Objectives

- Illustrate selection of modeling approach for evaluating treatment pathways in mCRPC.
- Review data needs for developing and evaluating treatment pathways.
**Brief Overview of mCRPC**

- Prostate cancer is most common non-skin cancer among men in the US.
  - 241,740 new cases of prostate cancer and 28,170 prostate cancer-related deaths were estimated for 2012.¹
- Estimated expenditures approached $11.9 billion,² making it the fifth most costly cancer.
- Disease course:
  - Typically slow disease course, and only a small percentage of patients eventually progress to metastatic phase.³
  - Nearly all metastatic prostate cancer ultimately becomes castration-resistant.
    - mCRPC is defined as disease progression with rising serum prostate-specific antigen (PSA) levels despite surgical or medical castration.
    - This stage typically begins as asymptomatic or mildly symptomatic disease; progression is associated with increasing symptoms and pain.
    - Median survival times reported from historical studies was <1 yr ⁴ but is now vastly improved, averaging 18–24 months or more.

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**2010 Treatment Recommendations in mCRPC**

![NCCN Practice Guidelines in Oncology - v.2.2010](image)
2013 Treatment Recommendations in mCRPC

- NCCN treatment guidelines show the treatment options are quickly increasing for the clinical states of mCRPC (asymptomatic/minimally symptomatic, symptomatic/rapid progression, and post-docetaxel).

NCCN Guidelines Version 2.2013 Prostate Cancer

ADVANCED DISEASE: ADDITIONAL SYSTEMIC THERAPY FOR CASTRATION-RECURRENT PROSTATE CANCER

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>No</td>
</tr>
</tbody>
</table>

- Docetaxel (category 1)
- Mitoxantrone
- Abiraterone acetate
- Enzalutamide
- Palliative RT or radionuclide for symptomatic bone metastases
- Clinical trial

- Abiraterone acetate or enzalutamide (category 1, post-docetaxel)
- Cabazitaxel (category 1, post-docetaxel)
- Salvage chemotherapy
- Docetaxel rechallenge
- Mitoxantrone
- Other secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Abiraterone acetate (category 1)
  - Enzalutamide
  - Ketoconazole
  - Steroids
  - DES or other estrogen
  - Sipuleucel-T
  - Clinical trial


Recently Approved Treatments

- A number of drugs have been recently approved in the US, each with a survival benefit versus the control, but at a higher drug cost.

<table>
<thead>
<tr>
<th>Clinical States in mCRPC</th>
<th>FDA Approval</th>
<th>Efficacy</th>
<th>Toxicity</th>
<th>Median Tx Duration (Months)</th>
<th>AWP/ASP Drug Cost/Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic/minimally symptomatic</td>
<td>Sipuleucel-T 2010</td>
<td>4.1 to 4.5 months (HR 0.76, 0.59)</td>
<td>Mild</td>
<td>3 doses at ~2 weeks</td>
<td>$70,842*</td>
</tr>
<tr>
<td>Symptomatic/rapid progression</td>
<td>Docetaxel 2004</td>
<td>2.4 months (HR 0.761)</td>
<td>Hematologic (neutropenia)</td>
<td>6.6 (every 3 weeks)</td>
<td>$1,547*</td>
</tr>
<tr>
<td>Post docetaxel</td>
<td>Cabazitaxel 2010</td>
<td>2.4 months (HR 0.70)</td>
<td>Hematologic (neutropenia)</td>
<td>4.1 (6 cycles)</td>
<td>$11,793*</td>
</tr>
<tr>
<td></td>
<td>Abiraterone 2010</td>
<td>3.9 to 4.6 months (HR 0.65 - 0.74)</td>
<td>Mild</td>
<td>8 (daily dosing)</td>
<td>$7,080</td>
</tr>
<tr>
<td></td>
<td>Enzalutamide 2012</td>
<td>4.8 months (HR 0.63)</td>
<td>Mild</td>
<td>8.3 (daily dosing)</td>
<td>$7,886</td>
</tr>
</tbody>
</table>

Rationale for Treatment Pathway Modeling

- Given the rapid emergence of several treatment options, the clinical question is how to best sequence these agents to optimize clinical and cost outcomes.
- Models are a framework that allow the synthesis of evidence from numerous sources and can be used to pull together inform clinical and cost implications as evidence becomes available.
- Other approaches to evaluating pathways have important limitations in mCRPC:
  - Clinical trials data alone only provide limited data on efficacy, and current mCRPC trials are not designed to explore sequences.
  - Database studies require data, but many of the relevant mCRPC treatments are only recently approved.
- Providing earlier evidence of the costs and outcomes associated with clinical pathways may help with decision making.

Considerations For Selecting Model Approach in mCRPC

<table>
<thead>
<tr>
<th>Modeling Objective</th>
<th>• Compare treatment pathway options over the course of mCRPC to reflect the new treatment paradigm.</th>
</tr>
</thead>
</table>
| Events of Interest/Outcome Measures | • Time on treatment, time to disease progression, OS  
  • mCRPC trials have shown that treatment benefits and survival differs by ECOG, number of previous therapies, level of pain, and presence of visceral disease. |
| Subsequent Treatments | • Subsequent treatments along the mCRPC spectrum have been shown to significantly prolong survival.  
  • Subsequent treatment options may depend on previous treatments and patient characteristics, such as comorbidities, previous toxicities, and age. |
| Heterogeneity of Patients | • Number of subgroups (age, comorbidities, PSA levels) |

These considerations point to the use of a DES/individual time-to-event simulation. Captures multiple courses of disease, can adjust OS benefit based on the drugs received, allows for testing different scenarios that were not observed in the trial, and can capture impacts of patient heterogeneity.
Modeling Steps – Develop Model Framework

- To capture benefits, the model needs to simulate individual clinical experiences, starting from first treatment through subsequent treatments until death.
- Example pathways using newly available drugs:

**Asymptomatic: minimally symptomatic**

- Sipuleucel or Abiraterone

**Symptomatic: Rapid progression**

- Docetaxel

**Post-docetaxel**

- Cabazitaxel or Abiraterone or enzalutamide

BSC: best supportive care

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**Steps for DES using Example Pathway**

1. **Patients enter simulation**
2. **Assign baseline profile**
3. **Clone patients**
4. **Start 1st line e.g. sipuleucel-T or abiraterone**
5. **Estimate time to treatment end/PFS**
6. **Update status, risk and time to next event**
7. **Start post docetaxel treatment**
8. **Estimate time to treatment end/PFS**
9. **Update status, risk and time to next event**
10. **Start next therapy e.g. docetaxel**
11. **Estimate time to treatment end/PFS**
12. **Update status, risk and time to next event**

**Equation predicting time-to-event (discontinuation from 1st line treatment, start of next therapy, death etc.)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coefficient</th>
<th>Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>2.5</td>
<td>–</td>
</tr>
<tr>
<td>Tx</td>
<td>0.5</td>
<td>Yes = 1, No = 0</td>
</tr>
<tr>
<td>Age</td>
<td>0.04</td>
<td>65</td>
</tr>
<tr>
<td>ECOG score</td>
<td>0.12</td>
<td>1</td>
</tr>
<tr>
<td>Scale</td>
<td>0.8</td>
<td>–</td>
</tr>
</tbody>
</table>

**Event times ($T_i$) explained by survival curves that follow a parametric distribution (e.g., Weibull)**

- Sample a random number (RND) UNIF(0,1) and compute time corresponding to the RND on the curve

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**Parameter Coefficient**

- **Patient Characteristics**
  - **Intercept**: 2.5
  - **Tx**: 0.5
  - **Age**: 0.04
  - **ECOG score**: 0.12
  - **Scale**: 0.8

- **Yes = 1, No = 0**

- Adjust intercept

- **Patient characteristics and disease status** (ECOG status over time, PSA progression, or radiographic progression or opiate use at time of treatment discontinuation)
Data Needed for Treatment Pathway Models

Asymptomatic/ minimally symptomatic e.g., sipuleucel-T or abiraterone

Symptomatic/Rapid progression e.g., docetaxel

Post-docetaxel e.g., abatzilat or abiraterone or enzalutamide

Death

Effectiveness Inputs
- Time to first-line end/progression
- Time to death (without next-line tx)
- Incidence of toxicities

Utilities
- On-treatment/PFS
- Disutility from toxicities

Effectiveness Inputs
- Time to second-line end/progression
- Time to death (without next-line tx)
- Incidence of toxicities

Utilities
- On-treatment/PFS
- Disutility from toxicities

Effectiveness Inputs
- Time to third-line end/progression
- Time to death
- Incidence of toxicities

Utilities
- On-treatment/PFS
- Disutility from toxicities
- Post-progression

Costs
- Administration costs
- Drug costs
- Toxicities
- Medical follow up
- Symptom management

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Summary

- In mCRPC, the treatment landscape has been quickly changing. With many more treatment options available along the mCRPC disease spectrum, the relevant question for decision makers is identifying the optimal pathways in terms of health outcomes and costs.
- An individual simulation modeling approach can better capture the multiple courses of therapy, apply impacts of drugs to quality of life and survival outcomes, and assign costs.
- It can also evaluate treatment pathways early on, before full implementation of the pathways.
- It can capture the important heterogeneity of the mCRPC population in terms of predictors of survival and treatment benefit (e.g., ECOG, level of pain, number of previous therapies received).
- However, this modeling approach requires individual-level data from at least some trials to inform the prediction equations.