Managing advanced HR-positive, HER2-negative breast cancer with CDK4/6 inhibitors in post-menopausal patients: is there a best sequence?

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Abstract: The current therapeutic landscape of luminal human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (mBC) is fundamentally evolving, particularly in the advent of molecularly targeted therapies, such as inhibitors of mammalian target of rapamycin and cyclin-dependent kinase 4/6 (CDK4/6). In the context of CDK4/6 inhibitors, landmark clinical trials for palbociclib [PALOMA-1, PALOMA-2, PALOMA-3], ribociclib [MONALEESA-2, MONALEESA-3, MONALEESA-7] and abemaciclib [MONARCH-1, MONARCH-2, MONARCH-3] have provided solid data regarding progression-free survival and overall response rate, justifying the introduction of this class of drugs into our therapeutic armoury. However, several clinical questions remain open. One of the most relevant issues faced in practice is that of the optimum sequencing of CDK4/6 inhibitors, particularly given the wide range of therapeutic options open to clinicians treating luminal mBC. In this brief commentary, we would like to focus on the best sequence for CDK4/6 inhibitors and their place in this growing, complex scenario.

Keywords: abemaciclib, best-sequence therapy, CDK4/6 inhibitors, metastatic breast cancer, palbociclib, ribociclib

The current therapeutic landscape of luminal HER2-negative (HR+/HER2−) metastatic breast cancer (mBC) is fundamentally evolving, particularly in the advent of molecularly targeted therapies, such as inhibitors of mammalian target of rapamycin (mTOR) and cyclin-dependent kinase 4/6 (CDK4/6). In the context of CDK4/6 inhibitors, landmark clinical trials for palbociclib [PALOMA-1, PALOMA-2, and PALOMA-3], ribociclib [MONALEESA-2, MONALEESA-3, and MONALEESA-7] and abemaciclib [MONARCH-1, MONARCH-2, and MONARCH-3] have provided solid data regarding progression-free survival and overall response rate (ORR), justifying the introduction of this class of drugs into our therapeutic armoury. However, several clinical questions remain open. One of the most relevant issues faced in practice is that of the optimum sequencing of CDK4/6 inhibitors, particularly given the wide range of therapeutic options open to clinicians treating luminal mBC.

The use of CDK4/6 inhibitors comes not only with considerable economic cost, but also with potential toxicity, which varies according to the agent used. The main toxicities encountered are largely cytopenias, particularly neutropenia (more common in palbociclib and ribociclib), nausea and diarrhoea (encountered more with abemaciclib), and fatigue.1–10 Considering that the combined objective of mBC therapy is to improve survival and to delay the progression of disease, whilst also postponing the onset or worsening of symptoms and improving or maintaining quality of life, it is questionable whether an upfront

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approach with endocrine therapy (ET) and CDK4/6 inhibitors is appropriate for all patients. Certain patients may derive more advantage with upfront CDK4/6 inhibition, whereas others may benefit from initial ET monotherapy, thus mitigating associated costs and side effects, saving the introduction of CDK4/6 agents until a later line of therapy.

All seminal CDK4/6 inhibition trials to date have demonstrated a clear advantage for CDK4/6 inhibitors plus ET over ET alone, in both the upfront and later-line settings. However, there is no definitive evidence to suggest upfront combination therapy is the optimal approach in all patients, in spite of this currently being the predominant clinical indication approved for licensing and recommended by international guidelines such as NCCN and ESMO.

Indeed, the trials that evaluated the efficacy of CDK4/6 inhibition as a subsequent-line therapy demonstrated high levels of activity and efficacy in favour of combination ET plus CDK4/6 inhibitors, notwithstanding previous progression on ET monotherapy. In PALOMA-3, the majority of the intention-to-treat (ITT) population had documented previous sensitivity to ET, with 48% having received one line of previous ET, and a further 39% having received two previous ET lines. Despite this pretreatment, the median PFS in PALOMA-3 was 9.5 months [95% confidence interval (CI) 9.2–11] for palbociclib plus fulvestrant versus 4.6 months [95% CI 3.5–5.6] in the fulvestrant plus placebo arm (p < 0.0001). Similarly, MONARCH-2, which enrolled patients whose disease had progressed on either neoadjuvant/adjuvant or first-line palliative ET (59% and 38%, respectively), showed a significant advantage in PFS (16.4 months for abemaciclib plus fulvestrant versus 9.3 months for fulvestrant alone, p < 0.001). Similar results for ribociclib were reported in MONALEESA-3, with a median PFS of 20.5 months (95% CI, 18.5–23.5) for dual therapy versus 12.8 months (95% CI, 10.9–16.3) for ET plus placebo (p < 0.001). Overall, 21% of those enrolled in MONALEESA-3 had received up to one line of prior endocrine therapy for advanced disease (PFS hazard ratio 0.565).

Contrastingly, although exploratory analyses from some trials have suggested that treatment benefit of ET+CDK4/6 inhibitors can extend to the next line of therapy after progression, a modest median time to progression (TTP) with treatment lines given subsequent to combination ET+CDK4/6 inhibitors in both the settings of cytotoxic chemotherapy and ET ± molecular therapies such as everolimus has been reported. These short periods of clinical efficacy observed with therapies given post-CDK4/6 inhibition, plus evidence of robust efficacy of ET+CDK4/6 inhibition as a subsequent-line therapy, stress once again that in some patients, the introduction of these inhibitors could safely be delayed. An answer to this fundamental question may emerge from the SONIA trial, an ongoing study primed to evaluate optimal sequencing of CDK4/6 inhibitors. SONIA randomizes subjects with advanced breast cancer (BC) not previously treated in the metastatic setting to receive either upfront combination aromatase inhibitors (AIs) + CDK4/6 inhibition in the first line, followed by fulvestrant in the second line, or the sequential approach of single-agent AIs followed by fulvestrant + CDK4/6 inhibitors following first progression.

Unfortunately, as crossover was not permitted in any of the PALOMA, MONALEESA or MONARCH trials, it is impossible to definitively comment as to whether upfront or subsequent-line CDK4/6 inhibition offers the greatest benefit overall. Consequently, subgroup analyses have to date been the only source of data in the context of identifying which patients stand to benefit most from upfront CDK4/6 inhibition, in those in whom a later introduction might be appropriate. The bottom-line message derived from the subgroup analyses of the first-line therapy trials (PALOMA-2, MONALEESA-2 and MONARCH-3) is that a proportional benefit in favour of the combination arm is observed in all the evaluated subgroups. However, in such subgroup analyses, it is appropriate to evaluate proportional as well as absolute benefits. The absolute benefit of receiving CDK4/6 inhibition, particularly during the first year of therapy, is expected to be less in subgroups with a clinicopathologically better overall prognosis, such as patients with bone-only disease. In such groups, any advantage gained from receiving combination ET+CDK4/6 inhibitors must be contrasted with the real risk of disease progression, which is comparatively less than that of patients with more aggressive disease.

Subgroup analyses within MONARCH-3 suggested patients with features of clinicopathological
low risk of progression (bone-only disease, absence of liver metastases, long treatment-free interval) single-agent ET in first line may represent an acceptable therapeutic option. Conversely, relatively rapid progression was observed in patients with adverse prognostic features, most notably that of a short treatment-free interval (TFI) and hepatic metastases, suggesting such clinical factors may prompt upfront introduction of CDK4/6 agents. This premise was reinforced by an exploratory subgroup pooled analysis of over 1000 patients treated in MONARCH-2 and MONARCH-3,16 which suggested that, despite proportional benefits from the combination therapy being observed in all subgroups, the largest absolute benefit for abemaciclib plus ET was seen in patients with poor prognostic features; namely, the presence of hepatic metastases, PR-negative status and high-grade tumours, wherein large increases in PFS (hazard ratios 0.4–0.5) and ORR (>30%) were observed. Conversely, bone-only disease was associated with a good prognosis, with less absolute benefit observed for dual treatment, particularly during the first year of therapy. Subpopulation treatment-effect pattern plot (STEPP) analysis of TFI data reported in MONARCH-3 suggested that patients with the shortest TFI (which may be regarded as a surrogate marker of poor disease response to ET) received more benefit from abemaciclib than those with a preceding long TFI. However, the duration of follow up is not sufficiently mature to consider these data as definitive. Moreover, conflicting results were found in a STEPP analysis of baseline TFI data from PALOMA-2, which showed a constant treatment effect on PFS, regardless of TFI.17 Additionally, updated data from MONALEESA-218 did not show an association between TFI and PFS, therefore TFI should be considered as only one of many factors to evaluate in the optimization of treatment. Similar to what was seen in the MONARCH-3 subgroup analysis, a prespecified analysis of PALOMA-2 demonstrated that patients with bone-only disease appeared to derive a modest absolute benefit from the combination therapy, particularly during the first 6–9 months of treatment. The advantage in favour of the combination therapy becomes progressively more evident after the first year of follow up, with a median PFS not yet reached.17

These subgroup analyses are limited by their exploratory nature, and as such, there remains ongoing need for specific trials with adequate statistical power, which allow for crossover, to answer the fundamental question of sequencing. Findings of subgroup analyses of the existing seminal trials so far appear to favour upfront CDK4/6 agents in metastatic disease with aggressive features, and ET monotherapy with a delayed introduction of CDK4/6 inhibition in the later line for patients with indolent disease. A general consensus exists about the need of combined treatment with a CDK4/6 inhibitor and ET in patients who have progressed on first-line ET monotherapy. Nevertheless, the question of where CDK4/6 agents fit in the bigger picture of sequencing within the many drug classes available in metastatic regimens remains unanswered and largely unaddressed. Although international guidelines11,12,19 suggest the use of chemotherapy in patients with visceral crises or in whom it is necessary to induce rapid disease control, subgroup data arising from the MONARCH and PALOMA trials suggest that the greatest benefit for upfront CDK4/6 inhibition was derived in patients with features of aggressive disease or a poor previous response to ET, which are also clinical grounds to consider first-line chemotherapy to obtain rapid disease control. However, patients at theoretical risk of life-threatening complications in the short term were excluded from enrolment in these trials, and no direct head-to-head data exist comparing the efficacy of CDK4/6 agents versus chemotherapy, though a meta-analysis of indirect comparisons has been recently published.20 As such, it is impossible to extrapolate the findings of these subgroup analyses to patients with the highest-risk features, and so chemotherapy is unlikely to be fully supplanted from its current role in first-line therapy of metastatic disease. However, in the context of quality of life, CDK4/6 inhibitors in the landmark trials provided impressive data on how quickly symptomatic patients become asymptomatic. This rapidity of action is a further element which must be taken into consideration when comparing these agents with chemotherapy.

There is currently lack of clinical data on the best therapeutic option to employ in the setting of CDK4/6 pretreated patients. Specific to the setting of failure on CDK4/6 inhibitors+AIAs, the myriad of available options, including single-agent fulvestrant, or the combination of everolimus and ET, complicates the scenario. In this instance, data from indirect comparisons of clinical trials in CDK4/6-inhibitor-naïve patients21,22 suggest that combinations of everolimus+ET may be superior to single-agent fulvestrant. However, little is known about the...
efficacy of these regimens after CDK4/6 inhibitors.

Limited preclinical evidence suggest that rechallenging Rb-proficient palbociclib-resistant cell lines with palbociclib may still be effective.\textsuperscript{23} Additional preclinical evidence suggests the existence of crosstalk between the PI3K/mTOR and CDK4/6 pathways, and that simultaneous inhibition of the two pathways may be more effective compared with single blockade.\textsuperscript{24,25} This has led to the question of whether it is viable to maintain CDK4/6 inhibitors beyond progression, by either modifying the backbone ET or adding mTOR inhibitors. The MAINTAIN [ClinicalTrials.gov identifier: NCT02632045]\textsuperscript{26} and TRINITI-1 [ClinicalTrials.gov identifier: NCT02732119]\textsuperscript{27} trials will provide preliminary clinical evidence to partially address these issues. Specifically, TRINITI-1 is a phase I/II trial aimed to evaluate the combination of ribociclib, everolimus and exemestane after previous progression on a CDK4/6 inhibitor and the phase II MAINTAIN randomizes patients who have previously progressed on AIs plus either ribociclib or palbociclib to receive either single-agent fulvestrant or fulvestrant+ribociclib.

In addition to the limited insight permitted by subgroup analyses or indirect comparisons between different classes of drugs, in order to identify the subgroup of patients who benefit most from early or later treatment with CDK4/6 inhibitors, the identification of biomarkers that predict sensitivity to this class of drug is of vital importance. Despite a growing number of analyses aimed at evaluating potential predictive biomarkers to respond to CDK4/6 inhibitors, currently available data are still scarce and inconsistent. More likely, it will be not from the identification of a single biomarker, but from clarification of an entire network of biomarkers, that a more rationalized and optimized therapeutic algorithm can be built in order to produce personalized treatment strategies that contain the side effects, improve or maintain the quality of life, reduce the costs of improper or un-needed treatment, and clarify the increasingly complex therapeutic landscape of this particular setting of BC.

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**References**

1. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol* 2015; 16: 25–35.

2. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med* 2016; 375: 1925–1936.

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, doubleblind, phase 3 randomised controlled trial. *Lancet Oncol* 2016; 17: 425–439.

4. O’Shaughnessy J, Petrakova K, Sonke GS, et al. Ribociclib plus letrozole versus letrozole alone in patients with de novo HR+, HER2– advanced breast cancer in the randomized MONALEESA-2 trial. *Breast Cancer Res Treat* 2018; 168: 127–134.

5. Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *J Clin Oncol* 2018; 36: 2465–2472.

6. 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: 904–915.

7. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer. *Clin Cancer Res* 2017; 23: 5218–5224.

8. Sledge GW, 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: 2875–2884.
19. Joy AA, Ghosh M, Fernandes R, et al. Systemic treatment approaches in HER2-negative advanced breast cancer—guidance on the guidelines. *Curr Oncol* 2015; 22(Suppl. 1): S29–S42.

20. Wilson FR, Varu A, Mitra D, et al. Systematic review and network meta-analysis comparing palbociclib with chemotherapy agents for the treatment of postmenopausal women with HR-positive and HER2-negative advanced/metastatic breast cancer. *Breast Cancer Res Treat* 2017; 166: 167–177.

21. Gianni L, Arcangeli V, Gianni C, et al. Everolimus-exemestane (EE) vs palbociclib-fulvestrant (PF) or abemaciclib-fulvestrant (AF) or everolimus-fulvestrant (EF) in the treatment of metastatic HR+, HER2- metastatic breast cancer and prior aromatase inhibitors treatment. An indirect comparison with netwoork meta-analysis [abstract]. Paper presented at 2017 San Antonio Breast Cancer Symposium, December 5–9, 2017; San Antonio, TX. Abstract no. P3-11-05.

22. Bachelot T, McCool R, Duffy S, et al. Comparative efficacy of everolimus plus exemestane versus fulvestrant for hormone-receptor-positive advanced breast cancer following progression/recurrence after endocrine therapy: a network meta-analysis. *Breast Cancer Res Treat* 2014; 143: 125–133.

23. Dean JL, Thangavel C, McClendon AK, et al. Therapeutic CDK4/6 inhibition in breast cancer: key mechanisms of response and failure. *Oncogene* 2010; 29: 4018–4032.

24. Michaloglou C, Crafter C, Siersbaek R, et al. Combined inhibition of mTOR and CDK4/6 is required for optimal blockade of E2F function and long-term growth inhibition in estrogen receptor-positive breast cancer. *Mol Cancer Ther* 2018; 17: 908–920.

25. Zahng J, Xu K, Liu P, et al. Inhibition of Rb phosphorylation leads to mTORC2-mediated activation of akt. *Mol Cell* 2016; 62: 929–942.

26. Kalinsky K, Mundi PS, Chiuusan C, et al. A randomized phase II trial of fulvestrant with or without ribociclib after progression on aromatase inhibition plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastatic hormone receptor positive, HER2 negative breast cancer. *J Clin Oncol* 2017; 35(Suppl. 5): Abstract TPS1112.

27. Bardia A, Hurvitz S, Yardley DA, et al. TRINITI-1: Ribociclib + everolimus (EVE) + exemestane (EXE) triplet combination in men or postmenopausal women with HR+, HER2- advanced breast cancer (ABC) following progression on a cyclin-dependent kinase (CDK) 4/6 inhibitor [abstract]. Paper presented at 2016 San Antonio Breast Cancer Symposium, December 6-10, 2016; San Antonio, TX. Abstract no. OT2-01-05.