ICER Public Meeting: Antiandrogen Therapies for Nonmetastatic Castration-Resistant Prostate Cancer

September 13, 2018

ICER

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

WIFI Network: Marriott Guests
Password: 0809

Welcome and Introduction

Why are we here this morning?

"There are two landmarks of significant changes for men with prostate cancer: becoming castrate resistant and developing metastatic disease…

…Men are angry, frustrated, frightened, and often depressed when they reach these points. As their disease progresses they come to the realization that all available treatments only work for a very limited period before resistance develops and the cancer progresses. *They have also gone through enough treatments to know that every one of them will have side effects and a likely diminution of their quality of life."*

--Anonymous Patient Comment to ICER

Welcome and Introduction

Why are we here this morning?

- New treatment options often raise questions about appropriate use, cost
  - *In a 2017 survey report from the Cancer Support Community, more than 50% of respondents reported having monthly prostate cancer-related out-of-pocket costs of more than $100, with 25% of respondents reporting over $500 of out-of-pocket costs per month*

- Need for objective evaluation and public discussion of the evidence on effectiveness and value

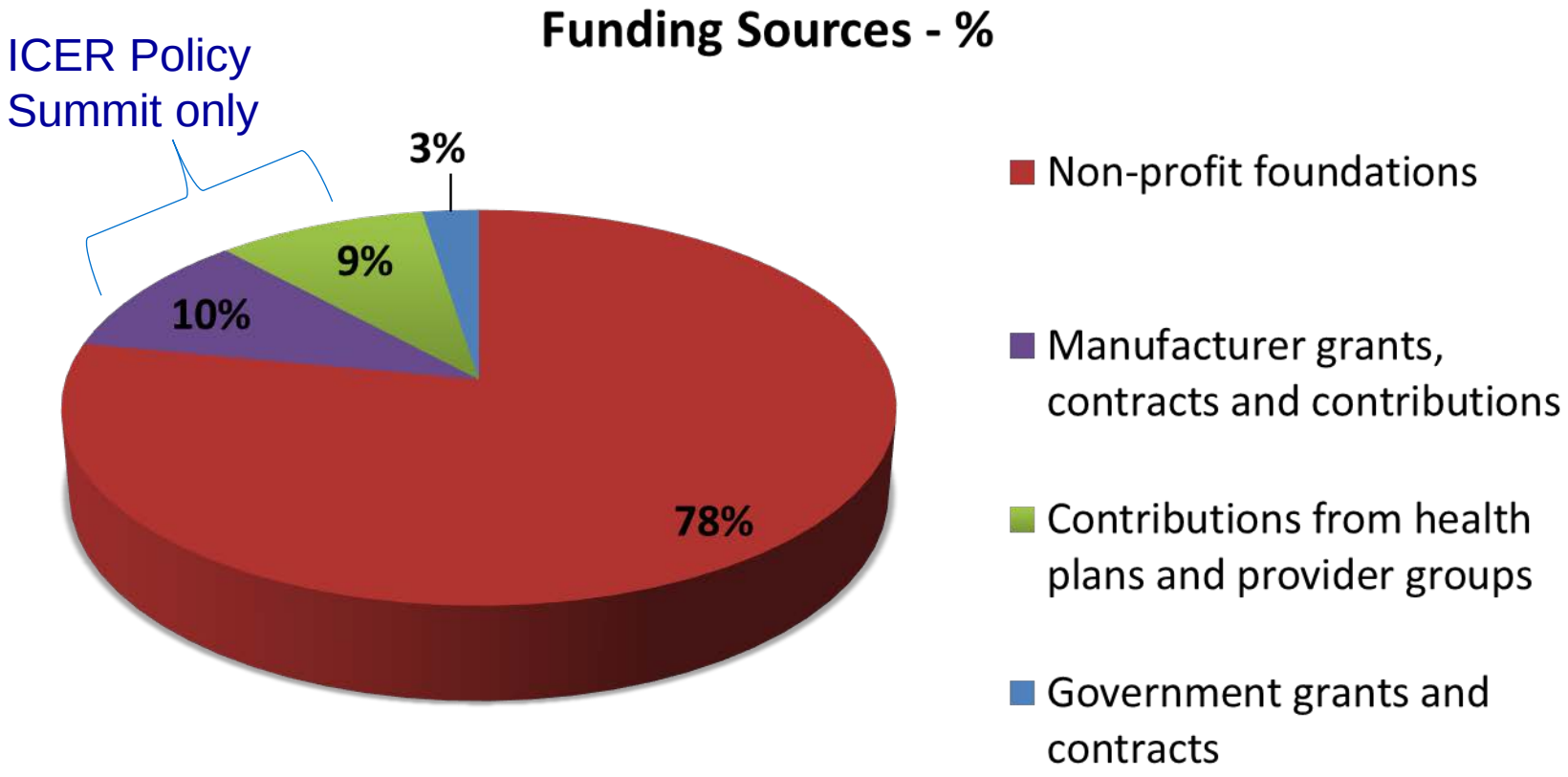
Welcome and Introduction

- Midwest Comparative Effectiveness Public Advisory Council (CEPAC)

- The Institute for Clinical and Economic Review (ICER)

Sources of Funding, 2018

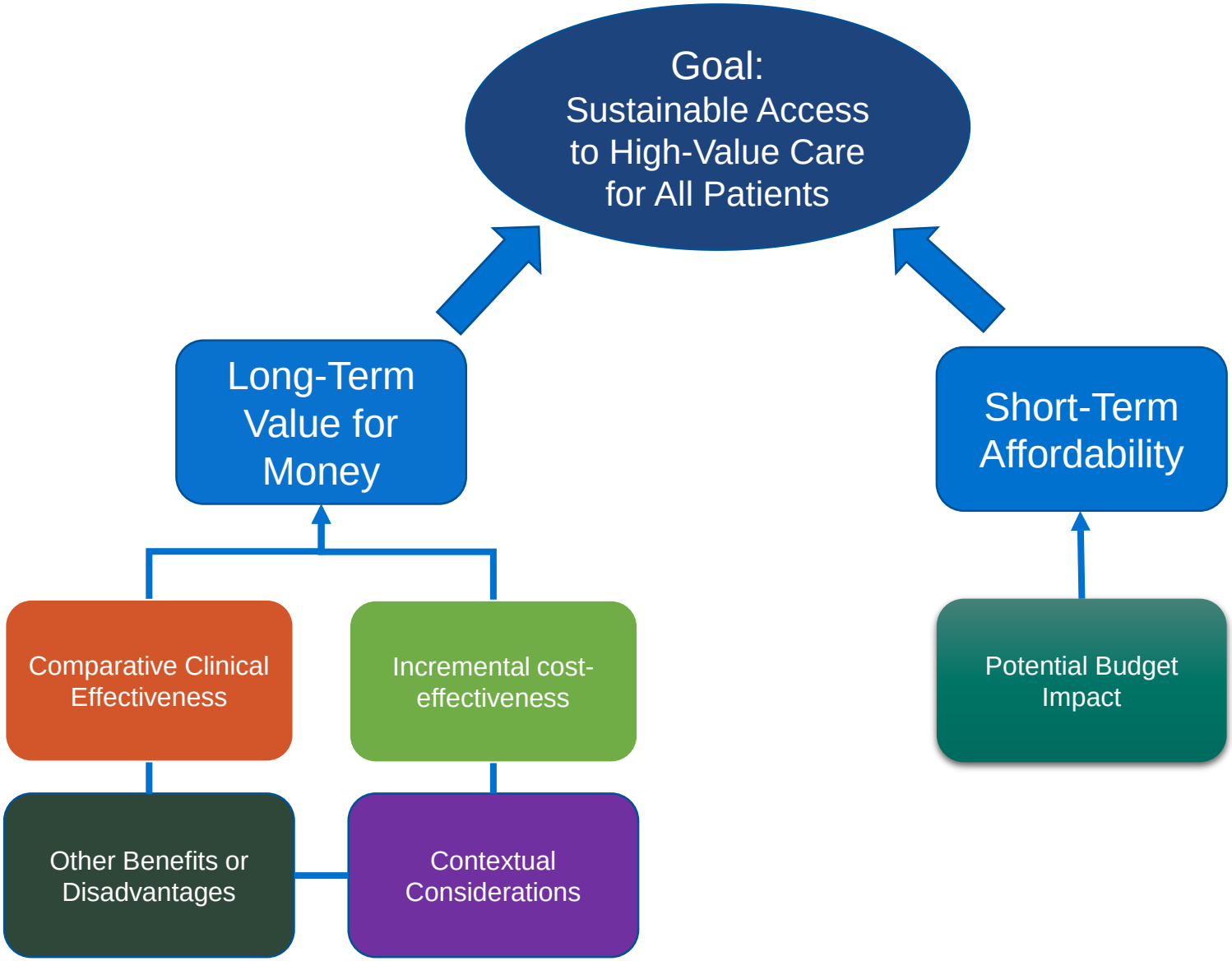
ICER Policy Summit only



Welcome and Introduction

How was the ICER report on therapies for prostate cancer developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis
- University of Washington cost-effectiveness modeling
- Public comment and revision
- Expert report reviewers
  - Jerome P. Richie, MD, Brigham And Women's Hospital
  - Matthew R. Smith, MD, Massachusetts General Hospital Cancer Center
- How is the evidence report structured to support CEPAC voting and policy discussion?


Goal:
Sustainable Access to High-Value Care for All Patients
Long-Term Value for Money
Short-Term Affordability
Comparative Clinical Effectiveness
Incremental cost-effectiveness
Potential Budget Impact
Other Benefits or Disadvantages
Contextual Considerations

Morning Agenda

9:00am: Welcome and Opening Remarks

9:15 am: Presentation of the Evidence and Economic Modeling
- David Rind, MD, MSc, Chief Medical Officer, ICER
- Greg Guzauskas, MSPH, PhD

10:15 am: Manufacturer Public Comments

10:30 am: MW CEPAC Vote on Clinical Effectiveness and Value

11:45 am: Reflections from Experts and MW CEPAC Panel

12:00 pm: Break for Lunch

Evidence Review

David Rind, MD, MSc

Chief Medical Officer

Institute for Clinical and Economic Review

ICER

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AND ECONOMIC REVIEW

Key review team members:

Patricia Synnott, MALD, MS

Aqsa Mugal, BA

Disclosures:

We have no conflicts of interest relevant to this report.

Prostate Cancer

- Second most common cause of cancer death in men in the US
- 2018 estimates:
  - 165,000 new cases
  - 30,000 deaths
- Disproportionate effects in black men:
  - 60% higher incidence
  - 110% higher mortality

Androgens and Prostate Cancer

- Prostate cancers are generally androgen responsive
- Androgen deprivation therapy (ADT) involves medical or surgical castration
- ADT is used in a number of clinical settings
- Castration-sensitive prostate cancer:
  - Never treated with ADT
  - Still responding to ADT

Castration-Resistant Prostate Cancer (CRPC)

- Clinical, radiographic, or biochemical progression despite ADT that has achieved low levels of testosterone
- First indication of CRPC is often a rise in PSA
- If metastases are found on conventional imaging, this is mCRPC
- Addition of “antiandrogen therapy” improves survival
  - Abiraterone acetate (androgen biosynthesis inhibitor)
  - Enzalutamide (androgen receptor inhibitor)

Nonmetastatic castration-resistant prostate cancer (nmCRPC)

- PSA is increasing despite ADT
- Metastases not found on conventional imaging
- Patients likely have metastatic disease but at an earlier stage
- Rate of PSA increase predicts risk
- Previously: continued ADT and surveillance

- Question: What are the benefits of starting antiandrogen therapy earlier?

Insights from Patients and Patient Groups

- Effect of the risks of morbidity and mortality on patients and their families
- Psychological effects on sense of self and benefits of having a treatment rather than waiting
- Sense of failure when PSA rises after burdensome therapies
- Variable tolerability of treatments, but fatigue a common substantial side effect
- Financial toxicities

Scope of the review

- **Population:** Men with nmCRPC
- **Intervention:** Adding one of the following to ADT:
  - Apalutamide
  - Enzalutamide
  - Abiraterone acetate + prednisone
- **Comparators:**
  - Continued treatment with ADT without antiandrogen therapy

Evidence

- Apalutamide
  - SPARTAN RCT
  - 1207 men with PSA doubling time ≤10 months
- Enzalutamide
  - PROSPER RCT
  - 1401 men with PSA doubling time ≤10 months
- Abiraterone acetate
  - IMAAGEN single arm study
  - 131 men with PSA ≥ 10 or PSA DT ≤10 months
  - Trials in mCRPC

What the RCTs show about benefits

- SPARTAN (apalutamide)
  - Overall survival: HR 0.70 (CI 0.47-1.04)
  - MFS: 40.5 vs 16.2 months (HR 0.28, CI 0.23-0.35)
  - Quality of life stable in both arms
- PROSPER (enzalutamide)
  - Overall survival: HR 0.80 (CI 0.58-1.09)
  - MFS: 36.6 vs 14.7 months (HR 0.29, CI 0.24-0.35)
  - Quality of life similar in both arms

Harms

- Fatigue is common (30-40%)
- Falls and fractures:
  - Apalutamide: 16% and 12% (vs. 9% and 7%)
  - Enzalutamide: 11% and 10% (vs 4% and 5%)
- Ischemic heart disease
  - Uncommon serious events in SPARTAN and PROSPER
  - FDA pooled analysis of three RCTs of enzalutamide showed more grade 3-4 events than with placebo (1.2 versus 0.5%) resulting in warning in label

Abiraterone acetate + Prednisone

- mCRPC without prior chemo
  - Abiraterone acetate OS HR: 0.81
  - Enzalutamide OS HR: 0.77
- mCRPC with prior chemo
  - Abiraterone acetate OS HR: 0.65
  - Enzalutamide OS HR: 0.66
- Single arm studies in nmCRPC (median time to PSA progression)
  - Abiraterone acetate: 28.7 months
  - Apalutamide: 24 months

Not all data suggest equivalence

- Median time to PSA progression was 28.7 months with abiraterone acetate in IMAAGEN
- SPARTAN (apalutamide): median time not reached (appears longer than 32 months)
- PROSPER (enzalutamide): 37.2 months

- Abiraterone acetate patent expiring
- ENABLE trial randomizing patients with CRPC to enzalutamide or abiraterone acetate being conducted in Japan (not sponsored by manufacturer)

Controversies and Uncertainties

- OS results are immature; MFS is a surrogate outcome
- SPARTAN and PROSPER only looked at PSA doubling times ≤10 months but FDA label is broad
- Black men underrepresented in SPARTAN (6%) and PROSPER (2%) and subgroup MFS HR in SPARTAN was 0.63 with wide CI vs 0.28 overall
- Data inadequate to compare antiandrogens to each other

ICER Evidence Ratings

- In men with nmCRPC and a rapid PSA doubling time (≤10 months):
  - High certainty that **apalutamide** + ADT provides a substantial net health benefit compared with ADT alone ("**A**").
  - High certainty that **enzalutamide** + ADT provides a substantial net health benefit compared with ADT alone ("**A**")
  - Moderate certainty that **abiraterone acetate** + ADT provides a small or substantial net health benefit and high certainty of at least a small net health benefit ("**B+**")
  - Insufficient evidence ("**I**") to conclude that the net health benefit of any of the three antiandrogens evaluated in men with nmCRPC is superior/inferior to either of the other two antiandrogens

Potential Other Benefits and Contextual Considerations

- Potential to reduce health disparities across racial and socio-economic categories in the US
- We heard from patient groups and clinical experts that there may be psychological benefits to having a therapy available for men who are experiencing rising PSA test results
- In the absence of more mature survival data, there is significant uncertainty about the survival benefit of treating men with nmCRPC with antiandrogen therapy

Public Comments Received

- B+ rating of abiraterone acetate not adequately explained
- MFS has been shown to be a valid surrogate for OS
- Lack of real world evidence and patient-reported outcomes in ICER report

- Additional comment about OS

“Meta-analysis” of SPARTAN and PROSPER

- Pooled estimate of overall survival:
  - Hazard ratio 0.76, 95% CI 0.59-0.97

Cost-Effectiveness

Greg Guzauskas, MSPH, PhD

Lotte Steuten, MsC, PhD

University of Washington

Department of Pharmacy

Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute

Disclosures

- Financial support was provided to the University of Washington by the Institute for Clinical and Economic Review (ICER) for this review.

- The University of Washington researchers report no industry funding related to prostate cancer.

Objective

To estimate the cost-effectiveness of antiandrogen therapies to treat non-metastatic castration resistant prostate cancer (nmCRPC), using a decision analytic model.

Methods in Brief

Methods Overview

- Population: Men diagnosed with nmCRPC, PSA doubling time ≤10 months
- Model: Hybrid of partitioned survival model, Markov model
- Setting: United States
- Perspective: Health sector
- Time Horizon: Lifetime
- Discount Rate: 3% per year (costs and outcomes)
- Cycle Length: Monthly

- Primary Outcomes:
  - Total cost
  - Quality adjusted life-years gained
  - Incremental cost-effectiveness ratios
    - (cost per quality-adjusted life year gained)

Modeled Interventions

Apalutamide (Erleada™; Janssen Biotech, Inc.)

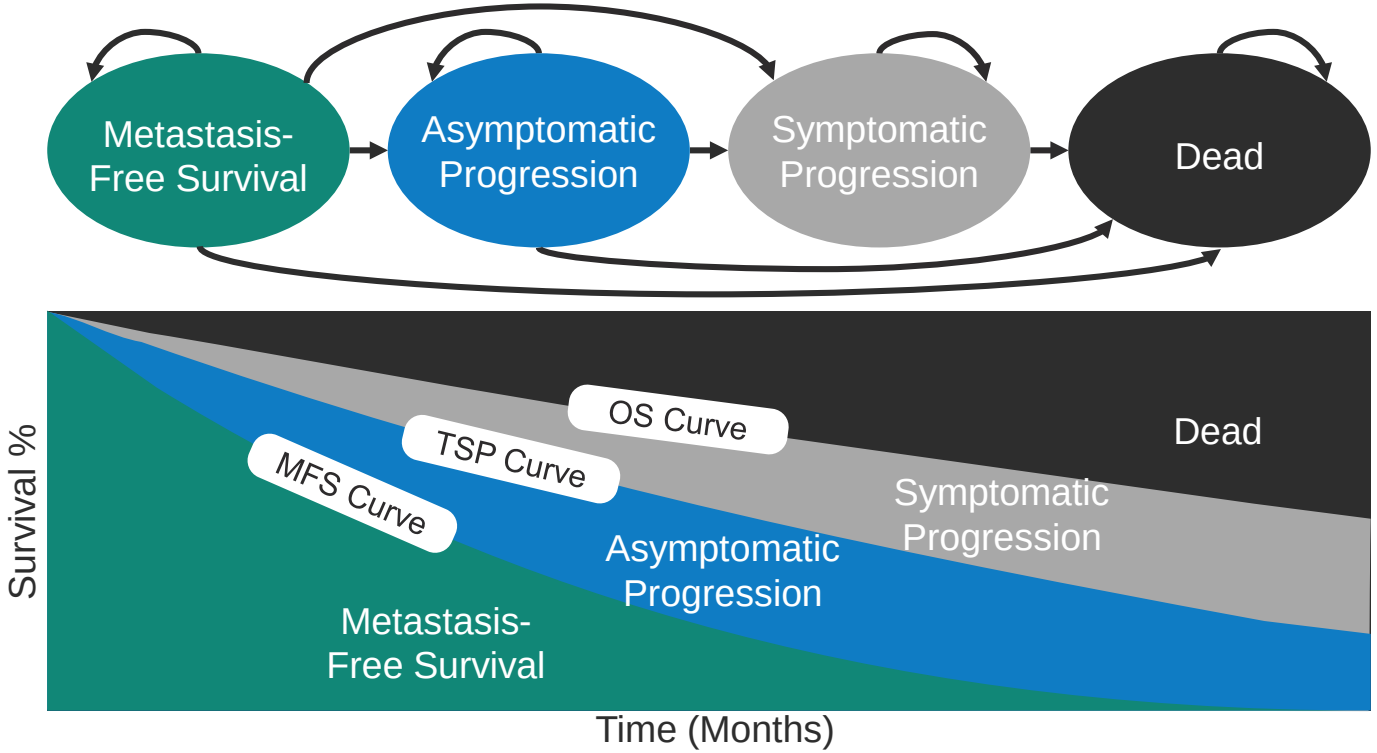
Enzalutamide (Xtandi®; Astellas Pharma, Inc. and Pfizer, Inc.)

Base case/standard of care comparator:

- Continued androgen deprivation therapy (ADT) alone until development of metastatic disease

Patients on each treatment are assumed to continue ADT until death.

Model Schematic

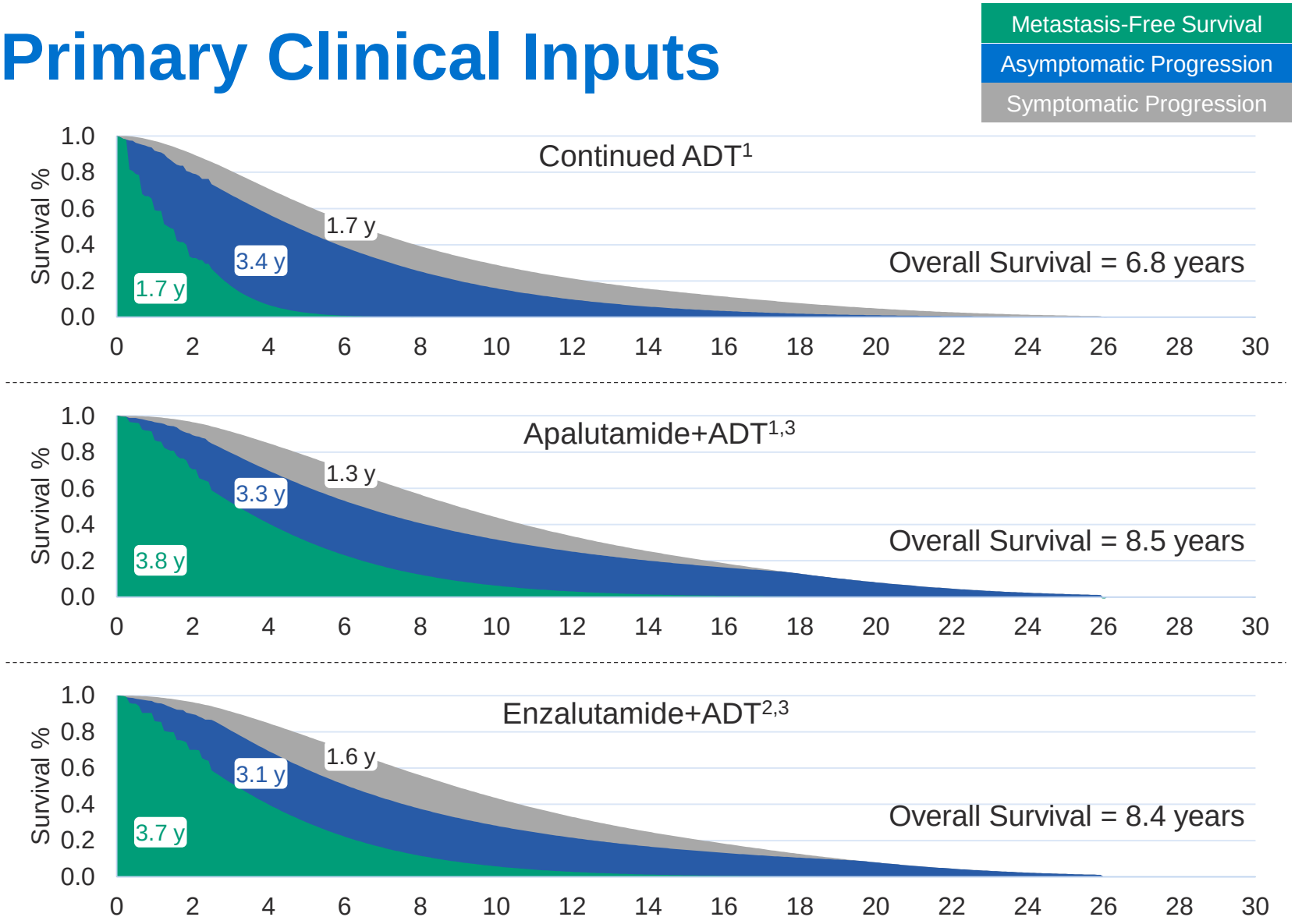


Key Model Assumptions

- Trial populations are similar, allowing for comparisons to a single baseline comparator (continued ADT from the SPARTAN trial[1]) using trial-reported hazard ratios.
- Time to symptomatic progression is similar between apalutamide and enzalutamide.
- Overall survival is modeled using a combination of trial-reported outcomes[1,2] and real-world 5-year survival data.[3]
- Instead of modeling trial-reported subsequent therapies, post-progression costs are informed by real-world data on subsequent approved treatments for mCRPC.

1. Smith MR, et al. N Engl J Med. 2018;378(15):1408-1418.
2. Hussain M, et al. N Engl J Med. 2018;378(26):2465-2474.
3. Surveillance, Epidemiology, and End Results (SEER) Program. 2018.

Primary Clinical Inputs



1. Smith MR, et al. N Engl J Med. 2018;378(15):1408-1418.
2. Hussain M, et al. N Engl J Med. 2018;378(26):2465-2474.
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Health State Utilities

Parameter	Value
Utility: Metastasis-Free Survival[1]	0.90
Utility: Asymptomatic Progression[2]	0.83
Utility: Symptomatic Progression[2]	0.69

1. Pataky R, et al. Int J Cancer. 2014;135(4):939-947.
2. Lobo JM, et al. Clinical Genitour Canc. 2017;15(3):e299-e309.

Adverse Events

Adverse Events of Interest	Continued ADT[1]	Apalutamide[1]	Enzalutamide[2,3]	AE Cost
Severe Rash	0.3%	5.2%	Not reported	$3,546[4]
Hypertension	11.8%	14.3%	4.6%	$3,746[4]
Fracture	6.5%	11.7%	9.8%	$4,529[5]
Dizziness	6.3%	9.3%	0.4%	$3,873[5]
Hypothyroidism	2.0%	8.1%	Not reported	$596[4]
Mental Impairment Disorder	3.0%	5.1%	5.2%	$3,000[4]
Cardiovascular-related Adverse Events*	0.5%	0.5%	1.2%	$9,664[5]

1. Smith MR, et al. N Engl J Med. 2018;378(15):1408-1418.
2. Hussain M, et al. N Engl J Med. 2018;378(26):2465-2474.
3. https://www.astellas.us/docs/us/12A005-ENZ-WPI.pdf?v=1
4. Wong w, et al. PLoS One. 2018;13(4):e0196007.
5. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/FY2018-IPPS-Final-Rule-Home-Page-Items/FY2018-IPPS-Final-Rule-Tables.html

Drug Costs

	Apalutamide[1]	Enzalutamide[2]
Recommended Dosing	240 mg (four 60 mg tablets) administered orally once daily	160 mg (four 40 mg capsules) administered orally once daily
Wholesale Acquisition Cost (WAC)[3]	$91.00/tablet	$90.88/capsule
Discount from WAC	29%*	29%
Net Price per Unit	$64.61/tablet	$64.45/capsule
Net Price per Month	$7,866	$7,848
Median Duration of Therapy	16.9 months	18.4 months

ICER

1. Smith MR, et al. N Engl J Med. 2018;378(15):1408-1418.
2. Hussain M, et al. N Engl J Med. 2018;378(26):2465-2474.
3. Redbook. US Brand Rx Net Price. 2018. Accessed May 21, 2018.

* Discount calculated based on discount for enzalutamide

Post-Progression Treatment Costs[1-4]

Treatment Received	Cost/month	%, Apalutamide	%, Enzalutamide	%, Continued ADT
Abiraterone + prednisone	$7,166	18%	32%	27%
Cabazitaxel	$12,088	0.3%	0.3%	0.5%
Docetaxel	$1,978	15%	15%	23%
Enzalutamide	$7,847	14%	0%	20%
Radium-223	$13,353	2%	2%	3%
Sipuleucel	$71,644	3%	3%	5%
No Treatment	--	*47%*	*47%*	*22%*
Total Cost/month Post-Progression*		**$5,579**	**$5,486**	**$8,151**

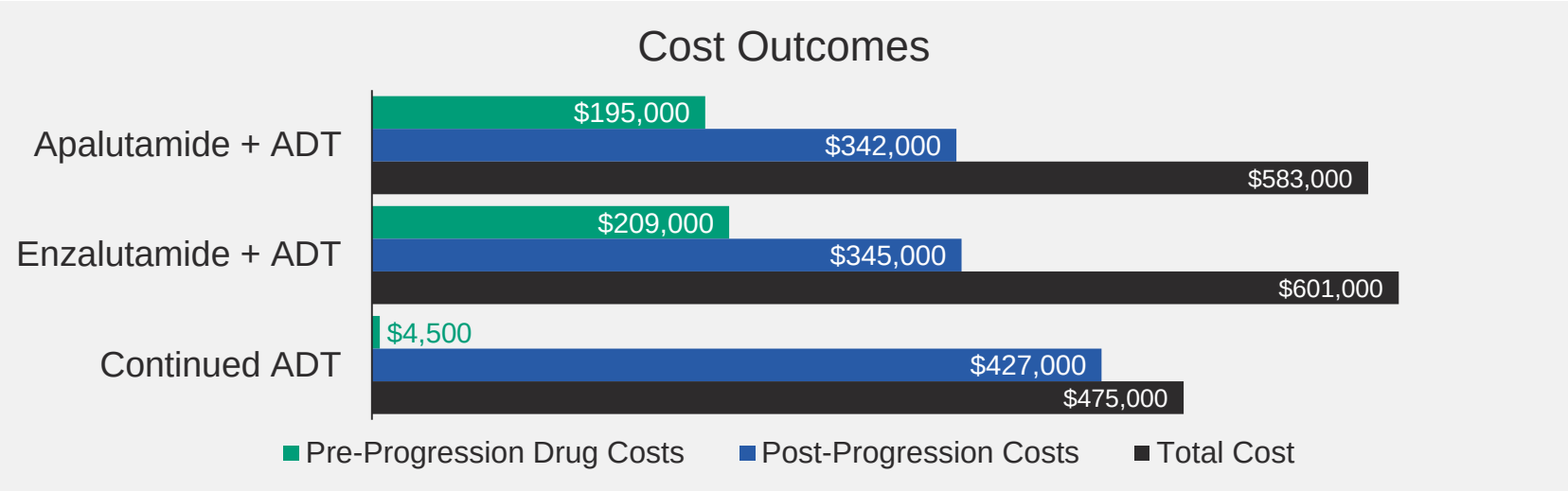
*includes cost of continued ADT (all regimens)

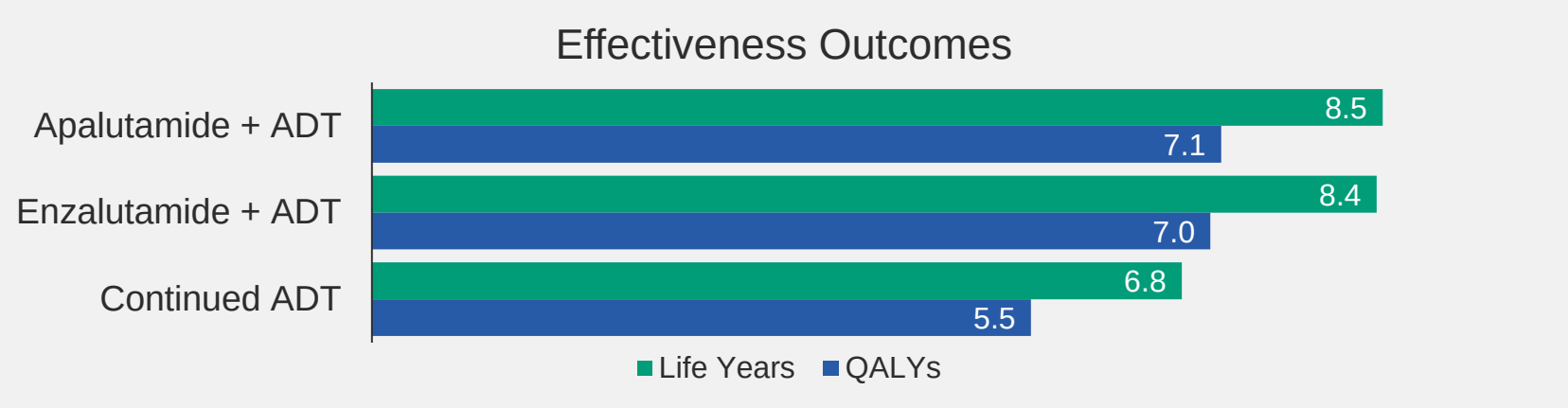
ICER

1. Smith MR, et al. N Engl J Med. 2018;378(15):1408-1418.
2. Caram MEV, et al. BMC Cancer. 2018;18(1):258.
3. Pollard ME, et al. Asian J Urol. 2017;4(1):37-43.
4. Li TT, et al. Cancer. 2017;123(18):3591-3601.

Results

Lifetime Outcomes





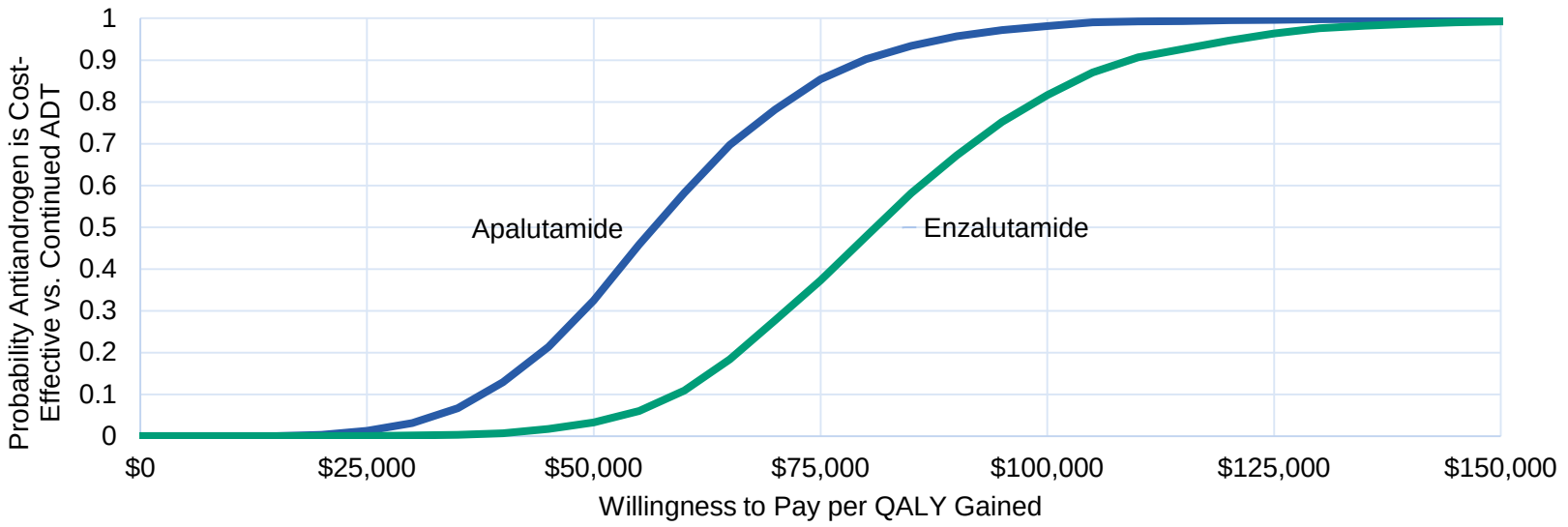
Incremental Results

Comparison	Incremental QALYs	Incremental Cost	ICER*
Apalutamide+ADT vs. Continued ADT	1.6	$108,000	**$68,000**
Enzalutamide+ADT vs. Continued ADT	1.5	$126,000	**$84,000**

*incremental cost-effectiveness ratio = incremental cost / incremental QALYs

Probabilistic Sensitivity Analysis

Comparator vs. Continued ADT	Probability ICER < $50,000 per QALY	Probability ICER < $100,000 per QALY	Probability ICER < $150,000 per QALY
Apalutamide + ADT	33%	99%	100%
Enzalutamide + ADT	3%	82%	99%



Scenario Analyses

Apalutamide and Enzalutamide were cost-effective (<$150K/QALY) in all scenario analyses:

- Extrapolations of trial-reported overall survival
- 3-state instead of 4-state (no TSP in PROSPER)
- Alternative parametric curve fits
- Continued ADT comparator based on PROSPER
- PSA doubling time subgroups
- Modified Societal perspective

Limitations

- The modeled lifetime outcomes are highly dependent on extrapolations of the short-term outcomes observed in the SPARTAN and PROSPER trials.

- Current lack of robust long-term data on post-antiandrogen overall survival.

- Modeled treatment duration, based on trial-reported medians, may overestimate real-world use (and thus antiandrogen cost).

Comments Received

- Model structure and modeled outcomes should better reflect specific trial-reported outcomes.

- Underlying differences in the patient populations of SPARTAN and PROSPER make comparisons between apalutamide and enzalutamide dubious.

Summary

- More costly, more effective: ICERs vs. continued ADT alone, for antiandrogen therapy with apalutamide+ADT or enzalutamide+ADT, are expected to fall within commonly cited thresholds of $50,000 to $150,000 per QALY gained.

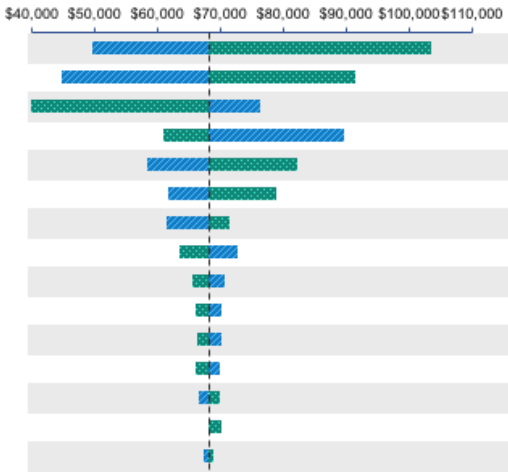
- Results were robust to all sensitivity and scenario analysis variation.

- Our findings are primarily driven by antiandrogen treatment duration, antiandrogen cost, and the costs of post-progression therapy.

Extra Slides

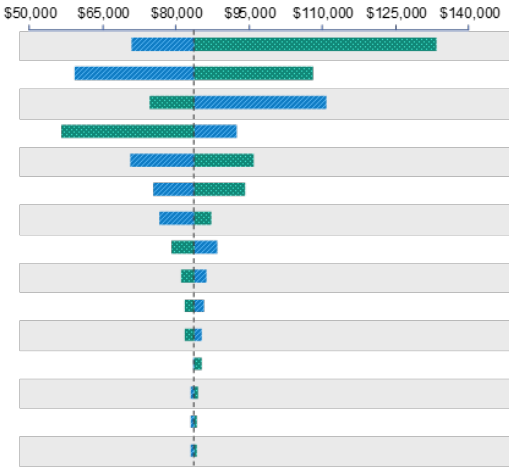
One-Way Sensitivity Analyses

Apalutamide+ADT vs. Continued ADT



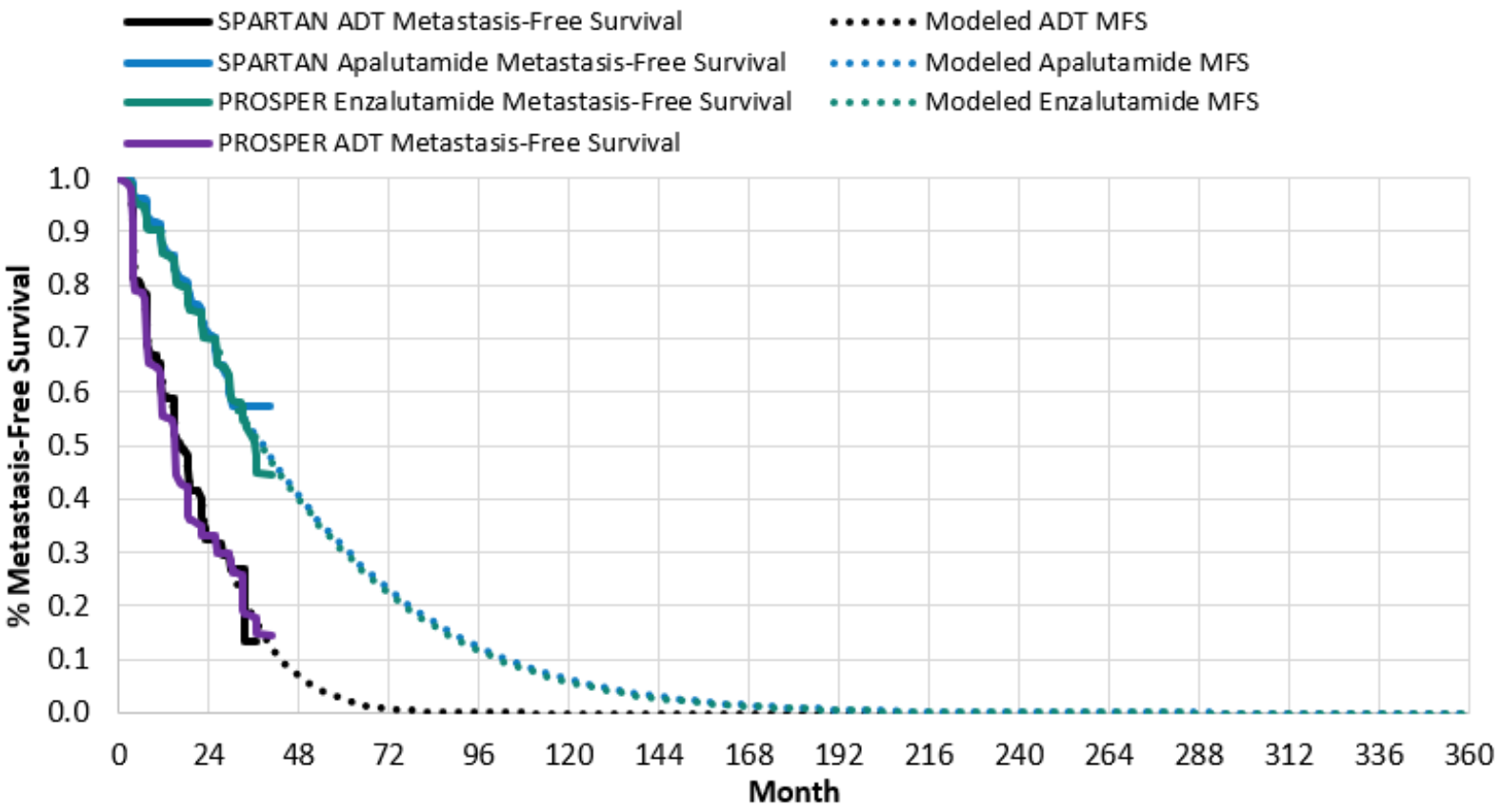
Parameter	Low Value	High Value	Low Result	High Result	Spread
Apalutamide Duration of Therapy	14.0 m	22.5 m	$49,681	$103,410	$53,729
Apalutamide Cost: 60 mg tablet	$52	$78	$44,898	$91,492	$46,594
Apalutamide Time to Subsequent Therapy	34.8 m	54.8 m	$76,286	$39,837	$36,449
Utility: Metastasis-Free Survival	0.72	0.99	$89,659	$60,905	$28,754
Apalutamide Hazard Ratio: MFS	0.23	0.35	$58,477	$82,132	$23,655
Apalutamide Hazard Ratio: OS	0.47	1.04	$61,686	$78,806	$17,120
ADT Time to Subsequent Therapy	14.6 m	17.6 m	$61,415	$71,543	$10,127
Cost/Month: Sipuleucel	$57,315	$85,973	$72,848	$63,542	$9,307
Abiraterone Cost: 250 mg tablet	$47	$70	$70,697	$65,693	$5,005
Enzalutamide Cost: 40 mg capsule	$52	$77	$70,285	$66,106	$4,179
ADT Proportion Subsequent Therapy	0.75	0.81	$70,122	$66,269	$3,853
SEER mCRPC 5-year Survival Rate	0.20	0.28	$69,954	$66,158	$3,795
Utility: Symptomatic Progression	0.59	0.80	$66,556	$69,917	$3,361
Apalutamide Hazard Ratio: TSP	0.32	0.63	$68,195	$70,175	$1,980
Cost/Month: MFS Supportive Care	$2,197	$3,295	$67,465	$68,926	$1,461

Enzalutamide+ADT vs. Continued ADT

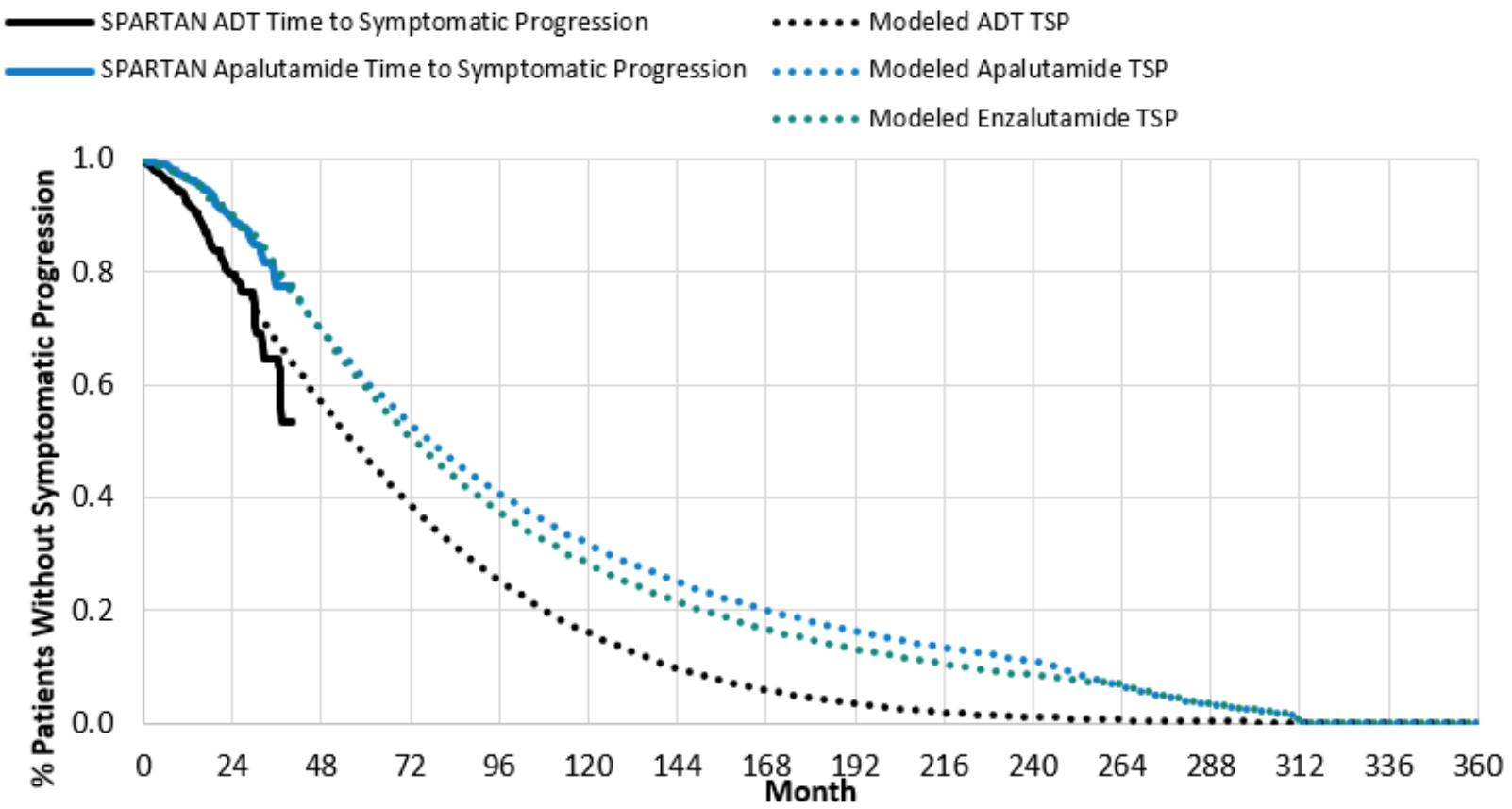


Parameter	Low Value	High Value	Low Result	High Result	Spread
Enzalutamide Duration of Therapy	16.5 m	26.1 m	$70,861	$133,416	$62,555
Enzalutamide Cost: 40 mg capsule	$52	$77	$59,230	$108,115	$48,885
Utility: Metastasis-Free Survival	0.72	0.99	$110,799	$74,547	$36,252
Enzalutamide Time to Subsequent Therapy	33.8 m	51.8 m	$92,383	$56,584	$35,799
Enzalutamide Hazard Ratio: MFS	0.24	0.35	$70,573	$95,832	$25,259
Enzalutamide Hazard Ratio: OS	0.58	1.09	$75,320	$94,094	$18,774
ADT Time to Subsequent Therapy	14.6 m	17.6 m	$76,507	$87,211	$10,704
Cost/Month: Sipuleucel	$57,315	$85,973	$88,399	$78,947	$9,452
Abiraterone Cost: 250 mg tablet	$47	$70	$86,214	$81,131	$5,083
ADT Proportion Subsequent Therapy	0.75	0.81	$85,629	$81,716	$3,913
SEER mCRPC 5-year Survival Rate	0.20	0.28	$85,280	$81,814	$3,466
Enzalutamide Hazard Ratio: TSP	0.33	0.63	$83,540	$85,133	$1,593
Cost/Month: MFS Supportive Care	$2,197	$3,295	$82,926	$84,420	$1,494
Utility: Asymptomatic Progression	0.80	0.87	$83,041	$84,314	$1,273
Utility: Symptomatic Progression	0.59	0.80	$83,129	$84,223	$1,094

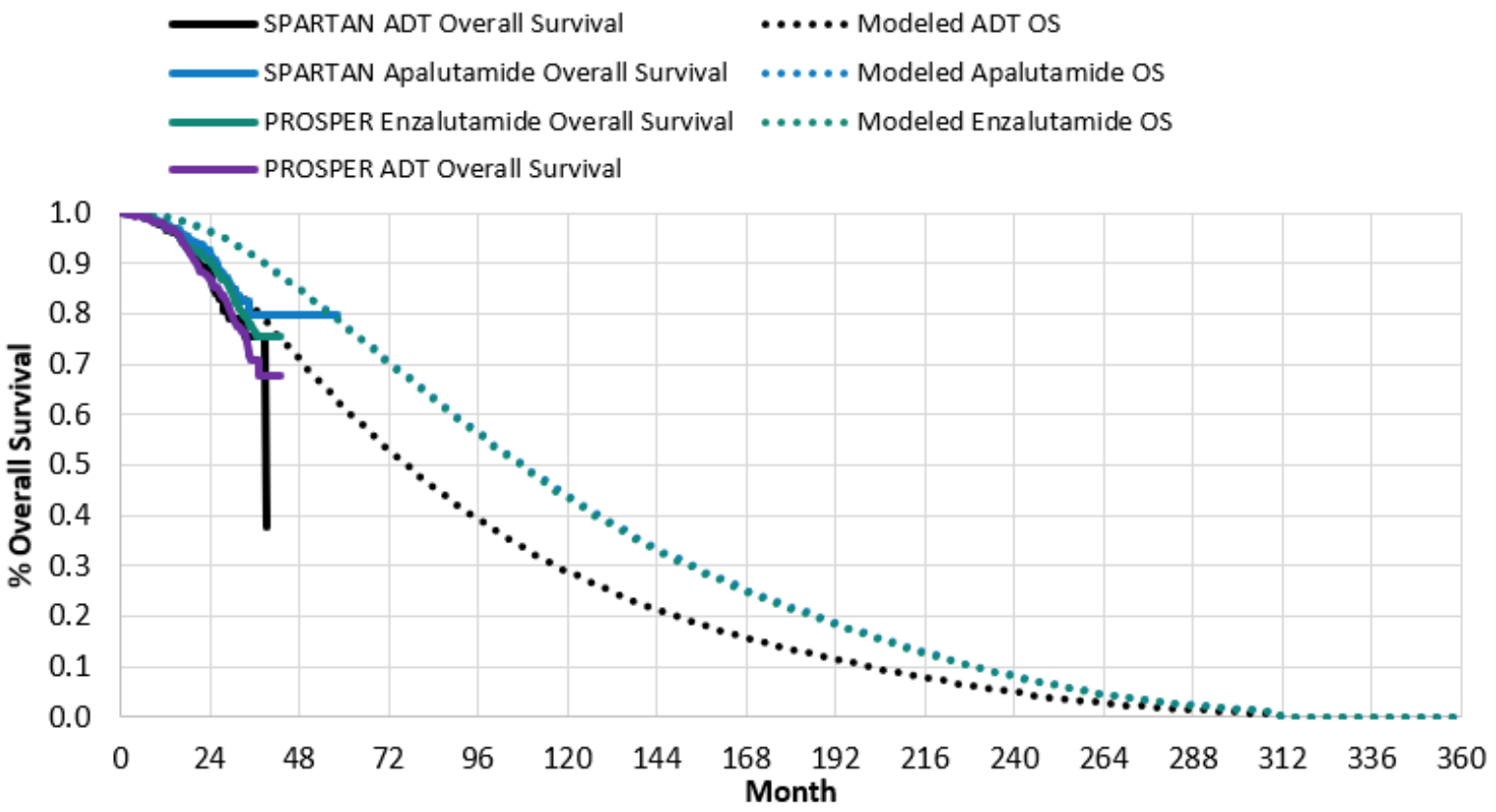
Modeled Metastasis-Free Survival Curves



Modeled Time to Symptomatic Prog. Curves



Modeled Overall Survival Curves



Manufacturer Public Comment and Discussion

Speaker

Name	Title	Company
Neil M. Schultz, PharmD, MS	Associate Director, Health Economics & Outcomes Research - Oncology	Astellas

Voting Questions

WIFI Network: Marriott Guests
Password: 0809

0. Which famous pastry was invented in Chicago?

A. Twinkie

B. Cronut

C. Bear claw

D. Cherry pie

Patient Population for all questions:

For each question, we are considering men with high risk (PSA doubling time ≤10 months) nonmetastatic castration-resistant prostate cancer being treated with androgen deprivation therapy. The comparator is waiting to add antiandrogen therapy with either abiraterone acetate or enzalutamide until the development of detectable metastatic disease

1. Is the evidence adequate to demonstrate a net health benefit of treating with apalutamide?

A. Yes

B. No

2. Is the evidence adequate to demonstrate a net health benefit of treating with enzalutamide?

A. Yes

B. No

3. Is the evidence adequate to demonstrate a net health benefit of treating with abiraterone acetate?

A. Yes

B. No

4. Is the evidence adequate to distinguish the net health benefits of apalutamide and enzalutamide?

A. Yes

B. No

5. Is the evidence adequate to demonstrate that abiraterone acetate has comparable efficacy to apalutamide and enzalutamide?

A. Yes

B. No

6. Does treating patients with antiandrogen therapies offer one or more of the following "potential other benefits?" (select all that apply)

A. Offers reduced complexity that will significantly improve patient outcomes.

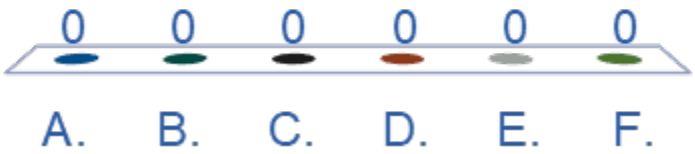
B. Will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.

C. Will reduce caregiver/family burden

D. Is a novel mechanism of action or approach

E. Will have a significant impact on improving return to work/overall productivity

F. Offers other important benefits or disadvantages.



7. Are any of the following contextual considerations important in assessing antiandrogen therapies' long-term value for money? (select all that apply)

A. Intended for care of individuals with condition of high severity in terms of impact on quality and/or length of life

B. Intended for care of individuals with condition with high lifetime burden of illness

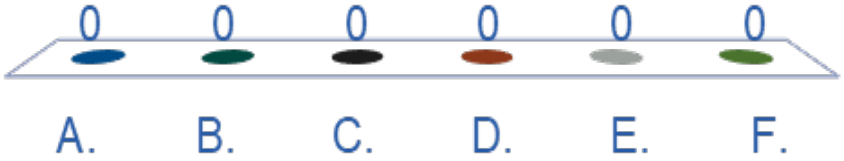
C. First to offer any improvement for patients

D. There is significant uncertainty about the long-term risk of serious side effects of this intervention.

E. There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.

F. Other important contextual considerations.

_____

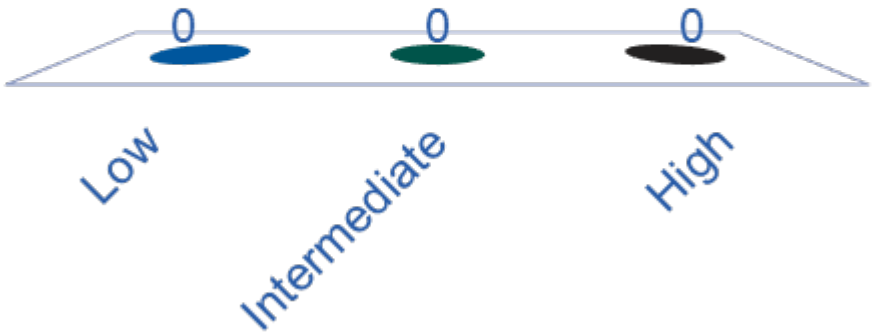


8. In men with high risk (PSA doubling time ≤10 months) non-metastatic castration resistant prostate cancer being treated with androgen deprivation therapy, given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering potential other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with apalutamide compared with waiting to add antiandrogen therapy with either abiraterone acetate or enzalutamide until the development of detectable metastatic disease?

A. Low

B. Intermediate

C. High

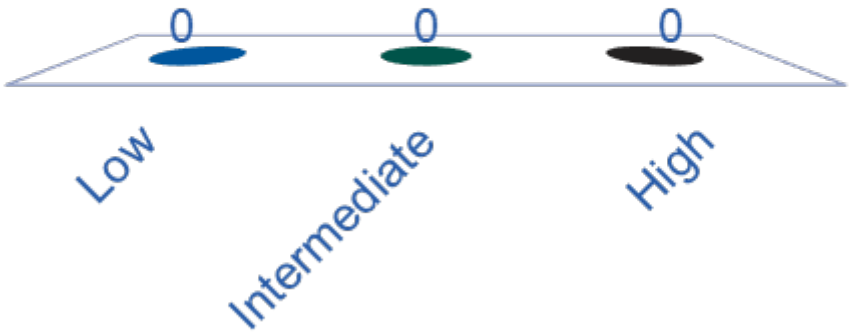


9. In men with high risk (PSA doubling time ≤10 months) non-metastatic castration resistant prostate cancer being treated with androgen deprivation therapy, given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering potential other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with enzalutamide compared with waiting to add antiandrogen therapy with either abiraterone acetate or enzalutamide until the development of detectable metastatic disease?

A. Low

B. Intermediate

C. High



Expert Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on/about
- Includes description of CEPAC votes, deliberation; policy roundtable discussion
- Materials available at

  https://icer-review.org/topic/prostate-cancer/

Break for Lunch.

Reconvene at 12:45pm.