What to do after failure of BCG?

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Making Cancer History®

Why is this important?

~ 1.2 Million Doses of BCG used globally for Bladder Cancer

How common is BCG failure?

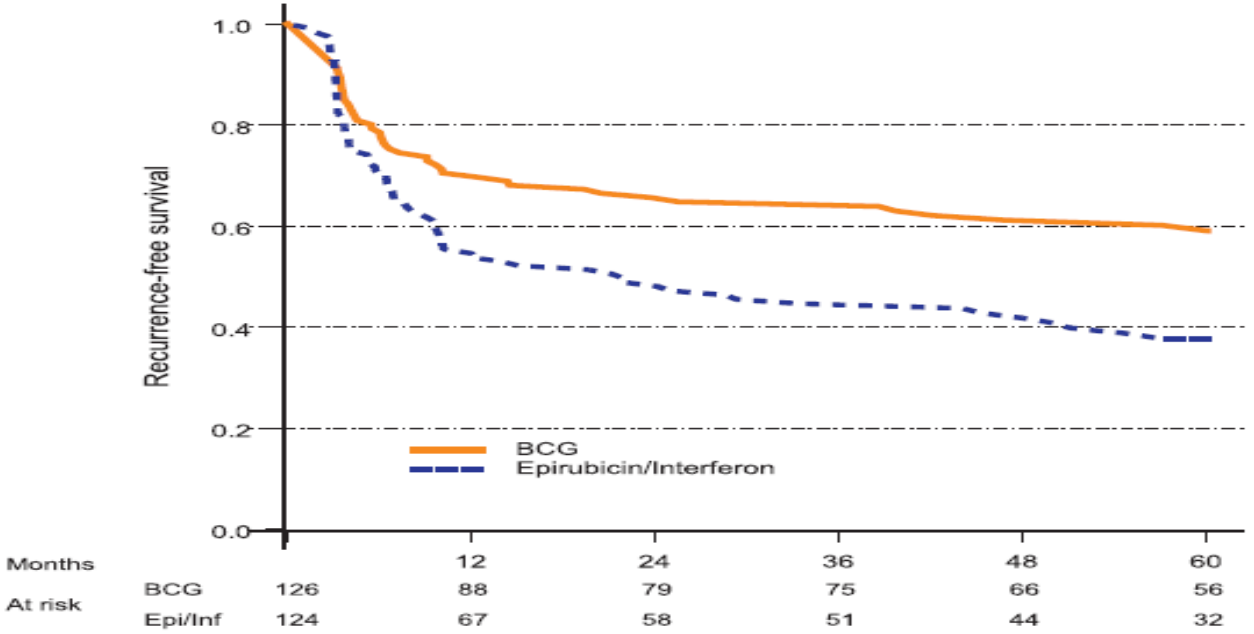


Figure 3. RFS according to randomization arm ($p = 0.001$)

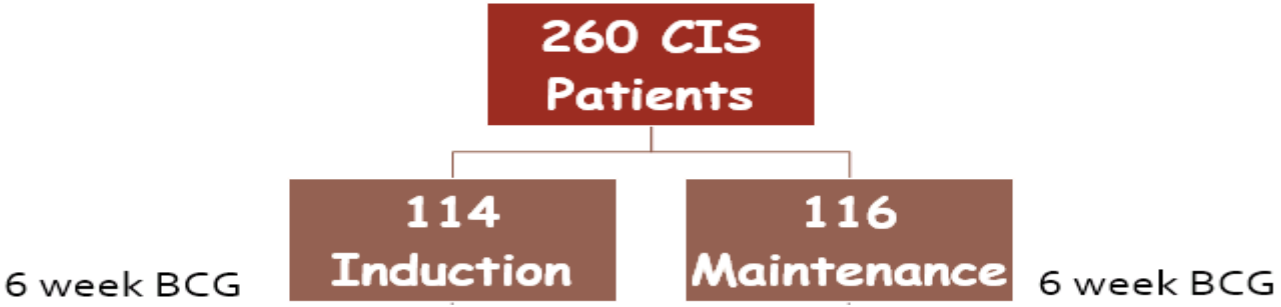
Hemdan et al. J Urol 2014; 191: 1244

Definition of BCG Failure

- Must include clear definition of ADEQUATE prior BCG therapy
- BCG Induction (6 weeks) plus at least one course of Maintenance BCG (3 weeks)
- Persistent disease at/after 6 month time point after initiation of therapy
  - Exception Ta/Tis -> T1 at 3 mos

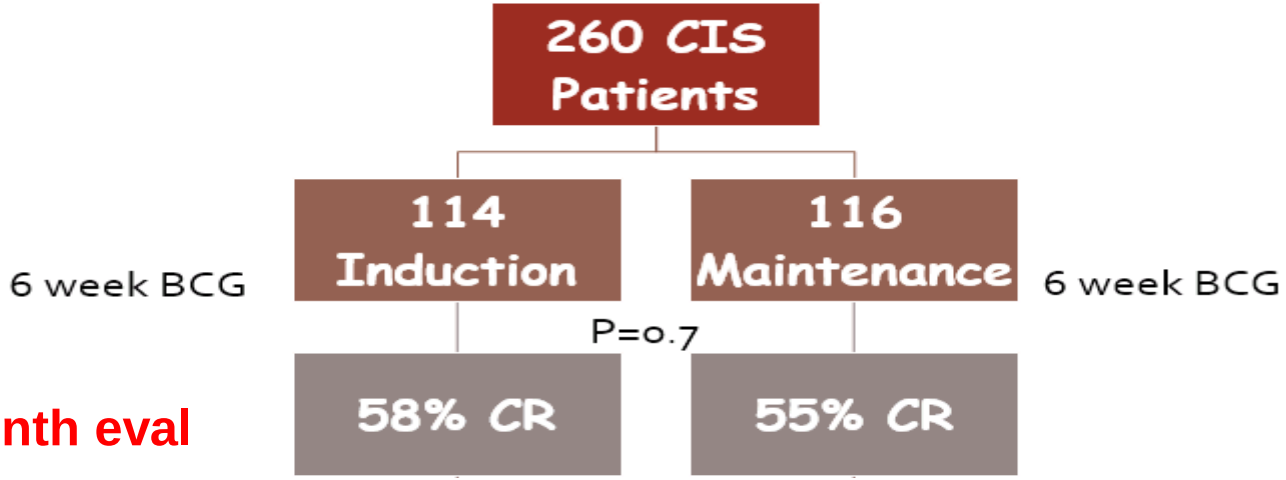
Martin and Kamat , Exp Reviews 2010

Why decision timing is important



Adapted from Lamm, JU 2000

Why decision timing is important



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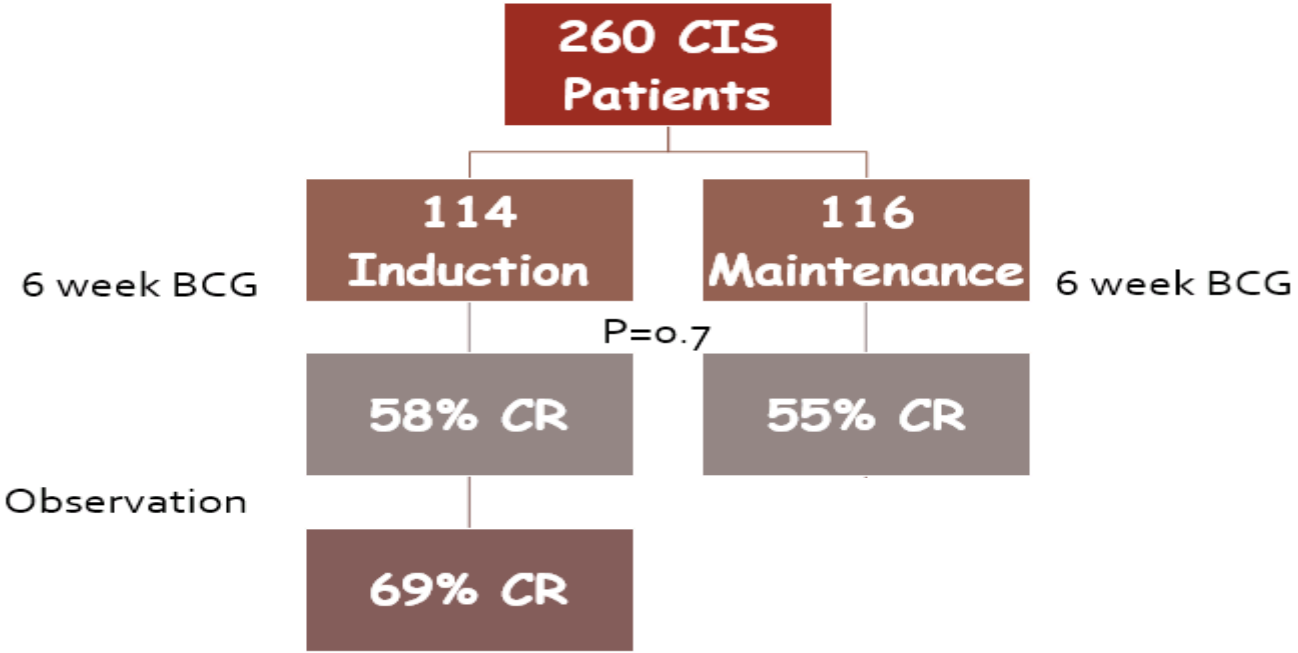

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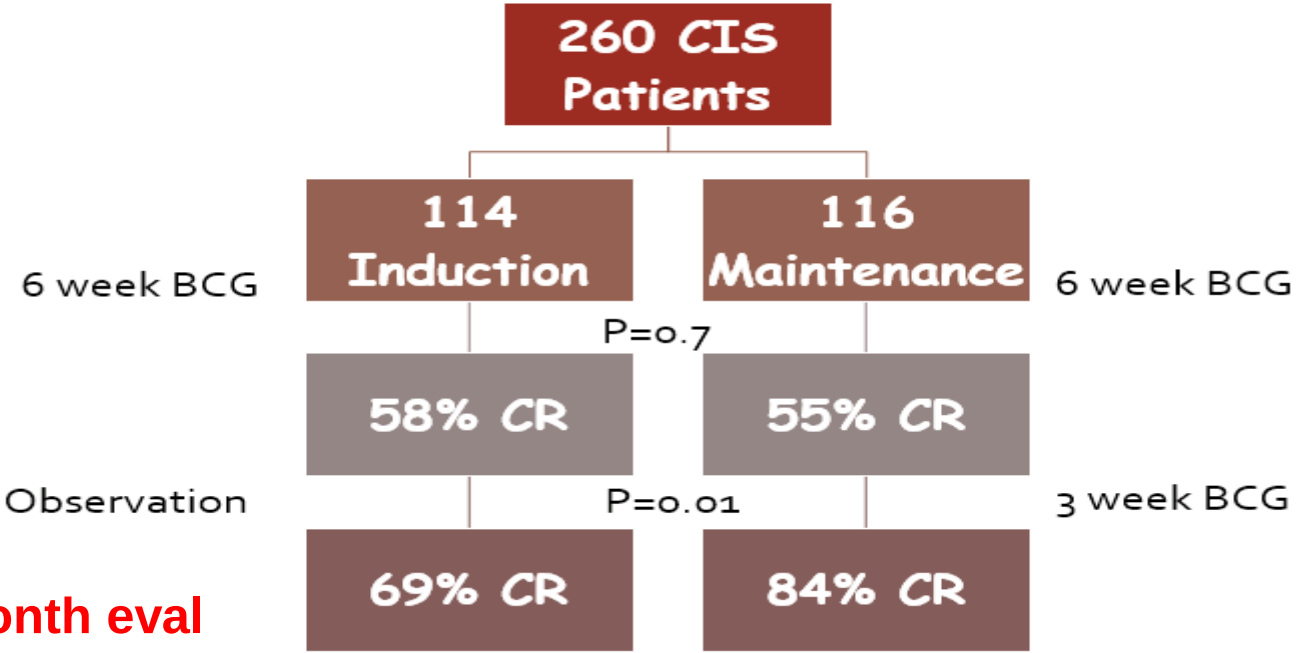
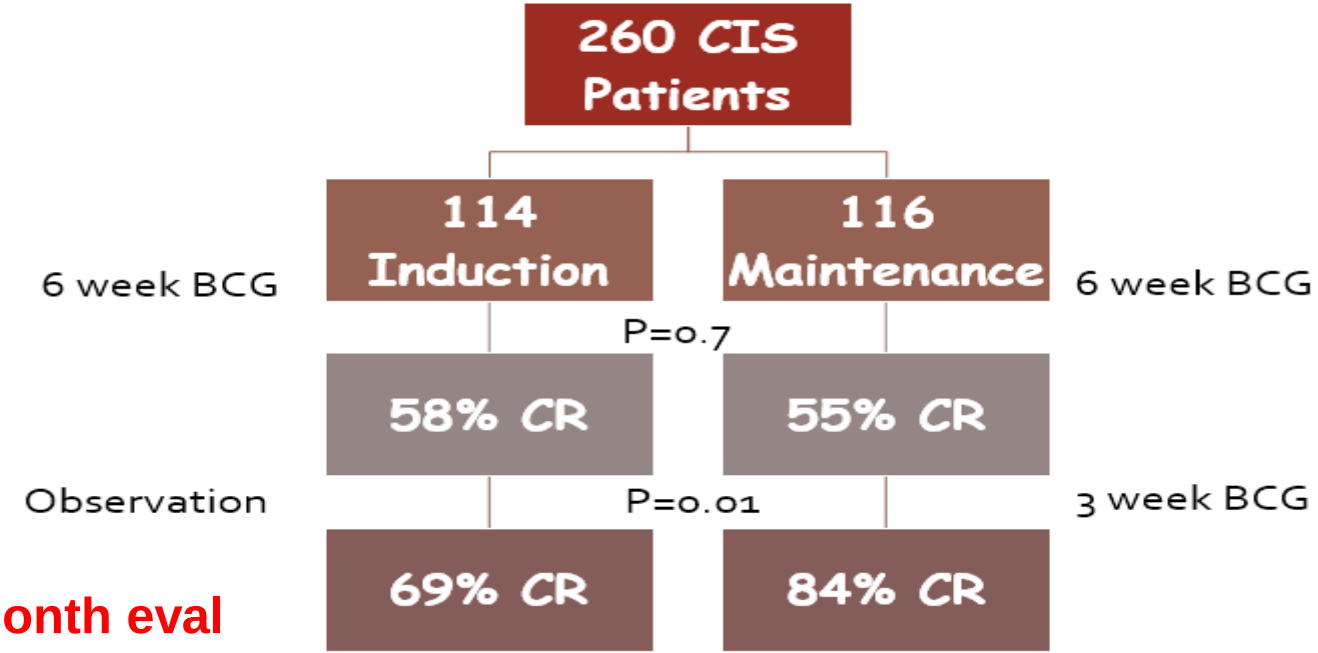


6 month eval

Adapted from Lamm, JU 2000

Why decision timing is important



64% of ‘failures’ salvaged with 3 weeks of BCG

Adapted from Lamm, JU 2000

BCG unresponsive NMIBC

- Persistent high grade disease at 6 months cysto
- Pro t 3 mos cys
- Recurrence of HG disease while on maintenance therapy

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

Guidance for Industry

DRAFT GUIDANCE

Kamat et al, JCO, 2016;
Lerner et al, Bladder Cancer, 2016

JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

Definitions, End Points, and Clinical Trial Designs for Non–Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group

Ashish M. Kamat, Richard J. Sylvester, Andreas Böhle, Joan Palou, Donald L. Lamm, Maurizio Brausi, Mark Soloway, Raj Persad, Roger Buckley, Marc Colombel, and J. Alfred Witjes

BCG Unresponsive CIS

Initial complete response (CR) **of 50% at 6 months;** durable response rate of at least **30% at 12 months** and **25% at 18 months**

BCG Unresponsive papillary disease

Recurrence free rate of **30% at 12 months** and **25% at 18 months**

J Clin Oncol 34.

Nat Rev Urol. 2017 Apr;14(4):244-255.

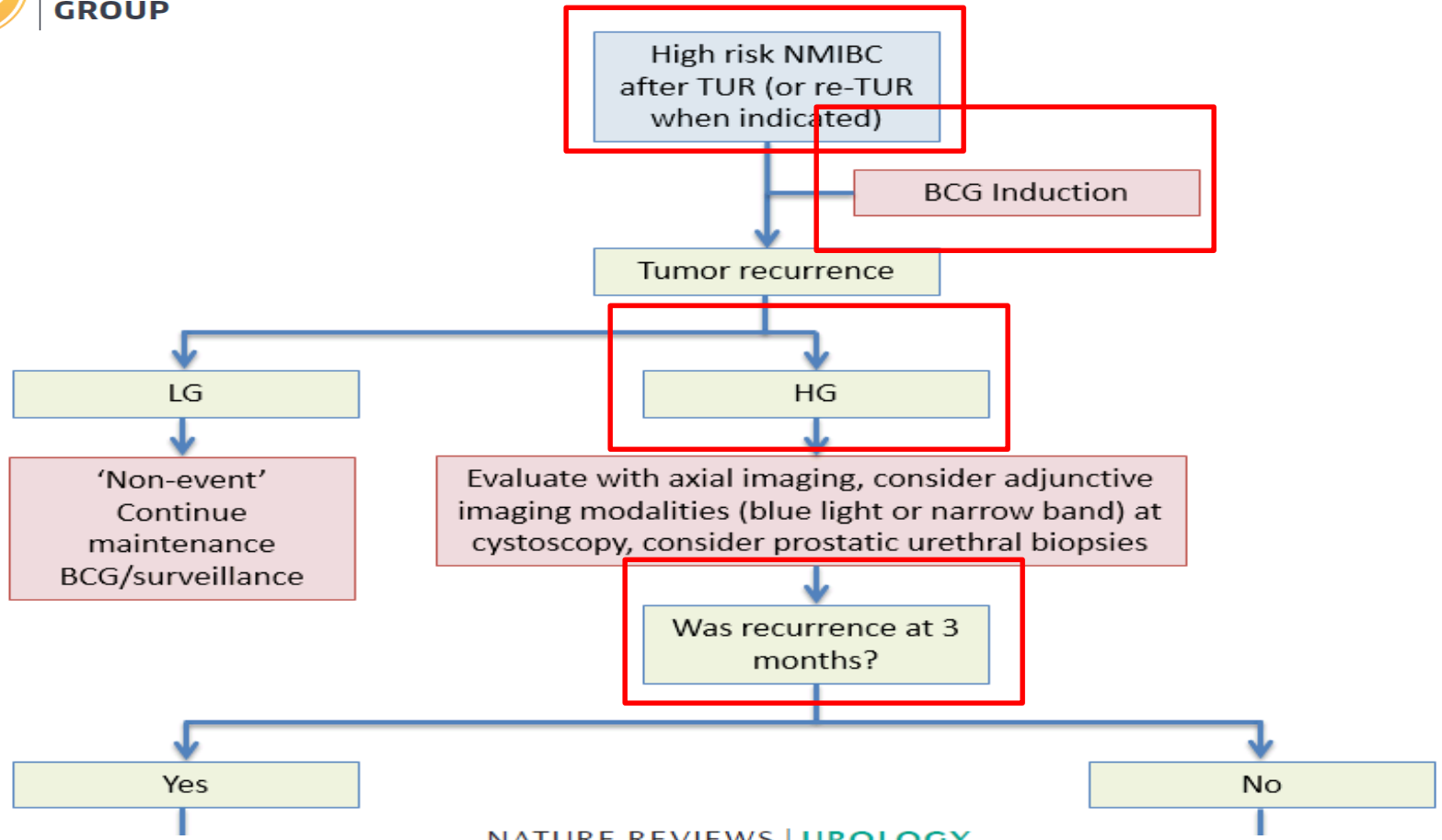
INTERNATIONAL BLADDER CANCER GROUP

BCG Unresponsive Non-muscle Invasive Bladder Cancer: Definition, Treatment Options and Management Recommendations from the IBCG

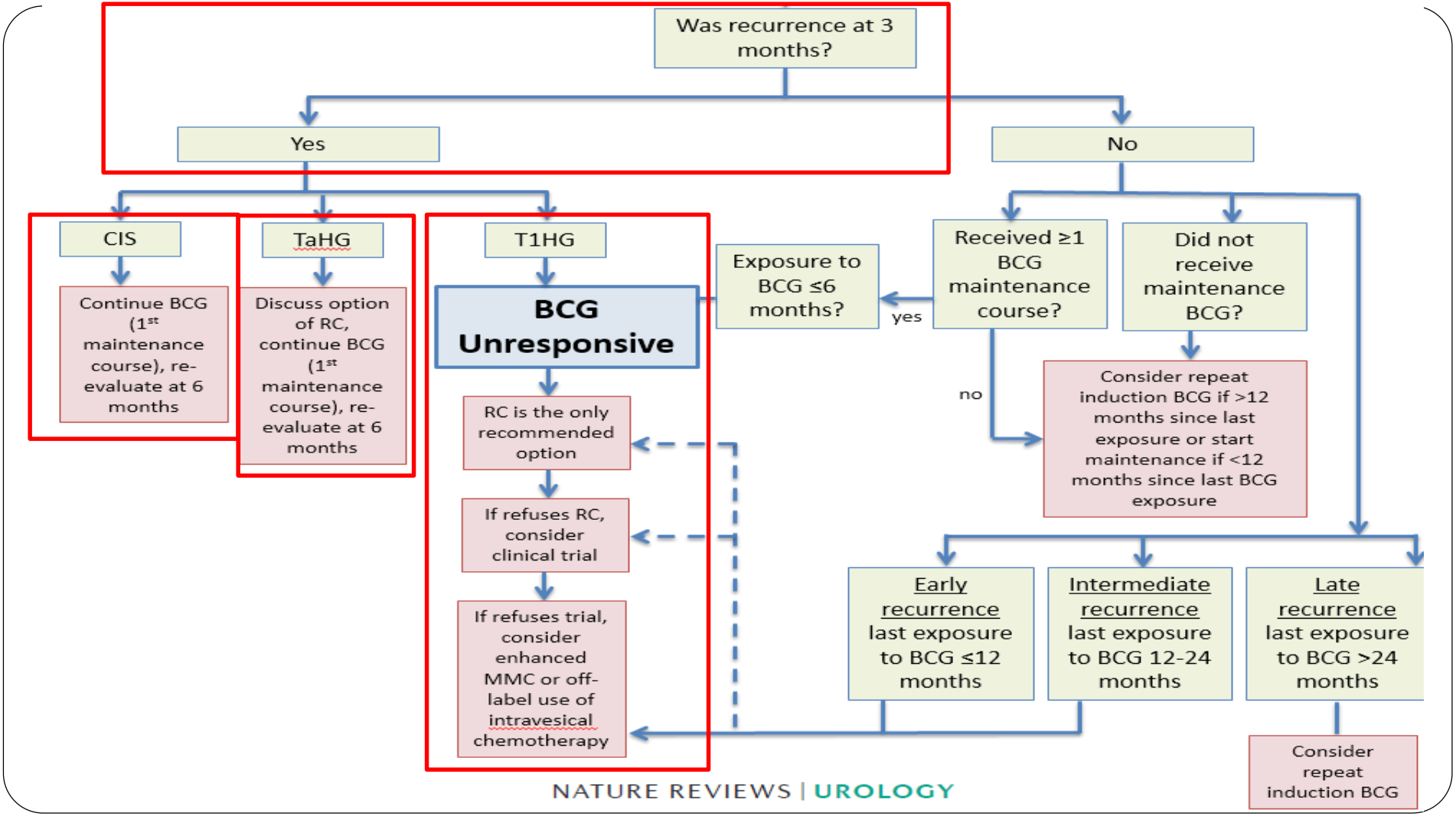
Ashish Kamat[1], Marc Colombel[2], Debasish Sundi[1], Donald Lamm[3], Andreas Boehle[4], Maurizio Brausi[5], Roger Buckley[6], Raj Persad[7], Joan Palou[8], Mark Soloway[9], J. Alfred Witjes[10]

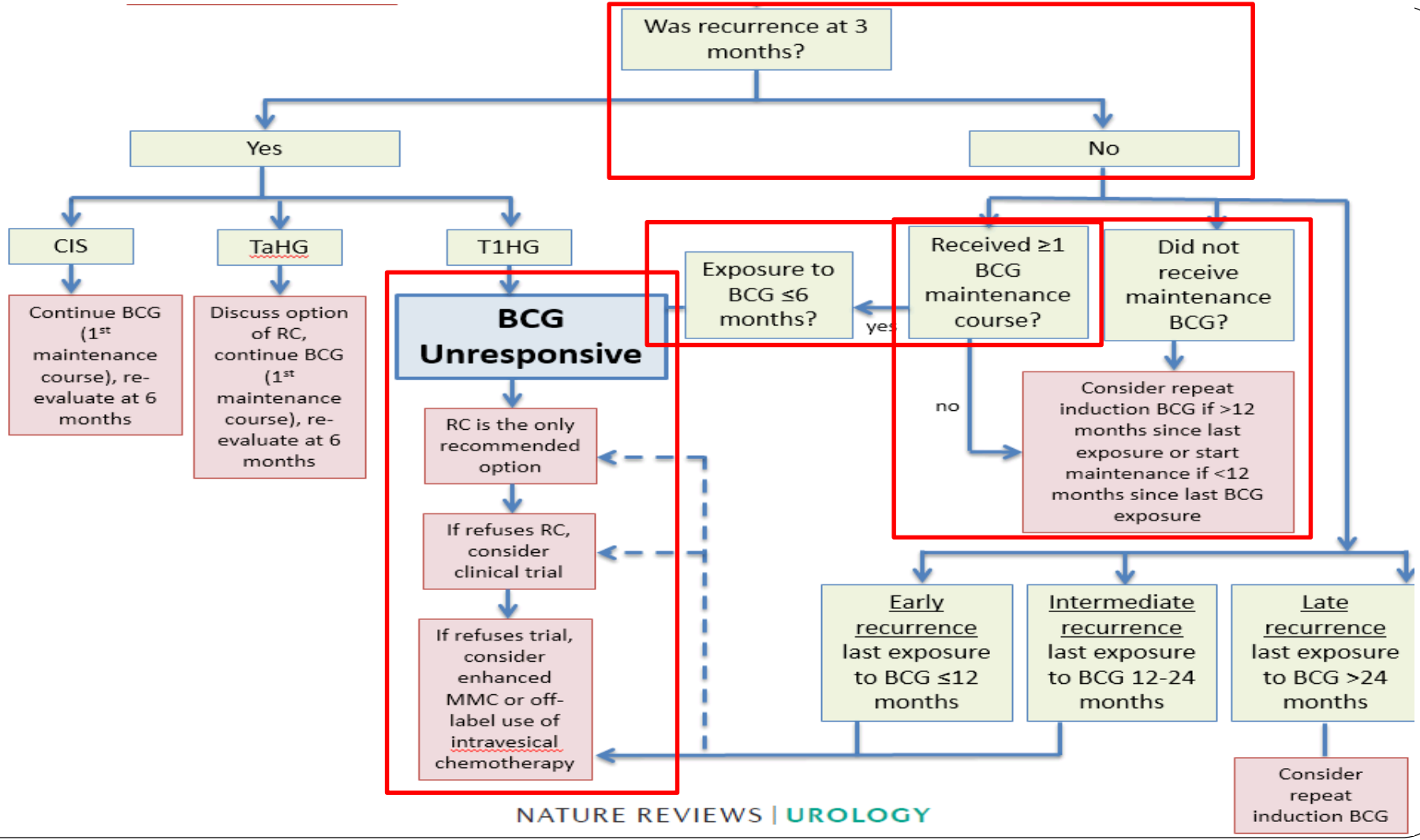
NATURE REVIEWS | UROLOGY

INTERNATIONAL
BLADDER CANCER GROUP



NATURE REVIEWS | UROLOGY


Was recurrence at 3 months?
Yes
No
CIS
TaHG
T1HG
Continue BCG (1st maintenance course), re-evaluate at 6 months
Discuss option of RC, continue BCG (1st maintenance course), re-evaluate at 6 months
BCG Unresponsive
RC is the only recommended option
If refuses RC, consider clinical trial
If refuses trial, consider enhanced MMC or off-label use of intravesical chemotherapy
Exposure to BCG ≤6 months?
yes
Received ≥1 BCG maintenance course?
Did not receive maintenance BCG?
no
Consider repeat induction BCG if >12 months since last exposure or start maintenance if <12 months since last BCG exposure
Early recurrence last exposure to BCG ≤12 months
Intermediate recurrence last exposure to BCG 12-24 months
Late recurrence last exposure to BCG >24 months
Consider repeat induction BCG
NATURE REVIEWS | UROLOGY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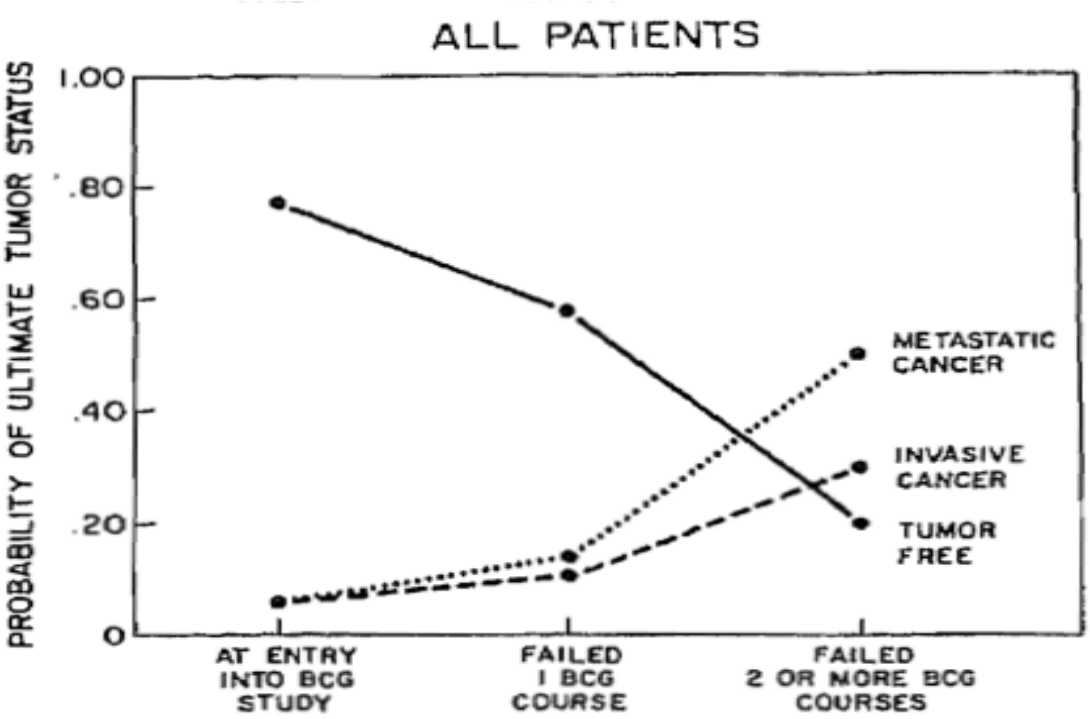
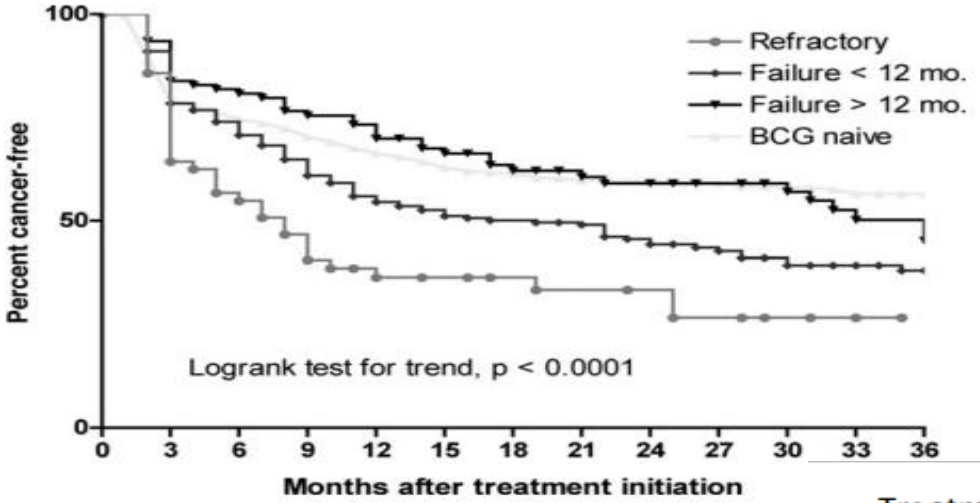
Options for Intravesical Therapy after BCG

What About Repeat BCG?



Catalona WJ, et al J Urol 1987

BCG plus interferon-α (INF-α)

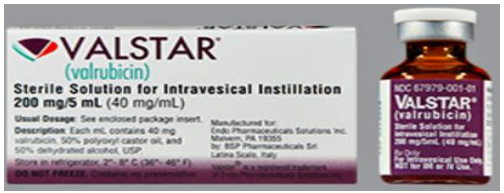


Treatment Group	2-yr Cancer-Free Survival Rate (%)	*P* Value*
BCG-N (n = 536)	59	
BCG refractory (n = 57)	34	<0.001
Recurrence (mo)		
≤6 (n = 167)	41	0.0011
6–12 (n = 129)	43	0.0006
12–24 (n = 68)	53	0.97
>24 (n = 46)	66	0.335

Gallagher BL et al, Urology, 20008

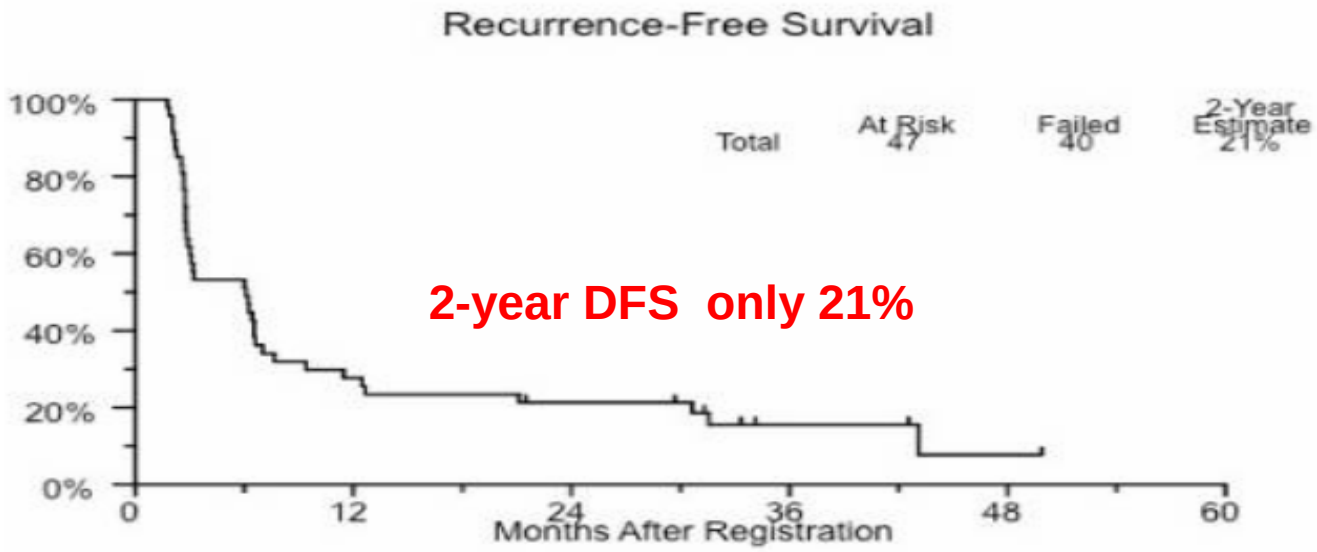
Valrubicin

- **FDA approved** in 1998 for BCG-refractory CIS in those who are not candidates for cystectomy
- CR at 6 months in 18% of patients
- **2-year DFS only 4%**



Steinberg et al, J Urol, 1998;
Dinney et al, Urol Onc, 2013.

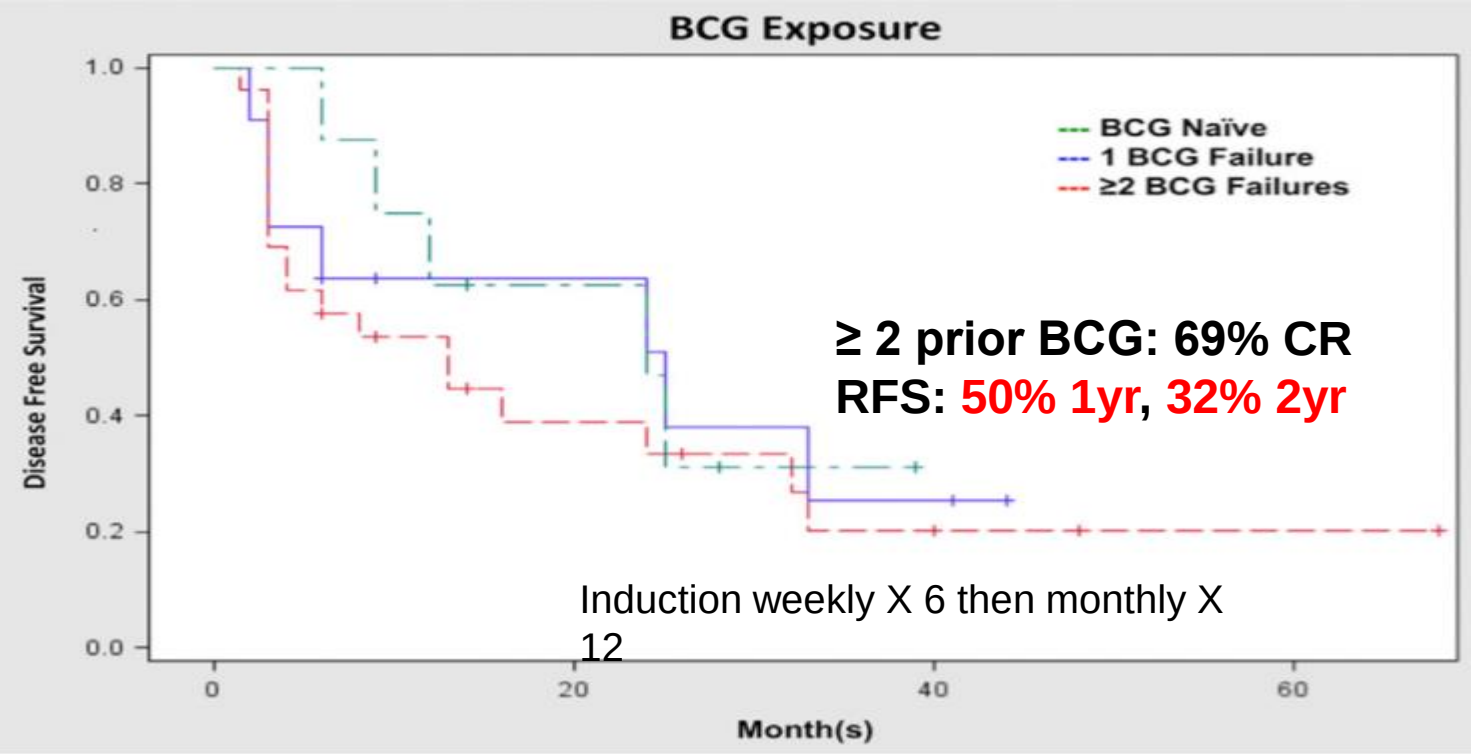
SWOG S0353 Phase II Gemcitabine



- Minimum of 2 courses of BCG
- Tis, T1, Ta high-grade, or Ta low-grade with >2 lesions
- 2gm Gem weekly x6, monthly to 12 months

Skinner , J Urol, 2013

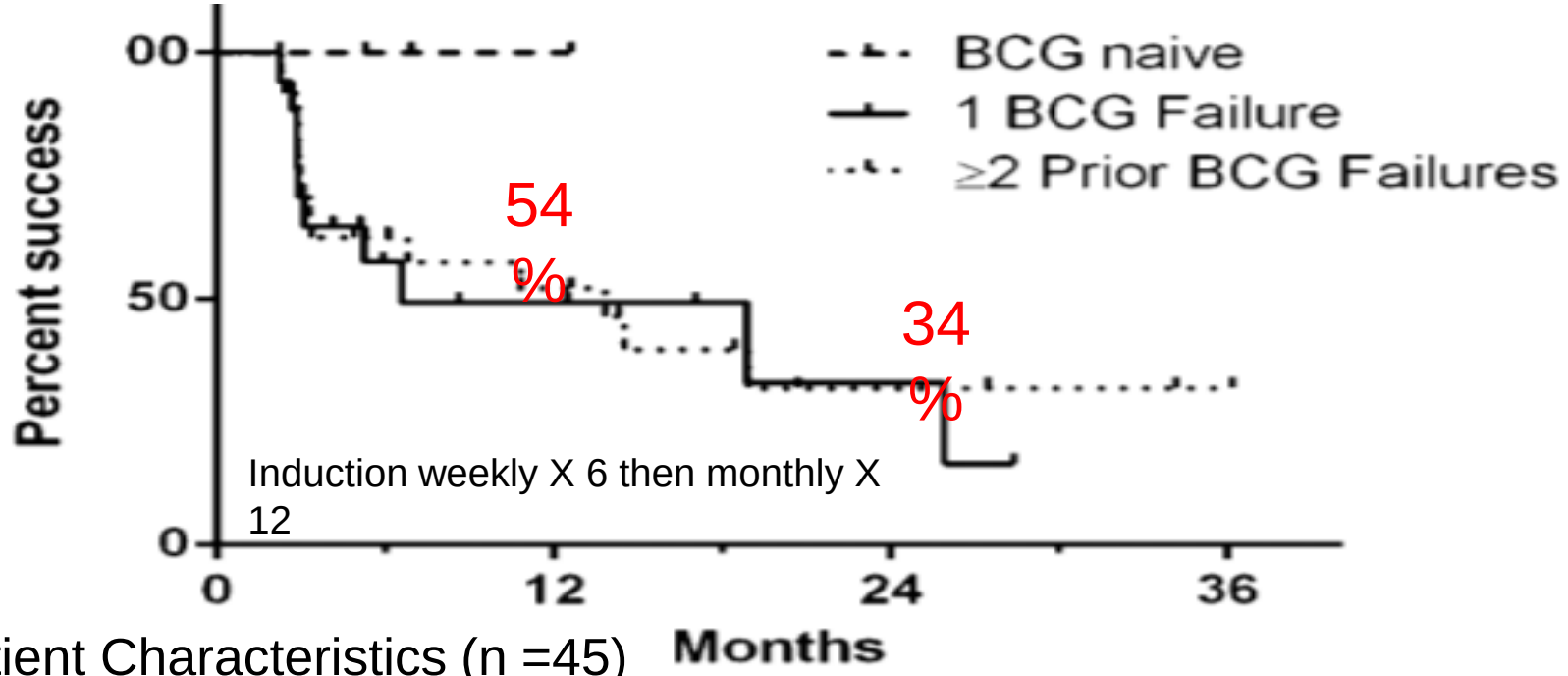
Sequential Doublet Chemotherapy with Gemcitabine – Mitomycin for HG BCG Refractory Patients (n=47)



Independent validation 37% NED at 22 months; n = 27 (Cockerill, BJUI 2015)

Lightfoot, O'Donnell, Urol Oncol 2014

Sequential Gemcitabine-Docetaxel



Patient Characteristics (n =45)

64% CIS; 91% HG

38% BCG Fx1; 53% BCG

Steinberg, O'Donnell, Bladder Ca, 2015

Gemcitabine Docetaxel Regimen

- Gemcitabine: 1 g in 50 ml of sterile water via catheter, plugged, and retained for 90 minutes.
- Docetaxel: drain bladder, then 37.5 mg of docetaxel in 50 mL of saline is instilled
- Catheter removed, patients are instructed to not urinate for 2 hrs

1300 mg oral sodium bicarbonate evening prior and morning of treatment to alkalinize their urine.

Prevent some side effects of acidic gemcitabine (pH 2.5); modify for sicker patients with sodium load.

Oral ondansetron prophylactically to patients who report nausea after their first instillation

Hyperthermic MMC post BCG

- 111 patients with recurrent papillary NMIBC after BCG

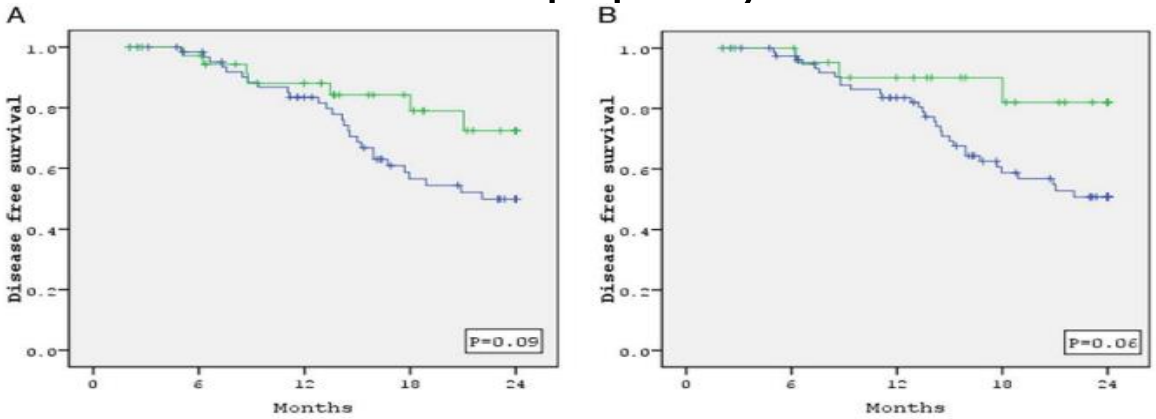


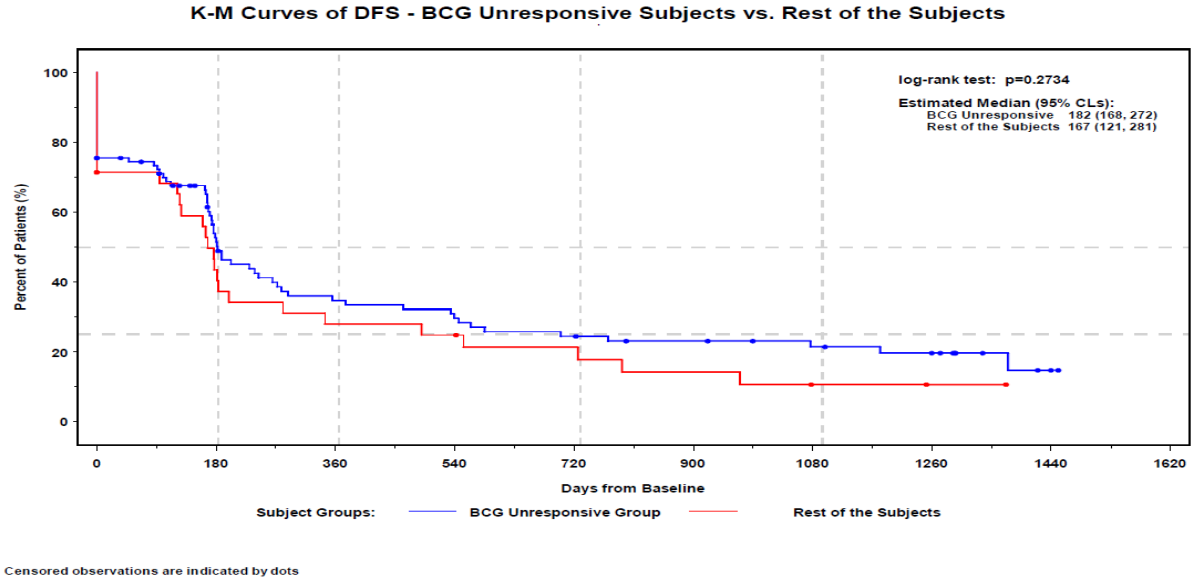
Figure 3. Disease-free survival. *A*, vs tumor recurrence history. Blue curve indicates highly recurrent. Green curve indicates other. *B*, vs EAU risk group. Blue curve indicates high risk. Green curve indicates intermediate risk. Vertical lines indicate censored.

- DFS estimates:
  - 85% and 56% after 1 and 2 years, respectively.
  - 38% were BCG refractory and 17% relapsed within 12 mos of BCG

Nativ O, Witjes at al J Urol. 2009

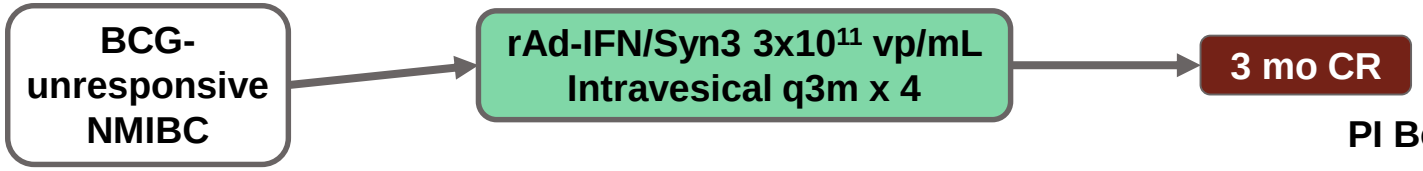
Mycobacterium cell wall-DNA complex

- Reanalysis of subset that was BCG Unresponsive
- 1 yr DFS: **35% in BCG unresponsive** vs. 25% overall
  - **Papillary: 61%** and 51% at 1 & 2 yrs, respectively



Plenary Session EAU 2016; Li & Kamat, Bladder Cancer. 2017 ;3(1):65

Instiladrin rAd-IFN-CS-003 – Phase 3 (n = 135)



PI Boorjian

Intravesical rAd–IFNα/Syn3 for Patients With High-Grade, Bacillus Calmette-Guerin–Refractory or Relapsed Non–Muscle-Invasive Bladder Cancer: A Phase II Randomized Study

Neal D. Shore, Stephen A. Boorjian, Daniel J. Canter, Kenneth Ogan, Lawrence I. Karsh, Tracy M. Downs, Leonard G. Gomella, Ashish M. Kamat, Yair Lotan, Robert S. Svatek, Trinity J. Bivalacqua, Robert L. Grubb III, Tracey L. Krupski, Seth P. Lerner, Michael E. Woods, Brant A. Inman, Matthew I. Milowsky, Alan Boyd, F. Peter Treasure, Gillian Gregory, David G. Sawutz, Seppo Yla-Herttuala, Nigel R. Parker, and Colin P.N. Dinney

- At 12 months: 40 patients (35%) free of high grade disease
  - No grade 4/5 AE
  - No treatment discontinuation due to AE

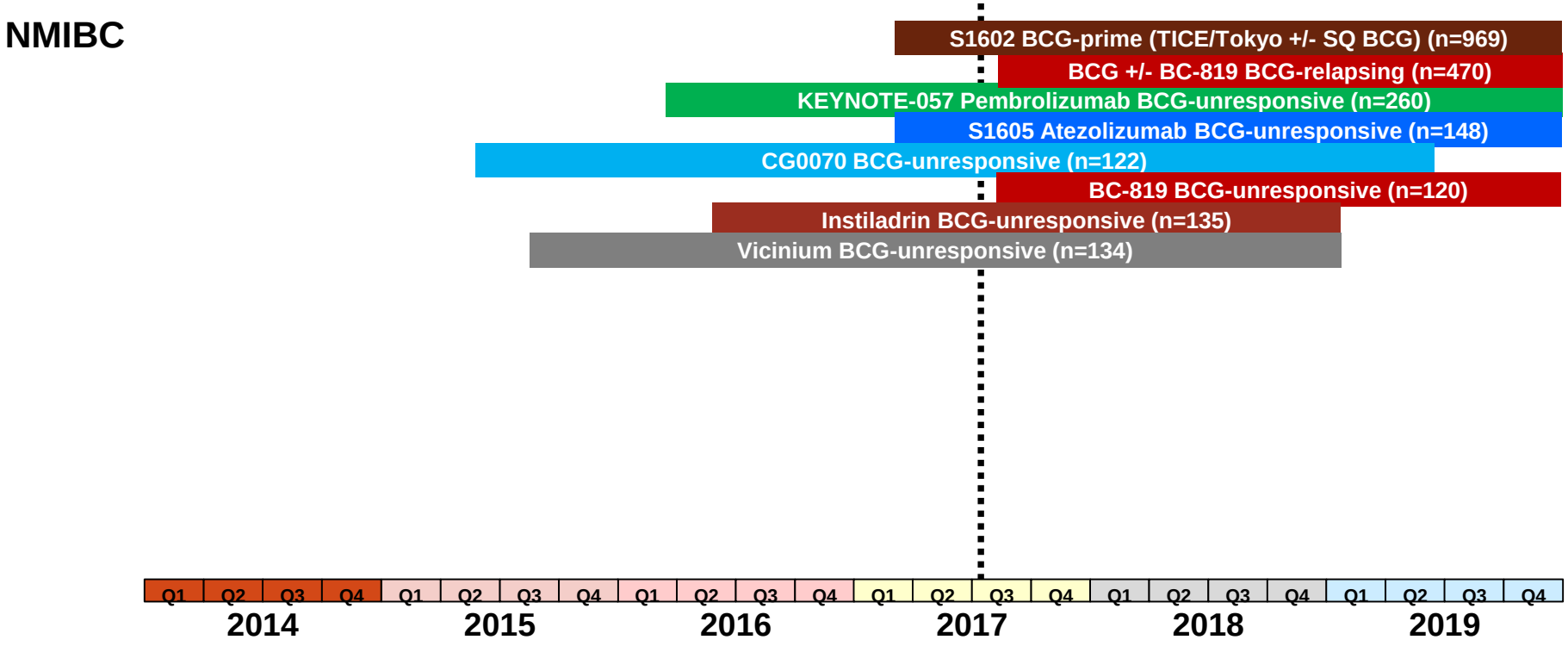
J Clin Oncol, Epub, 2017

Pembrolizumab in Patients With Bacillus Calmette Guérin (BCG)–Unresponsive, High-Risk Non–Muscle-Invasive Bladder Cancer (NMIBC): Phase 2 KEYNOTE-057 Study

Ashish M. Kamat,[1] Ronald de Wit,[2] Joaquim Bellmunt,[3] Toni K. Choueiri,[4] Kijoeng Nam,[5] Maria De Santis,[6] Robert Dreicer,[7] Noah M. Hahn,[8] Rodolfo Perini,[5] Arlene Siefker-Radtke,[2] Guru Sonpavde,[9] J. Alfred Witjes,[10] Stephen Keefe,[5] Dean Bajorin[11]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [3]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [4]Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, MA, USA; [5]Merck & Co., Inc., Kenilworth, NJ, USA; [6]University of Warwick, Coventry, United Kingdom; [7]University of Virginia School of Medicine, Charlottesville, VA, USA; [8]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA; [9]University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL, USA; [10]Radboud University, Nijmegen, Netherlands; [11]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Localized UC Registration Trials



Slide: Noah Hahn, JHU, Feb 2018

BCG Failure - Summary

- Make sure patient is truly BCG Unresponsive
- Radical Cystectomy treatment of choice
  - recommended by AUA, EAU, IBCG guidelines
- Options for intravesical therapy
  - Combination chemotherapy
  - Hyperthermic chemotherapy
- Enroll in clinical trials!

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