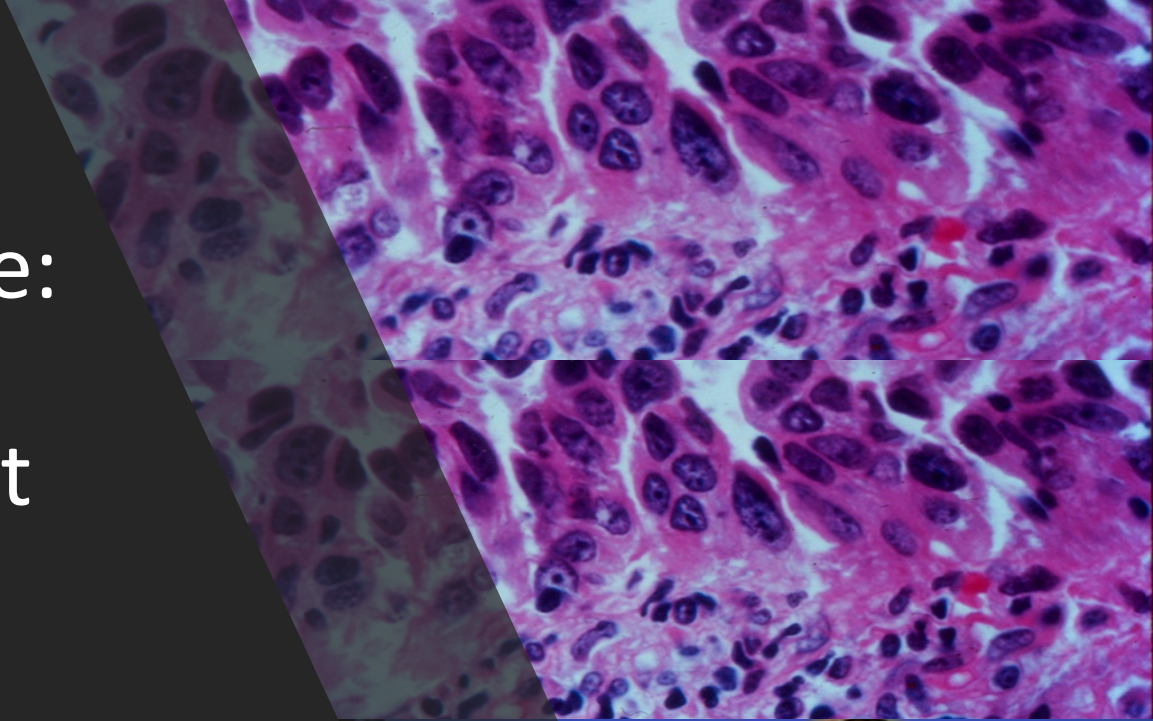
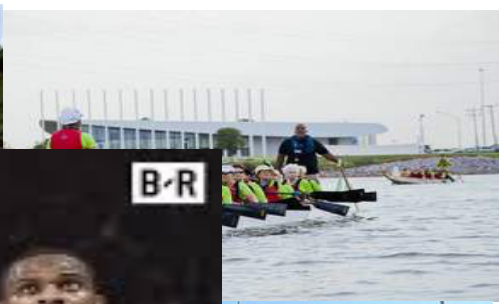


# BCG Failure or BCG Unresponsive: Defining and Managing Difficult Patients

Michael S. Cookson, MD,  
Professor and Chair  
Department of Urology  
University of Oklahoma





# Non-muscle Invasive Bladder Cancer

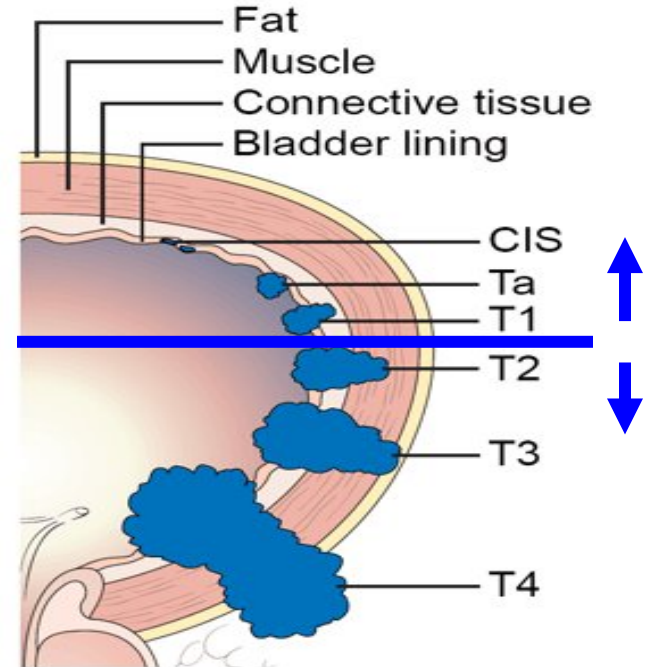
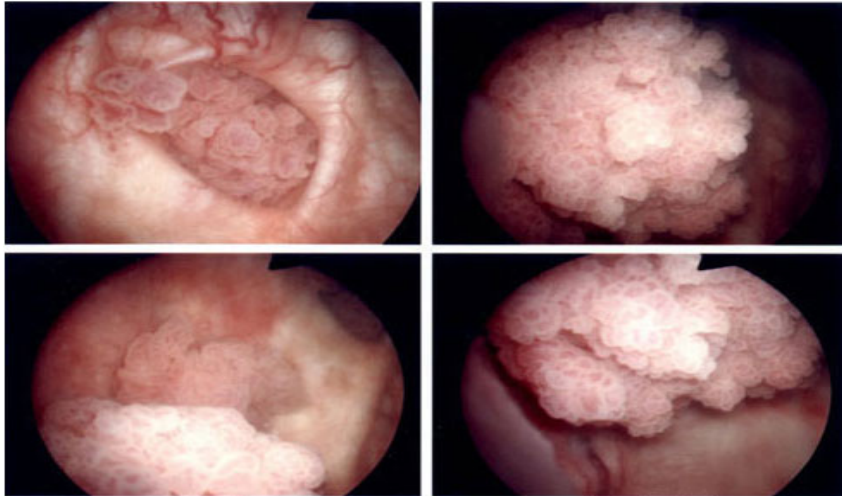
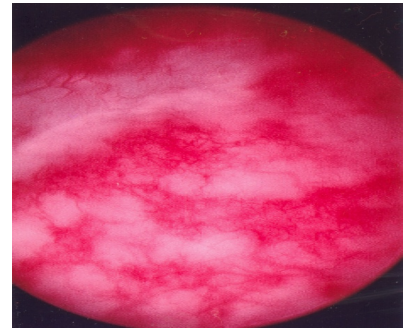


Diagram showing the T stages of bladder cancer  
© CancerHelp UK

# Bladder Cancer: Facts

- 80% present with NMIBC:
  - 70% Ta (papillary)
  - 20% T1 (lamina propria)
  - 10% CIS (high grade, flat)



# Natural History

- Difficult to predict (tumor heterogeneity)
- Two characteristic features:
  1. Recurrence:
    - 70% recurrence with TUR alone
  2. Tumor progression:
    - 30% tumor progression w/TUR alone

# Treated Natural History of NMIBC

## 15 Year Follow-up

- 86 high-risk patient with NMIBC
- Treated with TUR alone or TUR+BCG
- Progression in 53%, 18% UTT
- 36% underwent cystectomy
- 15-yr DSS was 63%, 34% dead of disease
- Life-long bladder and UTT surveillance

Cookson MS, Herr HW, et al: J. Urol. 1997; 158: 62–67.



## APPROXIMATE PROBABILITY OF RECURRENCE AND PROGRESSION

<b>Pathology</b>	<b>Approximate Probability of Recurrence in 5 years</b>	<b>Approximate Probability of Progression to Muscle Invasion</b>
<b>Ta, low grade</b>	<b>50%</b>	<b>Minimal</b>
<b>Ta, high grade</b>	<b>60%</b>	<b>Moderate</b>
<b>T1, low grade (rare)</b>	<b>50%</b>	<b>Moderate</b>
<b>T1, high grade</b>	<b>50- 70%</b>	<b>Moderate- High</b>
<b>Tis</b>	<b>50%- 90%</b>	<b>High</b>

# BCG Is Standard of Care

- Most intermediate and all high risk NMIBC
- Superior to intravesical chemotherapy
- Supported by meta-analysis (9 RCTs)
  - 68% initial CR
  - 47% durable CR (3.6 yr median f/u)
- Endorsed by AUA, EAU NCCN Guidelines
- Best results with maintenance

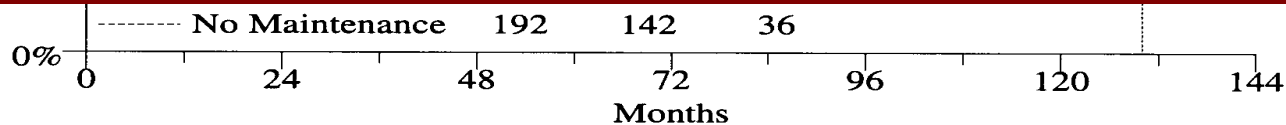


# Has Become U.S. Standard of Care

## SWOG 8507 - BCG Maintenance

2-year RFS 82% vs. 62% with/without maintenance

5-year RFS 60% vs. 41% with/without maintenance



# The Problem: Some Will Fail BCG

- Despite the benefits of BCG, long-term disease-free and progression-free survival may be difficult to achieve
- 50% will recur after induction BCG, and  $\cong$ 30% salvaged with additional BCG
- But, BCG failure may be lethal if untreated
- Key: identify early those failures

# Potential Causes of BCG Failure

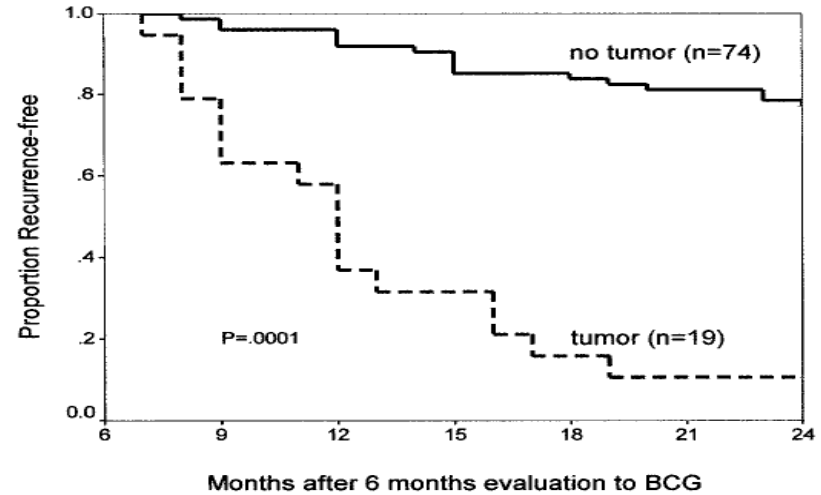
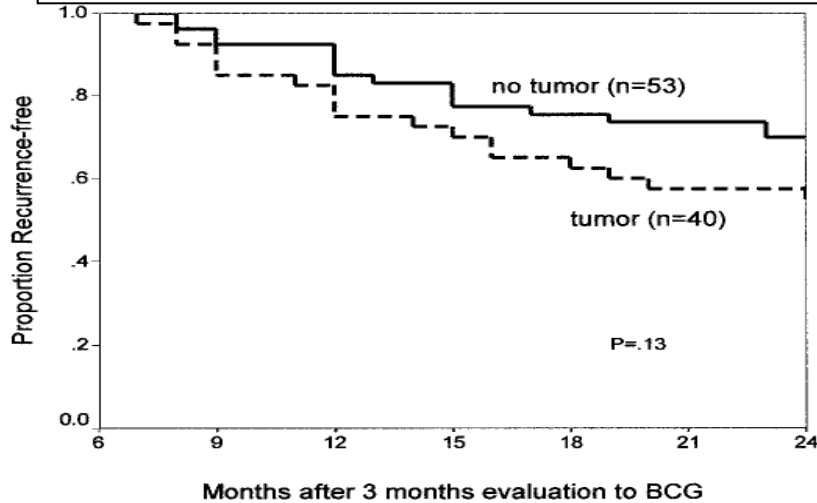
- Host immune incompetence
- Inadequately resected or occult invasive
- Resistant or non-antigenic tumor
- Inadequate treatment schedule
- Inadequate dose: too few CFU
- Inadequate contact of BCG and UCC
- Excess BCG inducing immunosuppression

# Definitions of BCG Failure

- **Intolerant:** recurrent disease in setting of inadequate BCG treatment due to side effects
- **Resistant:** recurrence of lesser or improving disease that resolves with further BCG
- **Relapsing:** recurrence after achieving 6 month CR, i.e. disease resolves after BCG then returns
- **Refractory:** No CR by 6 months after BCG... not improving or worsening disease despite two courses of BCG or maintenance

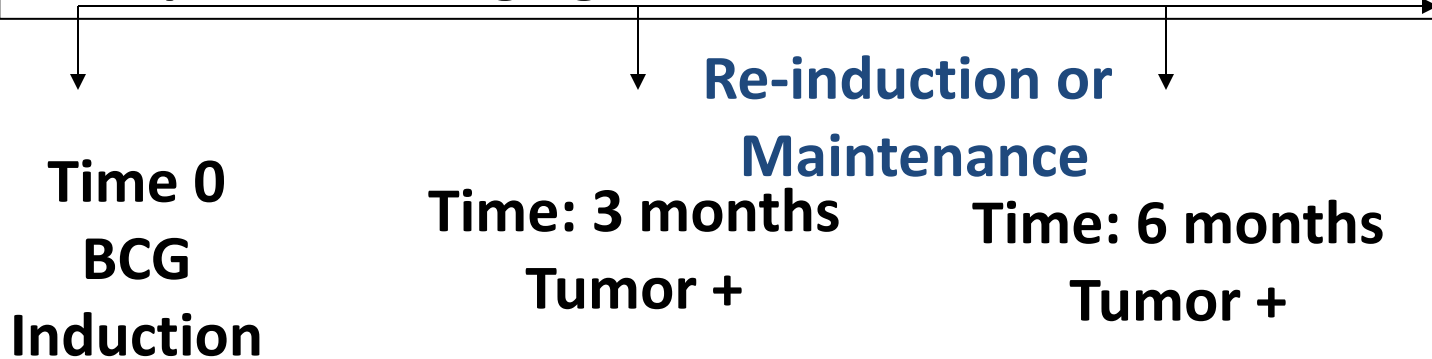
# Determining BCG Resistance: BCG Response over Time

- 6 months is the treatment period to identify high-risk tumors as truly refractory



# BCG Refractory

- Failure to achieve a disease free state 6 months after initial BCG therapy with either maintenance or retreatment at 3 months due to either rapidly recurrent or persistent high grade disease



Herr HW. J Urol 169:1706-1708, 2003  
Nieder AM, et al. Urology 66(S6A):108-125, 2005

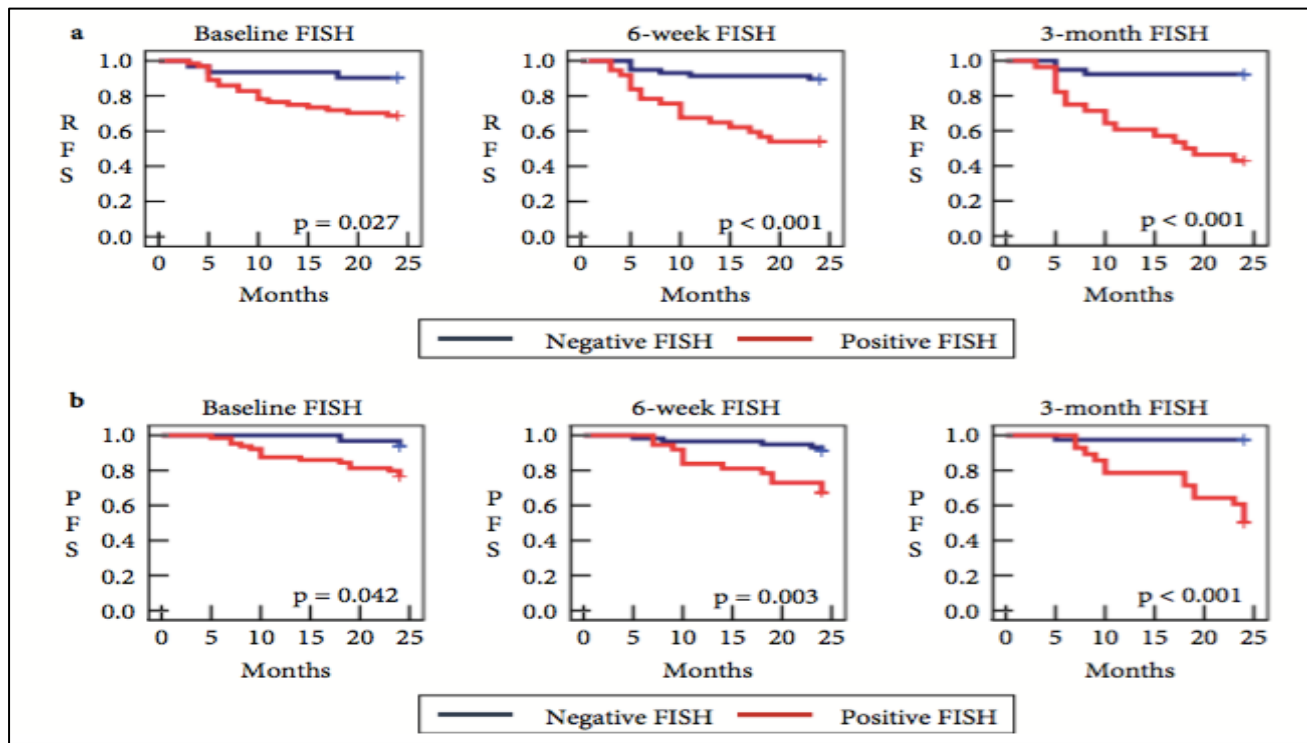
**Ultimately, determining when a patient  
has “failed” BCG is a shared decision  
between urologist and patient**

# Novel Definition: Molecular Failure

- Goal: Incorporate FISH testing to predict BCG failure before it becomes clinically apparent
- 143 patients treated with BCG live therapy followed prospectively for 2 years
- FISH assays collected at 6 weeks and 3 months
- Results of the FISH assays were correlated with clinical outcomes



# Recurrence and Progression-Free Survival based on FISH



# Novel Definition: Molecular Failure

- Result: FISH results correlated with recurrence
- Conclusion: Patients with an early positive FISH and a negative cystoscopy at 3 months should be considered “molecular BCG failures” and could enroll in prospective RCT’s

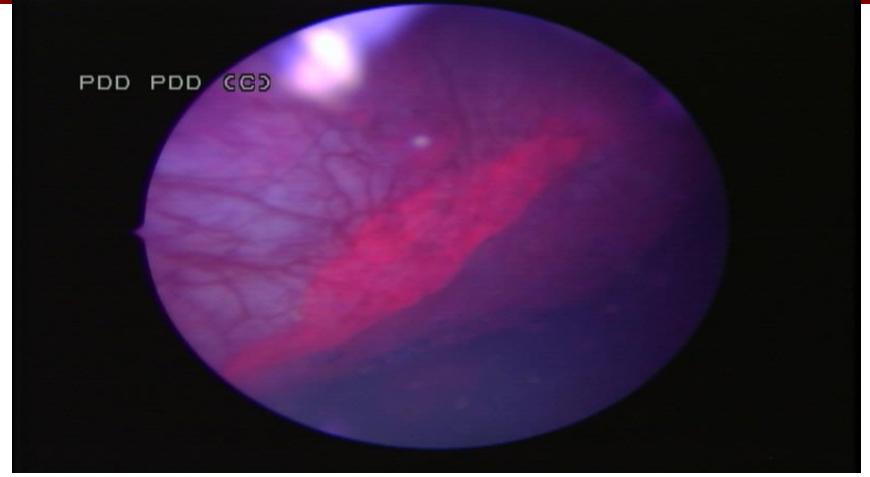
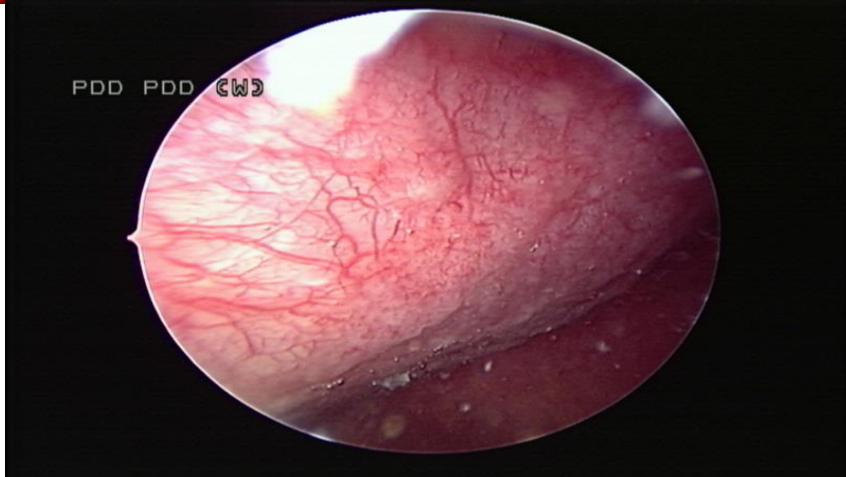
# Treatment Dilemma

- Cystectomy recommended as a standard of care after BCG failure
- Cystectomy has high rate of cure if before progression to muscle invasion
- Unfortunately, morbidity remains high
- And, many with high risk NMIBC who fail BCG are not candidates for cystectomy

# Strategies to Reduce Persistence and Recurrence of BCG Refractory CIS

- Better Surgery → Enhanced detection and more complete fulguration
- Better Agents → Enhanced IVe chemotherapy and immunotherapy
- Better Delivery System → Enhanced Bladder Penetration
- Better Diagnostics → Enhanced Predictive and Prognostic Tools

# Photodynamic Diagnostic Cystoscopy



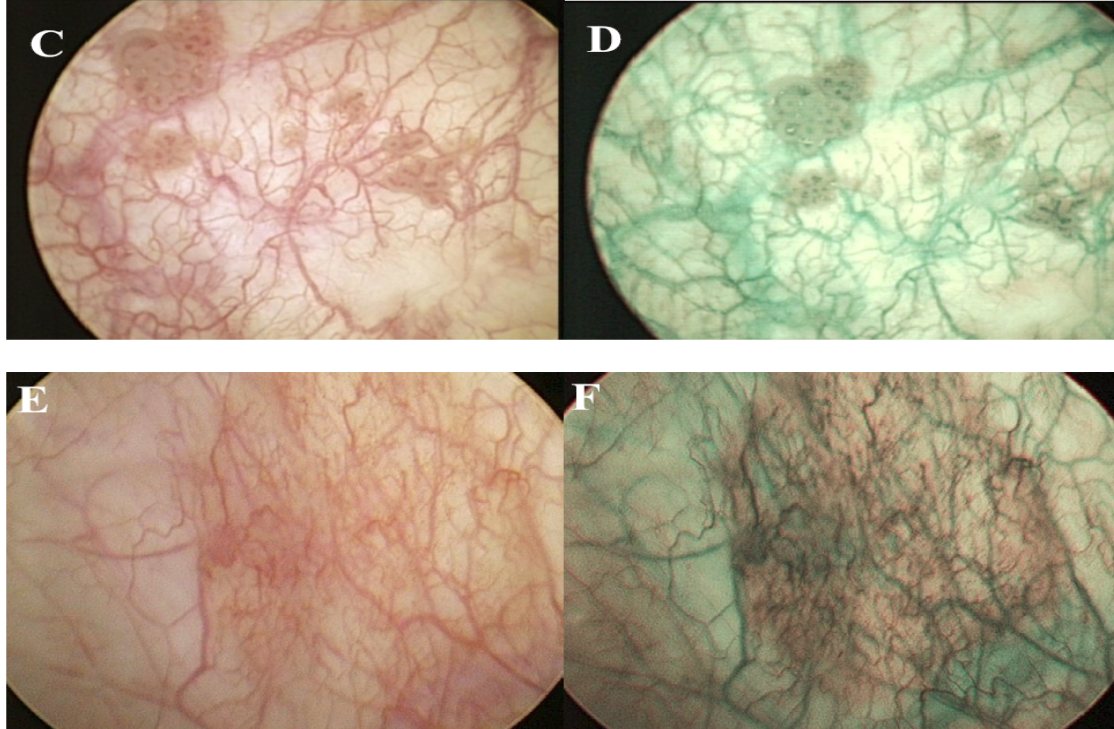
PDD exploits the photoactive properties of compounds such as hexaminolevulinate (HAL) (Hexvix™, Cysview™). Following instillation, HAL accumulates in neoplastic tissue. Illumination with blue-violet light produces a clearly demarcated red fluorescence from malignant tissue.

# Photodynamic Diagnosis of Non-muscle-invasive Bladder Cancer with Hexaminolevulinate Cystoscopy: A Meta-analysis of Detection and Recurrence Based on Raw Data

*Maximilian Burger<sup>a,\*</sup>, H. Barton Grossman<sup>b</sup>, Michael Droller<sup>c</sup>, Joerg Schmidbauer<sup>d</sup>, Gregers Hermann<sup>e</sup>, Octavian Drăgoescu<sup>f</sup>, Eleanor Ray<sup>g</sup>, Yves Fradet<sup>h</sup>, Alexander Karl<sup>i</sup>, Juan Pablo Burgués<sup>j</sup>, J. Alfred Witjes<sup>k</sup>, Arnulf Stenzl<sup>l</sup>, Patrice Jichlinski<sup>m</sup>, Dieter Jocham<sup>n</sup>*

- Prospective studies: 1345 patients
- FC cystoscopy used as an adjunct to white light (WL) cystoscopy
- Outcome: Detection of NMIBC up to 1 year
- FC cystoscopy detected significantly more tumors than WL
  - Ta tumors (14.7%;  $p < 0.001$ )
  - CIS lesions (40.8%;  $p < 0.001$ )
- In 26.7%, CIS was detected only by FC ( $p < 0.001$ )
- Recurrences were significantly lower with FC
  - 34.5% vs. 45.4% ( $p = 0.006$ )

# Narrow Band Imaging™ (NBI)



- Olympus Optical imaging technology enhances visibility of vessels on mucosal surfaces
  - Filters WL into specific light wavelengths that penetrate only surface of human tissue and are absorbed by HgB
  - Bluish light enhances **superficial capillary network (brown)**
  - Greenish light enhances **deeper vessel visibility: vessels are greenish-blue (cyan)**
- Cauberg EC et al. Urol 76: 658, 2010

# Detection of CIS by Cystoscopy WL and NBI

Series	No.	Cysto	Sens.	Spec.	PPV	NPV
Herr & Donat	67	WL/NBI	83/100	72/76	36/36	97/100
Tatsugami	30	WL/NBI	50/90	83/75	76/78	61/87
Cauberg	14	WL/NBI	55/69			
Shen	11	WL/NBI	68/77	82/77		75/83

Herr HW. Curr Urol Rep 2014



# Strategies to Reduce Persistence and Recurrence of BCG Refractory CIS

- Better Agents → Enhanced IVe chemotherapy and immunotherapy

# Valrubicin: Pivotal Study

- Open-label, phase III trial
- 90 patients with CIS after prior IVe therapy
- 21% CR at 6 months
- 32% CR at 6 months if you consider that with low grade recurrences (10 pts)
- Overall progression was low
- But, only 8% remained NED at 30 months

# Valrubicin: Take Home Message

- FDA-approved for patients with CIS who fail BCG and are unfit or unwilling to undergo a radical cystectomy
- Despite FDA approval, long-term DFS remains poor and highlights the need for additional bladder-conserving therapies

# Gemcitabine Trials

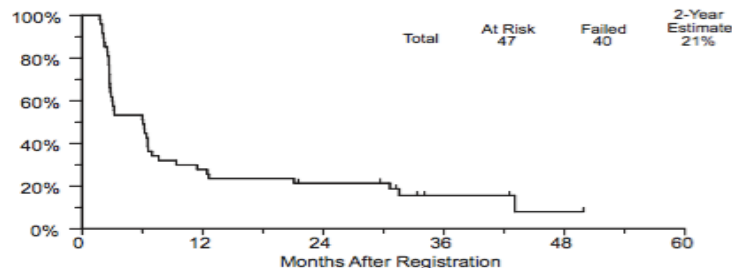
- Inhibits DNA synthesis
- Introduced by Dalbagni (2002) as safe
- Efficacy demonstrated in multiple Phase II trials with

Author	CR	Recurrence	Median time to recurrence	Comments	n
Dalbagni 2002 <sup>[15]</sup>	39% at 8-week follow-up	NA	NA	Phase I trial, no serious adverse events	18
Dalbagni 2006 <sup>[15]</sup>	50% at 8-week follow-up	90% of patients at 2 years	3.6 months	All patients had failed BCG	30
Sternberg 2013 <sup>[16]</sup>	39.1% at 8-week follow-up	62% DFS at 12 months	NA	Cumulative 5-year incidence of progression was 20%	69
Bartoletti 2005 <sup>[14]</sup>	Not reported	74.6% DFS at 12 months	7 months	Progression in 7/116 patients; 70 of 116 patients in this trial were naïve to BCG	116
Skinner 2013 <sup>[17]</sup>	47% at 12 weeks	27.6% DFS at 12 months 21% DFS at 24 months	6.1 months	Induction with 10-month maintenance Progression occurred in 2/47 patients	47
Perdona 2010 <sup>[19]</sup>	NA	45% DFS at median 15.2 months	3.5 months	Induction and maintenance therapy	20

CR=Complete response, NA=Not assessed, DFS=Disease-free survival, BCG=Bacillus Calmette-Guérin

# Gemcitabine: SWOG S0353

- U.S. Phase 2 Trial
- 47 patients with HG Ta, T1 and/or CIS who has received at least 2 prior courses of BCG
- Received 2 grams in 100cc NS q week x 6 weeks and the q month x 10 months
- Results: Recurrence-free
  - 3 months: 47% CR
  - 12 months: 28% CR
  - 24 months: 21% CR



# Taxane Trials

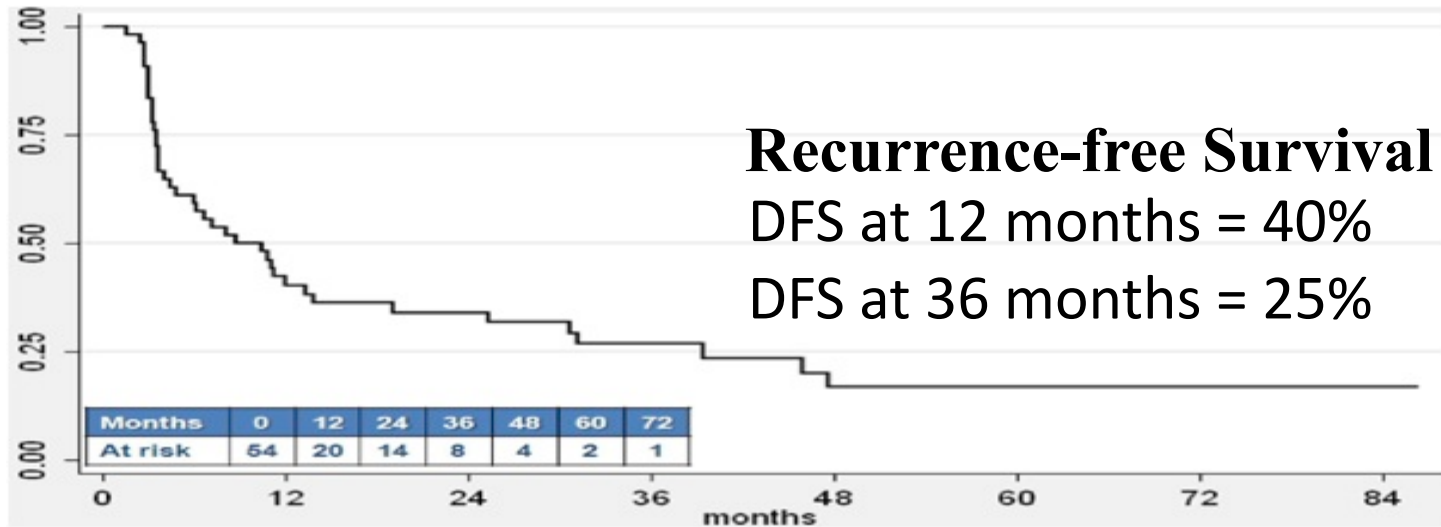
- Inhibits microtubule depolymerization
- Introduced in BCG failures by McKiernan (2006) with no dose-limiting toxicity at 75 mg
- Efficacy demonstrated in several Phase I / II studies, most with some form of maintenance

Author	CR	Recurrence	Median time to recurrence	Comments	n
McKiernan 2006 <sup>[23]</sup> Laudano 2010* <sup>[24]</sup>	55% at 4 weeks	22.2% DFS at 28 months	Not reported	Phase I trial, no dose-limiting toxicities, follow-up demonstrated progression in 11.1% of patients	18
Barlow 2009 <sup>[25]</sup>	61%	1 year DFS: 45% 2 year DFS: 32%	Not reported	Induction with 9-month maintenance therapy in select patients	33
Barlow 2009 <sup>[26]</sup>	76.9%	46.2% DFS at 13 months	Not reported	Received induction and 9 months of maintenance	13
Barlow 2013 <sup>[27]</sup>	59%	1 year DFS: 40% 3 year DFS: 25%	With docetaxel maintenance 39.3 vs 19.0 months in those without maintenance		54

\*Long-term follow-up of phase I study cohort. CR=Complete response, DFS=Disease-free survival, BCG=Bacillus Calmette-Guérin

# Docetaxel

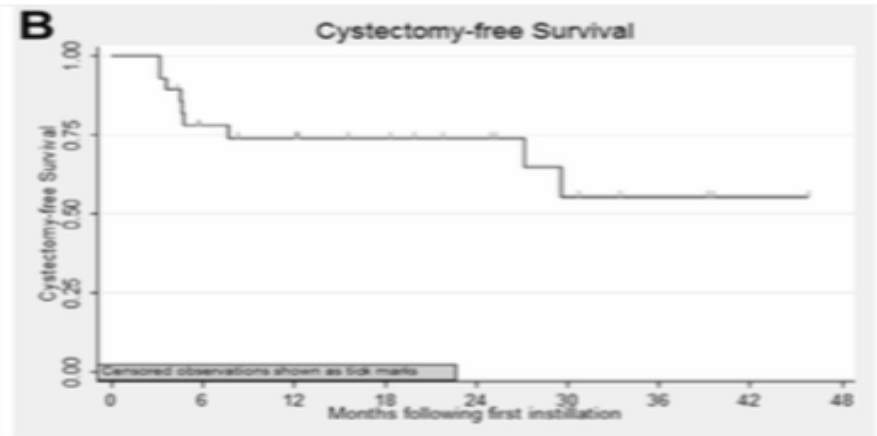
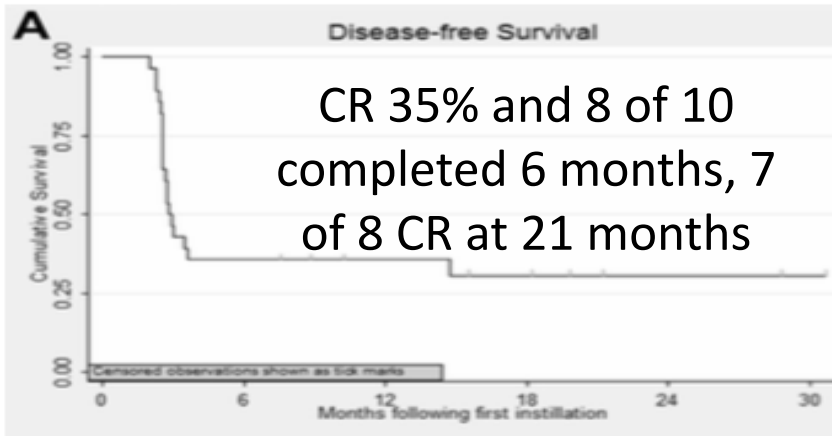
- 54 patients
- All failed prior BCG – 22 had only one prior course
- 83% high grade, 53% with CIS



Barlow et al, J Urol 189:834, 2013

# Paclitaxel

- Phase II study of 28 patients recurrent Tis, T1 and Ta who failed at least 1 cycle of BCG
- 6 weekly nab-paclitaxel 500 mg/100 ml, and monthly maintenance for 6 months



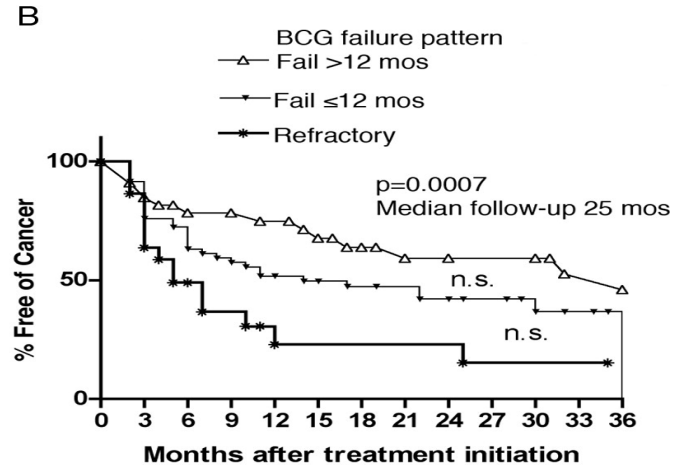
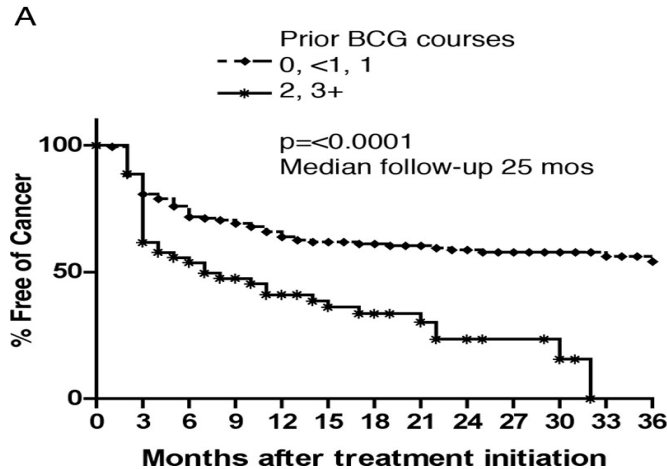


# BCG + IFN in BCG Failures

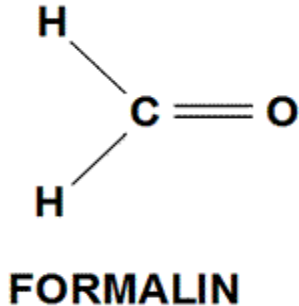
- Luciani, Urol. 2001:
  - 9/15 (60%) CR (NED) with median F/U 18 months
- Lam, Urol Oncol, 2003:
  - 12/20 (60%) NED with median F/U 22 months
- Punnen, Can J Urol, 2003:
  - 6/12 (50%) NED at 12 months
- O' Donnell, 2004:
  - 231 pts: 42% remaining disease-free at 24 months

# BCG + IFN

- Multicenter Phase II: 1,007 pts BCG naïve and failure
- At 24 months, 45% of BCG failure were disease-free
- Those with  $\geq 2$  prior courses of BCG or BCG-refractory had worse outcomes



# For Certain High Risk, NMIBC: The Most Definitive Therapy

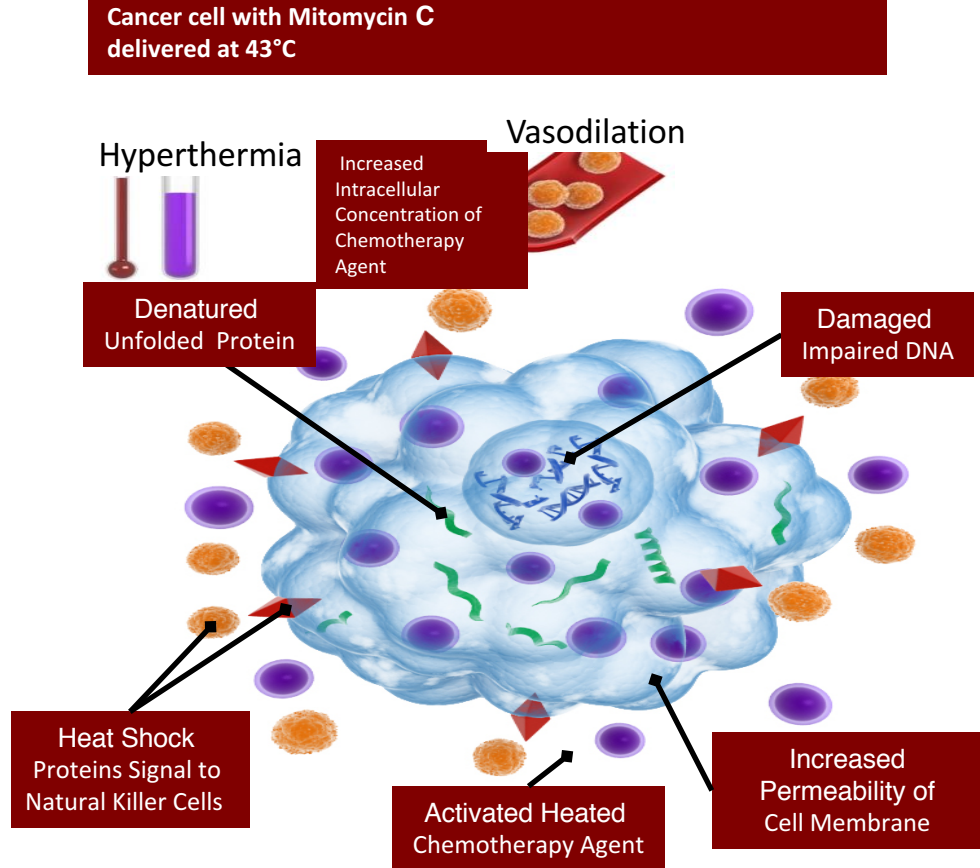


# Strategies to Reduce Persistence and Recurrence of BCG Refractory CIS

- Better Delivery System → Enhanced Bladder Penetration

# Hyperthermia Synergy

- Delivery of hyperthermic chemotherapy with temp  $41^{\circ}$  -  $44^{\circ}$  C
- Mechanism:
  - Direct cytotoxic effects
  - Enhanced penetration of chemo agent



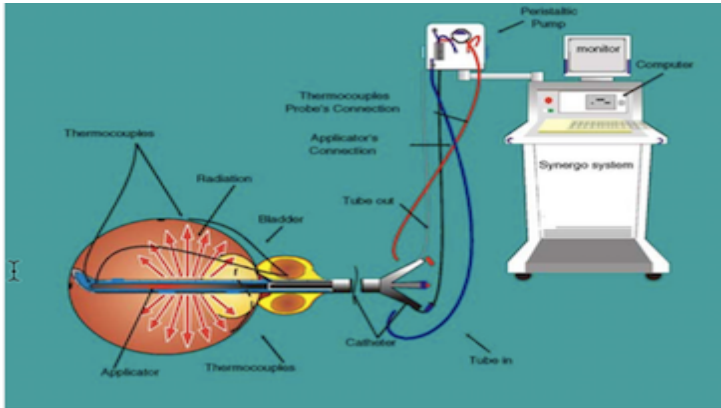
# MMC and Hyperthermia

- 160 patients: 129 (80.6%) BCG failures from a combined “10-year single center experience”
- MMC induction plus maintenance
- Median F/U 75 months
- RFS: 60% (1 year)
- RFS: 47% (2 years)
- Progression to MIBC: 4.3%
- 6.3% discontinued due to side-effects

# Hyperthermia Systems

## Synergo

- Intravesical microwave applicator
- 5 thermocouplers deliver hyperthermia to the bladder via direct contact



## Combat BRS

- Bladder Recirculation System
- External warmer



van der Heijden AG et al. Eur Urol 2004  
Souas A et al. Int J Hyperthermia 2014

# Photodynamic Therapy (PDT)

- Photosensitizing agent with activation by light
- Initial report w/BCG failures with 5-ALA by Waidelich (2001) with 60% CR in Cis and 21% papillary tumors
- ALA may cause hypotension requiring intervention
- Pilot studies with HAL and Radachlorin show promise

Agent	CR	Recurrence	Comments	n
5 ALA <sup>[35]</sup>	19/24 patients	DFS of 60% of patients with CIS at publication DFS of 21% without CIS at publication	Good response seen in CIS	24
5 ALA <sup>[37]</sup>	7/11 patients at 3 months	DFS in 5/11 patients at median of 18 month follow-up	Systemic toxicity with hypotension and skin sensitization	11
HAL <sup>[38]</sup>	52.9%	DFS at 21 months was 11.8%	No dose-limiting toxicity in phase 1 study	17
Radachlorin <sup>[39]</sup>	100% at 12-week follow-up	DFS at 30 months of follow-up was 60.1%	Prospective trial, safe with no dose-limiting toxicity All patients had high-grade disease	34

PDT=Photodynamic therapy, CR=Complete response, DFS=Disease-free survival, BCG=Bacillus Calmette-Guérin, CIS=Carcinoma *in situ*, ALA=Aminolevulinic acid, HAL=Hexaminolevulinic acid



# Lots of Medications In Trials

Drug	Trial Number	Phase	Description
rAd-IFN/Syn3 (Instiladrin)	NCT01687244	II	Interferon- $\alpha$ 2b transfected into urothelial cells via adenovirus vector
RAD001 (Everolimus)	NCT01259063	I/II	Intravesical gemcitabine + oral everolimus (mTOR inhibitor)
Dovitinib	NCT01732107	II	Oral dovitinib (tyrosine kinase inhibitor) for patients with FGFR3 over-expression/mutation
Sunitinib	NCT01118351	II	Oral sunitinib (tyrosine kinase inhibitor)
EN3348	NCT01200992	III	Mycobacterial cell wall-DNA complex Vs. Mitomycin C
ALT-801	NCT01625260	I/II	Recombinant protein – IL-2 + anti-p53-receptor
DTA-H19/PEI	NCT00595088	II	dsDNA plasmid – diphtheria toxin gene under H19 regulation (upregulated in tumor cells)
CG0070	Pending	II	GM-CSF transfected into urothelial cells via adenovirus vector
nab-rapamycin	Pending	I/II	Intravesical nanoparticle albumin-bound rapamycin (mTOR inhibitor)

# BCG Unresponsive Trials

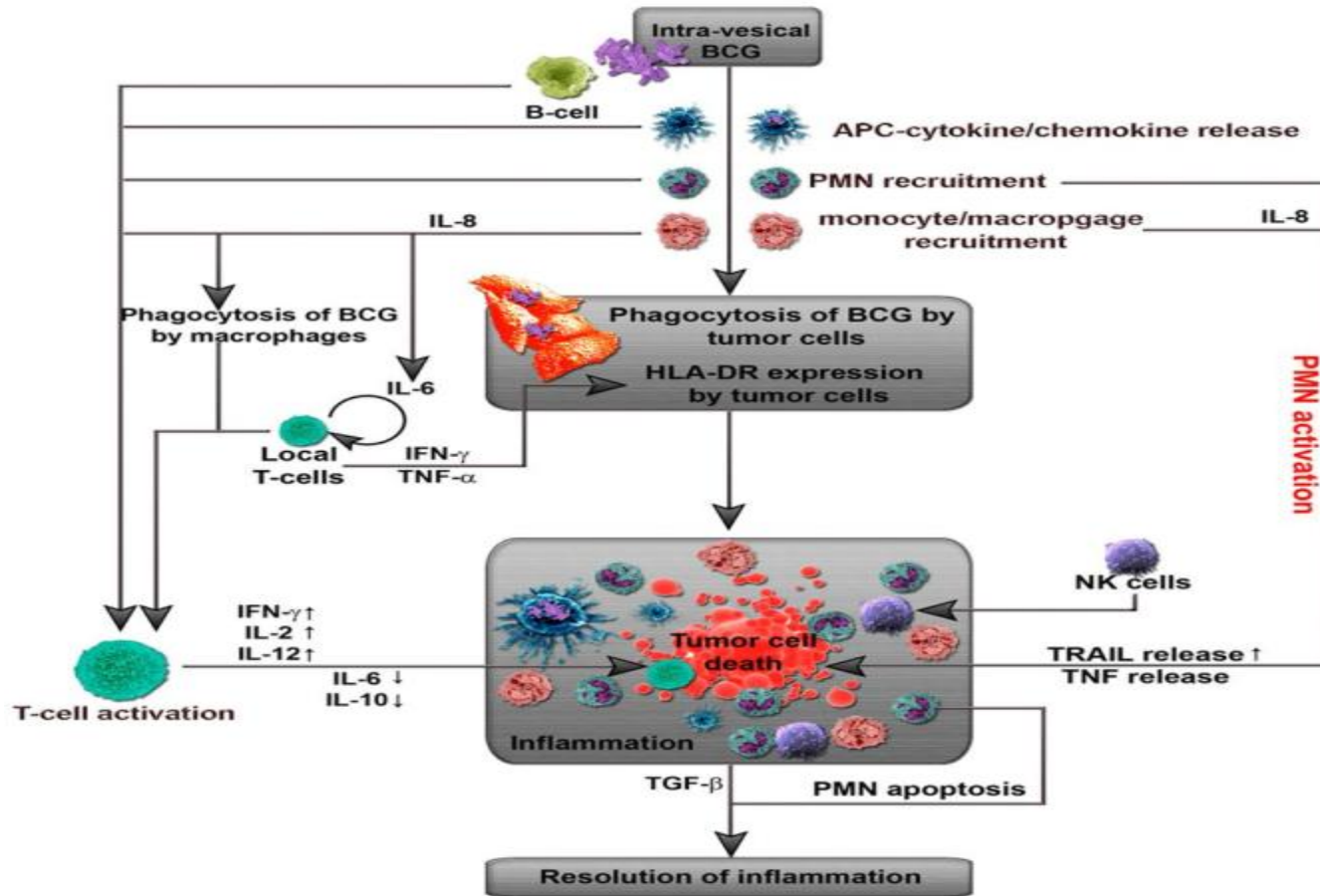
- Ad-IFN gene therapy (FKD) – SUO-CTC
- Viccinium (Viventia)
- Atezolizumab (SWOG S1605 - Roche/GNE)
- Pembrolizumab (Merck)
- ABI-009 Phase I/II (AADi LLC)
- Cabazitaxel, gemcitabine, and cisplatin Phase I (Columbia)
- BGJ 398 FGFR targeted therapy (MSKCC)
- ChemoXRT for T1 (RTOG 0926)

# Strategies to Reduce Persistence and Recurrence of BCG Refractory CIS

- Better Diagnostics → Enhanced Predictive and Prognostic Tools

# Optimizing BCG Therapy

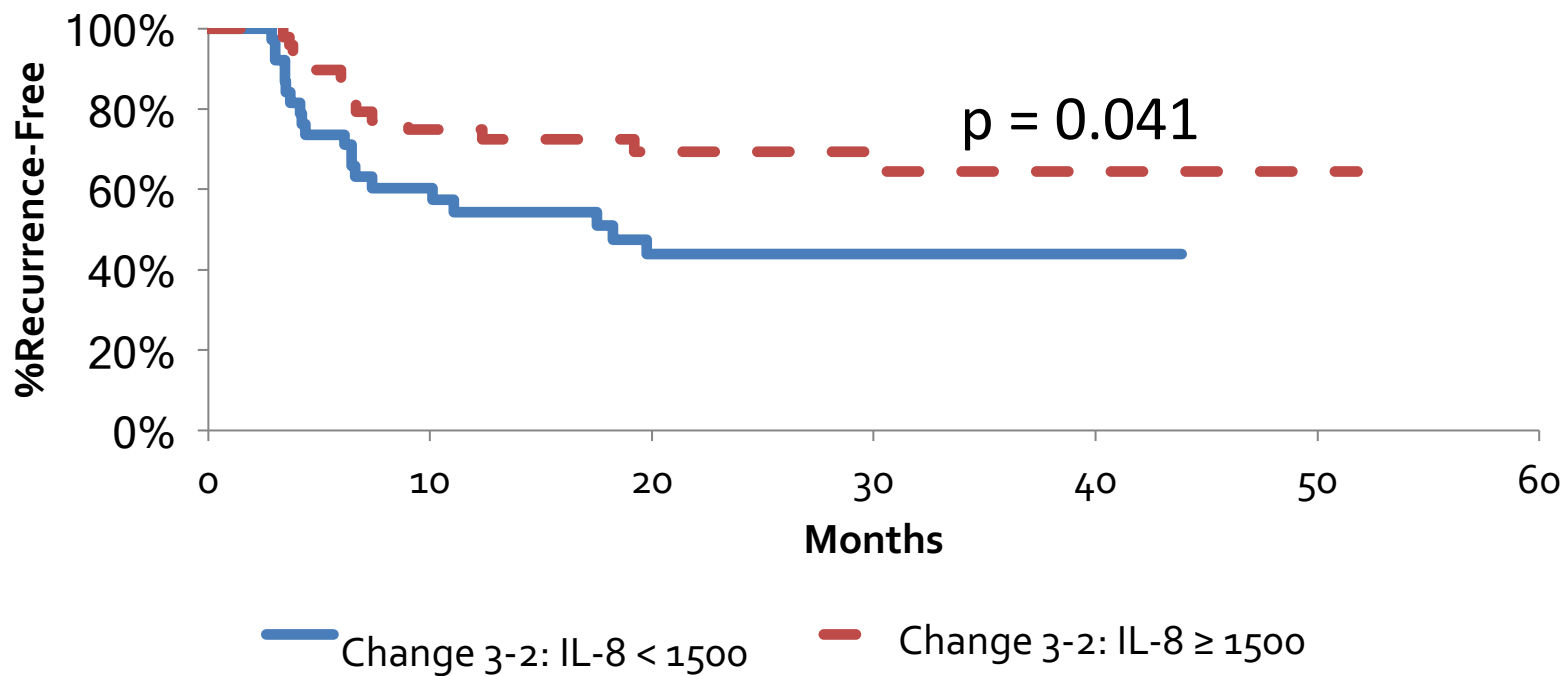
- BCG reduces recurrence and progression
- ~30% patients fail BCG therapy
  - In non-responders, disease often progresses before curative cystectomy
  - Decreased survival
- If we can identify non responders early, offer alternate therapy at earlier time point



# Cytokines and BCG Response

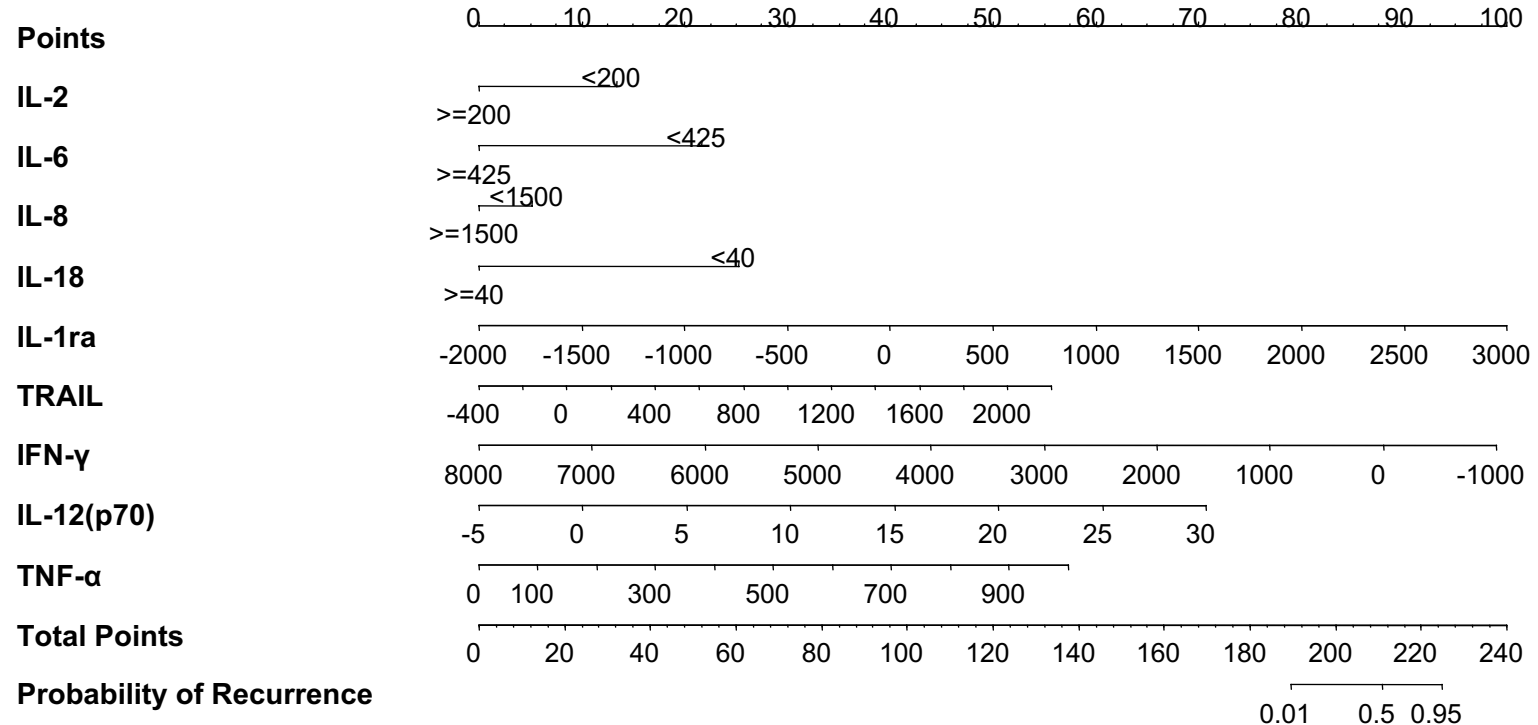
- Cytokine response to BCG does differentiate responders from non-responders
- Responders have higher levels of BCG induced cytokines at BCG – 6
- Magnitude of induction of cytokines correlates with recurrence rate and time to recurrence
- Complex interplay of cytokines

# $\Delta$ IL-8 with 6<sup>th</sup> BCG



Courtesy of Dr. Ashish Kamat, MDACC

# Cytokine Nomogram



Courtesy of Dr. Ashish Kamat, MDACC



# Recommendations

- Repeat TURBT with PPD or NBI technology
- Fulgurate all abnormal appearing areas
- If > 1 year from BCG, attempt BCG again
- If it has been < 1 year since BCG: Consider RC
- If unwilling or unfit for cystectomy
  - Clinical trial preferred
  - If HG Ta, IVe chemo gemcitabine, taxotere
  - For CIS, IVe valrubicin

# Conclusions: BCG Failure

- BCG failure group remains poorly defined
- Best salvage therapy to be determined, modest durable response rates modest
- Risk of progression is significant, increasing with each round of failed therapy
- Cystectomy remains the most durable option for appropriate surgical candidates

# Forecast for the Future: We need to develop...

- Markers that predict response or failure
- Better surgical strategies to eradicate CIS
- More effective, less toxic salvage regimens
- Enhanced delivery for salvage therapy
- Personalized therapy tailored to individual patient and tumor risk profiles

# Stephenson Cancer at OU Health Sciences Center

