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ORIGINAL RESEARCH ARTICLE

Cost Effectiveness of Ribociclib and Palbociclib in the Second-Line Treatment of Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer in Post-Menopausal Indian Women

Nidhi Gupta[1] · Dharna Gupta[2] · Jyoti Dixit[2] · Nikita Mehra[3] · Ashish Singh[4] · Manjunath Nookala Krishnamurthy[5,12] · Gaurav Jyani[2] · Kavitha Rajsekhar[6] · Jayachandran Perumal Kalaiyarasi[3] · Partha Sarathi Roy[7] · Prabhat Singh Malik[8] · Anisha Mathew[8] · Pankaj Malhotra[9] · Sudeep Gupta[10,12] · Lalit Kumar[8] · Amal Kataki[11] · Shankar Prinja[2]

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Abstract

Background In this study, we evaluate the cost and outcomes of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) plus fulvestrant, fulvestrant alone, and conventional chemotherapy as the second-line therapy for hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) metastatic breast cancer (MBC) in India.

Methods Using a Markov model, the clinical effectiveness of managing HR+, HER2− MBC in postmenopausal women with either a CDK4/6i (either ribociclib or palbociclib) and fulvestrant, fulvestrant alone, and chemotherapy (single-agent paclitaxel or capecitabine) was measured in terms of quality-adjusted life-years (QALYs). The costs were estimated from two different points of view: scenario I, as per the prevailing market prices of the drugs; and scenario II, as per the reimbursement rates set up by the publicly financed national health insurance scheme. Incremental cost per QALY gained with a given treatment option was compared against the next best alternative and was assessed for cost effectiveness using a threshold of 1-time the per capita gross domestic product (GDP) in India from a societal perspective.

Results In scenario I, an MBC patient was found to incur a lifetime cost of Indian Rupees (₹) 2.54 million ($34,644), ₹2.53 million ($34,496), ₹512,598 ($6,984), ₹326,026 ($4,442) and ₹237,115 ($3,230) for the ribociclib and palbociclib combination arms, fulvestrant monotherapy, single-agent paclitaxel and the single-agent capecitabine treatment arms, respectively. The lifetime cost for CDK4/6i (ribociclib and palbociclib) combination therapy, fulvestrant monotherapy, paclitaxel, and capecitabine arms was estimated to be ₹1.94 million ($26,459), ₹1.92 million ($26,220), ₹315,387 ($4,296), ₹187,392 ($2,553) and ₹153,263 ($2,088), respectively, in scenario II. The mean QALYs lived per MBC patient with CDK4/6i (either ribociclib or palbociclib) combination therapy, fulvestrant, paclitaxel and capecitabine were estimated to be 1.4, 1.0, 0.9 and 0.7, respectively. None of the treatment arms are cost effective at current prices and reimbursement rates at a threshold of 1-time the per capita GDP of India. However, a 78% reduction in the current market price or a 72% reduction in the reimbursement rate of fulvestrant in the government-funded insurance program will make it a cost-effective treatment option for HR+, HER2− MBC patients in India.

Conclusion CDK4/6i (ribociclib and palbociclib) therapy is not a cost-effective treatment option for MBC patients. A 72% reduction in the reimbursement rate for fulvestrant monotherapy will make it a cost-effective treatment option in the Indian context.

1 Introduction

Breast cancer is the most prevalent cancer among women worldwide. It is estimated that nearly 2.4 million new cases of cancer and 623,000 deaths were attributed to breast cancer among Indian women in 2018 [1]. The age-adjusted incidence and mortality rates are as high as 25.8/100,000 and 13.3/100,000 women in India, respectively [2, 3].

✉ Shankar Prinja
shankarprinja@gmail.com

Extended author information available on the last page of the article

Key Points for Decision Makers

The combination of CDK4/6 inhibitors (ribociclib and palbociclib) and endocrine therapy (fulvestrant) has proven to improve survival outcomes among hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer patients.

In this study, we evaluated the cost effectiveness of ribociclib/palbociclib combination therapy, fulvestrant monotherapy, single-agent paclitaxel and single-agent capecitabine in the Indian context from two different point of views: scenario I, as per the prevailing market prices of the drugs; and scenario II, as per the reimbursement rates set up by the publicly financed national-level health insurance scheme.

The use of ribociclib/palbociclib is not a cost-effective treatment option in the Indian context. A 78% and 72% reduction in the price of fulvestrant monotherapy in both scenarios, respectively, is required to make it the most cost-effective treatment option for MBC patients in India.

Unfortunately, 20–25% of breast cancer patients in India present with upfront metastatic disease [4]. Among patients with metastatic breast cancer (MBC), hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) breast cancer is the most common subtype [4, 5]. Endocrine therapy (ET) is the mainstay of management of HR+, HER2− MBC.

HR+, HER2− MBC is considered to be an incurable disease with treatment aimed at increasing the patient's lifespan and maintaining a good quality of life [6, 7]. The median overall survival (OS) is reported as 36 months [8, 9]. The National Cancer Grid (NCG) and Indian Council of Medical Research (ICMR), as well as the top-most panel of oncologists in India, recommend the use of ET with or without targeted therapies for HR+, –HER2− MBC, with chemotherapy being reserved for patients with visceral crisis [10–12]. First-line ET among postmenopausal women predominantly consists of tamoxifen or aromatase inhibitors (AIs) with or without cyclin dependent kinase-4/6 inhibitors (CDK4/6i) [10], while in second-line therapy, the treatment options vary from the use of fulvestrant as a single agent, fulvestrant in combination with CDK4/6i, or AIs in combination with mammalian target of rapamycin (mTOR) inhibitors [10]. However, due to the high costs associated with these agents, the majority of patients in India have to resort to chemotherapy [13].

The introduction of targeted agents such as CDK 4/6i (ribociclib, palbociclib, and abemaciclib) have added another option for the management of HR+, HER2− MBC. Various trials have shown that the use of CDK4/6i along with ET in this subset of MBC patients improves disease-free survival (DFS) and OS [14–17]. With various available options, the treatment of HR+, HER2− MBC is personalized in the developed world based on prior ET received, severity of the disease (visceral crisis), and the adverse effects (AEs) profile of the drug, influencing the quality of life among these patients with limited survival. However, in developing and low-income countries such as India, in addition to the factors discussed above, cost becomes paramount for decision making with newer expensive agents such as CDK 4/6i [18, 19].

Ayushman Bharat-Pradhan Mantri Jan Aarogya Yojana (AB-PMJAY) [48], the flagship health insurance scheme of the government of India, aims to reduce the financial hardship and catastrophic expenditure associated with cancer treatment in India. Treatment options such as single-agent paclitaxel, single-agent capecitabine and fulvestrant have been added as part of the scheme's Health Benefit Package (HBP) [20]. Therefore, it is necessary to assess these packages designed by experts from the perspective of cost effectiveness so as to make value-based policy decisions.

Few studies have assessed the cost effectiveness of CDK4/6i; however, a majority of the studies have evaluated first-line therapy only, while none have assessed the comparison between CDK4/6i and chemotherapy [21–24]. Furthermore, a majority of the studies have not included updated DFS and OS rates from recent updated clinical trials [21, 22, 24]. In view of the limitation of existing evidence, we undertook this study to determine the most cost-effective treatment strategy for second-line treatment of HR+, HER2− MBC among postmenopausal women in India.

2 Materials and Methods

2.1 Overview of the Analysis

We undertook this cost-effectiveness analysis (CEA) using the societal perspective to determine the most cost-effective treatment strategy in the second-line setting for HR+, HER2− MBC patients in India, taking into consideration two different points of views: (1) as per the prevailing market and procurement prices (scenario I: market price scenario); and (2) as per the reimbursement rates set up by the national-level health insurance scheme in India (scenario II: publicly financed health insurance scenario) (Table 1) [20]. The lifetime costs and consequences of the combination of CDK4/6i (both ribociclib and palbociclib) and fulvestrant, single-agent fulvestrant and chemotherapy: single-agent injection

paclitaxel and single-agent oral capecitabine, respectively, were calculated using standardized methods. The incremental cost-effectiveness ratios (ICERs) were compared against the next best alternative. 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) [25]. We used the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist to report our findings [26].

2.2 Model Structure

A Markov model was developed in Microsoft Excel (Microsoft Corporation, Armonk, NY, USA) to estimate the lifetime costs and consequences among 1000 hypothetical patients (Fig. 1). 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 [14, 27].

After the failure of first-line therapy, the patient enters the model in the PFS health state, where they receive the treatment. Subsequently, the patient can either stay in the PFS health state or progress to PD2 or die. Patients in the PD2 health state remain in that health state until death. Subsequent treatment for the PD2 health state comprised chemotherapy or hormone therapy, or best supportive care. Disease-specific mortality was assumed to occur for the PD2 health state only, while all patients in both the PFS and PD2 health states were assumed to die due to all-cause mortality. The patient enters the model at 50 years of age, which is the median age of presentation of breast cancer in India [28].

Table 1 Description of the two scenarios

Scenario	Scenario name	Description	Cost assumptions	Effects
I	Market price scenario	As per the prevailing market prices of the drugs and treatment in the Indian context	• Market prices and procurement prices for all treatment arms • OOPE: direct non-medical expenditure (including user/procedure fees) for OPD consultation and day-care visits • Diagnostics: CGHS reimbursement rates	• LYs • QALYs
II	Publicly financed health insurance scenario	From the point of view of the publicly financed national health insurance program	• Reimbursement rates as per ABPM-JAY HBP • Direct non-medical expenditure for OPD consultation and day-care visit	• LYs • QALYs

OOPE out-of-pocket expenditure, *LYs* life-years, *QALYs* quality-adjusted life-years, *OPD* Out-patient Department, *CGHS* Central Government Health Scheme, *ABPM-JAY* Ayushman Bharat Pradhan Mantri Jan Aarogya Yojana, *HBP* health benefit package

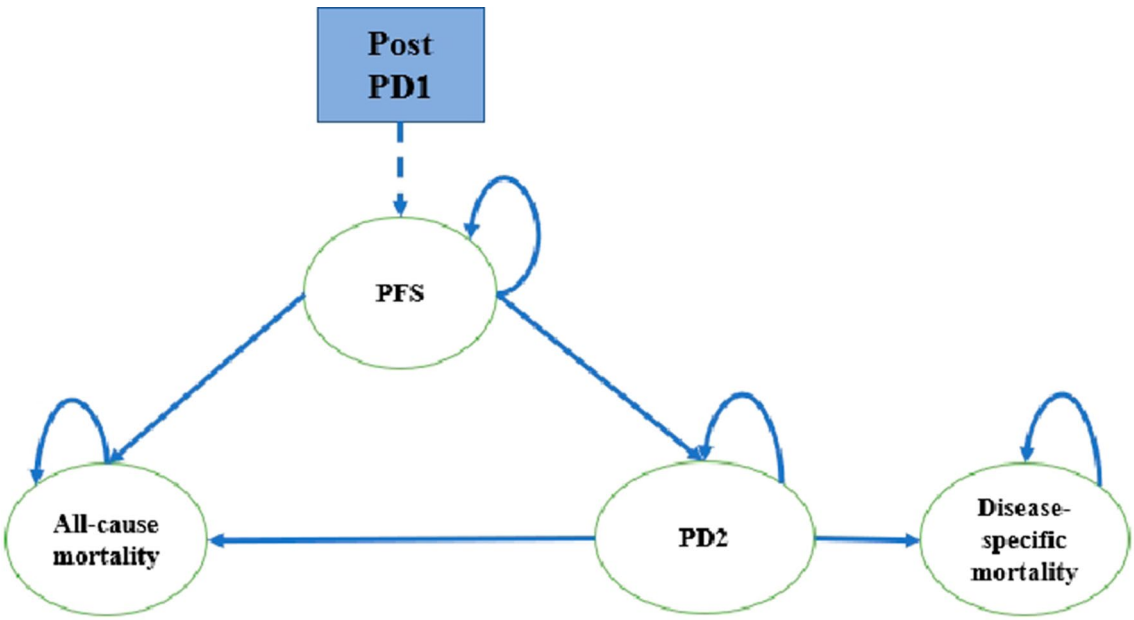

Fig. 1 Schematic of the Markov state transition model. *PFS* progression-free survival, *PD* progressive disease

All future costs and outcomes were discounted at a rate of 3% [25].

2.3 Treatment Scenarios

Five treatment scenarios were modeled: (1) ribociclib (600 mg/day orally on days 1–21 in a 28-day cycle) plus fulvestrant (500 mg intramuscularly on day 1 of each 28-day cycle, with an additional dose on day 15 of cycle 1); (2) palbociclib (125 mg/day orally on days 1–21 in a 28-day cycle) plus fulvestrant (500 mg intramuscularly on day 1 of each 28-day cycle, with an additional dose on day 15 of cycle 1); (3) fulvestrant 500 mg intramuscularly on days 1 and 15 of cycle 1, followed by 500 mg on day 1 of a 28-day cycle and (4) paclitaxel 175 mg/m^2 three-weekly; and (5) capecitabine 1250 mg/m^2 orally for a 2 weeks on/1 week off cycle. The latter two chemotherapy arms were simulated to make the analysis mimic the real-world situation as very few people are able to afford the high cost associated with CDK4/6i in India [13].

2.4 Cost of Treatment of Metastatic Breast Cancer

The costs were estimated from a societal perspective for all treatment arms; however, in this analysis, we did not take into account the productivity losses incurred by the patients and their caregivers due to the cancer treatment. This is in concurrence with the reference case guidelines to undertake economic evaluation by India's HTA agency [25].

In scenario I, we took into account the prevailing market prices for the different treatment arms in the PFS and PD2 health states. The cost of treatment in the PFS state included drug acquisition costs, cost of drug administration (inpatient/day-care), direct out-of-pocket expenditure (OOPE; including travel, board/lodgings, food, user fees, informal payment, and other) per outpatient department (OPD) consultation, recurrent investigations, and the management of grade 3/4 AEs (Table 2). Locally published studies and existing national health system cost databases were used to elicit the unit health system cost of services provided to patients in the PFS and PD2 health states, including the outpatient consultation, day-care visits, and hospitalization [29, 30]. Scenario II included reimbursement rates and direct non-medical expenditure (excluding user fees) (Table 2) in the PFS state. The reimbursement rates set up under the ambit of national publicly funded health insurance—Ayushman Bharat Pradhan Mantri Jan Aarogya Yojana (ABPM-JAY)—were applied, which includes the cost of the drugs, administration costs (day-care and OPD visits), supportive care, and routine follow-up [31]. A detailed description of the two scenarios is given in Table 1.

Separate incidence rates for grade 3–4 AEs were applied for the intervention and comparator arms using the published literature (electronic supplementary Table 1) [27, 32]. MONALEESA-3 and PALOMA-3 trial data were used to determine the incidence of AEs in the ribociclib and palbociclib arms, respectively [14, 15]. The costs were applied separately in each cycle using the treatment protocol obtained from subject experts and standard treatment guidelines [12].

A similar methodology was applied in the PD2 health state for both scenarios. The cost of out-patient consultation, routine laboratory and diagnostic tests, third-line therapy, best supportive care, and end-of-life hospitalization were included in scenario I, while for scenario II, the reimbursement rates and direct non-medical expenditure for third-line therapy were modeled. Third-line treatment included chemotherapy (either paclitaxel or capecitabine for the other three arms), hormone therapy, and palliative care (electronic supplementary Appendix I). It was assumed that third-line treatment (chemotherapy and hormone therapy) will be administered to PD2 patients for an average of 6 months, after which all patients were provided with best supportive care/palliative care till death.

The OOPE component was derived from primary data collected from 843 breast cancer patients, including 105 MBC cases, across six Indian states [33]. The data was analyzed to compute direct non-medical expenditure (travel, food, board/lodgings, informal payment, others, etc.) and user fees/procedure charges incurred on outpatient consultation, per bed-day hospitalization, and per day-care visit. The expenditure incurred on drugs was computed using procurement rates of the Medical Services Corporation in Rajasthan state [34] and treatment protocols based on expert opinion and standard treatment guidelines [12]. For the diagnostic services in scenario I, we used the provider payment rates under the Central Government Health Scheme (CGHS), a publicly financed national insurance scheme [35]. All costs are reported in Indian National Rupee (₹) and converted to US dollars (US$) using an exchange rate of US$1 = ₹73.4, for the years 2020–2021 [36].

2.5 Valuation of Consequences

The outcomes were assessed in terms of both life-years (LYs) and quality-adjusted life-years (QALYs). The transition rates of a patient moving from the PFS to PD2 health state in the ribociclib arm were obtained from the subgroup analysis reported among second-line HR+, HER2− MBC patients [14]. For palbociclib, we assumed a similar transition probability from the PFS to PD2 health state, based on evidence from a recently published network meta-analysis [32] and consultation with expert oncologists. Furthermore, due to the absence of any clear-cut subgroup analysis in the PALOMA-3 trial [15], we assumed similar efficacy for both palbociclib and ribociclib. The rates were converted to monthly transition probabilities using standard methods

Table 2 Cost parameters for assessing the cost effectiveness of CDK4/6 inhibitor combination therapy

Input cost parameter	Scenario I Unit cost in ₹ (US$)	Scenario II Cost per cycle in ₹ (US$)	Source	Distribution
Drug costs/reimbursement rates				
Ribociclib tablet 600 mg	4,357 (59)	4,357 (59)	Market price	γ
Palbociclib tablet 125 mg	4,286 (58)	4,286 (58)	Market price	γ
Fulvestrant injection 500 mg	15,840 (215)	12,000 (163)	Market price; [20]	γ
Paclitaxel injection 280 mg	684 (9)	11,800[a] (161)	Market price; [20]	γ
Capecitabine tablet 500 mg	12.48 (0.2)	7,400[a] (101)	Market price; [20]	γ
Tamoxifen tablet 20 mg	1.6 (0.02)	1,200[a] (16)	Market price; [20]	γ
Letrozole tablet 2.5 mg	3.4 (0.04)	3,900[a] (53)	Market price; [20]	γ
Exemestane tablet 25 mg	43 (0.6)	3,900[a] (53)	Market price; [20]	γ
Anastrozole tablet 1 mg	7.6 (0.1)	3,900[a] (53)	Market price; [20]	γ
Loperamide tablet	0.18 (0.002)	0.18 (0.002)	[34]	γ
ORS pouches	2.02 (0.03)	2.02 (0.03)	[34]	γ
Emset tablet 4 mg	0.145 (0.002)	0.145 (0.002)	[34]	γ
Cremaffin syrup	83.8 (1.1)	83.8 (1.1)	[37]	γ
Ibuprofen tablet	1.0 (0.01)	1.0 (0.01)	[34]	γ
GCSF injection 300 µg	89.9 (1.2)	89.9 (1.2)	[34]	γ
Paracetamol tablet 650 mg	0.73 (0.01)	0.73 (0.01)	[37]	γ
Cefipine injection 2 g	275 (3.7)	275 (3.7)	[37]	γ
Amikacin injection 750 mg	26.1 (0.3)	26.1 (0.3)	[34]	γ
Fluconazole tablet 150 mg	1.12 (0.01)	1.12 (0.01)	[34]	γ
Ciplox tablet 500 mg	1.24 (0.02)	1.24 (0.02)	[34]	γ
Udiliv tablet 200 mg	6.7 (0.09)	6.7 (0.09)	[34]	γ
Pyridoxine tablet 100 mg	1.33 (0.02)	1.33 (0.02)	[34]	γ
Amlodipine tablet 5 mg	0.1 (0.01)	0.1 (0.01)	[34]	γ
Augmentin tablet 625 mg	3.89 (0.05)	3.89 (0.05)	[34]	γ
Gabapentin tablet 300 mg	0.97 (0.013)	0.97 (0.013)	[34]	γ
Betadine mouthwash	184 (2.5)	184 (2.5)	[34]	γ
Mucopain ointment	51 (0.7)	51 (0.7)	[34]	γ
Metformin tablet 500 mg	0.23 (0.003)	0.23 (0.003)	[34]	γ
Lasilactone tablet 20 mg	2.54 (0.03)	2.54 (0.03)	[34]	γ
Megastrol syrup 800 mg	12.7 (0.17)	12.7 (0.17)	[34]	γ
Omeprazole tablet 20 mg	0.31 (0.004)	0.31 (0.004)	[34]	γ
Celecoxib tablet 200 mg	6.16 (0.08)	6.16 (0.08)	Market price	γ
Tramadol tablet 50 mg	0.37 (0.005)	0.37 (0.005)	[34]	γ
Morphine tablet 10 mg	6 (0.08)	6 (0.08)	[34]	γ
Health system cost				
Outpatient consultation	266.2 (3.6)	Included in the reimbursement costs	Unpublished data	γ
Day-care visit	1,038 (14.1)		[30]	γ
Bed-day hospitalization	1,439 (19.6)		Unpublished data	γ
Out-of-pocket expenditure (OOPE)				
Per outpatient consultation	3,905[b] (53)	1,844[c] (25)	Primary data	γ
Per day-care visit	4,279[b] (58)	1,854[c] (25)	Primary data	γ
Per episode of hospitalization	9,637[b] (131)	9,637[b] (131)	Primary data	γ
Cost of diagnostics (reimbursement rates)				
Complete blood count	135 (1.8)	Included in the reimbursement costs	[35]	γ
Liver/renal function tests	225 (3.1)		[35]	γ
Serum electrolytes (Na, K, Ca, P, Mg)	370 (5)		[35]	γ
Electrocardiogram	50 (0.68)		[35]	γ

Table 2 (continued)

Input cost parameter	Scenario I Unit cost in ₹ (US$)	Scenario II Cost per cycle in ₹ (US$)	Source	Distribution
Echocardiography	1,200 (16)		[35]	γ
CECT chest/abdomen	4,500 (61)		[35]	γ
Chest x-ray	60 (0.8)		[35]	γ
Urine routine/microscopy	35 (0.5)		[35]	γ
Urine culture	50 (0.7)		[35]	γ
Blood culture	100 (1.4)		[35]	γ
Sputum gram staining	150 (2)		[35]	γ

₹ Indian Rupees, *US$* US dollars, *OOPE* out-of-pocket expenditure, *ORS* oral rehydrating solution, *GCSF* granulocyte-colony stimulating factor, *CECT* contrast-enhanced computed tomography

[a]Total reimbursement cost (6 cycles: paclitaxel and capecitabine; 20 cycles: tamoxifen; 21 cycles: letrozole; 3-monthly: exemestane and anastrozole)

[b]Including the OOPE on travel, food, user fees, boarding/lodging, informal payments, and others (excluding the drugs and diagnostics)

[c]Including OOPE on travel, food, boarding/lodging, informal payments and others (excluding the user fees, drugs and diagnostics)

[38]. We also accounted for time-dependent risk in the model. In the case of the chemotherapy arms, the transition rates were adjusted using hazard ratios obtained from a systematic review comparing the CDK4/6i with various chemotherapeutic regimens [39]. Age-specific all-cause mortality rates from each health state were obtained from the Sample Registration System (SRS) life tables [40]. The disease mortality rate for the PD2 health state in the fulvestrant-alone arm was obtained from published Indian literature [41] and adjusted using the hazard ratios obtained from the MONALEESA-3 trial to obtain the probability of dying due to breast cancer for the intervention arm (Table 3) [14].

Baseline utility values were obtained from the National Cancer Database for Cost and Quality of Life (CaDCQoL) primary data collected from 843 breast cancer patients across India, consisting of a subset of 105 MBC patients [33]. Patients were administered the EQ-5D-5L tool to measure health-related quality of life (HRQoL). The Indian tariff values were used to calculate the index utility score, which was considered as a base value [25]. This base value was then used to compute the utility scores for different health states (PFS and PD2) and AEs (hematological and non-hematological) using the gradient obtained from the published literature (Table 3) [42]. We used the data on the proportion of patients who reported having AEs to determine the utility for each type of AE (electronic supplementary Appendix I).

The comparative cost effectiveness was assessed in terms of incremental cost per QALY gained.

2.6 Sensitivity and Threshold Analyses

A probabilistic sensitivity analysis (PSA) was undertaken to test parameter uncertainty. The probability of CDK4/6i being cost effective was assessed at a willingness to pay (WTP) threshold equal to the per capita gross domestic product (GDP) as per the guidelines for HTA in India [25, 43]. The per capita GDP of India was considered to be ₹141,493 (US$1,927) for the years 2020–2021 [44].

For undertaking PSA, we used gamma distribution for parameters related to cost, and beta distribution for parameters related to risk of complications, OS, and utility scores. For the remaining parameters, we used uniform distribution to simulate random values. The upper and lower bounds were computed from the standard error estimated in the primary data, or estimates provided in the literature. Wherever the upper and lower bounds were not available, we assumed a variation of 20% on either side of the base estimate for clinical parameters, and 30% variation for risk of mortality and treatment patterns, and 50% for cost parameters. The Monte Carlo method was used for simulating the results, and the number of iterations were restricted to 10,000 times. The median was computed along with the 2.5th and 97.5th percentile to estimate the 95% confidence interval (CI).

A dominance analysis was undertaken in which each treatment arm was compared against the next best alternative to assess the comparative cost effectiveness between various scenarios. Due to the high cost of CDK4/6i in India, we undertook multiple PSAs at different price levels for ribociclib and palbociclib, in order to assess the probability of a combination of CDK4/6i and ET to be cost effective, at different price reduction levels in the Indian context.

A univariate price threshold analysis was also undertaken at various prices for different treatment arms so as to determine the price at which a particular treatment is cost effective at a WTP threshold of one times the per capita GDP (₹141,493) for India.

Table 3 Monthly input parameters used in estimating effectiveness of treatment arms

Input variables	Ribociclib + fulvestrant	Palbociclib + fulvestrant	Fulvestrant	Paclitaxel	Capecitabine	Distribution	Source
Clinical parameters							
Average proportion of patients with non-hematological AEs	0.806	0.824	0.992	0.754	0.962	β	[14, 32]
Average proportion of patients with hematological AEs	0.194	0.176	0.008	0.246	0.038	β	[14, 32]
Transition probabilities							
PFS to PD2 (0–2 months)	0.107	0.107	0.133	0.218	0.382	β	[14, 39]
PFS to PD2 (2–4 months)	0.057	0.057	0.103	0.117	0.204	β	[14, 39]
PFS to PD2 (4–6 months)	0.024	0.024	0.030	0.049	0.086	β	[14, 39]
PFS to PD2 (6–8 months)	0.051	0.051	0.075	0.105	0.183	β	[14, 39]
PFS to PD2 (8–10 months)	0.035	0.035	0.068	0.072	0.126	β	[14, 39]
PFS to PD2 (10–12 months)	0.058	0.058	0.128	0.118	0.206	β	[14, 39]
PFS to PD2 (12–14 months)	0.060	0.060	0.106	0.124	0.217	β	[14, 39]
PFS to PD2 (14–16 months)	0.059	0.059	0.055	0.120	0.210	β	[14, 39]
PFS to PD2 (16–18 months)	0.033	0.033	0.041	0.067	0.117	β	[14, 39]
PFS to PD2 (18–20 months)	0.078	0.078	0.044	0.159	0.278	β	[14, 39]
PFS to PD2 (20–22 months)	0.034	0.034	0.183	0.070	0.123	β	[14, 39]
PFS to PD2 (22–24 months)	0.083	0.083	0.074	0.170	0.297	β	[14, 39]
PFS to PD2 (24–26 months)	0.017	0.017	0.074	0.035	0.062	β	[14, 39]
PFS to PD2 (26–28 months)	0.036	0.036	0.183	0.074	0.130	β	[14, 39]
PFS to PD2 (28–30 months)	0.019	0.019	0.183	0.040	0.070	β	[14, 39]
PFS to PD2 (30–32 months)	0.030	0.030	0.065	0.062	0.109	β	[14, 39]
PFS to PD2 (32–34 months)	0.066	0.066	0.065	0.135	0.236	β	[14, 39]
PFS to PD2 (34–36 months)	0.189	0.189	0.345	0.385	0.673	β	[14, 39]
PFS to PD2 (36–38 months)	0.161	0.161	0.345	0.329	0.575	β	[14, 39]
PFS to PD2 (38–40 months)	0.312	0.312	0.423	0.636	0.575	β	[14, 39]
PFS to PD2 (40–42 months)	0.333	0.333	0.423	0.680	0.575	β	[14, 39]
PFS to PD2 (42 months onwards)	0.293	0.293	0.423	0.598	0.575	β	[14, 39]
PD2 to death due to the disease (50 years)	0.034	0.034	0.046	0.025	0.025	β	[14, 28, 41]
PD2 to death due to the disease (51 years)	0.034	0.034	0.046	0.059	0.059	β	[14, 28, 41]
PD2 to death due to the disease (52 years)	0.034	0.034	0.046	0.053	0.053	β	[14, 28, 41]
PD2 to death due to the disease (53 years)	0.034	0.034	0.046	0.071	0.071	β	[14, 28, 41]
PD2 to death due to the disease (54 years onwards)	0.034	0.034	0.046	0.187	0.187	β	[14, 28, 41]
Utility values							
Post-progression PD1 (base value)	0.659	0.659	0.659	0.659	0.659	β	Primary data
PFS (without AEs)	0.773	0.773	0.773	0.773	0.773	β	[42]
PFS (non-hematological AEs)	0.671	0.692	0.671	0.667	0.661	β	[32, 42]
PFS (hematological AEs)	0.590	0.588	0.579	0.579	0.579	β	[32, 42]
PD2	0.246	0.246	0.246	0.246	0.246	β	(42)

PFS progression-free state, *PD* progressive disease, *AEs* adverse events

3 Results

3.1 Cost and Outcomes

In scenario I, we estimated that an MBC patient incurs a lifetime cost of ₹2.54 million ($34,644) and ₹2.53 million ($34,496) when treated with a combination of ribociclib plus fulvestrant and palbociclib plus fulvestrant, respectively (Table 4). The lifetime costs incurred by an MBC patient were estimated to be ₹512,598 ($6,984), ₹326,026 ($4,442), and ₹237,115 ($3,230) when treated using fulvestrant

Table 4 Per person lifetime cost and health outcomes for all treatment arms

Outcome variable	Ribociclib + fulvestrant (95% CI)	Palbociclib + fulvestrant (95% CI)	Fulvestrant alone (95% CI)	Single-agent paclitaxel (95% CI)	Single-agent capecitabine (95% CI)
LYs Undiscounted Discounted	3.9 (3.2–4.7) 3.6 (3.0–4.2)	3.9 (3.3–4.7) 3.6 (3.0–4.2)	2.8 (2.3–3.4) 2.6 (2.2–3.1)	2.3 (2.1–2.5) 2.2 (2.0–2.4)	2.1 (1.9–2.3) 2.0 (1.8v2.2)
QALYs Undiscounted Discounted	1.6 (1.3–1.8) 1.4 (1.2–1.7)	1.6 (1.3–1.9) 1.5 (1.3–1.7)	1.1 (0.9–1.3) 1.0 (0.9–1.2)	0.9 (0.8–1.0) 0.87 (0.7–0.99)	0.71 (0.61–0.82) 0.7 (0.6–0.8)
Total lifetime cost (in ₹): scenario I Undiscounted Discounted	2,653,862 (1,946,873–3,612,050) 2,542,859 (1,859,251–3,461,113)	2,642,607 (1,973,980–3,508,313) 2,531,980 (1,895,996–3,364,063)	536,581 (445,950–722,315) 512,598 (426,125–683,620)	339,826 (281,041–411,967) 326,026 (270,106–394,357)	248,132 (193,236–318,061) 237,115 (185,296–303,147)
Total lifetime costs (in ₹): scenario II Undiscounted Discounted	2,027,361 (1,394,949–2,861,491) 1,942,108 (1,332,396–2,745,553)	2,009,228 (1,387,397–2,816,556) 1,924,593 (1,319,656–2,709,734)	332,286 (248,631–440,525) 315,387 (236,517–414,602)	196,276 (155,886–248,035) 187,392 (149,308–235,997)	160,890 (120,481–214,372) 153,263 (115,165–203,459)

CI confidence interval, *LY* life-years, *QALYs* quality-adjusted life-years, ₹ Indian Rupees

monotherapy, single-agent paclitaxel, and single-agent capecitabine, respectively.

In scenario II, we estimated that an MBC patient incurs a lifetime cost of ₹1.94 million ($26,459), ₹1.92 million ($26,220), ₹315,387 ($4,296), ₹187,392 ($2,553), and ₹153,263 ($2,088) when treated using ribociclib plus fulvestrant, palbociclib plus fulvestrant, fulvestrant monotherapy, single-agent paclitaxel, and single-agent capecitabine, respectively (Table 4).

An MBC patient treated with CDK 4/6i (either ribociclib or palbociclib and fulvestrant) combination therapy, fulvestrant monotherapy, paclitaxel, and capecitabine has an overall mean survival of 3.6, 2.6, 2.2, and 2.0 LYs respectively. After factoring in quality of life, this would translate to 1.4, 1.0, 0.9, and 0.7 QALYs, respectively.

3.2 Cost Effectiveness

The combination of ribociclib and fulvestrant was dominated by the combination of palbociclib and fulvestrant for both scenarios (Table 5). The combination of palbociclib and fulvestrant incurs an incremental cost of ₹4.85 million ($66,131) and ₹3.9 million ($52,698) per QALY gained compared with fulvestrant monotherapy for scenarios I and II, respectively, which is not cost effective at the current WTP threshold of one times the per capita GDP (₹141,493) of India. Therefore, at a threshold of one times the per capita GDP (₹141,493), the use of both ribociclib and palbociclib is not a cost-effective treatment modality in the Indian context.

In scenario I, single-agent paclitaxel is a non-dominated treatment strategy that incurs an incremental cost of ₹505,732 ($6,890) compared with single-agent capecitabine, which is not cost effective at the current WTP threshold of one times the per capita GDP (₹141,493) of India. Similarly, fulvestrant monotherapy offers better health outcomes at an incremental cost of ₹963,208 ($13,123) per QALY gained compared with single-agent paclitaxel. In scenario II, single-agent paclitaxel is a non-dominated strategy and offers better health outcomes than single-agent capecitabine at an incremental cost of ₹194,127 ($2,519) per QALY gained, which is nearly 1.3 times the WTP threshold of India. Finally, fulvestrant monotherapy incurs an incremental cost of ₹660,797 ($9,003) per QALY gained compared with single-agent paclitaxel.

3.3 Sensitivity and Threshold Analysis

At the current WTP threshold of one times the per capita GDP (₹141,493) of India, both ribociclib and palbociclib have zero probability of being cost effective in both scenarios. The probability of fulvestrant monotherapy being cost effective at a WTP threshold of one times the per capita GDP is estimated to be 2% and 3% in scenarios I and II, respectively, whereas the probability of single-agent paclitaxel being cost effective is estimated to be 0.1% and 23% in scenarios I and II, respectively.

A 95% reduction in the price of palbociclib is insufficient to make palbociclib and fulvestrant combination therapy cost effective in the Indian context at a WTP threshold of one times the per capita GDP. However, when the drug price and reimbursement rate of fulvestrant 500 mg was reduced by 78% (₹17,520–₹3,854) and 72% (₹12,000–₹3,360), respectively, it becomes a cost-effective treatment option when compared with single-agent paclitaxel at a WTP threshold of one times the per capita GDP (Fig. 2).

Table 5 Cost effectiveness of the treatment strategies for both scenarios

Treatment arms	Scenario I (as per the current market prices)			Scenario II (as per the reimbursement rates in HBP 2.0)			Interpretation
	Costs in ₹ (US$)	QALYs	Incremental cost per QALY gained (US$)	Costs in ₹ (US$)	QALYs	Incremental cost per QALY gained (US$)	
Single-agent capecitabine	237,115	0.69	–	153,264	0.69	–	ND
Single-agent paclitaxel	326,026	0.86	505,732	187,392	0.86	194,127	ND
Fulvestrant alone	512,598	1.06	963,208	315,387	1.06	660,797	ND
Palbociclib + fulvestrant	2,531,980	1.47	4,854,037	1,924,593	1.47	3,868,085	ND
Ribociclib + fulvestrant	2,542,859	1.45	–	1,942,108	1.45	–	D

HBP Health Benefit Package, ₹ Indian Rupees, US$ US dollars, *QALYs* quality-adjusted life-years, *ND* non-dominated, *D* dominated

4 Discussion

Breast cancer is a rising health problem in India with 1 in 22 women in urban India and 1 in 60 women in rural India being diagnosed with the disease [45]. A significant number of patients in India still present with locally advanced and metastatic disease [4, 46], with the incidence of HR+ tumors in India varying between 20 and 45% [4, 10, 47].

Our study assessed the most cost-effective treatment option for the second-line treatment of HR+, HER2− MBC patients in India as per the prevailing market prices (scenario I), as well as from the point of view of the national-level publicly financed health insurance schemes (scenario II). CDK4/6i is not a cost-effective treatment modality in India even if the price is significantly reduced compared with the current price in both scenarios. When the market price and reimbursement rate of fulvestrant is reduced by 78% and 72%, respectively, fulvestrant becomes a cost-effective treatment option for HR+, HER2− MBC patients in India (Fig. 2). Hence, we recommend a more than 70% reduction in the existing reimbursement rates and market prices of fulvestrant for inclusion in treatment guidelines and reimbursement under publicly funded programs.

Chemotherapy should not be the treatment of choice in HR+, HER2− MBC until endocrine resistance or visceral crisis occur. Our study recommends the use of fulvestrant (ET) for second-line treatment as it provides more favorable health outcomes than the chemotherapeutic agents. Various meta-analyses have shown that although CDK 4/6i combined with ET have superior efficacy to ET alone, their superiority to chemotherapy has not been found to be statistically significant with respect to chemotherapy. In the meta-analysis by Wilson et al., palbociclib plus fulvestrant showed statistically significant improvement in PFS relative to capecitabine, mitoxantrone, and pegylated liposomal doxorubicin, and non-statistically significant improvement in PFS relative to paclitaxel, docetaxel, and other monotherapy or combination chemotherapy agents [39].

When chemotherapy is used for HR+, HER2− MBC, single-agent chemotherapy is recommended over combination chemotherapy in view of the fewer AEs associated with single-agent chemotherapeutic regimens. Among single-agent regimens, paclitaxel and capecitabine are the most commonly used drugs. Real-world evidence shows that chemotherapy is used as first-line therapy in HR+, HER2− MBC irrespective of visceral crisis and contrary to the recommended guidelines [10]. Our analysis indicates that single-agent paclitaxel has the lowest incremental cost per QALY gained compared with all other treatment strategies in both scenarios, but it is still not a cost-effective treatment option. Fulvestrant monotherapy is the next best treatment strategy and can be cost effective at a price reduction of 78% and 72% from the point of view of scenarios I and II, respectively.

AB-PMJAY [48] also introduced the use of fulvestrant for MBC patients as part of HBP 2.0 [20]. Our analysis indicates that the reimbursement rates set up in HBP 2.0 should be revised and updated so as to make them more cost effective from both a payers' and societal perspective. This will not only increase efficiency but will also be helpful in expanding the coverage for the scheme in terms of number of beneficiaries.

4.1 Model Validation

The findings of our model are in concurrence with existing clinical and epidemiological evidence for both ribociclib and palbociclib (electronic supplementary Appendices I and II). The median OS in our model for the CDK4/6i combination arm is estimated to be 40 months, which is consistent with the estimates reported in the MONALEESA-3 (median OS = 40.2 months) and PALOMA-3 (median OS = 38 months) clinical trials [14, 15]. Furthermore, in our model, we estimated a median OS of 28 months for the fulvestrant arm, which concurs with the findings of the PALOMA-3 (median OS = 33.8 months) and MONALEESA-3 (median OS = 32.5 months) clinical trials. Another study by Vaikundaraja

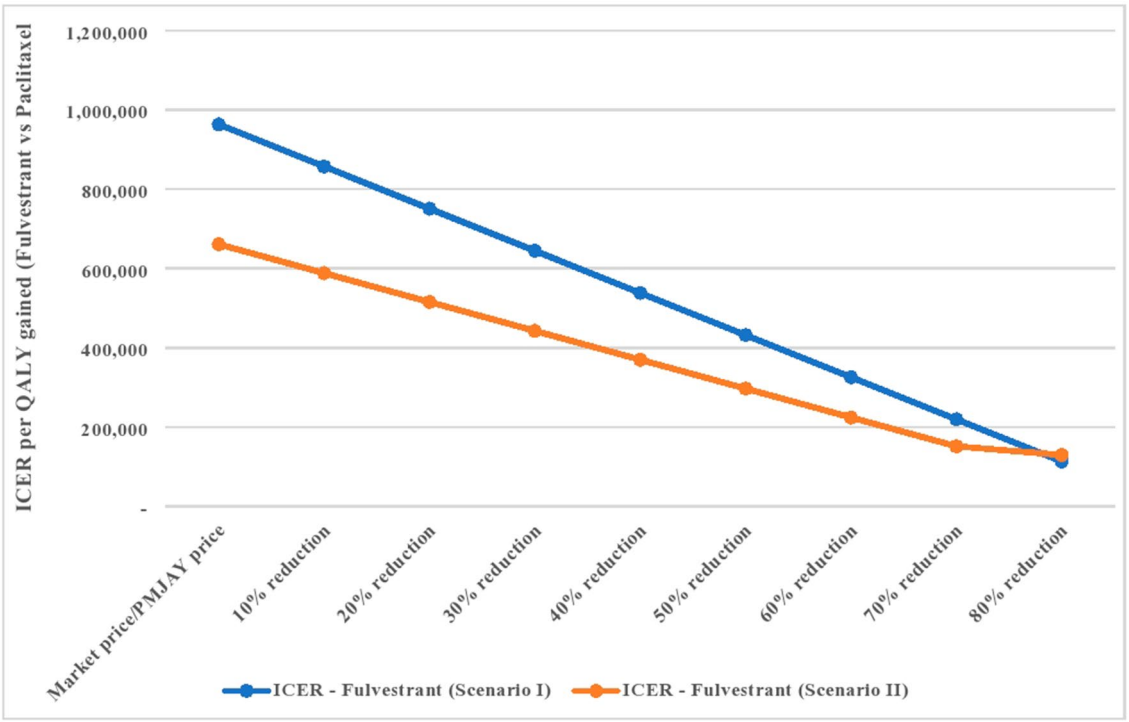

Fig. 2 Price threshold analysis for fulvestrant monotherapy. *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year

et al. reports a median OS of 21 months (95% CI 8.9–33.1) for fulvestrant patients [49, 50]. Therefore, our results are very much in line with the existing real-world evidence in the Indian context. The study by Agrawal et al. reported a median PFS of 12 months among second-line palbociclib patients, whereas our model estimated a median PFS of 13 months in the CDK4/6i (both ribociclib and palbociclib) combination therapy arms [50]. Compared with a median PFS of 10 months reported for fulvestrant monotherapy among Indian women, we estimated the median PFS in the fulvestrant arm to be 9 months [49].

Our study findings report lower QALYs compared with LYs for cancer treatment, which is in line with the findings published by other model-based evaluations of cancer treatment in the Indian context [30, 51, 52]. We estimated an incremental gain of 0.44 and 0.45 QALYs for ribociclib and palbociclib combination therapy, respectively, compared with fulvestrant monotherapy, which is in line with the findings reported by Yang et al. (0.47 incremental QALYs) [21]. The incremental gain of 1.1 LYs concurs with a recently published Canadian study that reported a gain of 1.19 incremental LYs for the ribociclib combination arm [53]. Yang et al. and Mamiya et al. also reported that CDK4/6i (ribociclib and palbociclib) are unlikely to be cost effective at the current prices of these drugs [21, 54]. Studies such as those by Mistry et al. [22] and Suri et al. [23] from a US and UK payer perspective, as well as Stellato et al. from a Canadian perspective [53], also report cost-effectiveness ratios which show that CDK4/6i in combination with letrozole is not a cost-effective treatment modality at their respective country-specific WTP thresholds.

4.2 Strengths and Limitations

We would like to highlight a few strengths of our study. First, our study is the first to report the cost effectiveness of treatment modalities for HR+, HER2− MBC patients in the Indian context from two distinct points of view (market prices and reimbursement rates). Second, we took into account all possible treatment options to make the analysis as robust as possible. Third, we have also incorporated the costs as well as the QoL associated with AEs due to cancer treatment. Fourth, we used the survival data from the published Indian literature to make the results as generalizable as possible, and lastly, we obtained the OOPE estimates from the primary data collected as a part of an ongoing multicentric study for assessing the economic burden and HRQoL among cancer patients in India [33]. The OOPE estimated in our primary data analysis is in line with the average medical expenditure reported in the National Sample Survey Organisation's (NSSO) 75th round [55]. Similarly, the share of OOPE is consistent with other studies reporting costs incurred due to cancer treatment in India [56–58]. We also took into account two of the most common

CDK4/6i currently being used in India, i.e. ribociclib and palbociclib. Abemaciclib was not included in this study as it was unavailable in the Indian market at the time of conceptualization of the study.

However, there are certain limitations of this analysis. First, this study does not look into specific subgroups within HR+, HER2− MBC patients, such as patients with endocrine resistance, prior disease-free interval, visceral metastases, and bone-only metastases, etc., which might help guide us to a more favorable patient population in whom these drugs may be more effective; however, we do not currently have robust data for such subgroup analysis. Second, we did not take into account the cost of grade 1–2 AEs, which might have slightly underestimated the costs; however, given the fact that CDK4/6i are not cost effective, the inclusion of such costs would have further strengthened our conclusions. Lastly, we also did not take into account the indirect costs due to loss of productivity incurred by both patients and caregivers. This was in agreement with Indian HTA guidelines [25], and also to avoid duplication [59].

5 Conclusion and Policy Implications

From the point of view of prevailing market prices (scenario I) and the reimbursement rates set-up under HBP 2.0 (scenario II), none of the treatment scenarios for second-line postmenopausal HR+, HER2− MBC patients are cost effective in the Indian context. We recommend a reduction in the market prices and reimbursement rates for fulvestrant monotherapy to ensure its use represents value for money. Future research should focus on identifying clinical markers such as endocrine resistance, prior disease-free interval, visceral metastases, bone-only metastases, brain metastases, tumor grade, progesterone receptor status, performance status, and age, etc., as well as molecular markers that point towards the inherent uncertainty regarding the cost effectiveness of CDK4/6i therapy, which should be further evaluated.

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Declarations

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Conflict of interest Sudeep Gupta has participated in research projects sponsored by Pfizer, Novartis, and Eli Lilly for which research funding was provided by these companies to his institution. Nidhi Gupta, Dharna Gupta, Jyoti Dixit, Nikita Mehra, Ashish Singh, Manjunath Nookala Krishnamurthy, Gaurav Jyani, Kavitha Rajsekhar, Jayachandran Perumal Kalaiyarasi, Partha Sarathi Roy, Prabhat Singh Malik, Anisha Mathew, Pankaj Malhotra, Lalit Kumar, Amal Kataki, and Shankar Prinja declare no conflicts of interest.

Availability of data and material (data transparency) The datasets generated and/or analyzed during the current study are available from the corresponding author on request.

Code availability (software application or custom code) The code that supports the findings of this study is available from the corresponding author on request.

Ethical approval The study protocol was approved by the Institutional Ethics Committee of the Post Graduate Institute of Medical Education and Research, Chandigarh, India (IEC-03/2020-1565).

Consent to participate Written informed consent was obtained from all study participants.

Consent for publication Not applicable.

Author contributions Study conception: SP, NG, DG and JD. Study design: NG, DG, SP and JD. Analysis: DG, JD, NG and SP. Writing (first draft): DG, NG and SP. Writing (review and editing): All authors.

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Authors and Affiliations

Nidhi Gupta[1] · Dharna Gupta[2] · Jyoti Dixit[2] · Nikita Mehra[3] · Ashish Singh[4] · Manjunath Nookala Krishnamurthy[5,12] · Gaurav Jyani[2] · Kavitha Rajsekhar[6] · Jayachandran Perumal Kalaiyarasi[3] · Partha Sarathi Roy[7] · Prabhat Singh Malik[8] · Anisha Mathew[8] · Pankaj Malhotra[9] · Sudeep Gupta[10,12] · Lalit Kumar[8] · Amal Kataki[11] · Shankar Prinja[2]

1 Department of Radiation Oncology, Government Medical College and Hospital, Chandigarh, India

2 Department of Community Medicine and School of Public Health, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

3 Department of Medical Oncology, Adyar Cancer Institute, Chennai, Tamil Nadu, India

4 Department of Medical Oncology, Christian Medical College, Vellore, Tamil Nadu, India

5 Department of Clinical Pharmacology, Tata Memorial Centre, Mumbai, Maharashtra, India

6 Department of Health Research, Ministry of Health and Family Welfare, New Delhi, India

7 Department of Medical Oncology, Dr. B. Booroah Cancer Institute, Guwahati, Assam, India

8 Department of Medical Oncology, All India Institute of Medical Sciences (AIIMS), New Delhi, India

9 Department of Internal Medicine, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

10 Department of Medical Oncology, Tata Memorial Centre, Mumbai, Maharashtra, India

11 Department of Gynaecologic Oncology, Dr. B. Booroah Cancer Institute, Guwahati, Assam, India

12 Homi Bhabha National Institute, Mumbai, Maharashtra, India