

# BCG-Refractory NMIBC Treatment: Present and Future

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LINEBERGER

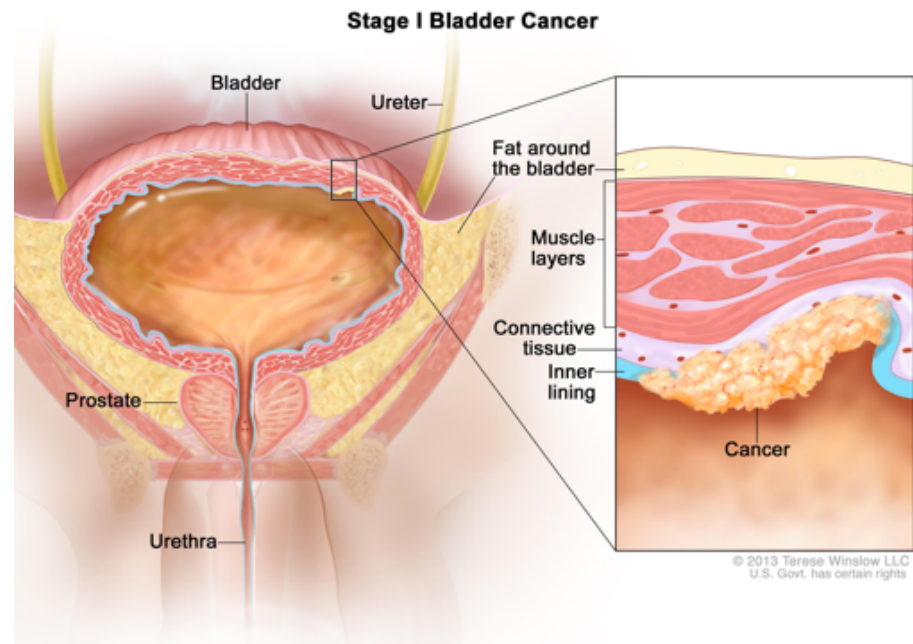


# Disclosures

- Research Funding
  - PCORI
- Advisory Board
  - Photocure
  - Urogen
- Consultant
  - Merck

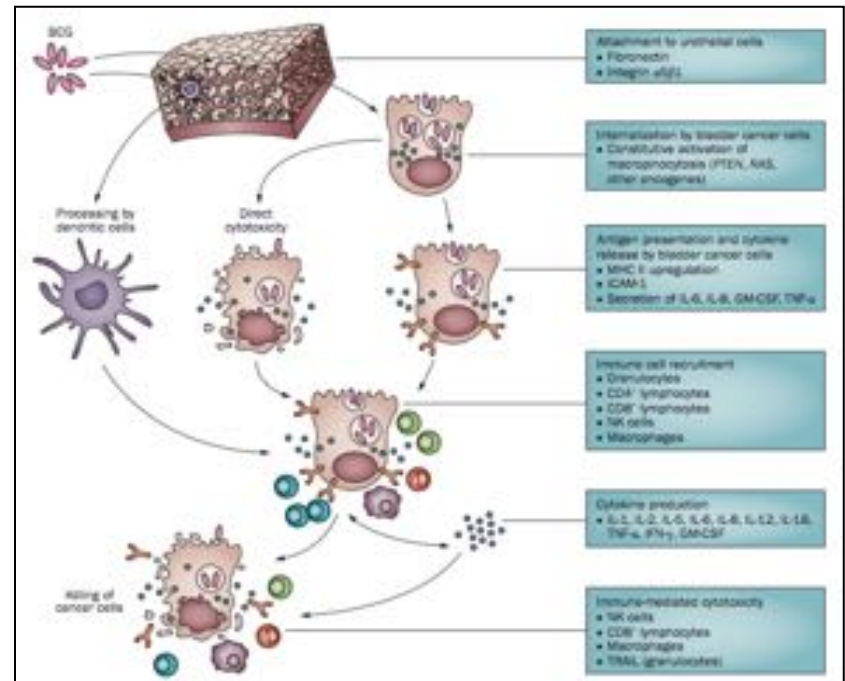
# Outline

- Definitions
- Evaluation
- Treatment
  - Surgery
  - Chemoradiation
  - Chemotherapy
  - Immunotherapy
- Future Directions



# BCG

- First reported by Morales et al. in 1976
- Superior to chemotherapy in both recurrence and progression



Redelman-Sidi et al. Nat Rev Urol 2014:154

Morales et al. J Urol 1976:180

Sylvester et al. J Urol 2002:1964

**American Urological Association (AUA)/  
Society of Urologic Oncology (SUO) Guideline**

**DIAGNOSIS AND TREATMENT OF NON-MUSCLE  
INVASIVE BLADDER CANCER: AUA/SUO GUIDELINE**

**Intravesical Therapy; BCG/Maintenance; Chemotherapy/BCG Combinations**

15. In a patient with suspected or known low- or intermediate-risk bladder cancer, a clinician should consider administration of a single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin) within 24 hours of TURBT. In a patient with a suspected perforation or extensive resection, a clinician should not use postoperative chemotherapy. (Moderate Recommendation; Evidence Strength: Grade B)
16. In a low-risk patient, a clinician should not administer induction intravesical therapy. (Moderate Recommendation; Evidence Strength: Grade C)
17. In an intermediate-risk patient a clinician should consider administration of a six week course of induction intravesical chemotherapy or immunotherapy. (Moderate Recommendation; Evidence Strength: Grade B)
18. In a high-risk patient with newly diagnosed CIS, high-grade T1, or high-risk Ta urothelial carcinoma, a clinician should administer a six-week induction course of BCG. (Strong Recommendation; Evidence Strength: Grade B)
19. In an intermediate-risk patient who completely responds to an induction course of intravesical chemotherapy, a clinician may utilize maintenance therapy. (Conditional Recommendation; Evidence Strength: Grade C)
20. In an intermediate-risk patient who completely responds to induction BCG, a clinician should consider maintenance BCG for one year, as tolerated. (Moderate Recommendation; Evidence Strength: Grade C)
21. In a high-risk patient who completely responds to induction BCG, a clinician should continue maintenance BCG for three years, as tolerated. (Moderate Recommendation; Evidence Strength: Grade B)

63yo M with history of HG1. He undergoes BCG induction. During his first surveillance, a bladder tumor is noted and found to be HG1a. How would you describe this patient?

- A. Inadequate BCG
- B. BCG intolerant
- C. BCG refractory
- D. BCG relapsing
- E. BCG unresponsive



Adequate BCG

# Adequate BCG

- 6 week induction + 3 week maintenance
  - SWOG protocol: 3, 6, 12, 18, 24, 30, 36 months
- “Adequate BCG” clinical trial design standpoint
  - At least 5 of 6 intended weekly induction treatments (one induction course) +
  - At least 2 additional weekly maintenance treatments or a second re-induction in a 6-month time period

Kamat et al, 2016 *J Clin Oncol* 34: 1935-1944



# terminology

[tur-muh-nol-uh-jee]

**noun, plural**

1. the system of specialized words used in a particular subject.
2. the science of the study of terms.

**Word Origin**

1, from German Terminologie (1786), a hybrid of *terminus* and *logia*, coined by C.G. Schütz of Jena, from Medieval Latin *terminus*, "word, expression" (see *terminus*); *logia*, "with, a speaking of"

- Intolerant
- Refractory
- Relapsing
- Unresponsive

# BCG Terminology

- BCG Intolerant
  - Cannot receive due to treatment-related adverse effects
- BCG Refractory
  - Persistent high grade cancer 6 months after start of induction therapy OR
  - Progresses grade/stage 3 months after start of induction
- BCG Relapsing
  - Recurrence after achieving disease-free state at 6 months
- BCG Unresponsive
  - Combination of BCG refractory + BCG relapsing whose tumors recur within 6 months of last BCG exposure (early)

# GUIDELINES

## EAU

Cystectomy preferred option  
Repeat BCG induction or  
intravesical chemo viable option  
for intermediate risk disease

## ICUD-EAU

Best option might be repeat  
induction BCG but cystectomy  
also indicated

## AUA

Radical cystectomy  
No additional BCG  
Consider clinical trials



# EVALUATION

- Optimally stage
- Evaluate sanctuary sites
  - Prostatic urethra
  - Upper urinary tract



A photograph of an operating room. In the center is a surgical table covered with a light blue drape. To the left, there is a medical cart with various equipment. In the background, there are stainless steel walls and a door. The overall scene is clean and clinical.

## Surgical Options for BCG-Refractory NMIBC

When?  
Why?

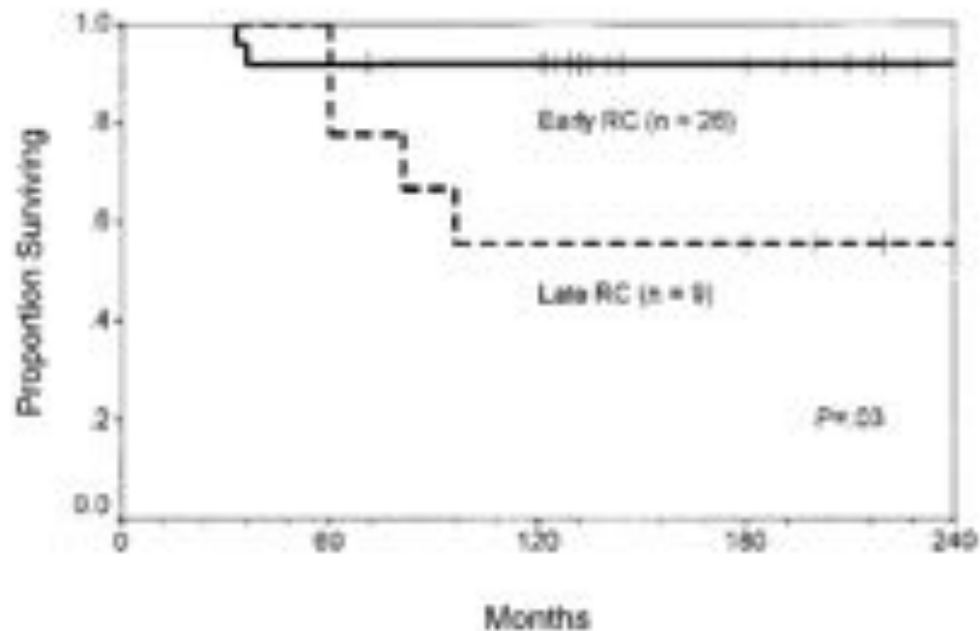


# Surgical Options

DOES EARLY CYSTECTOMY IMPROVE THE SURVIVAL OF PATIENTS WITH HIGH RISK SUPERFICIAL BLADDER TUMORS?

HARRY W. HERR AND PRAMOD C. SOGANI

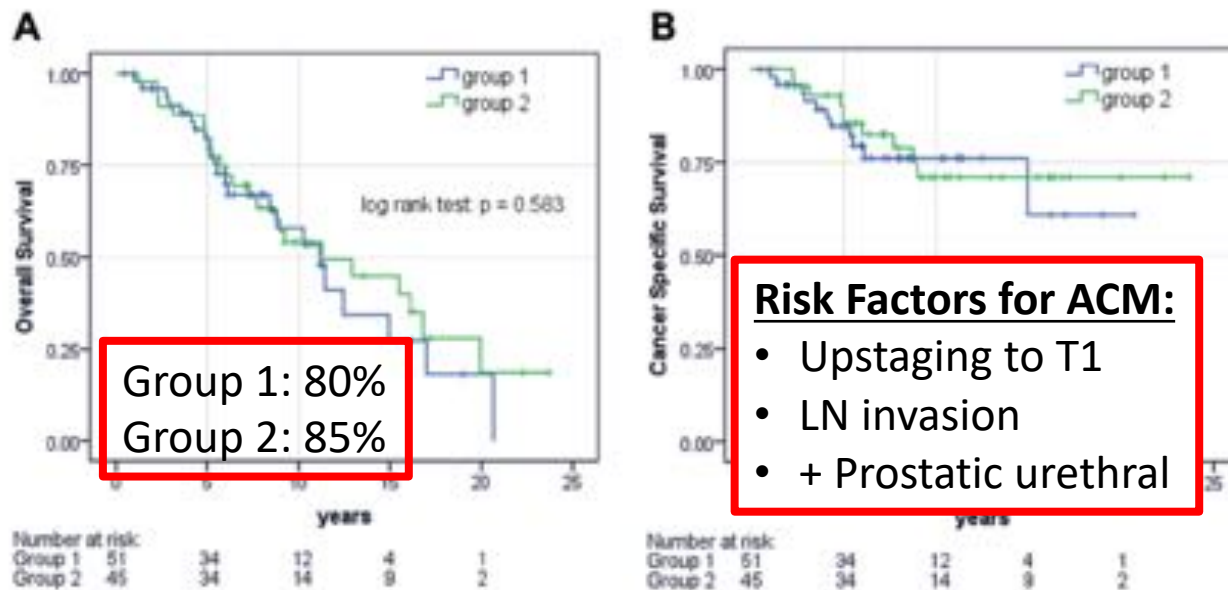
*From the Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, New York*





# The Timing of Radical Cystectomy for bacillus Calmette-Guérin Failure: Comparison of Outcomes and Risk Factors for Prognosis

Christopher R. Haas,\* LaMont J. Barlow, Gina M. Badalato, G. Joel DeCastro, Mitchell C. Benson and James M. McKiernan



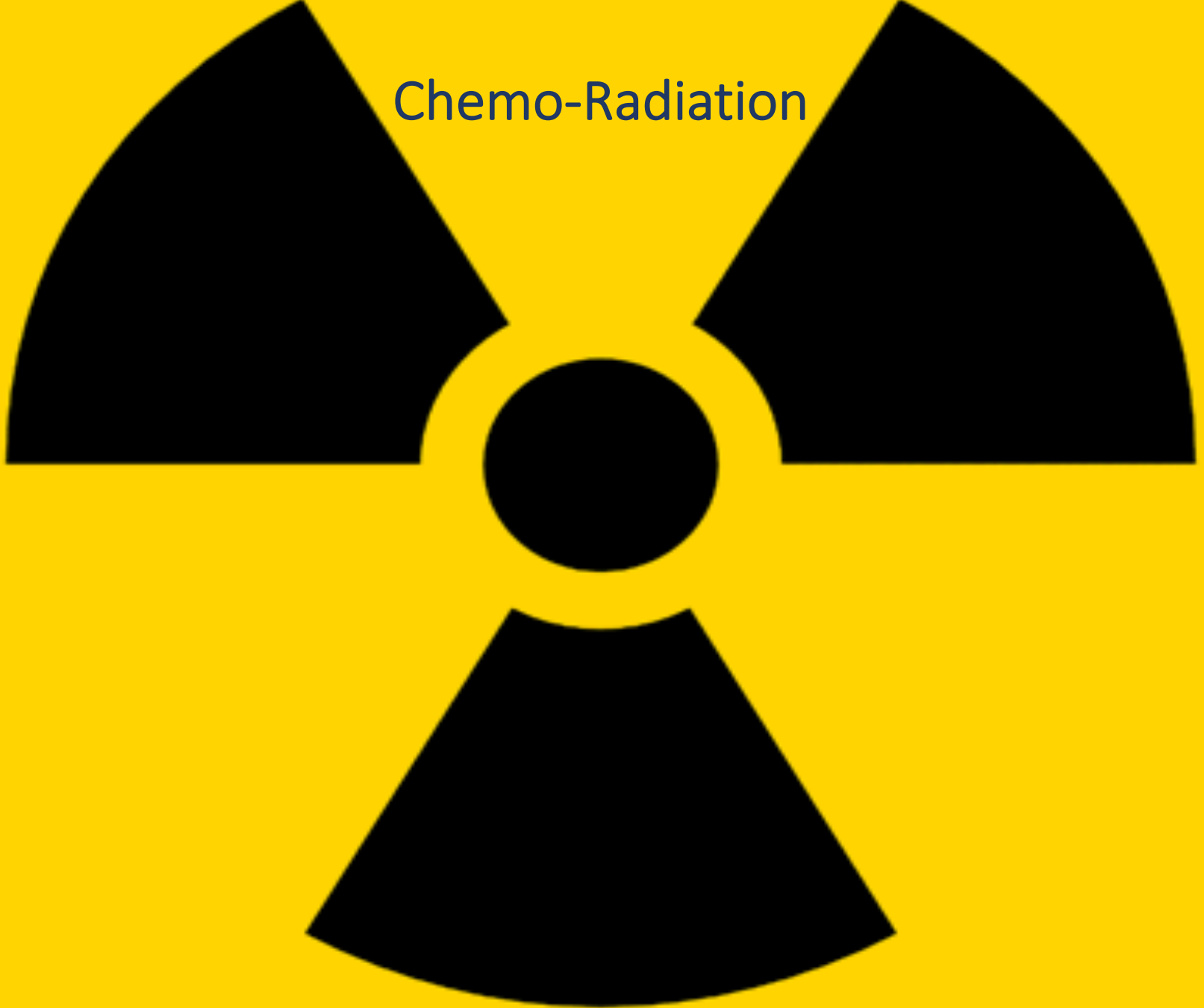
Group 1 (n=61): BCG with or without IFN  
Group 2 (n=56): At least 1 additional salvage IVC after BCG

A photograph of an operating room with a surgical table, medical equipment, and blue drapes.

# Surgical Options for BCG-Refractory NMIBC

- Immediate cystectomy not mandatory if expeditious cystectomy after salvage attempt
- Staging is critical

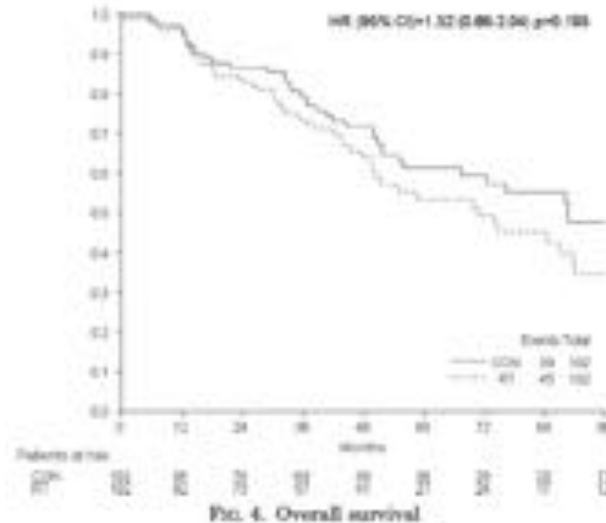
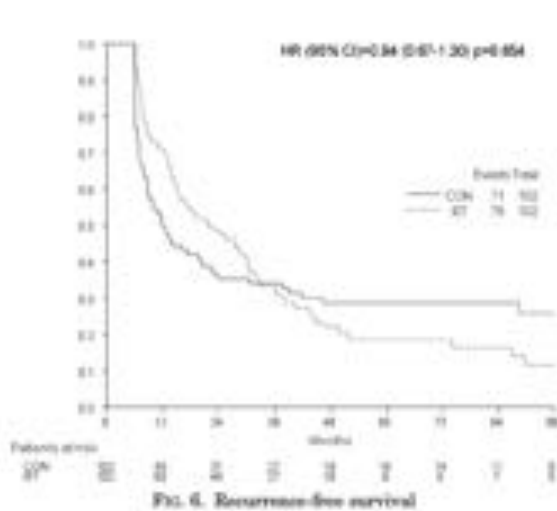
Chemo-Radiation



# A Randomized Trial of Radical Radiotherapy for the Management of pT1G3 NXM0 Transitional Cell Carcinoma of the Bladder

S. J. Harland,<sup>\*,†,‡</sup> H. Kynaston,<sup>†</sup> K. Grigor, D. M. Wallace, C. Beacock, R. Kockelbergh, S. Clawson, T. Barlow, M. K. B. Parmar and G. O. Griffiths on behalf of the National Cancer Research Institute Bladder Clinical Studies Group

*From the Institute of Urology and Department of Oncology, University College London (SjH) and Cancer Group, Medical Research Council Clinical Trials Unit (SC, TB, MKBP, GOG), London, Department of Urology, University Hospital of Wales, Heath Park, Cardiff (HK), Department of Pathology, Western General Hospital, Edinburgh (KG), Department of Urology, Queen Elizabeth Hospital, Birmingham (DMW), Department of Urology, Royal Shrewsbury Hospital, Shrewsbury (CB), and Department of Urology, Leicester General Hospital, Leicester (RK)*

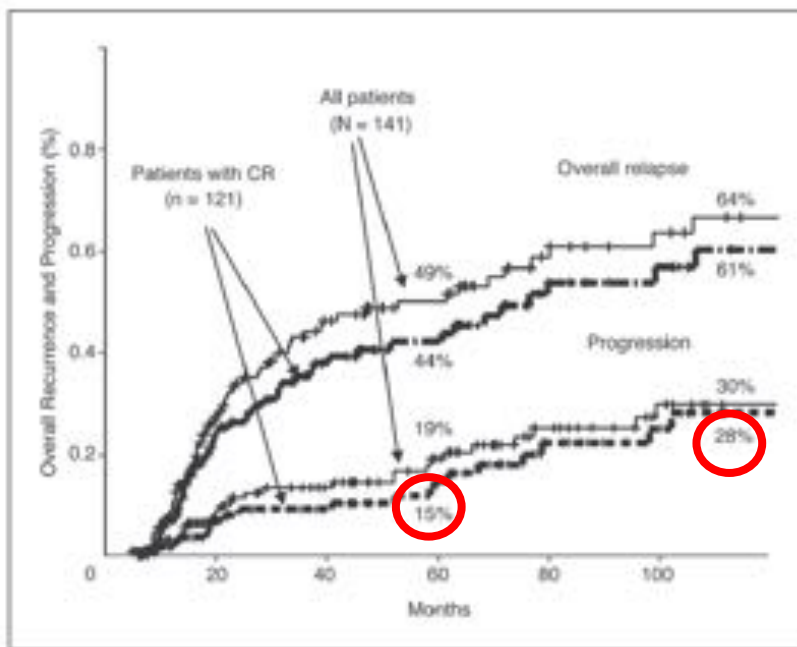


- Group 1: New HGT1, no CIS
  - Observation vs. radiotherapy
- Group 2: CIS
  - Intravesical therapy vs. radiotherapy

No difference between radiotherapy and conservative management in progression, recurrence or survival

# Radiochemotherapy After Transurethral Resection for High-Risk T1 Bladder Cancer: An Alternative to Intravesical Therapy or Early Cystectomy?

Christian Weiss, Carolin Wolze, Dirk Gerhard Engehausen, Oliver J. Ott, Frens S. Krause, Karl-Michael Schrott, Jürgen Dunst, Rolf Sauer, and Claus Rödel



**Fig 2.** Overall recurrence and progression ( $\geq$  T2; N1, M1) for all 141 patients with high-risk T1 bladder cancer, and for 121 patients with complete response (CR) after transurethral resection of bladder tumor and radiotherapy or radiochemotherapy.

Non-randomized

CR achieved in 88%

70% “pleased” or “delighted” with urinary function

80% preserved bladder



RTOG 0926:

A PHASE II PROTOCOL FOR PATIENTS WITH STAGE T1 BLADDER CANCER TO EVALUATE SELECTIVE BLADDER PRESERVING TREATMENT BY RADIATION THERAPY CONCURRENT WITH RADIOSENSITIZING CHEMOTHERAPY FOLLOWING A THOROUGH TRANSURETHRAL SURGICAL RE-STAGING

**Patient Population:** (See [Section 3.0](#) for Eligibility) (3/31/14)

- Operable patients with non-muscle invading tumors and with at least one being a high grade Stage T1 urothelial carcinoma for whom radical cystectomy is being considered as the next conventional step in therapy by standard urologic guidelines
- AJCC Stages T1, NX or N0, M0, only transitional cell histology
- Restaged by a urologist in the participating institution with an aggressive, visibly complete TURBT with muscularis propria in the specimen but with no evidence of its invasion by tumor
- Failed standard treatment with, or is medically ineligible for, intravesical biological therapy or chemotherapy
- No evidence of prostatic stromal invasion by tumor

- Single arm study to evaluate chemoradiation in patients with HGT1 UCC bladder
- Primary endpoint: Radical cystectomy rate at 3 years
- Accrual is closed, estimated completion 2023



# Chemo after BCG Failure



# Valrubicin

EFFICACY AND SAFETY OF VALRUBICIN FOR THE TREATMENT OF  
BACILLUS CALMETTE-GUERIN REFRACTORY CARCINOMA IN SITU  
OF THE BLADDER

GARY STEINBERG, ROBERT BAHNSON,\* STANLEY BROSMAN, RICHARD MIDDLETON,  
ZEV WAJSMAN,† MICHAEL WEHLE AND THE VALRUBICIN STUDY GROUP‡

- Only approved intravesical agent for BCG-Refractory CIS when cystectomy not an option
- Single-arm study of patients with BCG Failure
  - 70% with  $\geq 2$  prior BCG courses
  - 81% with 3-24mo interval between last tx and valrubicin
  - Unclear % BCG unresponsive
- Primary outcomes DFR 6 months = 21%
- Suboptimal salvage therapy for BCG failure

# BCG Failure: Gemcitabine

## **SWOG S0353: Phase II Trial of Intravesical Gemcitabine in Patients with Nonmuscle Invasive Bladder Cancer and Recurrence after 2 Prior Courses of Intravesical Bacillus Calmette-Guérin**

Eila C. Skinner,\* Bryan Goldman, Wael A. Sakr, Daniel P. Petrylak,† Heinz-Josef Lenz, Cheryl T. Lee, Shandra S. Wilson, Mitchell Benson, Seth P. Lerner, Cathy M. Tangen and Ian M. Thompson‡

THE JOURNAL OF UROLOGY®

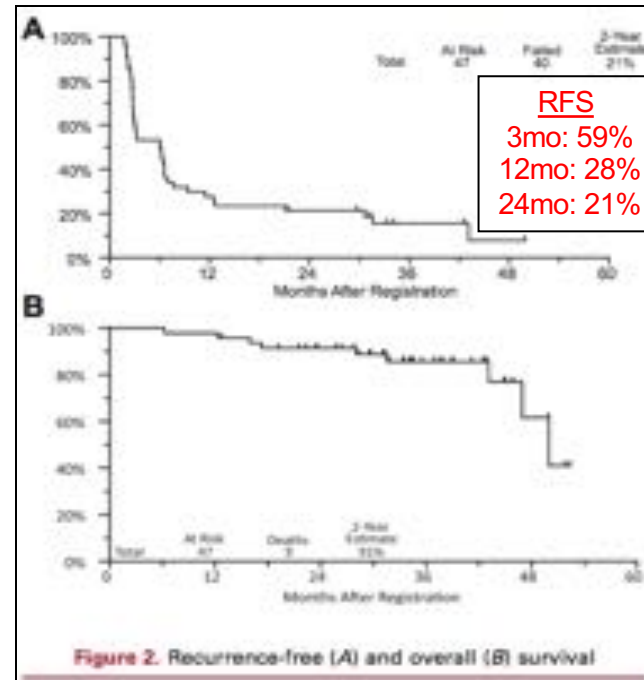
Vol. 190, 1200-1204, October 2013

- Single arm study, 55 patients
- 2g gemcitabine/100cc NS
  - Weekly x 6
  - Maintenance: monthly x 1
  - Dwell time: 1hr

## SWOG S0353: Phase II Trial of Intravesical Gemcitabine in Patients with Nonmuscle Invasive Bladder Cancer and Recurrence after 2 Prior Courses of Intravesical Bacillus Calmette-Guérin

### Baseline patient characteristics

	No. (%)
Male	33 (79)
Race:	
White	43 (91)
Asian	3
Mixed	1
Zubrod performance status:	
0	39 (83)
1	7 (15)
2	1 (2)
Multifocal low grade Ta	6 (13)
High grade Ta	11 (23)
High grade T1	2 (4)
CIS:	29 (60)
With papillary lesions	8 (17)
Prior BCG treatments:	
6 + 6 Wks or more	26 (55)
6 + 3 Wks	15 (32)
Less than 6 + 3 Wks (intolerance)	6 (13)
Not since last BCG:	
3 (refractory)	9 (19)
4-12	29 (60)
Greater than 12	10 (21)



Intravesical gemcitabine may be better than BCG for Refractory NMIBC

# BCG Failure: Nab-Paclitaxel

**Phase II Trial of Intravesical Nanoparticle Albumin Bound Paclitaxel for the Treatment of Nonmuscle Invasive Urothelial Carcinoma of the Bladder after bacillus Calmette-Guérin Treatment Failure**

James M. McKiernan,\* Dara D. Holder, Rashed A. Ghandour, LaMont J. Barlow, Jennifer J. Ahn,† Max Kates, Gina M. Badalato, Arindam Roychoudhury,‡ G. Joel Decastro and Mitchell C. Benson

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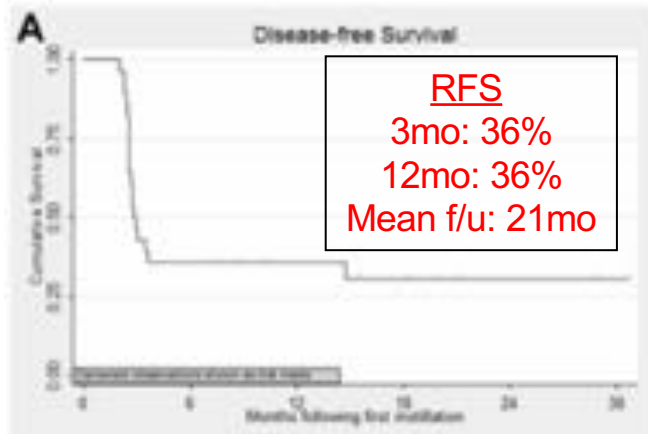
Vol. 192, 1633-1638, December 2014

- Prospective single institution: 28 patients
- Regimen:
  - Nab-Paclitaxel 500mg/100ml NS
  - Induction weekly x 6
  - Maintenance monthly x 6

	No. (%)
Gender:	
F	6 (21)
M	22 (79)
Clinical stage:	
Ta	4 (14)
Ta + Tis	2 (7)
T1	4 (14)
T1 + Tis	5 (18)
Tis only	13 (48)
Tumor grade:	
Low grade/multifocal Tis	1 (4)
High grade	27 (96)

	No. (%)
BCG alone induction	27 (96)
BCG alone reinduction	6 (21)
BCG maintenance	0
BCG + interferon	13 (48)
Intravesical chemotherapy:	
Mitomycin	1 (3.8)
Gemcitabine	3 (11)
Mitomycin+gemcitabine	1 (3.8)
Vinorelbine	1 (3.8)
No. cycles:	
1	7 (25)
2	12 (43)
3	8 (29)
4	1 (3.8)



Toxicity

9/28 (32%) grade 1-2

NO discontinuation of therapy



# BCG Failure: Combo Chemo

## Sequential Intravesical Gemcitabine and Docetaxel for the Salvage Treatment of Non-Muscle Invasive Bladder Cancer

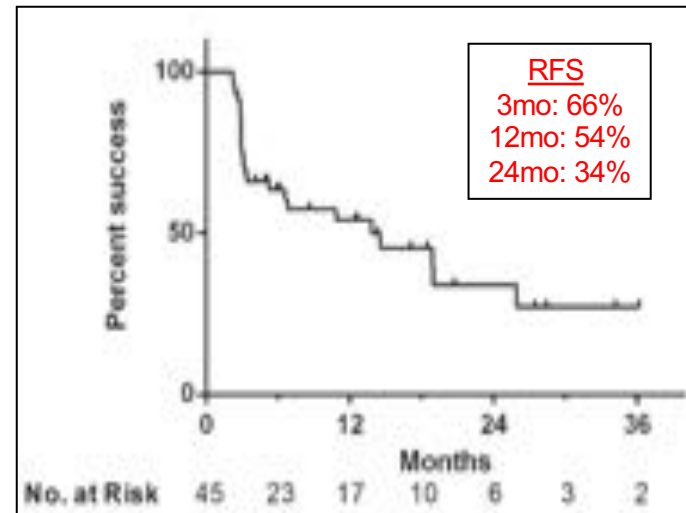
Ryan L. Steinberg, Lewis J. Thomas, Michael A. O'Donnell\* and Kenneth G. Nepple  
*University of Iowa Department of Urology, Iowa City, IA, USA*

**Bladder Cancer 1 (2015) 65–72**

- Retrospective case series: 45 patients
- Regimen:
  - Gemcitabine 1g/50cc NS x 90min
  - Followed by docetaxel 37.7mg/50ml NS x 2hrs
  - Induction weekly x 6
  - Maintenance monthly x 24

# Sequential Intravesical Gemcitabine and Docetaxel for the Salvage Treatment of Non-Muscle Invasive Bladder Cancer

<b>Stage</b>	
CIS alone	20 (44%)
TaLG	4 (9%)
TaLG + CIS	0
TaHG	8 (18%)
TaHG + CIS	5 (11%)
T1HG	4 (9%)
T1HG + CIS	4 (9%)
T1LG	0
T1LG + CIS	0
<b>Prior treatments</b>	
Median induction courses (range)	2 (0-4)
BCG naïve	4 (9%)
1 prior BCG failure	17 (38%)
≥2 prior BCG failures	24 (53%)



40/45 (89%) tolerated full induction  
28/45 (62%) with symptoms during induction  
7/45 (16%) impacted treatment schedule

# BCG Failure: Combo Chemo

Multi-institutional analysis of sequential intravesical gemcitabine and mitomycin C chemotherapy for non-muscle invasive bladder cancer

Andrew J. Lightfoot, M.D.<sup>a</sup>, Benjamin N. Breyer, M.D.<sup>b</sup>, Henry M. Rosevear, M.D.<sup>a</sup>,  
Bradley A. Erickson, M.D., M.Sc.<sup>a</sup>, Badrinath R. Konety, M.D., M.B.A.<sup>c</sup>,  
Michael A. O'Donnell, M.D.<sup>a,\*</sup>

Urologic Oncology: Seminars and Original Investigations 32 (2014) 35.e15–35.e19

- Multi-institutional retrospective series: 47 patients
- Regimen:
  - Gemcitabine 1g/50cc NS x 90min
  - Followed by MMC 40mg/20ml NS x 90min
  - Induction weekly x 6
  - Maintenance monthly x 12

## Multi-institutional analysis of sequential intravesical gemcitabine and mitomycin C chemotherapy for non-muscle invasive bladder cancer

Andrew J. Lightfoot, M.D.<sup>a</sup>, Benjamin N. Breyer, M.D.<sup>b</sup>, Henry M. Rosevear, M.D.<sup>a</sup>,  
Bradley A. Erickson, M.D., M.Sc.<sup>a</sup>, Badrinath R. Konety, M.D., M.B.A.<sup>c</sup>,  
Michael A. O'Donnell, M.D.<sup>a,\*</sup>

- 87% high grade
- Median # prior tx: 2
  - 55%  $\geq$  2 prior tx
- 30% grade 1-2 toxicity
  - 4/47 (9%) discontinued induction

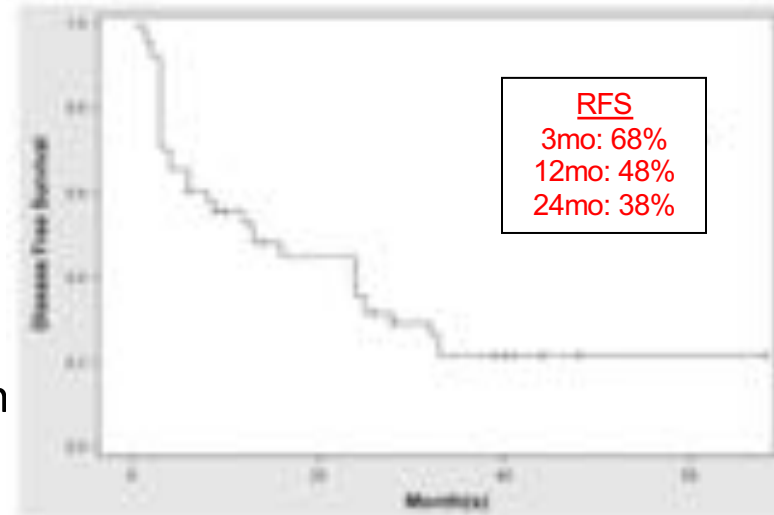


Fig. 1. Recurrence-free survival for all patients. (A) RFS based on stage: 68% CR, 48% 1-RFS, and 38% 2-RFS.

Lightfoot et al. Urol Oncol 2014;35:e15

# Immunotherapy



- BCG
- Interferon
- Emerging Therapies

# Repeat BCG

- Persistent disease after single induction course, repeat induction
  - 43-63% response rate
- Additional  $\geq 3$  courses not recommended
  - 20% response rate
  - 80% rate of progression/metastasis
  - Increased toxicity

Bui, *Urology* 1997:49

Reijke et al, *J Urol* 2005; 173



# BCG + Interferon

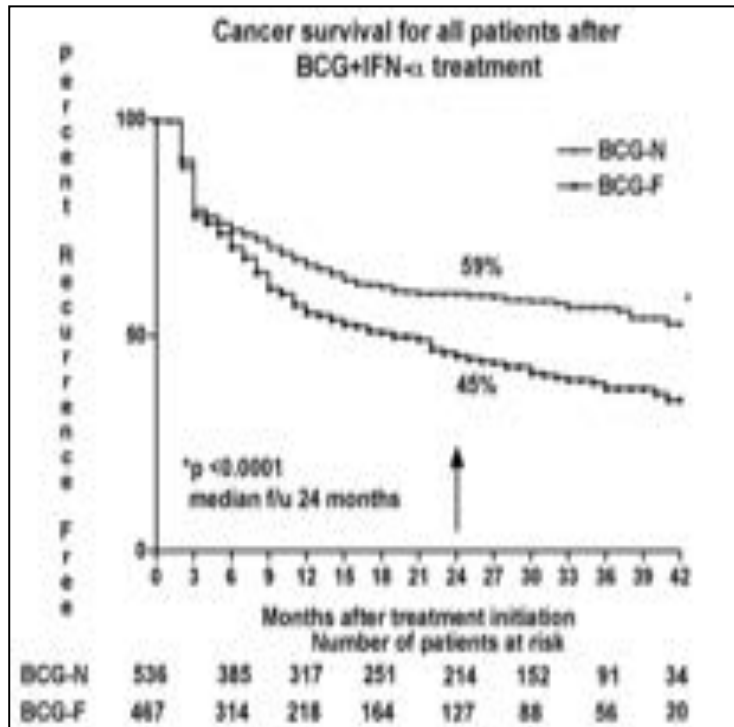
Seminar article

Final results from a national multicenter phase II trial of combination bacillus Calmette-Guérin plus interferon  $\alpha$ -2B for reducing recurrence of superficial bladder cancer<sup>☆</sup>

Fadi N. Joudi, M.D.<sup>a</sup>, Brian J. Smith, Ph.D.<sup>b</sup>, Michael A. O'Donnell, M.D.<sup>a,\*</sup>, and the National BCG-Interferon Phase 2 Investigator Group

- Large non-randomized phase 2
  - Group 1- BCG Failure (n=467)
    - 1/3D BCG + 50m u INF- $\alpha$  (+maintenance)
  - Group 2- BCG Naive (n=536)
    - FD BCG + 50m u INF- $\alpha$  (+maintenance)

# BCG + Interferon



- Consideration for BCG failure after 1 course (HR 1.5 for failure after  $\geq 2$  courses)
- Not directly compared to BCG re-induction alone
- Multiple design concerns (BCG naïve patients)

# BCG + Interferon

- Further data demonstrate that BCG-IFN no more effective than BCG alone<sup>1</sup>
- Response rate at 24 months 23% for truly BCG unresponsive disease<sup>2</sup>
  - Similar to historic BCG rates
- Bottom line: **BCG+IFN has a limited role** in treatment of BCG refractory NMIBC

<sup>1</sup>Nepple, J Urol 2010; 184.

<sup>2</sup>Roseveat, J Urol 2011; 186

A microscopic image showing a cluster of cells. On the left is a large, bright green, spherical cell cluster with a fuzzy, fibrous surface. To its right is a larger, more complex cluster of cells in shades of blue and cyan, with some cells appearing more rounded and others more elongated. The background is black.

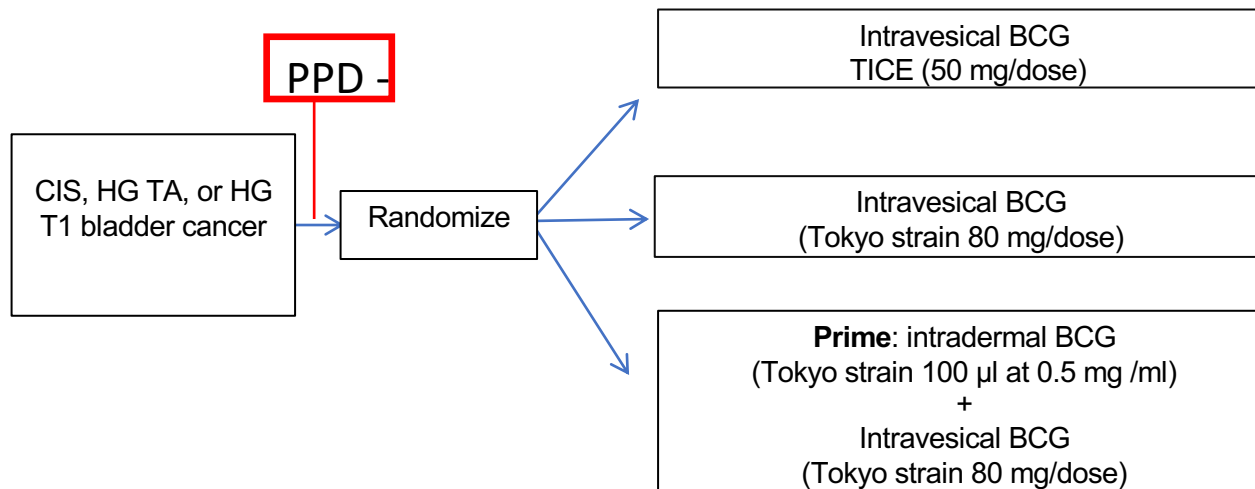
# Emerging Immunotherapies

# SWOG S1602 (PRIME)

PI: Rob Svatek



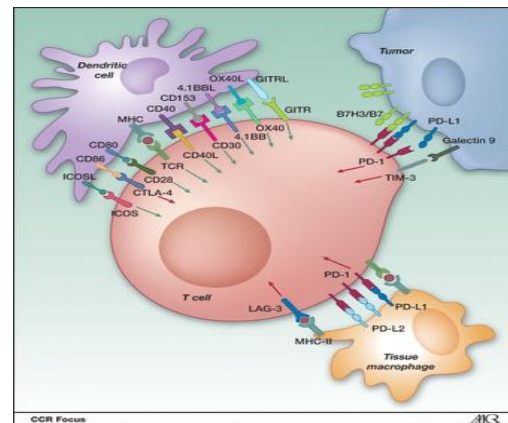
- Intradermal injection to augment BCG response
- Leads to BCG-specific memory T cell response → increased bladder infiltration by cytotoxic CD8+ T cells upon repeated BCG exposure



# SWOG 1605

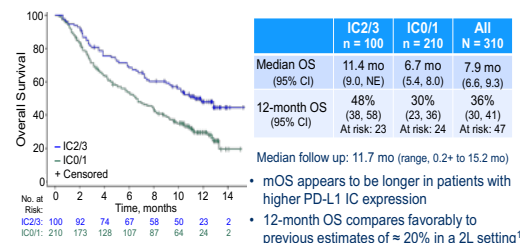
## Phase 2 trial of Atezolizumab in BCG-unresponsive NMIBC

- Single agent IV Atezolizumab
  - Antibody targets PD-L1
- BCG unresponsive population
- Building on success seen in metastatic UCC
- Opened first quarter 2017



PI: Peter Black

IMvigor 210: Overall Survival in mUC



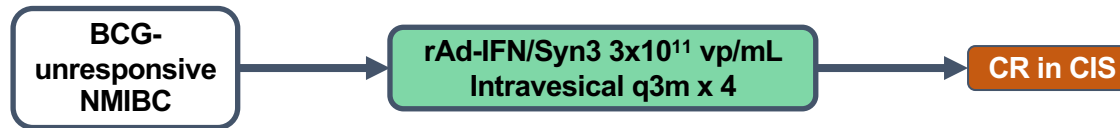
NE, not estimable. Data cutoff September 14, 2015.  
Reference: 1. Agarwal N, et al. Clin Genitourin Cancer. 2014; 12(2):130-137.



# Viral Gene Therapy: CG00700

- CG0070 – oncolytic adenovirus
  - Expresses GMCSF transgene
  - Selectively replicates in Rb-deficient cells
- Phase I: 49% RR at 10.4 months
- Phase III: Single arm study, RR at 18 months
  - NCT02365818
  - PD-1 and PD-L1 immunohistochemistry scores of tumor cells and infiltrating immune cells

# Instiladrin rAd-IFN-CS-003



PI Boorjian

- Adenovirus vector harboring human IFN alpha2b gene
  - Gene incorporated into bladder lining → expression of large amount of protein
- 40 patients
- 35% high-grade 12mo RFS
- No grade 4/5 AE or tx discontinuation
- Phase III trial now completed accrual (n=157)

Intravesical rAd-IFN $\alpha$ /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. Sawatz, Seppo Yla-Herttuala, Nigel R. Parker, and Colin P.N. Dinney

J Clin Oncol, 2017

# Future Directions

- Targeted therapy
  - VEGFR3-FGFR3 inhibitor (dovitinib) (NCT01732107)
  - mTOR inhibitor (everolimus) + gemcitabine (NCT01259063)
  - Vicinium (EpCam Ab conjugate)
  - Oral sunitinib (NCT 01118351)
  - ALT-801 + gemcitabine (NCT 01625260)
- Drug delivery
  - MitoGel – thermosensitive hydrogel MMC
  - Taris GemRIS

# Ongoing Trials: BCG-Refractory NMIBC

Agent	Mechanism	Sponsor	Phase	NCT#
Panvac +/-BCG	Vaccine	NCI	II	NCT02015104
ALT-801 + gem	Vaccine	Altor Bioscience	I/II	NCT01625260
rAD-IFN/Syn3	Gene therapy	FKD Therapies Oy	III	NCT02773849
CG0070	Oncolytic virus	Cold Genesys	III	NCT02365818
Pembrolizumab	PD-1 blockade	Merck	II	NCT02625961
Atezolizumab +/- BCG	PD-L1 blockade	Hoffmann-La Roche	I/II	NCT02792192
Vicinium	Ab target EpCAM	Viventia Bio	III	NCT02449239
VPM1002BC	Modified BCG	Swiss Group for Clinical Research	I/II	NCT02371447

# Take-Home Points

- BCG + maintenance remains first-line standard of care therapy for high risk NMIBC
- Defining BCG unresponsive disease consistently is paramount
- Cystectomy is standard of care for BCG unresponsive disease *for now*
- Bladder-preserving regimens available - including intravesical chemo, immunotherapy and radiation
- Large amount of clinical investigation ongoing for improving outcomes for BCG unresponsive patients





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