Regulatory Considerations for Trial Design: BCG-Unresponsive CIS

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Disclosures

- No financial or other disclosures

FDA Approved Treatments for Patients with BCG-Unresponsive CIS

- Valrubicin approved BCG-refractory CIS “for whom immediate cystectomy would be associated with unacceptable morbidity or mortality”
  - CR rate 18%, median DOR ~13.5 months

- Pembrolizumab approved for BCG-unresponsive CIS at high risk of progression
  - CR rate 41%, median DOR ~16 months

Considerations for BCG-Unresponsive CIS

- No currently accepted standard of care non-cystectomy therapies after BCG
- BCG-unresponsive patients are at high risk of progression
- Radical cystectomy is associated with significant morbidity and mortality
- Lack of alternative treatment options for patients who refuse or are ineligible for surgery
- A durable complete response is a measure of clinical benefit in this setting
  - Delay or stop progression→ delay or avoid cystectomy→ delay or avoid morbidity/mortality → clinically meaningful

Defining Clinical Benefit: Expert Opinion

- FDA and AUA workshop, May 6, 2013, San Diego, CA*
  - Single-arm trial could provide sufficient benefit
  - BCG-refractory CIS: CR rate of 40-50% at 6 months and a durable response rate of at least 30% for 18-24 months...”
- Recommendations from International Bladder Cancer Group†
  - BCG-unresponsive CIS: CR rate of 50% at 6 months and durable response rates of 30% at 12 months and 25% at 18 months clinically meaningful

*Jarow et al, Urology 2014
†Kamat et al, JCO 2016

FDA Guidance: BCG-Unresponsive NMIBC

- Single arm trial appropriate where randomized trial is unethical or not feasible
- Randomizing BCG-unresponsive patients to placebo or minimally effective drug raises ethical concerns
- Single arm trials appropriate because “currently, no effective medical therapies are available and the only alternative is radical cystectomy”
- If effective therapies become available, “a randomized trial may be appropriate”

FDA Guidance for Industry: BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment

ODAC on Pembrolizumab for NMIBC

- Assenting opinions:
  - Responses clinically meaningful in patients who want to delay cystectomy and have another option for treatment
  - Patient-physician can have informed discussion re: benefit-risk
- Dissenting opinions:
  - Unclear clinical meaningfulness of demonstrated CR and DOR
  - Follow up duration too short
  - Systemic toxicity concerns
  - Deferral of cystectomy resulting in older or more frail patient at surgery
- 9-4 vote in favor of CR/DOR representing favorable risk/benefit profile

Oncologic Drugs Advisory Committee (ODAC) Meeting: December 17, 2019

Trial Design Considerations

	Single Arm Trials	Randomized Trials
Benefits	• Shorter completion time • Smaller sample size • Early efficacy signal detection	• Minimize bias • Allow evaluation of time to event endpoints • Robust safety characterization
Limitations	• Possible selection bias • Comparison to historical control can be problematic • Distinguishing adverse events due to drug vs. disease can be difficult	• Takes longer to complete trial • Potential loss of equipoise when early activity noted • Time to event endpoints (e.g. PFS, RFS, etc.) may be confounded by censoring methods

FDA Guidance for Industry: Clinical Trials Endpoints for the Approval of Cancer Drugs and Biologics

Single Arm Trials in Patients with BCG-Unresponsive CIS

- Variability in trial procedures can bias interpretation of trial results
  - Biopsy for erythematous lesions at investigator discretion
  - Confirmation of presence of baseline disease
  - Prior BCG received
  - Detection methods (blue light, narrow band, etc.)

- Randomization avoids systematic differences with respect to known and unknown variables that could affect outcomes

FDA Guidance for Industry: E10, Choice of Control Group and Related Issues in Clinical Trials

Selection Bias and Historical Control

- Selection bias: Sample selection may not represent target population
  - Heterogeneity within patient population
  - Incompletely understood disease characteristics
- Historical Control: Cross trial comparisons can be misleading
  - Differing study conduct, duration of treatments, missing data, etc.
  - Standard of practice and patient populations enrolled change over time
  - Must ensure appropriate historical control to evaluate results
- Randomization can mitigate these issues by
  - Accounting for selection bias
  - Balancing known and unknown prognostic factors
  - Enabling evaluation of observed treatment effect relative to chance

Sullivan & Keyes-Elstein. Nature Reviews Rheumatology 2020

Minimizing Bias in Single Arm Trials: BCG-Unresponsive CIS

- Protocol should specify bladder mapping and biopsy triggers
- Presence of baseline disease and prior BCG received should be adequately documented
- Detection method used at baseline should be used throughout trial
- Central pathology review
- Need adequate number of patients with mature follow up
  - # of patients depends on several factors
  - Should allow for precise estimation of the treatment effect
  - Generally, at least 12 months follow up after CR is recommended

Randomized Trials: BCG Unresponsive CIS

- There is no comparative efficacy requirement
- Several control therapies may be acceptable
- Comparator does not have to be FDA approved
- Considerations for comparator arm:
  - If being used by community, may be considered as a control
  - What would the patient have gotten if there was no investigational agent?
  - Equipoise should exist between arms
  - Can consider 2 to 1 randomization to investigational agent
  - Consider physician's choice control arm

FDA Guidance for Industry: E10, Choice of Control Group and Related Issues in Clinical Trials

Time to Event Endpoints: BCG-Unresponsive CIS

- Results of time to event endpoints in single arm trials are uninterpretable
  - Results may be due to differences in patient, disease, or other factors
- Time to event endpoints can be assessed in randomized trials
  - Progression-free survival, recurrence-free survival, etc.
- Can't evaluate recurrence in patients with CIS if disease still present
- Use of RCTs may allow for more clinically meaningful outcomes to be assessed in BCG-unresponsive CIS

FDA Guidance for Industry: Clinical Trials Endpoints for the Approval of Cancer Drugs and Biologics

Single Arm vs. Randomized Trials: BCG-Unresponsive CIS

- Single arm trial designs should consider:
  - Sources of bias should be minimized
  - Substantial variability in trial conduct can adversely affect interpretation of results
  - Can’t assess time to event endpoints
  - Adequate safety data needed to characterize benefit-risk
- Randomized trials appear feasible and should consider
  - Comparator doesn’t need to be FDA approved
  - Equipoise should exist between arms
  - Investigator’s choice may be appropriate
  - Allows for robust safety characterization
  - Time to event endpoints can be assessed

Discussion Points

- Assessment of CR and duration of follow up in single arm trials should be reliable
  - What are the challenges in single arm trials and how can bias be minimized?
- Single arm and randomized trial designs each have benefits and drawbacks
  - What are the challenges to an RCT and how can these be overcome?
- There may be more than one appropriate comparator arm
  - What comparators may be reasonable and for what duration?

Thank You

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