Use of CDK4/6 inhibitors in the treatment of Metastatic Breast Cancer: "Is the cost worth it?"

Health Technology Assessment in India (HTAIn)
Postgraduate Institute of Medical Education & Research, Chandigarh

Policy Brief

Executive Summary:

Breast cancer is the most prevalent cancer among women all over the world. Nearly, 13.3 out of per 1 lakh women die of the metastatic breast cancer (MBC) every year (1). Endocrine Therapy is the mainstay of treatment for the Hormone Receptor-positive (HR+), Human Epidermal growth factor Receptor 2-negative (HER2-) MBC.

In this analysis, we aimed to determine the cost-effectiveness of newly launched Cyclin dependent kinase-4/6 inhibitors (CDK4/6i) : Palbociclib and Ribociclib for the second-line treatment of MBC among postmenopausal Indian women. Using a Markov model, the clinical effectiveness and costs either CDK4/6i (both Ribociclib and Palbociclib) and Fulvestrant, Fulvestrant, and chemotherapy (single-agent Paclitaxel or Capecitabine) was determined. Incremental cost per QALY gained with a given treatment option was compared against the next best alternative, and assessed for cost-effectiveness.

Image source: Internet

We found that CDK4/6 inhibitors are not cost-effective in the Indian scenario even if the cost of Ribociclib and Palbociclib are reduced by 95%. In contrast, Fulvestrant offers better health outcomes at a lower cost than Paclitaxel. As compared to Capecitabine, Fulvestrant incurs an incremental cost of ₹ 16,137 ($ 220) per QALY gained, and is hence cost-effective treatment modality.

Policy Recommendations:

- From the societal perspective, we recommend that Fulvestrant monotherapy should be the treatment of choice for second-line MBC patients in India.
- We recommend Fulvestrant for standard treatment guidelines and reimbursement under national publicly funded insurance schemes.
- The use of CDK4/6 inhibitors – Ribociclib and Palbociclib is not cost-effective as per current prices.
- Use of these drugs for certain specific subgroups and subtypes should be explored and evaluated further.

Policy Brief

Background and Gap in Literature:

The introduction of targeted agents like CDK 4/6i (**Ribociclib and Palbociclib**) have added a new option in the management of HR+ HER2- MBC. Various trials have shown that use of CDK4/6i along with ET improves disease-free survival (DFS) and overall survival (OS) (2,3). However, in countries like India, it is important to determine whether the cost of treatment using CDK4/6i plus Fulvestrant is justified given the extent of treatment success, as compared to Fulvestrant alone, or the conventional chemotherapy which is currently offered to majority of the patients. Majority of the studies have either evaluated the first line therapy only, or did not include the comparison between CDK4/6i and chemotherapy. In view of the limitation of existing evidence, we undertook this study to determine the cost effectiveness of CDK4/6i (Ribociclib and Palbociclib) as compared to **Fulvestrant monotherapy** as well as **single-agent chemotherapeutic regimens** in order to determine the most cost-effective treatment modality for MBC among post-menopausal Indian women.

Aims and Objective

This policy brief addressed the policy question of whether using Ribociclib and Palbociclib for treatment of MBC would be cost-effective in the Indian context. It summarizes the results of a Economic evaluation study on various MBC treatment regimens, conducted by the HTA Resource Hub, PGIMER, Chandigarh.

Number of new cases in 2020, both sexes, all ages

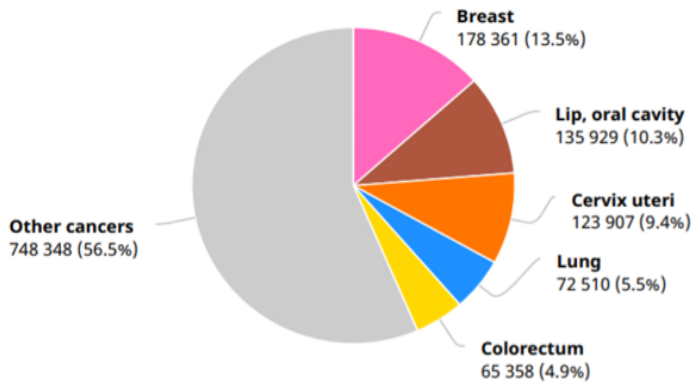

Image Source: GLOBOCON India Factsheet 2020

Treatment arms:

1. Tab. Ribociclib 600mg OD daily + Inj. Fulvestrant 500mg monthly
2. Tab. Palbociclib 125mg OD daily + Inj. Fulvestrant 500mg monthly
3. Inj. Fulvestrant 500mg monthly
4. Inj. Paclitaxel 175mg/m^2 three weekly
5. Tab. Capecitabine 1250mg/m^2 OD daily for two weeks

Methods and Approach

We undertook this cost-effectiveness analysis (CEA) using a disaggregated societal perspective, which accounted for both health system and patients' costs. We compared the combination of CDK4/6i (both Ribociclib and Palbociclib) and Fulvestrant with single-agent Fulvestrant as well as with chemotherapy (Paclitaxel and Capecitabine) respectively. Our methodological principles are consistent with the Indian reference case for conducting economic evaluations used by the agency for Health Technology Assessment in India (HTAIn).

The analysis was performed under the following components:

1. **Markov model** was developed in Microsoft Excel to estimate the lifetime costs and consequences (in terms of Quality Adjusted Life-years (QALYs)* and Life-years). The model consisted of three mutually exclusive health states: Progression-free survival (PFS), Progressive disease (PD2) and death. A monthly cycle length based on the treatment schedules in the MONALEESA-3 trial was considered (Figure 1).
2. Costs related to the treatment and the adverse effects were estimated for all the health states. In order to obtain the Out-of-Pocket Expenditure (OOPE), the primary data was analysed from 843 MBC patients as a part **CADCQoL database** (4).
3. Transition probabilities and effectiveness parameters were obtained from the Ribociclib pivotal trial – **MONALEESA-3** and published systematic review and network meta-analysis by **Wilson et al. (2017)** (5).
4. The Quality of Life (QoL) scores were estimated from the **CADCQoL** primary data collected from 843 breast cancer patients which was then adjusted to obtain the utility scores for different health states and adverse effects.

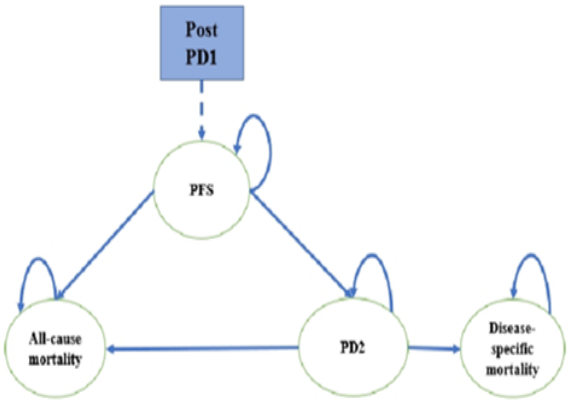

Figure 1: Schematics of the Markov state transition model. PFS: Progression-free state; PD: Progressive Disease

***Quality Adjusted Life-years:**

- QALY is a generic measure of health and is used to compare the health gains across different diseases and hence provide a uniform platform to compare effectiveness across all the different areas of healthcare.
- EQ5D is the most utilised tool worldwide to measure QoL.

Policy Brief

Results:

- The combination of Ribociclib and Fulvestrant incurs an incremental cost of ₹ 610,428 ($ 8,316) per QALY gained and the Palbociclib and Fulvestrant combination incurs an incremental cost of ₹ 385,003 ($ 5,245) per QALY gained compared to the Fulvestrant monotherapy arm which is not cost-effective at 1-time per capita GDP.
- Single-agent Paclitaxel incurs a higher cost and results in a loss of QALYs as compared to the Fulvestrant arm and is therefore dominated by Fulvestrant monotherapy.
- When compared to single-agent Capecitabine, use of Fulvestrant incurs and additional cost of ₹ 16,138 ($ 220) per QALY gained.
- Hence, Fulvestrant monotherapy is a cost-effective treatment modality for HR+ HER2- MBC patients in the Indian context.

Price Threshold Analysis

- At the current WTP threshold of one-time per capita GDP (₹ 141,225) of India, both Ribociclib and Palbociclib have a **zero probability** to be cost-effective.
- Even when the market price of Ribociclib and Palbociclib are reduced by 95%, the probability for the combination therapy to be cost-effective was estimated to be 53% and 57% respectively (Figure 2).
- When compared with single-agent Paclitaxel and Capecitabine, a 90% reduction in the price of Palbociclib and Ribociclib resulted in 95% and 99% probability of being cost-effective respectively.

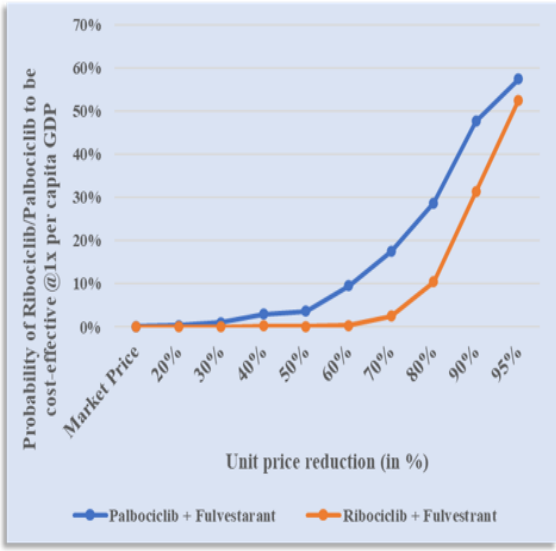

Figure 2: Price threshold analysis for Ribociclib and Palbociclib combination therapy

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