COST-EFFECTIVENESS ANALYSIS AND VALUE BASED PRICING OF ANTICANCER DRUGS IN INDIA

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Executive summary

The present research work includes cost-effectiveness analysis of targeted therapies (crizotinib and ceritinib) as compared to pemetrexed-based chemotherapy in patients with newly diagnosed advanced/metastatic non-small cell lung cancer (NSCLC), and cost-effectiveness analysis of enzalutamide for treatment intensification for metastatic hormone-sensitive prostate cancer (mHSPC) patients in India.

The former study estimated that Crizotinib and Ceritinib offer higher health gains as compared to chemotherapy, however, the high additional health gain is not cost-effective in the Indian context. Nearly 92% and 81% reduction in the price of ceritinib and crizotinib respectively, is required to make it a cost-effective treatment option for ALK and ROS1-positive NSCLC. Therefore, targeted therapies should be included in India's publicly financed health insurance scheme at the recommended value-based prices. Institutional structures for strategic purchasing and price negotiation should be established.

The second analysis aimed to determine the most cost-effective drug for treatment intensification for mHSPC patients in India. Androgen-deprivation therapy is the mainstay of treatment for newly-diagnosed metastatic hormone-sensitive prostate cancer (mHSPC) patients. However, the intensification of treatment with either docetaxel or novel anti-androgens (NAA) (abiraterone-acetate plus prednisone (AAP), enzalutamide and apalutamide) is being recommended based on the improved clinical outcomes and quality-of-life among patients. This study aimed to determine the most cost-effective drug for treatment intensification for mHSPC patients in India.

A Markov model was developed with 4 health states: Progression-free survival, progressive disease, best supportive care, and death. Lifetime costs and consequences were estimated for 4 treatment sequences: AAP-first, enzalutamide-first, apalutamide-first, and docetaxel-first. Incremental cost per quality adjusted life year (QALY) gained with a given treatment option was compared against the next best alternative and assessed for cost-effectiveness using a willingness to pay (WTP) threshold of 1 x per capita gross domestic product (GDP) in India.

We estimated that the total lifetime cost per patient was ₹ 1,367,454 (US$ 17,487), ₹ 2,168,885 (US$ 27,735), ₹ 7,678,501 (US$ 98,190), and ₹ 1,358,746 (US$ 17,375) in the AAP-first, enzalutamide-first, apalutamide-first, and docetaxel-first treatment sequence, respectively. The

mean QALYs lived per patient were 4.78, 5.03, 3.22, and 2.61, respectively. AAP-first sequence incurs an incremental cost of ₹ 4,014 (US$ 51) per QALY gained as compared to the docetaxel-first sequence, with a 87% probability of being cost-effective at the WTP threshold of 1 x per-capita GDP of India. The use of AAP-first also incurs an incremental net monetary benefit (NMB) of ₹ 396,491 (US$ 5,070) as compared to the docetaxel-first treatment sequence. Nearly 48% reduction in the price of enzalutamide is required to make it a cost-effective treatment sequence as compared to AAP-first in India.

As a whole, we concur with the inclusion of standard dose AAP in India's publicly financed health insurance scheme for intensification of treatment in mHSPC as it is the only cost-effective sequence among the various NAA when compared to docetaxel-first treatment sequence. Furthermore, a systematic reduction in the price of enzalutamide would further help to improve clinical outcomes among mHSPC patients.

Chapter I: Economic Evaluation of Targeted Therapies for ALK- and ROS1-Fusion Positive Non-Small Cell Lung Cancer in India

Abstract

Background: Targeted therapies, such as crizotinib and ceritinib (both standard and low dose), have shown promising results in treating non-small cell lung cancer (NSCLC) with specific oncogenic drivers like Anaplastic Lymphoma Kinase (ALK) and c-ros (ROS1) oncogene etc. This study aims to assess the cost-effectiveness of these therapies for patients with NSCLC in India.

Methods: The Markov model consisted of three health states: Progression-free survival (PFS), progressive disease (PD) and death. Lifetime costs and consequences were estimated for three treatment arms: Crizotinib, Ceritinib and chemotherapy for patients with ALK- and ROS1-positive NSCLC. Incremental cost per QALY gained with crizotinib and ceritinib was compared to chemotherapy and assessed using a willingness to pay (WTP) threshold of 1-time per capita gross domestic product in India.

Results: The total lifetime cost per patient for ALK-positive NSCLC was ₹ 332,456 ($ 4,054), ₹ 1,284,100 ($ 15,659) and ₹ 2,337,779 ($ 28,509) in the chemotherapy, crizotinib and ceritinib arms respectively. The mean QALYs lived per patient was 1.20, 2.21 and 3.34, respectively. For patients with ROS1-positive NSCLC, the total cost was ₹ 323,011 ($ 3,939) and ₹ 1,763,541 ($ 21,507) for chemotherapy and crizotinib, with mean QALYs lived per patient of 1.16 and 2.73, respectively. Nearly 92% and 81% reduction in the price of ceritinib and crizotinib is required to make it a cost-effective treatment option for ALK- and ROS1-positive NSCLC, respectively.

Conclusion: Our study findings suggest that the prices of ceritinib and crizotinib need to be reduced significantly to justify their value for inclusion in India's publicly financed health insurance scheme for treatment of patients with locally advanced/ metastatic ALK- and ROS1-positive NSCLC, respectively.

Introduction

Lung cancer accounts for 5.9% and 11.7% of all cancer cases, and 8.1% and 18% of cancer deaths in India and the world respectively [1]. Nearly 70% of patients with lung cancer in India present with locally advanced and metastatic disease [2] with adenocarcinoma being the predominant histology.

With the development of precision oncology, the determination of targetable oncogenic drivers in NSCLC such as epidermal growth factor receptor (EGFR) mutations, or the anaplastic lymphoma kinase (ALK) and c-ros oncogene (ROS1) rearrangements has become important. The prevalence of EGFR mutations and ALK rearrangements is approximately 30% and 10%, respectively. Similarly, the prevalence of ROS1 rearrangement is reported between 2.82 – 4.1% [3–5]. ALK inhibitors like crizotinib, ceritinib and lorlatinib have shown promise in treating patients with ALK-positive advanced/metastatic NSCLC [6–8]. However, treatment options for ROS1-positive disease are limited, crizotinib is a promising ALK inhibitor for ROS1-positive NSCLC. Molecular testing and the targeted drugs are expensive and inaccessible to the majority of patients in LMICs [9]. Targeted drugs like crizotinib and ceritinib can cost nearly ₹ 40,000 - ₹ 50,000 a month in the Indian setting. In the absence of targeted therapy, treatment of patients with ALK and ROS1-positive advanced/metastatic NSCLC is typically limited to cytotoxic chemotherapy regimens. In view of the above, economic evaluation becomes necessary to guide decision-makers about treatment choice, resource allocation and value for money [10]. Therefore, we undertook this analysis to determine the cost-effectiveness of crizotinib and ceritinib for treatment of newly diagnosed advanced/metastatic NSCLC and harbouring either ALK- or ROS1 gene rearrangement.

Methodology

Overview of the analysis

A Markov model was developed in Microsoft Excel to evaluate the lifetime costs and outcomes of treating patients with newly diagnosed advanced/metastatic NSCLC (patients with metastases at presentation or those who progress or recur after previous definitive therapy) and harbouring either ALK- or ROS1- gene rearrangement. ALK inhibitors, Crizotinib and Ceritinib were compared with pemetrexed-based platinum doublet chemotherapy followed by maintenance single agent pemetrexed until disease progression in patients with advanced/metastatic NSCLC (Supplementary Appendix). The methodological principles of the

economic evaluation are consistent with the Indian reference case for conducting economic evaluations used by the agency for Health Technology Assessment in India (HTAIn) [11].

Markov model structure

The model consists of three different health states: Progression-free survival (PFS), progressive disease (PD) and death (including all-cause mortality and disease-specific mortality) (Figure 1). A patient with newly diagnosed NSCLC with either ALK- or ROS1- gene rearrangement will undergo first-line treatment in the PFS health state. The PD health state involves second-line therapy after progression. The second-line therapy continues for 6 cycles or 4 months, after which all the patients receive the best supportive care. A lifetime horizon (15-years) and a monthly cycle length were considered for this analysis. A discount rate of 3% was applied for future costs and outcomes [11].

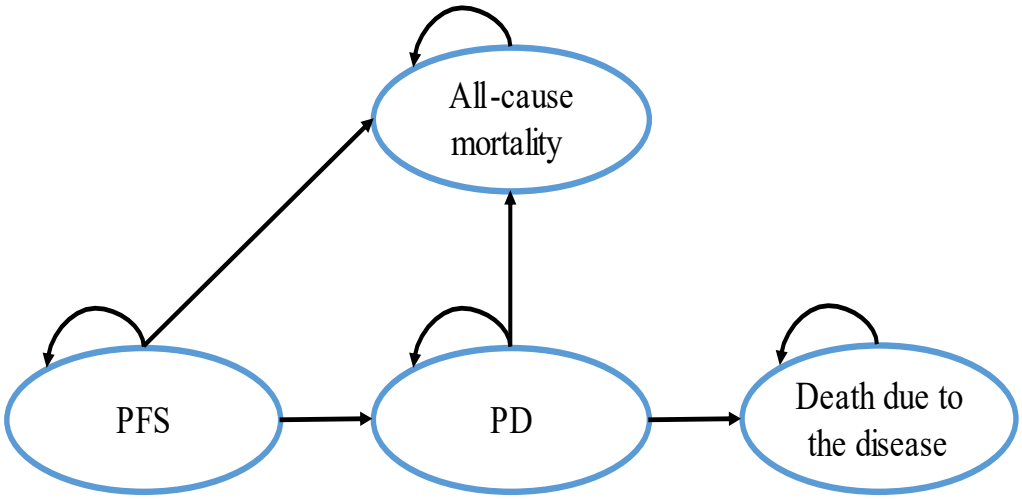

Figure 1: Markov model to determine the most cost-effective treatment option for NSCLC

Valuation of consequences

The health benefits for each treatment arm were measured in terms of life-years (LYs) and quality-adjusted life-years (QALYs). Treatment efficacy for the first-line treatment with Crizotinib and pemetrexed-based chemotherapy was obtained from the published PROFILE-1014 clinical trial for patients with ALK positive NSCLC [8]. For the ceritinib arm, the hazard ratio for the PFS health state was obtained from published systematic reviews and meta-analyses comparing crizotinib and ceritinib [10]. For patients with ROS1 positive NSCLC, the Kaplan-Meier PFS curves from different clinical studies were pooled, given the comparable eligibility criteria and baseline patient characteristics in the two studies [12,13]. The probability of

patients in the PFS state was estimated using the standard extrapolation technique derived by Guyot et al. (2012) [14]. In this method, the reported PFS curves were digitized using web-based software to extract the survival data to generate pseudo-individual patient-level data, and was then fit to standard parametric models (exponential, Weibull, Gompertz, lognormal and log-logistic), and the suitable survival distribution selected for each curve based on the goodness of fit (Akaike Information and Bayesian Information Criterion) and visual inspection [14] (Figure S1-S2). The age-specific risk of all-cause mortality was obtained from the Indian Sample Registration system lifetables [15]. Disease-specific mortality was obtained from published clinical literature [16] (Table 1).

The utility values for the PFS & PD health states, and impact of treatment-related adverse effects were obtained from the primary data collected from 521 patients with advanced/metastatic NSCLC as a part of the larger multi-centric 'National Cancer Database for Costs and Quality of Life (CADCQoL)' study [17]. To estimate the quality of life (QoL) scores associated with each health state, Indian tariff values were utilized [18]. The data on the decrement in the utility value due to the occurrence of different adverse effects reported in the literature [6,8,12,13] (Table S1 & S2) was health state utility derived from the CADCQoL database [17] (Table 1).

Table 1: Input parameters to determine the effectiveness of the different treatment arms

Input variable	Parameter (95% CI)	Distribution	Source
Median age of presentation of NSCLC in India	50 years	-	[9]
Discount Rate	3%	Beta	[30]
PFS function parameters (For ALK-positive group)			
Chemotherapy	• Shape: 0.04 (0.02 – 0.06) • Scale: 0.42 (0.29 – 0.55)	Weibull	[8]
Crizotinib	• Shape: 2.39 (2.19 – 2.60) • Scale: 0.15 (0.008 – 0.30)	Lognormal	[8]
PFS function parameters (For ROS1 positive group)			
Chemotherapy	• Shape: 2.02 (1.87 – 2.17)	Loglogistic	[12,13]

	• Scale: -0.32 [(-0.47) – (-0.17)]		
Crizotinib	• Shape: 2.96 (2.67 – 3.24) • Scale: 0.14 (-0.07 – 0.35)	Loglogistic	[12,13]
Disease-specific mortality			
Probability to die among PD patients (Chemotherapy)	0.064 (0.045 – 0.083)	Beta	[50]
Probability to die among PD patients (Crizotinib and Ceritinib)	0.032 (0.022 – 0.042)	Beta	[32]
Age-specific mortality			
46-50	0.00045 (0.00036 – 0.00054)	Beta	[15]
51-55	0.00072 (0.00057 – 0.00087)	Beta	[15]
56-60	0.001 (0.0008 – 0.0013)	Beta	[15]
61-65	0.0016 (0.0013 – 0.002)	Beta	[15]
66-70	0.0025 (0.002 – 0.003)	Beta	[15]
71-75	0.0039 (0.003 – 0.005)	Beta	[15]
76-80	0.0059 (0.0045 – 0.0073)	Beta	[15]
80+	0.009 (0.007 – 0.012)	Beta	[15]
Utility values			
Utility score for PFS state (with AEs)	0.672 (0.538 – 0.806)	Beta	Primary data
Utility score for PFS state (without AEs)	0.704 (0.563 – 0.845)	Beta	Primary data
Utility score for PD state	0.496 (0.397 – 0.595)	Beta	Primary data

NSCLC: Non-small cell lung cancer; PFS: Progression-free survival; PD: Progressive disease; AE: Adverse events; LL: Lower limit; UL: Upper Limit

Cost of treatment of NSCLC

The cost of treatment of NSCLC was estimated using an abridged societal perspective. We didn't consider the indirect expenditure incurred by the patients and their caregivers. This aligns with the guidance for base case analysis as per the Indian reference case for HTA [11]. The treatment and supportive care regimen for all the arms, along with the management of AEs, were obtained from the published clinical protocols [19,20] and stakeholder consultations for each health state. For the crizotinib and ceritinib treatment arms, drug costs, direct patient out-of-pocket (OOP) expenditure per out-patient department (OPD) consultation (including travel, boarding/lodging, food, informal payment, and user fees), management of grade 3-4 AEs, and the cost of routine follow-up was included. Routine follow-up cost includes the cost per outpatient consultation, laboratory investigations and diagnostic tests. For the chemotherapy treatment and its subsequent maintenance arm, the reimbursement rates under AB – PMJAY were used [21]. The reimbursement rates include the drug acquisition and administration costs and the management cost of acute adverse events [21]. The direct non-medical OOP expenditure (excluding user fees) incurred on OPD consultations, diagnostic and laboratory investigations, and follow-up was incorporated. Separate incidence rates for each grade 3-4 AEs and their management cost were applied for all the arms using the published literature (Table S1 & S2; Supplementary Appendix).

Health system costs of outpatient consultation and day-care visits for PFS and PD patients were derived using data from published studies [22,23] and the nationally representative 'National Health System Cost Database'(NHSCD) [24]. The estimates on OOP expenditure were derived from primary data collected from 521 patients with advanced/metastatic NSCLC [17]. The data were analysed to compute both direct medical and non-medical expenditures. We used the reimbursement rates [21], market prices [25] and procurement rates of the Rajasthan Medical Service Corporation [26] for estimating expenditures on drugs. For the diagnostic services, we used the provider payment rates from the social health insurance scheme for central government employees in India i.e., Central Government Health Scheme [27] [Table 2]. All costs are reported in Indian National Rupee (₹) and converted to United States Dollar ($) using an exchange rate of 1$ = ₹ 82 for the year 2023 [28].

Table 2: Input cost parameters

Input Parameter	Cost per cycle in ₹ (Min-Max)	Cost per cycle in US$ (Min-Max)	Distribution	Source
Monthly cost of the drugs				
Crizotinib 250mg bottle (60 capsules)	42,000 (21,000 – 63,000)	512 (256 – 767)	Gamma	Market price
Ceritinib 150mg bottle (150 capsules)	42,000 (21,000 – 63,000)	512 (256 – 767)	Gamma	Market price
Inj. Pemetrexed 500 mg/m2 + Inj. Carboplatin AUC 5	10,125 (5062 - 15187)	123 (62 – 185)	Gamma	[21]
Inj. Pemetrexed 500/m^2	7,612 (3,806 – 11,419)	93 (46 – 139)	Gamma	[51]
Inj. Zoledronic Acid 4mg	3,500 (1,750 – 5,250)	43 (21 – 64)	Gamma	[21]
Inj. Denosumab 120mg	18,000 (9,000 – 27,000)	219 (110 – 329)	Gamma	Market price
Conventional radiotherapy – Brain, Bone, Lung	11,000 (5,500 – 16,500)	134 (67 – 201)	Gamma	[21]
SBRT – Brain, Bone, Lung	82,000 (41,000 – 123,000)	999 (499 – 1,498)	Gamma	[21]
Out-of-Pocket Expenditure (OOPE)				
Per Out-patient consultation*	2,823 (2,435 – 3,211)	34 (30 – 39)	Gamma	Primary data
Per Out-patient consultation**	2,413 (2,084 – 2,742)	29 (25 – 33)	Gamma	Primary data
Cost of diagnostic tests				
Molecular testing: IHC	1,500 (750 – 2,250)	18 (9 – 27)	Gamma	[52]
Molecular testing: FISH	5,000 (2,500 – 7,500)	61 (30 – 91)	Gamma	[52]
PET scan	21,000 (10,500 – 31,500)	256 (128 – 384)	Gamma	CGHS rate list [27]
Bone scan	3,500 (1,750 – 5,250)	43 (21 – 64)	Gamma	CGHS rate list [27]
CT scan (Chest, Abdomen and Pelvis)	6,945 (3,472 – 10,417)	85 (42 – 127)	Gamma	CGHS rate list [27]
MRI Brain	3,450 (1,725 – 5,175)	42 (21 – 63)	Gamma	CGHS rate list [27]
CECT Brain	1,350 (675 – 2025)	16 (8 – 25)	Gamma	CGHS rate list [27]

Biopsy	1,725 (862 – 2,587)	21 (10 – 31)	Gamma	[52]
MRI (Abdomen and Pelvis)	5,000 (2,500 – 7,500)	61 (30 – 91)	Gamma	CGHS rate list [27]
Complete Blood count	138 (69 – 207)	2 (1 – 3)	Gamma	CGHS rate list [27]
Renal Function Tests	261 (130 – 391)	3 (2 – 5)	Gamma	CGHS rate list [27]
Liver Function Tests	275 (137 – 412)	3 (2 – 5)	Gamma	CGHS rate list [27]
Serum electrolytes	370 (185 – 555)	5 (2 – 7)	Gamma	CGHS rate list [27]
Serum Calcium	63 (31 – 94)	1 (0.4 – 1.2)	Gamma	CGHS rate list [27]

OOPE: Out-of-Pocket Expenditure; Inj.: Injection; Tab.: Tablet; IHC: Immuno-histochemistry; FISH: Fluorescence in situ hybridisation; CGHS: Central government health scheme

** Including the OOPE on travel, user fees, boarding/lodging, food, informal payments and others (excluding the drugs and diagnostics) – direct expenditure (for crizotinib and ceritinib treatment arms)*

*** Including the OOPE on travel, boarding/lodging, food, informal payments, and others (excluding the drugs, diagnostics, and user fees) – direct non-medical expenditure (for chemotherapy treatment arm)*

The comparative cost effectiveness was assessed in terms of incremental cost per QALY gained. A WTP threshold equal to per capita gross domestic product (GDP) of India was used to assess the cost-effectiveness. The per capita GDP of India of was ₹ 185,267 (US$ 2,256.6) for the year 2021 [29].

Sensitivity and Scenario Analyses

A probabilistic sensitivity analysis (PSA) was undertaken to test parameter uncertainty. Probability of a treatment sequence to be cost effective was assessed at a WTP threshold equal to per capita GDP as per the guidelines for health technology assessment in India [30]. Under PSA, we used gamma distribution for cost parameters and beta distribution for parameters related to effectiveness, risk of complications, mortality, and utility scores. For rest of the parameters, we used uniform distribution. Model results were simulated 1000 times and median value (ICER) along 95% confidence interval was generated for base estimates using percentile method.

A univariate price threshold analysis was also undertaken at various prices for crizotinib and ceritinib to determine the price at which these are a cost-effective option at the WTP threshold of 1-time per capita GDP (₹ 185,267) for India.

A separate scenario analysis for ceritinib arm was also undertaken by altering the standard dose of 750mg daily (empty stomach) with low-dose ceritinib 450mg (low fat meal) once daily. The efficacy of low-dose ceritinib was assumed to be the same as the standard-dose as per the published clinical literature [31] and market price was used to estimate the cost of the drug.

Results

Costs and consequences

The treatment of patients with newly diagnosed ALK positive advanced/metastatic NSCLC incurred a lifetime discounted cost of ₹ 332,456 ($ 4,054), ₹ 1,284,100 ($ 15,659) and ₹ 2,337,779 ($ 28,509) in the chemotherapy, crizotinib and ceritinib arms respectively. The mean QALYs lived in each treatment arm were 1.20, 2.21 and 3.34 respectively.

Similarly, patients with ROS1 positive NSCLC incurred a lifetime cost of ₹ 323,011 ($ 3,939) and ₹ 1,763,541 ($ 21,507) for chemotherapy and crizotinib treatment arms respectively. The mean QALYs lived were 1.16 and 2.73 respectively [Table 3(a) and (b)].

Table 3 (a): Costs and Cost-effectiveness of different treatment strategies for ALK positive NSCLC in India

Treatment sequence	Total lifetime cost in ₹ (95% CI)	Total LYs (95% CI)	Total QALYs (95% CI)	ICER, ₹/QALY	Interpretation
Chemotherapy (Pemetrexed + Carboplatin)	332,456 (258,460 – 708,667)	2.06 (1.64 – 4.13)	1.20 (0.89 – 2.56)	-	ND
Crizotinib	1,284,100 (844,810 – 1,853,764)	3.79 (3.06 – 4.73)	2.21 (1.71 – 2.85)	936,459	ND (vs chemotherapy)
Ceritinib	2,337,779 (1,198,141 – 3,192,849)	5.31 (3.72 – 6.16)	3.35 (2.16 – 4.11)	931,928	ND (vs chemotherapy)

ALK: Anaplastic lymphoma kinase-positive; NSCLC: Non-small cell lung cancer; CI: Confidence Interval; LY: Life-year; QALY: Quality-adjusted Life-years; ICER: Incremental cost-effectiveness ratio; ND: Non-dominated

Table 3 (b): Costs and Cost-effectiveness of different treatment strategies for ROS1 positive NSCLC in India

Treatment sequence	Total lifetime cost in ₹ (95% CI)	Total LYs (95% CI)	Total QALYs (95% CI)	ICER, ₹/QALY	Interpretation

Chemotherapy (Pemetrexed + Carboplatin)	323,011 (266,807 – 387,416)	2.01 (1.67 – 2.46)	1.16 (0.91 – 1.47)	-	ND
Crizotinib	1,763,541 (1,144,802 – 2,618,855)	4.49 (3.57 – 5.76)	2.73 (2.02 – 3.67)	917,184	ND (vs chemotherapy)

ROS1: c-ros oncogene; NSCLC: Non-small cell lung cancer; CI: Confidence Interval; LY: Life-year; QALY: Quality-adjusted Life-years; ICER: Incremental cost-effectiveness ratio; ND: Non-dominated

Cost-effectiveness

The chemotherapy regimen incurs the lowest costs and health benefits for patients with ALK and ROS1 positive NSCLC in India. Crizotinib incurs an incremental cost of ₹ 936,459 ($ 11,420) and ₹ 917,184 ($ 11,185) per QALY gained as compared to chemotherapy for patients with ALK- and ROS1- positive NSCLC respectively. Similarly, ceritinib incurs a lower incremental cost of ₹ 931,928 ($ 11,365) per QALY gained as compared to chemotherapy treatment arm. At the current prices of the drugs, none of the treatment options are cost-effective at the WTP threshold of 1-time per capita GDP of India.

Scenario Analyses

The use of low-dose ceritinib (450 mg once daily) for the first-line treatment of patients with ALK positive NSCLC resulted in an incremental cost of ₹ 591,002 ($ 7,207) per QALY gained as compared to chemotherapy which is also not cost-effective (Table S3).

Sensitivity and Threshold Analysis

ICER value is most sensitive to the market price of crizotinib and ceritinib in the model. A 50% change on either side in the market price of crizotinib and ceritinib resulted in a 50% and 44% change in the ICER values of crizotinib and ceritinib respectively as compared to the chemotherapy treatment arm.

At a WTP threshold of 1-time per capita GDP, there is only 3.6% probability for crizotinib and ceritinib to be cost-effective at its current price. Nearly 81% reduction in the market price of crizotinib (from ₹ 42,000 to ₹ 7,980 per bottle of 60 capsules) is required to make it a cost-effective treatment option for Indian patients with NSCLC (Figure 2).

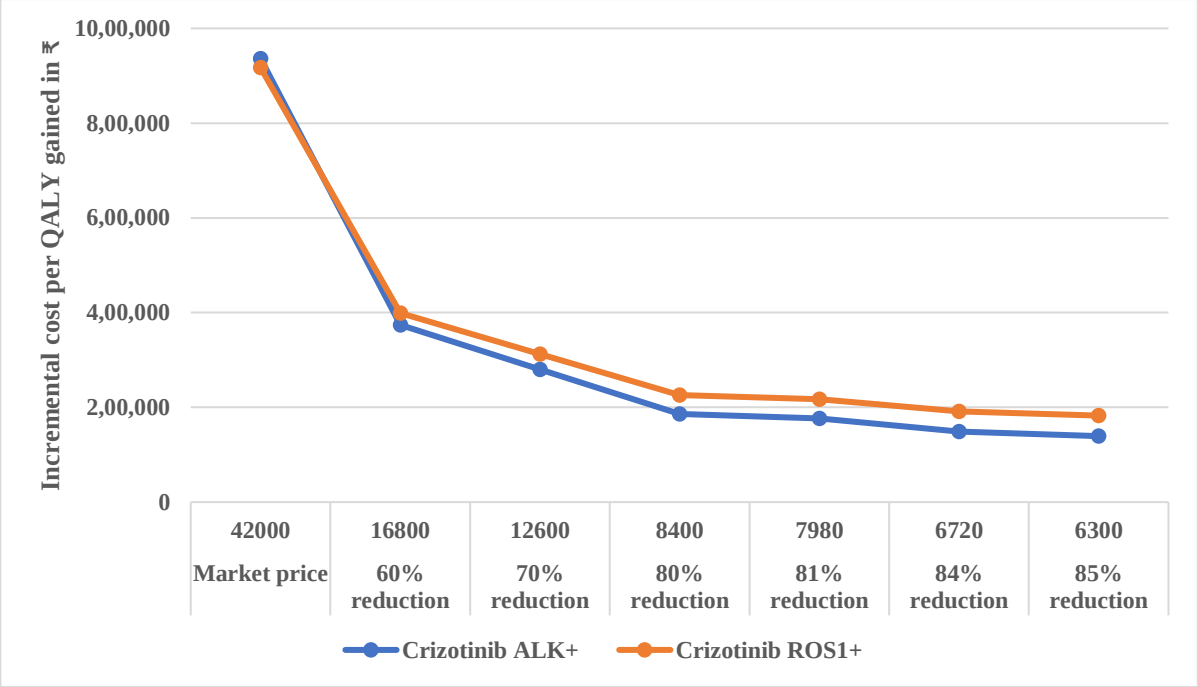

Figure 2: Price threshold analysis for crizotinib for patients with ALK and ROS1 positive NSCLC

Similarly, for the standard dose of ceritinib (750mg daily) to be cost-effective at the WTP threshold of 1-time per capita GDP, nearly 92% reduction in the market price of the drug (from ₹ 42,000 to ₹ 3,360 per month) is required. However, if the low dose ceritinib (450mg once daily) is being used, an 78% reduction in the market price of ceritinib (from ₹ 25,200 to ₹ 5,544 per month) is required to make it a cost-effective treatment option for patients with ALK positive NSCLC in India (Figure 3).

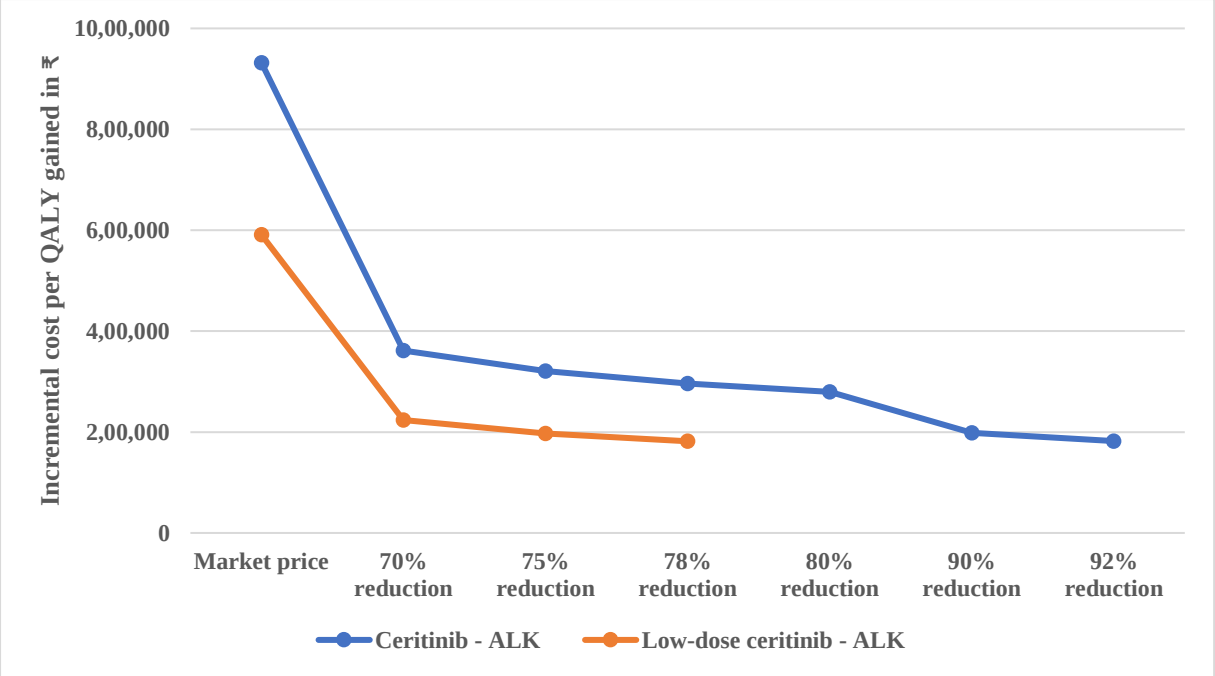

Figure 3: Price Threshold Analysis – Ceritinib for patients with ALK positive NSCLC

Model validation

Our study results are consistent with the published clinical and epidemiological literature. Our study estimates median PFS as 7, 10 and 16 months for chemotherapy, crizotinib and ceritinib arms respectively in patients with ALK positive NSCLC. These findings are concurrent with existing clinical trials (PROFILE 1014 and ASCEND-4) that report median PFS to be 7, 10.9 and 16.6 months respectively [6,8]. Similarly, published literature from India report a median PFS ranging from 6-11 months for chemotherapy and ALK inhibitors (crizotinib, ceritinib etc.) which is in line with our model output [32,33]. There is a significant dearth of epidemiological data for clinical outcomes among patients with ROS1 positive NSCLC. A study reports 1-year PFS rate to be 56.2% which is in line with our analysis that reports a 62.3% PFS rate at the end of 12 months [5]. Another published study reports a median overall survival (OS) of 45.5 months among patients with ALK positive NSCLC who received first-line crizotinib treatment. This concurs with our estimated median OS of 42 months for patients with ALK positive NSCLC and crizotinib as first-line treatment [34].

Several published cost-effectiveness analyses from Ecuador, China, and Portugal report high ICERs for crizotinib which are nearly 3-20 times the WTP threshold of GDP of the respective countries [35–37]. This is in line with our study findings with respect to crizotinib and ceritinib. Published literature comparing different TKIs for patients with ALK positive NSCLC report

LYs and QALYs in the range of 3.8-5.9 and 2.7-4.1 respectively for the crizotinib treatment arm [38–41]. Similarly, for ceritinib, studies report QALYs ranging from 2.7-3.22 in patients with ALK positive NSCLC [41,42]. This aligns with our study findings of 3.78 and 5.3 LYs and 2.21 and 3.34 QALYs respectively for patients treated with crizotinib and ceritinib respectively. Furthermore, for patients with ROS1 positive NSCLC, a study reported 3.35 and 2.4 LYs and 2.5 and 1.77 QALYs for crizotinib and chemotherapy treatment arms respectively [43] which is in with our estimates of 4.5 and 2.01 LYs and 2.73 and 1.16 QALYs respectively.

Discussion

Our study aimed to determine the most cost-effective targeted drug therapy for the treatment of patients with newly diagnosed ALK- and ROS1- positive advanced/metastatic NSCLC in India.

Overall, while the crizotinib and ceritinib offer higher health gains compared to chemotherapy, the high additional cost is not a good value for money. In our analysis, the targeted drugs account for nearly 80-85% of the total cost of management among patients with ALK- and ROS1- positive NSCLC. Therefore, the high cost of these targeted drugs makes this biomarker directed therapy potentially inaccessible to a substantial percentage of patients in LMICs. This is further concurred by another study which reports first line crizotinib in patients with ALK rearrangement could be started in only 22% eligible patients mainly due to financial constraints [44].

The access to molecular testing in India is limited by the cost and its availability in referral and tertiary centres. Majority centres use IHC and FISH for molecular testing as against the standard preferred method of NGS which is more expensive. We have included the cost of molecular testing using IHC and FISH in our analysis and these tests should be included in the high-end diagnostic packages of PMJAY to deliver molecular directed therapy.

A phase I trial has shown that a lower dose of 450mg once a day with food has a higher efficacy and lower GI toxicity as compared to ceritinib 750mg once a day in fasting state, particularly in Asian patients [31]. The physicians in India commonly prescribe low dose ceritinib and further research with phase III trials in Indian patients need to be undertaken to validate this. In our analysis, the monthly cost of ceritinib 450mg once daily accounts for ₹ 25,200 ($ 307) which significantly reduces the cost of treatment.

The current market prices for crizotinib and ceritinib is a poor value for public money for a LMIC like India. The health benefits (QALYs) from crizotinib (2.73), and ceritinib (3.34) are significantly higher as compared to other molecules like sorafenib for HCC (0.5) [45], temozolamide (1.45) [46], bevacizumab for carcinoma cervix (0.13) [47], CDK4/6i (1.6) for breast cancer [23]. Hence, we recommend nearly 81% reduction in market price of crizotinib to make it a cost-effective treatment option to be included in India's publicly financed health insurance scheme.

Strengths & Limitations

Our study is the first to examine the cost-effectiveness of the treatment options for both ALK and ROS1 positive NSCLC for India. Secondly, we obtained the OOPE and QoL estimates from the primary data collected as part of the nationally representative CADCQoL database making our estimates generalizable. Thirdly, we incorporated the reimbursement rates set up under India's ABPM-JAY wherever available making our analysis policy-relevant [21,48]. Fourthly, we included the efficacy of pemetrexed maintenance therapy among patients treated with chemotherapy patients, even though such data was not available in the PROFILE 1014 clinical trial, to mimic the real-world clinical practice [49]. Lastly, we used the survival data from Indian literature to make our results generalizable.

There are certain limitations to this analysis. Firstly, we didn't consider the productivity losses incurred by the patients and the caregivers for the cancer treatment as per the Indian HTA guidelines [30]. Secondly, due to the lack of evidence on mortality, we used similar survival data for both these subgroups of lung cancer namely, patients with ALK and ROS1 positive NSCLC. Thirdly, crizotinib and ceritinib are not the preferred TKIs for treatment of patients with ALK positive NSCLC and have been superseded with other more-effective TKIs like alectinib, brigatinib and lorlatinib but we did not include these in our analysis as their cost is nearly 6-8 times higher than crizotinib and ceritinib which makes it unlikely for them to be cost-effective. Similarly, entrectinib has not been evaluated for ROS1-positive NSCLC.

Conclusions & Policy Implications

Targeted agents (crizotinib and ceritinib) offer greater health benefits as compared to chemotherapy for patients with ALK- and ROS1- positive advanced/metastatic NSCLC in India. But this comes at a very high cost. Therefore, a significant reduction in the prices of these agents is needed to make their use cost-effective. Access to biomarker directed therapy along

with inclusion of molecular testing in the PMJAY is a positive step for advanced/metastatic NSCLC. The study findings may help both clinical practice and reimbursement policy for this condition that is relatively expensive to treat at current drug prices.

Declarations

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

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

Authors' contribution: Study conception: DG, NG, NS and SP. Study design: NG and DG. Analysis: DG, NG, and SP. Writing (first draft): DG, NG, NS and SP. Writing (review and editing): DG, NG, NS and SP.

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Supplementary Appendix I

Treatment strategies

A hypothetical cohort of newly diagnosed, treatment naïve NSCLC patients with either ALK- or ROS1- gene rearrangement will undergo one of the following treatments:

1. Crizotinib 250mg as oral medication taken twice daily until disease progression.
2. Ceritinib 750mg as oral medication taken once daily until disease progression.
3. Pemetrexed 500mg/m^2 and Inj. Carboplatin AUC 5 administered intravenously 3 weekly for 4 cycles, followed by maintenance with pemetrexed 500mg/m^2, 3 weekly, till disease progression

For patients with ROS1-positive NSCLC, only crizotinib and chemotherapy treatment were compared, as the efficacy and safety of ceritinib have not been proven in this group.

Table S1: Probabilities of Individual Adverse events in the PFS health state (ALK-positive NSCLC patients)

Type of Grade 3-4 adverse event	Pemetrexed 500mg/m^2 and Inj. Carboplatin AUC 5	Crizotinib 250mg	Ceritinib 750mg (standard dose)	Ceritinib 450mg (low dose)
Vision disorder (includes visual impairment, photopsia, blurred vision, vitreous floaters, reduced visual acuity, diplopia, and Photophobia)	-	0.006 (0.005 – 0.006)	-	-
Diarrhoea	0.006 (0.005 – 0.006)	0.023 (0.021 – 0.026)	0.053 (0.048 – 0.058)	-
Edema	0.006 (0.005 – 0.006)	0.006 (0.005 – 0.006)	-	-
Vomiting	0.029 (0.026 – 0.032)	0.017 (0.016 – 0.019)	0.053 (0.048 – 0.058)	0.034 (0.031 – 0.038)
Constipation	-	0.017 (0.016 – 0.019)	-	-
Alanine transferases increased	-	-	0.307 (0.276 – 0.338)	0.182 (0.164 – 0.2)
Aspartate aminotransferase increased	-	-	0.169 (0.152 – 0.186)	0.114 (0.102 – 0.125)

Gamma-glutamyltransferase increased	-	-	0.286 (0.257 – 0.314)	0.023 (0.023 – 0.035)
Elevated aminotransferases	0.023 (0.021 – 0.026)	0.140 (0.126 – 0.154)	-	-
Upper respiratory infections	0.006 (0.005 – 0.006)		-	-
Headache	-	0.017 (0.011 – 0.013)	-	-
Pyrexia	0.006 (0.005 – 0.006)		-	-
Dizziness	0.012 (0.011 – 0.013)		-	-
Fatigue	0.023 (0.021 – 0.026)	0.029 (0.026 – 0.032)	0.042 (0.038 – 0.046)	-
Neutropenia	0.152 (0.137 – 0.167)	0.111 (0.1 – 0.122)	-	-
Stomatitis	0.012 (0.011 – 0.013)	0.006 (0.005 – 0.006)	-	-
Asthenia	0.012 (0.011 – 0.013)	-	0.026 (0.024 – 0.029)	-
Anaemia	0.088 (0.079 – 0.096)	-	0.021 (0.019 – 0.023)	-
Leukopenia	0.053 (0.047 – 0.058)	0.017 (0.016 – 0.019)	-	-
Thrombocytopenia	0.064 (0.058 – 0.071)	-	-	-
Nausea	0.017 (0.016 – 0.019)	0.017 (0.011 – 0.013)	0.026 (0.024 – 0.029)	-
Decreased appetite	0.006 (0.005 – 0.006)	0.023 (0.021 – 0.026)	0.011 (0.009 – 0.0120)	-
Neuropathy	-	0.012 (0.011 – 0.013)	-	-
Dyspnea	0.023 (0.021 – 0.026)	0.029 (0.026 – 0.032)	0.021 (0.019 – 0.023)	-
Blood alkaline phosphatase increased	-	-	0.074 (0.066 – 0.081)	-
Abdominal pain	-	-	0.021 (0.019 – 0.023)	-
Decreased weight	-	-	0.037 (0.033 – 0.041)	-
Blood creatinine increased	-	-	0.021 (0.019 – 0.023)	-

Table S2: Probabilities of Individual Adverse events in the PFS health state (ROS1-positive NSCLC patients)

Type of Grade 3-4 adverse event	Pemetrexed 500mg/m^2 and Inj. Carboplatin AUC 5	Crizotinib 250mg
Leukopenia	0.106 (0.096 – 0.117)	0.033 (0.03 – 0.037)
Neutropenia	0.064 (0.057 – 0.070)	0.033 (0.03 – 0.037)
Alanine aminotransferase elevation	-	0.1 (0.09 – 0.11)
Creatine kinase-MB elevation	-	0.033 (0.03 – 0.037)
Sinus bradycardia	-	0.033 (0.03 – 0.037)
Anemia	0.021 (0.019 – 0.023)	-
Fatigue	0.042 (0.038 – 0.047)	-
Nausea	0.021 (0.019 – 0.023)	-

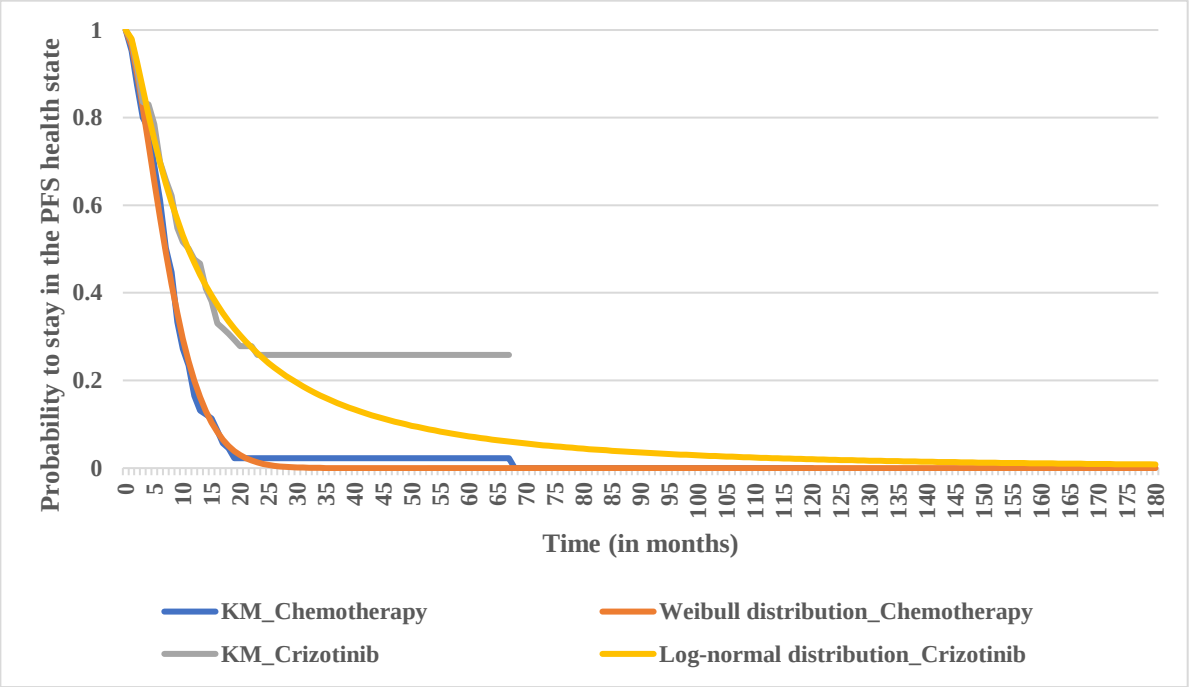
Table S3: Percentage of patients undergoing palliative radiotherapy in the PFS health state (For ALK- and ROS1-positive NSCLC patients)

Location of distant mets	Conventional hypofractionation	Stereotactic body radiation therapy (SBRT)
Brain	25%	5%
Bone	15%	5%
Lungs	0%	5%

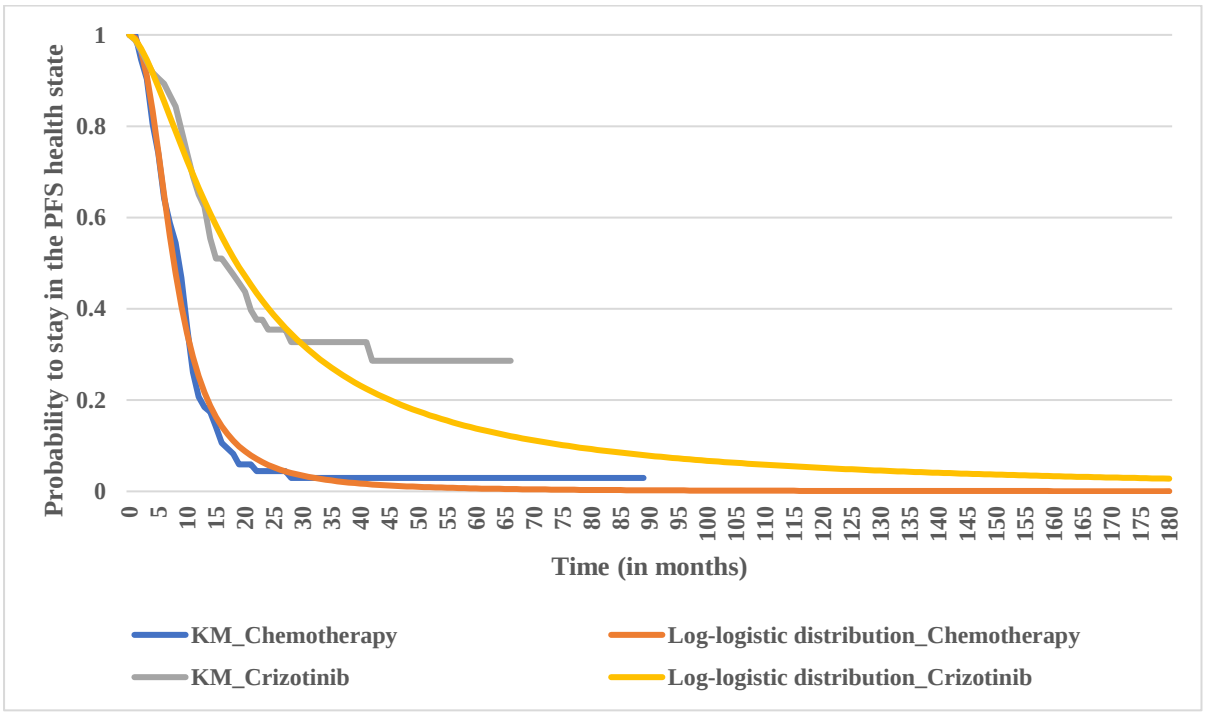
Table S4: Costs and Cost-effectiveness of different treatment strategies for ALK positive NSCLC in India

Treatment sequence	Total lifetime cost in ₹ (95% CI)	Total LYs (95% CI)	Total QALYs (95% CI)	ICER, ₹/QALY	Interpretation
Chemotherapy (Pemetrexed + Carboplatin)	332,456 (258,460 – 708,667)	2.06 (1.64 – 4.13)	1.20 (0.89 – 2.56)	-	ND
Crizotinib	1,284,100 (844,810 – 1,853,764)	3.79 (3.06 – 4.73)	2.21 (1.71 – 2.85)	936,459	ND (vs chemotherapy)
Low dose Ceritinib	1,606,501 (1,453,000 – 2,323,001)	5.31 (4.02 – 6.87)	3.35 (2.34 – 4.64)	591,002	ND (vs chemotherapy)

ALK: Anaplastic lymphoma kinase-positive; NSCLC: Non-small cell lung cancer; CI: Confidence Interval; LY: Life-year; QALY: Quality-adjusted Life-years; ICER: Incremental cost-effectiveness ratio; ND: Non-dominated



Supplementary Figure 4: Parametric survival analysis for ALK-positive NSCLC patients



Supplementary Figure 5: Parametric survival analysis for ROS1-positive NSCLC patients

Chapter II: Cost-effectiveness analysis of systemic therapy for intensification of treatment in metastatic hormone-sensitive prostate cancer in India

Abstract

Background: Androgen-deprivation therapy is the mainstay of treatment for newly-diagnosed metastatic hormone-sensitive prostate cancer (mHSPC) patients. However, the intensification of treatment with either docetaxel or novel anti-androgens (NAA) (abiraterone-acetate plus prednisone (AAP), enzalutamide and apalutamide) is being recommended based on the improved clinical outcomes and quality-of-life among patients. This study aimed to determine the most cost-effective drug for treatment intensification for mHSPC patients in India.

Methods: A Markov model was developed with 4 health states: Progression-free survival, progressive disease, best supportive care, and death. Lifetime costs and consequences were estimated for 4 treatment sequences: AAP-first, enzalutamide-first, apalutamide-first, and docetaxel-first. Incremental cost per quality adjusted life year (QALY) gained with a given treatment option was compared against the next best alternative and assessed for cost-effectiveness using a willingness to pay (WTP) threshold of 1 x per capita gross domestic product (GDP) in India.

Results: We estimated that the total lifetime cost per patient was ₹ 1,367,454 (US$ 17,487), ₹ 2,168,885 (US$ 27,735), ₹ 7,678,501 (US$ 98,190), and ₹ 1,358,746 (US$ 17,375) in the AAP-first, enzalutamide-first, apalutamide-first, and docetaxel-first treatment sequence, respectively. The mean QALYs lived per patient were 4.78, 5.03, 3.22, and 2.61, respectively. AAP-first sequence incurs an incremental cost of ₹ 4,014 (US$ 51) per QALY gained as compared to the docetaxel-first sequence, with a 87% probability of being cost-effective at the WTP threshold of 1 x per-capita GDP of India. The use of AAP-first also incurs an incremental net monetary benefit (NMB) of ₹ 396,491 (US$ 5,070) as compared to the docetaxel-first treatment sequence. Nearly 48% reduction in the price of enzalutamide is required to make it a cost-effective treatment sequence as compared to AAP-first in India.

Conclusion: We concur with the inclusion of standard dose AAP in India's publicly financed health insurance scheme for intensification of treatment in mHSPC as it is the only cost-effective sequence among the various NAA when compared to docetaxel-first treatment sequence. Furthermore, a systematic reduction in the price of enzalutamide would further help to improve clinical outcomes among mHSPC patients.

Introduction

As per the latest estimates, prostate cancer (PC) has the fifth highest incidence rate among males in India (4.8 per 100,000) (1). PC features among the top 10 cancers in urban cancer registries of Bangalore, Delhi, Bhopal and Mumbai (2). Furthermore, the incidence of PC is expected to increase from 41,532 cases in 2020 to over 47,000 in 2025 (2). This constitutes roughly 3% of total cancer cases in the country. It is generally a disease of the elderly population, with a mean age at presentation reported to be 69.7 years (3).

Even though the 5-year survival among localized PC patients is estimated be approximately 99%, metastatic PC is incurable (4). About 3% of PC cases present with de nova metastatic disease, which has the worst prognosis as compared to patients presenting with metastatic disease after recurrence (5). The health states preceding the terminal stage of the disease are metastatic hormone-sensitive prostate cancer (mHSPC) and metastatic castration resistant prostate cancer (mCRPC).

Standard treatment for mHSPC has been long term androgen deprivation therapy (ADT) without much progress over decades (6,7). Recently there has been a paradigm shift in the management of mHSPC, with a call for intensification of treatment with docetaxel-based chemotherapy or novel anti-androgen (NAA) agents like abiraterone acetate, enzalutamide, apalutamide. Results from various trials have been consistent with about 20% improvement in overall survival (OS) when docetaxel is combined with ADT, and 35% improvement in OS when NAA have combined with ADT over ADT alone for mHSPC (8–12). This intensification of treatment with either the chemotherapy or NAA along with long term ADT is the new standard of care (8,9,11).

The standard treatment guidelines, however, do not recommend or prioritize the use of docetaxel or either one of the NAA over the other. Neither do the guidelines recommend the preferred sequence for the use of these therapies when mHSPC progresses to mCRPC. There are many differences between these different agents including mechanism of action, route of administration, duration of treatment, adverse effect profile and cost of therapy. Choice of the agent for intensification of treatment in low middle income countries (LMICs) like India is usually based on the affordability and accessibility to these agents.

The increasing incidence of PC is expected to put a significant burden on the healthcare system in terms of high cost of treatment and compromised quality of life (QoL) in the country (13).

Intensification of treatment for mHSPC improves OS, delays progression to CRPC and improves the quality of life (14). Hence, it is important to evaluate the cost effectiveness of these multiple agents used for treatment intensification and incorporate this evidence in standard treatment guidelines to help in clinical decision making.

Several studies have evaluated the cost-effectiveness for intensification of treatment in metastatic PC. Sung et al. (2021) and Wang et al. (2021) compared the combination therapies with ADT alone from the US payers' perspective and reported that abiraterone acetate (AA) is most cost-effective treatment option among the mHSPC patients at a willingness to pay (WTP) threshold between $50,000 and $200,000 per QALY gained (15,16). Furthermore, they also reported that enzalutamide is not a cost-effective treatment option from the US healthcare sector perspective (16).

However, these results cannot be generalised in the Indian healthcare setting due to wide variations in the cost of the drugs, and other health system costs and out-of-pocket (OOP) expenditure. Therefore, there is a need for conducting health economic evaluation to assess the costs and benefits associated with intensification of treatment for mHSPC in order to better prioritize the use of a particular drug based on its cost effectiveness and optimize the use of limited resources especially in low- and middle-income countries such as India. This is even more pertinent since the AAP and docetaxel are included for free cashless treatment under India's tax-funded health insurance program – *Ayushman Bharat* Pradhan Mantri Jan Aarogya Yojana (ABPM-JAY). Further, enzalutamide has been nominated for inclusion in health benefit packages (HBP) as part of the National Health Authority's topic nomination process. As a result, a detailed cost-effectiveness analysis was commissioned by India's Health Technology Assessment Agency (HTAIn) to assess the value for money of different systemic therapies for treatment intensification for the first-line treatment of metastatic mHSPC patients. In view of this, we undertook this analysis to determine the most cost-effective treatment for a newly-diagnosed mHSPC patient in India.

1. Methodology

2.1 Overview of the analysis

A Markov state-transition model was developed to evaluate the lifetime costs and health outcomes of treating newly diagnosed, mHSPC patients from an abridged societal perspective (17,18). Various options available for the treatment of mHSPC patients until progression to

mCRPC were evaluated. These include addition of different first-line treatment options to ADT with either abiraterone acetate plus prednisone (AAP), enzalutamide, apalutamide or docetaxel. The methodological principles of the economic evaluation are consistent with the Indian reference case for conducting economic evaluations used by the HTAIn (17). The latest edition of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) have been used to report the findings (19).

2.2 Treatment sequences

A hypothetical cohort of newly diagnosed, treatment naïve, mHSPC patients after receiving ADT were assumed to undergo one of the following treatment sequences as shown in the Figure 1.

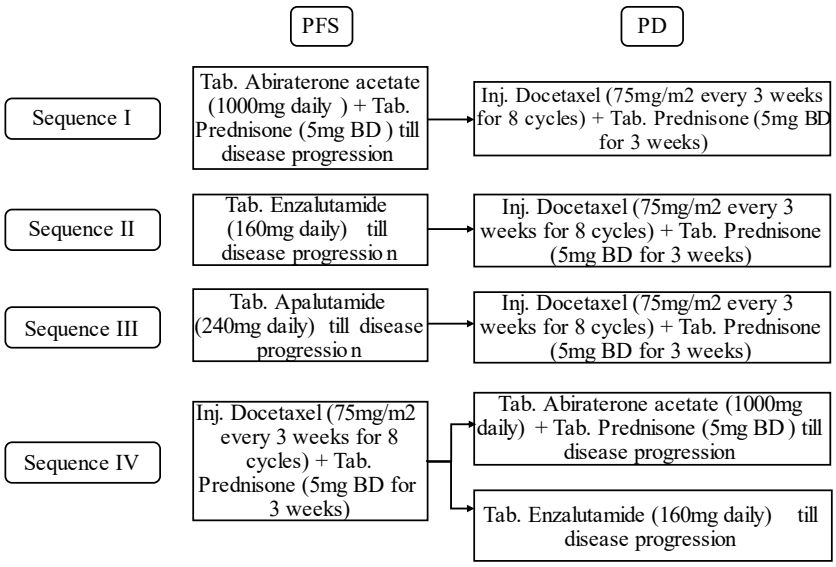


Figure 1: Treatment strategies for newly diagnosed metastatic hormone-sensitive prostate cancer. PFS: Progression-free survival; PD: Progressive disease; BD: twice a day; Inj.: Injection; Tab.: Tablet

2.3 Markov model structure

A state-transition Markov model was developed with four different health states: Progression-free survival (PFS), progressive disease (PD), best supportive care (BSC) and death (including all-cause mortality and disease-specific mortality) (Figure 2). A mHSPC patient in PFS health state can progress to PD health state, or transition to BSC or die due to all-cause mortality. The PD patient can remain in the same health state, or transition to BSC or die. The PD health state

involves second-line therapy after progression. The patients who received either AAP, enzalutamide or apalutamide in the PFS health state will undergo second-line treatment with docetaxel in the PD health state. Similarly, patients who received docetaxel as the first-line treatment are eligible for both AAP and enzalutamide in the second-line treatment. The BSC health state comprises of patients from both the PFS and PD health states. Those PFS patients who discontinue the treatment for reasons other than progressive disease move to BSC. Similarly, those PD patients who progress on second-line therapy move to the BSC health state. In our model, no disease-specific mortality was assumed in PFS state as PFS is defined as the time from randomization to progression or death wherein deaths without progression are censored observations rather than counted as events (20). Death both from mCRPC and all-cause mortality was considered for PD and BSC health states. A lifetime horizon and a monthly cycle length was considered for this analysis. A discount rate of 3% was applied for both costs and effectiveness parameters according to the methodological guidelines set up by the HTAIn (17).

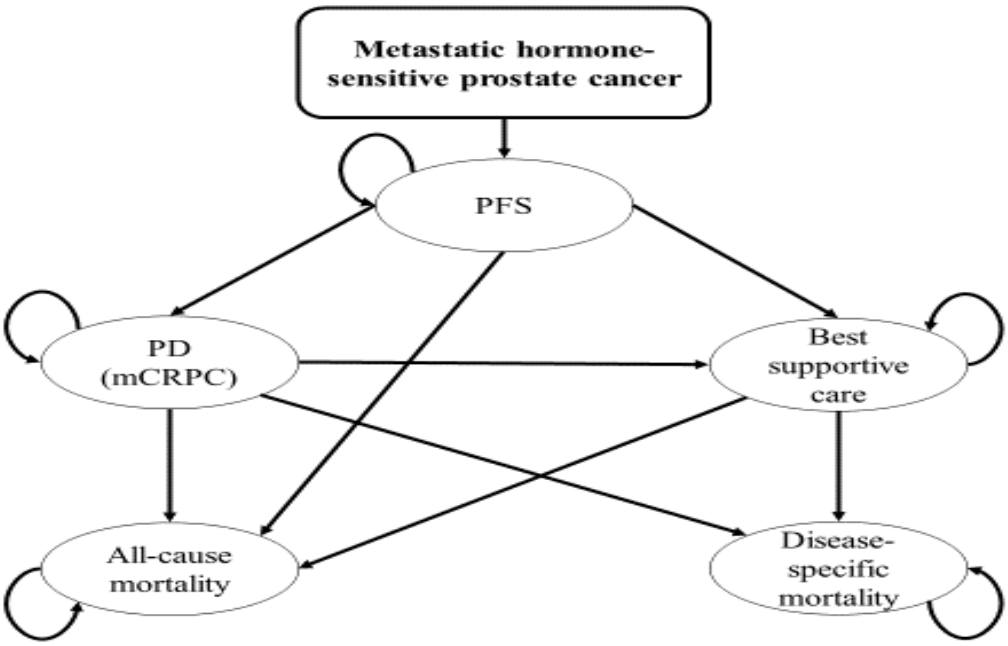


Figure 6: Markov model to determine the most cost-effective treatment sequence for metastatic prostate cancer. PFS: Progression-free survival; mCRPC: metastatic Castrate-resistant Prostate Cancer; PD: Progressive disease

2.4 Valuation of consequences

Treatment efficacy for the first-line treatment with AAP-first, enzalutamide-first, apalutamide-first and docetaxel-first was obtained from the published results of the STAMPEDE, ARCHES, TITAN and CHAARTED clinical trials respectively (8–10,12). For AAP-first treatment sequence, STAMPEDE (21) trial was chosen over the LATITUDE (22) trial due to multiple reasons. Firstly, the LATITUDE trial included the high-risk mHSPC patients with a more aggressive disease than mixed set of patients considered in the STAMPEDE trial. Secondly, in the LATITUDE trial, nearly 72 patients were allowed to cross-over to the abiraterone arm from the control group which further raises questions on the quality of data. Similarly, for the enzalutamide-first treatment sequence, the updated results of the ARCHES trial published in 2022 were given preference over the ENZAMET trial (23,24). This is because the early use of docetaxel treatment was permitted in the ENZAMET trial. A cohort of patients (65%) in the enzalutamide treatment arm were allowed to receive docetaxel concurrent with enzalutamide (24), which is not in line with our inclusion criteria of newly diagnosed mHSPC patients. In addition, the patients in the control arm of the ENZAMET trial received an additional anti-androgen drug along with the standard care. For docetaxel-first treatment sequence, CHAARTED trial was preferred over STAMPEDE trial as the latter clinical trial included both metastatic (61%) and non-metastatic (39%) prostate cancer patients while CHAARTED trial included only metastatic prostate cancer patients.

The reported PFS Kaplan-Meier curves were digitized using a web-based software to estimate the individual patient time-to-event data (25). The curves were then fitted for the one of the following parametric distributions: exponential, Weibull, gompertz, log-normal and log-logistic (26). The best fit was chosen according to Akaike Information criterion (AIC), Bayesian Information Criterion (BIC) and visual inspection (26). Similarly, the probability to stay in the PD health state was obtained from COU-AA-301, AFFIRM and PROSTY for AAP, enzalutamide and docetaxel arms in the second-line therapy respectively (27–29) [Fig. S1(a-f)]. Patients who discontinued first line treatment in the PFS state for reasons other than disease progression (adverse effects, poor affordability etc.), received second-line therapy or moved to BSC health state. The discontinuation rates were obtained from the individual clinical trials for each treatment sequence (10–12,21,30). Additionally, as per the stakeholder consultation with the clinicians (including 5 oncologists and 2 urologists), nearly 15% of the patients that transition to BSC from PFS health state will still undergo second-line treatment. The Sample

Registration System abridged lifetables were used to estimate the age-specific risk of all-cause mortality in the model (31). Disease-specific mortality in the PD and supportive care state were obtained from published clinical literature (32). The efficacy parameters are listed in the Table 1.

The baseline utility values for each health state (PFS, PD and BSC) were obtained from the primary data collected from 68 metastatic PC patients using EQ-5D-5L questionnaire, as a part of the larger multi-centric 'National Cancer Database for Cost and Quality of Life' (CADCQoL) study (33). The Indian tariff values were used to estimate the quality of life scores associated with each health state (34). The primary data from the CADCQoL study was used to estimate the disutility due to treatment-related adverse events (33) (Table 1). The data on incidence of AEs in both the PFS and PD health states for each treatment arm was obtained from the published clinical literature (8,11,12,27–30) (Table S3).

Table 1: Input parameters to determine the effectiveness of the different treatment arms

Input variable	Parameter	Distribution	Source
Median age of presentation of PC in India	65 years	-	(30)
Discount Rate	3%	Beta	(18)
Proportion of patient undergoing AA plus prednisone in PD state	0.9	Beta	Expert opinion
Proportion of patient undergoing enzalutamide in PD state	0.1	Beta	Expert opinion
PFS function parameters			
Abiraterone acetate plus Prednisone	• Shape: 3.93 (3.76 – 4.10) • Scale: 0.35 (0.24 – 0.46)	Log-normal	(8)
Enzalutamide	• Shape: 4.01 (3.91-4.37) • Scale: 0.12 (-0.04 – 0.30)	Log-normal	(9)
Apalutamide	• Shape: 0.005 (0.003-0.01) • Scale: 0.31 (0.15 – 0.46)	Weibull	(10,11)
Docetaxel	• Shape: 2.80 (2.68-2.93)	Log-normal	(12)

	• Scale: 0.014 (-0.08 – 0.112)		
Survival function for PD health state			
Enzalutamide	• Shape: 2.08 (2.02 – 2.16) • Scale: -0.14 [-0.2 – (-0.08)]	Log-normal	(23)
Docetaxel	• Shape: 0.007 (0.004 – 0.015) • Scale: 0.53 (0.40 – 0.66)	Weibull	(24)
Disease-specific mortality			
Probability to die among PD patients (Abiraterone acetate treatment)	0.043 (0.03 – 0.06)	Beta	(22)
Probability to die among PD patients (Enzalutamide treatment)	0.037 (0.026 – 0.048)	Beta	(23)
Probability to die among PD patients (Docetaxel treatment)	0.04 (0.03 – 0.05)	Beta	(24)
Probability to die among patients in best supportive care	0.046 (0.032 – 0.060)	Beta	(26)
Age-specific mortality			
66-70	0.0025 (0.002 – 0.003)	Beta	(25)
71-75	0.0039 (0.003 – 0.005)	Beta	(25)
76-80	0.0059 (0.0045 – 0.0073)	Beta	(25)
80+	0.009 (0.007 – 0.012)	Beta	(25)
Utility values			
Overall mean utility score for PC patients	0.636 (0.555 – 0.717)	Beta	Primary data
Utility score for PFS state (without AEs)	0.770 (0.598 – 0.942)	Beta	Primary data
Utility score for PFS state (with AEs)	0.565 (0.452 – 0.678)	Beta	Primary data

Utility score for PD state (without AEs)	0.596 (0.439 – 0.754)	Beta	Primary data
Utility score for PD state (with AEs)	0.391 (0.313 – 0.470)	Beta	Primary data
Utility score BSC state	0.431 (0.345 – 0.517)	Beta	Primary data

PC: Prostate cancer; PFS: Progression-free survival; PD: Progressive disease; AE: Adverse events; BSC: Best supportive care

2.5 Cost of prostate cancer treatment

The cost of treatment of mHSPC and mCRPC was estimated from an abridged societal perspective. This means that we included both direct medical and non-medical costs borne by the healthcare payer as well as the patient. We did not consider the indirect expenditure incurred by the patients and their care givers. This is in line with the guidance for base case analysis as per the Indian reference case for HTA (17,18). The treatment protocol for all the four interventions along with the management of AEs were obtained from the published clinical treatment guidelines (7) and expert opinion for each health state. For the AAP and docetaxel treatment arms, the reimbursement rates set up as the part of the HBP under Ayushman Bharat – Pradhan Mantri Jan Aarogya Yojana (AB – PMJAY) were used (35). The reimbursement rates include the drug acquisition and administration costs, and cost of management of acute adverse events (35). The direct non-medical OOP expenditure (including travel, boarding/lodging, food, informal payment etc.) incurred on out-patient department (OPD) consultations, diagnostic and laboratory investigations, and follow up was also incorporated. For the enzalutamide and apalutamide treatment arms, drug acquisition costs, direct patient OOP expenditure per OPD consultation (including user fees), management of grade 3-4 AEs and the cost of routine follow-up was included. Routine follow-up cost includes the cost per outpatient consultation, laboratory investigations and diagnostic tests. Separate incidence rates for each grade 3-4 AEs and cost for their management were applied for all the arms using the published literature (Table S2) (8,11,12,27–30).

Health system costs of outpatient consultation and day-care visit for PFS and PD patients were elicited using data from published studies (36,37) and nationally representative 'National Health System Cost Database'(NHSCD) (38). The estimates on OOP expenditure were derived from primary data collected from 68 metastatic PC patients (33). The data was analysed to compute both direct medical (user fees/procedure charges incurred on outpatient consultation) and non-medical expenditures (travelling, food, boarding/lodging, informal payment, others

etc.). We used the reimbursement rates (35),generic & market prices and procurement rates of the Rajasthan Medical Service Corporation (RMSC) (39),for estimating expenditures on drugs. For the diagnostic services, we used the provider payment rates from the social health insurance scheme for central government employees in India i.e., Central Government Health Scheme (CGHS) (40) (Table 2). All costs are reported in Indian National Rupee (₹) and converted to United States Dollar ($) using an exchange rate of 1$ = ₹ 78.2 for the year 2022 (41).

The comparative cost effectiveness was assessed in terms of incremental cost per QALY gained. A WTP threshold equal to per capita gross domestic product (GDP) of India was used to assess the cost-effectiveness as per the guidelines for HTA in India (17). The per capita GDP of India for the year 2021-22 was ₹ 186,788 (US$ 2,388.6) (42).

Table 2: Input cost parameters

Input Parameter	Cost per cycle (in ₹)	Cost per cycle (in US$)	Distribution	Source
Monthly cost of the drugs				
Abiraterone acetate 1000mg plus Prednisone 5mg	13,000 (6,500 – 19,500)	166 (83 – 249)	Gamma	(34)
Enzalutamide 160mg	22,286 (11,143 – 33,429)	285 (142 – 427)	Gamma	Market Price
Apalutamide 240mg	180,000 (90,000 – 270,000)	2,301 (1151 – 4,603)	Gamma	Market Price
Docetaxel 75mg/m^2	8,500 (4,250 – 12,750)	18 (9 – 36)	Gamma	(34)
Inj. Zoledronic Acid 4mg	3,500 (1,750 – 5,250)	7 (4 – 14)	Gamma	(34)
Inj. Denosumab 120mg	18,000 (9,000 – 27,000)	230 (114 – 460)	Gamma	(34)
Palliative radiotherapy	10,000 (5,000 – 15,000)	128 (64 – 256)	Gamma	(34)
Inj. Cabazitaxel 20mg/m^2	42,222 (21,111 – 63,333)	540 (270 – 1080)	Gamma	Market Price
Inj. Mitoxantrone plus Tab. Prednisone 5mg	4,200 (2,100 – 6,300)	6 (3 – 9)	Gamma	(34)
Tab. Bicalutamide 50mg	127 (57 – 209)	2 (1 – 3)	Gamma	Market Price
Tab. Abiraterone 250mg	1,242 (621 – 1,863)	16 (8 – 32)	Gamma	(38)

Out-of-Pocket Expenditure (OOPE)				
Per Out-patient consultation*	1798 (1251 – 2344)	23 (16 – 30)	Gamma	Primary data
Per Out-patient consultation**	2,279 (984 – 3,575)	29 (13 – 46)	Gamma	Primary data
Cost of diagnostic tests				
PSMA PET scan	22,264 (11,132 – 33,395)	285 (142 – 569)	Gamma	Market Price
Bone scan	3,500 (1,750 – 5,250)	45 (22 – 89)	Gamma	CGHS rate list (39)
CT scan (Chest, Abdomen and Pelvis)	6,945 (3,472 – 10,417)	89 (44 – 178)	Gamma	CGHS rate list (39)
MRI (Abdomen and Pelvis)	5,000 (2,500 – 7,500)	64 (32 – 128)	Gamma	CGHS rate list (39)
Complete Blood count	138 (69 – 207)	2 (1 – 3)	Gamma	CGHS rate list (39)
Renal Function Tests	261 (130 – 391)	3 (2 – 5)	Gamma	CGHS rate list (39)
Liver Function Tests	275 (137 – 412)	3 (2 – 5)	Gamma	CGHS rate list (39)
Serum electrolytes	370 (185 – 555)	5 (2 – 7)	Gamma	CGHS rate list (39)
Serum Calcium	63 (31 – 94)	1 (0.4 – 1.2)	Gamma	CGHS rate list (39)
PSA levels (Total)	319 (159 – 478)	4 (2 – 6)	Gamma	CGHS rate list (39)

OOPE: Out-of-Pocket Expenditure; Inj.: Injection; Tab.: Tablet

** Including the OOPE on travel, boarding/lodging, food, informal payments, and others (excluding the drugs, diagnostics, and user fees) – direct non-medical expenditure (for AA plus prednisone and docetaxel treatment sequences)*

*** Including the OOPE on travel, user fees, boarding/lodging, food, informal payments and others (excluding the drugs and diagnostics) – direct expenditure (for enzalutamide and apalutamide treatment sequences)*

2.6 Sensitivity and Scenario Analyses

A univariate (Figure S2) and a probabilistic sensitivity analysis (PSA) were undertaken to test parameter uncertainty. Probability of a treatment sequence to be cost effective was assessed at a WTP threshold equal to per capita GDP as per the guidelines for health technology assessment in India (17). Under PSA, we used gamma distribution for cost parameters and beta distribution for parameters related to effectiveness, risk of complications, overall survival, and utility scores. For rest of the parameters in the model, we used uniform distribution. Uncertainty ranges for input parameters were computed from the standard error estimates from the primary data, or data available in the literature. Wherever the measures of dispersion were not available, based on reported variation in values for various parameter types in different Indian economic

evaluations (43–45) regarding uncertainty in parameter values, a variation of 20% for clinical parameters; 30% variation for mortality risks, utility scores and treatment patterns; and 50% variation for cost parameters was assumed on either side of base parameter values. Model results were simulated 5000 times and median value (ICER) along 95% confidence interval was generated for base estimates using percentile method.

A separate scenario analysis for the AAP-first treatment arm was undertaken by altering the standard dose of 1000mg daily (empty stomach) with low-dose abiraterone 250mg administered with low fat breakfast in mHSPC patients. The efficacy of low-dose abiraterone was assumed to be the same as the standard-dose abiraterone as per the published clinical literature (46) and the procurement prices were used to estimate the cost of drug (39).

A dominance analysis was also undertaken in which each treatment sequence was compared against the next best alternative to assess the comparative cost-effectiveness between various treatment strategies. Additionally, the incremental Net Monetary Benefit (iNMB) approach was also used to compare different treatment sequences along with the dominance analysis.

3.Results

3.1 Base-case analysis

Over a lifetime horizon, treatment of newly-diagnosed mHSPC patients incurred a total discounted cost of ₹ 1,367,454 (US$ 17,487), ₹ 2,168,885 (US$ 27,735), ₹ 7,678,501 (US$ 98,190), and ₹ 1,358,746 (US$ 17,375) in the AAP-first, enzalutamide-first, apalutamide-first, and docetaxel-first treatment sequence, respectively. The mean LYs lived in each treatment sequence were 6.7, 6.9, 4.7 and 4.0 respectively. This translated to 4.78, 5.03, 3.22, and 2.61 mean QALYs lived per patient for AAP-first, enzalutamide-first, apalutamide-first, and docetaxel-first treatment sequence, respectively. The detailed results are given in Table S5 of the supplementary appendix.

The discounted cost-effectiveness results are reported in Table 3. In the base case, docetaxel-first, AAP-first and enzalutamide-first are non-dominated treatment sequences for mHSPC patients. The AAP-first treatment sequence incurs the lowest incremental cost of ₹ 4,014 (US$ 51) per QALY gained compared to the docetaxel-first treatment sequence and is cost effective given the threshold for cost effectiveness in India (1 x GDP). Similarly, the enzalutamide-first treatment sequence incurs an incremental cost of ₹ 3,147,770 (US$ 40,253) per QALY gained

when compared to the AAP-first treatment sequence, which is not cost-effective at the current WTP threshold of 1 x per capita GDP (₹ 186,788) of India. Furthermore, the AAP-first treatment sequence incurs the highest incremental NMB of ₹ 396,491 (US$ 5,070) as compared to the docetaxel-first treatment sequence. Enzalutamide incurs a negative NMB and is therefore not cost-effective in the Indian context. A minimum reduction in price of 48% is required for enzalutamide to be cost-effective for use in Indian patients (Figure S3).

Table 3: Costs and Cost-effectiveness of different treatment strategies for mHSPC in India

Treatment sequence	Total lifetime cost in ₹	Total LYs	Total QALYs	ICER, ₹/QALY gained	iNMB (as per dominance analysis)	iNMB (vs Docetaxel)	iNMB (vs Abiraterone acetate)
Docetaxel-first sequence	1,358,746	3.99	2.61	ND	ND	-	-
Apalutamide-first sequence	7,678,501	4.73	3.22	D	D	D	D
Abiraterone acetate plus Prednisone-first sequence	1,367,454	6.65	4.78	4,014 (vs docetaxel)	396,491	396,491	-
Enzalutamide-first sequence	2,168,885	6.90	5.03	3,147,770 (vs AAP)	-753,874	-357,382	-753,874

mHSPC: metastatic hormone-sensitive prostate cancer; LY: Life-Years; QALY: Quality-adjusted Life-years; ICER: Incremental cost-effectiveness ratio;iNMB: incremental Net Monetary Benefit; ND: Non-dominated; D: Dominated; AAP: Abiraterone acetate plus prednisone

3.2 Scenario Analysis

The use of low-dose AA for the treatment of a newly-diagnosed mHSPC patient resulted in a total lifetime cost of ₹ 642,865 (US$ 8,221). Therefore, the use of low dose abiraterone incurs lower cost and better health outcomes as compared to the docetaxel-first treatment sequence. This resulted in an incremental NMB of ₹ 1,121,081 (US$ 14,336) which is cost-effective for India. The docetaxel-first and apalutamide-first treatment sequences are dominated treatment strategies in this scenario. The detailed results are shown in the Table S6 of the Supplementary Appendix.

3.3 Sensitivity Analysis

In the base-case analysis, the probability of AAP-first treatment sequence to be cost-effective is estimated to be nearly 87% at the current WTP threshold of 1-time per capita GDP (₹ 186,788) of India (Figure 3). The cost-effectiveness of the AAP-first treatment sequence is mainly affected by the package cost of AAP, probability stay in PD health state in docetaxel arm, reimbursement rate for docetaxel, probability to die in the PD and BSC health states, and probability to transition from PFS to BSC (Figure S2). However, these variations do not change the overall study conclusion as the ICER value is still below the WTP threshold of 1-time per capita GDP of India.

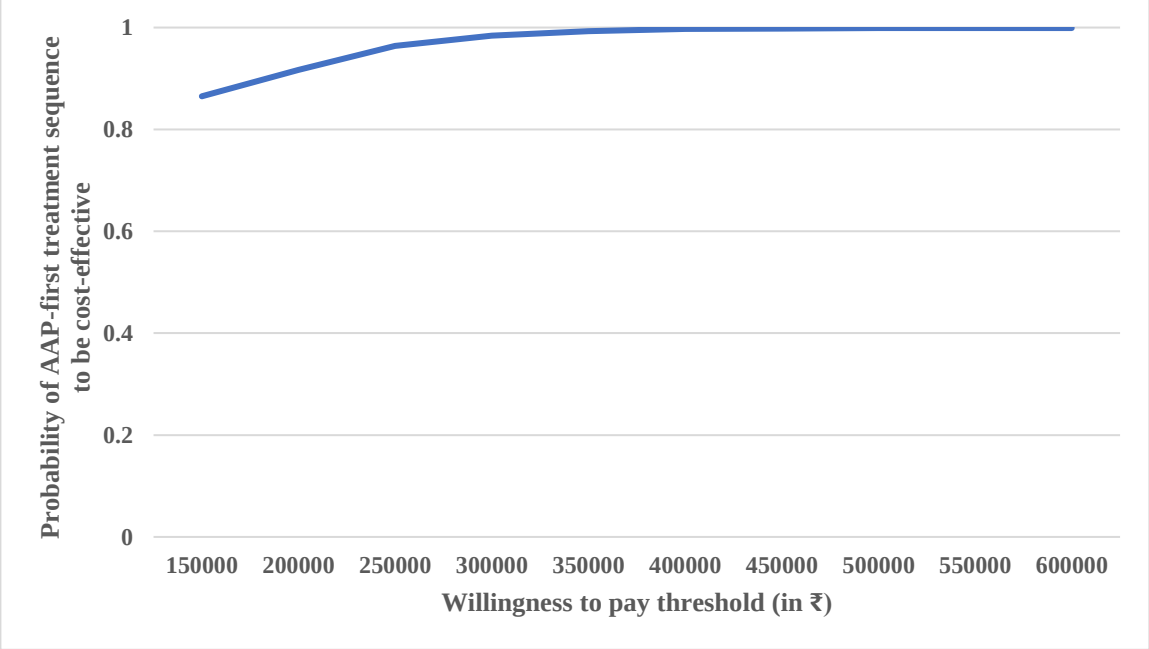


Figure 3: Cost-effectiveness Acceptability curve: Abiraterone acetate plus Prednisone vs. Docetaxel

4. Discussion

Our study aimed to determine the most cost-effective drug to be used along with ADT for treatment intensification for newly diagnosed mHSPC patients in India. Neither any randomized trials are available to compare the efficacy of chemotherapy and different NAAs in mHSPC nor any guidelines recommend the use of one agent over the other.

Majority of the previous cost-effectiveness studies have compared ADT alone with ADT combined with docetaxel or NAA (15,47). However, since ADT has been the established standard of care for decades, the dilemma exists over the choice of intensification agents, which need to be compared among themselves. Certain published NMAs report superiority of AAP

treatment over docetaxel and enzalutamide treatment options for mHSPC patients (48,49), but these do not report data from updated published analysis of drugs such as enzalutamide. However, we used results from long-term analysis for enzalutamide (23). Moreover, we did not compare combination of ADT and docetaxel or NAA with ADT alone. Apart from the drug to choose in the first line, our analysis also provides evidence about the most cost-effective sequence of drugs after progression from mHSPC to mCRPC which is a more real-world guidance as patients are likely to have treatment during the progression phase of the disease. When standard treatment guidelines do not give an insight into use of a particular agent over multiple options available, cost effectiveness analysis can help physicians make an appropriate choice by picking up the option which is the best value for money, thus making optimal use of limited resources in LMICs like India.

In LMICs, docetaxel remains a preferred agent due to its low cost, easy availability, finite number of cycles/ duration and a manageable toxicity profile. On the other hand, NAA are expensive, need be given indefinitely till disease progression, come with their own set of adverse effects, and are inaccessible for majority of patients from LMICs. Compliance to NAA also remains poor for all these reasons. However, our analysis shows that AAP-first treatment sequence offers better health outcomes compared to docetaxel- first sequence and is cost-effective. It incurs an incremental cost of ₹ 4,014 (US$ 51) per QALY gained as compared to docetaxel-first treatment sequence, which is cost-effective at the current WTP threshold of 1-time per capita GDP (₹ 186,788) of India. Enzalutamide-first sequence offers higher health benefits as compared to AAP-first sequence, however it is not cost effective at the current prices. A minimum of 48% price reduction is required to make enzalutamide-first sequence cost effective in India. Apalutamide-first is the dominated treatment sequence as it incurs a higher lifetime cost and offers lesser health outcomes than AAP-first treatment sequence.

With the availability of generic molecules for abiraterone acetate, and enzalutamide, cost of these drugs has significantly come down in India. In the light of these lowered drug prices, our analysis becomes even more significant to help oncologists in clinical decision making. Treatment selection based on adverse effect profile may be considered for patients not tolerating a particular drug.

Docetaxel was already approved in the AB-PMJAY and recent inclusion of AAP in the HBP should encourage physicians to prefer its use over docetaxel in the light of this evidence. Abiraterone is better tolerated than docetaxel in terms of its adverse effects and there is ease of

administration with AAP. Abiraterone acetate has a greater positive food effect which relates with an increase in the drug amount absorbed when taken with food. Phase II trials have shown that when low dose of AA is taken with high/ low fat diet, there is increased bioavailability (50). The use of low-dose AA (250mg) following a low-fat breakfast in mHSPC patients can significantly improve optimal utilisation of limited resources available with AB-PMJAY. Moreover, for those not covered under AB-PMJAY, it can decrease the economic burden for the patients. Our analysis shows that a 75% reduction in the drug dose for AA (from 1000mg to 250mg) provides better health outcomes at a lower cost as compared to the docetaxel-first treatment sequence in India, which significantly brings down the cost and may further improve compliance to this treatment. Though phase III data for this scenario is not available, the recommendation for low dose AA with low fat diet is still available in the internationally followed NCCN guidelines 2023 (51). The Indian Council Medical Research (ICMR) needs to encourage multicentric phase III trials for low dose AA in our country to achieve cost reductions for the treatment of metastatic prostate cancer. A survey has shown that of the 251 medical oncologists interviewed on the use of low dose AA in India, 55% were already prescribing it when patient resources were limited (52).

Cost effectiveness analysis for drugs specific to high volume or low volume metastatic burden patients, use of radiation therapy with or without NAA to primary prostate for low volume metastatic disease, use of triple drug therapy combining ADT with NAA and docetaxel needs robust data and remains a question for future analysis (12,53–55).

4.1 Model validation

Our study results are consistent with the published clinical and epidemiological literature. As per the published literature, the percentage of patients with radiographic PFS at 24 months was reported to be 68.2% with apalutamide, which is in line with our model estimates (66.9%) (11). Our study estimates a median PFS of 16 months in the docetaxel treatment arm which is line with the published evidence that report the median time to CRPC as 19.4 months (16.8 – 22.6) (12). Furthermore, we report a 2-year overall survival rate of 85% in the enzalutamide treatment arm, which is on par with the most recent report from the ARCHES trial that estimates a 2-year OS rate of 86.19% (9). Similarly, the recent evidence shows that 60% (55% - 64%) of mHSPC patients undergoing AAP are still alive at 5-years (21). Our study also reports a 57% survival in the AAP arm. We estimated a 5-year survival of 57%, 49.5%, and 45.3% in the AAP-first, enzalutamide-first, and apalutamide-first treatment sequences respectively. This is line with the

published Indian epidemiological studies that report a 5-year survival among metastatic PC to be 47.7% (56).

A recently published cost-effectiveness analysis that compared similar treatment combinations among mHSPC patients reported 4.76, and 3.92 QALYs among the AAP and enzalutamide arms respectively (16). However, it is important to note that this analysis relied on previously published effectiveness data for enzalutamide. Use of updated data, as shown in our analysis, rather shows that the QALYs lived are highest with enzalutamide. This study represents a notable advancement in the existing literature, incorporating long-term outcomes with enzalutamide.

4.2 Strengths & Limitations

Our study is a unique analysis that aimed to determine the cost-effectiveness of NAA and chemotherapy for treatment intensification in newly-diagnosed mHSPC patients in the Indian context. Firstly, the study captured the lifetime costs associated with the entire clinical course of the disease to make our analysis as close to the real-world as possible. Secondly, we also considered the costs and consequences associated with an additional BSC health state to mimic the actual clinical practice. Thirdly, we also performed a scenario analysis considering the use of low-dose AA instead of the standard AA regimen which has serious cost implications especially in developing economies such as India. Moreover, we incorporated the reimbursement rates set up under AB PM-JAY wherever available to make our analysis policy relevant (35,57). Lastly, we obtained the cancer-specific OOPE and quality of life estimates from the primary data collected as a part of an ongoing multicentric study for assessing the economic burden among cancer patients in India (33).

However, there are certain shortcomings of this analysis. Firstly, we did not use the India-specific disease mortality rates due to the lack of relevant literature in the country. Secondly, we did not consider the productivity losses incurred by the patients as well as the caregivers for the cancer treatment. This is in accordance with the Indian reference case and HTA guidelines which do not recommend the inclusion of indirect costs in the base-case results (17,18). Thirdly, we did not include the use of radiotherapy in our comparison for low-volume disease as robust data is not available. Similarly, metastatic burden-based analysis was not done due to heterogeneity in outcomes. Finally, while we obtained the updated efficacy data from original trials for different treatment sequences, we did not perform a network meta-analysis (NMA).

The published NMAs which has used the papers which reported the original trial results, showed superiority of AAP treatment over docetaxel and enzalutamide treatment options for mHSPC patients (48,49). However, these NMAs have not used updated trial results for enzalutamide, which show better efficacy than abiraterone on longer follow up. Hence, we recommend future research to aim at undertaking an NMA using the updated trial findings in order to derive more accurate and robust estimates (9).

4.3 Conclusions & Policy Implications

From the perspective of the Indian context, the AAP first treatment sequence is the cost effective treatment compared to other novel treatment combinations for newly-diagnosed mHSPC patients. Therefore, we concur with the inclusion of AAP treatment option in the India's publicly financed health insurance scheme as its use represent a true value for money. Findings from our study may help both clinical practice and reimbursement policy for this relatively common and costly condition. The use of low-dose AA (250mg/day) following a low-fat breakfast also shows promise in terms of lower overall cost and similar health benefits as the standard dose AA and should be considered where standard dose treatment is not feasible. Moreover, enzalutamide has the potential to be cost-effective at a 48% reduction in the current market price of the drug. Thus, from within the NAA, choice of drug should be determined by cost effectiveness evidence, which should also help to guide financing of treatment by the national health insurance scheme.

Declarations

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Conflict of Interest: The authors declare no conflicts of interest.

Availability of data and material (data transparency): The datasets generated during 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 statement: The study protocol was approved by the Institute Ethics Committee of the Post Graduate Institute of Medical Education and Research, Chandigarh, India (IEC-03/2020-1565).

Consent to participate: A written informed consent was obtained from all the study participants for quality of life and out of pocket expenditures and their consent was taken for using the data for publication.

Authors' contribution: Study conception: DG, NG, and SP. Study design: NG and DG. Analysis: DG, NG, and SP. Writing (first draft): DG, NG, and SP. Writing (review and editing): DG, NG, SP and KGV.

Key points for Decision Makers:

1. AAP-first sequence, which incurs an incremental cost of ₹ 4,014 (US$ 51) per QALY gained, has an 87% probability of being cost-effective at a WTP threshold of 1-time per capita GDP of India. Additionally, AAP-first treatment sequence incurs the highest incremental NMB of ₹ 396,491 (US$ 5,070) as compared to docetaxel-first treatment sequence. We, therefore, concur with the inclusion of AAP within PMJAY health benefit packages.
2. A 48% reduction in the price of enzalutamide is required to make enzalutamide-first treatment sequence cost-effective as compared to AAP-first treatment sequence in India.
3. Furthermore, low-dose AA dominates the docetaxel-first treatment sequence with lesser costs and better health outcomes.

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Supplementary Appendix

Cost-effectiveness analysis of systemic therapy for intensification of treatment in metastatic hormone-sensitive prostate cancer in India

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Model descriptions and methodology

We used a state-transition Markov model to analyse the cost-effectiveness of combination novel systemic regimens with androgen deprivation therapy (ADT), namely (i) Abiraterone acetate and prednisone (AAP); (ii) Docetaxel; (iii) Enzalutamide; and (iv) Apalutamide for newly diagnosed metastatic castrate-sensitive prostate cancer (mCSPC). The health states include: (1) newly diagnosed, progression-free (PFS) mCSPC, (2) progressed disease (PD) mCRPC, (3) best supportive care (BSC) and (4) death (inclusive of disease-specific and all-cause). The model is irreversible in the sense that the patients in the PD health state would not return to the PFS health state.

We incorporated four randomized controlled trials (RCTs; ARCHES, TITAN, STAMPEDE and CHAARTED) (1–4) for first-line treatment (PFS health state) with enzalutamide, apalutamide, abiraterone acetate and docetaxel respectively and three RCTs (AFFIRM, COU-AA-301 and PROSTY) (5–7) for second-line treatment (PD health state) to estimate the transition probabilities between health states (Table S1).

Table S1: Summary of the studies used to determine the efficacy of different treatment regimens

Treatment strategies for mHSPC patients (First line)				
Study characteristics	**Enzalutamide +ADT**	**Apalutamide + ADT**	**AAP + ADT**	**Docetaxel + ADT**
Author, year	Armstrong et al. (2022) (1)	Chi et al. (2019) (2)	James et al. (2017) (3)	Kyriakopoulos et al. (2018) (4)
Trial name	ARCHES	TITAN	STAMPEDE	CHAARTED
Sample size	574	525	500	397
Treatment strategies for mCRPC patients (Second line)				
	Enzalutamide/ AAP to Docetaxel	**Docetaxel to Enzalutamide**	**Docetaxel to AAP**	
Author, year	Kellokumpu-Lehtinen et al. (7)	Loriot et al. (5)	Fizazi et al. (6)	
Trial name	PROSTY	AFFIRM	COU-AA-301	
Sample size	184	800	797	

We firstly digitized the reported PFS curves and estimated the individual patient time-to-event data (including occurrence time of all the events) from the reconstructed curves. We then extrapolated the reconstructed curves to the appropriate parametric distributions (Exponential, Weibull, gompertz, log-normal and log-logistic). The goodness of fit was assessed according to Akaike Information criterion (AIC), Bayesian Information Criterion (BIC) and visual inspection. From these extrapolated curves, we determined the probability to stay in a particular health state (PFS or PD) using standard techniques. Figure S1 [(a)-(f)] presents the model calibration for all the different treatment regimens. The outcomes generated from the estimated transition probabilities were well-fitted with the reported survival outcomes for each treatment sequence.

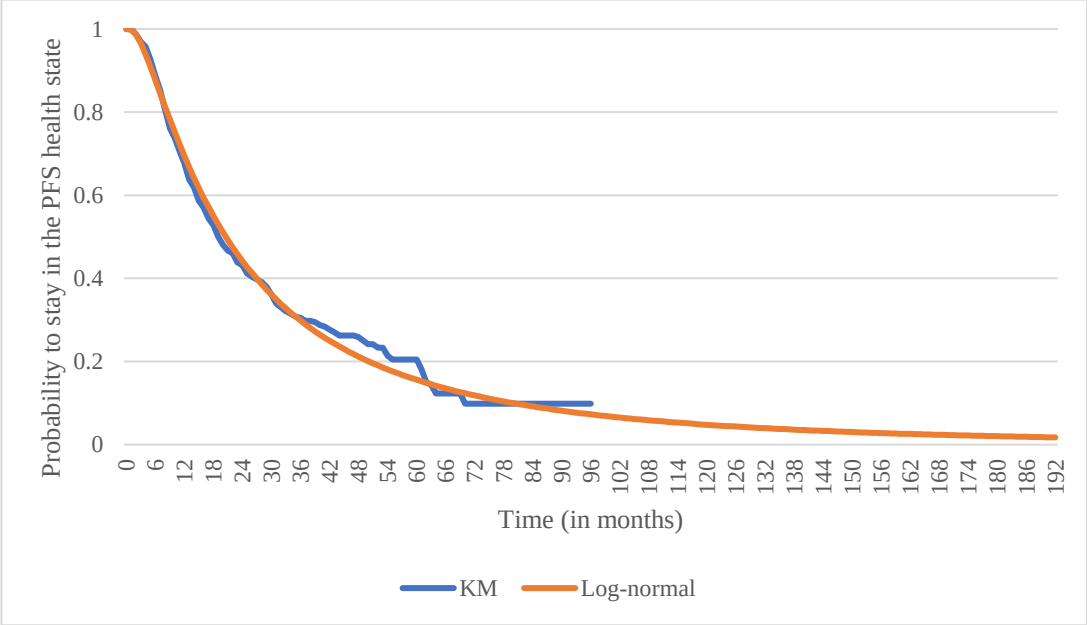

Figure S7(a): Kaplan Meier and Log-normal PFS survival curve for Docetaxel treatment in the PFS health state

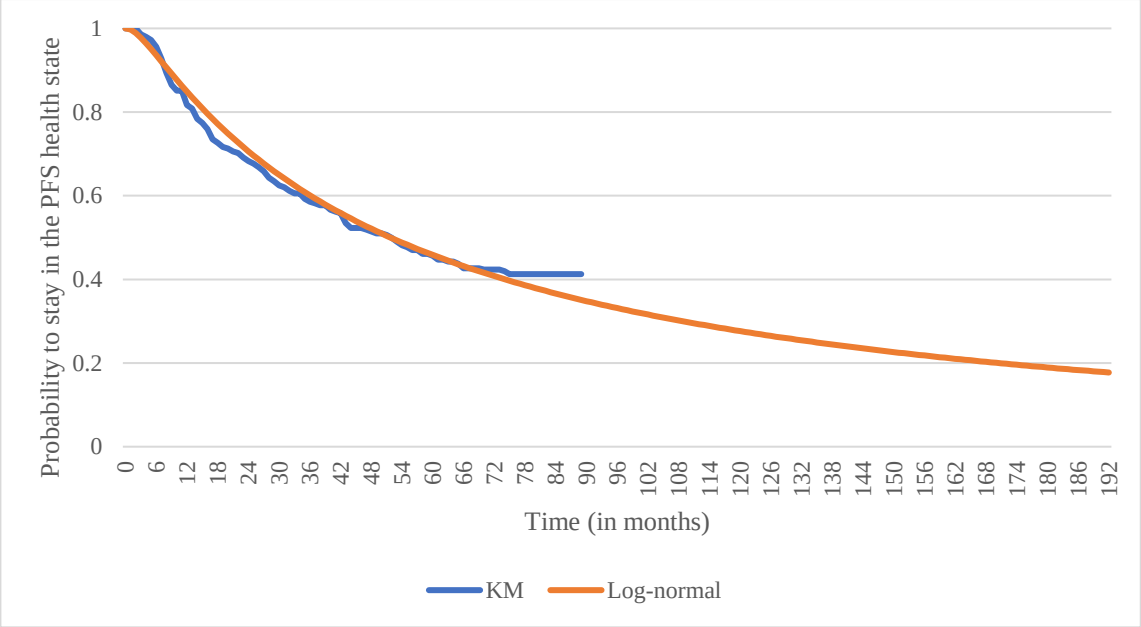

Figure S8(b): Kaplan Meier and Log-normal PFS survival curve for Abiratertone acetate plus prednisone treatment in the PFS health state

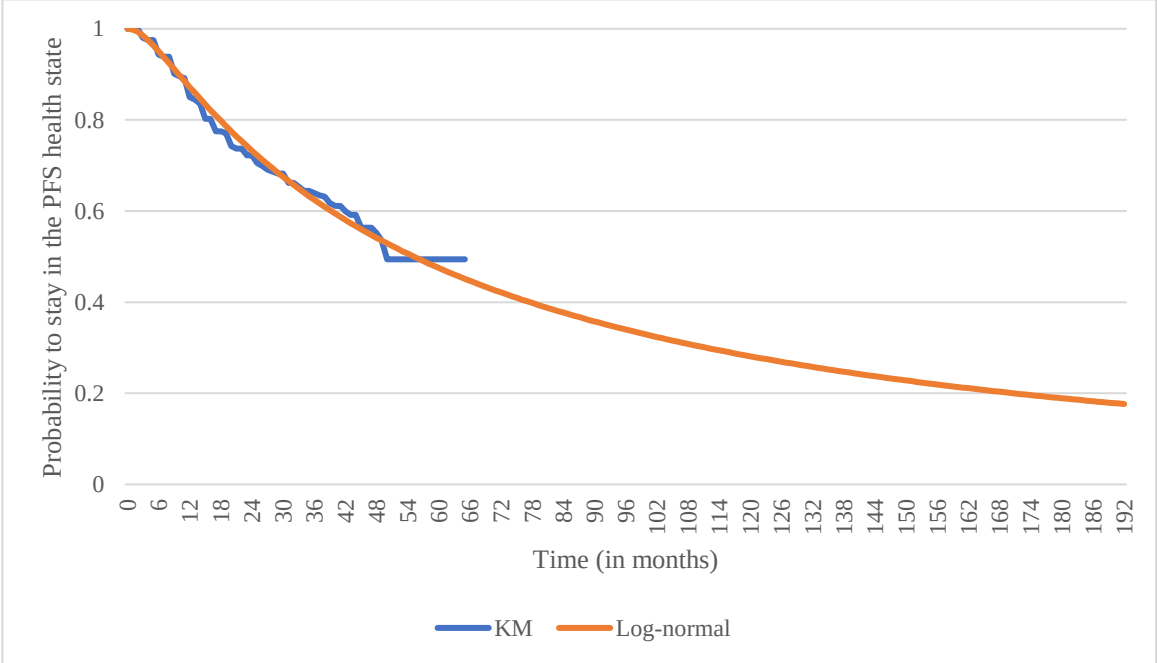

Figure S9(c): Kaplan Meier and Log-normal PFS survival curve for Enzalutamide treatment in the PFS health state

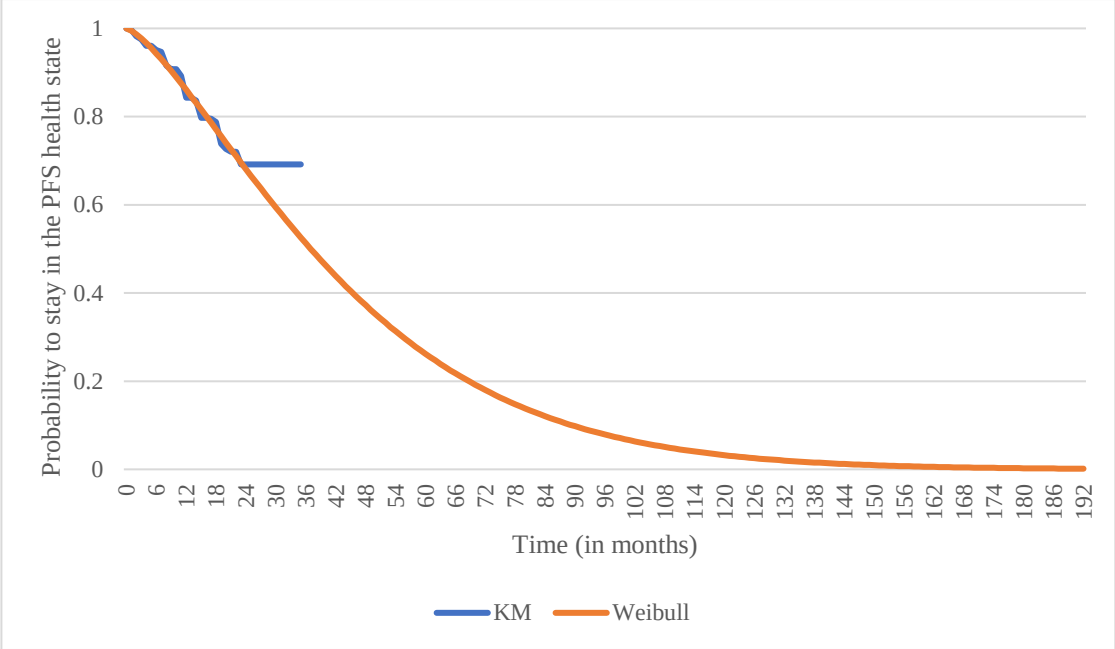

Figure S10(d): Kaplan Meier and Log-normal PFS survival curve for Apalutamide treatment in the PFS health state

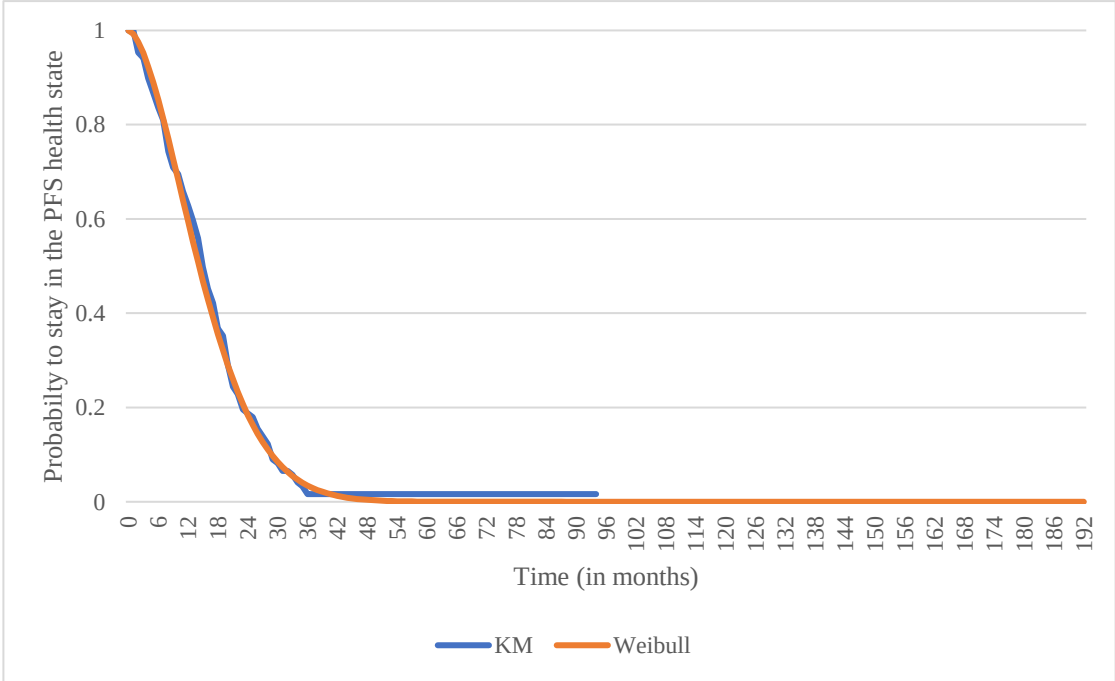

Figure S11(e): Kaplan Meier and Log-normal PFS survival curve for Docetaxel treatment in the PD health state

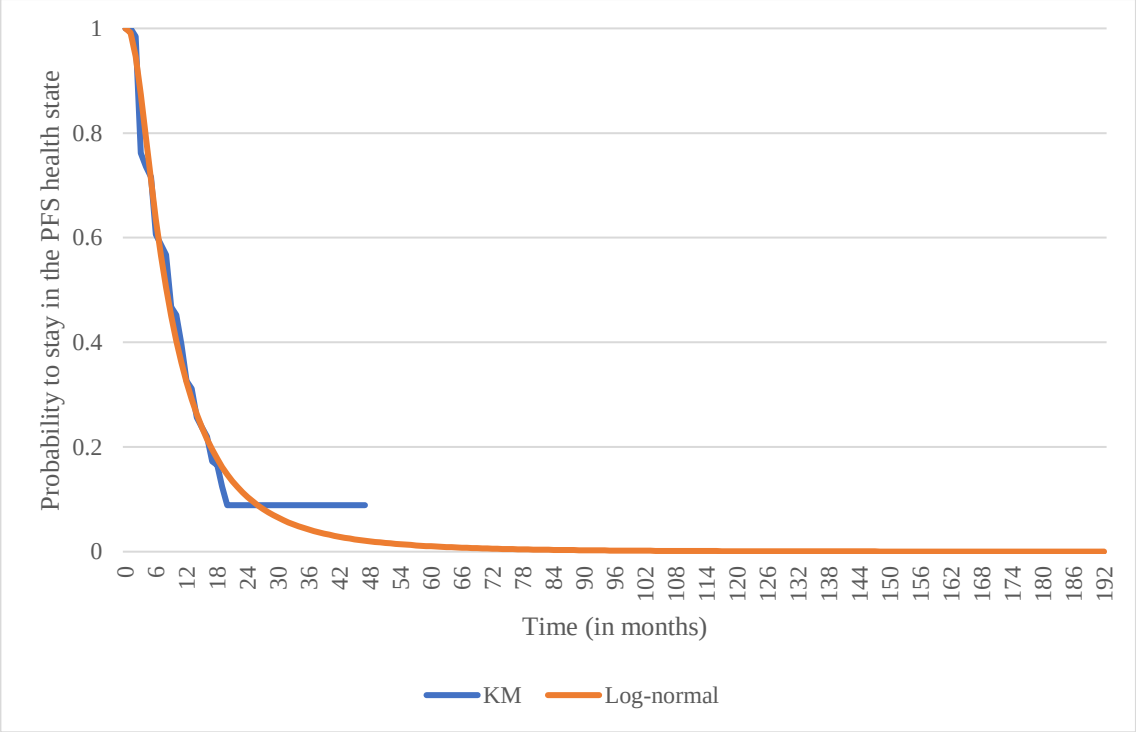

Figure S12(f): Kaplan Meier and Log-normal PFS survival curve for Enzalutamide treatment in the PD health state

Table S2. Costs of Individual Adverse Events

Type of Grade 3-4 adverse event	Mean cost, 2022 (₹)	Standard Error, 2022 (₹)	Distribution	Source
Hypertension	3.6	0.9	Gamma	(8)
Selected cardiovascular event	17,900	4,566.3	Gamma	(9)
Fractures	6,300	1,607.1	Gamma	(9)
Pain (Back pain/ Arthralgia/ Bone pain/ Musculoskeletal pain)	16.8	4.3	Gamma	(8)
Hypokalaemia	44.7	11.4	Gamma	(8)
Hepatotoxicity (Alanine plus aspartate)	421.6	107.6	Gamma	(8)
Hyperglycaemia (plus diabetes)	31.2	7.9	Gamma	(8)
Anaemia	2,000	510.2	Gamma	(9)
Spinal cord compression	15,000	3,826.5	Gamma	(9)
Haematuria	17.1	4.4	Gamma	(8)
Cataract	4,000	1,020.4	Gamma	(9)
Urinary Tract Infection	15.7	4.0	Gamma	(8)
Hyperkalaemia	12.1	3.1	Gamma	(8)
Rash	8.8	2.2	Gamma	(8)
Neutropenia	3,888.9	992.1	Gamma	(8)
Leucopenia	505	128.8	Gamma	(8)
Febrile neutropenia	33,250	8,482.1	Gamma	(9)

Infection without neutropenia	65.4	16.7	Gamma	(8)
Infection with neutropenia	33,250	8,482.1	Gamma	(9)
Diarrhoea	24.7	6.3	Gamma	(8)
Nausea	14.6	3.7	Gamma	(8)
Raised alkaline phosphatase concentration	421.6	107.6	Gamma	(8)
Watery eyes	11	2.8	Gamma	(8)
Thrombocytopenia	2,000	510.2	Gamma	(9)
Vomiting	14.6	3.7	Gamma	(8)
Constipation	83.8	21.4	Gamma	(8)
Neuropathy	32.7	8.3	Gamma	(8)

Table S3. Probabilities of Individual Adverse Events in the mHSPC state

Type of Grade 3-4 adverse event	Docetaxel + ADT	AAP + ADT	Enzalutamide + ADT	Apalutamide + ADT	Distribution	Source
Hypertension	-	0.216 (0.194 – 0.238)	0.033 (0.029 – 0.036)		Beta	(3,10)
Asthenia/ Fatigue/ Musculoskeletal weakness	-	0.038 (0.035 – 0.042)	0.028 (0.025 – 0.031)	0.034 (0.031 – 0.038)	Beta	(3,10,2)
Selected cardiovascular event	-	-	0.010 (0.009 – 0.011)	-	Beta	(10)
Fractures	-	-	0.010 (0.009 – 0.011)	0.063 (0.057 – 0.069)	Beta	(2,10)
Loss of consciousness	-	-	0.010 (0.009 – 0.011)	-	Beta	(10)
Musculoskeletal events	-	-	0.016 (0.014 – 0.017)	-	Beta	(10)
Secondary primary malignancies	-	-	0.016 (0.014 – 0.017)	-	Beta	(10)
Pain (Back pain/ Arthralgia/ Bone pain/ Musculoskeletal pain)	-	0.1 (0.090 – 0.111)	-	0.044 (0.039 – 0.038)	Beta	(3,2)
Hypokalaemia	-	0.117 (0.105 – 0.129)	-	-	Beta	(3)
Hepatotoxicity (Alanine plus aspartate)	-	0.104 (0.093 – 0.114)	-	-	Beta	(3)
Hyperglycaemia (plus diabetes)	-	0.059 (0.053 – 0.064)	-	-	Beta	(3)
Anaemia	-	0.028 (0.026 – 0.031)	-	0.017 (0.015 – 0.019)	Beta	(3,2)
Blood lactate dehydrogenase increased	-	0.022 (0.020 – 0.024)	-	-	Beta	(3)
Spinal cord compression	-	0.02 (0.018 – 0.022)	-	-	Beta	(3)
Urinary retention	-	0.018 (0.017 – 0.020)	-	-	Beta	(3)
Pneumonia	-	0.015 (0.014 – 0.017)	-	-	Beta	(3)
Haematuria	-	0.015 (0.014 – 0.017)	-	-	Beta	(3)
Cataract	-	0.013 (0.012 – 0.015)	-	-	Beta	(3)
Urinary Tract Infection	-	0.010 (0.009 – 0.011)	-	-	Beta	(3)
Weight increased	-	0.010 (0.009 – 0.011)	-	0.011 (0.010 – 0.013)	Beta	(3,2)
Hyperkalaemia	-	0.012 (0.010 – 0.013)	-	-	Beta	(3)
Rash	-	-	-	0.090 (0.081 – 0.099)	Beta	(2)

Neutropenia	0.528 (0.475 – 0.581)	-	-	-	Beta	(4)
Leukopenia	0.290 (0.261 – 0.319)	-	-	-	Beta	(4)
Febrile neutropenia	0.142 (0.128 – 0.156)	-	-	-	Beta	(4)
Infection without neutropenia	0.119 (0.11 – 0.131)	-	-	-	Beta	(4)
Infection with neutropenia	0.244 (0.220 – 0.269)	-	-	-	Beta	(4)
Diarrhoea	0.023 (0.204 – 0.025)	-	-	-	Beta	(4)
Nausea	0.114 (0.010 – 0.012)	-	-	-	Beta	(4)
Raised alkaline phosphatase concentration	0.062 (0.056 – 0.069)	-	-	-	Beta	(4)
Watery eyes	0.017 (0.015 – 0.019)	-	-	-	Beta	(4)

Table S4. Probabilities of Individual Adverse Events in the mCRPC state

Type of Grade 3-4 adverse event	Enzalutamide/ AAP to Docetaxel	Docetaxel to Enzalutamide	Docetaxel to AAP	Distribution	Source
Hypertension	-	-	0.013 (0.011 – 0.014)	Beta	(6)
Asthenia/ Fatigue/ Musculoskeletal weakness	0.041 (0.037 – 0.045)	0.062 (0.056 – 0.069)	0.124 (0.111 – 0.136)	Beta	(7,5,6)
Selected cardiovascular event	-	-	0.052 (0.047 – 0.057)	Beta	(6)
Pain (Back pain/ Arthralgia/ Bone pain/ Musculoskeletal pain)	-	0.01 (0.009 – 0.011)	0.248 (0.223 – 0.272)	Beta	(5,6)
Hypokalaemia	-	-	0.044 (0.040 – 0.049)	Beta	(6)
Hepatotoxicity (Alanine plus aspartate)	-	-	0.038 (0.034 – 0.041)	Beta	(6)
Anaemia	0.013 (0.011 – 0.014)	-	0.078 (0.070 – 0.086)	Beta	(7,6)
Neutropenia	0.120 (0.108 – 0.132)	-	-	Beta	(7)
Febrile neutropenia	0.085 (0.076 – 0.093)	-	-	Beta	(7)
Diarrhoea	0.010 (0.009 – 0.011)	-	0.011 (0.010 – 0.012)	Beta	(7,6)
Nausea	-	-	0.021 (0.019 – 0.024)	Beta	(6)
Thrombocytopenia	-	-	0.014 (0.012 – 0.015)	Beta	(6)
Vomiting	-	-	0.026 (0.024 – 0.029)	Beta	(6)
Dyspnoea	-	-	0.018 (0.016 – 0.019)	Beta	(6)
Constipation	-	-	0.013 (0.011 – 0.014)	Beta	(6)
Fluid retention/Oedema	-	-	0.025 (0.023 – 0.028)	Beta	(6)
Allergic reaction	0.020 (0.018 – 0.022)	-	-	Beta	(7)
Neuropathy	0.010 (0.009 – 0.011)	-	-	Beta	(7)

Table S5. Discounted cost and consequences with different treatment regimens for mHSPC health state

Treatment	Total Life-Years (95% CI)	Total QALYs (95% CI)	Total Costs (95% CI) in ₹
Docetaxel-first sequence	4.0 (3.2 – 4.9)	2.6 (1.9 – 3.5)	1,358,746 (786,081 – 2,587,998)
Abiraterone acetate plus Prednisone-first sequence	6.6 (4.4 – 9.5)	4.8 (2.9 – 7.3)	1,367,454 (777,051 – 2,174,383)
Enzalutamide-first sequence	6.9 (4.5 – 10.1)	5.03 (2.9 – 8.0)	2,168,885 (1,110,804 – 3,966,971)
Apalutamide-first sequence	4.7 (3.7 – 5.8)	3.2 (2.3 – 4.2)	7,678,501 (3,916,571 – 12,550,585)

mHSPC: metastatic hormone-sensitive prostate cancer; QALYs: Quality-Adjusted Life-Years; CI: Confidence Interval

Table S6. Discounted cost-effectiveness results: Scenario Analyses (Low-dose abiraterone)

Treatment sequence	Total lifetime cost in ₹	Total LYs	Total QALYs	ICER, ₹/QALY gained	iNMB (as per dominance analysis)	iNMB (vs Docetaxel)	iNMB (vs Abiraterone acetate)
Docetaxel-first sequence	1,358,746	3.99	2.61	D	ND	-	-
Apalutamide-first sequence	7,678,501	4.73	3.22	D	D	D	D
Low-dose abiraterone	642,865	6.65	4.78	-	-	1,121,081	-
Enzalutamide-first sequence	2,168,885	6.90	5.03	5,993,731 (vs AAP)	-1,478,464 (vs AAP)	-357,382	-1,478,464

mHSPC: metastatic hormone-sensitive prostate cancer; LY: Life-Years; QALY: Quality-adjusted Life-years; ICER: Incremental cost-effectiveness ratio; iNMB: incremental Net Monetary Benefit; ND: Non-dominated; D: Dominated; AAP: Abiraterone acetate plus prednisone

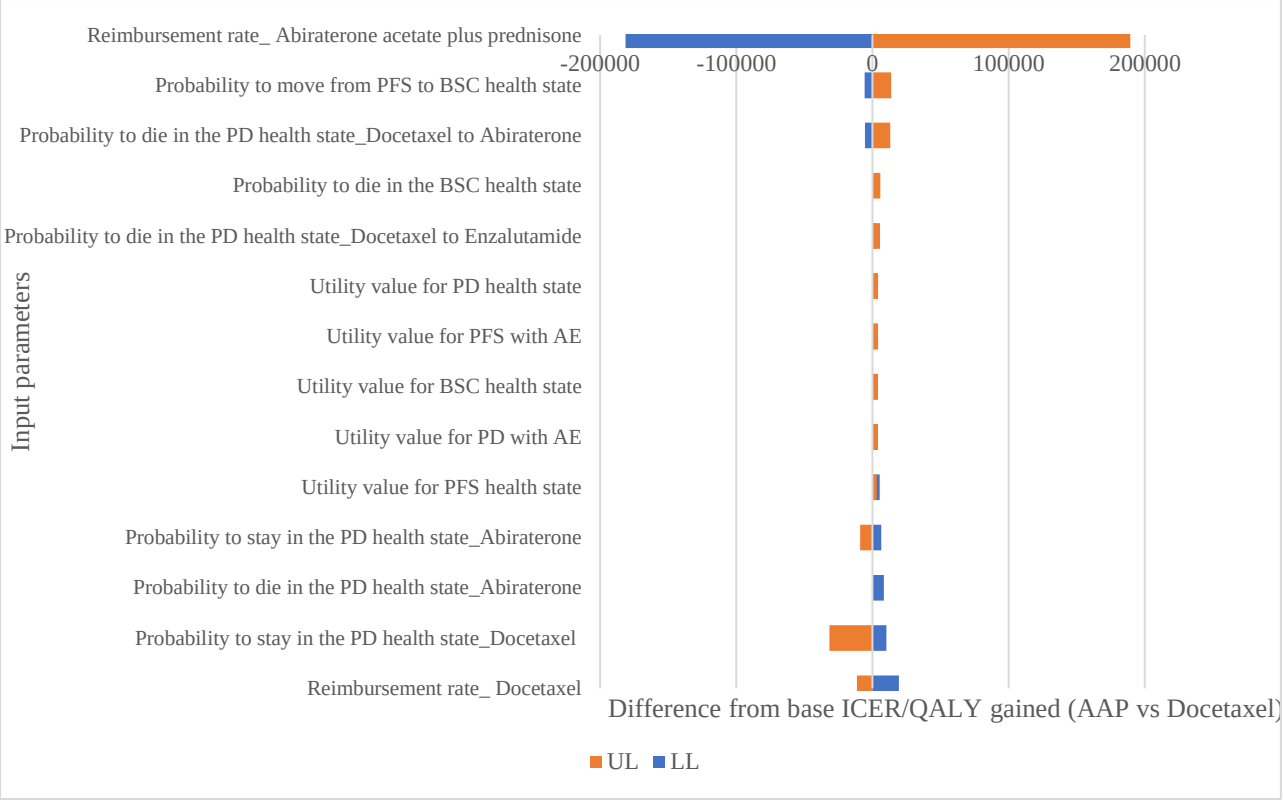

Figure S2: Univariate sensitivity analysis for Abiraterone acetate plus prednisone-first treatment sequence. ICER: Incremental cost effectiveness ratio; QALY; Quality-Adjusted Life-Years; PFS: Progression-free state; PD: Progressive disease; AE: Adverse events; BSC: Best supportive care; UL: Upper Limit; LL: Lower Limit

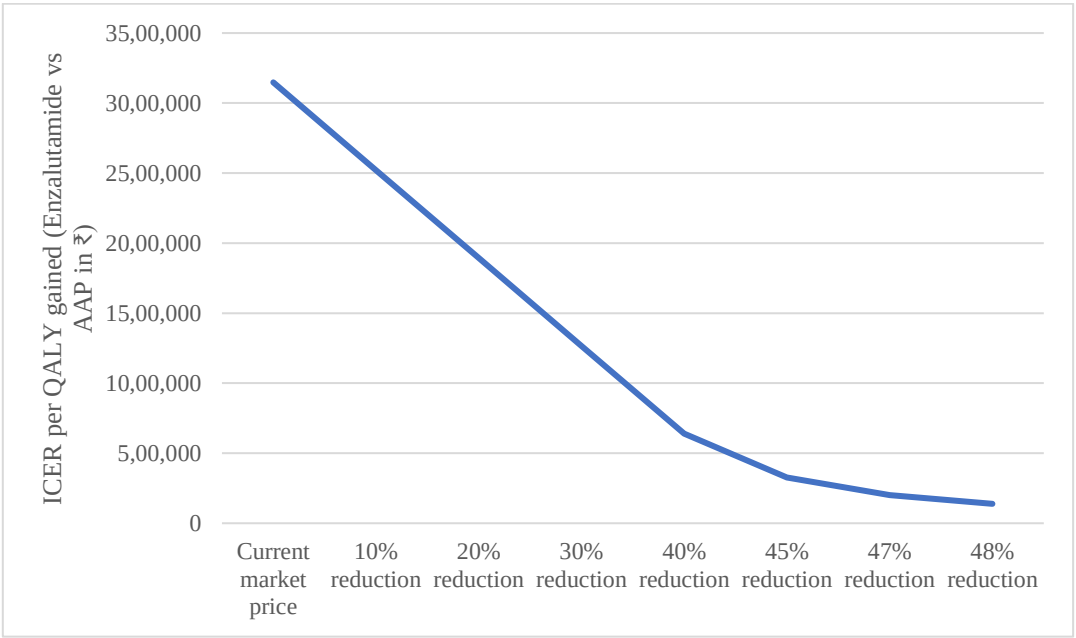

Figure S3: Price threshold analysis for Enzalutamide

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