Apaziquone
for Intravesical Instillation
NDA 208714

Spectrum Pharmaceuticals, Inc.

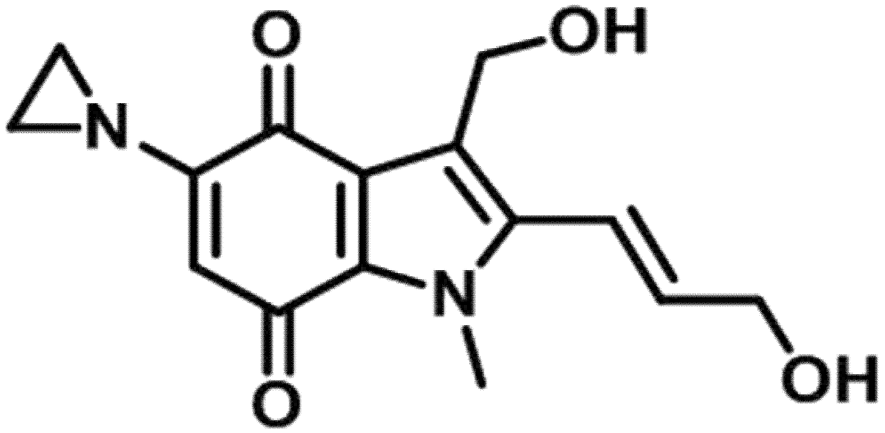
Oncologic Drugs Advisory Committee

September 14, 2016

Introduction

Anil K Hiteshi, RAC
Vice President, Global Regulatory Affairs & Pharmacovigilance
Spectrum Pharmaceuticals

Apaziquone



INN:	Apaziquone
Proprietary Name:	Qapzola
Previously:	EOquin
Also Known as:	EO9

Proposed Indication

- Apaziquone is indicated for intravesical instillation post-transurethral resection of bladder tumors (post-TURBT) in patients with low- and intermediate-risk non-muscle invasive bladder cancer (NMIBC)

- The drug is instilled as a single 4 mg dose into the bladder at least 30 minutes post-TURBT and retained in the bladder for a period of 1 hour

Apaziquone Positive Efficacy and Safety

- Strong anti-tumor activity demonstrated in marker lesion studies
- Reproducible treatment effect demonstrated in two large clinical trials
- Excellent safety profile – treatment arm is indistinguishable from placebo arm
- Positive benefit-risk fills an unmet medical need

Presentation Agenda

Introduction	**Anil K. Hiteshi, RAC** *Global Regulatory Affairs* *Spectrum Pharmaceuticals, Inc*
Post-Operative Intravesical Therapy	**Neal Shore, MD*** *Medical Director* *Carolina Urologic Research Center*
Efficacy and Safety	**Gajanan Bhat, PhD** *Biostatistics* *Spectrum Pharmaceuticals, Inc*
Benefit – Risk and Clinical Utility	**Alfred Witjes, MD*** *Professor of Oncological Urology* *Radboud University, Nijmegen Medical Centre*
Clinical Perspective	**Mark Soloway, MD*** *Chief of Urological Oncology* *Memorial Cancer Institute*
Concluding Remarks	**Rajesh Shrotriya, MD** *Chairman and CEO* *Spectrum Pharmaceuticals, Inc*

*** Clinical Investigators and Experts**

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Post-Operative Intravesical Chemotherapy

Neal Shore, MD, FACS

Medical Director, Carolina Urologic Research Center

Myrtle Beach,South Carolina

Bladder Cancer

- Incidence: 76,960 new cases/year in USA[1]
  - 70% of these are Non-Muscle Invasive Bladder Cancer (NMIBC)
  - Mostly in age ≥65
- Prevalence: 600,000 cases[2]
  - Requires long term cystoscopic surveillance
  - Frequent transurethral resection

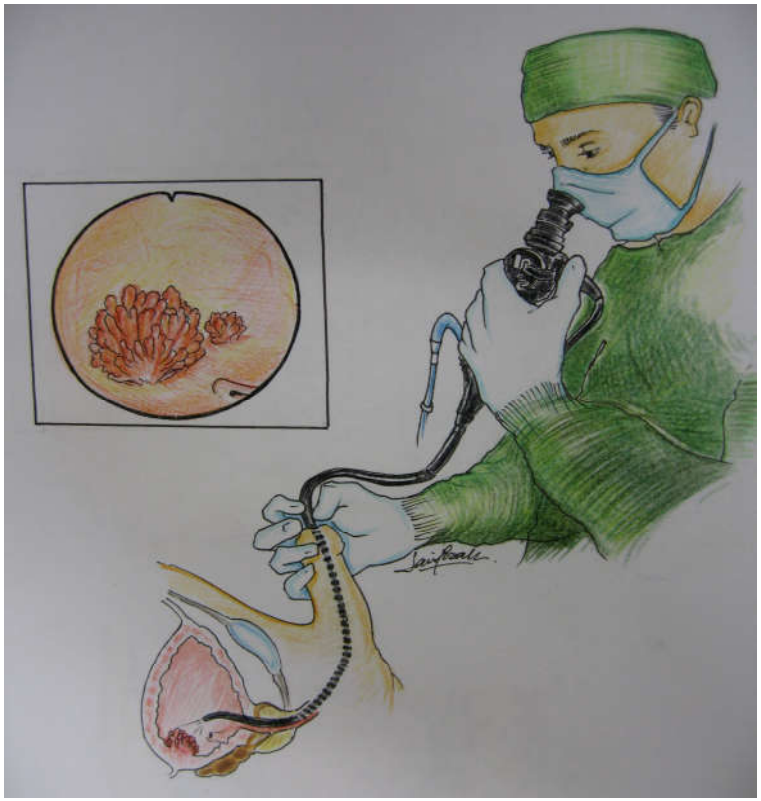
1. Howlader, et al. SEER Cancer Statistics Review. 1975-2013. 2016;Table 1.1
2. NCI SEER Cancer Statistics Review. 1975-2013.

Bladder Cancer Risk Stratification

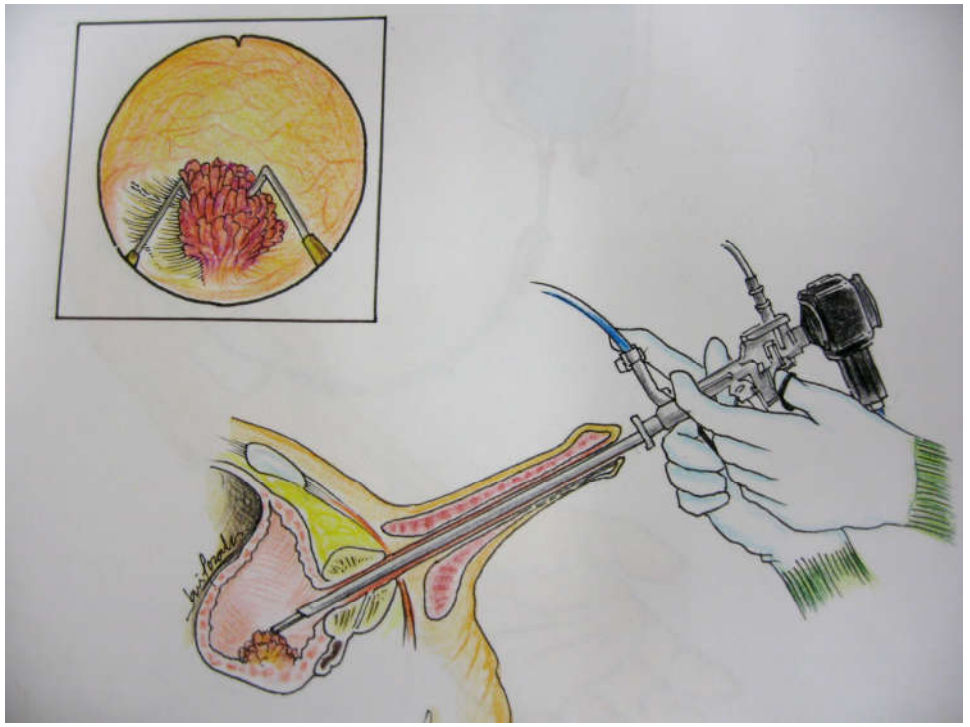
- **Low risk**
  - Solitary Ta low grade ≤3cm
- **Intermediate risk**
  - Any recurrent Ta low grade
  - Low Grade Ta multifocal
  - Low Grade solitary Ta >3 cm
  - High Grade Ta ≤3 cm
  - Low Grade T1

Surveillance Cystoscopy vs. TURBT

Flexible Cystoscope



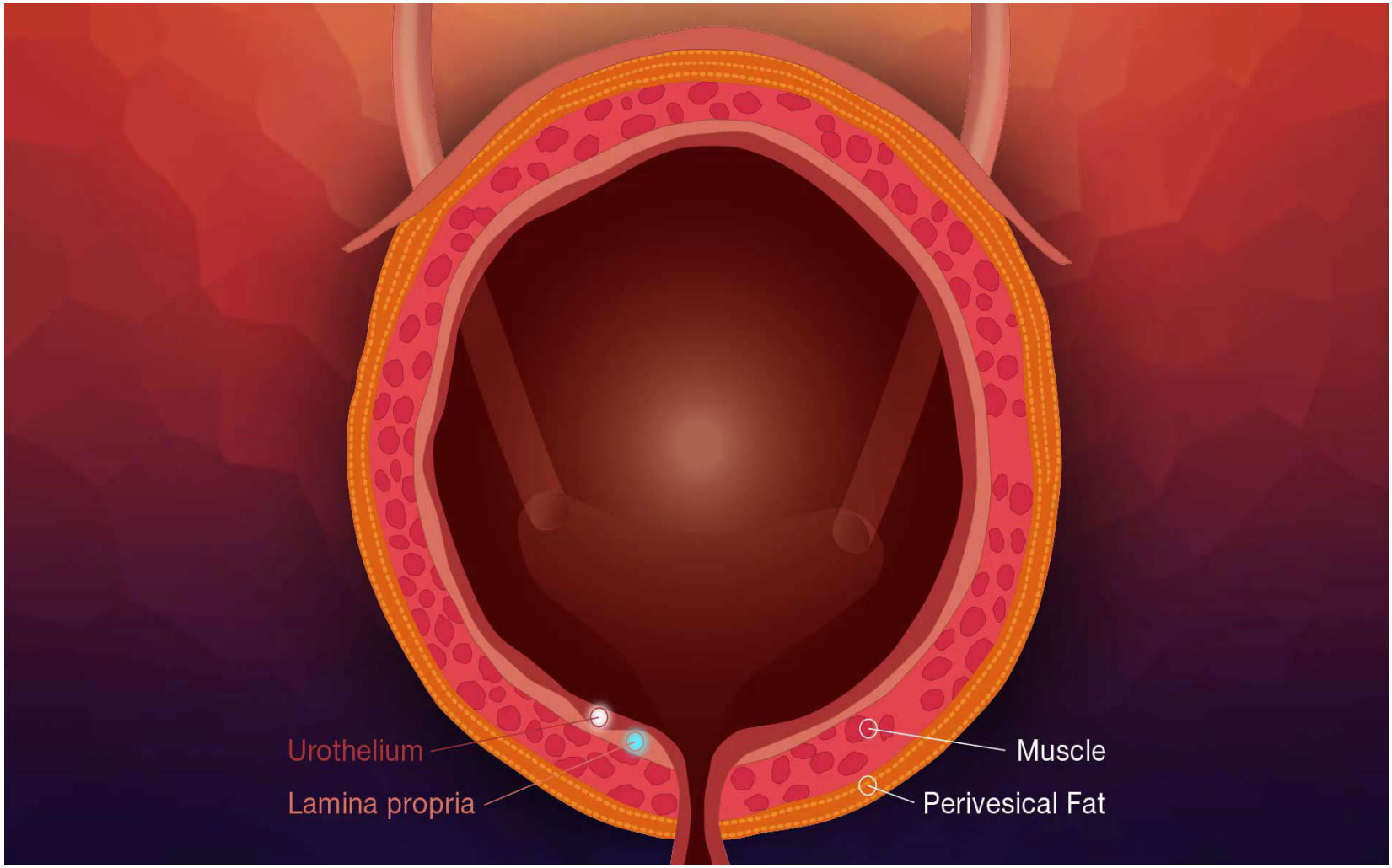
Rigid Resectoscope



TURBT Procedure

A video of a TURBT procedure was shown

Reason for Recurrence



All Guidelines Support Single Dose Post-Operative Intravesical Chemotherapy

American Urological Association

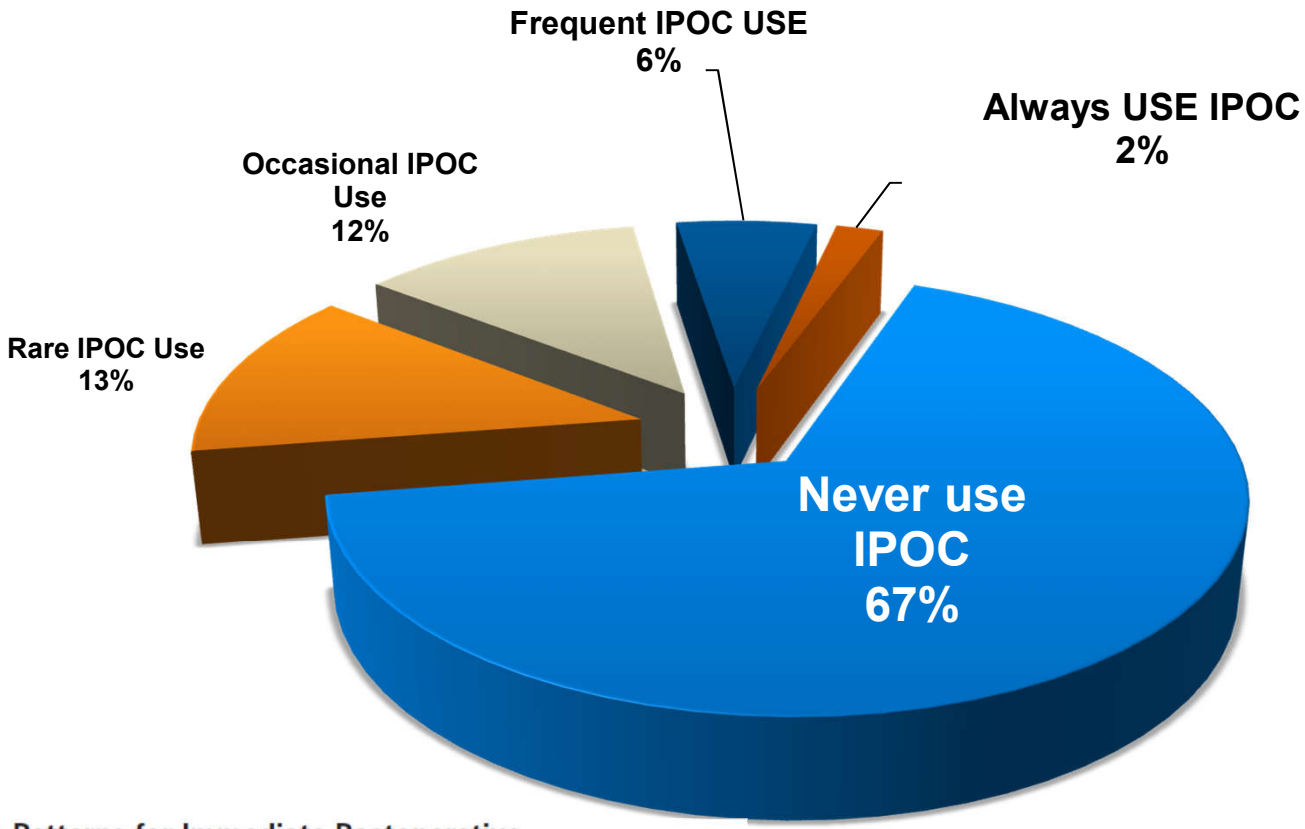
European Association of Urology

Canadian Urological Association / Association des urologues du Canada

NCCN National Comprehensive Cancer Network®

- **All International guidelines recommend/consider post-operative chemotherapy**

Under-Utilization of Post-Operative Intravesical Chemotherapy



National Practice Patterns for Immediate Postoperative Instillation of Chemotherapy in Nonmuscle Invasive Bladder Cancer

Michael S. Cookson,* Sam S. Chang,† Michael G. Oefelein,‡,§ Jack R. Gallagher,‖ Brent Schwartz§ and Kylee Heap‖

Cookson, et al. *J Urol.* 2012;187(5):1571-1576.

Why is Post-Operative Intravesical Chemotherapy Under-Utilized in the US?

- FDA Briefing Document suggests underutilization may be due to perceived low efficacy of current treatments[1]
- In peer reviewed publications the reasons most commonly reported include[2,3]:
  - Fear of bladder perforation
  - Net benefit
  - Reluctance of staff for handling, mixing and instilling agents
  - Inconvenience of ordering in the hospital setting
  - Lack of reimbursement without approved labeling
  - Toxicity

1. FDA Briefing Document
2. Burks, et al. *J. Urol.* 2012;188:2108.
3. Cookson, et al. *J Urol.* 2012;187(5):1571-1576.

Toxicity of Single Instillation of Mitomycin C

- Cystitis[1]
- Calcifications[2]
- Reduced bladder capacity[3]
- Extravasation leading to peritonitis
- Rare cases of cystectomy due to severe bladder contracture[4]

1. Barocas, et al. *Adv Urol.* 2012;2012:421709.
2. Liu, et al. *The Kaohsiung Journal of Medical Sciences.* 2001;17(5):274-277.
3. Kamat and Lamm, *J Urol.* 2000;55(2):161-168.
4. Panach-Navarrete, et al. *Arch Esp Uro.* 2015;68(7):633-636.

What is the Efficacy of Post-Operative Intravesical Chemotherapy ?

- Efficacy of single post-operative chemotherapy tested in multiple studies – Meta-analysis[1]
  - Variable treatment effect
  - Many studies used TUR alone as control arm (TUR ≠ placebo)
  - Placebo-controlled studies showed lower treatment effect
- Recent studies showed absolute reduction of 5% in recurrence rate in recent study[2]
- International Bladder Consortium: 6% absolute reduction is clinically meaningful[3]

1. Sylvester, et al. *J Urol.* 2004;171(6 Pt 1):2186-2190, Sylvester, et al. *Eur Urol.* 2016;69(2):231-244.
2. Di Stasi, et al. *The Lancet Oncology.* 2011;12(9):871-879.
3. Kamat, et al. *J Clin Oncol.* 2016;34(16):1935-1944.

What Does 6.7% Reduction in Recurrence Really Mean to Patients with NMIBC?

- Avoids ~20,000 Trans-Urethral Resections under general anesthesia per year
- Avoids major anesthetic complications
- Avoids up to ~1,000 bladder perforations with subsequent prolonged catheterization
  - Based on 1.3 - 5% incidence of bladder perforations[1]
- Avoids ~1,100 secondary hospitalizations
  - Based on 5.7% incidence of secondary hospitalizations[2]

1. Nieder, et al. *J of Urol.* 2005;174;2307-2309
2. Mezei and Chung. Ann. *Surg.* 1999;230(5):721-728.

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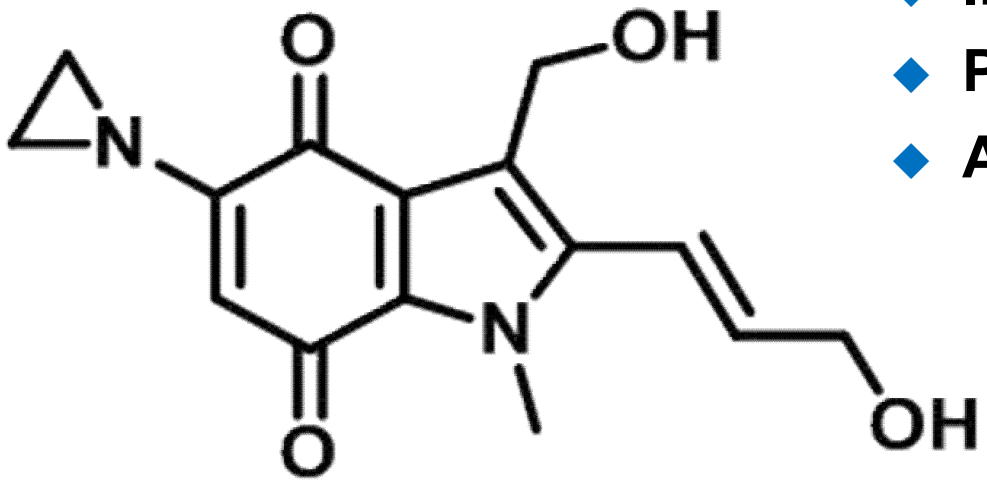
Clinical Efficacy and Safety

Gajanan Bhat, PhD
Biostatistics
Spectrum Pharmaceuticals, Inc

Apaziquone



- INN: Apaziquone
- Proprietary Name: Qapzola
- Also known as: EO9

- Fully synthetic bioreductive alkylating indoloquinone
- Activated by DT-diaphorase & other reductases
- Active in both hypoxic and aerobic conditions
- Minimal systemic absorption after intravesical instillation & rapid elimination

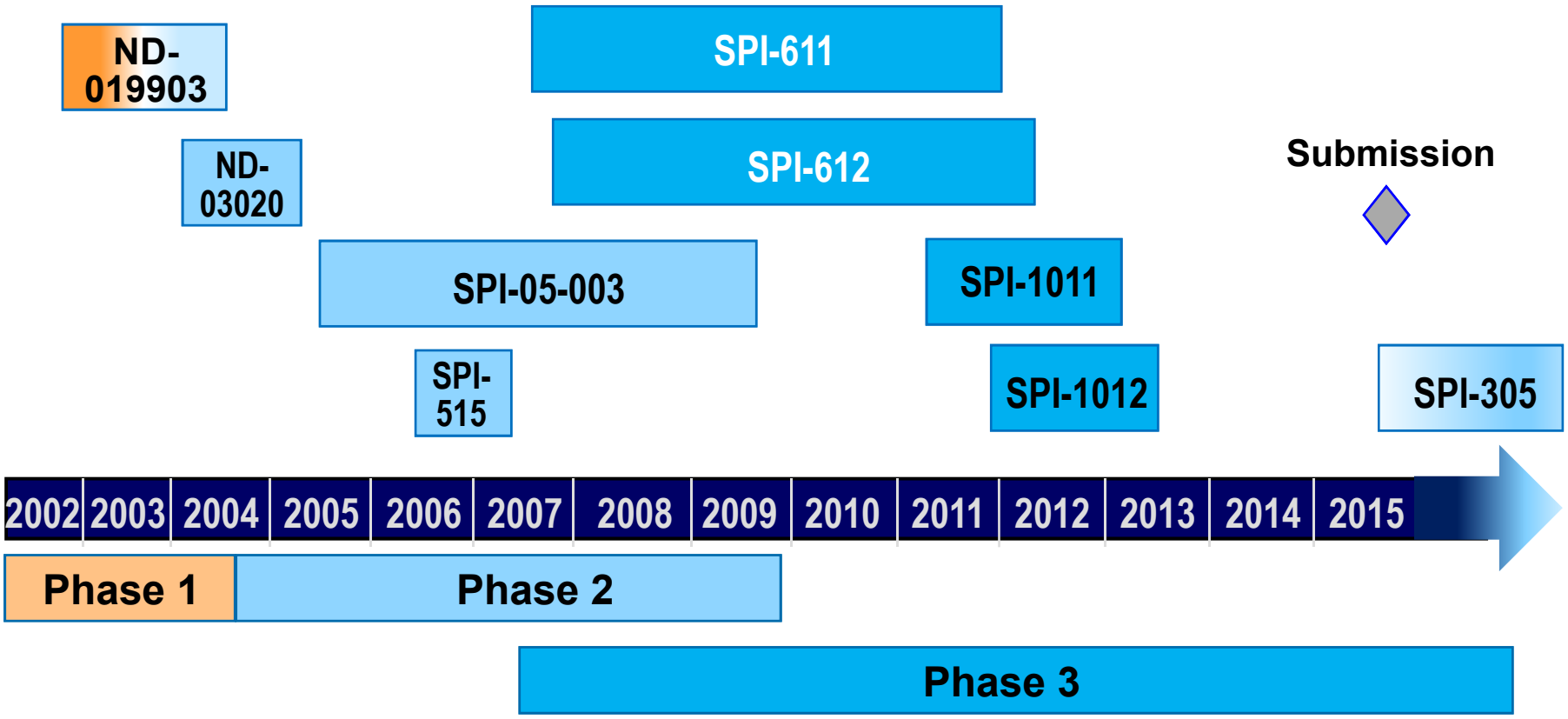
Apaziquone: Most Potent Intravesical Agent *In Vitro*

Intravesical Agent	Cell Line (LD_{50} µM)*			
	RT112	T24	253J	RT4
Mitomycin C	99	210	280	35
Epirubicin	26	1827	100	21
Gemcitabine	21	26	27	23
Apaziquone	**3.3**	**9.9**	**3.6**	**6.4**

Apaziquone is 10-30× more potent than MMC

*** van der Heijden, et al. *J Urol*. 2005;173:1375-1380.**

Clinical Development (N=1859)



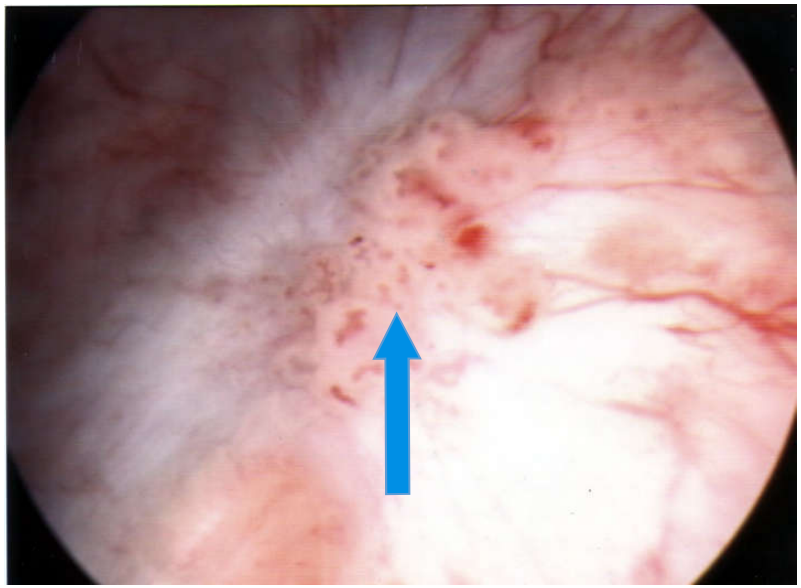
In Total, 1859 patients were enrolled in 8 clinical studies

Early Phase Studies – Established Dose and Antitumor Activity

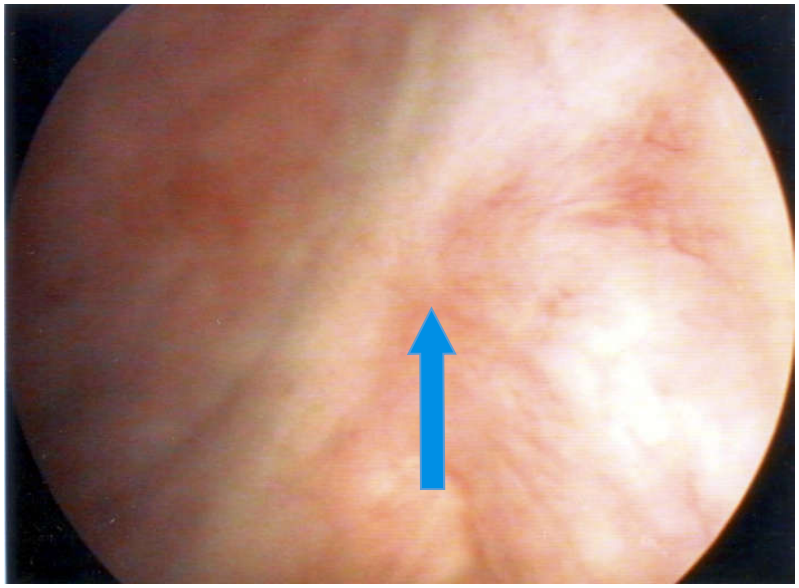
- **Phase 1 – Dose (4mg/40mL)**
  - 12 patients with multifocal Ta, T1, G1-G2 bladder cancer
  - Apaziquone not detected in plasma at doses up to 16 mg
  - 67% (8/12) histology confirmed CR
- **Phase 2 – Marker Lesion Study**
  - 46 recurrent, multifocal, Ta-T1, G1-G2 bladder cancer patients
  - 6 weekly doses of 4 mg/40mL
  - Doses well tolerated

*Study ND-019903, ND-03020

Established Efficacy in Marker Lesion Study



Before Apaziquone Treatment



After Apaziquone Treatment
(Complete Response)

Response	N (%)	95% CI
Complete Response (CR)	31 (67)	51 to 80
NR (stable marker lesion)	15 (33)	20 to 49
No patient had progressive disease		

Van der Heijden, et al. 2006.

Pivotal Studies 611 and 612 (N=1614)
Single Dose Apaziquone vs. Placebo post-TURBT

- Nearly identical in design
- Global, multi-center, double-blind, randomized study
  - Time of instillation 0-6 hours post-TURBT
- Recurrence assessed every 3 months for 2 years
- Blinded central tumor pathology
  - Identify target population – Ta, G1-G2 NMIBC
  - Recurrence within 2 years
- Target Ta, G1-G2, no additional intravesical therapy
- Each study powered to detect an absolute difference of 12% at 5% level of significance

Primary and Secondary Endpoints

- **Analysis Population – Ta, G1-G2**
  - **Histologically confirmed by independent review**
- **Primary Endpoint – 2 Year Recurrence Rate**
  - **Proportion of patients with documented recurrence on or before 2-years**
  - **Chi-square test at 5% level of significance**
- **Secondary Endpoint – Time to Recurrence**
  - **Kaplan-Meier estimate and Cox proportional hazard model**
  - **Log-rank test, HR and 95% CI**

Study Results

Largest Studies Ever Undertaken in NMIBC

	Country	Sites, n	Patients, n (%)
Study 611	United States	72	756 (94.3)
	Poland	7	46 (5.7)
Study 612	United States	23	167 (20.6)
	Canada	30	438 (53.9)
	Poland	20	207 (25.5)
Total		152	1614 (100)

Majority of patients (84%) enrolled in US/Canada; 57% in the US

Demographics and Baseline Status

Parameter (%)	Study 611 N=802		Study 612 N=812	
	APZ N=406	PBO N=396	APZ N=402	PBO N=410
Male	73.4	74.2	73.9	73.7
Median age (yrs)	68 (29, 90)	68 (32, 94)	68 (24, 94)	68 (22, 89)
≥65 yrs	60.8	63.1	60.9	60
Race, White	96.6	96.7	97.5	97.6
Primary tumor	63.8	63.4	61.7	63.7
Single tumor	62.6	62.6	57.7	56.3
G1-2 grade	79.0	75.0	75.3	77.3

Patient population is elderly with Grade 1-2 disease

Primary Endpoint: Reproducible Effect

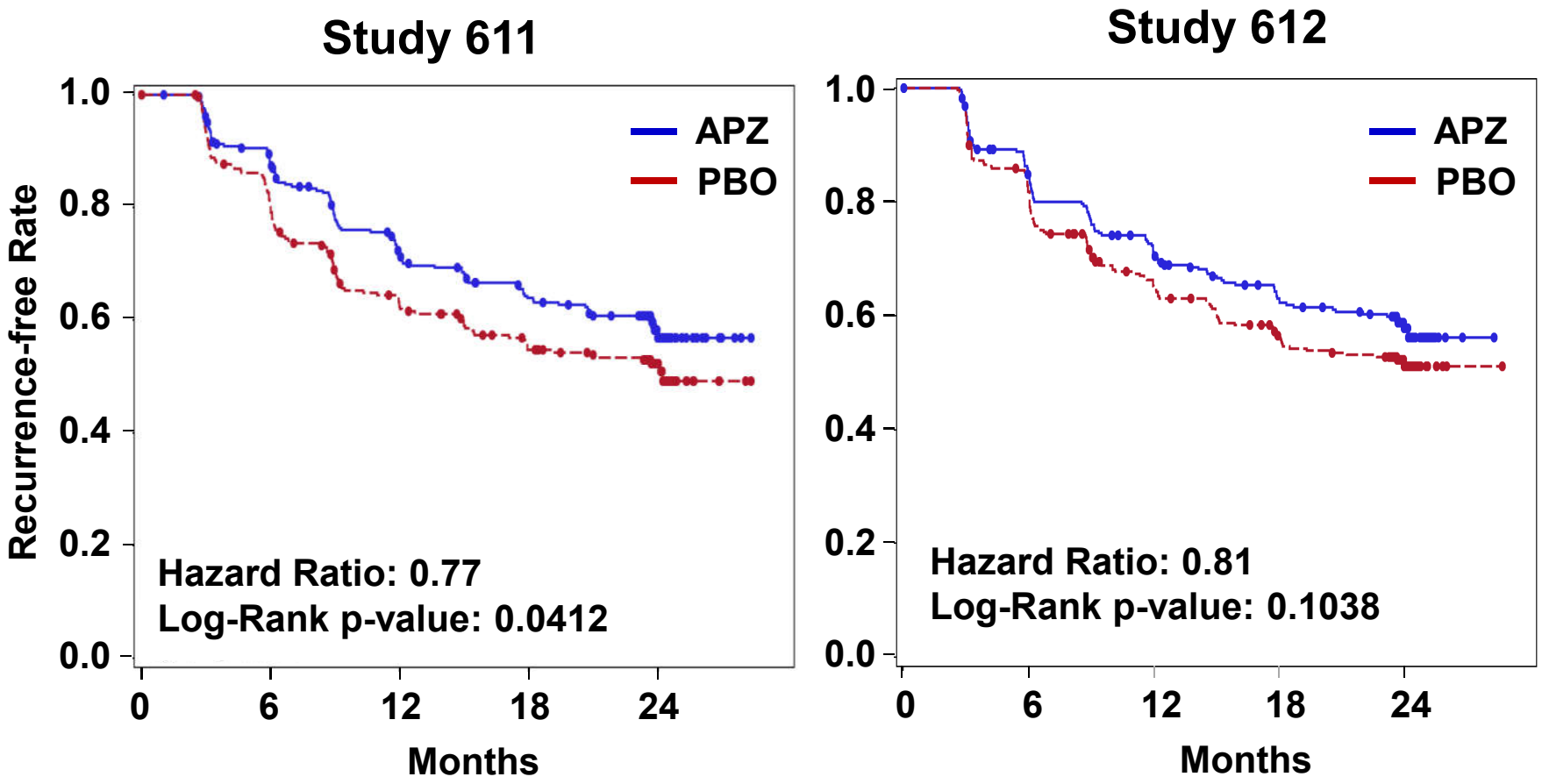
2-Year Recurrence Rate: Ta, G1-G2 Population

Parameter	Study 611 APZ N=295	Study 611 PBO N=271	Study 612 APZ N=282	Study 612 PBO N=298	Overall APZ N=577	Overall PBO N=569
Recurrence, %	38.0	44.6	39.7	46.3	38.8	45.5
p-value	0.1068		0.1094		0.0218	
Difference, % (95% CI)	-6.7 (-14.8, 1.4)		-6.6 (-14.6, 1.4)		-6.7 (-12.4, -1.0)	
Odds ratio	0.76		0.76		0.76	
Relative change, %	–15.0		–14.2		–14.7	

Consistent treatment effect in both studies

Secondary Endpoint: Reproducible Effect

Time to Recurrence: Ta, G1-G2 Population



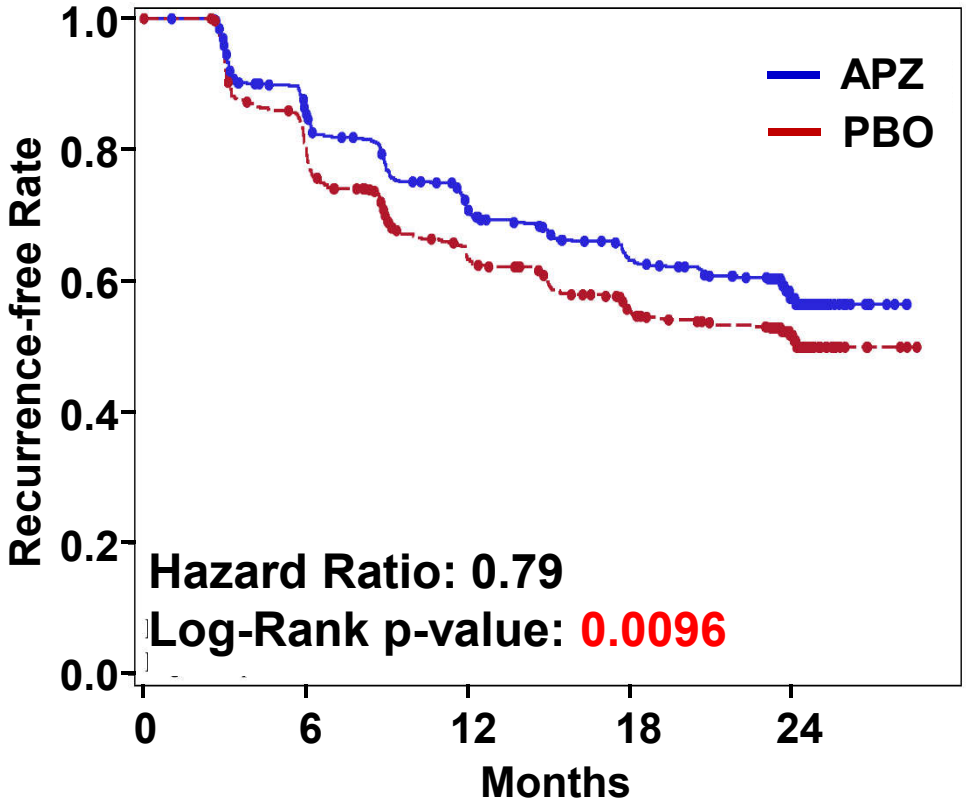
Significant improvement in 611, positive difference in 612

Pooled Analysis of Efficacy Ta, G1-G2 Population

2-Year Recurrence Rate

Parameter	Overall APZ N=577	Overall PBO N=569
Recurrence, %	38.8	45.5
p-value	0.0218	
Difference, %	-6.7	
Odds ratio (OR) (95% CI)	0.76 (0.60, 0.96)	
OR stratified (95% CI)	0.70 (0.54, 0.89)	

Time to Recurrence



Significant Improvement in both Recurrence Rate and Time to Recurrence

Clinical Trial Design Challenges

- No precedence for study design
- Time to recurrence vs. 2 year recurrence as endpoint
- Treatment effect based on literature in 2004
  - Significant heterogeneity in design, control, treatment effect and study size[1]
  - TURBT alone ≠ placebo as control
  - 2-year recurrence data was not available
- Clinically relevant treatment effect of immediate intravesical therapy was not well understood for a 2-year recurrence endpoint

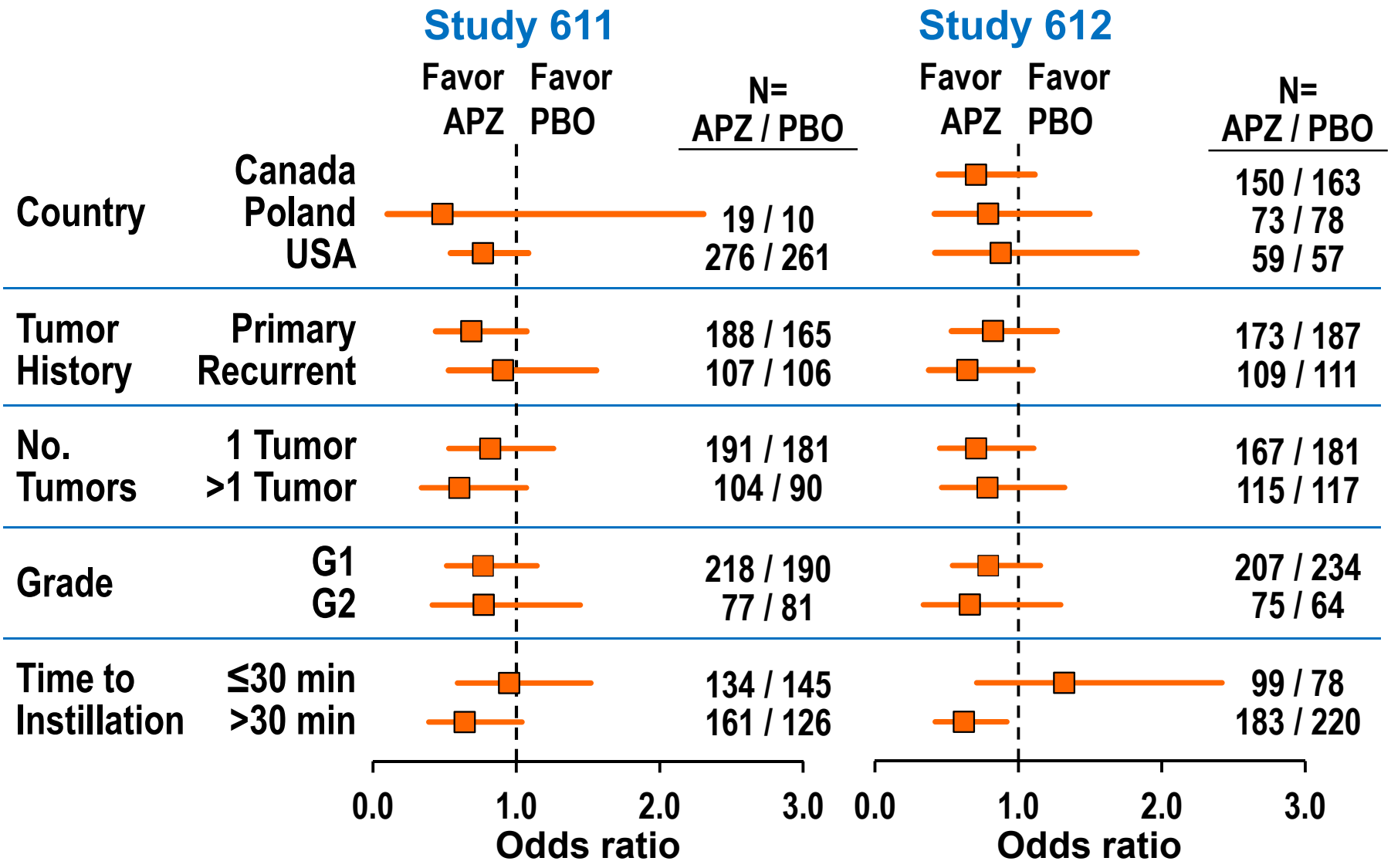
1. Sylvester. et al, *J Urol.* 2004

Positive Reproducible Study Results

- Remarkable consistency of 2 adequate and well-controlled studies overall
- Largest database of blinded, randomized placebo-controlled trials
- Estimated effect is clinically meaningful
  - Relative reduction of ~15% (~6.7% absolute difference) observed from both studies
  - Supported by International Bladder Cancer Group[1]

1. Kamat. et al, *JCO.* 2016

Recurrence Rate
Baseline and Dosing Subgroups
Ta, G1-G2 Population



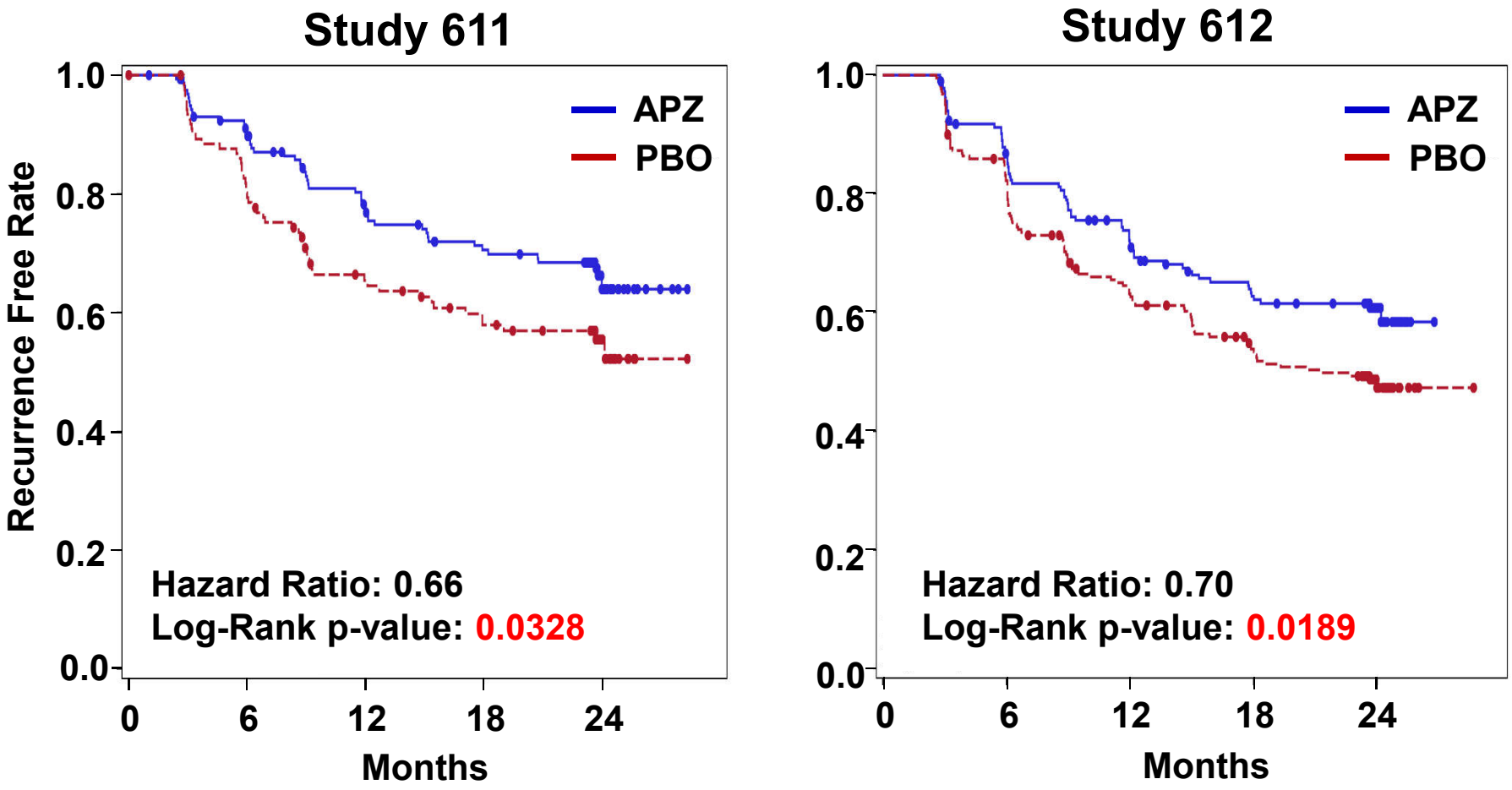
Recurrence Rate and Time to Recurrence
Ta, G1-G2 Population, >30 minutes

Parameter	Study 611 APZ N=161	Study 611 PBO N=126	Study 612 APZ N=183	Study 612 PBO N=220
Recurrence Rate				
Recurrence, %	31.1	41.3	38.3	50.0
Nominal p-value	0.0733		0.0183	
Difference, %	-10.2		-11.7	
Odds ratio (95% CI)	0.64 (0.39, 1.04)		0.62 (0.42, 0.92)	
Time to Recurrence				
First quartile (months)*	12.5	8.3	11.6	6.3
Hazard ratio (95% CI)	0.66 (0.45, 0.97)		0.70 (0.52, 0.95)	
Nominal p-value	0.0328		0.0189	

Significant improvements in time to recurrence in both studies (nominal p<0.05) if dosed >30 min post-TURBT

*Median time to recurrence not reached.

Time to Recurrence
Ta, G1-G2 Population: >30 Minutes



Significant improvements in time to recurrence in both studies (nominal $p<0.05$) if dosed >30 min post-TURBT

Substantial Evidence of Efficacy

- Demonstrated marked antitumor activity (67%) in 2 marker lesion studies in bladder cancer patients
- Reproducible efficacy overall
  - Reduction in 2 year recurrence (6.7%, 6.6%)
  - Improved time to recurrence (HR 0.77, 0.81) in two studies
  - Statistically significant improvements in pooled analyses
  - Supported by International Bladder Cancer Group[1]
- Consistent efficacy in subgroups
  - Significant improvement in time to recurrence (HR of 0.66, 0.70) when instilled >30 min post-TURBT

1. Kamat, et al. *JCO.* 2016.

Safety

Overview of Safety Studies

- Total 1859 patients enrolled in 8 studies
  - 1053 patients treated with apaziquone
    - 808 patients in pivotal studies
    - 245 patients in supportive studies
  - 806 patients treated with placebo

Adverse Events – Pivotal Studies

Category	Study 611		Study 612	
	APZ N=406	PBO N=396	APZ N=402	PBO N=410
Any TEAE, n (%)	326 (80.3)	298 (75.3)	320 (79.6)	335 (81.7)
Grade ≥3	79 (19.5)	89 (22.5)	71 (17.7)	87 (21.2)
Any Treatment-Related AE, n (%)	51 (12.6)	50 (12.6)	42 (10.4)	40 (9.8)
Grade ≥3	1 (0.2)	0	5 (1.2)	2 (0.5)
Any SAE, n (%)	93 (22.9)	98 (24.7)	96 (23.9)	108 (26.3)
All SAEs Other Than Death	92 (22.7)	96 (24.2)	93 (23.1)	101 (24.6)
All Treatment-Related SAEs	0	0	2 (0.5)	0
Deaths	11 (2.7)	13 (3.3)	14 (3.5)	14 (3.4)
Any AE Leading to Study Disc, n (%)	14 (3.4)	17 (4.3)	18 (4.5)	17 (4.1)

All AEs, SAEs, discontinuations, and deaths are similar between treatment groups

Most Common Treatment-Related AEs

Preferred Term	Study 611		Study 612	
	APZ N=406	PBO N=396	APZ N=402	PBO N=410
Any treatment-related AE	**51 (12.6)**	**50 (12.6)**	**42 (10.4)**	**40 (9.8)**
Dysuria	20 (4.9)	19 (4.8)	17 (4.2)	14 (3.4)
Bladder Spasm	8 (2.0)	5 (1.3)	3 (0.7)	4 (1.0)
Micturition Urgency	5 (1.2)	13 (3.3)	6 (1.5)	3 (0.7)
Bladder Pain	5 (1.2)	3 (0.8)	5 (1.2)	1 (0.2)
Hematuria	1 (0.2)	12 (3.0)	7 (1.7)	2 (0.5)
Urinary Tract Infection	4 (1.0)	1 (0.3)	4 (1.0)	0
Pollakiuria	4 (1.0)	10 (2.5)	2 (0.5)	5 (1.2)

Common AEs are similar between groups and were less than 5% incidence

Overall Safety Conclusions

- In >1800 patients studied
  - Apaziquone was well-tolerated
  - Safety profile indistinguishable from placebo in pivotal studies
  - No study discontinuation due to treatment-related AEs
  - No deaths within 30 days of study drug dose
  - No effect of apaziquone on bladder capacity
  - No clinically meaningful differences in hematology, chemistry or vital signs

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Benefit-Risk and Clinical Utility of Apaziquone

J.Alfred Witjes, MD
Professor of Oncologic Urology, Radboud University Nijmegen Medical Centre, Netherlands

Radboudumc

Efficacy of Apaziquone

- Individual trials did not reach statistical significance
  - Better bladder resections (digital equipment) → fewer recurrences → less difference between study arms
  - Placebo treatment ≠ no treatment

- However
  - Results are consistent
  - Combined analysis is significant
  - Significant increased time to recurrence if dosed >30 minutes
  - Considered clinically relevant (Kamat, JCO 2016)

Apaziquone is effective

Ofer N. Gofrit,* Kevin C. Zorn, Sergey Shikanov and Gary D. Steinberg

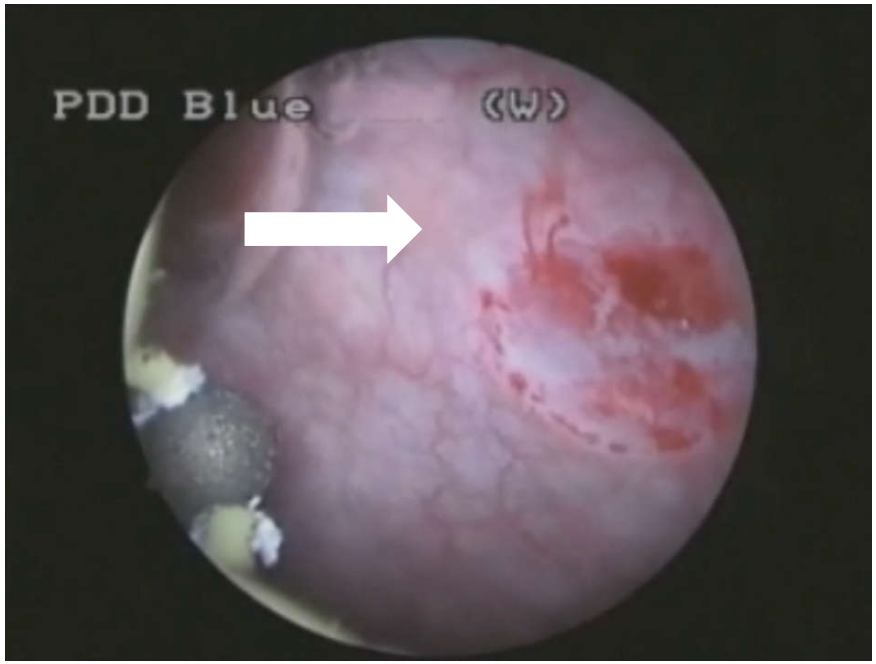
0022-5347/10/1835-1678/0
THE JOURNAL OF UROLOGY®

Vol. 183, 1678-1685, May 2010
Printed in U.S.A.
DOI:10.1016/j.juro.2009.12.104

ulocyte-macrophage colony-stimulating factor). The highest complete response rate in intermediate risk patients (67%) was attained with apaziquone. Patients who achieved a complete response with this agent also had a prophylactic benefit with a 2-year recurrence-free rate of 45.2% compared to 26.7% in those who did not achieve a complete response. The complete response rate in bacillus

The <30 minutes issue

- The timing of instillation might be a logistic problem in some US hospitals
- But the effect of some bleeding on apaziquone 4 mg seems obvious

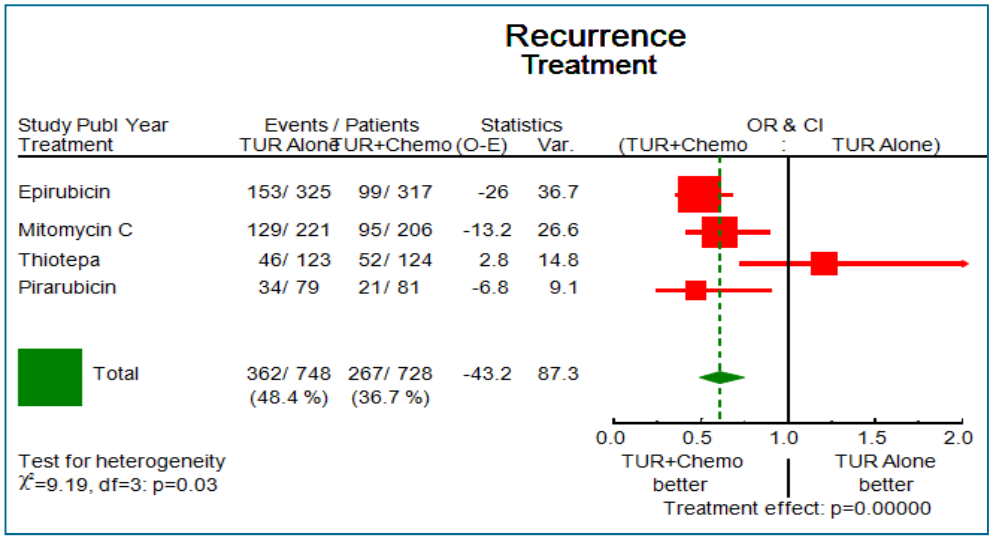


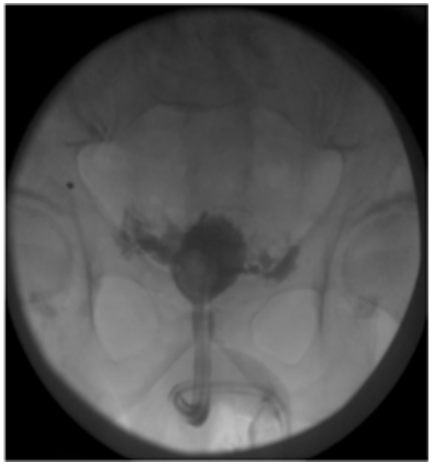
APZ safety: important for my patients

- Fortunately this is a non issue
- Important in a non-lethal disease
- Very important for my patient population
  - Elderly
  - (ex)smokers
  - Cardio vascular disease
  - Pulmonary disease

The US alternatives for an immediate instillation

- **Thiotepa (1959): does not work**
- **Mitomycin C (never registered): potentially toxic, availability problems**
- **BCG (1989, 1990) contraindicated in the post-operative setting**





Clinical arguments

- Although it is in all guidelines, it is dramatically underused in the US
  - Chamie (2011): only 1 out of 4500 patients had all guideline therapy and follow up advice followed

- Jarow 2015, Bladder cancer journal: only 3 drugs registered, so there is a large unmet need

- Now there is a possibility to register a new drug for an unmet indication: opportunity for education

What's in it for my patients

- **The low risk cohort is by far the largest cohort (US: 55%) with many many events**
  - **Low and intermediate risk is 85% of prevalent bladder cancer cases**
  - **In the US, overall prevalence (#TUR's) is 600,000 every year**
    - **80-90% is NMIBC; 80% low/int risk; 6-7% reduction**

- **I can spare for my patients**
  - **Many cystoscopies (less follow up because I treat better)**
  - **17,000 – 22,000 TUR procedures (a real operation under anesthesia)**

CR-9

Radboudumc

What's in it for my patients

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  - **In the US, overall prevalence (#TUR's) is 600,000 every year**
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My conclusion: clinical benefit

- Yes, this **reduction** in recurrence rate and TURBT procedures and follow up cystoscopies is **very safe** in **these older patients** and clinically **relevant** in **2016**

Presentation Agenda

Introduction	**Anil K. Hiteshi, RAC** *Global Regulatory Affairs* *Spectrum Pharmaceuticals, Inc*
Post-Operative Intravesical Therapy	**Neal Shore, MD** *Medical Director* *Carolina Urologic Research Center*
Efficacy and Safety	**Gajanan Bhat, PhD** *Biostatistics* *Spectrum Pharmaceuticals, Inc*
Benefit – Risk and Clinical Utility	**Alfred Witjes, MD** *Professor of Oncological Urology* *Radboud University, Nijmegen Medical Centre*
Clinical Perspective	**Mark Soloway, MD** *Chief of Urological Oncology* *Memorial Cancer Institute*
Concluding Remarks	**Rajesh Shrotriya, MD** *Chairman and CEO* *Spectrum Pharmaceuticals, Inc*

Clinical Perspective

Urothelial Cancer of the Bladder

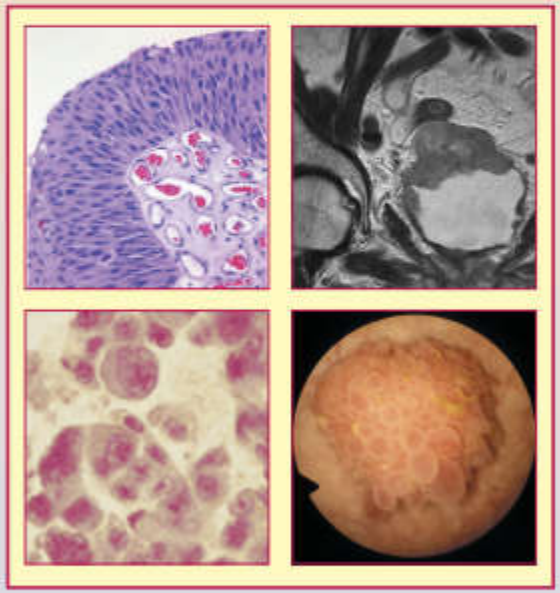
Mark Soloway, MD

Chief of Urological Oncology,
Memorial Cancer Institute

Bladder Tumors

EDITORS

MARK SOLOWAY,
ADRIENNE CARMACK, SAAD KHOURY



1st INTERNATIONAL CONSULTATION ON BLADDER TUMORS - HAWAII OCTOBER 3-7, 2004

CO-SPONSORED BY

SIU (International Society of Urology),
ICUD (International Consultation on Urological Diseases),
EORTC Urology (European Organisation for Research and Treatment of Cancer)

BLADDER CANCER

EDITORS

MARK SOLOWAY - SAAD KHOURY

2nd International Consultation on Bladder Cancer - Vienna

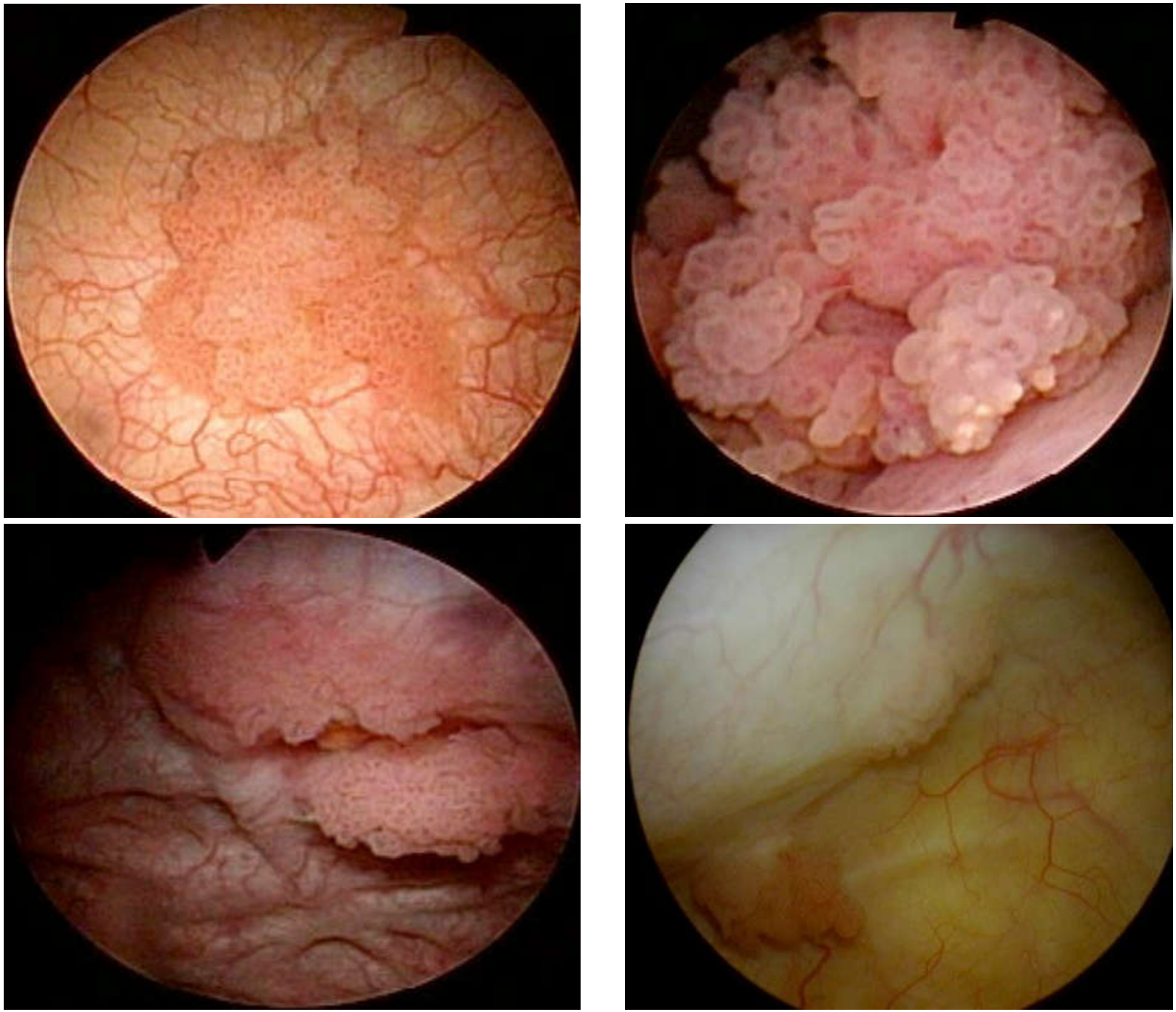
Second Edition

2012

eau European Association of Urology

ICUD

CP-3



Key Facts

- Most common bladder tumors are Ta G1-G2
- These patients *rarely* have a tumor which is of higher grade or stage
- Most “recurrences” are small tumors

Natural History of Papillary TCC Based on Grade

Gilbert et al, Kaiser of So. Calif. *J Urol.* 1978

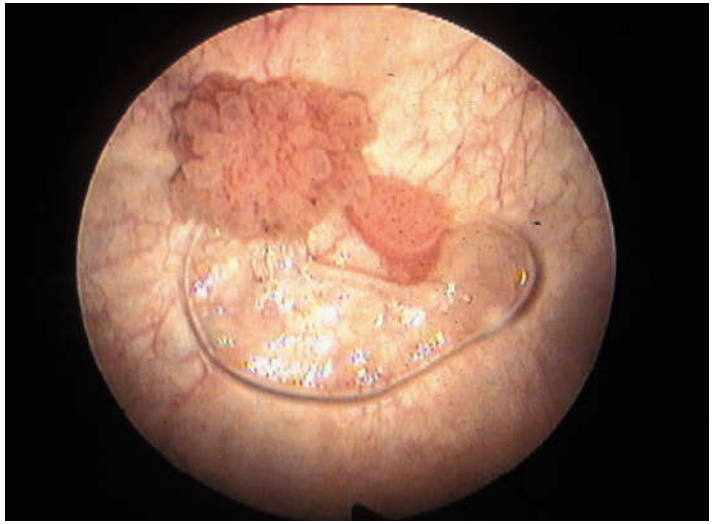
- 365 consecutive patients
- 1950-1965
- Long follow up (10-25 years)
- Almost all treated only with a TURBT

Natural History of Grade 1 Gilbert, 1978

155

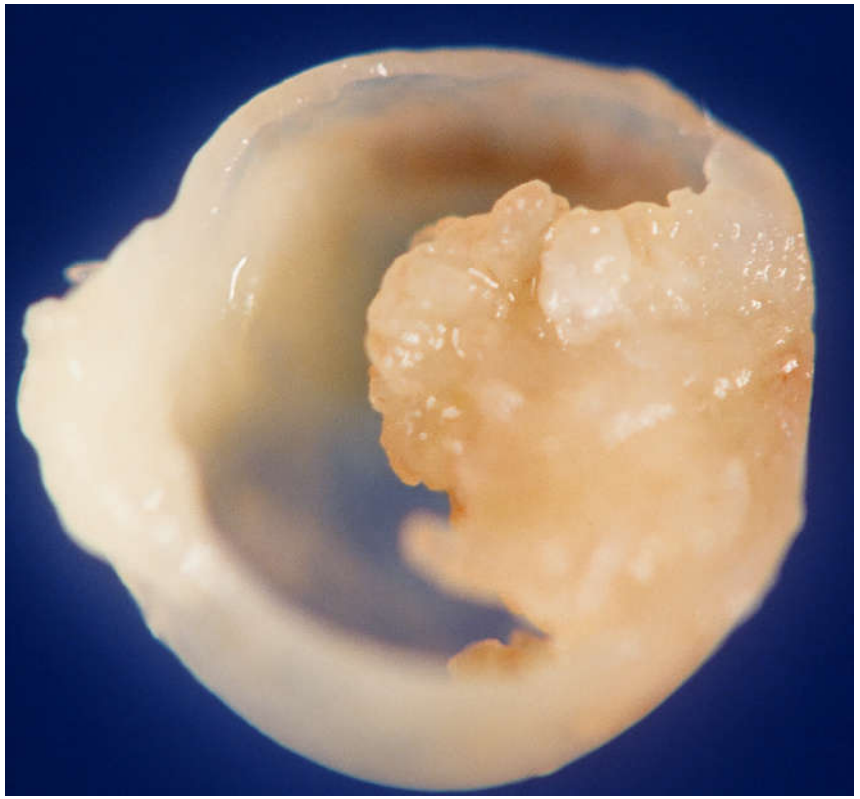
5% died of TCC or other causes

95% alive



My Research in Bladder Cancer

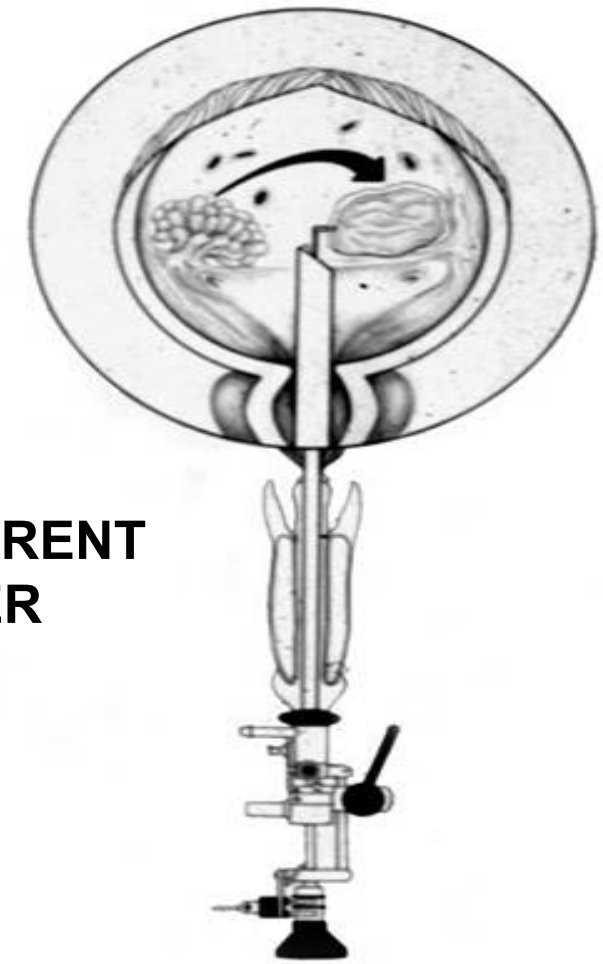
- NCI
- Developed animal model for BC
- Identified cisplatin



Subsequent Tumors – Why?

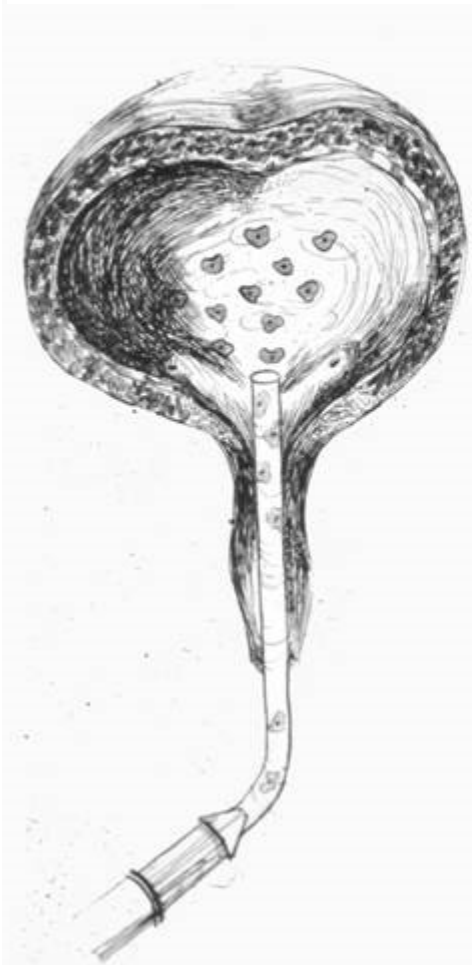
- Incomplete removal
- New tumor (carcinogen)
- Tumor implantation

Implantation

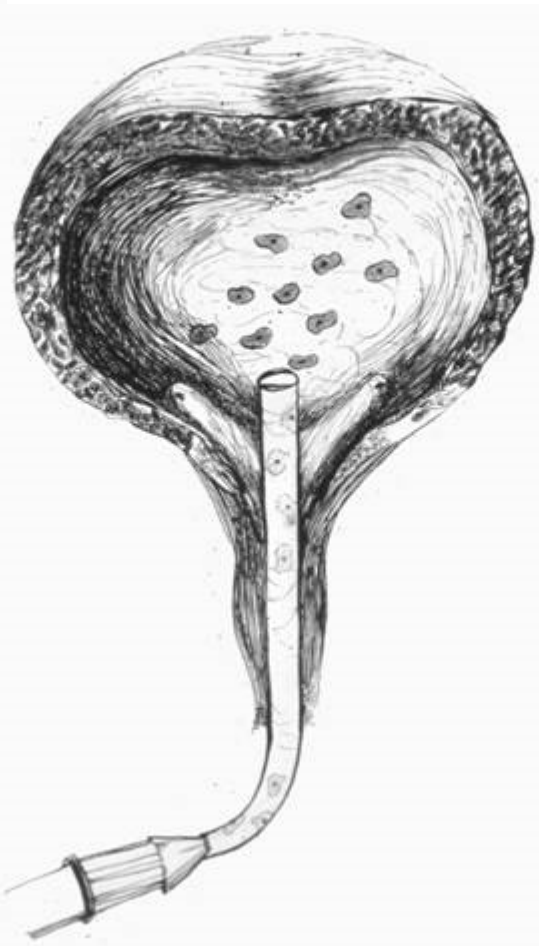


ETIOLOGY OF RECURRENT
BLADDER CANCER

Normal Bladder +10^6MBT-683 cells



Cauterized Urothelium +10^6MBT-683 cells



Cauterized Urothelium Only

CP-11

Susceptibility of Urothelium to Neoplastic Cellular Implantation

Weldon, T.E. and Soloway, M.S.

Urol 5:824-827, 1975

CP-12

Prophylaxis of Bladder Tumor Implantation – Intravesical and Systemic Chemotherapy

Soloway, M.S. and Martino, C.

Urol 79:29-34, 1976

Rationale for Intensive Intravesical Chemotherapy for Superficial Bladder Cancer

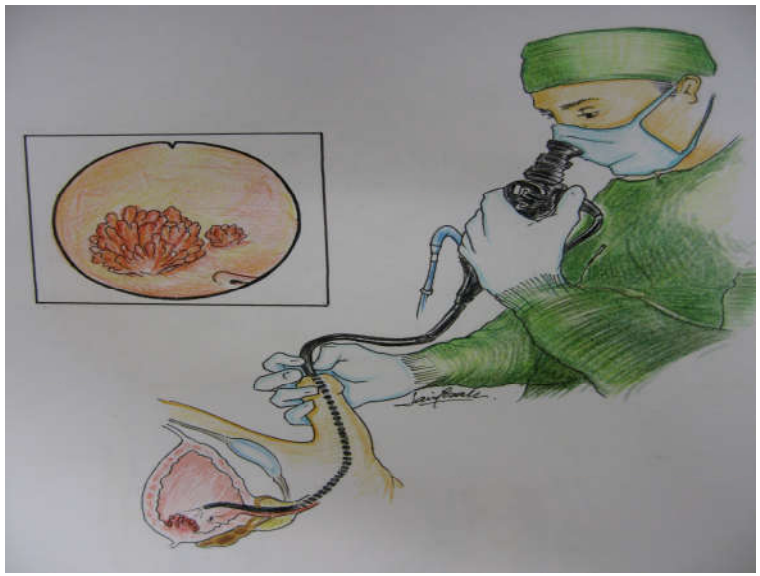
Soloway, M.S.

***J Urol.* 123:461-466, 1980**

Based on animal work and patients that intravesical chemotherapy decreases recurrence rate. More than 10 yrs later to become a guideline for treatment of Ta BC.

Typical Patient

- 70 year old man; former cigarette smoker
- Prior cardiac stents, on Plavix; COPD
- Gross hematuria
- Office cystoscopy – papillary UC, appears Ta



Typical Patient (cont'd)

- TURBT planned
- Medical clearance (H/PE, blood work, EKG, chest imaging, off anticoagulation)
- TURBT performed

1993 AUA

- **Mitomycin C treatment long term results of the MRC study (D. Tolley, MKB Parmar)**
  - **Lower recurrence rate with 1 or 5 doses**

Intravesical Therapy

- EAU guidelines
- Review of trials on early post op instillation
- "All arguments are in favor of an immediate instillation in all with papillary Ta/T1 tumors"

Oosterlinck et al, Euro Urol 2009

AUA/SUO 2016

- **Suspected or known low or intermediate risk bladder tumors consider single intravesical chemotherapy within 24 hrs**

Intravesical Chemotherapy

- Thiotepa (P. Riddle, R. Veenema)
- Animal model proves implantation is real
- Mitomycin C
- MRC trial – Tolley et al
- EORTC GU group
- Scandinavian trials
- Post TURBT IC accepted by all guidelines

AUA/SUO and EAU Risk Groups

- **Low risk**
  - Solitary Ta low grade ≤3cm
- **Intermediate risk**
  - Any recurrent Ta low grade
  - Low Grade solitary Ta >3 cm
  - Low Grade Ta multifocal
  - High Grade Ta ≤3 cm
  - Low Grade T1

Use of BCG for Low Grade Ta

Poor choice

Side effects common

Does not change Recurrence Rate

Why Apaziquone for Low Grade Ta

- Need for FDA approved drug for intravesical chemotherapy
- Safe
- Effective in large prospective placebo controlled randomized trial with only a single 4 mg dose

New FDA Approved Therapy Needed Now

- Waiting for the new study will take at least 5-6 years
- Potential to improve utilization of post-operative chemotherapy
- Potential to reduce the need for thousands of repeat TURBTs a year in this elderly population

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Concluding Remarks

Rajesh Shrotriya, MD
Chairman and CEO
Spectrum Pharmaceuticals, Inc

Current Therapeutic Landscape

- Low and intermediate risk NMIBC
  - No new drug for 50 years
  - No approved drugs currently available
  - Off label drugs rarely used by Urologists

Why Apaziquone?

- Goal of therapy is to reduce visits to operating room
- Extremely safe
- Consistent clinically meaningful treatment effect

Proposed Indication

- **Apaziquone is indicated for intravesical instillation post-transurethral resection of bladder tumors (post-TURBT) in patients with low- and intermediate-risk non-muscle invasive bladder cancer (NMIBC)**

Support Slides

Follow-up Cystoscopy Compliance

Follow-up Status	Study 611 APZ N=295 n (%)	Study 611 PBO N=271 n (%)	Study 612 APZ N=282 n (%)	Study 612 PBO N=298 n (%)
Complete Last Cystoscopy @ Month 24	243 (82.4)	216 (79.7)	239 (84.8)	263 (88.3)
Miss Last Cystoscopy @ Month 24	52 (17.6)	55 (20.3)	43 (15.2)	35 (11.7)
After Recurrence	14 (4.7)	18 (6.6)	17 (6.0)	12 (4.0)
Due to Death	7 (2.4)	7 (2.6)	4 (1.4)	8 (2.7)
Due to AE	1 (0.3)	3 (1.1)	0	1 (0.3)
Due to Other Reason	30 (10.2)	27 (10.0)	22 (7.8)	14 (4.7)

Recurrence Rate
Ta, G1-G2 Population
Sensitivity Analyses – Handling Missing Data

	APZ		PBO		Difference, %	
	N	Recur, n (%)	N	Recur, n (%)	(95% CI)	
Study 611						
Original Analysis	295	112 (38.0)	271	121 (44.6)	-6.7	(-14.8, 1.4)
Sensitivity Analysis 1	295	150 (50.8)	271	158 (58.3)	-7.5	(-15.6, 0.7)
Sensitivity Analysis 2	257	112 (43.6)	234	121 (51.7)	-8.1	(-16.9, 0.7)
Study 612						
Original Analysis	282	112 (39.7)	298	138 (46.3)	-6.6	(-14.6, 1.4)
Sensitivity Analysis 1	282	138 (48.9)	298	161 (54.0)	-5.1	(-13.2, 3.0)
Sensitivity Analysis 2	256	112 (43.8)	275	138 (50.2)	-6.4	(-14.9, 2.0)

Sensitivity Analysis 1: treat all patients who did not recur and missed last visit as failure.
Sensitivity Analysis 2: exclude all patients who did not recur and missed last visit.

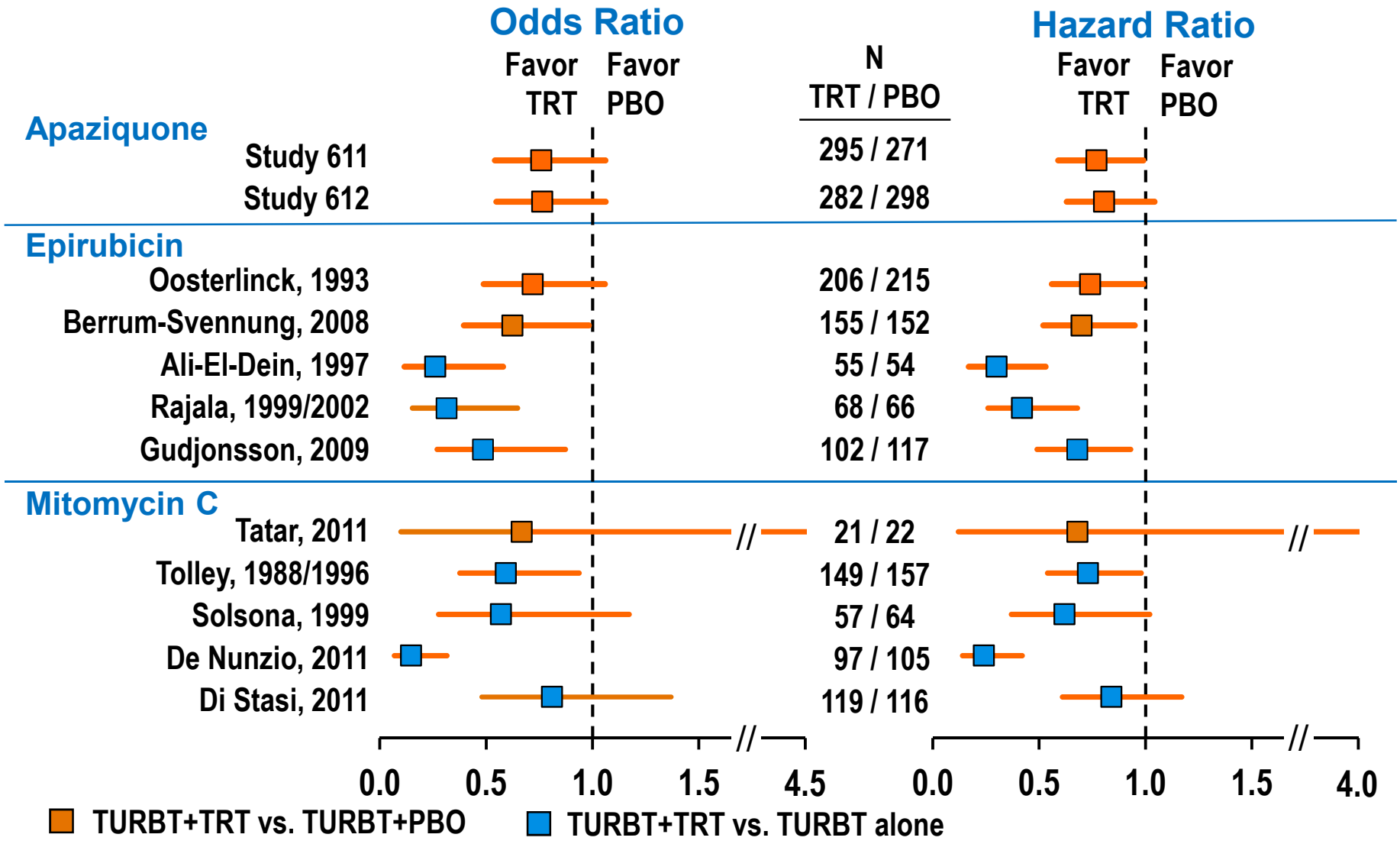
Demographics
Ta, G1-G2 Population

	Study 611 N=566		Study 612 N=580	
	APZ N=295	PBO N=271	APZ N=282	PBO N=298
Male, %	71.2	73.4	72.0	69.8
Female, %	28.8	26.6	28.0	30.2
Median Age	68 (29, 90)	68 (32, 94)	68 (24, 94)	68 (22, 89)
<65 years, %	41.7	38.7	40.4	41.9
≥65 years, %	58.3	61.3	59.6	58.1
Race, %				
White	97.3	97.0	97.5	97.0
Smoking Status, %				
Current	23.7	20.3	30.9	22.8
Former	58.6	56.1	48.9	52.0
Never	17.6	23.6	20.2	25.2

Recurrence Rate & Time to Recurrence
ITT Population

Parameter	Study 611 APZ N=406	Study 611 PBO N=396	Study 612 APZ N=402	Study 612 PBO N=410
Recurrence Rate				
Recurrence, %	36.9	42.2	40.0	46.1
p-value	0.1304		0.0821	
Difference, %	-5.2		-6.0	
Odds ratio (95% CI)	0.80 (0.61, 1.07)		0.78 (0.59, 1.03)	
Time to Recurrence				
Hazard ratio (95% CI)	0.84 (0.67, 1.05)		0.84 (0.68, 1.04)	
p-value	0.1169		0.1058	

Efficacy in Intravesical Therapy



Recurrence Rate
Ta, G1-G2 Population
Dr. Karsh Site (#048)

Parameter	Site #048 APZ N=24	Site #048 PBO N=21
Recurrence, %	3 (12.5)	5 (23.8)
p-value	0.3276	
Difference, %	-11.3 (-33.8, 11.2)	
Odds ratio (95% CI)	0.46	
Relative recurrence %	-47.5	