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 Bellete, President & Head of US Cancer Commercial Operations
AGENDA

• 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
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

Surgeon General's Report 2004
Bladder cancer is associated with a high risk of:

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

High rate of residual tumor after TURBT:

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

Patients with incomplete initial resection are at high risk of recurrence:

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

Direct medical costs of cancer care (US)

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

Diagnosis and Presentation
Bladder Cancer Segmentation

- Muscle Invasive: ~30%
- Non-muscle Invasive: ~70%
- Low-risk: 70-80%
- Med/High-risk: 20-30%
Bladder Cancer Staging

Prevalence of Bladder Cancer Staging at Diagnosis\(^1,2\)

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>% of Patients</th>
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<tbody>
<tr>
<td>Non-muscle invasive</td>
<td>75%</td>
</tr>
<tr>
<td>Ta</td>
<td>60%</td>
</tr>
<tr>
<td>T1</td>
<td>30%</td>
</tr>
<tr>
<td>Tis</td>
<td>10%</td>
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<tr>
<td>Muscle invasive</td>
<td>20%</td>
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<tr>
<td>Metastatic</td>
<td>5%</td>
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</table>


Bladder Cancer

Symptoms, Diagnosis, Surveillance & Follow-up

Symptoms
- Hematuria
  - Gross, Microscopic, High Risk
- Urinary frequency or urgency
- Dysuria

Outpatient Setting
Pre-diagnosis
- Urine cytology
- Urinalysis
- CT Scan
- Urine Culture
- White light cystoscopy

Operating Room
Diagnosis & Treatment
- White light cystoscopy
- Blue Light Cystoscopy with Cysview
- Biopsies
- Resection of lesions (TURB)

Suspicions for Recurrence
- ≥ T2
- Ta high grade, T1, CIS
- Ta low grade

Adjuvant Treatment
- Cystectomy
- Chemotherapy
- Immunotherapy
- BCG

Surveillance
- Outpatient Setting
- White light cystoscopy
- Every 3 months

Complete resection, correct grading and staging is essential for optimal patient management
Non-muscle Invasive Bladder Cancer

Standard of Care: Life-long Follow-up

TURBT + single-dose chemotherapy - (Blue Light Cystoscopy with Cysview – can be utilized in the TURB procedure)

- Induction BCG or MMC
- Follow-up including cystoscopy, urine cytology, urinalysis

- After 24 mos, follow-up every 6 mos for another 2-3 yrs
- Annual follow-up after 5 yrs unless recurrence
- 50% recurrence rate Ta low grade within 5yrs
- All patients undergo lifetime surveillance, a major cost driver

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%

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

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

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<tr>
<th>Genes</th>
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<td>Christoph et al, Int J Cancer, 2006</td>
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<td>Lin et al, Int J Urol, 2010</td>
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<td>DAPK1</td>
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<td>Tada et al, Cancer Res, 2002</td>
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<td>DAPK2</td>
<td>NA</td>
<td>0.04</td>
<td>Christoph et al, Int J Cancer, 2006</td>
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<td>IGBP1</td>
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<td>Kim et al, Clin Genetison, Cancer, 2012</td>
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<td>BUNX3</td>
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<td>TIMP3</td>
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<td>Friedrich et al, Eur J Cancer, 2003</td>
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<td>TIMP3</td>
<td>0.01</td>
<td>NA</td>
<td>Hoque et al, JNCI, 2006</td>
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</table>

Comparison of Mutation Frequency in NMIBC vs MIBC

- DNA Methylation marker associated with progression and recurrence

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

Hematuria → CT Scan, Cystoscopy, Cytology

- TURBT
  - large, multiple tumors, high grade
    - 4-6 wks
    - Repeat TURBT
  - small non-invasive tumor, low grade
    - 3 months
    - Surveillance – Cystoscopy, Cytology, FISH
      - Negative cystoscopy
        - F/U surveillance
      - Positive, low grade, low stage
        - Peri TURBT MMC?
        - Cystectomy or additional 3 weeks BCG Therapy

- Upstaged
  - Negative or same stage, grade
    - 3-4 wks
    - 6 weeks BCG
  - 6 wks Cystoscopy / Bladder Bx
    - (-)
      - 3 weeks BCG ± Maintenance
    - (+)
      - Cystectomy or additional 3 weeks BCG Therapy

- Surveillance – Cystoscopy, Cytology, FISH
  - Negative cystoscopy
    - F/U surveillance
  - Positive, low grade, low stage
    - Peri TURBT MMC?
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

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
Cancer Immunotherapy

Recognition of cancer cells by T cells

Normally -- upregulation of immune checkpoint receptors

Cancer Immunotherapy

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

Chen ED. Immunity 68 (2013): 267-279
## Current Clinical Trials


<table>
<thead>
<tr>
<th>Trial/Sponsor</th>
<th>Drug</th>
<th>Target/Design</th>
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<td>Open?</td>
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<td>BCG refractory/CIS</td>
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<td>BCG + HS 410</td>
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<td>High risk</td>
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<td>BioCancell</td>
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<td>Table 3</td>
<td>Novel drug delivery systems</td>
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<td>• Adenoviral mediated</td>
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<td>• Nanoparticles</td>
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<td>• Implantable osmotic pump</td>
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<td>• Conjugated antibody/payload</td>
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<td>• Bacterial minicells</td>
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<tr>
<td>• Iontophoresis</td>
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<tr>
<td>• Muco-adhesive molecules</td>
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</table>

Invasive Bladder Cancer

• Lethal disease if not treated appropriately

• Surgery remains cornerstone therapy

Cystoscopic view of papillary bladder cancer
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

- **TURBT**
- **MCV**, XRT + concurrent cisplatin
- **urologic evaluation**
- **incomplete response**: recommend radical cystectomy
- **complete response**: MCV, XRT

**Induction therapy**

**Consolidation therapy**

*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

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 tumor are classified into 2 separate pathways with distinct histopathology patterns, molecular alterations, and clinical behavior.

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>% RELATIVE FREQUENCY</th>
<th>% PROGRESSION</th>
<th>% DEATHS</th>
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<td>Secondary</td>
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</table>
Recurrence after Radical Cystectomy

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


Shariat et al. BCRC J Urol. 2006 Dec
US Drug Approvals in GU Cancers

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

(Castillo-Martin 2010)
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
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
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

Shariat et al., ICUD Guidelines 2012
Improved Prediction of Outcomes
Many Pathways result in Cancer development and Spread
Using Tissue Markers to Predict Outcomes after Cystectomy

MORE ALTERATIONS = WORSE OUTCOMES

Combined cell-cycle biomarkers
Shariat et al., J Clin Oncol 2003

Combined apoptosis biomarkers
Karam et al., Lancet Oncol 2007
Understanding the Biology of Cancer Improves Prediction of Behavior

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

<table>
<thead>
<tr>
<th></th>
<th>Base nomogram model</th>
<th>Base model + Nb altered markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>p = 0.1</td>
<td>Age</td>
</tr>
<tr>
<td>Path grade</td>
<td></td>
<td>Path grade</td>
</tr>
<tr>
<td>Path T</td>
<td></td>
<td>Path T</td>
</tr>
<tr>
<td>LVI</td>
<td></td>
<td>LVI</td>
</tr>
<tr>
<td>Concomitant Cis</td>
<td></td>
<td>Concomitant Cis</td>
</tr>
<tr>
<td>Nb altered markers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

200 bootstrap corrected predictive accuracy:

- Base nomogram model: 72.6%
- Base model + Nb altered markers: 83.4%
Performance of individual clinicopathologic variables and classifiers in the validation set for predicting cancer recurrence.

Genomic classifiers will likely be commercially available soon.
Predict Response to Therapy
Recurrence after Radical Cystectomy

*20-30% of T1-T2 patients recur after cystectomy*
SWOG 8710 Randomized Neoadjuvant MVAC Chemotherapy Trial

Grossman et al., NEJM 2003
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% in contemporary series) have excellent survival following RC alone (**80% cure**)
  
  – NAC favors advanced tumors: **42 mo cT3/4 vs 19 mo cT2**

• Problem: current staging is inadequate and > 50% under-staged

• Chemotherapy is toxic

Identify those patients most likely to benefit from NAC

COXEN Gene Expression Model

Evaluation of Model on Human Tumors

MSKCC & UVA

NCI-60 Panel

Gene Expression

MSKCC & UVA

NCI-60 Panel

COXEN

Ref: Clin Can Res 2005;11(7): 2625

Tx: Neoadjuvant MVAC (N=45) + surgery or XRT

Outcome: Downstaging, Overall survival

Downstaging vs. COXEN Score

Downstaged

NO Downstage

COXEN Score

Downstaging defined as ≤pT1 or ≤T1 after two courses of MVAC

MSKCC & UVA

NCI-60 Panel

Gene Expression

Ref: Clin Can Res 2005;11(7): 2625

Tx: Neoadjuvant MVAC (N=45) + surgery or XRT

Outcome: Downstaging, Overall survival

Use Genomic Information to Identify Tumors that Respond to Therapy

Proportion Surviving

P = 0.000656

0.0 0.2 0.4 0.6 0.8

0 12 24 36 48 60 72

Disease-Free Survival Time (Months)

Predicted Responders (34)

Predicted Nonresponders (11)
**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 urothelial cancer

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

**Purpose:** Biomarker validation and Biomarker discovery

**Primary study objective:** To characterize the relationship of MVAC-and GC-specific COXEN scores vs. pT0 rate in patients treated with neoadjuvant MVAC or GC

**Tumor Sample TURBT**

**Randomize to chemo n=184**

**Gem-Cis**

**DD-MVAC**

**Assessment**

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

**Collection**

Tissue (>P0), blood, urine

**Molecular Analysis**

Gene expression, Sequencing, microRNA, SNP

**Discovery**

**Impact**: Transform thinking about patient selection for neoadjuvant chemotherapy in urothelial cancer
Identification of Distinct Basal and Luminal Subtypes of Muscle-Invasive Bladder Cancer with Different Sensitivities to Frontline Chemotherapy

Woonyoung Choi, Sima Porten, Seongchan Kim, Daniel Willis, Elizabeth R. Plimack, Beat Roth, Tiewei Cheng, Mai Tran, I-Ling Lee, Jonathan Melquist, Jolanta Ruchala, Shizhen Zhang, Shanna Pretzsch, Keith Baggerly, Arlene Siefker-Radtke, and David J. McConkey

Need Better Understanding of Subtypes of Bladder Cancer
**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

CDK4/6 inhibitors:
- Palbociclib
- LEE001
- LY2835219

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

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%)
RTK/Ras/PI3K pathways
HER2/ERBB2 Activation as a potential therapeutic target

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

Natl Academy of Sciences 2011
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 Pathway

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.


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

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 (≥1% but <5%), and IC2/3 (≥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

<table>
<thead>
<tr>
<th>OLD MODEL: Treatment determined by a tumor's location</th>
<th>NEW MODEL: Treatment determined by key molecular “hubs” targeted within cells</th>
</tr>
</thead>
</table>

![Diagram showing molecular hubs in cancer 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

<table>
<thead>
<tr>
<th>OLD MODEL: Large numbers of patients, not selected by molecular characteristics</th>
<th>NEW MODEL: Small patient populations with relevant molecular defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>➔ lower chance of effectiveness</td>
<td>➔ all participants potential to respond</td>
</tr>
</tbody>
</table>
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
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.
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.

Davis 2012; Dimashkieh 2013; Schroeder 2004
STAGING & GRADING

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

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.
Grade important prognostic factor for recurrence and progression.

WHO/ISUP 2004 grading system most widely accepted in the United States.

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

Eble 2004
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.

<table>
<thead>
<tr>
<th></th>
<th>Risk of Progression (%)</th>
<th>Risk of Recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Grade Ta</td>
<td>6</td>
<td>55</td>
</tr>
<tr>
<td>High-Grade T1</td>
<td>17</td>
<td>45</td>
</tr>
</tbody>
</table>

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.

Palou 2012; Cookson 1997; Leblanc 1999
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
<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>LG&lt;sup&gt;a&lt;/sup&gt; solitary Ta ≤ 3cm</td>
<td>Recurrence within 1 year, LG Ta</td>
<td>HG T1</td>
</tr>
<tr>
<td>PUNLMP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Solitary LG Ta &gt; 3cm</td>
<td>Any recurrent, HG Ta</td>
</tr>
<tr>
<td></td>
<td>LG Ta, multifocal</td>
<td>HG Ta, &gt;3cm (or multifocal)</td>
</tr>
<tr>
<td></td>
<td>HG&lt;sup&gt;c&lt;/sup&gt; Ta, ≤ 3cm</td>
<td>Any CIS&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>LG T1</td>
<td>Any BCG failure in HG patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any variant histology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any LVI&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any HG prostatic urethral involvement</td>
</tr>
</tbody>
</table>

<sup>a</sup>LG = low grade; <sup>b</sup>PUNLMP = papillary urothelial neoplasm of low malignant potential; <sup>c</sup>HG = high grade; <sup>d</sup>CIS = carcinoma in situ; <sup>e</sup>LVI = lymphovascular invasion
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
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
15. In a patient with suspected or known low- or intermediate-risk bladder cancer, a clinician should consider administration of a single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin) within 24 hours of TURBT. In a patient with a suspected perforation or extensive resection, a clinician should not use postoperative chemotherapy. (Moderate Recommendation; Evidence Strength: Grade B)
16. In a low-risk patient, a clinician should not administer induction intravesical therapy. (Moderate Recommendation; 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)
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)
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

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

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 reduced\(^1\)

<table>
<thead>
<tr>
<th>Table 6 - Overall recurrence rates up to 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated with BL, n (%)</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Herrmann et al. [24]</td>
</tr>
<tr>
<td>Stefic et al. [21]</td>
</tr>
<tr>
<td>Drăgănescu et al. [25]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>At least one T1 or CIS</td>
</tr>
<tr>
<td>At least one Ta</td>
</tr>
<tr>
<td>High-risk subgroup</td>
</tr>
<tr>
<td>Intermediate-risk subgroup</td>
</tr>
<tr>
<td>Low-risk subgroup</td>
</tr>
</tbody>
</table>

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).

Rate of recurrence is reduced by 10.9% \( p < 0.006 \)

Time to recurrence prolonged\(^2\)


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

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).
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.
Summary

• NMIBC heterogenous and dangerous disease

• Although complex guidelines and risk groupings aid in decision making

• All decisions are based upon stage and grade of tumor as well as interaction with prior treatments

• Thorough cystoscopic exam and complete TURBT are the cornerstone of all decision making

• Life long surveillance is a critical for ensuring favorable outcomes and limiting the risk of progression
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

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