Chapter 9

Management of Hormone Receptor-Positive Metastatic Breast Cancer

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Additional information is available at the end of the chapter

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Abstract

Hormone-receptor positive HER2-negative breast cancer constitutes about 2/3 of breast cancer. Hormonal therapy such as tamoxifen and aromatase inhibitors has been the main stay of treatment which gives favorable quality of life compared with traditional chemotherapy. However, the efficacy of subsequent hormonal therapy declines rapidly after the patients develops resistance to first line hormonal therapy. In recent years, there have been many breakthrough in the treatment of this cancer. A number of targeted agents including CDK4/6 inhibitor and mTOR inhibitor are now part of standard treatment paradigm to help prolong the use of hormonal therapy. New understanding in potential biomarker of resistance such as *ESR1* mutation or *PIK3CA* mutation has also empowered us to develops personalized approach in treatment. This article will explain the treatment logistic for this cancer, current knowledge in hormonal resistance, findings of key clinical trials that define the current treatment paradigm, efficacy and major side effect precaution of the targeted agents, and the unmet needs.

Keywords: metastatic breast cancer, hormone-receptor positive, CDK4/6 inhibitor, SERD, mTOR inhibitor

1. Introduction

Breast cancer is a common cancer in female with a high chance of recurrence even after curative treatment. The goal for treatment in metastatic disease is life prolongation and preservation of quality of life. Breast cancer is defined by the overexpression of hormone receptor (HR), either estrogen and/or progesterone receptors, and human epidermal growth factor receptor 2 (HER2) receptor. HR-positive HER2-negative ($HR^{+ve}/HER2^{-ve}$) breast cancer accounts for 70% of breast

cancer [1]. For patients with HR^{+ve}/HER2^{-ve} metastatic breast cancer (MBC), the choice between chemotherapy versus endocrine therapy depends on the disease load especially the presence of visceral crisis – patients with impending visceral crisis should be treated with systemic chemotherapy, whereas patients with stable condition should be given endocrine therapy. As hormonal stimulation is known to be the underlying driving force and these tumors tend to be slow growing, endocrine therapy is considered the mainstay of treatment for most patients.

The first endocrine therapy described for treatment of MBC was tamoxifen which dated back in year 1971 [2]. It is a selective estrogen receptor modulator (SERMs) that binds competitively to estrogen receptors, and can have both antagonistic and agonistic effect depending on the tissue of action. Nowadays tamoxifen and raloxifen are the most commonly used SERMs clinically. SERMs can be used in both pre- and post-menopausal women. These drugs are well tolerated and have favorable toxicity profile. The use of aromatase inhibitor (AI) was started in early 2000s for post-menopausal women. AI blocks the action of peripheral aromatase, preventing conversion of androgens to estrogen. Letrozole and anastrozole are non-steroidal reversible AIs, whereas exemestane is a steroidal irreversible AI. The initial evidence to support the use of AI was by the TARGET trial, which showed equivalent efficacy of anastrozole and tamoxifen in the first line treatment of HR-positive MBC but with lower incidence of side effects such as thromboembolic events and vaginal bleeding [3]. Subsequently letrozole was demonstrated to have superior time to progression (9.4 versus 6.0 months, $p < 0.0001$), improved objective response rate (ORR) (32 versus 21%, p −0.0002) and a trend toward longer overall survival (OS) (34 versus 30 months) compared with tamoxifen [4]. The third class of endocrine therapy is selective estrogen-receptor degrader (SERD), and fulvestrant is the only SERD approved by the U.S. Food and Drug Administration (FDA) so far. In the CONFIRM trial, it has been defined that fulvestrant should be given at a higher dose of 500 mg instead of 250 mg for its better benefit in overall survival [5]. In the recently published phase 3 FALCON trial in which endocrine therapy-naïve patients were randomized to receive fulvestrant 500 mg monthly or anastrozole 1 mg daily [6]. The progression-free survival (PFS) in the fulvestrant group was 16.6 months compared with that of 13.8 months in the anastrozole group. The p-value was at a borderline of 0.0486 and the overall survival data is not available yet. As such, both AI and fulvestrant are acceptable option for initial treatment of HR^{+ve}/HER2^{-ve} MBC, yet the use of fulvestrant is often limited by the need for monthly intramuscular injection and its high cost.

Traditional endocrine therapy at the frontline setting achieves an overall response rate in the range of 25–45% and median PFS around 8–10 months [3, 4, 7]. Second line endocrine therapy often yields unfavorable response. With improving understanding in this disease, more and more evidence suggests that combining endocrine therapy with targeted therapy could overcome endocrine resistance and significantly prolong the time on endocrine therapy, delaying the needs for chemotherapy. This chapter will discuss the latest development in the targeted therapy for HR^{+ve}/HER2^{-ve} MBC and the future direction.

2. Endocrine resistance

Endocrine resistance is a major obstacle for treatment of HR^{+ve}/HER2^{-ve} MBC. Multiple mechanisms have been implicated. Based on these knowledge we now have a number of

targeted therapy that can help overcome this problem. The more clinically relevant mechanisms are discussed as below.

2.1. Dysregulation of cell cycle checkpoints

In mammalian cells, cell cycle progression is determined by the checkpoint regular retinoblastoma protein (Rb), which itself is controlled by a number of cyclin-dependent kinases (CDK) [8]. In quiescent state, Rb in its hypo-phosphorylated state suppresses the cell cycle progression from G1 phase into S (synthesis) phase. In proliferative state, CDK subtypes 4 and 6 complexes with cyclin D1, D2, or D3, triggering Rb phosphorylation [9]. Hyperphosphorylation of Rb leads to increased activity of the E2F family of transcription factors and promotes cell cycle progression. Cyclin D1 amplification is common in HR-positive breast cancer. Cyclin D1 is encoded by *CCDN1*. *CCND1* and cyclin D1 have been found to be amplified in 15–20 and 28–58% of luminal breast cancer respectively [10, 11]. Preclinical research suggested dysregulated cell cycle checkpoint regulation could lead to abnormal cell cycle progression and loss of endocrine responsiveness. Treatment of antiestrogen in breast cancer cells was associated with suppressed cyclin D1 expression, and emergence of endocrine resistance was accompanied by persistent cyclin D1 expression and Rb phosphorylation [12, 13]. Subsequent *in vitro* study further demonstrated that in breast cancer cell lines, CDK4/6 inhibitor palbociclib had preferential activity in reversing treatment resistance in luminal cells [14]. A number of CDK4/6 inhibitors have been tested clinically, and have become standard treatment of HR^{+ve}/$HER2^{-ve}$ MBC.

2.2. Crosstalk growth factor receptor and PI3K/AKT/mTOR pathway

Phosphatidylinositol-3-kinasd (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway is an important signal transduction system on which many growth factor receptors pathways converge. Crosstalk between the PI3K/Akt/mTOR pathway and growth factor receptors such as EGFR, HER2, HER2, FGFR1, and IGF1R have been described in endocrine resistance [15–18].

Abnormal activation of the PI3K pathway could result in factitious cell proliferation. The PI3K complex is composed of a regulatory subunit and a catalytic subunit p110. P110 has four isoforms – α, β, γ, and δ. *PIK3CA* mutation is found in up to 40% of breast cancer and is likely to be present in early cancer development [19, 20]. Abnormal PK3K signaling was found in up to 70% of breast cancers [21]. Besides *PIK3CA* mutation, hyperactivation of this pathway can result from aberration other PI3K subunits, mutation or phosphorylation of effectors Akt, loss of inhibitory signal from PTEN or INPPR4B, leading to activation of downstream effector mTOR protein. As hyperactivation of PI3K pathway could promote estrogen-independent ER transcriptional activation, inhibition of PI3K or its downstream effectors is an attractive target to overcome endocrine resistance [21, 22].

2.3. Changes in the estrogen receptor (ER) and HER2 status

Loss of HR expression, although uncommon, has been reported in hormone-resistant breast cancer. Study of paired primary and metastatic HR-positive breast cancer found a positive-to-negative change in HR status in 10% of metastatic breast tumor [23]. In the P024 neoadjuvant endocrine therapy trial that recruited 228 post-menopausal women with HR-positive stage 2 or 3 breast cancer, those who lost ER status after AI treatment had worse recurrence-free

survival compared with those who had no change in ER status (HR of relapse = 2.4, p = 0.03) [24]. Another study of paired sample analysis of primary cancer and liver metastases post-treatment showed ER status and HER2 status change in 30% and 10% of patients [25]. How these changes in receptor status affect management and outcome is not well understood.

2.4. Molecular changes secondary to the use of aromatase inhibitor

Molecular changes in the target receptors after treatment causing treatment failure is a well-known phenomenon in many malignancies. For HR-positive breast cancer, the target of interest is *ESR1*, which encodes for ERα. *ESR1* mutation has not been detected in sequencing analysis of 390 treatment-naïve primary breast cancer tissues in the Cancer Genome Atlas project [11]. In another study, tissue of patients with hormone-resistance breast cancer were sequenced, and showed 14 or 80 these cases showed *ESR1* mutations affecting the ligand-binding domain [26]. The mutations were the highly recurrent mutations encoding p.Tyr537Ser, p.Tyr537Asn and p.Asp538Gly alterations. p.Tyr537Ser and p.Asp538Gly play a role in hydrogen bonding of the mutant amino acid with Asp351 and favors the agonist conformation of the ER receptor. As a result the mutant ER becomes active in the absence of hormonal stimulation, and renders ER antagonists ineffective. The clinical significance of *ESR1* mutation will be further discussed in Section 3.4.

3. New clinical therapy and emerging treatment

3.1. CDK4/6 inhibitor is now a new standard treatment

3.1.1. Palbociclib

Palbociclib is a first-in-class CDK4/6 inhibitor [27]. Based on the impressive PFS found in the phase 2 study PALOMA-1 [28], palbociclib was granted accelerated approval in 2015 by the Food and Drug Administration (FDA) for treatment of $HR^{+ve}/HER2^{-ve}$ MBC in the first line setting.

3.1.1.1. Key results of phase 3 PALOMA studies

PALOMA-2, is a double-blind, placebo-controlled, randomized phase 3 study of palbociclib plus letrozole in women with $HR^{+ve}/HER2^{-ve}$ MBC patients who had no prior treatment for advanced disease [29]. Patients were randomized to receive palbociclib plus letrozole or placebo plus letrozole. The primary end point was PFS. Secondary end points included OS, objective response rate (ORR), clinical benefit response (CBR) and safety. The study recruited 666 women within 17 months. The primary endpoint was met – the addition of palbociclib to letrozole, as compared with placebo-letrozole, increased the median PFS from 14.5 months (95% confidence interval [CI], 12.9–17.1) to 24.8 months (95% CI, 22.1 to not estimable) (hazard ratio [HR] 0.58, 95% CI, 0.46–0.72; $p < 0.001$). Subgroup analyses of PFS confirmed a consistent benefit across all subgroups evaluated including different race, prior disease-free survival, visceral involvement, prior

hormonal therapy, the type of recent hormonal therapy, or prior chemotherapy (HR ranges, 0.35–0.67). The ORR for all randomly assigned patients in palbociclib-letrozole group versus placebo-letrozole group was 42.1% (95% CI, 37.5–46.9) and 34.7% (95% CI, 28.4–41.3) (odds ratio 1.4, 95% CI, 0.98–2.01; p = 0.06). CBR among all patients randomized was 84.9% (95% CI, 81.2–88.1) for palbociclib-letrozole group and 70.3% (95% CI, 63.8–76.2) for placebo-letrozole group (odds ratio 2.39 (95% CI, 1.58–3.59; p < 0.0010). The most frequent grade 3 and 4 adverse event (AE) in the palbociclib-letrozole group was neutropenia (66%), but febrile neutropenia occurred in 1.8% of patients only. Other common AE included fatigue (37%), nausea (35%), arthralgia (33%), alopecia (33%) and diarrhea (26%) and all these were mild.

PALAMO-3 is another indication-defining phase 3 study of palbociclib [30]. Patients with HR^{+ve}/$HER2^{-ve}$ HER2-negative MBC who had relapsed or progressed during prior endocrine therapy were randomized to receive fulvestrant with placebo or fulvestrant with palbociclib. A total of 521 patients were randomized. The median PFS was 9.2 and 3.8 months in the fulvestrant-palbociclib and fulvestrant-placebo groups respectively (95% CI, 2.5–5.5) (HR 0.42, 95% CI, 0.32–0.56; p < 0.001). ORR was 10.4% with fulvestrant-palbociclib and 6.3% with fulvestrant-placebo, and the CBR was 34% with fulvestrant-palbociclib and 19% with fulvestrant-placebo. In the fulvestrant-palbociclib group, grade 3 or 4 neutropenia was found in 62%. Other common AEs were fatigue (38%), nausea (29%), anemia (26%), and headache (21%).

The results of PALOMA-2 echo those of PALOMA-1 that led to FDA approval. PALOMA-1 differs from PALOMA-2, besides being a phase 2 trial, in that it adopted a 1:1 randomization. There were also small differences in the subgroup analysis, such as inclusion of the newly diagnosed metastatic disease subgroup. Nevertheless, both studies showed significant survival benefit of palbociclib and similar toxicity profiles.

3.1.2. Ribociclib

Ribociclib is the second CDK 4/6 inhibitor received the U.S. FDA approval in March 2017. The first approval study was MONOLEESA-2 for first line setting. MONOLEESA-7, which is also a first line trial, had special interest in pre- and peri-menopausal women. The data also became available recently.

3.1.2.1. Key results of phase 3 MONOLEESA studies

MONOLEESA-2 is a double-blind, placebo-controlled, phase 3 study of ribociclib plus letrozole [31]. It mirrors PALOMA-2 for the target patient population. Patients were randomized 1:1 to ribociclib-letrozole or placebo-letrozole. The study demonstrated that the addition of ribociclib to letrozole significantly improved PFS from 14.5 months to over 25 months giving a HR of 0.56 for disease progression or death (95% CI, 0.43–0.72; p < 0.001). The ORR was 40.7% in the ribociclib group and 27.5% in the placebo group in the intention-to-treat population. The CBR was 79.6% in the ribociclib group and 72.8% in the placebo group (p = 0.02) respectively in the intention-to-treat population. The most common grade 3 and 4 AEs were neutropenia (60%), elevated alanine aminotransferase (9%), elevated aspartate aminotransferase (6%), infection (4%) and vomiting (4%). Other common AEs were minor and mild.

The results of MONOLEESA-7 was first released in the San Antonio Breast Cancer Symposium (SABCS) 2017 [32]. Unlike other studies of CDK4/6 inhibitors, this study recruited pre- or perimenopausal $HR^{+ve}/HER2^{-ve}$ MBC patients who had received no prior endocrine therapy for advanced disease, but allowed up to 1 line of chemotherapy. Patients were randomized to receive standard treatment of goserelin, plus either tamoxifen or AI, together with ribociclib or placebo. The median age of recruited patients were 44 years old, and 40% had *de novo* metastatic disease. For those who developed metastasis after primary resection, more than 50% had disease-free interval for more than 12 months. Median PFS turned out to be 13.0 months for the placebo group and 23.8 months for the ribociclib group (HR 0.553; 95% CI, 0.441–0.694; $p < 0.001$). About ¼ of the patients received tamoxifen, and there was no difference from those who received AI in term of PFS benefit gained with addition of ribociclib. Goserelin was an effective method for ovarian suppression for treatment of pre/peri-menopausal $HR^{+ve}/HER2^{-ve}$ MBC, and tamoxifen was as good as AI partnering with ribociclib.

3.1.3. Abemaciclib

In September 2017, abemaciclib was approved by the U.S. FDA to be used in combination with fulvestrant for HR-positive MBC progressed following endocrine therapy. It was also approved as monotherapy for HR-positive MBC with disease progression following endocrine therapy and chemotherapy in the metastatic setting.

3.1.3.1. Important clinical trials of abemaciclib

MONARCH-2 is a randomized placebo-controlled trial to study the combination of abemaciclib with fulvestrant in patients with $HR^{+ve}/HER2^{-ve}$ MBC who have progressed on or had less than 12 months from end of adjuvant endocrine therapy [33]. Patient received abemaciclib daily without resting period. The original study dose was 200 mg BD, but the protocol amended to reduce the dose to 150 mg BD as there were many clinically significant diarrheas. Abemaciclib plus fulvestrant significantly prolonged median PFS versus fulvestrant alone (16.4 versus 9.3 months; HR 0.553; 95% CI, 0.449–0.681; $p < 0.001$). In the intention-to-treat population, abemaciclib plus fulvestrant achieved an ORR of 35.2% compared with 16.1% in the control arm ($p < 0.001$), and it included 14 patients with complete response (3.1%). The treatment gave durable response with 12-month duration of response rate of 67.8 and 66.9% in the abemaciclib and the placebo arm respectively. After 12 cycles of treatment, the mean change in tumor size for the abemaciclib arm and placebo arm were − 62.5% and − 32.8% respectively. The most common adverse events in the abemaciclib arm were diarrhea (all grade 86.4%, grade 3 & 4 13.4%), neutropenia (all grade 46.0%, grade 3 & 4 26.5%), nausea (all grade 45.1%, grade 3 2.7%), and fatigue (all grade 39.9%, grade 3 2.7%).

The results of MONARCH-3 came after MONARCH-2. MONARCH-3 is a double-blind randomized phase 3 study of abemaciclib or placebo plus a non-steroid AI in $HR^{+ve}/HER2^{-ve}$ MBC patients who had no prior systemic therapy in the advanced setting [34]. Patients were randomized to receive either abemaciclib 150 mg BD continuously or placebo with anastrozole 1 mg or letrozole 2.5 mg daily. Median PFS was significantly longer in the abemaciclib arm compared with placebo arm (HR 0.54; 95% CI, 0.41–0.72; $p < 0.001$). The ORR in the

intention-to-treat population was 48.2% and 34.5% for abemaciclib and placebo arms respectively (p = 0.002). Diarrhea was reported in 81.3% but most was grade 1. The most common grade 3 or 4 toxicity was neutropenia (21.1%) and diarrhea (9.5%).

While most clinical trials of palbociclib and ribociclib focused on first or early line treatment for metastatic disease, abemaciclib is the only CDK4/6 inhibitor that has proven to have meaningful activity in refractory disease. MONARCH-1 is a phase II single-arm open-label study for $HR^{+ve}/HER2^{-ve}$ MBC patients who had progressed on or after endocrine therapy, and had 1 or 2 chemotherapy regimens [35]. Abemaciclib was given at 200 mg BD continuously as monotherapy. The primary objective was ORR. Other endpoints included CBR, PFS, and OS. This study recruited 132 patients. Median line of treatment was 3. ORR was 19.7%, CBR was 42.4%, median PFS was 6.0 months, and median OS was 17.7 months. Major treatment-related AEs were diarrhea (all grade 90.2%, grade 3 & 4 19.7%), fatigue (all grade 65.2%, grade 3 12.9%), and nausea (all grade 64.4%, grade 3 4.5%). Neutropenia was reported in 87.5% of patients of which 26.9% were grade 3 or 4.

3.1.4. Biomarker of response

At the age of precision medicine, we aim to understand the potential biomarker of response that can guide us on treatment. For palbociclib, investigated biomarkers include cyclin D1 amplification and p16 loss, ER expression, Rb level, and Ki67 index [28, 36], as well as hormone-receptor expression level, *PIK3CA* mutation status, and plasma circulating tumor DNA *ESR1* mutation status [37, 38]. No biomarker of response has been identified for palbociclib.

As to ribociclib, ctDNA was collected for MONALEESA-2 study at baseline. Although patient with *PIK3CA* variants had shorted PFS compared with those with wild-type *PIK3CA*, they derived similar PFS benefit to the addition of ribociclib (Altered *PIK3CA* HR 0.53, wild-type *PIK3CA* HR 0.44) [31]. Similarly, altered *TP53* was a poor prognostic factor, yet both wild-type *TP53* and altered *TP53* had similar response to added benefit of ribociclib. There was a week trend toward limited PFS benefit with ribociclib was observed in patients with alteration in CDH1 and FGFR1/ZNF7–3. The incidence of these genetic events was found in only 5–11% of patients, thus the results still inconclusive. A better understanding in biology of endocrine resistance and obtaining study biopsy at the time of starting treatment or upon disease recurrence or progression might provide valuable insight in this field.

3.1.5. Discussion for CDK4/6 inhibitor

PALOMA-2 showed superior efficacy of adding palbociclib to letrozole in first line treatment of $HR^{+ve}/HER2^{-ve}$ MBC with an unprecedented PFS of over 2 years. This benefit extended to all subgroups, including those with prior exposure to hormonal therapy or chemotherapy. This study confirms the new standard of adding CDK4/6 inhibitor in this disease.

The most concerning toxicity of palbociclib and ribociclib was neutropenia. It happened in 80–90% of patients of which grade 3 or 4 neutropenia was reported in 60%. Patients who developed neutropenic fever, grade 4 neutropenia, or prolonged neutropenia would require dose reduction. The significance of dose reduction is not clear. PALOMA-3 is a

study of palbociclib in combination with fulvestrant in patients who progressed on first line hormonal therapy [30]. Detailed analysis showed that dose modification of palbociclib for grade 3 and 4 neutropenia had no adverse effect on PFS [39]. Together with improved quality of life (QoL), and low incidence of neutropenic fever of less than 2%, palbociclib and ribociclib are drugs very well tolerated.

While PALOMA-1, PALOMA-2, and MONALEESA-2 provided the evidence to the use of CDK4/6 inhibitor in the first line setting, all these trials were done in post-menopausal women. In fact the last randomized trial dedicated to premenopausal women with MBS was published almost 2 decades ago. It is estimated that around 1/5 of newly diagnosed breast cancer in the U.S. was found in women younger than 50 years old [40]. In Asia-Pacific region, 40% of breast cancer patients were of age less than 50 years [41]. Breast cancer in young patients is believe to be more aggressive and has distinct tumor biology. MONALEESA-7 is the first of the series to explore the activity of CDK 4/6 inhibitor in these patients. It extended the use of CDK4/6 inhibitor in pre/peri-menopausal women in combination with GHRH agonist as the mean of ovarian suppression. It also proved that tamoxifen was an as effective hormonal partner as AI with CDK4/6 inhibitor.

The hazard ratios for all first line trials of CDK4/6 inhibitor were similar, ranging between 0.49 and 0.58. It appeared that these drugs had comparable efficacy. The choice of drug would probably depend on their toxicity profile, dosing regimen, or dosage form. The 3 CDK4/6 inhibitors were not made equal. Palbociclib and ribociclib are structurally similar, basing off a pyrido [2,3-d]pyrimidin-7-one scaffold that was optimized for selectivity toward CDK4/6 [42, 43]. Abemaciclib, on the other hand, derived from a 2-anilino-2,4-pyrimidine-[5-benzimidazole] scaffold. This compound not only has potent activity against CDK4 and 6, it also inhibits multiple kinases *in vitro* a concentration less than 100 nM [44]. Neutropenia is the most common side effect of palbociclib and ribociclib. It appeared that anemia, thrombocytopenia and possibly stomatitis were more common in patients given palbociclib. For ribociclib, results from MONOSEESA-2 showed grade 3 or 4 elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in up to 9% of the patients. Prolonged QTcF was also a concern for a small proportion of patients in the study. Although palbociclib and ribociclib have comparable spectrum of CDK activity [45], the small disparities in their chemical structure might explain the differences in their toxicities. Abemaciclib, being structurally distinct from the other 2 CDK4/6 inhibitors, has diarrhea being the most reported adverse event. Grade 3 and 4 neutropenia was at around 21–25%, half of that reported in the PALOMA or MONALEESA trials. Due to the lower incidence of bone marrow toxicity, this drug is taken twice per day continuously without the need for a resting week. It is also the only CDK4/6 inhibitor with an indication in heavily pretreated patients as a monotherapy.

Although $HR^{+ve}/HER2^{-ve}$ breast cancer is regarded as a less aggressive form of breast cancer, a significant proportion of patients after curative resection ultimately relapse. The impressive response in metastatic setting and decent QoL data of palbociclib suggest that this drug might have a role as adjuvant therapy and help prevent recurrence. A number of adjuvant trials are ongoing. For instance, PALLAS evaluates the outcome of adding 2 years of palbociclib to standard endocrine therapy [NCT02513394]. PENELOPE-B studies the role of adding

palbociclib to standard endocrine therapy in patients with high risk of relapse after neoadjuvant chemotherapy [NCT01864746]. MonarchE [NCT03155997] is also recruiting. It studied the effect of adding 2 years of abemaciclib to standard adjuvant endocrine therapy in high-risk node-positive early stage patients post-resection.

CDK4/6 inhibitors revolutionized how $HR^{+ve}/HER2^{-ve}$ MBC should be treated. There is an unmet need for biomarker of response to guide management decision. Further studies on the benefit of continuing CDK 4/6 inhibitors beyond progression or the optimal time to add these targeted agents would also be needed.

3.2. Traditional mTOR inhibitor remains a standard treatment

mTOR is a downstream effector of the PI3K/AKT pathway. Targeting mTOR is a rational strategy to reverse endocrine resistance. TAMRAD is a phase 2 study that explored the combination of oral mTOR inhibitor everolimus with tamoxifen versus tamoxifen in patients with $HR^{+ve}/HER2^{-ve}$ MBC who have progressed on AI [46]. The dosage of everolimus was 10 mg daily. This primary end point was CBR. Everolimus significantly improved the CBR from 42–61%. Time to progression increased from 4.5 months with tamoxifen alone to 8.6 months with addition of everolimus (HR 0.54; 95% CI, 0.36–0.81). Significant adverse reaction included fatigue (72%), stomatitis (56%), rash (44%), anorexia (43%), and diarrhea (39%). Second line AI is a common strategy upon progression on first line AI. BOLERO-2 is a phase 3 trial which randomized patients who have receive exemestane plus everolimus or everolimus alone [47]. Patients had recurrence or progression while on previous endocrine therapy with a nonsteroidal AI in the adjuvant setting or to treat advance disease. The primary end point was PFS. The study stopped early after the interim analysis, as median PFS was 6.9 months with everolimus plus exemestane, versus 2.8 months with exemestane alone (HR 0.43; 95% CI, 0.35–0.54; $p < 0.001$) based on assessments by local investigators. These patients were heavily pretreated – besides nonsteroidal AI, 57% had received an antiestrogen, 26% had chemotherapy in the advance setting, and 54% had 3 or more lines of therapies. Stomatitis was the most frequent and debilitating adverse events (all grades 56%, grade 3 8%), followed by rash (add grades 36%, grade 3 1%), fatigue (all grades 33%, grade 3 3%), and diarrhea (all grades 30%, grade 3 2%). As everolimus is an immunosuppressant, the incidence of infection cannot be under-estimated and there were 2 cases of deaths from sepsis. Other class-specific severe toxicities included anemia (grade 3 5%), hyperglycemia (grade 3 4%), pneumonitis (grade 3 3%), and elevated AST (grade 3 3%) and elevated ALT (grade 3 3%). The study was not powered to detect a difference in OS, and the analysis of OS was negative [48]. Subsequent molecular analysis of archival tissue showed that the mutational status of *PIK3A*, amplification of *FGFR1*, or P3K/AKT/mTOR pathway alteration did not affect treatment response to everolimus [49]. This analysis reviewed some potential quantitative differences in the efficacy of everolimus among tumors of specific *PIK3CA* exons, *FGFR2*, *mTOR*, and chromosomal instabilities. These remains to be further investigated. BOLERO-2 also included analysis of plasma cell-free DNA (cfDNA) for 2 *ESR1* mutations [50]. *ESR1* D538G mutation was detected in 21% and *ESR1* Y537S mutation was found in 13%. Interestingly, patients with D538G mutation had PFS benefit with addition of everolimus (HR 0.34; 95 CI, 0.02–0.57), while those carrying Y537S mutation did not.

Everolimus is an inhibitor of mTORC1. It is postulated that mTORC1 inhibition by everolimus set off negative feedback mechanism via AKT signaling, and leads to treatment resistance. Vistusertib is a small molecule ATP competitive dual inhibitor of mTORC1 and mTORC2. Preclinical model demonstrated that vistusertib had superior activity to everolimus in suppressing tumor growth [51]. MANTA is a randomized phase 2 study of fulvestrant in combination with vistusertib or everolimus or fulvestrant alone in HR-positive HER2-negative MBC patients who have disease resistance to AI [52]. No more than 1 line prior chemotherapy was allowed in advanced setting. Primary end point was PFS. At median follow up of 17 months, it showed that addition of vistusertib did not add PFS benefit compared with fulvestrant alone (7.6 versus 5.4 months; HR 0.88; 95% CI, 0.63–1.24, p = 0.46). In fact, the fulvestrant-everolimus arm had superior PFS compared with the fulvestrant-vistusertib arm (12.3 versus 7.6 months; HR 0.63; 95% CI, 0.45–0.9, p = 0.01). Stomatitis and rash were the most common adverse effects of this dual mTOR inhibitor, and the frequency was comparable to that of everolimus. In summary, dual inhibition of mTOR did not derive superior effect. Everolimus remains the only mTOR inhibitor approved by the U.S. FDA for $HR^{+ve}/HER2^{-ve}$ MBC.

3.3. PI3K inhibitors as an emerging treatment

Intracellular signaling pathways have complex interaction. Targeted inhibition of a particular component in the pathway might cause relief of upstream feedback inhibition. Inhibition of the effector mTOR in the PI3K/AKT/mTOR pathway, could result in adaptive hyperactivation of the upstream AKT activity and leads to treatment failure [53]. As *PIK3CA* mutation is the most common genetic changes in breast cancer and represents a more proximal target, targeting *PIK3CA* might exert upstream halt of growth signaling. A number of PI3K inhibitors have been developed. Pictilisib is an orally active pan-inhibitor of class 1 PIK3K. FERGI is a randomized phase 2 study which recruited $HR^{+ve}/HER2^{-ve}$ MBC patients who have progressed on or after AI [54]. Patients were given either fulvestrant or fulvestrant with pictilisib. The primary end point was PFS. There was no difference between 2 groups, both in the intention-to-treat population or patients with *PIK3CA* mutation. Pictilisib-associated serious adverse events in the original study dose of 340 mg per day were reported in 16%, whereas those leading to discontinuation were rash, pneumonitis, diarrhea, abdominal pain, stomatitis or elevated AST or ALT. Close to half the patients required dose modification. Toxicities greatly limited drug exposure of the patients. Although in the second part of the study dosage has been reduced and toxicity profile improved, the drug was not further developed due to its lack of PFS benefit.

Another extensively studied PI3K inhibitor is buparlisib. It is also a pan-class I PI3K inhibitor. It showed encouraging results in early clinical studies and it was ultimately brought to a number of phase 3 trials. BELLL-2 combined fulvestrant with buparlisib or placebo in $HR^{+ve}/HER2^{-ve}$ MBC patients who have progressed on or after AI, and had received up to 1 line of chemotherapy in the advanced setting [55]. The median PFS was 6.9 months in the buparlisib group versus 5.0 months in the placebo group (HR 0.78; 95% CI, 0.67–0.l89; one sided p < 0.001). In patients with PI3K pathway-activation, median PFS was 6.8 months in the buparlisib group versus 4.0 months in the placebo group (HR 0.76; one sided PFS p −0.014). The most common grade 3 or 4 toxicities in the buparlisib group was increased ALT (25%), increased AST (18%), hyperglycemia (15%), and rash (8%). As preclinical data showed that

buparlisib in combination with fulvestrant can reverse resistance mTOR inhibitor (Novartis data), BELLE-3 studied the combination of fulvestrant with or without buparlisib in HR^{+ve}/$HER2^{-ve}$ MBC patients who have progressed on or after mTOR inhibition [56]. It demonstrated that addition of buparlisib to fulvestrant prolonged the median PFS 1.8 months to 3.9 months (HR 0.67; 95% CI, 0.53–0.84, one-sided $p < 0001$). Circulating tumor DNA (ctDNA) analysis of *PIK3CA* status was available. Of the 432 subjects, 34% carried PIK3CA mutation. Among these patients, the median PFS was 4.7 months for those in the buparlisib arm versus 1.6 months for those in the placebo arm, thus those who received the PI3K inhibitor were 50% less likely to have disease progression. Despite these encouraging findings, grade 3 or 4 adverse events related to buparlisib were alarming – they included elevated ALT (22%), elevated AST (18%), and hyperglycemia (12%). Other toxicities potentially related to the drug such as depression, anxiety, and rash were also concerning. The company decided not to pursue further development of the drug due to its safety profile.

On the other hand, the company has turned its focus to a α-specific PI3K inhibitor alpelisib. Early phase study showed preliminary preferential antitumor activity in *PIK3CA*-altered tumor treated with alpelisib [57]. A presentation of the preliminary results for the combination of alpelisib and fulvestrant demonstrated encouraging early efficacy [58]. The study recruited 87 patients with HR^{+ve}/$HER2^{-ve}$ MBC. Alpelisib was given at 300 mg on a continuous daily schedule. In the PIK3A-altered population, the CBR was 45%. Median PFS was 9 and 5 months in the *PIK3CA*-altered groups and *PIK3CA* wild-type group respectively. This drug appeared to be better tolerated than pan-PI3K inhibitors. At the moment, the phase III SOLAR-1 trial [NCT02437318] studying the same combination in patients who have progressed on or have failed AI is ongoing. First PFS analysis is expected to be available later the year.

3.4. SERDS and its new role

Fulvestrant is the only clinically available SERD. It targets the ER for proteasomal degradation and halts the action of estrogen. It is capable of binding to the ligand-binding domain of ERα, converting it to a form incapable with transcriptional activity [59, 60]. Fulvestrant is given by intramuscular injection on day 1, 15, 29, then every 28 days. The initial studied and market dose was 250 mg. At first line setting, as in the FACT study (SWOG S0226 trial), fulvestrant at 250 mg did not demonstrate survival advantage over AI [61]. As second line treatment, fulvestrant at 250 mg showed similar time to progression (TTP) to anastrozole. Yet the later CONFIRM study demonstrated that doubling the dose to 500 mg gave a superior PFS and OS compared with 250 mg [5, 62]. FALCON is a phase 3 study which further brings fulvestrant at 500 mg to first line setting in comparison with anastrozole. The PFS was 16.6 and 13.8 months for the fulvestrant and anastrozole groups respectively with a p value of 0.0486 [6].

Given the special property of SERD on receptor degradation and conformation, it would be interesting to explore if patients with *ESR1* mutation respond differently from those with *ESR1* wild type. SoFEA is a study comparing exemestane with fulvestrant-containing regimens in patients with prior sensitivity to nonsteroidal AI. Prospective-retrospective analysis of plasma ctDNA from SoFEA found *ESR1* mutation in 39% of patients, of which half were polyclonal [63]. Those with *ESR1* mutation had better PFS after giving fulvestrant compared

with exemestane (HR 0.52, p = 0.02). Patients with *ESR1* wild type had similar benefit given either drug. PALOMA3 is a study that compared fulvestrant plus placebo with fulvestrant plus palbociclib in patients with progression after prior endocrine therapy. Plasma ctDNA analysis showed *ESR1* mutation rate of 25%, of which 28% where polyclonal. Fulvestrant plus palbociclib gave rise to better PFS compared with fulvestrant alone in both *ESR1* mutant (HR 0.43, p = 0.002) and *ESR1* wild type patients (0.49, p < 0.001) [63]. Analysis of ctDNA from the BOLERO2 study also supported that *ESR1* mutation can be found in around 30% of patients who have failed prior endocrine therapy [50]. Patients with *ESR1* mutation had shorted OS compared with wild type. This study did not involve the use of fulvestrant.

While fulvestrant is non-inferior to AI in the first line setting, more data on OS is awaited. Yet emerging evidence suggest that testing of *ESR1* mutation could probably guide us in the choice of hormonal therapy in patients who have failed prior endocrine therapy. The approach is limited by the availability of ctDNA analysis, sensitivity of different ctDNA methodology, often difficult-to-obtain tissue biopsy upon the time of progression, and accessibility to *ESR1* test in local laboratory as it is still not a standard practice.

4. The sequence of endocrine therapy and targeted drugs

AI has been the standard of care for first line treatment of patients with $HR^{+ve}/HER2^{-ve}$ MBC. The role of fulvestrant has been controversial. Due to the high cost, the need for monthly injection, and similar efficacy in the first line setting, fulvestrant is often an option rather than the preferred choice. Yet much remained to be learnt from this SERD. In the phase 3 FALCON trial, patients given monthly injection of fulvestrant at 500 mg had borderline statistically longer median PFS of 16.6 months (95% CI, 13.83–20.99) compared with those of 13.8 months (95% CI, 11.99–16.59) given oral anastrozole 1 mg daily (HR 0.797, 95% CI, 0.637–0.999; p = 0.0486) [6]. This approach showed that the ceiling PFS ceiling of hormonal therapy could be stretched to 20 months in some patients. More interestingly, subgroup analysis suggested that most of the survival benefit was derived from patients who had bone-only metastatic disease, with a median PFS of 22.3 month in the fulvestrant group versus 13.8 months in the anastrozole group (HR 0.59; 95 CI, 042–0.84). Reanalysis of SOG S0226 according to prior exposure to adjuvant adjuvant tamoxifen, showed that those without prior endocrine exposure had longer median PFS when given fulvestrant compared with anastrozole (16.7 versus 12.7 months; HR 0.73; 95% CI, 0.60–0.89, p = 0.002), which further translated into improved median OS by 1 year (40.3 versus 52.2 months, p = 0.0067) [64]. With the emergence of new treatment option of multiple CDK4/6 inhibitors, and the increasing financial burden associated with them, the practical questions would be how to choose the first line hormonal therapy. There have been international guidelines to lay the general clinical principle that treatment recommendation should be based on if the patient is naïve to endocrine therapy, the type of adjuvant therapy, length of disease free interval and if disease relapsing less than 12 months from the end of adjuvant AI [65, 66]. More updated and detailed guidelines are anticipated in light of new findings.

As to the choice of agent in the second line setting or beyond, the choice would largely depend on prior treatment. Some general principles are becoming apparent. First of all, there is

enough data to suggest that CDK4/6 inhibitor should be part of standard treatment in patients with $HR^{+ve}/HER2^{-ve}$ MBC, be it first line (PALOMA-2, MONALEESA-2, MONARCH-3, MONALEESA-7), second line (PALOMA-3, MONARCH-2), or later line in refractory cases (MONARCH-1). Since PI3K/AKT/mTOR plays an important role in hormonal resistance, mTOR inhibitor should also be considered in all patients. The only approved choice currently is everolimus. For the choice of hormonal partner in patients who have progressed on or failed prior AI, testing of *ESR1* mutation status might provide some guidance as to if switching to SERD would be helpful. It is still not clear if patients who progress on first line CDK4/6 inhibitors should be continued this targeted agent with a switch of hormonal partner. Chemotherapy should be reserved for patients who have exhausted the options for hormonal therapy and these targeted therapies, or patients with impending visceral crisis.

5. Conclusion

Although we are becoming increasingly equipped to overcome resistance to hormonal therapy, these treatment would fail nevertheless. The preliminary OS data for the phase II PALOMA-1 trial was presented in June 2017. It showed that the median OS was 37.5 months in patients who received palbociclib and AI versus 34.5 months in those who received AI (HR 0.897) [67], suggesting the impressive gain in median PFS after adding palbociclib might not translate into long term survival. Interestingly, analysis of OS for BELL2 appears to be trending toward similar observation. The median OS for patients who received buparlisib and fulvestrant versus those who received placebo and fulvestrant was 33.2 and 30.4 months respectively (HR 0.87; 95% CI, 0.74 to 1.02; $p = 0.045$) [68]. Even in patients who had PI3K pathway activated or PIK3CA mutation, the improvement in median PFS with addition of buparlisib did not translate into better median OS (HR 0.81, $p > 0.05$). These might be explained by two reasons. Firstly, post-progression survival can be affected by availability and effectiveness of subsequent therapy. Second, progression on CDK4/6 inhibitor might have selected out patients who then became refractory to other treatment especially chemotherapy. More understanding in the mechanism of resistance to hormonal therapy and targeted therapy is needed to overcome these barriers.

$HR^{+ve}/HER2^{-ve}$ MBC is the most common type of breast cancer. The main stay of treatment is hormonal therapy, and the choice of hormonal therapy includes SERM, AI, and SERD. SERD might play a more important role in selected patients, as development of *ESR1* mutation could render patients resistant to AI. Addition of targeted therapy such as CDK4/6 inhibitor or mTOR inhibitor can help prolong the use of hormonal therapy, and should be part of standard treatment for all patients in their treatment journey. Future research would focus on strategies to overcome resistance to these therapies.

Conflict of interest

Dr. Chiu has no conflict of interest to declare.

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