Endpoints, Safety and Benefit

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FDA NMIBC Workshop
I have no financial conflicts
Non-Muscle Invasive Bladder Cancer

What Outcomes Can We Assess?

- Treatment
  - Complete Response
  - Local Progression
- Cystectomy
- Metastasis
- Death

Risk for Muscle Invasion

Symptom and Functional Impacts

TIME

NMIBC
BCG-Refractory
Strength of Efficacy Endpoint Results

• **What** is being Measured? *(Endpoint Selection)*
  – Direct Benefit (Feels/Functions/Survives) considered more meaningful

• **How** accurately is it being measured? *(Measurement Characteristics)*
  – Accuracy of the measure
  – Susceptibility to Bias
  – Accuracy of the Timing of the Event

• **How Much** effect on the endpoint is observed? *(Magnitude of Effect)*
How is the efficacy endpoint measured?

- How much interpretation / subjectivity associated with the event?
  - More interpretation / subjectivity = more risk for bias / variability

  - Delay/Prevention of a Morbid Procedure:
    - rPFS (PCWG-2): Interpret two new lesions on a bone scan
    - PFS: Interpret target lesion increases by 20%
    - Survival: No interpretation required
Many Factors In Decision to Undergo a Procedure

- Clinician’s assessment of risk of disease progression and subsequent morbidity/mortality
- Patient’s willingness to undergo procedure
- Insurance / financial issues
- Other Unknown Factors?
# No Free Lunch: Strengths and Limitations of Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Clinical Meaningfulness</th>
<th>Low Risk of Bias</th>
<th>Feasibility</th>
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</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Tumor Endpoints</td>
<td>+/−</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Clinical Outcome-PRO</td>
<td>+</td>
<td>+/−</td>
<td>+</td>
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<tr>
<td>Clinical Outcome-Reduction in Healthcare Utilization (e.g. Steroid Use, morbid procedure)</td>
<td>+</td>
<td>-</td>
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Delaying Cystectomy- Benefits and Risks

• **BENEFIT** of delaying or avoiding cystectomy
  – Cystectomy is a significantly morbid procedure
  – Delaying or avoiding cystectomy reduces this morbidity

• **RISK** of delaying or avoiding cystectomy
  – The investigational treatment itself has toxicity
  – Delaying a curative treatment might reduce the cure rate
Example: Localized Prostate Cancer

• Incorporating a delay/prevent endpoint for a curative morbid procedure has been discussed before in the localized prostate cancer setting
Localized Prostate Cancer- Outcomes and Approximate Timing

Clinical Outcomes (Morbidity or Mortality)

Biomarkers and Imaging

** 40% of this series had Gleason >=7

Based on Pound et al: JAMA 1999
Trial Challenges for an Active Surveillance Population

• **Efficacy-** Overall survival or metastases (MFS) impractical
• **Efficacy-** Delay/Avoidance of prostatectomy or radiation is meaningful, but introduces potential for bias
• **Acute/subacute safety-** Must be well tolerated in context of surveillance
• **Long term safety-** Could delaying curative treatment reduce cure rate?
Addressing the Issues- Efficacy

• **Issue**
  – Delay/Prevention of prostatectomy (RP) or radiation (XRT) introduces potential for bias

• **Potential Path Forward**
  – Primary Endpoint- Local Progression Free Survival
  – Secondary Endpoint- Delay/Prevention of RP/XRT
  – Comparative Long Term Urinary and Sexual Function
Addressing the Issues- Acute/Subacute Safety

• Issues
  – Acute and Subacute Toxicity of the Intervention must be less than the procedure you are seeking to avoid!

• Potential Path Forward
  – Clinical and patient-reported (PRO) safety and tolerability
  – Acceptable toxicity *in context of an active surveillance control arm*
  – LESS toxicity than the curative treatment you are trying to delay/avoid
Addressing the Issues - Missing Chance for Cure

• **Issues**
  – Potential for delayed harm
    • Reduced cure rate, or increased post surgical relapses

• **Potential Path Forward**
  – Rates of relapse for those who undergo curative RP/XRT
Localized Prostate Cancer Patients Eligible for Active Surveillance

- Surveillance + Intervention
- Surveillance Alone

Primary
- Objective Risk Progression

Secondary
- Curative Therapy (XRT or RP)

LONG TERM FOLLOW UP
Comparative Symptom/Function
Outcomes for Curative Treatments

Acute and Subacute Safety/Tolerability
Delayed Harm
Clinical Benefit:
More than Just the Primary Endpoint

- Efficacy
- Safety
- Clinical Context

Primary and Secondary Endpoints
Example: Metastatic Prostate Cancer-> Abiraterone and *Multiple Efficacy Endpoints*

• COU-302 trial- co-primary rPFS and OS
  – Large statistically significant rPFS advantage
  – Nonsignificant trend for benefit on OS
  – Time to cytotoxic chemotherapy was delayed
  – Time to first opiate use was delayed
  – Time to PRO pain also supportive
  – Time to ECOG decline supportive
  – Favorable safety profile

Low Risk Prostate Cancer is NOT the same as BCG-Refractory Bladder Cancer

NMIBC is different than Low Risk Local Prostate Cancer in many ways:

1. Prognosis if window of cure is missed
2. Morbidity of cystectomy versus prostatectomy
3. Surveillance frequency and morbidity
Take Home Points

- All endpoints have strengths and limitations balancing meaningfulness with objectivity and feasibility
- The primary efficacy endpoint is not the only evidence taken into account in a risk:benefit decision
- Mitigate bias where you can (blinding, objective triggers for clinical events, independent review)
Background
Questions to Panel:

• Is delaying or avoiding cystectomy a useful event to capture as a primary or key secondary endpoint?

• Can objective triggers for cystectomy be agreed upon by urologic community?

• Do patients think this would be a meaningful endpoint?