FDA Clinical Trial Design for Non-Muscle Invasive Bladder Cancer Workshop

BCG-Naïve Clinical Trial Designs

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BCG-Naïve NMIBC Outcomes

**EORTC 30962**
(n=338, full-dose BCG arm, 3-yrs maintenance)
- 1-yr RFS ~ 75%
- 2-yr RFS ~ 62%
*Larger sample size, No CIS patients*

**MMC CHT vs BCG**
(n=95, full-dose BCG arm, 1-yr maintenance)
- 1-yr RFS ~ 75%
- 2-yr RFS ~ 65%
*Smaller samples size, 22% w/CIS*

Arends TJH et al, Eur Urol 2016;69:1046-52
BCG-Naïve NMIBC – Most Recent FDA Guidance


Development of Systemic and Topical Drugs to Treat Non-muscle Invasive Bladder Cancer


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Abstract: There are few approved drugs available for the treatment of patients with non-muscle invasive bladder cancer (NMIBC) and none have been approved in the twenty-first century. Four drugs, ifosfamide in 1959, BCG Tice in 1989, BCG Connaught in 1990, and mitomycin in 1996, have been approved for the treatment of NMIBC. In addition, these four agents are not commonly used off label as an intravesical treatment for NMIBC. New drugs are needed for the management of NMIBC. This article outlines important aspects of the design and conduct of clinical trials to develop new therapies for these tumors and to obtain marketing approval. It includes a discussion of the patient population, BCG-unresponsive disease, and the appropriate endpoints for drug approval. It is hoped that this article will spur drug development in NMIBC within the Center for Drug Evaluation and Research at the Food and Drug Administration.

Keywords: Non-muscle invasive bladder cancer, drug development, clinical trial design

INTRODUCTION

Non-muscle invasive bladder cancer (NMIBC) is a localized disease of the bladder urothelium generally managed with surgical excision and/or intravesical therapies. The main goals of these therapies are to prevent recurrence and progression of the patient’s bladder cancer. More effective drugs and drugs that are active in refractory patients are needed in NMIBC. This article outlines important aspects of the design and conduct of the clinical trials necessary to obtain marketing approval.

PATIENT POPULATION

Non-muscle invasive bladder cancer includes the following clinical stages of disease:

- Ta: Non-invasive papillary cancer
- T1: Tumor invades the subepithelial connective tissue
- Tis: Carcinoma in situ

Among patients with bladder cancer, approximately 45% present with Ta, 24% with T1, and 19% with Tis. The remainder of the patients present with ≥T2 disease (muscle-invasive bladder cancer) [12]. To fully establish the tumor stage, it is important that the biopsy specimen contain muscle tissue. To this end, patients who have undergone resection of a T1 lesion should undergo biopsy of the base of the lesion before study entry to confirm the absence of muscle-invasive risk of progression such as patients with low-risk and possibly intermediate-risk disease. For intermediate- and high-risk disease, a randomized superiority trial against an appropriate active control or a randomized trial in which the experimental therapy is added to the standard of care (e.g., BCG ± experimental therapy) is recommended. For example, patients with persistent/recurrent disease after a single induction course of BCG could be randomized to additional BCG vs. experimental therapy or to BCG ± experimental therapy. In patients with BCG-unresponsive disease, radical cystectomy should not be unduly delayed while awaiting a response to an experimental agent.

Single-arm trials may be considered when an appropriate control does not exist (e.g., patients with BCG-unresponsive disease). The statistical analysis plan...
BCG-Naïve NMIBC – Design #1
Novel Tx vs BCG

- BCG-Naïve NMIBC
- Novel Tx
- SOC BCG
- 1° Endpoint - EFS

R
BCG-Naïve NMIBC – Design #1
Novel Tx vs BCG

- IR and HR vs HR only
- Uniform PreTx staging
- Photodx staging
- CIS vs CIS+Pap vs Pap

- SOC BCG Strains
- BCG Supply
- Maintenance Tx

- Qualifying Events
  - HG EFS
  - UTUC Events?
  - Superior vs Noninferior
  - Relevant EFS Changes
  - Toxicity
BCG-Naïve NMIBC – Design #1 Novel Tx vs BCG: Current and Planned Trials

S1602 – BCG PRIME
PI: Svatek
N=969

HR BCG-Naïve NMIBC

R

Tokyo BCG

SQ Prime + Tokyo BCG

SOC BCG

1° Endpoint - TTHGR

EA8212 – BRIDGE
PI: Kates
N=870

HR BCG-Naïve NMIBC

R

Gem/Doc

SOC BCG

1° Endpoint - EFS

• Stratification
  • Age < 75 vs > 75
  • Ta vs T1 vs CIS vs Ta/T1 + CIS
• Noninferiority Design
  • Margin 1.34 (Tokyo vs SOC)
  • 1 yr HGEFS 68% vs 75%
  • 84% power
  • Margin 1.40 (Prime + Tokyo vs Tokyo)
  • 1 yr HGEFS 81% vs 75%
  • 83% power

BCG-Naïve NMIBC – Design #2
Novel Tx + BCG vs BCG
BCG-Naïve NMIBC – Design #2
Novel Tx + BCG vs BCG

- BCG-Naïve NMIBC
- Novel Tx + BCG
- Novel Tx + Reduced Maintenance BCG
- SOC BCG
- 1° Endpoint - EFS
BCG-Naïve NMIBC – Design #2
Novel Tx + BCG vs BCG

- Qualifying Events
- HG EFS
- UTUC Events?
- Superior EFS Changes
- Toxicity Profile
- PROMs

https://clinicaltrials.gov/ (accessed 10/15/21)
BCG-Naïve NMIBC – Design #2 Novel Tx + BCG vs BCG: Current and Planned Trials

POTOMAC
N=1020

HR BCG-Naïve NMIBC → SOC BCG → Durvalumab + BCG → 1st Endpoint EFS

CREST
N=999

HR BCG-Naïve NMIBC → SOC BCG → Sasanlimab + BCG → 1st Endpoint EFS

KEYNOTE-676
N=1525

HR BCG-Naïve NMIBC → SOC BCG → Pembrolizumab + BCG → 1st Endpoint CIS CR rate / EFS

ALBAN
N=516

HR BCG-Naïve NMIBC → SOC BCG → Atezolizumab + BCG (1-yr only) → 1st Endpoint - EFS

https://clinicaltrials.gov/ (accessed 10/15/21)
BCG-Naïve NMIBC – Design #2 Novel Tx + BCG vs BCG: Current and Planned Trials

- None require CIS
- All combine Systemic anti-PD-(L)1 Tx w/BCG
- All aim for Superior EFS (1 w/CIS CR rate co-1°)
- All require BCG in all arms

https://clinicaltrials.gov/ (accessed 10/15/21)
BCG-Naïve NMIBC – Design #3 Single Arm Novel Tx Accelerated Approval

BCG-Naïve NMIBC → Novel Non-BCG Tx → 1º Endpoint CIS CR rate
BCG-Naïve NMIBC – Design #3 Single Arm Novel Tx Accelerated Approval

- Possible pathway during BCG supply shortages?
- Safety and Efficacy required 1st in BCG-unresponsive NMIBC
- Appropriate Efficacy Metric?
Summary

• Accepted BCG-naïve Trial Designs include:
  – Novel Tx vs BCG
  – BCG + Novel Tx vs BCG

• Trials with practice changing potential are ongoing that incorporate
  – Non-inferiority designs
  – Systemic PD-(L)1 + BCG regimens
  – Reduced BCG maintenance arm

• Need for alternative BCG-strains and acceptable non-BCG alternatives remains high
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