INTERNATIONAL
BLADDER CANCER GROUP (IBCG)

IBCG

International Bladder Cancer Group

Newsletter

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Index

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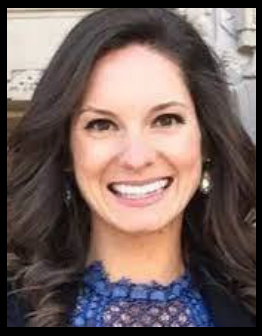
IBCG Retreat 2024



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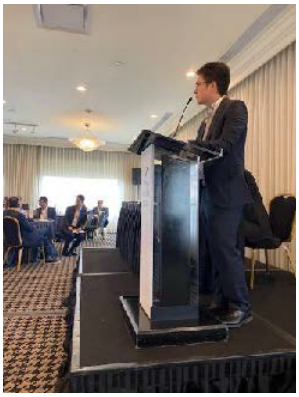


Wei Shen Tan,
MD, PhD

The annual International Bladder Cancer Group (IBCG) Retreat was held in Houston, Texas, from August 23-24, 2024. Co-chaired by Drs. Shilpa Gupta, Roger Li and Patrick Hensley, the event brought together over 90 international bladder cancer clinicians, scientists and patient advocates, with IBCG representation spanning five continents.

The aim of the retreat was to develop consensus statements on two disease processes.

First, the group sought to define optimal sequencing of therapy in muscle-invasive bladder cancer. Several phase 3 trials with perioperative immunotherapy offer an opportunity for a paradigm change in both cisplatin-eligible and-ineligible patients. Given the increasing interest in bladder preservation, there was debate surrounding how best to define clinical complete response. However, the group agreed that the current curative intent treatment of muscle-invasive bladder cancer (MIBC) includes either radical cystectomy or trimodal therapy (TMT).

Emerging markers of response to therapy, including circulating tumor DNA (ctDNA) and multi-parametric MRI using the VI-RADS scale, show promise and may aid in patient selection for bladder sparing and adjuvant therapy moving forward.

Sarah Psutka,
MD

Laura Mertens,
MD

Rick Bangs,
Patient Advocate

In the locally advanced or metastatic setting, there was consensus that enfortumab vedotin plus pembrolizumab, when available, should represent the preferred treatment choice. The nuances and challenges of managing patients with oligometastatic disease were also addressed, highlighting the opportunity for cure in select patients. However, the optimal treatment modality and timing of treatment remains undefined.

Additional topics in the session included:

- Trial design endpoints for neoadjuvant/adjuvant therapy
- Biomarkers for patient selection for neoadjuvant/adjuvant therapay or surgery alone
- The multi-disciplinary management of metastatic disease.

Secondly, the group tackled intermediate risk non-muscle-invasive bladder cancer (IR NMIBC), focusing on definitions, risk stratification, management strategies and trial design.

Currently, cystoscopic surveillance remains the standard of care for follow-up of patients with IR NMIBC, as no urinary biomarkers have achieved the required sensitivity or specificity to serve as a replacement. There is ongoing debate regarding the optimal length and intensity of surveillance schedules. The group explored strategies for de-intensification of surveillance and treatment in order to reduce the need for multiple TURBTs.

Regarding trials of IR NMIBC agents, whilst treatment efficacy is essential, length and duration of follow-up are equally important, as is quality of life. Given that IR NMIBC is not lethal, there was broad consensus that trial design should be patient-centered and include validated quality of life questionnaires.

Patient advocates from the Bladder Cancer Advocacy Network (BCAN) and the World Bladder Cancer Patient Coalition (WBCPC) concluded the working group presentations by providing valuable insights, highlighting the need to eliminate restrictive eligibility criteria in clinical trials. Age should not be a barrier, as excluding older patients solely based on age may deny them effective treatments they might tolerate well if otherwise fit. Advocate groups also emphasised the importance of addressing survivorship challenges in IR NMIBC. Notably, the discontinuation of surveillance cystoscopies can induce significant patient anxiety, as many seek reassurance from continued specialist care.

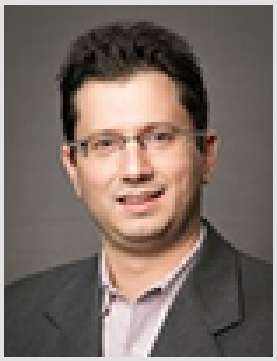
In this context, shared decision-making is crucial for discussing patients' ongoing needs and preferences for care over time.

The retreat utilized a process of literature review, expert opinion-based recommendation synthesis, and pre-meeting voting by IBCG members. Recommendations were revised based on discussion, and final statements underwent live voting at the conclusion of the meeting, with ratification of statements achieving consensus.

The resulting publications on both the optimal sequencing of therapy in MIBC and IR NMIBC are forthcoming.

Highlights from

ESMO'24 Presidential Symposium: Bladder Cancer in the Forefront



Petros Grivas, MD PhD

Professor, Dept. of Medicine, Division of Hematology Oncology
Clinical Director, Genitourinary Cancers Program University of Washington Professor, Clinical Research Division Fred Hutch Cancer Center

In Barcelona this past September, we witnessed another major milestone in the rapid development of bladder cancer therapeutics. The practice changing data of the phase III NIAGARA trial showed that perioperative (neoadjuvant and adjuvant) durvalumab (anti-PD-L1) plus neoadjuvant gemcitabine/cisplatin improved both event-free survival (EFS) and overall survival (OS) vs chemotherapy alone, without jeopardizing the ability of patients to pursue curative-intent radical cystectomy.

The NIAGARA trial, which enrolled over 1,000 patients, is the largest conducted trial in this patient population, representing a "paradigm shift" in the management of localized muscle-invasive bladder cancer (MIBC). It is impressive to see such a large trial conducted in this therapy setting and patient population, while we had seen challenges in the accrual of randomized trials in the past, example evaluating adjuvant chemotherapy. It is noteworthy that the trial's accrual period included the Covid19 pandemic, which introduced major challenges and barriers in conducting clinical research globally.

Bladder cancer accounts for many thousands of global deaths annually, representing a major cause of mortality, morbidity, and economic burden in healthcare systems worldwide. The conventional standard of care for MIBC involves neoadjuvant cisplatin-based chemotherapy (in fit patients) followed by radical cystectomy and pelvic lymph node dissection in patients who pursue the surgical approach (not the bladder preservation strategy). However, this approach has been associated with relatively high recurrence rates, underlining a significant and major need in this curable patient population. As we get

more effective systemic therapies in the metastatic disease setting, "moving" those combinations in the localized disease setting is attractive, interesting and logical.

Durvalumab is an anti-PD-L1 agent with approved indications in other cancer types (its previous indication in metastatic urothelial carcinoma was withdrawn). The perioperative (neoadjuvant and adjuvant) strategy has a robust biological rationale and has shown positive results in other cancer types, example breast and lung cancers, aiming to eradicate micro-metastases and the primary tumor, and, thus, reduce the risk of recurrence and death.

The NIAGARA trial was a randomized phase III trial involving over 1,000 patients with localized muscle-invasive bladder cancer (clinical stage T2–T4aN0–N1). Patients were randomized to either four cycles of gemcitabine/cisplatin neoadjuvant chemotherapy followed by radical cystectomy (standard of care) or four cycles of gemcitabine/cisplatin neoadjuvant chemotherapy combined with durvalumab followed by radical cystectomy, followed by adjuvant durvalumab for up to eight monthly doses. Primary endpoints were event-free survival (EFS) and pathologic complete response rate. EFS was defined as the time from randomization to cancer recurrence, progression or death from any cause (patients who did not undergo cystectomy were counted as having an event regarding the EFS endpoint).

NIAGARA showed a significant improvement in EFS with durvalumab, which translated to a significant reduction in the risk of cancer recurrence, progression or death (HR 0.68). At the two-year landmark, EFS rates were 68% for durvalumab arm vs 60% for standard of care arm. Overall survival (OS) also showed a significant benefit, with a significant reduction in the risk of death (HR 0.75); the two-year OS rates were 82% for durvalumab arm vs 75% for standard of care arm.

Pathologic complete response rates were numerically higher with durvalumab (37% vs 27%). Although this did not reach statistical significance in the primary analysis due to alpha allocation in the statistical analysis plan and a clerical error in the initial analysis (59 cases were not appropriately analyzed); this trend implied increased rate of primary tumor eradication with durvalumab added to chemotherapy. The benefit with added durvalumab was consistent across patient subgroups with likely different degrees/magnitudes of benefit.

The toxicity profile was similar between the arms without notable additional toxicity from durvalumab. Grade 3-4 adverse events occurred in 69% of patients in the durvalumab arm vs 68% in the standard of care arm. Treatment-related grade 3-4 adverse events were observed in 41% of patients in each arm, while adverse events leading to death were really rare, occurring in < 1% of patients in each arm. In the adjuvant phase, only 6% of patients experienced grade 3-4 treatment-related adverse events, with a similarly low proportion of patients discontinuing adjuvant durvalumab due to toxicity. Notably, the addition of durvalumab did not delay curative intent surgery or lower the prospect of patients undergoing radical cystectomy (approximately 85% of patients in each arm successfully underwent cystectomy). Interestingly, 'patient choice' was the most common reason for not proceeding to the planned radical cystectomy.

The NIAGARA trial opens new paths for the treatment of muscle-invasive bladder cancer, while we wait the results of two additional phase III trials evaluating other checkpoint inhibitors (pembrolizumab or nivolumab) combined with gemcitabine/cisplatin as well as three trials evaluating checkpoint inhibitors plus the antibody drug conjugate, enfortumab-vedotin.

While the NIAGARA trial is practice-changing, there are several very important questions that remain unanswered:

- The individual contribution of the neoadjuvant vs adjuvant phase of therapy is not certain. Do we need either or both? Future three-arm or four-arm clinical trial designs, despite being complex, long, costly, and challenging, can help clarify these questions.

- The impact of pathologic stage on survival needs further exploration; an exploratory analysis of disease-free and overall survival in each arm stratified by pathologic stage can provide useful insights. There is concern about over-treatment and under-treatment; therefore, adding granular data in key patient subsets can help inform this dialogue.

Highlights from ESMO'24 Presidential Symposium: Bladder Cancer in the Forefront

- The potential impact of prior systemic checkpoint inhibitor given in non–muscle invasive bladder cancer setting, as well as the potential of rechallenge with a checkpoint inhibitor in cases of later recurrence, remain unanswered urgent questions.

- The impact of potential adjuvant checkpoint inhibitor, example nivolumab, in the standard-of-care arm, as well as access to effective salvage therapies upon cancer recurrence / progression can affect the performance of the control arm and, therefore, the results of this trial regarding EFS and OS. That is an inherent limitation of NIAGARA also based on the timing of the accrual period (prior to adjuvant nivolumab regulatory approval).

- Upper tract urothelial carcinoma (UTUC) is a separate, major unmet need. Results from the ongoing ECOG ACRIN 8192 phase II/III trial will help answer that question; therefore, accrual in that trial is critical and highly encouraged across the U.S. centers.

- The role of accelerated or dose-dense (dd) MVAC is a relevant question since many experts use this regimen in the neoadjuvant setting. While gemcitabine/cisplatin is the most commonly used neoadjuvant regimen and is a very reasonable and acceptable control arm in NIAGARA trial, results from the AURA phase II trial, among others, raise the interesting hypothesis whether ddMVAC may be a preferred partner for checkpoint inhibitors. This question is being asked in the ECOG ACRIN 8192 phase II/III trial in UTUC.

- There is significant interest in viewing health-care utilization, patient-reported outcomes and quality- of-life data in future analyses from the NIAGARA trial. There is also a considerable curiosity regarding tissue-based molecular biomarkers, example DNA repair genes, and circulating tumor DNA, which could possibly inform the discussions on decision-making about adjuvant therapy and potentially help avoid both over- and under- treatment.

Despite these remaining questions, overall, we are very excited about the practice-changing data from the NIAGARA trial and eagerly await ongoing and future trials for further advancements and optimization in the care of people with bladder cancer.

IBCN 2024: Highlights

Amanda Myers, MD,

Fellow of Urologic Oncology,
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The IBCN 2024 occurred in Bern, Switzerland, from September 19th to September 21st, 2024. The even featured a keynote lecture on Friday morning by Niko Beerenwinkel, Professor of Computational Biology ETH Zurich, on "Inferring Tumor Evolution from Single-Cell Data." Dr. Beerenwinkel discussed the evolutionary process of cancer, which can be visualized through tumor phylogeny and cell lineage trees. Phylogenetic tree reconstruction can be performed by using single-cell sequencing from a tumor biopsy. This is a powerful tool applicable to bladder cancer that can help identify evolutionary biomarkers and patient subgroups with similar tumor evolution patterns.

The highlight of day two was a thematic session discussing antibody-drug conjugates (ADCs). Srikala Sridhar discussed the toxicity of different agents and ongoing clinical trials. Markus Eckstein discussed mechanisms of resistance of ADCs, including target plasticity,

microenvironment factors, and acquired or preexisting payload and binding site resistance mechanisms.

Several impactful abstracts were presented over the weekend, including the following highlights:

Comprehensive Genomic Characterization of Early-Stage Bladder Cancer

Philippe Lamy presented a study of comprehensive genomic characterization from 438 patients with NMIBC, including cohorts from UROMOL (n=296) and Aarhus University Hospital (n=142). Whole exome sequencing, shallow whole exome sequencing, and total RNA sequencing were performed. The most frequent mutations were seen in FGFR3, KDM6A, and KMT2D. Whole genome doubling was found in 15% of tumors and associated with increased risk of progression. An integrative clustering analysis comprised copy number alterations, mutations, and gene expression to develop new genomic subtypes. This includes low-risk iClus1, 2, and 3, as well as iClus4, which is defined as high-risk. These groups improve risk discrimination compared to previously used transcriptomic classes in NMIBC.

Correlation of Circulating Tumor DNA (ctDNA) Dynamics with Clinical Response in Muscle-Invasive Bladder Cancer (MIBC) Patients Undergoing Trimodality Therapy (TMT)

Kent Mouw presented one of the first studies describing ctDNA dynamics following TMT. The study evaluated pretreatment ctDNA results using the commercially available Signatera assay from 30 patients undergoing TMT. Of these, 22 patients had

both pre- and post-RT ctDNA available. Of the 13 patients initially ctDNA negative, all remained negative. Of the nine patients who were ctDNA positive, five converted to ctDNA negative post-RT, and four remained ctDNA positive. The study was noted to be limited by its retrospective nature, limited sample size, and follow-up. We look forward to seeing future directions from expanded cohorts and follow-up in the future.

Spatial Proteomics and Transcriptomics Reveal an Altered Immune Cell Landscape in Bladder Cancer Patients Unresponsive to BCG Treatment

Trine Strandgaard presented data from spatial analyses of patients treated with BCG. This included immunohistochemistry (PD-1/PD-L1) from 168 tumors from 105 patients, GeoMx Digital Spatial Profiling (DSP) whole transcriptome analysis (WTA), and proteomics from 152 tumors from 101 patients, and imaging mass cytometry (IMC) from 68 tumors from 58 patients. After BCG treatment, patients showed increased CD4 ($p<0.001$), CD8 ($p=0.004$), and macrophages ($p=0.020$) compared to pretreatment cell counts. Spatial analysis revealed tissue localization of cells with enrichment after treatment. The authors concluded that BCG treatment alters immune cell infiltration, and pre-BCG immune cell abundances may affect outcome. Improving our understanding of the tumor microenvironment may deepen insights into the biological basis for patient outcomes.

First Translational Correlates Using Urinary Genomic Disease Burden to Assess Cretostimogene Grenadenorepvec: Comprehensive Analysis from the BOND-003 Trial in BCG Unresponsive, High Risk, Non-Muscle Invasive Bladder Cancer

Colin Dinney presented data on urinary genomic disease burden from patients in the BOND-003 trial using urine cell-free DNA (UroAmp). Pretreatment baselines were available for 64 patients, and post-treatment analysis was available for 51 patients at three months. The genomic disease burden response showed a reduction in aneuploidy and altered ERBB2, TP53, and RB1 mutations at three months compared to baseline. Patients who had reinduction at three mos and achieved a complete response had a significant reduction in genomic disease burden. Patients classified as UroAmp negative at three months had an 80% RFS at 12 mos. Patients classified as UroAmp positive at three mos had a 33% RFS at 12 mos ($p=0.012$). Longitudinal urinary genomic disease burden assessment using urine cell-free DNA can be used to quantify treatment response and may be used to support future treatment allocation trials to guide treatment intensity.

BCAN
Bladder Cancer Advocacy Network

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Promoting BCAN's 2025 Walks to End Bladder Cancer: Join the Fight Against Bladder Cancer

Bladder cancer is one of the most common cancers in the United States, impacting approximately 83,000 Americans each year. It is a disease that shocks not only the individuals diagnosed but also their families, caregivers, and communities. For healthcare providers, medical researchers, and doctors, bladder cancer deserves significant attention due to its prevalence and the urgent need for better treatments and outcomes.

One of the most impactful ways you can contribute to the fight against this disease is by supporting the Bladder Cancer Advocacy Network's (BCAN) 2025 Walks to End Bladder Cancer.

What is BCAN's Walk to End Bladder Cancer?

BCAN's Walk to End Bladder Cancer is an annual event that brings together thousands of individuals nationwide to raise awareness and funds for bladder cancer research, education, and support. The Walks provide a platform for patients, survivors, caregivers, doctors, researchers, and supporters to unite and take a stand against bladder cancer.

In 2025, BCAN will host 19 Walks across the United States, including first-time events in Cleveland, Tampa, and St. Louis. These Walks are a powerful way to amplify the voices of those affected by bladder cancer, raise much- needed funds, and foster community support.

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Why Healthcare Providers Should Get Involved?

As healthcare providers and researchers, your involvement in BCAN's Walks to End Bladder Cancer is invaluable. You play a critical role in the fight against bladder cancer, not only through your work in patient care and research but also by educating and empowering patients and their families. By participating in or promoting the Walks, you can have a direct impact on the bladder cancer community and help further the mission of improving outcomes for those affected by the disease.

Here's how you can make a difference:

- **Raise Awareness**: Bladder cancer remains underrepresented in the public discourse compared to other cancers. By spreading the word about BCAN's Walks, you can help bring bladder cancer into the spotlight, ensuring it receives the attention it deserves.
- **Engage Your Patients**: Encourage your patients, especially those who are bladder cancer survivors, to participate in a Walk. Walking is a great form of physical activity for many and these events provide an opportunity to connect with others who understand their experiences.
- **Support Research**: Funds raised through BCAN's Walks augment BCAN's ability to support groundbreaking bladder cancer research. As medical professionals, you understand the importance of funding innovative research to develop better treatments and find a cure.
- **Show Your Solidarity**: By walking alongside your patients and their families, you demonstrate your commitment to their journey, fostering trust and providing a source of hope and encouragement.

Where the 2025 Walks Will Take Place

BCAN is excited to host 19 Walks to End Bladder Cancer in 2025 across major cities in the U.S. This year's Walks will take place in the following locations:

Albany, NY	Clevland, OH (New)	Philadelphia, PA	Seattle, WA
Austin, TX	Columbus, OH	Pittsburg, PA	St. Louis, MO (New)
Baltimore, MD	Denver, CO	Portland, ME	Tampa, FL (New)
Boston, MA	Myrtle Beach, SC	Richmond, VA	Washington, DC
Chicago, IL	New York City, NY	San Diego, CA	

In addition to these events, BCAN will continue to offer a virtual Walk option for those who cannot attend in person, ensuring that everyone, regardless of location, can participate.

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Promoting BCAN's 2025 Walks to End Bladder Cancer: Join the Fight Against Bladder Cancer

Registration and Fundraising Opportunities

In addition to the Walk itself, participants can engage in fundraising efforts to support bladder cancer research and awareness. BCAN has made it easy for participants to raise funds through their Walk with BCAN mobile app, available in the Apple Store and Google Play.

By raising $100 or more, participants will receive an official 2025 Walk to End Bladder Cancer t-shirt. For those who raise higher amounts, there are additional incentive prizes, offering an exciting way to encourage participation.

First-Time Walk Locations: Cleveland, Tampa, and St. Louis

We are particularly excited to announce that for the first time, BCAN will host Walks in Cleveland, Tampa, and St. Louis. These new locations represent an important expansion of the Walks to End Bladder Cancer, allowing more communities to come together to support bladder cancer patients and families. If you are a healthcare provider or researcher in one of these areas, this is a perfect opportunity to help establish a new tradition in your community. Your involvement can help ensure the success of these inaugural Walks, while also showing your patients and colleagues that you are committed to advancing bladder cancer care in your region.

How You Can Promote the Walks to Your Patients

As trusted healthcare providers, you have a unique opportunity to promote the Walks to your patients, particularly those directly impacted by bladder cancer.

Here are a few ways you can get involved and spread the word:

- Share Information in Your Clinic: Display flyers, posters, or brochures about the Walks in your clinic or hospital. You can also provide patients with direct links to registration information. If you would like promotional materials, please contact BCAN's Walk team at Walk@BCAN.org.

- Encourage Patients to Form Teams: Suggest that patients and their families form teams to walk together. This creates a sense of community and support, helping patients feel less isolated in their journey.

- Lead by Example: Register as a participant in your local Walk, and let your patients know that you'll be walking alongside them. This gesture can have a profound impact on patients, showing them that you are invested in their well-being both inside and outside the clinic.

Let's Walk Together Toward a Brighter Future

The fight against bladder cancer is a shared responsibility, and together, we can make a lasting impact. BCAN's 2025 Walks to End Bladder Cancer provide an incredible opportunity for healthcare professionals to get involved, advocate for their patients, and contribute to life-saving research.

Register today and join us in one of the 19 cities (or virtually) for the 2025 Walk to End Bladder Cancer. Together, we can work toward a future free from bladder cancer.

For more information and to register, visit BCANWalk.org or scan the QR code on this page. Let's walk together toward a brighter future for everyone impacted by this disease.

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**.

Systemic treatment in bladder cancer

State of art in 2024 and challenges in Morocco

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I. BACKGROUND

Bladder cancer treatment has evolved from traditional surgery and chemotherapy to include immunotherapy, targeted therapies, and antibody drug conjugates. These therapeutic innovations, along with advances in surgical techniques and multimodal approaches, continue to reshape clinical practice and improve outcomes for bladder cancer patients. However, the high cost of these treatments poses a significant challenge in low-income countries such as Morocco.

II. IMMUNOTHERAPY IN NON-METASTATIC BLADDER CANCER

Neoadjuvant cisplatin-based chemotherapy (NAC) with radical cystectomy (RC) improves overall survival (OS) versus RC alone and has been the recommended treatment for muscle-invasive bladder cancer (MIBC) for the past 40 years[1].

Perioperative immune checkpoint inhibitors (ICIs) could improve long-term clinical outcomes by priming anti-tumor immunity before surgery and eradicating micrometastatic disease.

Systemic treatment in bladder cancer
State of art in 2024 and challenges in Morocco

Numerous phase II studies are showing promising activity of neoadjuvant immunotherapy with complete pathologic response rates (pT0 ~ 30-45%).

1. Neoadjuvant Setting

a. Durvalumab = NIAGARA Trial

Durvalumab is a selective, high-affinity, human IgG1 kappa monoclonal antibody that binds to programmed death ligand 1 (PD-L1) and blocks the interaction of PD-L1 with programmed death 1 and CD80. The phase III NIAGARA trial was onducted to evaluate the efficacy and safety of perioperative durvalumab in combination with neoadjuvant gemcitabine–cisplatin followed by radical cystectomy, as compared with neoadjuvant gemcitabine–cisplatin followed by radical cystectomy alone, in cisplatin-eligible patients with MIBC. Event-free survival was one of two primary end points. Overall survival was the key secondary end point[2].

The estimated event-free survival at 24 months was 67.8% (95% CI, 63.6 to 71.7) in the durvalumab group and 59.8% (95% CI, 55.4 to 64.0) in the comparison group (95% CI, 0.56 to 0.82; p<0.001). The estimated overall survival (OS) at 24 months was 82.2% (95% CI, 78.7 to 85.2) in the durvalumab group and 75.2% (95% CI, 71.3 to 78.8) in the comparison group (95% CI, 0.59 to 0.93; p=0.01).

A pathological complete response occurred in 37.3% (95% CI, 33.2 to 41.6) of the patients in the durvalumab group and in 27.5% (95% CI, 23.8 to 31.6) of those in the comparison group (risk ratio, 1.34; 95% CI, 1.13 to 1.60). NIAGARA supports perioperative durvalumab with NAC as a potential new standard treatment for patients with cisplatin-eligible MIBC.

b. Pembrolizumab = PURE-01 Trial

The PURE-01 trial of neoadjuvant pembrolizumab prior to RC initially pioneered the use of neoadjuvant ICI in patients with MIBC[3]. Both cisplatin eligible and ineligible patients were included.

The 36-month event-free survival (EFS) and OS were 74.4% [95% CI, 67.8-81.7] and 83.8% (95% CI, 77.8-90.2) in the ITT population, respectively. Within the cohort of patients who did not receive additional chemotherapy (N = 125), the 36-month RFS was 96.3% (95% CI, 91.6-100) for patients achieving ypT0N0, 96.1% (95% CI, 89-100) for ypT1/a/isN0, 74.9% (95% CI, 60.2-93) for ypT2-4N0, and 58.3% (95% CI, 36.2-94.1) for ypTanyN1-3 pathologic responses. EFS was significantly stratified among PD-L1 tertiles (lower tertile: 59.7% vs. medium tertile: 76.7% vs. higher tertile: 89.8%, P = 0.0013). PURE-01 results further confirm the sustained efficacy of neoadjuvant pembrolizumab before RC. PD-L1 expression was the strongest predictor of sustained response post-RC.

2. Adjuvant Immunotherapy

The goal of adjuvant immunotherapy is to eliminate residual cancer cells, reduce risk of relapse, and improve overall survival. Immune checkpoint inhibitors may play an important role if there is residual disease post-NAC, or in patients who did not receive NAC.

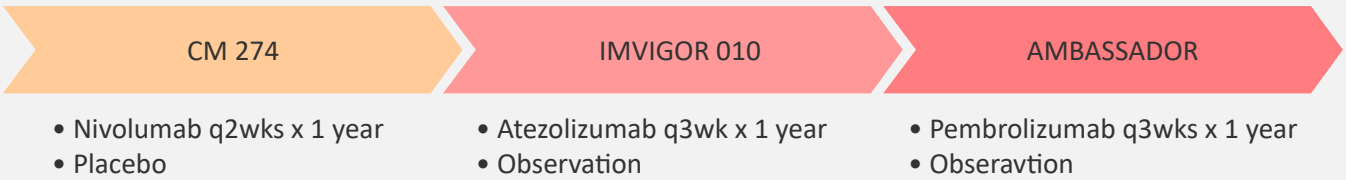

Figure 1 : Adjuvant immunotherapy studies

a. Nivolumab = Checkmate 274 Trial

The phase 3 CheckMate 274 trial of adjuvant nivolumab reported positive results for its primary endpoints across the entire study population, although the authors note the possibility of a larger effect size for bladder compared to UTUC. EFS was the primary endpoint and OS was the key secondary endpoint[4].

DFS was 20.8 months with nivolumab compared to 10.8 months with placebo (HR, 0.70; 98.22% CI, 0.55–0.90; P < .001). For patients with a programmed death-ligand 1 (PD-L1) expression level of 1% or more, DFS was 74.5% with nivolumab and 55.7% with placebo (HR, 0.55; 98.72% CI, 0.35–0.85; P < .001).

Treatment-related adverse events of grade 3 or higher occurred in 17.9% of the nivolumab group and 7.2% of the placebo group. Two treatment-related deaths due to pneumonitis and one treatment-related death due to bowel perforation were noted in the nivolumab group.

Adjuvant Nivolumab should be offered as adjuvant therapy for patients with MIBC with pT3/4 and /or pN+ stage or who have residual muscle-invasive tumor (ypT2-4 or ypN+) after RC and prior cisplatin-based neoadjuvant chemotherapy.

b. Pembrolizumab = AMBASSADOR Trial

The efficacy of adjuvant Pembrolizumab was examined by the AMBASSADOR trial as compared with observation in patients with high-risk muscle-invasive urothelial carcinoma after radical surgery. The coprimary end points were DFS and OS[5].

The median DFS was 29.6 months (95% CI, 20.0 to 40.7) with pembrolizumab and 14.2 months (95% CI, 11.0 to 20.2) with observation (hazard ratio for disease progression or death, 0.73; 95% CI, 0.59 to 0.90; two-sided P=0.003).

Grade 3 or higher adverse events (regardless of attribution) occurred in 50.7% of the patients in the pembrolizumab group and in 31.6% of the patients in the observation group. Among patients with high-risk muscle-invasive urothelial carcinoma after radical surgery, disease-free survival was significantly longer with adjuvant pembrolizumab than with observation.

Therefore, adjuvant pembrolizumab may be considered after its approval as adjuvant therapy for patients with MIBC with pT3/4 and /or pN+ stage or who have residual muscle-invasive tumor (ypT2-4 or ypN+) after radical cystectomy and prior cisplatin-based neoadjuvant chemotherapy.

3. Ongoing phase II/III Trials:

a. Enfortumab vedotin = KEYNOTE-905/EV-303 Trial

This phase III trial is designed to evaluate the efficacy and safety of perioperative pembrolizumab alone or in combination with enfortumab vedotin compared with RC + pelvic lymph node dissection alone in patients with MIBC who are cisplatin-ineligible or decline cisplatin-based treatment (T2-T4aN0M0 or T1-T4aN1M0)[6].

Dual primary endpoints are pathologic complete response as assessed by central pathologic review and EFS. Secondary endpoints include OS, DFS, pathologic downstaging rates, safety, and tolerability.

b. KEYNOTE-866 Trial

KEYNOTE-866 is a randomized phase III study to assess efficacy and safety of chemotherapy with perioperative pembro versus chemotherapy with perioperative placebo for patients with MIBC (T2-T4aN0M0) who are cisplatin-eligible[7].

Primary endpoints are pathologic complete response and EFS in all patients and patients with PD-L1 CPS ≥10. Secondary endpoints are overall survival, disease-free survival, and pathologic downstaging rate stratified by CPS as well as safety.

C. Sacituzumab govitecan = SURE-02 Trial

The multi-cohort, open-label, phase II SURE study is evaluating neoadjuvant Sacituzumab govitecan + pembrolizumab followed by adjuvant pembrolizumab in patients with cT2-4N0M0 MIBC who were ineligible for or refused cisplatin-based neoadjuvant chemotherapy. Patients receive 4 cycles of neoadjuvant Sacituzumab govitecan on days one and eight, Q3W, followed by RC.

The primary endpoint of the study is to assess the proportion of complete pathologic response (ypT0N0). Secondary end points include event-free survival (EFS), clinical complete response rate and OS[8].

III. IMMUNOTHERAPY IN ADVANCED BLADDER CANCER

1. EV302/ Keynote – A39 Trial

Enfortumab vedotin and pembrolizumab was investigated in the phase III EV-302 trial, which randomized 886 patients with previously untreated locally advanced or metastatic urothelial carcinoma to either enfortumab vedotin plus pembrolizumab or gemcitabine in combination with either cisplatin or carboplatin[9]. The primary end points were PFS, as assessed by blinded independent central review, and OS.

Median PFS was significantly longer with enfortumab vedotin plus pembrolizumab compared to chemotherapy (12.5 months vs. 6.3 months; HR, 0.45; 95% CI, 0.38–0.54; P < .001). Median OS was also significantly longer with enfortumab vedotin plus pembrolizumab (31.5 months vs. 16.1 months; HR, 0.47; 95% CI, 0.38– 0.58; p < .001). Confirmed ORR was 67.7% and 44.4% for enfortumab vedotin plus pembrolizumab and chemotherapy, respectively (P < .001), with complete responses observed in 29.1% of patients in the enfortumab vedotin plus pembrolizumab group and 12.5% of those in the chemotherapy group.

Treatment-related AEs grade ≥3 occurred in 55.9% of patients receiving enfortumab vedotin plus pembrolizumab and 69.5% of those receiving chemotherapy.

Based on these results, the combination of pembrolizumab plus enfortumab vedotin is the preferred first-line systemic therapy option for patients with advanced or metastatic urothelial carcinoma.

2. Nivolumab = CM901 Trial

The multinational, phase III CheckMate901 study compared nivolumab plus gemcitabine-cisplatin to gemcitabine-cisplatin alone in 608 patients with previously untreated unresectable or metastatic urothelial carcinoma. Patients who received the nivolumab combination also received maintenance nivolumab for up to 2 years. The primary outcomes were OS and PFS. The objective response rate and safety were exploratory outcomes[10].

Nivolumab plus gemcitabine-cisplatin showed longer median OS compared to gemcitabine-cisplatin alone (21.7 vs. 18.9 months; HR, 0.78; 95% CI, 0.63–0.96; P = 0.02). The median PFS was similar for the two arms (7.9 vs. 7.6 months; P = 0.001), but the PFS curves separated over time. At 12 months, the PFS was 34.2% with the nivolumab combination compared to 21.8% with chemotherapy alone. The ORR was 57.6% with the nivolumab combination compared to 43.1% with chemotherapy alone. For those in the nivolumab plus gemcitabine-cisplatin group, 21.7% had complete responses.

Grade ≥3 AEs occurred in 61.8% of those in the nivolumab combination group and 51.7% of those who received chemotherapy alone.

Combination therapy with nivolumab plus gemcitabine-cisplatin resulted in significantly better outcomes in patients with previously untreated advanced urothelial carcinoma than gemcitabine-cisplatin alone.

3. Avelumab = JAVELIN Bladder 100 Trial

For patients who show either response or stable disease through their full course of platinum-based first-line chemotherapy, maintenance therapy with the PD-L1 inhibitor avelumab is recommended[11].

The randomized, phase III JAVELIN Bladder 100 trial showed that avelumab significantly prolonged OS in 700 randomized patients compared to best supportive care alone (median OS 21.4 vs. 14.3 months; HR, 0.69; 95% CI, 0.56–0.86; P = .001). The OS benefit was observed in all prespecified subgroups, including patients with PD-L1–positive tumors.

Grade ≥3 AEs were reported in 47.4% of patients treated with avelumab compared to 25.2% of those with best supportive care alone. Maintenance avelumab plus best supportive care significantly prolonged overall survival, as compared with best supportive care alone, among patients with urothelial cancer who had disease that had not progressed with first-line chemotherapy.

4. Sacituzumab govitecan = TROPHY-U-01 Trial

Sacituzumab govitecan has been evaluated in cohort 1 of TROPHY-U01, a phase II open-label study with 113 patients in cohort 1. Patients within this cohort had locally advanced, unresectable, or metastatic urothelial carcinoma that had progressed following prior platinum-based and PD-1/PD-L1 checkpoint inhibitor therapy and were treated with sacituzumab govitecan[12].

The ORR was 27% (95% CI, 19.5%–36.6%) and 77% of participants showed a decrease in measurable disease. The median DOR was 7.2 months (95% CI, 4.7–8.6 months), median PFS was 5.4 months (95% CI, 3.5– 7.2 months), and median OS was 10.9 months (95% CI, 9.0–13.8 months).

Key grade ≥3 treatment-related AEs were neutropenia (35%), leukopenia (18%), anemia (14%), diarrhea (10%), and febrile neutropenia (10%). Six percent of patients in the study discontinued treatment because of treatment-related AEs.
SG monotherapy demonstrated a high ORR with rapid responses. Treatment was feasible with a manageable toxicity profile.

5. Pembrolizumab = KEYNOTE-045 Trial

The phase III KEYNOTE-045 study showed a superior overall survival (OS) benefit of pembrolizumab, a programmed death 1 inhibitor, versus chemotherapy in patients with advanced UC that progressed on platinum-based chemotherapy[13].

Median 1- and 2-year OS rates were higher with pembrolizumab (44.2% and 26.9%, respectively) than chemotherapy (29.8% and 14.3%, respectively). The objective response rate was also higher with pembrolizumab (21.1% versus 11.0%). Median duration of response to pembrolizumab was not reached (range 1.6+ to 30.0+ months) versus chemotherapy (4.4 months; range 1.4+ to 29.9+ months).

Pembrolizumab had lower rates of any grade (62.0% versus 90.6%) and grade ≥3 (16.5% versus 50.2%) treatment-related adverse events than chemotherapy. Pembrolizumab continues to demonstrate superior survival over chemotherapy in patients with advanced UC after failure of platinum-based therapy, irrespective of PD-L1 status.

6. Erdafitnib = THOR Trial

THOR is a phase III trial of erdafitinib as compared with chemotherapy in patients with metastatic urothelial carcinoma with susceptible FGFR3/2 alterations who had progression after one or two previous treatments that included an anti–PD-1 or anti–PD-L1[14].

The median OS and PFS were significantly longer with erdafitinib than with chemotherapy (12.1 and 5.6 months versus 7.8 and 2.7 months, respectively). The incidence of grade 3 or 4 treatment-related adverse events was similar in the two groups (45.9% in the erdafitinib group and 46.4% in the chemotherapy group).

Erdafitinib therapy resulted in significantly longer overall survival than chemotherapy among patients with metastatic urothelial carcinoma and FGFR alterations after previous anti–PD-1 or anti–PD-L1 treatment.

Table 1 : Therapies/indications in UC

Therapy	Disease setting	Trial	Control	Absolute survival gain
First line therapy				
Enfortumab vedotin – pembrolizumab	Treatment of patients with locally advanced or metastatic UC who are not eligible for cisplatin containing Chemotherapy.	EV-302/KN-A39 Phase III	Platinum-based ChT Median PFS: 6.3 months Median OS: 16.1 months	PFS gain: 6.2 months OS gain: 15.4 months
Nivolumab – gemcitabine – cisplatin	First-line treatment of adult patients with unresectable or metastatic UC	CheckMate 901 Phase III	Gemcitabine - cisplatin Median PFS: 7.6 months Median OS: 18.9 months	PFS gain: 0.3 months OS gain: 2.8 months
Maintenance therapy				
Avelumab	First-line maintenance treatment of patients with locally advanced or metastatic UC who are progression-free following	JAVELIN Bladder 100 Phase III	Best supportive care Median OS: 15.0 months	OS gain : 8.8 months
Further – line therapy				
Enfortumab vedotin	Treatment of patients with locally advanced or metastatic UC who have previously received a platinum-containing Chemotherapy and a PD-1 or PD-L1 inhibitor	EV-301 Phase III	Investigator's choice of ChT (standard docetaxel, paclitaxel or vinflunine) Median OS: 8.94 months	OS gain : 3.97 months
Pembrolizumab	Treatment of locally advanced or metastatic UC in adults who have received prior platinum containing Chemotherapy	KEYNOTE-045 Phase III	Investigator's choice of ChT (paclitaxel, docetaxel or vinflunine) Median OS: 7.2 months 2-year OS: 14.3%	OS gain : 4.3 months

Therapy	Disease setting	Trial	Control	Absolute survival gain
Further – line therapy				
Sacituzumab govitecan	Treatment of patients with locally advanced or metastatic UC who have previously received a platinum-containing Chemotherapy and either PD-1 or PD-L1 inhibitor	TROPHY-U-01 Phase II	Single arm	ORR: 27.4% Median DoR: 7.2 months Median PFS: 5.4 months
Erdafitinib	Treatment of patients with metastatic urothelial carcinoma with susceptible FGFR3/2 alterations who had progression after one or two previous treatments that included an anti–PD-1 or anti–PD-L1.	THOR	Investigator's choice of chemotherapy (docetaxel or vinflunine).	Gain OS: 4,3 months. Gain PFS: 2,9 months

IV. Barriers to Advanced Bladder Cancer therapies:

Access to modern treatments for bladder cancer in Morocco, in particular immunotherapies, ADC, and targeted therapies, remains extremely limited. These new therapies, which offer increased hope of survival for patients with aggressive cancers, are inaccessible to most Moroccans for several reasons:

High cost of treatment and impact on accessibility: ADCs and immunotherapies generally cost several thousand dirhams per month. For example, pembrolizumab and atezolizumab, which are the only immunotherapy treatments currently available for bladder cancer in Morocco, remain financially inaccessible to the majority of patients without specific health insurance or substantial financial resources[15]. Worldwide, the efficacy of these drugs has been shown to significantly improve survival rates of patients with advanced bladder cancer[16], but their high price makes access difficult for Moroccans. Other bladder cancer drugs used elsewhere, such as nivolumab or antibody-drug conjugates (such as enfortumab vedotin), are not available in Morocco.

Health insurance issues: Social insurance in Morocco, although expanding with programs such as RAMED and AMO, often does not cover expensive oncology treatments, particularly those of the latest generation[17]. Immunotherapies and ADCs for bladder cancer are not included in the standard reimbursement lists, and patients often must pay the full cost of treatment themselves. This severely limits treatment options for middle-class and low-income patients, who simply cannot afford such treatments without additional financial support[18]. Private insurers, although sometimes offering broader cover options, do not systematically include immunotherapies and ADCs in their contracts, leaving the majority of patients with limited choices[19].

Access to new bladder cancer therapies is strikingly uneven worldwide. In high-income countries, these therapeutic advances now represent an increasingly standard treatment option for advanced or metastatic bladder cancer, with

promising results in terms of OS and PFS. However, in low- and middle-income countries, access to these innovations remains limited or non-existent due to a number of factors, including prohibitive cost, lack of adequate reimbursement systems and lack of specialized infrastructure[20].

Scientific advances in oncology should benefit all patients, regardless of their country of origin or financial resources. Unequal access to cutting-edge therapies for bladder cancer represents a major ethical and public health challenge. Indeed, the World Health Organisation (WHO) emphasises the need for equity in healthcare and recommends concerted efforts to facilitate access to essential medicines and new therapies in low- and middle-income countries[21]. International funding initiatives, partnerships between governments and the pharmaceutical industry, and differential pricing policies could help to reduce this inequality[22]. In addition, the development of clinical research networks in countries with limited resources could facilitate the introduction of innovative therapies by providing access to clinical trials[23].

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