NMIBC Trial Design for Patients with Papillary Disease and Patients with CIS from Statistical Perspective

Zhou Feng, PhD
FDA/CDER/OTS/OB

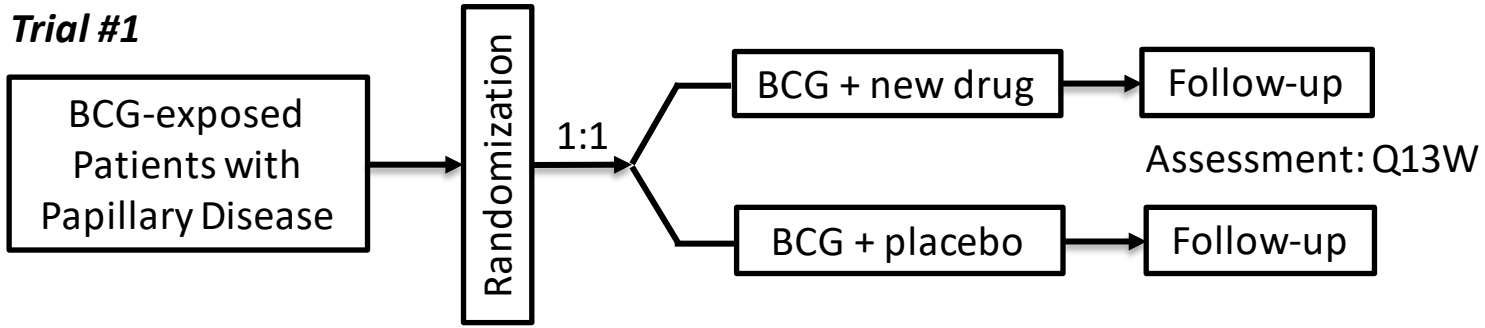
NMIBC Workshop Day 2
11/19/2021

Introduction

- NMIBC patients tend to fall into two pathological groups with different primary objectives: Patients with papillary disease focusing on disease recurrence, and patients with CIS focusing on complete response and the duration of response.
- Trials of NMIBC may include both patients with papillary disease and patients with CIS, however, there is limited consensus whether these two groups should be studied together.
- Key question — ***What are the pros and cons of studying patients with papillary disease and patients with CIS in a 1-trial vs. 2-trial approach?***

Two-Trial Approach – Papillary

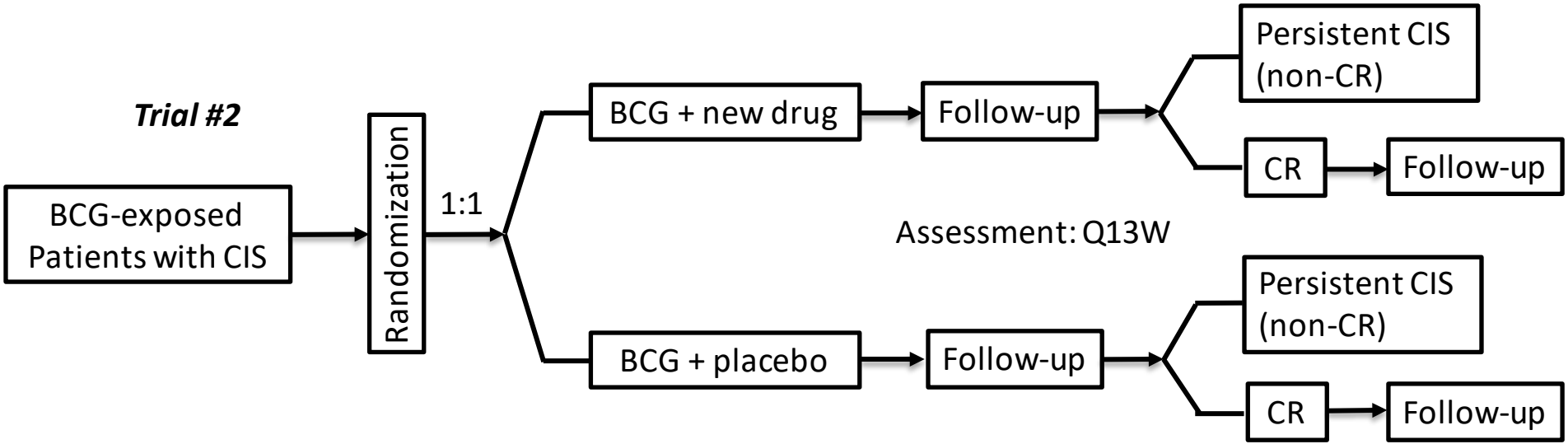
Hypothetical example: To study the efficacy of a new drug on BCG-exposed patients.



Primary endpoint: EFS
2-year accrual & 4-year readout
24-month EFS rate: 52% vs. 40% (HR = 0.7)
Power = 90%, 1-sided alpha = 2.5%

→ Sample size = ~600

Two-Trial Approach – CIS



Primary endpoint: 6-month CR rate
6-month CR rate: 75% vs. 55%
Power = 90%, 1-sided alpha = 2.5%

→ Sample size = ~250

Two-Trial Approach – Pros & Cons

Pros

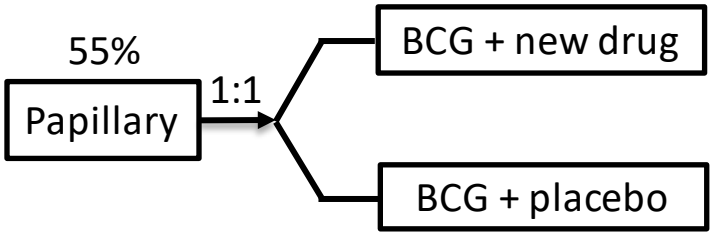
- More straightforward data analyses
  - EFS: log-rank test, hazard ratio (95% confidence interval)
  - CR rate: odds ratio, risk ratio or risk difference (95% confidence interval)
- Clearer interpretation and conclusion: Efficacy needs to be demonstrated in each population
- Statistically powered test in each population
- Routine futility analysis in each trial

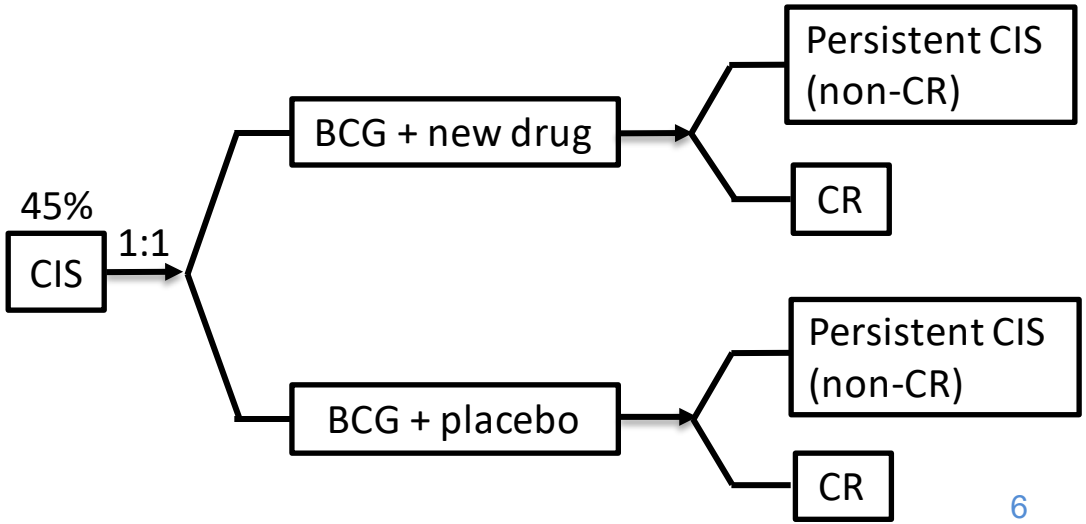
Cons

- Requires a larger sample size

One trial approach – Design

- It is like combining the two trials for analysis.
- EFS will be the primary endpoint.
  - EFS is a typically used endpoint for patients with papillary disease.
  - It is challenging to define EFS for patients with CIS, especially persistent CIS.





One trial approach – Sample Size

- For sample size considerations, assuming same parameters as the two-trial approach, 45% prevalence of patients with CIS, and an EFS of 6 months for patients with persistent CIS, a sample of ~450 patients will be needed.
- This smaller sample size is likely due to a large number of EFS events at 6 months provided by patients with persistent CIS.
- There may be only limited power to show a benefit in each population.
  - ~50% power for patients with papillary disease (EFS)
  - ~70% power for patients with CIS (6-month CR rate)

One-Trial Approach – Pros & Cons

Pros

- Reduction in sample size
- Operational benefits

Cons

- Challenges in handling patients with CIS, especially persistent CIS
- ITT results may be driven by one patient population
- Subgroup analyses may be underpowered
- Challenging to conduct a futility analysis within papillary/CIS population

BCG-unresponsive Population

Consider a head-to-head trial to study the efficacy of a new drug on BCG-unresponsive patients by comparing to a positive control

- Sample sizes follow from previous pattern where the one-trial approach saves overall sample size, however subgroup analyses may be underpowered
- Trial arms may have similar toxicity, so efficacy considerations may need to be adjusted.

60% patients with persistent CIS
6-month CR rate: 70% vs. 50%
24-month EFS rate in patients with papillary disease and patients with CIS reached CR: 52% vs. 40% (HR = 0.7)

→

Two-trial approach:
Patients with papillary disease = ~500
Patients with CIS = ~270

One-trial approach = ~400
Power of subgroup analyses = ~45% and ~80%

Summary

	Two-Trial Approach	One-Trial Approach
Pros	• More straightforward data analysis • Clearer interpretation and conclusion • Statistically powered test for each population • Routine futility analysis	• Reduction in sample size • Operational benefits
Cons	• Requires a larger sample size	• Challenge in handling patients with persistent CIS • ITT results may be driven by one population • Subgroup analyses may be underpowered • Challenging futility analyses


FDA
U.S. FOOD & DRUG
ADMINISTRATION