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”
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
Trial Design Considerations

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

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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