Applying the Estimand Framework to High-Risk Non-Muscle Invasive Bladder Cancer Trials: Considerations for Populations with CIS and Papillary Disease
Take Home Messages

• Different clinical questions imply different trial designs and analyses
• Defining the endpoint should be relevant within clinical context
• Estimand thinking is a team sport and requires an iterative process
High-Risk Non-Muscle Invasive Bladder Cancer (NMIBC)

- Frequent recurrence, low risk mortality

<table>
<thead>
<tr>
<th>AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer</th>
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<tbody>
<tr>
<td><strong>Low Risk</strong></td>
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<tr>
<td>LG a solitary Ta ≤ 3cm</td>
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<td>PUNLMP</td>
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LG = low grade  
PUNLMP = papillary urothelial neoplasm of low malignant potential  
HG = high grade  
CIS = carcinoma in situ  
LVI = lymphovascular invasion  
BCG = Bacillus Calmette-Guerin
How is High-Risk NMIBC Treated?

• Goals of therapy to minimize risk of recurrence and disease progression to muscle-invasive and/or metastatic disease
• Complete TURBT
• Six-week induction course of BCG followed by up to 3 years of maintenance
• Cystectomy (or pembrolizumab) for BCG unresponsive disease
Transurethral Resection of Bladder Tumor (TURBT)
### CIS vs. Papillary

#### Similarities of Papillary and CIS
- CIS and papillary may co-exist
- Treated similarly

<table>
<thead>
<tr>
<th>Papillary</th>
<th>CIS</th>
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<tbody>
<tr>
<td>Papillary disease fully resected at baseline</td>
<td>CIS remains present at baseline</td>
</tr>
<tr>
<td>Randomized trial necessary</td>
<td>Single arm trial may be acceptable with complete response (CR) and duration of response (DOR)</td>
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<td>- Potentially curable disease</td>
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<td>- CIS expected to continue to progress to muscle-invasive without treatment</td>
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Different Clinical Questions Imply Different Trial Designs: Two-Trial Approach

1. Patients with high-risk NMIBC with **papillary** disease, resected at baseline
   - **Primary endpoint:** Recurrence-free survival (RFS)
   - BCG + new drug
   - BCG + placebo

2. Patients with high-risk NMIBC with **CIS** at study entry +/- papillary
   - **Primary endpoint:** Complete response (CR) rate
   - **Key secondary endpoint:** Duration of response
   - BCG + new drug
   - BCG + placebo

Source: Adapted from Feng 2021
Different Clinical Questions Imply Different Trial Designs: One-Trial Approach

Patients with **papillary** disease, resected at baseline (70%)

Patients with **CIS** at study entry +/- papillary (30%)

1:1

- BCG + new drug
- BCG + placebo
- BCG + new drug
- BCG + placebo

Primary endpoint: Event-free survival (EFS)

Clinical Question: ?

Source: Adapted from Feng 2021
Estimand Example
One-Trial Approach: Pool CIS and Papillary

**Example Clinical Question:** Does BCG + new drug delay time to first recurrence, progression, persistence of CIS, or death compared to BCG + placebo for patients with CIS (+/- papillary disease) at study entry or patients with papillary disease who have had their disease resected at baseline, regardless of treatment discontinuation or initiating subsequent anti-cancer therapy?

- **Estimand Attributes:**
  - Population: Patients with CIS (+/- resected papillary disease) at study entry or with fully resected papillary disease as defined by protocol inclusion/exclusion criteria
  - Treatments: BCG + new drug vs. BCG + placebo
  - Endpoint: EFS defined as time from randomization to recurrence, progression, persistent CIS (treatment failure), or death
  - Intercurrent Events:
    - Discontinuing study treatment (treatment policy strategy)
    - Initiating subsequent anti-cancer therapy (treatment policy strategy)
  - Population-Level Summary: Hazard ratio
Persistent CIS

- **Definition:** Continued existence of CIS at earliest post-baseline time point if CR not observed at next assessment
- **How Collected:** Cystoscopy or cytology
- **Consequence of persistent CIS:** Move to other treatment options or cystectomy
- **Interpretation Impact:** Unclear interpretation since CIS was already present at baseline

How does timing of a persistent CIS event impact interpretation of EFS?
Timing of Persistent CIS: Example

Patient 1

Randomization → Persistent CIS → CR

Week 12 → Week 24

• **No Event:** If CR at Week 24, assumes we want to evaluate EFS regardless of persistent CIS at Week 12

Patient 2

Randomization → Persistent CIS → Persistent CIS

Week 12 → Week 24

1. **Event at Week 12:** Assumes that persistent CIS is not meaningful before Week 12 vs.
2. **Event at Baseline:** Assumes CIS existed at baseline and there was no response
Timing of Persistent CIS

• **Clinical question:** What is the treatment effect of BCG + new drug relative to BCG + placebo in EFS where persistent CIS is considered treatment failure (event)?

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<thead>
<tr>
<th>Reasons for Event at Baseline</th>
<th>Reasons for Event at Week 12</th>
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<tbody>
<tr>
<td>• Considered treatment failure</td>
<td>• If persistent CIS after 2 inductions cycles with BCG considered BCG unresponsive disease</td>
</tr>
<tr>
<td>• Risk of progression at all time points</td>
<td>• Arbitrary, not consistent with approach to non-BCG therapy</td>
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<tr>
<td>• Less subjectivity as patients may or may not continue treatment after persistent CIS at Week 12</td>
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Considerations Using the One-Trial Approach

- Heterogeneous population, some patients have disease at baseline
- Pooled results may be driven by papillary population
- Challenges with interpreting and defining timing of persistent CIS
- CIS: Complete Response Rate and Duration of Response supportive

Patients with **papillary** disease, resected at baseline (70%)

Patients with **CIS** at study entry +/- papillary (30%)
Discussion

- Unique solid tumor setting due to endpoints and populations
  - Event definitions may also be heterogeneous across trials
- Understanding clinical relevance of statistical details is important when thinking through non-standardized endpoints
  - Statisticians translate assumptions of endpoint definition to clinical context
  - Clinicians and statisticians discuss advantages and limitations of approaches
  - Work together to craft recommendations on trial design and analysis
Take Home Messages

• Different clinical questions imply different trial designs and analyses
• Defining the endpoint should be relevant within clinical context
• Estimand thinking is a team sport and requires an iterative process
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