AUCTORES
Globalize your Research

New Medical Innovations and Research

Anthony Kodzo-Grey Venyo *

Open Access

Research Article

Immunotherapy in the Scenario of Urothelial Cancer an Update

Anthony Kodzo-Grey Venyo

Educational Supervisor Certificate Rcp London and Accreditation Medical Examiner Member Rc Path London.

***Corresponding Author:** Anthony Kodzo-Grey Venyo. Educational Supervisor Certificate Rcp London and Accreditation Medical Examiner Member Rc Path London.

Received date: July 19, 2025; Accepted date: July 25, 2025; Published date: July 30, 2025

Citation: Anthony Kodzo-Grey Venyo, (2025), Immunotherapy in the Scenario of Urothelial Cancer an Update, *J New Medical Innovations and Research,* 6(7); **DOI: 10.31579/2767-7370/160**

Abstract:

Urinary bladder cancer is the commonest urinary tract malignancy. Platinum-based chemotherapy is the first line of treatment in locally advanced or metastatic bladder cancer. Immunotherapy has become a new treatment option in a broad variety of malignancies including bladder cancer. Immunotherapy has been approved as first line of treatment in patients who are ineligible for platinum-based chemotherapy and second-line treatment for metastatic urothelial cancer who progressed after platinum-based treatments. Within the United States of America, about 80 000 new cases and 17 000 deaths occur each year due to bladder cancer. Within Western Europe and the United States of America, urothelial carcinoma is the common histologic type. Muscle-invasive bladder cancer is defined when the tumour involves the detrusor muscle and it has a higher metastatic potential. The most common presenting symptom in patients with bladder cancer is painless visible or non-visible haematuria, even though irritative voiding symptoms including urinary frequency, urgency, dysuria could also be the manifestation symptom. Depending on the age, comorbidities, functional status of the patient, and stage of the malignancy, treatment options include surgery, radiotherapy, chemotherapy, and most recently immunotherapy and targeted therapies had been included as effective treatment options.

Keywords: urothelial cancer; bladder cancer; immunotherapy; check point inhibitors

Introduction

Urinary Badder Cancer (BCa) in 2022 was stated to be the seventh most common cancer worldwide [1] [2]. Men are stated to be three to four times more likely to be diagnosed than women [1] [3], who often have more aggressive tumours at diagnosis [1] [4]. At the time of diagnosis, over 70% of tumours are classified as non–muscle-invasive bladder cancer (NMIBC). [1] Intravesical bacillus Calmette-Guerin (BCG) is commonly utilised to decrease the risk of recurrence of high-grade NMIBC [1] [5]. Nevertheless, about 35% of patients who receive BCG still do subsequently develop recurrences. [1] [6]. More recently, inhibition of programmed cell death protein-1 (PD-1) or programmed cell death-ligand 1 (PD-L1) had emerged as effective BCa immunotherapeutic treatment. [1] [7] [8] Nevertheless, only 20% to 30% of patients have a significant response to inhibition of these immune checkpoints. [1] [9] These incomplete response rates to both BCG and checkpoint inhibitors had highlighted the need for novel approaches to improve response rates of bladder cancer. [1] The importance of sex and hormonal differences upon BCa treatment response has remained relatively unexplored. Large contemporary series do not indicate sex differences in response to BCG treatment had been reported in previous series. [10] [11] Sociological, health system, and presentation differences nonetheless confound the assessment of biological treatment differences. [1] [12]. Existing studies had indicated that hormonal differences might impact upon outcomes, with oestrogens being potentially protective against BCa development but possibly supportive of BCa progression. [13]. Androgens and the androgen receptor (AR) had been more robustly implicated in the carcinogenesis urinary bladder and BCa progression. [1] [14]. Furthermore, androgens had been identified to have immunosuppressive properties, [1] [1] [15], which likely contribute to sex differences in various pathologies. [1] [16] Recent studies had found AR-suppressive therapy to be associated with improved BCa outcomes, highlighting the potential for clinical impact. [1] [17].

Radical surgery entailing cystectomy for tumours that arise within the urinary bladder or nephroureterectomy for tumours that arise within the upper urinary tract is the standard of care for patients who have muscle-invasive urothelial carcinoma. [18] [19] [20] Even though radical surgery is undertaken with curative intent, more than 50% of patients with pathology examination evidence of cancer invading through the muscularis propria or involving the regional lymph nodes would have lethal metastatic recurrence. [18] [19] [20] [21] [22] Adjuvant chemotherapy may prolong disease-free survival among patients with locally advanced upper tract urothelial carcinoma; [18] [23] nevertheless, no consensus decision had emerged regarding routine adjuvant cisplatin-based chemotherapy, and some patients with urothelial carcinoma are noted to be ineligible for or decline neoadjuvant cisplatin-based chemotherapy. [18] [19] [20] [24] [25] [26] [27] In addition, despite a high risk of metastatic recurrence, no standard adjuvant systemic therapies had been demonstrated to improve outcomes in patients with pathological evidence of residual disease pursuant to undergoing neoadjuvant cisplatin-based chemotherapy. [18] [28] [29]

Nivolumab is a fully human IgG4 monoclonal antibody which is directed against programmed death 1. At a dose of 3 mg per kilogram of body weight every 2 weeks, nivolumab had been demonstrated to have anti-tumour activity in patients with metastatic urothelial carcinoma who had previously received platinum treatment;[18] It was approved in this population upon the basis of the results of the CheckMate 275 trial. [18] Nevertheless, to 2021, no immune-checkpoint inhibitor had demonstrated efficacy as adjuvant therapy in patients who have urothelial carcinoma at high risk for metastatic recurrence after radical surgery with curative intent. [18] Hence, the phase 3 CheckMate 274 trial was undertaken to ascertain the efficacy and safety of adjuvant nivolumab, in comparison with placebo, in patients with muscle-invasive urothelial carcinoma after radical surgery (with or without previous neoadjuvant cisplatin-based combination chemotherapy). [18]

The ensuing article contains a review and update of the literature which is divided into two parts: (A) Overview and (B) Miscellaneous narrations and discussions from case reports, case series, and studies related to immunotherapy in the treatment of urinary bladder cancer.

Aim

To provide an update on immunotherapy in the treatment of urinary bladder cancer.

Method

Internet databases were searched including: Google; Google scholar; Yahoo; and PUBMED. The search words that were used included: Immunotherapy in bladder cancer; Immunotherapy in urothelial cancer; urinary bladder cancer immunotherapy. Ninety-seven (97) references were identified which were used to write the article which has been divided into two parts: (A) Overview and (B) Miscellaneous narrations and discussions from case reports, case series, and studies related to immunotherapy in the treatment of urinary bladder cancer.

[A] Overview Of Urothelial Carcinoma.

Definition / general statements related to urothelial carcinoma

- The new WHO 2022 classification of urinary and male genital tumours (5th edition) replaces the previous WHO 2016 classification
- Diagnostic criteria of urothelial carcinoma, molecular correlates and nomenclature of urothelial carcinoma had been updated.

Major updates

- 5th edition of WHO classification for bladder cancers is organized based on tumour lineage: urothelial, squamous and glandular tumours.
    - Exceptions for urachal, diverticular and urethral accessory gland tumours
    - Separate chapters for neuroendocrine neoplasms, mesenchymal tumours, haematolymphoid malignancies, melanocytic tumours and metastatic tumours
    - Genetic tumour syndromes of urinary and male genital tract are covered in dedicated chapter
- Histology subtypes are now preferred over variants
    - Standardized terminology: genetic alterations as variants, distinct morphologies as histologic patterns and significant morphologies as tumour subtypes
    - All subtypes of urothelial carcinoma and those with divergent differentiation are classified as high-grade tumours, regardless of bland morphology (e.g., microcystic / tubular, small or large nested)
    - WHO 5th edition stresses reporting the presence and percentage(s) of different subtypes and divergent differentiation in urothelial carcinomas
- Papillary tumours are deemed high grade if containing ≥ 5% high grade component; < 5% is noted as low grade with < 5% high grade component, prompted by poor interobserver reproducibility,
- The descriptor inverted is reserved for papillary tumours with almost exclusively inverted architecture
- Urothelial proliferation with undetermined malignant potential is no longer considered a distinct entity but rather an early low grade non-invasive papillary urothelial carcinoma or extension at the tumour edge / shoulder lesion.
- Urothelial dysplasia no longer has a separate section; the term has been retained for preneoplastic lesions falling short of carcinoma in situ diagnosis,
- Clear cell urothelial carcinoma was renamed clear cell urothelial carcinoma (glycogen rich) for clearer distinction from clear cell adenocarcinoma with Müllerian differentiation.
- Signet ring / diffuse has been removed from plasmacytoid subtype terminology. [39]
- New edition advocates for pT1 tumour sub-staging via histo-anatomical (tumour relative to muscularis mucosa and vascular plexus) or micrometric approach (measuring of invasive tumour component); however, it does not favour any specific methodology of subcategorization or tier system.
- Predictors of immune checkpoint inhibitor response: PDL1 expression in tumour and host immune cells, tumour mutation burden and microsatellite instability / mismatch repair defect status.

WHO (2022) – A variety of tumours of the urinary tract had been documented under different classification codes due to the fact that based upon their histopathology examination features they are different and they also portend different biological behaviour patterns. Some of the tumour types and their coding have been summated as follows:

Urothelial tumours	ICD-O	ICD-11
• Non-invasive urothelial tumours	•	
○ **Urothelial papilloma**	8120/0	2F35 & XH5M82
○ **Inverted Urothelial Papilloma**	8121/0	2F35 & XH5A08
○ **Papillary Urothelial Neoplasm of low malignant potential**	8130/1	2F78 & XH5UU5
○ **Non-Invasive Papillary Urothelial Carcinoma, low grade**	8130/2	2C91.0 & XH12F0
○ **Non-Invasive Papillary Urothelial Carcinoma, high grade**	8130/2	2C91.0 & XH12F0
○ **Urothelial Carcinoma In situ**	8120/2	2C91.0 & XH5GH8
• **Invasive urothelial neoplasms**		
○ **Invasive Urothelial Carcinoma**	8120/3	2C91.0 & XH8EH1
Squamous cell neoplasms of the urinary tract		
○ **Squamous papilloma of the urothelial tract**	8052/0	2F35 & XH50T2
• **Squamous cell carcinomas of the urinary tract**	•	
○ **Verrucous carcinoma of the bladder**	8051/3	2C9Y & XH5PM0
○ **Pure squamous carcinoma of the urothelial tract**	8070/3	2C94.1
Glandular neoplasms		
• Adenomas	•	
•	•	
○ **Villous adenoma**	8261/0	2F35 & XH90D6
• Adenocarcinomas	•	
○ **Adenocarcinoma, NOS**	8140/3	2C94.0
Urachal and diverticular neoplasms		
○ **Urachal carcinoma**	8010/3	2C9Y & XH74S1
○ **Diverticular carcinoma**	8120/3	GC01.2 & XH8EH1
Urethral neoplasms		
• Urethral accessory gland carcinomas	•	
○ Littre gland adenocarcinoma of the urethra	8140/3	2C93.0 & XH22Z8
○ Skene gland adenocarcinoma of the urethra	8140/3	2C93.0 & XH22Z8
○ Cowper gland adenocarcinoma of the urethra	8140/3	2C93.0 & XH22Z8
Tumours of the Müllerian type		
○ **Clear cell adenocarcinoma of the urinary tract**	8310/3	2C9Y & XH6L02
○ Endometrioid carcinoma of the urinary tract	8380/3	2C94.Y & XH0SD2

[A2] OVERVIEW OF URINE CYTOLOGY

Definition / general statements related to urine cytology

- Urine Cytology represents a significant portion on non-gynaecologic cytology specimens in daily practice, primarily because of the simplicity and ease of specimen procurement and its significant impact on management.
- However, there was no consensus on the various categories and their cytomorphologic features used for reporting.
- Paris System for reporting urinary cytology was an effort to standardize terminology with standardized cytomorphologic criteria for reporting urine cytology (2016)
- Paris System is based upon the principle that the ultimate goal of urine cytology is detection of high-grade urothelial carcinoma.

Essential features of urine cytology

- Identification of high-grade urothelial carcinoma (**HGUC**) is the ultimate goal of urinary cytology and should always be kept in mind while reporting urine cytology; these patients will receive active investigation to find the lesion.
- Suspicious for High Grade Urothelial Carcinoma (SHGUC) has similar management due to its strong association with **HGUC**.
- Carcinoma in Situ (**CIS**) cannot be differentiated from HGUC within urine cytology. [56]
- Low grade urothelial neoplasia (**LGUN**) can only be definitively diagnosed in the presence of 3 dimensional cellular papillary clusters with fibrovascular cores; if not present, report as negative for high grade urothelial carcinoma (**NHGUC**) with a possible comment for consideration of **LGUN.**
- Atypical urothelial cells (AUC) should be reported using strict morphologic criteria with 1 major and 1 minor criterion.

Clinical features related to urine cytology in the scenario of urothelial carcinoma

- Cytology is useful to detect carcinoma in situ or marked chronic inflammation (i.e. when there is no specific lesion to biopsy), carcinoma hidden in diverticula or for detecting residual tumour from urine specimens.
- Cystoscopy biopsy of visible lesions is more sensitive than cytology in most cases.

- Bladder irrigation is superior to collecting voided urine.
- Urine cytology is most sensitive and highly specific for high grade tumours (diagnosis or follow-up) whether flat (carcinoma in situ), papillary or mixed
- Urine cytology is stated to have a low sensitivity (difficult to diagnose) for papilloma and low malignant potential lesions because they have normal histology.
- Follow up examination of urine with FISH may improve sensitivity and specificity of cytology

Types of urine specimens obtained by the clinician for the assessment of urothelial carcinoma

Voided urine:

- Voided urine is non-invasive, easiest to obtain.
- Obtaining 3 second morning voided midstream urine samples collected over 3 consecutive days appears to optimize the detection of urothelial malignancies.

Instrumented urine:

- Catheterization of the bladder or irrigation of bladder.

Ileal conduit urine:

- Ileal conduit and neobladder are the most common urine diversion techniques used in patients who have undergone cystectomy and urine can be obtained from ileal conduit,
- A portion of the ileum is anastomosed with the ureters to the skin or to the urethra.

Processing / preservation of urine specimen

- Immediate processing is recommended or refrigerate if immediate processing cannot be done.
- If fixation if needed, use equal volumes of 50% ethanol or a methanol-based fixative (Cytolyt® or similar)

Format of diagnostic report by the pathologist in the assessment for urothelial carcinoma.

Recommendations for Diagnostic Format and Categories for Urinary Cytology Specimens Papanicolaou Society of Cytopathology Practice Guidelines Task Force include the ensuing:

I. Adequacy Statement (Optional). Satisfactory for evaluation

- List any quality factors affecting specimen
- Unsatisfactory for evaluation (give reason)

II. General Categorization

- Negative for epithelial cell abnormality.
- Epithelial cell abnormality present.

III. Descriptive Diagnosis.

In reporting on the urine cytology specimen pursuant to the examination, the pathologist documents the ensuing regarding presence or absence:

- Negative for epithelial cell abnormality
- Infectious agents
- Bacterial organisms
- Fungal organisms
- Viral changes (CMV, herpes, adenovirus, polyomavirus)
- Nonspecific inflammatory changes
- Acute inflammation
- Chronic inflammation
- Changes consistent with xanthogranulomatous pyelonephritis
- Cellular changes associated with:
  Chemotherapeutic agents
  Radiation
- Epithelial Cell Abnormalities
  Atypical urothelial cells
  Low-grade urothelial carcinoma
  High-grade urothelial carcinoma (invasive carcinoma vs. carcinoma in situ)
  Squamous cell carcinoma
  Adenocarcinoma
  Other malignant neoplasms (specify type)

IV. Other -Other iterations that tend to be included by the pathology report of urine cytology include the ensuing:

- An optional comment section should be used to list additional findings or further clarification of findings

Specimen adequacy

The ensuing iterations had been made about adequacy of urine cytology specimen.

- Adequacy refers to the usefulness of the specimen to diagnose or raise suspicion of urothelial carcinoma
- Adequacy is determined by the interplay of 4 specimen characteristics: collection type, cellularity, volume and cytomorphologic findings
- Of these, the cytomorphologic findings must be considered first because any atypical, suspicious or malignant cells make the specimen intrinsically adequate regardless of the volume, cellularity or collection type
- Similar to Pap smear adequacy, any atypical, suspicious or malignant cells on cytology automatically becomes an adequate specimen
  - Adequate number of benign urothelial cells also supersedes any volume requirements for adequacy
  - Volume is only considered for voided specimens; low volume samples are less likely to have adequate urothelial cells, but an optimal volume has not been established
  - The Paris system indicates that for SurePath®, 30 ml is an optimal volume for voided urines but specimens should not be rejected based on low volume
  - Benign urothelial cellularity cut offs should be validated for instrumented and voided urines

Negative for High Grade Urothelial Carcinoma (NHGUC)

- To minimize lumping everything into the "atypical" category, the terminology Negative for High Grade Urothelial Carcinoma includes all entities that pose no significant risk to the patient for developing HGUC based upon available studies
- This term also clarifies the goal of the Paris System - to highlight those cases at risk for HGUC
- For example, radiation associated atypia is classified as Negative for High Grade Urothelial Carcinoma and not atypical
- A urine sample (voided or instrumented) is considered Negative for High Grade Urothelial Carcinoma if any of the following components are present:
  - Benign urothelial, squamous and glandular cells
  - Benign urothelial tissue fragments

- Changes associated with stones
- Viral cytopathic effect due to polyoma virus
- Post therapy effect, including epithelial cells from urinary diversions

Atypical Urothelial Cells (AUC)

- Defined as cellular changes that fulfil the major (required) criterion and only 1 minor criterion
  - Note: the presence of 2 or more minor criterion including nuclear hyperchromasia is diagnostic of Suspicious for HGUC (see below)
- Major criterion (required):
  - Non superficial and non-degenerated urothelial cells with an increased N/C ratio (> 0.5)
- Minor criteria (one required):
  - Nuclear hyperchromasia
  - Irregular nuclear membranes
  - Irregular, coarse and clumped chromatin
- Diagnosis of AUC is appropriate when cells are more abnormal than NHGUC
- AUC is appropriate when there is suspicion of HGUC but also extensive degeneration

Note:

- Normal intermediate and basal urothelial cells, typically seen in instrumented urine, have high N/C ratio and frequently occur in groups; should be regarded as NHGUC

Atypical urothelial cells

Suspicious for High Grade Urothelial Carcinoma (SHGUC)

- Reflects the presence of urothelial cells with severe atypia that falls short for a diagnosis of high-grade urothelial carcinoma but beyond atypical urothelial cells
- A diagnosis of SHGUC is defined as non-superficial and non-degenerated urothelial cells showing:
  - Increased N/C ratio, at least 0.5 - 0.7 (required criterion)
- Moderate to severe nuclear hyperchromasia (required criterion) and at least one of the following:
  - Irregular clumpy chromatin
  - Marked irregular nuclear membranes

High Grade Urothelial Carcinoma (HGUC)

- Sensitivity of urine cytology for HGUC is 50% to 85%
- Positive urine cytology is clinically meaningful, is significantly associated with tumour recurrence and is independent of other clinicopathologic variables
  - Hence, positive urine cytology in primary upper urinary tract urothelial carcinoma is valuable to predict prognosis and preoperative positive urine cytology may be associated with higher prevalence of tumour recurrence
- It can be useful to predict tumour progression

The ensuing are wort noting:

- Urine cytology cannot distinguish invasive **HGUC** and **carcinoma in situ (CIS)**
- Squamous or glandular differentiation of urothelial carcinoma may be seen in urine cytology but a diagnosis of **squamous cell carcinoma** or **adenocarcinoma** of the urinary tract can only be made after examination of biopsy or cystectomy specimens
- HGUC is diagnosed on the basis of this criteria according to the Paris System consensus:
  - Cellularity; at least 5 - 10 abnormal cells
  - N/C ratio: 0.7 or greater
  - Nucleus: moderate to severe hyperchromasia
  - Nuclear membrane: markedly irregular
  - Chromatin: coarse / clumped
- Other notable cytomorphologic features of HGUC are:
  - Cellular pleomorphism
  - Marked variation in cellular size and shapes. i.e. oval, rounded, elongated or plasmacytoid (comet cells)
  - Scant, pale or dense cytoplasm
  - Prominent nucleoli
  - Mitoses
  - Necrotic debris
  - Inflammation

High grade urothelial carcinoma (HGUC)

Low Grade Urothelial Neoplasia (LGUN)

- LGUN is a combined cytologic term for low grade papillary urothelial neoplasms, which includes: urothelial papilloma, papillary urothelial neoplasm of uncertain malignant potential **(PUNLMP)** and low grade papillary urothelial carcinoma **(LGPUC)**
- Definitive diagnosis of **LGUN** is possible only in the presence of this cytologic criteria (regardless of voided urine or instrumented urine):
  - 3 dimensional cellular papillary clusters with fibrovascular cores including capillaries
  - Cellular papillary clusters are defined as clusters of cells with nuclear overlapping forming papillae
- The following cytologic features should be categorized as NHGUC:
  - 3 dimensional cellular clusters without fibrovascular cores
  - Increased numbers of single monotonous (non-umbrella) cells
- Cytoplasmic homogeneity
- Nuclear border irregularity
- Increased N/C ratio
- A comment may be added to suggest LGUN in these cases without definitive cytomorphologic features

- Rate of progression is 0% for papillomas, 3.6% for PUNLMP and 5 - 25% for LGPUC

Squamous Cell Carcinoma (SCC)

- Accounts for 2 - 5% of all bladder cancer in West
- In North Africa and Middle East where Schistosoma haematobium infestation is endemic, it accounts for 25 - 30% of bladder malignancies
- Cases not associated with Schistosoma (non-bilharzial) are usually associated with conditions causing urinary stasis with epithelial injury, such as spinal cord injury or paraplegia
- Cytologic features of bladder SCC are similar to SCC elsewhere
- Diagnostic criteria for SCC:
    - Cellular specimen with numerous individual and nests of squamous cells
    - Tumour cells are large, polygonal with keratinized cytoplasm, sharp borders and mildly to markedly atypical hyperchromatic nuclei
    - Fiber and tadpole cells, squamous pearls and "cell in cell" arrangement may be present
    - Background may show fragments of a-nucleated squamous cells, small atypical parakeratotic cells, necrosis, RBCs and neutrophils
    - Nonkeratinizing malignant cell groups with metaplastic appearance may be present
    - Liquid based preparations show similar morphology but the background is cleaner so cell details are better preserved

Adenocarcinoma

- Accounts for 0.5% to 2.5% of all primary bladder malignancies and includes vesical and urachal subtypes.
- Urachal adenocarcinoma develops within urachal remnants located in bladder dome.
- Primary urinary tract adenocarcinoma is less common than secondary involvement from adjacent organs.
- Risk factors for the development of adenocarcinoma of urinary tract / bladder include cystitis glandularis of intestinal type and bladder exstrophy.
- Diagnostic criteria:
    - Variable cellularity
    - Enteric / colonic type columnar cell clusters and single degenerated cells in a background of necrosis and mucin
    - Nuclei are large vesicular or hyperchromatic, with irregular shapes and prominent nucleoli
    - Cytoplasm may be vacuolated
- Mucinous / colloid type has rounded 3-D clusters of crowded, bland cells with small to moderate amounts of lacy cytoplasm with occasional mucin vacuoles and medium sized nuclei with visible nucleoli in mucinous background.
- **Signet ring cell adenocarcinoma**: cells with large cytoplasmic mucin filled vacuole that appear optically clear or finely vacuolated, pushing the nucleus to the periphery. [56]
- **Clear cell carcinoma**: cells with abundant vacuolated cytoplasm and centrally located nuclei that may be present in clusters with hobnail configuration.

Small cell carcinoma

- Accounts for less than 1% of all bladder malignancies.
- Diagnostic criteria:
    - Moderate to high cellularity.
    - Haemorrhagic and necrotic background with apoptosis, isolated or small groups of small, undifferentiated malignant cells, mitoses and numerous neutrophils.
    - Cells are arranged singly, in linear pattern with rosettes, loosely or tightly cohesive clusters.
    - The tumour cells are round to oval or irregular and small to medium in size (2 - 3 x lymphocytes).
    - Nuclei are small to oval, hyperchromatic with finely granular evenly distributed or smudged chromatin, ill-defined membranes, prominent moulding and display crush artifact.
    - Nucleoli are inconspicuous.
    - Scanty cytoplasm.
    - High Nuclear / Cytoplasmic ratio (High N:C ratio)

Secondary neoplasms

- **Renal cell carcinoma**:
    - May be seen in cases of renal pelvis invasion by renal cell carcinoma
    - Degenerated cells
    - Cells maintain the same morphology as the tumours in the kidney
- **Prostatic carcinoma**:
    - Bladder neck involvement by prostatic carcinoma
    - Large cells in clusters with ill-defined cell borders, vacuolated cytoplasm, round nuclei and prominent nucleoli
    - Immunohistochemistry may be helpful
- **Colonic carcinoma**:
    - Direct extension to the urinary bladder with possible fistulae formation
    - Cells arranged in acinar configuration
    - Coarse chromatin pattern and prominent nucleoli
    - Necrosis and abundant red blood cells
    - Fecal material present

[B] Miscellaneous Narrations and Discussions from Some Case Reports, Case Series and Sudies Related to Immunotherapy in Urothelial Carcinoma

In 1997, Nseyo and Lamm made the ensuing iterations:

- Intravesical therapy had been used in the management of superficial transitional cell carcinoma (TCC) of the urinary bladder (i.e., Ta, T1, and carcinoma in situ) with specific objectives which include treating existing/residual tumour, preventing recurrence of tumour, preventing disease progression, and prolonging survival.
- The initial clinical stage and grade of the tumour remain the main determinant factors in survival irrespective of the treatment.
- At the time of publication of their article in 1997, bacillus Calmette-Guerin (BCG) immunotherapy had remained the most effective treatment and prophylaxis for TCC (Ta, T1, CIS) and had positive outcomes on tumour recurrence rate, disease progression, and prolongation of survival.
- Prostatic urethral mucosal involvement with urinary bladder cancer could be effectively treated with BCG intravesical immunotherapy in that it had demonstrated a reduction in tumour recurrence rates, but had had no positive impact upon disease progression or prolongation of survival.
- Interferons, keyhole-limpet hemocyanin (KLH), bropirimine, and PHOTOFRIN®-photodynamic therapy (PDT) were under investigation in the management of TCC and early results were encouraging.

Bajorin et al. stated that the role of adjuvant treatment in high-risk muscle-invasive urothelial carcinoma after radical surgery is not clear. Bajorin et al. reported that in a phase 3, multi-centre, double-blind, randomized, controlled trial, they had assigned patients with muscle-invasive urothelial carcinoma who had undergone radical surgery to receive, in a 1:1 ratio, either nivolumab (240 mg intravenously) or placebo every 2 weeks for up to 1 year. Neoadjuvant cisplatin-based chemotherapy before trial entry was allowed. The primary end points were disease-free survival among all the patients (intention-to-treat population) and among patients with a tumour programmed death ligand 1 (PD-L1) expression level of 1% or more. Survival free from recurrence outside the urothelial tract was a secondary end point. Bajorin et al. summated the results as follows:

- A total of 353 patients were assigned to receive nivolumab and 356 to receive placebo.
- The median disease-free survival in the intention-to-treat population was 20.8 months (95% confidence interval [CI], 16.5 to 27.6) with nivolumab and 10.8 months (95% CI, 8.3 to 13.9) with placebo.
- The percentage of patients who were alive and disease-free at 6 months was 74.9% with nivolumab and 60.3% with placebo (hazard ratio for disease recurrence or death, 0.70; 98.22% CI, 0.55 to 0.90; P<0.001).
- Among patients who had a PD-L1 expression level of 1% or more, the percentage of patients was 74.5% and 55.7%, respectively (hazard ratio, 0.55; 98.72% CI, 0.35 to 0.85; P<0.001).
- The median survival free from recurrence outside the urothelial tract in the intention-to-treat population was 22.9 months (95% CI, 19.2 to 33.4) with nivolumab and 13.7 months (95% CI, 8.4 to 20.3) with placebo.
- The percentage of patients who were alive and free from recurrence outside the urothelial tract at 6 months was 77.0% with nivolumab and 62.7% with placebo (hazard ratio for recurrence outside the urothelial tract or death, 0.72; 95% CI, 0.59 to 0.89).
- Among patients with a PD-L1 expression level of 1% or more, the percentage of patients was 75.3% and 56.7%, respectively (hazard ratio, 0.55; 95% CI, 0.39 to 0.79).
- 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 were noted in the nivolumab group.

Bajorin et al. made the ensuing conclusion:

- In this trial involving patients who had high-risk muscle-invasive urothelial carcinoma who had undergone radical surgery, disease-free survival was longer with adjuvant nivolumab than with placebo in the intention-to-treat population and among patients with a PD-L1 expression level of 1% or more. (Funded by Bristol Myers Squibb and Ono Pharmaceutical; CheckMate 274 ClinicalTrials.gov number, NCT02632409.)

Alexandroff et al. made the ensuing iterations:

- In the year of publication of their article, about 13000 patients in the USA would die of urinary bladder cancer and another 54000 new cases would appear.
- The situation is similar for most industrialised western nations, with incidence rates of 18 to 30 new cases per 100000 men placing urinary bladder cancer among the top five cancers in this sex.
- It was unclear why women are affected a third to a quarter less often than men.
- In 75% of patients the disease is diagnosed in its early superficial stage, usually as a result of visible or non-visible blood in the urine.
- Nevertheless, with an overall 65% recurrence rate and 30% progression rate, even these patients need lifelong medical vigilance entailing periodic internal inspections of their urinary bladders.

Vasekar et al. made the ensuing iterations:

- With the advent of Bacille Calmette Guerin (BCG), urinary bladder cancer was one of the earliest cancers where the concept of immunotherapy was used.
- While this is true, recent advances in the use of immunotherapy had been enabling oncologists to expand the armamentarium for the treatment of bladder cancer.
- Unacceptable side effects and failure to produce a durable response with the use of chemotherapeutic agents in urinary bladder cancer had led to the evaluation of more targeted and personalized approaches.

- Increased understanding of the underlying carcinogenesis of urinary bladder cancer, coupled with the ability to engineer targeted agents implicated in bladder cancer associated pathways had provided new avenues for the management of this disease.

- Newer immunotherapy approaches had generated a great deal of interest in urinary bladder cancer together with other diseases

Butt, et al. made the ensuing iterations:

- As research focus in oncology had recently shifted from oral targeted therapy to immunomodulation, the era of successful drug development in urinary bladder cancer had just commenced.

- This had led to unprecedented approval of five immunotherapeutic agents by regulatory agencies for metastatic bladder cancer within a span of 12 months.

- With an initial triumph of anti-programmed cell death-1 (anti-PD-1) and anti-programmed cell death ligand-1 (anti-PDL-1) drugs, ongoing efforts are aimed at identification and validation of new druggable immune targets to consolidate the initial gains

Grados et al made the ensuing iterations:

- For nearly 50 years, immunotherapy had been utilised in patients with urinary bladder cancer in the form of Mycobacterium bovis Bacillus Calmette-Guerin (BCG), which is still the first-line therapy for non-muscle invasive disease.

- Nevertheless, the remarkable results obtained with checkpoint inhibitor drugs, including Pembrolizumab and Atezolizumab, had fuelled the quest to optimize these and other forms of immunotherapy for both non-muscle invasive as well as advanced bladder cancer.

Konala et al. made the ensuing iterations:

- Urinary bladder cancer is the fifth most common cancer within the United States of America.

- Cisplatin-based chemotherapy is the current standard of care in stage IV urinary bladder cancer.

- It has increased overall survival but rarely results in complete remission, with an overall survival of 14 months to 15 months.

- The most significant breakthrough in cancer treatment over the last decade was the development of immunotherapy.

Konala **et al.** declared the ensuing data sources for their iterations**:**

- KEYNOTE-045, IMvigor211, CheckMate275, Javelin Solid Tumor, MEDI4736, and KEYNOTE-0528 clinical trials.

Konala also stated the ensuing areas of uncertainty**:**

- There are ongoing clinical trials utilising combination of immunotherapy and chemotherapy as first line of therapy in the setting of metastatic urothelial cancer and also to ascertain the duration of treatment.

Konala et al. also summated the ensuing therapeutic Advances**:**

- Immunotherapy was approved as a second-line treatment for metastatic urothelial cancer.

- Their use as a first-line agent was only limited to patients who are ineligible for cisplatin-based treatments.

- Five medicaments were approved by Food and Drug Administration for metastatic urothelial cancer including 3 Programmed cell-death protein 1 (PD-1) inhibitors and 2 programmed cell-death ligand 1 (PD-L1) inhibitors in patients who have progressed during or after platinum-based therapy. Pembrolizumab, nivolumab, and atezolizumab are PD-1 inhibitors. Durvalumab and avelumab are PD-L1 inhibitors.

- Nevertheless, only 2 medicaments were approved based upon phase III clinical trials—pembrolizumab and atezolizumab, of which only

- KEYNOTE study undertaken with pembrolizumab had demonstrated overall survival difference.

- Atezolizumab and pembrolizumab are the Food and Drug Administration–approved checkpoint inhibitors in cisplatin-ineligible patients.

Rhea et al. made the ensuing iterations:

- The role of immunotherapy in urinary bladder urothelial cancers is rapidly expanding.

- Since the initial second-line therapy approval for patients who fail prior platinum-based chemotherapy, utilisation of immunotherapy with checkpoint inhibitors had been rapidly evolving.

- There are approved indications for first-line metastatic disease in the platinum-ineligible patients or the cisplatin-ineligible PD-L1 positive patients, and there is a label for high-risk non-muscle-invasive bladder cancer who are BCG-refractory.

- In addition, a trial on maintenance immunotherapy with avelumab had demonstrated positive findings with improvement in overall survival that has also changed standard of care for these patients.

- There were ongoing clinical trials evaluating its use in the neoadjuvant and adjuvant perioperative muscle-invasive bladder cancer setting.

Wołącewicz et al. highlighted the ensuing lessons which clinicians need to learn:

- ❖ Checkpoint inhibitors are an established treatment for second-line therapy in metastatic urothelial cancers.

- ❖ Maintenance therapy with avelumab after complete response, partial response or stable disease after platinum-based chemotherapy had demonstrated improvement in overall survival and had been established as standard of care.

- ❖ First-line immunotherapy for metastatic urothelial cancer is appropriate for patients who have PD-L1 high or those who are platinum in-eligible.

- ❖ Pembrozulimab is an option for patients with high-risk BCG-refractory patients who are ineligible or refuse to undergo cystectomy.

- ❖ The role of immunotherapy in urinary bladder urothelial cancers is rapidly expanding.

- ❖ Since the initial second-line therapy approval for patients who had failed prior platinum-based chemotherapy, utilisation of immunotherapy with checkpoint inhibitors had been rapidly evolving.
- ❖ There are approved indications for first-line metastatic disease in the platinum-ineligible patients or the cisplatin-ineligible PD-L1 positive patients, and there is a label for high-risk non-muscle-invasive bladder cancer who are BCG-refractory.
- ❖ Furthermore, a trial on maintenance immunotherapy with avelumab had demonstrated positive findings with improvement in overall survival that had also changed standard of care for these patients.
- ❖ There were ongoing clinical trials evaluating its utilisation in the neoadjuvant and adjuvant perioperative muscle-invasive bladder cancer setting.

Wołącewicz et al. made the ensuing iterations:

- Urinary bladder cancer is one of the most significant genitourinary-cancer, causing high morbidity and mortality in a great number of patients.
- Over the years, a variety of treatment methods for this type of cancer had been developed.
- The commonest treatment is the highly efficient method using Bacillus Calmette-Guerin, giving a successful effect in a high percentage of patients.
- Nevertheless, in view of the genetic instability of urinary bladder cancer, together with individual needs of patients, the search for different therapy methods has been ongoing.
- Immune checkpoints are cell surface molecules that influence the immune response and decreasing the strength of the immune response.
- Among those checkpoints, the PD-1 (programmed cell death protein-1)/PD-L1 (programmed cell death protein ligand 1) inhibitors aim at blocking those molecules, which results in T cell activation, and in bladder cancer the use of Atezolizumab, Avelumab, Durvalumab, Nivolumab, and Pembrolizumab has been described.
- The inhibition of another pivotal immune checkpoint, CTLA-4 (cytotoxic T cell antigen), might result in the mobilization of the immune system against urinary bladder cancer and, among anti-CTLA-4 antibodies, utilisation of Ipilimumab and Tremelimumab had been discussed.
- Furthermore, many different approaches to successful urinary bladder cancer treatment exists, such as utilisation of ganciclovir and mTOR (mammalian target of rapamycin) kinase inhibitors, IL-12 (interleukin-12) and COX-2 (cyclooxygenase-2).
- Utilisation of gene therapies and the disruption of different signalling pathways were currently being investigated.
- Research had indicated that the combination of many methods increases treatment efficiency and the positive outcome in an individual.

In 2015, Fuge et al. made the ensuing iterations:

- It was nearly 40 years since Bacillus Calmette–Guérin (BCG) was first used as an immunotherapy to treat superficial bladder cancer.
- Despite its limitations, up to 2015 it had not been surpassed by any other treatment.
- As a better understanding of its mechanism of action and the clinical response to it have evolved, some of the questions around optimal dosing and treatment protocols had been answered.
- Nevertheless, its potential for toxicity and failure to produce the desired clinical effect in a significant cohort of patients presents has been an ongoing challenge to clinicians and researchers alike.
- They had summarized the evidence behind the established mechanism of action of BCG in urinary bladder cancer, highlighting the extensive array of immune molecules that had been implicated in its action.
- They had discussed the clinical aspects of BCG including its role in reducing recurrence and progression, the optimal treatment regime, toxicity and, in light of new evidence, whether or not there is a superior BCG strain.
- The problems of toxicity and non-responders to BCG had led to development of new techniques that had been aimed at addressing these pitfalls.
- The progress made in the laboratory had led to the identification of novel targets for the development of new immunotherapies. This includes the potential augmentation of BCG with various immune factors through to techniques that avoid utilisation of BCG altogether; for example, utilising interferon-activated mononuclear cells, BCG cell wall, or BCG cell wall skeleton.
- The potential role of gene, virus, or photodynamic therapy as an alternative to BCG was also reviewed.
- Recent interest in the immune check point system had led to the development of monoclonal antibodies against proteins involved in this pathway.
- Early findings had indicated benefit in metastatic disease, even though the role in superficial bladder cancer had remained unclear at the time of publication of their article.

Boegemann et al. made the ensuing iterations:

- With recent advances in immune-oncology and the introduction of checkpoint inhibitors into clinical practice for many cancers, the treatment landscape of urothelial carcinoma had changed dramatically and will continue to change further.
- Currently, a number of compounds and combinations were under investigation in numerous clinical trials and various clinical scenarios for bladder cancer.
- They had provided in their review, an overview of the history and rationale for immunotherapy in urinary bladder cancer.
- They had also provided the currently available data evaluating checkpoint inhibitors for bladder cancer, and discuss ongoing trials and future perspectives for urothelial carcinoma treatment.

- The introduction of checkpoint inhibitors into the management of bladder cancer had marked a significant milestone for this disease.
- Checkpoint inhibitors have the potential to impact patients across multiple disease states from non-muscle-invasive disease to metastatic tumours refractory to conventional treatment.
- That being said, validated biomarkers, including genetic signatures, to accurately predict response, and the establishment of optimal sequencing and combination of these immunotherapeutic agents with chemo/radiotherapy are urgently required.

In 2020, Lenfant et al. reported the available information on the current status and future direction of the use of checkpoint inhibitors as novel immunotherapeutic agents in bladder cancer. Lenfant et al. made the ensuing iterations:

- Over the past 3 years, five immunotherapies targeting programmed cell death 1 (Pembrolizumab and Durvalumab) or programmed cell death-ligand 1 (PD-L1) (Atezolizumab, nivolumab and Avelumab) pathways had been approved in second-line setting for patients who had progressed during or after cisplatin-based chemotherapy.
- According to the most recent update, these patients should be PD-L1-positive to be eligible for immunotherapy.
- Utilisation of novel checkpoint inhibitors was also very promising in other settings: Metastatic urothelial carcinoma without prior systemic treatment (IMvigor-130), as neoadjuvant treatment before radical cystectomy in patients with muscle invasive disease (PURE-01), and in Bacillus Calmette-Guérin (BCG) refractory non-muscle invasive bladder cancer (KEYNOTE 057).

Lenfant et al. [73] made the ensuing summations:

- Ongoing trials on the role of checkpoint inhibitors in bladder cancer may change clinicians' approach to different stages of bladder cancer.
- For metastatic urothelial carcinoma, the role of combined immune and chemotherapy might improve survival.
- For localized bladder cancer, immunotherapy as neoadjuvant therapy might be associated with less toxicity and better tolerability.
- Finally, in the setting of a BCG-refractory or BCG-naïve non-muscle invasive disease checkpoint inhibitors might reduce/delay the risk of progression and subsequent cystectomy.

Ghasemzadeh et al. made the ensuing iterations:

- Urothelial bladder cancer (UBC) had remained one of the most common and deadly cancers globally, and platinum-based chemotherapy, which has been the standard-of-care in metastatic bladder cancer, has had limited success in improving outcomes for patients.
- The recent development and translation of therapeutic strategies which had been aimed at harnessing the immune system had led to durable and prolonged survival for patients with several different cancers, including UBC.
- In a malignancy in which no major treatment advances had occurred over the preceding 30 years, clinicians are now witnessing a second coming of immunotherapy in the form of PD-1/PD-L1 blockade.
- But modern immunotherapy was still in its infancy in UBC; in addition to immune checkpoint blockade, a number of new metabolic, vaccine, agonist and tumour microenvironmental approaches were in development.
- Ultimately the application of these agents in UBC should be driven by a more comprehensive understanding of the factors limiting an anti-tumour immune response, both in patients as well as in physiologically relevant animal models.

Fakhrejahani et al. reviewed recent data on immunotherapies for urinary bladder cancer and discussed strategies to maximize the antitumor effect of immunotherapy in solid tumours. Fakhrejahani et al. reported their findings as follows:

- Anti-programmed death ligand 1 had shown promise in advanced bladder cancer.
- Clinical trials of immune checkpoint inhibitors as monotherapy or in combination were underway.
- They had reviewed strategies for enhancing antitumor immunity using immunomodulating agents or combination treatments that may increase tumour response.

Fakhrejahani et al. made the ensuing summation:

- Combining immune checkpoint inhibitors with other treatment modalities might lead to the development of new treatment strategies in advanced bladder cancer; nevertheless, identifying predictive biomarkers is essential for appropriate patient selection.

Rouanne et al. made the ensuing iterations:

- Over the preceding 3 decades, no major treatment breakthrough had been reported for advanced urinary bladder cancer.
- Recent Food and Drug Administration (FDA) approval of five immune checkpoint inhibitors in the management of advanced urinary bladder cancer had represented new treatment opportunities.
- They had examined the available data of the clinical trials leading to the approval of ICIs in the management of metastatic bladder cancer and the ongoing trials in advanced and localized settings.

Rouanne et al. undertook a literature search on PubMed and ClinicalTrials.gov combining the MeSH terms: 'urothelial carcinoma' OR 'bladder cancer', and 'immunotherapy' OR 'CTLA-4' OR 'PD-1' OR 'PD-L1' OR 'atezolizumab' OR 'nivolumab' OR 'ipilimumab' OR 'pembrolizumab' OR 'avelumab' OR 'durvalumab' OR 'tremelimumab'. Rouanne et al. included prospectives studies evaluating anti-PD(L)1 and anti-CTLA-4 monoclonal antibodies. Rouanne et al. made the ensuing iterations:

- Evidence-data related to early phase and phase III trials evaluating the 5 ICIs in the advanced urothelial carcinoma were detailed in their review.
- Anti-tumour activity of the 5 ICIs supporting the FDA approval in the second-line setting were reported.

- The activity of PD(L)1 inhibitors in the first-line setting in cisplatin-ineligible patients were also presented.
- Ongoing trials in earlier disease-states including non-muscle-invasive and muscle-invasive bladder cancer had been discussed.

. Rouanne et al. made the ensuing conclusions:

- Blocking the PD-1 negative immune receptor or its ligand, PD-L1, results in unprecedented rates of anti-tumour activity in patients with metastatic urothelial cancer.
- Nevertheless, a large majority of patients did not respond to anti-PD(L)1 drugs monotherapy.
- Investigations exploring the potential value of predictive biomarkers, optimal combination and sequences were ongoing to improve such treatment strategies.

Bellmunt et al. made the ensuing iterations:

- The treatment of bladder cancer has evolved over time to encompass not only the traditional modalities of chemotherapy and surgery, but it has been particularly impacted by utilisation of immunotherapy.
- The first immunotherapy was the live, attenuated bacterial Bacillus Calmette–Guérin vaccine, which had been the standard of care non-muscle-invasive bladder cancer since 1990.
- Modern immunotherapy has focused upon inhibitors of checkpoint proteins, which are molecules which impede immune function, thereby enabling tumour cells to grow and proliferate unregulated.
- Several checkpoint targets (programmed death ligand-1 [PD-L1] programmed cell death protien-1 [PD-1], and cytotoxic T-lymphocyte associated protein 4 [CTLA4]) had received the most attention in the treatment of urinary bladder cancer, and had inhibitor agents either approved or in late-stage development.
- They had described in their most recent data on agents that inhibit PD-L1, found on the surface of tumour cells, and PD-1 found on activated T and B cells and macrophages.
- Atezolizumab is the only member of this class currently which had been approved at the time of publication of their article for the treatment of urinary bladder cancer, but nivolumab, pembrolizumab, durvalumab, and avelumab all had positive results for this indication, and approvals were anticipated in the near future.
- The checkpoint inhibitors do offer an effective alternative for patients for whom previously there were few options for durable responses, including those who are ineligible for cisplatin-based regimens or who are at risk of significant toxicity.
- Research was ongoing to further categorize responses, define ideal patient populations, and investigate combinations of checkpoint inhibitors to address multiple pathways in immune system functioning.

Aggen et al. made the ensuing iterations:

- Treatment options for metastatic urothelial carcinoma (mUC) had remained relative unchanged over the preceding 30 years with combination chemotherapy as the mainstay of treatment.
- Within the preceding year the landscape for mUC had seismically shifted following the approval of five therapies targeting the programmed cell death protein (PD-1)/programmed cell death ligand 1 (PD-L1) axis.
- Notably, the anti-PD-1 antibody pembrolizumab had shown improved OS relative to chemotherapy in a randomized phase III study for second line treatment of mUC; this level 1 evidence had led to approval from the U.S. Food and Drug Administration (FDA).
- The PD-1 antibody nivolumab also had shown an overall survival benefit, in this case in comparison to historical controls.
- Similarly, antibodies that target PD-L1 including atezolizumab, durvalumab, and avelumab had now received accelerated approval from the FDA as second line treatments for mUC, with durable response lasting more than 1 year in some patients.
- Some of these agents had been approved in the first line setting as well - based upon single-arm phase II studies atezolizumab and pembrolizumab had received accelerated approval for first-line treatment of cisplatin ineligible patients.
- Despite these multiple approvals, the development of clinically useful biomarkers to ascertain the optimal treatment for patients had remained somewhat elusive.

Simons et al. made the ensuing iterations:

- Urinary bladder cancer accounts for about 13,000 deaths annually, and more than 60,000 new cases would appear 2008, making it the fourth and tenth most common cancer among men and women, respectively.
- The majority of the newly diagnosed cases would be diagnosed prior to muscle invasion, and are thus potentially completely curable.
- Unfortunately, more than 20% of patients initially diagnosed with non-muscle invasive bladder cancer will eventually die of their disease despite local endoscopic surgery.
- Mycobacterium bovis bacillus Calmette-Guérin (BCG) has been used for the treatment of bladder cancer since 1976, and continues to be at the forefront of therapeutic options for this malignancy. Despite its success and worldwide acceptance, the antitumor effector mechanisms remain elusive. BCG therapy induces a massive local immune response characterized by the expression of multiple cytokines in the urine and bladder tissue [83], and the influx of granulocytes and mononuclear cells into the bladder wall. Findings from our laboratory have demonstrated that tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is induced by BCG treatment, and TRAIL was expressed on polymorphonuclear neutrophils (PMN) in the urine obtained from patients after intravesical BCG instillation. Subsequently, we have determined that BCG and components of the mycobacterial cell wall can directly stimulate the release of soluble TRAIL from PMN through toll-like receptor-2 (TLR2) recognition that is augmented by interferon (IFN) . Based on our work and that of others implicating the need for T helper type 1 (Th-1) cytokine responses to BCG therapy for therapeutic results, we propose

that TRAIL is released by PMN migrating to the bladder in response to BCG treatment. In addition, IFN acts to augment and prolong the amount of TRAIL released by PMN, resulting in an effective therapeutic outcome.

Pettenati and Ingersoll made the ensuing iterations:

- BCG immunotherapy is the gold-standard treatment for non-muscle-invasive urinary bladder cancer at high risk of recurrence or progression.
- Pre-clinical and clinical studies had demonstrated that a robust inflammatory response to BCG involves several steps: attachment of BCG; internalization of BCG into resident immune cells, normal cells, and tumour urothelial cells; BCG-mediated induction of innate immunity, which is orchestrated by a cellular and cytokine milieu; and BCG-mediated initiation of tumour-specific immunity. As an added layer of complexity, variation between clinical BCG strains might influence development of tumour immunity.
- Nevertheless, more than 40 years after the first use of BCG for urinary bladder cancer, many questions regarding its mechanism of action had remained unanswered.
- Clearly, a better understanding of the mechanisms that underlie BCG-mediated tumour immunity could lead to improved efficacy, increased tolerance of treatment, and identification of novel immune-based therapies.
- Indeed, enthusiasm for urinary bladder cancer immunotherapy, and the possibility of combining BCG with other therapies, has been increasing due to the availability of targeted immunotherapies, including checkpoint inhibitors.
- Understanding of the mechanism of action of BCG immunotherapy had advanced greatly, but many questions had remained, and further basic and clinical research efforts are required to develop new treatment strategies for patients with urinary bladder cancer.

Pettenati and Ingersoll [88] summated the ensuing key points:

- BCG immunotherapy is the gold-standard treatment for high-risk non-muscle-invasive bladder cancer (NMIBC) in order to prevent disease recurrence and progression.
- BCG induces a robust innate immune response over many weeks is ensued by lasting antitumour adaptive immunity.
- Different BCG sub-strains are in clinical use around the world; however, whether these strains have varying efficacies in the induction of tumour immunity has not been clear.
- Efforts to improve BCG immunotherapy had largely failed, and up to the time of publication of their article, no existing therapy had outperformed BCG for treatment of high-risk NMIBC.
- New approaches, which incorporate novel immunotherapies such as checkpoint inhibitor antibodies, might successfully synergize with BCG to improve patient outcomes.

Song et al. made the ensuing iterations:

- With the mechanistic understanding of immune checkpoints and success in checkpoint blockade utilising antibodies for the treatment of certain cancers, immunotherapy had become one of the hottest areas in cancer research, with promise of long-lasting therapeutic effect.
- Currently; nevertheless, only a proportion of cancers have a good response to checkpoint inhibition immunotherapy.
- Better understanding of the cancer response and resistance mechanisms is essential to fully explore the potential of immunotherapy to cure the majority of cancers.
- Urinary bladder cancer, which is one of the most common and aggressive malignant diseases, had been successfully treated both at early and advanced stages by different immunotherapeutic approaches, bacillus Calmette–Guérin (BCG) intravesical instillation and anti-PD-1/PD-L1 immune checkpoint blockade, respectively.
- Therefore, it does provide a good model to investigate cancer immune response mechanisms and to improve the efficiency of immunotherapy.
- They had reviewed urinary bladder cancer immunotherapy with equal weight on BCG and anti-PD-1/PD-L1 therapies and demonstrate why and how bladder cancer could be used as a model to study the predictors and mechanisms of cancer immune response and shine light on further development of immunotherapy approaches and response predictive biomarkers to improve immunotherapy of bladder cancer and other malignancies.
- They reviewed the success of BCG and anti-PD-1/PD-L1 treatment of bladder cancer, the underlying mechanisms and the therapeutic response predictors, including the limits to our knowledge.
- They then highlighted briefly the adaptation of immunotherapy approaches and predictors developed in other cancers for bladder cancer therapy.
- Finally, they had explored the potential of using bladder cancer as a model to investigate cancer immune response mechanisms and new therapeutic approaches, which may be translated into immunotherapy of other human cancers.

Gan et al. made the ensuing iterations:

- Genetic mutations had been progressively introduced to BCG by repeated serial passage over many decades of its culture and global dissemination.
- Hence, marked differences exist in the phenotype, antigenicity, reactogenicity, and clinical characteristics of the numerous sub-strains of BCG currently in use for bladder cancer immunotherapy.
- These differences influence proposed mycobacterial antitumour mechanisms and toxicity, potentially resulting in variations in clinical efficacy and adverse effects.
- Nevertheless, even though there is evidence of sub-strain-related differences in the clinical efficacy of BCG as a tuberculosis vaccine, evidence of an effect on bladder cancer immunotherapy remains elusive, owing to the lack of appropriately powered head-to-head comparative clinical trials, the non-standardization of BCG manufacture, and variation in treatment protocols—possibly itself a response to underlying sub-strain differences.

- Advances in the understanding of mycobacterial genetics, structure and function, and host–pathogen interactions might explain differences in clinical practice and outcomes.
- These advances are guiding the identification of biomarkers for reactogenicity and efficacy, and the rational design of immunotherapeutic strategies to eliminate the use of live bacilli for bladder cancer therapy.

Besançon et al. made the ensuing iterations:

- Men are three to four times more likely to be diagnosed with bladder cancer (BCa) than women, who often have more aggressive tumours.
- Intravesical bacillus Calmette-Guerin (BCG) for non-muscle-invasive bladder cancer (NMIBC) is one of the first immunotherapies, with use of immune checkpoint inhibitors for BCa immunotherapy expanding.
- Sex hormones, and notably androgens, might impact upon the outcome of these therapies.

Besançon et al. undertook a study to understand immunological sex differences in BCa and to investigate androgen receptor (AR) inhibition as a novel strategy to improve the response to BCa immunotherapy. Besançon et al. freshly collected Human NMIBC tumours following transurethral resection. They used in vivo studies, the subcutaneous MBT-2 BCa model in male and female C3H mice. The AR antagonist enzalutamide was given alone or in combination with anti-programmed cell death protein-1 (anti-PD-1) or intra-tumoral BCG + poly(I:C) treatments. Besançon et al. evaluated tumour growth and survival in vivo as well as they computed the outcome measures utilising statistical analysis. Flow cytometry and RNA sequencing characterized the immune cells present in murine and human tumours. They performed descriptive comparisons for MBT-2 tumours between sexes and with human NMIBC tumours. Besançon et al. summated the results as follows:

- The MBT-2 model shows multiple similarities to the immune composition of human NMIBC tumours and recapitulates previously observed human tumour immune cell sex differences.
- Enzalutamide in combination with either anti-PD-1 or BCG + poly(I:C) treatment in male mice had synergized to improve response rates.
- Notably, the proportion of complete responses in male mice treated with the combination treatment resembles that observed in female mice with either immunotherapy alone.
- Limitations of their study included the sample size for murine experiments.

Besançon et al. made the ensuing conclusions and patient summary:

- Their results suggested that combining AR antagonism with immunotherapy in male BCa patients may potentiate the antitumor immune response and increase response rates.
- The MBT-2 model appears relevant to investigate immunological BCa sex differences.
- Their studies had suggested that combining antiandrogen treatments with BCa immunotherapy may improve response rates in men.
- They had also demonstrated the utility of the MBT-2 mouse model to study sex differences in BCa.

Kaur et al. made the ensuing iterations:

- The standard treatment for non-metastatic muscle-invasive bladder cancer (MIBC) is cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy or tri-modality therapy with chemoradiation in select patients.
- Pathology complete response (pCR) to neoadjuvant chemotherapy is a reliable predictor of overall and disease-specific survival in MIBC.
- A pCR rate of 35% to 40% is attained with neoadjuvant cisplatin-based chemotherapy.
- With the approval of immune checkpoint inhibitors (ICIs) for the treatment of metastatic urothelial cancer, these agents are now being studied in the neoadjuvant setting for MIBC.

Kaur et al. [91] reported the results from clinical trials using single agent ICI, ICI/ICI and ICI/chemotherapy combination therapies in the neoadjuvant setting for MIBC. These single-arm clinical trials had demonstrated safety and pCR comparable to cisplatin-based chemotherapy. Kaur et al. [91] made the ensuing conclusions:

- Neoadjuvant ICI is a promising approach for cisplatin-ineligible patients, and the role of adding ICIs to cisplatin-based chemotherapy was also being investigated in randomized phase III clinical trials.
- Ongoing biomarker research to suggest a response to neoadjuvant ICIs would also guide appropriate treatment selection.

Li, et al. made the ensuing iteration:

- There is a critical unmet need for safe and efficacious neoadjuvant treatment for cisplatin-ineligible patients with muscle-invasive bladder cancer.

Li, et al. launched a phase 1b study using the combination of intravesical cretostimogene grenadenorepvec (oncolytic serotype 5 adenovirus encoding granulocyte-macrophage colony-stimulating factor) with systemic nivolumab in cisplatin-ineligible patients with cT2-4aN0-1M0 muscle-invasive bladder cancer. The primary objective was to measure safety, and the secondary objective was to assess the anti-tumour efficacy as measured by pathology complete response along with 1-year recurrence-free survival. Li, et al. summarised the results as follows:

- No dose-limiting toxicity was encountered in 21 patients who were enrolled and treated.
- Combination treatment had achieved a pathological complete response rate of 42.1% and a 1-year recurrence-free survival rate of 70.4%.
- Pathological response was associated with baseline free E2F activity and tumour mutational burden but not PD-L1 status.
- Even though T cell infiltration was broadly induced after intravesical oncolytic immunotherapy, the formation, enlargement and maturation of tertiary lymphoid structures was specifically associated with complete response, supporting the importance of coordinated humoral and cellular immune responses.

Li, et al. concluded that:

- Together, these results had highlighted the potential of this combination regimen to enhance therapeutic efficacy in cisplatin-ineligible patients with muscle-invasive bladder cancer, warranting additional study as a neoadjuvant therapeutic option. ClinicalTrials.gov identifier: NCT04610671 .

Yan et al. [93] made the ensuing iterations:

- Neoadjuvant immunotherapy-driven bladder preservation (Neoimmu-CMT), despite its prominence, is constrained in application due to the absence of robust clinical evidence.
- Currently, there is a lack of comparative studies on the efficacy of Neoimmu-CMT versus the traditional trimodal therapy (TMT) or neoadjuvant chemotherapy- driven bladder preservation (NAC-CMT).
- To address this gap, their study (ChiCTR2300069303) had aimed to assess Neoimmu-CMT's viability and identify suitable candidates through a multicenter, propensity score-matched analysis.

Yan et al. undertook a study which included 163 patients from 14 hospitals, who were categorized into Neoimmu-CMT (n=97), TMT (n=30), and NAC-CMT (n=36) subgroups. PSM was utilized to mitigate baseline variability. Primary outcomes were disease-free survival (DFS), urinary bladder-intact DFS (BI-DFS), and overall survival (OS) Univariate and multivariate Yan et al. [93] used Cox analyses to identify potential prognostic factors. Biomarker assessment comprised immunohistochemistry and single-cell RNA sequencing. Yan et al. [93] summarised the results as follows:

- Post-PSM, Neoimmu-CMT significantly had outperformed NAC-CMT in DFS (HR: 2.112, 95% CI: 1.247-3.576, P=0.005) and BI-DFS (HR: 2.329, 95% CI: 1.138-4.770, P=0.021), with a 2-year BI-DFS rate of 90.28% compared to NAC-CMT's 71.59%.
- Nevertheless, Neoimmu-CMT and TMT demonstrated no significant difference in DFS and BI-DFS, with Neoimmu-CMT marginally surpassing TMT in 2-year BI-DFS rates (86.42% vs. 80.89%).
- Clinical complete response to neoadjuvant treatment and lower clinical T stage were positive prognostic factors for Neoimmu-CMT.
- Biomarker analysis showed the tumour microenvironment immune phenotype closely related to bladder preservation outcomes.

Yan et al. [93] made the ensuing conclusions:

- Neoimmu-CMT is a promising bladder preservation strategy, comparable to TMT and superior to NAC-CMT.
- Its advancement could significantly broaden urinary bladder preservation treatment options.

Tomita et al. made the ensuing iterations:

- The phase 3 CheckMate 274 trial had demonstrated superiority of adjuvant nivolumab over placebo after radical surgery in patients with high-risk muscle-invasive urothelial carcinoma.
- Nevertheless, the efficacy and safety of adjuvant nivolumab in Japanese patients with muscle-invasive urothelial carcinoma had not been clarified.

Tomita et al. [94] randomized patients who had muscle-invasive urothelial carcinoma to adjuvant nivolumab 240 mg or placebo (every 2 weeks via intravenous infusion) up to 120 days after radical surgery in CheckMate 274. Tomita et al. summarised the results as follows:

- Out of 49 patients in the Japanese subgroup, 27 and 22 patients were randomized to nivolumab and placebo, respectively.
- Eleven and 8 patients, respectively, had tumour PD-L1 expression level of 1% or more.
- The median disease-free survival times in the nivolumab and placebo groups were 29.67 months (95% confidence interval 7.79–not reached) and 9.72 months (95% confidence interval 4.73–not reached), respectively (hazard ratio 0.77, 95% confidence interval 0.35–1.69).
- The corresponding values in patients with tumour PD-L1 expression level of 1% or more were 29.67 months (95% confidence interval 2.63–not reached) and 25.95 months (95% confidence interval 5.59–not reached) (hazard ratio 1.10, 95% confidence interval 0.31–3.92), respectively.
- Treatment-related adverse events of Grade 3–4 had occurred in 25.9 and 13.6% of patients in the nivolumab and placebo groups, respectively.
- The commonest treatment-related adverse events in the nivolumab group were lipase increased, amylase increased and diarrhoea.
- The changes in quality-of-life scores from baseline over time were similar in both groups.

Tomita et al. concluded that:

The efficacy and safety results in the Japanese subgroup were found to be consistent with the overall population of CheckMate 274.

Powles et al. made the ensuing iterations:

- Neoadjuvant chemotherapy which is ensued by radical cystectomy is the standard treatment for cisplatin-eligible patients with muscle-invasive bladder cancer.
- Adding peri-operative immunotherapy might improve outcomes.

In this phase 3, open-label, randomized trial, Powles et al. assigned, in a 1:1 ratio, cisplatin-eligible patients with muscle-invasive bladder cancer to receive neoadjuvant durvalumab plus gemcitabine-cisplatin every 3 weeks for four cycles, followed by radical cystectomy and adjuvant durvalumab every 4 weeks for eight cycles (durvalumab group), or to receive neoadjuvant gemcitabine-cisplatin ensued by radical cystectomy alone (comparison group). Event-free survival was one of two primary end points. Overall survival was the key secondary end point. Powles et al. summarised the results as follows:

- In total, 533 patients were assigned to the durvalumab group and 530 to the comparison group.
- The estimated event-free survival at 24 months was found to be 67.8% (95% confidence interval [CI], 63.6 to 71.7) in the durvalumab group and 59.8% (95% CI, 55.4 to 64.0) in the comparison group (hazard ratio for progression, recurrence, not undergoing radical cystectomy, or death from any cause, 0.68; 95% CI, 0.56 to 0.82; P<0.001 by stratified log-rank test).
- The estimated overall survival 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 (hazard ratio for death, 0.75; 95% CI, 0.59 to 0.93; P = 0.01 by stratified log-rank test).
- Treatment-related adverse events of grade 3 or 4 in severity had occurred in 40.6% of the patients in the durvalumab group and in 40.9% of those in the comparison group; treatment-related adverse events leading to death occurred in 0.6% in each group.

- Radical cystectomy was undertaken in 88.0% of the patients in the durvalumab group and in 83.2% of those in the comparison group.

Powles et al. concluded that: Perioperative durvalumab plus neoadjuvant chemotherapy had led to significant improvements in event-free survival and overall survival in comparison with neoadjuvant chemotherapy alone.

Romero et al. [96] made the ensuing iterations:

- Eligible patients with muscle-invasive bladder cancer (MIBC) typically receive cisplatin-based chemotherapy prior to undergoing radical cystectomy; even though about 50% would develop disease relapse within 3 years.
- Now, newly published data from the phase III NIAGARA trial which was simultaneously presented at the ESMO Congress 2024 had demonstrated that adding perioperative durvalumab to neoadjuvant chemotherapy improves outcomes in this setting.

Romero et al. randomly allocated a total of 1,063 patients (1:1) to receive neoadjuvant gemcitabine–cisplatin followed by radical cystectomy with or without neoadjuvant and adjuvant durvalumab (durvalumab and control group, respectively). Pathological complete response (pCR) and event-free survival (EFS) were the co-primary end points.

Singh et al. reported the case of an 83-year-old female who presented to the emergency department because she had lower abdominal pain. The pain commenced 1 month preceding her presentation and progressively got worse. She had a computed tomography (CT) scan of the abdomen and pelvis, which demonstrated significant left-sided hydronephrosis, hydroureter, mass in left side of the base of her urinary bladder (see figure 1), and 4.6 cm × 4.7 cm mass medial to the left common femoral artery (see figure 2). She underwent transurethral resection of the bladder tumour, which demonstrated a large necrotic mass involving the left posterior bladder/trigone and left side of bladder wall which was adjudged to be the likely cause of her left-sided hydronephrosis, and hydroureter, and pathology examination features of the tumour was consistent with high-grade urothelial carcinoma with invasion of muscularis propria. The patient was diagnosed with metastatic bladder cancer. The patient was not a chemotherapy candidate based upon her age and performance status and immunotherapy was commenced with pembrolizumab. She received 7 cycles of pembrolizumab (every 3 weeks) and then she presented to hospital for breathing difficulty and she had CT scan of the chest which showed pneumonitis. She was commenced on steroids, pembrolizumab permanently stopped, and eventually she was discharged home. The patient continued to follow-up as outpatient off therapy and her repeat CT scan of her chest, abdomen, and pelvis 6 month post her last treatment showed no evidence of metastatic disease in chest, abdomen, and pelvis–complete response (see figure 3).

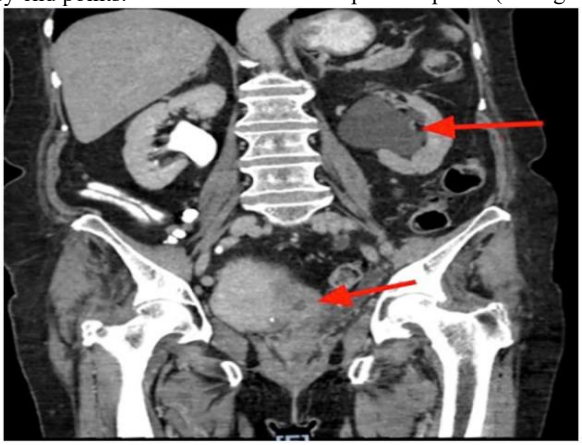


Figure 1: Computed tomography scan of the abdomen and pelvis showing significant left-sided hydronephrosis, hydroureter, and mass in left side of the base of the bladder. Reproduced from: under the Creative Commons Attribution License.

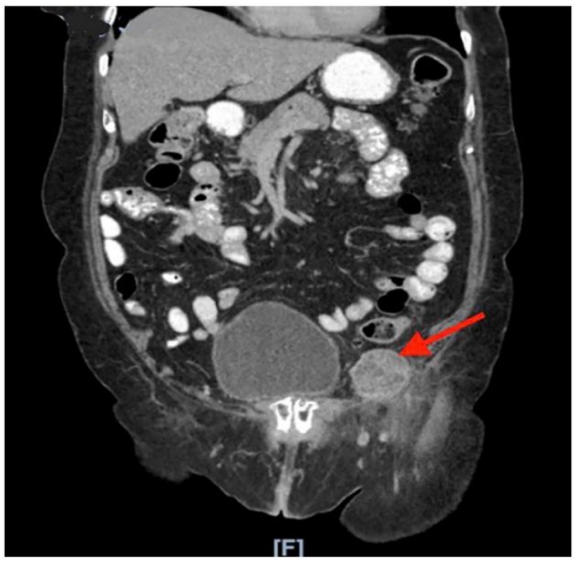
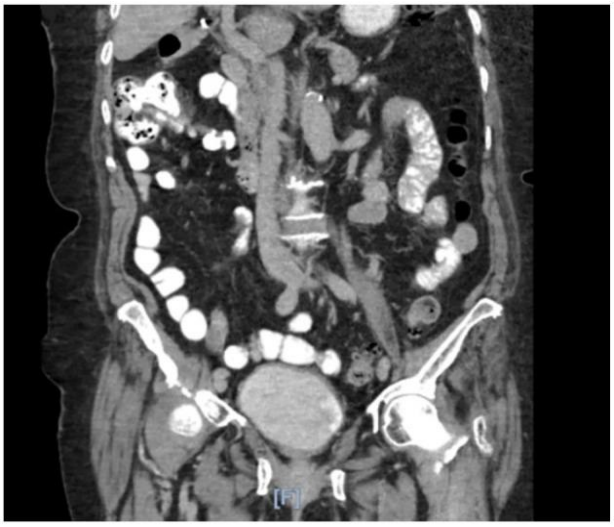


Figure 2: Computed tomography scan of the abdomen and pelvis showing 4.6 × 4.7 cm mass medial to the left common femoral artery. Reproduced from: under the Creative Commons Attribution License.



Computed tomography scan of the chest, abdomen, and pelvis showing no evidence of metastatic disease–complete response. Reproduced from: under the Creative Commons Attribution License.

Singh et al. concluded that:

- They had reported the case of an elderly female with metastatic bladder cancer who was chemotherapy ineligible and hence was given immune checkpoint inhibitor pembrolizumab and complete response was achieved.

conclusions and summation of salient points related to immunotherapy for urinary bladder cancer

Immunotherapy is a terminology that is used for medicaments that are utilised to help an individual's own immune system to recognize and destroy cancer cells. This type of treatment is sometimes used to treat urothelial carcinoma of urinary bladder**.** Intravesical immunotherapy treatments are instilled directly into the urinary bladder. They are utilised mainly for early-stage bladder cancers that have not extended deeply into the wall of the bladder and these tumours are staged PTA and PT1 tumours. Intravesical immunotherapy treatments are instilled directly into the urinary bladder. They are used mainly for non-muscle invasive early-stage bladder cancers that have not grown deeply into the wall of the urinary bladder. Bacillus Calmette-Guerin (BCG) has been in use for many years in an attempt to reduce the recurrence of high-grade / high-risk non-muscle invasive urinary bladder tumours. While BCG does not usually make a person sick, it can help trigger an immune response. BCG can be instilled right into the urinary bladder as a liquid. This activates immune system cells in the bladder, which then attack the bladder cancer cells. **Nadofaragene firadenovec (Adstiladrin)** is made up of a virus which contains the gene to make interferon alfa-2b, an important immune system protein. When the virus is instilled into the urinary bladder as part of a liquid, it delivers the gene into the cells lining the bladder wall. The cells then commence making extra interferon alfa-2b, which helps the body's immune system to attack the cancer cells. Nogapendekin alfa inbakicept (Anktiva**)** is an interleukin-15 (IL-15) receptor agonist. When Anktiva is instilled into the bladder as a liquid, it activates some of the body's immune cells, including natural killer (NK) cells and T cells, which then attack the cancer cells.

Immune checkpoint inhibitors represent an important part of the immune system due to its ability to keep itself from attacking normal cells within the body. To do this, it utilises "checkpoint" proteins on immune cells, which act like switches that need to be turned on or off to start an immune response. Cancer cells sometimes utilise these checkpoints so as to keep from being attacked by the immune system. But medicaments that target these checkpoints, which are referred to as checkpoint inhibitors, can help restore the immune response against cancer cells.

PD-1 and PD-L1 inhibitors, Avelumab (Bavencio) and durvalumab (Imfinzi) target PD-L1, a protein upon cells (including some cancer cells) that help keep the immune system from attacking them. By blocking PD-L1, these medicaments boost the immune system's response against the cancer cells. This could shrink some tumours or slow their growth.

Nivolumab (Opdivo) and pembrolizumab (Keytruda) target PD-1, a protein on certain immune cells (called T cells) which normally helps keep these cells from attacking other cells within the body. Blocking PD-1 can enable the immune system to attack the cancer cells, which could shrink some tumours or slow down their growth.

These medicaments can be utilised in different scenarios to treat urinary bladder cancer. Some of the utilizations of the aforementioned medicaments include the ensuing:

- ❖ Pembrolizumab can be utilised with enfortumab vedotin, to treat advanced urinary bladder cancer.
- ❖ Nivolumab can be utilised together with chemotherapy to treat advanced urinary bladder cancer.
- ❖ Avelumab can be utilised as an additional maintenance treatment in people who have advanced urinary bladder cancer which did not worsen during their initial chemotherapy treatments.
- ❖ Most of these checkpoint inhibitors could be utilised in individuals who have advanced urinary bladder cancer which commences to grow again pursuant chemotherapy.
- ❖ Pembrolizumab could be utilised to treat certain urinary bladder cancers which are not growing into the muscle wall of the urinary bladder (non-muscle-invasive), are not getting smaller with intravesical BCG, and are not being treated with the undertaking of a cystectomy.
- ❖ Nivolumab might be offered to individuals who have muscle-invasive bladder cancer (MIBC, cancer which has invaded the muscle wall of the bladder) which has been removed with surgery but is at high risk of recurring. In this scenario, it is administered for one year.
- ❖ Durvalumab can be used together with chemotherapy preceding the undertaking of a cystectomy in people with MIBC, and then again by itself pursuant to the cystectomy, for up to about 8 months.
- ❖ These drugs are usually administered as intravenous (IV) infusions, every 2 weeks to 6 weeks, depending upon the

medicament. Some can now be administered subcutaneously under the skin over many minutes as well.

Possible side effects of checkpoint inhibitors can include the ensuing:

- Fatigue
- Nausea
- Loss of appetite
- Fever
- Urinary tract infections (UTIs)
- Rash
- Diarrhoea
- Constipation

Some of the possible side effects and complications of the aforementioned that occur less often, including more serious side effects that could occur include the ensuing:

- **Infusion reactions:** Some people might have an infusion reaction while receiving one of these medicaments. The infusion reaction is like an allergic reaction, and could include: fever, chills, flushing of the face, rash, itchy skin, feeling dizzy, wheezing, and trouble breathing.
- **Autoimmune reactions:** These medicaments work by basically removing one of the safeguards on the body's immune system. Sometimes the immune system commences attacking other parts of the body, which could cause serious or even life-threatening problems within the lungs, intestines, liver, hormone-making glands, or other organs.
- **Antibody-drug conjugates:** Man-made versions of antibodies which are called **monoclonal** antibodies, are designed to attach to a specific target, such as a protein upon the surface of the urinary bladder cancer cells.
- **Antibody-drug conjugates (ADCs)** are monoclonal antibodies which are linked to a chemo drug. Once inside the human body, the antibody part of the ADC acts like a homing device, bringing the chemo directly to the cancer cells.

Enfortumab vedotin (Padcev) is another medicament**.** Urinary bladder cancer cells usually have the Nectin-4 protein upon their surface. Enfortumab vedotin is an anti-Nectin-4 antibody which is attached to a chemotherapy medicament. The antibody part acts like a magnet to bring the chemotherapy medicament to the bladder cancer cells with Nectin-4 on them. The chemotherapy medicament enters the cancer cells and kills them. This medicament can be used together with the immunotherapy drug pembrolizumab in individuals who have advanced urinary bladder cancer. Enfortumab vedotin could also be used by itself to treat individuals who have advanced bladder cancer who:

- Have already been treated with a platinum-based chemotherapy medicament including cisplatin and immunotherapy (specifically, a PD-1 or PD-L1 inhibitor), OR

Enfortumab vedotin is infused intravenously (IV), typically once a week for 2 weeks or 3 weeks, followed by a week off. Common side effects of Enfortumab vedotin include: fatigue, peripheral neuropathy (a type of nerve damage that can lead to numbness or tingling in the hands or feet), nausea, taste changes, decreased appetite, diarrhoea, rash, hair loss, dry eyes or vision changes, dry skin, itching, and high blood sugar levels. Less common but more serious side effects of Enfortumab vedotin could include severe skin reactions, inflammation and swelling within the lungs, and very high blood sugar levels.

.Bacillus Calmette-Guerin (BCG) can help trigger an immune response. BCG can be instilled into the bladder. This activates immune system cells within the urinary bladder, which then attack the bladder cancer cells.

Nadofaragene firadenovec (Adstiladrin) is made up of a virus that contains the gene to make interferon alfa-2b, an important immune system protein. When the virus is instilled into the bladder as part of a liquid, it delivers the gene into the cells lining the bladder wall. The cells then commence making extra interferon alfa-2b, which helps the body's immune system attack the cancer cells.

Nogapendekin alfa inbakicept (Anktiva) is an interleukin-15 (IL-15) receptor agonist. When put into the bladder as a liquid, it activates some of the body's immune cells, including natural killer (NK) cells and T cells, which then attack the cancer cells.

Conflict Of Interest – Nil

Acknowledgements

Acknowledgements to:

- Journal of Investigative Medicine High Impact Case Reports and the American Federation of Medical Research: For granting permission for reproduction of figures and contents of their journal article under the Creative Commons Attribution License under the ensuing copyright statements: © 2021 American Federation for Medical Research This article is distributed under the terms of the Creative Commons Attribution-Non-Commercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (https://us.sagepub.com/en-us/nam/open-access-at-sage)

References

1. Besançon M, Gris T, Joncas FH, Picard V, Bergeron A, Fradet Y, Toren P. Combining Antiandrogens with Immunotherapy for Bladder Cancer Treatment. European Urology Open Sci. 2022 Jul 26; 43:35-44.
2. Hayashi T, Fujita K, Hayashi Y, Hatano K, Kawashima A, McConkey DJ, Nonomura N. Mutational landscape and environmental effects in bladder cancer. International journal of molecular sciences. 2020 Aug 23;21(17):6072.
3. Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, Kassouf W, Kiemeney LA, La Vecchia C, Shariat S, Lotan Y. Epidemiology and risk factors of urothelial bladder cancer. European urology. 2013 Feb 1;63(2):234-41.
4. Mungan NA, Kiemeney LA, van Dijck JA, van der Poel HG, Witjes JA. Gender differences in stage distribution of bladder cancer. Urology. 2000 Mar 1;55(3):368-71.
5. Guallar-Garrido S, Julián E. Bacillus Calmette-Guérin (BCG) therapy for bladder cancer: an update. ImmunoTargets and therapy. 2020 Feb 13:1-1.
6. Zlotta AR, Fleshner NE, Jewett MA. The management of BCG failure in non-muscle-invasive bladder cancer: an update. Can Urol Assoc J. 2009 Dec;3(6 Suppl 4):S199-205.
7. Ott PA, Hu-Lieskovan S, Chmielowski B, Govindan R, Naing A, Bhardwaj N, Margolin K, Awad MM, Hellmann MD, Lin JJ, Friedlander T. A phase Ib trial of personalized neoantigen therapy plus anti-PD-1 in patients with advanced melanoma, non-small cell lung cancer, or bladder cancer. Cell. 2020 Oct 15;183(2):347-62.
8. de Jong FC, Rutten VC, Zuiverloon TC, Theodorescu D. Improving anti-PD-1/PD-L1 therapy for localized bladder cancer. International journal of molecular sciences. 2021 Mar 10;22(6):2800.

9. Sunshine J, Taube JM. Pd-1/pd-l1 inhibitors. Current opinion in pharmacology. 2015 Aug 1; 23:32-8.
10. Bree KK, Hensley PJ, Brooks N, Matulay J, Nogueras-Gonzalez GM, Navai N, Dinney CP, Kamat AM. Impact of sex on response to BCG in non-muscle invasive bladder cancer patients: a contemporary review from a tertiary care center. World journal of urology. 2021 Nov;39(11):4143-9.
11. Uhlig A, Strauss A, Hosseini AS, Lotz J, Trojan L, Schmid M, Uhlig J. Gender-specific differences in recurrence of non–muscle-invasive bladder cancer: a systematic review and meta-analysis. European Urology Focus. 2018 Dec 1;4(6):924-36.
12. Bilski K, Zapała Ł, Skrzypczyk MA, Oszczudłowski M, Dobruch J. Review on gender differences in non-muscle invasive bladder cancer. Transl Androl Urol. 2019 Feb;8(1):12-20.
13. McGrath M, Michaud DS, De Vivo I. Hormonal and reproductive factors and the risk of bladder cancer in women. American journal of epidemiology. 2006 Feb 1;163(3):236-44.
14. Miyamoto H, Yao JL, Chaux A, Zheng Y, Hsu I, Izumi K, Chang C, Messing EM, Netto GJ, Yeh S. Expression of androgen and oestrogen receptors and its prognostic significance in urothelial neoplasm of the urinary bladder. BJU international. 2012 Jun;109(11):1716-26.
15. Ben-Batalla I, Vargas-Delgado ME, Von Amsberg G, Janning M, Loges S. Influence of androgens on immunity to self and foreign: effects on immunity and cancer. Frontiers in immunology. 2020 Jul 2;11:1184.
16. Moradi F, Enjezab B, Ghadiri-Anari A. The role of androgens in COVID-19. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020 Nov 1;14(6):2003-6.
17. Kourbanhoussen K, McMartin C, Lodde M, Zlotta A, Bryan RT, Toren P. Switching cancers: a systematic review assessing the role of androgen suppressive therapy in bladder cancer. European Urology Focus. 2021 Sep 1;7(5):1044-51.
18. Bajorin DF, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y, Bamias A, Lebret T, Shariat SF, Park SH, Ye D, Agerbaek M, Enting D, McDermott R, Gajate P, Peer A, Milowsky MI, Nosov A, Neif Antonio J Jr, Tupikowski K, Toms L, Fischer BS, Qureshi A, Collette S, Unsal-Kacmaz K, Broughton E, Zardavas D, Koon HB, Galsky MD. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. N Engl J Med. 2021 Jun 3;384(22):2102-2114.
19. Alfred Witjes J, Lebret T, Compérat EM, Cowan NC, De Santis M, Bruins HM, Hernández V, Espinós EL, Dunn J, Rouanne M, Neuzillet Y, Veskimäe E, van der Heijden AG, Gakis G, Ribal MJ. Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. Eur Urol. 2017 Mar;71(3):462-475.
20. Benson AB, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Garrido-Laguna I, Grem JL, Gunn A, Hoffe S, Hubbard J, Hunt S, Kirilcuk N, Krishnamurthi S, Messersmith WA, Meyerhardt J, Miller ED, Mulcahy MF, Nurkin S, Overman MJ, Parikh A, Patel H, Pedersen K, Saltz L, Schneider C, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Johnson-Chilla A, Gurski LA. NCCN Guidelines Insights: Rectal Cancer, Version 6.2020. J Natl Compr Canc Netw. 2020 Jul;18(7):806-815.
21. Rouprêt M, Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM, Cowan NC, Dominguez-Escrig JL, Gontero P, Hugh Mostafid A, Palou J, Peyronnet B, Seisen T, Soukup V, Sylvester RJ, Rhijn BWGV, Zigeuner R, Shariat SF. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2020 Update. Eur Urol. 2021 Jan;79(1):62-79.
22. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, Skinner E, Bochner B, Thangathurai D, Mikhail M, Raghavan D, Skinner DG. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol. 2001 Feb 1;19(3):666-75.
23. Birtle A, Johnson M, Chester J, Jones R, Dolling D, Bryan RT, Harris C, Winterbottom A, Blacker A, Catto JWF, Chakraborti P, Donovan JL, Elliott PA, French A, Jagdev S, Jenkins B, Keeley FX Jr, Kockelbergh R, Powles T, Wagstaff J, Wilson C, Todd R, Lewis R, Hall E. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. Lancet. 2020 Apr 18;395(10232):1268-1277.
24. Dash A, Galsky MD, Vickers AJ, Serio AM, Koppie TM, Dalbagni G, Bochner BH. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer. 2006 Aug 1;107(3):506-13.
25. Necchi A, Lo Vullo S, Mariani L, Moschini M, Hendricksen K, Rink M, Sosnowski R, Dobruch J, Raman JD, Wood CG, Margulis V, Roupret M, Briganti A, Montorsi F, Xylinas E, Shariat SF; European Association of Urology-Young Academic Urologists (EAU-YAU), Urothelial Cancer Group and the Upper Tract Urothelial Carcinoma Collaboration group. Adjuvant chemotherapy after radical nephroureterectomy does not improve survival in patients with upper tract urothelial carcinoma: a joint study by the European Association of Urology-Young Academic Urologists and the Upper Tract Urothelial Carcinoma Collaboration. BJU Int. 2018 Feb;121(2):252-259.
26. Xylinas E, Rink M, Margulis V, Clozel T, Lee RK, Comploj E, Novara G, Raman JD, Lotan Y, Weizer A, Roupret M, Pycha A, Scherr DS, Seitz C, Ficarra V, Trinh QD, Karakiewicz PI, Montorsi F, Zerbib M, Shariat SF; UTUC Collaboration. Impact of renal function on eligibility for chemotherapy and survival in patients who have undergone radical nephro-ureterectomy. BJU Int. 2013 Aug;112(4):453-61.
27. Donat SM, Shabsigh A, Savage C, Cronin AM, Bochner BH, Dalbagni G, Herr HW, Milowsky MI. Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy: a high-volume tertiary cancer center experience. Eur Urol. 2009 Jan;55(1):177-85.
28. Sternberg CN, Skoneczna I, Kerst JM, Albers P, Fossa SD, Agerbaek M, Dumez H, de Santis M, Théodore C, Leahy MG, Chester JD, Verbaeys A, Daugaard G, Wood L, Witjes JA, de Wit R, Geoffrois L, Sengelov L, Thalmann G, Charpentier D, Rolland F, Mignot L, Sundar S, Symonds P, Graham J, Joly F, Marreaud S, Collette L, Sylvester R; European Organisation for Research and Treatment of Cancer Genito-Urinary Cancers Group; Groupe d'Etude des Tumeurs Urogénitales; National Cancer Research Institute Bladder Cancer Study Group; National Cancer Institute of Canada Clinical Trials Group; German Association of Urologic Oncology. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. Lancet Oncol. 2015 Jan;16(1):76-86.
29. Cognetti F, Ruggeri EM, Felici A, Gallucci M, Muto G, Pollera CF, Massidda B, Rubagotti A, Giannarelli D, Boccardo F; Study Group(†). Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. Ann Oncol. 2012 Mar;23(3):695-700.

DOI:10.31579/2767-7370/160