INTERNATIONAL
BLADDER CANCER GROUP (IBCG)

IBCG

International Bladder Cancer Group

Newsletter

Volume 1
2023

Index

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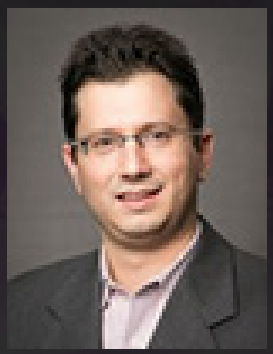

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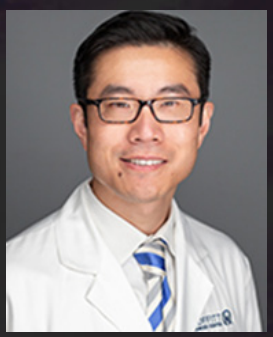

Roger Li

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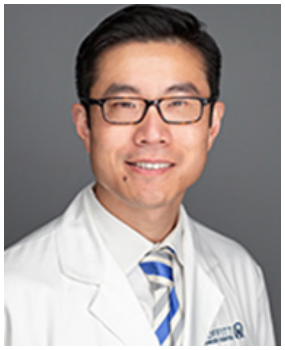
Articles

GU ASCO Update

BCG Unresponsive Disease
(KEYNOTE-57 Long-Term Results)



Roger Li, MD

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BCG unresponsive disease is a well-described, difficult-to-treat disease, for which the standard-of-care is radical cystectomy. Following guidance from the IBCG [1], there has been a flurry of clinical trials investigating various bladder-sparing strategies in this disease space. The results from KEYNOTE-57 demonstrated an overall complete response rate of 41% in carcinoma in situ (CIS)-containing BCG unresponsive patients treated with IV pembrolizumab2, leading to its approval in 2020. At GU ASCO 2023, Andrea Necchi discussed the long-term follow-up results gathered from Cohort B of the study, in which patients with BCG unresponsive papillary-only disease were treated with pembrolizumab.

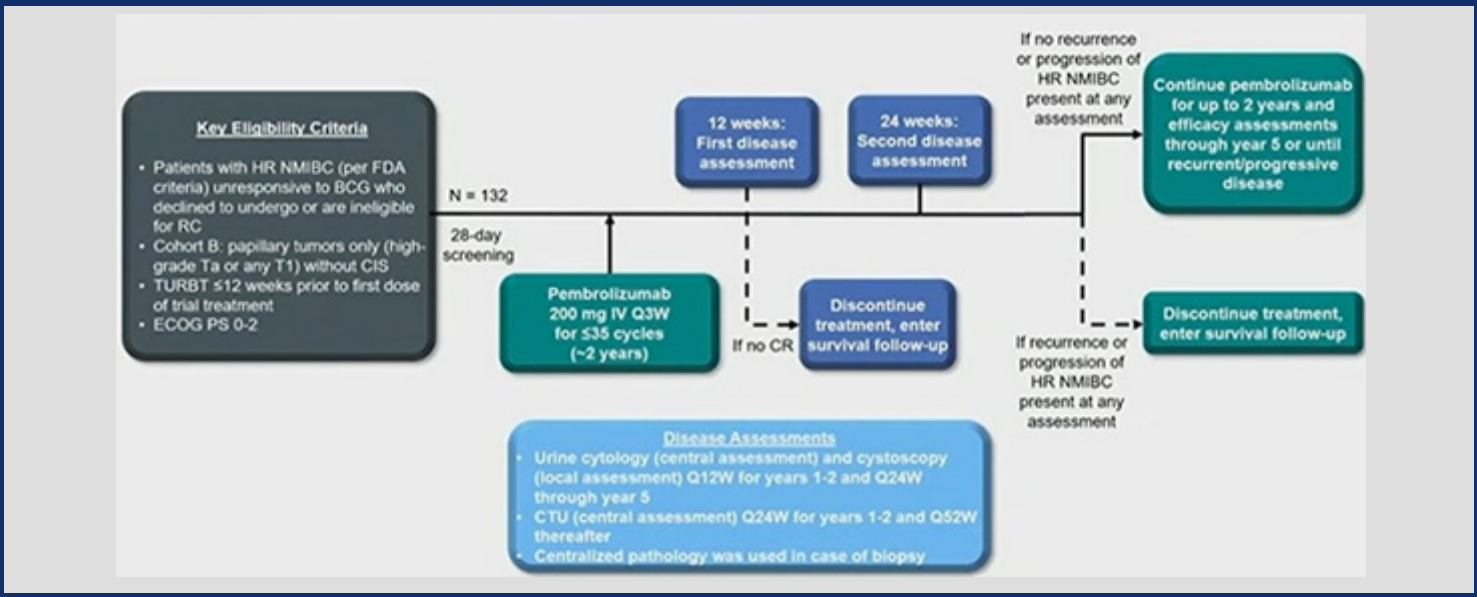
In the study, 135 patients received pembrolizumab 200mg every three weeks for up to 35 cycles (~2 years). Patients were assessed per standard-of-care using cystoscopy and urine cytology every 12 weeks without a mandated random bladder biopsy. The primary endpoint of the study, HR NMIBC disease-free survival rate, was found to be 43.5% (95% CI 35-52%) at 12 months, 34.9% at 24 months, and 34.9% at 36 months, after a median follow-up of 45.4 months (range 14.9-77.1). Progression-free survival, a key secondary endpoint in the study, was found to be 88.2% (95% CI 80-93%).

Following disease recurrence, 36 patients (26.7%) underwent radical cystectomy, with 9 of them (25%) were discovered to have no residual disease while only 4 progressed to muscle-invasive bladder cancer (MIBC).

BCG Unresponsive Disease

Moreover, treatment-emergent adverse event rates were similar to those reported in the past for pembrolizumab monotherapy trials, with 14.4% Grade 3/4 AE's and 10.6% discontinuation rate due to toxicity. Importantly, no death occurred due to treatment.

These preliminary results show an encouraging benefit/risk ratio for pembrolizumab in the BCG unresponsive papillary-only population. It begs the question of why pembrolizumab seems to have a numerically higher efficacy level in the papillary-only cohort vs. patients with pure or concomitant CIS. Effective therapies in both settings are sorely needed.

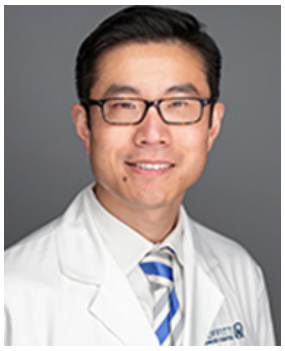


Reference

1. Kamat AM, Sylvester RJ, Bohle A, et al. Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group. J Clin

2. Balar AV, Kamat AM, Kulkarni GS, et al. Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. The Lancet Oncology. 2021;22(7):919-930.

Urinary Biomarker



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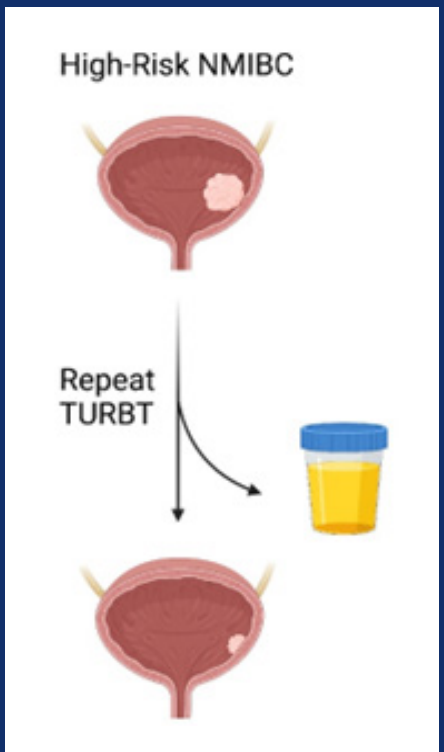
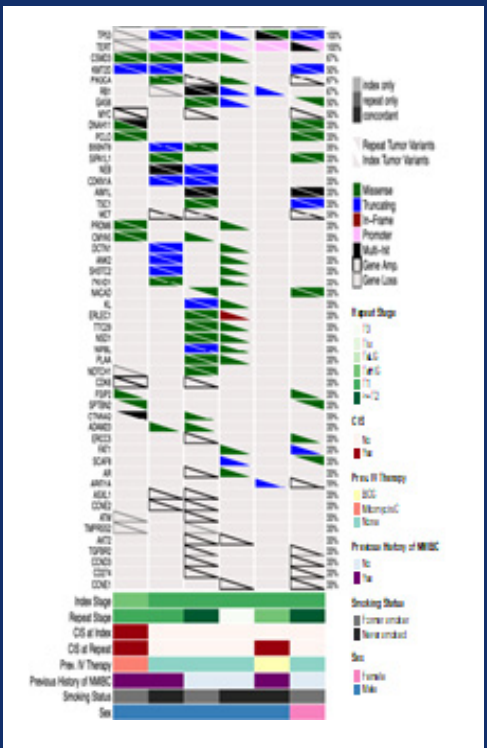
An accurate urinary biomarker for the detection of bladder cancer has been the object of much research over the past several decades. As bladder cancer constantly interfaces with the urine, it stands to reason that it will leave traces within the urine that can reflect disease identity and burden. However, due to the molecular heterogeneity seen across the spectrum of bladder cancer, such tests remain elusive.

In the preliminary study conducted at Moffitt Cancer Center, Rose et al. presented results of using the urine-based circulating tumor DNA assay to predict minimal residual disease. The investigators collected urine samples from 11 patients with high-risk non-muscle-invasive bladder cancer (NMIBC) undergoing re-TURBT to complete initial staging. An ultra-deep sequencing platform (PredicineBEACON™) was used and the threshold for ctDNA positivity was set at the detection of 2 or more tumor concordant variants, using whole exome sequencing of the index TURBT tissue as reference standard.

First, concordance between the index and repeat TURBT tissue samples were assessed, finding a high concordance rate of 83%. The observed high concordance rate established that the index TURBT can be reliably used to generate the bespoke genomic panel for testing within the urine. ctDNA alterations found within the urine reflected the mutational landscape previously described for NMIBC – with alterations in TP53 (45%), KMT2D (36%), and RB1 (27%) being the most prevalent. Elevated urinary ctDNA tumor fractions were observed in 8 patients with the residual disease compared to 3 patients without minimal residual disease (MRD) (25% vs. 0.2%), indicating potential clinical utility.

Albeit preliminary, this test brings exciting data on a personalized urine test that may be used to detect minimal residual disease in the context of bladder cancer. The study is currently ongoing with data collected on more robust cohorts pending.





BCAN Announces Awardees of First-Ever $3 Million Translational Clinical Trial Award

(Award aims to transform bladder cancer care and patient outcomes.)

March 29, 2023

The Bladder Cancer Advocacy Network (BCAN) today announced the recipients of its first-ever Translational Clinical Trial Award (TCTA). The TCTA was created to fund early-phase patient-oriented research projects aimed at reducing the burden of care and over-treatment for bladder cancer patients. This three-year award provides up to $3 million to support research with the potential to make significant impacts on bladder cancer patient care and outcomes, leading to changes in clinical practice, guidelines, or standards of care.

The 2022 TCTA awardees are Sarah Psutka, MD, MSc, Associate Professor of Urology at the University of Washington, and Amir Horowitz, Ph.D., a cancer immunologist in a translational research program focused on bladder cancer and Assistant Professor of Oncological Sciences at the Icahn School of Medicine at Mount Sinai. Dr. Horowitz's co-principal investigators are Matthew Galsky, MD, and John Sfakianos, MD, both of Mt. Sinai.

Sarah Psutka
MD, MSc.

Amir Horowitz
PhD

Dr. Horowitz's team's proposal seeks to establish proof-of-concept for a novel immunotherapy combination of two drugs, durvalumab and monalizumab, that may delay or prevent the need for a radical cystectomy in patients with BCG-unresponsive, non-muscle invasive bladder cancer. Dr. Psutka's "Get Moving" clinical trial will enroll patients who have muscle-invasive bladder cancer and are undergoing chemotherapy followed by radical cystectomy. Her project aims to study how personalized exercise intervention and pragmatic prehabilitation can improve patient outcomes and health-related quality of life.

Dr. Horowitz said, "My team and I are very grateful to BCAN for this opportunity. Not all non-muscle invasive bladder cancer patients respond to BCG treatments, and it is our hope that this trial helps to delay or eliminate the need for a life-altering radical cystectomy for many."

The TCTA is part of BCAN's ongoing efforts to advance bladder cancer research and support those impacted by the disease. Since 2009, BCAN has funded over $5 million in bladder cancer research grants.

"BCAN is delighted to announce the awardees of our first-ever Translational Clinical Trial Award," said Andrea Maddox-Smith, CEO of BCAN. "These innovative research projects have the potential to transform bladder cancer care and improve patient outcomes. We are proud to support Dr. Psutka and Dr. Horowitz and his team in their important work."

Dr. Psutka added," Our team is thrilled to have this opportunity to undertake a pragmatic prehabilitation trial. This trial was born out of the critical need vocalized by our patients and patient advocates at the 2022 BCAN Think Tank scientific meeting. We look forward to advancing our understanding of how we can meet this need and develop scalable tools that can make personalized prehabilitation available to all."

Funding for this award comes from BCAN board member and philanthropist Duncan Alexander. BCAN is very grateful for his support.

The Bladder Cancer Advocacy Network Announces Five Awardees of Its Prestigious 2023 Young Investigator Awards

Outstanding early-career researchers acknowledged for novel studies to enhance the well-being of bladder cancer patients

In May 2023, The Bladder Cancer Advocacy Network (BCAN) announced the five recipients of its prestigious Young Investigator Awards, recognizing exceptional early-career scientists and clinical cancer investigators who are committed to making a positive impact on the lives of bladder cancer patients.

Each Young Investigator Award includes a $75,000 grant to support one year of bladder cancer research. Over the years, BCAN has provided more than $5 million in grants to promising scientists and researchers, underscoring the urgent need to advance our understanding of bladder cancer.

The distinguished recipients of this year's Young Investigator Awards are Jonathan Chou, MD, Ph.D., an Assistant Professor of Medicine in Hematology/Oncology at the University of California, San Francisco; Kathryn Gessner, MD, Ph.D., a Postdoctoral Fellow in Urologic Oncology at the University of North Carolina at Chapel Hill; Sean Clark-Garvey, MD, MPH, a Postdoctoral Fellow in Medical Oncology at the University of North Carolina at Chapel Hill; and Soonbum Park, Ph.D., a Postdoctoral Research Scientist focusing on Molecular Pharmacology and Therapeutics at the Columbia University Medical Center.

Dr. Chou's project is titled "Targeting advanced bladder cancer with NECTIN4-directed CAR T cell therapy," while Dr. Gessner's project explores "Dissecting the impact of E-cadherin loss on the immune microenvironment and response to immune checkpoint blockade in plasmacytoid urothelial carcinoma." Dr. Clark-Garvey's is titled, "Investigating novel mechanisms and therapeutic options for metastatic bladder cancer," and Dr. Park's project focuses on "Unveiling novel therapeutic targets for non-muscle invasive bladder cancer."

The 2023 Patient-Centered Clinical Research Young Investigator Award is presented to Rishi Sekar, MD, a Postdoctoral Fellow and Clinical Instructor of Urologic Oncology at the University of Michigan. Dr. Sekar's project is titled "Identifying individual and community-level drivers of disparities in bladder cancer clinical trials participation."

"We are delighted to invest in the innovative ideas and approaches of today's promising bladder cancer researchers who are dedicated to improving the lives of patients and caregivers," said Andrea Maddox-Smith, the CEO of the Bladder Cancer Advocacy Network. "These awards are made possible thanks to the incredible generosity of our donors."

The Bladder Cancer Advocacy Network's (BCAN's) mission is to increase public awareness about bladder cancer, advance bladder cancer research and provide educational and support services for the bladder cancer community.

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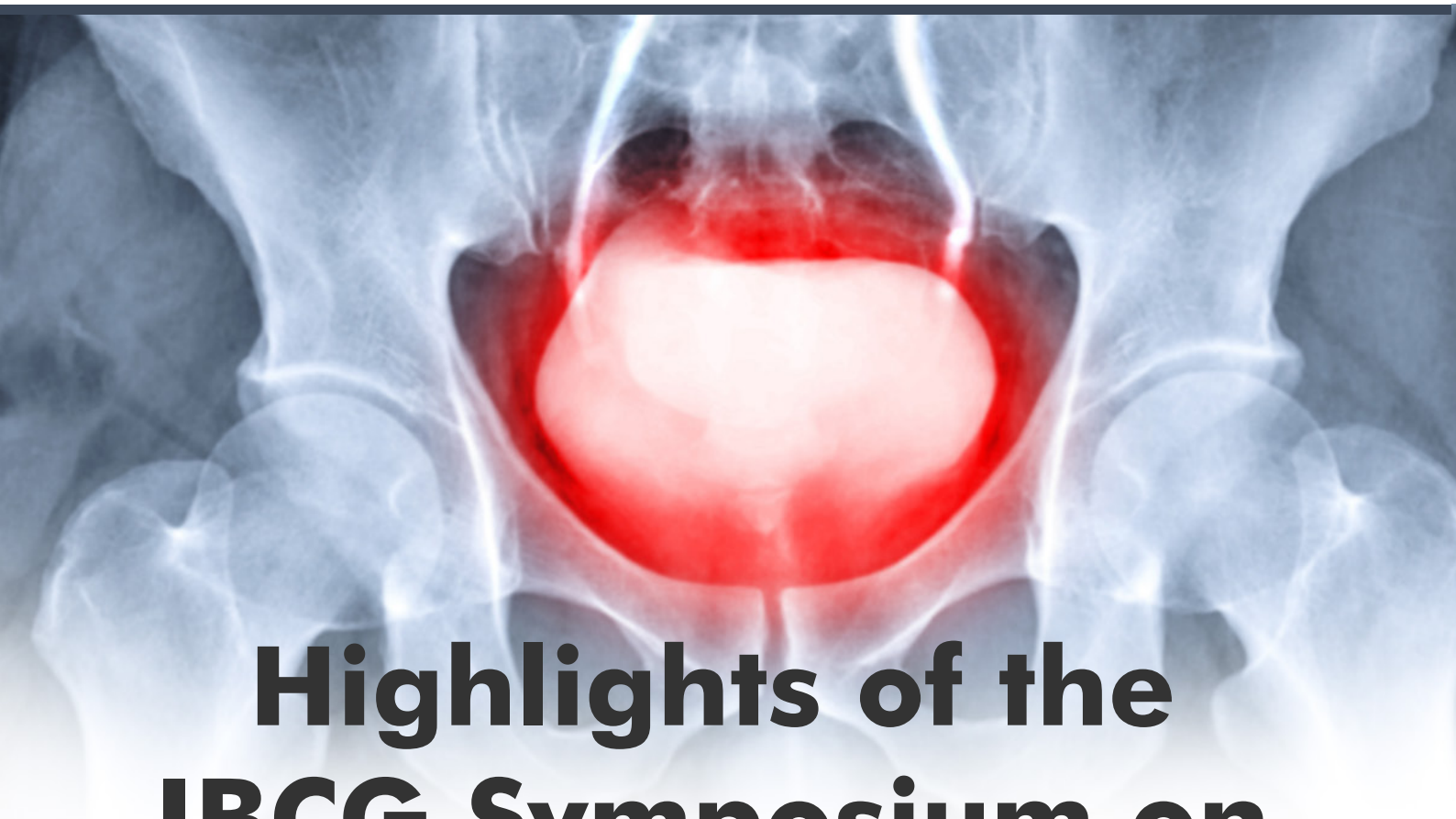


Highlights of the IBCG Symposium on Bladder Cancer

Part of the Annual Course of the Chilean Society of Urology 2023

Mario Fernández

MD, Urologist of Clínica Alemana de Santiago, Director of the Chilean Society of Urology, and IBCG Coordinator for Latin America

Cristian Alliende

MD, Department of Urology- Clínica Alemana de Santiago

Valentina Grajales

MD, MS, Fellow of Urologic Oncology, MD Anderson Cancer Center, Houston, TX

Highlights of the IBCG Symposium on Bladder Cancer Part of the Annual Course of the Chilean Society of Urology 2023

In April of this year, the IBCG Symposium took place in Santiago de Chile as a part of the Annual Course organized by the Chilean Society of Urology. The event drew a significant crowd of over 250 attendees, where five distinguished members of the IBCG faculty delivered presentations on various aspects of bladder cancer (BC) management. The IBCG lecturers who shared their expertise at the symposium were:

- Ashish M Kamat, MD, MBBS, Urologist, University of Texas MD Anderson Cancer Center, USA; President of IBCG
- Shilpa Gupta, MD, Medical Oncologist, Cleveland Clinic, USA
- Joan Palou MD, PhD, FEBU, FRCS, Urologist, Fundació Puigvert, Barcelona, Spain
- Peter Black MD, FACS, FRCSC, Urologist, University of British Columbia, Vancouver, Canada
- Roger J Buckley, MD, Urologist, North York Hospital, Canada

The symposium was preceded by a Consensus Meeting of IBCG experts and fifteen Chilean BC experts. During this meeting, a thorough evaluation of the national BC clinical guidelines was conducted, and a consensus was reached regarding recommendations for revisions and updates. Dr. Valentina Grajales (Fellow of Urologic Oncology, MDACC), who served as the meeting secretary, presented these recommendations to the symposium attendees the following day. These recommendations will be compiled into a document and subsequently shared with the Chilean Ministry of Health.

Epidemiology and Clinical Landscape of Bladder Cancer in Chile

The symposium began with a presentation by Dr. Mario Fernández, Urologist of Clínica Alemana de Santiago, Director of the Chilean Society of Urology, and IBCG Coordinator for Latin America. His presentation shed light on the global and local epidemiological and clinical landscape of bladder cancer (BC). He emphasized that BC is a highly prevalent disease with a protracted course, exhibiting low lethality but imposing significant burdens on healthcare systems. In fact, when calculated per patient, BC stands as the costliest among all malignant neoplasms. Dr. Fernández underscored a noteworthy trend in Chile, where the incidence of BC is increasing, primarily due to the high prevalence of smoking and the progressive aging of the population. He also highlighted a staggering fourfold increase in the country's BC surgeries (TUR-B and cystectomy) over the past two decades.

Introduction of IBCG

Next, Dr. Ashish Kamat delivered a presentation on the IBCG. He provided insights into the organization's core objectives, which focus on enhancing outcomes for bladder cancer (BC) patients by offering evidence-based recommendations. Additionally, the IBCG strives to develop educational tools that are tailored to the unique needs of diverse urological communities worldwide.

Low and Intermediate-Risk NMIBC

Subsequently, Dr. Joan Palou chaired the panel on presenting cases of low and intermediate-risk NMIBC. Joining him on the panel were Drs. Roger Buckley, Mario Fernández, Alvaro Vidal (Urologist, Instituto Oncologico FALP), Ashish Kamat, and Peter Black.

The discussion began with the diagnostic evaluation of hematuria, encompassing invasive and noninvasive tests. The panel engaged in a dynamic exchange of viewpoints regarding using bladder ultrasound (US) as the initial diagnostic approach before cystoscopy or CT Urography. North American urologists favored CT Urography as the primary diagnostic option. The discussion then shifted toward the utility of cytology in the preoperative setting. Dr. Palou advocated for including urinary cytology as part of the initial assessment because if cytology is positive for high-grade disease, he recommended conducting random bladder biopsies to identify the presence of carcinoma in situ (CIS). Additionally, Dr.

Black discussed the benefit of sparing high-risk patients from a single bladder instillation of chemotherapy, while Dr. Kamat highlighted the advantage of avoiding a very deep resection in a low-risk tumor by using cytology.

The panel unanimously recognized the importance of standardizing urinary cytology by implementing the PARIS classification for accurate interpretation. The panel briefly discussed various aspects, such as the risk classification of non-muscle invasive bladder cancer (NMIBC), transurethral resection of bladder tumor (TUR-B) checklists, and the immediate administration of intravesical instillations. They also discussed the importance of utilizing bacillus calmette-guérin (BCG) therapy with maintenance for intermediate-risk tumors when this treatment option is chosen over intravesical chemotherapy regimens. Then, Dr. Palou delved into photodynamic diagnosis (PDD) and its limitations. While acknowledging its superiority to white light in detecting Ta and CIS tumors, he emphasized that PDD does not identify all CIS lesions. In contrast, Dr. Palou pointed out that random biopsies alone have a 25% detection rate for CIS.

The panel concluded their discussion by exploring follow-up strategies. Dr. Palou asked the experts about the future role of urinary markers and cytology in reducing the need for follow-up cystoscopy. Specifically, he inquired whether a strong negative predictive value (NPV) or high sensitivity should be prioritized. In response, Dr. Black suggested that these markers would be most helpful in low-risk tumors and recommended prioritizing a reliable NPV.

Techniques in TUR-B

Dr. Palou provided a comprehensive overview of various surgical techniques through instructional videos. He demonstrated different scenarios, including tumors located at the bladder dome, ureteral orifice, bladder wall perforations, and en-bloc resection. Shifting the focus to optical diagnosis optimization, Dr. Kamat underscored the benefits of PDD and its impact on recurrence, progression, and residual tumor rates compared to traditional white light techniques. Additionally, he reviewed the evidence on using narrow-band imaging (NBI), particularly for low and intermediate-risk tumors, as it has shown efficacy in reducing recurrence rates. Both experts emphasized the importance of performing a high-quality TUR-B as the initial step in managing all patients with bladder cancer. They stressed that TUR-B should not be underestimated or considered a simple surgery, as it plays a pivotal role in determining the course of the disease and directly impacts patient management.

High-Risk NMIBC

Dr. Buckley chaired a panel consisting of Drs. Ashish Kamat, Shilpa Gupta, Peter Black, Joan Palou, Rodrigo Pinochet (Urologist, Clínica Alemana de Santiago) and Patricio Valdebenito (Urologist, Hospital Regional de Antofagasta). Dr. Buckley presented cases of high-grade NMIBC and solicited insights from the panel members regarding diagnostic approaches, indications for random biopsies, and prostatic urethra biopsies.

The panel briefly touched upon en-bloc resections, indications for a second TURB, and immediate intravesical instillations during the discussion. Dr. Buckley further mentioned the European Association of Urology (EAU) recommendation in 2023, which suggests continuous bladder irrigation with saline for patients unsuitable for immediate chemotherapy bladder instillation. Dr. Kamat shared that he tends to avoid immediate intravesical treatment in cases involving deep resections or resections of the ureteral orifice. He argued that the number of recurrences prevented by such treatment is limited and can be effectively monitored through active surveillance, thereby minimizing the potential toxicity associated with intravesical treatment. Dr. Buckley commented that in his experience, intravesical instillations with MMC can generate significant toxicity, such as chronic pelvic pain. He then proceeded to present comprehensive information about intravesical BCG, including its history, mechanism of action, manufacturing process, dosage, and treatment schedules. Dr. Pinochet recommended using 4 vials of 30 mg of the BCG Danish strain, which is the full dose. Dr. Palou encouraged the audience not to fear adverse reactions and emphasized the importance of administering full doses in line with the available evidence. Dr. Kamat expanded on this, discussing positive outcomes observed in Chilean patients who received the full dosage of BCG. He also discussed BCG shortage scenarios. Dr. Buckley reminded the audience about the results of

trials such as CUETO 98013, EORTC 30962, and NIMBUS, underscoring the importance of adhering to the standard BCG treatment regimens and dosages.

The panel also deliberated on the possibility of utilizing reduced dose schemes and durations of BCG treatment in cases of shortage or for specific patients. They then reviewed the adverse effects associated with BCG and discussed various management strategies. The panel agreed on the efficacy of administering fluoroquinolones on the day of BCG instillation to prevent and treat post-BCG cystitis. In conclusion, the panel discussed the classification of BCG failure and explored corresponding treatment options. These options included repeating BCG regimens, considering radical surgery, or implementing alternative bladder preservation strategies.

BCG Complications

Dr. Fernandez provided a comprehensive overview of the complications associated with BCG treatment. He presented findings of the EORTC 30962 study, demonstrating that approximately 70% of patients experienced some form of adverse reaction to treatment, with 62% being local and 30% systemic. In addition, there was no significant difference in adverse reactions between full and reduced doses of BCG, and treatment discontinuation due to toxicity was only 7.8%. Dr. Fernandez highlighted the challenges in diagnosing and studying these complications, as clinical assessment is the primary method. He shared data from his center, aligning with existing literature, where only 12% of patients needed to discontinue treatment due to toxicity when receiving full doses of BCG. He then discussed the management of various complications such as BCG cystitis, hematuria, orchiepididymitis, malaise and fever, persistent fever, allergies, and the severe complication of sepsis. Dr. Fernandez outlined preventive measures to prevent these complications, including proper drug instillation through atraumatic and low-pressure catheterization. He also discussed administering quinolones at 6 and 18 hours post-instillation, as it has been shown to reduce moderate and severe side effects in 10-20% of cases.

Localized MIBC

Dr. Black chaired the panel on locally advanced MIBC, which included Dr. Carolina Ibañez (Medical Oncologist, P. Universidad Católica), Dr. Nicolas Isa (Radiotherapist IRAM), Dr. Gupta and Dr. Rodrigo Ledezma (Urologist, Hospital Clínico Universidad de Chile). They discussed clinical scenarios, indications for bladder-sparing therapy, histological variants, and neoadjuvant chemotherapy. The panel examined the VESPER trial, noting that the 6-cycle dose-dense MVAC scheme was not commonly used, with 4 cycles being the standard practice. Dr. Gupta and Dr. Ibañez emphasized that younger patients may benefit more due to better treatment tolerance. Regarding histological subtypes, Dr. Isa mentioned that patients with the small cell variant could receive radiotherapy with neoadjuvant chemotherapy using etoposide and cisplatin, similar to the approach in lung cancer.

A case of a patient with locally advanced multifocal disease was presented by Dr. Black and the question of whether radiotherapy would be appropriate after a good response to neoadjuvant therapy was raised. Dr. Isa stated that while there may not be strong scientific literature supporting this indication, it was not uncommon in real-world scenarios for patients to opt out of surgery or for anesthesiologists to deem patients unfit for surgery. Thus, in his experience, it was a reasonable approach.

The panel also discussed pre-habilitation for frail patients, staging, maximum TURB, and salvage surgery. Dr. Black mentioned the variability in the impact of radiotherapy on pelvic tissues during surgery, noting instances where he had performed neobladders since the periurethral tissues were less exposed to radiation. Overall, the panel explored various aspects of locally advanced MIBC management, providing insights based on their experiences and current practices.

Open vs. Robotic Cystectomy

In the following presentation, Dr. Palou discussed open and robotic cystectomy, focusing on oncologic outcomes as well as urinary and sexual function. He highlighted perioperative treatment management changes over the past decades,

particularly with the implementation of the ERAS protocol. Dr. Palou presented findings from a systematic review comparing open versus robotic cystectomy, indicating a lower risk of transfusion, shorter hospital stays, and longer surgical time for the robotic technique. However, he emphasized the limited evidence supporting these findings. He also reviewed the evidence on similar local recurrence rates, intracorporeal surgery benefits, the learning curve, and secondary outcomes from the iROC trial, which showed lower infection rates, hernias, and thromboembolic events with robotic surgery. Dr. Palou discussed the importance of neurovascular preservation, especially for patients with localized disease who desire to preserve sexual function and achieve better continence with neobladder reconstruction. He also touched upon lymphadenectomy, emphasizing the usefulness of sending lymph node samples in packages to increase lymph node count. The discussion included different dissection templates, with extended lymphadenectomy showing improved survival, particularly for pT3 patients, compared to limited lymphadenectomy.

Urinary Diversion and ERAS

Dr. Black discussed urinary diversions, noting the increasing preference for ileal conduits over neobladders worldwide. He highlighted the factors to consider when selecting the type of diversion, stating that age, previous radiotherapy, and T stage should not be considered absolute contraindications. Dr. Black emphasized that the risk of complications should not solely determine the choice of diversion. He mentioned potential complications associated with ileal conduits and neobladders, such as parastomal hernias, stenosis, incontinence, retention, and urolithiasis. Regarding the quality of life, he stated that retrospective series have not shown the superiority of one technique over the other. Dr. Black discussed the components of the ERAS protocol, emphasizing the importance of multidisciplinary coordination, audits, and measuring goals. He acknowledged criticisms of the ERAS protocol for radical cystectomy, including the lack of prospective evidence, extrapolation of evidence from colorectal surgery, and inconsistency in the application of ERAS principles among the different studies. Despite this, retrospective evidence suggests a benefit of ERAS application in cystectomy, including faster bowel movement recovery, reduced need for nasogastric tubes for postoperative ileus, and lower readmission rates. Dr. Black also mentioned the potential addition of pre-habilitation to enhance the benefits of the ERAS protocol.

Bladder Preservation in MIBC

Dr. Gupta discussed bladder preservation strategies as an alternative to radical cystectomy. She highlighted the need for therapies with lower toxicity and comparable efficacy. Although prospective evidence is limited, meta-analyses and cohort analyses suggest similar survival outcomes between trimodal therapy (TMT) and radical cystectomy in selected patients. Dr. Gupta presented updated data from the Phase III BC2001 trial, showing that TMT achieved better locoregional control, cancer-specific survival, and lower salvage cystectomy rates compared to radiotherapy alone, without increased toxicity. She also mentioned ongoing studies exploring the addition of immunotherapy to TMT in high-risk NMIBC. These studies include SWOG/NRG1806 (Atezolizumab), KEYNOTE-992 (Pembrolizumab), EA 8185 (Durvalumab), and CCTG BL13 (adjuvant Durvalumab post-TMT).

Dr. Gupta highlighted trials exploring the possibility of avoiding cystectomy for patients who show a good response to neoadjuvant chemotherapy, with or without immunotherapy. She mentioned completed trials, such as RETAIN and HCRN GU16-257, as well as ongoing trials, including A031701 and RETAIN-2. The non-randomized RETAIN study enrolled patients with cT2-T3 N0 M0, ECOG 0-1, and predominant urothelial histology. After three cycles of MVAC chemotherapy, patients were assigned to active surveillance, intravesical therapy, TMT, or cystectomy based on T stage, follow-up TUR-B status, and sequencing of the primary tumor. The study showed a 2-year overall survival rate of 82%, with no statistically significant differences between surveillance and the other treatment approaches. However, the HCRN GU16-257 trial failed to show non-inferiority of bladder sparing compared to radical cystectomy. In this trial, patients received Gemcitabine + Cisplatin + Nivolumab for 4 cycles, and those with a complete clinical response skipped cystectomy and continued with 4 months of Nivolumab. The complete clinical response rate was 48%, and the primary outcome of 2-year metastasis-free survival is still pending.

Locally Advanced and Metastatic Urothelial Cancer

Dr. Gupta presented the new treatment standards for locally advanced and metastatic urothelial cancer. She discussed optimizing the use of immunotherapy and new treatments in these settings. Recent advances were reviewed, including the approval of immunotherapy drugs, FGFR inhibitors (Erdafitinib), and antibody conjugates (Enfortumab Vedotin and Sacituzumab Govitecan). She then discussed the importance of platinum-based regimens as first-line treatments for locally advanced and metastatic patients. Dr. Gupta mentioned the limited utilization of second-line treatment, even in developed countries. She also referred to the negative results of the IMvigor 130 (Atezolizumab) and Keynote-361 (Pembrolizumab) studies regarding the combination of chemo- and immunotherapy in advanced disease, with the pending results of the NILE study in this area. In addition, Dr. Gupta discussed studies investigating the combination of immunotherapies compared to standard treatment. She mentioned that the DANUBE study (Durvalumab + Tremillimumab) showed negative results for overall survival, while the Checkmate-901 study (Nivolumab + Ipilimumab) is still ongoing.

Shifting the focus to patients with advanced cisplatin-ineligible disease, she highlighted the therapeutic options over the past 6 years. Initially, the standard was Gemcitabine + Carboplatin, then single-agent immunotherapy (Atezolizumab, Pembrolizumab). However, FDA restrictions now limit its use to patients with high PD-L1 expression or platinum-ineligible status. The current standard treatment is still Gemcitabine-Carboplatin with maintenance Avelumab, based on the JAVELIN Bladder 100 trial findings. This phase III study showed that in platinum-treated metastatic patients who did not progress, maintenance Avelumab improved overall and progression-free survival. After 38 months of follow-up, the Avelumab group had a median overall survival of 23 months compared to 15 months in the standard care group. However, patients with visceral metastases showed less benefit from the maintenance of Avelumab, leading to the development of the Avelumab intensification concept. Another Phase III trial, MAINCAV, is currently underway, comparing maintenance Avelumab with Avelumab + Cabozantinib, using similar selection criteria as JAVELIN Bladder 100. Dr. Gupta also mentioned Pembrolizumab as the only immunotherapy agent with a Phase III trial (KEYNOTE-045) demonstrating improved overall survival compared to chemotherapy in the second-line treatment of metastatic disease.

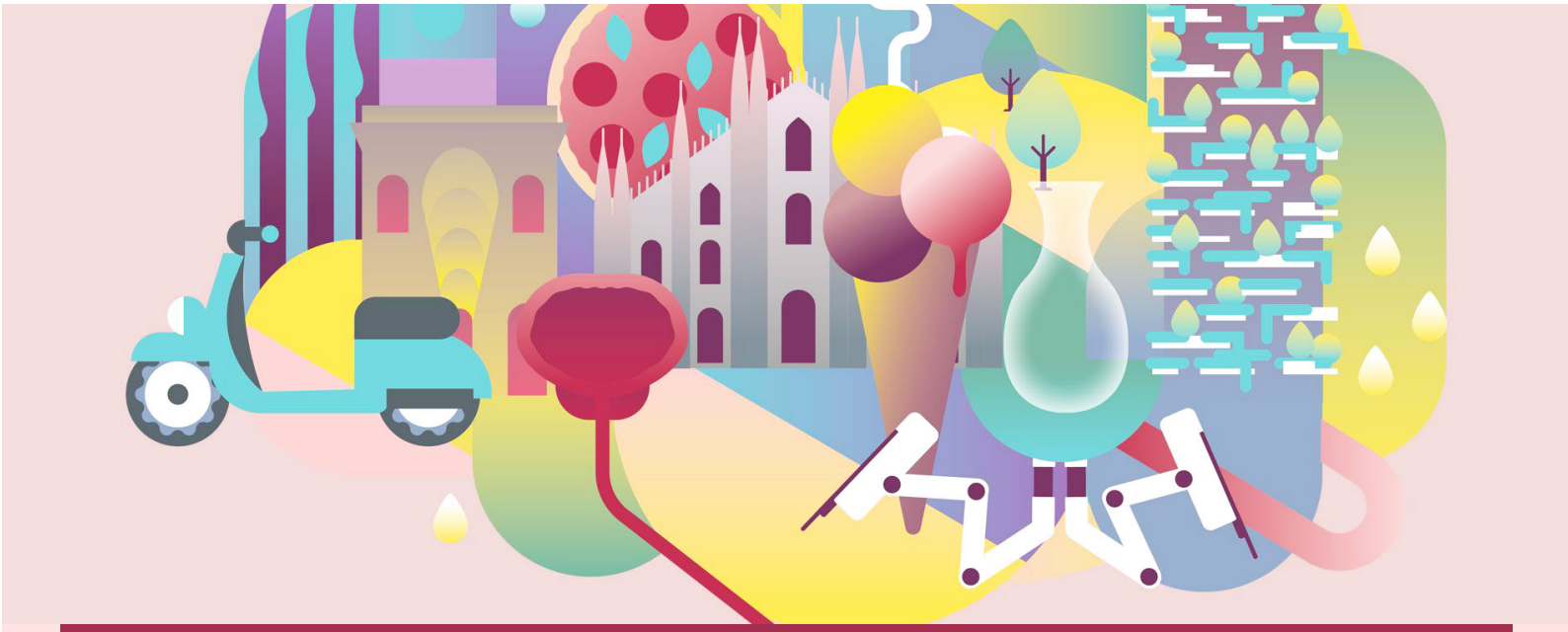
Dr. Gupta then introduced two new antibody conjugates, Enfortumab Vedotin (EV) and Sacituzumab Govitecan. She highlighted the EV-301 trial, a Phase III clinical trial that included patients who had progressed on prior chemotherapy and immunotherapy. The trial compared Enfortumab Vedotin with chemotherapy, and at 24 months of follow-up, Enfortumab Vedotin showed an overall survival of nearly 13 months, compared to 9 months in the chemotherapy arm. As a result, Enfortumab Vedotin has become a standard of care in Europe and North America. Dr. Gupta mentioned that the agent has a rapid onset of action but also cautioned about potential adverse events, including the risk of severe rash, hyperglycemia, and the development of diabetes. She noted that these drugs are not yet available in Chile.

She also discussed Erdafitinib, a promising FGFR inhibitor that has shown a high overall response rate in a single-arm study of patients with progression after chemotherapy and/or immunotherapy. The FDA has approved Erdafitinib for locally advanced or metastatic urothelial cancer. However, it is important to note that ocular toxicity is a potential side effect that resolves after the drug's discontinuation. Dr. Gupta also shared her definition of "platinum ineligible" criteria, which she presented at ASCO 2022 and will soon be published as guidelines for future clinical trials. These criteria apply to approximately 10% of patients, and currently, Pembrolizumab or Atezolizumab are the standard treatments for this subgroup. In the future, combinations of Enfortumab Vedotin (EV) and Pembrolizumab may receive approval for patients who meet the platinum-ineligible criteria, pending results from the EV-103 study. Additionally, the results of the EV-302 study, comparing Gemcitabine + Cisplatin to EV + Pembrolizumab, are expected to be presented within the next two years, potentially leading to a replacement of the current standard treatment. Dr. Gupta concluded her presentation by mentioning other promising novel agents, including the VEGF tyrosine kinase inhibitor Cabozantinib and the anti-HER2 conjugated antibody Trastuzumab Deruxtecan, which may have indications in combination with immunotherapy.

At the conclusion of the meeting, Dr. Kamat chaired a round table discussion on MIBC cases, joined by Drs. Suraj Samtani (Medical Oncologist, Clínica las Condes), Sergio Guzmán (Urologist, Clínica Universidad de Los Andes), Peter Black, Shilpa

Highlights of the IBCG Symposium on Bladder Cancer Part of the Annual Course of the Chilean Society of Urology 2023

Gupta, Joan Palou, and Diego Reyes (Urologist, Clínica BUPA, and Clínica las Condes). The panel deliberated on neoadjuvant chemotherapy regimens, the optimal number of cycles, and patients who may be eligible for neoadjuvant treatment avoidance. Dr. Kamat stated that at his center, pT2 patients without lymphovascular invasion, histological subtypes, or hydronephrosis are not offered neoadjuvant treatment, a stance supported by Dr. Palou. The urologists also discussed bimanual examination under anesthesia. During the discussion, Dr. Black noted the usefulness of a bimanual exam under anesthesia after completing a TURB for suspected muscle-invasive disease to distinguish between a complete resection and higher stages. Dr. Kamat presented a case of a patient with no disease after neoadjuvant treatment and questioned the appropriateness of bladder preservation, leading again to a discussion on the RETAIN trial. The consensus among Dr. Guzman, Drs. Palou and Kamat were that patients who achieve a T0 status benefit the most from standard treatment with radical cystectomy. The follow-up of pT0 patients after radical cystectomy was also discussed, with Dr. Samtani suggesting the incorporation of a multimodal follow-up and new tumor markers such as ct-DNA. Lastly, there was a brief mention of open versus robotic radical cystectomy and different types of urinary diversion.



European Association of Urology (EAU) 2023 Bladder Cancer Summary

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Non-Muscle Invasive Bladder Cancer

Two randomized studies investigated the efficacy of en bloc transurethral resection of the bladder tumor (TURBT) versus conventional TURBT in NMIBC patients. Diana et al (A0283) randomized 219 patients with stage < cT2 tumors, <3 cm, <4 lesions without variant histology and found the 1 year recurrence rate to be 8.9% versus 12.5% for en bloc versus conventional TURBT (p=0.88). Teoh et al (A0707) conducted a multicentre study, EB-STaR, including 276 NMIBC patients with <3 cm tumors who were randomized between both techniques. The 1 year recurrence rate was 38.1% versus 28.5% in favor of en bloc resection (p=0.007). The difference between these study outcomes might partly be explained by the heterogeneity in the populations studied. However, looking at the recurrence rate at different time points in the EB-STaR study it is striking that at the 3 month time point evaluation, the curves immediately diverge in favor of en bloc TURBT, indicating that the proportion of patients having residual tumors after conventional TURBT was much higher. This could be a reflection of the quality of surgery performed in the standard-of-care arm. In addition, the relapse curves converge strongly after the 12 months endpoint and with longer follow-up, the difference between both treatment arms might resolve.

Menguel et al (A0422) presented a small study (N=69, median follow-up 26 months) on the EpiCheck urine test in NMIBC patients treated with BCG. Positive EpiCheck post-BCG instillations were correlated with a 14-times higher risk of tumor recurrence. This study provides a rationale to initiate a study randomizing patients with negative post-BCG EpiCheck test results to surveillance with EpiCheck versus standard follow-up with cystoscopies +/- cytology.

Necchi et al presented in late-breaking abstract 06 the results of cohort B of the Keynote-057 study on pembrolizumab in patients with BCG-unresponsive papillary NMIBC without CIS and showed after a median follow-up of 45 months of the 12 months disease-free survival to be 43.5%. In patients with PD-L1 positive tumors, this was 54.1%. Previously, pembrolizumab was approved by the US Food and Drug Administration for BCG-unresponsive CIS of the bladder based on the results of cohort A of Keynote-057, which demonstrated a complete response rate of 41% at 3 months and 20% at 1 year. So, pembro seems to be an option in BCG-unresponsive papillary NMIBC patients, however, the costs, the intravenous administration, and the toxicity profile are not neglectable and should be weighed against novel intravesical therapies, such as nadrofaragene firadenovec and BCG + IL15 superagonist.

Muscle-Invasive Bladder Cancer

Heck et al presented the long-term results of the German LEA trial (LB07) in which patients with bladder cancer undergoing radical cystectomy were randomized between standard versus extended lymph node dissection (LND). Previously, the study was reported to be negative for the primary endpoint, which was the time to progression. Remarkably, the lymph node yield in the standard LND was high with a median yield of 19 versus 31 in the extended LND group. At EAU23, Heck et al demonstrated that the 5 year time to progression, overall and cancer-specific survival were all better in the eLND group: 68%, 57%, and 76% versus 60%, 51%, and 65%, although only the latter was statistically significantly different ($p = 0.03$). At the costs of more grade >II complications and longer operation time, a more extensive LND had a positive impact on the prognosis of bladder cancer patients undergoing radical cystectomy.

Abstract A1297 by Marcq et al reported a large inverted probability treatment weighted analysis of almost 600 patients who received whole-pelvis versus bladder-only radiation with curative intent. After a median follow-up of 34 months, both cancer-specific and overall survival was better in the whole-pelvis treated group. So, both extensive surgery and radiation seem to contribute to patient outcomes.

Lymph Node-Positive Bladder Cancer

Von Deimling et al (A0547) reported 269 clinically node-positive bladder cancer patients who received induction chemotherapy, either cisplatin- or carboplatin-based. The pathological complete response (pCR) rate was 18% versus 13% for cisplatin versus carboplatin ($p = 0.4$) but the overall survival of cisplatin-treated patients was significantly better. Whether this reflects a true difference in the efficacy of the therapy administered in this high-risk population remains questionable given the similar pCR rates of both regimens. In addition, cisplatin-fit patients have better performance overall, better kidney function, and fewer comorbidities. Therefore, the results of this retrospective study have to be interpreted with caution.

Metastatic Bladder Cancer

Klumper et al (A0541) performed a translational study on the immunohistochemistry expression of Nectin-4 among 137 matched primary-metastatic biopsied samples. Nectin-4 is a target of Enfortumab Vedotin (EV), an antibody-drug conjugate that was recently approved as second-line therapy in patients with metastatic urothelial cancer. EV binds to Nectin-4 leading to the release of the cytotoxic payload MMAE, leading to disruption of microtubules and eventually cell death. It was previously assumed that Nectin-4 expression was ubiquitous in urothelial cancer but this study showed that 40% of metastatic urothelial cancer samples did not express Nectin-4 and that the level of expression decreased from primary to metastases in 50% of cases. The findings were translated into the clinical setting showing that the progression-free survival was worse in patients with tumors harboring attenuated Nectin-4 expression and who were treated with EV. These results provide a rationale to biopsy all patients with metastatic urothelial cancer who are candidates for treatment with EV given the significant toxicity of EV and accompanying costs.

Now in our 18th year, **the Bladder Cancer Advocacy Network has provided more than $6 million in research funding** to end bladder cancer. And we're just getting started.

At the Bladder Cancer Advocacy Network (BCAN), we believe that today's medical research is the engine that drives tomorrow's better lives for patients and those who love them.

Our goal is to identify the best and most promising medical research to advance our understanding of bladder cancer. BCAN awards grants to support early and seasoned investigators performing innovative research to develop lifesaving treatments and improve patient outcomes.

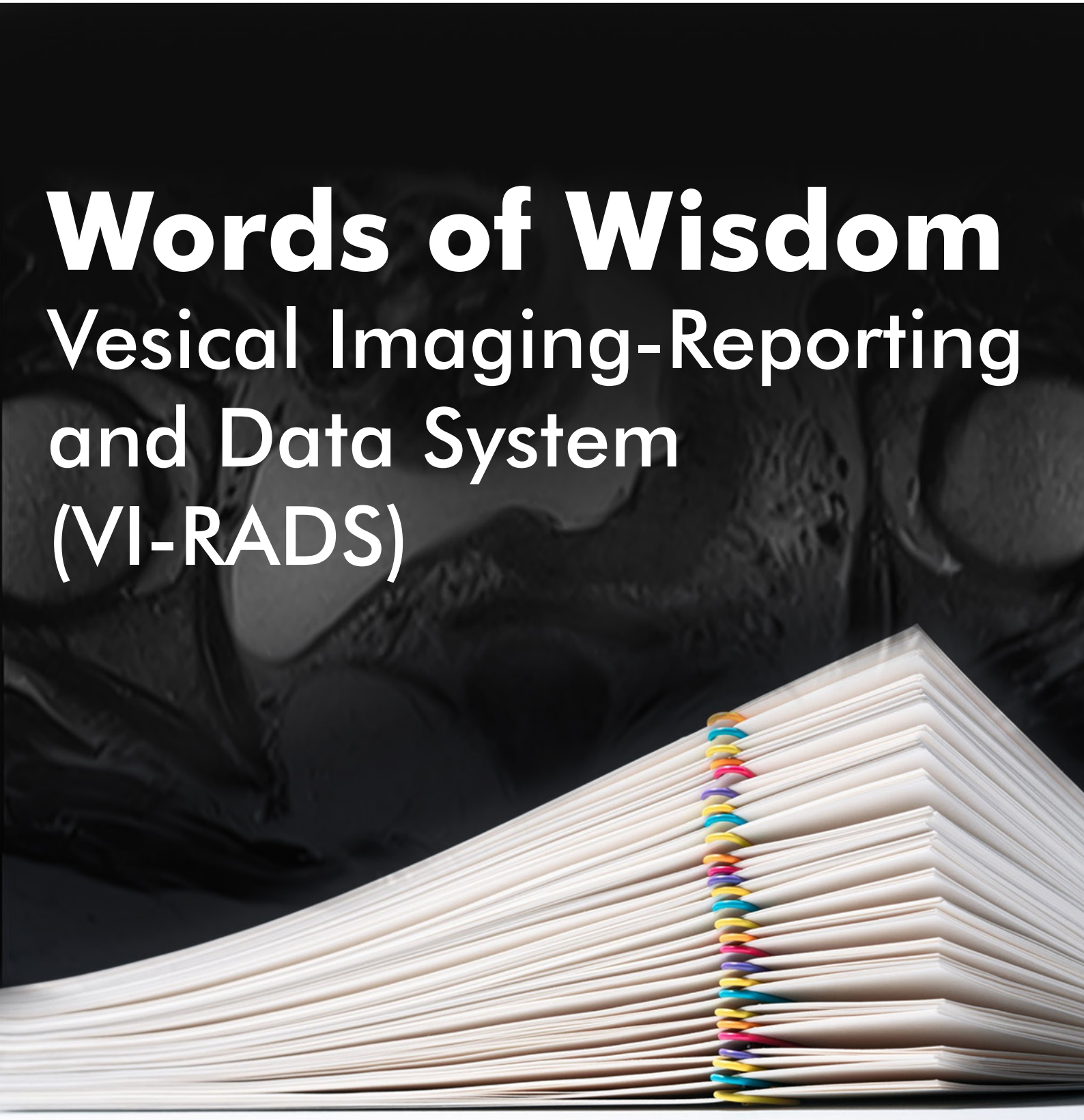
To learn more about BCAN's research program and grant funding, please visit **bcan.org/research**.

BCAN
Bladder Cancer Advocacy Network

Join us for our **Walks to End Bladder Cancer** in the Spring of 2023. Our in-person and virtual walks raise spirits and raise funds to defeat bladder cancer. Please visit **bcanwalk.org**.

Words of Wisdom

Vesical Imaging-Reporting and Data System (VI-RADS)



Diagnostic Value of the Vesical Imaging-Reporting and Data System in Bladder Urothelial Carcinoma with Variant Histology

Word of Wisdom - Vesical Imaging-Reporting and Data System (VI-RADS)

Experts' Summary:

This retrospective analysis of 360 consecutive patients (255 pure urothelial carcinoma (UC), 69 variant UC) with bladder cancer evaluated Vesicle Imaging-Reporting and Data System (VI-RADS) scores which were accessed by four readers. In a pair-matched analysis of 122 patients, there were no differences between VI-RADS between pure UC and variant UC. The receiver operating characteristic (ROC) curve for pure UC and variant UC for muscle-invasive bladder cancer (MIBC) was 0.93–0.94 and 0.89–0.92 respectively with no significant difference in the performance between the two cohorts. The authors suggest that VI-RADS achieves excellent diagnostic performance for the detection of MIBC in both pure UC and variant UC.

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Experts' Comments:

In this retrospective analysis of patients undergoing MRI pre-Transurethral resection of bladder tumor (TURBT), Arita et al. provide evidence that the diagnostic performance of VI-RADS for the identification of MIBC in variant UC is excellent and comparable to that of pure UC. It is important to appreciate that the authors did not evaluate patients with non-UC pathology such as pure adenocarcinoma and squamous cell carcinoma of the bladder. The study was conducted across two different centers using 1.5 T MRI machines and VI-RADS was accessed by four blinded board-certified radiologists. The authors also performed a propensity score match analysis of 122 patients (1:1 ratio) in their attempt to minimize differences in patient and pathological variables.

Utilizing a threshold of VI-RADS of ≥3 the sensitivity and specificity for the detection of MIBC ranges from 88-94% and 75-82% respectively. Adopting a VI-RADS threshold of ≥4 reports a sensitivity of 76-85% and specificity of 86-93% for the identification of MIBC. There was no difference between pure UC and variant UC. There was a good agreement based on Fleiss' kappa values of 0.84/0.81 for the overall VI-RADS score, 0.75/0.68 for T2WI scores, 0.84/0.74 for DWI scores, and 0.84/0.77 for DCE-MRI scores suggesting results were generalizable. The radiologists should be commended restricted use of VI-RADS score 3 (pure UC: 8-12%, variant UC: 12-13%) following propensity score matching. They also appropriately used radical cystectomy as the reference standard for MIBC diagnosis in patients without preoperative chemotherapy and TURBT histology as the reference standard if radical cystectomy was not performed or if preoperative chemotherapy was administered.

However, it is important to appreciate important limitations in the study. Prior to propensity score matching, there were clear differences in the two patient cohorts. Patients with variant UC were less likely to be male (77% vs 88%, p=0.04), had a larger tumor diameter (21 mm vs 15 mm, p=0.01), higher rate of T3-4 (20% vs 6%, p<0.001), higher rate of high-grade cancer (62% vs 47%, p=0.03). Despite, propensity score matching for sex, lesion diameter, pathological muscle invasion status, and pathological tumor grade, sessile/broad-based tumors (69% vs 36%, p<0.001) and use of perioperative chemotherapy (28% vs 12%, p=0.02) were more common in the variant UC cohort compared to pure UC. Additionally, squamous and glandular differentiation accounted for 77% of the entire variant UC cohort hence results may not be generalizable for all variant histology.

Moreover, it is important to consider the significance of identifying MIBC before TURBT. The ongoing BladderPath Study, which reported outcomes for their first 100 patients in their evaluation of an MRI pathway to expedite patients with MIBC by avoiding a TURBT and proceeding straight to radical treatment [1]. While the performance of MRI for the detection of MIBC is commendable, it remains inferior to TURBT in terms of staging, and

decisions made solely based on MRI would risk over treatment. Further, it is estimated that 80% of new bladder cancer patients diagnosed are NMIBC which would be managed by TURBT anyway even after an MRI-based approach [2]. Hence, the proposal to perform a preTURBT MRI on all newly diagnosed bladder cancer patients for the betterment of 25% of MIBC seems like an excessive waste of healthcare resources. Rather, it would make more sense to invest in expediting current early diagnosis pathways and rapid access to a urology consult and prompt TURBT rather than advocate for a preTURBT MRI. Unless a more effective method is identified utilizing serum or urinary biomarkers or the current standard of care imaging such as CT scans to identify the patients who are at higher risk of MIBC, we suspect that there will be low uptake for the role of preTURBT MRI for bladder cancer [3, 4].

Conflict of Interest:

AM owns equities of Oltre Medical Consulting, LLC, Toulouse (FR).

References

1. Bryan RT, Liu W, Pirrie SJ, Amir R, Gallagher J, Hughes AI, et al. Comparing an Imaging-guided Pathway with the Standard Pathway for Staging Muscle-invasive Bladder Cancer: Preliminary Data from the BladderPath Study. European Urology. 2021;80:12-5.
2. Nielsen ME, Smith AB, Meyer A-M, Kuo T-M, Tyree S, Kim WY, et al. Trends in stage-specific incidence rates for urothelial carcinoma of the bladder in the United States: 1988 to 2006. Cancer. 2014;120:86-95.
3. Tan WS, Tan WP, Tan M-Y, Khetrapal P, Dong L, deWinter P, et al. Novel urinary biomarkers for the detection of bladder cancer: a systematic review. Cancer treatment reviews. 2018;69:39-52.
4. Khetrapal P, Lee MWL, Tan WS, Dong L, de Winter P, Feber A, et al. The role of circulating tumor cells and nucleic acids in blood for the detection of bladder cancer: A systematic review. Cancer Treatment Reviews. 2018;66:56-63.

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