INTERNATIONAL
BLADDER CANCER GROUP (IBCG)

IBCG

International Bladder Cancer Group

Newsletter

Volume 2

Index

Chief Editor

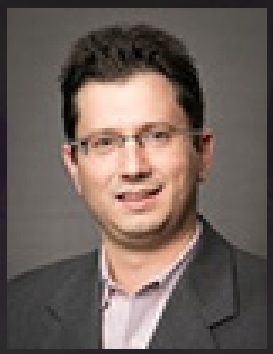
Prof. J.A. Witjes

Professor in oncological urology,
Radboud University Medical Center, Netherlands

Editorial Team

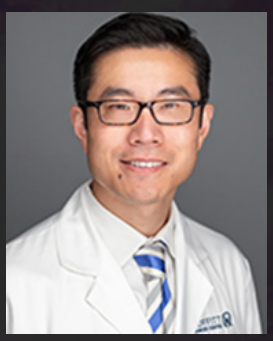
Sima Porten

Chair, 2022 BCAN Bladder Cancer Think Tank
Member, Multidisciplinary urologic oncology team,
UCSF Helen Diller Family Comprehensive Cancer Center



Dr. Petros Grivas

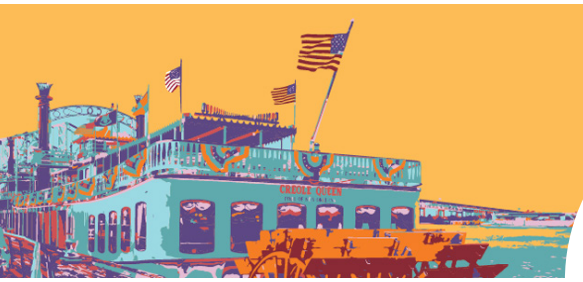
MD, Division of Oncology,
Seattle Cancer Care Alliance and Fred Hutchinson Cancer Research Center



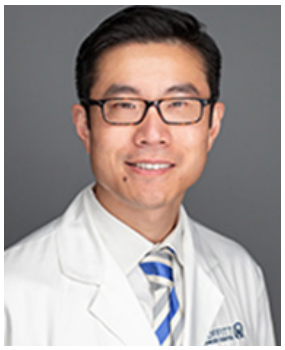
Dr. Roger Li

Assistant Member-
Department of Genitourinary Oncology H.LEE. MOFFIT Cancer Center

Articles



NMIBC Roundup



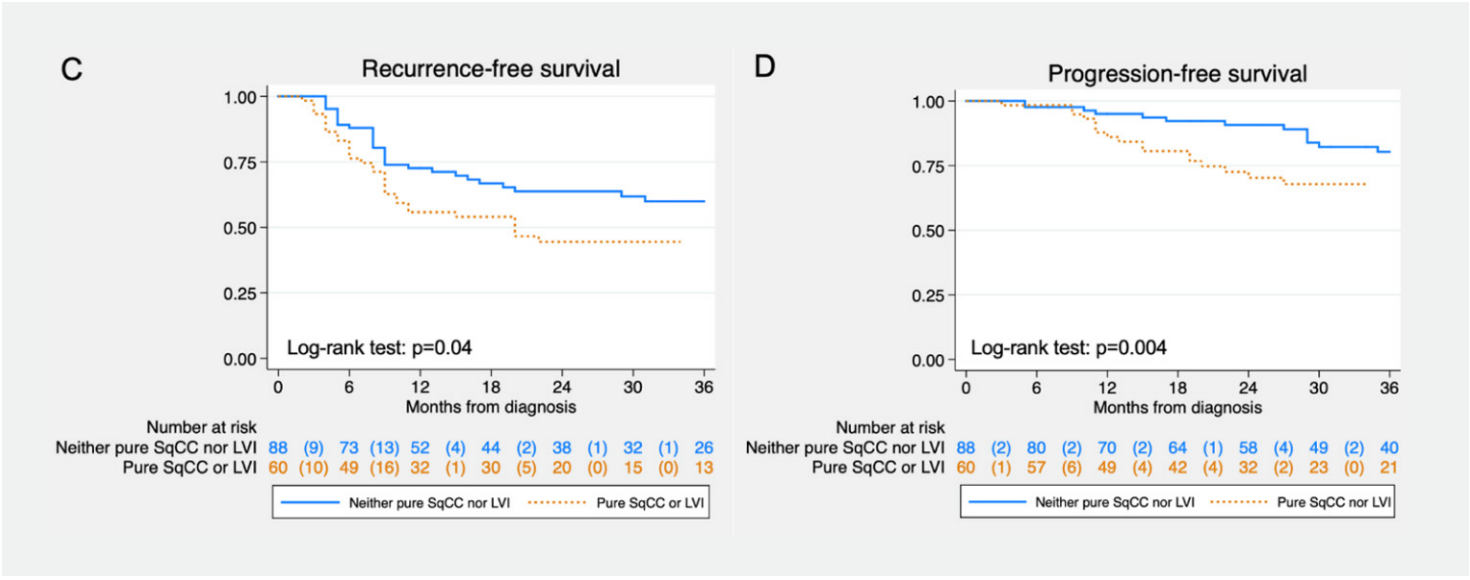
Roger Li, MD

Assistant
Member- Department of Genitourinary Oncology
H.LEE. MOFFIT Cancer Center

To Cystectomy or Not to Cystectomy

T1HG bladder tumors always present a management conundrum. Although these tumors exhibit signs of invasion and high propensity to progress, a significant proportion of the patients will respond to Bacillus Calmette-Guerin (BCG), and keep their bladders intact. This is especially the case in the setting of variant subtypes, whose response to BCG, the standard of care, is less known.

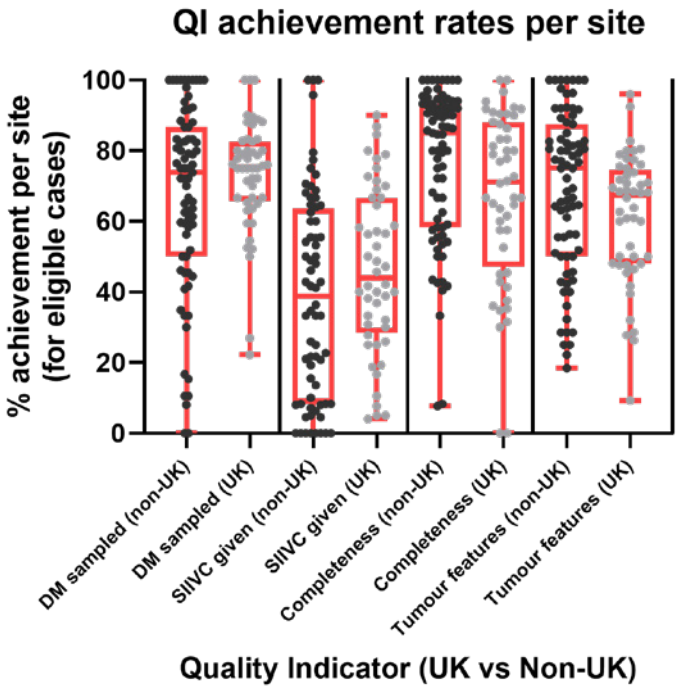
Lonati et al reported on a retrospective study comparing survival outcomes following upfront radical cystectomy vs. conservative management for T1HG squamous bladder cancer. The authors report no cancer specific or overall survival differences in the two studies. 41% of the patients treated conservatively suffered cancer recurrence, while 24% had tumor progression. On multivariate analysis, pure squamous tumors (HR 2.40, p=0.04) and the presence of lymphovascular invasion (HR 2.19, p=0.04) were independent predictors of cancer progression. These results suggest possible resistance to intravesical BCG treatment in patients with tumors that are of pure squamous histology and/or with LVI. When these are detected, upfront cystectomy or other novel conservative treatment agents should be considered.



Resect

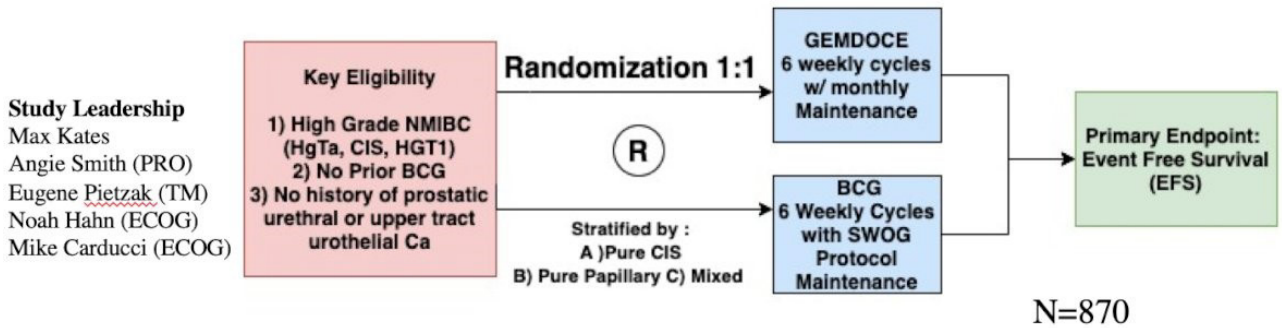
The technique for Transurethral Resection of a Bladder Tumor (TURBT) has long been recognized to be one of the main drivers of quality management of bladder cancer. Transurethral REsection and Single instillation intra-vesical chemotherapy Evaluation in bladder Cancer Treatment (RESECT) is a global, multi-centered observational study aimed to determine whether audit and feedback can improve the quality of TURBT surgery and reduce early recurrence rates. In a baseline analysis, the investigators attempted to evaluate the quality of the TURBT by measuring 4 pre-determined quality indicators (QI)– sampling of the detrusor muscle (in tumors >5mm), instillation of perioperative intravesical chemotherapy within 24 hours, documentation of completeness of TURBT, and documentation of tumor number, size, and location. Altogether,

documentation from 3,193 TURBTs from 175 sites in 40 countries were examined. There was wide variation both within and between countries in the quality of the TURBT. Median achievement of obtaining detrusor muscle was 75%, 41.7% for perioperative intravesical chemotherapy, 80% for documentation of completeness of resection, and 68.4% of all other tumor characteristics. Through establishing the baseline in the variability of the quality of resection and documentation, the
the investigators are now poised to assess whether targeted feedback may improve the performance of TURBT and to reduce recurrence rates.



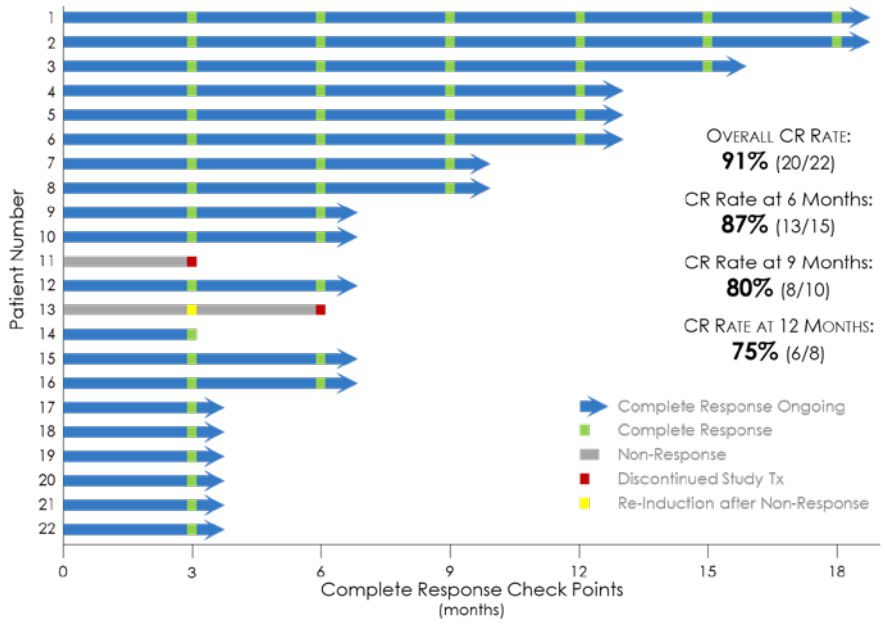
Gem/Doce takes center stage for the treatment of high-risk NMIBC

For over four decades, intravesical BCG has remained the gold standard adjuvant treatment for high risk, non-muscle invasive bladder cancer (NMIBC). Hampered by the current shortage in North America, many patients are getting inadequate treatment and there is a dire need for an alternative treatment. Previously, a combination intravesical chemotherapy using gemcitabine and docetaxel (gem/doce) was deployed in the BCG refractory setting and demonstrated effectiveness. Spurred on by its success in the BCG refractory setting, several investigators have transplanted gem/doce's use into the BCG-naïve setting, particularly during the contemporary era of BCG shortage. From the birthplace of this combination (University of Iowa) came a study led by Dr. Ian McElree on the effectiveness of gem/doce in 107 patients with BCG-naïve high-risk NMIBC treated between 2013-2021. Induction course consisted of 6 weekly intravesical infusions, while monthly maintenance of 2 years were attempted. Recurrence free survival at 6, 12, and 24 months were 89%, 85%, and 82%, respectively. Impressively, no patient experienced disease progression. Common symptoms included urinary frequency/urgency (36%), hematuria (11%), and dysuria (8%). Another Phase 2 study led by Dr. Sunil Patel from Johns Hopkins in 14 patients with BCG-naïve high risk NMIBC, 100% had CR at 3 month follow-up, and 3 patients demonstrated durable CR at 12 months. These results further solidify the accumulating clinical data on the efficacy of intravesical gem/doce as frontline treatment in BCG-naïve high-risk NMIBC patients. We look forward to the launch of the phase 3, randomized, cooperative group sponsored BRIDGE trial to test the efficacy of intravesical BCG vs. gem/doce in BCG naïve NMIBC patients.



Combination CG0070 and Pembrolizumab in patients with BCG unresponsive CIS

CG0070 is an Ad-5 based oncolytic virus engineered to express GM-CSF and replicates selectively in tumor cells with mutated or deficient RB proteins. It acts through a dual pronged attack, causing tumor cell lysis and subsequent immunogenic cell death. Intravesical CG0070 has previously demonstrated efficacy in an open label phase 2 study in BCG refractory patients, demonstrating CR rate of 62% and 29% at 12 months. IV pembrolizumab, a PD-1 inhibitor, has demonstrated 40% CR rate at 3 months in patients with BCG unresponsive CIS, with a durable response of ~20% at 12 months. The investigators hypothesized mechanistic synergism between CG0070 + pembrolizumab, and launched CORE1, a phase 2 open label study combining these two agents treating patients with BCG unresponsive CIS. This study aims to accrue 35 patients to be treated with intravesical CG0070 (1x1012vp) in combination with pembrolizumab at the standard, q6 weekly dosing. CG0070 is administered weekly x 6 as induction, followed by weekly x 3 maintenance instillations at months 3, 6, 9, 12, and 18. Primary endpoint of the study is CR at 12 months as obtained via cystoscopy, urine cytology and random bladder biopsy. At the time of presentation, 22 patients have reached 3 months mark, with 20/22 (91%) achieving CR. Of 8 patients reaching the 12 months mark, 6 had durable CR. Adverse events were mainly limited to bladder related toxicity, including polyuria, bladder spasms, and dysuria. No drug related serious adverse events were found. CG0070 and pembrolizumab represent a promising combination in the treatment of BCG Unresponsive CIS.



Urine microRNA as liquid biopsy predictive of response to BCG

Despite its success, 30-50% of the patients treated with intravesical BCG fail to derive durable response and up to 15% of the patients progress to muscle invasive/metastatic disease. As tissue samples prior to BCG treatment may be too scant for molecular profiling, Mitra and colleagues attempted to explore the use of urinary microRNA (miRNA) as a liquid predictive biomarker. Using the amplification-free nCounter platform, the investigators analyzed miRNA profiles in a discovery cohort of 52 responders and 28 non-responders and validated their findings in a cohort of 26 responders and 14 non-responders. A 233-feature random forest classifer was constructed to achieve a sensitivity of 81% and specificity of 64%. Using the 35 highest ranked features, another abridged classifier was able to achieve sensitivity of 85% and specificity of 68%. Urinary miRNA profiling appears to be a promising predictive platform to predict response to BCG.

MIBC highlights of the 2022 New Orleans AUA

Fred Witjes
Nijmegen, NL

MP 03-02 from a group from Florida, looked at the value of a visibly complete TURBT in case in invasive bladder cancer (BCa), something urologists are inclined to pursue. Interestingly they found that a visibly complete transurethral resection (TURBT) was NOT associated with final pathologic response following neoadjuvant chemotherapy (NAC) and radical cystectomy (RC). These results, for example, do not support the need for a repeat TURBT to achieve a visibly complete resection of a muscle-invasive tumor if NAC and RC are planned. Data from the ongoing randomized phase II/III (BladderPath) study are awaited.

The discussion about the advantage of a PET/CT above a "normal" CT is ongoing. MP 03-06 from the Netherlands found that FDG-PET/CT was not more accurate than conventional enhanced CT for assessment of response to NAC. However, both imaging techniques were not very accurate and response was often overestimated, suggesting other techniques are needed.

One of these techniques might be MRI. The recently published VI-RADS (Vesical Imaging-Reporting And Data System) score, is thought to be useful in discriminating T1 and T2a tumors and in the follow up of tumors during chemotherapy. PD 42-08 from Texas evaluated the value of bladder cancer MRI in the real-world setting. Indeed, MRI showed high performance in ruling out MIBC in patients undergoing re-TURBT, but also in predicting the presence of residual disease prior to cystectomy. These findings support the continued refinement of MRI in bladder cancer and as a potentially important adjunct in specific scenarios, such as monitoring tumors during NAC.

RC, still being the standard of care for MIBC patients, was highlighted in PD 42-02, a multicenter study from the UK on intracorporeal versus open RC and diversion (iROC trial). The results of this trial showed that patients undergoing intracorporeal robot assisted RC (iRARC) spent fewer days in hospital within 90 days of surgery, and may have quicker recovery than open RC. No difference was detected in overall or cancer specific survival. The full publication can be found in JAMA June 2022.

However, besides RC multi-modality or tri modality treatment (TURBT and chemotherapy as radiosensitizer and radiotherapy, TMT) is becoming more and more popular as bladder preserving alternative. A comparison between RC and TMT was presented in PD 42-01. This large multi-institutional study supports that TMT for select MIBC patients, eligible for both RC and TMT, provides oncologic outcomes equivalent to RC. TMT should therefore not be reserved to candidates not eligible for surgery, but offering TMT to all suitable candidates could provide patients with a choice of treatments.

A Japanese group presented their results on the relevance of side effects during pembrolizumab treatment in MP 03-19. I remember that for a long time urologists thought that for example more BCG toxicity in NMIBC treatment was a good sign and suggested a better treatment outcome, which was not true in the end. This Japanese multi-institutional study showed that presence of immune related adverse events (AE's) was significantly associated with progression free survival (PFS) and overall survival (OS) in metastatic urothelial cancer patients treated with pembrolizumab. Their suggestion was that presence of immune related AE's may be used as a surrogate prognostic marker for PFS and OS in this treatment regime. I assume we need more data to support this, but the findings are not illogical and interesting.

Finally, in another presentation on immunotherapy, an international group confirmed in PD10-01 the effect of nivolumab (NIVO) after surgery for muscle invasive urothelial carcinoma, in patients with still tumor present after RC, with or without NAC, and with longer follow-up as the original publication, NIVO continued to show clinically meaningful improvement in DFS vs placebo for these patients at high-risk after surgery for muscle invasive urothelial carcinoma. The advantage was confirmed in both ITT pts and in points with PD-L1>1%. Again, supporting adjuvant NIVO as a standard of care for high-risk MIUC points after radical surgery.

BCAN
Bladder Cancer Advocacy Network

THINK TANK 2022

BCAN Think Tank 2022

Patrick J. Hensley

Department of Urology, University of Kentucky College of Medicine, Lexington, KY, USA

Petros Grivas

Division of Medical Oncology, Department of Medicine, University of Washington Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Sima P. Porten

Department of urology, University of California San Francisco, San Francisco, CA, USA

After a several-year hiatus of in-person meetings, the 17th annual Bladder Cancer Advocacy Network (BCAN) Think Tank was held from August 3-5, 2022 in Denver, Colorado. Since its inception in 2006, the Think Tank has become the premier bladder cancer meeting in North America, marked by a gathering of thought leaders in bladder cancer clinical care, research, and patient advocacy disciplines. This year's meeting was chaired by Drs. Sima Porten (UCSF) and Bishoy Faltas (Weill Cornell Medical College). In addition to the plenary sessions discussed below, this year's meeting exhibited state-of-the-art breakout discussions on topics including next generation trials in NMIBC, exposures to environmental contaminants associated with bladder cancer, survivorship challenges, and health equity in bladder cancer care and access to care.

The meeting was kicked off on Wednesday with a compelling Patient Voice Panel lead by BCAN co-founder Diane Zipursky Quale, where patients who have survived bladder cancer along the spectrum of non-muscle invasive disease to recurrent, metastatic disease after radical cystectomy, discussed their experiences from diagnosis to survivorship. The patients provided their testimonials on their emotional and physical preparedness for their bladder cancer journey and some of the fundamental and lasting changes that their treatments have had on their lives.

The first night concluded with research funding announcements supported by BCAN, including the new Bladder Cancer Career Development Award which supports junior investigators who have not yet received major independent research funding for up to three years of translational, clinical or epidemiological bladder cancer research

https://bcan.org/bcan-research/grants-and-research-funding-opportunities/bladder-cancer-career-development-award/

Day two included presentations by the 2020 and 2021 BCAN Young Investigator awardees, Dr. Rusty Johnson, MD, PhD, a Medical Oncology Fellow at the Johns Hopkins Greenberg Bladder Cancer Institute ("Gender-specific Stratification of Survival Following Immune Checkpoint Inhibitor Therapy Based on Intratumoral Expression of a B cell Gene Signature") and Dr. Yuki Kita, MD, PhD, a Medical Oncology Fellow at the University of North Carolina ("NRF2 activation promotes a basal-like phenotype but a fitness disadvantage in normal urothelium"). Presentations were also given by the 2020-2021 Patient Centered Clinical Young Investigators Dr. Matthew Mossanen, MD, MPH, a urologic oncologist at the Brigham and Women's Hospital and Dana Farber Cancer Institute ("Factors Associated with Smoking Cessation: A Survey of Bladder Cancer Patient and Provider Perspectives on How to Quit") and Dr. Svetlana Avulova, MD, a urologic oncologist at Albany Medical Center ("Sexual Function in Women Undergoing Radical Cystectomy").

Presentations were also given by the 2019 and 2020 BCAN Bladder Cancer Research Innovation Awardees. Dr. Philip Beachy, PhD, from Stanford University School of Medicine in Stanford, CA received the award in 2019 and his team's work titled "Targeting Urothelial Basal Cells in Transdifferentiation and Non-muscle Invasive Bladder Cancer" was presented by his college Dr. Kris Prado, MD, a urologic oncologist also at Stanford University. The authors presented a proof of principal concept that that urothelial stem cells can be engineered from fibroblasts using a minimal set of transcription factors. Additionally, basalization of the non-tumor urothelium, often considered an early step to urothelial carcinogenesis, was modifiable and reversable with pharmacologic intervention. Dr. Jeffrey Ravetch, MD, a Professor of Immunology, Virology, and Microbiology at Rockefeller University in New York, NY received the award in 2020. His work titled "Defining and testing

novel immunotherapy combinations for NMIBC" was presented by Dr. David Knorr, MD, PhD, a medical oncologist a Memorial Sloan Kettering Cancer Center. CD40 stimulation drives anti-tumor immunity and is highly expressed on B cells. The investigators evaluated novel strategies for CD40 agonism as a therapeutic strategy in NMIBC, which is currently being investigated in a Phase I/II study at Memorial Sloan Kettering for BCG unresponsive disease.

The second day's sessions concluded with two plenary discussions on novel bladder cancer screening and diagnostic paradigms. Drs. Yair Lotan (UT Southwestern), Philip Abbosh (Fox Chase Cancer Center) and Minetta Liu (Natera) discussed the role of early bladder cancer screening in high-risk populations. The panel discussed the balance between the benefits of early detection, including early-stage migration and how this might correlate with improved survival outcomes vs. the costs associated with broad screening programs. They discussed how novel biomarkers, including urine and serum-based markers, may better inform at-risk populations compared to conventional hematuria screening. The session concluded with a discussion on the use of artificial intelligence in bladder cancer research and clinical care, lead by panelists Drs. Randy Sweis (University of Chicago), Shilpa Gupta (Cleveland Clinic), Alexander Pearson (University of Chicago) and Bishoy Faltas (Weill Cornell Medicine).

Day three was kicked off by presentations from 2021 BCAN Young Investigator Awardees Dr. Filipe LF Carvalho, MD, PhD, a urologic oncologist at the Brigham and Women's Hospital in Boston, MA ("Clonal architecture and tumor microenvironment of cisplatin resistant localized muscle-invasive bladder cancer"), Dr. Brendan Guercio, MD, a medical oncology fellow at the Memorial Sloan Kettering Cancer Center in New York, NY ("Investigating diet and benefit from immune checkpoint blockade in urothelial cancer"), Dr. Benjamin Miron, MD, a urologic oncology fellow at the Fox Chase Cancer Center in Philadelphia, PA ("Relationship of Circulating Tumor DNA in Patients with Muscle Invasive Bladder Cancer to Pathologic Staging and Disease Prognosis"), and Dr. Eugene Pietzak, MD, a urologic oncologist at the Memorial Sloan Kettering Cancer Center in New York, NY ("Defining the Clinical Impact and Molecular Drivers of "Secondary" Muscle-Invasive Bladder Cancer").

The meeting concluded with a captivating, interactive discussion on the current state of bladder preservation in muscle-invasive disease. The panel included expert urologic oncologists, medical oncologists, radiation oncologists as well as testimonials from patient advocates who detailed their personal experience with urinary diversion. The limitations of contemporary clinical staging modalities, including imaging and post-chemotherapy bladder biopsies, as well as ongoing trials investigating predictive molecular biomarkers for cisplatin-sensitivity to inform patient selection for bladder preservation were discussed.

BCAN will also be hosting the Bladder Cancer Summit for patients and families September 30 – October 1, 2022 at the Westin Baltimore Washington Airport (BWI) Hotel. This event brings together bladder cancer patients, survivors, and caregivers to share stories, experiences, and information about the disease with this year's theme being "Staying well and thriving while surviving".

Patient Forum 2022 Bladder Cancer Advocacy Network (BCAN) Think Tank

BCAN
Bladder Cancer Advocacy Network

BCAN Funds Two **New Research Awards** to Provide a Better Tomorrow for Patients

Bladder cancer research is critical to improve the prevention, detection, and treatment of the disease and ensure that survivors live longer, better quality lives. To continue propelling research and creating new possibilities, during the annual Think Tank meeting held in August of 2022, BCAN announced that it is funding two new bladder cancer research awards to help build a better tomorrow for patients and those who love them.

BCAN Funds Two New Research Awards to Provide a Better Tomorrow for Patients

BCAN
Bladder Cancer Advocacy Network

Translational Clinical Trial Award

The first award announced is the first-ever Translational Clinical Trial Award (TCTA) that supports patient-oriented research to transform bladder cancer care. The award will provide a maximum of $3 million in funding over 36 months to spark changes to the standard of care in bladder cancer, decrease overtreatment, and significantly impact patient outcomes.
This award is being funded through a generous grant from BCAN Board Member Mr. Duncan Alexander, a business leader with a long history of giving back through his philanthropic contributions.

Through this award, BCAN seeks to bring enhanced urgency to the process of bladder cancer research and to support projects with novel approaches unlikely to be funded by industry or other sponsors. Rather than supporting basic research which results in general knowledge and understanding of a disease, this award will fund translational research and clinical trials and have a more immediate impact on bladder cancer treatments and approaches to medical care.

Applications closed on October 18,2022 and TCTA award recipients will be announced in February 2023.

Career Development Award

In September 2022, BCAN began accepting applications for its first-ever Career Development Award (CDA). This award will support junior investigators who have yet to secure their first major research funding who aim to establish an independent bladder cancer research program and successful career path. The CDA is a three-year grant totaling $250,000 that will fund research that has direct relevance to bladder cancer.

The CDA is designed is designed to compliment BCAN's other research awards and address the research needs of investigators who are in the middle part of their careers. BCAN's Young Investigator Awards provide funding for early-career investigators and its Research Innovation Award is presented to seasoned bladder cancer medical professionals.
Applications closed on October 18, 2022 and the awardee will be announced in January 2023.
Generosity fuels bladder cancer research

BCAN raises funds and awards to develop lifesaving treatments and improve patient outcomes. None of our research awards would be possible without the generosity of our wonderful donors and corporate partners. We are very grateful.

To learn more about BCAN's grants and research funding opportunities, Please visit

https://bcan.org/bcan-research/grants-and-research-funding-opportunities/

Scan this QR Code

Now in our 17th year, **the Bladder Cancer Advocacy Network has provided more than $5 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 2022. Our in-person and virtual walks raise spirits and raise funds to defeat bladder cancer. Please visit www.bcanwalk.org

IBCG Health Services Research and Population Health

Patrick J. Hensley

Department of Urology, University of Kentucky College of Medicine, Lexington, KY, USA

Sima P. Porten

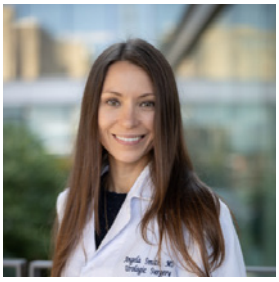
Department of urology, University of California San Francisco, San Francisco, CA, USA

A mission of the International Bladder Cancer Group is to improve global bladder cancer outcomes through evidence-based treatment. The Health Services Research (HSR) arm of the IBCG is fundamental to this mission, and aims to be a collaborative source for global clinicians and researchers to improve population health of bladder cancer patients.

The HSR arm is lead by Dr. Stephen Williams, Professor and Chief of Urology at the University of Texas Medical Branch, USA. This multidisciplinary, international HSR team includes Sia Daneshmand (University of Southern California, USA), Petros Grivas (University of Washington, USA), Shilpa Gupta (Cleveland Clinic, USA), Patrick Hensley (University of Kentucky, USA), Niyati Lobo (London, UK), Yair Lotan (University of Texas Southwestern, USA), Hugh Mostafid (Nuffield Health, UK), Sima Porten (University of California, San Francisco, USA), Sarah Psutka (University of Washington, USA), Shahrokh Shariat (Medical University of Vienna, Austria), and Angela Smith (University of North Carolina, USA).

There have been several high-impact publications from this group, highlighted by a recent study by Bree et al. published in JAMA Network Open. The authors evaluated surveillance and treatment practices, cancer outcomes, and associated costs of care for low-grade non muscle-invasive bladder cancer in over 13,000 patients in the SEER-Medicare database. Throughout the study period from 2003 to 2013, there was uniformly increased overutilization of surveillance testing (cystoscopy, cytology, and imaging) resulting in a 60% increased treatment cost despite low rates of disease progression in the cohort. The authors conclude that adherence to current bladder cancer guidelines in low-risk disease will mitigate these increased costs.

Ongoing projects within the HSR team include critical evaluation of global high value care options to improve bladder cancer care delivery. We aim to learn, understand, and inform value care models by leveraging the innate talent within the IBCG to improve oncologic outcomes, develop novel therapies, and also study the economic impact of bladder cancer care. The ultimate goal of these studies is to improve population-based bladder cancer outcomes by informing practice guidelines and improved care delivery on a global scale.



Angela Smith

University of North Carolina, Chapel Hill, NC, USA

Stephen B. Williams

University of Texas Medical Branch, Galveston, TX, USA