INTERNATIONAL
BLADDER CANCER GROUP (IBCG)

April 2022

Quarterly Newsletter

IBCG

International Bladder Cancer Group

Dear colleague, friend, or patient

You are looking at the first newsletter of the international bladder cancer group, the IBCG. A short history, explaining what the IBCG has been standing for, is included in this first newsletter. After a longer than expected due to the pandemic preparation, we aim at the first two to three issues in 2022, obviously dealing with all aspects of non-invasive, invasive and metastatic bladder cancer, the respective treatments, the doctors and the patients.

The target audience for this newsletter is anyone interested in bladder cancer, such as patients, urologists, medical oncologists, radiotherapists, and other doctors. We are also actively supporting patient advocacy. For e.g. in this current issue, we have excellent submission from Bladder Cancer Advocacy Network (BCAN), apart from contributions from patients and patient organizations in the patient's corner, we aim at including educational work, congress reports, a platform for young urologists to feature their work and provide exposure, case studies or challenging clinical scenarios, reviews of clinical trials, reviews of important publications, interviews with key opinion leaders, updates on IBCG publications and registries, preview on selected (IBCG) future meeting activities, and a pharma corner.

Of course, during the first year, we will keep an eye on how this is received and are open for other "unmet needs" and ideas.

We certainly hope that you enjoy reading this IBCG initiative and newsletter as much as we enjoyed making it, and let's all stay focussed on the unmet needs in bladder cancer.

- On behalf of the editorial board, Fred Witjes, Urologist, Nijmegen, The Netherlands.

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The History and Future of IBCG

The International Bladder Cancer Group (IBCG) began as an association of international urologists that was formed with the primary objective to address global educational needs and learning gaps in order to improve the care and management of patients with urothelial carcinoma. The initial end product in 2006 was a CD-ROM on case studies regarding the management of NMIBC (Yes, a CD-ROM, we all remember them, It was 2006). The initial group consisted of international urologists who were chosen for their expertise and from different geographic areas of the world in order to provide a global representation.

Over the subsequent years, the Strategic Mission of the IBCG has been to improve outcomes of patients suffering from bladder cancer through critical evaluation and leveraging of existing data to drive evidence based treatment. An additional goal was to develop practical educational tools that are applicable to the global urological community and thus enhance the care of patients with bladder cancer on a global level.

Towards this end, the IBCG has published numerous peer-reviewed articles in high-impact urological journals such as Journal of Urology, European Urology, BJU International, and the Journal of Clinical Oncology. The first few articles published by the IBCG were in European Urology in 2008 and included topics such as clinical practice recommendations for the prevention and management of intravesical therapy - associated adverse events. The next was a Review of the Guidelines and Best Practice Recommendations for the Management of non-muscle invasive bladder cancer in the Journal of Urology 2011. This remains one of the most downloaded articles for that Journal.

The IBCG then discussed many different topics over the next few years with publications addressing the Definition of Progression in NMIBC and Defining and Treating the Spectrum of Intermediate Risk NMIBC both published in the Journal of Urology in 2014. The IBCG's white paper published in the Journal of Clinical Oncology in 2016 "Definitions, Endpoints and Clinical Trial Designs for non-muscle-invasive bladder cancer: Recommendations from the International Bladder Cancer Group" is being used by regulatory bodies as well as the industry as a guide in the development of clinical trials. The IBCG made recommendations for the management of BCG-unresponsive NMIBC in Nature Reviews in 2017 and also addressed the management of low-grade bladder tumors in BJU international in 2020. Recently in late 2021, the IBCG published its "Consensus Statement on Clinical Trial Designs for Patients with IBCG exposed NMIBC" in European Urology to serve as a guide for this emerging space in the NMIBC spectrum.

The IBCG is currently working in partnership with the Society for Immunotherapy of Cancer (SITC) for a definitive white paper guidance document for clinical trial designs and all stages of muscle-invasive and non-muscle-invasive bladder cancer. The IBCG has expanded its membership in the past few years to include many additional globally recognized experts in the field of bladder cancer. This expansion has included a wide range of healthcare professionals such as medical oncologists, radiation oncologists, statisticians, and researchers with representation to include all the continents. In 2021, the IBCG created a Health Services Research group led by Dr. Steven B Williams, which aims to be a collaborative source for clinicians and researchers.

The IBCG will continue to support ongoing initiatives including clinical trial designs, clinical research, national and international guidelines, and assistance and conference or symposium organization. These initiatives and projects will help continue the IBCG Mission which will always remain, which is to improve outcomes of patients suffering from bladder cancer through critical evaluation and leveraging of existing data to drive evidence-based treatment.

For more information on IBCG, please click on the link below

www.ibcg.info

Chief Editor

Chief Editor
Prof. J.A. Witjes

J.A. Witjes is professor in oncological urology at Radboud university medical center, Netherlands.

His research interest is translational and clinical research in bladder, prostate, and testicular cancer.

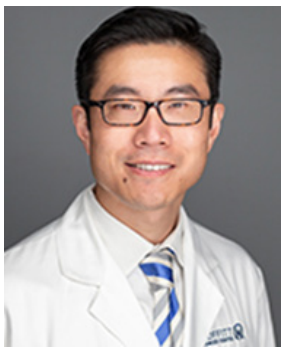
He has many training and teaching activities. He is a member of several international societies, and he chairs, amongst others, the Dutch guidelines committee on bladder cancer and the EAU guidelines committee on metastatic and muscle-invasive bladder cancer.

He is a reviewer and editor of several urological and oncological journals. He is involved in and leads many studies and projects which has resulted in many lectures and over 600 (peer-reviewed) publications, reviews, and book chapters.

Editorial Team

Sima Porten
MD, MPH

Sima Porten received her undergraduate, doctoral, and public health degrees from Northwestern University completing her education in June 2006. She was inducted into the Alpha Omega Alpha Honor Society during medical school and completed a Howard Hughes Medical Institute-NIH Research Scholars fellowship during that time. She then completed her urology residency training at the University of California, San Francisco where she received the Julius R. Krevans Award for Clinical Excellence. She completed her Urologic Oncology Fellowship at The University of Texas, MD Anderson Cancer Center. During the fellowship, she was awarded the John Quale Travel Fellowship for her research in Bladder Cancer. Currently, she is part of the multidisciplinary urologic oncology team of the UCSF Helen Diller Family Comprehensive Cancer Center where she continues to pursue her clinical and research interests in bladder cancer, upper tract urothelial cancer, and kidney cancer. She was named the Young Investigator of the year in 2021 by the Society of Urologic Oncology and is the Chair of the 2022 BCAN Bladder Cancer Think Tank. She is an active member of many professional societies (American College of Surgeons, American Urologic Association, Society of Urologic Oncology) and is the current urologic oncology fellowship director at UCSF.



Roger Li
MD

Roger Li is a genitourinary oncologist whose clinical practice focuses on the surgical treatment of bladder, prostate, kidney, and penile cancers. He offers a variety of treatment options, including open, laparoscopic, and robotic-assisted procedures, as well as nerve-sparing approaches based on the clinical scenario.

Prior to joining Moffitt, Dr. Li completed advanced urologic oncology training at the MD Anderson Cancer Center in Houston, Texas. Dr. Li's research interest includes the genomic characterization of genitourinary malignancies in attempt to tailor therapy specific to the patient, as well as the development of novel immunotherapeutic strategies in treating early-stage bladder cancer. Dr. Li's work has previously been highlighted in several national and international urology meetings.

He has authored numerous peer-reviewed manuscripts and book chapters on urologic oncology. In addition, he serves as reviewer for many international urologic journals,

including British Journal of Urology International, European Urology Oncology, Journal of Clinical Genitourinary Cancer, and BMC Cancer. A native of California, Dr. Li received his medical degree from the University of California, Irvine, and completed his urologic residency training at Loma Linda University Medical Center. In his spare time, he enjoys spending time with his family, traveling, and watching and playing basketball.

Petros Grivas
MD, Ph.D

Petros Grivas is a board-certified medical oncologist with expertise and experience in treating genitourinary (GU) cancers. He is the Clinical Director of the Genitourinary Cancers Program at the University of Washington and Associate Professor in the Dept of Medicine, Division of Oncology.
Department of Medicine, Division of Oncology, Seattle Cancer Care Alliance, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA.

Dr. Grivas completed his training at the University of Patras Medical School and took his M.D. degree in 2005; he then pursued Ph.D. in Medical Oncology under the mentorship of key academic faculty and defended his thesis successfully in late 2008. He completed his Residency in Internal Medicine at Hahnemann University Hospital/Drexel University College of Medicine (Philadelphia, USA) in 2010. He then completed his Fellowship in Hematology/Oncology at the University of Michigan (Ann Arbor, USA) in 2013. He stayed there as Clinical Lecturer for another year before he was recruited as Assistant Professor at the Cleveland Clinic (Cleveland, USA), where he was leading the bladder/urothelial cancer program, pursuing clinical and translational research, teaching trainees, and seeing patients with GU cancers.

He has had main role in clinical trials that led to the FDA approval of new drugs for bladder/urothelial cancer, and is considered a key opinion, thought leader and international expert, giving lectures in several countries, educating oncologists, other healthcare providers and trainees, leading innovative clinical trials, reviewing grant proposals and manuscripts, and publishing novel and important research. He is dedicated to efficient, personalized and outstanding patient care and believes in optimal patient-physician relationship as well as community outreach.

AUA 2022 Spotlight: Inaugural Bladder Cancer Forum

The 2022 AUA Annual Meeting to be held in New Orleans, LA will not only mark the first in person meeting by the organization since 2019, but also will feature a Bladder Cancer Forum hosted by the International Bladder Cancer Group (IBCG) on Sunday, May 15 from 2:00-5:00 pm and is open to all meeting attendees. This dedicated forum will feature expert International panelists across bladder cancer disciplines, led by moderators Dr. Ashish Kamat (MD Anderson Cancer Center), Dr. Sima Porten (UCSF), and Dr. Patrick Hensley will deliver State of the Art Lectures on contemporary management as well as debate treatment strategies in challenging disease states. Across the spectrum of non-muscle invasive disease, discussion topics will include the role of surveillance for low-risk NMIBC as well as the impact of variant histology on NMIBC management. Panelists will discuss current and emerging therapeutic options for BCG unresponsive disease and the role of timely cystectomy for high-risk NMIBC. In the MIBC setting, the role for neoadjuvant systemic therapy will be debated, along with the emerging relevance of defining clinical complete response to systemic therapy in bladder preservation strategies. Over the past decade, new drug therapies, improvements in technology, and guideline updates have revitalized and pushed progress forward in the treatment of bladder cancer. As May marks Bladder Cancer Awareness month, this forum marks the recognition of the dedication and perseverance of many in the IBCG community, and the importance of moving the bar forward to improve outcomes for patients facing this terrible disease.

For the agenda on AUA Bladder Cancer Forum, please click on the link below:
www.tinyurl.com/2y69vzy9

For more information on IBCG, please click on the link below
www.ibcg.info

Highlights of the EAU 2021, bladder cancer

J Alfred Witjes, MD, PhD
Professor Oncological Urology
Radboud University Medical Center, Netherlands.

The NMIBC guideline

The NMIBC's risk classification is changed. Some clinical risk factors for progression have been added; age over 70, multiple papillary tumors, and tumors larger than 3 cm. Patients may therefore fall into a different risk group than before and belong to a different follow-up/treatment group. The risk group is easy to determine via the risk calculator on www.NMIBC.net. Next to this, there is a “very high risk” group added to the guideline, where immediate cystectomy should be discussed because of the high risk of progression.

Immunotherapy

In the NMIBC setting, Nadofaragene Firadenovec was discussed. It is a non-replicating adenoviral vector with human IFN-α 2b gene and Syn3, which incorporates virus into the cellular DNA and causes synthesis and expression of IFN-α2b protein. It is a 3-monthly intravesical therapy. A phase 3 study in BCG unresponsive patients showed a complete response in 53% after 3 months (45% after 12 months).

Systemic immunotherapies were also presented

(Neo-)adjuvant immunotherapy has not yet compared to the standard (neo-) adjuvant chemotherapy and is therefore not recommended outside of a trial.

In metastatic urothelial carcinomathe JAVELIN bladder 100 trial, with avelumab switch maintenance, showed an overall survival benefit of 7 months as compared to best supportive care, in patients without progression after chemotherapy. It is now recommended in the guideline. In 2nd line after platinum-based chemotherapy, pembrolizumab was shown to give an, overall survival advantage of 3 months compared to second-line chemotherapy. Also, atezolizumab, avelumab, durvalumab, and nivolumab are mentioned in the guideline with also a better side effects profile compared to second-line chemotherapy.

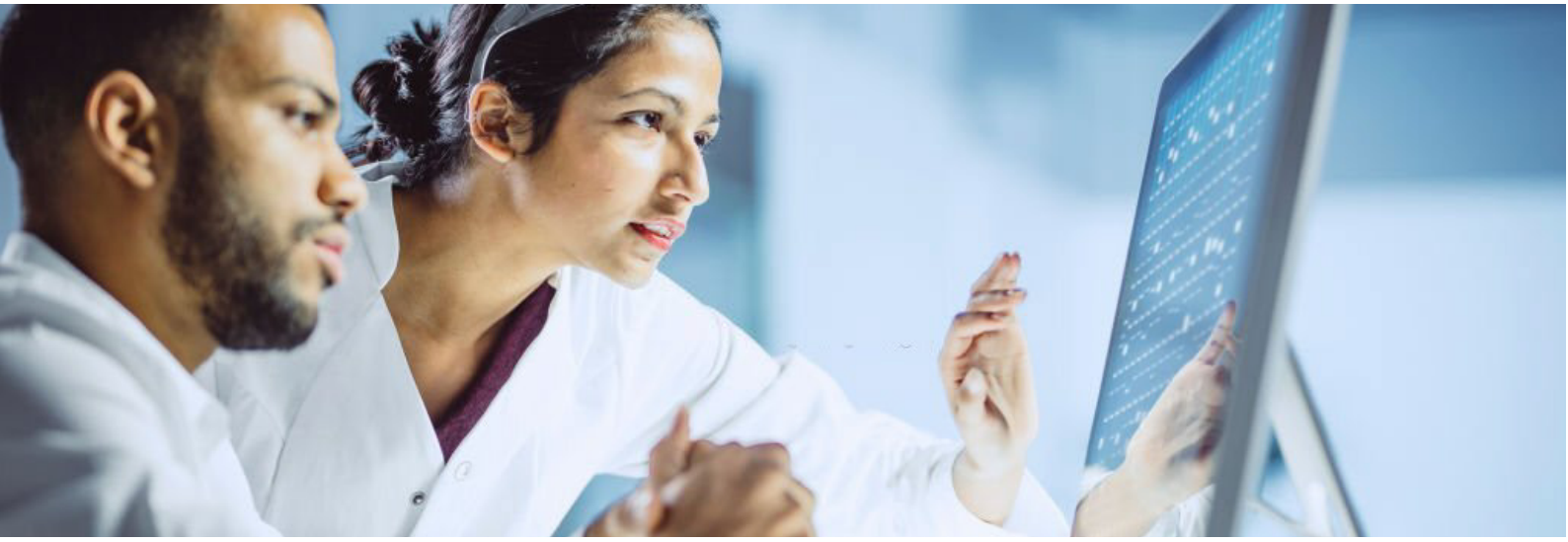
Enfortumab Vedotin was used as later-line therapy and presented in a phase 3 trial, where an overall survival benefit of 4 months was achieved with acceptable toxicity. This treatment remedy is currently only available in clinical trials.

Biomarkers

A hot topic this year were biomarkers at different stages of the disease. For diagnosis and follow-up of the NMIBC urinary biomarkers were presented, which generally high negative predictive values up to 99% if TaLG tumors were excluded. The question remains whether these biomarkers can replace a cystoscopy. No biomarkers that are prognostic of a response toneo-adjuvant therapy have been identified yet. Circulating Tumor DNA and Circulating Tumor Cells seem to predict early recurrence after cystectomy, enabling early treatment with the aim of better survival.

Some practical tips for daily practice

1. NO antibiotic prophylaxis in TURT (without catheter of nefro drain) gave no increased risk of infection or post-bleeding in an RCT: so we can stop antibiotic prophylaxis in TURT.
2. Music during cystoscopy leads to lower heart rate, VAS, and anxiety score afterwards. A simple out patient trick in an uncomfortable situation for the patient.



BCAN
Bladder Cancer Advocacy Network
Leading the way to awareness and a cure

BCAN Fuels Bladder Cancer Research

The Bladder Cancer Advocacy Network (BCAN) is a US-based community of patients, caregivers, survivors, advocates, medical and research professionals united in support of people impacted by bladder cancer. Its research goal is to identify the best and most promising studies that will provide the greatest opportunity to advance the understanding of bladder cancer and improve management and treatment of this disease. BCAN raises funds and awards grants to support early investigators as well as innovative bladder cancer research to develop lifesaving treatments and improve patient outcomes. Supporting bladder cancer research is an integral part of BCAN's mission. Its research grant program attracts "the best and the brightest" who apply their talent, knowledge, and experience to improve the understanding and treatment of bladder cancer.

To date, BCAN has invested more than $6 million in bladder cancer research through its research grants and the Bladder Cancer Genomics Consortium (BCGC) program and plans to invest over $1 million in additional award funding through its 2022 research award programs. BCAN's research funding is making a tremendous impact on the bladder cancer research field that will translate to better outcomes for bladder cancer patients and their families.

Bladder Cancer Genomics Consortium

To help propel bladder cancer research forward, BCAN launched the Bladder Cancer Genomics Consortium (BCGC) in 2017. The BCGC is an innovative collaboration between BCAN and eight leading medical centers to develop an enriched understanding of the genomic profile of bladder cancer and to accelerate the development of novel treatments. The BCGC's goal is to provide the opportunity for every patient to be an exceptional responder to personalized therapy while advancing collaborative research to support the development of life-saving treatments for bladder cancer.

Bladder Cancer Think Tank

BCAN has been hosting its annual Think Tank since 2005, which is the largest bladder cancer specific meeting in North America. Meeting attendees include leading urologists, oncologists, researchers, pathologists, social scientists, patient advocates and industry representatives, all of whom are dedicated to improving the diagnosis, treatment and survivorship of bladder cancer. The invitation-only Think Tank facilitates important discussions to define some of the current priorities for advancing bladder cancer research, including all parts of the patient and caregiver journey, from diagnosis to treatment to survivorship.

This year's Think Tank will be held in Denver, CO from August 3-5, 2022.

Clinical trials database

BCAN helps connect patients and caregivers with actively recruiting bladder cancer clinical trials in the U.S. via its Clinical Trials Dashboard. Using the dashboard, visitors can search by the type of bladder cancer they or their loved one has, by their state of residence, and users can sort the results by those clinical trials that are closest to them. Patients can also print out a copy of information about a clinical trial and take it with them to their next doctor's appointment.
Please visit bcan.org/clinicaltrials.

Research funding

BCAN has funded more than $6 million in bladder cancer research grants. BCAN works to identify and fund the work of clinicians and researchers who bring novel approaches, innovation, and out-of-the-box ideas that propel progress in bladder cancer research. BCAN's grants and research funding mechanisms include:

John Quale Travel Fellowships

The John Quale Fellowship Program supports, early career investigators with a demonstrated interest in bladder cancer research to attend BCAN's annual Bladder Cancer Think Tank. The travel fellowships awarded each year are intended to defray travel-related costs for attending the meeting.

Young Investigator and Patient-Centered Clinical Research Awards

BCAN launched its Young Investigator Awards (YIA) in 2013, and the Patient Centered Clinical Research Young Investigator Awards in 2018. The YIA grants support the work of early career researchers working in basic, translational, clinical, epidemiologic, bioengineering, or any other scientific or research field. Each awardee must be working in a research environment capable of supporting transformational bladder cancer research.

The Patient-Centered Clinical Research Young Investigator Award (PCC-YIA) supports early-career scientists and clinical cancer researchers investigating transformational patient-oriented clinical bladder cancer and/or upper tract urothelial cancer research. Examples include studies of shared decision making, access to care, quality of care, quality of life, health disparities, comparative effectiveness research, patient-centered outcomes research, and survivorship.

Research Innovation Awards

Since 2014, BCAN's Bladder Cancer Research Innovation Award (RIA) has supported high risk, high reward science, providing $300,000 over a two-year period to experienced investigators breaking new ground with novel and creative projects with great potential to spur breakthroughs in the management of bladder cancer.

Career Development Award (New in 2022)

In the Fall of 2022, the Bladder Cancer Advocacy Network will offer a Career Development Award to support junior investigators who have received their initial faculty appointment to establish an independent bladder cancer research program and career path but have not yet secured their first major research funding.

For more information or questions about BCAN's research funding, visit:
www.bcan.org/bcan-research/grants-and-research-funding-opportunities/

e-mail
grants@bcan.org?

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

Long time BCAN Patient Advocate Describes the Value of Research

Bladder cancer patient and Bladder Cancer Advocacy Network's (BCAN's) longstanding volunteer, Robert Lipman, first heard about John and Diane Quale and the Bladder Cancer Advocacy Network (BCAN) in 2005. Bob was diagnosed with high-grade non-muscle invasive bladder cancer that year, and like BCAN's co-founders, John and Diane Quale, were surprised at the lack of information available about the disease.

The importance of bladder cancer research

The meaning and value of bladder cancer research became apparent to Bob when he read his first scientific paper about a medical study using BCG and Interferon. Bob took the paper to his local urologist and after reading the paper carefully, the doctor agreed to treat Bob using the combination of the two drugs. One of the paper's authors was Dr. Michael O'Donnell, who serves on BCAN's Scientific Advisory Board. Bob noted that after some initially disappointing results, treatments with BCG and Interferon ultimately prevented the tumor in his bladder from recurring and he has remained cancer-free for the last 16 years.

Having been one of the original BCAN patient advocates, Bob has a unique view on the value of bladder cancer medical research. He told BCAN, "It gives me and all the other patients and caregivers a lot more hope. Thanks to research, now there are many more treatments and therapies for bladder cancer patients in all stages of the disease." He added, "When I had bladder cancer, my options were limited to BCG and having my bladder removed."

Bob as a bladder cancer patient advocate

On two occasions, Bob testified for more and better bladder cancer treatments at the U.S. Food and Drug Administration. He told BCAN, "I testified as the patient voice, advocating for better research and better treatments."

Bob's volunteering to help bladder cancer patients goes even further. He is also a volunteer in BCAN's Survivor to Survivor (S2S) program that connects newly diagnosed bladder cancer patients with trained volunteers who offer their perspectives on what it was like for them to be diagnosed and treated. S2S is about lending a sympathetic and knowledgeable ear to those who could benefit from someone who has "been there, done that." He enjoys helping others in their bladder cancer journeys.

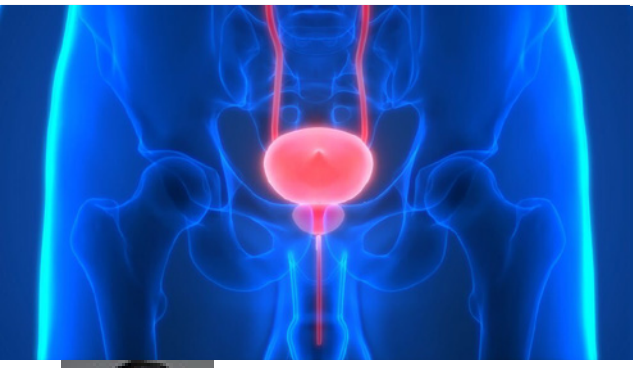
The value of research collaboration

Bob also sees the value in BCAN's contributions to bladder cancer research outside of the financial grants that the organization gives to develop new and innovative ways to treat bladder cancer. Bob told BCAN, "A lot of bladder cancer research has come about because of the work that BCAN has done to bring together the researchers who collaborate and share information." An example of enhanced collaboration is BCAN's annual bladder cancer Think Tank, the premier bladder cancer scientific meeting in North America. Since its inception in 2005, the Think Tank meeting has focused on identifying obstacles and creating solutions in bladder cancer research. Think Tank attendees have told BCAN that the very nature of the meeting helps make collaboration possible, and that many attendees form professional relationships that last for their entire careers.

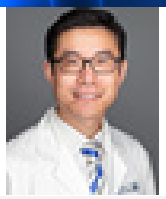
Bob noted that the quantity of people researching improved bladder cancer treatments has changed over the years as well. He told BCAN, "In the beginning, bladder cancer research was being conducted primarily by doctors and researchers at academic institutions. Now, with enhanced collaboration, pharmaceutical companies and others have invested in bringing new treatments to the market." For those 732,000 people who are living with bladder cancer in the United States, this increased focus means more treatment options and improved patient outcomes.

Patient involvement in clinical trials

Having been a bladder cancer patient turned volunteer and advocate, Bob feels strongly about another important research-related topic: getting patients involved in bladder cancer research. Patients offer crucial perspectives that create better clinical trial designs that improve the lives of those suffering from the disease. Bob believes that successful treatments and promising clinical trials mean involving patients from the outset to hear their perspectives. He said, "I have been involved in clinical trial designs to help ensure the patient perspectives are heard. It's been very gratifying to be able to make an impact on the medical community with the patients' perspective. Never in my wildest dreams would I ever think that I would be a co-author on papers in medical journals."



GU-ASCO 2022 Round up



Roger Li, MD
Assistant Member- Department of Genitourinary Oncology
H.LEE. MOFFIT Cancer Center

SWOG S1314: A Randomized Phase II Study of Co-Expression Extrapolation (COXEN) with Neoadjuvant Chemotherapy for Localized, MIBC with Overall Survival Follow Up

The SWOG1314 trial assessed a gene expression model (COXEN – CO-eXpression ExtrapolatioN) as a predictive biomarker for response to Gemcitabine-Cisplatin or dose-dense Methotrexate-Vinblastine-Adriamycin/doxorubicin-Cisplatin (ddMVAC) in patients with muscle-invasive bladder cancer. This predictive model was developed using a comparison of correlation matrices to identify gene expression patterns concordantly expressed in both cell lines and relevant human samples. In the SWOG1314 trial, COXEN scores for GC and MVAC were tested for prediction of pathologic downstaging, progression free survival (PFS) and overall survival (OS) among patients with MIBC undergoing neoadjuvant chemotherapy followed by surgery. Amongst 167 patients, the COXEN scores were not significantly prognostic for OS or PFS in their respective arm. However, the COXEN GC score was a significant predictor for OS in the pooled arm. Another important finding emerging from the study was that no significant different in OS or PFS was observed in patients treated with ddMVAC vs. GC (OS HR 0.87, 95% CI 0.54-1.40, p=0.57). The investigators concluded that the COXEN score may be prognostic of survival in patients receiving platinum-based neoadjuvant chemotherapy and that ddMVAC and GC provided comparable oncologic outcomes.

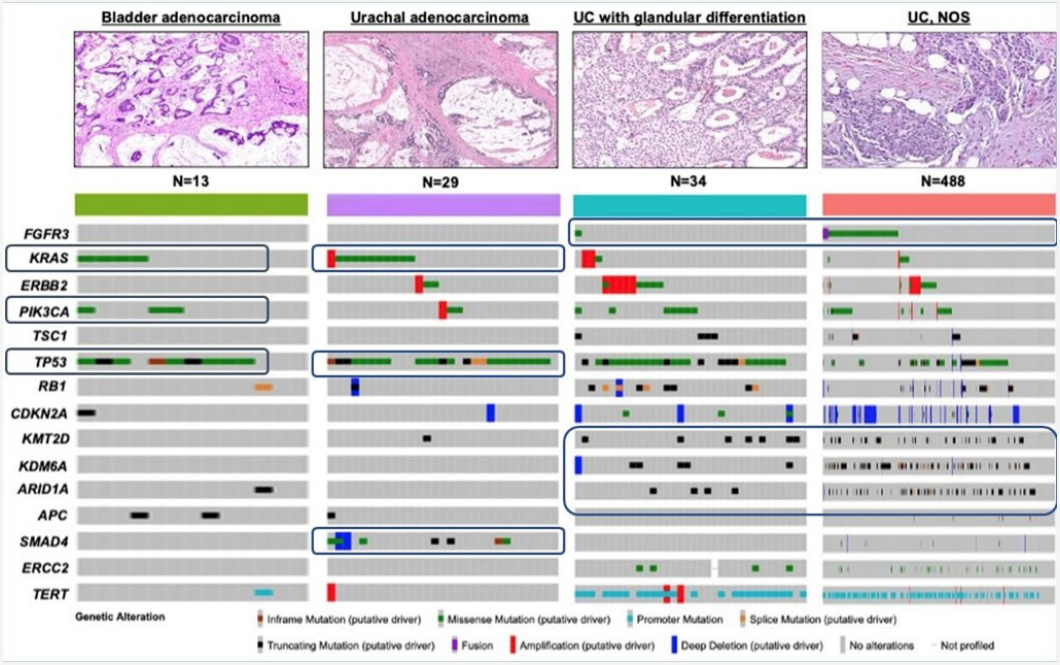
COXEN Score	Treatment Arm	Outcome	Sample Size	Hazard Ratio*	HR 95% CI*	2-sided p value *
GC-specific	GC	OS	82	0.33	0.10, 1.13	0.08
GC-specific	GC	PFS	82	0.45	0.17, 1.20	0.11
MVAC-specific	MVAC	OS	85	0.99	0.40, 2.45	0.98
MVAC-specific	MVAC	PFS	85	1.56	0.75, 3.27	0.23
GC-specific	Both	OS	167	0.45	0.20, 0.99	0.047
GC-specific	Both	PFS	167	0.77	0.42, 1.40	0.39

*Adjusted for two stratification factors – clinical stage at baseline (T2 vs T3, T4a), PS (0 vs 1). Funding: NIH/NCI grant U10CA180888, U10CA180819, U10CA180820, U10CA180821.

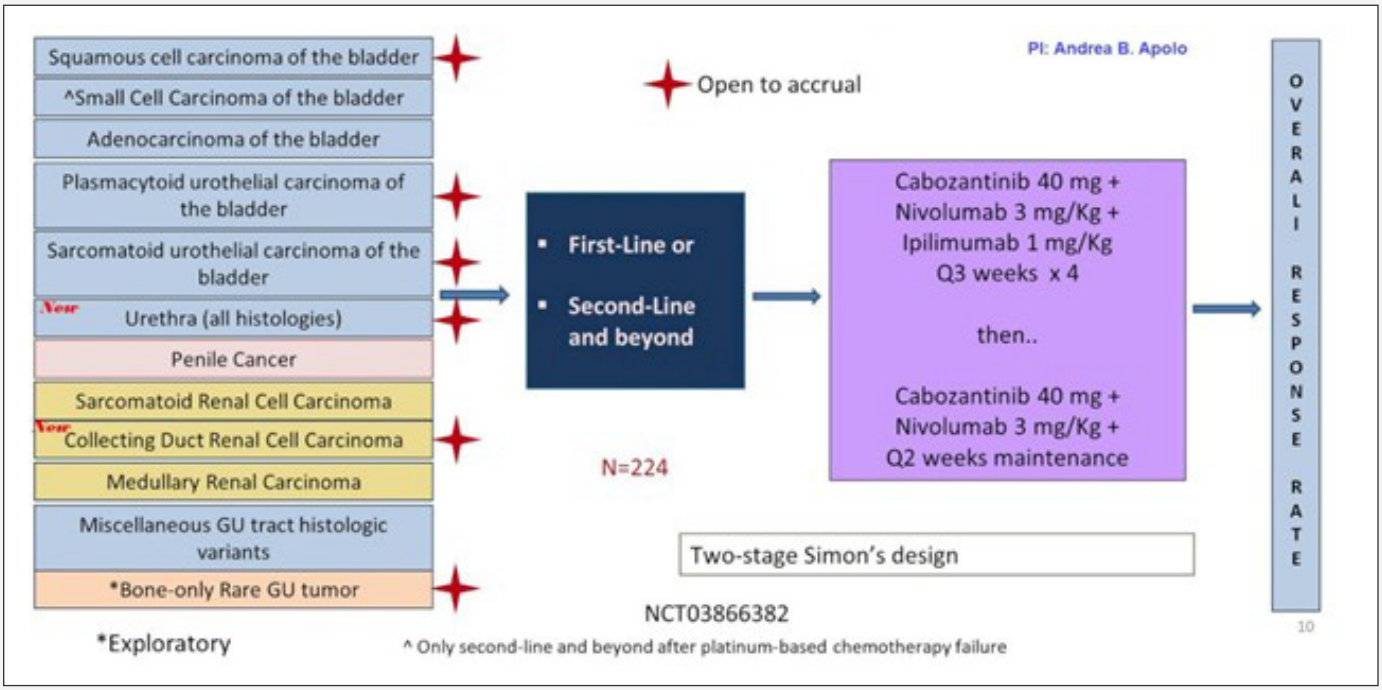
Systemic Therapy for Rare Variants of Urothelial Cancer

In a session on the management of rare variants in genitourinary cancers, Dr. Jonathan Rosenberg discussed the role of systemic therapy for the management of patients with urothelial cancers of variant histology. Pure variants are rare tumors. Within the current treatment paradigm, mixed histology tumors are generally treated in a one-size-fits-all manner along with conventional urothelial carcinoma, with some inferences made from extrapolations from case series, databases, or expert opinions. To define efficacious treatments for the rare variants, studies are needed to investigate their unique biological properties and eventually enable clinical trials. Dr. Rosenberg highlighted the often-used treatments for a few variants to provide context. For small cell or neuroendocrine carcinoma, it is known that early systemic therapy improves survival. The survival benefit associated with systemic therapy, typically using a platinum/etoposide regimen, can be extended to tumors with focal small cell histology or with lower stage presentation. Micropapillary bladder cancer is known to be associated with HER2 overexpression and amplification, thus making it a preferable candidate for HER2-directed therapies. On the other hand, bladder adenocarcinoma is associated with alterations in KRAS, PIK3CA, and TP53.

However, those with glandular features share similar genetic alteration patterns as conventional urothelial carcinoma, with much more frequent alterations seen in chromatin remodeling genes such as KMT2D, KDM6A, and AIRD1A. These tumors should thus be treated with conventional systemic regimens for urothelial carcinoma, while 5-FU based regimens as well as FOLFOX may be reserved for the pure adenocarcinomas.

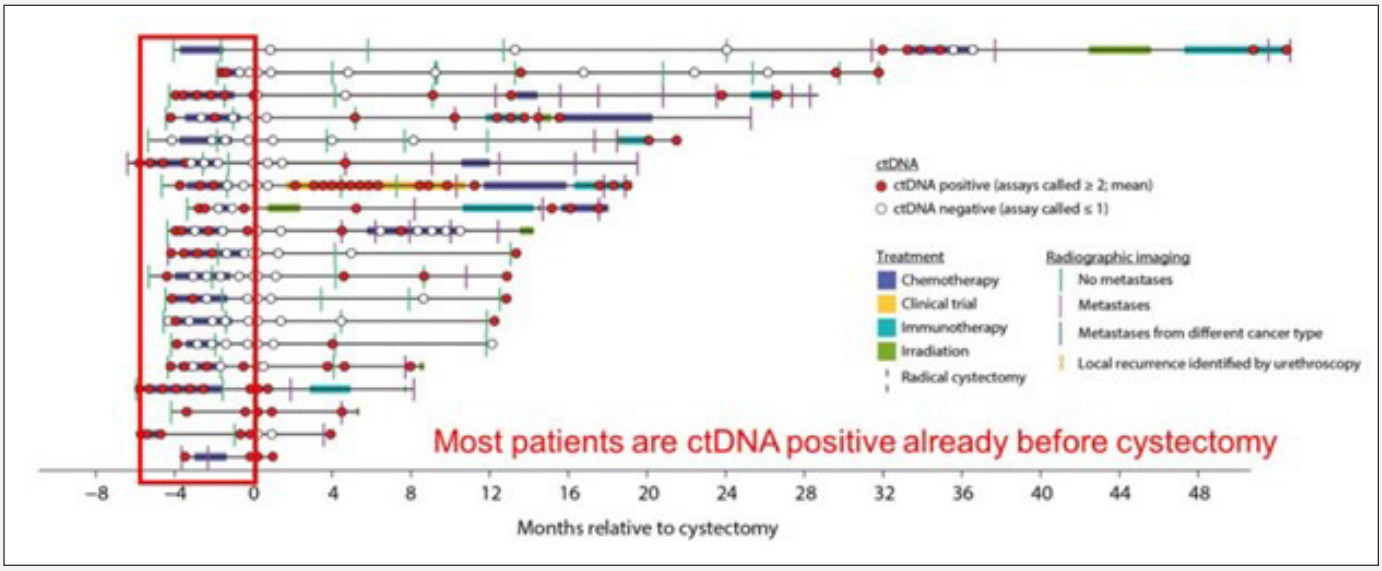


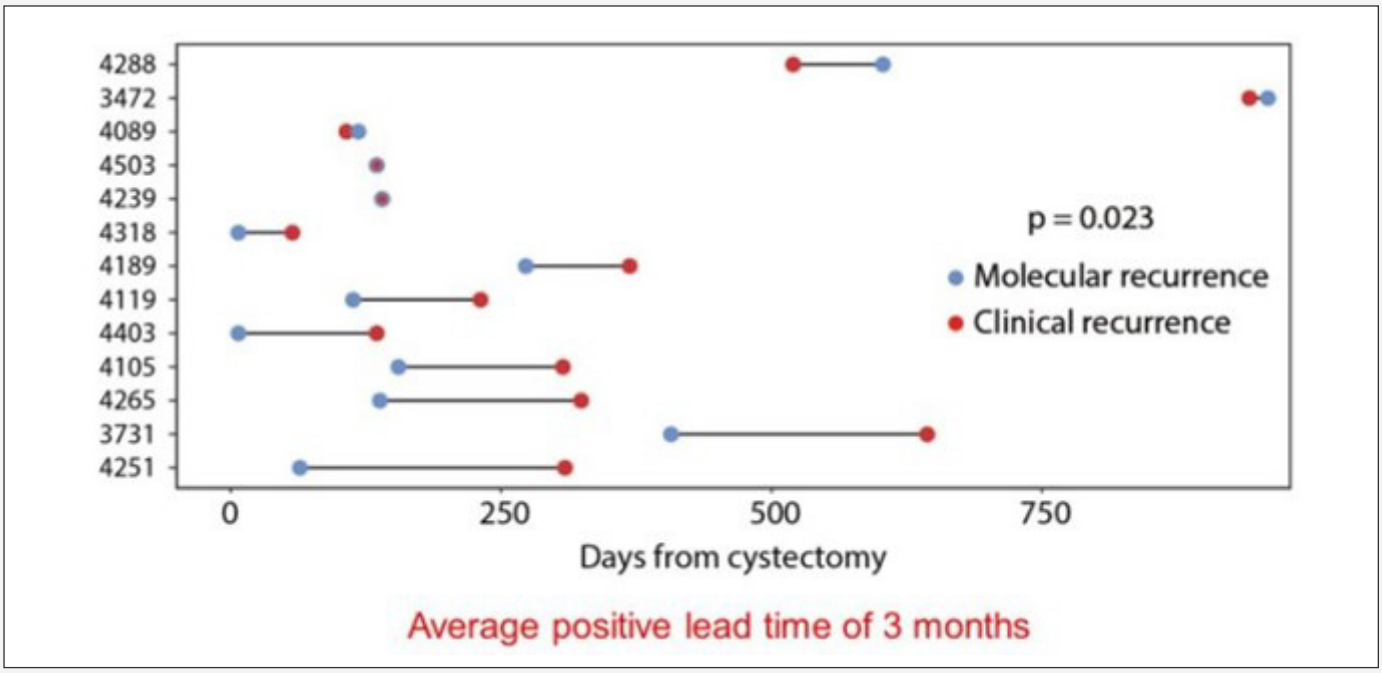
In addition, targeted agents such as VEGF or EGFR inhibition may be used against tumors harboring these genomic alterations. Plasmacytoid urothelial carcinoma has been classically characterized by E-cadherin loss (CDH1 loss of function mutation, methylation, etc.), enabling locoregional spread via direct extension. Upstaging is common at the time of radical cystectomy, with high rates of positive surgical margins. Retrospective data demonstrate a less than usual benefit derived from conventional systemic chemotherapy, thought to be attributed to occult disease present at the time of treatment. There is emerging data demonstrating the effectiveness of immunotherapy on par with chemotherapy for the treatment of this rare variant. There are limited available prospective data on the efficacy of immunotherapy in the treatment of urothelial cancer of variant histology. In the SAUL study, where bladder cancer patients not eligible for other trials were accrued and treated with atezolizumab, 47 patients harboring variant histology demonstrated a disappointing ORR of 9%. On the other hand, combination treatment using nivolumab and ipilimumab demonstrated an ORR of 37% in 19 patients. There is an ongoing trial led by Dr. Andrea Apolo investigating the efficacy of ipilimumab, cabozantinib, and nivolumab in rare genitourinary cancers as either first-line or subsequent-line therapy, with a target accrual of 224 patients using a Simon's Two-stage design.

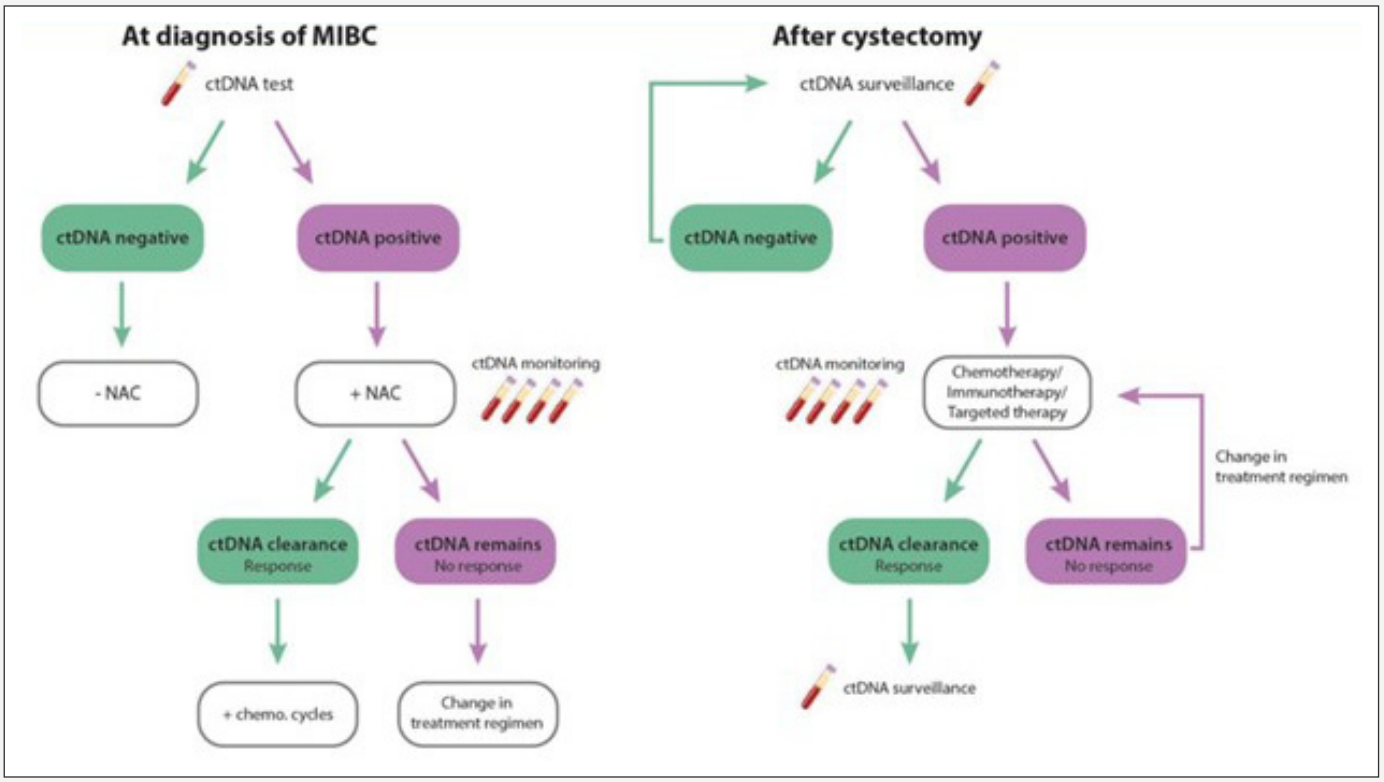


ctDNA Analysis in Muscle-Invasive Bladder Cancer

Dr. Lars Dyrskjot discussed the role of ctDNA and its prognostic and predictive implications in the treatment of muscle invasive bladder cancer (MIBC). ctDNA is released from necrotic cells due to apoptosis, or via active release by cancer cells. The half-life of ctDNA is very short (<2 hours), thus allowing for real-time monitoring of tumor burden. In addition, specific mutational profiles found within the ctDNA may also be leveraged to predict response to treatment and to monitor clonal evolution through the course of treatment. In the context of MIBC, a study was conducted using tumor informed ctDNA collected serially before, during and after neoadjuvant chemotherapy and radical cystectomy. The investigators found powerful prognostic implications from ctDNA collected both before the start of chemotherapy and before cystectomy. ctDNA was also used in the measurement of treatment response while chemotherapy was ongoing, and was demonstrated to dynamically track the response of tumor to treatment. Furthermore, ctDNA detection following surgery predated clinical recurrence, and thus may serve as a non-invasive mechanism for disease surveillance. Extending from these exciting results, Dr. Dyrskjot and others from Denmark have launched the TOMBOLA trial, a non-randomized ctDNA based intervention study to investigate whether a ctDNA guided treatment paradigm may improve outcomes in patients with MIBC. The study assesses the hypothesis that early treatment implementation upon "biochemical recurrence" of detectable ctDNA can lead to superior oncologic outcomes than conventional therapeutic delivery schedules. This study will include approximately 282 patients to be enrolled between 2020-2022, with >6,000 ctDNA samples collected at various timepoints before and after radical cystectomy. In sum, ctDNA is emerging as a powerful biomarker and offers many opportunities to improve upon the current treatment paradigm.



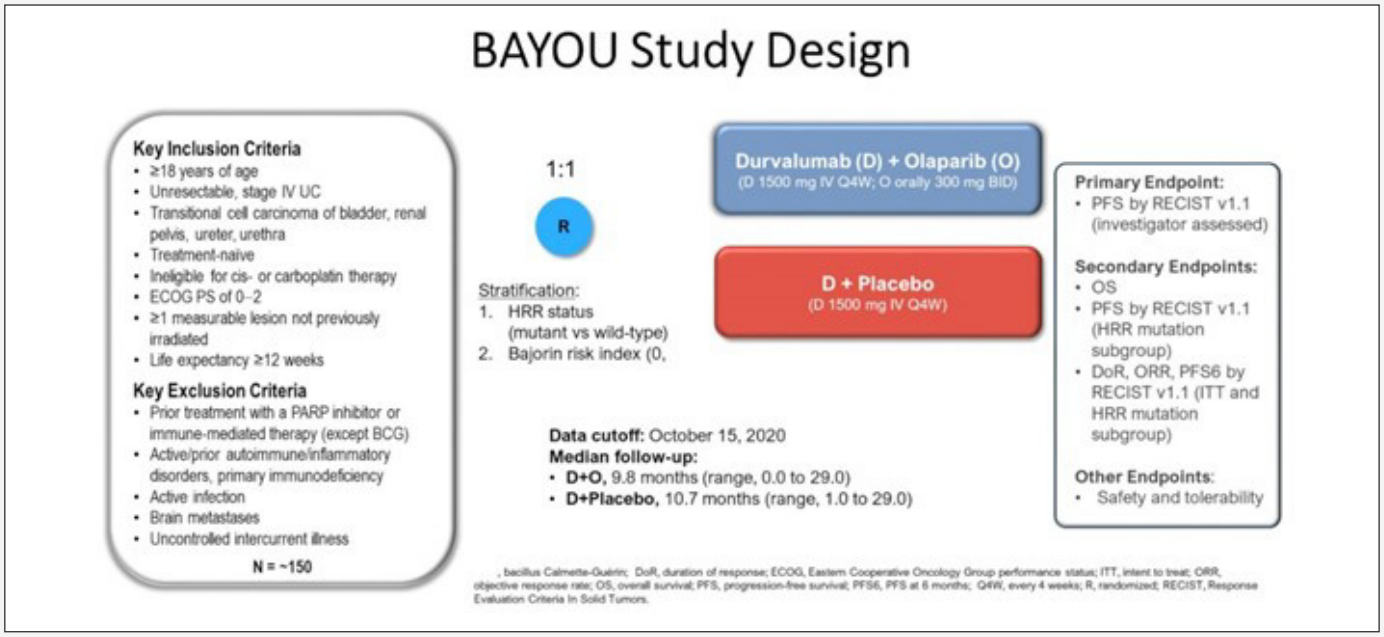


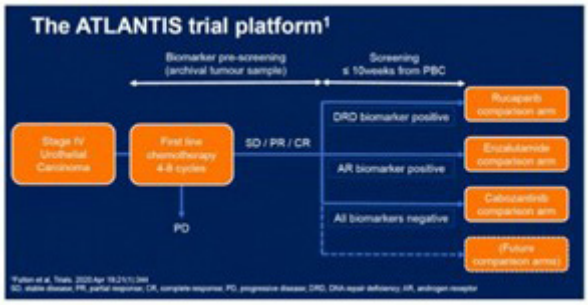


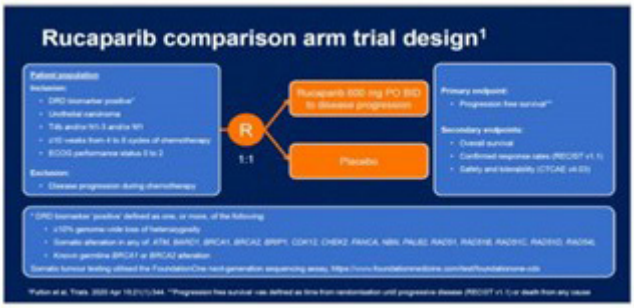
The Role of PARP Inhibitors in the Management of Advanced/Metastatic Urothelial Carcinoma

There has been a recent explosion of novel therapeutic agents for metastatic urothelial carcinoma, with several immune checkpoint inhibitors, targeted agents, and antibody-drug conjugates gaining approval. However, to date, there has not been any established role for PARP inhibitors in this disease space. Two trials involving PARP-inhibitors were reported at GU-ASCO2022. In the BAYOU study presented by Dr. Jonathan Rosenberg, combination therapy using PD-L1 inhibitor durvalumab, and PARP inhibitor Olaparib was tested against durvalumab monotherapy in patients with metastatic urothelial cancer who were treatment naïve but ineligible for platinum-based chemotherapy. In a cohort of patients with heavy disease burden (>60% visceral metastases), the combination did not improve PFS (median 4.2mo) vs. durvalumab alone (3.5mo). Notably, 22% of the patients in the combination group had homologous recombination repair (HRR) gene mutations, compared to 18% in the durvalumab monotherapy arm. Among a subset of patients with HRR mutations, combination therapy was found to provide PFS benefit of 5.6 vs. 1.8 mo, p<0.001. Interestingly, HRR mutations may also serve as a prognostic biomarker as OS was shown to be worse in the HRR mutants than in WT patients in both the combination and durvalumab monotherapy arms. No additional grade 3/4 treatment-related adverse events occurred with the combination treatment. Results from the BAYOU trial sets the benchmark for PFS/OS in platinum ineligible patients.

In the ATLANTIS trial presented by Dr. Cabb, metastatic urothelial carcinoma patients with DNA repair deficiency (DRD) were randomized to maintenance using the PARP inhibitor rucaparib or placebo following response to chemotherapy. The selection of DRD was based on somatic alterations in DRD associated genes as well as ≥10% genomic loss of heterozygosity. Of the 248 patients pre-screened, 74 (26.5%) were biomarker positive. Unfortunately, the study was stopped following accrual of 40 patients due to a combination of COVID-19 pandemic and the approval of avelumab in the switch-maintenance setting. Median PFS was 35.3 wks (8.8mo) in patients receiving rucaparib vs. 15.1 wks in those receiving placebo (HR 0.53, CI 0.30-0.92, 1 sided p = 0.07). The PFS (8.8mo) seen in this trial compares favorably to that seen from the JAVELIN trial using avelumab as switch maintenance, providing only 3.7mo of PFS benefit. While maintenance avelumab did demonstrate a 7-mo OS benefit, it remains to be seen whether PARP inhibitors can provide a similar if not better OS benefit when compared to BST. Despite this, no OS benefit was seen in the rucaparib arm (NR vs. 72.3wks, HR 1.22, 80% CI 0.62-2.38, p=0.35)at data cutoff with relatively short follow-up period. TEAE were mainly low grade, predominated by fatigue, nausea, and rash. Previously, the ATLAS (rucaparib monotherapy as 3rd line therapy) and BISCAY (Olaparib in combination with durvalumab in chemo-refractory patients) trials both failed to demonstrate a meaningful survival benefit associated with the administration of PARP inhibitor.





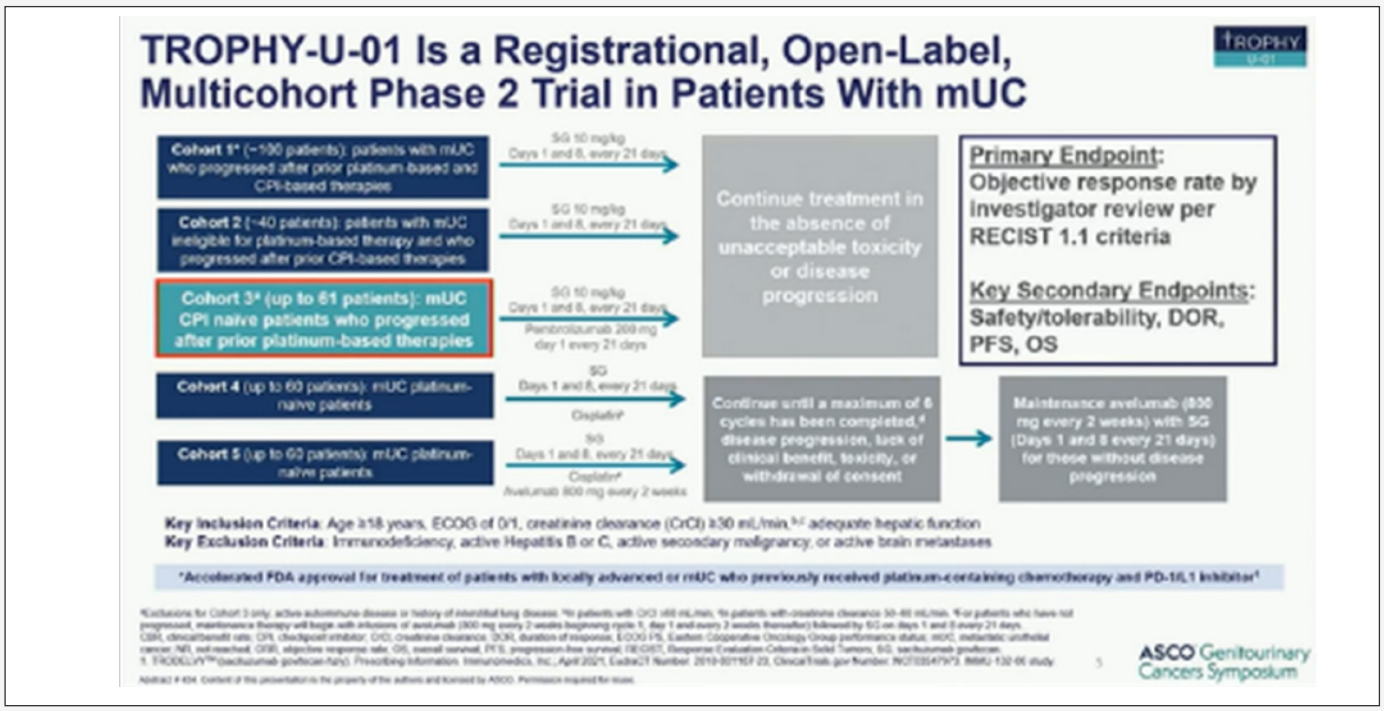


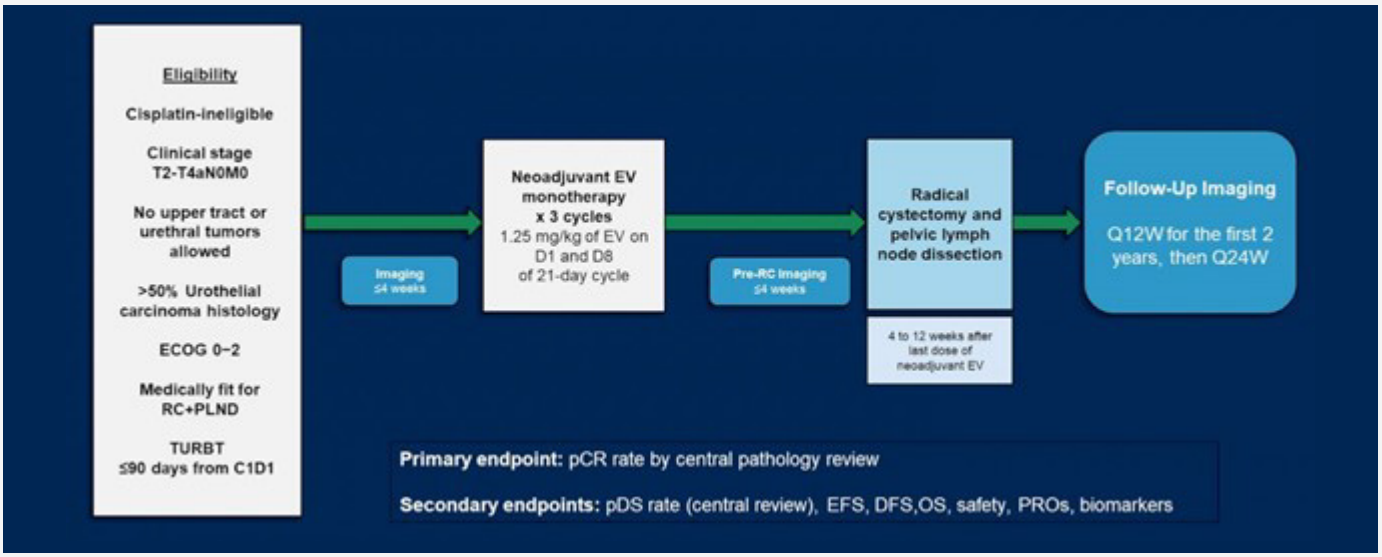
Antibody Conjugates Come of Age

Several antibody drug conjugates have gained prominence in the treatment of locally advanced and metastatic urothelial cancer. Enfortumab vedotin (EV) in combination with pembrolizumab has demonstrated remarkable ORR of >70% and PFS of 12.3mo in the frontline setting in cisplatin ineligible patients with locally advanced and metastatic UC. Sacituzumab govitecan (SG) is an antibody-drug conjugate that targets trophoblast cell-surface antigen 2 (Trop2) with a SN-38 (topoisomerase-I inhibitor) payload. SG monotherapy has previously demonstrated significant activity and manageable safety in patients with metastatic urothelial cancer after progressing on platinum-based chemotherapy and immune checkpoint blockade. In cohort 3 of the TROPHY-U-01 study, SG was administered in combination with pembrolizumab in patients with metastatic urothelial cancer progressing after platinum-based chemotherapy to investigate its ORR by a blinded independent central review per RECIST1.1. As reported by Dr. Petros Grivas, at the time of data cutoff, 41 patients received treatment at RP2D (10mg/kg). At a median follow-up of 5.8mo, the investigator-assessed ORR was 34% (95% CI 20.1-50.6), with 1 CR and 13 PRs, significantly lower than ORR observed following combination EV + pembrolizumab. TEAE were similar to those seen in previously reported trials using SG, predominated by diarrhea (76%), nausea (59%), anemia (56%), neutropenia (44%), and asthenia (41%). Grade ≥3 adverse events occurred in 59% of patients. In correlative studies, TROP2 mRNA/protein is highly expressed across all molecular subtypes of bladder cancer except neuroendocrine subtypes. TROP2 mRNA were also found to be co-expressed on cancer cells with NECTIN4, the target of EV. In a recent preclinical study, CRISPR/Cas9 knockdown of TROP2 reduced sensitivity to SG. However, following prolonged EV exposure, cells downregulated NECTIN4 expression while maintaining TROP2 expression, rationalizing the use of SG in EV resistant tumor strains.

In the EV-103 phase 1b/2 trial, patients received 3 cycles of EV in the neoadjuvant setting prior to radical cystectomy and pelvic lymph node dissection. Of 22 patients enrolled, 19 completed all three planned cycles of EV and 21 patients underwent cystectomy. A 36.4% pathologic complete response (95% CI 17.2-59.3) was seen, with pathological downstaging observed in 50% (95% CI 28.2-71.8) of the patients. Of note, perioperative mortality was observed in 3 patients that were deemed to be unrelated to EV.

In sum, antibody drug conjugates have demonstrated remarkable activity in several urothelial cancer settings. They offer a targeted approach to delivering precision chemotherapeutic treatment to patients with advanced urothelial cancer. Despite the early enthusiasm, optimal combinatory therapy partner, disease setting, and several other important clinical questions remain undefined.



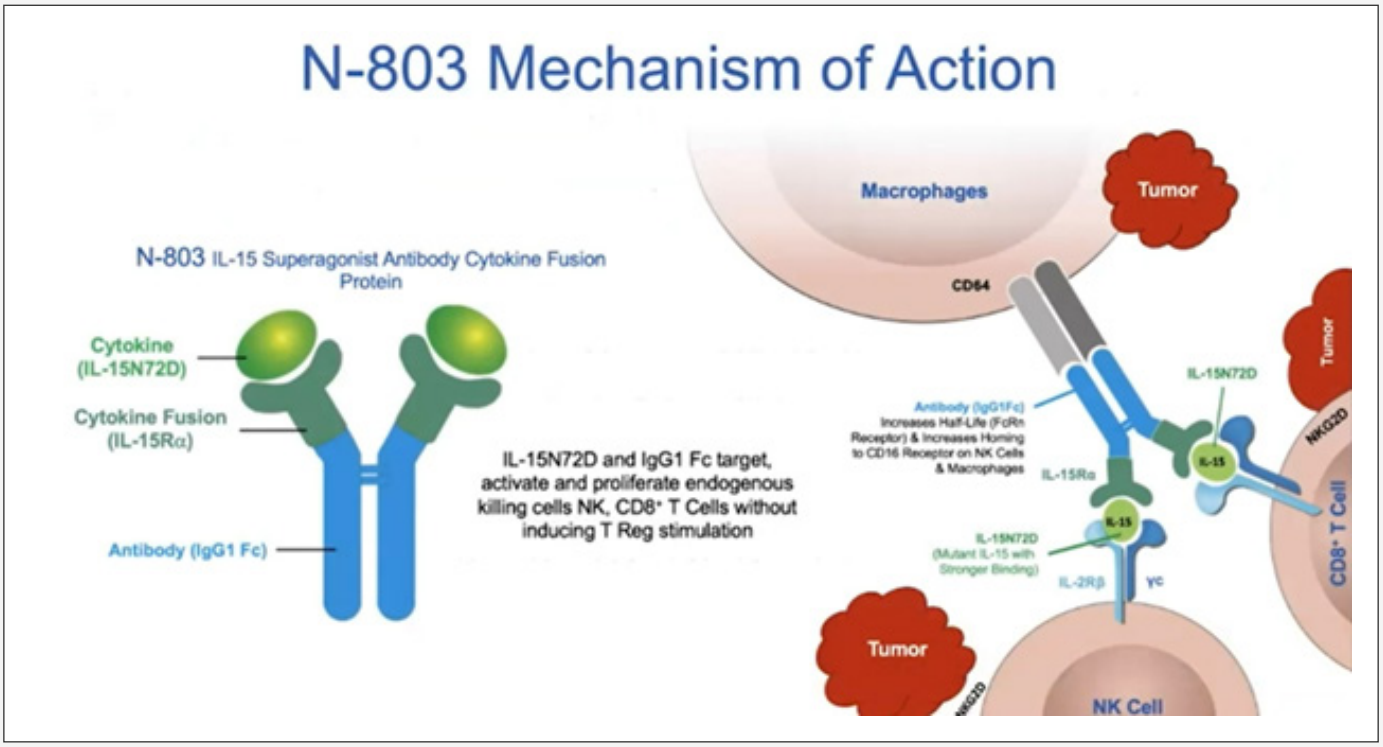


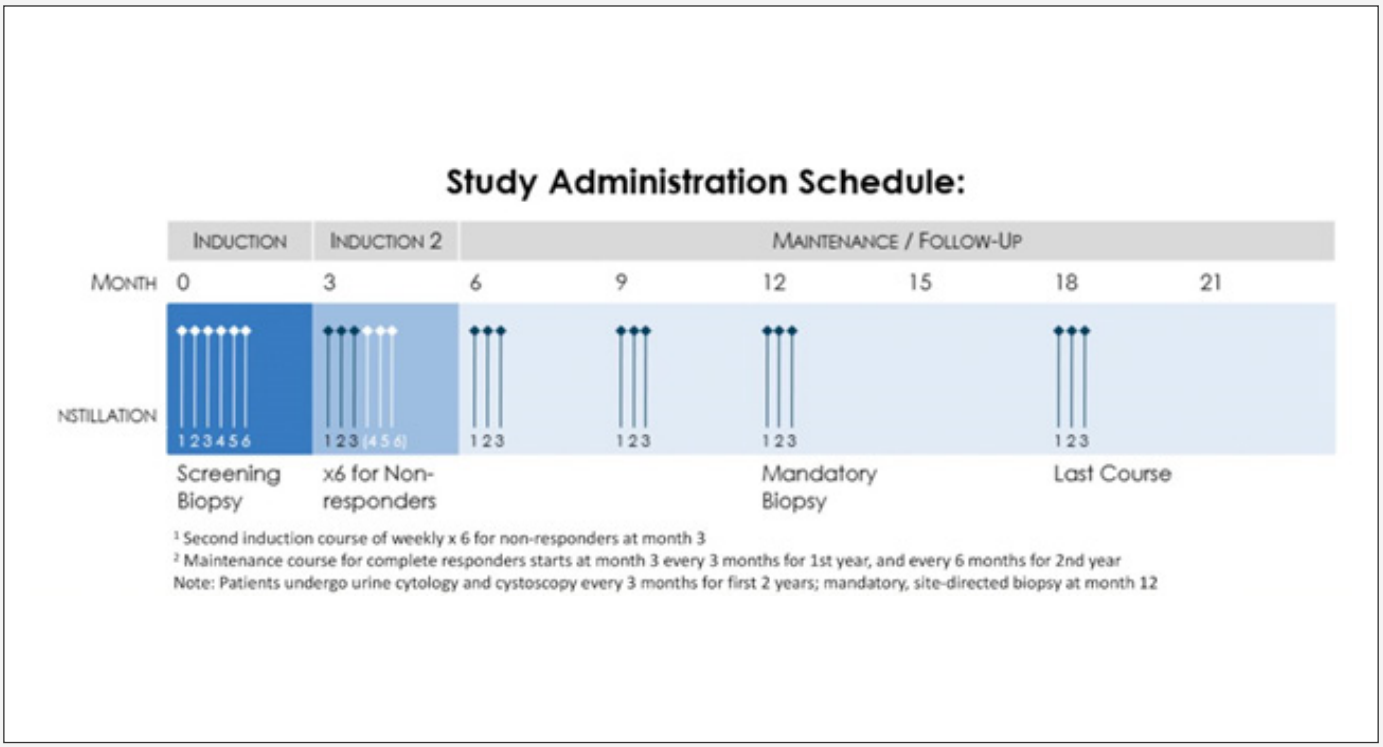
New activity in the BCG Unresponsive Space

Despite its success, many patients with high-risk non-muscle-invasive bladder cancer treated with BCG eventually develop BCG-unresponsive disease. Bladder sparing therapeutic options for these patients remains limited. Two studies were reported in the BCG Unresponsive space at ASCO-GU 2022. In a phase 3 trial assessing combination therapy using IL-15Rα Fc superagonist N-803 (Anktiva) and BCG, Dr. Sam Chang reported complete response rates of 71% (95% CI 60.1 – 80.5%) at any time, with median duration of response of 24.1mo and a 55% probability of maintaining response for ≥18mo in a cohort of 83 patients with CIS containing BCG Unresponsive NMIBC. The cystectomy-free rate in responders was 93%. Among 77 patients with papillary only disease, the 12-month disease free rate was 57% and 53% at 18-month. Similarly, a 95% cystectomy-free rate was seen at 20.7-month median follow-up. The treatment combination was also well tolerated, with no treatment-related grade 4/5 adverse events, and no immune-related adverse events. Despite these exciting results, treatment efficacy does depend on combination with BCG, and administration of this combination will be impacted by the ongoing global BCG shortage.

GU-ASCO 2022 Round up

Dr. Edward Uchio presented a trial in progress for a Phase III trial using an intravesical oncolytic virus CG0070 for the treatment of BCG-unresponsive CIS patients. The study aims to accrue a total of 110 patients to be treated with an intravesical dose of 1x1012vp of CG0070 weekly x 6, followed by weekly x 3 maintenance instillations at months 3, 6, 9, 12, and 18, with patients having persistent CIS or HG Ta at 3mo eligible for re-induction. The primary endpoint of the study is the complete response rate at any time as assessed by cystoscopy, urine cytology, and for-cause biopsy. These two trials are at the forefront of an exciting disease space with several different agents currently being investigated. Final results from these trials are anxiously awaited.





SIU Master Class by IBCG

IBCG's proposal for an instructional course has been accepted by the SIU for 2022 and will be held at its 42nd Congress in Montreal, Canada - November 9-13, 2022. (details listed below)
Please mark your calendars and we will have additional information soon.

Course: IBCG Master Class on BCG (and beyond)

Co-Chairs:

- Ashish Kamat, MD MBBS
  - o Tenured and Endowed Professor of Urologic Oncology (Surgery) and Cancer M.D. Anderson Cancer Center

- Roger Li, MD
  - o Assistant Member- Department of Genitourinary Oncology H.LEE. MOFFIT Cancer Center

Speakers:

- Roger Li, MD

- Andrea Kokorovic, MD
  - o Urologic oncologist at University of Montréal Hospital Center

- Patrick J. Hensley, MD
  - o Urology-M.D. Anderson Cancer Center

Learning objectives:

- Familiarize with literature on diverse BCG dosing regimens and oncologic efficacy to optimize dosing schedule during BCG shortage
- Understand the existing and emerging intravesical therapy regimens for high-risk (HR) non-muscle invasive bladder cancer (NMIBC) in the age of BCG shortage
- Define BCG Unresponsive NMIBC
- Understand the existing and emerging bladder sparing therapies for BCG unresponsive NMIBC
- Understand timing and indications for radical cystectomy (RC) in HR NMIBC

https://www.siu-urology.org/congress

Improved therapies in non-muscle invasive bladder cancer

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Current bladder cancer management is far from optimal. Adjuvant therapy after macroscopic complete transurethral resection of bladder tumors (TURBT) for non-muscle invasive bladder cancer (NMIBC) consists of the intravesical instillation of a cytotoxic drug or bacillus Calmette-Guerin (BCG) immunotherapy(1). Regardless of these bladder instillations, 5-year recurrence rates and progression to muscle-invasive disease (MIBC) rates of up to 52% and 20%, respectively, are common(2).

A recent thesis defended on 11th June 2021 at the Radboudumc, The Netherlands, describes several techniques for the treatment of bladder cancer, with an emphasis on prolonging intravesical drug exposure and on the use of hyperthermia in non-muscle-invasive and localized muscle-invasive disease. Three general principles were evaluated, i.e. the prolongation of drug exposure, improved drug tissue penetration using hyperthermia, and systemic drug application with localized drug release using intravesical hyperthermia. A summary of the discussion of this thesis was made in a series of three. Here, part one of this summary is presented.

Prolonged drug exposure

A short intravesical residence time, air bubbles, local adverse events such as urinary frequency and urgency, drug dilution or degradation by urinary production or acidity, the urothelial barrier function, and tumor-related factors such as decreased drug sensitivity all contribute to a suboptimal efficacy. Basic measures such as decreasing urine production and acidity, prescription of anticholinergic drugs, and positionary changes for air bubbles are important but will only modestly influence bladder tumor exposure(3). Techniques to improve tumor exposure time to intravesical drugs might improve treatment efficacy(4, 5).

The use of polymer hydrogels to slowly release drugs such as mitomycin C (MMC) has potential to improve tumor exposure time: exposure time is increased 3-48h depending on the gel type, the instilled volume and the optional combination with other techniques(6, 7). Since the cell cycle time of human bladder cancer cells is about 48-72h(8), this might be still too short to achieve additional benefit. The use of a thermosensitive hydrogel which solidifies at body temperature has shown good efficacy in rats(9). However, efficacy was similar to the MMC control group which was most likely caused by a too high dose of MMC to detect any difference. Toxicity of hydrogel encapsulated MMC was high and was regarded as a surrogate marker for a higher systemic exposure supporting the prolonged drug release mechanism. Toxicity in humans is expected to be lower compared with rats, which are known to be more sensitive to MMC(10). In other preclinical studies investigating hydrogels with different physical characteristics(6, 7, 11-13), materials were combined with nanoparticles (11, 13), epirubicin(12), doxorubicin(6) and BCG(7). These studies also suggested prolonged exposure or enhanced drug penetration (7, 11-13) with some hydrogels prolonging exposure to up to 7 days if combined with other encapsulating techniques such as liposomes(11). A single recent study on the use of 6 weekly instillations of MMC in hydrogel in low grade intermediate risk NMIBC patients showed a complete response rate at 3 months of 65% (41/63) with sustained short term response (14). However, comparison with MMC in water was lacking. Altogether, more convincing evidence for the additive value of hydrogels in bladder cancer patients is needed before clinical implementation is justified. Future studies with hydrogels should evaluate the effect of the increased exposure time on local and systemic toxicity as well as anti-tumor efficacy in humans. Extension to application of hydrogels for urothelial carcinoma in the upper urinary tract, which to date has only been evaluated in one single-arm study of 74 patients showing complete response in 59% of patients but a high rate of adverse events, would then also become interesting(15).

Improved therapies in non-muscle invasive bladder cancer

Similar to hydrogels, the Gemcitabin Releasing Intravesical System (GemRIS) provides a mechanism to prolong drug exposure. Gemcitabin is a commonly used drug in MIBC(16) and has been used in NMIBC bladder instillations(17, 18), although not as first choice due to more adverse events and less clinical experience compared to the other agents (i.e. MMC and epirubicin) (1). The small molecular structure and quick systemic metabolization make it suitable for loading into the GemRIS providing a constant cytotoxic concentration (> 10 µg/mL) of urinary gemcitabine for at least 4-5 days.

Although the GemRIS proved safe and generally well-tolerated in a phase 1b study, the preliminary efficacy in low grade pre-TURBT patients was low (unpublished data). Evaluation of GemRIS' ability to reduce tumor recurrence by eliminating re-implantation of tumor cells and residual tumor in the adjuvant setting for NMIBC would be interesting. In addition, since high grade NMIBC or MIBC cells are highly dedifferentiated and exert a short cell-cycle time, it might make them more susceptible to prolonged exposure to chemotherapeutic agents in a neoadjuvant setting prior to either TURBT or radical cystectomy. Preliminary data on treatment of cN0M0 MIBC patients in the neoadjuvant setting showed clinical down-staging and reduction of the tumor size in 80% (8/10) of patients(19). The next logical step would be to evaluate a larger patient cohort for short- and long term efficacy. Effect on the presence of (microscopic) node metastasis should be carefully included in these studies as gemcitabine might exert its effect also on lymph nodes via the lymphatic vessels or immune stimulation. Since current neoadjuvant chemotherapy in MIBC disease should be cisplatin based(16), loading of GemRIS with cisplatin might further increase clinical relevance of these studies. Combination of GemRIS with systemic therapy such as immunotherapy with PD-L1 or PD-1 inhibitors(19), might prove even more effective as a neo-adjuvant or even bladder preserving option in the future.

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