

UPDATE ON THE MANAGEMENT OF BLADDER CANCER: KOL BREAKFAST

LE PARKER MERIDIEN
NEW YORK

Thursday 25th August

Kjetil Hestdal, MD, President & CEO

Erik Dahl, CFO

Ambaw Belle, President & Head of US Cancer Commercial Operations



AGENDA

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- Welcome by **Kjetil Hestdal**, *President & CEO, Photocure ASA*
- **Cancer of the Urinary Bladder**
 - **Dr. Gary Steinberg**; Bruce & Beth White Family Professor of Surgery & Vice Chairman of Urology & Director Urologic Oncology, University of Chicago
- **Genomic Landscape of Bladder Cancer**
 - **Dr. Yair Lotan**; Professor, Chief Urologic Oncology, Holder of the Helen J. & Robert Strauss Professorship, Univ. of Texas Southwestern Medical Center
- **Risk Stratification and Guidelines for Management of NMIBC**
 - **Dr. James McKiernan**; John K. Lattimer Professor & Chairman Dept. of Urology, College of Surgeons & Urologist-in-Chief at NY Presbyterian Columbia Hospital & Vice Chair, AUA Guidelines Committee
- Company Update by **Kjetil Hestdal**
- Q&A Session

DR. GARY STEINBERG

BRUCE & BETH WHITE FAMILY PROFESSOR OF SURGERY & VICE
CHAIRMAN OF UROLOGY & DIRECTOR UROLOGIC ONCOLOGY,
UNIVERSITY OF CHICAGO





THE UNIVERSITY OF
CHICAGO
MEDICINE &
BIOLOGICAL
SCIENCES

Cancer of the Urinary Bladder

Dr. Gary D. Steinberg

Director of Urologic Oncology

Vice Chairman Section of Urology

Bladder Cancer Natural History & Etiologic Factors

Bladder Cancer Epidemiology (US 2016)

- 76,960 new cases
- 16,390 deaths
- Prevalent population > 550,000 patients

Risk Factors for Bladder Cancer

- Cigarettes
- Occupation: dyes, rubber, textile, diesel, exhaust
 - Aromatic amines
 - Nitrates / Nitrosoamines
- Chronic cystitis
- Cyclophosphamide
- Radiation therapy

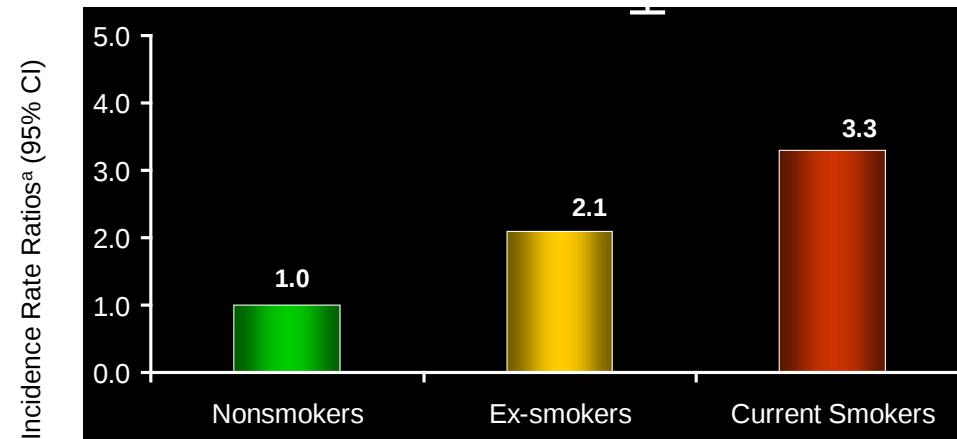
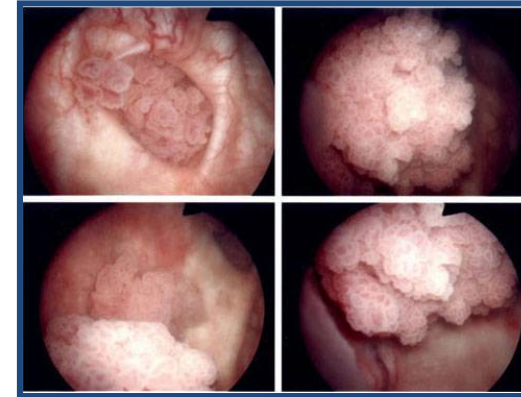
Lifetime risk of developing bladder cancer:¹

- 1 in 26 men
- 1 in 84 women



Increased Risk of Bladder Cancer Among Smokers and Ex-Smokers

- Smoking is one of the most important risk factors associated with bladder cancer
- Prevention of cigarette smoking would result in 50% fewer men and 23% fewer women with bladder cancer
- Current cigarette smokers have approximately 3-fold greater risk of bladder cancer than nonsmokers
- Successfully quitting smoking before 50 years of age reduces the risk by about 50% after 15 years



Zeegers et al. *World J Urol.* 2004;21:392-401; Urology channel.

<http://www.urologychannel.com/bladdercancer/index.shtml>. Accessed September 20, 2007

Surgeon General's Report 2004



Unmet Medical Needs

Bladder cancer is associated with a high risk of:

- Recurrence:²
 - Up to 61% at 1 year
 - Up to 78% at 5 years for NMIBC
- Progression to muscle-invasive disease:²
 - Up to 17% at 1 year
 - Up to 45% at 5 years
 - Common in patients with CIS, which are often difficult to detect³

High rate of residual tumor after TURBT:

- 34%–76% of patients have evidence of tumor on repeat TURBT at 2–6 weeks⁴⁻⁶

Patients with incomplete initial resection are at high risk of recurrence⁵

- Continued growth of microscopic lesions which were not observed at initial TURBT⁷
- New growth of small residual traces of tumor, often at surgical margins⁸

Direct medical costs of cancer care (US)

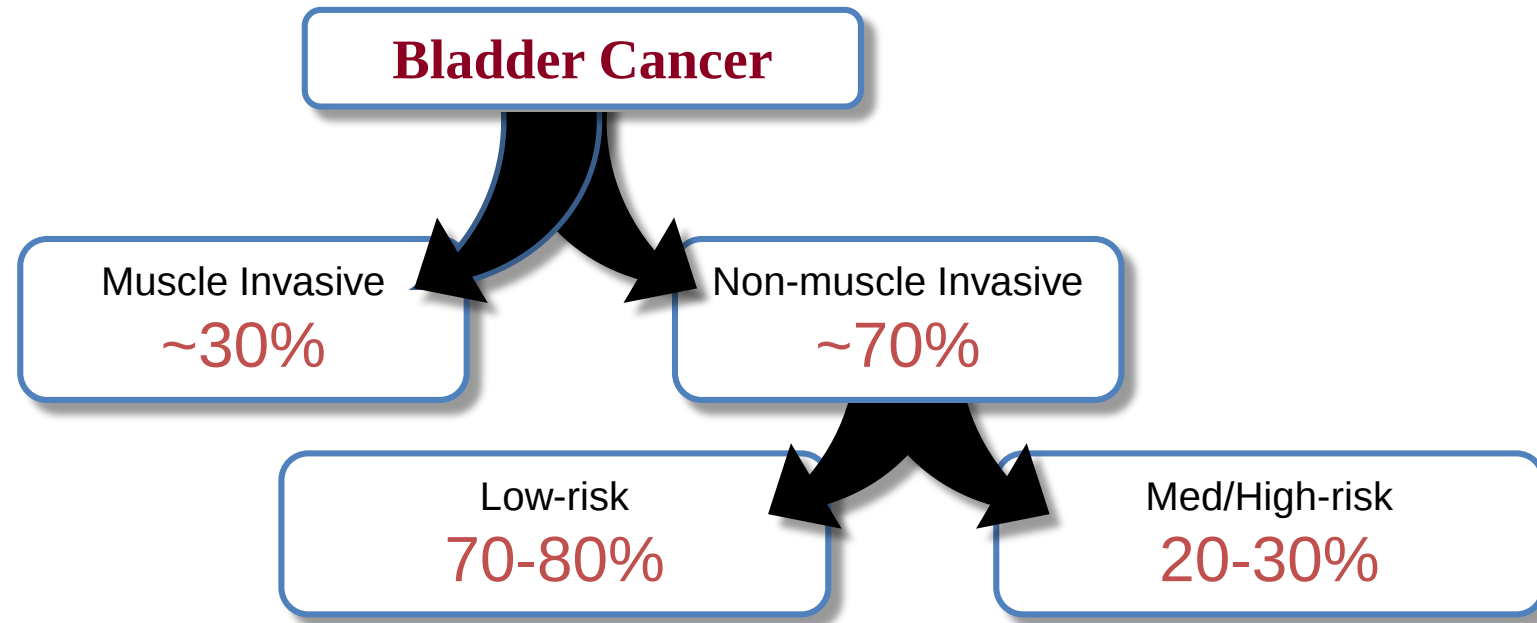
- Estimated at **\$125 billion** in 2010
- Expected to rise to **\$155 billion** in 2020**



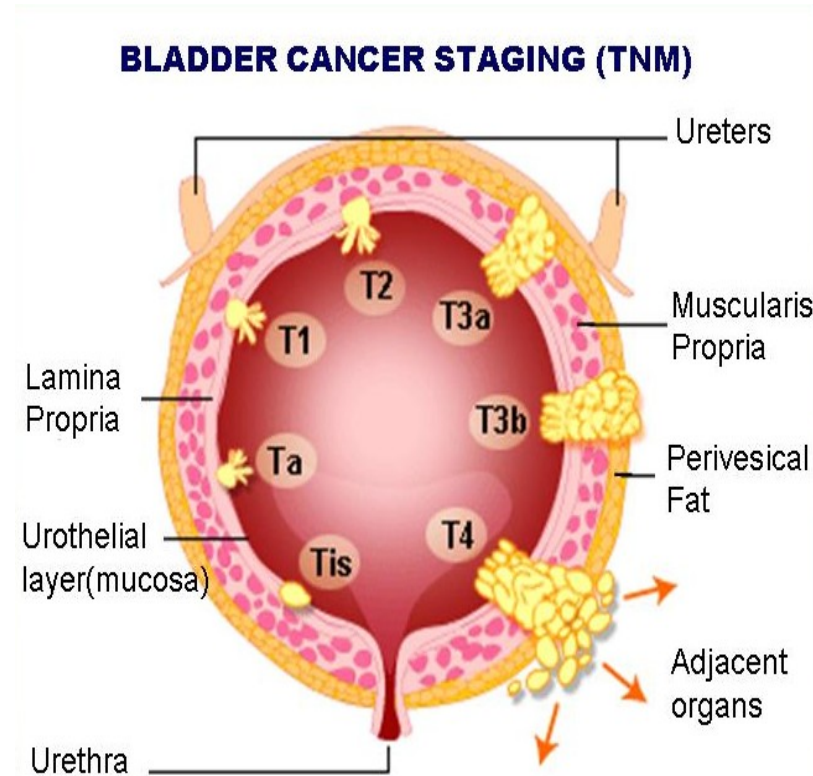
Diagnosis and Presentation



Bladder Cancer Segmentation



Bladder Cancer Staging



Prevalence of Bladder Cancer Staging at Diagnosis^{1,2}

Stage at Diagnosis	% of Patients
Non-muscle invasive	75%
Ta	60%
T1	30%
Tis	10%
Muscle invasive	20%
Metastatic	5%

AJCC Cancer Staging Manual 6th Edition; 2002.

NCI 2009 - <http://www.cancernet.nci.nih.gov/cancertopics/pdq/treatment/bladder/HealthProfessional/page4#Reference4.4>.

Accesses 21 July, 2009.

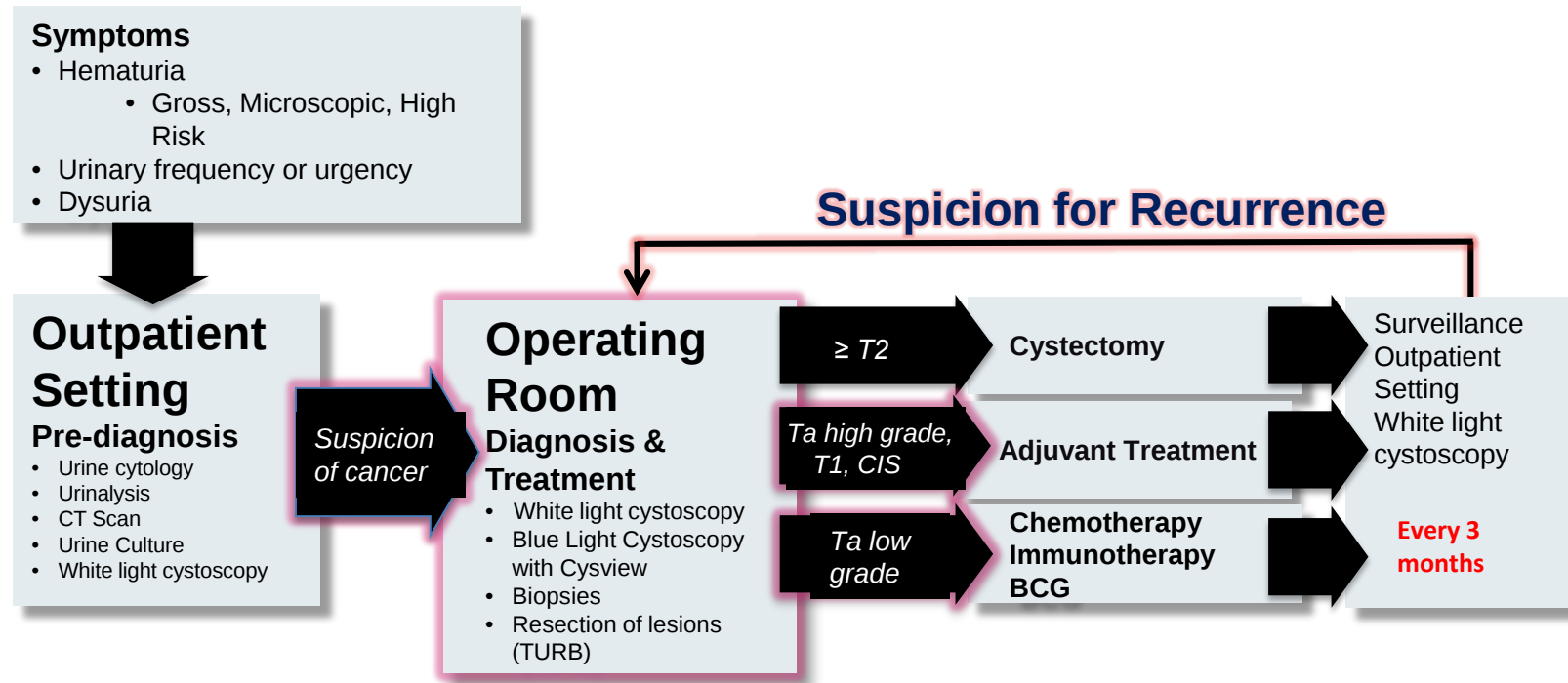
1. Sonpavde G. *Postgrad Med.* 2005;119(3):30-37.

2. Dalbagni G. *Nat Clin Pract Urol.* 2007;4(5):254-260.



Bladder Cancer

Symptoms, Diagnosis, Surveillance & Follow-up

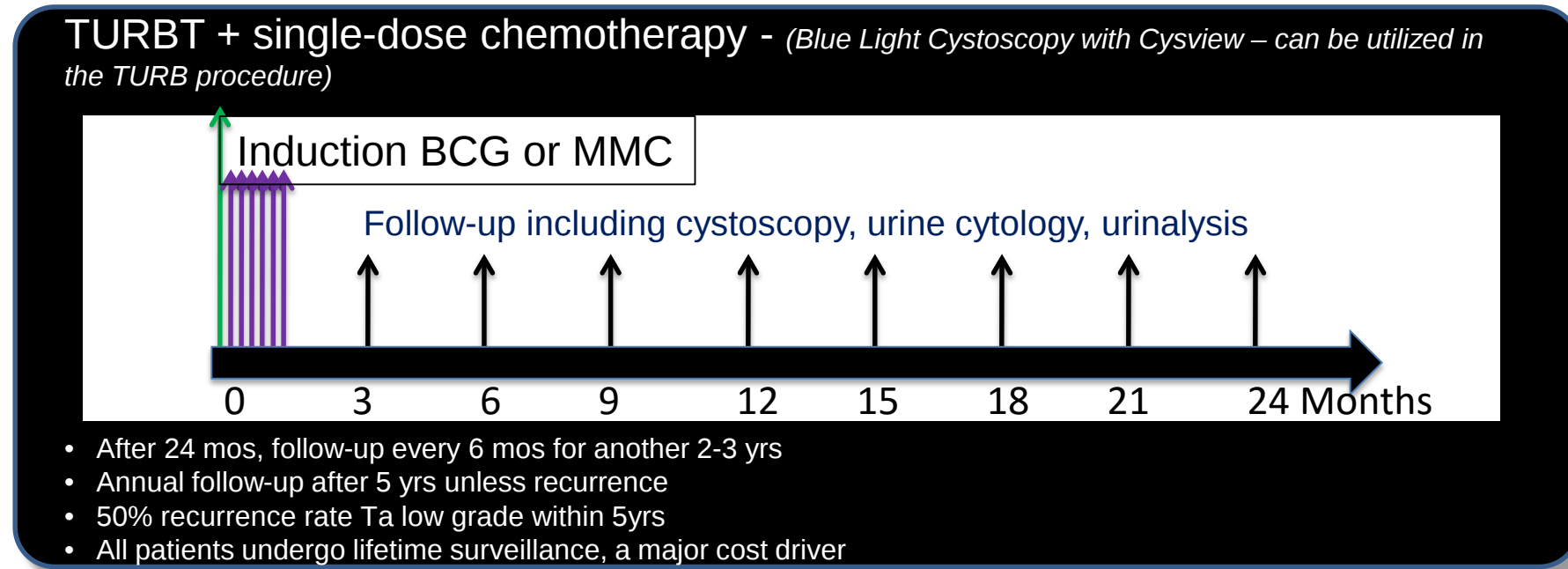


Complete resection, correct grading and staging is essential for optimal patient management



Non-muscle Invasive Bladder Cancer

Standard of Care: Life-long Follow-up⁹



9. 2007 Update of the AUA Guideline for the Management of Nonmuscle Invasive Bladder Cancer.



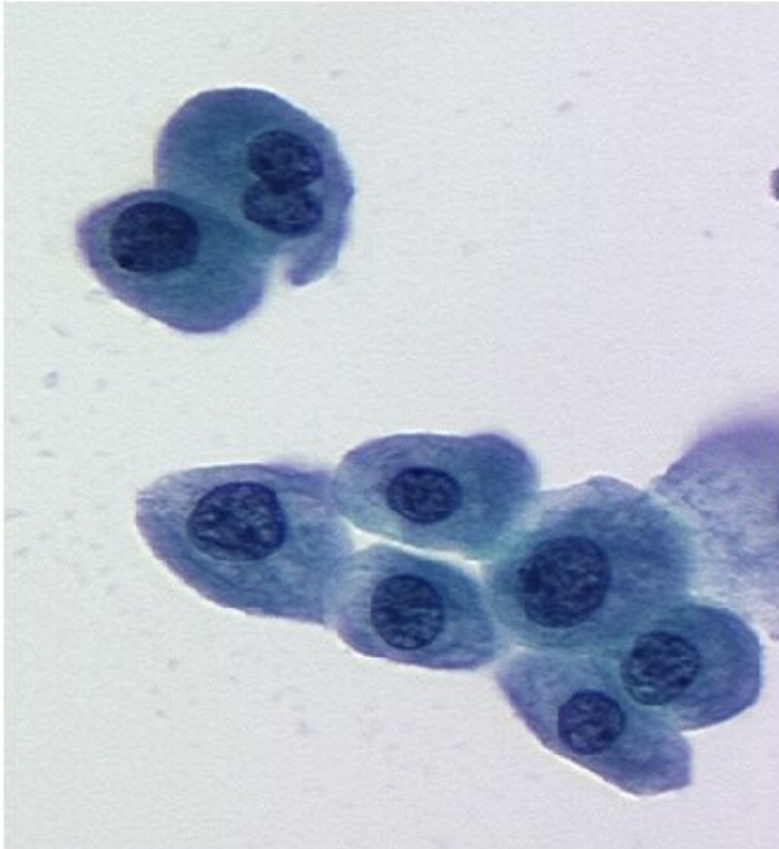
Bladder Cancer Surveillance

- Cystoscopy
 - Sometimes misses High-Grade CIS
 - 28% increased detection rate using Cysview*
 - Unable to detect Upper Tract Disease
- Urine Cytology
 - Detects High-Grade CIS
 - Frequently misses Low-Grade Papillary Tumors
 - Overall sensitivity 30%, overall Specificity = 95%

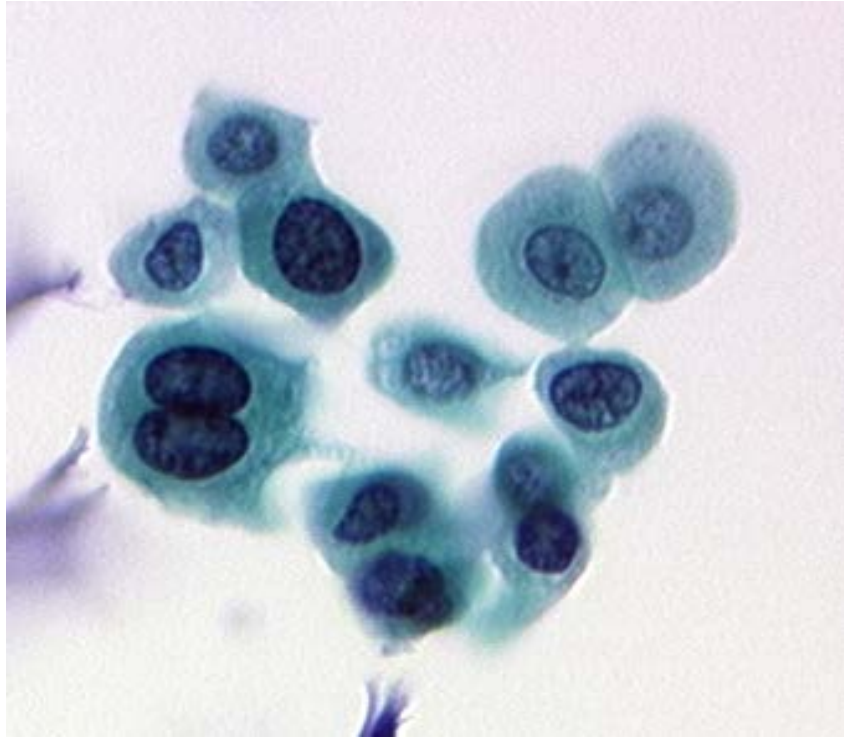
*Schmidbauer, et al, PCB301/01 Study Group. "Improved Detection of Urothelial Carcinoma in Situ with Hexaminolevulinate Fluorescence Cystoscopy." *The Journal of Urology* 171, no. 1 (January 2004)



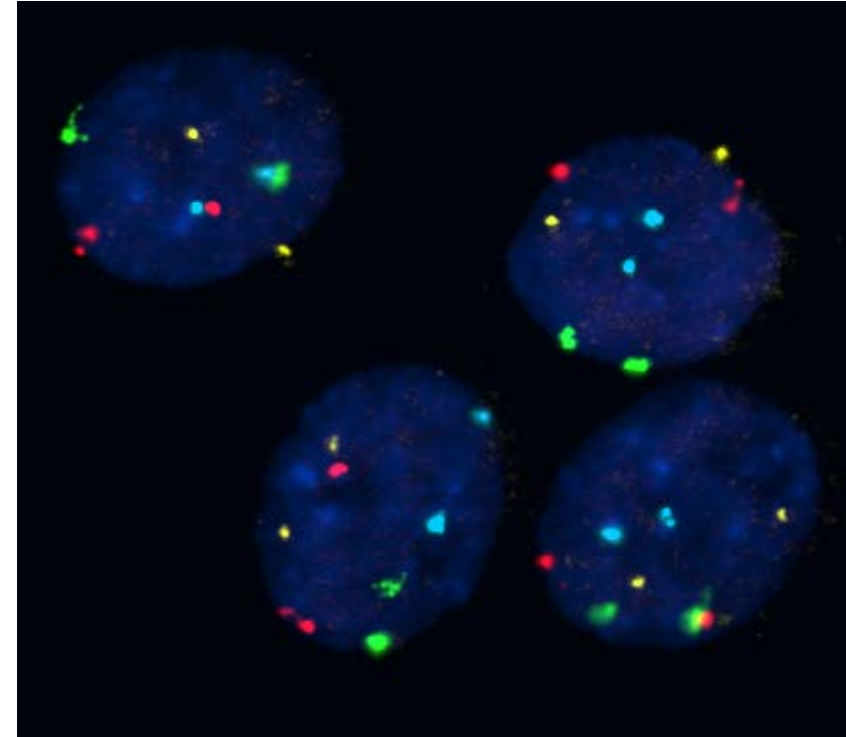
Urine Cytology



Combining Morphology with DNA Technology: Molecular Cytology



Cytology



Molecular Cytology



Imaging



Rationale for Early Detection

- Good cure rates for non-muscle invasive disease
- Treatment of early tumors is relatively less complicated but high cost due to number of diagnostic procedures
- Opportunity exists to detect tumors destined to invade muscle before they actually do so



Office Cystoscopy

- Thorough Endoscopy of Urethra and Bladder
- Local Anesthesia
- Photography of Bladder
- Cytology – to assess for Cancer Cells



Bladder Tumor - Cystoscopy

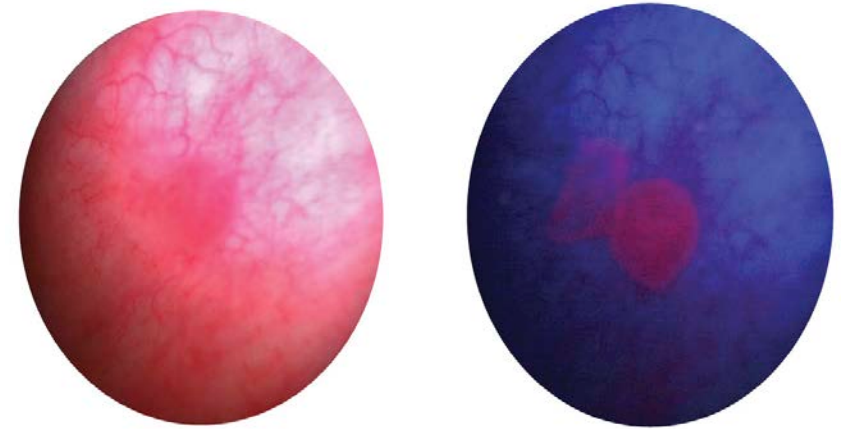


Blue Light Cystoscopy with Cysview

- Diagnostic tool to aid detection of bladder tumors
- Technology
 - Instill a photosensitizing agent into the bladder via a catheter
 - The agent induces preferential intracellular accumulation of photoactive porphyrins (PAPs), mainly protoporphyrin IX (PpIX), in malignant as opposed to non-malignant cells of urothelial origin
 - Under subsequent blue light illumination, neoplastic cells fluoresce enabling visualization of the tumor

Ref: Frampton JE, Plosker GL. Hexyl aminolevulinate in the detection of bladder cancer. Drugs 2006; 66:571-8.

Standard White Light Cystoscopy
Mode 1

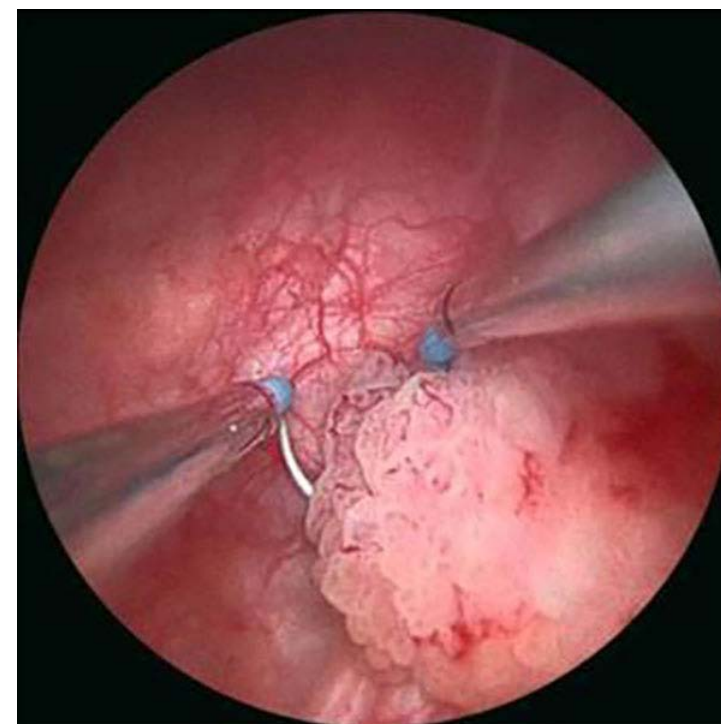


Blue Light Cystoscopy with Cysview
Mode 2



TURBT: Diagnostic and Therapeutic

- Establishes pathologic diagnosis, including grade and stage of disease
- Also should be viewed as a complete oncologic procedure, especially in low grade non-muscle invasive disease
 - Repeat TURBT
 - May upstage from T1 to T2 in up to 40-50%
 - Residual disease or early recurrence



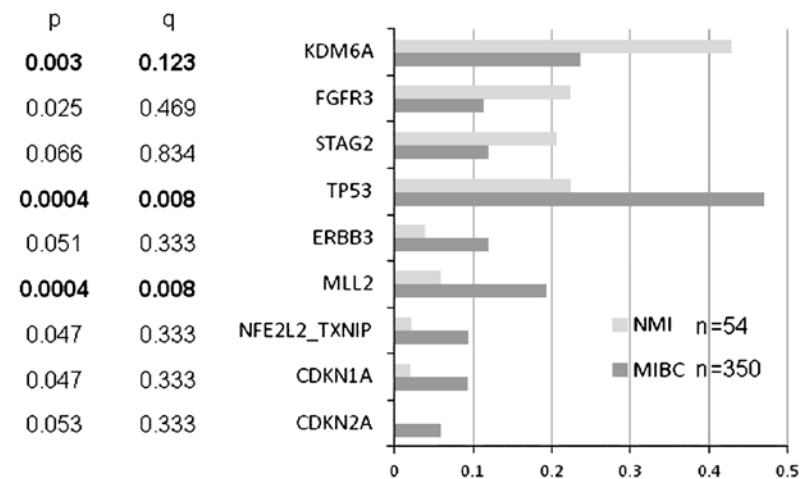
Bladder Cancer Diagnosis: Challenges and Future Directions

- Molecular markers: Detection, Risk Stratification, Prediction of Response to Treatment
 - Whole genome sequencing
 - Epigenetics
 - miRNA microarrays

DNA Methylation marker associated with progression and recurrence

Genes	Progression	Recurrence	Study
APAF1	NA	0.05	Christoph et al, Int J Cancer, 2006
CDH13	0.00	0.01	Lin et al, Int Urol Nephrol, 2012
CDKN2A	NA	0.05	Lin et al, Urol Oncol, 2010
DAPK1	NA	0.001	Tada et al, Cancer Res, 2002
DAPK1	NA	0.04	Christoph et al, Int J Cancer, 2006
IGFBP3	NA	0.02	Christoph et al, Int J Cancer, 2006
RASSF1A	0.004	NA	Kim et al, Clin Genitourin Cancer, 2012
RASSF1A	0.04	NA	Catto et al, J Clin Oncol, 2005
RASSF1A, CDH1, APC, TNFSR25, EDNRB	0.05	NA	Yates et al, Clin Cancer Res, 2007
RUNX3	0.01	0.02	Kim et al, Cancer Res, 2005
RUNX3	0.006	0.04	Yan et al, J Surg Oncol, 2012
RUNX3	0.013	NA	Kim et al, J Urol, 2008
SYMPO2	0.05	NA	Cebrian et al, Cancer Res, 2008
SYMPO2	0.03	0.01	Alvarez-Mugica et al, J Urol, 2010
TBX2, TBX3, GATA2, ZIC4	0.003	NA	Kandimalla et al, Eur Urol, 2012
TBX4	0.05	NA	Reinert et al, Clin Cancer Res, 2011
TIMP3	NA	0.036	Friedrich et al, Eur J Cancer, 2005
TIMP3	0.01	NA	Hoque et al, JNCI, 2006

Comparison of Mutation Frequency in NMIBC vs MIBC



S.P. Lerner et al. / Summary of NMIBC Trials Planning Meeting

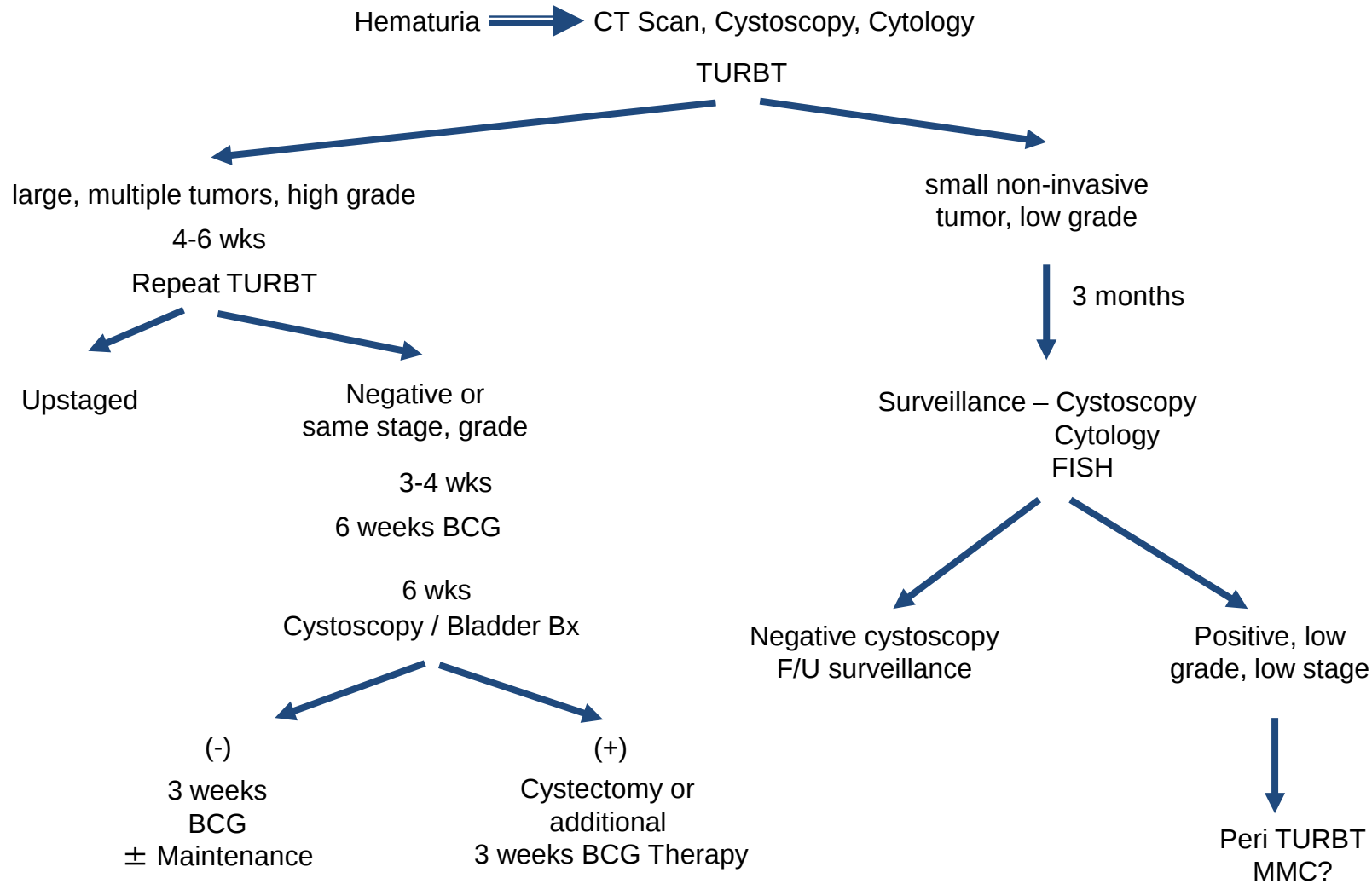


Non-Muscle Invasive Disease

- TURBT
- Chemotherapy / Immunotherapy
- Detection / Surveillance
- Watchful Waiting



NMIBC: Evaluation / Treatment



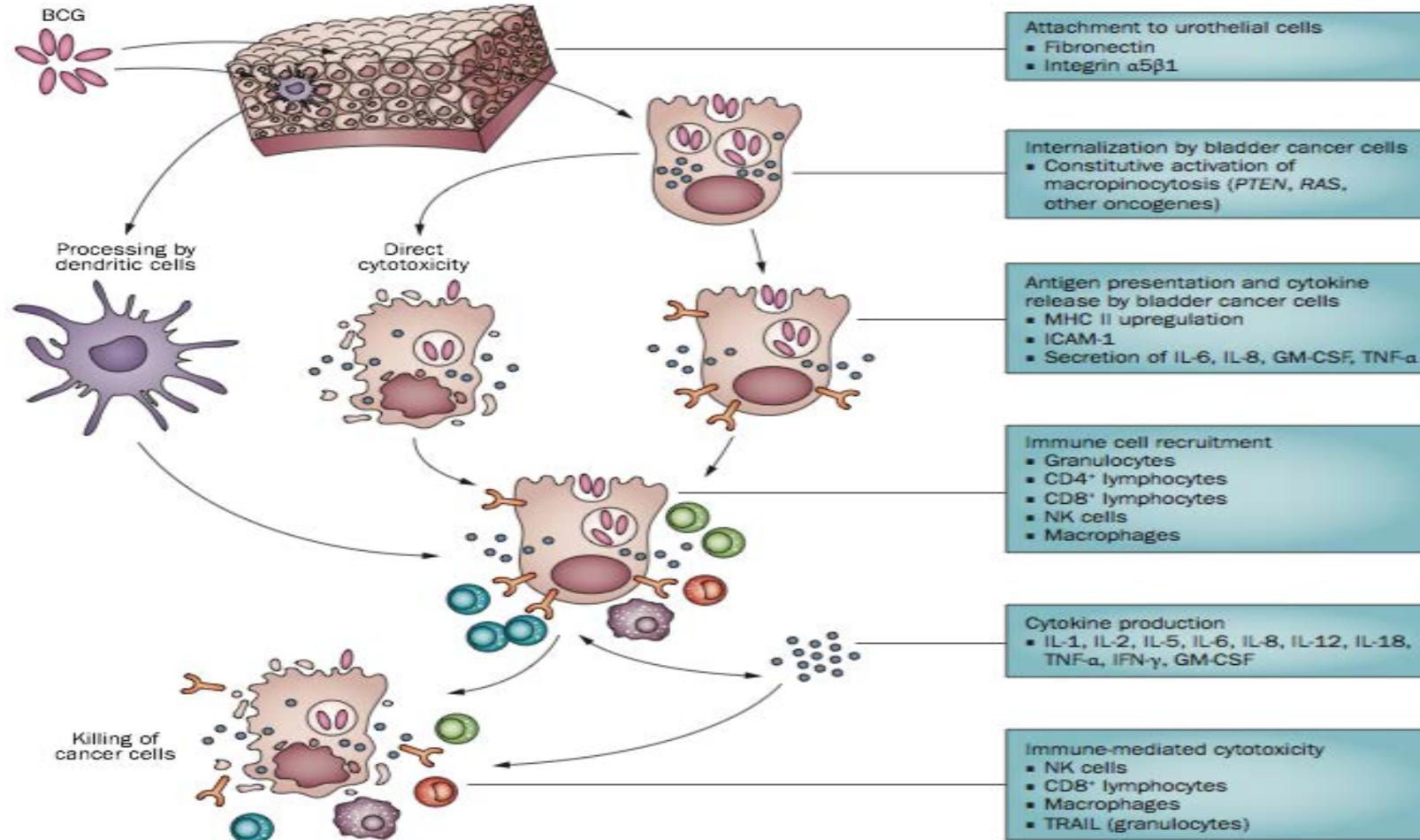
NMIBC: Current Challenges

- Urinary markers to replace cystoscopy
- 2nd line therapies for BCG-failure
 - Intravesical
 - When to proceed to cystectomy
- Biomarkers of disease aggressiveness – predicting progression and recurrence
 - **NMIBC – 60-80% chance of recurrence at 5 years with surgery alone**
 - **Exception – first time, solitary, small, TaG1 papillary tumors**

Millan-Rodriguez et al. JUrol 2000



BCG: Mechanism of Action



Redelman-Sidi et al. The mechanism of action of BCG therapy for bladder cancer—a current perspective. Nat. Rev. Urol. 11, 153–162 (2014).



Biomarkers to Predict Response to BCG?

- glutathione S-transferase theta 1 (GSTT1)
 - Genomic polymorphisms may predict response
 - GSTT1-positive up to 14-fold higher risk of early BCG failure
- Urinary cytokine panel – CyPRIT
 - 9 inducible cytokines in urine
 - Predict recurrence with 85.5% accuracy

*Kang et al. Urologic Oncology, 2014

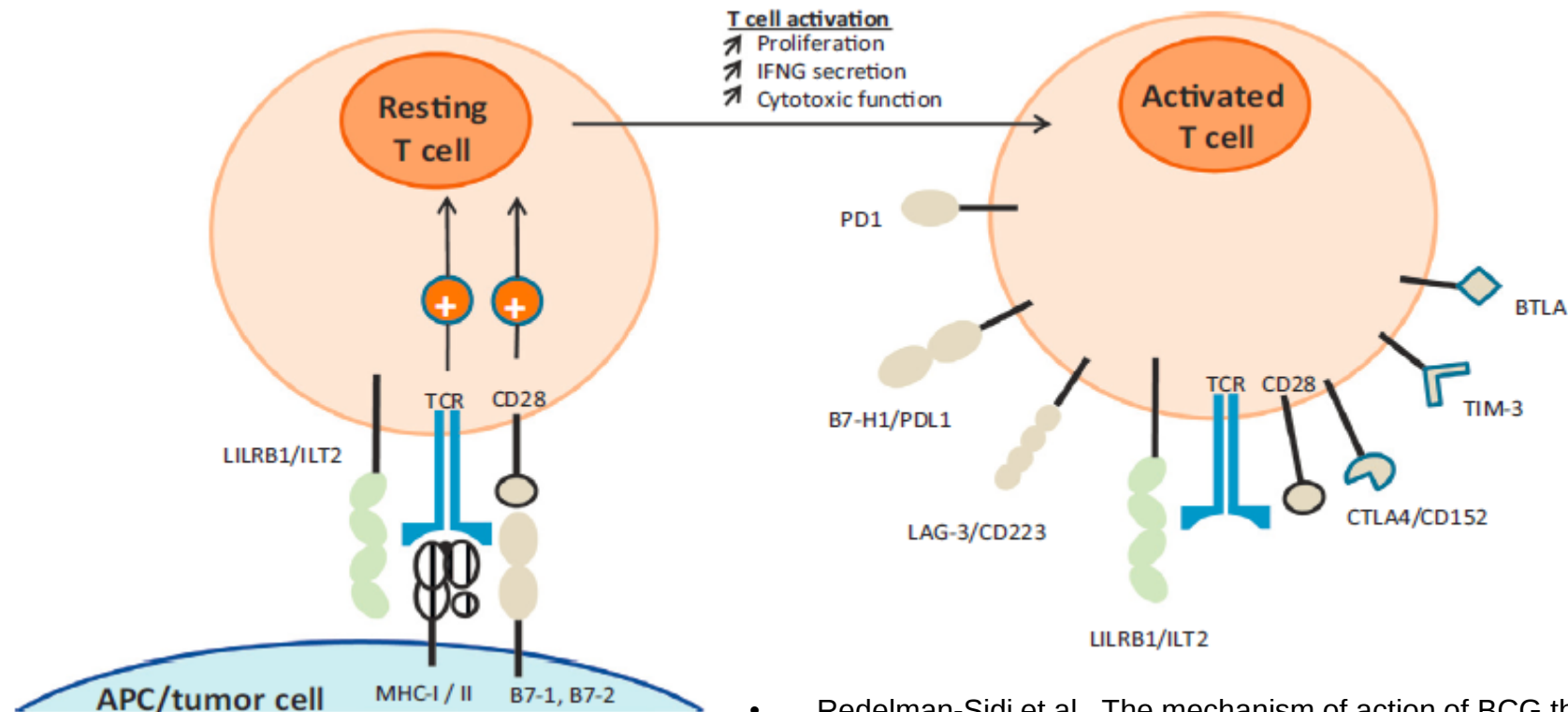
* Kamat et al. European Urology, 20161111



Cancer Immunotherapy

Recognition of cancer cells by T cells

Normally -- upregulation of immune checkpoint receptors

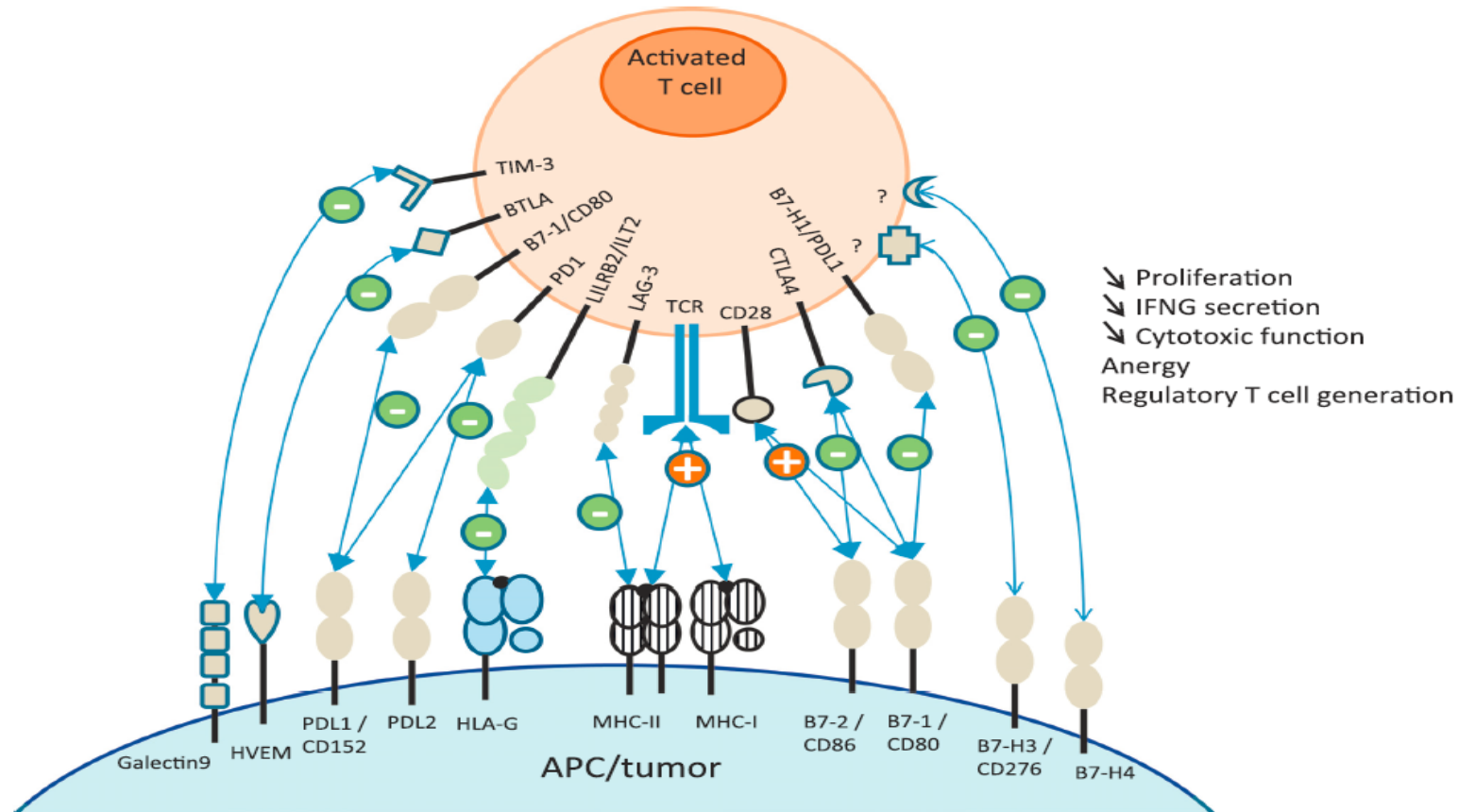


- Redelman-Sidi et al. The mechanism of action of BCG therapy for bladder cancer—a current perspective. Nat. Rev. Carosella ED. Eur Urol 68 (2015): 267-279

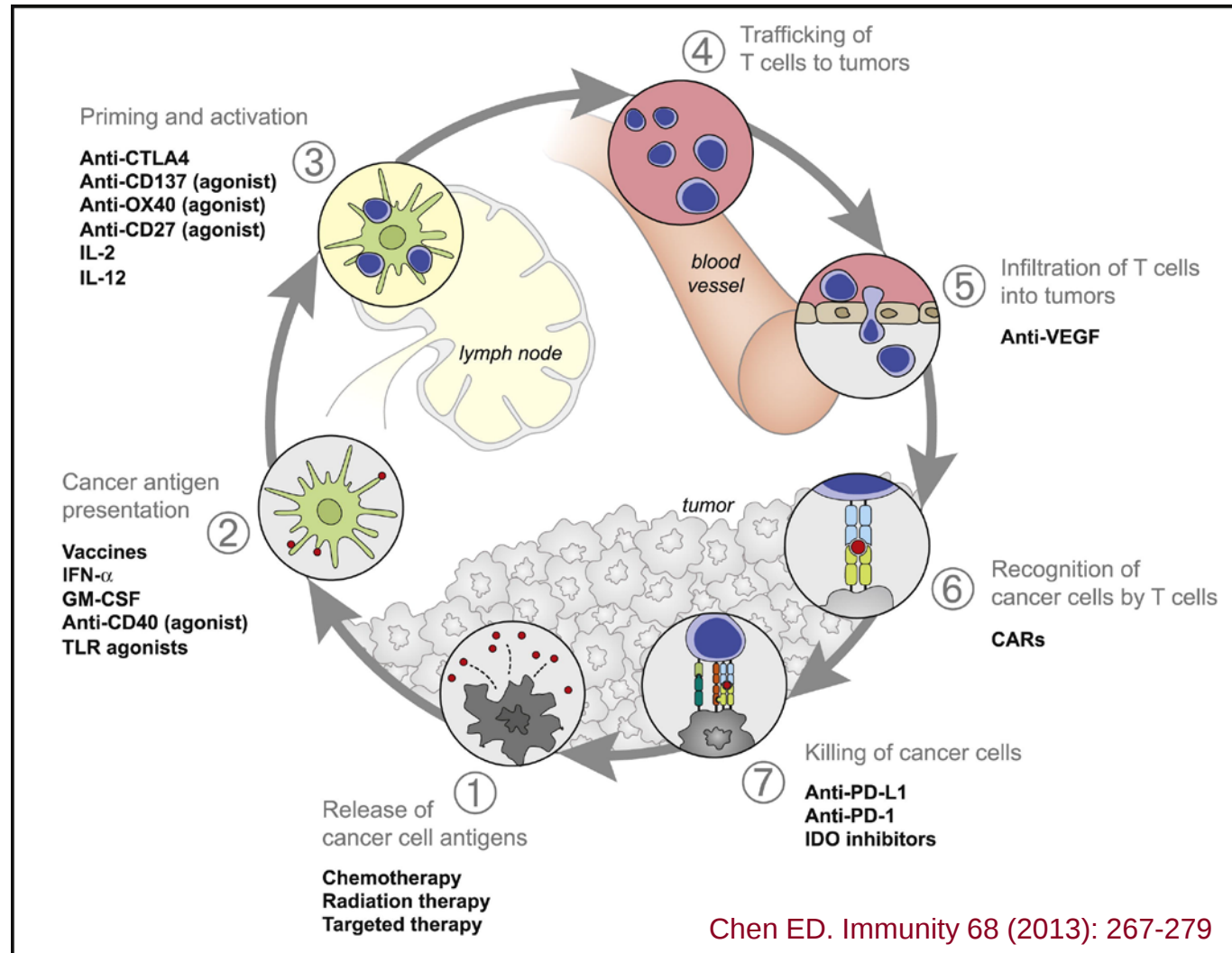


Cancer Immunotherapy

Tumors can escape response by direct or indirect (APC) inhibition of various immune checkpoint proteins



Therapeutic Targets



Current Clinical Trials

Table 2
Current clinical trial landscape

Trial/Sponsor	Drug	Target/Design	Phase	Status
S0337	Gemcitabine	Peri-op single dose	III	Completed
NCT00974818	MMC vs. Gem			Closed early?
NCT00461591	Apaziquone	Peri-op single dose	III	Closed
NCT00598806				
RTOG-0926	Chemo/XRT	T1	II	Open
NCT01732107	Dovitinib (FGFR3)	BCG refractory	II	Closed
Cold Genysis	CG 0070	Rep competent ADV GMCSF	III	Open?
NCT02009332	Rapamycin (mTOR)	BCG refractory	I/II	Open
NCT01259063	Everolimus/Gem	BCG refractory/CIS	I/II	Open
NCT02197897	Tamoxifen	ER – TaLG marker lesion	II	Open
NCT02010203	HS 410 (vaccine)	BCG + HS 410	I/II	Open
Heat Biologics		(BCG naïve)		
Viventia	Vicinium	High risk	I/II	Ph II planned
FKD	AD-IFN	BCG refractory	II	Completed
				Ph III planned
BioCancell	BC 819 (H19/DTA)	BCG failure/refractory	II	Completed
				Ph III planned
NCT02015104	PANVAC+BCG vs. BCG	BCG failure	II	Open
Telesta Therapeutics	MCNA	Failure/Unresponsive	III	Completed
Altor Bioscience	ALT-803 (IL15)	BCG naïve	I/II	Completed

Lerner, Seth P., et al. "Summary and Recommendations from the National Cancer Institute's Clinical Trials Planning Meeting on Novel Therapeutics for Non-Muscle Invasive Bladder Cancer." *Bladder Cancer* 2, no. 2.



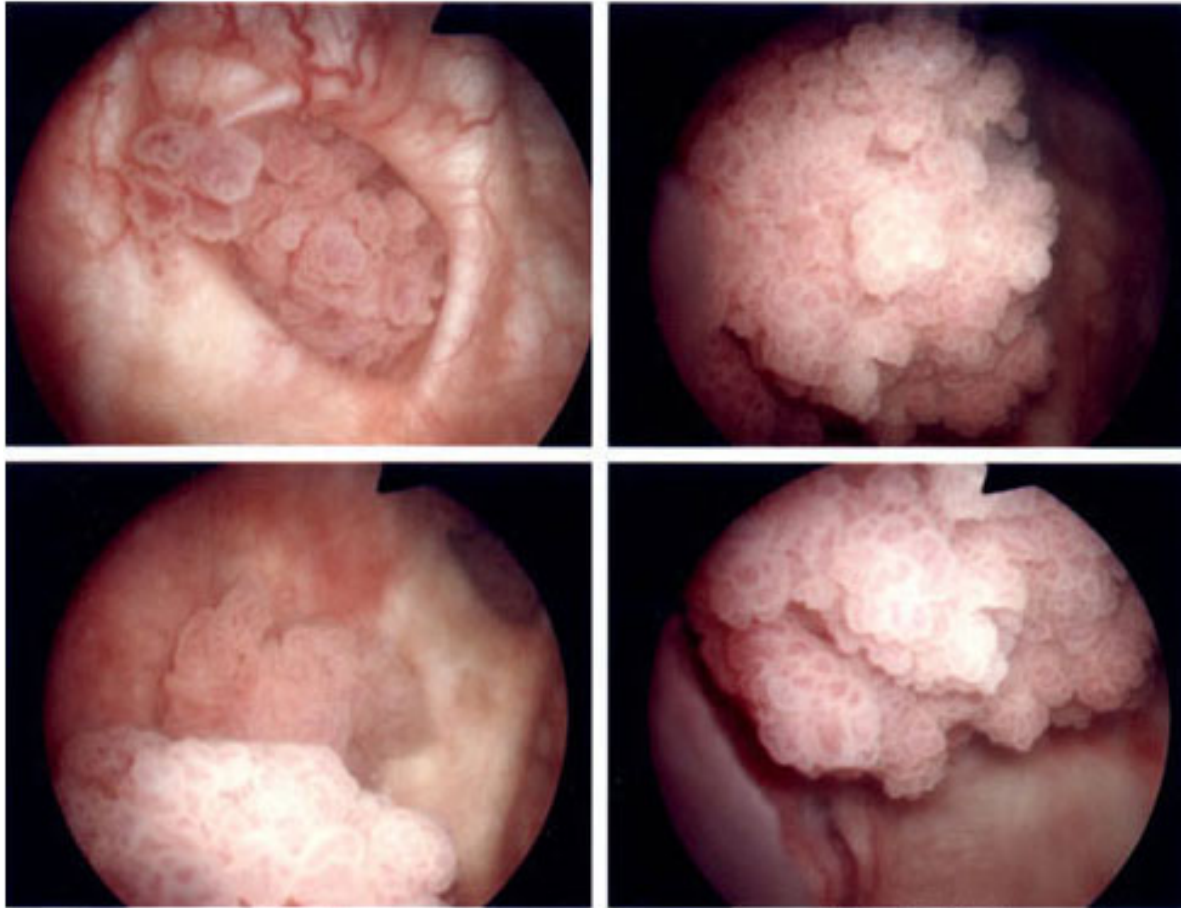
Table 3
Novel drug delivery systems

-
- Adenoviral mediated
 - PEI/DNA plasmid
 - Liposomal complex
 - Nanoparticles
 - Implantable osmotic pump
 - Conjugated antibody/payload
 - Bacterial minicells
 - Heat
 - Iontophoresis
 - Muco-adhesive molecules
-

Lerner, Seth P., et al. "Summary and Recommendations from the National Cancer Institute's Clinical Trials Planning Meeting on Novel Therapeutics for Non-Muscle Invasive Bladder Cancer." *Bladder Cancer* 2, no. 2.



Invasive Bladder Cancer



Cystoscopic view of papillary bladder cancer

- Lethal disease if not treated appropriately
- Surgery remains cornerstone therapy

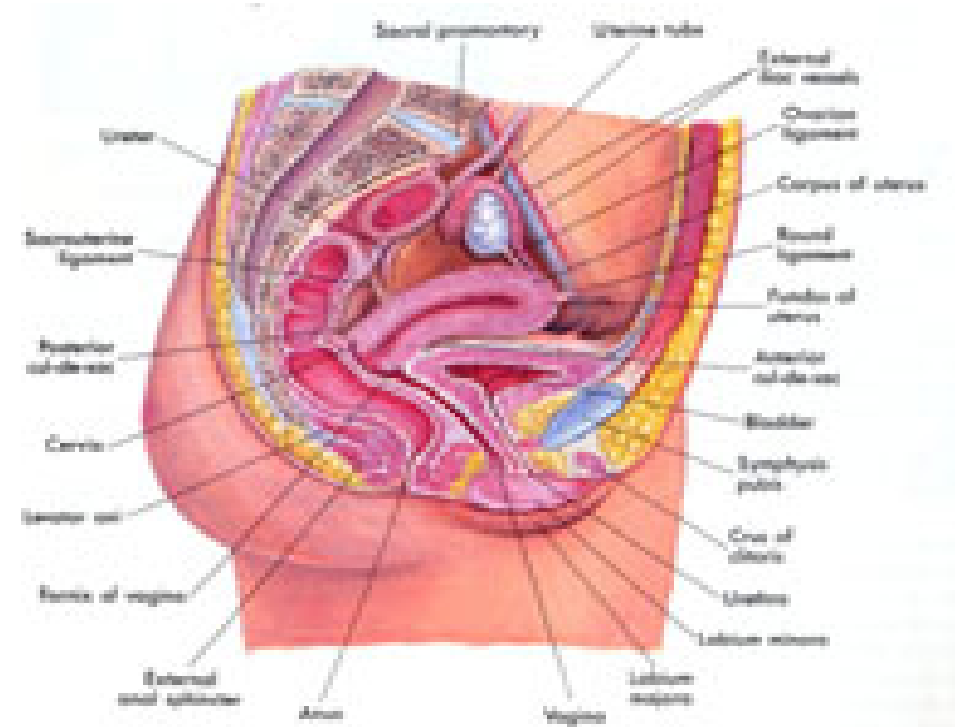


Muscle Invasive Disease

- Radical Cystectomy
- Lymph Node Dissection
- Chemotherapy



Radical Cystectomy

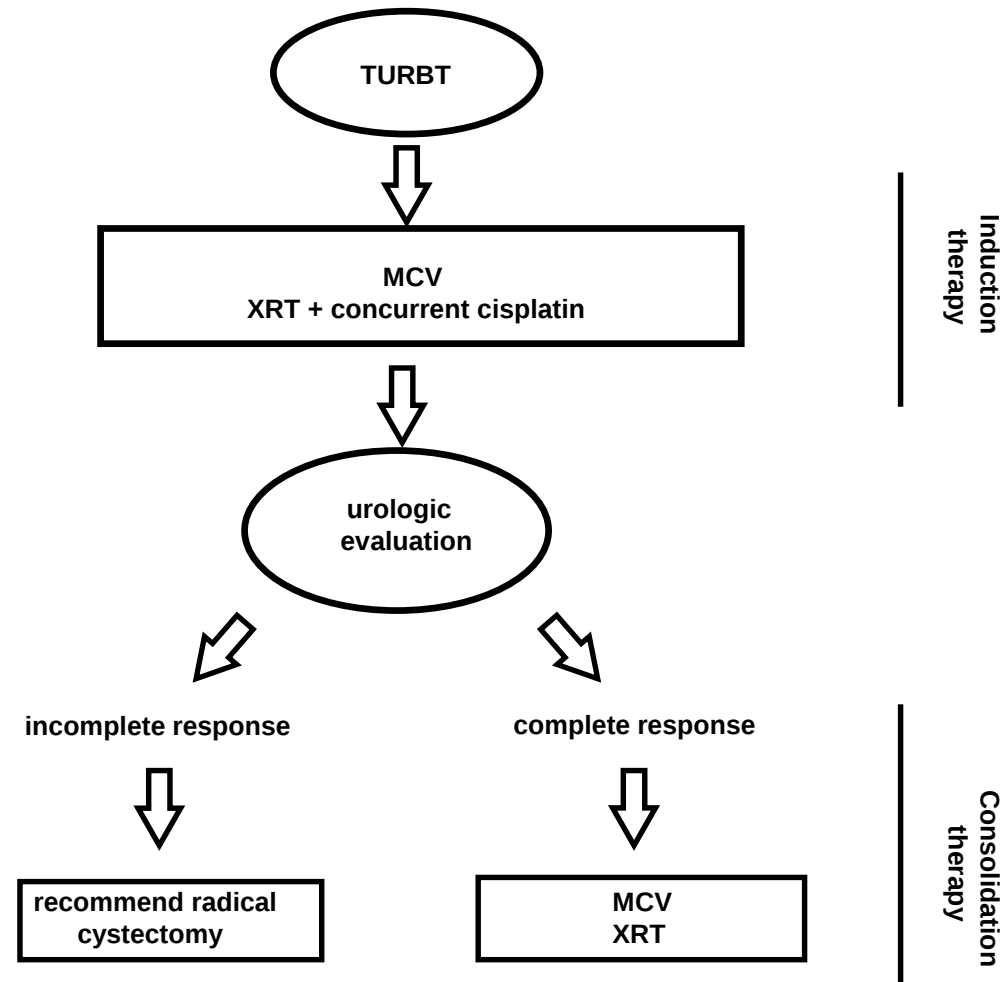


Treatment of Invasive Bladder Cancer: Bladder Preservation

- TURBT
- Chemotherapy
- Radiation Therapy



Treatment of Invasive Bladder Cancer: Bladder Preservation



TURBT: Transurethral resection of bladder tumor, MCV: Methotrexate, Cisplatin, Vinblastine, XRT: External beam irradiation



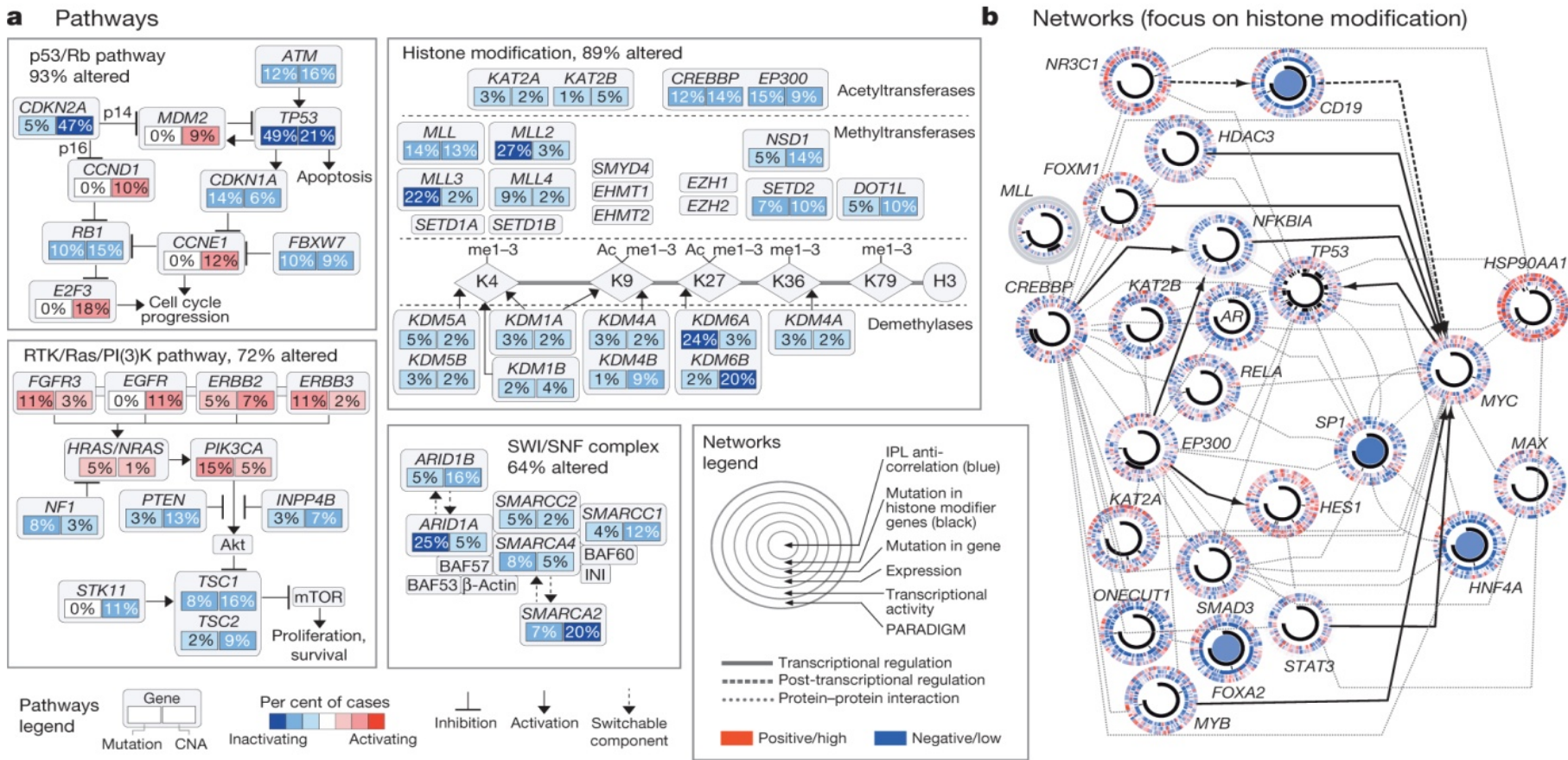
Future Directions: The Cancer Genome Atlas Project

- 2014: First 131 patients sequences
 - Somatic mutation, DNA copy number variants, mRNA and microRNA expression, protein expression, DNA methylation
 - One of the highest somatic mutation rates across cancers
 - 32 significantly mutated genes involved with multiple pathways
- 2015: Cohort increased to 412 tumors
 - 54 significantly mutated genes now identified



Future Directions: The Cancer Genome Atlas Project

Large opportunity for translational research & Targeted Therapy



The Cancer Genome Atlas Research Network *Nature* **507**, 315-322 (2014) doi:10.1038/nature12965



Take Home Points

- Bladder carcinoma is a common and deadly cancer usually diagnosed in the elderly and costs \$4 billion per year in the US
- Non-muscle invasive disease requires resection and often intravesical therapy with close follow up
- Gold standard treatment for muscle invasive disease remains cystectomy
- Knowledge of the molecular mechanisms underlying bladder carcinoma has recently increased exponentially – vast opportunity for translational research



DR. YAIR LOTAN

PROFESSOR, CHIEF UROLOGIC ONCOLOGY, HOLDER OF THE
HELEN J. & ROBERT STRAUSS PROFESSORSHIP, UNIV. OF
TEXAS SOUTHWESTERN MEDICAL CENTER



Genomic Landscape of Bladder Cancer

Yair Lotan

Professor of Urology



Acknowledgement

- Seth Lerner, BCM
- Shahrokh Shariat, Univ. of Vienna
- William Kim, UNC

Disclosures

- **Research Studies:**
 - Abbott
 - Cepheid
 - Genomedx
 - Pacific Edge
 - MDxHealth
 - Photocure

Outline

- **Background**
- **State of genomics**
- **Potential Applications**
- **Future directions**

BLADDER CANCER: Epidemiologic Features

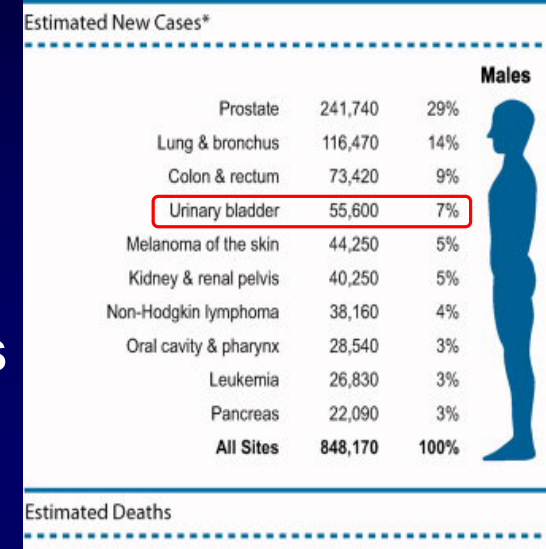
USA in 2015: 74,690 new cases

➡ 553,496 prevalence ➡ 15,580 deaths

Europe in 2012: 118,280 new cases

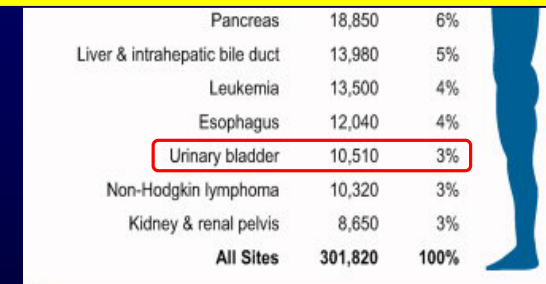
➡ >600,000 prevalence ➡ >20,000 deaths

- 4th most common in ♂ and 11th in ♀



Women with BCa have worse mortality than man!

→ Enormous challenge due to the growth of our aging population



Causes: genetic, epigenetic, hormonal factors?

unequal health care access and processes?

Likelihood of Tumor Progression

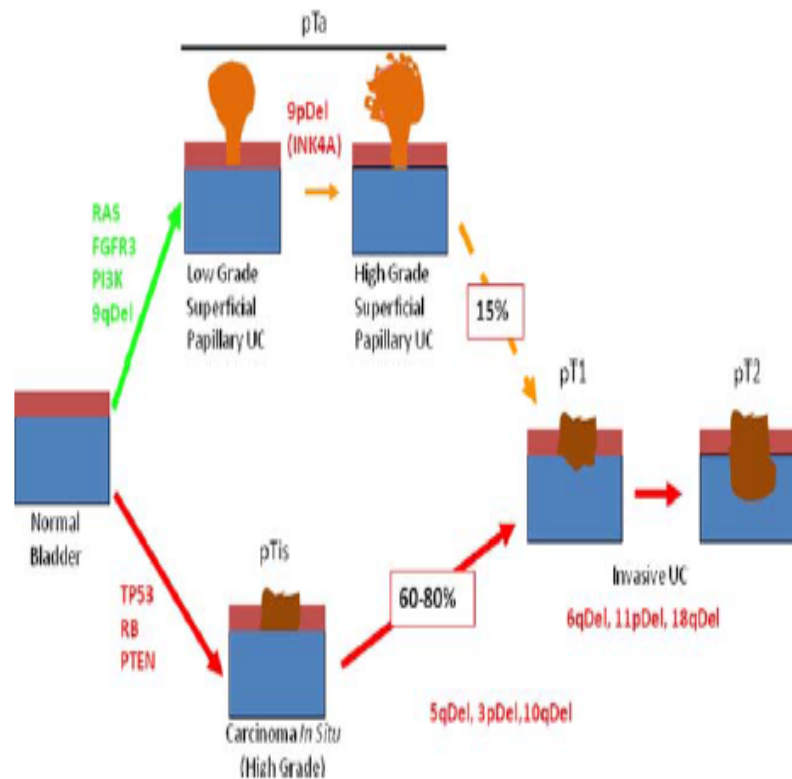
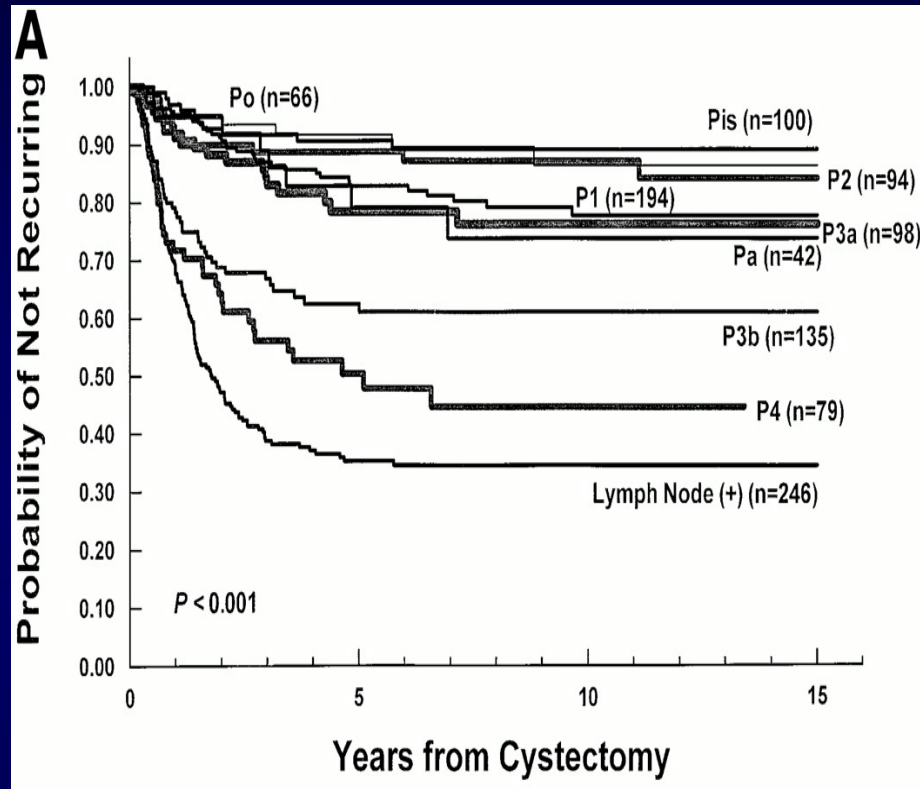


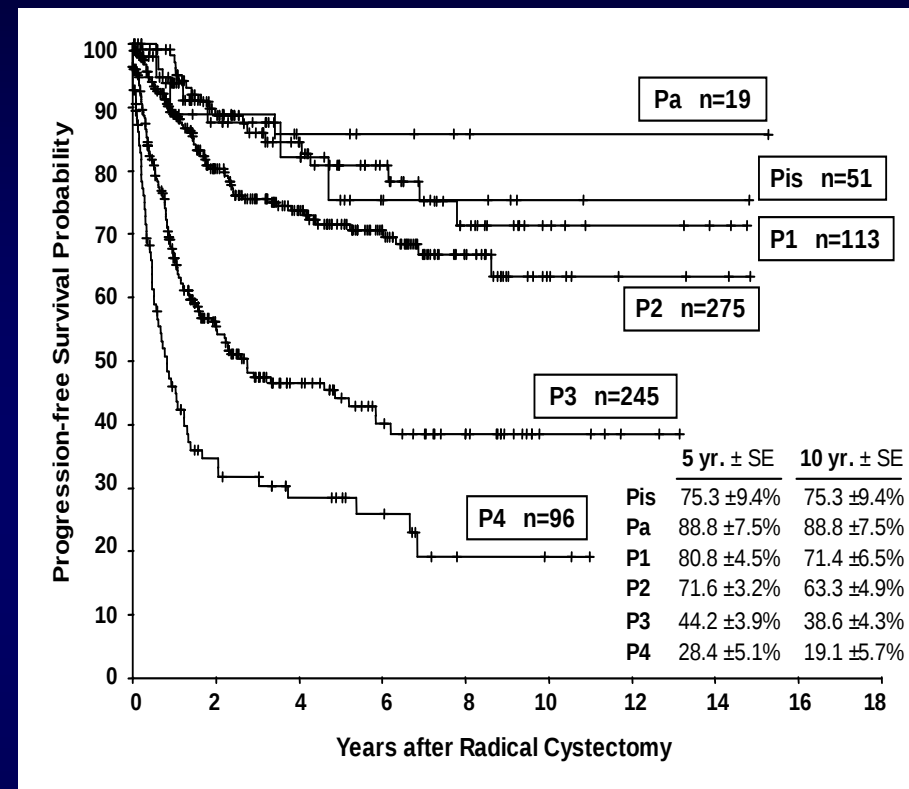
Fig. 1. Molecular pathways of urothelial tumorigenesis and bladder cancer progression. Bladder tumors are classified into 2 separate pathways with distinct histopathology patterns, molecular alterations, and clinical behavior.

TUMOR TYPE	% RELATIVE FREQUENCY	% PROGRESSION	% DEATHS
Noninvasive			
Papilloma	10	0-1	0
Papillary urothelial neoplasm of low malignant potential	20	3	0-1
Papillary cancer low grade (TaG1)	20	5-10	1-5
Papillary cancer high grade (TaG3)	30	15-40	10-25
Invasive			
Papillary cancer (T1G3)	20	30-50	33
Carcinoma in Situ			
Primary	10	>50	—
Secondary	90		

Recurrence after Radical Cystectomy



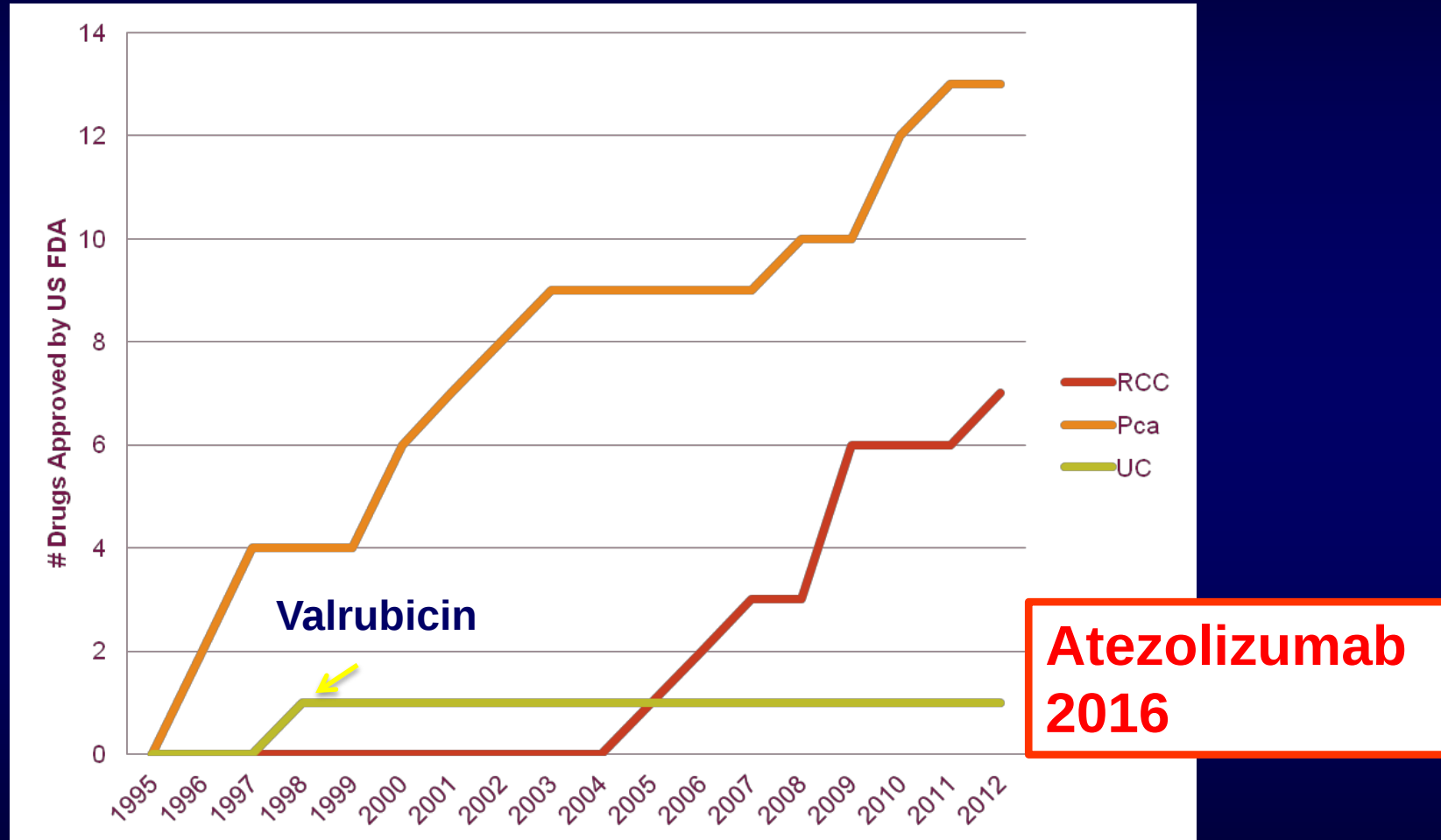
Stein, J. P. et al. J Clin Oncol;
19:666-675 2001



Shariat et al. BCRC J Urol.
2006 Dec

•20-30% of T1-T2 patients recur after cystectomy

US Drug Approvals in GU Cancers



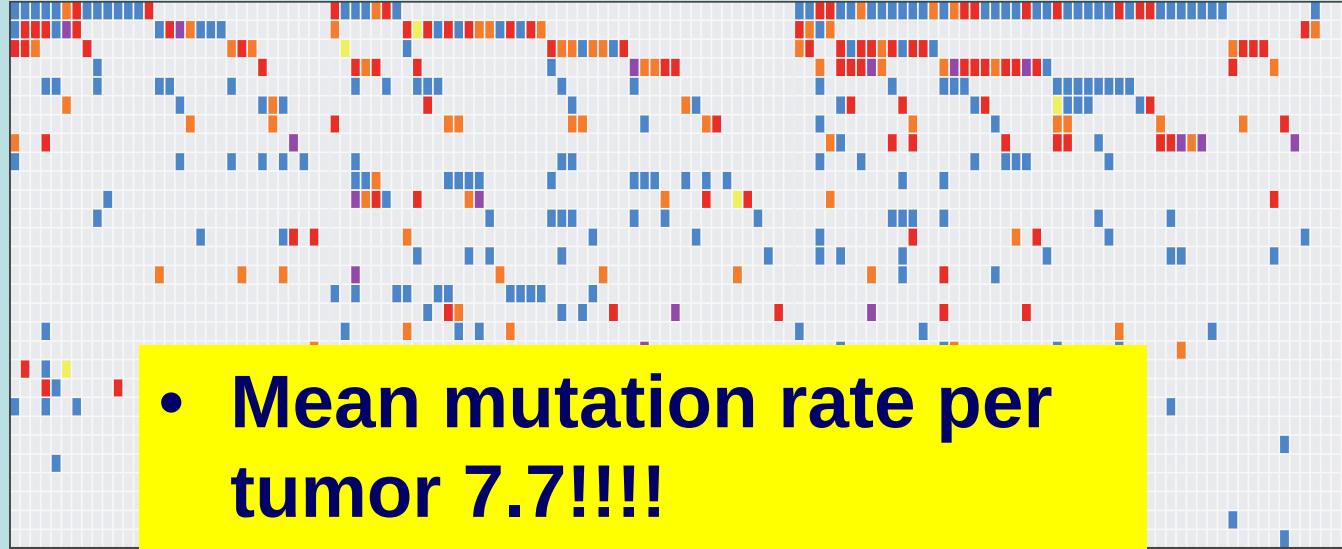
Galsky et al, Clinical Advances in Hematology & Oncology, 2013

Comprehensive molecular characterization of urothelial bladder carcinoma

The Cancer Genome Atlas Research Network*

Urothelial carcinoma of the bladder is a common malignancy that causes approximately 150,000 deaths per year worldwide. So far, no molecularly targeted agents have been approved for treatment of the disease. As part of The Cancer Genome Atlas project, we report here an integrated analysis of 131 urothelial carcinomas to provide a comprehensive landscape of molecular alterations. There were statistically significant recurrent mutations in 32 genes, including multiple genes involved in cell-cycle regulation, chromatin regulation, and kinase signalling pathways, as well as 9 genes not previously reported as significantly mutated in any cancer. RNA sequencing revealed four expression subtypes, two of which (papillary-like and basal/squamous-like) were also evident in microRNA sequencing and protein data. Whole-genome and RNA sequencing identified recurrent in-frame activating *FGFR3-TACC3* fusions and expression or integration of several viruses (including HPV16) that are associated with gene inactivation. Our analyses identified potential therapeutic targets in 69% of the tumours, including 42% with targets in the phosphatidylinositol-3-OH kinase/ AKT/ mTOR pathway and 45% with targets (including *ERBB2*) in the RTK/ MAPK pathway. Chromatin regulatory genes were more frequently mutated in urothelial carcinoma than in any other common cancer studied so far, indicating the future possibility of targeted therapy for chromatin abnormalities.

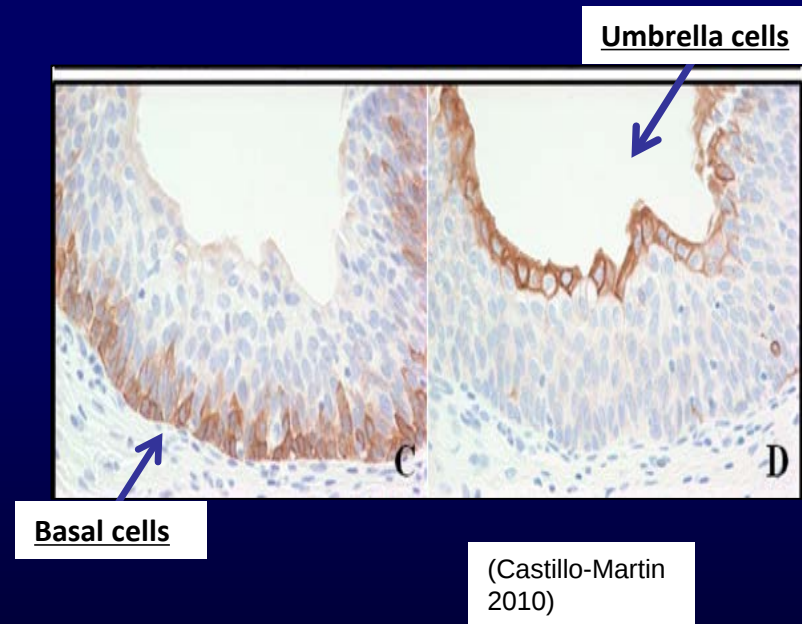
Three clusters - mutation/copy number data



- Mean mutation rate per tumor 7.7!!!!
- No unique mutation for all cancers
- Not Prostate Cancer

Subtypes of High Grade Bladder Cancer

- High grade tumors segregate into clusters
- Differences in genetics drive:
 - Prognosis
 - Basal cell worse
 - Response to therapy
 - Gender
 - Basal resemble breast
 - More common women
 - Immune response



How Do We Use Genomic Information?

- **Diagnosis**
 - Urine markers
- **Prediction of Outcomes**
 - Tissue markers
- **Predict Response to Therapy**
- **Identify Novel Therapeutics**

Improved Bladder Cancer Detection

Current Diagnosis/Surveillance of Bladder Cancer

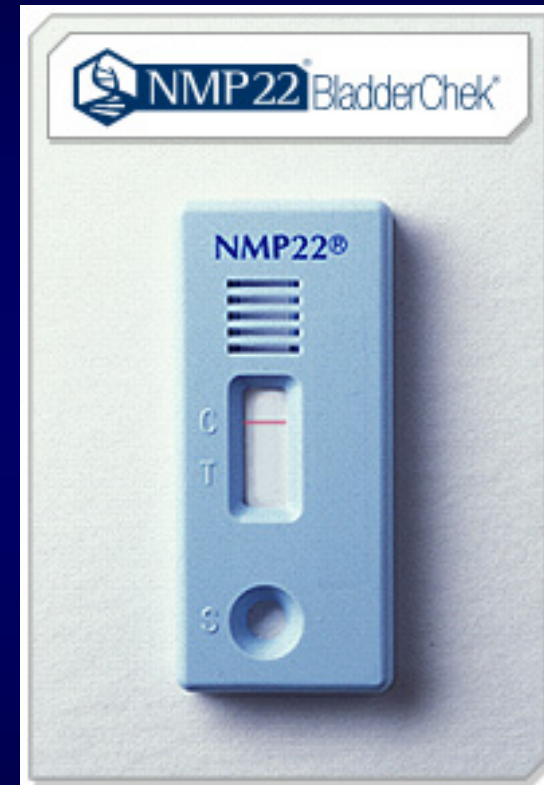
- Visual inspection of bladder (Cystoscopy) and pathologic inspection of urine (Cytology)
- Cystoscopy Limitations
 - Miss lesions especially carcinoma in situ
 - Can't see upper tract disease
 - Invasive
- Cytology is inconsistent
 - Misses 20% of HG disease
 - Negative for most LG disease
 - 10-15% atypical
 - Not point of care

Tumor Marker Approaches

- *Biochemical* detection of proteins or other urinary compounds
 - NMP22
- Detection of cellular *antigen* by immunohistochemistry or cytochemistry
 - ImmunoCyt™
- Detection of *genetic alterations*
 - FISH

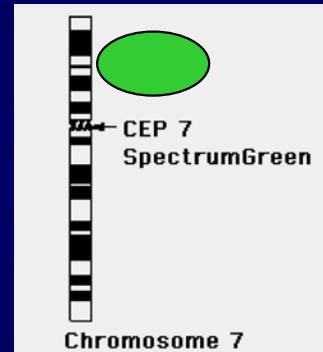
NMP22 BladderChek Test

- Detects elevated amounts of the nuclear matrix protein
- Point-of-care test
- FDA-approved for diagnosis of bladder cancer in high-risk patients.

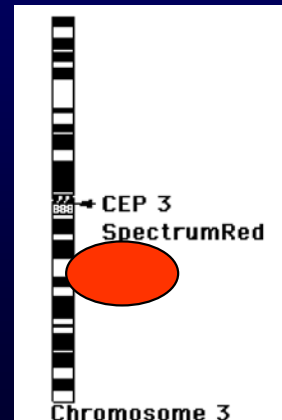
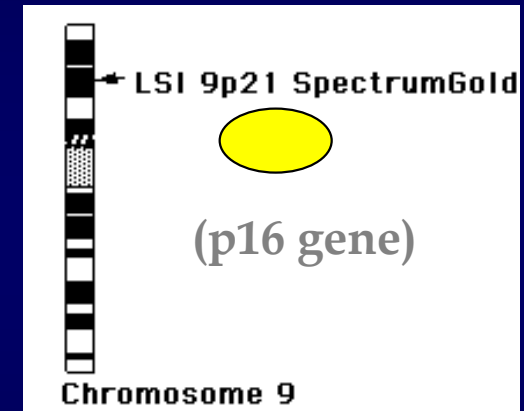
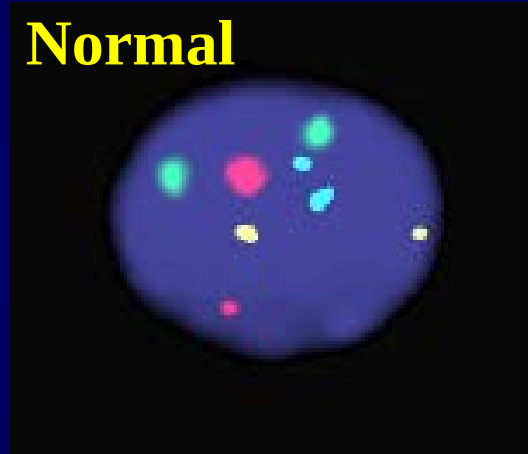


UroVysion

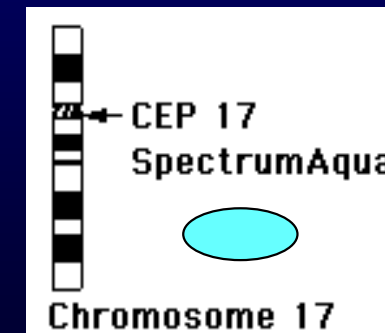
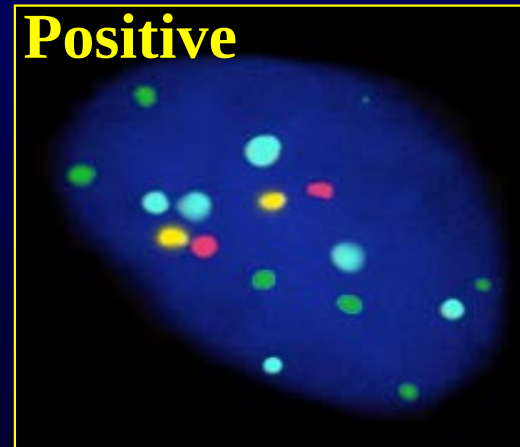
- Detects aneuploidy via Fluorescence in situ Hybridization
- Abnormal result
 - More than 2-4 cells with multiple chromosomal gains
 - More than 9-11 cells with loss of both copies of 9p21



Normal

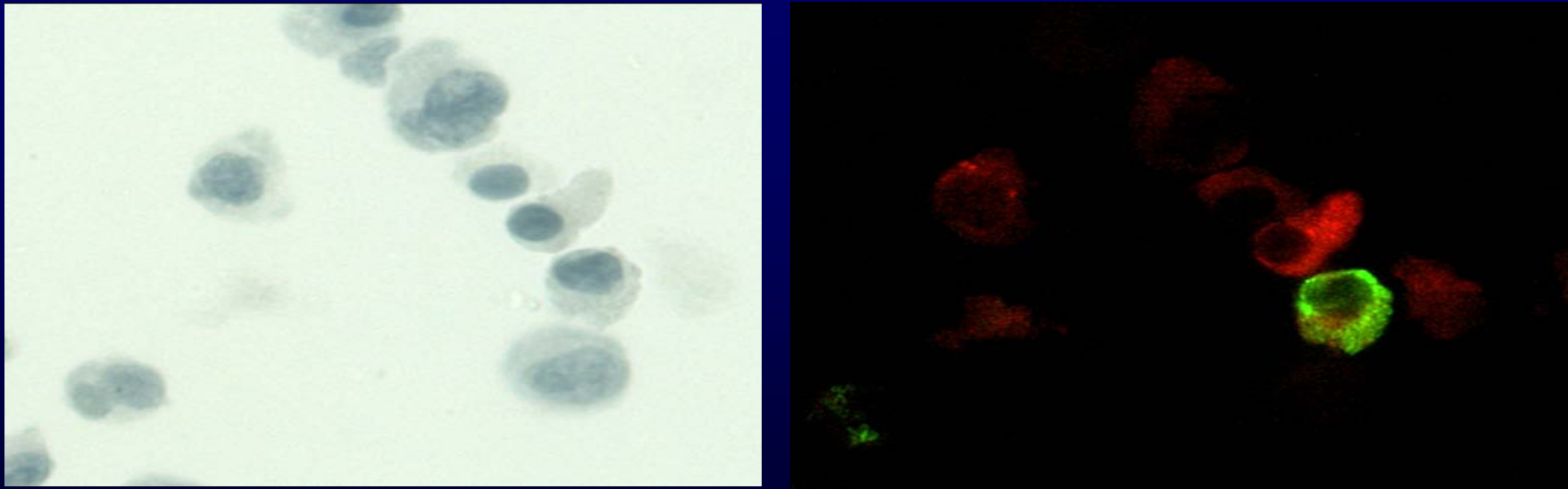


Positive



ImmunoCyt™/uCyt+™

- Uses antibodies labeled with fluorescent markers
 - a mucin glycoprotein
 - carcinoembryonic antigen (CEA)
- Any cells expressing tumor antigen are then detected by fluorescence microscopy.
- Recommended in combo with cytology



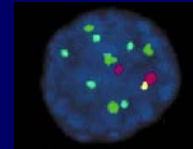
Atypical Cells in Voided Urine
Positive with the Green and Red
Antibodies of the ImmunoCyt Test

Cxbladder Monitor

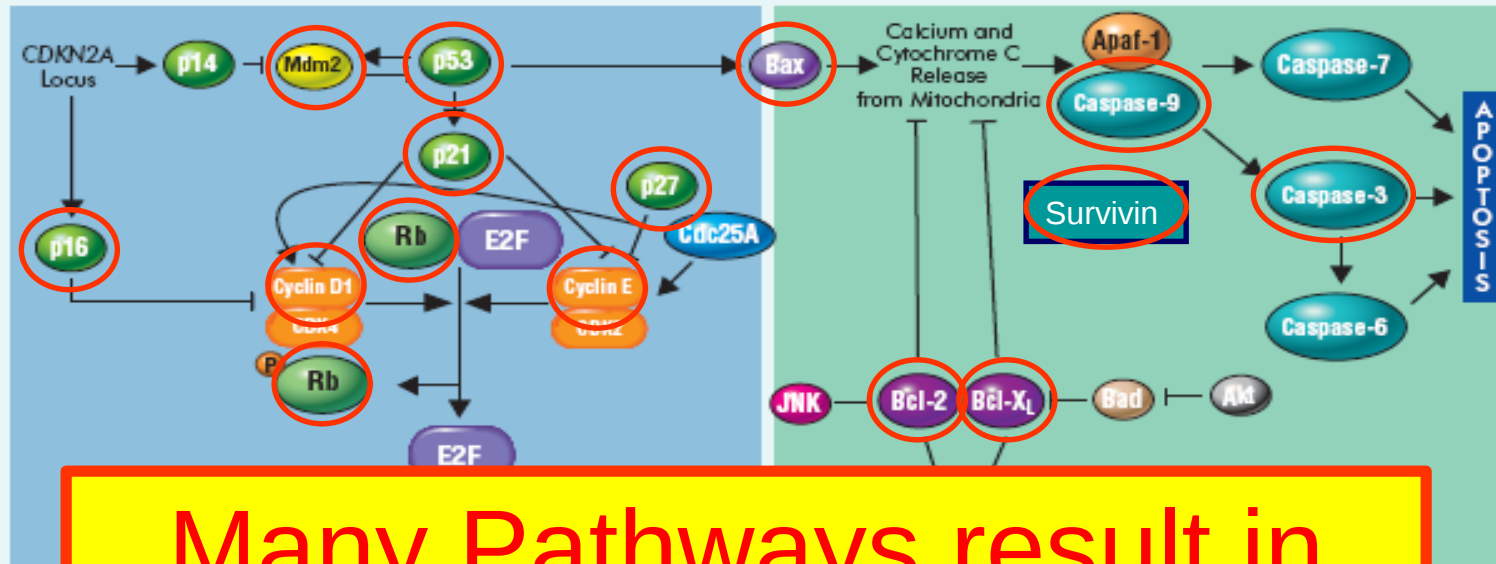
- Measures the gene expression levels of five biomarkers and incorporates previous UC occurrence to represent a bladder cancer signature used to:
 - **MDK: Cell proliferation, migration, and angiogenesis in cancer cells**
 - **HOXA13: Cell differentiation and the morphogenesis and differentiation of the genitourinary tracts**
 - **CDC2 (CDK1): Essential to mitotic cell cycle: cell proliferation**
 - **IGFBP5: Anti-apoptotic gene**
 - **CXCR2: Mitigates neutrophil migration to areas of inflammation**

Urinary Markers – *selection of appropriate markers according to clinical needs*

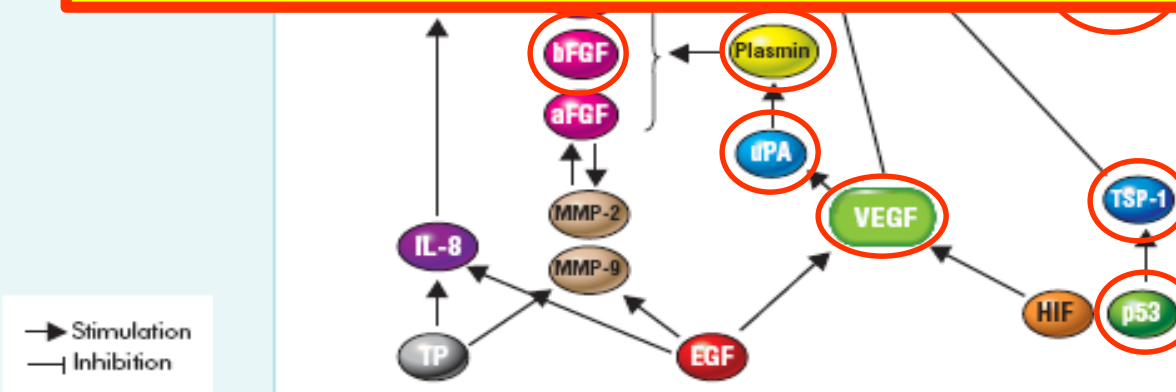
- No single marker has demonstrated superior clinical utility over cytology and cystoscopy
 - All test sensitivities > cytology (low grade!)
 - All test specificities < cytology
- There is no “**ideal**” marker
- Not Recommended by EAU or AUA guidelines



Improved Prediction of Outcomes



Many Pathways result in
Cancer development and
Spread



Using Tissue Markers to Predict Outcomes after Cystectomy



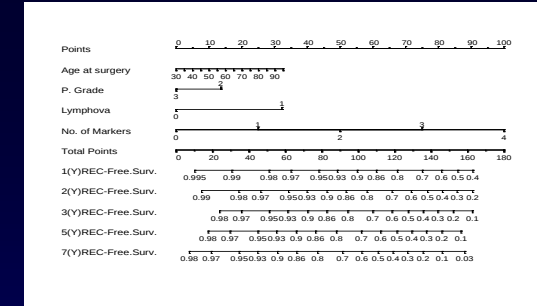
Combined cell-cycle biomarkers

Shariat et al., J Clin Oncol 2003

Combined apoptosis biomarkers

Karam et al., Lancet Oncol 2007

Prediction of disease recurrence in 191 patients with pT1-T3 N0 M0



Base nomogram model

Base model + Nb altered markers

Age

$p = 0.1$

Age

$p = 0.7$

Path g

$p = 0.08$

Path T

$p = 0.004$

LVI

$p = 0.046$

Conco

$p = 0.2$

Understanding the Biology
of Cancer Improves
Prediction of Behavior

Nb altered markers $p < 0.001$

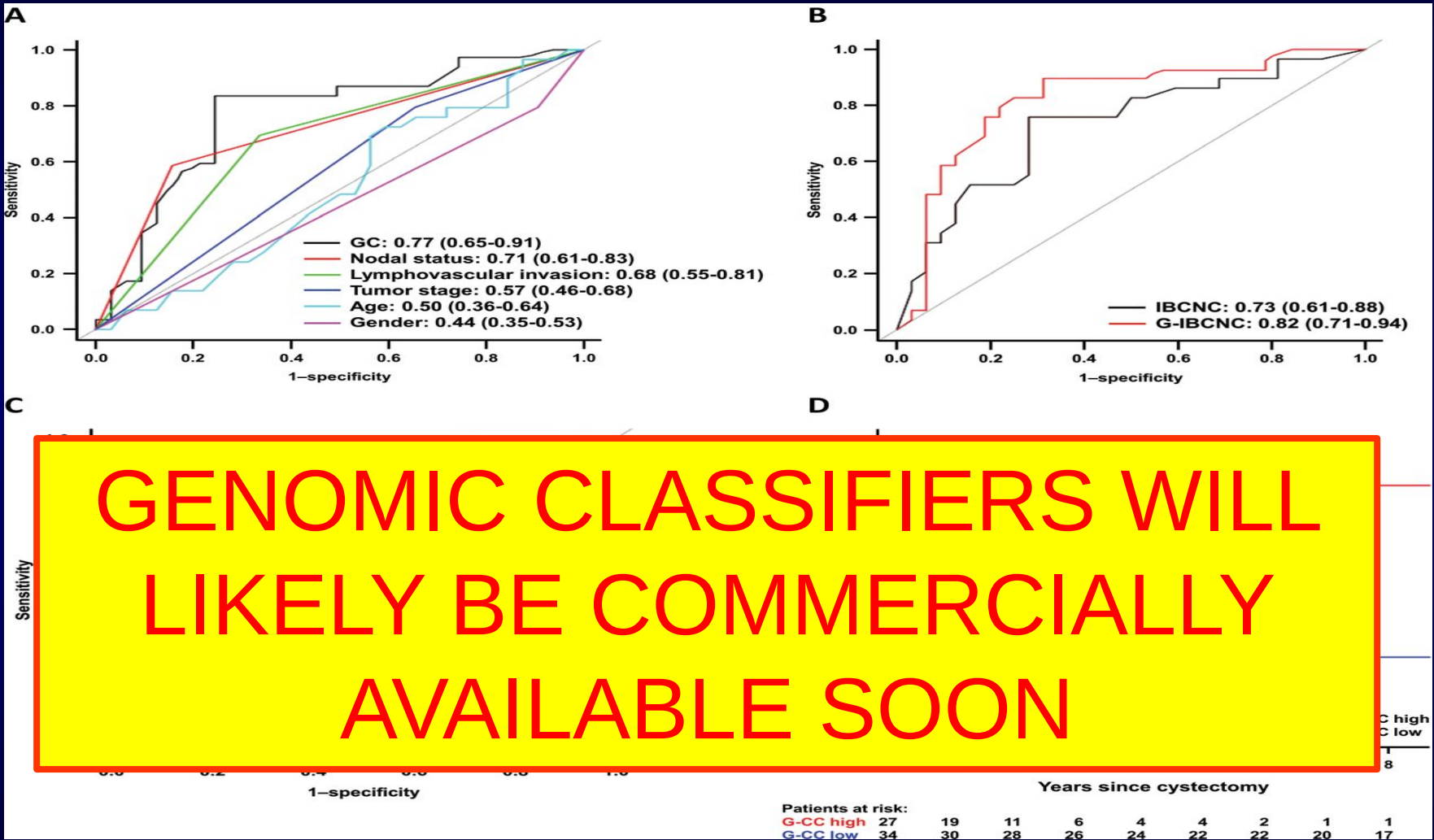
200 bootstrap corrected
predictive accuracy:

72.6 %

200 bootstrap corrected
predictive accuracy:

83.4 %

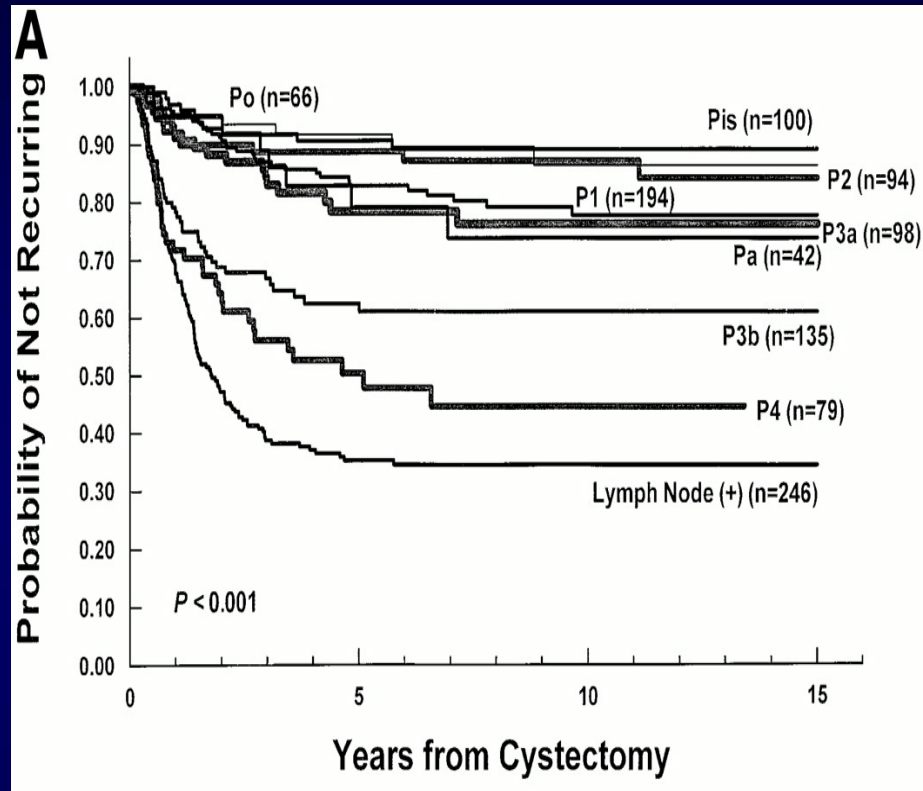
Performance of individual clinicopathologic variables and classifiers in the validation set for predicting cancer recurrence.



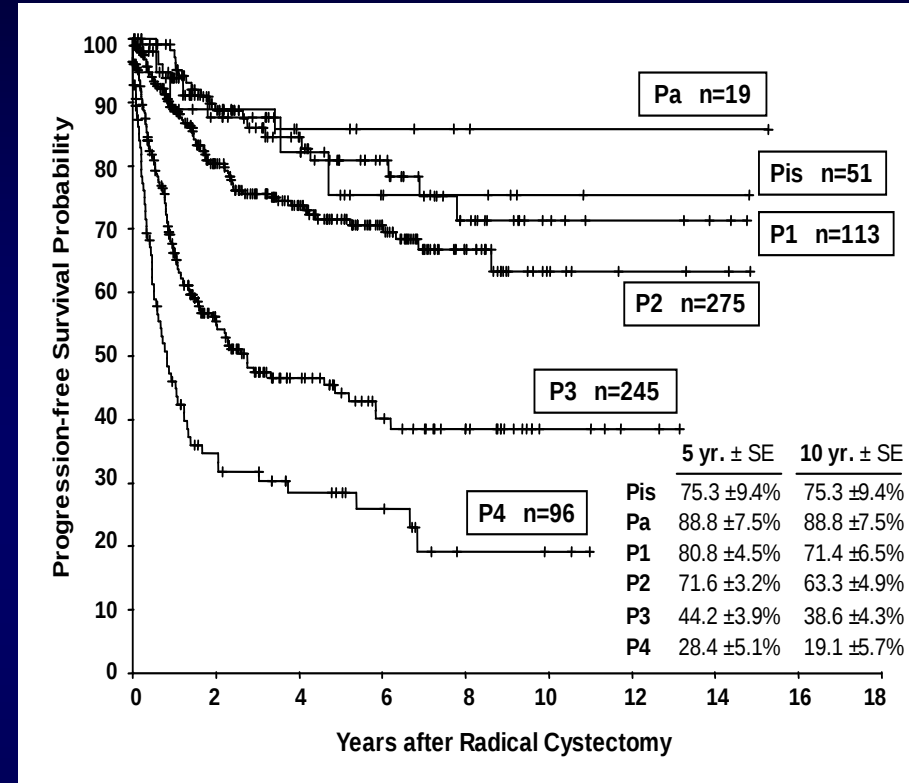
Anirban P. Mitra et al. JNCI J Natl Cancer Inst
2014;106:dju290

Predict Response to Therapy

Recurrence after Radical Cystectomy



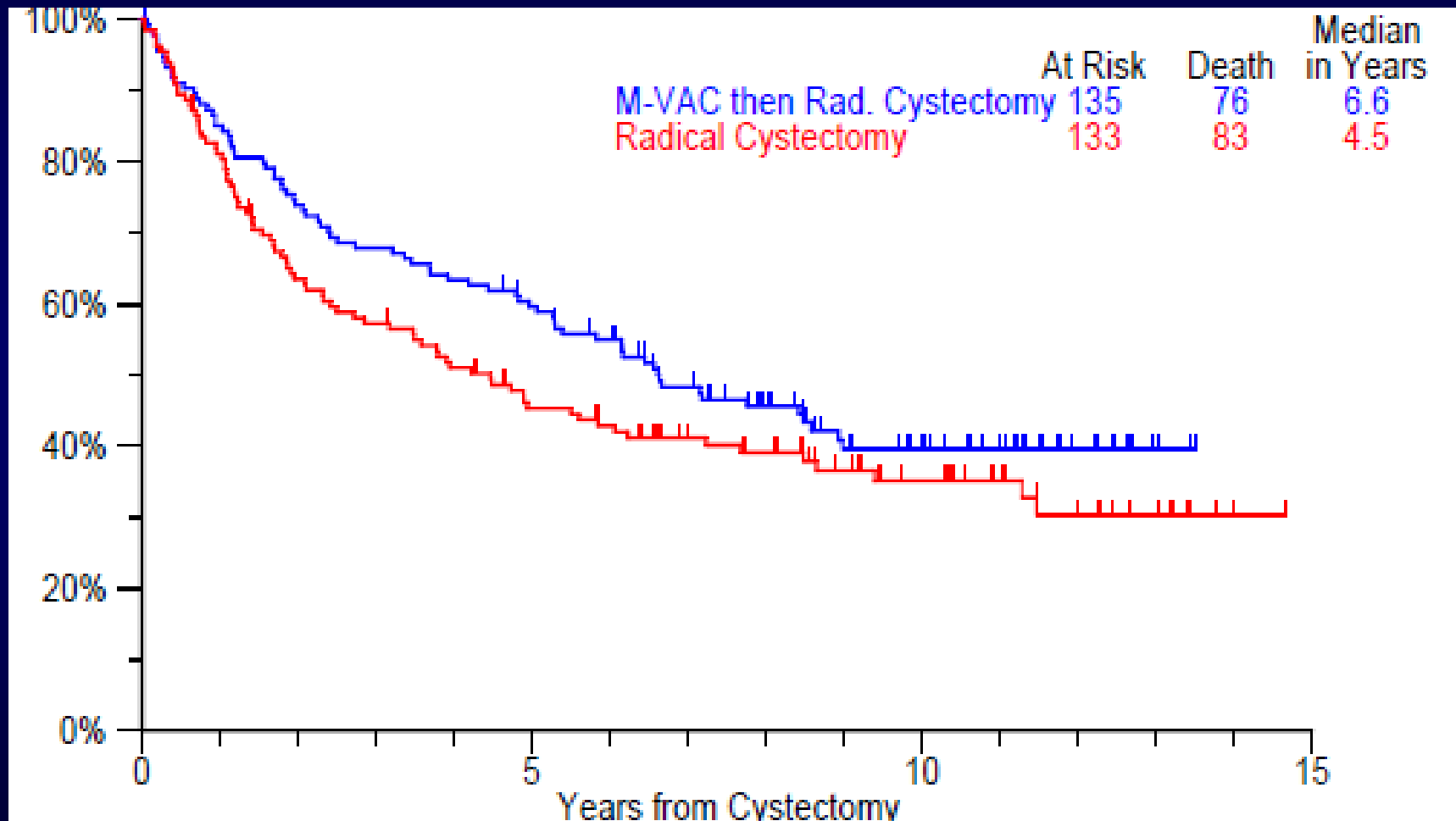
Stein, J. P. et al. J Clin Oncol;
19:666-675 2001



Shariat et al. BCRC J Urol.
2006 Dec

•20-30% of T1-T2 patients recur after cystectomy

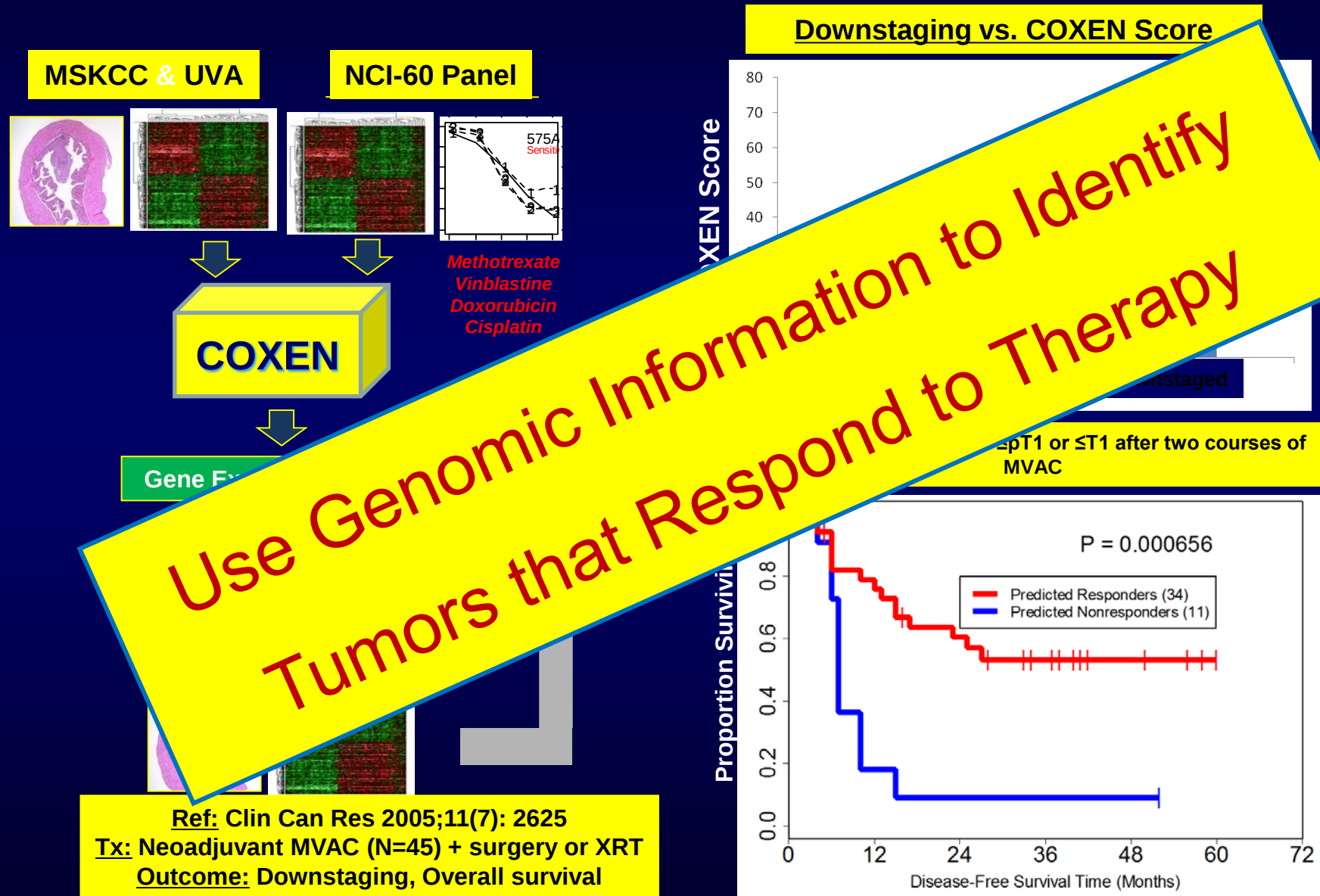
SWOG 8710 Randomized Neoadjuvant MVAC Chemotherapy Trial



Dilemma of Neo-adjuvant Chemotherapy

- Level 1 evidence shows improvement in survival
- 6% ↑ in 5yr survival → only 20-25% of unselected
- **Not everyone seems to need NAC**
 - Organ-confined BC (~50%)
excellent survival
 - NAC for vs 19 mo cT2
- Identify those patients most likely to benefit from NAC
- Chemo and > 50% under-staged
- Chemo

The COXEN Principle: Prediction of treatment outcome (Theodorescu et. al, Proc Natl Acad Sci U S A. 2007;104(32):13086)



SWOG 1314: A Randomized Phase II Study of COXEN with Neoadjuvant Chemotherapy for Localized Muscle-Invasive Bladder Cancer

Impact: Transform thinking about patient selection for neoadjuvant chemotherapy in muscle-invasive urothelial cancer

Selection Criteria SWOG 8710
(T2-T4a N0M0, cisplatin eligible)

Tumor Sample
TURBT

Randomize
to chemotherapy

Collection
Tissue (>P0), blood, urine

Molecular Analysis
Gene expression
Sequencing
microRNA
SNP

Discovery

Collection
Tissue (>P0), blood, urine

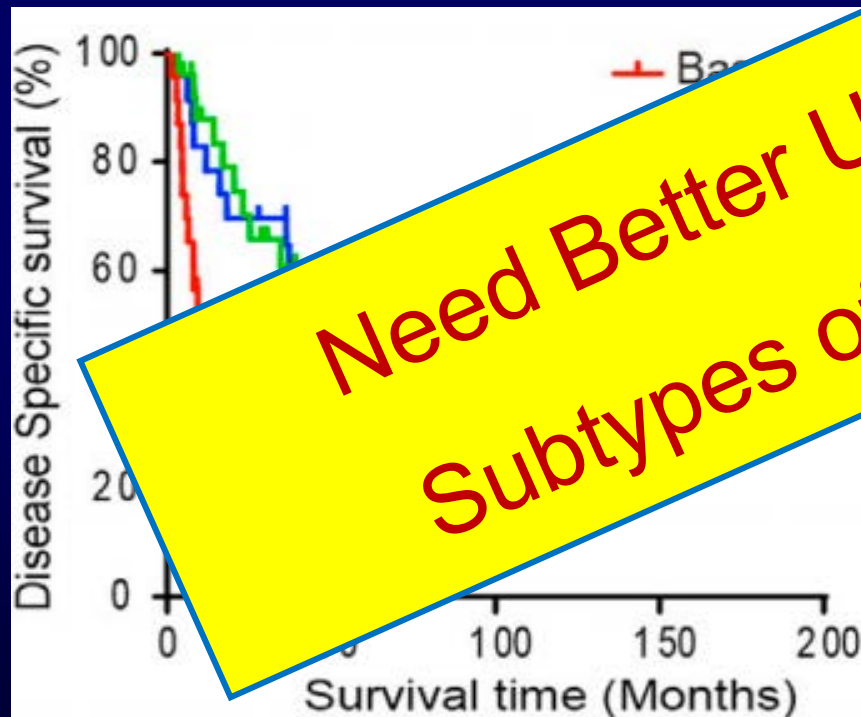
Molecular Analysis
Gene expression
Sequencing
microRNA
SNP

Characterize the relationship of MVAC- and GC-specific COXEN scores in terms of pT0 rate

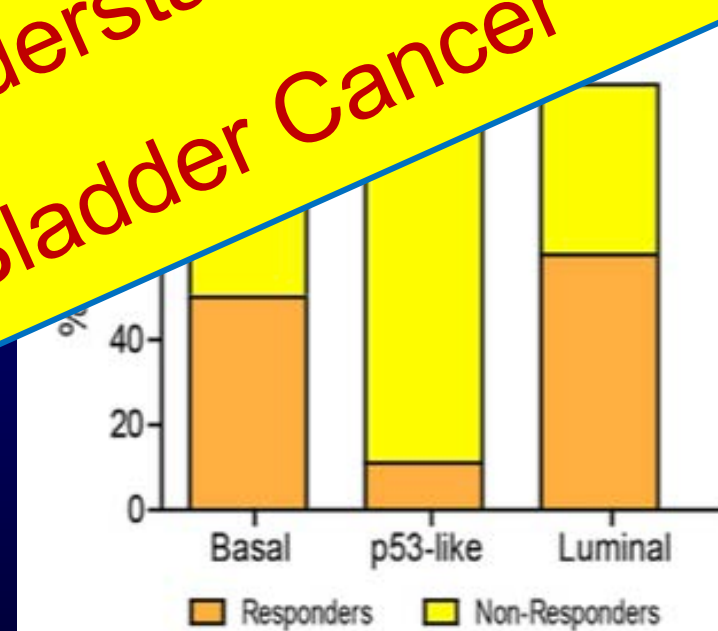
Cooperative Group Study will
Determine if COXEN Principle Works

Identification of Distinct Basal and Luminal Subtypes of Muscle-Invasive Bladder Cancer with Different Sensitivities to Frontline Chemotherapy

Woonyoung Choi,¹ Sima Porten,¹ Seungchan Kim,⁶ Daniel Willis,¹ Elizabeth R. Plimack,⁷ Beat Roth,¹ Tiewei Cheng,^{1,5} Mai Tran,^{1,5} I-Ling Lee,¹ Jonathan Melquist,¹ Jolanta P. Shizhen Zhang,³ Shanna Pretzsch,¹ Keith Baggerly,⁴ Arlene Siefker-Radtke,² P. and David J. McConkey^{1,5,*}

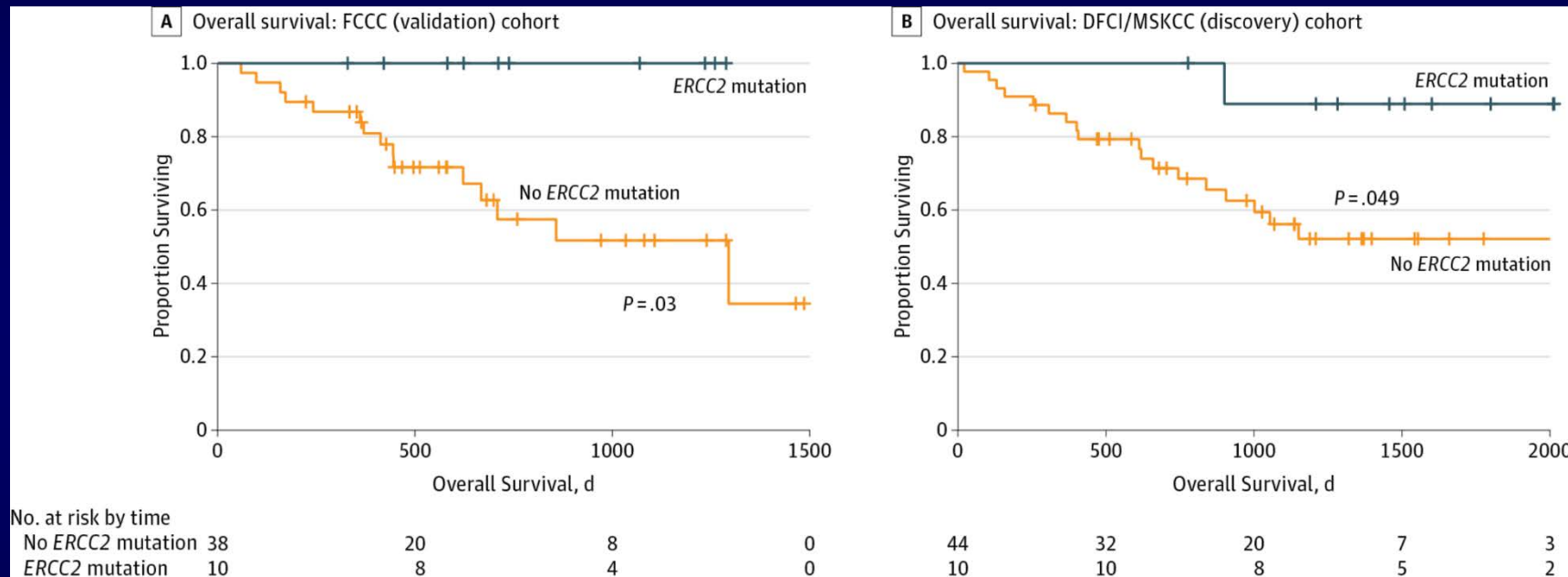


Need Better Understanding of Subtypes of Bladder Cancer



From: **Clinical Validation of Chemotherapy Response Biomarker ERCC2 in Muscle-Invasive Urothelial Bladder Carcinoma**

JAMA Oncol. Published online June 16, 2016. doi:10.1001/jamaoncol.2016.1056



- *ERCC2* is the helicase that unwinds DNA for repair via the nucleotide excision repair pathway
- Important for repair of platinum-induced DNA damage.
- Loss-of-function mutations leading to cisplatin sensitivity.

Summary

- Need to improve selection of patients for multi-modal therapy
- Cooperative group trial on COXEN will provide important information but not for years
- Understanding biology using genomics is best chance to select patients

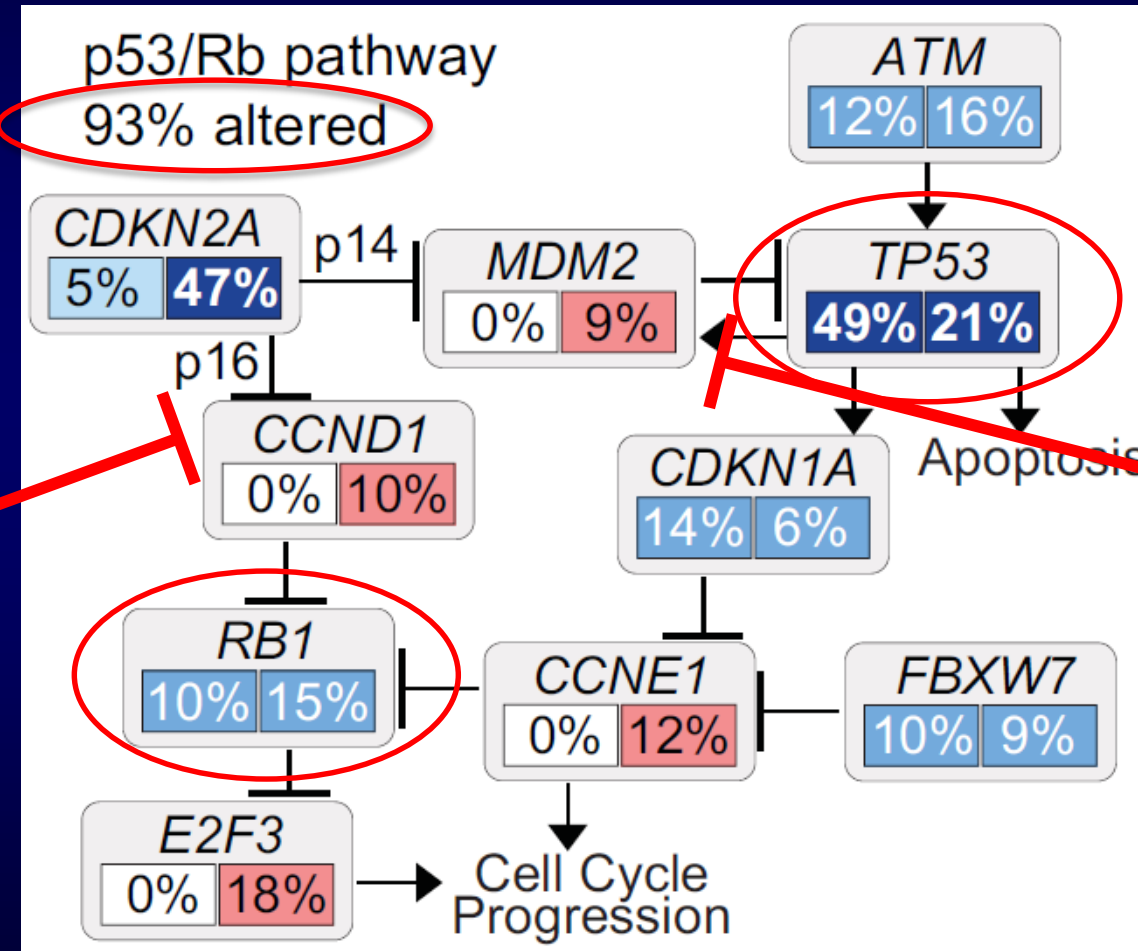
Identify Novel Therapeutics

How can TCGA Inform Clinical Questions

- 69% of tumors harbor potential therapeutic targets
 - PI3K/AKT/mTOR (42%)
 - RTK/MAPK (44%)
 - Chromatin regulatory genes
 - Novel biomarkers/targets – STAG2?
- Should cancer treatment be organ specific or target/pathway specific?
- Molecular classifier

Majority of samples have cell cycle regulatory pathways altered

Left box: mutation
Right box: copy number
Red: activated or amplified
Blue: inactivated or deleted



CDK4/6 inhibitors:
Palbociclib
LEE001
LY2835219

MDM2 inhibitors:
RG-7112
RO5503781
DS-3032b
CGM097
MK-8242
SAR405838

Reverse translation from clinic to lab

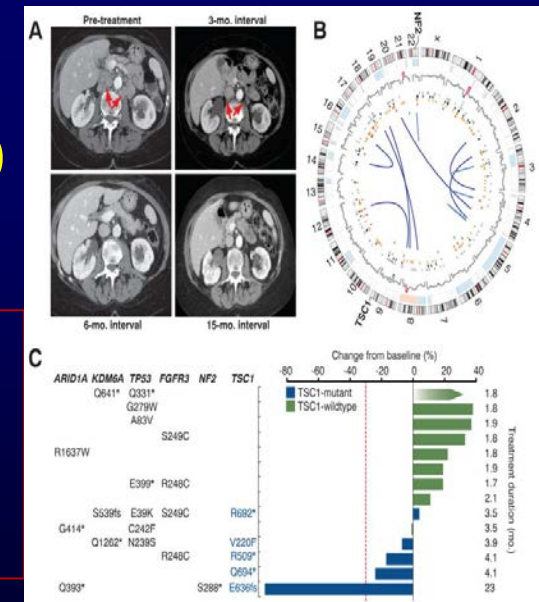
- E.g. Everolimus (mTORC1 inhibitor) in relapsed bladder cancer
 - Negative trial: 1 CR+1PR in 45 patients
 - Pt. with CR remained NED on drug for 36 mos



Milowsky et al., BJUI 2013

- MSKCC lab: whole genomic sequencing identified 2 gene mutations in this patient: NF2 and TSC1
 - 1 CR: both gene mutations
 - 2 minor responses: one gene mutation (TSC1)
 - 9 Progressive disease: wild type TSC1

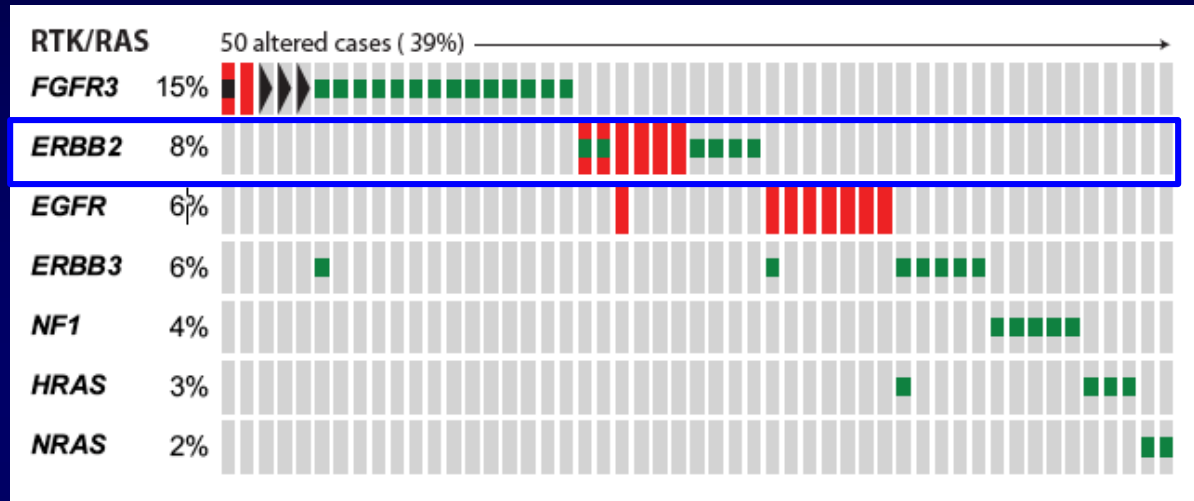
→ Everolimus is an active agent in metastatic
UC harboring TSC1 mutations (6.2%)



Iyer et al., Science 2012

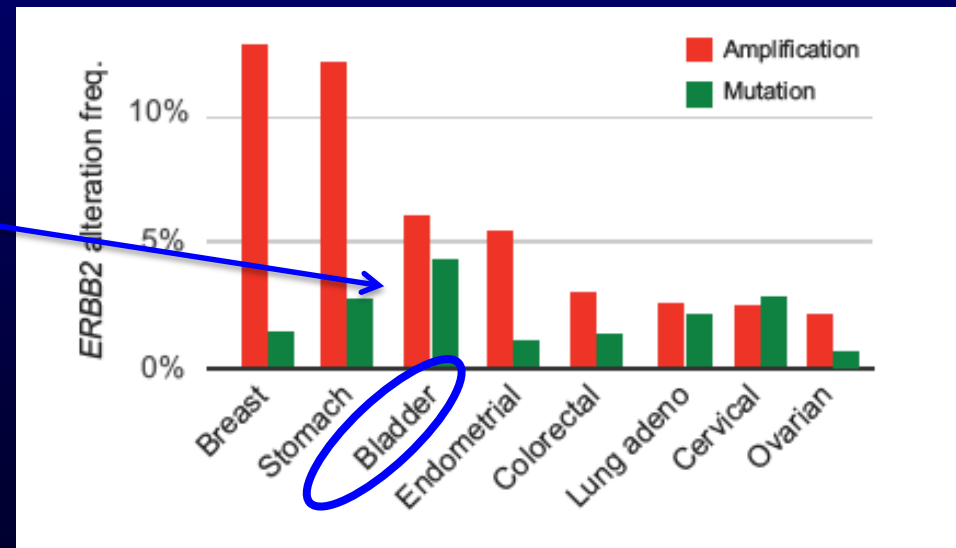
RTK/Ras/PI3K pathways

HER2/ERBB2 Activation as a potential therapeutic target



Trastuzumab
Trastuzumab-DM1
Lapatinib [NCT00447226]
Neratinib [NCT01953926]
DN24-02 [NCT01353222]
Her2 – CAR (CAGT/BCM)

Her2 levels comparable
to Her2+ breast cancer

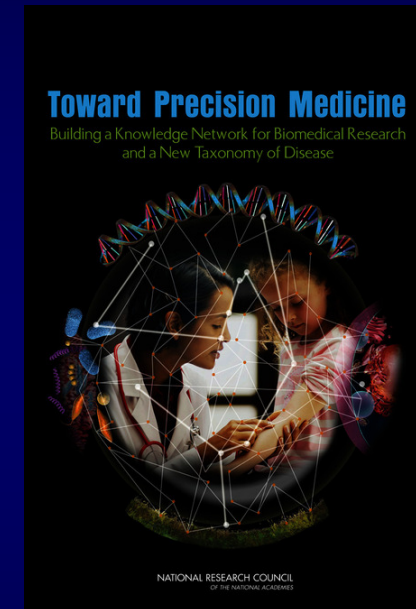


NCI MATCH

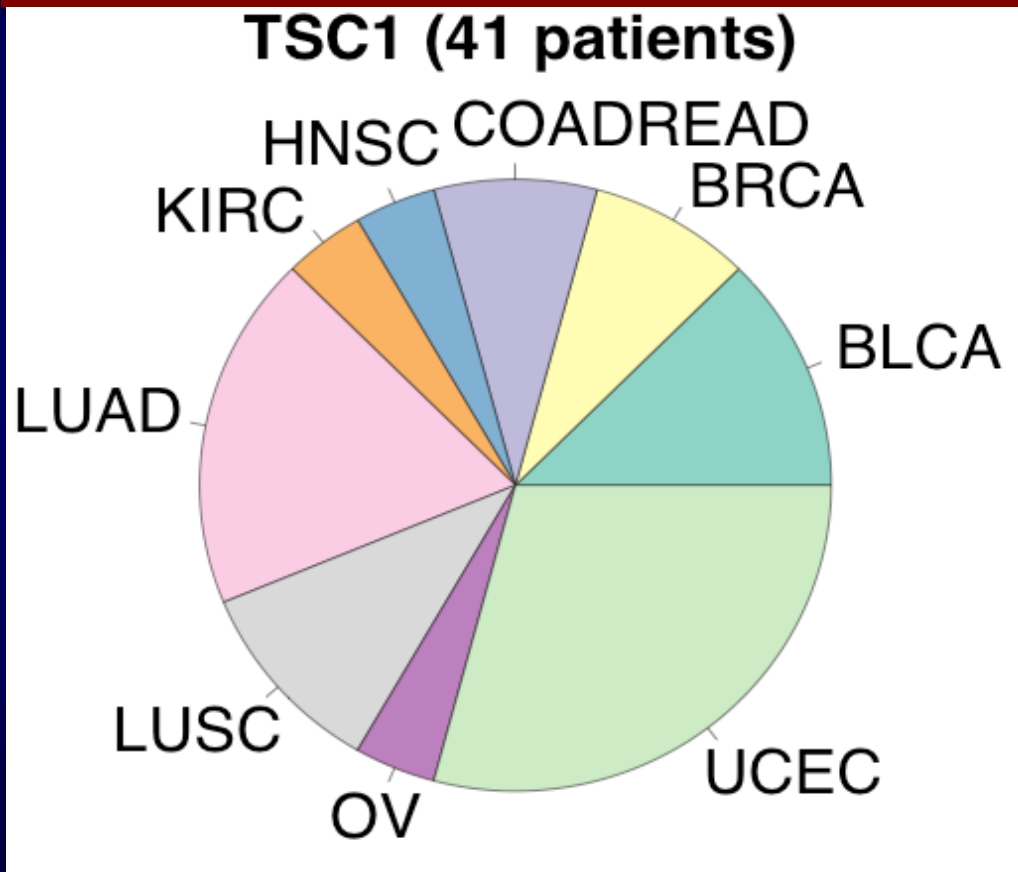
Molecular Analysis for Therapy Choice

Precision medicine working group

- Precision medicine clinical trial
- Genotype to phenotype
- Led by ECOG-ACRIN with NCI
- Multiple (up to 30) Phase II arms
- Eligibility based on molecular characteristics

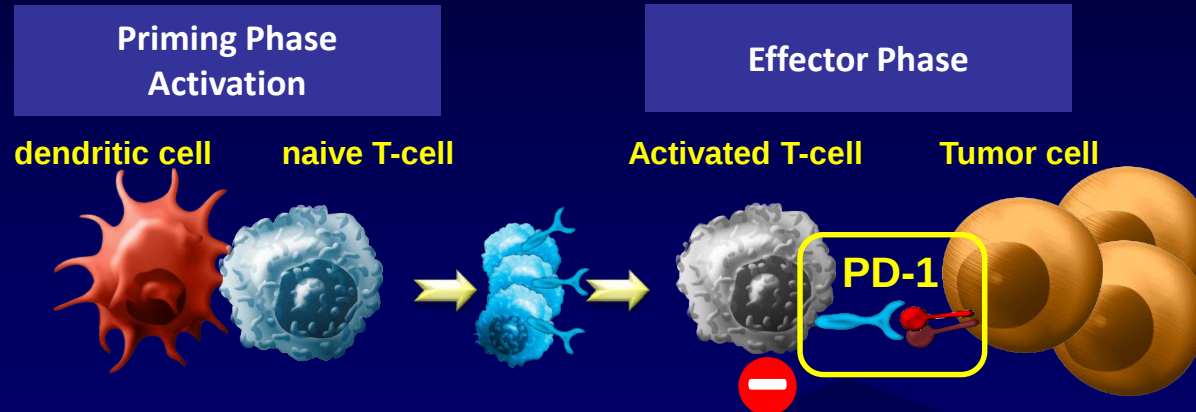


Genes that are rarely mutated in one tumor type occur frequently across tumor types

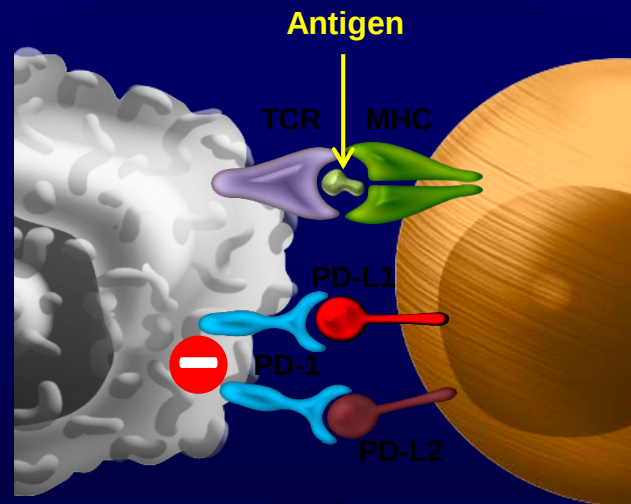


- Alterations in MTOR may also predict sensitivity to everolimus [Wagle et al. Cancer Discovery 2014]
- Low frequency alterations in aggregate and across pathways are even more powerful.

Avoiding the PD-1 Immunecheckpoint Pathway¹



- PD-1 is expressed more on activated T-cells during the effector phase of the immune response



- PD-L1 and PD-L2 turn off the T-cell activity through the PD-1 receptor on the T-cells

T-cell activation

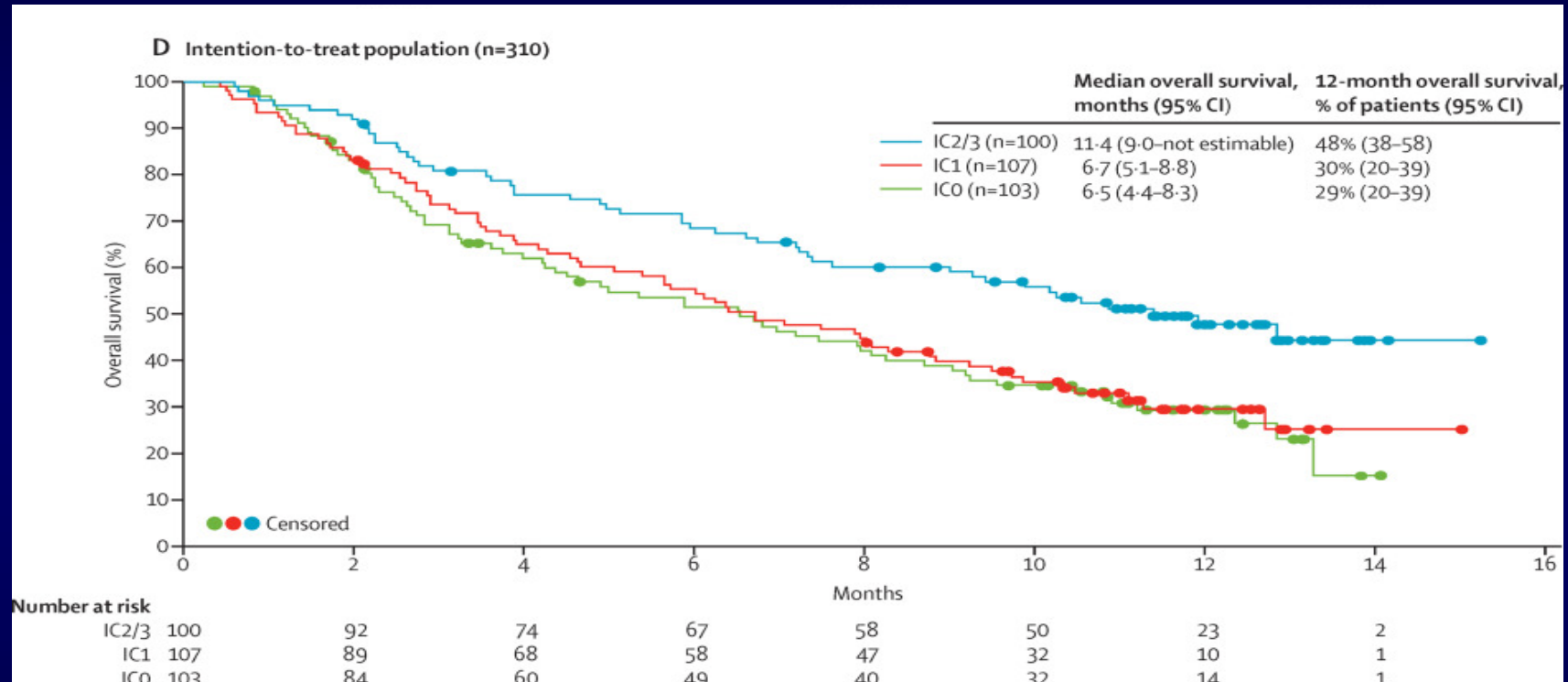
Tumor cells avoid the immune response

Reprinted by permission from Macmillan Publishers Ltd: *Nat Rev Cancer*,¹ copyright 2012.

PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; PD-L2 = programmed cell death ligand 2.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial



The PD-L1 tumour-infiltrating immune cell (IC) status was defined by the percentage of PD-L1-positive immune cells in the tumour microenvironment: IC0 (<1%), IC1 ($\geq 1\%$ but <5%), and IC2/3 ($\geq 5\%$).

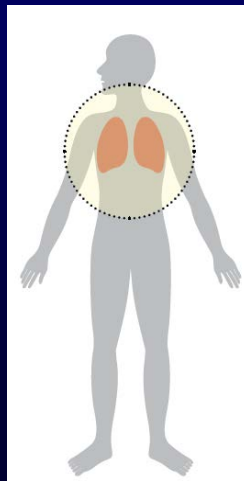
Summary

- Delineation of the genomic landscape and molecular subtypes will accelerate biomarker and drug development
- NCI leading in design and support for “basket-type” clinical trials for Phase I/II

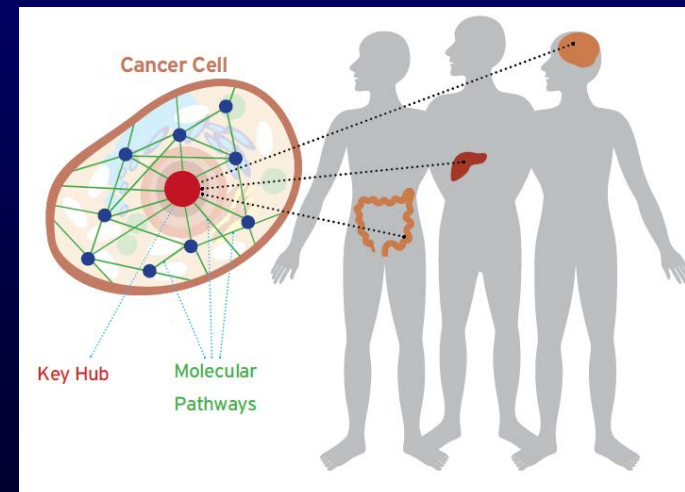
Molecularly-Driven Diagnostic & Therapeutic Development

- Therapies will increasingly target the key molecular hubs that drive cancer growth - not just individual mutations
- Treatments more personalized taking into account
 - when and how to intervene to hit the right targets
 - how treatments are likely to affect each patient
- Future genetic modification: CRISPER/CAS9

OLD MODEL: Treatment determined by a tumor's location



NEW MODEL: Treatment determined by **key molecular “hubs”** targeted within cells



Flexible clinical research guided by biomarkers

- **Criteria for entry in a trial based on molecular characteristics**
 - Inclusion only of the participants most likely to respond **based on molecular characteristics**
 - Faster & more conclusively answers
- Need to screen larger numbers of pts to identify participants

OLD MODEL: Large numbers of patients, not selected by molecular characteristics
→ lower chance of effectiveness

NEW MODEL: Small patient populations with **relevant molecular defects**
→ all participants potential to respond



Genomic Based Trial Design Key Hurdles

- Biomarker validity
- Next-Gen sequencing CLIA approved lab
- Regulatory/FDA
- Pharma/Biotech support
- Funding
- Trial leadership
- Target/pathway prioritization

DR. JAMES MCKIERNAN

JOHN K. LATTIMER PROFESSOR & CHAIRMAN DEPT. OF UROLOGY,
COLLEGE OF SURGEONS & UROLOGIST-IN-CHIEF AT NY
PRESBYTERIAN COLUMBIA HOSPITAL &
VICE CHAIR, AUA GUIDELINES COMMITTEE



Risk Stratification and Guidelines for Management of NMIBC

James McKiernan M.D.
John K. Lattimer Professor and Chair

Department of Urology
Columbia University



Guidelines in NMIBC 2016

A case study

- 57 year-old-male executive with first ever TURBT with white light
- Reveals HG T1 UCC with squamous variant histology no muscle in the specimen no perioperative chemo
- Waits 5 weeks and begins BCG therapy
- Receives antibiotics with each BCG infusion
- Does not have a repeat TURBT
- Does not have squamous histology reported on first TURBT



Guidelines in NMIBC

- Levels of evidence and strength of recommendation
- Risk Stratification
CUETO, EAU, WHO 1973 vs 2004
- Initial evaluation
- TURBT and re-TURBT
- Intravesical therapy
- Enhanced cystoscopy
- Surveillance schedules



EPIDEMIOLOGY

NMIBC represents approximately 75% of the 74,000 estimated new bladder cancer cases diagnosed in the United States in 2015. Bladder cancer is more common in males than females with a ratio of approximately 3:1, and it is the fourth most common solid malignancy in men.

Estimated New Cases

			Males
Prostate	220,800	26%	
Lung & bronchus	115,610	14%	
Colon & rectum	69,090	8%	
Urinary bladder	56,320	7%	
Melanoma of the skin	42,670	5%	
Non-Hodgkin lymphoma	39,850	5%	
Kidney & renal pelvis	38,270	5%	
Oral cavity & pharynx	32,670	4%	
Leukemia	30,900	4%	
Liver & intrahepatic bile duct	25,510	3%	
All Sites	848,200	100%	

PRESENTATION & DIAGNOSIS

The most common presenting symptom is painless hematuria

- Urinary cytology
- Bimanual exam
- Imaging
 - CT
 - MRI

A diagnosis of bladder cancer is confirmed by direct visualization of the tumor using cystoscopy and TURBT. An adequate TURBT requires complete resection of all visible tumor with adequate sampling to assess the depth of invasion.

STAGING & GRADING

Staging of primary tumors (T) in bladder cancer

TX	Primary tumor cannot be assessed
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ (CIS)
T1	Tumor invades lamina propria
T2	Tumor invades muscularis propria
T2a	Tumor invades superficial muscularis propria (inner half)
T2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue/fat
T3a	Tumor invades perivesical tissue/fat microscopically
T3b	Tumor invades perivesical tissue fat macroscopically (extravesical mass)
T4	Tumor invades prostate, uterus, vagina, pelvic wall, or abdominal wall
T4a	Tumor invades adjacent organs (uterus, ovaries, prostate stoma)
T4b	Tumor invades pelvic wall and/or abdominal wall

Staging for bladder cancer is separated into clinical and pathologic stage, as outlined by the American Joint Committee on Cancer (AJCC), also known as the Tumor-Node-Metastases (TNM) classification. Clinical stage reflects the histologic findings at TURBT; the clinician's physical exam, including bimanual exam under anesthesia; and findings on radiologic imaging.

STAGING & GRADING

Grade important prognostic factor for recurrence and progression
WHO/ISUP 2004 grading system most widely accepted in the United States.

2004 World Health Organization/ International Society of Urologic Pathologists: Classification of Non-muscle Invasive Urothelial Neoplasia
Hyperplasia (flat and papillary)
Reactive atypia
Atypia of unknown significance
Urothelial dysplasia
Urothelial CIS
Urothelial papilloma
Papillary urothelial neoplasm of low malignant potential
Non-muscle invasive low-grade papillary urothelial carcinoma
Non-muscle invasive high-grade papillary urothelial carcinoma

PROGNOSIS

The survival prognosis for patients with NMIBC is relatively favorable, with the cancer-specific survival (CSS) in high-grade disease ranging from approximately 70-85% at 10 years and a much higher rate for low-grade disease.

The rates of recurrence and progression to MIBC are important surrogate endpoints for prognosis in NMIBC, as these are major determinants of long-term outcome.

	Risk of Progression (%)	Risk of Recurrence (%)
Low-Grade Ta	6	55
High-Grade T1	17	45

Risk stratification in NMIBC aids personalized treatment decisions and surveillance strategies as opposed to a generalized ‘one-size fits all’ approach.

The survival rate for patients with localized Bladder Cancer is less in patients with localized prostate cancer

Levels of Evidence

- 1 - Evidence from meta-analysis or randomized trial
 - Should or will (Standard)
- 2 - Evidence from a controlled study without randomization or from well-designed quasi-experimental study
 - May consider
- 3 - Evidence from comparative studies, correlation studies and case reports
- 4 - Evidence from expert committee reports or opinions or clinical experience of respected authorities



○ Option

AUA RISK STRATIFICATION SYSTEM

Low Risk	Intermediate Risk	High Risk
LG ^a solitary Ta ≤ 3cm	Recurrence within 1 year, LG Ta	HG T1
PUNLMP ^b	Solitary LG Ta > 3cm	Any recurrent, HG Ta
	LG Ta, multifocal	HG Ta, >3cm (or multifocal)
	HG ^c Ta, ≤ 3cm	Any CIS ^d
	LG T1	Any BCG failure in HG patient
		Any variant histology
		Any LVI ^e
		Any HG prostatic urethral involvement
^a LG = low grade; ^b PUNLMP = papillary urothelial neoplasm of low malignant potential; ^c HG = high grade; ^d CIS=carcinoma <i>in situ</i> ; ^e LVI = lymphovascular invasion		

GUIDELINE: RISK STRATIFICATION

5. At the time of each occurrence/recurrence, a clinician should assign a clinical stage and classify a patient accordingly as “low-,” “intermediate-,” or “high-risk.”
(Moderate Recommendation; Evidence Strength: Grade C)

EORTC/CUETO Model → Tumor size, tumor focality, grade, stage

AUA/SUO Additions → Lymphovascular invasion, prostatic urethral involvement, variant histology, poor response to BCG

GUIDELINE: TURBT/REPEAT RESECTION

12. In a patient with non-muscle invasive disease who underwent an incomplete initial resection (not all visible tumor treated), a clinician should perform repeat transurethral resection or endoscopic treatment of all remaining tumor if technically feasible. (Strong Recommendation; Evidence Strength: Grade B)
13. In a patient with high-risk, high-grade Ta tumors, a clinician should consider performing repeat transurethral resection of the primary tumor site within six weeks of the initial TURBT. (Moderate Recommendation; Evidence Strength: Grade C)
14. In a patient with T1 disease, a clinician should perform repeat transurethral resection of the primary tumor site to include muscularis propria within six weeks of the initial TURBT. (Strong Recommendation; Evidence Strength: Grade B)

Routine Re-TUR

Can it make BCG better?

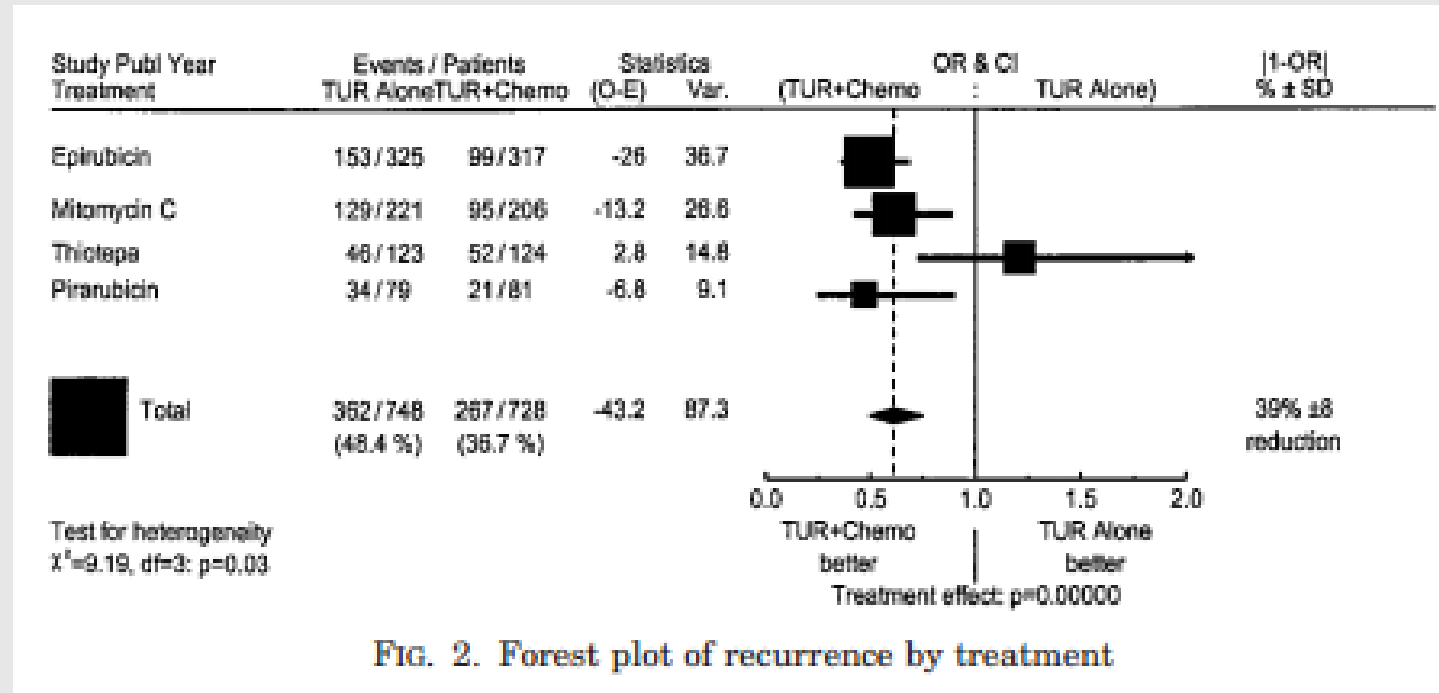
- 1,021 patients treated with BCG at MSKCC
- Viable disease found in 55%
- 44% relapse if no re-TUR and 9% if re-TUR
- Only significant predictor of 5 -yr cure was re-TUR!!

Sfakianos and Herr J Urol 2013



GUIDELINE: INTRAVESICAL THERAPY

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)



GUIDELINE: INTRAVESICAL THERAPY

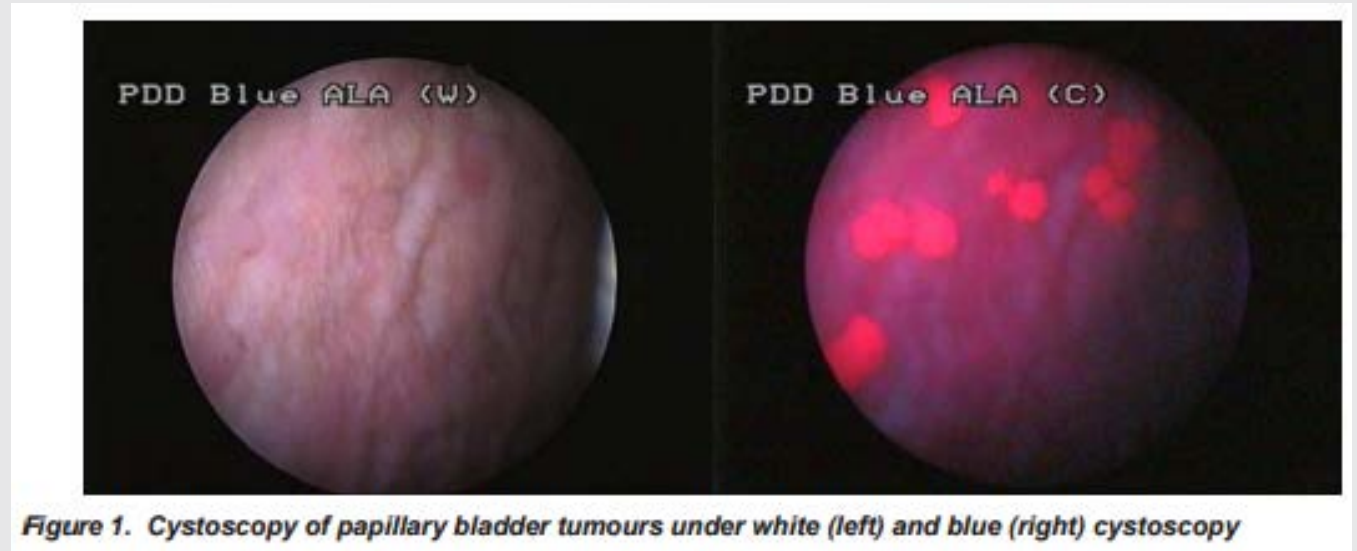
16. In a low-risk patient, a clinician should not administer induction intravesical therapy. (Moderate Recommendation; Strength of Evidence Grade C)
17. In an intermediate-risk patient a clinician should consider administration of a six week course of induction intravesical chemotherapy or immunotherapy. (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)

GUIDELINE: INTRAVESICAL THERAPY

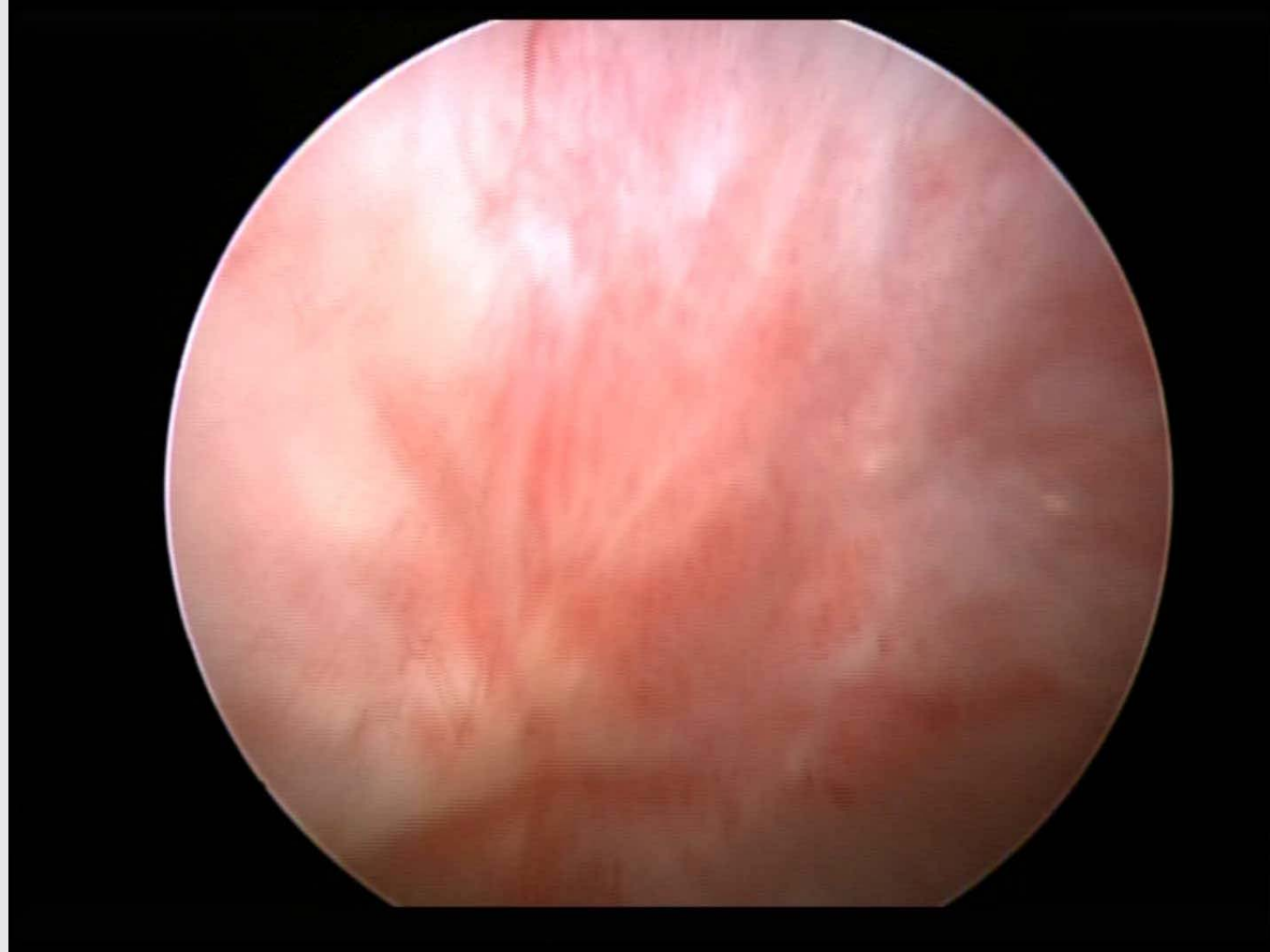
19. In an intermediate-risk patient who completely responds to an induction course of intravesical chemotherapy, a clinician may utilize maintenance therapy. (Conditional Recommendation; Evidence Strength: Grade C)
20. In an intermediate-risk patient who completely responds to induction BCG, a clinician 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)

GUIDELINE: ENHANCED CYSTOSCOPY

30. In a patient with NMIBC, a clinician should offer blue light cystoscopy at the time of TURBT, if available, to increase detection and decrease recurrence. (Moderate Recommendation; Evidence Strength: Grade B)
31. In a patient with NMIBC, a clinician may consider use of NBI to increase detection and decrease recurrence. (Conditional Recommendation; Evidence Strength: Grade C)



Enhanced Cystoscopy Revealing the Unseen Enemy



Blue Light Cystoscopy with Cysview

Results from meta-analysis in 9 studies and > 2000 patients

Table 5 – Detection of additional tumours in patients with at least one Ta or T1 tumour and additional carcinoma in situ (CIS) lesions in patients with at least one CIS lesion

Tumour type	Patients in whom at least one Ta or T1 tumour was detected only by BL, n (%)	Meta-analysis event rate	Patients in whom at least one CIS lesion was detected only by BL, n (%)	Meta-analysis event rate
Total	188/831 (22.6)	24.9%; $p < 0.001$ (0.184–0.328)	68/268 (25.4)	26.7%; $p < 0.001$ (0.183–0.371)
Primary cancer	66/360 (18.3)	20.7%; $p < 0.001$ (0.131–0.312)	31/111 (27.9)	28.0%; $p < 0.001$ (0.193–0.388)
Recurrent cancer	122/471 (25.9)	27.7%; $p < 0.001$ (0.218–0.343)	37/157 (23.6)	25.0%; $p < 0.001$ (0.168–0.354)
High risk	97/397 (24.4)	27.0%; $p < 0.001$ (0.168–0.402)	–	–
Intermediate risk	84/250 (33.6)	35.7%; $p = 0.004$ (0.271–0.453)	–	–
Low risk	7/183 (3.8)	5.4%; $p < 0.001$ (0.026–0.106)	–	–

BL = blue light.

At least one additional Ta/T1 was found in 24.5% of the patients $p < 0.001$

26.7% of the CIS patients were diagnosed with BLCC only $p < 0.001$

Burger M et al., European Journal of Urology 2013



Blue Light Cystoscopy with Cysview impacts recurrence of bladder cancer

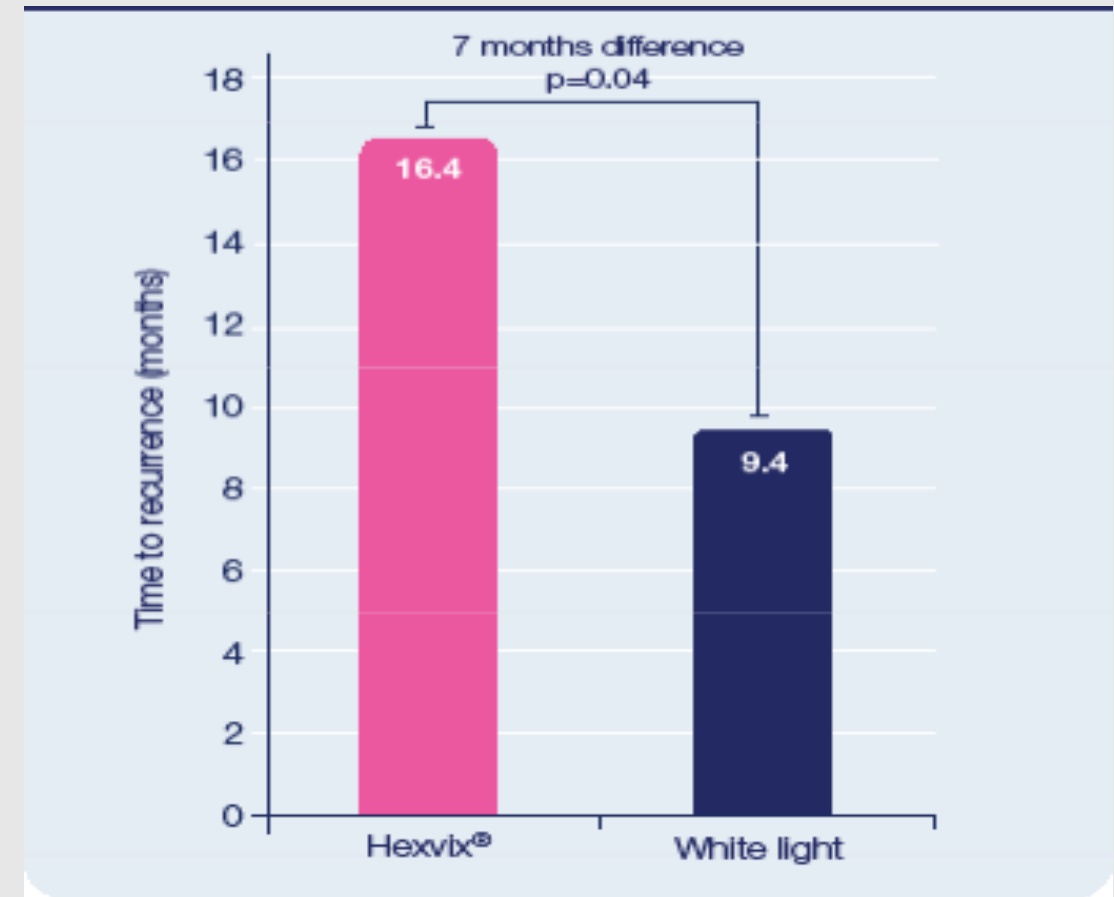
Rate of recurrence reduced¹

Table 6 - Overall recurrence rates up to 12 months

	Patients treated with BL, n (%)	Patients treated with WL, n (%)	Total	Follow-up period
Hermann et al. [24]	27/68 (39.7)	38/77 (49.4)	145	12 mo
Stenzl et al. [21]	72/200 (36.0)	92/202 (45.5)	402	9 mo
Drăgoescu et al. [25]	8/42 (19.0)	17/45 (37.8)	87	12 mo
Total	107/310 (34.5)	147/324 (45.4)	634*	p = 0.006; RR = 0.761 (0.627-0.924)
At least one T1 or CIS	26/74 (35.1)	45/87 (51.7)	161*	p = 0.052; RR = 0.696 (0.482-1.003)
At least one Ta	92/256 (35.9)	119/268 (44.4)	524*	p = 0.040; RR = 0.804 (0.653-0.991)
High-risk subgroup	46/126 (36.5)	70/144 (48.6)		p = 0.05; RR = 0.752 (0.565-1.000)
Intermediate-risk subgroup	43/95 (45.3)	40/74 (54.1)		p = 0.246; RR = 0.836 (0.617-1.132)
Low-risk subgroup	14/78 (17.9)	34/98 (34.7)		p = 0.029; RR = 0.561 (0.334-0.944)

BL = blue light; CIS = carcinoma in situ; RR = risk ratio; WL = white light.
Some patients appear in both subgroups (at least one T1 or CIS and at least one Ta).

Time to recurrence prolonged²



Rate of recurrence is reduced by 10.9% p= <0.006

1. Burger et al: European Journal of Urology 2013

2. Grossman et al: Journal of Urology 2012



Blue light cystoscopy with Cysview impacts progression of bladder cancer

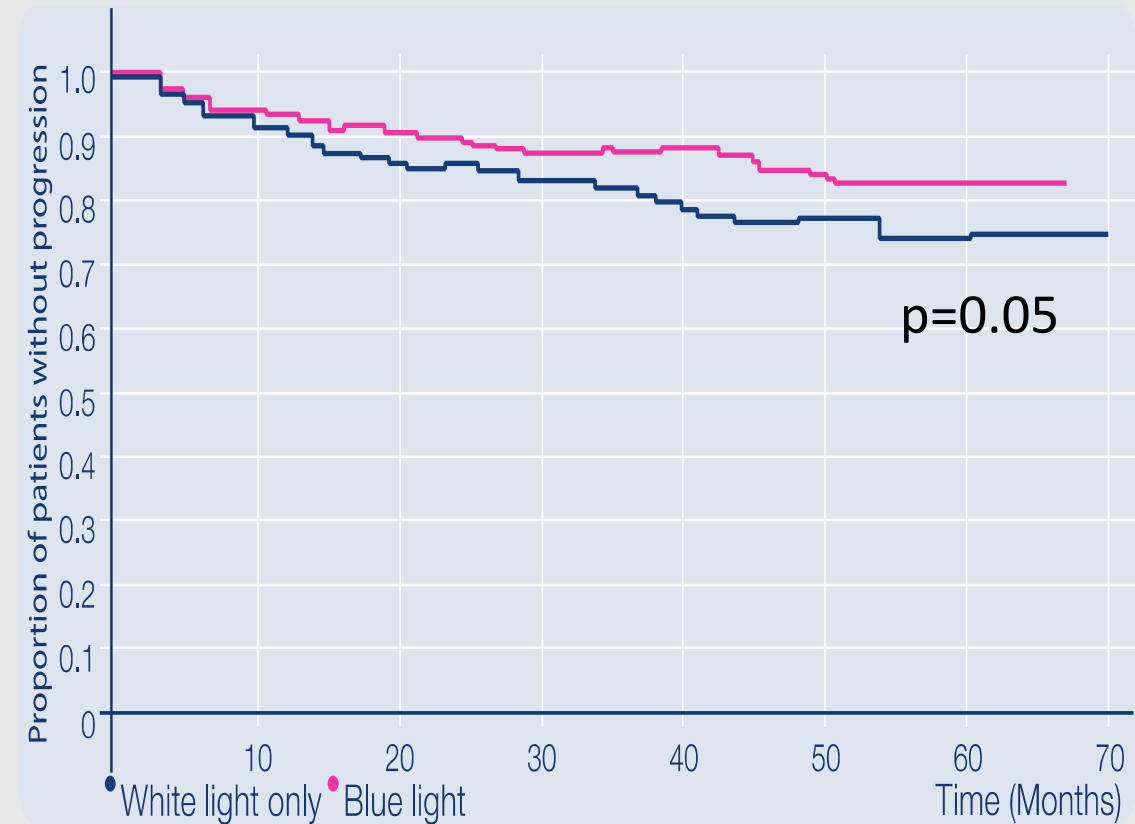
Rate of progression reduced¹

Meta analysis in 5 studies and 1301 patients:

- **BLCC**: 44/644 patients (6.8%)
- **WLC**: 70/650 patients (10.7%), $p=0.01$

“This meta-analysis supports the assumption that the detection of NMIBC with BLCC reduces the risk of progression. Therefore patients should receive BLCC at their first resection as this might allow more patients at risk of progression to be treated timely and adequately”

Time to progression prolonged²



1 Gakis et al, Bladder Cancer July 2016

2. Kamat et al. The Bladder Cancer Journal, April 2016



EAU Guidelines 2013

Enhanced Cystoscopy

- If equipment is available, use fluorescence-guided (PDD) biopsy instead of random biopsies when bladder CIS or HG tumor is suspected (e.g., positive cytology, recurrent tumor with previous history of a HG lesion).

GUIDELINE: SURVEILLANCE & FOLLOW UP

32. After completion of the initial evaluation and treatment of a patient with NMIBC, a clinician should perform the first surveillance cystoscopy within three to four months. (Expert Opinion)
33. For a low-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent surveillance cystoscopy six to nine months later, and then annually thereafter; surveillance after five years in the absence of recurrence should be based on shared-decision making between the patient and clinician. (Moderate Recommendation; Evidence Strength: Grade C)
34. In an asymptomatic patient with a history of low -risk NMIBC, a clinician should not perform routine surveillance upper tract imaging. (Expert Opinion)

EAU Guidelines 2013

Surveillance

- Low-risk Ta cysto at 3 months. If negative, subsequent cysto 9 months later, then yearly for 5 years.
- High-risk cysto and urinary cytology every 3 months for 2 years, every 6 months until 5 years, then yearly.
- Intermediate-risk Ta in-between follow-up scheme using cysto and cytology, adapted according to personal and subjective factors.



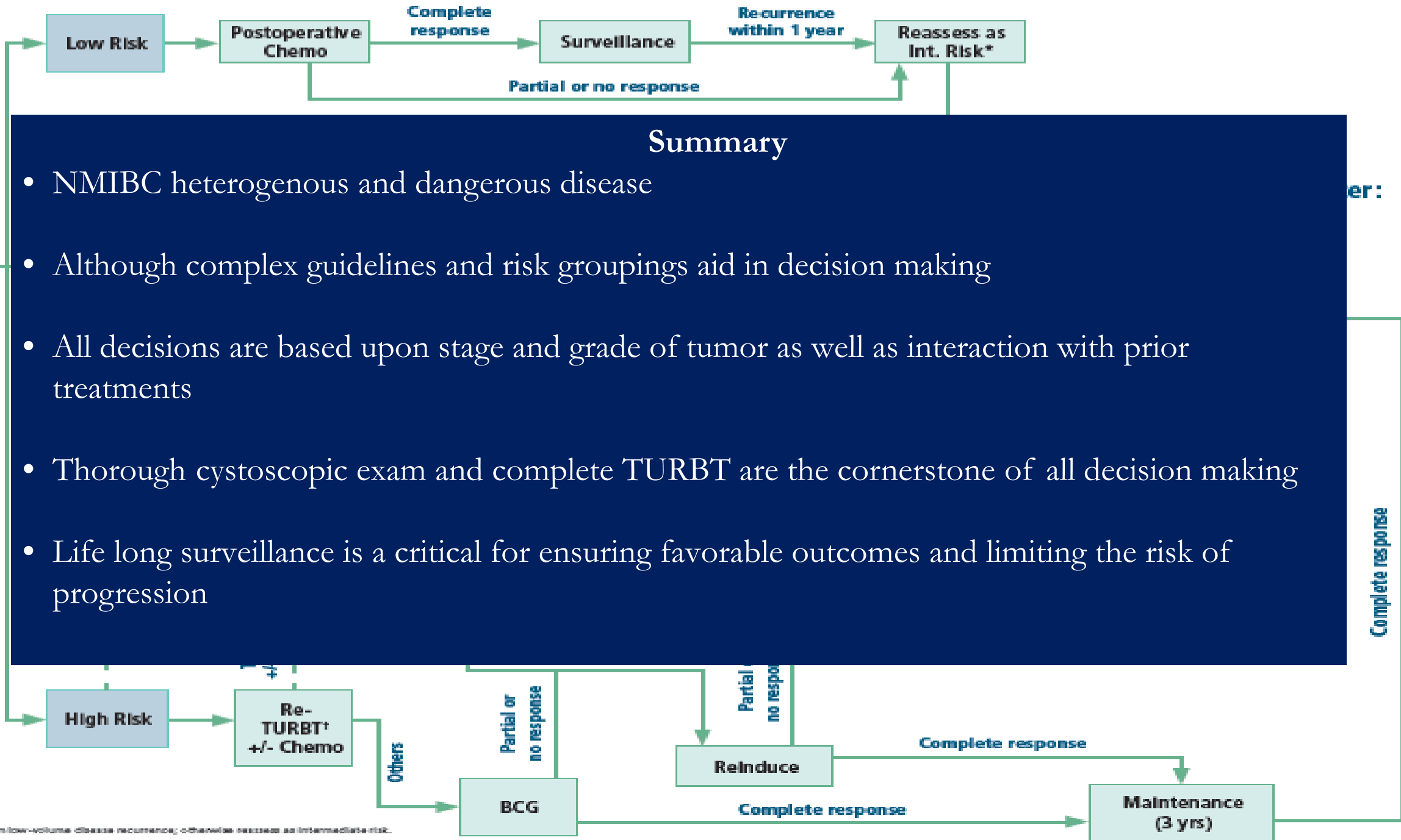
EAU Guidelines 2013

Surveillance

- Yearly upper tract imaging for high-risk tumors.
- After BCG for CIS consider R-biopsies or biopsies with PDD at 3 or 6 months.
- Positive cytology and no visible tumor in the bladder, R-biopsies or biopsies with PDD (if equipment is available) and CT urography, prostatic urethra biopsy.



TURBT



*Consider fulguration in low-volume disease recurrence; otherwise reassess as intermediate risk.

†Timely re-TURBT (within six weeks) should be performed if there are concerns regarding an incomplete resection and/or if bladder sparing treatment (e.g., intravesical therapy or surveillance), is being planned.

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AMAZING
THINGS
ARE
HAPPENING
HERE



— NewYork-Presbyterian

COMPANY UPDATE

Kjetil Hestdal, MD, President & CEO

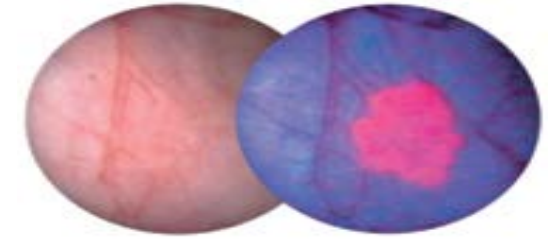


DISCLAIMER



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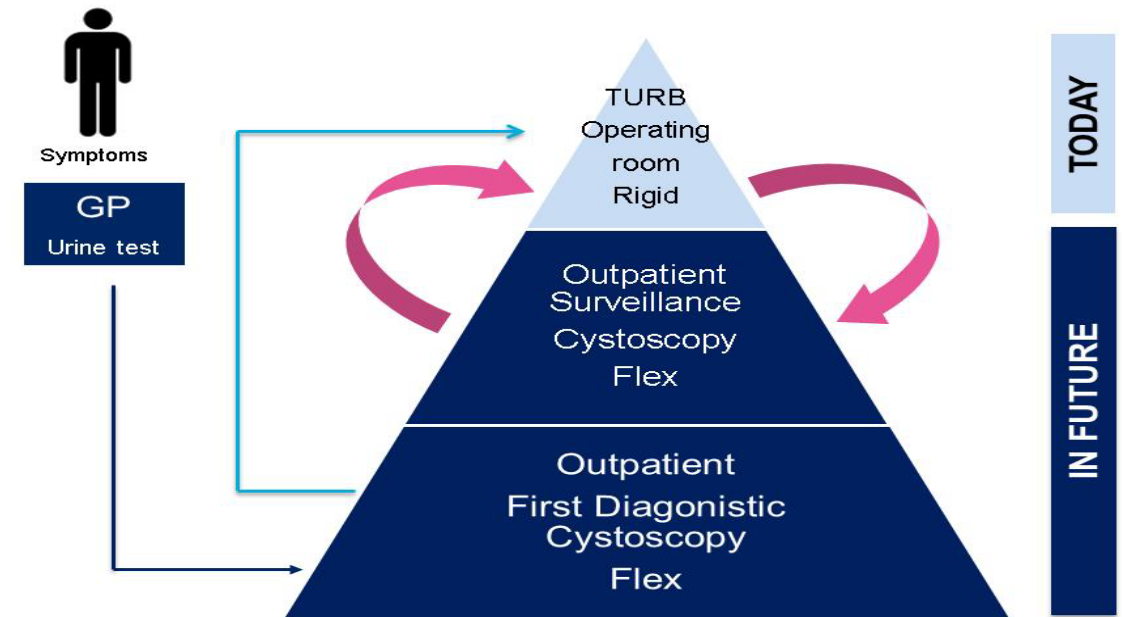
HEXVIX / CYSVIEW: CURRENT STATUS IN US AND EU



- Hexvix® (EU) / Cysview® (US) first approved drug-device procedure for improved detection and management of bladder cancer
- Commercialized by Photocure in US and Nordic regions
 - Strategic partners in other regions
- LTM in market sales growth of 18% to NOK 230 M (~USD 30 M)
 - Market penetration in Nordic at more than 40%
- PHO launched Cysview in the US in 2012 - a significant market opportunity
 - > 300,000 bladder cancer resections (TURB) procedures yearly
 - Majority of TURBs done at 400 hospitals and in 50 top major metropolitan areas (MSA)
 - Currently at 79 hospitals up from 65 at end of 2015; Top 20 BLC accounts current estimated market penetration is 25%
 - BLFCC ongoing Phase 3 study in the US to support market expansion into the flexible surveillance market with more than 1 million procedures in the US market
 - Continued progress on passage of bill in US to provide separate payment to hospitals
- Clinical trials ongoing to expand use in to larger “surveillance” market

HEXVIX / CYSVIEW: EXPANDING INTO THE SURVEILLANCE SEGMENT

- Surveillance following initial diagnosis represents a significant growth opportunity
 - Utilizes flexible cystoscope
 - Market potentially 2 -3 times as large as TURB
- Secured alignment with FDA on study design necessary to obtain label extension
- Phase 3 market expansion study ongoing
- Study results expected 2017



PHOTOCURE SUMMARY

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Profitable Commercial Franchise

- Driven by Hexvix / Cysview for detection and management of bladder cancer
 - NOK 230 M (\$ ~30M) global in market sales LTM

Established own sales operations

- Strong position in US and local market
- Potential to expand urology portfolio to leverage commercial infrastructure

Significant growth prospects within Urology

- Large untapped potential for Hexvix / Cysview in current and near term market segments and territories

Further value potential in late-stage pipeline

- Seeking partnerships for Phase 3 ready non-urology assets
 - Cevira® (HPV related disease of cervix) and Visonac® (inflammatory acne)

Financials

- Cash and equivalents of NOK 104.4 M (\$~15M) as at June 2016
- Listed Nasdaq OMX Oslo: PHO (Mkt cap: approx. US\$ 120 M)

Q&A

