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

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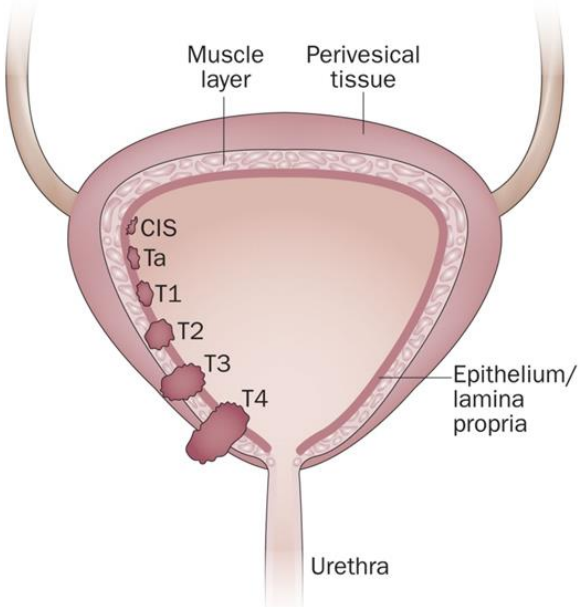
Take Home Messages

- 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)



Mertens, L. S. *et al.* (2014) Landmarks in non-muscle-invasive bladder cancer *Nat. Rev. Urol.* doi:10.1038/nrurol.2014.130

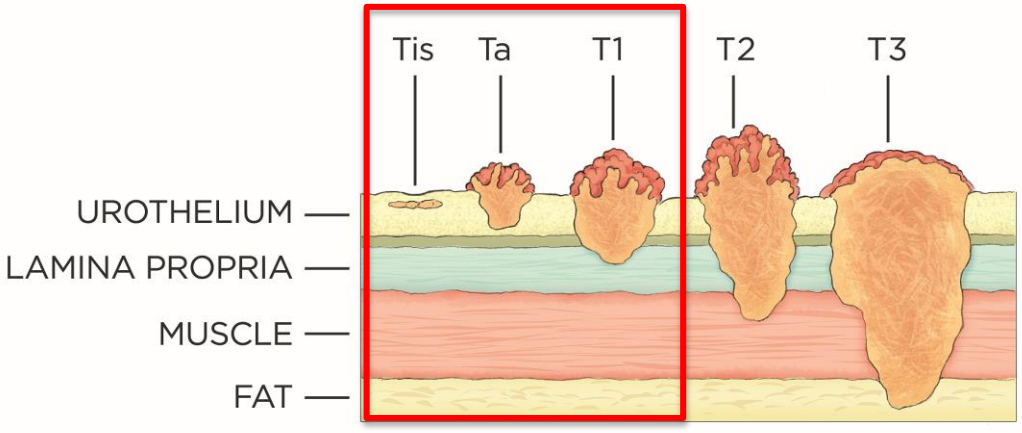
AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer		
Low Risk	Intermediate Risk	High Risk
LG a solitary Ta ≤ 3cm	Recurrence within 1 year, LG Ta	HG T1
PUNLMP	Solitary LG Ta > 3cm	Any recurrent, HG Ta
	LG Ta, multifocal	HG Ta, >3cm (or multifocal)
	HG c Ta, ≤ 3cm	Any CIS
	LG T1	Any BCG failure in HG patient
		Any variant histology
		Any LVI
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		Any HG prostatic urethral involvement

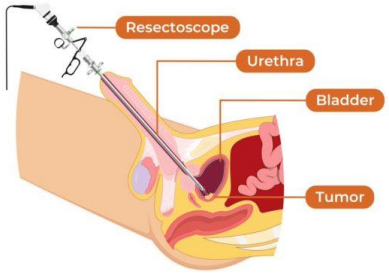
- Frequent recurrence, low risk mortality

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)



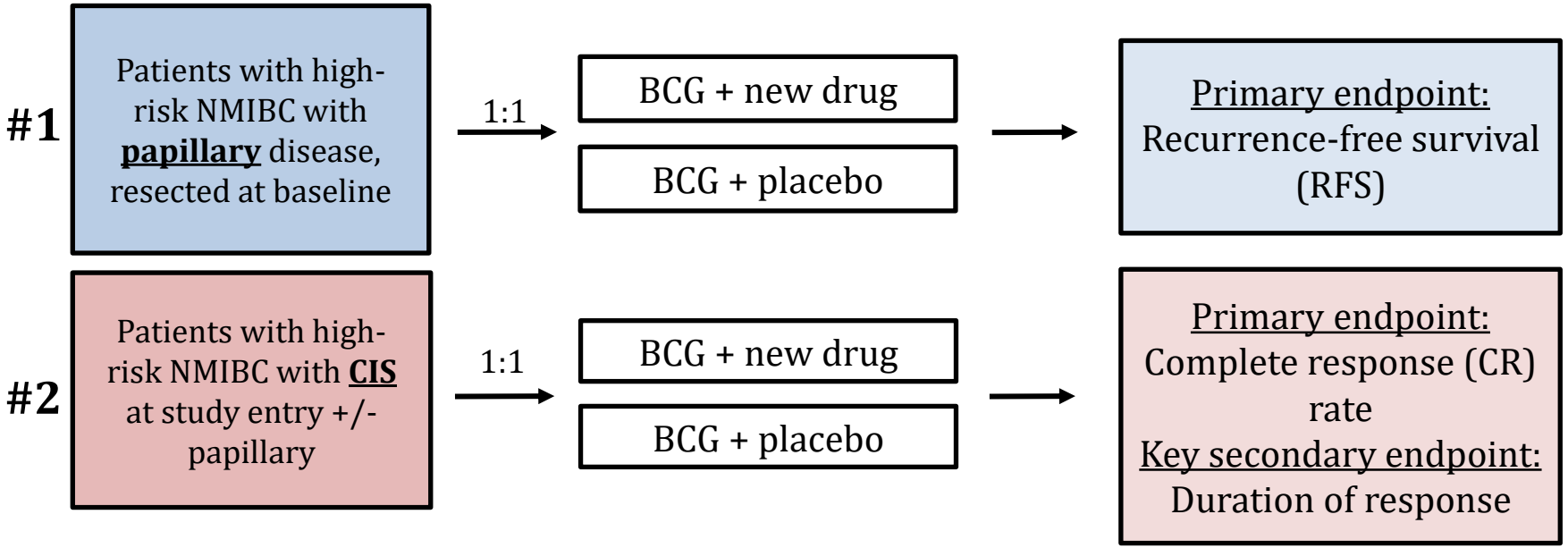


CIS vs. Papillary

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

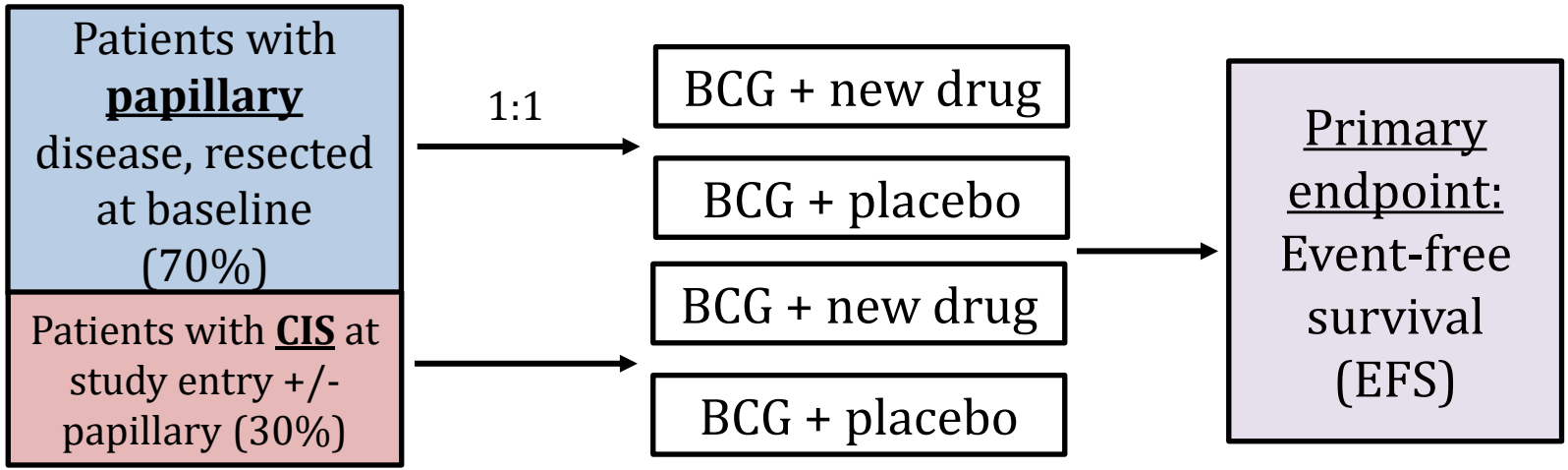
• Papillary disease fully resected at baseline
• Randomized trial necessary
	• CIS remains present at baseline
	• Single arm trial may be acceptable with complete response (CR) and duration of response (DOR)
	  • Potentially curable disease
	  • CIS expected to continue to progress to muscle-invasive without treatment

Different Clinical Questions Imply Different Trial Designs: Two-Trial Approach



Source: Adapted from Feng 2021

Different Clinical Questions Imply Different Trial Designs: One-Trial Approach



Source: Adapted from Feng 2021

Clinical Question: ?

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

Interpret persistent CIS?

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

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

1. **Event at Week 12:** Assumes that persistent CIS is not meaningful before Week 12

   vs.

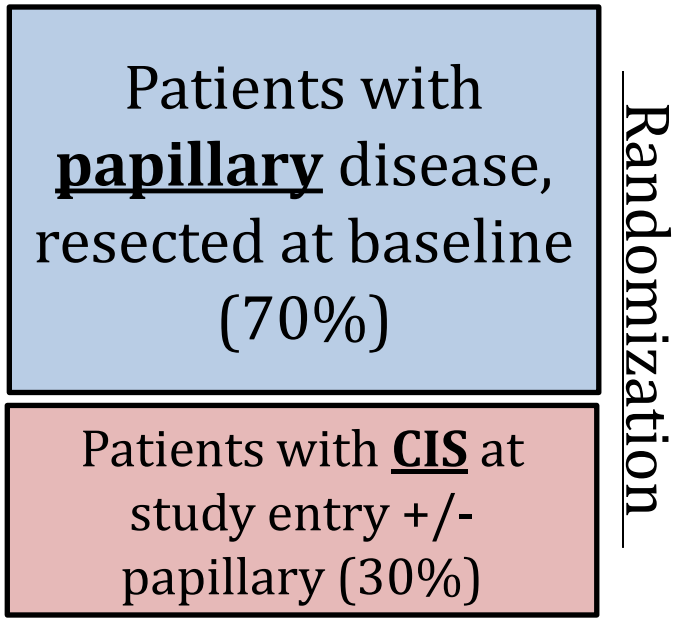
2. **Event at Baseline:** Assumes CIS existed at baseline and there was no response

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)?

Reasons for Event at Baseline	Reasons for Event at Week 12
• Considered treatment failure • Risk of progression at all time points • Less subjectivity as patients may or may not continue treatment after persistent CIS at Week 12	• If persistent CIS after 2 inductions cycles with BCG considered BCG unresponsive disease • Arbitrary, not consistent with approach to non-BCG therapy

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

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

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Acknowledgments

- Yuan-Li Shen
- Erik Bloomquist
- Zhou Feng
- Alexei Ionan
- Elaine Chang
- Chana Weinstock
- Shenghui Tang


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