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

BCG-Naïve Clinical Trial Designs

Noah M. Hahn MD

Professor of Oncology and Urology

Johns Hopkins Greenberg Bladder Cancer Institute

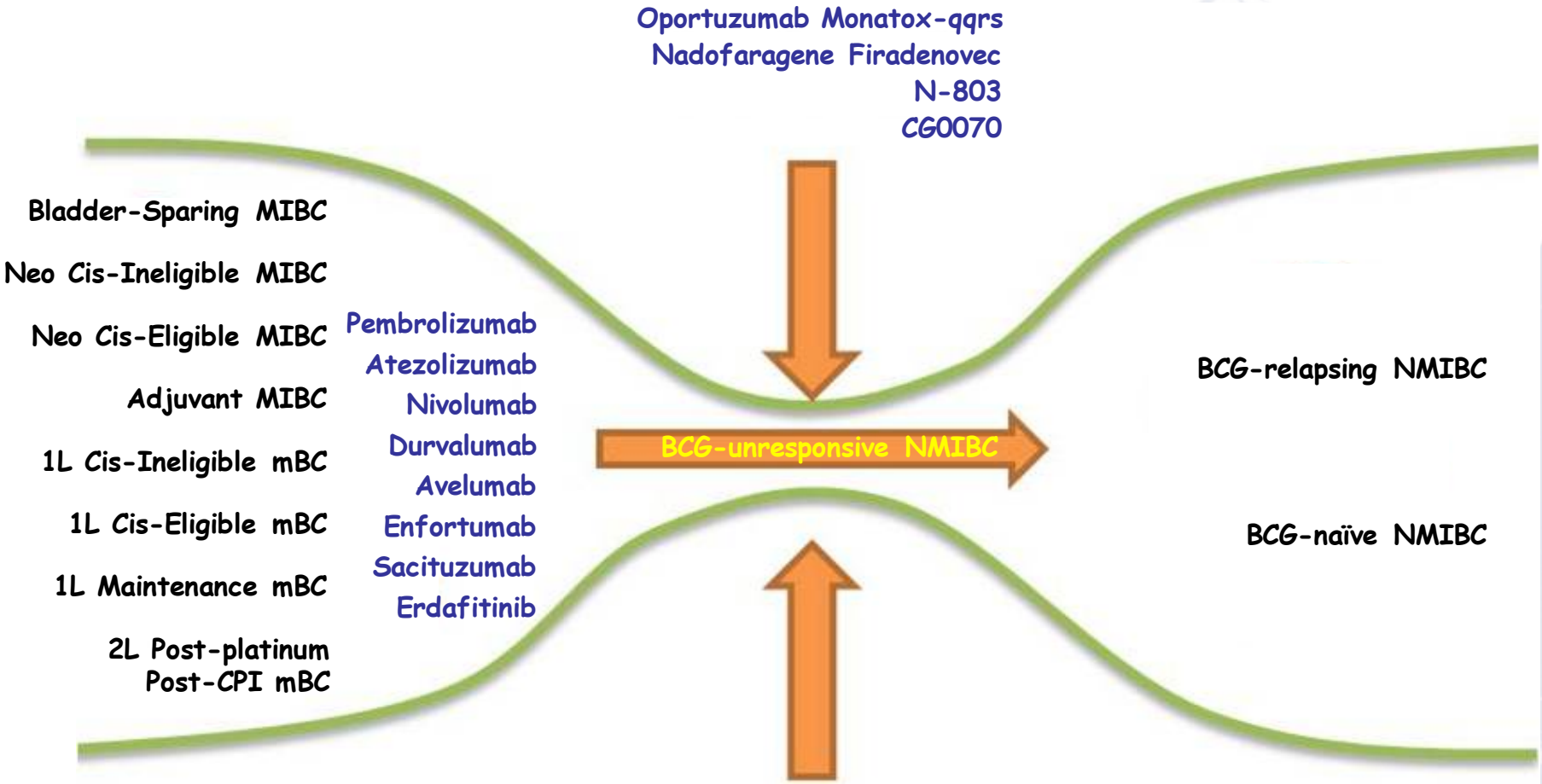
JOHNS HOPKINS MEDICINE

Disclosures

- **Research to Institution**
  - AstraZeneca, Incyte, Inovio, Genentech, BMS, Merck, Seattle Genetics, Astex, Pieris, HTG Molecular Diagnostics
- **Consulting**
  - Merck, Genentech, GlaxoSmithKline, Ferring, Champions Oncology, EMD Serono, Health Advances, Keyquest Health, Guidepoint Global, Seattle Genetics, Incyte, Mirati, TransMed, CicloMed, Janssen, Pfizer, Boehringer Ingelheim, RemeGen, BioGears
- **Honoraria**
  - Bladder Cancer Academy, Large Urology Group Practice Association, Creative Educational Concepts

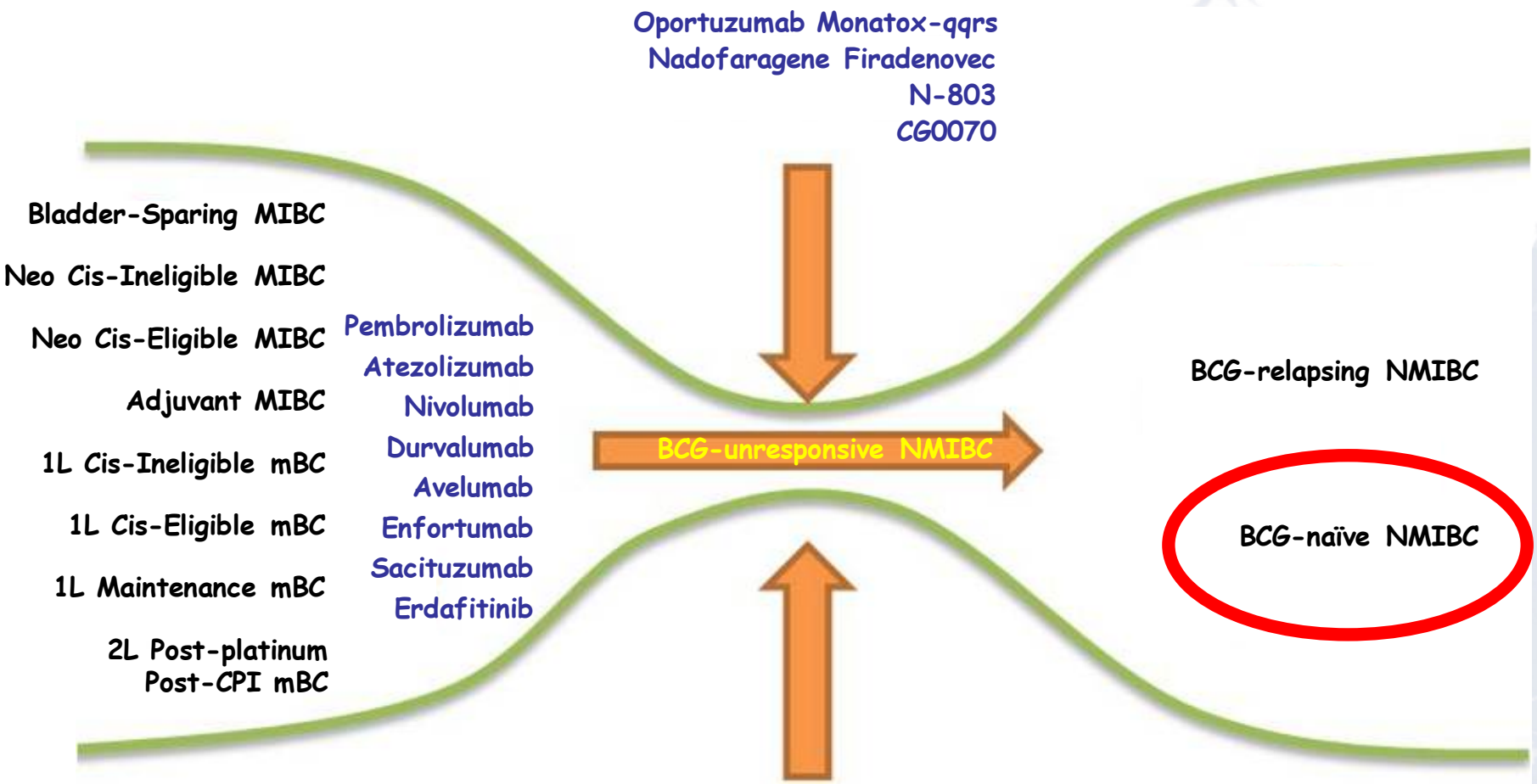
JOHNS HOPKINS MEDICINE

NMIBC Drug Development



JOHNS HOPKINS MEDICINE

NMIBC Drug Development

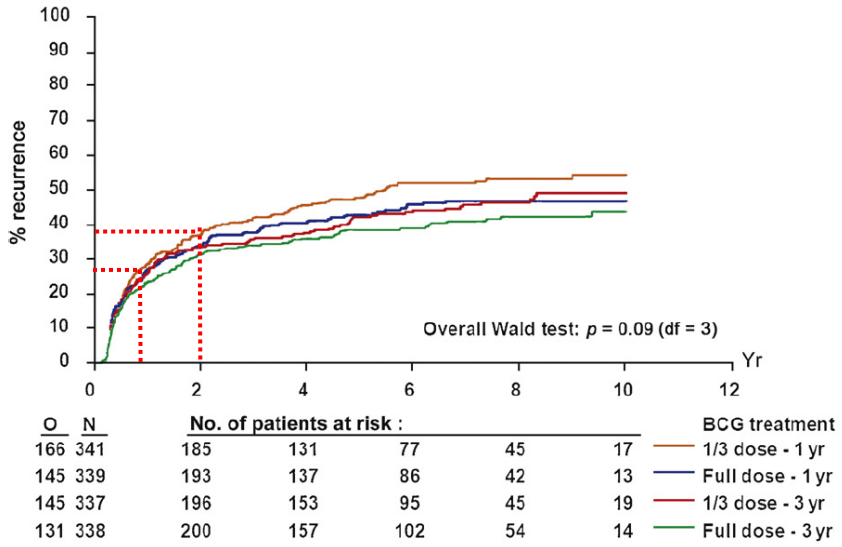


JOHNS HOPKINS MEDICINE

BCG-Naïve NMIBC Outcomes

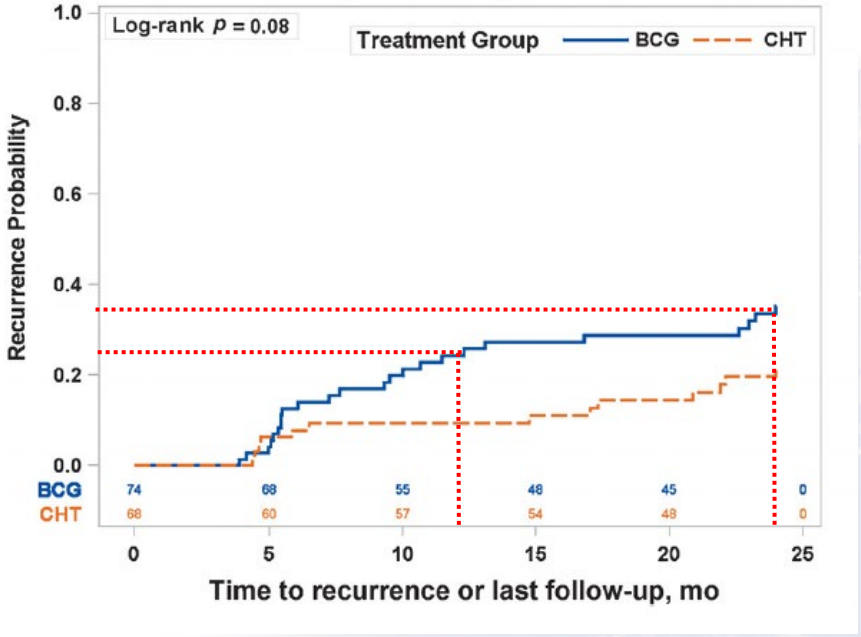
EORTC 30962
(n=338, full-dose BCG arm, 3-yrs maintenance)

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)

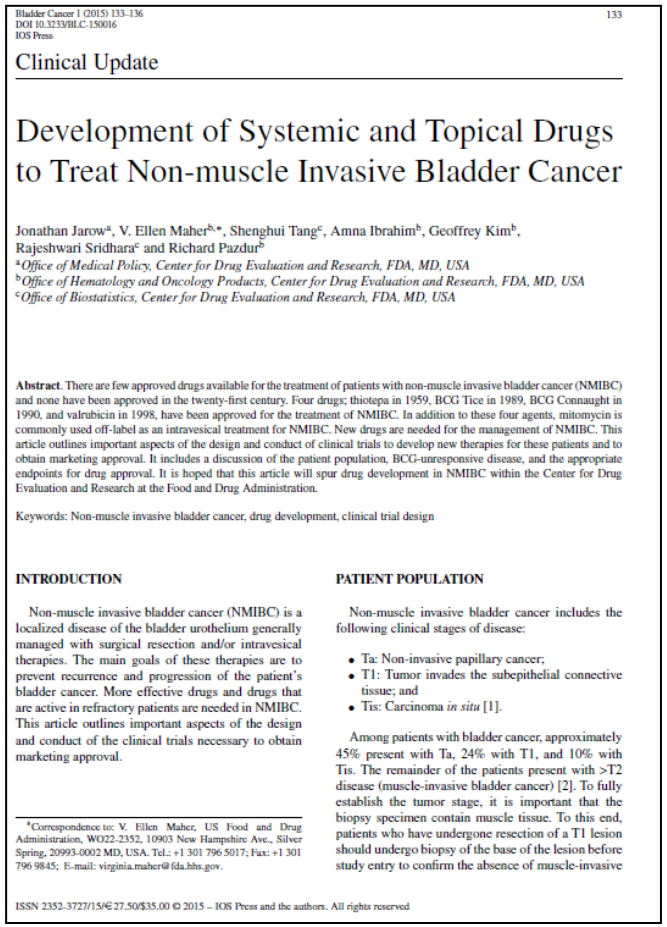
1-yr RFS ~ 75%
2-yr RFS ~ 65%
Smaller samples size, 22% w/CIS



Oddens J et al, Eur Urol 2013;63:462-72
Arends TJH et al, Eur Urol 2016;69:1046-52

JOHNS HOPKINS MEDICINE

BCG-Naïve NMIBC – Most Recent FDA Guidance



Bladder Cancer 1 (2015) 133–136
DOI 10.3233/BLC-150016
IOS Press

Clinical Update

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

Jonathan Jarow[a], V. Ellen Maher[b,*], Shenghui Tang[c], Amna Ibrahim[b], Geoffrey Kim[b], Rajeshwari Sridhara[c] and Richard Pazdur[b]
[a]*Office of Medical Policy, Center for Drug Evaluation and Research, FDA, MD, USA*
[b]*Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, FDA, MD, USA*
[c]*Office of Biostatistics, Center for Drug Evaluation and Research, FDA, MD, USA*

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; thiotepa in 1959, BCG Tice in 1989, BCG Connaught in 1990, and valrubicin in 1998, have been approved for the treatment of NMIBC. In addition to these four agents, mitomycin is 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 patients 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 resection 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.

*Correspondence to: V. Ellen Maher, US Food and Drug Administration, WO22-2352, 10903 New Hampshire Ave., Silver Spring, 20993-0002 MD, USA. Tel.: +1 301 796 5017; Fax: +1 301 796 9845; E-mail: virginia.maher@fda.hhs.gov.

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; and
- Tis: Carcinoma *in situ* [1].

Among patients with bladder cancer, approximately 45% present with Ta, 24% with T1, and 10% with Tis. The remainder of the patients present with >T2 disease (muscle-invasive bladder cancer) [2]. 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

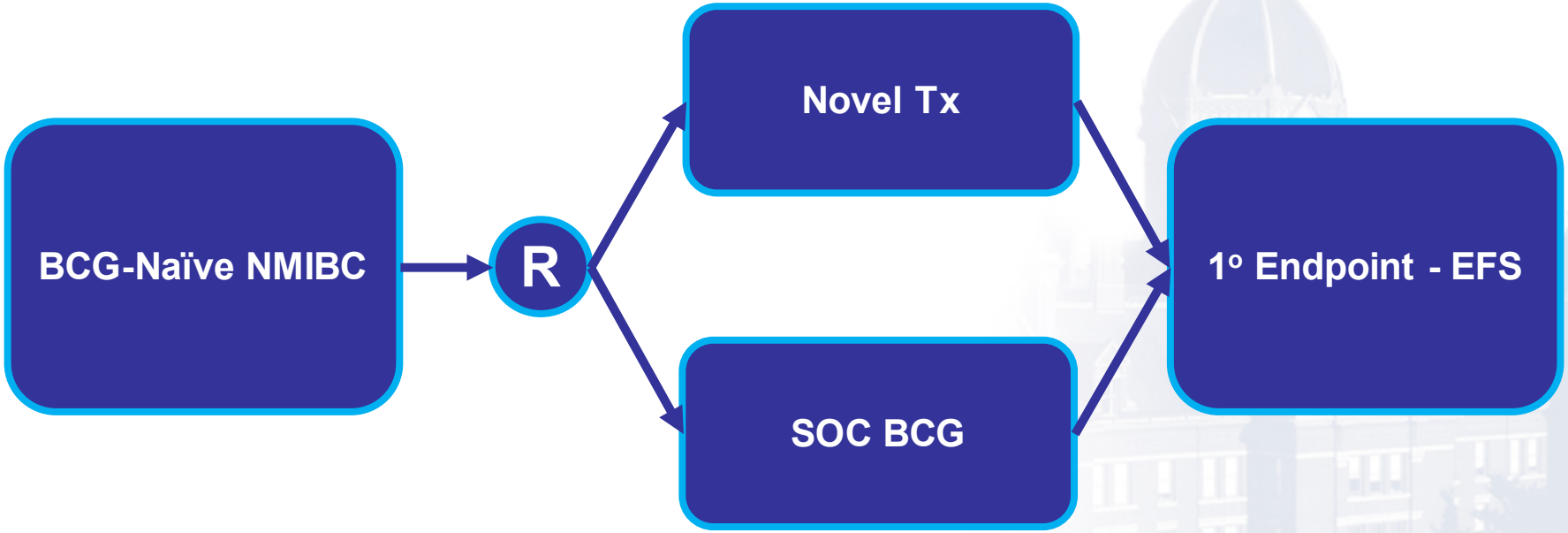
risk of progression such as patients with low-risk and possibly intermediate-risk disease. For intermediate- and high-risk disease, a randomized superiority trial against an appropriate active control or a randomized trial in which the experimental therapy is added to the standard of care (e.g., BCG ± 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

Jarrow J et al, Bladder Cancer 2015;1:133-36

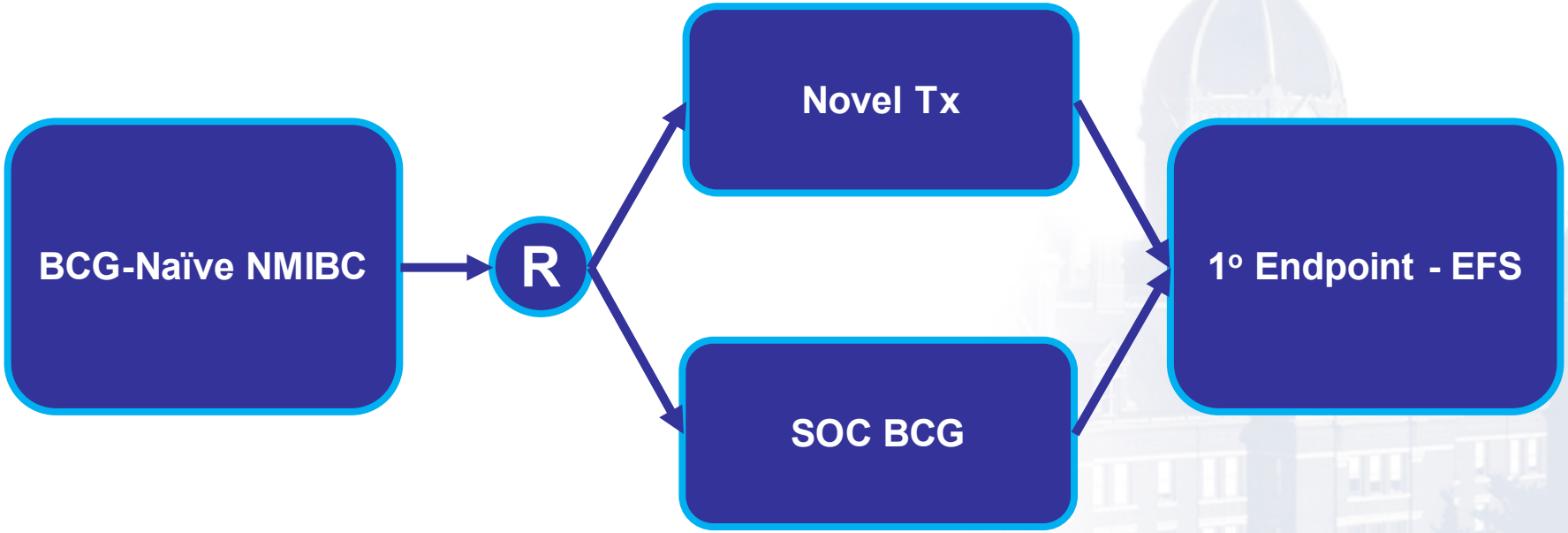
JOHNS HOPKINS MEDICINE

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



JOHNS HOPKINS MEDICINE

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



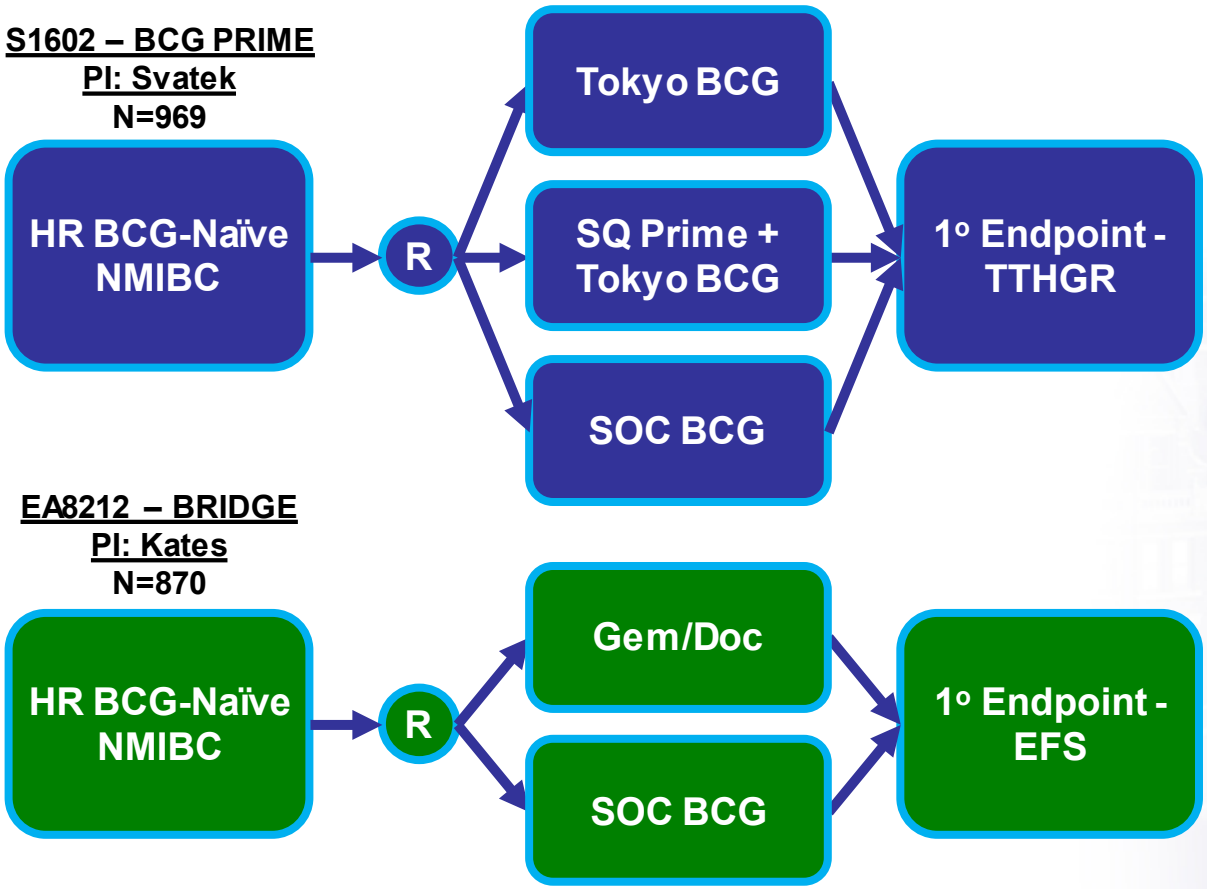
- IR and HR vs HR only
- Uniform PreTx staging
- Photodx staging
- CIS vs CIS+Pap vs Pap

- SOC BCG Strains
- BCG Supply
- Maintenance Tx

- Qualifying Events
  - HG EFS
  - UTUC Events?
- Superior vs Noninferior
- Relevant EFS Changes
- Toxicity

JOHNS HOPKINS MEDICINE

BCG-Naïve NMIBC – Design #1 Novel Tx vs BCG: Current and Planned Trials

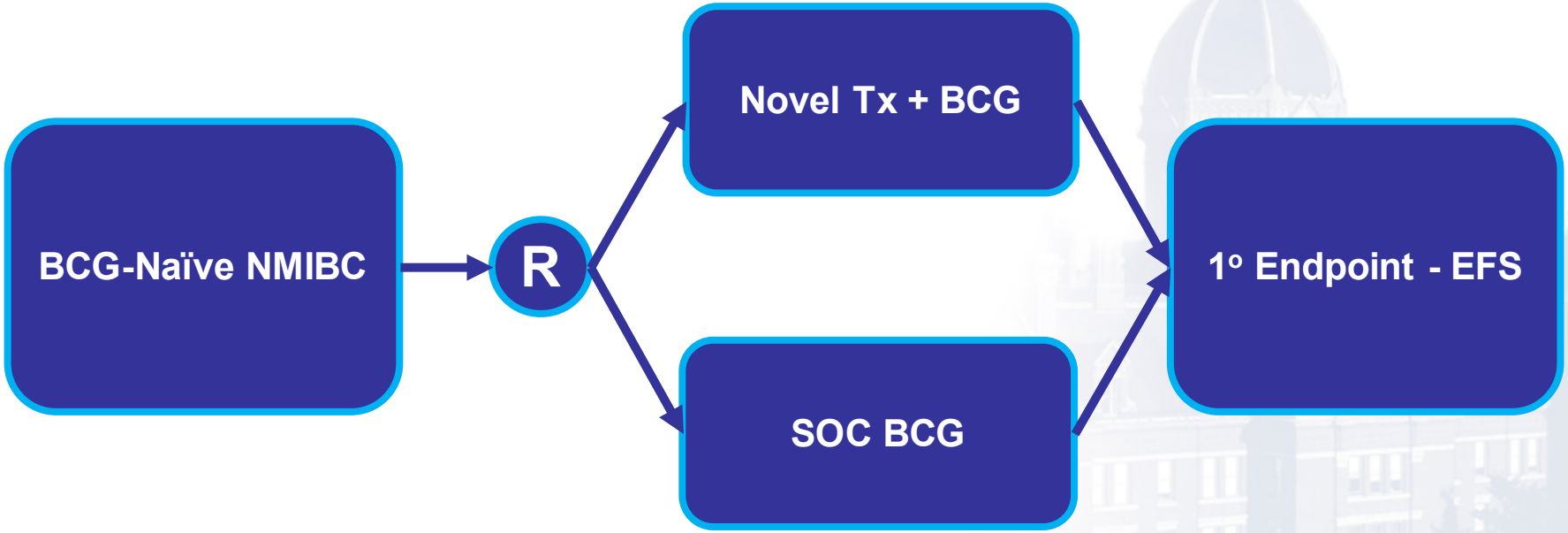


- Stratification
  - Age ≤ 75 vs > 75
  - Ta vs T1 vs CIS vs Ta/T1 + CIS
- Noninferiority Design
  - Margin 1.34 (Tokyo vs SOC)
  - 1 yr HGEFS 68% vs 75%
  - 84% power
  - Margin 1.40 (Prime + Tokyo vs Tokyo)
  - 1 yr HGEFS 81% vs 75%
  - 83% power

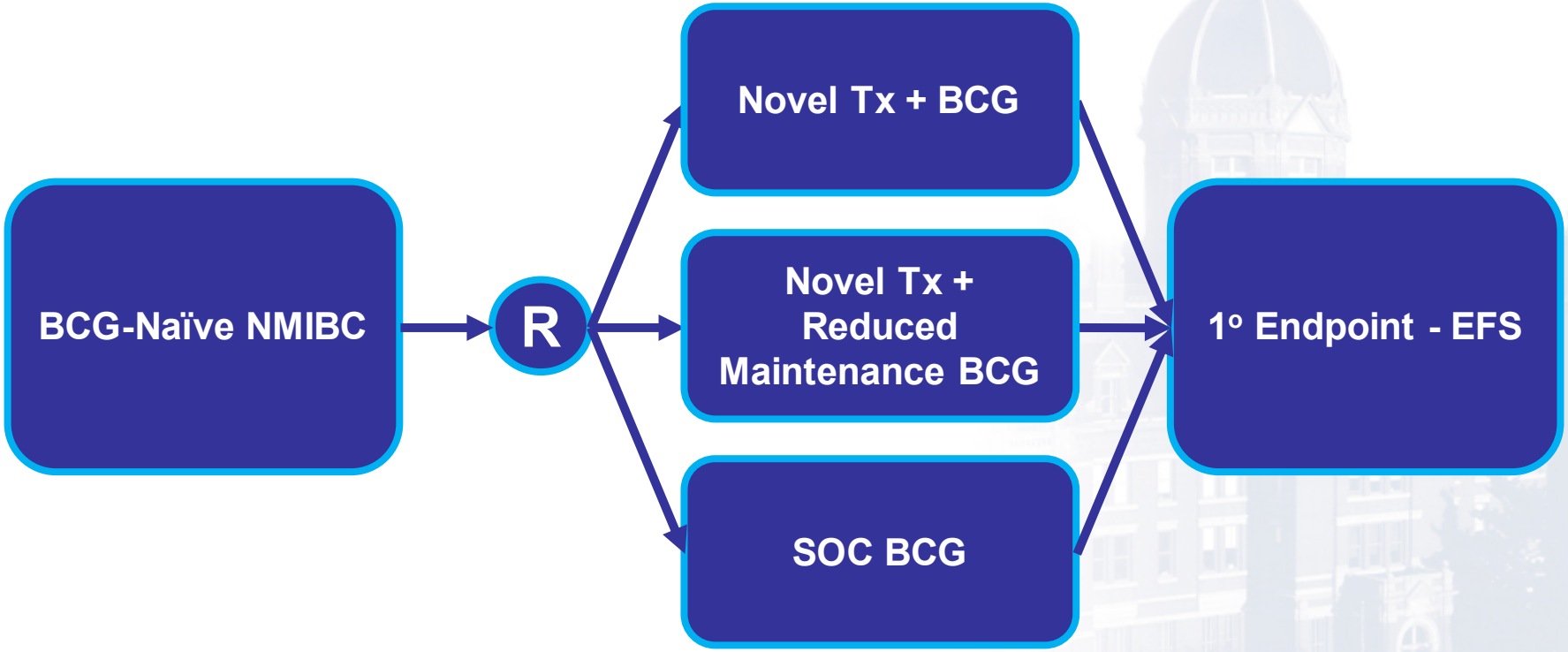
- Stratification
  - Ta/T1 vs CIS vs Ta/T1 + CIS
- Noninferiority Design
  - Margin 1.25 (Gem/Doc vs SOC)
  - 2 yr HGEFS 58% vs 65%
  - 85% power

https://www.ctsu.org/Public/Default.aspx?ReturnUrl=%2f *(accessed 10/15/21)*

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

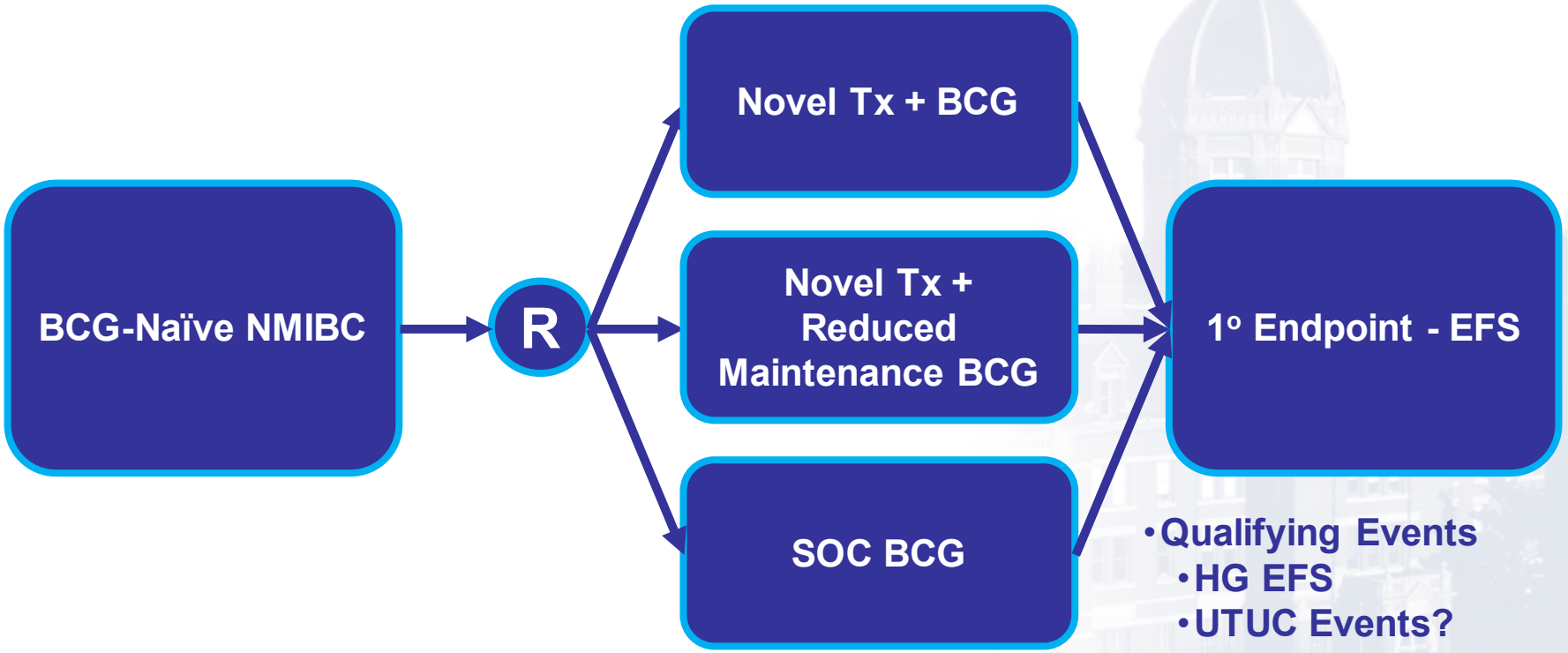


BCG-Naïve NMIBC – Design #2
Novel Tx + BCG vs BCG



JOHNS HOPKINS MEDICINE

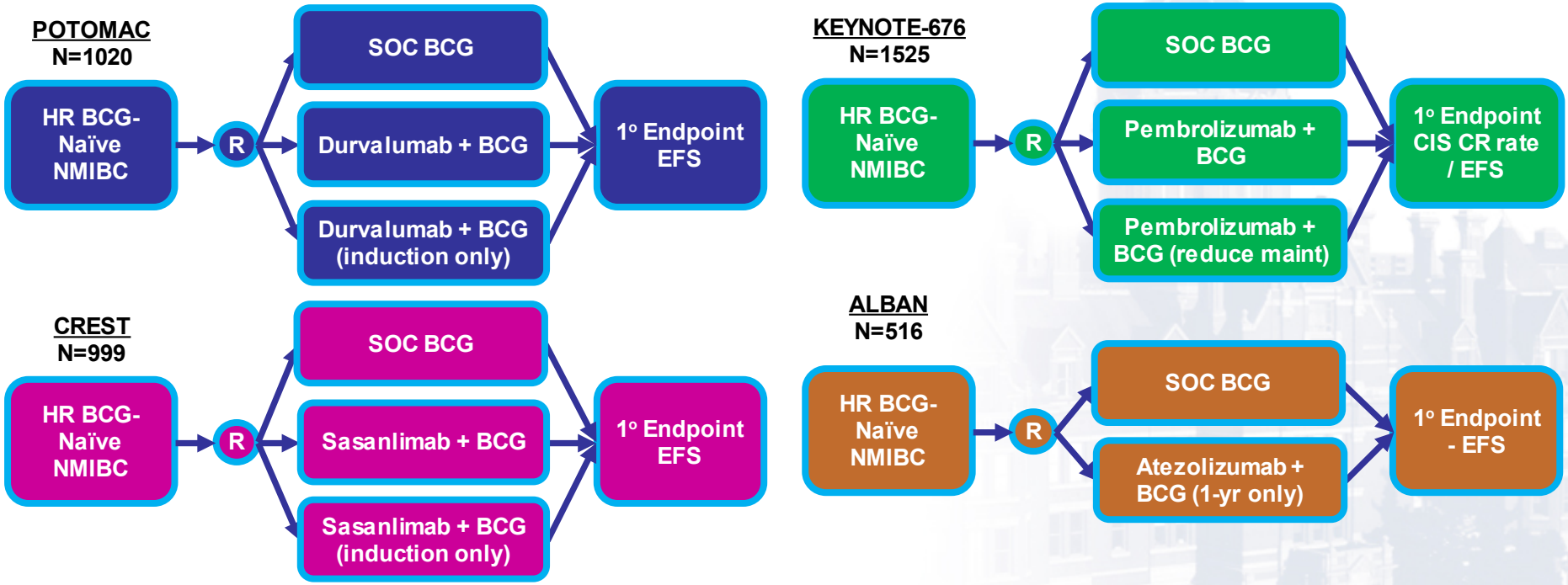
BCG-Naïve NMIBC – Design #2
Novel Tx + BCG vs BCG



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

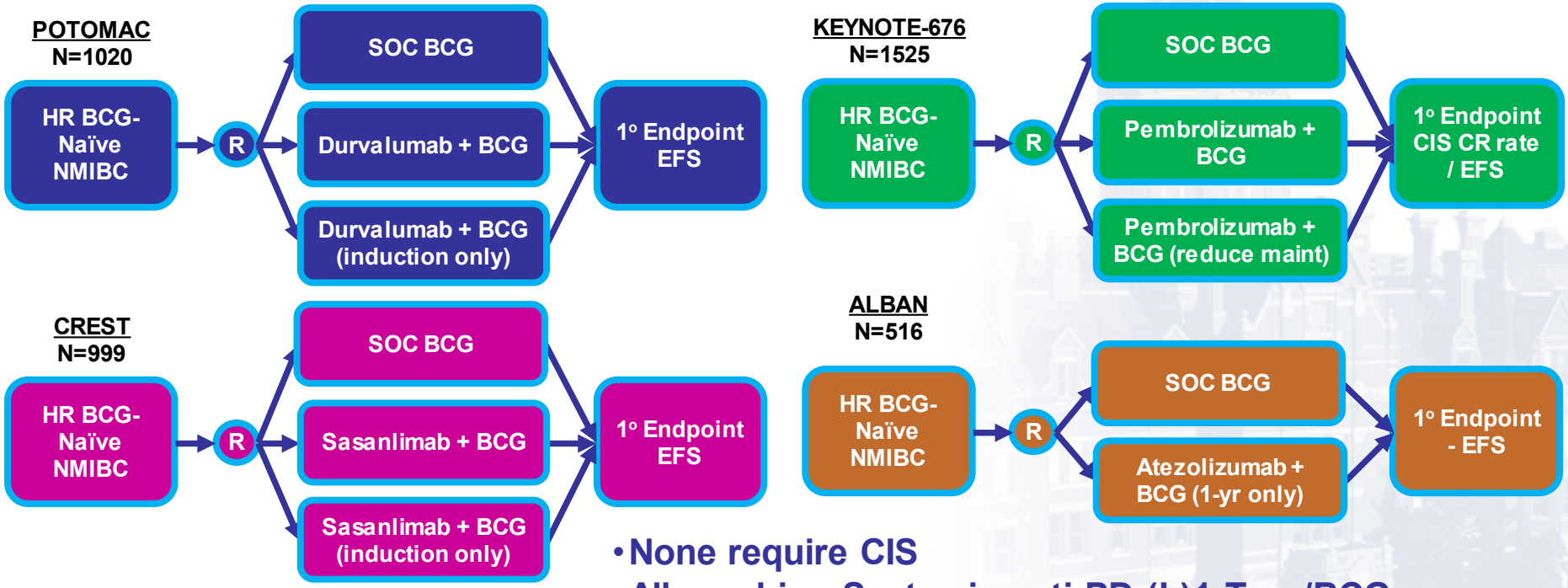
https://clinicaltrials.gov/ (accessed 10/15/21)

BCG-Naïve NMIBC – Design #2 Novel Tx + BCG vs BCG: Current and Planned Trials



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-1º)
- 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 – 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

Acknowledgments

- Hahn Lab
  - Mary Grace Phelan
  - Bridget McGuire
  - Catherine Kagemann
  - Samantha Steigerwald
  - Will Langbo
  - Hui Zhao
  - Jong Chul Park
- McConkey Lab
  - David McConkey
  - Bryan Wehrenberg
  - Megan Fong
  - Kara Lombardo
  - David Neal
  - Kai Aragaki
  - Gabe Epstein
  - Jack Mountain
- Immunology
  - Kellie Smith
  - Drew Pardoll
- Computational Biology
  - Luigi Marchionni
- Epigenetics
  - Steve Baylin
  - Vasan Yegnasubramanian
  - Mohammad Hoque
- GBCI
  - Erwin and Stephanie Greenberg
- Urology
  - Trinity Bivalacqua
  - Woonyoung Choi
  - Max Kates
  - Nirmish Singla
  - Michael Johnson
  - Armine Smith
  - Phil Pierorazio
- Medical Oncology
  - Jean Hoffman-Censits
  - Burles Johnson
- Otolaryngology
  - Mohammad Hoque
- Pathology
  - Alex Baras
  - Andres Matoso
  - Vamsi Parini
- Radiation Oncology
  - Phuoc Tran
  - Danny Song
  - Ted DeWeese
- HTG Molecular Diagnostics
  - BJ Kerns
  - Yong Lee
- Hoosier Cancer Research Network
  - Chris Fausel
  - LeaEtta Hyer
  - Anita Borek
  - Karen Dutcher
  - Tim Breen
  - Anita Camic
  - Cyndi Burkhardt
  - Lisa Wood
  - Ahran Lee
  - Robyn Lillie
- Funding
  - NCI R01R01CA235681
  - NCI P30CA006973
  - NCI UM1CA186691
  - HTG Molecular Diagnostics

JOHNS HOPKINS MEDICINE