INTERNATIONAL
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IBCG

International Bladder Cancer Group

Newsletter

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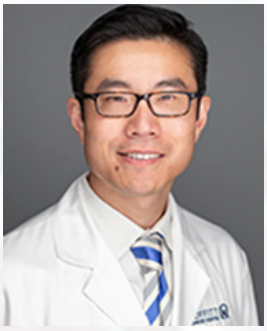

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AUA-2024 Summary

The American Urological Association Annual Meeting was held May 3-6, 2024, in San Antonio, Texas. The meeting included a number of notable plenaries, didactic, and clinical trial sessions dedicated to bladder cancer.

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During Friday's plenary session, a debate-style discussion, moderated by Dr. Eila Skinner, highlighted patient selection for ileal neobladder vs. ileal conduit urinary reconstruction after radical cystectomy for bladder cancer. Dr. Anne Shuckman argued that there are few absolute contraindications for neobladder, including severe renal or hepatic dysfunction, compromised intestinal function (including inflammatory bowel disease), and urethral stricture disease. Notably, these contraindications do not include oft-referenced age and sex. Additionally, several retrospective studies have exhibited similar renal functional decline between continent diversion and ileal conduit urinary diversion following surgery, in addition to similar post-operative infectious complications. The rate of stoma-related complications, including retraction/stenosis, parastomal hernia, prolapse, and skin irritation are not to be understated. From a quality of life standpoint, there have been conflicting data in the literature when comparing neobladder vs. conduit. However, Dr. Mark Tyson argued that significant lifestyle advantages exist to neobladder reconstruction, including improved physical function, sexual function, as well as mental and social health related to positive body image. With an estimated long-term catheterization rate of 10% necessary for neobladder patients, voiding dysfunction is often over-emphasized during patient counseling.

Dr. Josh Meeks took the counterargument, citing patient expectations that their neobladder will be physiologically similar to their native bladder, can be a source of frustration. Neobladder function declines with time, characterized by worsening daytime continence and increased nocturnal incontinence. Notably, the rates of urinary incontinence or hypercontinence requiring catheterization are much higher in women, with nearly half of women relying on intermittent self-catheterization in longitudinal follow-up. Dr. Amy Luckenbaugh discussed that ileal conduit urinary diversion is associated with shorter operative time, shorter length of stay, as well as decreased post-operative complications and unplanned readmissions.

Ultimately, while we guide our patients through thoughtful education, our discussions regarding urinary diversion techniques should be fair, balanced, and patient-centered to improve patient outcomes and limit decisional regret.

AUA 2024 Summary

On the heels of the FDA's approval of ANKTIVA for BCG-unresponsive NMIBC, Dr. Patrick Soon-Shiong, Chairmen of ImmunityBio, provided a comprehensive discussion on next generation immunotherapy for non-muscle-invasive bladder cancer (NMIBC). To frame the discussion, Dr. Soon-Shiong discussed mechanisms for BCG and immuno-oncologic (IO) failure. Through the expression of MHC on the surface of tumor cells, dendritic cells are trained to recognize BCG-infected bladder cancer cells to generate killer T cells. CD8+ memory T cells exhibit therapeutic failure upon loss of MHC expression on the cancer cell surface, a so-called "cold" tumor, with MHC-negative clonal selection resulting in T cell immune evasion.

Targeting MHC-negative cells is a novel therapeutic approach to overcoming acquired resistance to traditional chemotherapy and immunotherapy. Natural killer (NK) cells are programmed to identify MHC-negative tumor cells. As a result, gamma interferon is released and acts in a paracrine fashion to restore MHC on the tumor cell surface, effectively converting a "cold" tumor to a "hot" tumor. ANKTIVA (N-803) is an IL-15 receptor superagonist consisting of an IL-15 mutant fused with an IL-15 receptor alpha, which binds with high affinity to IL-15 receptors on NK, CD4+, and CD8+ T cells. Mimicking the role of a dendritic cell, intravesical instillation results in the generation of both memory and killer CD8+ T cells, leading to a durable response.

Based on results from the QUILT 3.032 trial, the drug has been FDA-approved when combined with BCG for BCG unresponsive NMIBC. To further parse out the additive effect of ANKTIVA over BCG alone in the combination trial, Dr. Soon-Shiong referenced data from QUILT 2.005, a randomized trial of BCG vs. BCG + ANKTIVA for BCG-naïve NMIBC. Accordingly, the complete response rate in Cohort A (CIS) at any time was 85% in the combination group and 61% in the BCG-alone group, with sustained complete response rates being higher for BCG + ANKTIVA (median duration not reached). Considering the global BCG shortage, ImmunityBio took the exciting step of partnering with the Serum Institute of India for large-scale BCG production.

On Sunday, Dr. Joseph Jacob presented results from Cohort 2 (TAR-200 alone) of the ongoing SunRISe-1 study in BCG unresponsive NMIBC. The complete response rates at 6 and 12 months were 75.7% and 61.9%, respectively, in the TAR-200 monotherapy group. Clinical response was characterized as rapid onset (98% of complete responses achieved at the first disease assessment at week 12) and durable (74.6% with an 18-month duration of response). The therapy was well tolerated, with mostly grade 1-2 toxicities and few treatment discontinuations.

Dr. Mark Tyson presented updated results from BOND-003, a phase 3 study of intravesical Cretostimogene Grenadenorepvec for BCG unresponsive NMIBC. In a cohort of 105 patients with BCG unresponsive CIS, the complete response rate at any time was 75.2%. Notably, 53.8% of patients achieved a complete response upon repeat induction, and there was a 96.7% progression free survival rate at 12 months. The treatment was very well tolerated, with no grade ≥3 toxicities.

A new program titled "Clinical Trials in Progress" was introduced at AUA 2024, highlighting ongoing trial design, methodology, and eligibility criteria. The bladder cancer session was chaired by Drs. Bernard Bochner and Karim Chamie. Several randomized trials in the intermediate-risk NMIBC disease space were discussed, including MoonRISe-1 (Phase 3 study of TAR-210 vs. chemotherapy in FGFR altered tumors) and PIVOT-006 (Phase 3 study of Cretostimogene vs. surveillance). Three ongoing single-arm BCG unresponsive trials were presented: BOND-003 (Cretostimogene) Cohort P (papillary-only disease), Orion-BC (paclitaxel-hyaluronic acid), and SSANTROP (Sasanlimab + Sacituzumab).

EAU 2024: Bladder Cancer Highlights

The **Rapid Fire Debates in Bladder Cancer**, chaired by Prof. Kamat and Prof. Stenzl, was the highlight of Friday's program – the most attended event, a testament to its value and relevance. The lively and thought-provoking debates, designed to foster a collaborative atmosphere, not only offered valuable insights into the current challenges faced in clinical practice but also ignited discussions on the most effective management strategies.

Over the weekend, a number of impactful abstracts on bladder cancer were presented, each contributing to our understanding of this complex disease.

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Non-Muscle Invasive Bladder Cancer

Guiding adjuvant instillation in intermediate risk NMIBC by drug screens in patient-derived organoids.

Egger et al. presented an update on a Phase II clinical trial aimed at guiding adjuvant instillation in IR-NMIBC using patient-derived organoids to determine tumor response to four chemotherapeutic agents (epirubicin, mitomycin C, gemcitabine, and docetaxel). Thirteen patients have enrolled with successful model and drug screen outcomes in all cases. Recruitment for the trial is ongoing. From a resource standpoint, the use of PDOs may not be practical for all IR-NMIBC cases, but it offers a promising individualized approach for patients with recalcitrant tumors and frequent recurrences. The final results are eagerly awaited.

Reducing the number of flexible cystoscopies in patients undergoing follow-up for non-muscle invasive bladder cancer with either flexible cystoscopy or the urinary biomarker test Bladder Cancer Monitor: A secondary outcome from a randomized clinical trial

Dreyer et al. presented an update from the DaBlaCa-15 non-inferiority RCT, comparing the number of cystoscopies in patients with HG-NMIBC undergoing cystoscopy q4 mos. vs urinary biomarker test Xpert® Bladder Cancer Monitor surveillance q4 mos. with one annual cystoscopy (n=313). Importantly, this study enrolled patients with high-grade tumors at various stages of their disease trajectory, including at the time of diagnosis, while receiving maintenance intravesical therapy, or up to two years after diagnosis. Patients with UTUC within 5 years and HGT1 tumor without re-resection were excluded. The intervention arm required significantly fewer cystoscopies (345) than the control arm (740). The authors suggest non-inferior RFS in the intervention arm and low risk of progression in the total study population, with data forthcoming later this year. Is the level-one evidence we need for routine clinical use of urinary markers on the horizon?

The impact of centralized uropathology review in the management of bladder cancer patients at the time of transurethral resection of the bladder.

Robersti et al. presented data examining 272 TURBT specimens from 231 patients seeking a pathologic second opinion from a fellowship trained uropathologist. Major discordance with changes in management according to European Association of Urology (EAU) guidelines was observed in 28% of cases. These findings support centralized pathologic review by an expert uropathologist in all cases; at the very least, patients should be informed of the option and its implications. Considering feasibility challenges and current resource limitations, we need to identify which patients benefit more precisely from a second opinion; perhaps future integration of AI for quality control and flagging specimens for central review could streamline this process.

Muscle Invasive Bladder Cancer

Clinical outcomes in patients with high-risk, post-cystectomy muscle-invasive bladder cancer (MIBC) with persistent circulating tumour DNA-negative (ctDNA-) status on serial testing: surveillance analysis from the IMvigor011 study

Powles et al. presented an analysis from the IMvigor011 surveillance cohort, focusing on high-risk post-cystectomy MIBC with persistent ctDNA negative status on serial testing. Over a median follow-up of 16 months, 17 DFS events occurred out of 171 patients. Serially negative ctDNA status demonstrated strong prognostic value, with an 18-month DFS rate of 88%. However, 10% of patients relapsed radiographically despite negative ctDNA, suggesting the inability to replace radiographic surveillance completely.

Extended follow-up from CheckMate 274 including the first report of overall survival outcomes.

Galsky et al. presented extended follow-up data from CheckMate 274 evaluating adjuvant nivolumab versus placebo after surgery for patients with ypT2-4a or pT3-pT4a or (y)pN+ MIBC. The trial previously met both its primary endpoints, DFS in the ITT population and patients with tumor PD-L1 expression ≥ 1%. With extended follow-up, the study continues to show DFS benefits. New interim OS data favors adjuvant nivolumab with a median OS of 70 months vs 50 months HR 0.76 (0.61-0.96). This is in contrast to trials evaluating pembrolizumab (OS HR 0.98) and atezolizumab (OS HR 0.85).

Positive ctDNA status before radical cystectomy predicts lymph node status and pathological upstaging.

Ben-David et al. presented a retrospective study of serial tumor informed ctDNA (Signatera) in 112 patients undergoing RC with a median follow-up of 8 months. Positive preoperative ctDNA status was associated with an increased risk of node-positive disease, variant histology, and locally advanced disease (≥ pT3). While prognostic, the clinical utility of preoperative ctDNA in guiding neoadjuvant treatment is not yet known. Notably, the tumor-informed ctDNA approach requires an adequate TURBT specimen and initial specimen processing takes 3-6 weeks.

The role of androgen response pathway in association with tumor biology and response to neoadjuvant ICI in MIBC.

Tateo et al. presented a retrospective transcriptome-wide expression profiling (Decipher) focusing on AR gene expression of 102 TURBT samples from patients in the PURE-01 study. The AR gene expression and androgen response signature were highly expressed in luminal tumors vs other subtypes ($p=0.005$ and $p<0.001$). Androgen response signature scores were significantly lower in ypT0N0 responders ($p=0.03$). While AR signaling is known to promote CD8 T cell exhaustion and

impair the efficacy of ICI in preclinical models, this is the first study to report the androgen response pathway as a potential biomarker of ICI benefit in MIBC. Nonetheless, these results require cautious interpretation without a comparator group not treated with ICI.

Metastatic Bladder Cancer

Enfortumab vedotin and pembrolizumab (EV+P) versus chemotherapy (chemo) in previously untreated locally advanced or metastatic urothelial carcinoma (la/mUC): Results from the global phase 3 EV-302/KEYNOTE-A39 study.

Powles et al. presented a subgroup analysis from the EV-302/KEYNOTE-A39 study. The PFS and OS benefit was consistent with the overall population in all pre-specified subgroups, including upper tract and lower tract disease groups, reaffirming EV+P as the standard first line treatment in both groups. For upper tract with EV+P vs chemo, mPFS was 12.7 mos vs 6.2 mos HR 0.50 (0.35–0.71), and mOS NR vs 18.4 mos HR 0.53 (0.34–0.83). For lower tract disease, mPFS was 12.5 mos vs 6.3 mos HR 0.44 (0.35–0.54), and mOS was 31.5 mos vs 15.6 mos HR 0.46 (0.36–0.59).

Membranous NECTIN-4 expression in metastasis versus matched primary tumor more accurately predicts enfortumab vedotin response.

Büttner et al. conducted a follow-up study to their previous investigation, examining NECTIN-4 expression in primary tumors versus distant metastatic sites. Their initial research revealed decreased NECTIN-4 expression in metastatic sites vs primary tumors. In this retrospective sample of 26 patients with metastatic UC treated with EV, they explored the predictive value of membranous NECTIN-4 expression in primary tumors versus distant metastasis. NECTIN-4 expression correlated with improved PFS, particularly when analyzing tissue from metastatic sites compared to primary tumors. Utilizing NECTIN-4 expression from metastatic tissue biopsies as a predictive biomarker has the potential to aid in treatment decision-making, potentially avoiding unnecessary costs and drug toxicity in patients unlikely to benefit from EV.

All stages

Development of the Bladder Utility Symptom Scale (BUSS utility): A novel tool to measure utilities and quality of life in bladder cancer patients.

Kulkarni et al. presented the development of the Bladder Utility Symptom Scale (BUSS utility). Patient utilities critically impact comparative effectiveness and cost-effectiveness analyses. The previously validated BUSS-P tool was utilized to elicit time tradeoff utilities. This is the first instrument to provide utilities derived from both patients (n=200) and the general public (n=200). These data in all phases of BCa will facilitate robust cost-effectiveness and decision-modeling work.

A patient-derived bladder cancer organoid biobank for translational research and precision oncology.

Garioni et al. aimed to establish an expandable living biobank of patient-derived organoid models. 95 samples were collected and processed from 52 patients with MIBC and 38 patients with NMIBC to generate organoids and tumor/organoid pairs. Of the 18 samples maintained for more than five passages, 10 PDO lines from different bladder cancer subtypes were selected and phenotypically characterized. Selected lines highly resembled their original tumors. PDOs displayed either a pure luminal (CK8+), a pure basal (CK5+), a mixed basal-luminal (CK5+ and CK8+ cells), or a sarcomatoid (Vimentin+) phenotype. Preliminary in vitro drug screens revealed significant differences in the response of each PDO line toward various therapeutics. This PDO biobank will serve as a valuable resource for translational research and precision oncology applications, offering insights into tumor response to therapeutics and potential biomarkers of drug sensitivity.

IBCG AT AUA-2024

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The International Bladder Cancer Group session at the AUA was held in San Antonio, Texas on May 5, 2024. The meeting was co-chaired by Drs. Janet Kukreja and Ashish Kamat. In true collaborative fashion, the meeting began with an energizing walk to end bladder cancer. The 2024 AUA session mission was to engage in discussing the complexities of diagnosing and managing bladder cancer, with particular emphasis on emerging treatments and techniques.

The session began with a debate-style format discussion of the role of urinary markers in the surveillance of NMIBC. A poll of the audience demonstrated that 85% of the audience members do not use additional markers besides cytology in intermediate-risk NMIBC. Several FDA approved urinary markers (CxBladder, UroVysion, ImmunoCyt, NMP22, etc.) demonstrate sensitivity of 60-70% but specificity lower than urinary cytology[1]. Dr. Kelly Bree argued for utilizing urinary markers in intermediate risk by alternating markers and spacing out the frequency of cystoscopy to reduce frequency of cystoscopy without compromising oncologic outcomes. Dr. Kamal Pohar highlighted that currently trials fall short of guidance, but a future randomized trial led by Dr. Florian Schroeck looking to answer this question, will be helpful. In higher-risk patients, a singular biomarker has not outperformed cystoscopy with cytology and there was agreement that one should not be used in place of a visual assessment.

Dr. Badrinath Konety and Dr. Jeremy Teoh continued the session discussing optimal TURBT technique and whether all HG NMIBC requires re-resection. An audience poll demonstrated that 29% recommended all receive re-TUR, 55% for T1 only, and 16% for none. The discussion centered on the presence of muscle in the specimen, visual completeness of resection, and utilizing the en-bloc resection technique. Dr. Konety highlighted a large systematic review which demonstrated that in patients with Ta disease 0-8% were upstaged and with T1 disease 0-32% were upstaged[2]. While en-bloc could be an effective methodology, it is feasible for tumors <3cm and is not universally adopted. While this is an evolving debate, at present there is still significant data to continue performing re-TUR.

The following session centered on the management of recurrent LG intermediate-risk bladder tumor. Dr. Sarah Psutka focused on de-escalation, given high recurrence rates, up to 80% at 5-years. Additionally, >95% of these recurrences low grade and costly, with perioperative risks and financial toxicity[3]. She focused on options for management including in office fulguration and chemoablative options without resection, highlighting improved benefits and low oncologic risks. Dr. Param Mariappan focused on the evidence heterogeneity, with up to 20% of tumors thought to be LG on visual inspection representing HG disease, high rates of surveillance failure and recurrences with chemoablation, and advocating for a nuanced approach focused on patient quality of life and symptoms[4].

Very high risk NMIBC with variant histology was addressed by Dr. Paolo Gontero and Dr. Michael Cookson, with the latter advocating for a thoughtful approach with proper staging, repeat resection, and vigilant surveillance when bladder sparing options are selected. Dr. Gontero highlighted the low-quality evidence available in variant histology and that conservative measures should prevail with early cystectomy, especially for plasmacytoid variants[5].

Next, we discussed BCG unresponsive disease with Drs. Sima Porten and Roger Li. Dr. Porten presented data to suggest that one line of therapy after being BCG unresponsive is reasonable, however significant delay to cystectomy can demonstrate worse oncologic outcomes. Dr. Li argued for repeat intravesical options, especially when clinical factors allow, and suggested focusing on the durability of subsequent intravesical treatments. This is an evolving area that was featured at the 2023 IBCG Forum.

Drs. Seth Lerner and Sia Daneshmand discussed the findings of S1011 and the LEA trials, describing standard template of lymph node dissection in radical cystectomy. Dr. Lerner described increased mortality risk for extended lymph node dissection with no benefit in overall survival. He suggested reasons to possibly explain these findings: very meticulous standard dissection, high use of neoadjuvant chemotherapy, use of adjuvant chemotherapy, and predominant T2-T4a disease/N0-2 inclusion[6]. Dr. Daneshmand discussed the retrospective data demonstrating the benefit of extended PLND of 5% in 5-year RFS, highlighting that the number needed to treat may not have been reached in powering the RCTs and that there are still select cases in which it has a role[7].

The next session focused on use of biomarkers and imaging to avoid local consolidation of MIBC after neoadjuvant chemotherapy or immunotherapy. The audience poll suggested that 75% of members did not think that markers can help patients avoid consolidative therapy. Dr. Petros Grivas presented data for future molecular biomarkers which could help select patients who have higher chance of achieving complete response with systemic therapy and avoid radical surgery/radiation. He highlighted use of mpMRI and ctDNA data to help predict clinical complete response in patients, but agreed that this is nascent work which is exciting but perhaps not yet ready for prime time.

Finally, the session concluded with a discussion of recently reported clinical trials, highlighting paradigm-shifting data for metastatic urothelial carcinoma with enfortumab+pembrolizumab. In the EV-302 trial comparing EV+P to cisplatin-based chemotherapy, overall survival for EV+P nearly doubled, 31 months versus 16 months for chemotherapy (HR 0.47), a significant mortality reduction for patients who received EV+P. Furthermore, they discussed patients who achieved complete response. In the trial, around 29% of patients achieved complete radiographic response in the arm of EV+pembrolizumab. If patients have a complete response, which is sustained, this presents a clinical challenge as the data is unclear on de-escalation protocols. Lastly, there will certainly be questions of sequencing as EV+pembrolizumab moves earlier in the treatment line and how this will impact response to further lines of therapy.

The session was lively, prompted excellent debate and engagement, and highlighted areas for further exploration. The IBCG retreat will be held on August 22- 24, 2024 in Houston, Texas and will focus on establishing recommendations for intermediate risk NMIBC as well as sequencing of therapy in MIBC.

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Now in our 19th year, **the Bladder Cancer Advocacy Network has committed more than $10 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 2025. Our in-person and virtual walks raise spirits and raise funds to defeat bladder cancer. Please visit **bcanwalk.org**.

Gem/Doce in 2024: What is Next?

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Sequential intravesical gemcitabine and docetaxel (Gem/Doce) has been a notable advancement in the treatment of non-muscle invasive bladder cancer (NMIBC) since Michael O'Donnell developed this regimen in 2009.[1] Following its initial publication in 2015, Gem/Doce has continued to gain traction in the urologic oncology community for various challenging situations. This therapy began as a long-needed option for disease unresponsive to bacillus Calmette-Guerin (BCG) and is now growing as an effective alternative first-line agent during chronic BCG shortages. As we move into an era of increasing therapy options for NMIBC, it is beneficial to evaluate the pros and cons of Gem/Doce, and what the future holds for this regimen.

When Gem/Doce was first utilized for treating disease refractory to bacillus Calmette-Guerin (BCG), it proved significantly more effective than available bladder-sparing alternatives of that time.[1] A landmark multi-institutional analysis by Steinberg et al. in 2020 demonstrated that the 2-year recurrence-free survival (RFS) for patients with BCG-unresponsive NMIBC was 50%, a rate that remains superior to the currently FDA approved and highly costly therapies such as Pembrolizumab, Adstiladrin, and Anktiva.[2–5] This efficacy has been replicated in subsequent studies.[6,7] Long-term evaluations have also shown that, compared to Adstiladrin, twice as many patients can avoid cystectomy at 5 years with Gem/Doce.[8,9]

As the ongoing BCG shortage persists, Gem/Doce has increasingly shown promise in the high-risk, BCG naïve setting. McElree et al. reported that a cohort of 107 patients receiving Gem/Doce for treatment-naïve high-risk NMIBC experienced a 2-year RFS of 82%.[10] A follow-up comparative study revealed that Gem/Doce provided superior 2-year high-grade RFS (81% Gem/Doce versus 69% BCG), although the majority of patients who received BCG in that study received 1 year of maintenance.[11] This result has been confirmed by other series and a prospective Phase II study of 25 patients who received Gem/Doce and had a 1-year RFS of 92%.[12,13] The ongoing ECOG prospective BRIDGE trial, which aims to randomize 870 patients to either BCG or Gem/Doce, is embraced by the bladder cancer community and has already completed over 50% of its accrual.[14]

Gem/Doce in 2024: What is Next?

The use of Gem/Doce has continued to expand beyond high-grade NMIBC to include intermediate-risk and low-grade tumors. Initial and multi-institutional reports indicate that the overall 2-year RFS of Gem/Doce ranges from 70-80%.[15,16] However, the regimen's effectiveness decreases in patients with a history of recurrent disease or when maintenance therapy is not used.[15] Furthermore, topical therapies have selectively been utilized for non-invasive completely ablated upper tract urothelial carcinoma (UTUC) or CIS of the upper tract.[17] During the BCG shortage, Gem/Doce for UTUC was explored and appears to have equivalent safety and efficacy.[18,19] Finally, the regimen has been tested in the context of resected prostatic urethral CIS, indicating its potential versatility in various bladder cancer scenarios.

Interestingly, the efficacy of Gem/Doce in treatment-naïve high-grade and low-grade NMIBC has been very comparable across studies.[11,15] This consistency, along with the regimen's favorable tolerance (<4% discontinuation), efficacy, low cost, and consistent availability, supports the argument for a non-risk adapted approach to its use.[20] In oncology, non-risk adapted management strategies have been successfully employed in some contexts, such as the recent widespread adoption of non-risk adapted surveillance of clinical stage I germ cell tumors. However, the broader trend in oncology is moving towards precision medicine and tailored treatment approaches, which holds true for NMIBC as a myriad of promising biomarkers and targeted therapies are emerging. While non-risk adapted utilization may be optimal now, there will be a future need to integrate Gem/Doce into evolving precision treatment paradigms.

Despite its advantages, Gem/Doce faces several challenges. The logistical demands of the regimen are cumbersome and financially burdensome, especially from the perspective of "tying up" rooms during dwell times. Additionally, most of the supportive data for Gem/Doce comes from retrospective studies, and prospective validation is needed for more contexts than the newly diagnosed high-grade setting, which is currently being evaluated by the BRIDGE trial. Several key questions remain about the optimal administration of Gem/Doce. For example, while the original protocol for Gem/Doce recommended 90-120 minute dwell time for each agent, recent studies have shown similar results using 1 hour dwell time for each.[12] Furthermore, the ideal duration and role of maintenance need further investigation. While the original 2-year maintenance is effective and necessary for high-grade disease, this may be overtreatment for intermediate-risk disease.[21] While there is a substantial ongoing body of research assessing predictors of response to BCG, similar efforts are needed for Gem/Doce to fully understand its mechanisms and optimization.

As we look to the future, Gem/Doce represents a promising treatment option for NMIBC, with ongoing studies and emerging data poised to further refine its role in bladder cancer management. The current enthusiasm for this regimen is tempered by practical challenges and unanswered questions. Novel research and future studies from the IBCG and others will be essential to address these questions and improve care for our patients. Much work remains to be done!

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ASCO 2024
Bladder Cancer Updates

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1. Patient-reported outcomes (PROs) from a randomized, phase 3 trial of enfortumab vedotin plus pembrolizumab (EV+P) versus platinum-based chemotherapy (PBC) in previously untreated locally advanced or metastatic urothelial cancer (la/mUC). S Gupta, Y Loriot, M Simon Van Der Heijden, et al

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EV+P nearly doubled median PFS and OS versus platinum-based chemotherapy in patients with previously untreated locally advanced or metastatic urothelial cancer in the phase 3 EV-302 trial, and is NCCN category 1 and ESMO guidelines preferred treatment option.
PRO assessments included the EORTC Quality of Life Questionnaire (EORTC QLQ-C30), and the Brief Pain Inventory Short Form (BPI-SF) completed at baseline, weekly for 12 weeks, then every 3 weeks through survival follow-up, inclusive of the time post-progression. This is the unique aspect of the PRO collection as typically PRO collection stops at the end of treatment. Time to pain progression and mean change from baseline in worst pain at week 26 using the BPI-SF were prespecified analyses statistically tested using a gatekeeping strategy. Mean change from baseline through week 26 and time to confirmed deterioration of EORTC-QLQ-C30 and BPI-SF domains were prespecified descriptive analyses. Time to pain progression and time to confirmed deterioration were assessed using Kaplan-Meier methods. Patients with moderate-severe pain at baseline (around 1/3rd) were of special interest and those treated with EV+P had a meaningful improvement from baseline in BPI-SF worst pain from weeks 3 through 26. The Global Health Status (GHS) and QOL was improved with EV+P for both cisplatin eligible and cisplatin ineligible patients and outperformed platinum chemotherapy.

Key Takeaways:

EV+P significantly improves PFS and OS compared to platinum-based chemotherapy without detriment to quality of life and functioning.

Patients with moderate to severe pain treated Ev+P demonstrated clinically meaningful improvements in worst pain and GHS/QOL.

Data collection across the entire patient journey was a notable approach and was associated with differences in compliance between treatment arms. Findings from this study may inform the design of future trials. Patient reported outcome data presented here complement the published clinical efficacy and safety data, add the patient perspective, and support the use of enfortumab vedotin + pembrolizumab for patients with previously untreated locally advanced or metastatic urothelial cancer.

2. Characterization of complete responders to nivolumab + gemcitabine-cisplatin vs gemcitabine-cisplatin alone and patients with lymph node–only metastatic urothelial carcinoma from the CheckMate 901 trial. MD Galsky, GP Sonpavde, T Powles, et al

https://doi.org/10.1200/JCO.2024.42.16_suppl.4509

The CheckMate 901 (NCT03036098) is a phase 3, multinational, open-label trial of Nivo-GC vs GC for up to 6 cycles, followed by nivolumab maintenance (at a dose of 480 mg) every 4 weeks for for up to 2 years.

Presented was a post hoc analysis of the subset of patients who had CR and had lymph node-only metastatic disease, a known favorable prognostic factor in UC. A total of 102/608 (16.8%) patients randomized achieved a CR, of whom 54 treated with Nivo-GC, and 56 in the GC alone group had lymph node-only mUC. The median OS in patients with lymph node-only mUC was 46.3 months with Nivo-GC vs 24.9 months with GC, and PFS was 30.5 months vs 8.8 months, respectively.

This analysis shows durable responses in with combination in lymphnode only mUC patients.

3. Perioperative sacituzumab govitecan (SG) alone or in combination with pembrolizumab (Pembro) for patients with muscle-invasive urothelial bladder cancer (MIBC): SURE-01/02 interim results. A Cigliola, M Moschini, V Tateo, et al

https://doi.org/10.1200/JCO.2024.42.17_suppl.LBA4517

SURE is a multi-cohort, open-label, phase 2 trial evaluating neoadjuvant SG in MIBC patients who were cisplatin-ineligible either as, monotherapy (SURE-01 trial, NCT05226117) or in combination with pembrolizumab, followed by postsurgical adjuvant pembrolizumab (SURE-02 trial, NCT05535218).

Patients with cT2-4N0M0 UC and ineligible for or refused neoadjuvant cisplatin-based chemotherapy received four 3-weekly cycles of SG at a dose of 10 mg/Kg on days 1 and 8 and subsequently underwent a radical cystectomy. The primary endpoint was ypT0N0 rate. Secondary endpoints included ypT≤1N0 rate, EFS, OS and safety. In the overall cohort of 21 patients, any grade treatment-related adverse events (TRAE) were observed in 81% of patients; grade 3 TRAEs in 33.3% and grade 4 TRAEs in 19.1% of patients. One patient experienced a treatment-related death from sepsis. The most common grade ≥3 TRAEs were neutropenia and diarrhea.

Eighteen out of twenty one patients completed all 4 cycles of SG; 11/18 patients underwent RC and 7 patients refused RC (6 due to clinical CR). The median time from end of SG to surgery was 6.9 weeks, pCR was seen in 4/11 (36.4%) and any ypT≤1N0 response was observed in patients (45%). One patient had disease relapse/progression during or post-SG. The protocol was amended to reduce dose of SG to 7.5 mg/kg and mandating primary G-CSF prophylaxis.

SIU Announcement

WE BRING UROLOGISTS TOGETHER

INTERNATIONAL BLADDER CANCER GROUP

The Société Internationale d'Urologie (SIU) announced that the IBCG will hold a Masterclass in Non-Muscle Invasive Bladder Cancer at the 44th Congress to be held from October 23 to 26, 2024 in New Delhi, India.

International Bladder Cancer Group (IBCG) Masterclass in Non-Muscle Invasive Bladder Cancer (NMIBC)

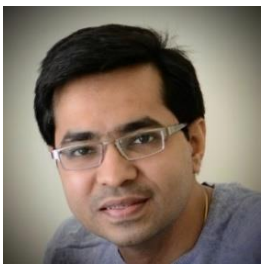
Chair- Shilpa Gupta, MD

Cleveland Clinic Foundation- Ohio, USA

Panel Members

Ashish Kamat, MD
MD Anderson Cancer Center
Houston, US

Andrea Necchi, MD
San Raffaele Research Hospital
Milan, Italy



Gagan Prakash, MD
Tata Memorial Centre
Mumbai- India

Instructional Course Description

NMIBC is a common and high-burden bladder cancer state, and an unmet need exists to advance treatments and maintain quality of life of patients worldwide. The IBCG Masterclass in NMIBC will review the risk classification of NMIBC, its nuances and how to select patients for the right approach. Novel treatments and strategies to allow for bladder preservation in BCG unresponsive NMIBC will be emphasized.
Dr. Gupta will present clinical cases for discussion with panelists, to get a global perspective on patient management.

Racial Disparities in Bladder Cancer

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Despite White patients exhibiting nearly twice the incidence of bladder cancer compared to Black patients, there exist well characterized disparate outcomes in bladder cancer-related mortality in Black patients[1-3]. These poor outcomes are thought to be multifactorial, with likely contributors including poor access to healthcare, implicit racial bias, and inherent genomic differences between White and Black patients. In a recent National Cancer Database study, Black patients with nonmetastatic muscle-invasive bladder cancer (MIBC) were significantly less likely to receive standard curative treatment, even when accounting for clinical factors and institutions[4]. Additionally, it is notable that racial differences exist in tumor biology[5-6], but high-quality genome-wide association studies have been stifled by underrepresentation of Black patients in publicly available genomic datasets.

The Veterans Affairs (VA) health system is the largest equal-access health system in the United States, and represents an ideal model to study the impact of access to care on outcomes. In their recent publication 'Racial disparities in stage at bladder cancer diagnosis in the US Veterans Affairs healthcare system', Bree at al. examined whether disparities in bladder cancer stage at diagnosis and stage-dependent survival exist in a racially admixed VA health system patient population[5].

The investigators identified nearly 70,000 VA patients diagnosed with bladder cancer over a 20-year period from 2000 to 2020. The cohort was comprised of 11% Black patients, which were characterized as having lower median household incomes and higher rates of comorbid illness compared to White or Hispanic patients. In univariable analysis, Black patients presented with higher rates of MIBC (≥cT2) compared to White patients (OR 1.15, 95% CI 1.04-1.28). However, on multivariable analysis controlling for socioeconomic factors, there was no significant different in stage at presentation between Black, White and Hispanic patients. Notably, after controlling for stage at presentation, Black and White patients exhibited similar all-cause and bladder cancer-specific mortality, with Hispanic patients having a lower risk of mortality.

These data suggest that in an equal-access healthcare system, there exist similar stage distribution at initial patient presentation as well as similar survival outcomes between White and Black patients with bladder cancer after controlling for clinical and socioeconomic factors. These data corroborate previous reports that up to 40% of excess bladder cancer mortality exhibited by Black patients can be explained by factors related to care access, including insurance status, education, income, and distance to a hospital[5].

Racial Disparities in Bladder Cancer

Despite due emphasis being placed on identifying inequalities in cancer outcomes based on sociodemographic factors, the root etiology of such inequalities remains poorly understood. Moving forward, we must be committed to broad inclusion of racially diverse patients in bladder cancer clinical trials and genomic studies to inform whether biologic differences contribute to therapeutic efficacy. While identifying sociodemographic inequalities in our healthcare systems are of utmost importance, this merely represents the initial step towards implementation of material change in healthcare access and delivery.

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