palbociclib (104,105) |
| • Steroidal AI+everolimus (108,109,110) |
| • Fulvestrant (63,64) |
| • Steroidal AI (97) |

| Completed adjuvant therapy and relapsed >12 months or long PFS on previous treatment |
| • Fulvestrant+abemaciclib (107) |
| • Fulvestrant+palbociclib (104,105) |
| • Steroidal AI+everolimus (108,109,110) |
| • Fulvestrant (63,64) |
| • Tamoxifen (46) |
| • Steroidal AI (98) |

| Completed adjuvant therapy and relapsed >12 months or long PFS on previous treatment |
| • Fulvestrant+abemaciclib (107) |
| • Fulvestrant+palbociclib (104,105) |
| • Steroidal AI+everolimus (108,109,110) |
| • Fulvestrant (63,64) |
| • Tamoxifen (46) |
| • Steroidal AI (103) |

#There is no specific preference in the order of options listed in the boxes.
HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2; NSAI: Non-steroidal aromatase inhibitor; AI: Aromatase inhibitor; PFS: Progression-free survival; TTP: Time to progression.


medical history of the patient, access to and availability of treatment, patients’ choice of formulation, toxicity associated with the treatment, lack of convincing clinical evidence or benefit in support of the treatment, and the need for frequent monitoring or follow-up during the treatment. The biology of the secondary tumor is also an important factor influencing treatment selection.

For the first-line management of postmenopausal HR+, HER2– advanced breast cancer, tamoxifen has been the standard-of-care, based on decades of established evidence. However, there has been a shift in the standard-of-care from tamoxifen therapy to AIs in the first-line setting, with both NSAIs and steroidal AIs clinically proven to provide superior TTP and PFS benefits compared to tamoxifen. Furthermore, emerging evidence from the FALCON study supports the use of fulvestrant high dose (500-mg) as a preferred and new first-line standard-of-care with superior PFS benefits versus anastrozole, a current standard-of-care. These benefits have been especially noted in patients with non-visceral disease and in endocrine therapy-naïve de novo advanced breast cancer patients or patients with early recurrent disease. Based on the findings from the FALCON trial, fulvestrant 500-mg has been approved by the European Commission and US FDA as monotherapy in postmenopausal women with HR+, HER2– advanced breast cancer, not previously treated with endocrine therapy[112,113].

There is conflicting evidence in the literature on the use of the combination therapy of fulvestrant plus anastrozole in the first-line setting. Therefore, combining two hormone therapies may not prove beneficial. Combination therapies
of endocrine agents with CDK4/6 inhibitors or mTOR inhibitors have shown considerable promise, and are more suitable for treating patients with more extensive disease, but not in crises.

For the second-line therapy of postmenopausal HR+, HER2− status advanced breast cancer, single-agent tamoxifen, steroidal AIs, and fulvestrant have shown considerable promise. Testing for ER, PR and HER2 status should be done prior to considering any of the recommended regimens to further guide treatment selection. Although, there is no strong clinical data to support the use of single-agent tamoxifen in second-line settings, anecdotal reports have suggested benefits from using tamoxifen, either alone or as a part of a combination regimen in these settings, especially in patients who have not received tamoxifen in the adjuvant setting or when there is no access to other available agents. The combination of fulvestrant and anastrozole may not be beneficial over hormone monotherapies. However, a subgroup of patients with both ER+ and PR+ status may benefit from treatment with this combination. The combination therapies of CDK4/6 inhibitors or mTOR inhibitors with endocrine therapies have demonstrated significantly superior PFS benefits over respective hormone monotherapies in the second-line setting, but with an increased risk of adverse effects, thus again reinforcing the importance of frequent monitoring and dose interruptions/reductions as well as appropriate patient selection.

Considering the clinical benefits demonstrated by fulvestrant, especially based on the results from the FALCON study, this drug may be an optimal endocrine therapy backbone choice for future combination therapies with new targeted agents such as CDK4/6 inhibitors. The use of these potential new combination strategies may, however, be restricted by affordability constraints in the local settings. Patient education on the usefulness of combination therapy and monitoring of side effects during treatment may enhance the adaptability of these therapies in the local context. Furthermore, the current use of chemotherapy in high-risk patients, such as in those with visceral crisis, may also change in future with the evolving role of the combination of hormone therapies with new targeted agents.

In order to ensure the optimal use of the proposed treatment-sequencing strategies in the local context, it is important to address the challenges of availability and access to emerging new treatments. Furthermore, in the Malaysian setting, lack of disease awareness and timely diagnosis, as well as increased use of traditional therapies, are also important challenges that need to be addressed. The other unmet need in the local context is the unavailability of reliable biomarkers to help predict the treatment outcomes. With growing research in this field, the treatment landscape may witness a progress towards personalized therapy, molecular profiling efforts, and detection of potential driver mutations in breast cancer such as ESR1. The proposed evidence-based treatment-sequencing strategies in this article may serve as a useful guide to clinicians for optimizing treatment selection for better outcomes of postmenopausal patients with HR+, HER2− status advanced breast cancer in the future. To the best of our understanding, this is the first initiative as of October 2017, that has been undertaken to develop proposed treatment-sequencing strategies for the management of postmenopausal women with HR+, HER2− or unknown HER2 status advanced breast cancer, with context on adaptability in the Malaysian setting.

Author Contributions

Both authors have equally contributed in the preparation and reviewing of manuscript.

Acknowledgments

We would like to thank AstraZeneca Malaysia for the medical writing financial support and Ms. Sirisha Madhu from BioQuest Solutions for medical writing support.

Conflicts of interest

Author Radzi, is an advisory board member for AstraZeneca, Roche, Novartis, Mundi Pharma, Pfizer, MSD, Bohringer Ingelheim.

Author Lee, none to declare.

References


68. Robertson JF, Lindemann JP, Llombart-Cussac A, Rolski J,


77. Ribociclib receives EU approval as first-line treatment for HR-positive, HER2-negative locally advanced or metastatic breast cancer. Available from: http://www.esmo.org/Oncology-News/

Ribociclib-Receives-EU-Approval-as-First-Line-Treatment-for-HR-positive-HER2-negative-locally-advanced-or-Metastatic-Breast-Cancer.


86. Rudloff J, Boulay A, Zumstein-Mecker S, Evans DB, O’Reilly
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106. Fasching PA, Jerusalem GHM, Pivot X, Martin M, Laurentiis MD, et al. Phase III study of ribociclib (LEE011) plus fulvestrant for the treatment of postmenopausal patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (aBC) who have received no or only one line of prior endocrine treatment (ET): MONALEESA-3. J Clin Oncol 2016; 34 (suppl; abstr TPS624).


