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Letter to Editor

Dynamics of Sequencing of Cyclin-Dependent Kinase Inhibitors and Cost Expenditure Analysis in the Management of Metastatic Hormone-Receptor Positive, Human Epidermal Growth Factor 2-Negative Advanced Breast Cancer

Sir,

Hormonal manipulation constitutes the backbone of management of advanced hormone-receptor-positive (HR+) breast cancer. The availability of cyclin-dependant kinase (CDK) 4/6 inhibitors has led to significant improvements in the outcome of this population. Palbociclib, ribociclib, and abemaciclib are now approved as first-line therapy for HR+ advanced breast cancer in combination with aromatase inhibitors (AIs) in postmenopausal women. Randomized Phase 3 trials have shown a significant increase in progression-free survival (PFS) of around 9–10 months when compared with anti-estrogen therapy alone when used in endocrine-naive patients [Table 1].[1-4] When used in the second-line setting, the PFS gain is in the range of 6–7 months. The overall survival (OS) gain of 7 months (statistically nonsignificant) in the PALOMA 3 study could not answer the question of optimal sequencing of CDK 4/6 inhibitors, as 18% of patients received subsequent CDK 4/6 inhibitors in placebo arm.[5] Thus, we have a situation of an effective drug that can be sequenced in both the frontline and second-line settings, with no definitive evidence to suggest that a particular strategy of sequencing produces a definite survival benefit. To add to the clinician's dilemma, there are data from the FALCON trial which bring out single-agent fulvestrant as another treatment option in the endocrine-naive setting.[6] In addition, a recent publication highlights improved PFS and OS with a combination of fulvestrant plus anastrozole.[7] The subsequent lines could never be evidence based after that as there is no data on how AI + CDK4/6 inhibition will work after exposure to fulvestrant. Thus, it is likely that the recommendations of use in first line will remain the same in future.

In this scenario, comparison of treatment costs can guide us to assess the optimal strategy in developing countries with resource limitations. In India, majority of the health-care expense is borne out of pocket by the patient, and further, the proportion of patients who present with metastatic disease is significantly higher than that in the Western population. Abemaciclib is not yet available in this region. In India, the monthly cost of ribociclib is INR ₹51,600 (USD 739) and palbociclib is INR ₹67,857 (USD 971) as on December 31, 2018. The direct cost comparison of palbociclib and ribociclib with median PFS benefit in months is depicted in Figure 1a and b. The costs of hospital visits, investigations, and hospitalizations are excluded. Per-day cost of these drugs is depicted in Figure 2. As per companies' compassionate access program after compulsory 10 cycles of palbociclib and 12 cycles of ribociclib consumption, these medicines are supplied at free of cost till disease progression or unacceptable toxicity. Presuming

Table 1: Summary of Phase 3 trials of cyclin-dependant kinase 4/6 inhibitors in metastatic hormone-positive breast cancer

Trial	*n* (randomization)	Sequence of treatment	Treatment	Median PFS (months)	HR	*P*
PALOMA 2 (postmenopausal only)	666 2:1	First line	Palbociclib + letrazole versus letrazole	24.8 versus 14.5	0.58 (0.46-0.72)	<0.001
PALOMA 3 (premenopausal - 21%)	521 2:1	Second line	Fulvestrant + palbociclib versus fulvestrant + placebo	11.2 versus 4.6	0.46 (0.36-0.59)	<0.000
MONALESSA 7 (premenopausal only)	672 1:1	First line	Ribociclib versus tamoxifen/ letrazole + goserelin	23.8 versus 13	0.55 (0.44-0.69)	<0.0001
MONALESSA 3 (postmenopausal)	484 2:1	First and second (48.8%)	Ribociclib + fulvestrant versus fulvestrant	20.5 versus 12.8	0.59 (0.48-0.73)	<0.001
MONALESSA 2 (postmenopausal)	668 2:1	First	Ribociclib + letrazole versus letrazole	25.3 versus 16	0.58 (0.45-0.70)	Log rank $P=9.63\times10^{-8}$
MONARCH 3 (postmenopausal)	493	First	Abemaciclib + AI versus anastrozole/letrazole	Median NR versus 14.7	0.54 (0.41-0.72)	0.004
MONARCH 2 (postmenopausal)	669 2:1	First	Abemaciclib + fulvestrant versus fulvestrant	16.4 versus 9.3	0.55 (0.44-0.68)	<0.001

PFS – Progression-free survival; HR – Hazard ratio; AI – Aromatase inhibitor; NR – Not reported

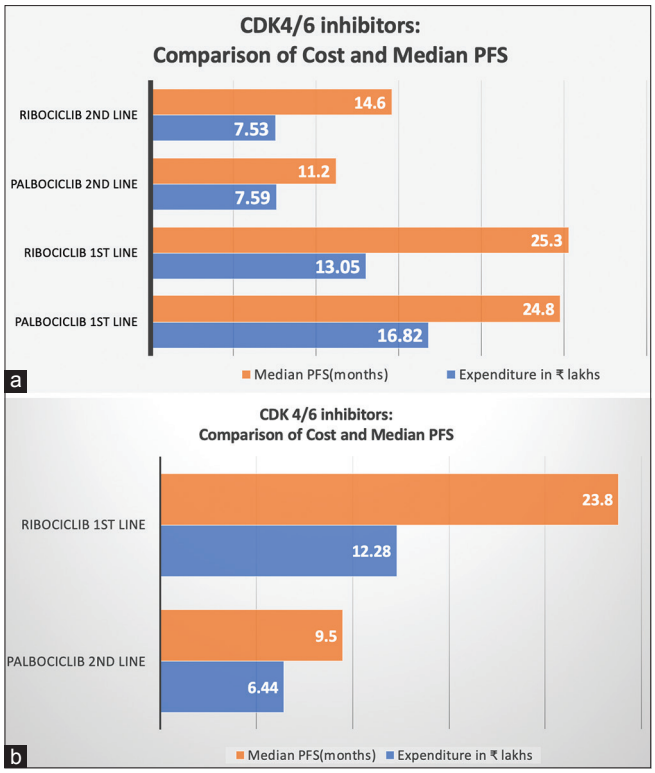

Figure 1: (a) Cyclin-dependent kinase 4/6 inhibitors in postmenopausal metastatic breast cancer: Comparison of cost and median progression-free survival. (b) Cyclin-dependent kinase 4/6 inhibitors in premenopausal metastatic breast cancer: comparison of cost and median progression-free survival

that the two molecules are equi-efficacious and equi-toxic and the reduction of dose/interruption of therapy due to toxicity is similar, for 10 and 12 cycles of palbociclib and ribociclib, the expenditures are ₹678,570 and ₹619,200, respectively.

In palliative setting, treatment is continued indefinitely till progression. Thus, if two ways of sequencing therapies generate equivalent overall outcomes, a strategy which uses any expensive drug for a shorter duration should be the clear winner. While the first-line use of CDK antagonists leads to an unprecedented PFS of 2 years with apparent better quality of life and psychological benefit to the patients, it involves the use of an expensive drug for a median duration of around 2 years, which significantly escalates the total cost of therapy. The National Institute for Health and Care Excellence has approved the first-line use of palbociclib and ribociclib with a caveat of cost agreement.[8,9] On the other hand, second-line use has a major advantage in terms of reduced costs [Figure 1a and b]. Further, endocrine resistance was present in 21.3% (111/521) of cases in the PALOMA 3 study, a subgroup where CDK inhibitor use was found to be ineffective in terms of improving survival. These patients may also be considered for fulvestrant alone or in a combination of exemestane and everolimus as the second-line regimen. Although it may be wise to choose exemestane + everolimus in this difficult set of patients,

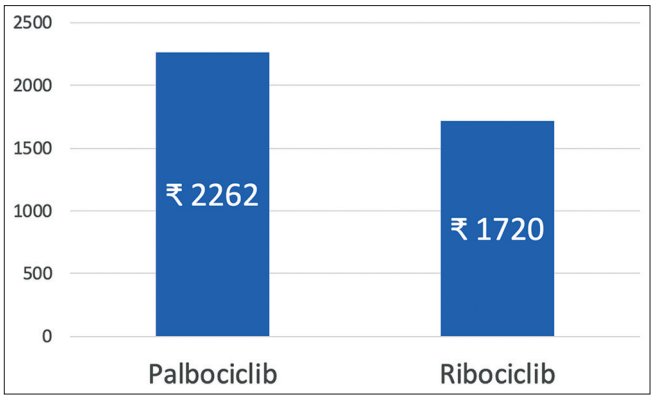

Figure 2: Cyclin-dependent kinase 4/6 inhibitors – per-day expenditure

using this regimen indiscriminately as a cheaper option in the hormone-naive population may be counterproductive and may jeopardize survival, as there is some evidence to suggest that CDK 4/6 inhibition works poorly after mammalian target of rapamycin (mTOR) inhibitors, not to mention the increased toxicity concerns with mTOR inhibitors.[10]

The scientific evidence pertaining to CDK 4/6 inhibitors has created a challenging situation for health-care providers for optimizing the sequence of CDK 4/6 inhibitors. The financial aspects are important for any health-care system. When the treatment is out of pocket, placing CDK 4/6 inhibitors in the second line will definitely reduce the financial toxicity across the world, especially in resource-limited countries.

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Conflicts of interest

There are no conflicts of interest.

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