Editorial Commentary

Monarch plus: a research review

Tao Sun[1,2], Junnan Xu[1,2], Jun Yang[1]

[1]Department of Breast Medicine, Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, Shenyang, China; [2]Department of Breast Medicine, Key Laboratory of Liaoning Breast Cancer Research, Shenyang, China

Correspondence to: Prof. Tao Sun. Department of Breast Medicine, Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, No. 44, Xiaoheyan Road, Dadong District, Shenyang 110042, China. Email: jianong@126.com.

Comment on: Zhang QY, Sun T, Yin YM, *et al*. MONARCH plus: abemaciclib plus endocrine therapy in women with HR+/HER2- advanced breast cancer: the multinational randomized phase III study. Ther Adv Med Oncol 2020;12:1758835920963925.

Received: 27 May 2021; Accepted: 02 July 2021; Published: 31 January 2022.

doi: 10.21037/tbcr-21-6

View this article at: https://dx.doi.org/10.21037/tbcr-21-6

Background

According to the most recent approximations of the global burden of cancer by the International Agency for Research on Cancer (IARC), breast cancer has exceeded lung cancer as the most commonly diagnosed malignancy worldwide. In China, the number of new breast cancer cases is 272,400 annually, with 69,500 deaths (1). Approximately 70% of breast cancers are hormone receptor (HR)-positive, which has a favorable prognosis with hormone-dependent and novel targeted drugs synergistically combined with antiestrogens. Inhibitors of cyclin-dependent kinases 4 and 6 (CDK 4/6$_i$) have been confirmed as the standard of treatment, combined with endocrine therapy (ET), in either the first-line setting or after progression on ET (2).

Several large randomized studies have shown that the standard therapy of CDK4/6$_i$s (with three FDA-approved agents: palbociclib, abemaciclib, and ribociclib) combined with ET exhibits enormous anti-cancer activity, and is affordable and safe in HR-positive, human epidermal growth factor 2 (HER2)-negative advanced breast cancer (ABC) (3-7). At present, the National Medical Products Administration (NMPA) has approved two CDK4/6$_i$s, palbociclib and abemaciclib. According to the *Chinese Society of Clinical Oncology (CSCO) Breast Cancer Diagnosis and Treatment Guidelines*, 2021 updated version, the preferred treatment recommendation is CDK4/6$_i$s combined with ET in HR-positive and HER2-negative ABC. Also, abemaciclib combined with fulvestrant was highlighted as level 1A—evidence for treatment after progression on a previous aromatase inhibitor (AI), which was separated from level 2A—evidence of palbociclib combined with fulvestrant.

Abemaciclib is a selective inhibitor of CDK4/6, and is the only CDK4/6$_i$ that may be given continuously and also be used as a monotherapy (8). In addition, abemaciclib seems to cross the blood-brain barrier, thereby activating the central nervous system (CNS) (9). Two large randomized studies (MONARCH3/2) (5,6) have shown that the progression-free survival (PFS) for abemaciclib combined with a non-steroidal AI or fulvestrant significantly improved in HR$^+$/HER2$^-$ ABC. Updated analyses have also demonstrated a marked improvement in overall survival (OS) with the combination of fulvestrant with abemaciclib. The recommendations of the CSCO 2021 guidelines were updated with a strong reference to the global MONARCH series clinical trials as well as a multinational, randomized, double-blind, placebo-controlled phase III trial—MONARCH plus (10). In this article, we review the key aspects of the MONARCH plus study.

Introduction

According to data from the 9th December, 2016 to 29th March, 2019, MONARCH plus was conducted in 45 sites, mainly in China, but also in India, Brazil, and South Africa. Postmenopausal women with HR$^+$/HER2$^-$ ABC who had not been systematically treated were assigned to cohort A to be given oral abemaciclib or a placebo daily combined with anastrozole or letrozole. Postmenopausal patients with HR$^+$/HER2$^-$ ABC who had progressed after ET were assigned to cohort B to be given oral abemaciclib or a placebo combined with fulvestrant. The primary endpoint was PFS in cohort A, and the secondary endpoints were

cohort B's PFS, objective response rate (ORR), and safety. Assuming a hazard ratio of 0.626 in cohort A and favoring abemaciclib plus AI, 119 and 170 PFS events were needed, with 80% power and a one-sided α =0.025.

In cohort A, 207 patients were randomly enrolled into the abemaciclib group, and 99 patients were included in the placebo group. The primary endpoint reached an expected hypothesis, and PFS was favored and significantly improved in the abemaciclib group [hazard ratio, 0.499; 95% confidence interval (CI), 0.346–0.719; P=0.0001]. Abemaciclib also exhibited considerable benefits in cohort B (median PFS was prolonged by approximately 6 months; hazard ratio, 0.376). The ORRs of abemaciclib-combined were 65.9% in cohort A and 50.0% in cohort B. The most common serious adverse event (SAEs) were neutropenia, leukopenia, and anemia in all patients treated with abemaciclib. Notably, in cohort B, the most common SAE was lymphopenia in the abemaciclib group. Any grade of diarrhea and ≥ grade 3 of neutropenia could be effectively treated by supportive drugs and/or dose adjustments. In summary, the PFS and ORR were clinically significant with abemaciclib plus ET, as well as significant and favorable safety in $HR^+/HER2^-$ ABC.

Discussion

More than 80% of patients in the MONARCH plus study were Chinese, which were recruited from 28 representative centers in China. MONARCH plus is the first randomized clinical trial to illustrate the significant improvement in PFS and favorable safety profile in four countries, including China, Brazil, India, and South Africa, which represent approximately 40% of the global population. The study demonstrated the efficacy and safety profile of abemaciclib in those countries where postmenopausal women with $HR^+/HER2^-$ ABC. The positive and consistent results present convincing evidence for the application of abemaciclib in this population, especially Chinese patients.

Before abemaciclib, the only $CDK4/6_i$ approved in China was palbociclib, and was indicated to be used in combination with AI, not with fulvestrant. The innovation of the MONARCH plus study is that it enrolled and evaluated cohorts with both endocrine-sensitive and endocrine-resistant populations in a single investigation, thereby yielding adequate power to investigate PFS, the primary endpoint. No alpha power was reserved for statistics in cohort B and the hypothesis for cohort B was just show the consistent tendency with global MONARCH 2 trial. Despite the small sample size of cohort B, its results suffice to show the consistent and robust improvement with MONARCH 2. As a bridging study, MONARCH plus provides sufficiently validated data and at the same time, avoids total replication of the large, expensive trials and shortens the clinical drug development period.

In terms of inclusion criteria, cohorts A and B adopted the standard scheme of the global MONARCH 3 and MONARCH 2 trials; however, some adjustments were made based on China's national condition. Firstly, the age of breast cancer diagnosis was at least 5–10 years earlier than that in American and other Western countries. More patients may receive tamoxifen treatment in adjuvant therapy and may be available for AIs (11). The MONARCH 3 trial mainly enrolled patients who were ET naïve or had relapsed 12 months after completion of adjuvant AI therapy. Thus, we did not show whether the population who progressed after other ET, including tamoxifen and toremifene, could benefit from abemaciclib in combination with nonsteroidal aromatase inhibitor (NSAI) treatment (6). In the MONARCH plus trial, the study design in cohort A enrolled patients who received adjuvant non-AI ET and relapsed within 12 months, and were still with available for AIs. Patients who had been treated with NSAIs during the adjuvant ET phase were enrolled in cohort B. Subgroup analysis showed that patients in cohort A who received non-NSAIs and relapsed within 12 months of completion of adjuvant ET could also benefit significantly (hazard ratio, 0.484) from the combination of abemaciclib and NSAIs. This hazard ratio was similar to that of fulvestrant in cohort B (0.407). Based on the study design and conclusion of the MONARCH plus trial, the CSCO guidelines recommend stratified treatment considering the previous ET for the first time.

The MONARCH plus interim analysis demonstrated that abemaciclib prolonged PFS in $HR^+/HER2^-$ ABC regardless of treatment with NSAI or fulvestrant, which was highly consistent with the results of the MONARCH 2 and 3 studies. Notably, ET-based therapies rarely rapidly inhibit and shrink hormone-dependent breast tumors, especially in patients who progressed during adjuvant ET. In both cohorts A and B, abemaciclib combined with ET significantly improved ORR, and the increase was greater in patients with measurable disease. In terms of disease control ratio (DCR) and clinical benefit ratio (CBR), we demonstrated a positive and consistent improvement. The Chinese subgroup analysis of the study was reported at the 2020 CSCO conference. Compared with ET alone,

abemaciclib combined with NSAI or fulvestrant significantly improved the PFS and ORR of Chinese women with ABC. These results are consistent with the intention to treat (ITT) population of the MONARCH plus study. It is especially worth noting that for patients with visceral metastasis and previous ET-resistance (primary resistance/secondary resistance), the PFS of patients who were combined with abemaciclib on the basis of ET was significantly improved.

Diarrhea was a specific safety signal of abemaciclib compared with other CDK4/6$_i$s (12). In the MONARCH plus study, the majority of diarrhea events were low-grade, and the occurrence rate of grade 3–4 SAEs was moderately less than that of the MONARCH 2 and 3 trials. This difference could be explained by raised awareness and improved administration. In other words, management of diarrhea should be active and controllable; the addition of antidiarrheal medication (e.g., loperamide) was orally administered when patients began to show early signs of loose stools. An important recommendation is that patients with grade ≥2 diarrhea should discontinue abemaciclib at the first cycle, which could be resumed at the original dose upon recovery from diarrhea (grade ≤1). However, if grade 2, or grade ≥3 diarrhea persists or recurs, dose reduction should be implemented (13).

The occurrence rate of treatment emergent adverse events (TEAEs) associated with neutropenia in the abemaciclib cohorts (cohort A: 80.0%; cohort B: 80.8%) in the MONARCH plus study was significantly higher than that of MONARCH 2 (46.0%) and MONARCH 3 (41.3%). The main cause for this difference may be the different patterns of reporting adverse events (AEs) in China and other countries. Moreover, the total occurrence rate of AEs and laboratory-based surveillance of grade ≥3 in this study was similar to that of MONARCH 2 and 3. In particular, discontinuation of abemaciclib due to neutropenia was rare, with only one patient reported with febrile neutropenia. Intermittent dosing schedules of other CDK4/6$_i$ due to neutropenia were defined as dose-limiting toxicity, with severe neutropenia being commonly reported in a series of phase III trials (3,4,14). The incidence of abemaciclib associated with severe neutropenia was infrequent; a potential reason for this may be the more substantial inhibition of cyclin D1/CDK 4 by abemaciclib compared with cyclin D3/CDK 6, as recognized by cell-free enzymatic assays (8).

In cohorts A and B in the MONARCH plus study, venous thromboembolic events (VTEs) were reported in four patients in the abemaciclib groups [cohort A: 2.0%, grade 1: one patient (0.5%), grade 2: three patients (1.5%); cohort B: 3.8%, grade 2: three patients (2.9%), grade 3: one patient (1.0%)]. Notably, no VTE was reported in the placebo groups. Following anticoagulant therapy, the cases of VTE recovered and only one patient was reported to have discontinued abemaciclib due to embolism in the abemaciclib combined with NSAI group (0.5%). No death owing to VTE was disclosed. The increased risk of VTE is a special toxicity of CDK4/6$_i$s. The PALOMA-3 tests reported that the incidence of VTE was 1.4% in palbociclib group and 0% in the control group (3). Tests to evaluate ribociclib identified a similar increase in the occurrence of VTE. The MONALEESA-7 final survival analysis demonstrated that ribociclib combined with AI increased the incidence of pulmonary embolism (PE) compared with the placebo group (2.7% *vs*. 0.9%) (7). For abemaciclib (MONARCH 2 and 3), the VTE rate was almost 5% in the abemaciclib group compared with less than 1% in the placebo group (0.6–0.9%). However, the risk of thrombosis in the real-world population may be higher than those received and managed in clinical trials, according to two recently published retrospective real-world studies. One study collected 424 metastasis breast cancer (MBC) patients who received any of the three CDKis approved by the FDA (palbociclib, ribociclib, abemaciclib), and 92% of patients received palbociclib. In this study, one out of five patients had visceral venous thromboembolism, which occurred in 90% of the palbociclib population (15). In another study, 266 patients were enrolled, with 79% receiving palbociclib, 14% receiving abemaciclib, and 7% receiving ribociclib. The data showed that 29 thrombotic AEs were reported in 26 female breast cancer patients (9.8%), including 72% venous-associated AEs and 34% arterial-associated AEs. The overall 1-year occurrence of thrombosis was 10.4%, including 10.9% in the palbociclib cohort, 8.3% in ribociclib cohort, and 4.8% in abemaciclib cohort (16). These inconsistent results indicate that there is a correlation between these three CDKis and VTEs. Further investigations regarding the mechanism of cancer-associated thrombosis are required to better understand this phenomenon.

Considering the clinical improvements exhibited in MBC, CDK4/6$_i$ studies have been initiated in the adjuvant setting for three CDK4/6$_i$s. In the phase III monarchE study, the addition of abemaciclib provided benefits in both invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) compared with mono-ET in high-risk early breast cancer patients (17). This is the first and only significant improvement seen yet in AI treatment in the

adjuvant population with estrogen receptor (ER)-positive early-stage breast cancer.

Despite the promising clinical progress with abemaciclib and other CDK4/6$_i$s, additional efforts should be made to determine the correct use of medications and optimal management of AEs. In routine clinical practice, conventional clinical monitoring (e.g., history of concomitant medications, electrocardiogram (ECG), and complete blood count) suffices to manage typical treatment-associated with AEs (e.g., prolongation, diarrhea, neutropenia, and hepatotoxicity). Clinicians should be aware to dose adjust and manage serious AEs with local labels. Above all, a clinical benefit/risk ratio should be considered to determine whether continue to receive treatment while occurring SAE (12,13). This is the essential approach to ensure that patients with HR$^+$/HER2$^-$ breast cancer are able to tolerate treatment with an oral CDK4/6$_i$ well.

Aside from widespread clinical experience with these agents, the clinical utility of putative biomarkers for routine medical decision-making has not been established (18). In the future, questions regarding the optimal population and dose with CDK4/6$_i$s, possible effective and feasible biomarkers for predictive value, and the potential resistance mechanisms of primary or acquired resistance to CDK4/6$_i$s should be addressed with large sample and well-designed randomized clinical trials. Meanwhile, the high cost of CDK4/6$_i$s hinders patient access. It is expected that CDK4/6$_i$s would be included in medical insurance reimbursement instead of being fully paid by patients.

Acknowledgments

We acknowledge A. Kassem for the language editing of this article.
Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-21-6/coif). TS serves as the unpaid editorial board member of *Translational Breast Cancer Research* from March 2020 to February 2022. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115-32.
2. Spring LM, Wander SA, Zangardi M, et al. CDK 4/6 Inhibitors in Breast Cancer: Current Controversies and Future Directions. Curr Oncol Rep 2019;21:25.
3. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016;17:425-39.
4. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 2016;375:1925-36.
5. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol 2017;35:2875-84.
6. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. J Clin Oncol 2017;35:3638-46.
7. Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol 2018;19:904-15.
8. Patnaik A, Rosen LS, Tolaney SM, et al. Efficacy and Safety of Abemaciclib, an Inhibitor of CDK4 and CDK6, for Patients with Breast Cancer, Non-Small Cell Lung Cancer, and Other Solid Tumors. Cancer Discov 2016;6:740-53.
9. Tolaney SM, Sahebjam S, Le Rhun E, et al. A Phase II

Study of Abemaciclib in Patients with Brain Metastases Secondary to Hormone Receptor-Positive Breast Cancer. Clin Cancer Res 2020;26:5310-9.
10. Zhang QY, Sun T, Yin YM, et al. MONARCH plus: abemaciclib plus endocrine therapy in women with HR+/HER2- advanced breast cancer: the multinational randomized phase III study. Ther Adv Med Oncol 2020;12:1758835920963925.
11. Breast cancer screening guideline for Chinese women. Cancer Biol Med 2019;16:822-4.
12. Rugo HS, Huober J, García-Sáenz JA, et al. Management of Abemaciclib-Associated Adverse Events in Patients with Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Safety Analysis of MONARCH 2 and MONARCH 3. Oncologist 2021;26:e53-65.
13. Ettl J. Management of Adverse Events Due to Cyclin-Dependent Kinase 4/6 Inhibitors. Breast Care (Basel) 2019;14:86-92.
14. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med 2016;375:1738-48.
15. Gervaso L, Montero AJ, Jia X, et al. Venous thromboembolism in breast cancer patients receiving cyclin-dependent kinase inhibitors. J Thromb Haemost 2020;18:162-8.
16. West MT, Smith CE, Kaempf A, et al. CDK 4/6 inhibitors are associated with a high incidence of thrombotic events in women with breast cancer in real-world practice. Eur J Haematol 2021;106:634-42.
17. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol 2020;38:3987-98.
18. Wander SA, Cohen O, Gong X, et al. The Genomic Landscape of Intrinsic and Acquired Resistance to Cyclin-Dependent Kinase 4/6 Inhibitors in Patients with Hormone Receptor-Positive Metastatic Breast Cancer. Cancer Discov 2020;10:1174-93.

doi: 10.21037/tbcr-21-6
Cite this article as: Sun T, Xu J, Yang J. Monarch plus: a research review. Transl Breast Cancer Res 2022;3:7.

