June 29th 2019

HONG KONG BREAST CANCER FOUNDATION

ANNUAL SCIENTIFIC MEETING 2019

Summary of Session 4

CDK4/6 inhibitors in Premenopausal Women with HR+ HER2- Advanced Breast Cancer

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PALOMA-2, MONARCH-3 and MONALEESA-2

PALOMA-2, MONARCH-2 and MONALEESA-2 evaluated the efficacy of a CDK4/6 inhibitor in combination with an aromatase inhibitor in postmenopausal patients without prior endocrine therapy for advanced disease in HR+ and HER2- advanced breast cancer. In these trials, adding a CDK4/6 inhibitor to an aromatase inhibitor significantly prolonged progression-free survival (PFS) to >2 years compared with an aromatase inhibitor alone. The hazard ratios were around 0.54 to 0.57.[1-3]

PALOMA-3, MONARCH-2 and MONALEESA-3

Three randomized trials, PALOMA-3, MONARCH-2 and MONALEESA-3, were conducted to investigate the efficacy of a CDK4/6 inhibitor in combination with fulvestrant in HR+ HER2- advanced breast cancer.[4-7] All three studies showed that the addition of a CDK4/6 inhibitor significantly improved PFS. Median PFS were 11.2 months in the palbociclib-fulvestrant group in PALOMA-3, 16.4 months in the abemaciclib-fulvestrant group in MONARCH-2, and 20.5 months in the ribociclib-fulvestrant group in MONALEESA-3. The variation in median PFS might be caused by different patient selection criteria in individual trial. In PALOMA-3, one previous line of chemotherapy or several previous lines of endocrine therapy in advanced disease was allowed.[4] Both PALOMA-3 and MONARCH-2 included patients in second-line setting only.[4,6] In MONALEESA-3, 19% of patients had de novo metastatic disease or relapsed >12 months after the completion of (neo)adjuvant endocrine therapy, whereas 81% of patients relapsed $\leqslant$12 months from completion of (neo)adjuvant endocrine therapy with no treatment for advanced or metastatic disease, relapsed >12 months from completion of (neo)adjuvant therapy with subsequent progression after 1 line of endocrine therapy for advanced disease, or had advanced or metastatic breast cancer at diagnosis that progressed after one line of endocrine therapy for advanced disease with no prior (neo)adjuvant treatment for early disease.[7] Nonetheless, the hazard ratios were similar in the three trials, ranging from 0.5 to 0.6. Overall survival (OS) data was available in PALOMA-3 only. Though it was shown that the addition of palbociclib resulted in an absolute improvement in OS by 6.9 months, the difference was not statistically significant.[5]

Premenopausal patients

The 4th ESO-ESMO International Consensus Guidelines (ABC 4) recommend that young premenopausal patients with advanced ER+ breast cancer should have adequate ovarian function suppression or ablation, and then be treated in the same way as post-menopausal women, with endocrine agents with or without targeted therapies.[10] As differences in tumour biology between premenopausal and postmenopausal patients, for example, molecular alterations of key driver genes, activity of signaling pathways and tumour cell proliferation status (i.e. Ki67 marker), may affect treatment efficacy, dedicated trials in the premenopausal population are warranted. Three of the seven CDK4/6 inhibitor trials included premenopausal patients. However, premenopausal patients only accounted for a small portion of the overall study populations in PALOMA-3 and MONARCH-2 (20.9% and 16.1% respectively),[4-6] whereas MONALEESA-7 was the only trial to entirely recruit premenopausal and perimenopausal patients.[8]

In PALOMA3, a pre-planned subgroup analysis of OS by menopausal status was performed. In the postmenopausal subgroup, the median OS in the palbociclib-fulvestrant group was longer than that in the placebo-fulvestrant group (34.8 months vs 27.1 months; HR 0.73, 95% CI 0.57-0.95).[4,5] However, in the pre/perimenopausal subgroup, the OS were 38.0 months in both treatment arms (HR = 1.07, 95% CI 0.61-1.86). Several reasons might contribute to the disparity between the two subgroups. For example, the pre/perimenopausal subgroup had small sample size, fewer lines of prior treatment in the control arm, and smaller number of ≤40-year-old patients in the control group. This demonstrates that if a trial does not have a sufficient sample size, it is hard to draw a definitive conclusion.

MONALEESA-7

MONALEESA-7 was a phase 3, randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ribociclib plus endocrine therapy in peri/premenopausal women with HR+, HER2- advanced breast cancer.[8] Eligible patients were premenopausal women aged 18–59 years who had histologically or cytologically confirmed HR+, HER2- advanced breast cancer; an ECOG performance status of 0 or 1; measurable disease as per Response Evaluation Criteria in Solid Tumors version 1.1 criteria, or at least one predominantly lytic bone lesion; and had not received previous treatment with CDK4/6 inhibitors. Endocrine therapy and chemotherapy in the adjuvant or neoadjuvant setting was permitted, as was up to one line of chemotherapy for advanced disease. Patients were randomly assigned (1:1) to receive ribociclib or placebo, with either tamoxifen or a non-steroidal aromatase inhibitor (NSAI), all with goserelin. The primary endpoint was investigator-assessed progression-free survival.

A. **Patients' characteristics**

   Patients' characteristics were well-balanced in both groups. Thirty percent of patients in the ribociclib group and 29% in the placebo group were Asians. Bone metastases were observed in 75% in the ribociclib group and 73% in the placebo group; visceral metastases were observed in 58% in ribociclib group and 56% in placebo group. Fourteen percent of patients in both groups received previous chemotherapy for advanced disease.[8]

B. **Results**

The median PFS was 23.8 months in the ribociclib group compared with 13.0 months in the placebo group (HR 0.55, 95% CI 0.44-0.69, P <0·0001).[8] The estimated OS at 42 months was 70.2% in the ribociclib group and 46.0% in the placebo group (HR 0.71, 95% CI 0.54-0.95, P=0.00973).[9] Improvement in OS was seen in the subgroup of 495 patients who received an aromatase inhibitor, but not yet seen in the subgroup of 177 patients who received tamoxifen.[9]

Concerning the resistance to subsequent therapy in patients who had been treated with a CDK4/6 inhibitor, MONALEESA-7 continued to follow up on patients who discontinued the study treatment. It was found that ribociclib significantly prolonged the time to first subsequent chemotherapy. At 42 months, the proportion of patients who had not yet received the first subsequent chemotherapy were 65.8% and 49.0% in the ribociclib group and the placebo group respectively (HR 0.60, 95% CI 0.46-0.77).[9] Thus, ribociclib can help delay the use of toxic chemotherapy in this patient population.

The estimated percentages of patients who were alive at 42 months and did not have disease progression while receiving second-line therapy (PFS2) were 54.6% in the ribociclib group and 37.8% in the placebo group (HR 0.69, 95% CI 0.55-0.87).[9] Similar observation was found in PALOMA-3, where the addition of palbocilib to fulvestrant prolonged the median time from randomization to the end of study treatment, the median time from randomization to the start of postprogression chemotherapy, and the median time from randomization to the end of the immediate subsequent line of postprogression therapy,[5] which reflected that the CDK4/6 inhibitor treatment did not interfere with the type or efficacy of the standard treatment after progression.

C. **Safety**

Median treatment duration was approximately 2 years in the ribociclib group and approximately 1 year in the placebo group. After 15 months of additional follow-up, safety profile for the ribociclib group in MONALEESA-7 was consistent with previous analyses. The rates of grade 3 or 4 adverse events of special interest in the ribociclib and placebo arms were: neutropenia (63.5% vs 4.5%), hepatobiliary toxicity (11% vs 6.8%), and prolonged QT interval (1.8% vs 1.2%).[9]

D. **Other endpoints**

MONALEESA-7 showed statistically significant improvement in the health-related quality of life (HRQoL) after the addition of ribociclib to endocrine therapy and goserelin.[8] Median time to definitive (≥10%) deterioration as measured by the global health status/quality-of-life scale score of the EORTC QLQ-C30 was not reached in the ribociclib group compared with 21.2 months in the placebo group (HR 0.70, 95% CI 0.53-0.92, P = 0.004). In addition, the mean changes of EORTC QLQ-C30 pain score from baseline was found to be -5.1 and -3.5 in the ribociclib group and the placebo group respectively,

demonstrating a clinically meaningful (>5 points) improvement in the ribociclib group which was observed as early as 8 weeks and was sustained.[8]

Young-PEARL

Young-PEARL study was a phase 2, randomized controlled trial. Premenopausal patients with ER+, HER2- metastatic breast cancer who received tamoxifen and up to 1 prior line of chemotherapy for advanced disease were eligible.[11] They were randomized to receive palbocicilb plus exemestane with a GnRH analogue, or capecitabine. It was found that palbociclib prolonged PFS compared with capecitabine (20.1 vs 14.4 months; HR 0.659, 95% CI 0.437-0.994, P = 0.0469).

Ongoing studies

Ongoing studies comparing endocrine therapy against chemotherapy include PEARL and RIGHT Choice. PEARL evaluates the safety and efficacy of palbociclib plus exemestane or fulvestrant versus capecitabine in postmenopausal patients,[12] whereas RIGHT choice evaluates the safety and efficacy of ribociclib, non-steroidal aromatase inhibitors plus a GnRH analogue versus chemotherapy in premenopausal patients with symptomatic disease or visceral crisis.[13]

Conclusion

In conclusion, MONALEESA-7 was the only phase 3 study to evaluate a CDK4/6 inhibitor plus endocrine therapy exclusively in premenopausal patients. Ribociclib plus endocrine therapy resulted in a statistically significant longer OS compared with endocrine therapy alone, with 29% risk reduction in death in the intention-to-treat population and 30% risk reduction in death in the NSAI cohort.[9] The benefit of ribociclib extended beyond initial treatment based on time to subsequent chemotherapy and PFS2. It was also the first study to demonstrate a statistically significant improvement in OS with a CDK4/6 inhibitor plus endocrine therapy in patients with HR+, HER2- advanced breast cancer.

Case Study from *Dr Wong Lai San, Cindy*

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A 48-year-old young premenopausal female presented with de novo metastatic breast cancer. The patient noted a painless right breast mass. Subsequent mammography and ultrasound showed that there was a 4-cm breast subareolar mass with multiple lesions in her right breast, right axillary lymph nodes and internal mammary nodes. Core biopsy showed low grade invasive ductal carcinoma, ER 8/8, PR 8/8, HER2 score 0 and Ki-67 30%.

PET-CT was performed in August 2018 and a 5.7-cm tumour was found on the right breast with skin involvement and abutting chest wall with satellite nodules. The patient had level I, II and internal mammary node involvement. Suspected multiple metastases of 5-8mm were found in right middle lobe, right lower lobe, left lower lobe and left lingular lobe. Multiple bone metastases at left iliac

bone, sacrum, L5, L4, L3, L2, T10, T6, T3, sternum, left scapula, right posterior 9th rib and right anterior 6th rib were observed. Peritoneal metastasis was suspected due to the finding of left adnexal uptake.

This patient was seen in a public hospital and offered a combination of LHRH agonist, letrozole and a CDK 4/6 inhibitor. She started subcutaneous goserelin 10.8mg in September 2018 and was scheduled to start letrozole and palbociclib after 1 month. She sought a second opinion from Dr Wong, who suggested her to consider radiotherapy for pelvic bone metastases and regular administration of denosumab. She was also suggested to receive tamoxifen and a CDK4/6 inhibitor before starting letrozole. However, she preferred being treated the public hospital due to financial concern.

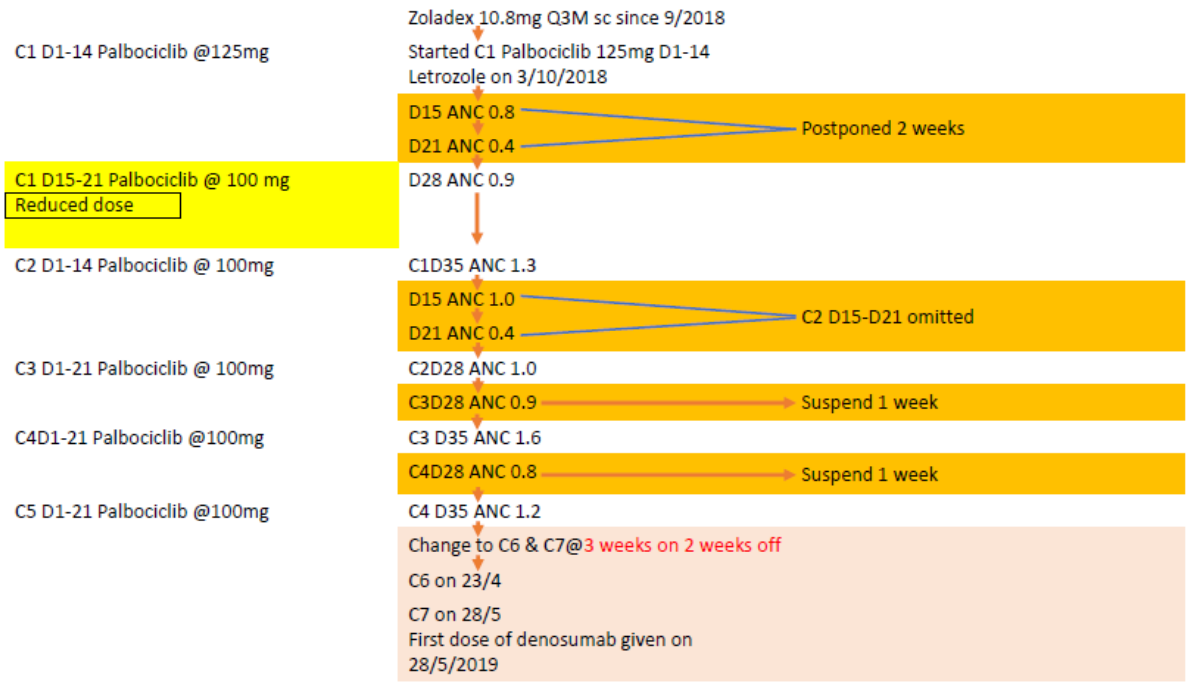

Figure 1. Treatment schedule of Dr Wong's patient

Figure 1 shows the treatment schedule of this patient. After the initiation of goserelin for 1 month, she started letrozole and palbocicilb 125mg. After 2 weeks of treatment, palbocicilb was interrupted due to neutropenia, and resumed after 2 weeks at a lower dose of 100mg. The patient received 14 days of palbociclib in the 2nd cycle and omitted the dose for 2 weeks due to neutropenia. In subsequent 3rd and 4th cycles, palbociclib was suspended for 1 week in each cycle because of low neutrophil count. Starting from the 6th cycle, she received palbociclib at a "3 weeks on, 2 weeks off" schedule.

The patient showed good clinical response. The tumour on her right breast shrank from 5cm to 2cm, and the mass in the right axillary lymph node decreased from 3cm to 1cm. Her left iliac pain was significantly reduced and painkiller was no long required. The carcinoembryonic antigen was within the normal range. The major side effects were hot flushes and arthralgia. The patient would have her first follow-up computed tomography in September 2019 due to limited resources in the public

hospital. She would continue the treatment of palbocicilb 100mg with a dosing schedule of "3 weeks on, 2 weeks off", with letrozole and goserelin as long as she is clinically stable.

Given the significant OS data demonstrated in MONALEESA-7 study,[8,9] Dr Wong agreed that upfront tamoxifen with ribociclib could also be a treatment option for her patient to spare her from arthralgia and hot flushes to improve her quality of life. She would also consider using radiotherapy for relieving pelvic pain due to bone metastases and ovarian oblation, followed by tamoxifen with a CDK4/6 inhibitor.

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