Hosted by: 香港乳癌基金會 HK Breast Cancer Foundation

Hong Kong-Taiwan Hormone-Receptor Positive (HR+) Advanced Breast Cancer Scientific Meeting

At a recent symposium held on 3rd August 2018, HK Breast Cancer Foundation invited two honorary speakers, Dr. Lu Yen-Shen and Dr. Joanne Chiu, to share their insights and opinions on the optimal treatment strategies for HR+ advanced breast cancer in the practices in Hong Kong and Taiwan.

New Treatment Strategies for HR+ Advanced Breast Cancer in Asians – Evidence to Practice

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Breast cancer evolution and progression are mainly influenced by estrogen receptors (ER). Approximately 60-80 % of breast tumors are dependent on estrogen for survival and progress through cell cycle for cell growth and proliferation[1]. Upon estrogen stimulation, ER signaling pathway and its downstream effectors cross-talk with other protein kinase pathways[2,3]. Estrogen stimulation leads to increased cellular proliferation via upregulation of cyclin D1 levels and CDK4/6 activity, causing the cells to progress from G1 to S phase[4,5]. It has been long established that blocking ER pathway represents the main approach to prevent cancer cells from proliferation and stop tumor growth. However, the response to endocrine therapy as first-line treatment is suboptimal for ER+ HER2- advanced breast cancer (ABC); it has been getting more and more common with resistance to endocrine therapy, and most patients face disease progression when given sufficient time[6,7]. Ongoing efforts over the past decade focused on alternative targeting pathways which interact with ER pathway and impact the cell proliferation, thus overcoming resistance to endocrine therapy (figure 1).

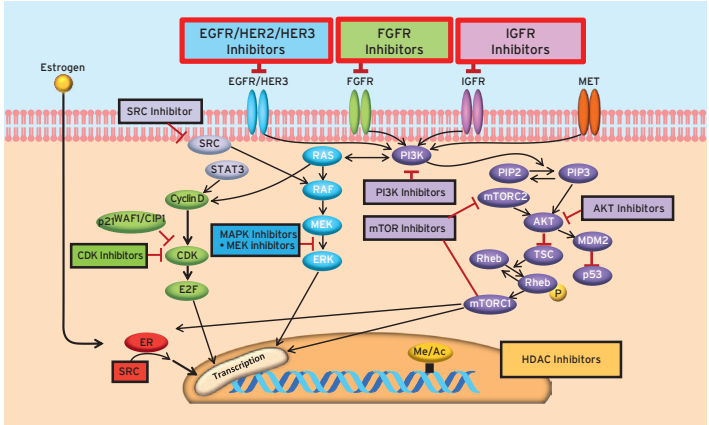


Figure 1: Mechanism of endocrine therapy resistance

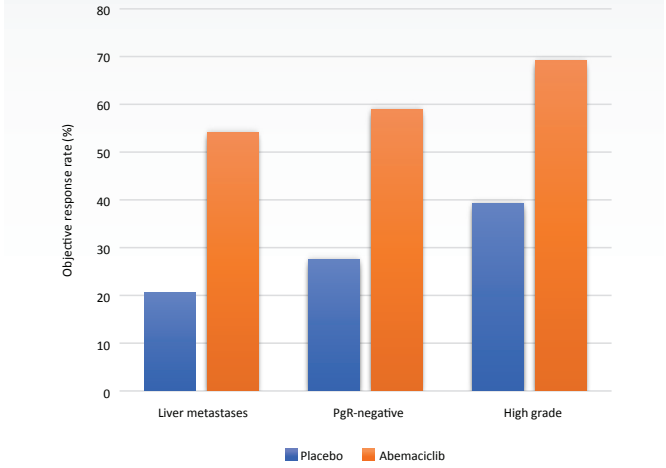
The first-line use of CDK4/6 inhibitors in postmenopausal HR+ HER2- ABC

There are currently many options in the therapy sequence in ER+ HER2- ABC. Treatment decisions should be based on medical comorbidities, prior adjuvant or endocrine therapies, and disease-free interval[8]. Particularly, the optimal treatment strategy must be carefully evaluated for extending progression-free survival (PFS) with first-line or second-line treatment, which ultimately delays the start of chemotherapy and translates into overall survival (OS) benefit. According to the real world data of HR+ HER2- ABC by Lobbezzo et al, 37% of the patients with visceral disease are given chemotherapy[9], in spite of indirect better overall response rate in patients with more severe clinical characteristics when using endocrine therapy plus CDK4/6 inhibitor[10,11]. Initial endocrine therapy is evidently more efficacious and less toxic compared to initial chemotherapy, and is heavily supported by the current guideline recommendations, with the exception of patients in need of immediate tumor reduction[12,13]. Therefore, unless in visceral crisis, endocrine therapy is always preferably considered as first-line treatment for HR+ HER2- ABC, including patients with visceral disease.

The fact that cell cycle regulators cyclin D1 or CDK4/6 converge with ER signalling pathway highlights the potential role of targeting cell proliferation in ER+ breast cancer (BC)[14]. In cancer development, cyclin D-CDK4/6-retinoblastoma (Rb) pathway is dysregulated upon upstream oncogenic mutations, leading to increased G1-S transition and uncontrollable cell-cycle progression[15, 16]. Endocrine resistance in HR+ BC is commonly associated with hyperactivation of cyclin D1-CDK4/6[17]; therefore rendering this downstream mediator a key target for alternative treatment. Inhibitors specific to CDK4/6, which suppress G1 to S phase transition before cells

irreversibly commit to mitosis and proliferation, have been extensively studied in large clinical trials and are under active ongoing clinical development. Particularly, the potential of CDK4/6 inhibitor in combination with endocrine therapy has been extensively explored in ER+ HER2- ABC. PFS was significantly doubled as shown by the consistently similar hazard ratios (HR) of about 0.5 using any three of the different CDK4/6 inhibitors as an add-on targeted agent in combination with letrozole, based on the results of PALOMA-2, MONALEESA-2 and MONARCH-3. Besides PFS, another secondary endpoint objective response rate (ORR) was also greatly improved, as evident from a rate of 42.1% in the palbociclib-letrozole vs. 34.7% in the placebo-letrozole group (p = 0.06); 42.5% in the ribociclib-letrozole vs. 28.7% in the placebo-letrozole group (p = $9.18X10^{-5}$); 61% in the abemaciclib-NSAI vs. 45.5% in the placebo-NSAI group (p = 0.003)[11,14,18].

Overall, results of clinical studies using add-on targeted agent CDK4/6 inhibitor in combination with any of the endocrine backbone therapies consistently showed a remarkable PFS benefit. Particularly, the first-line treatment of CDK4/6 inhibitor in combination with AI offers a greater than 24-month, compared to endocrine monotherapy with AI (14.5 - 16 months)[11,14,18]. Moreover, latest data show favorable efficacy of CDK4/6 inhibitors among Asian population and patients with more aggressive disease. Subgroup analysis showed patients with clinical characteristics associated with poor prognosis achieved greater overall response rate in the CDK4/6 inhibitor plus endocrine therapy group in the MONARCH-2 and MONARCH-3 studies (figure 2)[19]; while another subgroup analysis of MONALEESA-2 showed more significant PFS benefit and higher overall response rate with ribociclib plus letrozole in Asian population compared to non-Asian population (figure 3)[20].



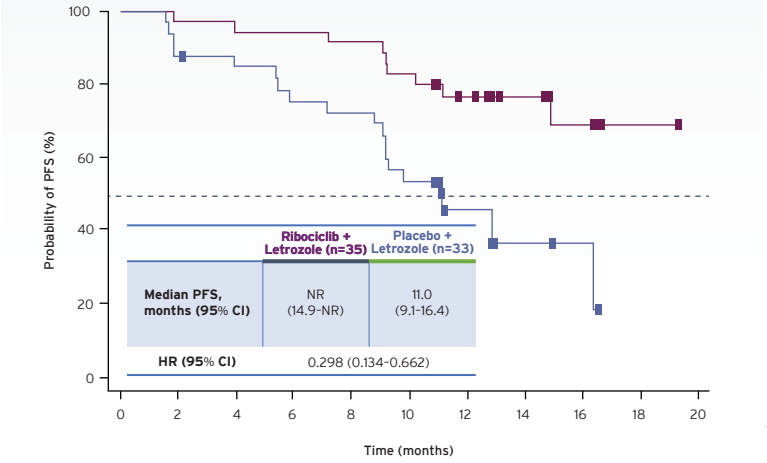


Figure 2: ORR comparing abemaciclib and placebo in patients with more concerning clinical characteristics including liver metastases, PgR negative, high grade tumor in MONARCH-3[19].

Figure 3: PFS curve comparing ribociclib plus letrozole and placebo plus letrozole in Asian subgroup of MONALESSA-2[20].

Nevertheless, patients' preferences and safety profile should be taken into account in selecting endocrine-based targeted combination. In general, CDK4/6 inhibitors demonstrated manageable safety profiles and were associated with low rates of febrile neutropenia[21].

The use of CDK4/6 inhibitors in premenopausal HR+ HER2- ABC

While BC predominantly occurs in older, postmenopausal women (age ≥50), the incidence of ABC in premenopausal women is increasing; BC in younger women (age <50) is often more aggressive and associated with poor prognosis. Treatment strategies for HR+ BC in premenopausal women are usually extrapolated from data of postmenopausal patients, with the addition of ovarian function suppression to endocrine therapy[22,23]. According to ESMO consensus guidelines, endocrine therapy is the preferred choice when combined with ovarian suppression/ablation in premenopausal ER+ HER2- ABC[12].

Recently, adding a CDK4/6 inhibitor to standard endocrine therapy for pre- and perimenopausal patients with ER+ HER2- ABC is evident by the ongoing MONALEESA-7 study, which is the first clinical trial having the statistical power to demonstrate significant clinical benefit using CDK4/6 inhibitor in premenopausal women[24]. Notably, this study recruited a rather high percentage of Asians (30%), and successfully showed that ribociclib can be effectively combined with either tamoxifen or NSAI together with ovarian function suppressant (OFS) using goserelin. The study met the primary endpoint in which median PFS was significantly improved with 23.8 months in the ribociclib plus endocrine therapy group versus 13.0 months in the endocrine therapy alone group (HR 0.55, 95% CI 0.44-0.69, p<0.0001, intention-to-treat population; figure 4). By subgroup analysis, both Asians and younger patients showed better benefit with ribociclib plus endocrine therapy (HR 0.40 for Asians vs. 0.66 for non-Asians; HR 0.44 for age <40 years vs. 0.59 for age ≥40 years)[24]. More interestingly, unlike previous studies on other CDK4/6 inhibitors showing no improvement in QoL[25], ribociclib plus endocrine therapy was associated with a reduction in EORTC QLQ-C30 pain score at week 8, which was maintained up to cycle 19 compared to endocrine

therapy alone as shown in figure 5[20]. The efficacy analysis showed that ribociclib in combination with endocrine therapy and OFS could represent a new first-line treatment option for pre-/perimenopausal patients. Another study, PALOMA-3, also highlighted the use of CDK4/6 inhibitor in second-line setting for premenopausal women; when patients were treated with fulvestrant plus palbociclib following progression on endocrine therapy, a median PFS of 9.5 months in the subgroup with pre-/perimenopausal status was observed (HR 0.5, 95% CI 0.29-0.87)[26].

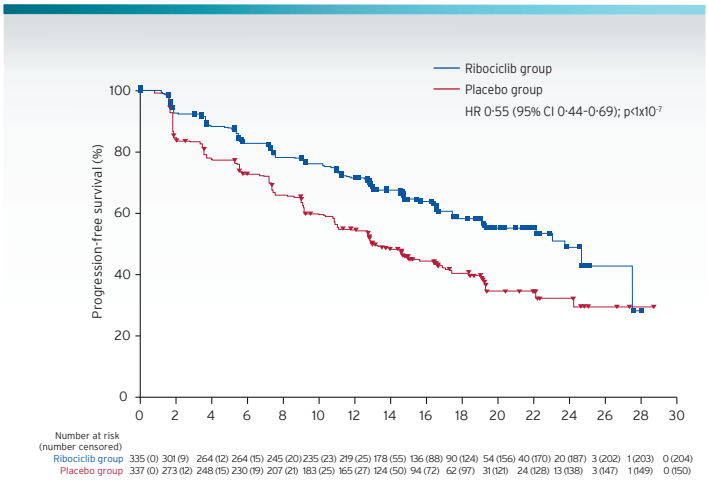


Figure 4: Primary endpoint, PFS in MONALEESA-7[24]

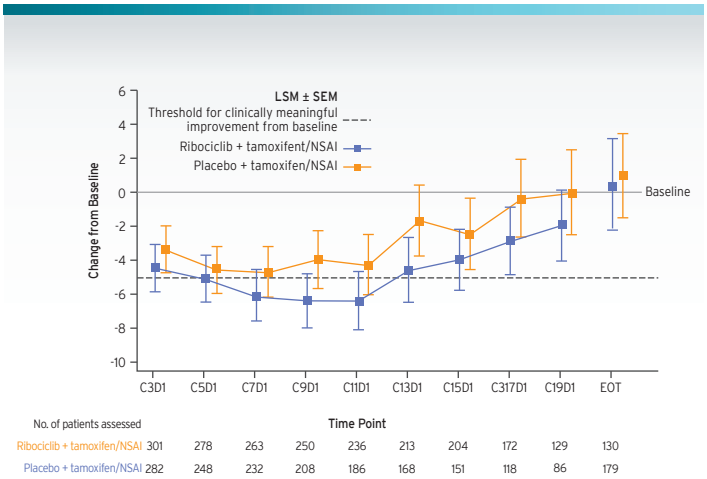


Figure 5: Patient-reported outcomes (EORTC QLQ-C30 pain score reduction) in MONALEESA-7[20]

Optimal Treatment Sequence in HR+ Advanced Breast Cancer – What Have We Learnt to Overcome Resistance

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Acquired mutations as part of the endocrine therapy resistance mechanism

In worldwide clinical practice, endocrine therapy is considered first-line for ER+ HER2- ABC. Unfortunately, 40% of patients show suboptimal response and do not benefit from endocrine therapy[27]. Recently, gene mutations have attracted particular interest as the underlying resistance mechanism, and detailed clinicopathologic data collected for each patient were linked to the genomic information using whole exome and transcriptome sequencing[28]. Tumor biopsies of resistant ER+ HER2- metastatic samples were analyzed and found that ESR1 mutation was acquired after treatment, suggesting a role of acquired mutation in treatment resistance in ER+ HER2- ABC. ESR1 mutation occurs rarely in primary BC[29], but more frequently in ABC patients who were previously treated with AI[30-32]. Particularly, plasma ESR1 mutations can help direct the choice of further endocrine-based therapy, as shown in SoFEA and PALOMA-3 studies[33]. ESR1 mutation in plasma DNA predicted the poor PFS on further AI therapy, which was suggestive of acquired resistance to prior AI pathway; whereas fulvestrant acts in a different pathway from AI, therefore ESR1-mutated patients remained sensitive to fulvestrant[34].

Other potential pathways to be targeted

PI3K mutation is often found enriched at the time of the disease progression and endocrine therapy resistance, therefore targeting PI3K is potentially the next therapeutic strategy[35].

The use of pan-PI3K inhibitor buparlisib with fulvestrant in BELLE-2 study showed significant PFS improvement to 7.0 months compared to 3.2 months with placebo plus fulvestrant in patients harboring ctDNA PIK3CA mutations. However serious side-effects occurred and the PFS benefit could not successfully translate into OS benefit[36]. Another PI3K isoform variant α-class inhibitor alpelisib might lead to differential safety profile from buparlisib and was developed to minimize off-target side-effects. According to an ongoing study (SOLAR-1), preliminary activity of the α-specific PI3K inhibitor alpelisib in combination with fulvestrant could overcome the endocrine therapy resistance (after the Scientific Meeting, the results of SOLAR-1 were presented at ESMO, which showed significant PFS improvement with alpelisib plus fulvestrant in patients with PIK3CA-mutated breast cancer compared with fulvestrant alone)[37].

The role of CDK4/6 inhibitors after progression on hormonal therapy

In ER+ HER2- ABC patients who were refractory to prior endocrine therapy, add-on with a CDK4/6 inhibitor significantly improved treatment efficacy[11,14,18], as evidenced by significant improvement in the rate of objective response and PFS. However, when comparing with the clinical trials using CDK4/6 inhibitor in combination with endocrine therapy as first-line (above 20 months PFS and over 50% objective response rate), the efficacy outcomes using CDK4/6 inhibitor across the second or later lines studies generally showed a smaller magnitude in terms of survival benefit and objective response

rate (median PFS 9.5 months and ORR 25% in PALOMA-3; median PFS 16.4 months and ORR 48% in MONARCH-2)[26,38]; however, careful consideration should be taken into account in indirect comparison among studies. The potential role of mTOR inhibitor in second-line setting after progression on endocrine therapy provides another clinical treatment option. Several ongoing studies such as BOLERO-2 showed 2.5 times longer in PFS using add-on everolimus when compared to endocrine therapy alone, and the efficacy was shown comparable to another targeted agent CDK4/6 inhibitor (HR 0.46 (95% CI: 0.36-0.59; p <0.001 for PALOMA-3 and HR 0.43 [95% CI: 0.35-0.54]; p < 0.001 for BOLERO-2)[26,39]. However, the response to mTOR inhibitor is significantly reduced when it is placed in third-line and beyond[40].

Conclusion

The importance of optimizing treatment strategies and identifying different clinical subgroups of patients with HR+ HER2- ABC was addressed by using an overall view from evidence-based clinical trials[20,33,37]; the broad implication of CDK4/6 inhibitors in different clinical settings of HR+ HER2- ABC was highlighted, particularly of the increasing potential of CDK4/6 inhibitor in combination with endocrine therapy for younger premenopausal patients[24]. The most recent findings on the underlying mechanism of resistance to endocrine therapy were summarized, including the acquired mutations as predictive prognostic markers for endocrine or CDK4/6 inhibitor treatment[33,36]. Continuous effort based on these most recent data is essential to help determine predictive factors for treatment outcome, although the results are not yet mature. Nevertheless, it is optimistic about more newly innovated targeted agents as add-on to the endocrine backbone therapy for improving the quality of care and outcomes of patients with HR+ HER2- ABC in the future.

Abbreviations list: AKT = protein kinase B. CDK4/6 = cyclin-dependent kinase 4/6. ctDNA = circulating tumour DNA. E2F = E2F transcription factor 2. EGFR = epidermal growth factor receptor. ERK = extracellular signal-regulated kinases. EROTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0. ESMO = European Society for Medical Oncology. ESR1 = estrogen receptor 1. FGFR = fibroblast growth factor receptors. HDAC = Histone deacetylases. HER2 = human epidermal growth factor receptor 2. HER3 = human epidermal growth factor receptor 3. IGFR = insulin-like growth factor 1. NSAI = non-steroidal aromatase inhibitor. NR = not reached. MAPK = mitogen activated kinase-like protein. MDM2 = E3 ubiquitin-protein ligase. MEK = mitogen-activated protein/extracellular signal-regulated kinase. MET = mesenchymal-epithelial transition. mTOR = mammalian target of rapamycin. mTORC1 = mammalian target of rapamycin complex 1. mTORC2 = mammalian target of rapamycin complex 2. Me/Ac = methyl/acetyl group. $p21^{WAF1/CIP1}$ = cyclin-dependent kinase inhibitor p21. RAS = Rat Sarcoma. p53 = tumor suppressor. PI3K = Phosphatidylinositol-4,5-bisphosphate 3-kinase. PIP2 = plasma membrane intrinsic protein 2. PIP3 = plasma membrane intrinsic protein 3. RAF = proto-oncogene serine/threonine-protein kinase. Rheb = Ras homolog enriched in brain. SRC = SRC proto-oncogene, non-receptor tyrosine kinase. STAT = signal transducer and activator of transcription. TSC = Tuberous Sclerosis Complex.

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