



Cost-effectiveness Analysis of Innovative Therapy for Patients with Newly Diagnosed Hormone-Sensitive Metastatic Prostate Cancer

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ARTICLE TITLE: Cost-effectiveness analysis of innovative therapy for patients with newly diagnosed hormone-sensitive metastatic prostate cancer

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ABSTRACT:

Background: The optimal therapeutic strategies for patients with metastatic hormone-sensitive prostate cancer (mHSPC) followed by metastatic castrate-resistant prostate cancer (mCRPC), in terms of cost and effectiveness remains unknown. This study aims to compare the cost-effectiveness of various potential strategies, from the start of first-line treatment in mHSPC to the death of the patients.

Methods: Two Markov decision-analysis models were developed, one for cohort A “asymptomatic/mildly symptomatic patients in mCRPC” and one for cohort B “symptomatic patients in mCRPC”. Each strategy reflects daily practice for mHSPC until progression in mCRPC from the start of first treatment regimen with either docetaxel or abiraterone acetate plus prednisone (AA) in mHSPC to the death of the patient. The cost-effectiveness analysis was performed from the French public healthcare system perspective. Only direct medical costs were included. Survival data were extracted from results of published randomized clinical trials.

Results: For cohort A, docetaxel followed by AA is the most cost-effective therapeutic strategy (€96,925 for 4.24 life-years). For cohort B, docetaxel followed by docetaxel is the most cost-effective therapeutic strategy (€81,463 for 4.05 life-years). Sensitivity analyses confirmed the robustness of our results except for a price reduction of 70% for AA or enzalutamide.

Conclusions: Our approach is innovative to the extent that our analysis takes into account various potential strategies for mPC. Our economic evaluation suggests that a price reduction of AA or enzalutamide impacts on the results. This approach must continue, including new drugs for patients with mPC.

KEY-WORDS: cost-effectiveness analysis; hormone-sensitive; castrate-resistant; metastatic; prostate cancer

INTRODUCTION

Prostate cancer is the second most common cancer with an estimated 1.1 million new cases worldwide in 2012 and the third most common cause of cancer death in men with 307,000 deaths in developed countries¹⁻⁴.

Treatment of metastatic prostate cancer (mPC) can be divided into two different stages: (1) metastatic hormone-sensitive prostate cancer (mHSPC), i.e. naive from androgen deprivation therapy (ADT); (2) metastatic castrate-resistant prostate cancer (mCRPC), when the cancer has progressed on ADT. Following drug labels and clinical trial design, patients are also treated according their symptomatic state (asymptomatic/mildly symptomatic or symptomatic) when their cancer becomes castrate resistant⁵.

For men with an initial diagnosis of mHSPC, continuous ADT represented the standard of care until 2015. In 2015, chemohormonal combination therapy with docetaxel became a new standard of treatment based on results of CHAARTED and STAMPEDE arm C randomized clinical trials (RCTs)^{6,7}. In 2017, abiraterone acetate plus prednisone (AA) has shown survival benefit in terms of overall survival (OS) and progression-free survival (PFS) in mHSPC setting^{6,8}. Adding AA to ADT in newly diagnosed mHSPC is an alternative standard of care to docetaxel with ADT³. After disease progression, multiple additional treatments have shown to improve OS, including docetaxel, AA, enzalutamide, radium-223, sipuleucel-T, and cabazitaxel after docetaxel⁹⁻¹⁵.

Despite these benefits, the use of androgen directed therapies in mHSPC and mCRPC strategies are likely to increase the already substantial economic burden associated with the management of mPC. Furthermore, the optimal strategy of treatment for these patients, in terms of cost and effectiveness, is unknown.

In the context of rational decision making in health care, a major challenge in economic evaluation (EE) is to provide cost-effectiveness data that are relevant to daily practice and that may optimize the consumption of healthcare resources. Thus, the purpose of this study was to compare the cost-effectiveness of various sequential strategies, from the start of first-line treatment in mHSPC to patient death.

MATERIAL AND METHODS

Two Markov decision-analysis models were developed to compare the cost and effectiveness of strategies, according to the presence or absence of symptoms in the mCRPC stage: cohort A with “asymptomatic or mildly symptomatic patients” and cohort B with “symptomatic patients”¹⁶. The rational is based on the eligibility criteria of the registration trials and the European label of AA and enzalutamide. All strategies reflect daily practice for mHSPC until progression in mCRPC from the start of first treatment regimen with either docetaxel plus prednisone or AA in mHSPC to the death of the patient³ (Figure 1).

Radium-223 dichloride has been excluded because in Europe, this treatment is currently only for patients with progression after at least two prior lines of systemic therapy for mCRPC, or who are ineligible for any available systemic mCRPC treatment.

MARKOV DECISION-ANALYSIS MODEL

For all strategies compared ($SA1_{DOCE} \rightarrow SA1_{ABI}$, $SA2_{DOCE} \rightarrow SA2_{ENZA}$, $SA3_{ABI} \rightarrow SA3_{ENZA}$, $SA4_{ABI} \rightarrow SA4_{DOCE}$, $SB1_{DOCE} \rightarrow SB1_{CABA}$, $SB2_{DOCE} \rightarrow SB2_{DOCE}$ and $SB3_{ABI} \rightarrow SB3_{DOCE}$), three potential mutually exclusive health states defined disease history: mHSPC, mCRPC and death. All patients started in the mHSPC state, with the introduction of ADT and were followed up, with the possibility to move to the mCRPC state or dying (death state) (Figure 2). Cycle length was set at 1 month to facilitate patient monitoring and the use of published survival data.

MODEL ESTIMATES: CLINICAL PARAMETERS

A systematic literature search was conducted in PubMed to identify published RCTs until February 2020 based on selected Medical Subject Heading (MeSH) (Appendix 1). Articles

were chosen according inclusion criteria: phase III RCT in mHSPC or mCRPC with treatment regimens matching with treatment regimens used in our EE. Concerning the first-line chemotherapy in mCRPC setting, we used data from the FIRSTANA phase III RCT because it is a more recent dataset than the TAX327 and TROPIC RCTs^{9,10}.

We retained (1) OS, defined as the time from initiation of first-line systemic therapy to death from any cause or to last monitoring for survivors, and (2) PFS, defined as the time from treatment initiation to one of the first of the following: death, biochemical clinical or radiological progression according to RCTs^{6-9,14}. Based on selection of the survival data published in the literature, transition probabilities were calculated using the Declining Exponential Approximation of Life Expectancy (DEALE) method for each health state (Table 1)^{17,18}.

MODEL ESTIMATES: COSTS

The cost-effectiveness analysis (CEA) was performed from the perspective of the French public healthcare system. Only direct medical costs were included, from the start of treatment until death of patient (lifetime horizon), including cost related to treatment (hospitalization, in- and outpatient treatments), monitoring (radiological, clinical and biological), medical consultations and management of adverse events (appendix 2, 3, 4, 5 and 6). Minor costs and costs considered independent of the treatment regimen were not taken into account. Costs are expressed in Euros (reference year 2020).

A healthcare resource utilization model was built based on data from summaries of product characteristics of selected drugs, international guidelines, RCTs and consensus conferences (Appendix 5)^{3,6-9,14,19,20}. A committee of 8 experts (medical oncologists, radiation oncologists, urologists) then validated it.

The cost of a treatment administrated in hospital (consultation, drug and administration) is included in a French public Diagnosis-Related Group (DRG), with the exception of drugs deemed as innovative and expensive such as cabazitaxel (<http://atih.sante.fr>). For instance, the DRG “28Z07Z” for outpatient chemotherapy session is estimated at €384.0.

For each reimbursed drug administered in ambulatory settings, the exact used number of units per patient has been determined according to the posology and multiplied by its unit purchase price (Appendix 2). Unit prices of drugs were obtained from wholesale price lists from official tariffs (<http://ameli.fr>). Because of the large number of options available to administer ADT, an average cost of €124.6 has been applied to represent ADT use. All drugs were reimbursed at 100%.

The cost of radiological, clinical and biological monitoring for each strategy during mHSPC and mCRPC were based on official tariffs (<http://ameli.fr>) (Appendix 3, Appendix 4).

Each medical consultation was valued according the specialty of physician: €23 for general practitioner, €28 for specialist physician such as medical or radiation oncologist or urologist (<http://ameli.fr>) (Appendix 5).

Based on the selected phase III RCTs, common adverse events for grade 3 and 4 ($\geq 2\%$) have been identified and associated with a principal diagnosis for the event according to the International Classification of Diseases 10th revision code (ICD-10 code) (Appendix 6). Each ICD-10 code is associated with one DRG and then one cost.

BASE-CASE PRESENTATION AND SENSITIVITY ANALYSES

The Markov decision-analysis model and sensitivity analyses were conducted using TreeAge Pro Suite software (TreeAge Software, Inc., Williamstown, MA, USA). Effectiveness and direct medical costs were measured over 12 months, discounted according to 2.5% rate according to the French recommendations¹⁶. Strategies were ranked using an efficiency frontier. To do this, four strategies in cohort A and three strategies in cohort B were ranked from the least expensive to the most one, respectively. Each dominated strategy (i.e. more expensive and less effective than the previous one) and each extended dominated strategy (i.e. with higher ICER, which is greater than that of a more effective strategy) were excluded from further analysis. Incremental Cost-Effectiveness Ratios (ICERs) were calculated using the following formula: $(\text{Cost}_{\text{StrategyA}} - \text{Cost}_{\text{StrategyB}}) / (\text{Effectiveness}_{\text{StrategyA}} - \text{Effectiveness}_{\text{StrategyB}})$.

The robustness of base-case analysis was assessed through a series of deterministic one-way sensitivity analyses. Firstly, the potential impact of STAMPEDE indirect comparison of docetaxel *versus* AA results was assessed by applying a new transition probability based on one-quarter decrease in PFS of first-line docetaxel²¹. Secondly, the potential cross-resistance between AA and enzalutamide were taken into account by applying the new transition probability based on a 50% decrease in PFS of second-line enzalutamide for the strategy SA3_{ABI→ENZA}^{22,23}. Thirdly, the introduction of generic cabazitaxel, AA and enzalutamide into the European market in the near future will be associated with a price reduction assumed to be between 30 and 70%. We investigated such a reduction from the original price of 30, 50 and 70%.

RESULTS

BASE-CASE ANALYSIS

For cohort A, the least costly strategy is SA1_{DOCE→ABI}, at a cost of €96,925 for 4.24 life-years (LYs) (Table 2). With the same effectiveness (4.25 LYs), the strategy SA2_{DOCE→ENZA} is more expensive, at a cost of €102,090. Strategies SA4_{ABI→DOCE} and SA3_{ABI→ENZA} are dominated due to the greater cost and lower effectiveness.

For cohort B, the least costly strategy is SB2_{DOCE→DOCE}, at a cost of €81,463 for 4.05 LYs (Table 3). With the same effectiveness (4.07 LYs), the strategy SB1_{DOCE→CABA} is more expensive, at a cost of €105,748. Strategy SB3_{ABI→DOCE} is dominated due to the greater cost and lower effectiveness.

SENSITIVITY ANALYSES

The robustness of the base-case result was confirmed for cohort A when either a 50% decrease of PFS of enzalutamide, or a cost reduction of AA and enzalutamide of 30% or 50% was applied (Table 2). However, a cost reduction of AA and enzalutamide of 70% influenced the base-case results; SA3_{ABI→ENZA} become efficient at the threshold value of social willingness to pay of €50,000/LY in comparison with SA4_{ABI→DOCE}.

It is also confirmed for cohort B (Table 3). Only, a cost reduction of AA and cabazitaxel of 70% influences the base-case result; the strategy SB3_{ABI→DOCE} is then the least costly and effective and SB2_{DOCE→DOCE} and SB1_{DOCE→CABA} are not efficient at the threshold value of

social willingness to pay of €50,000/LY in comparison with $SB3_{ABI \rightarrow DOCE}$ and $SB2_{DOCE \rightarrow DOCE}$ respectively.

DISCUSSION

Cost-utility analysis is the preferred EE method whether health-related quality of life is identified as an important health effect of interventions. Unfortunately, not all health state utility values (HSUV) essential to develop one were available in the literature. In addition, the choice of population used to elicit HSUVs is heterogeneous, and none are reported for French patients specifically. As a consequence, we conducted a CEA.

The chosen model dividing into two cohorts based on symptoms when patient becomes castrate resistant can be criticized, when currently majority of patients receive either AA or enzalutamide in first-line castrate resistant. From that perspective our model is covering this possibility as shown in figure 1a, therefore the main patients' flow is covered. However, the choice to describe this 2 possible scenarii was deliberate while taking into account the European label of AA and enzalutamide as the first-line in castrate resistant stage. On the same line, the eligibility criteria of the phase III registration trials COUAA302 and PREVAIL selected patient asymptomatic or mildly symptomatic from mPC, without opioid consumption^{13,14}.

The results of our CEA suggest that docetaxel for patient with mHSPC is cost-effective in comparison with AA. This result is consistent with the literature²⁴⁻²⁸. Strategies SA1_{DOCE→ABI} and SA2_{DOCE→ENZA} are dominant for cohort A, while SB2_{DOCE→DOCE} and SB1_{DOCE→CABA} are dominant for cohort B.

For cohort A, the choice of first-line treatment in mCRPC can be either AA, or enzalutamide, but enzalutamide is €5,165 more when compared with AA (€102,090 *versus* €96,925). However, because enzalutamide does not require corticosteroids, and does not require

frequent blood work to assess liver function and electrolytes, it may be easier to use and a more practical choice for some patients.

For cohort B, the choice of first-line treatment in mCRPC can be either docetaxel, or cabazitaxel, but cabazitaxel is €24,285 more when compared with docetaxel (€105,748 *versus* €81,463). Cabazitaxel was developed for use in patients who had disease progression after treatment with docetaxel, and has significant benefit in the post-docetaxel setting due to lack of complete cross-resistance²⁹.

The uncertainty related to clinical estimates and cost estimates and assumptions were taken into account in the sensitivity analyses (only deterministic not probabilistic) to assess the robustness of results. The latter was confirmed. However, a cost reduction of AA, enzalutamide and cabazitaxel by 70% influenced the base-case result. The introduction of generic AA, enzalutamide and cabazitaxel into the European market in the near future is expected to be associated with a price reduction of 70%, and will modify the results of the CEA and may influence daily practice. More recently, trials led to the use of additional androgen receptor directed therapies (enzalutamide and apalutamide) to be used in combination with ADT for mHSPC^{30–32}. These results will also need to be updated by the availability and coverage of new treatments such as apalutamide or enzalutamide in mHSPC setting.

However, our results need to be viewed within its limited context, i.e. a Markov decision-model with hypothetical cohort of patients with characteristics derived from selected RCTs. Clinical parameters of both models derived from results of selected phase III RCTs and may not be generalizable to the broader patient population. It was possible to choose between the results of FIRSTANA and PROSELICA to calculate transition probabilities related to cabazitaxel for strategy SB1DOCE→CABA. The model incorporated data from FIRSTANA

because it allowed homogenization in terms of first-line of chemotherapy in mCRPC whereas PROSELICA included second-line chemotherapy in mCRPC¹⁵. Moreover, there are no large-scale published prospective data detailing the sequence of docetaxel in mHSPC followed by cabazitaxel as first-line therapy for mCRPC.

The assessment of PFS differed according to selected RCTs (clinical, radiological or tumor) at the origin of a potential bias. We can also underline that we expect only limited benefit to treatment with enzalutamide in patients previously treated with AA for mHSPC (SA3_{ABI}→ENZA), due to similar mechanisms of cross resistance for these treatments²³. The choice of DEALE method is questionable as long as other methods exist to extrapolate survival data.

Out-of-pocket, indirect and intangible medical costs were not taken into account as costs for loss of productivity. The cost for each strategy has therefore been underestimated. Nevertheless, large out-of-pocket costs related to things like missed work and other indirect expenses are relatively unlikely given the mean age of patients with mHSPC.

To our knowledge, no EE has previously been published describing the cost-effectiveness of two successive lines of treatment in patients with mPC. Published EE have been restricted to one line of treatment: either treatment for mHSPC, or first- or second-line treatment for mCRPC^{24–28,33–37}. In addition, none of these were developed from a French or European healthcare system perspective. Thus, comparison with our study is limited due to our inclusion of multiple lines of therapy, and the populations assessed. We believe the innovative approach of this study in defining optimal sequencing for patients moving from mHSPC to mCRPC is unique, and the results add useful information to clinician and patients facing treatment decisions in the real world.

In conclusion, the management of mPC has been significantly modified by the availability of effective but expensive treatments. The best therapeutic sequence in terms of cost and effectiveness has not been previously defined. Our CEA suggests that docetaxel in the mHSPC setting is cost-effective, and can be followed by either AA, or a second round of docetaxel. Making choices based on the degree of symptomatology may lead clinicians to use more docetaxel followed by another taxane in patients with a greater symptom burden. In the next version of this analysis, we will incorporate newer treatments such as apalutamide and enzalutamide in patients with mHSPC.

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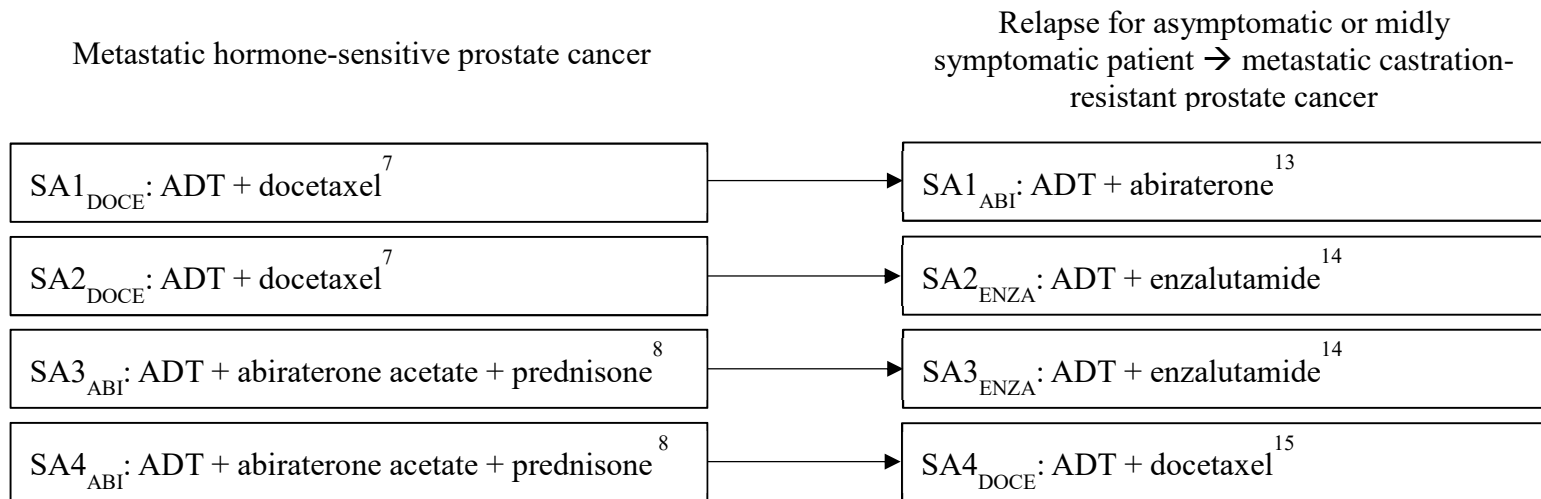
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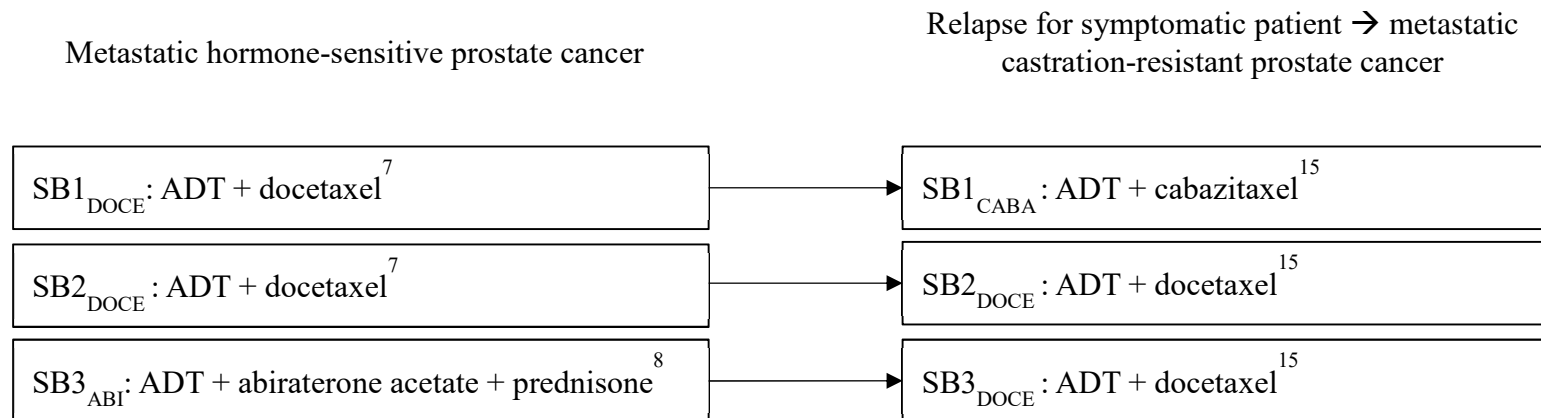
FIGURES

Figure 1: Compared strategies in the economic evaluation for cohorts A and B

1a) mHSPC then asymptomatic or mildly symptomatic patient in mCRPC setting

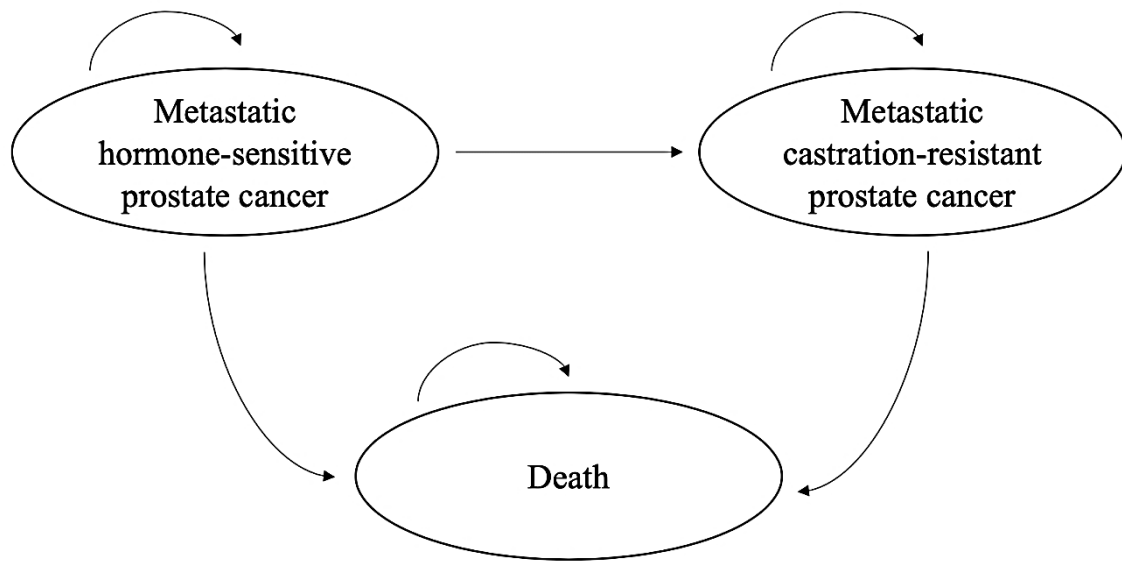


1b) mHSPC then symptomatic patient in mCRPC setting



Abbreviations: ADT = Androgen Deprivation Therapy; SA = Strategy for cohort A; SB = Strategy for cohort B; mHSPC = metastatic hormone-sensitive prostate cancer; mCRPC = metastatic castrate-resistant prostate cancer

Figure 2: Markov Health states and transitions



TABLES

Table 1: Randomized clinical trials used to determine transition probabilities

Study	Treatment	Line of treatment	Regimen	Median PFS, month [95% CI]	Median OS, month [95% CI]	Strategies*
CHAARTED	ADT + docetaxel (n = 397)	First-line	ADT + docetaxel 75	cPFS: 33.0 [29.1 – 40.9]	57.6 [52.0 – 63.9]	SA1 _{DOCE} , SA2 _{DOCE} ,
Sweeney <i>et al.</i>		(mHSPC)	mg/m ² /day for 6 cycles			SB1 _{DOCE} , SB2 _{DOCE}
N Engl J Med 2015 ⁷	vs. ADT alone (n = 393)		ADT alone	cPFS: 19.8 [17.8 – 22.5]	47.2 [41.8 – 52.8]	
LATITUDE	ADT + abiraterone acetate plus prednisone	First-line	abiraterone acetate	rPFS: 33.0 [NR – NR]	53.3 [48.2 – NR]	SA3 _{ABI} , SA4 _{ABI} ,
Fizazi <i>et al.</i>	(n = 602)	(mHSPC)	1000 mg/day			SB3 _{ABI}
N Engl J Med 2017 ⁸	vs. ADT alone (n = 597)		ADT alone	rPFS: 14.8 [NR – NR]	36.5 [33.5 – 40.0]	
COU-AA-302	ADT + abiraterone acetate plus prednisone	First-line	abiraterone acetate	rPFS: 16.5 [NR – NR]	34.7 [32.7 – 36.8]	SA1 _{ABI}
Ryan <i>et al.</i>	(n = 546)	(mCRPC)	1000 mg/day			
N Engl J Med 2013 ¹³	vs. ADT alone (n = 542)		ADT alone	rPFS: 8.2 [NR – NR]	30.3 [28.7 – 33.3]	
PREVAIL	ADT + enzalutamide (n = 872)	First-line	enzalutamide 160 mg/day	rPFS: 20.0 [18.9 – 22.1]	35.3 [32.2 – NR]	SA2 _{ENZA} , SA3 _{ENZA}
Beer <i>et al.</i>		(mCRPC)				
N Engl J Med 2014 ¹⁴	vs. ADT alone (n = 845)		ADT alone	rPFS: 5.4 [4.0 – 5.6]	31.3 [28.8 – 34.2]	

FIRSTANA	ADT + cabazitaxel 20mg/m ² (n = 389)	First-line	cabazitaxel 20 mg/m ²	tPFS: 13.4 [11.4 – 14.8]	24.5 [21.8 – 27.2]	
Oudard <i>et al.</i>		(mCRPC)				
J Clin Oncol 2017 ¹⁵	vs. ADT + cabazitaxel 25mg/m ² (n = 388)		cabazitaxel 25 mg/m ²	tPFS: 13.1 [11.7 – 14.3]	25.2 [22.9 – 27.0]	SB1 _{CABA}
	vs. ADT + docetaxel (n = 391)		docetaxel 75 mg/m ²	tPFS: 12.1 [11.3 – 13.8]	24.3 [22.3 – 27.6]	SA4 _{DOCE} ,
			every 3 weeks			SB2 _{DOCE} , SB3 _{DOCE}

Abbreviations: ADT = Androgen Deprivation Therapy; CI = Confidence Interval; cPFS = clinical Progression-Free Survival, mCRPC = metastatic Castration Resistant Prostate Cancer; mHSPC = metastatic Hormone Sensitive Prostate Cancer; NR = not reached; rPFS = radiological Progression-Free Survival; SA = Strategy of cohort A; SB = Strategy of cohort B; tPFS = tumor Progression-Free Survival; vs = versus

*all strategies are described in Figure 1

Table 2: Base-case results and deterministic one-way sensitivity analyses for cohort A

Strategy*	Cost (€)	Effectiveness (LYs)	Incremental cost (€)	Incremental effectiveness (LYs)	ICER (€/LYs)
Base-case analysis					
SA1 _{DOCE→ABI}	96,925	4.24	-	-	Reference
SA2 _{DOCE→ENZA}	102,090	4.25	5,165	0.01	476,769
SA4 _{ABI→DOCE}	149,865	3.97	47,775	-0.27	Dominated
SA3 _{ABI→ENZA}	168,383	4.15	18,518	0.17	Dominated
Sensitivity analysis: 25% decrease of PFS of first-line docetaxel used in the base-case analysis					
SA1 _{DOCE→ABI}	86,641	3.73	-	-	Reference
SA2 _{DOCE→ENZA}	92,485	3.75	5,844	0.01	Ext. dominated
SA4 _{ABI→DOCE}	149,865	3.97	57,380	0.23	Ext. dominated
SA3 _{ABI→ENZA}	168,383	4.15	18,518	0.17	198,966
Sensitivity analysis: 50% decrease of PFS of second-line enzalutamide post-abiraterone acetate plus prednisone used in the base-case analysis					
SA1 _{DOCE→ABI}	96,925	4.24	-	-	Reference

SA2 _{DOCE→ENZA}	102,090	4.25	5,165	0.01	476,769
SA4 _{ABI→DOCE}	149,865	3.97	47,775	-0.27	Dominated
SA3 _{ABI→ENZA}	156,211	3.83	54,121	-0.41	Dominated

Sensitivity analysis: cost reduction of abiraterone acetate plus prednisone and enzalutamide of 30%

SA1 _{DOCE→ABI}	90,708	4.24	-	-	Reference
SA2 _{DOCE→ENZA}	94,076	4.25	3,368	0.01	310,892
SA4 _{ABI→DOCE}	115,909	3.97	21,833	-0.27	Dominated
SA3 _{ABI→ENZA}	127,241	4.15	33,165	-0.10	Dominated

Sensitivity analysis: cost reduction of abiraterone acetate plus prednisone and enzalutamide of 50%

SA1 _{DOCE→ABI}	86,560	4.24	-	-	Reference
SA2 _{DOCE→ENZA}	88,730	4.25	2,170	0.01	200,308
SA4 _{ABI→DOCE}	93,299	3.97	4,569	-0.27	Dominated
SA3 _{ABI→ENZA}	99,836	4.15	11,106	-0.10	Dominated

Sensitivity analysis: cost reduction of abiraterone acetate plus prednisone and enzalutamide of 70%

SA4 _{ABI→DOCE}	70,649	3.97	-	-	Reference
SA3 _{ABI→ENZA}	72,392	4.15	1,743	0.17	10,153

SA1 _{DOCE→ABI}	82,421	4.24	10,029	0.09	Ext. dominated
SA2 _{DOCE→ENZA}	83,384	4.25	963	0.01	109,012

Abbreviations: ADT = Androgen Deprivation Therapy; Ext. dominated = Extended dominated; ICER = Incremental Cost Effectiveness Ratio;

LYs = Life-Years; SA = Strategy of cohort A

*all strategies are described in Figure 1

Table 3: Base-case results and deterministic one-way sensitivity analyses for cohort B

Strategy*	Cost (€)	Effectiveness (LYs)	Incremental cost (€)	Incremental effectiveness (LYs)	ICER (€/LYs)
Base-case analysis					
SB2 _{DOCE→DOCE}	81,463	4.05	-	-	Reference
SB1 _{DOCE→CABA}	105,748	4.07	24,285	0.02	1,267,043
SB3 _{ABI→DOCE}	149,865	3.97	44,117	-0.10	Dominated
Sensitivity analysis: 25% decrease of PFS of first-line docetaxel used in the base-case analysis					
SB2 _{DOCE→DOCE}	69,473	3.53	-	-	Reference
SB1 _{DOCE→CABA}	96,228	3.55	26,755	0.02	Ext. dominated
SB3 _{ABI→DOCE}	149,865	3.97	53,637	0.43	179,982
Sensitivity analysis: cost reduction of abiraterone acetate plus prednisone and cabazitaxel of 30%					
SB2 _{DOCE→DOCE}	81,463	4.05	-	-	Reference
SB1 _{DOCE→CABA}	98,629	4.07	17,166	0.02	895,617
SB3 _{ABI→DOCE}	115,909	3.97	17,280	-0.10	Dominated
Sensitivity analysis: cost reduction of abiraterone acetate plus prednisone and cabazitaxel of 50%					

SB2 _{DOCE→DOCE}	81,463	4.05	-	-	Reference
SB3 _{ABI→DOCE}	93,299	3.97	11,836	-0.08	Dominated
SB1 _{DOCE→CABA}	93,885	4.07	586	0.10	648,104
Sensitivity analysis: cost reduction of abiraterone acetate plus prednisone and cabazitaxel of 70%					
SB3 _{ABI→DOCE}	70,649	3.97	-	-	Reference
SB2 _{DOCE→DOCE}	81,463	4.05	10,814	0.08	133,781
SB1 _{DOCE→CABA}	89,141	4.07	7,678	0.02	400,591

Abbreviations: ADT = Androgen Deprivation Therapy; Ext. dominated = Extended dominated; ICER = Incremental Cost Effectiveness Ratio;

LYs = Life-Years; SB = Strategy of cohort B

*all strategies are described in Figure 1