Editorial Commentary

MONARCH-plus: the evidence of efficacy and safety of abemaciclib in countries with limited clinical research opportunities

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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 August 2021; Accepted: 26 September 2021.

doi: 10.21037/tbcr-21-25

View this article at: https://dx.doi.org/10.21037/tbcr-21-25

Estrogen receptor positive (ER+)/ human epidermal growth factor receptor 2 negative (HER2–) breast cancer is the most frequent subset, accounting for around 70% of all breast cancer cases (1).

Cyclin dependent kinase 4/6 (CDK 4/6) inhibitors (palbociclib, abemaciclib and ribociclib) combined with endocrine therapy (ET), non-steroidal aromatase inhibitors (NSAI) or fulvestrant became a standard treatment in ER+/HER2– advanced breast cancer (ABC) and represents one of the major breakthrough in metastatic breast oncology during the past two decades. This is based on the substantial and clinically meaningful progression free survival (PFS) benefit seen in all trials conducted using CDK 4/6 inhibitors + ET [hazard ratio (HR): 0.55–0.56], the improvement in overall survival (OS) seen in several trials (HR: 0.72–0.75) and the good safety profile (2-10). Although some differences can be noticed in the inclusion criteria of these pivotal trials mainly regarding anticancer treatment history, results can be considered similar with the three different drugs and are consistent through all subgroups of patients. Main results and the most important characteristics of patient population included are summarized in *Table 1*. Current guidelines recommend that every advanced luminal breast cancer patient be treated with CDK 4/6 inhibitors (11).

Two of the above-mentioned pivotal phase III trials used abemaciclib (Verzenio™, Eli Lilly and Company, Indianapolis, IN, USA) + ET based combinations. MONARCH-2 enrolled 669 women with ER+/HER2– ABC who had disease progression during prior ET. Patients were treated with fulvestrant plus either placebo (n=223) or abemaciclib 150 mg twice daily (n=446). Median PFS was prolonged from 9.3 to 16.4 months with abemaciclib plus fulvestrant (HR: 0.55; P<0.001), the response rate was 35.2% *vs.* 16.1% in the placebo group (7). The trial showed also a significant improvement in OS with the combination: 46.7 *vs.* 37.3 months (HR: 0.757, P =0.01) (8).

MONARCH-3 was a phase III trial using abemaciclib (n=328) or placebo (n=165) plus an aromatase inhibitor (AI) in 493 postmenopausal women with ER+/HER2– ABC with endocrine-sensitive disease who haven't received any prior systemic therapy for ABC. Abemaciclib plus AI showed a significantly longer median PFS than the AI plus placebo (28.18 *vs.* 14.76 months; HR: 0.540, P=0.000002). The response rate was 61% with abemaciclib and 45.5% with placebo (P=0.003) (12). Survival data are still immature.

Abemaciclib is the latest oral CDK 4/6 inhibitor to receive FDA approval, being granted breakthrough therapy designation in September 2017 as a 2nd-line treatment, combined with fulvestrant [+ luteinizing hormone-releasing hormone agonist (LHRHa) in pre-menopausal patients], for ER+/HER2– metastatic breast cancer (mBC) who progressed on prior ET. In February 2018, abemaciclib received FDA approval as a 1st-line treatment in combination with an AI. Contrary to other CDK 4/6 inhibitors, is also approved as a single agent (200 mg twice daily) for ER+/HER2– mBC who progressed after prior chemotherapy and ET (13).

In the current issue of *Translational Breast Cancer*

Table 1 Available data on phase III trials assessing the efficacy of CDK 4/6 inhibitors in combination with ETs in mBC

	PALOMA-2	MONALEESA-2	MONARCH-3	MONALEESA-7	PALOMA-3	MONARCH-2	MONALEESA-3
Study design	Phase III; placebo-controlled; 1st-line; (n=666); postmenopausal	Phase III; placebo-controlled; 1st-line; (n=668); postmenopausal	Phase III; placebo-controlled; 1st-line; (n=493); postmenopausal	Phase III; placebo-controlled; 1st-line; (n=672); premenopausal	Phase III; placebo-controlled; ≥2nd-line; (n=521); pre- and postmenopausal	Phase III; placebo-controlled; 2nd-line; (n=672); pre- and postmenopausal	Phase III; placebo-controlled; 1st- and 2nd-line; (n=726); postmenopausal
ET	Letrozole	Letrozole	NSAI	Tamoxifen, NSAI/LHRHa	Fulvestrant	Fulvestrant	Fulvestrant
CDK 4/6 inhibitor	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Palbociclib	Abemaciclib	Ribociclib
Prior therapy	No prior systemic therapy for ABC	No prior systemic therapy for ABC	No prior systemic therapy for ABC	No prior ET up to one CT for ABC	Prior ET up to one CT for ABC	No more than one ET; no prior CT for ABC	1st-line: no ET for mBC; 2nd-line: one line ET; no prior CT for ABC
HR PFS	0.58	0.56	0.54	0.55	0.46	0.55	0.59
Median PFS (mo)	24.8 *vs.* 14.5	25.3 *vs.* 16.0	28 *vs.* 14.7	23.8 *vs.* 13.0	11.2 *vs.* 4.6	16.4 *vs.* 9.3	20.5 *vs.* 12.8
HR OS	NA	NA	NA	0.71	0.81	0.75	0.72
Median OS	NA	NA	NA	NR *vs.* 40.9	34.9 *vs.* 28	46.7 *vs.* 37.3	NR *vs.* 40

CDK, cyclin dependent kinase; ET, endocrine therapy; mBC, metastatic breast cancer; HR, hazard ratio; PFS, progression free survival; OS, overall survival; NSAI, non-steroidal aromatase inhibitors; LHRHa, luteinizing hormone-releasing hormone agonist; ABC, advanced breast cancer; CT, chemotherapy; NA, not available; NR, not reported.

Research, Zhang *et al.* reports a pre-specified interim analysis of a randomized, double blind phase III trial conducted in China, Brazil, India and South Africa assessing the efficacy and safety of the combination of abemaciclib with either AI (cohort A, n=306) or fulvestrant (cohort B, n=157) compared to ET alone (14). Patients in cohort A had no prior systemic therapy for advanced/recurrent breast cancer and relapsed >1 year after adjuvant AI (if received), whereas patients in cohort B were refractory to NSAI (adjuvant or 1st-line metastatic setting) and had no prior chemotherapy for metastatic disease. Sixty percent of the patients had visceral involvement. Only 10% had prior AI and 40% did not received adjuvant ET in cohort A. As per inclusion criteria, almost all patients (98.7%) in cohort B were previously treated with an AI and 35% of them showed primary resistance according to ABC consensus guideline definition (11). Enrollment took place between December 2016 and August 2018 and most of the participating patients are originating from China (80% in cohort A and 85% in cohort B).

This paper reports an interim analysis after 119 events of the primary endpoint with a median follow-up up of 16 months (investigator assessed PFS in cohort A). Moreover, data on a number of secondary endpoints such as PFS in cohort B, objective response rate (ORR), disease control rate (DCR), clinical benefit rate (CBR) and safety are included.

Median PFS was not reached in the abemaciclib arm and it was 14.7 months in the placebo arm [HR: 0.499, 95% confidence interval (CI): 0.346–0.719, P=0.0001]. In cohort B, 82 events occurred at the time of this interim analysis, median PFS was also significantly better in the abemaciclib arm: 11.5 *vs.* 5.6 months (HR: 0.376, 95% CI: 0.240–0.588, P<0.0001). As in other pivotal trials, a significant improvement was observed with abemaciclib in all secondary endpoints such as ORR, DCR and CBR. The authors report a subgroup analysis, which show no differential efficacy of abemaciclib in relation to disease characteristics. Nevertheless, this analysis should be interpreted with caution given the small number of patients in each group.

In terms of safety profile, patients receiving abemaciclib experienced higher rates of neutropenia [80%, 30% grade 3 (G3)], diarrhea (80%, 4% G3), anemia (62%, 11% G3), thrombocytopenia (44%, 5.4% G3), liver function test and blood creatinine increase (35% and 12% respectively). A surprisingly high rate of pneumonitis was observed in both arms (6.3% with abemaciclib and 3% with ET alone). Venous thromboembolic events occurred in 2% and 3.8% of patients treated with abemaciclib in cohorts A and B respectively. Of note, treatment discontinuation due to adverse events was 10.7% in cohort A and 3.8% in cohort B.

The main strength of MONARCH-plus is that it has been conducted in countries with much limited clinical research opportunities and particularly in a population which was underrepresented in pivotal phase III trials. Data reassures oncology community that abemaciclib has potentially the same activity in these populations. Furthermore, and of importance no signals of differential toxicity profile were seen. The real-life data can be used to report antitumor activity of new drugs in specific patient populations such as patients in specific countries. This approach suffers from a substantial clinical and statistical bias. MONARCH-plus is a more valid approach to document activity and mainly safety profile. Hopefully, these results can foster the availability of CDK 4/6 inhibitors in these and similar countries for all ER+/HER2– breast cancer patients.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Breast Cancer Research*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-21-25/coif). AA reports that he receives grants and takes participation on a Data Safety Monitoring Board or Advisory Board held by Roche, Lilly, Amgen, EISAI, BMS, Pfizer, Novartis, MSD, Genomic Health, Ipsen, AstraZeneca, Bayer, Leo Pharma, Merck, and Daiichi. AG reports advisory fees from Lilly, and Daiichi Sankyo, honoraria for presentation from Daiichi Sankyo, support for attending meetings from Pfizer. The authors have no other 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.

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doi: 10.21037/tbcr-21-25
Cite this article as: Awada A, Gombos A. MONARCH-plus: the evidence of efficacy and safety of abemaciclib in countries with limited clinical research opportunities. Transl Breast Cancer Res 2022;3:5.