Title

Cost-Effectiveness of Metastasis-Directed Therapy in Oligorecurrent Hormone-Sensitive Prostate Cancer.

Journal

International Journal of Radiation Oncology - Biology - Physics, 108(4)

Authors

Parikh, Neil
Chang, Eric
Nickols, Nicholas
et al.

Publication Date

2020-11-15

DOI

10.1016/j.ijrobp.2020.06.009

Peer reviewed

HHS Public Access

Author manuscript

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2024 September 10.

Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2020 November 15; 108(4): 917–926. doi:10.1016/j.ijrobp.2020.06.009.

Cost-Effectiveness of Metastasis-Directed Therapy in Oligorecurrent Hormone-Sensitive Prostate Cancer

Neil R. Parikh, MD, MBA[*], **Eric M. Chang, MD**[*], **Nicholas G. Nickols, MD, PhD**[*,†,‡], **Matthew B. Rettig, MD**[†,§], **Ann C. Raldow, MD, MPH**[*], **Michael L. Steinberg, MD**[*], **Bridget F. Koontz, MD**[‖], **Neha Vapiwala, MD**[¶], **Curtiland Deville, MD**[#], **Felix Y. Feng, MD**[**], **Daniel E. Spratt, MD**[††], **Robert E. Reiter, MD**[‡], **Ryan Phillips, MD, PhD**[#], **Piet Ost, MD, PhD**[‡‡], **Phuoc T. Tran, MD, PhD**[#], **Amar U. Kishan, MD**[*,‡]

[*]Department of Radiation Oncology, University of California Los Angeles, Los Angeles, California

[†]VA Greater Los Angeles Health System, Los Angeles, California

[‡]Department of Urology, University of California Los Angeles, Los Angeles, California

[§]Department of Medical Oncology, University of California Los Angeles, Los Angeles, California

[‖]Department of Radiation Oncology, Duke University School of Medicine, Durham, North Carolina

[¶]Department of Radiation Oncology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

[#]Department of Radiation Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland

[**]Department of Radiation Oncology, University of California San Francisco, San Francisco, California

[††]Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan

[‡‡]Department of Radiotherapy, Ghent University Hospital, Ghent, Belgium

Abstract

Purpose: Oligorecurrent prostate cancer has historically been treated with indefinite androgen deprivation therapy (ADT), although many patients and providers opt to defer this treatment at the time of recurrence given quality-of-life and/or comorbidity considerations. Recently, metastasis-directed therapy (MDT) has emerged as a potential intermediary between surveillance and immediate continuous ADT. Simultaneously, advanced systemic therapy in addition to ADT has also been shown to improve survival in metastatic hormone-sensitive disease. This study aimed to compare the cost-effectiveness of treating oligorecurrent patients with upfront MDT before standard-of-care systemic therapy.

Corresponding author: Amar U. Kishan, MD; aukishan@mednet.ucla.edu.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Supplementary material for this article can be found at https://doi.org/10.1016/j.ijrobp.2020.06.009.

Methods and Materials: A Markov-based cost-effectiveness analysis was constructed comparing 3 strategies: (1) upfront MDT → salvage abiraterone acetate plus prednisone (AAP) + ADT → salvage docetaxel + ADT; (2) upfront AAP + ADT → salvage docetaxel + ADT; and (3) upfront docetaxel + ADT → salvage AAP + ADT. Transition probabilities and utilities were derived from the literature. Using a 10-year time horizon and willingness-to-pay threshold of $100,000/quality-adjusted life year (QALY), net monetary benefit values were subsequently calculated for each treatment strategy.

Results: At 10 years, the base case revealed a total cost of $141,148, $166,807, and $136,154 with QALYs of 4.63, 4.89, and 4.00, respectively, reflecting a net monetary benefit of $322,240, $322,018, and $263,407 for upfront MDT, upfront AAP + ADT, and upfront docetaxel + ADT, respectively. In the probabilistic sensitivity analysis using a Monte Carlo simulation (1,000,000 simulations), upfront MDT was the cost-effective strategy in 53.6% of simulations. The probabilistic sensitivity analysis revealed 95% confidence intervals for cost ($75,914-$179,862, $124,431-$223,892, and $103,298-$180,617) and utility in QALYs (3.85–6.12, 3.91–5.86, and 3.02–5.22) for upfront MDT, upfront AAP + ADT, and upfront docetaxel + ADT, respectively.

Conclusions: At 10 years, upfront MDT followed by salvage AAP + ADT, is comparably cost-effective compared with upfront standard-of-care systemic therapy and may be considered a viable treatment strategy, especially in patients wishing to defer systemic therapy for quality-of-life or comorbidity concerns. Additional studies are needed to determine whether MDT causes a sustained meaningful delay in disease natural history and whether any benefit exists in combining MDT with upfront advanced systemic therapy.

Introduction

There is been a growing consensus that the oligometastatic disease state, characterized by a limited number of clinically detectable metastases, may be an intermediary state between patients with curable localized disease and incurable widely metastatic disease.[1] As appreciation of the oligometastatic disease state in general has grown, 2 parallel developments have emerged in the treatment of metastatic, hormone-sensitive prostate cancer (mHSPC).

First, several randomized trials have established a survival advantage in patients with mHSPC with the upfront use of advanced systemic therapy in addition to androgen deprivation therapy (ADT) over standard ADT alone. These advanced systemic agents include both second-generation antihormonal drugs—abiraterone acetate plus prednisone (AAP) (LATITUDE[2] and STAMPEDE arm G[3]), enzalutamide (ENZAMET[4]), and apatalutamide (TITAN[5])—as well as docetaxel chemotherapy (CHAARTED[6] and STAMPEDE arm C[7]). Recent post hoc analyses of STAMPEDE arms C and G, in which patients with M1 disease were dichotomized by metastatic burden per the CHAARTED definition,[6] confirmed the survival benefit (regardless of volume of disease) of adding AAP to ADT or docetaxel to ADT, respectively.[8,9] Notably, the vast majority of patients enrolled on these studies had a de novo diagnosis of metastatic prostate cancer.

Contemporaneously, 5 small prospective studies have evaluated the use of metastasis-directed therapy (MDT), primarily using stereotactic body radiation therapy (SBRT) also

referred to as stereotactic ablative radiotherapy (SABR), in patients with oligometastatic disease that was discovered after prior definitive local therapy (oligorecurrent disease).[10–14] Overall, these studies suggest that up to 45% to 50% of patients may be free from use of ADT or other systemic treatment 2 years after MDT and that treatment itself is safe, with only 1 patient (0.3%) with grade 3 toxicity reported across all studies. Additionally, the randomized phase 2 SABR-COMET trial identified an overall survival benefit to metastasis-directed SABR in addition to standard-of-care systemic therapy in patients with a variety of primary malignancies, including breast, lung, colorectal, and prostate cancer.[15] A follow-up study examining quality of life (QoL) in SABR-COMET patients showed no QoL detriment in patients receiving SABR versus standard of care.[16] Thus, there exists substantial level I evidence for the intensification of systemic therapy for patients with de novo mHSPC, and promising level II evidence suggests that patients with limited-volume, oligometastatic prostate cancer that recurs after definitive therapy may derive freedom from systemic therapy of any kind(and its accompanying side effects) with the use of MDT.

Given the rapid increase in expected expenditures on prostate cancer care in the United States,[17] it has become increasingly important to identify opportunities to preserve high-level care while improving value. Although numerous cost-effectiveness studies have been performed comparing treatments in the metastatic castrate-resistant prostate cancer (mCRPC) setting, only a handful relate to the mHSPC setting and none to the oligorecurrent setting. Considering the synchronous developments described, this study aimed to estimate the cost-effectiveness of treating oligorecurrent patients with MDT before standard-of-care systemic therapy versus standard-of-care systemic therapy alone. Both upfront AAP + ADT and upfront docetaxel + ADT were chosen as standard-of-care comparators. Because AAP is now available in generic form and much less expensive than enzalutamide or apalutamide, albeit with a grossly similar efficacy profile versus ADT alone as seen in hazard ratios of patients with low-volume mHSPC, it was chosen to represent the second-generation antihormonal therapeutic option.

Methods and Materials

Model overview and analytical methods

A Markov-based cost-effectiveness analysis was developed to compare treatment strategies for men with recurrent, limited-volume oligometastatic prostate cancer, defined as having 1 to 3 extracranial metastases, no visceral disease, and no local recurrence. As shown in Figure 1, 3 treatment strategies were evaluated: (1) upfront MDT → salvage AAP + ADT → salvage docetaxel + ADT; (2) upfront AAP +ADT → salvage docetaxel + ADT; and (3) upfront docetaxel + ADT → salvage AAP + ADT.

A Markov model was constructed in TreeAge Pro 2020, version 1.0 (TreeAge Software, Inc, Williamstown, MA) to calculate the total costs and effectiveness associated with each treatment strategy, ultimately allowing for net monetary benefit (NMB) to be calculated for each strategy. The NMB approach was selected over the incremental cost-effectiveness ratio approach given the NMB approach's ease of interpretability and ability to rank multiple strategies.[18] Given work by Cameron et al correlating purchasing power parity–adjusted cost-effectiveness thresholds with health-adjusted life expectancy, a willingness-

to-pay (WTP) threshold of $100,000 per quality-adjusted life year (QALY) was chosen for this United States–centric analysis.[19] The analysis used a 10-year time horizon to simultaneously account for the follow-up intervals in STOMP[10] and STAMPEDE arms C/G subanalyses (36, 78, and 42 months, respectively) while also accounting for long-term differences in effectiveness between the various treatment strategies. The cycle length was 3 months, with half-cycle correction used for costs and utility estimates. Cost and utility were both discounted by 3% annually. In addition to base-case analysis, 1-way sensitivity and probabilistic sensitivity analyses were also performed, the latter of which was run with 1,000,000 simulations.

Methodology of deriving transition probabilities

Transition probabilities between various health states in the aforementioned treatment strategies were based on extant prospective data from randomized trials. Kaplan-Meier curves from individual studies were digitized with DigitizeIt software (DigitizeIt; Braunschweig, Germany), and subsequently fed through an R-based algorithm published by Guyot et al to reconstruct interval-specific survival data.[20] Beta distributions were subsequently constructed from these parameters (Table 1).

Target populations

In strategy 1, MDT consisted of 3-fraction SBRT to each metastatic lesion. The probability of failure into high-volume mHSPC was modeled from ADT-free survival in the M1 subset of STOMP patients receiving MDT (n = 17). Retreatment with SBRT was allowed if patients developed 1 to 3 new lesions not previously treated. Based on data from STOMP M1 patients, a 23.5% re-treatment probability was included in SBRT cost assumptions. Upon progression to high-volume mHSPC, patients received AAP + ADT with failure-free survival (FFS) modeled after high-volume M1 STAMPEDE arm G patients.

In strategy 2, patients received upfront AAP + ADT with FFS modeled after low-volume M1 STAMPEDE arm G patients. In strategies 1 and 2, after progression on AAP + ADT, patients were modeled to receive treatment with salvage docetaxel for 10 cycles and ADT with survival patterns modeled after overall survival from TAX-327.[21] In strategy 3, patients received upfront docetaxel for 6 cycles and ADT with FFS modeled after low-burden M1 STAMPEDE arm C patients.[8] Upon progression on docetaxel + ADT, patients were modeled to receive treatment with salvage AAP + ADT, with survival patterns modeled after COU-AA-301.[22]

For all treatment arms, the probability of death from other causes was derived from the death rates published in the 2016 Social Security actuarial life table,[23] with the initial probability of death from other causes initially set to that of a 66-year old man (ie, median age of low-volume M1 STAMPEDE patients receiving AAP + ADT),[9] with adjustments made at each subsequent cycle reflecting increasing age. To avoid double-counting, the probability of death from other causes was deducted from the probability of death in TAX-327 and COU-AA-301, as well as the initiation of ADT in the STOMP study. ADT consisted of leuprolide 22.5 mg injections administered every 3 months; abiraterone dosing was 1000 mg

daily; docetaxel was dosed 75 mg/m^2 intravenously over 60 minutes once on day 1 of each cycle.

Cost assumptions

This study was conducted from the perspective of a US payor, with cost estimates taken directly from the Medicare physician fee schedule,[24] Medicare laboratory fee schedule,[25] Medicare Part B pricing for injectable drugs,[26] and Medicare Federal Upper Limits for oral drugs (Table 1),[27] each updated as of March 2020. A freestanding center was assumed. Recurring interval costs included cost of treatment, level 4 follow-up visits, laboratory testing, and imaging for each treatment strategy. Patients undergoing MDT were modeled to have a follow-up visit with prostate-specific antigen (PSA) testing every 3 months and diagnostic choline positron emission tomography (PET)-computed tomography (CT) at PSA progression to look for additional lesions.

Patients receiving AAP + ADT were modeled to have follow-up visits every 3 months with PSA and comprehensive metabolic panel testing at each visit. Patients receiving docetaxel + ADT were initially followed every 3 weeks with PSA and complete blood count tested at each infusion visit, and subsequently every 3 months with PSA and total testosterone levels tested at each visit. Surveillance imaging with bone scan was performed every 6 months if mHSPC and every 3 months if mCRPC. Additional costs from grade ≥3 toxicity related to AAP ($410/month) and docetaxel treatment ($786/month) were derived from adverse event rates as published in COU-AA-301 and TAX-327, respectively (Table E1). Patients with mCRPC were modeled to receive denosumab. Additional inpatient and hospice costs from prostate cancer death of $36,554 were adapted from a prior analysis of end-of-life costs after adjustment for inflation.[28] All cost estimates were converted into 2020 US dollars by using a Consumer Price Index inflation calculator from the US Bureau of Labor Statistics. For the probabilistic sensitivity analysis, costs were assumed to be in a gamma distribution with standard deviation set as 25% of the mean.

Effectiveness assumptions

The effectiveness of interventions was based on transition probabilities and from utility estimates derived from the literature. Baseline utility values for mHSPC and mCRPC were respectively set at 0.90[29] and 0.830.[30] Incremental utility estimates were then set for each treatment, specific to baseline health state. Given no grade 2 to 5 adverse events in the MDT arm and comparable health-related QoL in the 2 STOMP arms, no disutility was assigned to SBRT. Incremental disutility estimates in patients receiving ADT (0.06) was based on long-term 5-level 5-dimensions EuroQuol utility scores derived from the LATITUDE study.[31] Additional disutility associated with abiraterone and docetaxel was derived from grade 3+ toxicities from each drug as published in COU-AA-301 and TAX-327, respectively (Table E1). For the probabilistic sensitivity analysis, baseline utility values were set to beta distributions with a standard deviation of 10% of mean. Incremental disutility values were set to normal distributions with a standard deviation of 25% of mean (Table 1).

Results

Total costs, total effectiveness, corresponding net monetary benefit (base case)

At 10 years, the total cost was $141,148, $166,807, and $136,154, with total QALYs of 4.63, 4.89, and 4.00, respectively, translating to NMB values of $322,240, $322,018, and $263,407 for upfront MDT, upfront AAP + ADT, and upfront docetaxel + ADT, respectively (Table 2). Given the markedly superior results of upfront MDT and upfront AAP + ADT strategies over upfront docetaxel + ADT at 10 years, subsequent 1-way sensitivity analyses directly compared upfront MDT versus upfront AAP + ADT using incremental NMB values with a WTP of $100,000 per QALY.

One-way sensitivity analysis—upfront MDT versus upfront AAP D ADT

To determine the influence of model inputs on the cost-effectiveness of upfront MDT versus upfront AAP + ADT (baseline comparator), 1-way sensitivity analyses were performed on key cost and utility estimate inputs. Baselines estimates were modified by ±50% for costs to represent modest variation. Upper/lower bounds for utility estimates were based on custom parameters taken from the literature. As seen in Figure 2, given the expected incremental NMB value of upfront MDT versus upfront AAP + ADT ($222) just slightly above 0, even modest variations in many cost and utility variables were enough to result in the NMB of upfront AAP + ADT being higher than the NMB of the upfront MDT strategy. Of all model inputs, the 3-month cost of AAP appears to have the greatest influence over the resulting incremental NMB value; modifying the base-case model input ($4047) by ±50% translates into incremental NMB changes of −$16,239 and $16,665, respectively. Of note, this base-case assumption price ($4047) represents the 3-month supply of generic abiraterone (updated as of March 2020) and already represents a significant price reduction compared with branded Zytiga (abiraterone), Xtandi (enzalutamide), and Erleada (apalutamide), for which 3-month supply costs are $21,080, $22,210, and $23,789, respectively, per the lowest March 2020 Veterans Affairs contracts. If Zytiga, Xtandi, and Erleada costs are substituted for generic abiraterone while holding all else constant, the incremental NMB value of upfront MDT versus upfront AAP + ADT dramatically increases to $138,741, $147,931, and $160,771, respectively.

Instead of the current 10-year time horizon, we studied the impact of shortening to 5 years or lengthening to 15 years. With a 5-year time horizon, the total costs were $90,800, $108,700, and $95,300 with total QALYs of 3.36, 3.26, and 2.93, translating to NMB values of $245,500, $216,900, and $197,700 for upfront MDT, upfront AAP + ADT, and upfront docetaxel + ADT, respectively. With a 15-year time horizon, total costs were $155,200, $192,200, and $148,400 with total QALYs of 4.97, 5.59, and 4.31, translating to NMB values of $341,500, $367,300, and $282,200 for upfront MDT, upfront AAP + ADT, and upfront docetaxel + ADT, respectively.

Multivariable probabilistic sensitivity analysis

To determine the effect of modifying multiple variables concurrently in cost-effectiveness analysis, a Monte Carlo simulation was run with 1,000,000 simulations. Distributions for cost, utility, and transition probability inputs were varied as per Table 1. As reflected

in Table 3, the simulation results showed a mean cost (95% confidence interval [CI]) of $133,873 ($75,914-$179,862), $167,827 ($124,431-$223,892), and $136,880 ($103,298-$180,617) and mean utility (95% CI) of 4.85 (3.85–6.12), 4.95 (3.91–5.86), and 4.09 (3.02–5.22) for upfront MDT, upfront AAP + ADT, and upfront docetaxel + ADT, respectively. The mean NMB values (95% CI) were $351,476 ($239,652-$531,551), $326,983 ($234,344-$417,815), and $272,437 ($174,239-$381,610) for upfront MDT, upfront AAP + ADT, and upfront docetaxel + ADT, respectively. A cost-effectiveness acceptability frontier comparing the probability of each strategy being cost-effective as a function of varying WTP shows upfront MDT as the cost-effective strategy in 53.6% of microsimulations at a WTP of $100,000 per QALY (Fig. 3).

Discussion

These results suggest comparable cost-effectiveness at 10 years of upfront MDT, followed by salvage AAP + ADT compared with upfront systemic therapy, in patients with oligorecurrent disease. This conclusion is especially supported by results from the probabilistic sensitivity analysis accounting for the wide range of model inputs likely to be seen distributed across a patient population. Given the overlapping 95% CIs of NMB values ($240,000–532,000, $234,000–418,000, and $174,000–382,000 for upfront MDT, upfront AAP + ADT, and upfront docetaxel + ADT, respectively), with upfront MDT being the cost-effective strategy 53.6% of the time, we safely conclude that upfront MDT has at least comparable cost-effectiveness compared with the other 2 treatment strategies. As more mature data become available in the future, we look forward to future studies to further reduce the uncertainty embedded in this study.

Although MDT portends cost-saving opportunities to a health system, such a strategy may also prove attractive to individual patients, particularly those hesitant to start systemic therapy due to QoL concerns or concurrent comorbidities. Although the base-case analysis incorporates utility estimates representative of a large population, patients particularly averse to systemic therapy—represented by lower utility values for health states involving systemic Therapy—stand to experience an even greater benefit from MDT. This is particularly evident from Figure 2, where the marked impact of variation of utility values is seen on cost-effectiveness outcomes.

Sensitivity analyses highlight the profound effect of abiraterone pricing on overall results. Although the recent introduction of generic abiraterone has led to a significant decrease in price already (Medicare Federal Upper Limit prices 81% lower than branded Zytiga currently available on Veterans Affairs formulary), the base-case cost-effectiveness estimates comparing upfront MDT versus upfront AAP + ADT continue to show comparable cost-effectiveness with incremental NMB values just above 0. Notably, a recently published phase 2 study compared the efficacy of low-dose (250 mg) abiraterone with low-fat meal versus standard-dose (1000 mg) with fasting in patients with mCRPC and suggested noninferiority of the low-dose regimen with respect to PSA metrics at 12 weeks.[32] It remains to be seen whether these findings will eventually translate into a survival endpoint and, more broadly, to an oligorecurrent mHSPC population with a smaller burden of disease

than the vast majority of patients enrolled on STAMPEDE; if so, this may lead to a substantial reduction in quantity of AAP purchased over time (and hence total cost).

Given recent evidence highlighting the efficacy of enzalutamide[4] and apalutamide[5] in patients with mHSPC, the number of systemic agents potentially available to patients with oligorecurrent disease continues to increase. No trials have directly compared abiraterone, enzalutamide, and apalutamide in the mHSPC population, but data do exist to reflect the efficacy of each drug (vs standard of care) in patients with low-volume disease as defined by CHAARTED or CHAARTED-like criteria. STAMPEDE, ENZAMET, and TITAN showed overall survival hazard ratios of 0.64 (0.42–0.97), 0.43 (0.26–0.72), and 0.67 (0.34–1.32) favoring AAP + ADT, enzalutamide + ADT, and apalutamide + ADT, respectively, over ADT alone in mHSPC with low-volume disease.[4,5,9] If enzalutamide + ADT and apalutamide + ADT are assumed to have similar efficacy profiles/toxicity burden as AAP + ADT and are then subsequently substituted for AAP in the current cost-effectiveness analysis, the cost of enzalutamide and apalutamide per the Veterans Affairs schedule (349% and 388% higher than that of generic AAP costs per Medicare Federal Upper Limit) would result in upfront MDT appearing significantly more cost effective than in the current analysis.

With highly sensitive imaging modalities, such as PSMA PET-CT now available in modern practice, the average disease burden for a patient with low- or high-volume metastatic disease is expected to become smaller. Based on STAMPEDE data associating lower metastatic burden with improved survival,[9] as well as ORIOLE data highlighting the improved efficacy of MDT with consolidative therapy targeting PSMA PET-CT lesions,[33] it stands to reason that the introduction of PSMA PET-CT will further improve outcomes in both populations. The relative improvement in outcomes and difference in downstream costs with PSMA PET-CT, however, is not entirely clear when comparing patients receiving AAP + ADT versus MDT.

Our study has several limitations that warrant discussion. First, given the limited number of STAMPEDE M1 patients (4.6%) with oligorecurrent disease, it remains unclear whether the efficacy of AAP + ADT is significantly different in de novo versus oligorecurrent disease. This is an important point because we assumed for the sake of modeling that patients with CHAARTED low-volume disease will follow a similar progression pattern on AAP + ADT and ADT alone as patients with oligorecurrent disease. It is somewhat reassuring that CIs in ENZAMET showing the benefit of advanced systemic therapy versus ADT alone appear remarkably similar for patients who had received previous local treatment versus those who had not (0.47–1.09 vs 0.47–0.89 for overall survival; 0.31–0.57 vs 0.31–0.50 for progression-free survival), although these subgroups are not stratified by volume.

Second, the M1 subset in STOMP receiving upfront MDT (n = 17) is considerably smaller than the M1 cohorts in STAMPEDE arms C/G. Additionally, beyond being completely composed of patients with oligorecurrent disease, the STOMP cohort also differs from its STAMPEDE counterpart in that choline PET was used to assess for disease, thereby potentially selecting for STOMP patients with a comparably lower burden of disease. Third, this study used multiple randomized trials to inform transition probabilities between

disease states. This approach was preferred over using STAMPEDE data alone to inform progression after development of mCRPC given the variability in “life-prolonging therapies” between the 2 STAMPEDE arms. Instead, the assumption was made that all patients after failing AAP + ADT will have similar outcomes regardless of prior treatments received.

Fourth, because treatment disutility estimates were calculated from rates of grade 3+ toxicity, these disutility estimates may be slightly understated because they do not account for various mild (grade 1–2) toxicities seen with treatment. Finally, utility estimates were not taken from a single study, but from multiple studies after extensive review of prior literature.

Conclusions

We found that at 10 years, upfront MDT followed by salvage AAP + ADT is comparably cost-effective compared with upfront standard-of-care systemic therapy and may be considered a viable treatment strategy, especially in patients wishing to defer systemic therapy for QoL or comorbidity concerns. Additional studies are needed to determine whether MDT causes a sustained meaningful delay in disease natural history and whether any benefit (in terms of cost effectiveness or survival) exists in combining MDT with a finite course of upfront advanced systemic therapy in the oligorecurrent setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures:

A.U.K. reports research funding from the Prostate Cancer National Institutes of Health Specialized Programs of Research Excellence (P50CA09213), the Radiological Society of North America (grant RSD1836), the STOP Cancer organization, the Jonsson Comprehensive Cancer Center, and the American Society of Radiation Oncology. N.G.N. reports research support from STOP Cancer and the Jonsson Comprehensive Cancer Center. A.U.K., N.G.N., P.T.T., F.Y.F., M.B.R., and D.E.S. report funding from the Prostate Cancer Foundation.

N.G.N. reports grants from Varian, Janssen, and Bayer; grants and personal fees from Progenics; and personal fees from Genes Science. M.B.R. reports grants from Novartis, Merck, Astellas, Medivation, and Progenics; grants and personal fees from Johnson & Johnson; personal fees from Bayer; and is a consultant for Constellation Pharmaceuticals. A.C.R. reports personal fees from Intelligent Automation. M.L.S. reports honoraria and travel support from ViewRay. B.F.K. has received research support from Janssen and has been on advisory boards for Blue Earth Diagnostics and Bayer. R.P. has received consulting fees and honoraria from RefleXion Medical, Inc.

N.G.N. reports grants from Varian, Janssen, and Bayer; grants and personal fees from Progenics; and personal fees from Genes Science. M.B.R. reports grants from Novartis, Merck, Astellas, Medivation, and Progenics; grants and personal fees from Johnson & Johnson; personal fees from Bayer; and is a consultant for Constellation Pharmaceuticals. A.C.R. reports personal fees from Intelligent Automation. M.L.S. reports honoraria and travel support from ViewRay. B.F.K. has received research support from Janssen and has been on advisory boards for Blue Earth Diagnostics and Bayer. R.P. has received consulting fees and honoraria from RefleXion Medical, Inc.

References

1. Rao A, Vapiwala N, Schaeffer EM, Ryan CJ. Oligometastatic prostate cancer: A shrinking subset or an opportunity for cure? Am Soc Clin Oncol Educ Book 2019;39:309–320. [PubMed: 31099652]
2. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017;377: 352–360. [PubMed: 28578607]

3. James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377:338–351. [PubMed: 28578639]
4. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med 2019; 381:121–131. [PubMed: 31157964]
5. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019;381:13–24. [PubMed: 31150574]
6. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373: 737–746. [PubMed: 26244877]
7. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): Survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387:1163–1177. [PubMed: 26719232]
8. Clarke NW, Ali A, Ingleby FC, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: Long-term survival results from the STAMPEDE trial. Ann Oncol 2019;30:1992–2003. [PubMed: 31560068]
9. Hoyle AP, Ali A, James ND, et al. Abiraterone in “high-” and “low-risk” metastatic hormone-sensitive prostate cancer. Eur Urol 2019;76: 719–728. [PubMed: 31447077]
10. Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: A prospective, randomized, multicenter phase II trial. J Clin Oncol 2018; 36:446–453. [PubMed: 29240541]
11. Siva S, Bressel M, Murphy DG, et al. Stereotactic abative body radiotherapy (SABR) for oligometastatic prostate cancer: A prospective clinical trial. Eur Urol 2018;74:455–462. [PubMed: 30227924]
12. Kneebone A, Hruby G, Ainsworth H, et al. Stereotactic body radiotherapy for oligometastatic prostate cancer detected via prostate-specific membrane antigen positron emission tomography. Eur Urol Oncol 2018;1:531–537. [PubMed: 31158100]
13. Bowden P, See AW, Frydenberg M, et al. Fractionated stereotactic body radiotherapy for up to five prostate cancer oligometastases: Interim outcomes of a prospective clinical trial. Int J Cancer 2020; 146:161–168. [PubMed: 31199504]
14. Pasqualetti F, Panichi M, Sainato A, et al. [(18)f]choline PET/CT and stereotactic body radiotherapy on treatment decision making of oligometastatic prostate cancer patients: Preliminary results. Radiat Oncol 2016;11:9. [PubMed: 26796633]
15. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): A randomised, phase 2, open-label trial. Lancet 2019;393:2051–2058. [PubMed: 30982687]
16. Olson R, Senan S, Harrow S, et al. Quality of life outcomes after stereotactic ablative radiation therapy (SABR) versus standard of care treatments in the oligometastatic setting: A secondary analysis of the sabr-comet randomized trial. Int J Radiat Oncol Biol Phys 2019;105: 943–947. [PubMed: 31470091]
17. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010–2020. J Natl Cancer Inst 2011;103:117–128. [PubMed: 21228314]
18. Paulden M. Why it’s time to abandon the ICER [e-pub ahead of print]. Pharmacoeconomics. 10.1007/s40273-020-00915-5. Accessed May 18, 2020.
19. Cameron D, Ubels J, Norstrom F. On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: A systematic review. Glob Health Action 2018;11:1447828.
20. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: Reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9. [PubMed: 22297116]
21. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–1512. [PubMed: 15470213]
22. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: Final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012;13:983–992. [PubMed: 22995653]

23. Social Security Administration. Actuarial life table. Available at: https://www.ssa.gov/oact/STATS/table4c6.html. Accessed March 11, 2020.
24. Centers for Medicare & Medicaid Services. Physician fee schedule search. Available at: https://www.cms.gov/apps/physician-feeschedule/license-agreement.aspx. Accessed April 20, 2020.
25. Centers for Medicare & Medicaid Services. 20clabq2. Available at: https://www.cms.gov/apps/ama/license.asp?fileZ/files/zip/20clabq2.zip. Accessed April 20, 2020.
26. Centers for Medicare & Medicaid Services. April 2020 ASP pricing file. Available at: https://www.cms.gov/apps/ama/license.asp?fileZhttps%3A//www.cms.gov/files/zip/april-2020-asp-pricing-file.zip. Accessed April 20, 2020.
27. Centers for Medicare & Medicaid Services. Federal upper limits e 2020.02. Available at: https://data.medicaid.gov/Drug-Pricing-and-Payment/Federal-Upper-Limits-2020-02/tfbh-fzkz. Accessed April 20, 2020.
28. Chastek B, Harley C, Kallich J, Newcomer L, Paoli CJ, Teitelbaum AH. Health care costs for patients with cancer at the end of life. J Oncol Pract 2012;8:75s–80s. [PubMed: 23598848]
29. Bayoumi AM, Brown AD, Garber AM. Cost-effectiveness of androgen suppression therapies in advanced prostate cancer. J Natl Cancer Inst 2000;92:1731–1739. [PubMed: 11058616]
30. Lloyd AJ, Kerr C, Penton J, Knerer G. Health-related quality of life and health utilities in metastatic castrate-resistant prostate cancer: A survey capturing experiences from a diverse sample of UK patients. Value Health 2015;18:1152–1157. [PubMed: 26686802]
31. Chi KN, Protheroe A, Rodriguez-Antolin A, et al. Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): An international, randomised phase 3 trial. Lancet Oncol 2018;19:194–206. [PubMed: 29326030]
32. Szmulewitz RZ, Peer CJ, Ibraheem A, et al. Prospective international randomized phase II study of low-dose abiraterone with food versus standard dose abiraterone in castration-resistant prostate cancer. J Clin Oncol 2018;36:1389–1395. [PubMed: 29590007]
33. Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: The ORIOLEphase 2 randomized clinical trial. JAMA Oncol 2020;6:650–659. [PubMed: 32215577]
34. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: Updated survival in the TAX 327 study. J Clin Oncol 2008;26:242–245. [PubMed: 18182665]

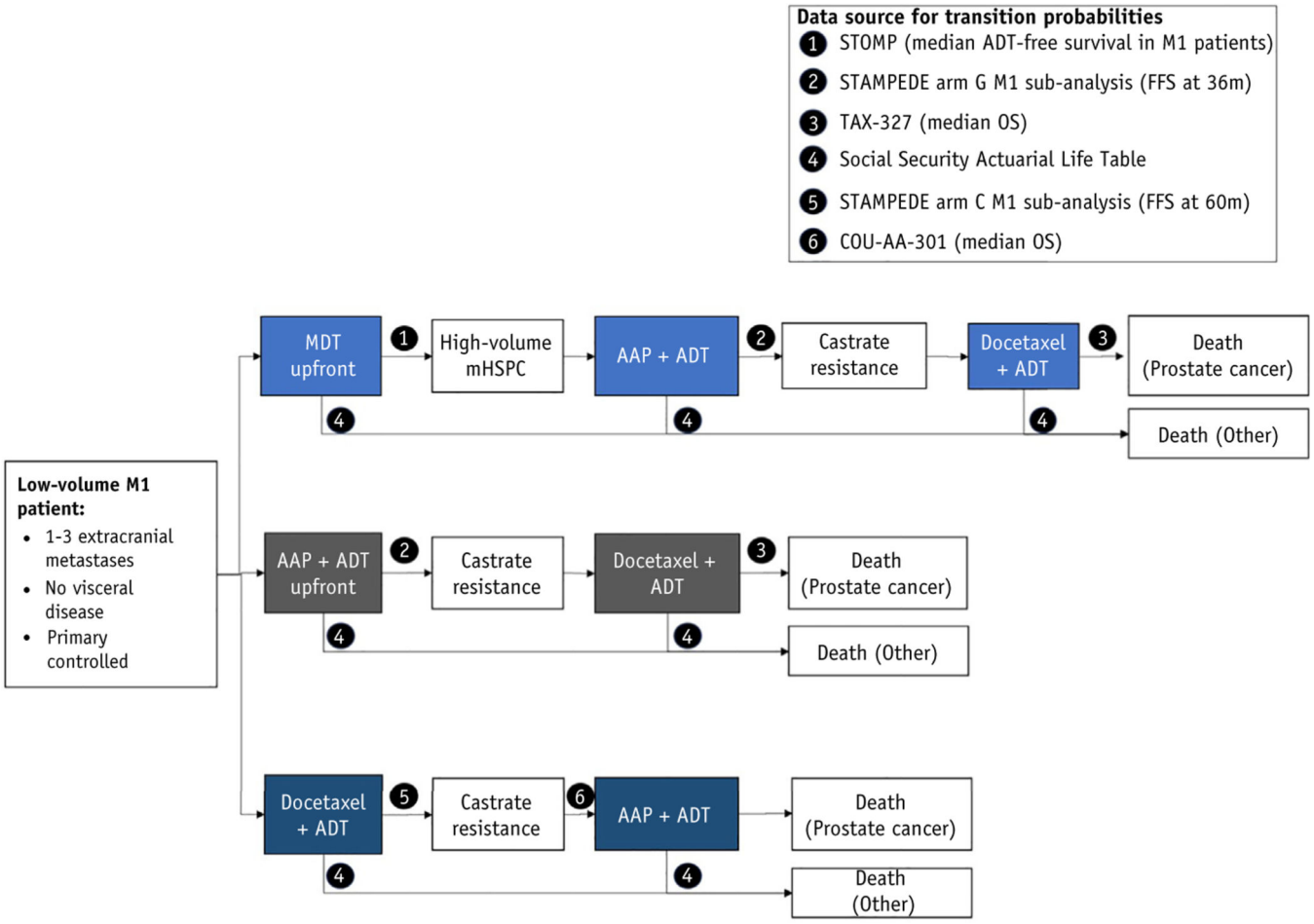

Fig. 1.

Schema for Markov model comparing 3 treatment strategies in patients with low-volume oligorecurrent disease: (1) upfront metastasis-directed therapy followed by salvage abiraterone acetate plus prednisone (AAP) + androgen deprivation therapy (ADT) followed by salvage docetaxel + ADT, (2) upfront AAP + ADT followed by salvage docetaxel + ADT, and (3) upfront docetaxel + ADT followed by salvage AAP + ADT.

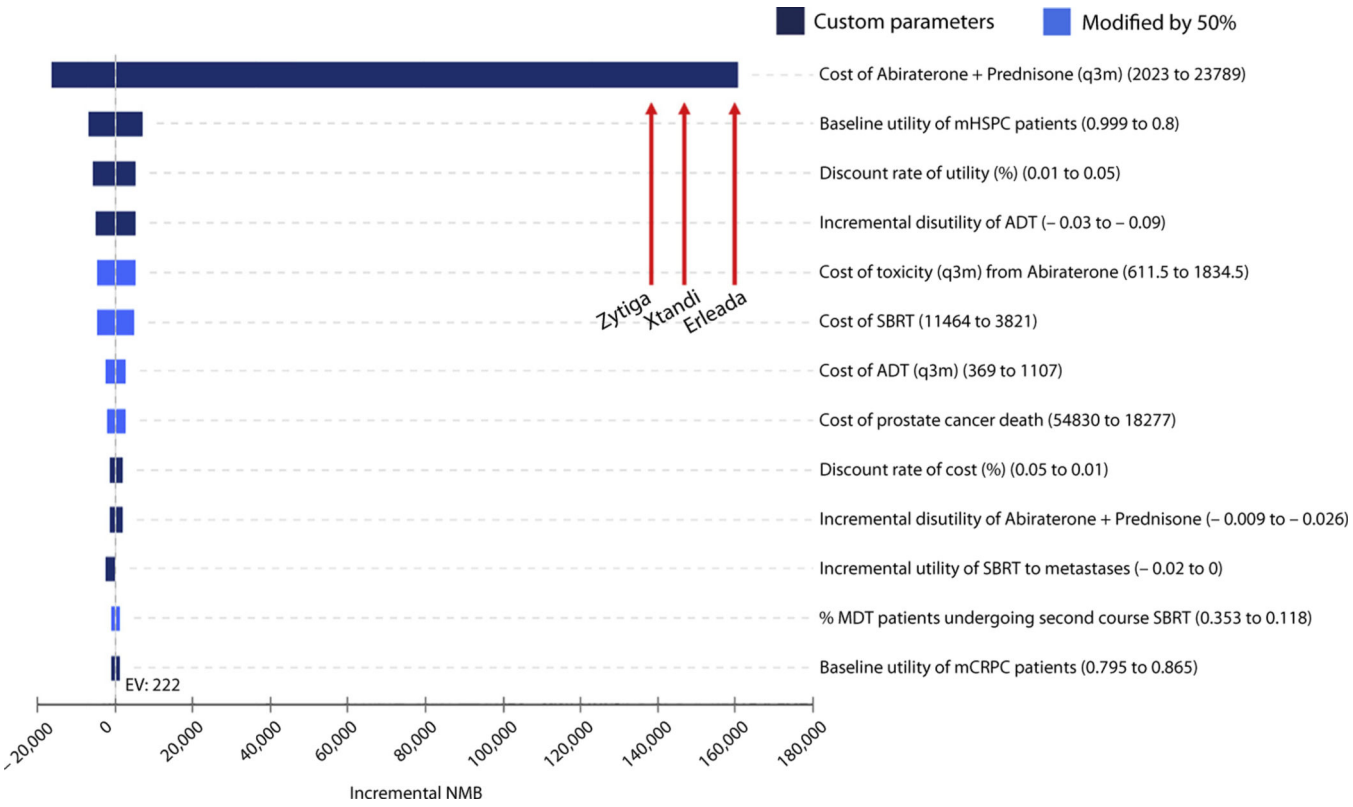

Fig. 2.

One-way sensitivity analyses reflecting effect of key model inputs on incremental net monetary benefit (NMB) of upfront metastasis-directed therapy versus upfront abiraterone acetate plus prednisone + androgen deprivation therapy (baseline comparator). Each key model input is shown with its lower/upper bounds in the sensitivity analysis and the corresponding effect on incremental NMB. The baseline expected value ($222) of incremental NMB is also shown.

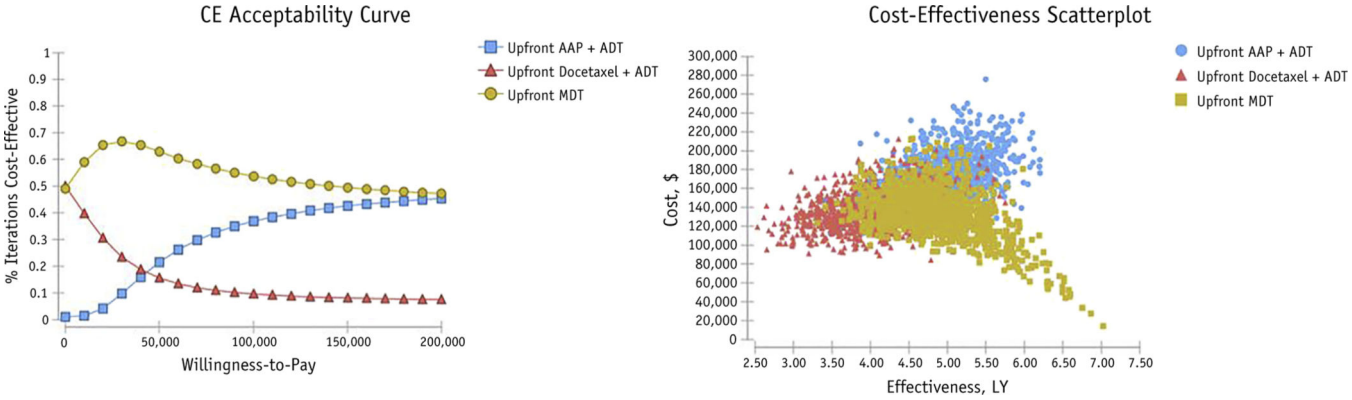

Fig. 3.

Results from probabilistic sensitivity analysis using Monte Carlo simulation (1,000,000 simulations) to compare each of the 3 treatment strategies. The cost-effectiveness acceptability frontier is displayed on the left, showing the probability of each strategy being the most cost effective at varying willingness-to-pay thresholds. The cost-effectiveness scatterplot is presented on the right for individual simulations.

Table 1

Costs, utilities, and probabilities used in the Markov model

Therapeutic or health state	Cost (base case)	Probabilistic distribution (SD)	Source
SBRT treatment	$7643	Gamma (25% of mean)	24*
AAP (3-month supply)	$4047	Gamma (25% of mean)	27
ADT (3-month supply)	$738	Gamma (25% of mean)	26†
Docetaxel (6 cycles / 10 cycles)	$1965→$3275	Gamma (25% of mean)	26‡
PC death (last 6 months)	$36,554	Gamma (25% of mean)	28§
Health state	**Baseline utility (base case)**	**Probabilistic distribution (SD)**	**Source**
mHSPC	0.90	Beta (10% of mean)	29‖
mCRPC	0.83	Beta (10% of mean)	30¶
Treatment	**Disutility**	**Probabilistic distribution (SD)**	**Source**
ADT	−0.06	Normal (25% of mean)	31#
Docetaxel	−0.041	Normal (25% of mean)	21**
AAP	−0.017	Normal (25% of mean)	22**
SBRT	0	—	10††
Intervention/health state	**Transition prob. (q3m)**	**Probabilistic distribution (α→β)**	**Source**
Low-volume mHSPC (MDT) → High-volume mHSPC	16.5%	Beta (α = 2.801; β = 14.199)	10‡‡,§§
Low-volume mHSPC (AAP + ADT) → mCRPC	2.5%	Beta (α = 5.174; β = 200.826)	9‖‖
Low-volume mHSPC (docetaxel + ADT) → mCRPC	4.5%	Beta (α = 5.671; β = 118.329)	8¶¶
High-volume mHSPC (AAP + ADT) → mCRPC	5.6%	Beta (α = 13.559; β = 229.441)	9‖‖
mCRPC (docetaxel + ADT) → PC death	11.8%	Beta (α = 39.466; β = 295.534)	34‡‡,##
mCRPC (AAP + ADT) → PC death	12.3%	Beta (α = 98.394; β = 698.606)	22‡‡,***
Death from other cause	0.42%−1.0% (varies with age)		23†††

Abbreviations: AAP = abiraterone acetate plus prednisone; ADT = androgen deprivation therapy; CPT = Current Procedural Terminology; mCRPC = metastatic castrate-resistant prostate cancer; MDT = metastasis-directed therapy; mHSPC = metastatic, hormone-sensitive prostate cancer; PC = prostate cancer; SBRT = stereotactic body radiation therapy; SD = standard deviation.

[*] Includes CPT codes: 77014, 77263, 77300, 77301, 77336, 77370, 77338, 77334, 77435, 77470, and 77373 (billed 3 times - once per fraction).

[†] Includes CPT code 96402.

[‡] Includes CPT codes 96360, 96365, and 96413.

[§] Total cancer-related costs ($29,962) in 2009 US dollars were converted to 2020 dollars with the U.S. Bureau of Labor Statistics inflation calculator.

[‖] Modeled after utility of asymptomatic patients with mHSPC.

[¶] Modeled after utility of asymptomatic patients with mCRPC.

[#] Modeled as difference (−0.06) between maximum/minimum utilities of LATITUDE patients while on ADT (+0.02 and e0.04, respectively).

[**] Additional disutility from docetaxel and AAP treatment derived from individual grade 3+ toxicities as noted in TAX-327 and COU-AA-301 (Table E1).

[††] Based on no grade 2 to 5 toxicity and comparable health-related quality of life at 3 and 12 months between 2 arms.

[‡‡] Transition probability further modified in Markov model (subtracted by rate of other death for that cycle) to avoid double counting.

[§§] Derived from reconstructed ADT-free survival curve in M1 STOMP patients receiving MDT; probability and beta distribution sampled at 29 months (time of last recorded event).

[‖‖] Derived from reconstructed failure-free survival curve in low-volume/high-volume M1 patients receiving AAP + ADT; probability and beta distribution sampled at 42 months (median follow-up).

[¶¶] Derived from reconstructed failure-free survival curve in low-volume M1 patients receiving docetaxel; probability and beta distribution sampled at 84 months (point on reconstructed curve closest to median follow-up).

[##] Derived from reconstructed overall survival curve from TAX-327; probability and beta distribution sampled at 24 months.

[***] Derived from reconstructed overall survival curve from COU-AA-301; probability and beta distribution sampled at 15.8 months (median overall survival).

[†††] Based on actuarial death tables for a US men over 10-year period from age ≥66 years.

Table 2

Total costs, effectiveness, and NMB (using willingness-to-pay threshold of $100,000/QALY) for each of the 3 strategies at 10 years

Strategy	Cost	Effectiveness, QALY	NMB
MDT → salvage AAP + ADT → salvage docetaxel	$141,148	4.63	$322,240
AAP + ADT → salvage docetaxel	$166,807	4.89	$322,018
Docetaxel + ADT → salvage AAP + ADT	$136,154	4.00	$263,407

Abbreviations: AAP = abiraterone acetate plus prednisone; ADT = androgen deprivation therapy; MDT = metastasis-directed therapy; NMB = net monetary benefit; QALY = quality-adjusted life year.

Both costs and effectiveness values include appropriate discount rates.

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2024 September 10.

Table 3

Total costs, effectiveness, and NMB (using willingness-to-pay threshold of $100,000/QALY) for each of the 3 strategies upon running Monte Carlo simulation with 1,000,000 microsimulations

Strategy	Cost, $ (95% CI)	Effectiveness, QALY (95% CI)	NMB, $ (95% CI)
MDT → salvage AAP + ADT → salvage docetaxel	133,873 (75,914–179,862)	4.85 (3.85–6.12)	351,476 (239,652–531,551)
AAP + ADT → salvage docetaxel	167,827 (124,431–223,892)	4.95 (3.91–5.86)	326,983 (234,344–417,815)
Docetaxel + ADT → salvage AAP + ADT	136,880 (103,298–180,617)	4.09 (3.02–5.22)	272,437 (174,239–381,610)

Abbreviations: AAP = abiraterone acetate plus prednisone; ADT = androgen deprivation therapy; CI = confidence interval; MDT = metastasis-directed therapy; NMB = net monetary benefit; QALY = quality-adjusted life year.

Both costs and effectiveness values include appropriate discount rates.