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COST EFFECTIVENESS ANALYSIS OF ENZALUTAMIDE, ABIRATERONE PLUS PREDNISONE AND CABAZITAXEL PLUS PREDINSONE FOR THE TREATMENT OF VISCERAL METASTATIC CASTRATION RESISTANT PROSTATE CANCER (MCRPC) AFTER DOCETAXEL THERAPY

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DEDICATION

This thesis is wholeheartedly dedicated to my lovely wife Nariman, adorable son Khaled, and my amazing parents Dr. Khaled Barqawi and Zeena Al-Hasani whose life-long indefatigable efforts have helped me in achieving this success. I am proud and glad to be part of this lovely family. They are my source of inspiration in life and whose unconditional love and support always motivate me to set higher goals and keep moving forward. I could not have reached this point without their support.

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ABSTRACT

Background: Prostate cancer is the second leading cause of death after lung cancer among men in the US. The America Cancer Society predicts 164,690 new cases and 29,430 prostate cancer deaths in 2018. Of those diagnosed with prostate cancer, about 10-20 % will develop castration-resistant prostate cancer (CRPC) within 5 years of diagnosis and 70 % of those cases will metastasize to mCRPC. In 2014, nearly US $13.4 billion was spent on prostate cancer in the US and expected to reach US $15.4 billion by 2020; making prostate cancer the fifth most costly cancer.

Objective: To conduct a cost-effective analysis of enzalutamide, abiraterone plus prednisone and cabazitaxel plus prednisone for the treatment of visceral mCRPC post-docetaxel failure from a US healthcare payer perspective utilizing life-time horizon Markov model. These medications received highest National Comprehensive Cancer Network (NCCN) guideline recommendation to treat visceral mCRPC post-docetaxel failure.

Methods: A pharmacoeconomic model was constructed using Microsoft Excel® supported by visual basic codes and macros functions to estimate the cost-effectiveness [cost per life year gained (LYG)] and cost-utility analyses [cost per quality adjusted life year (QALY)] of visceral mCRPC therapies from a US healthcare perspective. We included direct medical costs in the model expressed in 2018 US dollars. All model costs were adjusted for

inflation through the medical consumer price index (MCPI) as per the 1st quarter of 2018 and future costs were discounted at 3 %, (i.e. drug costs, grade (≥3) adverse events that occurred at least in 5 % of visceral mCRPC patients, costs of physician follow up, needed blood and imaging investigations). We calculated overall survival (OS) and progression-free survival (PFS) transition probabilities for each of the alternatives (abiraterone plus prednisone, enzalutamide and cabazitaxel plus prednisone) from the Kaplan-Meier survival curves of phase III trials using a digitizing program (Webplotdigitizer). Incremental cost-effectiveness ratios (ICERs) [cost per life year gained (LYG)] and incremental cost-utility ratios (ICURs) [cost per quality adjusted life year (QALY)] were calculated. Probabilistic sensitivity analysis was conducted to assess the robustness of base-case analysis and provide cost-effectiveness acceptability curve at various willingness-to-pay thresholds.

Results: Model results indicate (98.7 %) of patients who receive abiraterone acetate plus prednisone, (83.8 %) who receive cabazitaxel plus prednisone and (86.8 %) who receive enzalutamide are expected to die in 3 years. In 1.5 years' time, patients who receive enzalutamide will have significantly higher rates (14.47 %) of PFS than cabazitaxel plus prednisone (0.27 %) and abiraterone acetate plus prednisone (0.51 %). Enzalutamide was found to be more effective (1.58 LYG and 0.79 QALY) compared to abiraterone plus prednisone (1.20 LYG and 0.58 QALY) and cabazitaxel plus prednisone (1.48 LYG and 0.56 QALY). Enzalutamide was also associated with lower total costs ($157,830) compared to abiraterone acetate plus prednisone ($235,853) and cabazitaxel plus prednisone ($496,756). Cabazitaxel plus prednisone had an ICER & ICUR of $931.7K/LYG and almost 13 million/QALY respectively when compared to the next lowest treatment, abiraterone acetate plus prednisone.

Conclusion: Enzalutamide is cost-effective compared to abiraterone acetate plus prednisone and cabazitaxel plus prednisone from a US healthcare perspective. Abiraterone acetate plus prednisone is less effective and less costly compared to cabazitaxel plus prednisone.

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CHAPTER 1: INTRODUCTION

Introduction

This chapter consists of four sections. First, we provide an overview of prostate cancer, treatment of prostate cancer and castration resistant prostate cancer (CRPC). In the second section, we discuss current therapeutic options used in metastatic castration resistant prostate cancer (mCRPC). In the third section, we explore the importance of conducting cost-effectiveness analysis (CEA) for healthcare and policy decision makers as well as the significance of this study to the current literature. Finally, we discuss the purpose of our study.

Overview of prostate cancer

Prostate cancer is the second leading cause of death after lung cancer among men and the most common noncutaneous cancer affecting males in the United States (US).[1,2] In 2016, 180,890 newly diagnosed cases and 26,120 prostate cancer deaths were reported.[2] The America Cancer Society (ACS) predicts 164,690 new cases and 29,430 prostate cancer deaths in 2018.[3] Of those diagnosed with prostate cancer, about 10-20 % will develop castration-resistant prostate cancer (CRPC) within 5 years of diagnosis and 70 % of those cases will metastasize to mCRPC.[4–6]

Prostate cancer creates a substantial medical and non-medical burden.[7] In 2006, nearly US $9.9 billion was spent on prostate cancer in the United States, increasing to US $11.9 billion in 2012, US $13.4 billion in 2014 and expected to reach US $15.4 billion by 2020; making prostate cancer the fifth most costly cancer.[7–9] There are several important clinical and economic implications for utilizing newer therapeutic options that show improved survival and minimize cost.

Although annual incidence of low-risk prostate cancer decreased from 25,708 to 16,223 (37 % reduction) from 2004 to 2013, annual incidence of metastatic prostate cancer increased from 1,685 to 2,890 cases during those years.[10] Metastatic prostate cancer cases were predominantly reported or diagnosed in men aged 55-69 years (92%).[10] In addition, although age-adjusted mortality of prostate cancer has declined by 51 % from 1993-2014, there is evidence that decreasing death rates are due to increased public awareness and earlier detection utilizing prostate specific antigen (PSA) screening and digital rectal examination (DRE).[11]

The National Comprehensive Cancer Network (NCCN) guideline highly recommends efficient use of PSA screening for early detection to decrease risk of over-detection and potential over-treatment while maintaining the reduction in age-adjusted mortality due to prostate cancer.[6]

Several underlying mechanisms have been reported in the literature to better inform healthcare providers about the pathogenesis of prostate cancer.[12] These include the ongoing androgen biosynthesis by the adrenal glands, upregulation of androgenic receptors and prostatic tumor-mediated cytochrome P17 (CYP17), and the activation of androgen receptors via different pathways.[13,14] For the case of metastatic prostate cancer, the mechanical theory and the seed-and-oil theory are two current theories that explain how locally invasive prostate cancer becomes metastatic.[12] The mechanical theory attributes the spread of prostate cancer through the lymphatic system.[12] Investigators or proponents of the seed-and-oil theory believe that tissue factors facilitate the growth and the spread of cancerous cells.[12] Genetic variation and mutation, positive family history of prostate cancer, diet and the use of 5-alpha reductase inhibitors for benign prostatic

hyperplasia (BPH) have been reported to be associated with causing high-grade aggressive prostate cancer.[15–17]

The main indicators of prostate cancer prognosis are well described in the literature. The first diagnostic indicator is the Gleason pattern. The Gleason Pattern is a scoring system used to determine the aggressiveness of prostate cancer and assists in choosing appropriate treatment options.[18] The literature has also reported that three consecutive increases in PSA levels after radiation therapy, or an increase in PSA level by 0.2 ng/ml after radical prostatectomy may indicate metastasis.[19] In addition, performing biopsy and the clinical stage of prostate cancer may indicate failure of localized prostate cancer treatment.[19]

Several organizations have issued screening guidelines for prostate cancer. Examples of these organizations are the ACS, American Urological Association (AUA) and NCCN. Although these organizations differ in their recommendation regarding PSA routine testing, age groups, and life expectancy, they all agree on the importance of an informed shared decision-making process that considers patient's values and preferences and quality of life.[6,20–23]

PSA screening, accessing PSA velocity and measuring free versus bound PSA are three different approaches used for detecting prostate cancer. Elevated PSA is proportionally associated with higher odds of having prostate cancer.[23] Assessing PSA velocity is the second approach where the velocity is calculated by assessing three consecutive PSA measurements over at least a period of 18-24 months.[23] Free versus bound PSA is another approach that is used to differentiate elevated PSA due to benign

prostate hyperplasia (BPH) from cancer.[24] A lower percentage of free PSA is associated with higher chances of having prostate cancer.

Most prostate cancer patients are asymptomatic.[25] Abnormal PSA level and/or DRE are diagnostic measures used to identify prostate abnormality and/or cancer by performing a biopsy.[25] Usually, multiple biopsies are required since false-negative results often happen.[26] DRE helps in detecting nodules, asymmetry or differences in texture which warrant the need for biopsy.[26] Most prostate cancer patients have negative DRE and elevated PSA.[26] Cancer can also be recognized incidentally when resection is done to manage BPH.[26]

Patients with advanced stages of prostate cancer may manifest skeletal abnormalities due to bone metastases. Other manifestations include weight loss, anemia and back pain due to spinal compression.[25,27] In addition to PSA, DRE and performing biopsy as part of diagnostic workup, kidney and liver function tests are also warranted in advanced stages.[24] Computed Tomography (CT) scan is also often required in case of lymph node involvement.[24]

The American Joint Committee on Cancer (AJCC) issued a staging system for prostate cancer based on Gleason score and grade group of staging.[28] Generally, the clinical staging of prostate cancer, PSA level, DRE findings, biopsy findings and imaging study results indicate prostate cancer prognosis.[28] The Tumor, Node and Metastases (TNM) staging of prostate cancer is based on the extent of tumor size, involvement of lymph nodes and whether the tumor is metastasized.

TNM staging helps physicians in determining not only the prognosis of the patient but selecting the most appropriate therapy. This also helps patients in understanding their

disease condition and sharing their thoughts and decisions with the healthcare provider regarding their disease condition and course of treatment.

Treatment of prostate cancer

Treating prostate cancer depends, as in other cancers, on disease prognosis and staging. Current available therapeutic options are hormonal or androgen deprivation therapy (ADT), radiation therapy, chemotherapy, radical prostatectomy, active surveillance and watchful waiting.[29] Other therapeutic options like whole-gland cryotherapy or high-intensity focused ultrasound have not been studied well in terms of survival benefit and rates of complications. AUA recommends considering the following factors when treating prostate cancer: 1) patient preferences and values, 2) risk category or staging of prostate cancer, 3) life expectancy, 4) post-treatment functional status 5) baseline organ and overall health status. [29]

Management of localized prostate cancer

Newly diagnosed prostate cancer patients are primarily treated with surgery and/or radiation before they are put on hormonal therapy or ADT. Hormonal therapies are usually considered if there are signs of recurrence like increased PSA levels and clinical progression. The main goals of treatment are to prolong survival, prevent recurrence, minimize complications and maintain patient quality of life.

Although localized prostate cancer is usually treated with ADT and radiation, radical prostatectomy may be suitable in some cases. The AUA (2017) guideline considers radical prostatectomy, radiation, and active surveillance as appropriate therapeutic options to treat localized prostate cancer. However, the guideline recommends patients be informed about potential therapeutic benefits and risks.[30]

Additionally, despite ADT being considered a therapeutic option for managing locally advanced prostate cancer, AUA does not recommend it because it did not improve overall survival and prostate cancer-specific survival in a large observational study that included 66,717 men with localized prostate cancer.[30,31]

In active surveillance, treatment or intervention is provided only if there are signs of disease progression. According to NCCN, this includes low risk patients who have life expectancy of ≥ 10 years, monitoring of PSA levels not more often than 6 months unless clinically indicated, DRE not more often than 12 months unless clinically indicated and performing biopsy every 12-24 months.[32,33]

Watchful waiting includes close-follow up and providing treatment based on symptoms and is recommended in older patients with poor prognosis or life expectancy of less than 10 years.[33] In 2009, Lu-Yao et al concluded in the largest study in the US, that the watchful waiting overall survival rate reached 94 % with men of median age 78 years.[29] Since 1990, only two randomized clinical trials reported radical prostatectomy compared to the watchful waiting approach in localized prostate cancer.[34,35] The first one was conducted in Sweden and concluded that surgery was able to prevent 6 % of prostate cancer related deaths. In addition, prostate-specific mortality was 14.7 % compared to 20.7 % in the watchful waiting arm. However, the subsequent analysis did not show any survival benefit for men over 65 years.[34,35] Similar results were reported in the Prostate Intervention Versus Observational Trial (PIVOT) randomized controlled trial that included 731 men aged 75 years or younger with localized prostate cancer and life expectancy of at least 10 years.[36]

A sub-analysis conducted in the PIVOT study reported that men with PSA level of at least 10 ng/ml at diagnosis had greater overall mortality reduction compared with men with PSA level less than 10 ng/ml. Additionally, long-term follow-up data of PIVOT reported that surgery did not reduce overall mortality compared to observation in patients with localized prostate cancer (HR=0.84, P <0.06).[36]

Regarding advanced prostate cancer, both of the 2017 NCCN and 2011 European association urology guidelines of managing advanced prostate cancer suggested the use of luteinizing hormone releasing hormone (LHRH) agonists or antagonists, with or without androgen blockage to manage advanced prostate cancer.[32,37] They also recommended performing bilateral orchiectomy in case of spinal compression. [32,37] Although current therapeutic options provided beneficial effects in reducing the progression of prostate cancer and relieving potential obstructive symptoms, other toxic adverse events were associated with the treatments. Thus, it is crucial to balance potential benefits and risks before initiating treatment as well as considering patient's preferences, values and quality of life. [6,20,21,23,38]

Castration Resistant Prostate Cancer (CRPC)

In this section, we will discuss castration resistant prostate cancer (CRPC) definition, types, diagnosis and treatment.

Castration resistant prostate cancer (CRPC) is a prostate cancer that is no longer responding or refractory to hormone therapy. Thus, there is disease progression either in rising PSA levels and/or clinical progression despite hormonal or ADT. [39,40]

Patients with CRPC tend to have low testosterone levels classically below 50 pg/ml or even less than 20 pg/ml. Castration resistant prostate cancer can be non-

metastatic or metastatic (mCRPC).[40] Non-metastatic form is usually called M0, whereas metastatic form is called M1. About four to seven percent of living prostate cancer patients in the European Union have M0. [40]

In addition, CRPC is characterized by two to three consecutive elevated PSA levels obtained at intervals of greater than 2 weeks and/or documented pathological findings of disease progression on CT scan despite pharmacological (ADT) and surgical interventions aimed to reduce testosterone levels.[23,41]

Castration is a treatment modality aimed at suppressing androgen production that contributes to stimulating growth of prostate cancer cells. Metastatic CRPC (mCRPC) mostly affects bones, and potential metastatic complications include skeletal-related events, such as pathological fractures, pain and spinal cord compression which impairs the quality of life of patients.[41] Despite hormonal or ADT, of those diagnosed with prostate cancer, about 10-20 % will develop castration-resistant prostate cancer (CRPC) within 5 years of diagnosis and 70 % of those cases will metastasize to mCRPC. [4–6]

Docetaxel

In 2004, docetaxel was introduced into the United States (US) market as the first chemotherapeutic agent with survival benefit to treating mCRPC after failure of traditional hormonal therapy or ADT.[42] Two randomized clinical trials have shown that docetaxel further improved survival in mCRPC despite known adverse events (e.g. cardiovascular and gastrointestinal) that forced patients to stop therapy earlier.[42] Both of TAX327 trial and SWOG 99-16 trials showed higher survival rates with docetaxel compared to prednisone plus mitoxantrone (17.4 vs. 16.5 months) and (17.5 vs 15.6 months) respectively.[42]

Our study focuses on evaluating current therapeutic options in the US market that received the highest NCCN level of recommendation to treat visceral mCRPC patients who progress after docetaxel treatment.[6] Figure 1 demonstrates the 2017 NCCN guidelines evidence blocks for managing mCRPC with visceral metastasis.[6]

Current therapeutic options of mCRPC

In the following discussion, we will explore current therapeutic options for managing mCRPC following docetaxel therapy.

Cabazitaxel

In 2010, as a result of the TROPIC study, cabazitaxel with prednisone received Food and Drug Administration (FDA) approval to treat visceral mCRPC for patients who progress following docetaxel.

Cabazitaxel plus prednisone showed a median survival of 15.1 months compared to 12.7 months with mitoxantrone plus prednisone. However, cabazitaxel plus prednisone was associated with significant stage III/IV neutropenia and febrile neutropenia.[43,44]

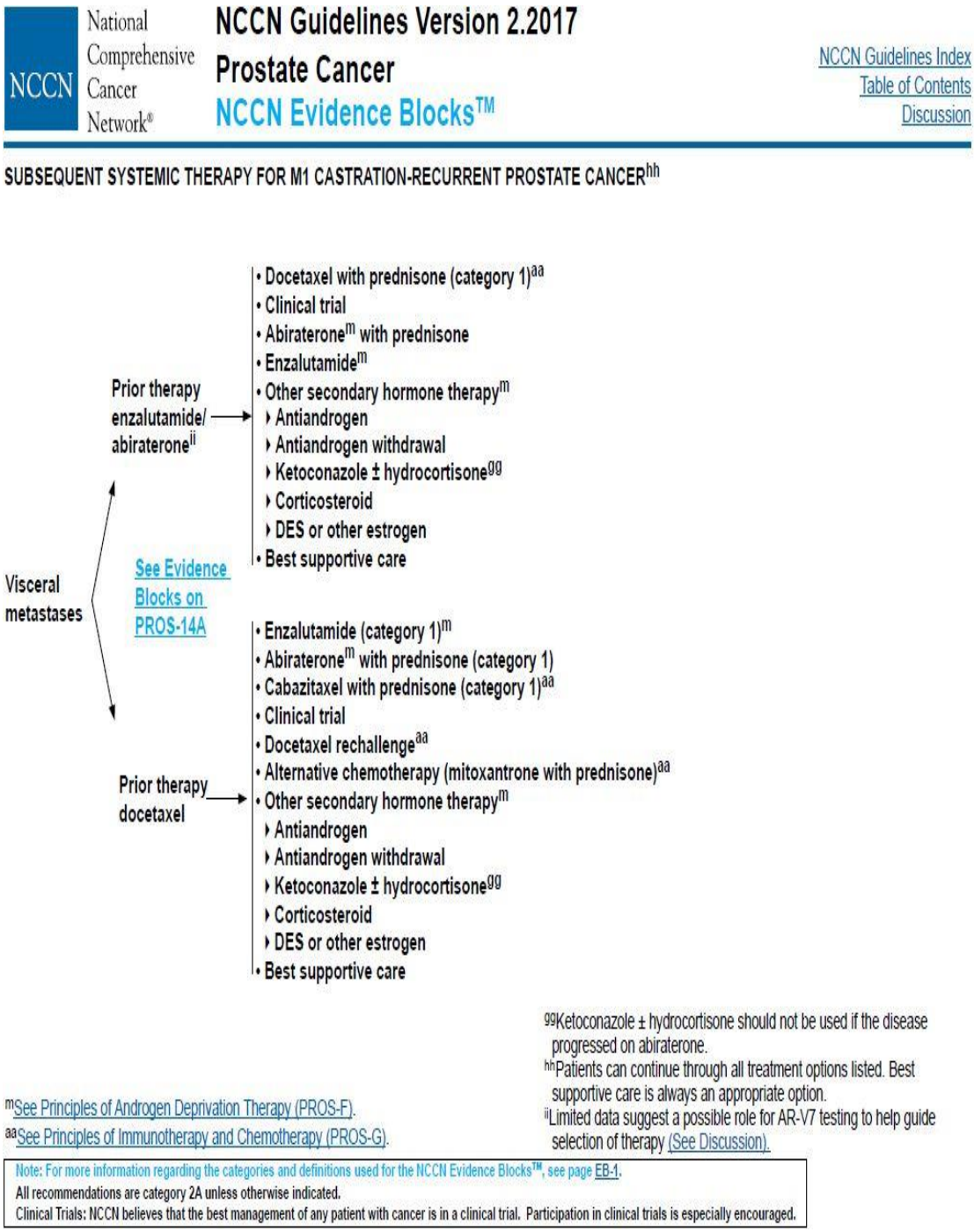
Abiraterone

In 2011, abiraterone with prednisone was granted FDA approval to treat visceral mCRPC. Abiraterone is a non-chemotherapeutic potent, selective, irreversible inhibitor of CYP17A1 that inhibits androgen biosynthesis and thus inhibits androgenic signaling which is important in the pathogenesis of mCRPC.[13,14,20,45–47]

Abiraterone plus prednisone approval was based on a large study that included 1195 men with CRPC treated with this combination. The median survival rate was 15.8 months for patients treated with abiraterone plus prednisone compared to 11.2 months for placebo. Men who received abiraterone plus prednisone showed prolonged progression-

Figure 1*

NCCN guidelines for treating mCRPC [6]



* Figure 1 [The figure describes NCCN guidelines for managing visceral mCRPC, version 2. February 2017]

free survival (PFS) rates, higher PSA response, and significantly longer time to PSA progression.[48,49]

In 2012, abiraterone received an additional FDA approval to be used in visceral mCRPC prior to receiving chemotherapy.[45,49] Given its prolonged overall survival benefit and convenient once-daily oral regimen, NCCN guidelines consider abiraterone plus prednisone as one of the first-line therapeutic options for visceral mCRPC. However, abiraterone is associated with serious cardiovascular disorders (i.e. cardiac arrhythmias, ventricular fibrillation and cardiac arrest).[48]

Enzalutamide

In 2012, enzalutamide was approved by the FDA for visceral mCRPC patients who progress despite docetaxel therapy. It works by inhibiting androgen receptors.[50] In 2013, It received an additional FDA indication approval for treating visceral mCRPC in chemotherapy-naïve patients. Enzalutamide prolonged survival relative to placebo in both post-docetaxel and chemotherapy-naïve arms.[51,52]

In addition, enzalutamide showed better quality of life response, higher PFS rates and longer time to develop skeletal manifestations. Enzalutamide showed 18-month median survival compared to 13.6 months on prednisone alone. However, five cases (0.6 %) of seizure including one case of status epilepticus were reported. [51,52]

Other therapeutic options

Sipuleucel-T and radium-223 were also introduced into the US market in 2010 and 2013 respectively and each agent showed a median survival benefit of 2-4 months compared to control.[45,53] Radium-223 which is a radioactive therapeutic modality that received FDA approval based on ALSYMPCA trial (ALpharadin in SYMptomatic

Prostate CAncer) to treat mCRPC, symptomatic bone metastasis with no known visceral metastasis.[54,55] Results demonstrated higher survival rates compared to placebo (14.9 vs 11.3 months). However, both radium and sipuleucel have not been studied in patients with visceral metastases.[56] Thus, the 2017 NCCN guideline of prostate cancer does not recommend either of both treatments to manage mCRPC with visceral metastasis.[6]

Radiation in metastatic prostate cancer

Radiation has been often used to treat metastatic prostate cancer in combination with ADT. In a large study that included 6,382 men with newly diagnosed prostate cancer, it was shown that combining both therapeutic modalities had better overall survival (55 vs 37 months), and 5-year survival outcomes compared to ADT alone. [31] Additionally, radiation has been also used as a palliative therapeutic modality in patients with mCRPC with painful bones, at higher risks of fractures and with patients with impending spinal compression.[57]

Significance of CEA for healthcare and policymakers

In this section, we discuss the importance of conducting CEA for healthcare and policymakers; and its role in introducing, assessing and maintaining health technologies.

CEAs in healthcare are conducted to provide decision makers with supplemental information that may be helpful in supporting their decision about introducing, maintaining, assessing or choosing the most cost-effective health technologies. CEAs may provide comparative effectiveness, safety, cost and cost-effectiveness information related to health technologies being considered or compared.

Based on 2017 NCCN guidelines of prostate cancer diagnosis and treatment, we aimed to conduct a CEA from a US healthcare payer perspective utilizing life-time

horizon Markov model between enzalutamide, abiraterone plus prednisone and cabazitaxel plus prednisone as they have the highest NCCN guideline recommendation to be used in visceral mCRPC based on significant survival benefits conducted in clinical trials.[6] To our knowledge, no published study has conducted a CEA comparing these therapies from a US healthcare payer perspective utilizing life-time horizon Markov model. Thus, it would be informative for decision makers to estimate costs, outcomes and cost-effectiveness between the three regimens by conducting CEA which assumes costs are related to a single, common effect (i.e., cost/life-year gained) that may differ in magnitude among alternative treatments or interventions.

Several organizations have utilized CEAs and health technology assessments to better inform health and policymakers about the most cost-effective strategy.[58,59] For example, pharmaceutical companies submit drug dossiers that provide budget-impact models and CEA studies to managed care organizations (MCOs) to facilitate formulary decisions.[58,59] In addition, in the UK, the National Institute of Clinical Excellence (NICE) believes that providing clinical effectiveness data is not sufficient to introduce or maintain health technology assessments (HTAs). Thus, there is a need to provide cost-effectiveness data to facilitate decision making regarding an HTA.[60,61]

Although clinical evidence has been given the greatest weight by health organizations and decision makers involved in resource allocation decisions, cost-effectiveness analyses may also play an important role by decision makers in health and medicine. For example, NICE has established procedures that incorporate the values of patients and the public in their CEA submission requirements of HTA. NICE has also

provided special consideration to end-of-life treatment and treatment for special populations (e.g. elderly and children).[62]

Overall, economic evaluations provide useful tools that help in making decisions about introducing or maintaining HTAs. Many world organizations and a few in the US have offered recommendations on how to perform these evaluations and control the growth of US health care expenditure in the future.[63]

The importance of the study to the literature

Since advanced stages of prostate cancer create substantial clinical and economic burden to patients, healthcare providers, and policymakers, there is an important need to conduct CEA comparing current therapeutic modalities that are used to treat visceral mCRPC.[7]

We chose to conduct the study from a US healthcare perspective and not from other perspectives (e.g. societal, patient or provider) for the following reasons. Studies from societal perspective require that all medical, non-medical and non-healthcare sector cost components be considered as recommended by the Second Panel of Cost-Effectiveness in Health and Medicine impact inventory.[62] However, it is difficult to obtain all cost components required to conduct the study from societal perspective.

The provider perspective was not considered as the US has a fragmented healthcare system and different providers have different allocated budgets and lists of covered formulary items by payers. Therefore, it is difficult to generalize our results for different healthcare providers. Whereas, different US payers may use CEAs results as a supplemental tool to decide on coverage/reimbursement decisions as results can be utilized by any payer and results can be generalized to different US healthcare payers.

Since clinical trials provide evidence regarding efficacy testing, there is still a need to translate clinical effectiveness endpoints into measures that are valued and crucial for different stakeholders.[61] The results may provide physicians, decision makers and healthcare payers valuable information to make appropriate treatment and payment decisions.

We found several published CEAs or economic evaluation studies that either evaluated different (from our proposed study) treatment regimens for mCRPC, utilized a different methodology (e.g. decision tree model) to conduct the evaluation, stated a different study perspective (e.g. societal), incorporated a shorter time horizon or were in non-US setting.[9,64–77]

To our knowledge, no published study has conducted a CEA that compared enzalutamide, abiraterone plus prednisone and cabazitaxel plus prednisone for the treatment of visceral mCRPC from a US healthcare payer perspective utilizing life-time horizon Markov model.[6]

The purpose of our study

The objective of our study is to conduct a CEA comparing enzalutamide, abiraterone plus prednisone and cabazitaxel plus prednisone for the treatment of visceral mCRPC post-docetaxel failure from a US healthcare payer perspective utilizing life-time horizon Markov model. The results of this study may help in evaluating the cost effectiveness between the different therapies. We considered these medication regimens they have the highest NCCN guideline recommendation to be used in visceral mCRPC based on significant survival benefits conducted in clinical trials.[6]

CHAPTER 2: LITERATURE REVIEW

Introduction

This chapter is divided into four sections. We will discuss first the anatomy of prostate gland, and the pathophysiology, epidemiology, etiology, prognosis, screening and diagnostic workup of prostate cancer as well as the management of advanced and metastatic castration resistant prostate cancer (mCRPC). In the second section, we will explore CRPC and current therapeutic options used to treat visceral mCRPC. This will include discussing the mechanism of action and pharmacokinetic profile of each therapeutic option, approved indications and dosage, contraindications and precautions, drug-drug interactions and dose adjustments, common side effects (>10%) and dosage forms and pricing. In the third section, we will focus on economic studies' methods, requirements and compare decision-tree to Markov models. In the last section, we will discuss the results of the literature review related to the economic evaluation of mCRPC.

Anatomy of the prostate gland

The prostate gland is surrounded by a capsule that is located below the bladder and separated from the rectum by a layer of fascia named the denovillers aponeurosis. Both of base of prostate gland and bladder are supplied by inferior vesicle artery.[78] The neurovascular bundle that lies on either side of the prostate is derived from the pelvic plexus that is important for erectile function. These nerve plexuses arose from thoracic (T 10-12) and sacral (S 2-4) nerve roots. Figure 2 describes the anatomy of the prostate gland.[78]

Figure 2*

Anatomy of the prostate gland [78]

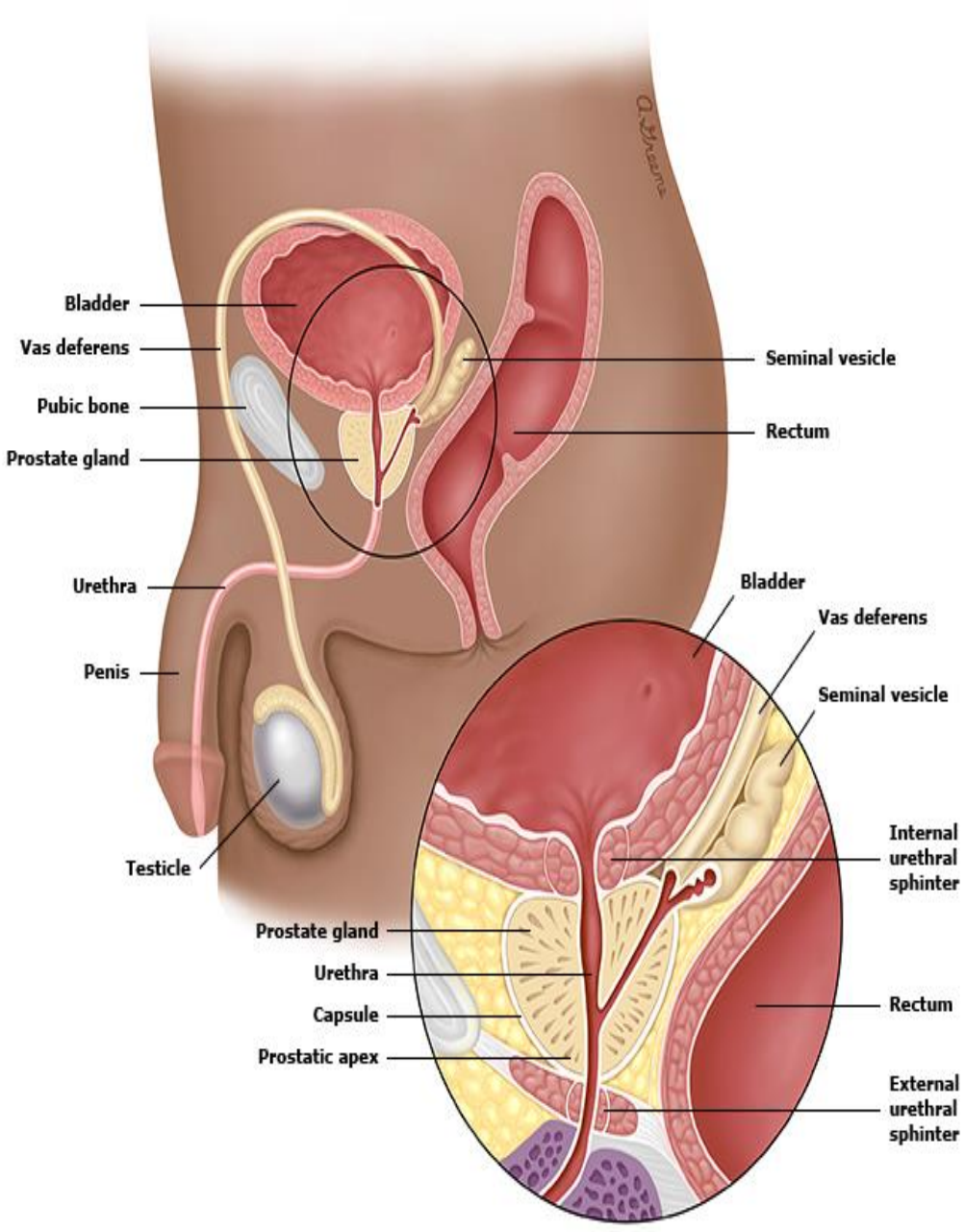


*Figure 2 [Reproduced with permission from: Benway BM, Andriole GL. Prostate biopsy. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on [July 11, 2018].) Copyright © 2018 UpToDate, Inc. For more information visit www.uptodate.com, see appendix for more information]

Pathophysiology of prostate cancer

Several underlying mechanisms have been reported by the literature to better inform healthcare providers about the pathogenesis of prostate cancer.[12] These include the ongoing androgen biosynthesis by the adrenal glands, upregulation of androgenic receptors and prostatic tumor-mediated cytochrome P17 (CYP17), and the activation of androgen receptors via different pathways.[13,14] Like other cancers, an imbalance between rates of cell death and growth can lead to prostate cancer. [12] However, this transformation is aggravated by subsequent gene mutations including the genes for retinoblastoma and P53 which will eventually cause tumor progression and metastasis.[12]

Nearly 95 % of prostate cancer cases are adenocarcinomas, 4 % have transitional cell morphology and are thought to arise from the urothelial lining of the prostatic urethra and 1 % have squamous cell carcinomas.[12] Although prostate cancer can arise either from the peripheral zone (70%), central zone (15-20%), or transitional zone (10-15%), most of prostate cancer cases involve multiple zones.[12] When prostate cancer is locally invasive, the transitional zone tumor cells spread to the bladder neck, whereas the peripheral zone tumor cells spread into the seminal vesicles and ejaculatory ducts.[12] For the case of metastatic prostate cancer, the mechanical theory and the seed-and-oil theory are two current theories that explain how locally invasive prostate cancer becomes metastatic.[12] The mechanical theory attributes the spread of prostate cancer through the lymphatic system. Investigators or proponents of the seed-and-oil theory believe that tissue factors facilitate the growth and the spread of cancerous cells.[12]

Although screening and earlier prostate cancer detection reduce mortality, long-term treatment complications may offset treatment benefits. This may include bowel

dysfunction, sexual and urinary complications which are common and long-lasting. For example, nearly 50-70 % of patients that underwent radical prostatectomy suffer from sexual impotence and about 40-50 % have urinary leakage.[79–82]

Epidemiology

Prostate cancer varies across geographical regions of the world, depending primarily on different diagnostic workups than on known risk factors (i.e. diet, lifestyle, race, age and androgen status).[83] The following are the reported prostate cancer case rates around the world: 104.2 cases of prostate cancer per 100,000 person-years in Australia and New Zealand, 93.1 cases per 100,000 person-years in western Europe, 73.1 cases per 100,000 person-years in northern Europe, 85.6 cases per 100,000 person-years in North America whereas the least is 7.2 cases per 100,000 person-years in Asia due to familial and dietary factors.[84] The age-adjusted mortality is the highest in Europe, 12 cases per 100,000 person-years and about 9.9 cases per 100,000 person-years in North America due to inherent genetic variation, although further studies are needed to confirm the underlying biological mechanism.[84]

Etiology

For many years, it was believed that testosterone which is a steroid hormone that is produced mainly by the testes and adrenal cortex is responsible for prostate rapid growth and cancer.[40] African Americans have higher incidence of prostate cancer, and studies had reported that African American men have 15 % higher levels of testosterone compared to Hispanics and whites.[85] However, a meta-analysis published by Boyle et al in 2015 concluded that both endogenous and exogenous testosterone are not risk factors for prostate cancer.[86]

Rates of prostate cancer vary among different geographical areas across the world, suggesting that genetic variation may be considered an important factor. For example, the risk of prostate cancer tends to be higher among individuals with sub-Saharan African ancestry.[15] Lower prostate cancer risks have been reported among native Asians. However, US immigrant Asians tend to have higher risks of prostate cancer compared to native Asians which suggests that diet and/or familial predisposition may be contributing factors of prostate cancer.[15]

Positive family history of prostate cancer increases the risk of developing the disease 6-7 years earlier than someone without a positive family history.[16] Familial predisposition is responsible for 5-10 % of prostate cancer cases.[16] A positive BRCA-2 mutation may also increase the risk of developing aggressive prostate cancer at younger age.[16] The use of 5-alpha reductase inhibitor for the treatment of BPH has been also attributed to increasing risks of developing aggressive high-grade prostate cancer compared to placebo. In 2011, the food and drug administration (FDA) issued a box warning for prescribing 5-alpha-reductase inhibitor products in patients with higher risks of developing prostate cancer.[15,17]

Prognosis

The main indicators of prostate cancer prognosis have been well described in the literature. The first diagnostic indicator is the Gleason pattern. The Gleason pattern is a scoring system used to determine the aggressiveness of prostate cancer and assists in choosing appropriate treatment options.[18] Scores may range from 1 to 10 .[18] Higher Gleason Patten scores (>7) are suggestive of poorly differentiated prostate cancer cells and/or poor prognosis.[24] Gleason pattern scores between 1 and 6 indicates well-

differentiated or low-grade tumor. Scores of 7 are suggestive of moderately-differentiated tumor.[24] Additionally, nearly 30 % of localized prostate cancer will spread despite treatment based on diagnostic PSA level, histologic grade and pathologic stage of the tumor.[18] Figure 3 demonstrates Gleason pattern for determining prostate cancer prognosis. However, Gleason pattern scores have changed recently because scores of 2-5 are rarely seen. Other important indicators are age at diagnosis, capsular penetration and the extent of tumor volume.[24]

The literature has also reported that three consecutive increases in PSA levels after radiation therapy, or an increase in PSA level by 0.2 ng/ml after radical prostatectomy may indicate metastasis.[19] In addition, performing biopsy and the clinical stage of prostate cancer may indicate failure of localized prostate cancer treatment.[19]

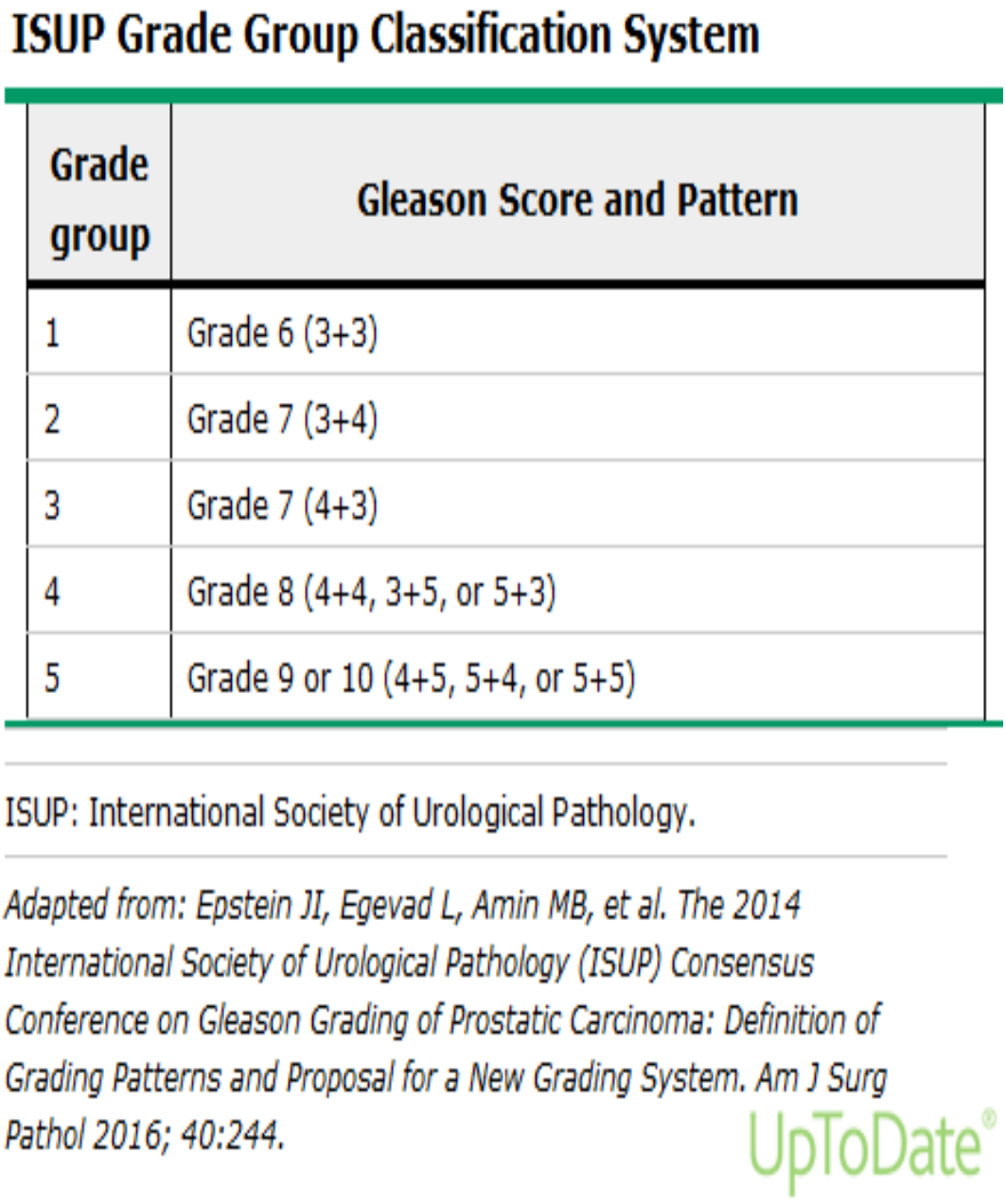
In a retrospective study that was conducted to evaluate the association of tumor progression due to anesthesia after radical retropubic prostatectomies, 1642 procedures were reviewed for patients who had general anesthesia and 1642 had opioid sparing approach to anesthesia (neuraxial block). Results showed that patients who had general anesthesia during prostatectomy had 30 % higher mortality risk and three times greater risk of systemic progression.[87,88]

The Literature has also identified several biochemical and genetic markers that help in determining the prognosis of prostate cancer. However, none of the following genetic measures is routinely used in practice; mutations in MYC, P53, PTEN and ERG-TMPRSS2 chromosomes.[89]

Figure 3*

Gleason's pattern of prostate cancer [90]

ISUP Grade Group Classification System



ISUP Grade Group Classification System

Grade group	Gleason Score and Pattern
1	Grade 6 (3+3)
2	Grade 7 (3+4)
3	Grade 7 (4+3)
4	Grade 8 (4+4, 3+5, or 5+3)
5	Grade 9 or 10 (4+5, 5+4, or 5+5)

ISUP: International Society of Urological Pathology.

Adapted from: Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol 2016; 40:244.

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*Figure 3 [Reproduced with permission from: Yang XJ. Interpretation of prostate biopsy. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on [July 11th, 2018].) Copyright © 2018 UpToDate, Inc. For more information visit www.uptodate.com. See appendix for more information]

Screening

Several organizations have issued screening guidelines for prostate cancer. Examples of these organizations are the ACS, AUA and NCCN. Although these organizations differ in their recommendation regarding PSA routine testing, age groups, and life expectancy, they all agreed on the importance of an informed shared decision-making process that considers patient's value, preferences and quality of life. [6,20,21,23,38]

Elevated PSA is proportionally associated with the odds of having prostate cancer. When PSA level is 1ng/ml, prostate cancer is detected in 8 % of men. This increases to 25 % if the PSA is between 4-10 ng/ml.[21]

The European Randomized Study of Screening for Prostate Cancer (ERSPC) recommends that a PSA value of 3 ng/ml or higher warrants the need for lateralized sextant biopsy.[91] Preston et al published a study reporting the association of high PSA levels in midlife and the odds of having deadly prostate cancer in the future.[31,38] The study included men, 40-59 years with PSA levels in the upper quartile versus those with levels below the 50th percentile. The odds of having deadly prostate cancer was 8.7 if the person is 40-49 years old, 12.6 if the person is 50-54 years old and 6.9 if the person is 55-59 years old.[38,91]

ACS recommends average-risk men who are at the age of 50 receive information about potential risks of prostate cancer and the importance of PSA screening. It further recommends men having a positive family history, high risk men at age 45 and African American men receive PSA screening. [2,21]

PSA retesting every 2 years is considered if PSA level falls below than 2.5 ng/ml. However, annual retesting is required if PSA level is ≥ 2.5 ng/ml. [3,21]

ACS recommends average-risk men who are at the age of 50 receive information about potential risks of prostate cancer and the importance of PSA screening as well as men having a positive family history, high risk men at age 45 and African.[2,3,21]AUA does not recommend routine PSA testing for the following categories:[23,92]

1. Men over 70
2. Men under 40
3. Men who are 40-54 years old with average risk
4. Men with at least a life expectancy of 10-15 years

Conversely, the NCCN guideline is more conservative and recommends baseline evaluation, physical examination and obtaining family history as well as baseline DRE for patients who are 45-75 years.[6] The published literature has also suggested other approaches that may help in determining the likelihood of developing prostate cancer. Assessing PSA velocity is the first approach where the velocity is calculated by assessing three consecutive PSA measurements over at least a period of 18-24 months.[23,92]

Free versus bound PSA is another approach that is used to differentiate elevated PSA due to benign prostate hyperplasia (BPH) from cancer.[21,24] A lower percentage of free PSA is associated with higher odds of having prostate cancer. The percentage is calculated relative to total PSA level. Measuring free PSA levels would help physicians to determine whether to perform a biopsy on a patient or not if PSA levels falls within 4-10 ng/ml. [21,24] This approach would also help in patients with either a large prostate gland and in whom who had one biopsy with negative results.[21,24] A percentage of free PSA

more than 25 % considered normal. However, a biopsy is considered recommended if free PSA level is below 18 % and others recommended a cutoff point of 12 %.[21,24]

Diagnostic workup

Most prostate cancer patients are asymptomatic.[25] Abnormal PSA level and/or DRE are diagnostic measures used to identify prostate abnormality and/or cancer by performing a biopsy.[25] Usually, multiple biopsies are required since false-negative results often happen.[26] DRE helps in detecting nodules, asymmetry or differences in texture which warrantee the need for biopsy.[26] Most prostate cancer patients have negative DRE and elevated PSA.[26] Cancer can also be recognized incidentally when resection is done to manage BPH.[26]

Prostate cancer patients can also present with urinary retention, urinary frequency, hematuria, adenopathy, bone pain, obstructive signs like decreased urine steam and over-distended bladder because of BPH.[25] However, patients with advanced stages of prostate cancer may manifest skeletal abnormalities due to bone metastases. Other manifestations include weight loss, anemia and back pain due to spinal compression.[25,27] In addition to PSA, DRE and performing biopsy as part of diagnostic workup, kidney and liver function tests are also warranted in advanced stages.[24] Computed Tomography (CT) scan is also often required in case of lymph node involvement.[24]

Tumor Node Metastases (TNM) Staging system of prostate cancer

The American Joint Committee on Cancer (AJCC) issued a staging system for prostate cancer based on Gleason score and grade group of staging.[93] Generally, the clinical staging of prostate, PSA level, DRE findings, biopsy findings and imaging study results indicate prostate cancer prognosis.[6,25] The TNM staging of prostate cancer is

described based on the extent of tumor size, involvement of lymph nodes and whether the tumor is metastasized. The classification below helps physicians in determining not only the prognosis of the patient but selecting the most appropriate therapy tailored for the stage of prostate cancer. This may also help patients in understanding their disease condition and share their thoughts and decisions with the healthcare provider regarding the course of treatment.

TNM Staging of prostate cancer [93]

A) T (primary tumor):

TABLE 1: 2010 TNM staging system of prostate cancer

Localized disease	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor neither palpable nor visible by imaging
T1a	Tumor incidental histologic finding in ≤ 5% of resected tissue
T1b	Tumor incidental histologic finding in > 5% of resected tissue
T1c	Tumor identified by needle biopsy (eg, because of elevated PSA level)
T2	Tumor confined within prostate
T2a	Tumor involves one-half of one lobe or less
T2b	Tumor involves more than one-half of one lobe but not both lobes
T2c	Tumor involves both lobes
Local extension	
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Bladder invasion, fixed to pelvic side wall, or invasion of adjacent structures
Metastatic disease	
N1	Positive regional lymph nodes
M1	Distant metastasis

From Edge SB, Byrd DR, Compton CC, et al (eds): AJCC Cancer Staging Manual, 7th ed. New York, Springer, 2010.

A) Nodal stages [93]

NX	Regional lymph node metastasis
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node or nodes

B) Metastasis [93]

M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s), with or without bone disease

Management of advanced /metastatic prostate cancer

Both of 2017 NCCN and 2011 European association urology guidelines of managing advanced prostate cancer suggested the use of LHRH agonists or antagonists, with or without androgen blockage to manage advanced prostate cancer. They also recommended performing bilateral orchiectomy in case of spinal compression.[6,32,37]

Although current therapeutic options provided beneficial effects in reducing the progression of prostate cancer and relieving potential obstructive symptoms, other toxic adverse events were associated with the treatments. Thus, it is crucial to balance potential benefits and risks before initiating treatment as well as considering patient preferences, values and quality of life.

The decision to start early hormonal treatment or defer treatment to later stage was controversial until the Veterans Administration Cooperative Urology Research Group (VACURG) recommended deferring hormone therapy until symptomatic progression occurs to prevent early androgen resistance in prostate tumors.[94–96] However, several clinical trials have shown that starting early may reduce potential obstructive complications and fractures.[94,95]

Advocates of intermittent ADT suggested this approach because of reduced adverse events. However, Crook et al found that in randomized study that included 770 men who received intermittent therapy and 765 men who received continuous therapy that intermittent approach is non-inferior to continuous in terms of overall survival and was not as effective as continuous in patients with metastatic castration hormone-sensitive prostate cancer (mCSPC). [95]

Combined androgen blockage therapy remains controversial because several randomized clinical trials did not show survival benefits. However, a limited number of studies reported a 3 to 6 month survival benefit with the use of complete androgen blockage therapy.[97] The number of negative studies was explained by the anti-androgen withdrawal phenomenon where PSA levels are reduced when ADT is stopped because of modifications in androgen's receptors that facilitate tumor growth. Thus, many patients' clinical condition was deteriorating because they did not stop ADT sooner. However, based on survival benefits provided by some clinical trials, it was suggested by the American Society of Clinical Oncology (ASCO) to consider combined androgen blockage therapy in patients with hormonal sensitive and resistant prostate cancer patients. Complete blockage of androgen receptors reduces symptoms of flare-ups (rise of testosterone levels) that may happen with LHRH agonist treatment. Blockage approach should be continued unless PSA progression occurs.[31,97,98]

In the following section, we will discuss CRPC and current therapeutic options for mCRPC management. This will include discussing the mechanism of action and pharmacokinetic profile of each therapeutic option, approved indications and dosage, contraindications and precautions, drug-drug interactions and dose adjustments, common side effects (>10%) associated with therapies; and dosage forms and pricing.

Castration Resistant Prostate Cancer (CRPC)

Newly diagnosed prostate cancer patients are usually treated with surgery and/or radiation before they are put on ADT. Hormonal therapies (ADT) are usually considered if there are signs of recurrence like increased PSA levels and clinical progression. However, Castration Resistant Prostate Cancer (CRPC) happens when the patient is no

longer responding or refractory to hormone therapy. Thus, there is disease progression either in rising PSA levels and/or clinical progression despite ADT.[40]

CRPC patients tend to have low testosterone levels classically below 50 pg/ml or even less than 20 pg/ml. CRPC can be non-metastatic or metastatic. Non-metastatic form is usually called M0, whereas metastatic form is called M1 or mCRPC. About four to seven percent of living prostate cancer patients in the European Union have M0.[40]

CRPC is characterized by two to three consecutive elevation of PSA levels obtained at intervals of greater than 2 weeks and/or documented pathological findings of disease progression on CT scan despite pharmacological (ADT) and surgical interventions aimed to reduce testosterone levels.[20,41]

Castration is a treatment modality aimed at suppressing androgen production that contributes to stimulating growth of prostate cancer cells. Metastatic CRPC (mCRPC) mostly affects bones, and potential metastatic complications include skeletal-related events, such as pathological fractures, pain and spinal cord compression which impairs the quality of life of patients.[20,41]

Main goals of treatment are prolonging survival, preventing recurrence, minimizing complications and maintaining patient quality of life. Despite ADT, most prostate cancer patients (70 %) will develop mCRPC in their lifetime. Thus, starting docetaxel would be warranted in these cases as a first line treatment for managing mCRPC.[4–6]

ACS predicts there are about 12-29 million of prostate cancer survivors living in the US. [40] It is also expected that there is about half a million non-metastatic prostate cancer patients in the US. [40] Clinicians should evaluate how risky the disease condition is

and how long it will take the patient to progress into metastatic stage. PSA doubling time and absolute PSA levels are critical indicators of disease progression. PSA doubling time is defined as the time needed for PSA level to increase by 100 % in the blood. The longer the duration is, the better the prognosis the patient has. If the PSA doubling time falls less than 10 months, the worse the prognosis the patient has.[40]

Figure 4 describes CRPC current therapeutic options indications, route and schedule of administration, contraindications, use of steroids and survival information. Until February 2018, there were no FDA approved novel therapeutic agents to treat non-metastatic CRPC and patients were treated with ADT alone.[39,99] However, apalutamide received FDA approval to treat non-metastatic CRPC patients based on a randomized double-blind multicenter trial that included 1,207 patients. About 401 patients received ADT alone and 806 patients received apalutamide 240 mg orally plus ADT. The main efficacy outcome was to assess metastasis free-survival (MFS). Results showed that patients who received apalutamide and ADT had longer survival duration compared to ADT alone (40.5 months vs. 16.5 months).[39,99]

All therapeutic options displayed in figure 4 are indicated for metastatic stages of CRPC except for apalutamide which is indicated for non-metastatic stage. All therapeutic options are given in conjunction with ADT. However, both abiraterone and docetaxel may be combined with ADT when cancer is disseminated. Additionally, patients who have higher risks of developing metastasis based on clinical and/or PSA progression may be started on enzalutamide, apalutamide and ADT.[43,45,51,100–103]

Many important factors play a role in determining the course of treatment. This includes site and rate of disease progression, patient preference, route of administration,

Figure 4*

Current therapies for CRPC [43,45,51,100–103]

Therapies for castration-resistant prostate cancer (CRPC)

Approach	Indications	Route, schedule	Steroids	Symptoms, disease burden	Contraindications	PSA response to treatment	Median overall survival benefit for men with metastatic disease*
Abiraterone	Metastatic CRPC	Oral, daily	Required	–	Severe liver dysfunction; hypokalemia; heart failure	Yes	Post docetaxel: 4.6 months[1] Chemotherapy naive: 4.4 months[2]
Enzalutamide	Metastatic CRPC	Oral, daily	Not required	–	Seizures	Yes	4.8 months[3]
Apalutamide	Non-metastatic CRPC	Oral, daily	Not required	–	–	Yes	Pending[4]
Sipuleucel-T	Pre or post docetaxel	IV, every 2 weeks x 3 doses	Possibly contraindicated	Asymptomatic or minimally symptomatic	Steroids; narcotics for cancer-related pain; GM-CSF; liver metastases	No	4.1 months[5]
Docetaxel	Metastatic CRPC¶	IV, every 3 weeks	Required	–	Moderate liver dysfunction; cytopenias	Yes	2.5 months[6]
Cabazitaxel	Post docetaxel	IV, every 3 weeks	Required	–	Moderate liver dysfunction; cytopenias	Yes	2.4 months[7]
Radium-223	Symptomatic bone metastases with no known visceral metastases	IV, every 4 weeks	Not required	Symptomatic bone metastases	Visceral metastases	Not reported	3.6 months[8]

PSA: prostate-specific antigen; IV: intravenously; GM-CSF: granulocyte macrophage colony-stimulating factor.
* The therapeutic approaches have not been compared with each other in large randomized trials. Only enzalutamide and apalutamide have been evaluated in men whose only evidence of disseminated disease is an elevated or rising serum PSA.
¶ Docetaxel is also indicated for castration-sensitive disease in combination with androgen deprivation therapy for metastatic prostate cancer.

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*Figure 4 [Reproduced with permission from: Dawson NA. Overview of the treatment of castration-resistant prostate cancer (CRPC). In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on [Date].) Copyright © 2018 UpToDate, Inc. For more information visit www.uptodate.com, see appendix.]

side effects profile, drug-drug interaction, regulatory and reimbursement statuses.[104] The site of metastatic involvement is the most crucial factor that affects survival in CRPC patients.[105] This was based on a large meta-analysis that included 8,820 men in different phase III clinical trials. Overall survival was the highest (31.6) months among men with only lymph node involvement. Survival decreased significantly among patients who had bone (21.3 months), lung (19.4 months) or liver (13.5 months) metastasis.[105]

In addition to site involvement, the presence of visceral metastasis, poor performance status, use of opioids, presence of circulating tumor cells, increased PSA, alkaline phosphatase (ALK) and lactic dehydrogenase (LDH) levels as well as low hemoglobin and serum albumin levels are all considered factors that affect survival among CRPC patients.[106] Several phase III clinical trials evaluated survival rates in patients who progress despite docetaxel treatment. Results showed that patients had longer overall survival rates when low number of serum circulating tumor cells was detected (<5 cells per 7.5 ml).[107–109]

Bone biomarkers have been also used to assess survival rates in patients with mCRPC since bone resorption and formation processes are disrupted in metastatic patients. Higher levels (>50th percentile) of bone resorption and formation markers like N-telopeptide, pyridinoline, C-terminal collagen propeptide and bone alkaline phosphatase were associated with poorer prognosis and shorter overall survival (22 months vs. 15 months) compared with patients with normal biomarkers level.[110]

Overall treatment goals for patients with bone metastasis include improving mobility, pain control and preventing complications such as spinal compression and pathological fractures.

Radiation has been used extensively in patients with bone metastasis as a pain reliever since it provides benefit in 80-90 % of cases.[104]

The literature identified other therapeutic options that are used for mCRPC. Sipuleucel-T and radium-223 were introduced into the US market in 2010 and 2013 respectively and both showed a median survival benefit of 2-4 months compared to control.[45,53] Radium-223 is radiopharmaceutical agent that improve patient quality of life by providing pain relief, improving overall survival and reducing complications. Radium-223 received FDA approval based on ALSYMPCA trial (ALpharadin in SYMptomatic Prostate CAncer) to treat mCRPC, symptomatic bone metastasis with no known visceral metastasis.[54,55] Results demonstrated higher survival rates compared to placebo (14.9 vs 11.3 months). However, since both radium and sipuleucel have not been studied in patients with visceral metastases, the 2017 NCCN guideline of prostate cancer does not recommend either of both treatments to manage mCRPC with visceral metastasis.[6]

Therapeutic options of visceral mCRPC

In this section, we will discuss NCCN highest level of recommendation therapies to treat visceral mCRPC.

Abiraterone (Zytiga®) [104]

It inhibits the biosynthesis of androgens in both testicles and androgen gland tissues by irreversibly inhibiting CYP17. Thus, it inhibits precursors of testosterone formation like dehydroepiandrosterone (DHEA) and androstenedione. It is metabolized by the liver and mostly excreted by feces (88 %). Abiraterone has a relatively a long half-life (14.4-16.5 hours) that is prolonged in case of liver failure. Abiraterone is indicated in both mCRPC and Castration Sensitive Prostate Cancer (CSPC). Unlike castration

resistant, CSPC is the initial phase of advanced prostate cancer where the disease is still sensitive to lowering testosterone levels or hormonal therapy.

Abiraterone has a convenient once daily regimen of 1,000 mg. It is given in combination with 10 milligrams (mg) of prednisone for mCRPC. However, a lower dose (5 mg) of prednisone is given for CSPC.

Abiraterone significantly interacts with CYP3A4 inducers. It is recommended to double the dose of abiraterone when a strong CYP3A4 inducer is concomitantly given with abiraterone. There is no dose adjustment required in case of renal impairment. However, a dose of 250 mg orally once daily is given if the patient has moderate liver failure (child-pugh class B).

Abiraterone is contraindicated in pregnant and breast-feeding women, severe liver failure (child-pugh class C) and when AST and/or ALT increases (>5) times during treatment. If the patient had (> 5) times the upper limit of AST and/or ALT, it is recommended to withhold the treatment until liver function tests return to normal, then reinitiate with 750 mg orally daily. If this continues, a dose reduction to 500 mg is required. Discontinuation of therapy is warranted if hepatotoxicity happens at a dose of 500 mg. In addition, since abiraterone is hepatotoxic, significant increases in liver function tests have been reported in the first 3 months of treatment. Therefore, liver functions are measured at baseline, every 2 weeks for 3 months then monthly. Patient may also develop significant hypertension as a result of CYP17 inhibition. Additionally, the drug is associated with risks of infections and adrenocortical insufficiency. Table 1 describes common side effects (≥ 10 %) associated with abiraterone use.

Table 1

Common side effects (of any grade) of abiraterone [104]

Cardiovascular	Hypertension (9% to 37%), edema (25% to 27%)
Central nervous system	Fatigue (39%), insomnia (14%)
Endocrine & metabolic	Hypertriglyceridemia (63%), hyperglycemia (57%), hypernatremia (33%), hypokalemia (17% to 30%), hypophosphatemia (24%), hot flash (15% to 22%)
Gastrointestinal	Constipation (23%), diarrhea (18% to 22%), dyspepsia (6% to 11%)
Genitourinary	Urinary tract infection (7% to 12%)
Hematologic & oncologic	Lymphocytopenia (20% to 38%; grades 3/4: 4% to 9%), bruise (13%)
Hepatic	Increased serum ALT (11% to 46%), increased serum AST (15% to 37%), increased serum bilirubin (7% to 16%)
Neuromuscular & skeletal	Joint swelling (30%), myalgia (26%)
Respiratory	Cough (7% to 17%), upper respiratory infection (5% to 13%), dyspnea (12%), nasopharyngitis (11%)

Abiraterone is available as 500 mg tablets. However, in May 2018, FDA approved a dosage form of 125 mg tablets (Yonsa®) yet not available in the US market (at the time of writing this thesis). The Average Wholesale Price (AWP) of one box (60's) of abiraterone 500 mg is US $12,278.59.

Enzalutamide (Xtandi®) [104]

Enzalutamide works by causing cellular death and reduction in tumor prostate volume through inhibiting DNA binding and nuclear translocation. Enzalutamide is primarily metabolized by the liver CYP2C8. In addition, it is mainly excreted by urine (71 %) and feces (14%). The prodrug half-life is 5.8 days whereas the terminal half-life of the metabolite N-desmethyl is 7.8 to 8.6 days.

A dose of 160 mg of Enzalutamide orally once daily is indicated for mCRPC. In July 2018, enzalutamide received an additional FDA indication to be used for non-

metastatic CRPC patients. The approval extends the indication for the oral therapy, which was previously approved for men with mCRPC.

Major drug-drug interactions are with CYP2C8 and CYP3A4 substrates. Enzalutamide is also an inducer of CYP2C19 and 2C9. However, no dose adjustment is required either in renal or hepatic impairment. Since enzalutamide is associated with risks of neurotoxicity, discontinuation of therapy is warranted in case of seizure. In addition, enzalutamide is contraindicated in pregnancy and breast-feeding women. The drug should be given with caution in the following conditions; posterior reversible encephalopathy syndrome, patients with predisposing risks for seizure or spermatogenesis as it may impair male fertility. Table 2 describes the most common side effects (>10%) associated with enzalutamide. The AWP of one box (120's) of enzalutamide 40 mg is US $13086.23.

Table 2

Common side effects (of any grade) of enzalutamide [104]

Cardiovascular	Peripheral edema (12% to 15%), hypertension (6% to 14%)
Central nervous system	Fatigue (≤51%), falling (5% to 13%), headache (11% to 12%), dizziness (10% to 11%)
Endocrine & metabolic	Hot flash (15% to 20%), weight loss (11% to 12%)
Gastrointestinal	Constipation (13% to 23%), diarrhea (12% to 22%), decreased appetite (19%), nausea (14%)
Hematologic & oncologic	Neutropenia (15%; grades 3/4: 1%)
Neuromuscular & skeletal	Weakness (≤51%), back pain (19% to 29%), arthralgia (21%), musculoskeletal pain (15% to 16%)
Respiratory	Upper respiratory tract infection (11% to 16%), dyspnea (11%)

Cabazitaxel (Jevtana®) [104]

Cabazitaxel is a taxane derivative that inhibits microtubule depolymerization and cell division. Therefore, it causes cell apoptosis and inhibits tumor proliferation. Cabazitaxel is metabolized by the liver CYP3A4,3A5 and has a terminal half-life of 95 hours. Cabazitaxel is given in combination with prednisone for mCRPC patients. The guideline recommends a dose of 25 mg/m2 once every 3 weeks (in combination with prednisone).

CYP3A inhibitors interact significantly with cabazitaxel. Thus, it is highly recommended to avoid this combination since it increases cabazitaxel concentration. If this combination cannot be avoided, a dose reduction of cabazitaxel by 25 % is required.

Cabazitaxel does not require dose adjustment in mild to moderate renal failure. However, it is recommended to use the drug with caution in patients with severe renal impairment (CrCl <15 ml/min). The use of cabazitaxel is contraindicated in severe hepatic failure (total bilirubin >3 times Upper Limit of Normal (ULN)), pregnancy, breast-feeding and neutrophil counts of ≤ 1,500 cells/mm3. It is also recommended to use the drug with caution in the following conditions: elderly patients with moderate renal failure, severe hepatic failure, neutropenia and pancytopenia, GI toxicity, hypersensitivity reactions, pulmonary toxicity, renal failure and urinary disorders. Therefore, it is recommended to monitor CBC, differential, platelet count at baseline and during treatment as clinically indicated. Table 3 describes the most common side effects (>10%) that are associated with cabazitaxel. The AWP of 60 mg/1.5 mL injection (1.5 mL) of cabazitaxel is US $12573.32.

Table 3

Common side effects (of any grade) of cabazitaxel [104]

Central nervous system	Fatigue (25% to 37%), peripheral neuropathy (13%; grades 3/4: <1%), peripheral sensory neuropathy (7% to 11%; grades 3/4: <1%)
Gastrointestinal	Diarrhea (27% to 47%), nausea (25% to 34%), vomiting (15% to 22%), constipation (18% to 20%), decreased appetite (13% to 19%), abdominal pain (6% to 17%), anorexia (16%), dysgeusia (7% to 11%)
Genitourinary	Hematuria (14% to 21%), urinary tract infection (7% to 11%)
Hematologic & oncologic	Anemia (98% to 100%; grades 3/4: 10% to 14%), leukopenia (80% to 96%; grades 3/4: 29% to 69%), neutropenia (3% to 94%; grades 3/4: 2% to 87%), thrombocytopenia (35% to 48%; grades 3/4: 3% to 4%)
Neuromuscular & skeletal	Weakness (15% to 20%), back pain (11% to 16%), arthralgia (7% to 11%)
Respiratory	Dyspnea (5% to 12%), cough (6% to 11%)
Miscellaneous	Fever (5% to 12%)

In the following section of this chapter, we will discuss economic studies' methods and requirements as well as compare decision-tree analysis to a Markov model analysis.

Pharmacoeconomic studies methods [111–117]

There are four main methods of pharmacoeconomic studies. Each of the following discussed method measures cost in monetary terms but differs regarding how health outcomes are measured and compared.

Cost-Minimization Analysis (CMA) is used when two medical interventions are comparable in effects but differ in cost. This analysis allows for the identification of the least costly alternative. For example, CMA may be used to compare the value of two generic medications rated as equivalent by FDA, but the cost varies due to different pricing.

Cost-Effectiveness Analysis (CEA) assumes costs are related to a single, common effect (i.e., cost/life-year gained) that may differ in magnitude among alternative treatments or interventions. CEA is widely used because outcomes are easy to quantify when compared to different pharmacoeconomic analyses types (e.g. CUA, CBA). However, CEA would not be appropriate to use when different units are used (e.g. blood glucose level versus prothrombin time). Clinicians, patients and decision-makers may decide on which agent is cost-effective based on the value differences of outcomes.

Cost-Utility Analysis (CUA) uses the same method as cost-effectiveness but is wider in scope, as it incorporates patient preferences into the cost model. This patient preference is called utility, which is expressed as cost/quality-adjusted life-year (QALY) gained. CUA measures outcomes based on years of life adjusted by utility weights which range from (0.0-1.0) where "1" indicates perfect health and "0" indicates death. Although some researchers consider CUA as a subset of CEA, there is no agreement on how to measure utility weights.

Cost-Benefit Analysis (CBA) is an economic comparison between two interventions that requires the conversion of all effect inputs (for example, reduced hospitalization) into monetary outputs, which helps to allocate health care resources. Both benefits and costs are measured in monetary terms which help clinicians and decision makers determine whether the benefits of an intervention exceed implementation costs. Thus, it helps in comparing different programs or interventions with similar or unrelated outcomes by predicting whether the dollar value of the added outcomes exceeds the cost required to obtain those outcomes.

Requirements of pharmacoeconomic studies

Jolicoeur et al (1992) had suggested the following requirements for a well-designed pharmacoeconomic analysis: define the problem, identify the study's perspective, determine outcomes and alternatives, select the appropriate method, place monetary values on the outcomes, identify study resources, establish outcomes probabilities, conduct decision analysis, perform sensitivity or incremental cost analysis or discounting and finally presenting the results with any limitations.[117]

Identifying the study's perspective (patient, payer, societal) is essential in any pharmacoeconomic study because results of evaluation depends heavily on the perspective taken. For example, alteplase may be of best-value from a societal perspective since it can cause 1 % reduction in mortality rates in a large population. However, streptokinase (cheaper option) may represent a better value from a hospital perspective because it provides similar outcomes for a cheaper price.

Patient perspective evaluates costs from the perspective of patients, what they pay for a product or service not covered by insurance. This may include copayments and out-of-pocket costs. This perspective may be considered when we assess the impact of drug therapy on patient quality of life.

Provider perspective evaluates actual costs of providing a service or a product regardless of what the provider charges. Providers can be Managed-Care Organization (MCO), hospitals or private-practice physicians.[118]

Payer perspective includes but is not limited to insurance companies, government or the employer. Payer perspective considers costs allowed or reimbursed by the payer. However, societal perspective is the broadest one because it is the only one which

considers the benefit of a product or service to the society. Societal perspective is mostly used in countries with nationalized medicine since it includes all direct and indirect costs in the economic evaluation. [118]

Discounting is another requirement of an economic evaluation with a time period longer than 1 year since there is a time value associated with money, and costs are estimated based on money spent or saved in future years. A 3-5 % is a generally accepted discount rate for healthcare interventions. However, it is recommended to conduct sensitivity analysis by including higher and lower estimates of various discount rates to account for variability.[62,118]

Time-horizon is another requirement to consider when conducting an economic evaluation because it should be long enough to reflect all important differences in outcomes and costs between comparisons. Time-horizon basically depends on the natural history of disease and the study objective.[62]

Sensitivity analysis is also important because it allows us to determine how results vary over a relevant range of values. Sensitivity analysis produces unbiased estimates of cost-effectiveness mean.[62] It identifies sources of parameter uncertainty, characterize uncertainty as probability distribution (e.g. beta & gamma distributions) and propagate it through model simulation providing robust analysis.[118] The following discussion will compare decision-tree analysis to Markov model.

Decision-Tree Analysis [119–121]

Decision-tree analysis is the process of systematically comparing different decision options by displaying choices that helps in calculating values needed to compare these options. Decision analysis helps in determining which option is more cost-effective

when decisions are complex, and uncertainty of information exists. Decision analysis starts with identifying the objective, perspective and duration of study. Second, specific alternatives should be selected for comparison (e.g. intervention versus no intervention, old versus new drug). Third, a decision structure analysis is drawn to represent either of the choices (e.g. treatment A versus B), chances (e.g. probability of adverse events due to different therapeutic options) and final outcomes of each option of interest. Fourth, obtained data of probabilities and costs are specified on the decision-tree and calculations are performed to estimate the Incremental Cost-Effectiveness Ratio (ICER) or incremental net-benefit ratio. Since some uncertainty surrounds the estimates, it is important to perform sensitivity analysis in the final step by including the highest and lowest range of probabilities and costs in the decision-tree to obtain the lower and higher range of answers.

Markov model [120,122]

Unlike decision-tree, Markov model is used to present complex scenarios with longer follow-up periods that occur over several repetitive intervals, or cycles. Markov model helps in situations where patients move back and forth, or between different health status over periods of time. We used Markov model to answer our research questions since cancer patients move into different health status based on their disease condition (e.g. progression-free survival, progression or death) where death is an absorbing stage where patient cannot move into any different health state later.

Markov model starts with determining different health situations a patient may experience (Markov states) where a patient cannot be in different health status at the same time. Second, all possible transitions between different health statuses are

determined based on obtained clinical data. Third, number and length of cycles are determined based on the disease status being evaluated. For example, for chronic diseases, a cycle length of 1 year is commonly used. Fourth, the proportion of patients who are likely to move from one health status to another during each cycle is determined based on provided clinical data. This is followed by calculating costs and outcomes in the fifth step. For example, percentage of patients who stay alive after cycle 1 get a value of 1 if the outcome of interest is years of life gained or saved. The total costs and outcomes are then summed for all cycles.

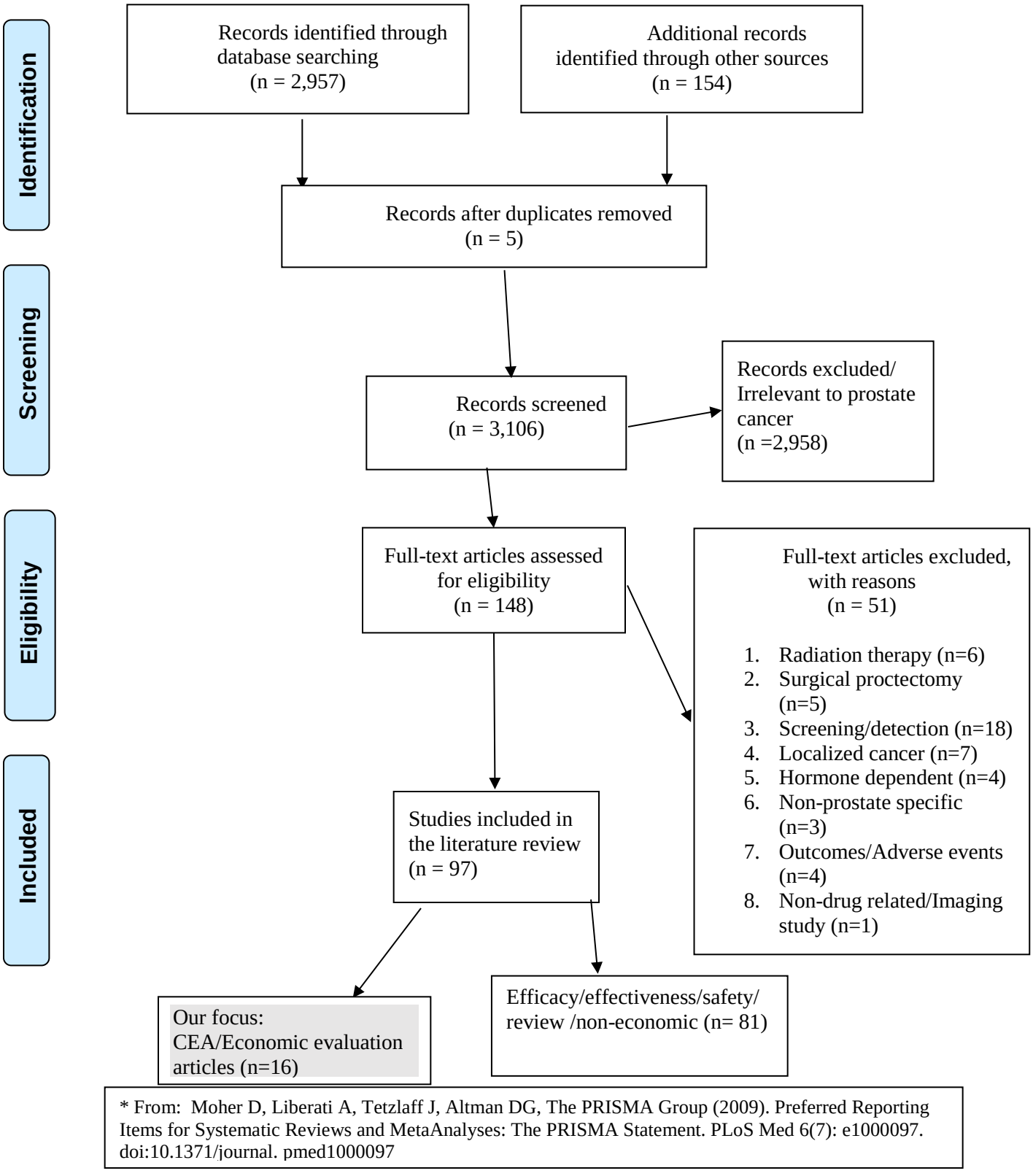
Costs are incorporated in any cost-effectiveness decision analytic method. Drummond et al has proposed in his book Methods for the Economic Evaluation of Health Care Programmes (3rd ed.) the following four categories of costs: health care sector costs, costs to other sectors, patient and family costs, and productivity costs. However, the literature has also reported different classification of costs known as direct medical and non-medical indirect; indirect costs; and intangible costs. Direct medical costs include but not limited to costs of medications, monitoring, administration, counseling, diagnostic tests, hospitalization, emergency visits, home medical costs and ambulance services. Indirect medical costs include travel costs to receive healthcare treatment, hotel stay for patient or family for out of town care and non-medical assistance related to a condition like home-making services. Indirect costs may include loss of productivity of patient, caregiver and due to premature mortality. Intangible costs may include but not limited to costs due to feeling pain, anxiety and fatigue.[123] The following section will explain results of the literature review related to economic evaluation of mCRPC.

Results of the literature review related to economic evaluations of mCRPC

We conducted a systematic review using PubMed to identify published economic evaluations and CEAs/CUAs of current therapeutic agents which received highest recommendation by the NCCN to treat visceral mCRPC patients. The medical subject headings (MeSH) terms ((((("Prostatic Neoplasms"[Mesh]) AND "Neoplasm Metastasis"[Mesh]) OR "secondary" [Subheading]) AND "Cost-Benefit Analysis"[Mesh]) OR "Quality-Adjusted Life Years"[Mesh] were used to identify relevant articles. Subheadings included cost-effectiveness and cost-utility analyses as well as published economic evaluations. Limitations were given for gender since prostate cancer affects males, human and articles published in English in the last 10 years since all medications of interest were introduced in the last 10 years. No additional limits were applied to the search strategy. The next page describes the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram that discusses the process of articles selection.

No studies were identified that conducted an economic evaluation of abiraterone acetate, enzalutamide and cabazitaxel to treat visceral mCRPC patients' refractory to docetaxel therapy from a US healthcare payer perspective utilizing life-time horizon Markov model. However, several economic evaluations compared different treatment paradigms for mCRPC, or had a different perspective (e.g. societal), or targeted different patient population, or utilized a different methodology (e.g. decision tree model) to inform decision makers or had a shorter time-horizon or were in non-US settings. [9,64–77] In addition, to our knowledge, our study is the first one that evaluated the above mentioned therapeutic agents from a US healthcare payer perspective.

PRISMA Flow Diagram*



* From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and MetaAnalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal. pmed1000097

The following discussion will explore published economic evaluations that included abiraterone plus prednisone, cabazitaxel plus prednisone and/or enzalutamide for the treatment of visceral mCRPC.

Abiraterone acetate

Ramaekers el al (2017) published an Evidence Review Group (ERG) perspective of the NICE single technology appraisal of abiraterone acetate as a treatment option of mCRPC among chemotherapy naïve patients.[110] The manufacturer Janssen was invited by NICE to submit evidence for clinical efficacy and cost-effectiveness of abiraterone acetate with prednisone compared to watchful waiting for chemotherapy naïve patients with mCRPC. The purpose was to evaluate whether the use of abiraterone acetate followed by docetaxel is more effective than watchful waiting followed by docetaxel.[64]

Both Maastricht University Medical Center and Kleijnen Systematic Reviews Ltd (KSR) were commissioned as an ERG. The main aim was to develop a NICE guidance by the appraisal committee for the use of abiraterone acetate plus prednisone to treat mCRPC in England and Wales since COU-302-AA clinical trial results for this group of patients were not presented. The ERG concluded in its final guidance that abiraterone acetate is a therapeutic option to treat mCRPC among chemotherapy naïve patients. Although the CEA of abiraterone was evaluated for mCRPC in this study, the population of interest were patients who did not receive chemotherapy before. In addition, it did not include enzalutamide and cabazitaxel in its comparison. [64]

Gong et al (2014) evaluated the CEA of abiraterone and sipuleucel-T in asymptomatic mCRPC using a Markov model from a US societal perspective. However,

the population of interest were patients who did not receive docetaxel (chemotherapy).[65] In addition, sipuleucel is not indicated for visceral mCRPC.[45,53]

Dellis et al (2014) had published a review article of economic evaluation of abiraterone acetate in mCRPC. The review mostly discussed previous work of prostate cancer economics, clinical efficacy of available therapeutic options, safety profile and budgetary impact of abiraterone. However, non-of the selected articles in that review conducted a comparative CEA of abiraterone plus prednisone, enzalutamide and cabazitaxel plus prednisone for visceral mCRPC.[67]

Wilson et al (2014) evaluated the CEA of cabazitaxel, enzalutamide and abiraterone acetate compared to placebo for the treatment of mCRPC. However, the authors utilized a decision-tree model to conduct the analysis over 18 months (short time-horizon). The CEA was conducted from a US societal perspective and no discounting has been used due to short-time horizon.[68]

Zhong et al (2013) evaluated the CEA of abiraterone, cabazitaxel, mitoxantrone and prednisone for mCRPC treatment in the US. The aim was to compare abiraterone and cabazitaxel to two placebos (prednisone and mitoxantrone). However, the analysis included different treatment modalities, utilized a decision-tree model from a US societal perspective and had a relatively short time-horizon (18 months).[66]

Dyer et al (2012) had published a NICE guidance of abiraterone acetate for mCRPC patients who progress despite docetaxel therapy. Clinical efficacy and cost effectiveness data of abiraterone were submitted by the manufacturer Janssen, UK that received evaluation by an ERG. COU-AA-301 trial compared abiraterone acetate plus prednisone to placebo with prednisone in patients who progress despite docetaxel

therapy. The main end-point was median overall survival over 12.8 months whereas secondary end-points were decline in progression-free survival (PFS) and PSA concentration. Abiraterone provided higher overall survival rates (14.8 vs. 10.9 months), prolonged PFS and reduced PSA concentration compared to placebo. The committee recommended abiraterone as a therapeutic option for mCRPC patients who progress despite docetaxel therapy.[124]

Pollard et al (2016) conducted a CEA of abiraterone, sipuleucel-T, enzalutamide, docetaxel, radium-223, and cabazitaxel for the treatment of mCRPC. However, the authors included chemotherapy naïve patients and treatments which are not indicated for visceral mCRPC like radium-223 and sipuleucel-T. They also utilized a decision-tree model to calculate the ICER from a US societal perspective.[69]

Pilon et al (2016) evaluated the cost per median overall survival month of abiraterone and enzalutamide for the treatment of mCRPC using three published phase III clinical trials data. Therefore, it was not a head-head study. Median treatment duration for patients who received enzalutamide was 18 months, whereas median treatment duration for patients who received abiraterone was 14 months. Overall median follow-up time of abiraterone was 49.2 months and 31 months for enzalutamide. Results showed that median overall survival of abiraterone plus prednisone was 34.7 months and 35.3 months for enzalutamide. The cost per median overall survival month was calculated by dividing the treatment cost by number of months needed to achieve overall survival for each treatment. Overall costs per median overall survival month and phase III clinical trials outcomes were lower with abiraterone plus prednisone compared to enzalutamide ($3231 versus 4512; 28% reduction).[70]

Massoudi et al (2017) evaluated associated incremental costs of enzalutamide versus abiraterone plus prednisone for the treatment of chemotherapy-naïve patients with mCRPC from a US payer perspective. They calculated the number needed to treat and associated costs of both treatments required to obtain an additional patient free of progression, chemotherapy or death over a year time-horizon. Clinical outcomes were obtained from COU-AA-302 and PREVAIL clinical trials. Main end-points were progression-free survival, time to initiate chemotherapy and overall one-year survival. Associated costs were calculated as number needed to treat multiplied by the difference in cost per treated patient. Results showed that enzalutamide is cost-effective compared to abiraterone for treating chemotherapy naïve patients with mCRPC.[71]

Restelli et al (2017) had explored the economic burden of mCRPC in Italy. The authors investigated all patients affected by mCRPC and treated with a single agent in an annual time horizon. Direct costs included adverse reactions, medications (abiraterone, enzalutamide, cabazitaxel and radium-223) and skeletal related event management (bony metastasis). They calculated associated costs per patient per year and multiplied it by number of patients with mCRPC in Italy. Nearly €196-228 millions of direct medical costs were associated with mCRPC in Italy mostly attributed to the cost of treatment.[72]

Peters et al (2016) evaluated the cost-effectiveness of radium-223 compared to abiraterone, cabazitaxel and enzalutamide for patients with mCRPC refractory to docetaxel from a Dutch societal perspective. Efficacy, safety and skeletal related event data were obtained from indirect treatment comparison. Authors utilized a life-time (5 years) Markov model to conduct the CEA using a specific Dutch resource use and costs for mCRPC. A time horizon of 5 years was employed, which can be considered lifetime,

given the short life expectancy of the patient population. Radium-223 was associated with lower costs (€6092 and €4465) and higher quality-adjusted life years (QALY) 0.02 and 0.01 compared to abiraterone and cabazitaxel respectively. However, radium-223 was associated with lower QALY (-0.06) and lower life-time costs (€7390) compared to enzalutamide. Authors concluded that radium-223 is a less costly agent and offering comparable health benefits compared to abiraterone, enzalutamide and cabazitaxel for the treatment of mCRPC from a Dutch societal perspective. However, radium-223 is not indicated to treat visceral mCRPC. [73]

Dragomir et al (2014) estimated drug costs of LHRH, denosumab, abiraterone and cabazitaxel for the management of mCRPC from a Quebec public healthcare system (Canada) perspective over a period of 28 months using a Markov model. The mean costs were C$48,428 per patient (95% CI: C$47,624 to C$49,232). Costs increased significantly to C$104,071 (95% CI: C$102,373 - C$105,770) per patient when abiraterone was given before docetaxel therapy. It was predicted that the annual drug costs for a cohort of 4,000 mCRPC patients in Canada is C$193.6 - C$416.3 million.[74]

Finally, Sorensen et al (2013) evaluated the budgetary impact of abiraterone acetate plus prednisone for mCRPC patients from a US healthcare payer perspective. The authors utilized a decision-tree model to compare treatment costs of mCRPC before and after docetaxel adoption based on a hypothetical 1,000,000 member-plan. The analysis concluded that abiraterone has a neutral impact on US health plan budget due to small number of eligible prostate cancer patients and lower toxicity-related costs compared with docetaxel.[9]

Our literature review included 13 articles that had abiraterone acetate as part of the economic evaluation for patients with mCRPC. Two of the 12 articles were ERG perspective of a NICE single technology appraisal. Three were for chemotherapy naïve patients with mCRPC. Nine included different treatment paradigms. One was a review article. One was a budget impact analysis. Three utilized a decision-tree model and had a short-time horizon (≤18 months). Five were evaluated from a societal perspective. Two were in a non-US setting. One had a life-time horizon (5 years). One was evaluated from a US healthcare payer perspective.

In summary, the review of abiraterone acetate economic evaluation included only two articles that were similar to our research question. Wilson et al (2014) conducted CEA of abiraterone, enzalutamide and cabazitaxel. However, it had a short-time horizon (18 months), utilized a decision-tree model with no discounting and included only the cost of major side effects.[68] Although Peters et al (2016) included the three therapies of interest in addition to radium-223 which is not indicated to treat visceral mCRPC, it utilized a Markov model and had a life-time horizon (5 years). However, it was a Dutch economic evaluation from a societal perspective.[73]

Cabazitaxel

In addition to the above discussed articles that included cabazitaxel (7 out of 13) articles as part of abiraterone acetate economic evaluation of mCRPC, the literature also identified the following two articles of cabazitaxel economic evaluation.

Kearns et al (2017) published an ERG perspective of the NICE single technology appraisal of cabazitaxel as a treatment option of mCRPC. The manufacturer Sanofi, UK was invited by NICE to submit clinical efficacy and cost-effectiveness data of cabazitaxel

for the treatment of mCRPC for patients who already received chemotherapy (docetaxel). The school of health and related research appraisal group at the University of Sheffield were commissioned as an independent ERG.[75]

Clinical efficacy data were derived from the TROPIC phase III clinical trial which compared cabazitaxel plus prednisone to mitoxantrone plus prednisone (placebo). Abiraterone plus prednisone, enzalutamide and radium-223 were further identified by NICE final scope for the subgroup of people with bone metastasis only. However, patients with visceral metastasis were not included.

Network meta-analysis (NMA) was conducted to create clinical evidence since no direct comparison of abiraterone or enzalutamide has been conducted with cabazitaxel. Cabazitaxel showed improved median overall survival and PFS compared to mitoxantrone (placebo). However, the NMA did not indicate any statistically significant differences among abiraterone, cabazitaxel and enzalutamide for both overall survival and PFS. The ERG recommended cabazitaxel as a treatment option of mCRPC for patients who progress despite docetaxel therapy.[122]

Flannery et al (2017) had conducted a budget impact analysis for the use of cabazitaxel for the treatment of mCRPC refractory to docetaxel therapy. Authors aimed to estimate one-year projected budget impact of using cabazitaxel as a second-line option for mCRPC following docetaxel therapy utilizing a hypothetical one million members of US private managed care plan. The model included radium-223, abiraterone acetate, cabazitaxel and enzalutamide with utilization rates derived from market research data. Both major side effects and treatment costs were incorporated into the model. Authors concluded that cabazitaxel may be a cost-saving therapeutic option to the health plan.[76]

Enzalutamide

In addition to the above discussed articles that included enzalutamide (9 out of 15) articles as part of abiraterone acetate and/or cabazitaxel economic evaluation of mCRPC, the literature also identified the following article of enzalutamide economic evaluation.

Bui et al (2016) evaluated the budget impact analysis of enzalutamide among chemotherapy naïve patients with mCRPC from a US payer perspective. A model was developed using a hypothetical one million-member US plan over one-year time horizon. The model included the cost of treatment and side effects of abiraterone acetate, radium-223, sipuleucel-T and docetaxel. Different sources of data were utilized to obtain costs of treatment, administration and monitoring, adverse events and rates of chemotherapy naïve mCRPC patients. The budget impact analysis included the calculation of the incremental aggregate budget impact, per patient per year (PPPY), per patient per month (PPPM) and per member per month (PMPM). Results showed that adopting enzalutamide in a population of 115 chemotherapy-naïve mCRPC patients would have an annual incremental budget impact of $510,641 ($4,426 PPPY, $369 PPPM, and $0.04 PMPM).[77]

Overall, since additional discussed articles did not conduct a CEA of the three therapies of visceral mCRPC from a US healthcare perspective utilizing life-time Markov model in the US setting; our economic evaluation will add to the previously published economic evaluations in this therapeutic area.

In summary, this chapter provided a detailed review of prostate cancer disease condition, screening, diagnosis, treatment, CRPC, therapeutic options of mCRPC, pharmacoeconomic studies' methods and requirements, compared decision-tree to

Markov model and discussed the results of literature review related to economic evaluation of mCRPC.

CHAPTER 3: METHODS

Introduction

In this chapter we discuss methods used to estimate the cost-effectiveness [cost per life year gained (LYG)] and cost-utility analyses [cost per quality-adjusted life-year (QALY)] comparing abiraterone acetate plus prednisone, enzalutamide and cabazitaxel plus prednisone in visceral mCRPC patients who progress despite docetaxel chemotherapy from a US healthcare payer perspective using a life-time horizon Markov model. The first section will discuss the research design. The second section will discuss the pharmacoeconomic model used in the study. This includes study comparators, population, time horizon, study perspective, discounting, transition probabilities, effectiveness measures, cost measures, adverse events and the calculation of an Incremental-Cost-Effectiveness Ratio (ICER) and an Incremental-Cost-Utility Ratio (ICUR). The third section will discuss probabilistic sensitivity analysis. In the last section, we will discuss human subjects' approval to conduct this study.

Research design

In this section, we will provide an overview of the research design. Our research design is a pharmacoeconomic model that was constructed using Microsoft Excel® and supported by visual basic codes and macros functions to estimate the cost-effectiveness [cost per LYG] and cost-utility analyses [cost per QALY] comparing abiraterone acetate plus prednisone, enzalutamide and cabazitaxel plus prednisone in visceral mCRPC patients who progress despite docetaxel chemotherapy from a US healthcare payer perspective using life-time horizon Markov model.

CEA assumes costs are related to a single, common effect (i.e., cost/life-year gained) that may differ in magnitude among alternative treatments or interventions. CEA is widely used because outcomes are easy to quantify when compared to different pharmacoeconomic analyses types (e.g. CUA, CBA). Clinicians, patients and decision-makers may decide on which agent is cost-effective based on the value differences of outcomes.[111–117]

CUA uses the same method as cost-effectiveness but is wider in scope, as it incorporates patient preferences and quality of life into the cost model. This patient preference is called utility, which is expressed as cost/QALY gained. CUA measures outcomes based on years of life adjusted by utility weights which range from (0.0-1.0) where "1" indicates perfect health and "0" indicates death.[111–117]

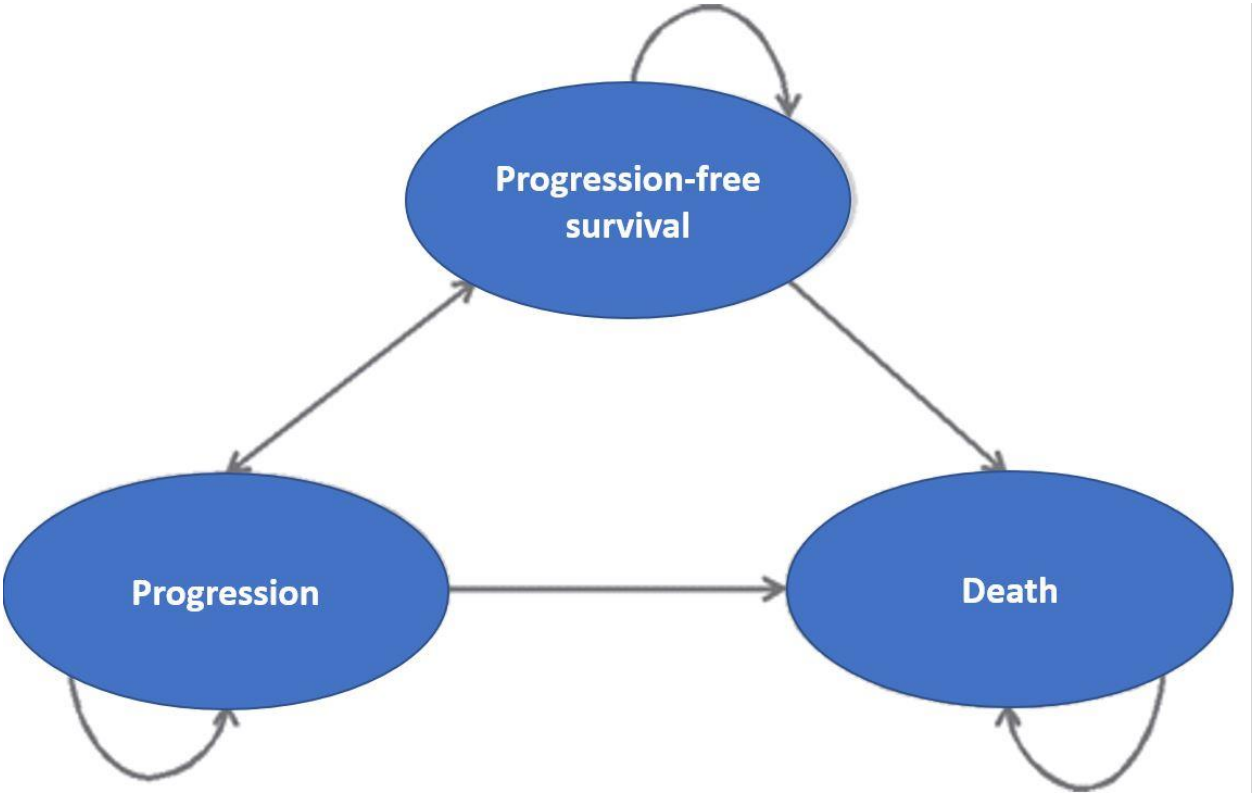
Model description

A life-time horizon Markov chain model was constructed from a US healthcare perspective using Microsoft Excel® and supported by visual basic codes and macro functions for a hypothetical cohort of visceral mCRPC patients who progress despite docetaxel therapy to receive either of abiraterone plus prednisone, enzalutamide and cabazitaxel plus prednisone based on 2017 NCCN highest level of recommendation for treating visceral mCRPC after docetaxel chemotherapy.

A three-health state [Progression-Free Survival (PFS), progression and death] transition model reflecting survival was developed as illustrated in Figure 5. The patient who starts in the PFS health state may stay in the same health state until the next cycle, progress to another state or die. However, a patient with disease progression may either stay in the same state until the next cycle, improve and go back to the PFS state, or die.

Figure 5

Health states transition model of a mCRPC patient



Cohort simulation was conducted for a hypothetical cohort of visceral mCRPC patients starting in the same health states. At each cycle, transition probabilities were applied. The proportion of patients in each cycle was calculated and summed using matrix algebra. Since mCRPC disease management and complications develop at a relatively fast time scale, a cycle of 7 days length was considered for cost-effectiveness modeling of mCRPC therapies.[73,125]

Since we are conducting an economic evaluation in the oncology setting, our approach allowed us to model overall-survival (OS) and PFS in a manner that reflected COU-AA-301 trial which compared abiraterone plus prednisone to placebo (prednisone), AFFIRM trial which compared enzalutamide to placebo and TROPIC trial which compared cabazitaxel plus prednisone to mitoxantrone plus prednisone (placebo).[43,48,51]

Since phase III clinical trials do not provide survival information beyond the data horizon, modeling OS and PFS using clinical trials data provided the transition probabilities of the different health states for a mCRPC patient reflecting primary sources of survival evidence provided by the clinical trials.[43,48,51]

We calculated OS and PFS transition probabilities for each of the alternatives (abiraterone plus prednisone, enzalutamide and cabazitaxel plus prednisone) from the Kaplan-Meier survival curves of phase III trials using a digitizing program (Webplotdigitizer).[126] Additionally, to generalize the findings from the trials and extrapolate survival beyond the data horizon, Weibull parametric modeling techniques were applied to approximate OS and PFS for abiraterone plus prednisone, enzalutamide and cabazitaxel plus prednisone for each cycle within the model's time horizon. Weibull parametric modeling was applied because it visually provided the best fit survival

distribution data beyond clinical trials survival information. Additionally, this was supported by analysis of variance results (ANOVA) results of R^2 and sum square of statistics for OS and PFS. Both gompertz and exponential distribution curves did not fit extrapolated survival data. The Weibull equation for estimating survival is: $S(t) = e^{-\lambda t^{\gamma}}$, where S(t) is the estimate of the survivor function at time (t), lambda (ג) the scale parameter, and gamma (γ) the shape parameter.[127]

Weibull distribution data of OS and PFS were then incorporated into the Markov model for each therapy. The proportion of dead individuals were calculated by subtracting OS from one (1-OS). Proportion of individuals with disease progression were calculated by subtracting 1 from the sum of proportion of dead and progression free survival patients [i.e. 1- (death+PFS)].

A 3% discounting rate was applied for all patients who survived (PFS and progressed patients) after the first year (52 weeks) as recommended by the US Panel on Cost-Effectiveness in Health and Medicine (USPCEHM).[62,128]

Our effectiveness measures LY and QALY (denominators) were calculated as follows: since we a weekly cycle for each of therapies, it was important to standardize the outcome measure LY into a weekly measure.

A constant value of 0.07692 was multiplied by PFS and progression transition probabilities for all patients who survived (PFS & progressed patients) at each cycle. The new values of PFS and progression were then discounted after the first year (52 weeks) and summed to provide a discounted LY gained for each therapy.

In addition, similar steps of Weibull parametric modeling, discounting after 52 weeks and weekly standardization were applied to obtain the QALY of each therapy at

each cycle. However, we provided the quality-adjusted life years (QALYs) by multiplying corresponding utilities by life expectancies. Specifically, we multiplied the utilities for PFS and progression by the proportion of PFS and progressed patients who responded to each therapy. We also considered disutilities due to adverse events in the model by subtracting those disutilities from PFS and progression utility values. We have finally summed all QALY of progressed and PFS patients at each cycle to yield the QALY for each therapy.

Health utility values of the three health states and disutility values due to adverse events were retrieved from published data of EuroQol, Five Dimensions questionnaire since it provides validated utilities in the US setting.[73,129,130] More details about utility values utilized in the model can be obtained from Table 4. We included utility values of PFS and progressed patients in the Markov model as well as the disutility values due to different adverse events from the literature.[129,131]

Table 4

Health Related Quality of Life (HRQoL) Utility values

Health states utility values	Utility value	95 % CI	Reference
Progression-free survival (PFS) of mCRPC patients	0.617	0.55-0.68	120
Progression (P) of mCRPC patients	0.37	0.33-0.41	132
Death	0		130

Cost Measures

Costs of therapies were obtained from RED BOOK Online® which is a resource of the latest drug product pricing of over-the-counter and prescription medications in the US.[133] Rates and costs of grade (≥3) adverse events that occurred in (≥5 %) of patients for the three therapies were obtained from clinical trials, package insert information and

literature.[43,48,51] We have also obtained costs of follow up visits and needed investigations from the literature.[134,135]

We included direct medical costs in the model expressed in 2018 US dollars based on the US healthcare payer perspective, all costs were adjusted for inflation through the medical consumer price index (MCPI) as per the 1st quarter of 2018.[136] We obtained the wholesale acquisition cost (WAC) of abiraterone, enzalutamide, cabazitaxel and prednisone from RED BOOK Online®.[133] Based on clinical trials and cost data, we calculated the cost per cycle (7 days) for each therapy or combination of therapy (when prednisone is given). We have assumed that the default body weight for an adult patient with mCRPC is 70 kg. Thus, cabazitaxel dose and cost were calculated based on body surface area of a 70-kilogram patient.[43]

We have also retrieved costs of grade (≥3) side effects that occurred in (≥5%) of patients in the model related to each of the therapies from the literature.[135,137] These costs were validated and adjusted based on reported percentages of adverse events by clinical trials.[43,48,51] We have standardized rates and costs of adverse events to a weekly percentage as reported by clinical trials using the equation (1-(1-p)^(1/52), where P is the probability of having grade (≥3) adverse events.[125]

Adverse events

Since clinical trials are conducted under controlled conditions, observed adverse events rates in clinical trials may not reflect the observed rates in clinical practice or directly compare to rates in the clinical trials of another drug. Thus, we aimed to include significant adverse events of grade (≥3) related to each of therapies that occurred in (≥5

%) of patients based on package insert information and literature since they may have a significant effect on the course of treatment, survival and costs.[50,104]

All included grade (≥3) adverse events were retrieved from the clinical trials COU-AA-301, AFFIRM and TROPIC clinical trials.[43,48,51] We have validated reported percentages by referring to package insert information.

Table 5 provides package insert raw percentages of grade (≥3) adverse events related to the three therapies. Table 6 describes related adverse events to each of the therapies, their frequencies, time affected (median exposure) and disutilities as reported by the clinical trials and literature. The following discussion will explain each of the therapies adverse events.

Abiraterone acetate plus prednisone

Abiraterone trial (COU-AA-301) included several adverse events of grade (≥3) associated with the use of abiraterone plus prednisone. However, none of the reported ones occurred in more than (10%) of patients in the abiraterone plus prednisone arm (the highest was 9 % associated with fatigue). The median follow-up in the overall study population was 12.8 months.[48]

Overall abiraterone was associated with the following grade (≥3) adverse events: (9 %) fatigue, (1 %) diarrhea, (<3 %) pain in the arm or leg, (7 %) anemia, (<2%) thrombocytopenia, (<1 %) neutropenia, (<3 %) nausea, (<3%) vomiting, (<1%) hematuria, (2%) abdominal pain, (<2%) dyspnea, (4%) arthralgia, (2 %) urinary tract infection and (<5 %) bone pain.[48,104]

Grade 3-4 arrhythmias occurred at similar rates in the placebo and abiraterone arms. Cardiac ischemia occurred in 2 patients in the active arm compared to 1 in the

placebo arm, cardiac death resulting in death occurred in 1 patient in both arms. Since rates of cardiovascular events were comparable in both arms, we did not include any of these adverse events and related cost data in the model. In addition, all grade (≥3) cardiac adverse events (i.e., ischemic heart disease, myocardial infarction, supraventricular tachyarrhythmias, ventricular tachyarrhythmias, cardiac failure, and possible arrhythmia-related tests, signs, and symptoms) associated with the use of abiraterone plus prednisone occurred in 4 % of patients.[48]

In summary, based on the above reported percentages of related adverse events to abiraterone plus prednisone, we decided to include costs of anemia, fatigue, diarrhea, neutropenia, back pain and bone pain in the model since they at least occurred in (≥5 %) of patients receiving either therapies.

Enzalutamide

Grade (≥3) adverse events were reported among (47 %) of enzalutamide-treated arm and (53 %) of placebo-treated arm. Additionally, about (18 %) of placebo-treated patients and (16 %) of enzalutamide-treated patients discontinued the medication. The median duration of follow up was 14.4 months.[51]

Most of enzalutamide-treated patients discontinued the drug due to seizure that occurred (0.9 %). Grade (≥3) enzalutamide-related adverse events were (6 %) fatigue, (1 %) diarrhea and (1 %) musculoskeletal pain. Grade (≥3) seizure, cardiac events and headache occurred in less than (1 %) of patients.

Overall, we have decided to include reported percentages and costs of fatigue and diarrhea related to enzalutamide therapy in the model since they at least occurred in (≥5) % of patients receiving either therapies.

Table 5

Grade (≥3) Adverse events raw percentages* [138–140]

Enzalutamide (grade≥3)	Abiraterone plus prednisone (grade≥3)	Cabazitaxel plus prednisone (grade≥3)
Fatigue 6 %	Fatigue < 9 %	Fatigue < 5 %
Diarrhea 1 %	Diarrhea < 1 %	Diarrhea 6 %
MS pain 1 %	Arm/leg pain < 3 %	Arm/leg pain 2 %
Headache <1%	****	****
CVS <1%	Arrhythmias 1 %, Cardiac failure 1.9 % Chest pain 0.5 %	****
Seizure <1%	****	****
	Anemia 7 %	Anemia < 11 %
	Thrombocytopenia <2%	Thrombocytopenia 4 %
	Neutropenia < 1 %	Neutropenia < 82 %
	Back pain < 6 %	Back pain < 4 %
	Nausea <3 %	Nausea 2 %
	Vomiting <3 %	Vomiting 2 %
	Hematuria < 1%	Hematuria 2 %
	Abdominal pain 2%	Abdominal pain 2%
	Dyspnea < 2%	Dyspnea 1 %
	Arthralgia 4 %	Arthralgia 1 %
	UTI 2 %	UTI 1%
	Bone pain < 6 %	Bone pain 1 %

*Raw percentages as reported by the package insert of each therapy. Note: values shaded in gray demonstrates all grade (≥3) adverse events included in the model that occurred at least in (≥5) of patients receiving either of therapies.

Cabazitaxel plus prednisone

We also included grade (≥3) adverse events that occurred in (≥5 %) of patients who received cabazitaxel plus prednisone as reported by TROPIC trial and package insert information.[140] Cabazitaxel plus prednisone regimen was mostly associated with (82%) neutropenia, (11 %) anemia, (6 %) diarrhea and fatigue (5 %). Other reported grade (≥3) adverse events occurred in (<5%) of patients in the cabazitaxel plus prednisone arm as described in Tables 5 and 6.

Table 6

Rates and utilities of grade (≥3) adverse events

Drug name	Grade (≥3) Adverse event	Frequency	Time affected*	Utility decrement	Reference
Abiraterone acetate plus prednisone	Anemia	0.0745	0.00148	0.119	48,131
	Diarrhea	0.0063	0.00012	0.212	48,131
	Fatigue	0.0834	0.00167	0.473	48,131
	Back pain	0.0594	0.00117	0.067	48
	Neutropenia	0.0100	0.00390	0.131	48,131
	Bone pain	0.0590	0.00110	0.067	48
Enzalutamide	Fatigue	0.0625	0.00124	0.473	51,131
	Diarrhea	0.0112	0.00021	0.212	51,131
Cabazitaxel plus prednisone	Neutropenia	0.8167	0.03210	0.131	43,129
	Anemia	0.1051	0.00213	0.119	43,131
	Diarrhea	0.0619	0.00123	0.212	43,131
	Fatigue	0.0485	0.00095	0.473	43,131
	Back pain	0.0377	0.00073	0.067	43
	Bone pain	0.0100	0.00390	0.067	43

*Time affected: All frequencies were converted to a weekly percentage that reflects weekly exposure to the adverse event using the equation (=1-(1-p) ^ (1/52)), where P reflects the probability/frequency of grade (≥3) adverse events.[125]

In summary, costs of fatigue, diarrhea, anemia, neutropenia, back pain and bone pain associated with abiraterone acetate plus prednisone were included in the model. Additionally, costs of fatigue, diarrhea, anemia, neutropenia, back pain and bone pain associated with cabazitaxel plus prednisone; and costs of fatigue and diarrhea associated with enzalutamide were also included in the model. No further adverse events were included in the model.

The model included costs of follow up visits and needed procedures obtained from the Centers for Medicare and Medicaid Services (CMS) physician and clinical

laboratory fee schedule which is a national pricing reference that uses medical Current Procedural Terminology (CPT) codes.[134,135] We have assumed that all therapies share the same follow up schedule and needed investigations (weekly physician visit and CBC check to check for anemia and neutropenia count); and performing CT scan when clinical or consistent and convincing biochemical progression is identified as recommended in 2017 by the prostate cancer Radiographic Assessment for Detection of Advanced Recurrence (RADAR) Working Group.[141] Based on the above recommendation and due to the aggressiveness of disease condition, we have assumed that CT scan and home nurse visits may be performed monthly.

We have also included the 95 % confidence interval estimate for costs of medications and adverse events to account for uncertainties in cost data. These estimates were used to conduct probabilistic sensitivity analysis. Table 7 provides more details related to cost data utilized in the model.

ICER & ICUR calculation

The cost-effectiveness outcome measures were ICER and ICUR expressed as cost per Life Year (LY) and cost per Quality Adjusted Life Years (QALY) gained for mCRPC patients as explained in tables (8-11) for the three therapies by dividing the incremental cost by the incremental effectiveness (LY or QALY) using the formula: (CostRx1-CostRx2)/ (LY)Rx1-LY) Rx2) and (CostRx1-CostRx2)/ (QALYs Rx1-QALY Rx2), respectively. Both outcome measures were endorsed as a reference case by NICE and USPCEHM in the UK.[62,128,142]

Table 7

Model Input for Costs

Medications	**WAC price per cycle (7 days) * (95 % CI) ****	**Reference**
Abiraterone acetate 1000 mg plus, prednisone 10 mg	$2861.614 ($2575.45, $3147.77)	Red Book[133]
Enzalutamide 40 mg	$2544.54 ($2290.08, $2798.99)	Red Book[133]
Cabazitaxel 25 mg/m2 plus prednisone 10 mg***	$8372.94 ($7535.6-$9,210.2)	Red Book[133]
Adverse events****	**Cost of adverse event (95 % CI)**	**Reference**
Fatigue	$6,946.00 ($6251.4, $7640.6)	Roy et al, CMS Acute Inpatient Prospective Payment System[135,137]
Diarrhea	$10,760.00 ($9684, $11836)	Roy et al, CMS Acute Inpatient Prospective Payment System[135,137]
Anemia	$1,038.00 ($934.2, $1141.8)	Roy et al, CMS Acute Inpatient Prospective Payment System[135,137]
Back pain	$10,914.00 ($9822.6, $12005.4)	Roy et al, CMS Acute Inpatient Prospective Payment System[135,137]
Neutropenia	$165.00 ($148.5, $181.5)	Roy et al, CMS Acute Inpatient Prospective Payment System[135,137]
Costs of follow up	**Costs**	**Reference**
Physician visit	$25.74 ($23.1-$28.3)	CMS physician service fee, clinical laboratory fee schedule search[134,135]
Complete blood count	$76.14 ($68.5-$83.7)	CMS physician service fee, clinical laboratory fee schedule search[134,135]
CT Scan	$230.98 ($207.8-$254)	CMS physician service fee, clinical laboratory fee schedule search[134,135]
Home nurse visit	$44.78 ($40.3-$49.8)	CMS physician service fee, clinical laboratory fee schedule search[134,135]

*The cost of cycle was calculated by multiplying the cost of each unit by the dose required per day by 7.
** Sensitivity analyses were performed by utilizing the assumed 95% Confidence Interval (CI).
*** The dose of cabazitaxel was calculated based on body surface area of a 70-kilogram patient.
****We have included grade III and above reported adverse events for each therapy in clinical trials. The unit costs for adverse events were obtained from published sources. **Note**: Both of adverse events and follow up visits costs were inflated to 2018 US dollars using the medical care component of the US Bureau of Labor Statistics Consumer Price Index.

Since it was recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guideline to provide the lowest cost treatment for each treatment comparison, we provided our cost-effectiveness outcome measures ICER and ICUR for each therapy starting with the lowest cost.[143,144] Base-case (deterministic) results of outcome measures were validated using probabilistic sensitivity analysis, which will be discussed in detail in a later section in this chapter.

Table 8
Base case (deterministic) results of the cost-effectiveness analysis

ENZ*		
$US/LY gained	**ABI+P****	
$US/LY gained	$US /LY gained	**CAB+P*****

*ENZ: Enzalutamide ** ABI+P: Abiraterone plus prednisone ***CAB+P: Cabazitaxel plus prednisone

Table 9
Probabilistic results of the cost-effectiveness analysis

ENZ		
$US/LY gained	**ABI+P**	
$US/LY gained	$US/LY gained	**CAB+P**

Table 10
Base case (deterministic) results of the cost-utility analysis

ENZ		
$US/QALY gained	**ABI+P**	
$US/QALY gained	$US/QALY gained	**CAB+P**

Table 11
Probabilistic results of the cost-utility analysis

ENZ		
$US/QALY gained	**ABI+P**	
$US/QALY gained	$US/QALY gained	**CAB+P**

Since cost-effectiveness of a health technology compared to an alternative is often determined if the ICER/ICUR falls below a specific threshold, we have considered a maximum value of $100,000 per QALY to determine if it is cost-effective as recommended by the Second Panel of Cost-Effectiveness in Health and Medicine.[62]

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis produces unbiased estimates of cost-effectiveness mean.[129] We performed this analysis since it identifies sources of parameter uncertainty, characterizes uncertainty as probability distributions (e.g. beta & gamma distributions) and propagates it through model simulation.

Probabilistic sensitivity analysis utilizes values from the Weibull distributions of OS, PFS, beta distribution of probabilities and utility estimates; and the gamma distribution of monetary inputs to provide an estimate of effects and costs through simulation. For example, since costs are expressed in positive numbers, gamma distribution was applied to address uncertainty in costs. The distribution considers the average cost per milligram and body surface area if applicable (e.g. cabazitaxel).

Beta distribution was applied to the proportion of patients who responded to the treatment with abiraterone acetate plus prednisone, cabazitaxel plus prednisone and enzalutamide. Beta distribution are often indicated for presenting uncertainty in probability parameters constrained within 0-1. In addition, beta-distribution was applied to manage uncertainty about the probability of adverse events for patients who received treatment and for both health-related quality of life utilities and disutilities.

We ran a probabilistic sensitivity analysis with 2,000 iterations to evaluate the combined effects of uncertainty in all model inputs, assess the robustness of deterministic base-case analysis and create the cost-effectiveness acceptability curve (CEAC) at various willingness to-pay thresholds (WTP).

Table 12 provides more details regarding model inputs that were validated through probabilistic sensitivity analysis.

Human subjects' approval

This study was approved by University of New Mexico Health Sciences Center (UNMHSC) Human Research and Review Committee (HRCC) under the exempt category. The approval letter is provided in Appendix B.

Table 12

Model Input of probabilistic sensitivity analysis

Parameters	Deterministic	Probabilistic Sensitivity Analysis Range of Values (+/-) 10 %
Utility values		
Utility value of PFS	0.617	0.55-0.68
Utility value of progressed patients	0.37	0.33-0.41
Disutility value due to adverse event	Varies based on Specific adverse events	Varies based on specific adverse events, please refer to table (6).
Costs of therapy		
Cost of 7 days cycle of Enzalutamide	$2544.54	($2290.0-$2798.9)
Cost of 7 days cycle of Abiraterone acetate plus prednisone	$2861.614	($2575.4-$3147.7)
Cost of 7 days cycle of Cabazitaxel plus prednisone	$8372.94	($7535.6-$9,210.2)
Costs of adverse events		
Fatigue	$6,946.00	($6251.4-$7640.6)
Diarrhea	$10,760.00	($9684-$11836)
Anemia	$1,038.00	($ 934.2-$1141.8)
Back pain	$10,914.00	($9822.6-$12005.4)
Neutropenia	$165.00	($148.5-$181.5)
Costs of follow up		
Weekly Physician visit	$25.74	($23.1-$28.3)
Weekly CBC	$76.14	($68.5-$83.7)
Monthly CT Scan	$230.98	($207.8-$254)
Monthly Home nurse visit	$44.78	($40.3-$49.8)

CHAPTER 4: RESULTS

Introduction

This chapter consists of five sections. In the first section, we discuss results of effectiveness measures which include results of overall survival and progression-free survival probabilities of enzalutamide, abiraterone acetate plus prednisone and cabazitaxel plus prednisone obtained from our life-time horizon Markov model. In the second section, we will discuss base-case results of cost measures This will be followed by a discussion of the calculation and comparison of the incremental cost-effectiveness ratios associated with each of the therapies. Fourth, we will discuss results of probabilistic sensitivity analysis. Finally, we will be providing a summary of study results in the last section.

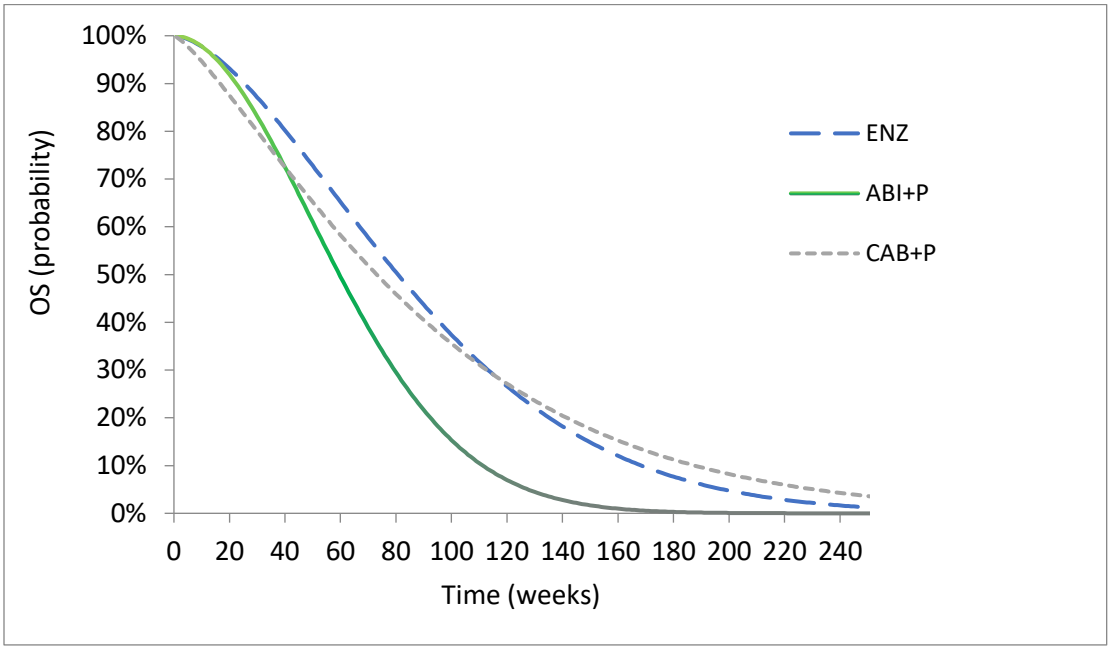
Results of Effectiveness measures and Survival Rates

The objective of this study was to estimate the cost-effectiveness between enzalutamide, abiraterone acetate plus prednisone and cabazitaxel plus prednisone for the treatment of visceral mCRPC patients who progress despite docetaxel therapy from a US health care perspective using life-time horizon Markov model.

Figures 6 & 7 provide the results of extrapolated survival curves of abiraterone acetate plus prednisone, enzalutamide and cabazitaxel plus prednisone using Weibull parametric modeling of phase III clinical trials OS and PFS curves. Results show that almost all visceral mCRPC patients are expected to die within 5 years which indicates the aggressiveness of the disease condition. Specifically, about (98.7 %) of patients who receive abiraterone acetate plus prednisone, (83.8 %) who receive

Figure 6

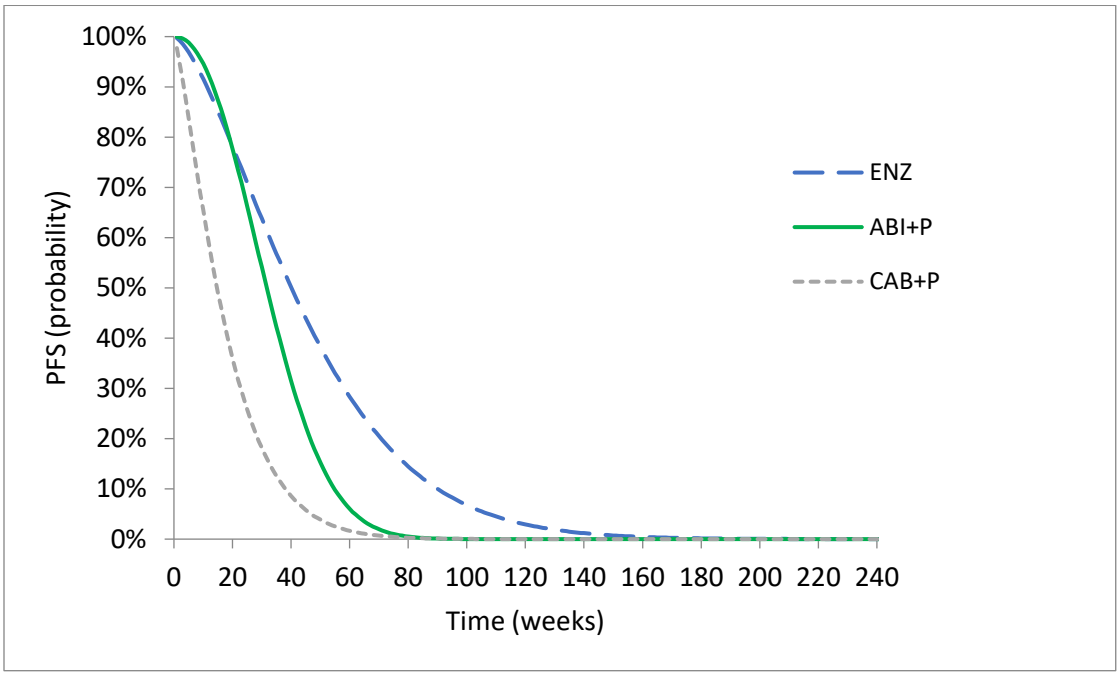
Overall survival (OS) Weibull distribution



*ENZ: Enzalutamide ** ABI+P: Abiraterone plus prednisone ***CAB+P: Cabazitaxel plus prednisone

Figure 7

Progression-Free Survival (PFS) Weibull distribution



*ENZ: Enzalutamide ** ABI+P: Abiraterone plus prednisone ***CAB+P: Cabazitaxel plus prednisone

cabazitaxel plus prednisone and (86.8 %) who receive enzalutamide are expected to die in 3 years. Additionally, in 1.5 years' time, patients who receive enzalutamide will have significantly higher rates (14.47 %) of PFS than cabazitaxel plus prednisone (0.27 %) and abiraterone acetate plus prednisone (0.51 %).

Overall, patients who receive enzalutamide have higher survival rates (1.58 LYG) compared to abiraterone plus prednisone (1.20 LYG) and cabazitaxel plus prednisone (1.48 LYG). However, abiraterone acetate was associated with better quality of life or outcomes (0.58 QALY) compared to cabazitaxel plus prednisone (0.56 QALY) due to a better side effect profile.

Base-case results of total cost measures

Our CEA utilized a US healthcare payer perspective. Therefore, we included direct medical costs in the model expressed in 2018 US dollars. All model costs were adjusted for inflation through the MCPI as per the 1st quarter of 2018 and future costs were discounted at 3 %.[62,136] We considered costs of drugs per cycle and grade (≥3) adverse events associated with abiraterone acetate plus prednisone, enzalutamide and cabazitaxel plus prednisone. We also included costs of physician follow-up visits, blood work and imaging studies (i.e. monthly CT) based on RADAR and NCCN recommendations for all visceral mCRPC patients receiving either therapies. Table 13 provides costs of enzalutamide, abiraterone acetate and prednisone whereas table 14 provides results of cabazitaxel since it poses different dosing profile. Table 15 explains base-case total cost measures of visceral mCRPC therapies.

Table 13

Costs of enzalutamide, abiraterone acetate and prednisone

Type of therapy	Strength (mg)	WAC price per tablet	Dose required daily	Cost per dose required daily*
Enzalutamide	40 mg	$90.87	160 mg	$363.5
Abiraterone acetate	250 mg	$85.26	1000 mg	$341.0
Prednisone**	10 mg	$67.73	10 mg	$67.73

*Cost per dose required daily equals to number of tablets required daily times Wholesale Acquisition Cost (WAC). **Cost of prednisone represent the average WAC price for multiple generic products

Table 14

Cost of Cabazitaxel

Body Surface Area	1.75
Strength	60/1.5 ml
Dose required	25 mg/m2
Number of units	1
Cost per unit	$10182.48
Cost per dose required every 3 weeks	$7424.725*

*Cost per dose required (every 3 weeks) assuming no wastage

Table 15

Base-case total cost measures of visceral mCRPC therapies

Type of therapy	Cost per dose required daily	Cost of therapy per cycle	Costs of grade (≥3) adverse events per cycle	Costs of follow-up visits and needed investigations per cycle	Total costs
Enzalutamide	$363.50	$2544,54	$555.175	$377.64	$157,830
Abiraterone acetate plus prednisone	$408.80	$2861,61	$1373.49	$377.64	$235,854
Cabazitaxel plus prednisone	***	$8372.94	$1659.78	$ 377.64	$496,756

***Cabazitaxel plus prednisone dose is given every 3 weeks.

Calculation and comparison of the incremental cost-effectiveness(ICERs) and incremental cost-utility ratios (ICURs) associated with each of the therapies

We estimated the cost-effectiveness [cost per LYG] and cost-utility analyses [cost per QALY] of visceral mCRPC therapies in patients who progress despite docetaxel chemotherapy from a US healthcare payer perspective using a life-time horizon Markov model.

Table 16 presents the base-case results of total LYG and QALY gained. Enzalutamide was found to be more effective (1.58 LYG) compared to abiraterone plus prednisone (1.20 LYG) and cabazitaxel plus prednisone (1.48 LYG). Additionally, Enzalutamide was associated with higher total QALY, (0.79 QALY), compared to abiraterone plus prednisone (0.58 QALY) and cabazitaxel plus prednisone (0.56 QALY). Enzalutamide was also associated with lower total costs ($157,830) compared to abiraterone acetate plus prednisone ($235,854) and cabazitaxel plus prednisone ($496,756).

Table 16

Base-case results of total costs and effectiveness measures

Comparator	Total Cost	Total LY gained	Total QALYs gained
ENZ	$157,830	1.58	0.79
ABI+P	$235,854	1.20	0.58
CAB+P	$496,756	1.48	0.56

ENZ: Enzalutamide, ABI+P: Abiraterone acetate plus prednisone, CAB+P: Cabazitaxel plus prednisone

ICER and ICUR calculation provide the ratio of the incremental difference in costs divided by the incremental difference in outcomes and used to determine the magnitude of the added cost for each unit in health improvement. However, based on the above results, enzalutamide dominated both abiraterone plus prednisone and cabazitaxel

plus prednisone as it provided more effectiveness at lower costs. Thus, enzalutamide was found to be cost-effective compared to abiraterone acetate plus prednisone and cabazitaxel plus prednisone.

However, abiraterone acetate plus prednisone was found to less effective and less expensive than cabazitaxel plus prednisone and therefore, the ICER and ICUR were calculated between these two options for the scenario where enzalutamide was not a dominant option. Cabazitaxel plus prednisone had an ICER & ICUR of $931.7K/LYG and almost 13 million/QALY respectively when compared to the next lowest treatment, abiraterone acetate plus prednisone.

Results of probabilistic sensitivity analysis

Probabilistic sensitivity analysis evaluates combined effects of uncertainty of all model input. This is achieved through repeated sampling of mean parameter values from a series of assigned distribution types, based on the standard error statistics and point estimates for each average parameter values. Each set of samples from all parameters generate a single estimate of expected effects and costs provided by the model.

Gamma distribution is useful to assess uncertainties of monetary inputs since they are constrained on an interval from zero to positive infinity.[145] Thus, we have used gamma distribution to assess uncertainties in costs of drugs per milligram per cycle and costs of grade (≥3) adverse events that occurred at least in (≥5%) of visceral mCRPC patients according to package insert information and phase III clinical trials data. Gamma distribution was also used to evaluate uncertainties in costs of follow up visits and any needed investigations as discussed in table 6.

Beta distribution was used to evaluate uncertainties in HRQoL utility estimates since they present uncertainty in probability parameters constrained between 0-1.[129] Beta distribution was also used to evaluate uncertainties in disutility values of grade (≥3) adverse events that occurred at least in (≥5%) of visceral mCRPC patients.

The analysis was run over 2000 iterations, at which point we evaluated the impact of further simulations on the mean probabilistic sensitivity analysis results. The results were also used to create the cost-effectiveness acceptability curve (CEAC).

Scatter plots were generated using Microsoft Excel® supported by macros and functions showing the four-quadrant plane that assesses the cost-effectiveness measures associated with abiraterone acetate plus prednisone, enzalutamide and cabazitaxel plus prednisone. Additionally, CEAC were plotted to show the probability of the three therapies to be cost-effective at various WTP thresholds. Figure 8. represent the probabilistic sensitivity analysis cost-effectiveness plane, which demonstrates the incremental costs and QALY difference between therapies. Figure 9. and 10. represent the CEAC for visceral mCRPC therapies. Enzalutamide dominated both therapies. Additionally, cabazitaxel plus prednisone becomes cost-effective compared to abiraterone plus prednisone (50 % cost-effective point estimate) at 12 million $US/QALY. Although the three therapies exceeded $100,000/QALY which is the recommended WTP threshold for cost-effectiveness by the second panel of cost-effectiveness in health and medicine, payers should be informed about these results and decide about payment conditions.

Table 17 presents the average reading of probabilistic sensitivity analysis results for both total costs and effectiveness measures for all visceral mCRPC therapies. Results

show that probabilistic sensitivity analysis are very comparable to base-case results which indicates that our base-case estimates are robust.

Table 17

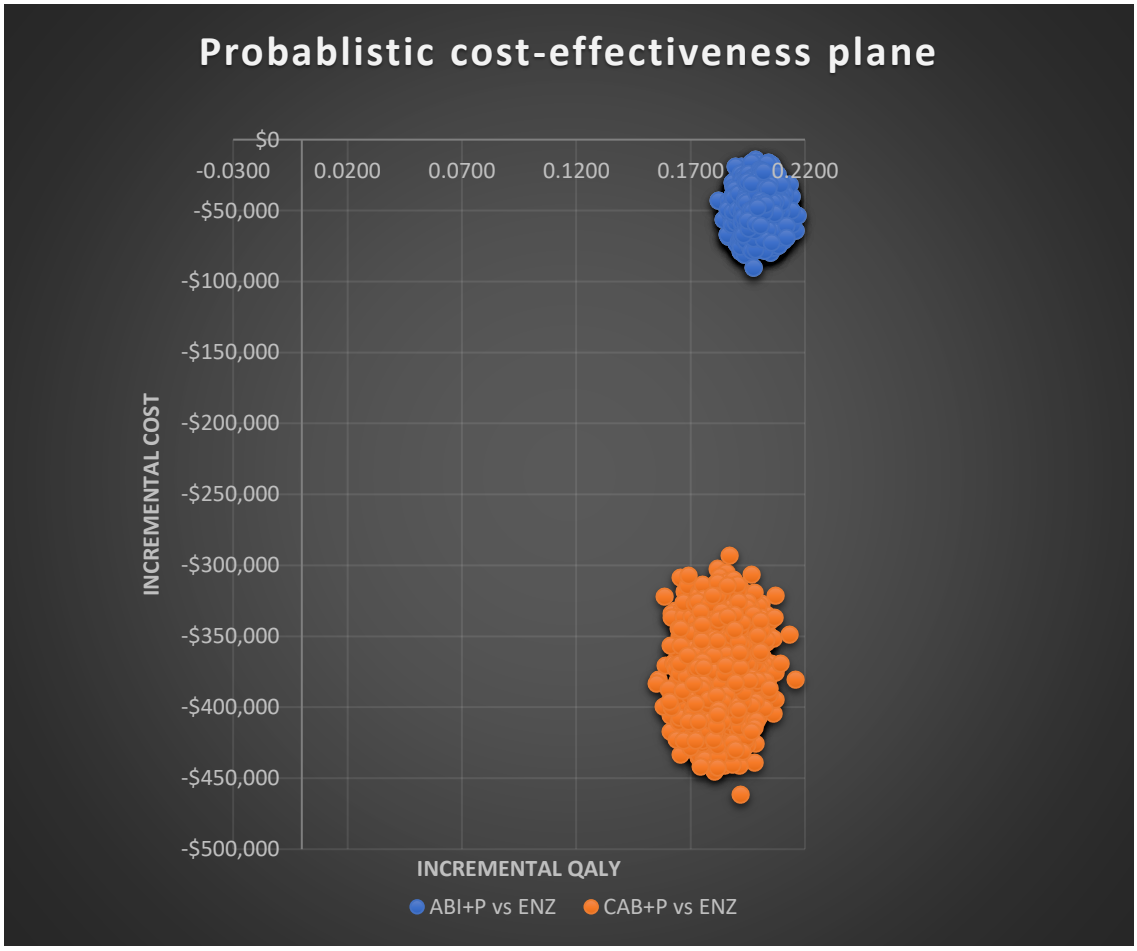
Probabilistic sensitivity results of total costs and effectiveness measures

Comparator	Total Cost	Total LYG	Total QALYs
ENZ	$157,903	1.58	0.79
ABI+P	$235,741	1.20	0.58
CAB+P	$496,370	1.48	0.56

ENZ: Enzalutamide, ABI+P: Abiraterone acetate plus prednisone, CAB+P: Cabazitaxel plus prednisone

Figure 8

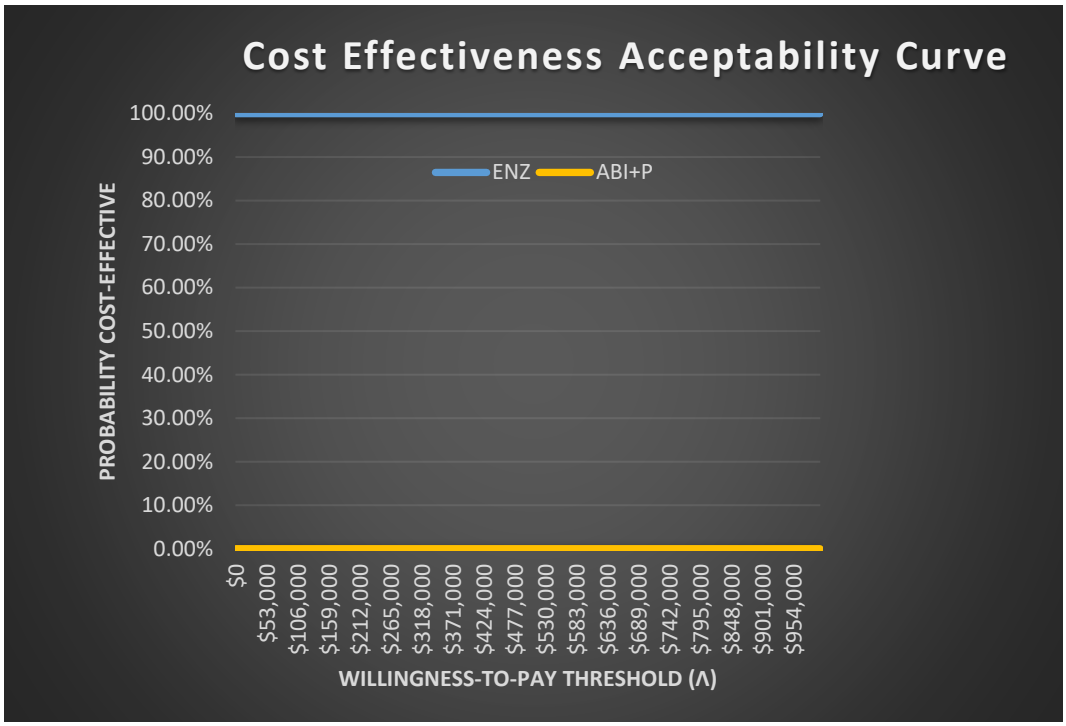
Probabilistic sensitivity analysis cost-effectiveness plane*



*ENZ: Enzalutamide, ABI+P: Abiraterone acetate plus prednisone, CAB+P: Cabazitaxel plus prednisone

Figure 9

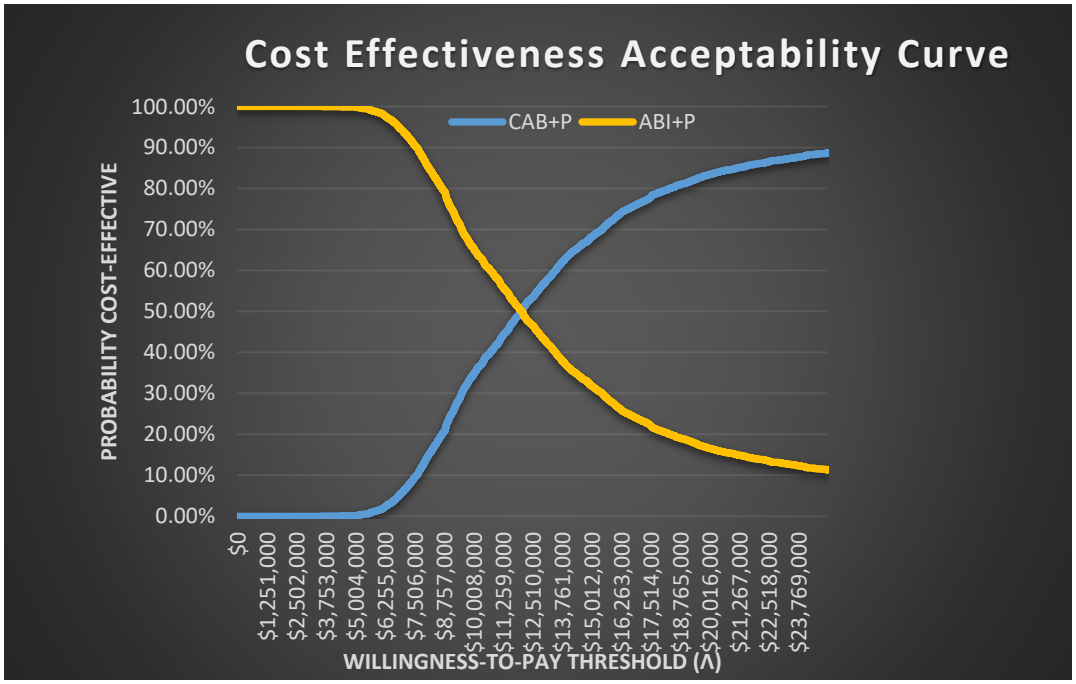
Cost-effectiveness acceptability curve*



*ENZ: Enzalutamide, ABI+P: Abiraterone acetate plus prednisone

Figure 10

Cost-effectiveness acceptability curve*



*ABI+P: Abiraterone acetate plus prednisone, CAB+P: Cabazitaxel plus prednisone

CHAPTER 5: DISCUSSION

This chapter consists of seven sections. In the first section, we will discuss the interpretation of the findings of our study. In the second section, our findings are compared to previous literature. This will be followed by discussing study's implications in the third section. Fourth, we will discuss the strengths of our study. Limitations of our study are discussed in the fifth section. This will be followed by discussing area of future research in the sixth section. Finally, we will close this chapter by providing a conclusion in the last section.

Interpretation of study findings

As recommended in the ISPOR Task Force Report of Consolidated Health Economic Evaluation Reporting Standards (CHEERS), [which provides recommendations in a checklist format to optimize reporting of health economic evaluations]; we discuss key findings of our study and describe how they support the conclusions reached as well as discuss limitations, generalizability of study findings and how findings fit with the current knowledge.[146]

Prostate cancer creates a substantial medical and non-medical burden. In 2006, nearly US $9.9 billion was spent on prostate cancer in the United States, increasing to US $11.9 billion in 2012, US $13.4 billion in 2014 and expected to reach US $15.4 billion by 2020; making prostate cancer the fifth most costly cancer.[7–9] There are several important clinical and economic implications for utilizing newer therapeutic options that show improved survival and minimize cost.

As cancer-related healthcare expenditures are increasing, the ASCO Value in Care Task Force proposed a framework to evaluate the value of new cancer drugs versus

standard of care treatments. The framework integrates incremental and nominal clinical benefit of cancer treatment with toxicity to determine the net health benefit, then compared against the cost of treatment.[7,8,147]

Visceral mCRPC is considered one of the major cancers with high cancer-related mortality rates. Our results have showed that almost all visceral mCRPC patients are expected to die within 5 years, which indicates the aggressiveness of the disease condition. Although docetaxel plus prednisone chemotherapy remains the gold standard therapy to treat those patients, most patients will progress and become resistant to chemotherapy, which mandates the initiation of novel treatments recommended by NCCN.[6]

Several controversial aspects related to prostate cancer management exist since limited data are available to support treatment recommendations. Many variables like predicted outcomes, patient clinical characteristics and preferences; and adjusted life expectancy should be considered by the healthcare provider and patient to tailor treatment according to patient clinical conditions, preferences and values.[6,20,21,23,38]

According to the 2017 NCCN guidelines, there is still no agreement for the best therapy for patients with visceral mCRPC who progress after docetaxel therapy. Available therapeutic options include enzalutamide, abiraterone acetate plus prednisone and cabazitaxel plus prednisone. These therapies received NCCN highest level of recommendations to treat patients with visceral mCRPC. Other therapeutic options like radium-223 and sipuleucel-T are not indicated for patients with visceral metastasis.

The decision to start treatment for patients who progress after docetaxel should be based on high level of efficacy and safety evidence as well as patient tolerability toward

therapy and potential side effects.[148–150] To our knowledge, there is no supportive data to inform the sequence for delivery of these treatments as there were no randomized head-head clinical trials have been reported. Additionally, no biomedical makers are available to help identify patients who are likely to benefit from any of these treatments.

Patients who are started on any of the treatments should be closely monitored for any signs of flare or evidence of clinical progression. NCCN and RADAR recommend periodic laboratory investigations (e.g. CBC, PSA tests) and radiological imaging to check for evidence of disease progression.[6,141]

Based on the above discussion, we aimed to estimate the cost-effectiveness of enzalutamide, abiraterone acetate plus prednisone and cabazitaxel plus prednisone for the treatment of visceral mCRPC patients who progress despite docetaxel therapy from a US health care perspective using life-time horizon Markov model.

Healthcare economic evaluations are conducted to inform healthcare resource allocation which has been defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences".[62] CEAs in healthcare are conducted to provide decision makers with supplemental information that may be helpful in supporting their decision about introducing, maintaining or assessing health technologies. CEAs provide comparative efficacy, safety and cost information related to health technologies being considered for the study.

Model-based CEA uses estimates of effects and costs from various sources, including retrospective databases (e.g. claims databases), observational studies, randomized controlled trials and meta-analyses to extend the analysis beyond clinical trials contrived settings and time frame to estimate ultimate outcomes and cost-

effectiveness. For example, model-based CEA may estimate costs and outcomes of measures not fully captured by the clinical trials horizon such as QALY and length of life. Decision analytic models are also useful in weighing outcomes and costs as well as assessing implications of evidential and other forms of uncertainty of decisions.[62]

Since clinical trials provide evidence regarding efficacy testing, there is still a need to translate clinical effectiveness endpoints into measures that are valued and crucial for different stakeholders. Our economic model utilized OS and PFS survival data, to extrapolate and generalize survival data beyond clinical trials time horizon to evaluate how therapies work in real-world practice. Both of outcomes and costs may be different under clinical trials conditions compared with when used in the general population. Thus, the results may provide physicians, decision makers and healthcare payers valuable information to make appropriate treatment and payment decisions. Since our study is from a US healthcare perspective, different US payers may use our CEAs results as a supplemental tool to decide on coverage/reimbursement decisions as results can be utilized by any payer and results can be generalized to different US healthcare payers.

Our literature review identified no studies that conducted an economic evaluation of abiraterone acetate, enzalutamide and cabazitaxel to treat visceral mCRPC patients' refractory to docetaxel therapy from a US healthcare payer perspective utilizing a Markov model. However, several economic evaluations compared different treatment paradigms for mCRPC, or had a different perspective (e.g. societal), or targeted different patient population, or utilized a different methodology (e.g. decision tree model) to inform decision makers or had a shorter time-horizon or were in non-US settings.[9,64–77]

Our Markov model included three-health state (PFS, progression and death) transition model reflecting survival. Given the short life expectancy of visceral mCRPC, we employed a life-time horizon Markov model. The patient who starts at the PFS health state may stay in the same health state until the next cycle or progress or die. However, a patient with disease progression may either stay at the same state until the next cycle or improve and go back to PFS or die. Since mCRPC disease management and complications develop at a relatively fast time scale, a cycle of 7 days length was considered for cost-effectiveness modeling of mCRPC therapies.[73,125]

A (3%) discounting was applied for all patients who survived (PFS and progressed patients) after the first year (52 weeks) as recommended by the US Panel on Cost-Effectiveness in Health and Medicine.[62]

Overall, results of our life-time horizon Markov model which estimated survival rates of visceral mCRPC patients showed that patients who receive enzalutamide will have higher OS and PFS rates (1.58 LYG) at total costs of ($157,830) compared to abiraterone plus prednisone (1.20 LYG) at total costs of ($235,853) and cabazitaxel plus prednisone (1.48 LYG) at total costs of ($496,756).

To interpret the findings of our study, enzalutamide was found to be cost-effective therapy compared to abiraterone acetate plus prednisone and cabazitaxel plus prednisone. Enzalutamide was associated with + 0.38 LYG compared to abiraterone acetate plus prednisone and + 0.10 LYG compared to cabazitaxel plus prednisone. Additionally, enzalutamide was associated with + 0.21 QALY compared to abiraterone acetate plus prednisone and + 0.23 QALY compared to cabazitaxel plus prednisone. We believe that

cabazitaxel plus prednisone was associated with least number of QALY because of larger associated grade (≥3) adverse events profile compared to other therapies.

Additionally, since abiraterone acetate plus prednisone was found to less effective (1.20 LYG) and less expensive ($235,853) than cabazitaxel plus prednisone (1.48 LYG) at total costs of ($496,756), cabazitaxel plus prednisone had an ICER & ICUR of $931.7K/LYG and almost 13 million/QALY respectively when compared to the next lowest treatment, abiraterone acetate plus prednisone.

Although Cabazitaxel plus prednisone was associated with higher total LYG compared to abiraterone, it was associated with 3.14 times higher total costs than enzalutamide and 2.1 times higher total costs than abiraterone acetate plus prednisone. We believe that the total costs of cabazitaxel plus prednisone was higher due to higher costs of drug per cycle and grade (≥3) adverse events.

Specifically, cabazitaxel plus prednisone was associated with 3.3 and 2.9 times higher drug costs per cycle than enzalutamide and abiraterone acetate plus prednisone respectively. Additionally, cabazitaxel plus prednisone was associated with 2.98 and 1.2 times higher costs of adverse events per cycle compared to enzalutamide and abiraterone acetate plus prednisone respectively mostly because of higher neutropenia events. Costs of physician follow up and needed investigations were similar across the three therapies because we have assumed that all visceral mCRPC patients will have comparable treatment plan and follow up schedule (e.g. weekly CBC, PSA test, monthly CT scan and home visit).

Results of probabilistic sensitivity analysis are very comparable to base-case results which favor the robustness of base-case estimates. CEACs showed that

enzalutamide dominated both therapies, and cabazitaxel plus prednisone becomes cost-effective compared to abiraterone acetate plus prednisone at 12 million $US/QALY. Although the three therapies exceeded $100,000/QALY which is the recommended WTP threshold for cost-effectiveness by the Second Panel of Cost-effectiveness in Health and Medicine, payers should be informed about these results and decide about payment conditions. Additionally, since we utilized an economic model to estimate the cost-effectiveness of visceral mCRPC therapies, we have utilized several assumptions to indicate the value for money of our interventions and therefore, economic models are subjected to problems and errors. However, they can still be valuable input for decision makers. The use of rigid cost-effectiveness threshold to determine funding decisions may encourage interested parties to tailor their estimates to trigger funding. On the other hand, we cannot leave our patients without getting appropriate evidence-based novel therapies that show improved survival rates. Therefore, our study results may be used to inform coverage/reimbursement decisions in this therapy area.

Overall, the greater economic benefit in terms of cost-savings and total cost-effectiveness and cost-utility favor enzalutamide therapy. Since our study is from a US healthcare perspective, this analysis should not be generalized to other settings or healthcare financing systems and countries. In addition, our economic evaluation intends to inform healthcare payers and policy makers – not to set policy or guide clinical practice. The following section will compare our study to previous literature.

Comparison with previous literature

Our literature review identified 16 economic evaluations. However, no studies were identified that conducted an economic evaluation of abiraterone acetate,

enzalutamide and cabazitaxel to treat visceral mCRPC patients' refractory to docetaxel therapy from a US healthcare payer perspective utilizing a Markov model. However, several economic evaluations compared different treatment paradigms for mCRPC, or had a different perspective (e.g. societal), or targeted different patient population, or utilized a different methodology (e.g. decision tree model) to inform decision makers or had a shorter time-horizon or were in non-US settings. In addition, to our knowledge, our study is the first one that evaluated the above mentioned therapeutic agents from a US healthcare payer perspective. Specifically, the review included only two articles that were close to our research question. Wilson et al (2014) conducted CEA of abiraterone acetate, enzalutamide and cabazitaxel compared to placebo (prednisone). However, it had a short-time horizon (18 months), considered QALY only as an effectiveness measure, utilized a decision-tree model with no discounting considered due to short-time horizon. Results showed that abiraterone acetate provided total QALY of 0.70 at total costs of $116,700. Enzalutamide provided total QALY of 0.73 at total costs of $129,769 and Cabazitaxel provided 0.76 of total QALY at total costs of $136,979. None of the therapies was dominant and the ICER for enzalutamide when compared to the next lowest treatment, abiraterone, is $437.6 K/QALY. Cabazitaxel had an ICER of $351.9K/QALY when compared to the next lowest treatment, enzalutamide. None fell below the generally accepted WTP threshold of $100,000 per QALY. They concluded that abiraterone is the most cost-effective treatment compared to placebo and other therapies.[68]

Although Peters et al (2016) included the three therapies of interest in addition to radium-223 which is not indicated to treat visceral mCRPC, it utilized a Markov model and had a life-time horizon (5 years). However, it was a Dutch economic evaluation from

a societal perspective. [56,73] Results of the study were more comparable and showed that radium-223 provided a total of 0.8 QALY and 1.39 LYG compared to 0.86 QALY and 1.5 LYG with enzalutamide, 0.78 QALY and 1.36 LYG with abiraterone; and 0.79 QALY and 1.38 LYG with cabazitaxel. However, enzalutamide was associated with higher total costs (€85,000) compared to (€84,410) with abiraterone acetate and (€82,783) with cabazitaxel.

Overall, since discussed articles did not conduct a comparative CEA of the three therapies of visceral mCRPC from a US healthcare perspective utilizing life-time Markov model, our economic evaluation will add to the previous efforts of published economic evaluation. The following section will discuss study's implications.

Study implications

The main objective of conducting CEA is exploring efficient ways for allocation of resources. In the light of currently available data, our results indicate the use of enzalutamide from a US healthcare payer perspective to treat visceral mCRPC patients post docetaxel failure as it provided higher total effectiveness at lower costs and dominated the other two therapies in our CEA. Enzalutamide dominated both abiraterone acetate and cabazitaxel plus prednisone in our CEA. In addition, from patient perspective, enzalutamide is associated with fewer grade (≥3) adverse events and therefore, poses better tolerability and safety profile compared to other therapies.

Study Strengths

Our study provides valuable information and adds a unique contribution to current knowledge of recommended visceral mCRPC treatments.

Our study has several strengths in comparison to previously published economic evaluations. Results of literature review identified no studies that conducted an economic evaluation of abiraterone acetate, enzalutamide and cabazitaxel to treat visceral mCRPC patients' refractory to docetaxel therapy from a US healthcare payer perspective utilizing a Markov model. However, several economic evaluations compared different treatment paradigms for mCRPC, or had a different perspective (e.g. societal), or targeted different patient population, or utilized a different methodology (e.g. decision tree model) to inform decision makers or had a shorter time-horizon or were in non-US settings.[9,64–77]

Therefore, to our knowledge, our study is the first one that estimated the cost-effectiveness of enzalutamide, abiraterone acetate plus prednisone and cabazitaxel plus prednisone for the treatment of visceral mCRPC after docetaxel therapy from a US healthcare perspective using life-time horizon Markov model.

In addition, since our study utilized phase III clinical trials data that provide evidence regarding efficacy testing, our study aimed to translate clinical effectiveness endpoints into measures that are valued and crucial for different US healthcare payers since both of outcomes and costs may be different under clinical trials conditions compared with when used in the general population. US healthcare payers may use our CEAs results as a supplemental tool to decide on coverage and reimbursement decisions as results can be utilized by any payer and results can be generalized to different US healthcare payers.

We also employed a life-time horizon Markov model as we believe visceral mCRPC is a complex and dynamic disease and people can move back and forth within different health states within a short time given the short expectancy of visceral mCRPC

patients. Other published economic evaluations adopted other decision analytic models like (e.g. decision tree) or considered shorter time horizon which would be more feasible in other disease conditions.

Study limitations

Although our study is the first to estimate the cost-effectiveness of visceral mCRPC therapies from a US healthcare perspective using life-time horizon Markov model, it has several limitations.

First, sampling uncertainty may exist in our study results since we obtained clinical efficacy data and rates of adverse events from COU-AA-301, AFFIRM and TROPIC phase III clinical trials. However, this issue was addressed by reporting the (95 %) confidence interval around point estimates for average costs of drugs, grade (≥3) adverse events; and follow up visits and investigations and utility estimates; and followed by conducting probabilistic sensitivity analysis for all model inputs to assess the robustness of base-case results and create the CEAC at various WTP thresholds.

Second, we only included adverse events of grade (≥3) that occurred at least in 5 % of visceral mCRPC patients who received either therapies in the model because they are associated with significant costs and may have greater impact on patient quality of life. Moreover, our economic model aimed to estimate the cost-effectiveness of visceral mCRPC therapies without inflating or underestimating costs of adverse events since all addressed medications were associated with a wide range of common adverse events of any grade (≥10%) addressed in the literature review chapter and this may not happen in real-world practice.

Third, although abiraterone acetate plus prednisone was associated with severe cardiovascular events, COU-AA-301 clinical trial did not explicitly provide categorized frequencies for various cardiovascular events. In addition, since rates of cardiovascular events were comparable in placebo and abiraterone plus prednisone arms, we did not include any of these adverse events and related cost data in the model. In addition, all grade (≥3) cardiac adverse events that included (ischemic heart disease, myocardial infarction, supraventricular tachyarrhythmias, ventricular tachyarrhythmias, cardiac failure, and possible arrhythmia-related tests, signs, and symptoms) associated with the use of abiraterone plus prednisone occurred in 4 % of patients whereas, we determined a cut-off of 5 % for all grade (≥3) adverse events to be included in the model.[48]

Fourth, we assumed costs of follow-up visits and needed investigations are similar across different visceral mCRPC therapies. One may argue that patients who receive cabazitaxel plus prednisone would incur more physicians 'office visits to receive treatment due to adverse events. Nonetheless, from the published literature, we did not find any evidence of the differences in the number of physicians' office visits between different therapies. Additionally, drop-out rates reported in COU-AA-301, AFFIRM and TROPIC trials due to adverse events were comparable. Specifically, drop-out rates for patients were 19 %, 18 % and 13 % for abiraterone acetate plus prednisone, cabazitaxel plus prednisone and enzalutamide respectively.[43,48,51] Thus, assumptions of equal number of physicians' office visits; CBC and PSA tests; and home nurse visits and CT scan was made for the purpose of our study. However, we determined number of visits and investigations based on RADAR recommendations.[141]

Fifth, our study did not consider the effect of different dosing of drugs due to potential differences in disease severity, patients' previous experience, preferences and values with any of visceral mCRPC therapies. We have followed treatment guideline recommendations with regards to initiating treatment post-docetaxel failure.

Sixth, although our study is from a US health perspective, we utilized a utility value of grade (≥3) anemia adverse events from NICE since we could find a relative one in the US setting. In addition, despite other utility values of adverse events were retrieved from published literature in the US setting, some of them were for different disease state (e.g. metastatic pancreatic cancer), although one may argue that utility values of adverse events would be the same regardless of the disease condition.

Finally, overall limitation of conducting a pharmacoeconomic study is using multiple components of evidence (e.g. clinical trials) and making assumptions to construct the model. In addition, study results are only as good as the components representing the truth or reality that are part of the model (i.e., if one of the probabilities or costs estimates were very wrong, it could have a huge impact on the model and CEA results).

Area of future research

The Second Panel of Cost-Effectiveness in Health and Medicine recommended that all studies report a reference case analysis based on healthcare sector perspective and another reference case based on societal perspective. [62] Reference cases should be defined by resources and components to consider for evaluation, methods to use and elements for reporting. To enhance consistency and comparability across studies, it is important to standardize methods and components within a perspective.[62] Thus, future areas of

research conducted from societal perspective to compare visceral mCRPC therapies after docetaxel therapy may be helpful to different stakeholders because of inclusion of mCRPC therapies costs to the society in the analysis as well as utilization of societal health utility values rather than of the healthcare payer. In general, conducting the study from a societal perspective may or may not change cost-effectiveness order of medications. Including societal costs and health utility values may have a significant impact on total costs and QALY estimates. However, they may not change cost-effectiveness order of medications in our study because cabazitaxel plus prednisone is the most expensive drug and causes wider range of side effect profile. Enzalutamide costs less and associated with least side effect profile.

Since cost-effectiveness analysis of health technologies may vary across different settings and countries because of differences in the incidence and severity of disease condition, clinical practice pattern, the availability of healthcare resources and relative prices of healthcare, we believe that conducting the study using the same methodology and patient population in different settings may be helpful in informing different stakeholders across different countries.[151,152]

Conclusion

We estimated the cost-effectiveness of enzalutamide, abiraterone acetate plus prednisone and cabazitaxel plus prednisone for the treatment of visceral mCRPC post-docetaxel failure from a US healthcare perspective using life-time horizon Markov model. In general, we found that enzalutamide is cost-effective compared to abiraterone acetate plus prednisone and cabazitaxel plus prednisone in the US setting.

Specifically, enzalutamide dominated other therapies and provided higher total effectiveness (1.58 LYG and 0.79 QALYs) at lower total costs ($157,830). Further, abiraterone acetate plus prednisone provided less total effectiveness (1.20 LYG) at lower total costs ($235,853) compared to cabazitaxel plus prednisone (1.48 LYG at total costs of $496,756).

LIST OF APPENDICES

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12 July 2018

Yazan K. Barqawi
University of New Mexico
10800 Cibola Loop NW
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Phone: 505-900-6004
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Dear Dr. Barqawi,

Figure(s): Therapies for castration-resistant prostate cancer (CRPC) [85716]
Topic: Dawson NA. Overview of the treatment of castration-resistant prostate cancer (CRPC).

Figure(s): Prostate anatomy [54803]
Topic: Benway BM, Andriole GL. Prostate biopsy.

Figure(s): ISUP Grade Group Classification System [107132]
Topic: Yang XJ. Interpretation of prostate biopsy.

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B. Human Subject Approval

HEALTH SCIENCES
OFFICE OF RESEARCH

Human Research Protections Program

October 15, 2018

Matthew Borrego
mborrego@salud.unm.edu

Dear Matthew Borrego:

On 10/15/2018, the HRRC reviewed the following submission:

Type of Review:	Initial Study
Title of Study:	Cost-effectiveness analysis of Enzalutamide, Abiraterone plus prednisone and Cabazitaxel plus prednisone for the treatment of Visceral Metastatic Castration Resistant Prostate Cancer (mCRPC) after Docetaxel therapy.
Investigator:	Matthew Borrego
Study ID:	18-669
Funding:	No Affiliated Company
Grant ID:	N/A
IND, IDE, or HDE:	None
Documents Reviewed:	• HRP 582 Protocol

The IRB determined that the proposed activity is not research involving human subjects. IRB review and approval is not required.

This determination applies only to the activities described in the submission and does not apply should any changes be made to these documents. If changes are being considered and there are questions about whether HRRC review is required, please contact the HRPO for guidance.

Sincerely,

Thomas F. Byrd, MD
HRRC Chair

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