

Endpoints, Safety and Benefit

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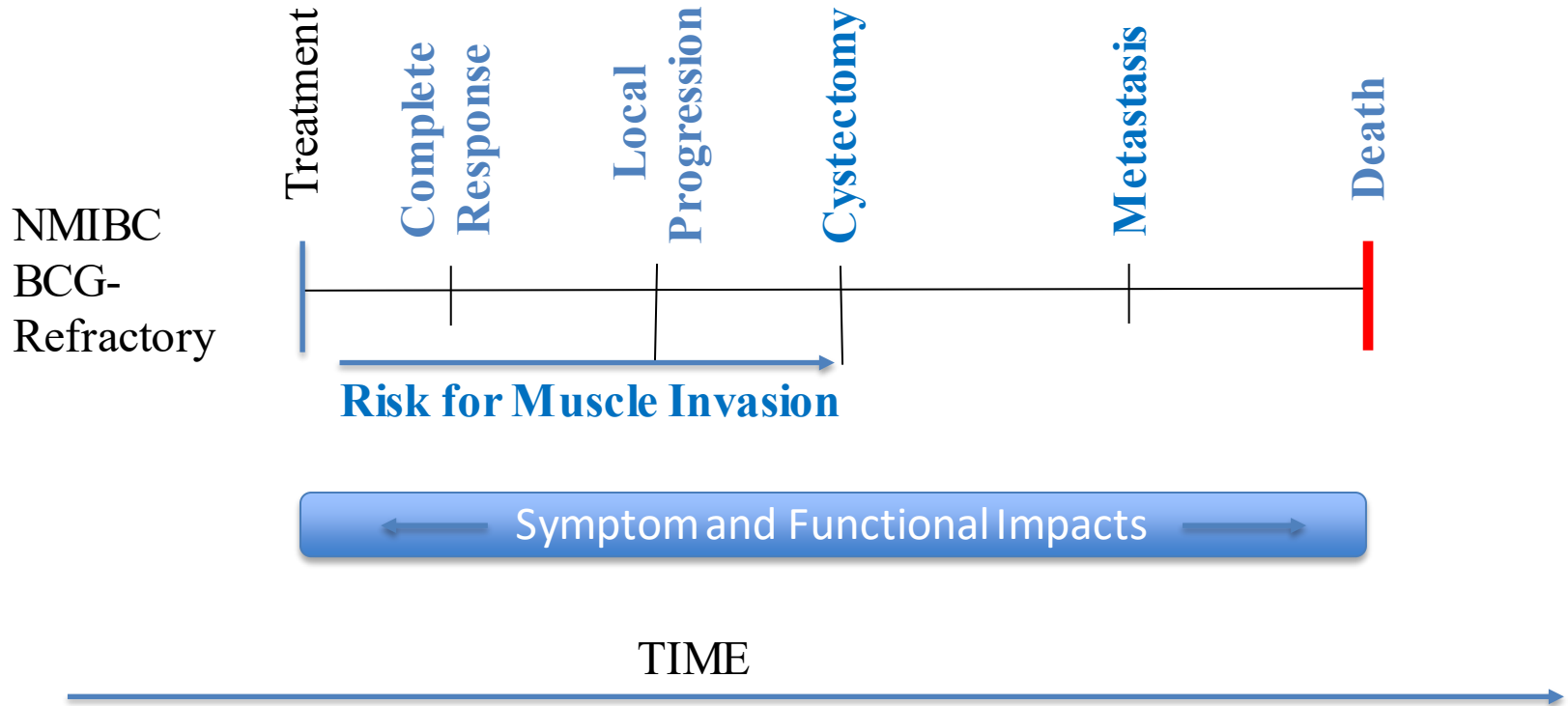
FDA NMIBC Workshop



- I have no financial conflicts

Non-Muscle Invasive Bladder Cancer

What Outcomes Can We Assess?



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

Interpretation / Subjectivity ↑



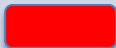













- Delay/Prevention of a Morbid Procedure:
 - rPFS (PCWG-2): Interpret two new lesions on a bone scan
 - PFS: Interpret target lesion increases by 20%
 - Survival: No interpretation required

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

	Clinical Meaningfulness	Low Risk of Bias	Feasibility
Overall Survival			
Tumor Endpoints	 / 		
Clinical Outcome-PRO		 / 	
Clinical Outcome-Reduction in Healthcare Utilization (e.g. Steroid Use, morbid procedure)			

Delaying Cystectomy- Benefits and Risks

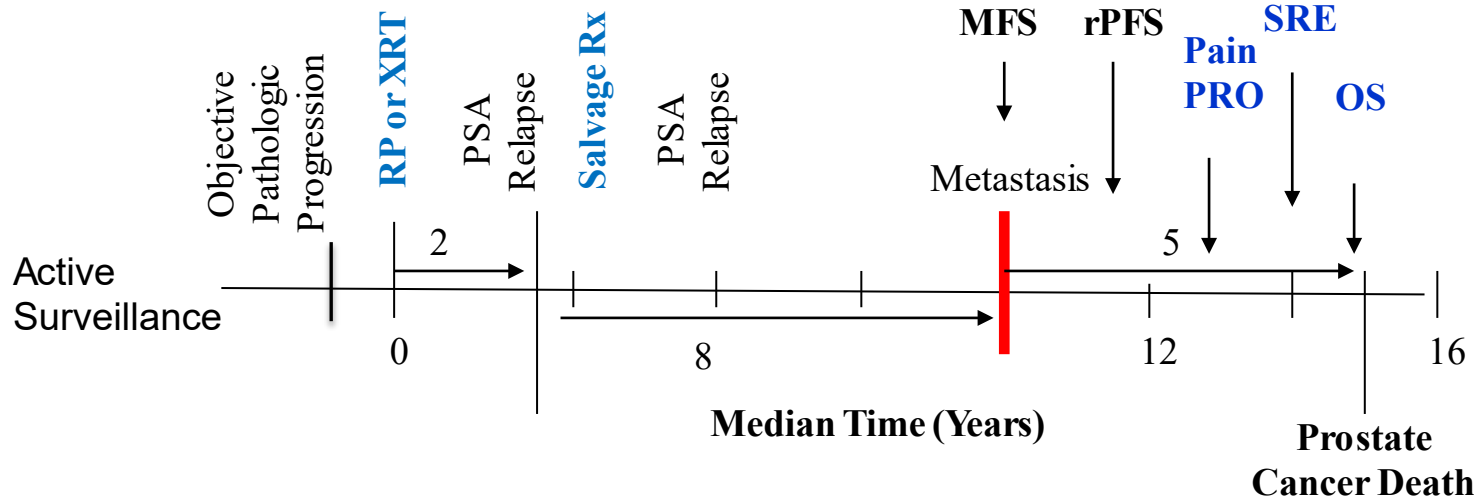
- BENEFIT of delaying or avoiding cystectomy
 - Cystectomy is a significantly morbid procedure
 - Delaying or avoiding cystectomy reduces this morbidity
- RISK of delaying or avoiding cystectomy
 - The investigational treatment itself has toxicity
 - Delaying a curative treatment might reduce the cure 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

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

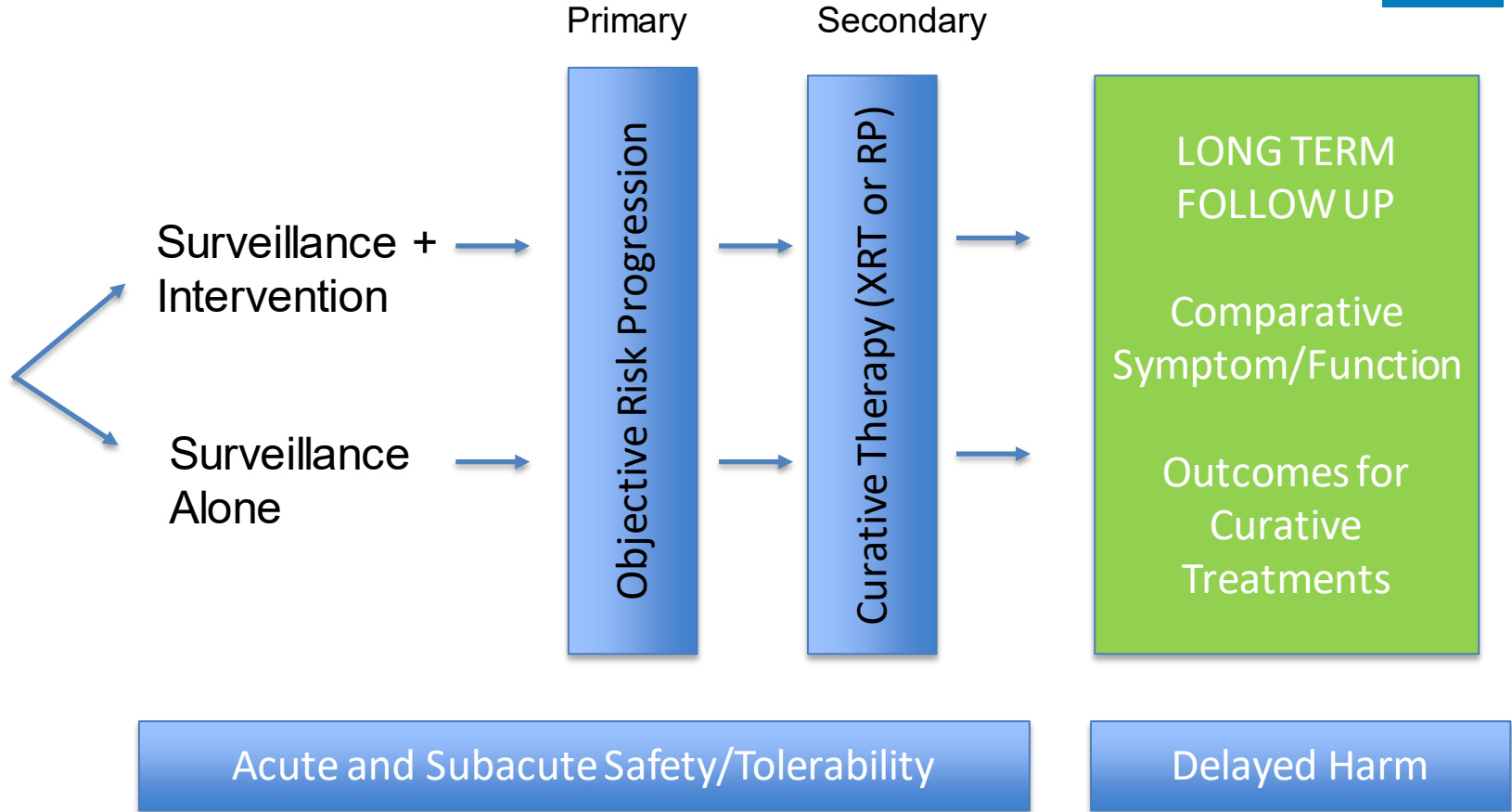
- **Issues**
 - Acute and Subacute Toxicity of the Intervention must be less than the procedure you are seeking to avoid!

- **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**

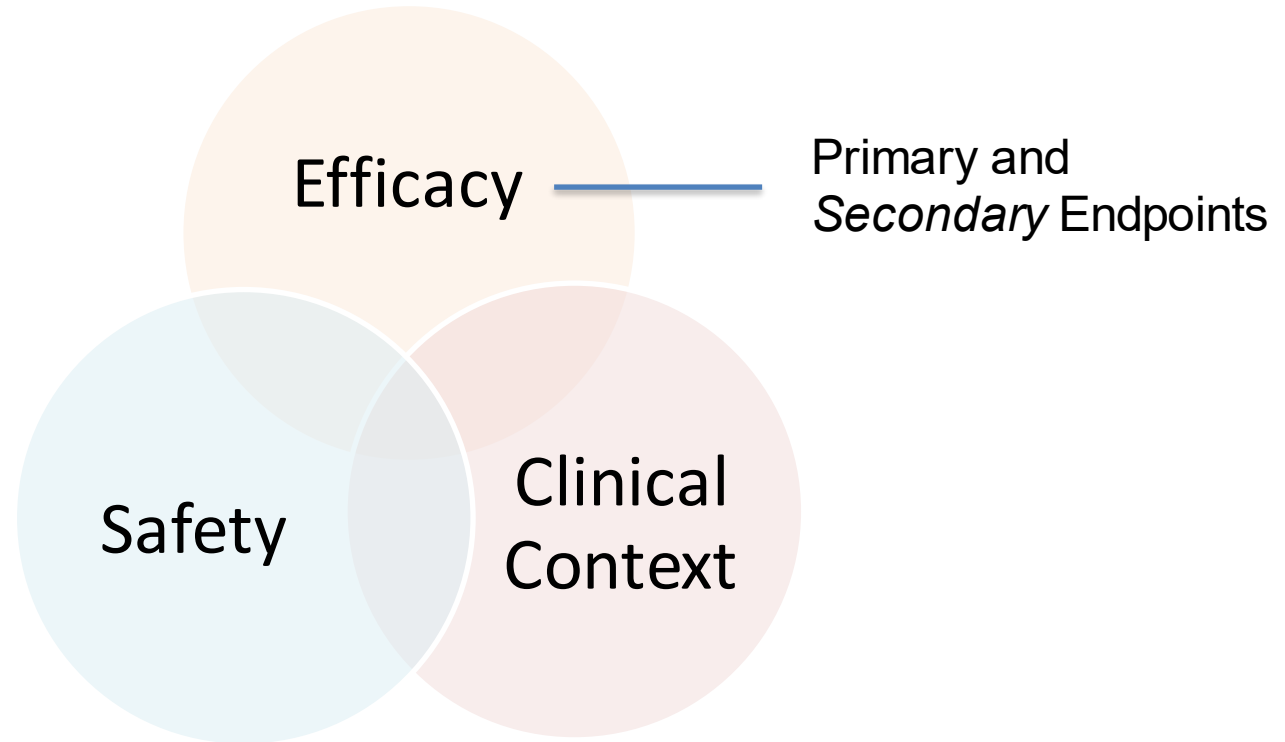
Addressing the Issues- Missing Chance for Cure

- **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



Clinical Benefit: More than Just the Primary Endpoint



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?