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Bladder Cancer Master Class

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The Bladder Cancer Master Class was created in collaboration with leading experts in the diagnosis and treatment of urothelial carcinoma. Below you will find the event sponsors, guest speakers, and other experts participating in the professional program.

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Prof. Álvaro Pinto, MD, PhD,
Hospital Universitario La Paz, Madrid, Spain

Prof. MUDr. Alexandr Poprach, Ph.D.,
Masarykův onkologický ústav, Brno, Czech Republic

Guest speakers and other experts

Prof. Dr. med. Jonas Busch
Vivantes Klinikum am Urban, Berlin, Germany

Prof. MUDr. Tomáš Büchler, Ph.D.
Onkologická klinika 1. LF UK a Fakultní Thomayerovy nemocnice, Prague, Czech Republic

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Institut molekulární a translační medicíny LF UP, Olomouc, Czech Republic

Doc. MUDr. Igor Hartmann, Ph.D.
Urologická klinika LF UP a FN Olomouc, Olomouc, Czech Republic

Doc. MUDr. Tomáš Kazda, Ph.D.
Masarykův onkologický ústav, Brno, Czech Republic

Doc. MUDr. Jindřich Kopecký, Ph.D.
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Urologická klinika LF UP a FN Olomouc, Olomouc, Czech Republic

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Wiener Gesundheitsverbund Klinik Ottakring, Vienna, Austria

Prof. Yann Neuzillet, MD, PhD
Université de Versailles Saint-Quentin-en-Yvelines, France

Prof. Javier Puente, MD, PhD
Hospital Clínico San Carlos, Madrid, Spain

Dr. Marzia Del Re
Saint Camillus International University of Health and Medical Sciences, Rome, Italy

Doc. MUDr. Michal Staník, Ph.D.
Masarykův onkologický ústav, Brno, Czech Republic

Prof. MUDr. Marek Svoboda, Ph.D.
Masarykův onkologický ústav, Brno, Czech Republic

Doc. MUDr. Hana Študentová, Ph.D.
Onkologická klinika LF UP a FN Olomouc, Olomouc, Czech Republic

Doc. MUDr. Vladimír Študent, Ph.D., FEBU
Urologická klinika LF UP a FN Olomouc, Olomouc, Czech Republic

OÄ Priv.-Doz. Dr. Hossein Taghizadeh, PhD, MSc
Wiener Privatklinik, Vienna, Austria

Doc. MUDr. Aleš Vidlář, Ph.D., FEBU
Urologická klinika LF UP a FN Olomouc, Olomouc, Czech Republic

Prof. Piotr Wysocki
Gdański Uniwersytet Medyczny, Gdańsk, Poland

Prof. MUDr. Roman Zachoval, Ph.D., MBA
Urologická klinika 3. LF UK a Fakultní Thomayerovy nemocnice, Prague, Czech Republic

Prof. Dr. med. Friedemann Zengerling
Universitätsklinikums Ulm, Germany

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MEDICAL TRIBUNE CZ, s.r.o.,
IČ: 26158299, DIČ: CZ26158299,
Radlická 37/901, 150 00 Praha 5,
Czech Republic
e-mail: remedia@remedia.cz
tel.: +420 224 916 916

Editorial processing of contributions
Mgr. Lucie Ondřichová, Bc. Eva Srbová,
Jitka Štěrbová

Editor-in-chief of the professional editorial office
PhDr. Nikola Homolová Richtrová, Ph.D.,
tel. +420 602 147 525
e-mail: richtrova@tribune.cz

Professional and language editorial office
PharmDr. Kateřina Viktorová
e-mail: viktorova@tribune.cz,
Mgr. Dagmar Fousková
e-mail: fouskova@remedia.cz

Graphic design and cover
David Weil, Petr Tkadlec, Barbara Fléglová,
Ivan Hořejší

Advertising and marketing
Martin Tomsa
tel.: +420 724 590 258
e-mail: tomsa@tribune.cz

Senior consultant:
MUDr. Marta Šimůnková

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Introduction

The Bladder Cancer Master Class was a three-day international expert colloquium focused on current and future trends in the diagnosis and treatment of bladder cancer, which took place on September 24–26, 2025, in Brno. The event responded to the dynamic developments in this field, where, after a long period of minimal changes in therapeutic algorithms and patient prognosis, fundamental shifts have been taking place across all stages of the disease in recent years.

The meeting was attended by an international community of leading experts who are involved in shaping current clinical practice in the field of uro-oncology. The program featured three dozen speakers from 18 countries, including authors of European guidelines and principal investigators of key clinical trials.

The Bladder Cancer Master Class was organized by the Masaryk Memorial Cancer Institute in Brno in collaboration with Merck. It was the first event of its kind held in the Czech Republic. It was endorsed by the Czech Oncology Society of the Czech Medical Association of J. E. Purkyně, the Uro-Oncology Section of the Czech Oncology Society of the Czech Medical Association of J. E. Purkyně, and the Czech Urological Society of the Czech Medical Association of J. E. Purkyně. The co-endorsers of the event were Prof. Alexandr Poprach, MD, PhD (Masaryk Memorial Cancer Institute, Brno) and Prof. Álvaro Pinto, MD, PhD (Hospital Universitario La Paz, Madrid).

The professional program focused on the comprehensive management of bladder cancer treatment in the context of increasing therapeutic variability and the need for interdisciplinary cooperation. The presentations covered, among other things, the advent of immunotherapy, new biomarkers, the use of liquid biopsy, the importance of maintenance therapy, bladder preservation strategies, and innovative endoscopic approaches in the treatment of early stages of the disease. Integral parts of the program were clinical case studies and discussions on the transfer of clinical trial results into real clinical practice.

The event focused on promoting an individualized approach to treatment that reflects the biological and clinical heterogeneity of individual patients, while also providing an opportunity to host an exceptional international professional meeting in the Czech Republic.

The Master Class also included a presentation on the care of patients with urological malignancies in the Czech environment and current research in this area. The program included professional excursions to the Masaryk Memorial Cancer Institute, the Olomouc University Hospital, and the Institute of Molecular and Translational Medicine of the Faculty of Medicine at the Palacký University in Olomouc.

Prof. Alexandr Poprach, MD, PhD

What was the main intention behind the Bladder Cancer Master Class? What was your goal when creating the program?

Jaký byl hlavní záměr programu Bladder Cancer Master Class? Jaký cíl jste měli při jeho tvorbě?

(prof. MUDr. Alexandr Poprach, Ph.D., a prof. Álvaro Pinto, MD, PhD).

https://www.remedia.cz/z-novinek/bladder-cancer-master-class-vse-co-se-deje-kolem-karcinomu-mocoveho-mechyre/#poprach

Masaryk Memorial Cancer Institute, Brno

Patients benefit from the centralization of care. It is appropriate to continue this in a meaningful way

On behalf of the Czech Urological Society of the Czech Medical Association of J. E. Purkyně, the chairman of this society, **Prof. Roman Zachoval, MD, PhD**, from the Urology Clinic of the Third Faculty of Medicine of Charles University and Thomayer University Hospital in Prague, took the floor and summarized the basic epidemiological data in his presentation and also addressed some important organizational aspects of care for these patients.

The good news about the level of Czech uro-oncology is that although the incidence of urological malignancies is rising, the mortality associated with them is stagnating, or even slightly declining.1,2 Specifically, bladder cancer is diagnosed in 2,100 people annually, predominantly in men (1,600 cases). In connection with this neoplasm, 900 people die each year. However, unlike other solid tumors (e.g., breast, kidney, or colorectal cancer), the five-year survival rate for bladder cancer has not improved significantly compared to the situation at the turn of the millennium. However, these data do not yet reflect the current shifts in the treatment algorithm. "Of course, our primary goal is the earliest possible diagnosis, which is true in oncology in general," said Prof. Zachoval.

The organization of care for this group of tumors largely mirrors the network of comprehensive cancer centers and regional cancer centers.1–4 Five years ago, in cooperation with the healthcare payers, the Ministry of Health, and the Czech Urological Society, centers for highly specialized uro-oncological care were established, of which there are currently sixteen.5 "Their regional distribution within the country is even," pointed out Prof. Zachoval. Around 60% of patients are treated at these centers, and this proportion has remained stable in recent years.1,6,7 He added: "When it comes to surgical treatment, it cannot be said that we are overly ambitious in this concentration. We are striving for consistent centralization only for a few extensive procedures.

This is also due to the fact that we do not want to damage the network of regional urology departments. Unfortunately, even with these selected extensive procedures, which include radical cystectomy, centralization is not working as we would like. There are still workplaces where these operations are performed on a smaller number of patients."

Even in the Czech Republic, if someone does something often, the chances of doing it well increase. For example, radical cystectomies performed in a highly specialized center have been shown to have better results than those performed in other facilities (Table 1).1,6 This can also be seen in the short term, when complications associated with the surgical procedure and access to them are taken into account to a greater extent. Three-month mortality is 7.7% in centers that perform at least 20 cystectomies per year, while in facilities with fewer than five procedures, it is almost double (12.66%) (Table 2).8,9 Prof. Zachoval further stated that they are the patients with advanced bladder cancer, who benefits most from centralization. This relationship does not apply to early-stage tumors, where treatment is based on endoscopic procedures.

TABLE 1 Comparison of one-year and three-year survival after radical cystectomy in a specialized center and in other centers

Radical procedure in a specialized center	One-year survival	Three-year survival
No (n = 4,192)	90.51% (89.70; 91.34)	78.93% (77.66; 80.22)
Yes (n = 123)	97.56% (94.87; 100.00)	82.82% (74.93; 91.55)
Radical procedure in a specialized center	**One-year survival**	**Three-year survival**
No (n = 1,214)	60.54% (57.86; 63.36)	40.85% (37.96; 43.97)
Yes (n = 311)	90.03% (86.76; 93.42)	73.48% (68.32; 79.03)

Source: adapted from citations 1 and 6

"The data from real clinical practice clearly show that centralization makes sense for our patients, and we are working with our partners to deepen this trend," said Prof. Zachoval.

According to him, it is positive that it has been possible to establish advanced specialized training in uro-oncology, which lasts two years and is completed with an exam. "Each of the highly specialized centers already has doctors trained in this way," said Prof. Zachoval.

TABLE 2 Comparison of survival after radical cystectomy at 30, 60 and 90 days after radical cystectomy in different centers and by type of cancer

	30 days after cystectomy		60 days after cystectomy		90 days after cystectomy	
	Died	Alive	Died	Alive	Died	Alive
Centers with ≤ 5 cystectomies per year	5.6%	94.4%	9.0%	91.0%	12.6%	87.4%
Centers with 6–20 cystectomies per year	2.8%	97.2%	6.3%	93.7%	9.5%	90.5%
Centers with more than 20 cystectomies per year	2.6%	97.4%	5.5%	94.5%	7.7%	92.3%
Stages I–II	2.7%	97.3%	5.7%	94.3%	7.6%	92.4%
Stages III–IV	3.6%	96.4%	7.4%	92.6%	11.2%	88.8%
T0–T2	2.7%	97.3%	6.2%	93.8%	8.1%	91.9%
T3–T4	3.5%	96.5%	6.8%	93.2%	11.0%	89.0%
N0 (nodal-free)	2.9%	97.1%	5.9%	94.1%	8.3%	91.7%
N1–N3 (nodal involvement)	4.2%	95.8%	8.7%	91.3%	12.2%	87.8%
M0 (no distant metastases)	2.9%	97.1%	5.9%	94.1%	8.4%	91.6%
M1 (distant metastases)	6.5%	93.5%	15.6%	84.4%	19.5%	80.5%

Source: adapted from citations 8 and 9

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Bladder cancer in 2025: How far has treatment progressed?

Bladder cancer is a disease for which the basic treatment algorithm has remained relatively stable for years. This included limited options for systemic therapy. This is now changing very rapidly. This malignancy is developing rapidly, affecting almost all patients regardless of tumor stage, which, among other things, places high demands on multidisciplinary collaboration. All this was summarized in the opening lecture of the Bladder Cancer Master Class colloquium by leading European uro-oncologist **Prof. Álvaro Pinto, MD, PhD,** from Hospital Universitario La Paz in Madrid, Spain.

In bladder cancer, too, time is the main factor determining the prognosis. The earlier the disease is detected, the more favorable the prognosis. Non-muscle-invasive bladder cancer (NMIBC), where the tumor is located only in the inner lining, is the most treatable. Since the 1980s, the BCG (Bacillus Calmette–Guérin) vaccine has been used to treat this type of cancer. The basis of non-pharmacological treatment is transurethral resection of the tumor tissue. In advanced stages, muscle-invasive bladder cancer (MIBC) and metastatic cancer, platinum-based chemotherapy is used, and radical cystectomy is performed for MIBC.

Immunotherapy and intravesical chemotherapy

However, new treatment options have emerged in recent years for all stages, whether local or systemic. This primarily involves the advent of immunotherapy, mainly immunotherapy based on the inhibition of immune response checkpoints, specifically programmed death-1 (PD-1) receptor and programmed death ligand-1 (PD-L1). "Today, we are in a completely different place than we were just a few years ago," said Prof. Pinto.

In this context, Prof. Pinto referred to the single-arm phase II KEYNOTE-057 study published in 2021.1 This study showed that pembrolizumab in monotherapy has promising antitumor activity. A total of 41% of patients achieved a complete response and 58% achieved an partial response. "These were the first results of their kind, although anti-PD-1 monotherapy is probably not the most effective option for NMIBC today," said Prof. Pinto.

Data supporting the combination of immunotherapy with BCG in patients with high-risk NMIBC were confirmed by the global randomized phase III CREST study published this year.2 The administration of the BCG vaccine and the PD-1 inhibitor sasanlimab in both the induction and maintenance phases statistically significantly and clinically meaningfully prolonged event-free survival (EFS) compared to the BCG vaccine alone. "This was the first study to prolong this parameter," commented Prof. Pinto.

Intravesical chemotherapy also has great potential in the early stages of the disease. In this context, Prof. Pinto spoke about the INLEXZO intravesical chemotherapy delivery system, which is designed for the administration of gemcitabine and has now been approved by the U.S. Food and Drug Administration.3 With its use, 82% of patients achieve a complete response without the need for reinduction. "For some patients with NMIBC who do not respond to BCG, this is a potentially practice-changing approach. We are seeing a high proportion of treatment responses that have persisted for a relatively long time," said Prof. Pinto, adding that other such systems working with the instillation of other substances are on their way into clinical practice.

According to Prof. Pinto, the new data also raise new questions: "For example, we must ask whether the recent evidence is sufficient to treat every patient with NMIBC with a combination of BCG and immunotherapy. We also do not yet know whether the new intravesical approaches should be the standard for BCG-refractory patients."

Immunotherapy in advanced stages

Immunotherapy has also advanced in patients who have already experienced muscle tissue invasion. In patients with high-risk MIBC, who have undergone radical surgery, adjuvant immunotherapy with a PD-1 inhibitor has proven effective. In a multicenter, randomized, double-blind, placebo-controlled phase III study, nivolumab administration in patients with PD-L1 expression ≥ 1% significantly prolonged disease-free survival compared to placebo (median 20.8 versus 10.8 months).4 After six months, 74.9% versus 60.3% of patients were alive (p<0.001).

In patients with MIBC, the standard of care is neoadjuvant chemotherapy followed by radical cystectomy. In the randomized, open-label phase III NIAGARA study, the addition of durvalumab perioperatively to chemotherapy, i.e., before surgery, followed by adjuvant monotherapy, proved effective.5 This approach led to an increase in EFS and estimated overall survival (after 24 months, 82.2% versus 75.2% of patients survived; p=0.01).

Antibody-drug conjugates (ADCs), i.e., preparations that combine a monoclonal antibody with a highly effective cytostatic drug, are also entering the treatment of urothelial carcinoma. In the EV-303/KEYNOTE-905 study, the combination of pembrolizumab with enfortumab vedotin, the ADC, administered before and after surgery in patients with MIBC significantly improved EFS and overall survival and achieved a pathological complete response (editor's note: the main conclusions of this study were presented at ESMO 2025 and clearly confirmed the initial positive results).6

It also appears that a personalized approach using ctDNA to detect molecular residual disease in patients with MIBC strongly predicted the benefit of adjuvant immunotherapy in terms of disease-free survival and overall survival. This is supported by preliminary data from the phase III IMvigor011 study with atezolizumab.7

A similar shift is also occurring in metastatic disease. Patients with advanced or metastatic urothelial carcinoma,

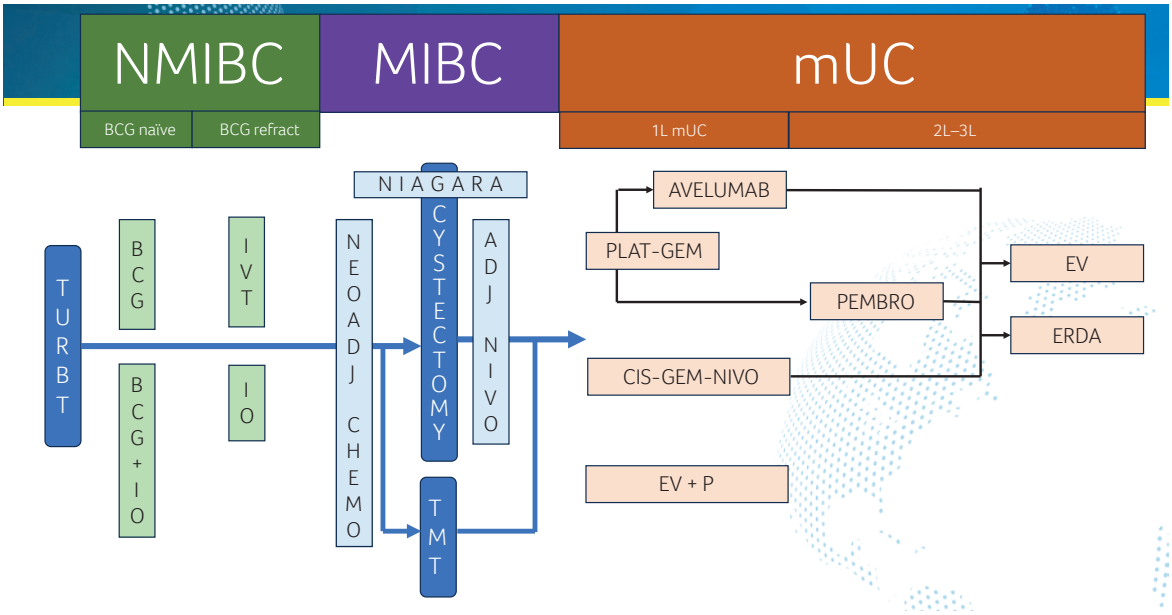

FIGURE 1 Algorithm of current therapeutic options for urothelial carcinomas

ADJ – adjuvant (therapy); **BCG** – Bacillus Calmette–Guérin; **BCG naïve** – previously untreated BCG; **BCG refractory** – BCG-refractory disease; **CIS-GEM-NIVO** – cisplatin + gemcitabine + nivolumab; **EV** – enfortumab vedotin; **EV + P** – enfortumab vedotin + pembrolizumab; **ERDA** – erdafitinib; **CHEMO** – chemotherapy; **IO** – immunotherapy; **IVT** – intravesical therapy; **mUC** – metastatic urothelial carcinoma; **MIBC** – muscle-invasive bladder cancer; **NEOADJ** – neoadjuvant (therapy); **NIVO** – nivolumab; **NMIBC** – non-muscle-invasive bladder cancer; **PEMBRO** – pembrolizumab; **PLAT-GEM** – platinum-based chemotherapy + gemcitabine; **TMT** – trimodal therapy; **TURBT** – transurethral resection of bladder tumor

Source: Prof. Pinto archive

who progressed after platinum-based chemotherapy, benefited more from pembrolizumab than from chemotherapy in second-line treatment.8 Pembrolizumab significantly improved median overall survival (10.3 versus 7.4 months, hazard ratio for death 0.73; p=0.002). In addition, there was less treatment-related toxicity in the immunotherapy group.

Data confirming the importance of immunotherapy for maintenance treatment are also available. Here, Prof. Pinto highlighted the importance of the JAVELIN Bladder 100 study, published in the New England Journal of Medicine in 2020.9 This was an international, open-label, phase III study that included 700 patients with histologically verified locally advanced unresectable/metastatic urothelial carcinoma, who had achieved disease stabilization, partial remission, or complete remission after first-line systemic therapy. Patients were then randomized (1:1) into two study arms: the avelumab arm and the best supportive care arm without avelumab. Overall survival was significantly higher in patients receiving maintenance treatment with avelumab compared to the control group. One-year survival was achieved in 71.3% of patients treated with immunotherapy and in 58.4% of the control group. The median overall survival was 21.4 versus 14.3 months (editor's note: according to the update, it was 23.8 versus 15.0 months).

ADC is also being added to the treatment arsenal, as shown by current data on enfortumab vedotin in patients with metastatic urothelial carcinoma.10

There is also room for targeted therapy in this patient population. For example, patients with alterations in fibroblast growth factor receptors (FGFR) may benefit from it. Compared to chemotherapy, the FGFR inhibitor erdafitinib prolonged overall survival in patients who had progressed on previous lines of treatment, including immunotherapy.11

At the end of his presentation, Prof. Pinto summarized the current therapeutic options for all stages in a single algorithm, noting that a number of unresolved issues remains (**Figure 1**).

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Modern diagnostic approaches in urothelial tumors: the role of molecular profiling, ctDNA, and pharmacogenetics in the era of personalized oncology

What does "modern diagnostics" mean in urothelial tumor oncology today, and why is a histopathological conclusion no longer sufficient? What added value do transcriptomic subtypes bring and what do they tell us about tumor biology and likely responses to immunotherapy? When can ctDNA be a practical tool for monitoring treatment and detecting minimal residual disease—and what are its limitations, including false negatives and preanalytical pitfalls? And why should pharmacogenetics and drug interactions be part of clinical reasoning as naturally as performance status or renal function? Are there differences in the treatment of patients with bladder and upper urinary tract tumors? These and many other questions were addressed in Section I of the Bladder Cancer Master Class colloquium, which emphasized that precision medicine is the result of comprehensive clinical reasoning that links various biological and clinical information over time and across treatment lines.

Modern diagnosis of bladder cancer: current approaches and innovations

In recent years, the diagnosis of bladder cancer has shifted from traditional histopathology to multiomic strategies that allow for a more accurate understanding of tumor biology and its response to treatment.1 As emphasized by **Dr. Marzia Del Re** of the Saint Camillus International University of Health and Medical Sciences in Rome, modern diagnostics is no longer just a "description of a cell under a microscope," but a comprehensive interpretation of genomic, transcriptomic, and dynamic circulating markers that together determine the prognosis and choice of optimal therapy. Her statement that "diagnostics means understanding how a tumor lives, how it changes, and how it responds to treatment pressure" aptly summarizes the current trend toward personalized oncology.

Molecular classification of MIBC: the significance of transcriptomic subtypes

The consensus molecular classification of muscle-invasive bladder cancer (MIBC), published by Kamoun and Chueh, is one of the pillars of this transformation.1,2 RNA-seq analyses of large cohorts (including cohorts from IMvigor studies) have shown that tumors can be simplified into four biologically distinct clusters—luminal, stromal, immune, and basal—with different signaling pathway activation and immune infiltration.3 Dr. Del Re described their characteristics in detail in her lecture: the luminal cluster is mainly associated with the activation of lipid metabolism, the stromal cluster is enriched with extracellular matrix components and transforming growth factor beta (transforming growth factor beta, TGF-β), while the immune and basal clusters are defined by significant infiltration of myeloid or granulocytic cells. These differences have a direct clinical impact. As she stated, "NMF1 and NMF2 are tumors without immune infiltration, while NMF3 and NMF4 are truly inflammatory tumors—they respond best to checkpoint inhibitors." This simplified biological stratification is therefore a useful tool for predicting response to immunotherapy and for the rational selection of treatment strategies (**Figure 1**).[1,3]

Genomic heterogeneity and clonal evolution during therapy

The genomic heterogeneity of urothelial carcinoma further increases the complexity of diagnostic decision-making. Chu et al. show that the spectrum of mutations varies significantly according to histological variants: neuroendocrine tumors more often carry TP53 mutations (and other

Dr. Marzia Del Re

SCHEME 1 Molecular subtypes of urothelial carcinoma – summary

B – B cells; **CDK4/6** – cyclin-dependent kinases 4 and 6; ***CDKN2A/B*** – *CDKN2A* and *CDKN2B* genes (cell cycle inhibitors); **DNA** – deoxyribonucleic acid; **ECM** – extracellular matrix; **FAB** – fatty acid biosynthesis; **FGFR3** – fibroblast growth factor receptor 3; **F-TBRS** – fibroblast TGF-beta response signature; **HER2** – human epidermal growth factor receptor 2; **ICs** – immune cells; **NMF** – non-negative matrix factorization; **NK** – natural killer cells; **PD-L1** – programmed death ligand 1; **RNA** – ribonucleic acid; **T/NK/B** – T cells / NK cells / B cells; **Teff** – effector T cells; **TGF-β** – transforming growth factor beta; ***TP53*** – tumor suppressor gene p53; **TROP2** – trophoblast cell surface antigen 2; UGTS – UDP-glucuronosyltransferase signature

Source: adapted from citation 3

alterations), while papillary tumors are characterized by changes in the fibroblast growth factor receptor (fibroblast growth factor receptor 3, FGFR3), and aggressive variants often show activation of the phosphatidylinositol-3-kinase (phosphoinositide 3-kinase, PI3K) pathway or amplification of the human epidermal growth factor receptor 2 (HER2).2 In this context, Dr. Del Re emphasized that "mutations are not static—the tumor accumulates new mutations under the pressure of therapy and often changes its histology as a mechanism of resistance." This development corresponds to the "trunk-and-branches" model, in which the primary driving alteration forms the "trunk" of the tumor, while changes that arise later during treatment determine the failure of specific therapies.2 Typical examples include mutations in the FGFR ligand-binding domain after targeted therapy, or changes in Nectin-4 expression or activation of transport mechanisms (e.g., MDR-1 pumps) leading to resistance to antibody-drug conjugate (ADC) therapies, such as enfortumab vedotin. An important practical aspect, as summarized by Dr. Del Re, is that "resistance to ADCs does not necessarily mean a new mutation—a different expression of the target protein or activation of transporters is sufficient."

Antibody-drug conjugates have meanwhile become an important part of the treatment of advanced bladder cancer. The presented work shows interindividual variability in the expression of TROP2 and Nectin-4.4,5 Dr. Del Re pointed out: "We are still discussing what is truly predictive—mRNA expression, or protein. In ADC treatment, resistance can arise even without a mutation—a change in the expression of the target protein is sufficient." These findings emphasize the need to combine molecular and proteomic approaches when interpreting ADC efficacy and failure.[4,5]

Liquid biopsy and ctDNA: clinical possibilities and practical pitfalls

Liquid biopsy, particularly the analysis of circulating tumor DNA (ctDNA), is an important pillar of modern diagnostics. The literature repeatedly emphasizes its role in monitoring treatment response, detecting minimal residual disease, identifying resistance mechanisms, and predicting early relapses.6–9 However, Dr. Del Re's practical interpretation added key context: one of the biggest limitations is false negatives. As she stated: "If you find a mutation in ctDNA, you can be sure that the tumor carries it. If you don't find it, you can't say anything at all." Low ctDNA concentrations are typical, for example, in bone metastases and intracranial involvement, where physiological barriers prevent its release into the circulation. Tumor-informed ctDNA tests have become a key part of monitoring of minimal residual disease in the early stages. The NIAGARA study showed that ctDNA clearance after neoadjuvant therapy and cystectomy significantly correlates with disease-free survival (DFS) and event-free survival.10

At the same time, however, it is important to emphasize that ctDNA negativity is not an absolute guarantee: "The curve of ctDNA-negative patients is not horizontal—we are still missing something, whether it's the panel, biology, or clonal dynamics," noted Dr. Del Re. This perspective supports the use of ctDNA as a sensitive tool for early identification of relapse risk, but also highlights the limitations of current panels.

Pharmacogenetics and drug interactions: a neglected, but critical factor in treatment

Pharmacogenetics is a less "visible" but clinically significant pillar of modern management. Zanger and Schwab report that up to 80% of oncology drugs, including supportive medications, are metabolized via the CYP450 system.[11] Interactions between drugs, dietary factors, and genetic polymorphisms may explain unexpected toxicity or treatment failure—for example, in the case of a cytidine deaminase mutation affecting gemcitabine metabolism or dietary CYP3A4 inhibitors (e.g., grapefruit).8 Dr. Del Re summed it up practically: "Sometimes we look for a resistance mechanism in the tumor, but the reason for failure is simply drug interaction." Pharmacogenetic testing should therefore be considered, especially in patients with comorbidities and polypharmacy.[11]

The closing message of the lecture underscored the importance of integrating diagnostic approaches. Precision medicine in bladder cancer does not arise from a single biomarker, but from the combination of histology, transcriptome, mutation profile, ctDNA dynamics, and pharmacogenetic information.1–11 Dr. Del Re summed up this need for integration succinctly: "We cannot think in isolation. We must integrate diagnostics, genomics, liquid biopsy, and pharmacogenetics. This is where artificial intelligence can help us. Not as a substitute, but as a tool that can handle large amounts of data."

The discussion raised the question of the routine availability of multiomic testing (next-generation sequencing, ctDNA, subtyping) in Italian practice. Dr. Del Re stated that "it is not standard for all patients" and that a significant portion of these approaches remains in the research sphere for now, although gradual implementation is underway—especially for first-line liquid biopsy.

Modern bladder cancer diagnostics is thus becoming a complex, data-rich discipline that allows for individualized treatment, prevention of resistance, and early detection of changes in tumor biology. Multiomic integration represents one of the most promising avenues for improving clinical outcomes in the coming years.

Comprehensive management of recurrent urothelial carcinoma: a case study of a young patient with ten years of follow-up

The presentation by **Fruzsina Fazekas, MD, PhD**, from the Péterfy Sándor Kórház-Rendelőintézet Urológiai Osztály in Budapest offered an exceptionally impressive view of the long-term course of aggressive urothelial carcinoma in a young patient. The patient was a 46-year-old man, originally completely healthy, whose disease over a period of ten years illustrated most of the major clinical challenges associated with the treatment of high-risk urothelial carcinoma. The speaker introduced the case with the words: "I have brought you a case that has been with me for many years. It is a story not only of medical decisions, but also of the great motivation of a patient who wanted to see his son's graduation."

First symptoms, early diagnosis, and high risk

The disease manifested itself in 2015 when the patient came to the emergency room with macroscopic hematuria. Until then, he had been completely healthy, with no comorbidities, no chronic medication, no smoking, and only a family history of kidney cancer on his maternal grandmother's side. Cystoscopy, cytology, and computed tomography (CT) confirmed a localized bladder tumor. During four transurethral resections, pT1 high-grade urothelial carcinoma, i.e., a high-risk non-invasive lesion, was repeatedly confirmed. After the fourth resection, the findings were negative for the first time, but according to the EORTC (European Organisation for Research and Treatment of Cancer) scoring, the risk of recurrence was 38% in one year and 62% in five years. The doctors therefore recommended early radical cystectomy, but the patient decided to preserve his bladder and opted for treatment with intravesical BCG instillations.

Rapid progression and complicated preparation for radical treatment

Despite BCG therapy, early recurrence occurred, this time in the form of muscle-invasive carcinoma localized in the urethra. Positive cytology, pT2 findings in urethral biopsy, and CT evidence of enlarged para-iliac lymph nodes and hydronephrosis indicated rapid disease progression. Preparation for radical cystectomy was further complicated by hospitalization for severe pyelonephritis. As Dr. Fazekas noted: "At that time, it seemed that surgery would not be possible because the patient's clinical condition was not favorable at all."

Radical treatment in two phases

After stabilizing the patient's overall condition, it was finally decided to perform a radical cystectomy, which, however, had to be carried out in two stages. In January 2017, a cystectomy with ileal conduit was performed, and the histological findings confirmed pT2, high-grade disease with positive para-iliac lymph nodes. This was followed by urethrectomy

Fruzsina Fazekas, MD, PhD

and, at the beginning of 2018, ureteral reimplantation with para-aortic lymphadenectomy, where metastasis of urothelial carcinoma was again confirmed. In March 2018, treatment with pembrolizumab was initiated. The patient was among the first in Hungary to receive this immunotherapy for his indication. Treatment lasted almost four years and was discontinued due to the development of immunologically-induced arthritis. Despite this complication, the patient remains in complete remission with no signs of disease to date.[12]

The subsequent discussion confirmed that, in this particular case, neoadjuvant cisplatin chemotherapy was not appropriate due to reduced renal clearance, which is in line with the recommendations of the European Association of Urology (EAU) for patients with urethral involvement, where the evidence for neoadjuvant chemotherapy is weaker than for primary MIBC.[12,13]

Discussion of therapeutic decisions

The case raised a number of professional questions regarding the optimal treatment sequence. In retrospect, it was suggested that urethral localization, early recurrence after BCG, and the patient's young age could support an earlier indication for radical cystectomy. The choice of adjuvant systemic therapy was also discussed, particularly the dilemma between carboplatin regimen and immunotherapy in patients with renal insufficiency. As one of the discussants noted: "In real-world practice, carboplatin is sometimes a more reasonable choice than immunotherapy if we do not have a clear benefit in PD-L1-negative patients."[14,15] However, another discussant argued that immunotherapy has a decent position in these patients, better than carboplatin.

This long-term follow-up case shows that the treatment of aggressive urothelial carcinoma is not linear. It requires flexibility, interdisciplinary collaboration, and the ability to individualize therapeutic decisions over time, but also to respect the life goals of the individual patient. The case study underscores the importance of immunotherapy in metastatic disease and demonstrates that even in high-risk patients, a combination of comprehensive care and personal motivation can lead to long-term survival without signs of disease. Dr. Fazekas concluded her presentation with the words: "It helps us to help. And most importantly, he really saw his son's graduation. And he's riding his motorcycle again." But the story doesn't end there—the patient has become actively involved in educational projects, where he shares his experience and helps other patients overcome their fears about treatment.12,[14–19]

Prof. Javier Puente, MD, PhD

Perioperative treatment of UTUC: neoadjuvant versus adjuvant chemotherapy in clinical practice

Prof. Javier Puente, MD, PhD, from Hospital Clínico San Carlos in Madrid presented a comprehensive overview of the current role of perioperative systemic treatment in patients with localized high-risk upper urinary tract cancer. In his introduction, he emphasized that the aim of his presentation was not only to present individual hazard ratios (HR) or response rates from clinical studies, but above all to show how the available data can be meaningfully implemented in everyday clinical practice. According to him, urothelial carcinoma of the upper urinary tract represents a specific oncological entity in which long-term treatment outcomes remain unsatisfactory despite radical nephroureterectomy with excision of the ureteral orifice. In invasive stages, five-year survival ranges are 43–75% for T2, 16–33% for T3, and only 0–5% for T4 or N+ disease, clearly underscoring the need for more effective perioperative strategies.[12,20]

Challenges of accurate staging and risk stratification

A major obstacle to the effective use of perioperative treatment remains the correct identification of patients who can truly benefit from it. Prof. Puente pointed out that in high-risk upper tract urothelial carcinoma (UTUC), accurate determination of the clinical stage prior to surgery is extremely difficult and that risk stratification is subject to significant limitations. Up to a quarter of ureteroscopic biopsies are inadequate and often do not allow reliable differentiation between non-invasive papillary tumors, carcinoma in situ, and invasive carcinoma.21,22 Clinical grading can partially aid decision-making, but its positive predictive value for muscle invasion is only approximately 60%.[21,23]

Traditionally reported risk factors include tumor size greater than 2 cm, hydronephrosis, high histological grade, positive cytology, and lymph node involvement. As summarized: "Patient selection is much more complex for upper urothelial tumors than for bladder tumors." A recently published American nomogram involving more than 6,000 patients identified age, histological grade, lymphovascular invasion, tumor size greater than 5 cm, and clinical lymphadenopathy as independent predictors of invasiveness.20,23 The accuracy of prediction reached 80% for muscle invasion and 88% for lymph node involvement, which represents a significant shift, but not a definitive solution to the problem.

Neoadjuvant chemotherapy: a rational concept with limited evidence

In the section on neoadjuvant chemotherapy, Prof. Puente explained the rational basis for this approach. Radical nephroureterectomy often leads to deterioration of renal function, and a significant proportion of patients become ineligible for platinum-based chemotherapy after surgery.[24] "Admin-

istering systemic therapy before surgery could therefore ensure that more patients receive the full dose of cisplatin and potentially achieve better outcomes," he said. Despite this logic, however, the level of evidence supporting neoadjuvant chemotherapy remains limited. Only a few small prospective studies and more than ten retrospective analyses are available. Meta-analyses report an average complete pathological response rate of around 11% and a partial response in approximately 43% of patients, with an improvement in overall survival suggested, but this is level 2 evidence.[14,16]

Prospective MSKCC data and differing transatlantic views

Prof. Puente identified the Memorial Sloan Kettering Cancer Center (MSKCC) study, which evaluated split-dose gemcitabine and cisplatin in patients with localized high-risk UTUC, as the most significant prospective study in this area.[14] According to the results presented, 63% of patients achieved a pathological response below ypT2 and 19% achieved complete pathological remission. Two-year progression-free survival was 89% and five-year progression-free survival was 72%, with overall five-year survival in respondents reaching nearly 80%. Although these data are very encouraging, their generalizability is limited by the small number of patients and the long recruitment period.

Prof. Puente also pointed out the difference in opinion between American and European experts. While some American authors consider these data strong enough to consider including neoadjuvant chemotherapy among standard procedures, European experts remain cautious and point out that staging inaccuracy can lead to both overtreatment and undertreatment. He was equally cautious in his assessment of neoadjuvant immunotherapy, for which the studies available to date have not provided convincing evidence of clinical benefit. According to Prof. Puente, there is therefore insufficient evidence in 2025 to routinely recommend neoadjuvant immunotherapy for UTUC.[25,26]

Adjuvant chemotherapy: the most robust evidence available

Adjuvant chemotherapy represents the strongest evidence base across the entire perioperative spectrum. Prof. Puente discussed in detail the groundbreaking POUT study, which demonstrated a significant prolongation of disease-free and metastasis-free survival with gemcitabine in combination with cisplatin or carboplatin compared to observation alone. The risk ratio for DFS was 0.45 in favor of adjuvant treatment, and toxicity was acceptable with no therapy-related deaths.[17,27] "The final analysis of overall survival showed a trend toward improvement (HR 0.76), although it did not reach statistical significance. Nevertheless, the study provided level 1 evidence and fundamentally influenced clinical recommendations," he emphasized.

Based on these data, both the EAU and NCCN clearly recommend platinum-based adjuvant chemotherapy for eligible patients with high-risk UTUC.26,28 Neoadjuvant chemotherapy, on the other hand, remains outside the EAU recommendations, while the NCCN—based on US data—allows it in selected patients.

Adjuvant immunotherapy: promising but still inconclusive

In the field of adjuvant immunotherapy, Prof. Puente summarized the results of three key studies. The IMvigor010 study with atezolizumab did not meet its primary endpoint and did not demonstrate an improvement in DFS.18 In contrast, the CheckMate 274 study with nivolumab showed a benefit in the entire urothelial carcinoma population, but a subanalysis focused on UTUC did not provide a convincing signal of efficacy.19 Similarly heterogeneous results were also observed with pembrolizumab.29 Although programmed death-1/programmed death ligand-1 (PD-1/PD-L1) inhibitors may be considered in patients who are not candidates for platinum-based chemotherapy, their role in the adjuvant treatment of UTUC remains unclear and the available data are currently limited.

Prof. Puente concluded by emphasizing that UTUC remains one of the most complex diagnoses in urogenital oncology and that even in 2025, there is no universal ideal algorithm for care. The best-supported approach remains adjuvant chemotherapy, whose benefit for DFS represents the strongest available evidence. Ongoing studies, such as the European URANUS study, offer hope for the future and should enable a more precise definition of the role of perioperative systemic treatment. According to Prof. Puente, each patient with UTUC should be assessed individually and ideally discussed within a multidisciplinary tumor board, as the right choice of treatment requires careful consideration of clinical factors and close cooperation between all specialists involved.[12,14–19,24–27,30]

Immunotherapy in the treatment of UTUC: from biological specifics to current clinical evidence

OÄ Priv.-Doz. Dr. Hossein Taghizadeh, PhD, MSc., from the Wiener Privatklinik presented a comprehensive and very practical view of the role of immunotherapy in UTUC in his lecture. Right at the beginning, he emphasized that UTUC cannot be perceived merely as an anatomical variant of urothelial carcinoma of the bladder. It is a biologically more aggressive disease that is often diagnosed at a more advanced stage and in patients with a deteriorated general condition. These characteristics have a fundamental impact on thera-

OÄ Priv.-Doz. Dr. Hossein Taghizadeh, PhD, MSc.

peutic decision-making. Upper urinary tract carcinoma accounts for approximately 5–10% of all urothelial carcinomas, but at the time of diagnosis, up to 60% of cases are invasive, which significantly affects the prognosis.[12,20]

Radical nephroureterectomy remains the standard of care, but data from large international cohorts, including the work of Margulis et al., show that even after adequate surgery, approximately one-third of patients experience relapse.20 At the same time, this is often a geriatric and polymorbid population, which further complicates the options for systemic treatment. As Dr. Taghizadeh pointed out, "it is not uncommon for patients to arrive with already reduced kidney function, which worsens further after surgery to the point that cisplatin cannot be administered." According to available data, approximately 40% of patients have chronic kidney disease stage ≥ 3 at the time of diagnosis, and up to 85% after surgery.[24]

Adjuvant chemotherapy as a basis, but with limited effect

A major milestone in the treatment of UTUC was the POUT study, which demonstrated that adjuvant chemotherapy significantly improves five-year disease-free survival (DFS 62% versus 45%; HR 0.55) and also shows a trend towards improved overall survival (66% versus 57%; HR 0.68).[17,27] Nevertheless, according to Dr. Taghizadeh, there is still room for further improvement: "Chemotherapy works, we know that. However, its effect is only partial and relapses are not uncommon. We need more effective systemic treatment that can target micrometastatic disease." This naturally turns attention to immunotherapy, which, thanks to its mechanism of action, can overcome some of the limitations of chemotherapy, especially in the context of renal insufficiency.

Immunogenomic characteristics of UTUC

A significant part of the presentation was devoted to an overview of the immunogenomic features of UTUC. Available studies show that UTUC generally has a higher mutation burden than bladder cancer and more often exhibits PD-L1 expression or a high microsatellite instability phenotype. Approximately 10% of cases are associated with a mismatch repair (MMR) deficiency, often in the context of Lynch syndrome.12,25 These characteristics suggest potential sensitivity to immunotherapy, but the clinical reality is more complex.

Upper urinary tract carcinoma exhibits significant molecular heterogeneity. Luminal-papillary tumors with FGFR3 mutations typically have an "immune-desert" microenvironment, characterized by low T-cell infiltration and a low likelihood of response to checkpoint inhibitors. In contrast, basal and inflammatory subtypes are associated with higher immune activity and potentially better response to immunotherapy.[1–3] Dr. Taghizadeh aptly summarized this ambivalence: "Upper urinary tract carcinoma is genetically rich but often immunologically silent. And it is precisely in this ambivalence that the key lies—understanding in whom immunotherapy can truly work."

Neoadjuvant immunotherapy: an interesting concept without convincing evidence

The lecture also discussed data from the field of neoadjuvant immunotherapy. The iNDUCT-V08 study, which evaluated the combination of durvalumab with chemotherapy, demonstrated downstaging in 42–50% of patients, but the rate of complete pathological remission remained low (5–13%) and the study was evaluated as negative.31 Similarly, the PURE-02 study with pembrolizumab did not produce the expected effect—no pathological response was observed and there was even one treatment-related death.[31]

In line with these results, the 2025 EAU guidelines state that there is insufficient evidence for the use of neoadjuvant immunotherapy in UTUC.26 Although the biological potential of this approach exists, clinical data have not yet provided clear support for its routine use.

Adjuvant immunotherapy: mixed and inconclusive results

Adjuvant immunotherapy has shown robust results in urothelial carcinoma as a whole, as demonstrated by the CheckMate 274 and AMBASSADOR studies.19,29 However, subanalyses focusing specifically on UTUC did not show a statistically significant benefit, probably due to the low number of patients enrolled. The EAU 2025 guidelines therefore take a cautious view of this area, stating that patients with UTUC did not clearly benefit from these studies.26 Dr. Taghizadeh commented: "We know that immunotherapy works in bladder cancer and metastatic urothelial carcinoma. But we don't yet have a clear answer in the adjuvant setting after surgery for UTUC."

An exception is the JAVELIN Bladder 100 study, which involves patients with metastatic disease. This study demonstrated prolonged overall survival with avelumab maintenance therapy after chemotherapy. This effect was consistent across subgroups, including patients with UTUC, who accounted for approximately 25% of the entire study population.[30]

Immunotherapy and ADC in the metastatic stage

A combination of immunotherapy and ADC has brought about a fundamental shift in the treatment of advanced urothelial carcinoma. Data for enfortumab vedotin, either as monotherapy or in combination with pembrolizumab (EV-103, EV-302), showed high efficacy regardless of the primary tumor site.32,34,35 The combination of enfortumab vedotin + pembrolizumab has become the new first-line standard of care for advanced disease. As Dr. Taghizadeh summarized: "In the metastatic stage, we no longer ask where the tumor originated—modern immunotherapy and ADCs work across urothelial carcinomas."

Immunotherapy is an important pillar of modern UTUC treatment, but its role varies depending on the clinical context. While evidence remains limited and inconclusive in the neoadjuvant and adjuvant settings, immunotherapy achieves significant clinical benefit in the metastatic stage, especially in combination with ADCs. 19,24–27,29–35 A key challenge for the future remains better biological stratification of patients, which will allow for more accurate identification of those who truly benefit from immunotherapy.

ADC in the treatment of UTUC: new clinical findings and their significance for practice

Prof. Tomáš Büchler, MD, PhD, from the Oncology Clinic of the 2nd Faculty of Medicine of Charles University and University Hospital Motol in Prague, presented a comprehensive overview of the role of ADC in the treatment of urothelial carcinoma, with a special focus on UTUC. He emphasized that although ADCs are among the fastest-growing therapeutic classes in contemporary oncology, their role in the treatment of UTUC has only been partially defined so far. Upper urinary tract carcinoma accounts for approximately 5–10% of all urothelial carcinomas, but it differs significantly from bladder tumors both biologically and clinically, which is also reflected in the response to systemic treatment.[36,37]

ADC in practice: efficacy, limitations, and data interpretation

Renal dysfunction is present in 30–40% of patients at the time of diagnosis, and after radical nephroureterectomy, a further significant decline in renal function may occur in up to 50–70% of patients. This fact significantly limits the possibilities of platinum chemotherapy and is one of the main reasons why ADCs are extremely attractive in the UTUC population.24,36 Their efficacy is not dependent on fully preserved renal function and, at the same time, they target molecular structures that are often expressed in UTUC.

The presentation noted that Nectin-4, the main target of enfortumab vedotin, is expressed in 65–80% of UTUC cases. Similarly, *HER2* positivity reaches 30–36% in UTUC, which is up to three times higher than in bladder tumors and points to significant biological differences between the two locations.4,5 These characteristics create an environment in which ADCs can potentially play a more significant role than in lower urinary tract urothelial carcinomas.

Prof. Büchler then summarized the current portfolio of ADCs used in the treatment of urothelial tumors: enfortumab vedotin (anti-Nectin-4), disitamab vedotin RC48 (anti-HER2), sacituzumab govitecan (anti-TROP2), and trastuzumab deruxtecan (anti-HER2).32–35 However, he pointed out that most registration studies have historically included both bladder and upper urinary tract tumors, and therefore purely UTUC-specific data have only become available in recent years, primarily from smaller prospective studies and real-world clinical practice.

Combination of enfortumab vedotin + pembrolizumab: a new standard with open questions

The combination of enfortumab vedotin and pembrolizumab (EV-302/KEYNOTE-A39) currently has the greatest clinical impact. This study demonstrated a significant prolongation of progression-free survival (12.5 versus 6.3 months; HR 0.45) and overall survival (31.5 versus 16.1 months; HR 0.47), with UTUC patients accounting for approximately 27% of the entire study population and the results achieved being consistent across individual subgroups.32,34,35

Prof. MUDr. Tomáš Büchler, Ph.D.

However, Prof. Büchler pointed out the need for cautious interpretation of these data. The control arm of the study underwent chemotherapy for only 18 weeks, while treatment with the combination of enfortumab vedotin + pembrolizumab continued until progression or toxicity. This led to significantly longer exposure to treatment, with a median of 12 cycles and up to 30 cycles in patients in complete remission. In addition, reliable data on subsequent maintenance treatment with avelumab were lacking in approximately one-third of patients, complicating the evaluation of optimal sequential strategies.34,35 As Prof. Büchler noted, "This lack of data is surprising, particularly in a population where information on sequencing would be most relevant."

ADC toxicity and the question of long-term treatment

Although enfortumab vedotin has a lower incidence of hematologic toxicities than conventional chemotherapy, it is associated with other types of adverse events that can be clinically significant.

As an example, Prof. Büchler cited toxic epidermal necrolysis, a rare complication occurring in approximately 0.8% of patients, with a mortality rate of around 50% and requiring intensive specialized care.33 At the same time, he emphasized that long-term administration of the combination of enfortumab vedotin + pembrolizumab may negatively affect patients' quality of life, especially with the accumulation of skin toxicity and peripheral neuropathy.

Clinical implications and future perspectives

Based on the available evidence, Prof. Büchler identified several clinical situations in which ADCs represent a rational and potentially highly effective treatment option. In the first line, the combination of enfortumab vedotin + pembrolizumab appears to be particularly suitable for patients who are unsuitable for cisplatin, which is a very common scenario in UTUC due to renal dysfunction. In the second line, enfortumab vedotin has a firm place based on the EV-301 study, but the optimal treatment sequence for patients who have already received enfortumab vedotin + pembrolizumab in the first line remains an open question.33

Patients with HER2-positive tumors may also theoretically benefit from disitamab vedotin or trastuzumab deruxtecan, with UTUC showing the highest rate of HER2 expression among urothelial carcinomas. Antibody-drug conjugates are also a suitable alternative for patients for whom chemotherapy would mean unacceptable toxicity or further deterioration of renal function.32–37

Prof. Büchler concluded his presentation by stating that the amount of evidence for the use of ADCs in the treatment of UTUC is growing rapidly but is still at a relatively early stage. All UTUC-only studies published to date are small and predominantly non-randomized, limiting the ability to draw definitive conclusions. Nevertheless, the available data suggest that the efficacy of ADCs in UTUC is comparable to or even higher than in bladder cancer, and that their safety profile is well manageable with early identification of specific toxicities. The lecture sounded like a call for continued UTUC-specific clinical research and a biomarker-driven approach that could enable more accurate patient selection.[32–37] As Prof. Büchler summarized: "Antibody-drug conjugates appear to be one

of the most promising ways to overcome the limitations of chemotherapy in the renally fragile UTUC population and to shape the future of treatment for this disease."

Metastatic UTUC: therapeutic strategies and clinical case report

Assoc. Prof. Jindřich Kopecký, MD, PhD, from the Department of Oncology and Radiotherapy, Faculty of Medicine of Charles University and University Hospital Hradec Králové, emphasized in his presentation that metastatic UTUC cannot be considered merely an anatomical variant of urothelial carcinoma of the bladder, but that it represents a biologically and clinically distinct entity. Patients with UTUC are usually older and already have poorer renal function at the start of treatment, which often deteriorates further after radical nephroureterectomy. This fact has a fundamental impact on the suitability of cisplatin administration and significantly influences the choice of first-line treatment sequence. At the same time, metastatic UTUC presents with different metastatic patterns, with retroperitoneal lymph node metastases and bone involvement being more common than in bladder cancer. Together, these factors create a specific clinical environment that requires an individualized therapeutic approach.[36,37]

Synchronous versus metachronous UTUC

One of the key messages of the presentation was the distinction between synchronous and metachronous UTUC. Data consistently show that the synchronous form of the disease has a significantly worse prognosis than metachronous UTUC.

Synchronous tumors are associated with a higher risk of early systemic dissemination and shorter overall survival, even when the extent of the primary disease is comparable. As Assoc. Prof. Kopecký stated, "this finding emphasizes the need for greater vigilance when deciding on the intensity of therapy and follow-up for synchronous tumors, regardless of their initial staging."

Insufficient representation of UTUC in clinical trials

Another fundamental problem is the significant discrepancy between the actual incidence of UTUC in the population and its representation in clinical trials. According to data from Nalla et al., UTUC accounts for only 5–10% of patients enrolled in randomized studies of first-line treatment for metastatic disease.37 In addition, in many studies, data for UTUC are combined with bladder cancer or are not analyzed separately. This approach significantly limits the robustness of conclusions for the UTUC population and forces clinical practice to extrapolate the results of studies that were primarily designed for a different biological entity. Assoc. Prof. Kopecký emphasized that this shortcoming is one of the main obstacles to the creation of high-quality evidence and that UTUC necessarily requires separate prospective clinical studies.

Treatment decisions in the context of renal function and guidelines

Although current recommendations from professional societies (EAU, NCCN, American Urological Association) formulate general principles of treatment common to both UTUC and bladder cancer, their application in UTUC patients is often limited by renal function.28 Assoc. Prof. Kopecký explained that a significant proportion of patients with UTUC are unable to undergo cisplatin chemotherapy, either due to pre-existing renal insufficiency or a subsequent decline in renal reserve after surgical treatment. For this reason, patients with UTUC more often switch to carboplatin regimens or to treatment combining immunotherapy and ADC. This is not necessarily the biologically optimal choice, but a consequence of the functional limitations of the organism. The treatment sequence for UTUC thus naturally differs from that for bladder cancer, even though it is broadly described in the same recommendations.

Oligometastatic UTUC and the role of local methods

Oligometastatic UTUC represents a specific subgroup. In patients with a limited number of metastatic sites, local treatment methods, in particular stereotactic radiotherapy or other focal approaches, can play an important role, with the potential for long-term disease control. Although there is a lack of randomized data for these strategies, their use is consistent with clinical practice and is based on smaller data sets and case reports. As mentioned, "local treatment may be beneficial especially in patients with painful bone metastases or isolated lymph node lesions," where it provides both symptomatic relief and support for systemic disease control.

Variant histology as a key prognostic factor

The presence of variant histology is a significant negative prognostic factor for metastatic UTUC. Studies by Deuker et al. and Douglawi et al. show that patients with variant histological types have significantly shorter overall survival, often in the range of 8–10 months, and a higher incidence of metastases, particularly lymph node and bone metastases.38,39 Although the presentation did not provide detailed numerical data, the available literature provides a consistent conclusion that variant histology has a significant impact on prognosis and choice of treatment strategy. In these patients, earlier initiation of more intensive systemic treatment or ear-

Doc. MUDr. Jindřich Kopecký, Ph.D.

lier use of ADCs, if available, may be rational given the high risk of rapid progression.

Clinical case study: typical course of UTUC in real practice

The presented case study of a 65-year-old patient with UTUC illustrated the typical course of metastatic disease in real clinical practice.

After radical nephroureterectomy, the patient underwent four cycles of chemotherapy with cisplatin and gemcitabine, followed by maintenance immunotherapy with avelumab. Despite this sequence, the disease progressed with the development of bone, lung, and retroperitoneal metastases. Painful bone lesions were treated with palliative radiotherapy, and enfortumab vedotin became the next line of systemic therapy. This course of events illustrates well the typical trajectory of advanced UTUC, where even with an optimal treatment sequence, the risk of relapse remains high and the treatment strategy must be planned with regard to renal function, tumor biology, and the patient's real possibilities.

Several key findings emerge from this case report: UTUC represents a biologically distinct entity with a higher risk of early metastatic progression; renal function fundamentally influences the choice of systemic therapy; variant histology worsens the prognosis and may require a more intensive therapeutic approach. Local methods, especially radiotherapy, can play an important role in controlling symptoms and maintaining the overall treatment trajectory. The case also highlights the need for multimodal and flexible thinking, as effective management of UTUC requires a combination of surgery, systemic therapy, immunotherapy, precise palliation, and modern drugs like ADC.[30,32,33]

The case described and the available literature show that although the treatment of metastatic UTUC is based on the general principles of urothelial carcinoma treatment, the actual therapeutic results are fundamentally influenced by the specific biological nature of this disease. Therefore, the success of care depends not only on the correct sequence of treatment modalities, but also on the ability to individualize therapy according to renal function, histological subtypes, progression dynamics, and patient preferences. Metastatic UTUC requires a multidisciplinary approach, rational use of local methods, and realistic planning of further lines of systemic treatment, including modern ADCs. This comprehensive approach offers the best chance of stabilizing the disease and maintaining an acceptable quality of life in patients with biologically aggressive tumors prone to early systemic progression.[28,36–39]

Key points

- Modern UC diagnosis requires the integration of histology, genomics, transcriptomics, proteomic correlates, and dynamic circulating markers, with interpretation over time and according to the treatment line, rather than isolated assessment of individual tests.
- Transcriptomic classification of MIBC enables biological stratification of tumors and prediction of response to immunotherapy; immune-inflammatory phenotypes generally benefit more from checkpoint inhibitor therapy than tumors without immune infiltration.
- Genomic heterogeneity and clonal evolution under the selective pressure of treatment explain treatment failure and support the need for repeated re-biopsy/re-escalation of molecular characterization upon progression; resistance is often due to changes in expression and phenotype, not just the emergence of new mutations.
- In ADC, the expression of functional target protein (e.g., Nectin-4, TROP2) is crucial, while mRNA levels may not be predictive; treatment failure can occur even without detectable genetic alteration.
- CtDNA can be used to monitor response, detect minimal residual disease, and detect relapse early; positivity is highly specific, while negativity does not rule out disease persistence and requires careful interpretation.
- Pharmacogenetics and drug interactions have a direct impact on the efficacy and toxicity of systemic treatment and should be a standard part of clinical decision-making, especially in polymorbid patients and patients on polypharmacy.
- UTUC represents a biologically specific entity with difficult staging and frequent renal limitation; the strongest perioperative evidence supports adjuvant platinum-based chemotherapy, while the role of neoadjuvant and adjuvant immunotherapy remains unclear.
- In metastatic UC, treatment algorithms are fundamentally changing with the combination of immunotherapy and ADC, which show high efficacy across locations, including UTUC, and redefine sequential treatment strategies.

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Treatment of advanced urothelial carcinoma in the era of new possibilities: How studies help and what practice looks like

What is the optimal treatment choice for patients with advanced urothelial carcinoma today? How important is the risk score for prognosis and treatment decisions? How should the results of key clinical studies be interpreted and translated into everyday practice? Where do chemotherapy, immunotherapy, and their combinations fit into individual lines of treatment? And how do quality of life, treatment toxicity, and patient preferences enter into decision-making? These and other questions were answered by speakers in Section II of the Bladder Cancer Master Class colloquium, which focused on the treatment of advanced urothelial carcinoma in the context of current and emerging therapeutic options.

The importance of risk scores

In the introductory lecture of the block, **Prof. Piotr Wysocki** from Gdański Uniwersytet Medyczny in Gdańsk, Poland, spoke about palliative care.[1] As he stated, we are in an era of new possibilities for the treatment of patients with advanced urothelial carcinoma (aUC) and, specifically, advanced bladder cancer (aBC). There is intense debate about how to incorporate them into guidelines, as "the answer is not simple." "It is not the case that the single systemic treatment that many international guidelines consider best is the optimal choice for every individual patient," he said.

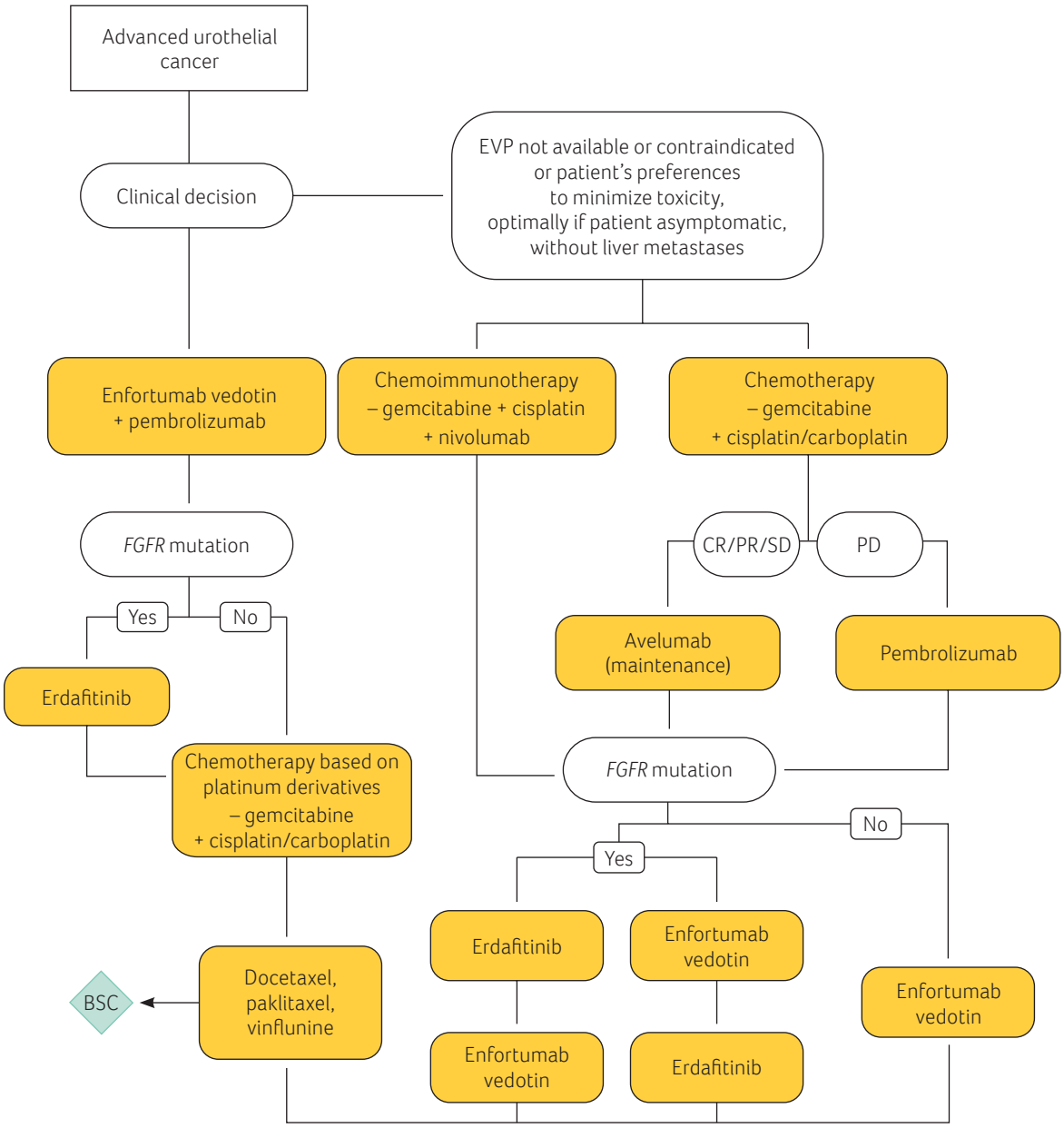
He pointed out that in patients with metastatic urothelial carcinoma (mUC), an updated risk score based on four negative prognostic factors—performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG PS) > 0, anemia (hemoglobin concentration < 10 g/dl), presence of liver metastases, and elevated C-reactive protein (CRP) concentration. Patients who do not have any of these factors have a one-year survival rate of 63%, while those with at least three factors have a survival rate of only approximately 15%.[2]

The 2025 guidelines of the Polish Society of Clinical Oncology place great emphasis on clinical decision-making together with the patient and point out that chemotherapy (CT) is still applicable to more patients than just those who are not candidates for the combination of enfortumab vedotin + pembrolizumab (scheme 1).[3] "We believe that patient preferences, their asymptomatic status, and the absence of liver metastases allow us to consider standard chemotherapy in combination with concurrent or sequential immunotherapy as a first-line treatment," added Prof. Wysocki. He reiterated the importance of the first choice with regard to subsequent lines of therapy.

Focus on the design of the EV-302 study

In the EV-302 study, the combination of enfortumab vedotin + pembrolizumab demonstrated better results than standard CT consisting of gemcitabine and cisplatin or carboplatin in patients with aUC. 4 However, standard CT was administered for 18 weeks, while enfortumab vedotin + pembrolizumab was administered until disease progression or unacceptable toxicity. Only later was maintenance therapy with avelumab added for patients who had at least stabilized. However, this was only 30% of the entire control group, and according to Prof. Wysocki, no data are available on these patients. The combination of enfortumab vedotin + pembrolizumab appears to be a very effective strategy in terms of progression-free survival (PFS) and overall survival (OS), and in the EV-302/KEYNOTE-A39 study, the benefit was consistent across subgroups, but we do not know the individual results of the 30% of patients who received CHT and maintenance therapy with avelumab. Furthermore, the study showed that CT is more toxic than enfortumab vedotin + pembrolizumab; however, according to the speaker, the difference was in the incidence of anemia, neutropenia, and thrombocytopenia, which he noted were "common side effects that we know how to treat."

Prof. Piotr Wysocki



SCHEME 1 Algorithm of palliative treatment in patients with urothelial carcinoma according to the Polish Society of Clinical Oncology from 2025

BSC – best supportive care; **CR** – complete response; **EVP** – enfortumab vedotin + pembrolizumab; **FGFR** – fibroblast growth factor receptor; **PD** – progressive disease; **PR** – partial response; **SD** – stable disease

Source: adapted from citation 3

However, he added that "on the other hand, in the enfortumab vedotin + pembrolizumab group, we see long-term toxicity that can significantly affect the quality of life of patients during long-term treatment when patients are actively treated." He emphasized the need to realize that the quality of life data for patients undergoing CT are presented only for the 18 weeks during which they were administered, and that these patients were not treated thereafter, while in the enfortumab vedotin + pembrolizumab combination group, they underwent continuous therapy for another 20 to 30 weeks.[5]

Overall survival and quality of life are significantly correlated, as demonstrated, for example, by a meta-analysis of data from 44,000 patients.[6] "It is therefore very important to realize that with the new drugs we are now using in clinical practice, there are also new toxic effects," Prof. Wysocki reminded. He drew attention to one of the very rare but life-threatening conditions – toxic epidermal necrolysis, which occurs in approximately 1 in 125 (approx. 0.8%) patients, but the risk of death is approximately 50%.[7]

How to improve the effectiveness of chemotherapy?

Data not including the combination of enfortumab vedotin + pembrolizumab show that the best results are achieved by patients undergoing cisplatin-based CT, while significantly worse results were achieved with platinum-free regimens, immunotherapy (IT) alone, and carboplatin-based regimens.[8] The guidelines of the Polish Society of Clinical Oncology emphasize the possibility of using CT alone or in combination with nivolumab based on the CheckMate 901 study (**Scheme 1**).[3,9] This study demonstrated that the CT + IT combination can achieve better OS and PFS than CT alone. In terms of response

rate, the speaker also considers the indirect comparison with the combination of enfortumab vedotin + pembrolizumab to be important. In both studies, the efficacy of the gemcitabine–cisplatin combination was similar, and the addition of IT significantly improved the overall response rate. Both regimens therefore enable significant improvement in disease control and its achievement in a similar proportion of patients.10,11

Although the concurrent administration of CT and IT is associated with increased toxicity, according to the speaker, this is something that current oncologists are familiar with and know how to treat. "And we know that patients not only tolerate it, but it is also known to improve treatment outcomes. Patients with immune-mediated adverse effects have better outcomes than patients without them," he said, again referring to the Polish recommendations, which assume that candidates for CT are only patients who cannot be offered IT at the beginning of treatment, i.e., those who have recently taken antibiotics, especially fluoroquinolones, but also proton pump inhibitors, corticosteroids, patients with poor ECOG PS, or patients with cachexia.[3]

Prof. Wysocki also pointed out that cisplatin may have similar benefits whether administered in standard doses (70 mg/m^2 every 3 weeks) or in split doses (35 mg/m^2 on days 1 and 8 of each 3-week cycle).[12] "The data clearly show that the combination of gemcitabine and cisplatin administered in split doses offers significant benefits to our patients. And it is also safe," the speaker assured.

Cisplatin and CKD

Recent data on the risk of chronic kidney disease (CKD) in patients treated with cisplatin show that stage IV CKD is rare. It was observed in 0.9% of patients who did not have CKD prior to CT; the average decrease in creatinine clearance (CrCl) was < 10 ml/min.[13] Cisplatin is contraindicated in patients with a glomerular filtration rate (GFR) < 40 ml/min, and in patients with GFR 40–60 ml/min only a divided dose of cisplatin should be used.14 Here, too, the optimal selection of patients for cisplatin plays an important role. The speaker emphasized that "it is always necessary to check whether our patients have reversible kidney disease that can be easily overcome with urological treatment."

Options for 2nd to 5th line treatment

Platinum-based CT can be followed by immunotherapy – either maintenance treatment with avelumab in patients without progression (CR/PR/SD), or, in the event of progression, immunotherapy as a 2nd line treatment – typically pembrolizumab. The procedure for 2nd and 3rd line treatment according to Polish recommendations is shown in Figure 1. Evidence for maintenance treatment with avelumab comes from the JAVELIN Bladder 100 study, and for pembrolizumab in the second line after progression from the KEYNOTE-045 study.[15–17] Today, there are a number of options to choose from; the key factors are quality of life, toxicity, and patient preferences. Enfortumab vedotin can also be selected in later lines of treatment, especially in patients who have not yet received it.

A large group (approximately 25%) of BC patients have a fibroblast growth factor receptor 3 (FGFR3) mutation that causes resistance to CT. FGFR inhibitors are available for these patients. Enfortumab vedotin in the EV-301 study and erdafitinib in the THOR study showed similar OS benefits compared to CT. At the time of the colloquium, there were no recommendations available as to whether enfortumab vedotin, or erdafitinib was more appropriate for patients with the *FGFR3* mutation. However, as enfortumab vedotin and erdafitinib differ in terms of toxicity, the speaker recommended optimizing treatment with these drugs based on the initial risk of toxicity.

There is also a place for enfortumab vedotin or erdafitinib in the fourth line, while the fifth line reopens the possibility of CT (**Figure 1**). "We know that chemotherapy is still effective. In patients who were treated with enfortumab and pembrolizumab in the third line, we still saw clinical benefit in every second patient," noted Prof. Wysocki.

He summarized that aBC treatment is long-term and sequential and that it is a therapy for a chronic disease. "There is currently no evidence that a cure is possible. No matter how hard we try, we cannot cure our patients. That is why wise and informed decisions about treatment are crucial," he said at the end of his lecture, emphasizing that decisions about sequential treatment must be based on comorbidities, toxicity, and patient preferences.

The role of pathology and proper patient selection

Prof. Dr. med. Arndt Hartmann from the Universitätsklinikum Erlangen, Pathologisches Institut in Erlangen, Germany, followed with a lecture on the importance of proper patient selection.[18] In his presentation, he explained that there are several types of BC from a molecular and histopathological point of view.

He described the development of UC as a complex process – papillary and solid or invasive UC arise in different ways. According to Prof. Hartmann, today the focus is mainly on aggressive solid BC, which develops from normal ectoderm via carcinoma in situ. This type accounts for about 30% of all BC cases, and its high instability and aggressiveness are due to many molecular changes. "Fortunately, most patients treated by urologists suffer from other bladder tumors," noted the speaker.

Papillary tumors are characterized by several mutations in genes controlling proliferation, particularly *FGFR3*, but also

Prof. Dr. med. Arndt Hartmann

PIK3CA and *STAG2*. They can progress to invasive disease. "So from the outset, we distinguish between two types of bladder cancer," added Prof. Hartmann.

Since 2012, efforts have been made to analyze gene expression for the possible definition of specific types of BC. In 2020, a meta-analysis of previous studies on this topic was performed.[19] Subsequently, six types of invasive bladder cancer (muscle-invasive bladder cancer, MIBC): three types of luminal tumors (papillary, unspecified, and unstable), a tumor in which the stroma plays a key role (stroma-rich), basal/squamous, and a small group of very aggressive neuroendocrine carcinomas.[20]

The urothelium is a specific epithelium with different cell types (umbrella cells, intermediate cells, basal cells) that express different immunohistochemical markers. Different types of BC can be derived from different cell populations, which may respond differently to CT, but also to new treatment options. There are also tumors with adenoid features, with different luminal and basal markers. A 2020 study then came up with a classification of BC based on gene expression, which shows a different prognosis for different types, with a very poor prognosis for neuroendocrine BC.[20] "This expression classification is used in many current neoadjuvant studies with new therapies to see if we can come up with a gene expression classifier that is already on the market and could predict which therapy would be best for a particular patient," added Prof. Hartmann.

Basal or luminal differentiation occurs during carcinogenesis. Molecular subtypes therefore differentiate during the transition from carcinoma in situ to invasive carcinoma and are then stable.21 "This is good news because the subtype does not change much after that," noted the speaker.

The histological variants are subtypes

Invasive carcinoma exhibits different histology and molecular subtypes. In the World Health Organization's 2022 pathological classification, there was a change in terminology—the term "histological variants" was changed to "histological subtypes." These reflect the fact that there are extremely diverse forms of differentiation in the urinary bladder (UB), with UC distinguishing between urothelial (conventional and unconventional) and non-urothelial (divergent) differentiation.

The speaker pointed out that histological subtypes are often associated with a poor prognosis, but according to a systematic review and meta-analysis from 2020, there is only retrospective data to support this claim, which shows a relatively small effect (risk ratio 1.37).22 "Many studies did not have reference pathology, drawing only from archives. It is therefore likely that some of these subtypes have a poor prognosis, but in reality there are no prospective data," said Prof. Hartmann. He expressed his opinion that subtypes will be important for prognosis and therapy prediction.

Tumor microenvironment and the development of muscle-invasive UC

Gene expression types are reflected in the tumor microenvironment, which in turn is very important for predicting response to IT. Based on the microenvironment, four types of BC are distinguished: immunologically "cold" (non-inflammatory) tumors, inflammatory tumors with low infiltration, immunologically "hot" tumors with high inflammatory infiltration, and inflammatory tumors with significant immune escape mechanisms (these are strongly positive for programmed death-ligand 1 [PD-L1] and are IT candidates).[23,24] Luminal/luminal papillary tumors that do not respond well to IT or CT are immunologically "cold" (non-inflammatory) tumors.[23] It is therefore clear that the microenvironment has prognostic significance in terms of survival. "The prognosis is much better for highly inflammatory tumors, while it is very poor for immunologically 'cold' tumors. This reflects the patient's immune response to the tumor," added the speaker.

The predictive significance for treatment remains unclear, "because we examine the primary tumor but treat the metastases" – this is associated with the hypothesis that the wrong material is being examined. Of all studies, a preliminary biopsy is required in less than 15% of cases. In a paper published in 2023, the authors paired primary tumors and metastases and found a discrepancy in immune infiltrate in 30% of patients.[25,26] In a group of 50 patients, there was no correlation between the response to second-line immune checkpoint inhibitors (ICIs) and patient outcomes on the one hand, and the phenotype of the primary tumor on the other. In contrast, biopsy of metastases made it possible to predict the tumor microenvironment and which patients could have very good results with immunotherapy alone. However, there are differences between different types of metastases—metastases in the liver or bones (stable, cold phenotype) respond poorly to therapy, while those in the lungs or kidneys (very unstable, hot phenotype) respond well.

Antibody-drug conjugates

Pathology can help in sequencing treatment or predicting the likely response to antibody-drug conjugates (ADCs), such as enfortumab vedotin. However, studies also show the importance of the age score – a high score is associated with a much better response to enfortumab vedotin.[27] "According to Tom Powles, everyone should receive enfortumab vedotin. However, in his studies, if you have a high age score, you have a much better response to treatment," said the speaker, adding that his team had also come to a similar conclusion in their patient cohort. "We see a very strong correlation between age score and response to enfortumab vedotin."

This opens up potential for further ADC targets. For example, the phase II DESTINY-PANTUMOR02 study points to the role of HER2-neu. According to the speaker, there will be several possible ADC targets in the future, such as Nectin-4, EGFR, HER2-neu, HER3, TROP2, etc., and predictive markers will be needed to respond to this targeted treatment.

The role of the multidisciplinary tumor board

Case study 1

Ap. Prof. Priv.-Doz. Dr. David D'Andrea, FEBU, from the Medical University and General Hospital in Vienna presented a case that progressed from non-muscle-invasive BC (NMIBC) to metastatic BC.28 In doing so, he highlighted the important role of the multidisciplinary tumor board.

The patient was a 62-year-old male, smoker, ECOG PS 0, married with three children, sporadically active, i.e., an atypical UC patient. The patient presented to the emergency room with macrohematuria. Computed tomography (CT) revealed thickening of the bladder but no distant metastases.

A cystoscopy performed several weeks earlier had revealed a 3 cm papillary tumor on the right wall of the bladder. The goal was to completely remove the tumor (the most important step in NMIBC), but not the bladder, to obtain a good sample for the pathologist and optimize oncological results, while performing a safe operation with minimal morbidity.

The patient therefore underwent transurethral resection of bladder tumor (TURB) en bloc, which, according to the literature, provides a better histological sample with fewer complications than standard BC resection. "During the operation, we also fill out a checklist, which is very important, and we did so with this patient as well. I recommend that you use it in your clinical practice. It consists of only 10 items that you include in your surgical report. It has been proven that this actually improves outcomes and recurrence-free survival in these patients," he said, adding that the report is very informative for the surgeon, but also for the physician who must subsequently decide on the type of adjuvant therapy.

The patient's pathology report therefore indicated UC pTa high grade, without concomitant carcinoma in situ and adverse features, with the presence of detrusor fragments in the sample; it was not another histological subtype.

In accordance with professional guidelines, a second TURB was performed, as up to 50% of residual tumor may be present in these patients. As this was negative, adjuvant treatment was initiated.

After discussion with the patient, intravesical instillation of Bacillus Calmette–Guérin (BCG) was chosen for the adjuvant phase. He completed the entire induction cycle, and the first follow-up cystoscopy, cytology, and biopsy showed recurrence during or after BCG instillation. As an aside, the speaker noted that all studies published up to 2024 on the absence of effect or failure of intravesical BCG instillation had recently been summarized, comprising a total of 68 different treatment arms.[29] "We therefore have a whole range of drugs and options to offer patients," he noted, referring in particular to the KEYNOTE-057 study with pembrolizumab monotherapy.[30] The recommendations of current European and American guidelines on how to proceed in the event of failure of intravesical BCG instillation are consistent—the patient must undergo radical cystectomy. However, the patient is young, active, has a family, wants to maintain his quality of life, and is asking for alternatives. In 2025, there are a number of options that could theoretically be offered to him, such as chemohyperthermia, to a certain extent also a second chance for BCG, ICI, FGFR inhibitor, interleukin 15 superagonist, and still also CT, which is probably the cheapest of all.

Based on data from a retrospective study, the patient was offered gemcitabine-docetaxel chemotherapy.[31] It is administered once a week for 6 weeks at a dose of 1 g of gemcitabine and 37.5 mg of docetaxel. The study shows a high response rate, which is also sustained, and a very high recurrence-free survival rate (60% after 1 year, 46% after 2 years).

A check-up after six months showed that the patient tolerated the therapy very well, with no adverse effects. A follow-up CT scan revealed a suspected pathology of one hip lymph node on the right. In addition, he had a papillary tumor filling his urostomy. Cytology was negative for high-grade tumor, and the bladder was without pathology.

A discussion took place in the multidisciplinary tumor board, which the presenter described as "very important for these patients," about what to offer. The patient again refused radical cystectomy. The tumor team proposed TURB, lymphadenectomy, and next-generation sequencing (NGS) of the tumor and/or lymph nodes. Histology after TURB showed invasive UC, laparoscopic lymphadenectomy showed one positive lymph node, and NGS panel of lymph node metastases showed mutations in four genes (FGFR, ERBB2, KRAS, HER2). "We therefore have some scope for targeted therapy," noted the speaker.

Ap. Prof. Priv.-Doz. Dr. David D'Andrea, FEBU

CtDNA was negative six weeks after surgery.

"There are therefore certain indications or signals that cancer could be cured in these patients," stated the speaker.

Case study 2

Another case was presented by **OÄ Dr. Dora Niedersüß-Beke, MBA,** from the Wiener Gesundheitsverbund Klinik Ottakring.[32]

This is a younger, 59-year-old man who was diagnosed with UC in 2014. He underwent 3 TURBs, the last one in 2015, and histology confirmed stage T1 G3. In 2019, he dropped out of follow-up.

It was not until June 2022 that he presented with pain and macrohematuria. He had grade 3–4 hydronephrosis on both sides, a creatinine concentration of 1.6 mg/dl, and a recurrence of localized BC; his ECOG PS was 1. His medical history included a stroke (2019), hypertension, non-insulin-dependent diabetes mellitus, and ischemic heart disease (stent implanted), all of which were adequately medicated.

A new TURB confirmed high-grade papillary UC, PD-L1 positivity, microsatellite stability, and NGS mutations in *PIK3CA* and *ERBB3*. The urologist scheduled a cystectomy for September 2022. Neoadjuvant CT was not appropriate for this patient.

An isotope nephrogram in August 2022 revealed a non-functional right kidney. However, the patient did not show up for surgery and disappeared from view again.

In July 2023, he came to the emergency room with the same problem. He had macrohematuria, was tired, had cramps, anemia, again elevated creatinine (5.5 mg/dL), and all the symptoms of acute renal failure.

A CT scan showed tumor progression. The bladder was filled with a tumor that had infiltrated the rectus abdominis muscle. The patient had pathological local, para-aortic, and para-iliac lymph nodes, but no visceral metastases. Radiologically, it was stage rT4N3M0.

The patient underwent left nephrostomy, and an oncology consultation was called for the first time, i.e., the lec-

turer's workplace. Supportive therapy was administered, and the patient underwent rebiopsy.

In August 2023, he was referred to a multidisciplinary tumor board. His ECOG PS was 2, and his kidney function improved slightly after nephrostomy (creatinine concentration 2.2 mg/dl). A combination of enfortumab vedotin + pembrolizumab was administered. "Even before the presentation at the European Society for Medical Oncology congress, we started treatment with a combination of enfortumab vedotin + pembrolizumab in this patient due to his poor kidney function, as we already had some data available in our department," explained the presenter.

After two doses of enfortumab vedotin (over 16 days), the patient came to the oncology department with fever, lower abdominal pain, and a huge abscess in the lower part of the abdominal wall. The cause was an infection at the site of the tumor after a large regression of the tumor mass. The patient was given antibiotics, underwent drainage, and "was doing well."

In the second cycle, only pembrolizumab was administered first, and then (on day 8) enfortumab vedotin was administered again at a reduced dose of 85%. In cycles 3 to 5, the patient was again given the full dose of enfortumab vedotin, but mild neuropathy developed. In December 2023, he received the sixth cycle of combination therapy with enfortumab vedotin + pembrolizumab, in which the dose was again reduced to 85%. As the speaker stated, "the patient tolerated the treatment quite well."

In January 2024, regression of the primary tumor and complete remission of all pathological lymph nodes were demonstrated. The MM, which still needed to be resolved, was also shrinking. "We found no further pathologies anywhere in the patient's body," added the presenter.

The patient was again presented to the multidisciplinary tumor board. "I think this is really important because times are changing and the condition of patients with metastases will continue to improve thanks to new therapeutic options.

OÄ Dr. Dora Niedersüß-Beke, MBA

We must therefore consider late radical cystectomy. And that's what we did with our patient because we knew that the main problem was the bladder and not the metastases in the lymph nodes, which disappeared during this therapy," added the speaker.

In March 2024, the man underwent extensive surgery with cystectomy, prostatectomy, and also ureterectomy and nephrectomy on the right side. Histologically, a ypT2a tumor (invasive undifferentiated papillary UC, chronic infectious infiltration, and myxoid degeneration) was still present, but all lymph nodes and all other sites were negative. The patient refused adjuvant IT, saying that he had "already undergone six cycles of systemic therapy and had had enough."

His most recent examination was performed three months earlier, when he was in ECOG 0 condition with a creatinine concentration of 2.0 mg/dl, and 1.5 years later he still showed no signs of disease.

Decision-making with individualized care

As a summary and recapitulation of what has been said, with an emphasis on personalized medicine using practical examples, two case studies were presented by **Prof. Dr. Javier Puente, PhD**, from the Institute of Oncology at Hospital Clinico San Carlos in Madrid.33

Case study 1

This was a 66-year-old man with hematuria, a history of well-controlled hypertension, a former smoker (20 pack-years), who had a very good ECOG PS 0 and good kidney function (estimated glomerular filtration rate [eGFR] 67 ml/min). Ultrasonography revealed thickening of the left bladder wall with suspected malignancy, and CT scan showed a 42-millimeter solid mass in the left part of the bladder with extension into the perivesical fat. TURB confirmed UC in stage cT3 and invasion into the lamina muscularis propria.

The patient underwent neoadjuvant gemcitabine-cisplatin-based CT with durvalumab, 4 cycles according to the NIAGARA study, followed by radical cystectomy + pelvic lymph node dissection. The lecturer justified the decision to remove the UB instead of attempting to preserve it with trimodal therapy based on the stage of the tumor.

The histopathological report revealed a high degree of infiltration with extensive squamous differentiation throughout the entire thickness of the UB wall, no metastases in the nodes, and PD-L1 positivity (combined positive score of 20). The stage was therefore T3N0M0.

The options available were simply monitoring, nivolumab administration for one year, radiotherapy, or adjuvant CT. Nivolumab was chosen based on the CheckMate 274 study.[34]

After 11 months of nivolumab use, progression occurred – metastasis to the lungs and lymph nodes. The patient still had an ECOG PS of 1 and an eGFR of 60 ml/min. The next steps could be enfortumab vedotin or IT with atezolizumab or pembrolizumab, or CT with a combination of gemcitabine and cisplatin, followed by avelumab or a combination of gemcitabine and cisplatin + nivolumab or a combination of enfortumab vedotin + pembrolizumab.

Due to the low response to neoadjuvant CT (the patient had a T3 stage tumor after treatment), the combination of enfortumab vedotin + pembrolizumab (not approved in the Czech Republic at the time of the colloquium) was chosen over the CT regimen.

The lecturer did not present any further developments.

Case study 2

The second clinical case involved a 72-year-old woman, ECOG PS 1, with metastatic UC, which was stabilized by gemcitabine-cisplatin-based CT as first-line treatment. She subsequently received avelumab as maintenance therapy. Her medical history also includes hypercholesterolemia and diabetes mellitus, CrCl around 45 ml/min (she takes enalapril 10 mg, omeprazole 20 mg, metformin 850 mg, and paracetamol as needed as concomitant medication).

"We perform molecular analysis at our facility, and the patient is microsatellite stable, has an *FGFR3* mutation, but also *ERBB2* amplification with a positive HercepTest," added the speaker.

Progression-free survival with first-line CT and avelumab was 21 months, then progression with metastases in the lungs, lymph nodes, and bones was observed. "However, the patient is in good performance status, has good creatinine clearance – 48 ml/min, and is mildly symptomatic," added the speaker.

The options now were enfortumab vedotin, pembrolizumab, erdafitinib, trastuzumab deruxtecan, or sacituzumab govitecan. The patient received enfortumab vedotin as a second-line treatment, administered intravenously at a dose of 1.25 mg/kg on days 1, 8, and 15 of a 28-day cycle. She suffered from dermatological toxicity (erythematous pruritic papules) and grade 2 peripheral neuropathy. She responded well to enfortumab vedotin, as demonstrated by imaging methods 12 weeks after its administration.

However, metastasis to the brain and progression in the lungs then occurred. At this point, the choice was between best supportive care, pembrolizumab, erdafitinib, trastuzumab deruxtecan, or sacituzumab govitecan. In addition, the patient could be enrolled in an open-label study in which the median PFS across cohorts was 6.9 months and the median OS was 13.4 months.[35,36]

The patient declined to participate in the study and was given erdafitinib as third-line treatment. She responded well to it, and 12 months after starting treatment, the response in her brain and lungs persisted, which the speaker described as a miracle. "These are exceptions. Most of our patients in these situations die within two to three months at the latest. She started taking erdafitinib and is still alive at this point," he concluded.

Key points

- The choice of first-line treatment for advanced/metastatic UC should be based on prognostic stratification (ECOG PS, hemoglobin < 10 g/dL, liver metastases, CRP), treatment goals (symptom control versus long-term survival), and the planned sequence of subsequent lines of treatment.
- Enfortumab vedotin + pembrolizumab is a highly effective regimen; however, interpretation of the EV-302/KEYNOTE-A39 study must take into account the design (time-limited CT in the control arm, non-universal use of avelumab maintenance therapy, continuous exposure in the enfortumab vedotin + pembrolizumab arm).
- The toxicity profiles differ fundamentally: the hematologic toxicity of CT is generally predictable and manageable, while the enfortumab vedotin + pembrolizumab regimen is dominated by cumulative long-term toxicity (skin adverse events, peripheral neuropathy), including rare but fatal toxic epidermal necrolysis.
- Cisplatin CT remains the reference standard in suitable patients; split-dose cisplatin allows for an expansion of the population eligible for cisplatin while maintaining efficacy and acceptable safety.
- Gemcitabine–cisplatin + nivolumab (CheckMate 901) improves OS, PFS, and ORR compared to CT alone and represents a clinically relevant first-line alternative with a well-known and manageable toxicity profile.
- Renal function is a key determinant of strategy: cisplatin is contraindicated in patients with GFR < 40 ml/min, and in patients with GFR 40–60 ml/min a split dose of cisplatin should be used; it is advisable to actively exclude reversible urological causes of renal function deterioration.
- After platinum, immunotherapy plays a key role: maintenance treatment with avelumab after response or stabilization (JAVELIN Bladder 100) or pembrolizumab in the second line (KEYNOTE-045), with an emphasis on quality of life and long-term disease control.
- In subsequent lines, decisions are based on various biomarkers and potential toxicity: for FGFR3 mutations, erdafitinib and/or enfortumab vedotin are considered; the optimal sequence is not universally established and depends on the clinical context.
- Pathology, molecular subtyping, and tumor microenvironment phenotype (cold/hot/leaking) support the prediction of response, especially to ICI; for decision-making in the metastatic stage, biopsy of the metastasis may be more beneficial than biopsy of the primary tumor.
- A multidisciplinary tumor board is essential for dynamic decision-making, treatment escalation or de-escalation, and possible conversion to local treatment after a deep systemic response (including the use of NGS/ctDNA, proper sequencing, and timing of cystectomy).

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MIBC in 2025: Where have diagnostics and treatment progressed, and what issues are currently being addressed?

What should the assessment, diagnosis, and treatment of invasive bladder cancer and urothelial carcinoma of the upper urinary tract look like today? What knowledge is available on bladder-sparing approaches? What do neoadjuvant treatment regimens offer patients, for whom are they suitable, and what should they include? Can liquid biopsy be helpful in patients with muscle-invasive bladder cancer? And is the current path that a patient with bladder cancer must take optimal? These and other questions were answered by speakers in Section III of the Bladder Cancer Master Class colloquium, which focused on muscle-invasive bladder cancer.

Staging, diagnosis, and endoscopic treatment of MIBC and UTUC

The first lecture was given by **Prof. Yann Neuzillet, MD, PhD**, from the Université de Versailles Saint-Quentin-en-Yvelines in France. He spoke about staging, diagnosis, and endoscopic treatment of muscle-invasive bladder cancer.[1]

Urothelial carcinoma (UC) essentially consists of two diseases – the vast majority (95%) of cases are bladder cancer (BC), with the remainder (5%) being upper tract urothelial carcinoma (UTUC). Global data on the incidence of UC therefore primarily reflect the incidence of BC. Bladder cancer differs from UTUC in several ways. For example, smoking is a major risk factor for BC, but only slightly increases the risk of UTUC, which is more likely to be caused by Lynch syndrome, for example. Patients with UTUC are older than those with BC. The mutations are also different – BC and UTUC share a number of mutations, but at different frequencies; UTUC more often has *H-RAS* and *FGFR3* mutations, while BC has *RB1*, *TP53*, and *ERBB2* mutations.[2,3] "Overall, although they have the same histological origin, UTUC and BC are two different diseases," said the speaker, adding that there are cases where BC and UTUC are clonally similar because they spread to different parts of the urinary system.

The differences also stem from the different thicknesses of the muscle layer of the bladder and upper urinary tract, which affects the histological prognosis and TNM (Tumor–Node–Metastasis) classification (in BC, stages T2 [spread to muscle) and T3 [spread to perivesical tissues) are further divided into sub-stages A and B, while in UTUC, stage T3 takes into account the location of the tumor in the renal pelvis or ureter – ureteral tumors have a poorer prognosis).[4]

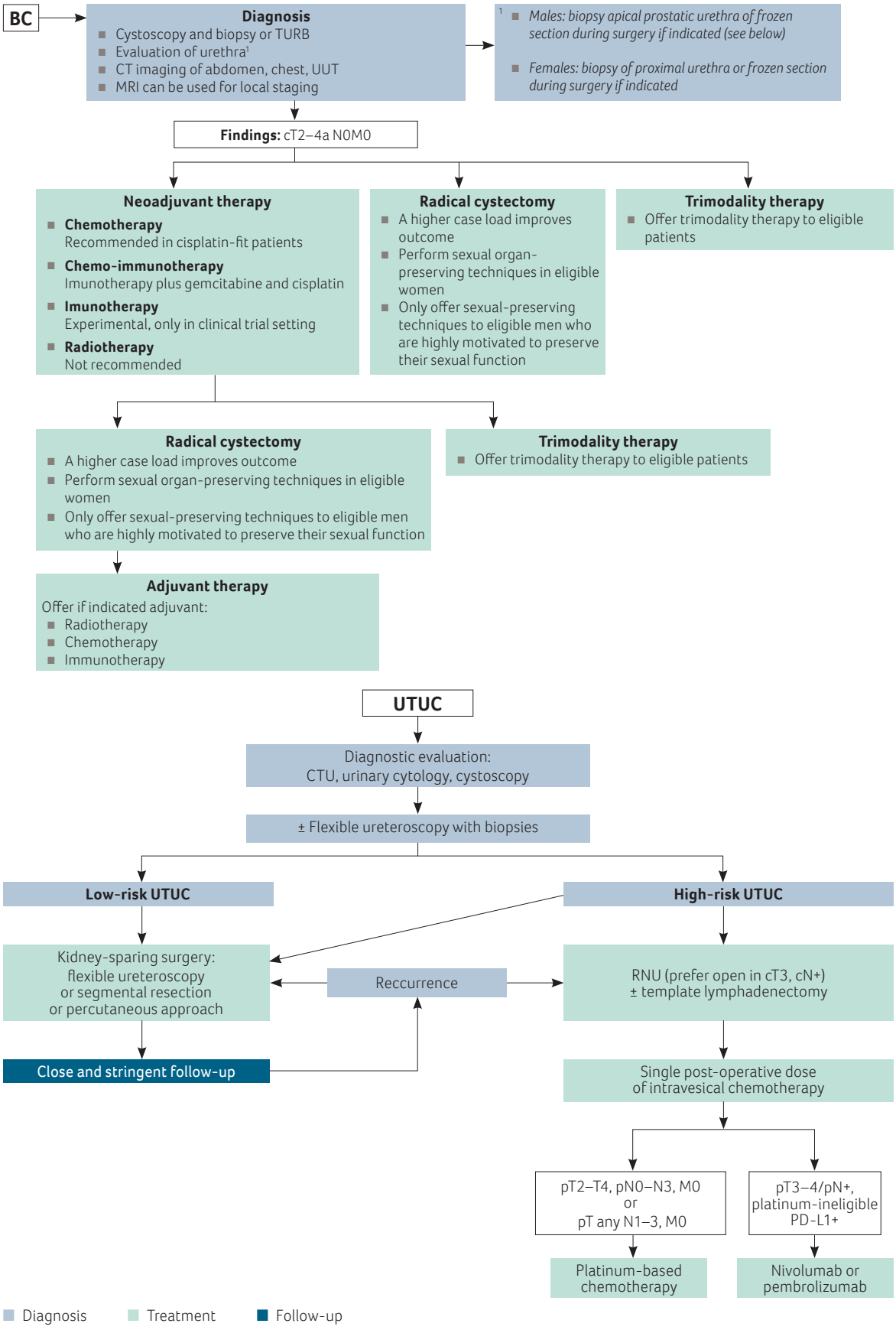
Diagnosis and staging of UC

Imaging methods are the main tool for detecting and staging BC and UTUC. For BC, magnetic resonance imaging (MRI) is more useful than computed tomography (CT). Staging according to multiparametric MR and VI-RADS classification has a sensitivity of 83% and a specificity of 90% for MIBC.[5] "It is therefore a good test for the early detection of bladder tumors with invasion into the muscle," said the speaker. Computed tomography is useful for detecting invasion into the perivesical tissue and adjacent organs. In the case of UTUC, he identified CT urography as better for tumor detection and staging, with a sensitivity of approximately 92% and a specificity of 95%.[6]

However, the speaker warned that staging using imaging tests is not optimal – it can underestimate the stage, i.e., the depth of invasion, resulting in a poor estimate of the En neoadjuvant chemotherapy," reflected Prof. Neuzillet. "So we have to perform the best possible resection. And if that's not possible, we have to hope that the patient will respond to cisplatin-based chemotherapy to improve the prognosis."

The situation is very different for UTUC. The decision to operate depends on the location of the tumor and the risk posed by its size, stage, and number (**Scheme 2**).11 In the case of a possible nephron-sparing surgery, it is necessary to ensure that renal function is preserved, which, however, is often a major problem in this disease, as it usually involves the oldest patients with comorbidities and already impaired renal function. There is therefore a risk of chronic renal failure and the need for dialysis, which, according to the speaker, has a higher mortality rate in comorbid elderly patients than urothelial carcinoma itself. "With this type of tumor, we must

Prof. Yann Neuzillet, MD, PhD



SCHEME 1 Algorithm of diagnostic and therapeutic approach to BC and UTUC

BC – bladder cancer; **CT** – computed tomography; **CTU** – computed tomography urography; **cN** – clinical nodal stage; **cT** – clinical tumor stage; **M0** – no distant metastases; **MR** – magnetic resonance imaging; **N0**–N3 – extent of regional lymph node involvement; **PD-L1** – programmed death-ligand 1; **pN** – pathological nodal stage; **pT** – pathological tumor stage; **RNU** – radical nephroureterectomy; **TURB** – transurethral resection of bladder; **UTUC** – upper tract urothelial carcinoma

Source: adapted from citations 10 and 11

therefore weigh the risk of dialysis against a conservative approach," warned Prof. Neuzillet, adding that with BC, and specifically MIBC, it is important to remove the entire tumor if possible, whereas this is not the case with UTUC.

Bladder-sparing treatment: Findings, advantages, and challenges

In addition to radical cystectomy, there are also several bladder-sparing options (maximal TURB, partial cystectomy, radiotherapy [RT], chemoradiotherapy [CRT], chemotherapy [CT], trimodal therapy [TMT]), but there is still skepticism among doctors. Data has long been limited, and fundamental questions remain: who is a suitable patient, and can the results match those of surgery? The current state of knowledge in this area was discussed by **Assoc. Prof. Michal Staník, MD, PhD**, from the Department of Urological Oncology at the Masaryk Memorial Cancer Institute in Brno.[13]

He emphasized that doctors' views on surgical procedures and bladder-preserving strategies differ significantly from those of patients.[14,15] "Removing every bladder is not exactly precision medicine. However, doctors are always concerned about the risk of recurrence and the impact on survival if the bladder is not removed. The data supporting TMT still tend to be for smaller, invasive tumors in selected patients. There is also a lack of multidisciplinary collaboration," said the speaker, adding that, conversely, for patients, bladder preservation is often the main goal. Ultimately, it is a matter of balance—focusing on oncological outcomes versus patients' wishes to preserve their bladder.

However, most bladder-sparing treatment options are only suitable for certain groups of patients, and the results in terms of five-year recurrence rates or five-year overall survival (OS) tend to be worse than in the case of RC. TMT, i.e., the triple combination of maximal TURB + CRT ± CT (neoadjuvant/adjuvant), is more promising. The optimal patient for this is a person with a *c*T2 unifocal tumor, without hydronephrosis and multifocal carcinoma in situ, good bladder function, and complete TURB.16 "If the patient responds well to trimodal therapy, they can be monitored. Otherwise, the next step would be salvage cystectomy," added the speaker.

Radical cystectomy versus TMT

Can trimodal therapy achieve the same results as surgery? Only one randomized controlled phase III study, SPARE, directly compared these two approaches, testing the effect of TMT and RC on overall survival.17 Unfortunately, only 45 patients could be randomized in 27 centers, mainly due to non-compliance with treatment. In the end, the results clearly favored surgery. The first meta-analysis of TMT versus RC was published in 2018.[18] It included 57 studies with approximately 30,000 patients, of whom 3,402 underwent TMT, with 10-year cancer-specific survival (CSS) also favoring RC.

However, in 2023, another analysis of TMT was published, this time conducted at two major institutions in Boston and Toronto.[19] It included 722 carefully selected patients with *c*T2–4N0M0. Most were ideal candidates for TMT – *c*T2 (90%), no carcinoma in situ (79%), no hydronephrosis (90%), after complete TURB. Only 33% were eligible for TMT. Chemotherapy (neoadjuvant/adjuvant) was administered to 56% versus 59% of participants. In the cystectomy group, 44% of patients had locally advanced T3 or T4 disease. The analysis showed no difference between TMT and cystectomy – metastasis-free survival (MFS) was 74% in both groups, and CSS was 81% versus 84%. "Based on these data, TMT can therefore produce comparable results to surgery in selected patients," summarized Assoc. Prof. Staník.

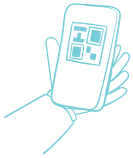
He stated that, based on the current evidence for bladder preservation options, trimodal therapy selected in appropriately selected patients represents the main real alternative to cystectomy.

What is needed to introduce TMT?

The speaker also added his view on the advantages and challenges that need to be overcome for the safe introduction of this method:

1. acceptance of TMT in real practice – currently, the actual target group is a maximum of 15 to 20% (patients with clinically localized carcinoma suitable for CT), the arrival of antibody-drug conjugate (ADC) combinations (ADC + immunotherapy) may expand it to 30–40% in the near future;[20]
2. infrastructure and access to treatment – expertise, centralization, and excellent multidisciplinary cooperation are needed to reproduce excellent results; according to the speaker, the patient's journey is very complex, and many practical factors (such as the distance between the patient's home and the cancer center) influence the choice of treatment;[20]
3. better definition of complete response – currently relies on cystoscopy and CT; circulating tumor DNA (ctDNA) should be better – however, according to Assoc. Prof. Staník, further studies are needed to determine how to integrate and use these biomarkers;[21]

Doc. MUDr. Michal Staník, Ph.D.

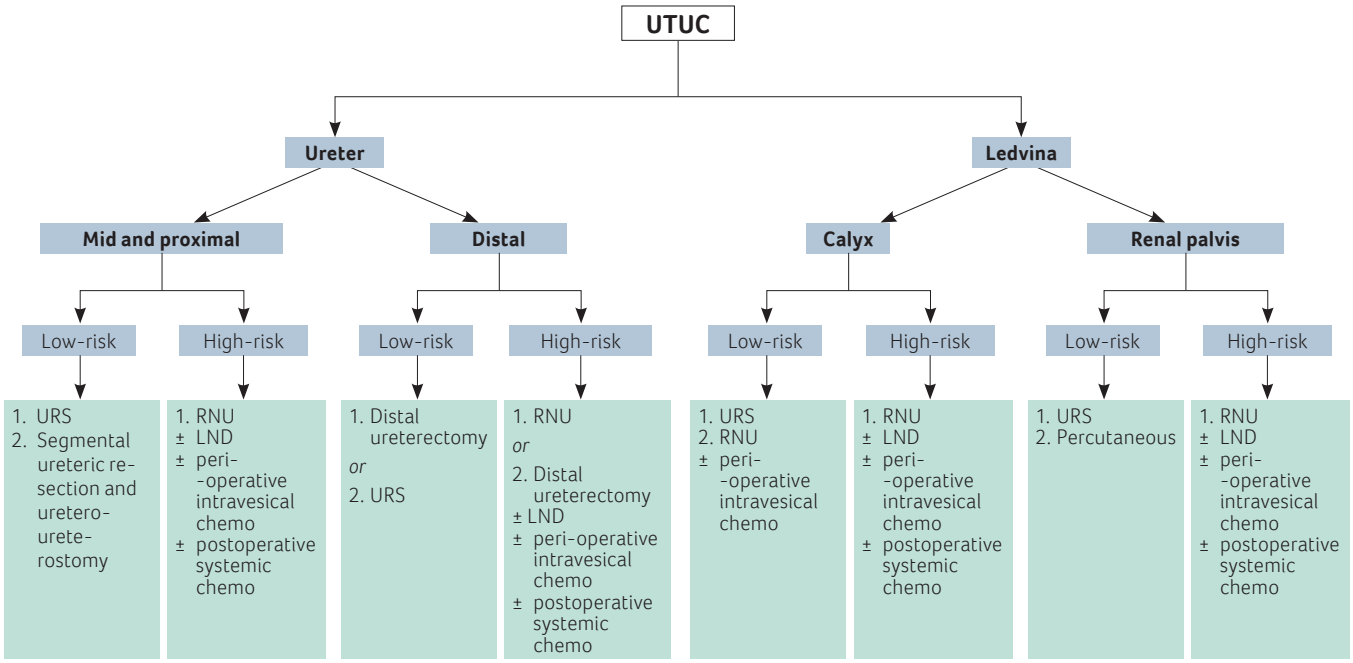


What do you think are the main trends in bladder-preserving surgeries of MIBC area?

Jaké jsou podle vás hlavní trendy v chirurgických postupech zachovávajících močový měchýř v oblasti MIBC?

(doc. MUDr. Michal Staník, Ph.D.)

https://www.remedia.cz/z-novinek/bladder-cancer-master-class-vse-co-se-deje-kolem-karcinomu-mocoveho-mechyre/#stanik



SCHEME 2 Algorithm for the approach to UTUC according to tumor characteristics

LND – lymphadenectomy; RNU – radical nephroureterectomy; URS – ureteroscopy; UTUC – upper tract urothelial carcinoma

Source: adapted from citation 11;

4. the need for careful lifelong monitoring (cystoscopy, biopsy and cytology, imaging, etc.) to check bladder function; some patients are at risk of chronic radiation toxicity, which can manifest itself, for example, as a reduction in bladder capacity or severe hemorrhagic cystitis and carries the risk of bladder loss even without signs of cancer;[22]
5. the answer to the question of whether salvage cystectomy is truly salvageable is: the data are limited, but in the words of the speaker, patients can probably be saved if they are carefully selected at the outset.[19]

What could bring about change in the near future?

As stated by Assoc. Prof. Staník, more effective systemic treatment (ADC + immunotherapy) is expected in the near future, which will bring a higher rate of complete response, as well as the use of better biomarkers (ctDNA kinetics in patients with TMT), which will allow for better definition of complete response and minimal residual disease. This will give greater certainty in physician decision-making and in choosing de-escalation strategies, which may one day allow to completely avoid local therapy in some patients with invasive bladder tumors.

"All these advances are likely to move us further towards personalized bladder treatment options," said Assoc. Prof. Staník, adding that careful patient selection will be absolutely essential. "We expect advances in biomarkers and strategies for de-escalating systemic treatment, but there will still be patient- and institution-related factors that may hinder their widespread implementation. We also need studies to validate all these new strategies."

Neoadjuvant chemotherapy, immunotherapy, and ADC

Prof. Dr. med. Jonas Busch from Vivantes Klinikum am Urban in Berlin-Kreuzberg began his presentation on the current role of NAC, immunotherapy, and ADC in the treatment of MIBC with a clinical case.[23]

Patient case study – and what it implies

This is a 70-year-old man with a slightly impaired performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG PS). He suffers from urinary retention (since March 2025), has hematuria, and has a catheter in place. His medical history includes hypertension, type 2 diabetes mellitus, back pain, and stroke; he has no allergies. Cystoscopy revealed a tumor, transurethral resection of the bladder tumor showed multifocal carcinoma, and MRI showed a cT4 tumor and one affected lymph node. He underwent four cycles of gemcitabine-cisplatin-based chemotherapy with durvalumab according to the NIAGARA study.[24] No immune-related adverse events occurred during administration, but severe neutropenia occurred in the fourth cycle. The patient ultimately underwent open RC, with the choice of open surgery based on the cT4 stage.

The speaker used this example to point out some of the weaknesses of the NIAGARA phase III randomized, controlled trial. In this trial, one arm received NAC (gemcitabine-cisplatin) + durvalumab and the other arm received NAC alone. After RC, the first arm continued with adjuvant monotherapy with durvalumab and the comparative arm remained without adjuvant treatment.

A number of target indicators (event-free survival [EFS], complete response [CR] rate, OS, MFS) and subgroup analysis demonstrated the benefits of adding durvalumab. The speaker rhetorically asked how the results would be affected if the comparator in the neoadjuvant phase was the ddMVAC regimen (dose-dense MVAC [methotrexate, vinblastine, doxorubicin, and cisplatin]), if the comparator group also received adjuvant therapy, such as nivolumab, or how many patients are likely to be overtreated with adjuvant durvalumab if they achieved pathological CR or did not respond to immune checkpoint inhibitors. He also paused at the fact that the study population had a creatinine clearance of ≥ 40 ml/min – according to the speaker, the question is whether we are convinced to treat this population. He expressed his belief that patients should

receive chemotherapy whenever possible, and that even the subgroup with mildly impaired renal function benefits from it.

He also pointed out that patients who did not undergo RC (due to postponement) accounted for only 1%. "These are classic arguments used by surgeons like me who have avoided neoadjuvant chemotherapy in the past. You have to show this data to surgeons and then tell them: Okay, neoadjuvant chemotherapy does not delay surgery, it does not prevent your patient from eventually having surgery, it helps your patient. So these data are important to convince surgeons about chemotherapy," Prof. Busch appealed, adding that surgeons should also be aware of other possible side effects. In the NIAGARA study, the addition of durvalumab to standard CT did not change the side effects, which he described as good news.

The NIAGARA study is currently the only published phase III study with convincing results. There is a lot of discussion about the administration of neoadjuvant immunotherapy alone. Phase II studies with pembrolizumab and atezolizumab have shown some efficacy, but no phase III studies have been published yet. Therefore, current guidelines state that neoadjuvant immunotherapy alone should only be used in studies. "However, I am quite sure that this area will change significantly in the future," he noted.

What to expect

The speaker also pointed to several studies that are expected to be published in the coming weeks, months, and years:[25]

- EV-303 – neoadjuvant pembrolizumab ± enfortumab vedotin before radical cystectomy in patients who are not eligible for cisplatin, followed by an adjuvant phase;
- EV-304 – see EV-303, but for patients suitable for cisplatin, pembrolizumab + enfortumab vedotin versus standard CT. "But even here, after standard chemotherapy, we don't have adjuvant treatment, which will probably be a minor problem in the final evaluation of these studies, because adjuvant immunotherapy is now the standard."
- VOLGA – triple combination of durvalumab + tremelimumab + enfortumab vedotin versus durvalumab + enfortumab vedotin versus cystectomy and adjuvant therapy – i.e., one group does not undergo cystectomy, the other does.
- ENERGIZE – NAC + nivolumab ± linrodostat mesylate, then cystectomy and nivolumab in the adjuvant phase.

"We know nivolumab from the adjuvant setting," he said, recalling the CheckMate 274 study.

"It is therefore important to remember that whenever you have a patient who has not yet received any neoadjuvant immunotherapy, they should receive it," said the speaker. He expressed the opinion that for cT2 tumors, discussion of the options within a multidisciplinary tumor board is necessary – he described this as good interdisciplinary practice.

Chemotherapy should be the standard for all patients who are "fit" for cisplatin. Currently, the new standard for patients suitable for cisplatin is the addition of durvalumab to CT. Immunotherapy alone is still only an experimental option. Outside the scope of MIBC, it can be added that in UTUC, in high-risk disease (e.g., from stage cT3), the role of neoadjuvant systemic therapy is being discussed, particularly in view of the high risk of micrometastatic involvement already at the time of diagnosis. In this context, neoadjuvant therapy is understood as a strategic tool for early intervention in systemic disease and achieving downstaging with prognostic significance.

Prof. Jonas Busch, MD.

"I am quite sure that we will see huge changes," Prof. Busch concluded.

The role of ctDNA

Biomarkers play an important role (not only) in oncology, and one of the important examination options is liquid biopsy – i.e., the ability to identify various components of body fluids, especially blood, such as circulating tumor cells, extracellular vesicles, or even cell-free DNA (cfDNA), which can be released into the bloodstream by several mechanisms, most often in connection with cell death. In patients with malignant tumors, the concentration rises from the usual < 10 ng/ml to > 1,000 ng/ml. **Dr. Brigida Anna Maiorano** from the San Raffaele Scientific Institute in Milan discussed this in more detail.[26]

As she stated, various studies have shown that specific genomic or epigenetic changes can be found in ctDNA, which make it possible to link it to the primary tumor. Liquid biopsy for ctDNA analysis is minimally invasive and easily repeatable, very useful in solid tumors for monitoring progression, identifying genetic changes, and is more representative of tumor heterogeneity compared to tissue biopsy. The methods used, droplet digital polymerase chain reaction (ddPCR) and next-generation sequencing (NGS), are relatively accurate. The main limitation of liquid biopsy analysis and its introduction into routine practice remains the amount of ctDNA released into the bloodstream, which is influenced by various preclinical and pathophysiological parameters.

Evidence of the benefits of liquid biopsy and ctDNA analysis in UC, especially MIBC, is growing. Various studies focus on the prognostic stratification of UC, the possibility of defining relapse by liquid biopsy or evaluating minimal residual disease that cannot be detected by current imaging tools, stratifying response or predicting resistance to treatment, but also using it for real-time evaluation during the course of the disease or to aid in decision-making about different lines of treatment within the continuum of care.[27]

Real-life example

The speaker shared a case study, which she introduced with the words, "how serial ctDNA monitoring can aid in treat-

ment decisions and response assessment and serve as a prognostic biomarker."

The case involved a 71-year-old woman with pT3N0M0 stage MIBC who underwent radical cystectomy, after which she was ctDNA negative. Approximately six months after surgery, she experienced unexplained weight loss with deterioration of her overall condition. CT scans were negative, but ctDNA concentrations began to rise and positron emission tomography showed progression. After another three months, ctDNA values were three times higher than baseline.

The patient entered a phase II clinical trial and began treatment with pembrolizumab. After starting treatment, ctDNA concentrations declined. After three months of pembrolizumab use, CT scan showed progression, but it was interpreted as pseudoprogression because ctDNA concentrations continued to decline. After another three months, pseudoprogression was confirmed on CT scan. CtDNA levels returned to zero.[28]

CtDNA in treatment decisions

In terms of biomarkers, there is growing evidence of the prognostic value of tumor mutation burden in UC. In MIBC, ctDNA has been shown to play a prognostic role in monitoring disease-free survival. Detection of ctDNA prior to cystectomy, in the minimal residual disease window, and in the surveillance window is prognostically associated with disease-free survival in patients with BC.

In the IMvigor010 study, the use of atezolizumab had a decisive impact on the survival of ctDNA-positive patients, and therefore the IMvigor011 study was designed as a biomarker-driven study.[29,30] In this context, Dr. Maiorano divided the studies into two generations—she designated those that use ctDNA to guide clinical decisions about the use of adjuvant therapy (such as IMvigor011) as the new generation.

Dr. Brigida Anna Maiorano

The ctDNA analysis in IMvigor010 confirmed that adjuvant atezolizumab is not necessary in patients with negative ctDNA, but in those with positive ctDNA, adjuvant therapy improved progression-free survival compared to observation. "That is why the IMvigor011 study has a new design," said the speaker. "Patients with negative ctDNA are therefore only monitored, but patients with positive ctDNA are randomized to receive adjuvant atezolizumab versus placebo."

In other words, ctDNA could be useful for improving the prognostic stratification of patients in bladder-sparing approaches or in deciding which patients should continue maintenance therapy or undergo treatment intensification.

According to Dr. Maiorano, it could be beneficial for the personalized treatment of patients with UC in the future if a molecular biologist were also part of multidisciplinary tumor boards. She added that before introducing ctDNA analysis into routine clinical practice, it is necessary to standardize the procedure and also to know the economic costs. "I think that in the future we will use ctDNA analysis more and more, both for invasive and metastatic tumors," she concluded.

How to improve care for patients with UC?

In the last lecture of the section, **Dr. Jorge Dias** from Centro Hospitalar de Vila Nova de Gaia in Espinho, Portugal, pointed out the difficulty of the journey of a patient with urothelial carcinoma towards diagnosis and treatment.[31] He discussed the difference between the ideal world and reality in clinical practice.

"We have guidelines from all societies, whether it's the European Association of Urology (EAU), the American Urological Association, the National Comprehensive Cancer Network, or the European Society for Medical Oncology, but the reality is sometimes very different," he said. Problems include delays in diagnosis and difficult access to treatment, which reflect the impact of socioeconomic differences. "We know that 75-90% of bladder cancer cases present with macrohematuria. But only 10-15% of diagnostic examinations of the inflammatory urinary tract reveal tumors. So it is still difficult to detect, especially in women." The delay may be due to factors on the part of the patient (low awareness of the disease, lower socioeconomic status associated with an unhealthy lifestyle, smoking, less frequent screening for cancer, limited access to healthcare) and healthcare professionals (incorrect diagnosis prior to BC diagnosis, failure to refer to a urologist, long waiting times – 6 to 12 months is too long for BC).

According to the speaker, the World Coalition of Bladder Cancer Patients reports that 57% of patients were misdiagnosed before BC was detected.

Low use of NAC and delays in cystectomy

Although NAC increases five-year OS by up to 8%, its overall global use is only 17% (!) according to data from a meta-analysis of 13 studies (n = 35,738) published in 2019. 32 There are geographical differences – for example, Japan and Sweden

Could you summarize the session dedicated to muscle-invasive bladder cancer? What were the key points discussed regarding diagnosis, treatment, and the organization of care?
Mohla byste shrnout sekci věnovanou svalovinu invadujícímu karcinomu močového měchýře? Jaká klíčová témata byla probírána v oblasti diagnostiky, léčby a organizace péče?
(Dr. Brigida Anna Maiorano)
https://www.remedia.cz/z-novinek/bladder-cancer-master-class-vse-co-se-deje-kolem-karcinomu-mocoveho-mechyre/#maiorano

have good data, while the Netherlands and Canada have low numbers. Reasons for not using NAC include advanced age, poorer ECOG PS, and a high burden of comorbidities, but also differences in healthcare systems, recommendations, and when the patient is referred to oncology. For example, the EAU recommends a maximum interval of three months between BC diagnosis and cystectomy. However, most of the 19 studies (n = 17,232) included in the 2019 meta-analysis and systematic review reported delays—reasons included patient condition (not "fit" for surgery, i.e., need to optimize comorbidities), need for a second opinion, socioeconomic factors (access to poorly equipped hospitals, the need to be referred to other hospitals), and, more often, lower education.33 "And let's be honest, cystectomy is no walk in the park. It's a very aggressive operation," the speaker noted, adding that mortality after radical cystectomy can still be as high as 3.2% within 30 days and up to 8% within 90 days, with a rehospitalization rate of 25% within 30 days and a complication rate of 30-40%. Minimally invasive surgery (laparoscopic or robotic) has reduced the need for transfusions and shortened hospital stays, but has made no difference in the rate of complications within 90 days or the time to recurrence. The number of surgeries performed at a given facility also plays a role. According to the EAU, at least 20 surgeries per year in each hospital are needed to optimize the complication rate. "And if we perform these surgeries in large centers, we also know that we will be able to provide more comprehensive care to patients," said Dr. Dias, pointing out that in colorectal cancer, a multimodal prehabilitation program—including nutrition, physical activity, psychological support, and smoking cessation—has already been shown to have a beneficial effect on reducing the incidence of complications. Certain results for this approach have also been seen in BC, and a study on this topic, ENHANCE, is currently underway in the Netherlands.[34] It is investigating the link between socioeconomic disadvantages, race, BC stage, diagnosis, and poorer survival prospects.

What can be done about this?

According to Dr. Dias, when it comes to delayed diagnosis, it is necessary to build on successful national public health awareness campaigns, improve professional knowledge in primary care, and ensure that diagnosis is rapid. "These patients cannot wait six months to go to the hospital. They must be referred as a priority, and cystoscopy should be performed as quickly as possible." He emphasized the importance of the role of a multidisciplinary tumor board from the very beginning. "Some studies show that re-evaluation of radiology and pathology can change the treatment plan in up to 44% of these patients." Patients with higher comorbidity indices should be treated in centers with high numbers of procedures. Treatment procedures must also be fast. It is also important to provide patients with accessible information in understandable language (most likely in the form of consultations with oncology nurses and assistance from patient organizations).

"Sometimes patients get lost in the amount of information and are afraid of what will happen," explained the speaker. The aforementioned socioeconomic factors must also be kept in mind. Teamwork is crucial in all aspects affecting UC patients—that is, the joint efforts of urologists, oncologists, nurses, physical therapists, psychologists, and possibly social workers.

Key points

- BC and UTUC are clinically and biologically different entities (risk factors, age, spectrum of mutations), which is reflected in different staging, prognosis, and treatment algorithms.
- Staging is primarily performed using imaging methods: for MIBC, multiparametric MR with VI-RADS is preferred (good accuracy for detecting muscle invasion), and for UTUC, CT urography; nevertheless, the stage, i.e., the depth of invasion, is often underestimated, especially in ureteral tumors.
- The variability of pathology can lead to incorrect stratification; centralized review would be beneficial. Percutaneous biopsy is under discussion (safety proven, indications and role are being defined).
- In MIBC, high-quality TURB is essential; there is no robust biomarker for predicting the benefit of neoadjuvant therapy, so practice is based on optimal local control and cisplatin neoadjuvant chemotherapy in eligible patients.
- UTUC requires a choice between radical and conservative/endoscopic procedures, taking into account the risk; decision-making is limited by renal reserve, and in older comorbide patients, the risk of dialysis may be prognostically dominant.
- In UTUC, adjuvant systemic therapy is being discussed for high-risk disease (e.g., from stage cT3), particularly with regard to the risk of micrometastatic involvement and the possibility of downstaging; there is no clear standard yet.
- Of the bladder-sparing approaches, trimodal therapy (TMT: maximal TURB + CT + CRT) has the strongest evidence in carefully selected patients (typically unifocal cT2, without hydronephrosis and carcinoma in situ, complete TURB) with salvage cystectomy in case of inadequate response.
- Data comparing radical cystectomy and TMT are heterogeneous; with strict selection, TMT may be oncologically comparable to surgical treatment at the cost of intensive lifelong monitoring and the risk of chronic radiation toxicity.
- Neoadjuvant treatment for MIBC is evolving: the results of the NIAGARA study support the addition of durvalumab to cisplatin chemotherapy in eligible patients, and this approach is becoming the new standard of perioperative treatment; neoadjuvant immunotherapy alone remains reserved for clinical trials.
- Ongoing studies of ADC and immunotherapy combinations (EV-303/304, VOLGA, ENERGIZE) may change treatment standards in the future; questions remain about optimal adjuvant treatment and the risk of overtreatment in patients with very good response.
- CtDNA is emerging as a tool for detecting minimal residual disease, early relapse, and biomarker-guided adjuvant treatment (e.g., IMvigor011); limitations remain in preanalytical factors and low ctDNA release in some patients.
- The patient pathway remains a weak point in care: low use of neoadjuvant therapy and delays in cystectomy; early multidisciplinary discussion, centralization of procedures, and prehabilitation are key.

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Modern treatment brings hope for better outcomes in patients with metastatic urothelial carcinoma – in clinical trials and in real-world practice

What is the significance of eligibility criteria for platinum-based chemotherapy today? What is known about first-line maintenance therapy for metastatic urothelial carcinoma? Why is it important to sequence the treatment of metastatic urothelial carcinoma and what does this entail? Do data from clinical trials correspond with data from real-world practice? What is current research focusing on? These topics were addressed in Section IV of the Bladder Cancer Master Class colloquium's professional program.

Eligibility criteria for patients with urothelial tumors for systemic treatment

The incidence of urothelial carcinoma (UC) in the European Union, including the Czech Republic, is rising. However, mortality remains relatively stable. The typical average age for this diagnosis in the Czech Republic is around 70 years. Similar data apply to the 18 countries represented by the foreign guests at the colloquium. **Prof. Alexandr Poprach, MD, PhD**, from the Comprehensive Cancer Care Clinic at the Masaryk Memorial Cancer Institute in Brno, began his lecture with this information.

Gupta versus Galsky criteria

Patients with UC, and especially with metastatic urothelial carcinoma (mUC), are frail. However, the speaker admitted that in his practice he does not have the time to use frailty questionnaires. He identified the eligibility criteria for platinum-based chemotherapy (CT) as a useful tool to help him decide on treatment. These criteria also take into account the very strong recommendations of the European Society for Medical Oncology (ESMO) from 2022 and 2024 for the treatment of UC, which are in line with the Czech recommendations in the Blue Book.[2,3] The patient's overall health, comorbidities, compliance, motivation for treatment, etc. are also important.

Prof. MUDr. Alexandr Poprach, Ph.D.

There are two sets of eligibility criteria for platinum-based CT – according to Gupta and according to Galsky.[4,5] The speaker himself says that he uses Galsky criteria in his clinical practice. He added his opinion that there is no doubt about the importance of indicators such as performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG PS), New York Heart Association (NYHA) functional class, and neuropathy, which include both criteria, but he considers hearing loss and renal insufficiency to be topics for discussion – Gupta criteria include creatinine clearance (CrCl) < 30 ml/min and do not mention hearing loss, while Galsky criteria include CrCl < 60 ml/min and hearing loss.

In this context, the speaker recalled the link between the severity of renal insufficiency and mortality and morbidity. He described CrCl values in the range of 40–60 ml/min as a gray area and a major challenge. He also touched on cisplatin-induced nephrotoxicity and pointed out that it may not be irreversible – it can be prevented by hydration and correction of hypomagnesemia with magnesium supplementation. Some strategies to mitigate nephrotoxicity emerged from the comprehensive work of Jiang et al.[6]

Hearing loss due to ototoxicity is a particular risk with cisplatin.[7] However, the speaker emphasized the need to consider what is truly important for the patient. "When you have a patient in the adjuvant or metastatic stage, I think it is necessary to discuss this potential toxicity with the patient in terms of treatment effects and survival; the role of this toxicity in the adjuvant indication is different from that in the palliative indication," said the speaker on the criterion of hearing loss.

In the current era of immunotherapy (IT) and antibody-drug conjugates (ADCs), the effects of cisplatin versus carboplatin are also being compared, as their effects on the immune system differ. The position of carboplatin is being reevaluated—a number of studies have shown that cisplatin does not provide a significant benefit in terms of treatment response and survival in mUC compared to carboplatin.[8,9] However, based on his experience, the speaker considers cisplatin to be more effective, especially in the era of modern immunotherapy.

EVITA criteria

The above-mentioned ESMO recommendations mention, among other things, the combination of pembrolizumab and enfortumab vedotin for the treatment of previously untreated patients with advanced or metastatic UC (stage IV). After progression during treatment with this combination, or in individuals for whom the combination is not suitable or is contraindicated, platinum-based CT should be administered. At the time of the colloquium, this option had not been approved in the Czech Republic. It offers a long duration of response and, in some patients, is capable of inducing long-term remission, but it has "certain specific toxicity for the patient," as the speaker said, and "financial toxicity," for example, according to data from the United States and Germany.

The EVITA criteria (EV-ineligible criteria) exist to determine eligibility for this combination, although they have not yet been validated. They include the following points:

- glycated hemoglobin value ≥ 8%,
- sensory or motor neuropathy grade ≥ 2,
- any corneal or retinal abnormality,
- CrCl or glomerular filtration rate ≤ 45 ml/min,
- ECOG PS ≥ 2.

The speaker stated that he is not in favor of these criteria, because according to them, a significant proportion of patients would not be suitable for pembrolizumab with enfortumab vedotin – given the expected toxicity profile, which includes neuropathy and skin diseases, people with comorbidities, aggressive tumors, uncontrolled or undiagnosed diabetes, alcohol abuse, etc. are considered unsuitable.[10] "The criteria are a tool, not a dogma," the speaker pointed out, explaining how the EVITA criteria are viewed in the Czech Republic.

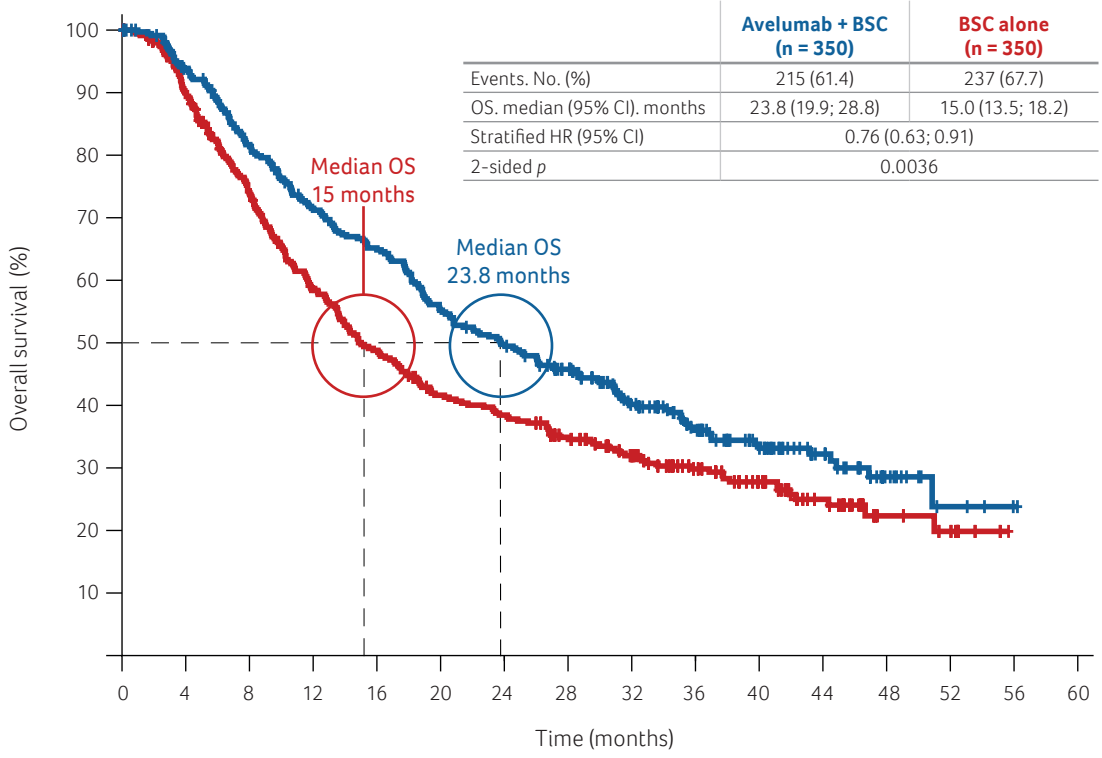
He concluded his presentation by emphasizing that the basis is the individualization of treatment and its adaptation to specific patients according to the subtype of their malignancy, metastases, extent of the disease, comorbidities, and the specifics of various treatment options.

The role of maintenance therapy in metastatic urothelial carcinoma

The fact that "one size does not fit all," i.e., that treatment needs to be individualized and that various options are available in the first line of mUC treatment, was also highlighted by **Prof. Álvaro Pinto, MD, PhD**, from Hospital Universitario La Paz in Madrid, Spain.[11]

There is currently a standard maintenance treatment that improves overall survival (OS), as demonstrated by the JAVELIN Bladder 100 study: patients who achieved disease control with first-line platinum-based chemotherapy and were randomized to receive avelumab plus best supportive care (BSC), achieved a significant improvement in OS compared to the BSC-only group (according to data from 2023, OS was 23.8 months versus 15 months) (**Graph 1**).[12,13] This was the first study to improve OS in this disease, including first-line platinum-based therapy. "The maintenance therapy strategy proved to be the most successful," said the speaker.

Furthermore, analysis of the JAVELIN Bladder study shows that the administration of avelumab to patients has no negative impact on the body. "So adding a substance that improves survival does not affect quality of life and safety pro-



GRAPH 1 Kaplan–Meier estimate of overall survival in the entire population in the JAVELIN Bladder 100 study

BSC – best supportive care; CI – confidence interval; HR – hazard ratio; No – number of patients; OS – overall survival; p – statistical significance value

Source: adapted from citation 13

Prof. Álvaro Pinto, MD, PhD

file," Prof. Pinto emphasized. "We are not adding any significant toxicity, and the rate of immune-related adverse events is really low, and they are usually low-grade adverse events."

The subgroup analysis showed the benefit of maintenance treatment with avelumab regardless of age, body mass index (BMI), and regardless of the choice of previous CT (cisplatin/carboplatin) and response to CT. "In cases of stable disease, we find partial response or complete response in all of these subgroups."

How to choose the right first-line treatment?

"It is good that we have various options for first-line treatment, but we have to choose, as this may be the last line of treatment the patient will undergo," Prof. Pinto pointed out. He reminded that sequential treatment for bladder cancer (BC) is not as successful as for prostate cancer because patients deteriorate with each progression they experience.

In various clinical trials and real-world studies, approximately 80% of patients achieve a response or at least stabilization of the disease after platinum-based CT, which means they are eligible for first-line maintenance treatment with avelumab. Since real-world studies may be biased, for example, in BC they suggest a lower rate of administration of first-line systemic therapy, the presenter recommended looking at clinical studies in which the control group was platinum-based CT.

For example, the addition of nivolumab to cisplatin-gemcitabine-based CT did not significantly slow disease progression.[14] Approximately 10% of patients will progress despite first-line CT. This was also shown in the EV-302/KEYNOTE-A39 study with the combination of pembrolizumab + enfortumab vedotin.[15] "The rate of disease progression is mostly the same, around 10%, whether you administer pembrolizumab + enfortumab vedotin or chemotherapy," noted Prof. Pinto. However, this means that 85–90% of patients will at least stabilize their disease and therefore be candidates for maintenance therapy with avelumab.

According to data published at the ESMO Congress 2024, patients receiving maintenance therapy with avelumab can achieve a long-term response. In the study, approximately 1 in 3 patients took avelumab for at least one year and approximately 1 in 5 patients took it for at least two years.

Toxicity of first-line treatment – an obstacle for avelumab

However, caution is needed due to the excessive toxicity of some treatment options, which may prevent maintenance therapy with avelumab. In the EV-302/KEYNOTE-A39 study, 35% of patients permanently discontinued treatment with this combination due to treatment-related adverse events and will therefore not be able to receive subsequent anticancer therapy. According to the speaker, the most concerning side effects are skin reactions and neuropathy—15% of patients treated with the pembrolizumab + enfortumab vedotin combination experience grade 3 or 4 skin toxicity, which is also difficult to manage, unpredictable, and often irreversible. In 42% of patients who experience high-grade skin reactions, complete resolution does not occur. Residual neuropathy persists in 89% of patients who have experienced it.

Prof. Pinto clarified that when choosing first-line treatment, it is necessary to find a balance between comorbidities, individualization of treatment, and what can be expected in terms of its efficacy and toxicity. He emphasized the need to listen to patients, especially in the case of mostly incurable patients with metastatic urothelial carcinoma.

"Do we listen to our patients, or do we just choose the first-line treatment and say, 'This is the best for you, it's okay'?" he asked rhetorically, followed by data from a clinical study comparing the preferences of oncologists versus patients at the start of first-line mUC treatment. Oncologists valued OS the most, but patients valued the treatment plan and fewer side effects.[16] "If you want the patient to choose one option, you know how to guide them to do so. But the patient must at least be informed about the different treatment options, what they can expect in terms of safety and efficacy, and then we need to agree with them if possible."

He summarized that there are three different options in the first line, and currently there is no data on which one is better because they have not been directly compared. Treatment should therefore be individualized based on clinical factors, expected toxicity, comorbidities, patient preferences, and availability. "And finally, I would like to quote a sentence that I really like: 'For every complex problem, there is a clear, simple, and wrong answer.' There is no single option for all our patients," concluded Prof. Pinto.

Maintenance therapy in real-world practice – four studies including Czech data

Evidence from real-world practice was presented by **Assoc. Prof. Jindřich Kopecký, MD, PhD,** from the Department of Oncology and Radiotherapy of Faculty of Medicine of Charles University and University Hospital Hradec Králové.[17] Like the previous speakers, he reminded the audience that UC remains a disease with a poor prognosis. The five-year survival rate is worse than for renal carcinoma or prostate cancer.18 However, modern therapies using immune checkpoint inhibitors (ICI) and ADC have improved the survival of patients with UC. "The last ten years have brought hope for our patients, but we are still not where we want to be, and perhaps we never will be. But every step, every improvement is good," he noted. The concept of maintenance therapy, i.e., the effort to maintain a long-term response with less toxic treatment known from other oncological diagnoses, is new in UC. It has become the new standard, but the question is how it is applied in practice.

When gathering evidence, data from clinical trials and real-world practice are important because they provide different information. Real-world data are now available on the benefits of maintenance therapy with avelumab in the first line of BC treatment. Worldwide, it has been used and properly registered in over 5,000 patients with locally advanced UC or mUC, including over 2,000 in Europe (including 107 in the Czech Republic).

The speaker focused on four studies – AVENANCE (France), READY (Italy), PATRIOT-II (USA), and data from the Czech registry (CZECHREG) – and specifically mentioned data from his workplace (UN HK).[17,19–22] The inclusion criteria and design are similar in all of them – participants had to have previously received CHT with a certain response or at least stabilization. He emphasized three aspects:

1. the proportion of cisplatin versus carboplatin in CT regimens: in the AVENANCE study, the largest of the four, only 28% used cisplatin, in the READY study 44.4%, 62.5% in the PATRIOT-II study, and 51% in the CZECHREG study (71% directly at UN HK);
2. UC localization: according to the speaker, upper tract urothelial carcinoma (UTUC) usually accounts for 20–30% of cases in clinical studies and 70–80% are BC, which was consistent with the AVENANCE and READY studies; these data are not available in the CZECHREG registry, while at UN HK the proportion of patients with UTUC was high (41% versus 59%);
3. Presence of visceral metastases: in the JAVELIN Bladder study, these occurred in 50% of patients, which was consistent with the patient group at UN HK (53%), but in AVENANCE and READY, the proportion was much higher (85% and 69.2%, respectively).

"It is important to keep this in mind when describing or interpreting data from real-world practice and not to compare them with each other," noted the speaker.

Despite these differences in clinical characteristics, however, the median time to progression after starting treatment with avelumab is quite similar, around two years, as in JAVELIN. Progression-free survival (PFS) is short, and the longest median PFS was in the Czech Republic (11 months in CZECHREG and 14 months in UN HK), as the speaker reflected, "perhaps because we had fewer patients with visceral metastases."

One-year OS in real-world data ranged from 67% (AVENANCE) to 87% (UN HK; 79.3% in CZECHREG), while two-year OS was significantly lower in both studies – only half of the patients who survived the first year survived the second. Overall survival after one year and median OS are consistent with the JAVELIN Bladder study.

According to the speaker, it would be highly desirable to have a tool to help identify patients who will not benefit from avelumab in two years. "Because these patients might be candidates for other, more aggressive treatments. However, I would like to have such data," he added.

According to him, toxicity in a real-world setting is underestimated.

What comes after avelumab, or is there still room for improvement?

Real-world data can provide information about subsequent therapy that "we don't usually get from clinical trials because they are not statistically powerful enough or no longer collect data from subsequent therapy," added the speaker. In his words, "there are signs" that after avelumab, there is still room for another line of treatment – ADC and enfortumab vedotin. A post hoc analysis of the AVENANCE study shows that the efficacy of ADC is not affected by previous lines of treatment. The median OS was 40.8 months.[23] The speaker noted that this is a retrospective study and many of the results are biased, but even real-world data show that further treatment after avelumab is still quite effective, with a response duration of usually around one year. He agreed with Prof. Pinto that "even a one-year extension of survival is not bad, and everything has its price."

Sad survival in the Czech Republic

Finally, Assoc. Prof. Kopecký addressed the problems faced in the treatment of UC patients in the Czech Republic. Mortality is high (in 2022, the incidence of BC was 2,352 people, with 935 patients dying from it), five-year survival has increased from 62% to 70%, and according to data from the National Cancer Registry, the Hradec Králové Region has the worst five-year survival rate in the Czech Republic.[24] According to the speaker, there are several explanations for this. He highlighted the fact that in the Czech Republic, there is a delay in referring patients from other cities for treatment to large centers where they can receive a full range of innovative therapies.

In addition to the comprehensive center in Hradec Králové, there are four oncology centers in the Hradec Králové Region (Jičín, Trutnov, Náchod, Rychnov nad Kněžnou) that can provide systemic treatment, but not innovative treatment. "The most problematic issue is the availability of care, especially for older patients with comorbidities who are unable or should not drive after receiving oncological treatment, because we administer drugs during chemotherapy that can impair their concentration," warned Assoc. Prof. Kopecký. "Getting to us by public transport means spending many hours just traveling and waiting for treatment. That's the reality, and it bothers us," added Assoc. Prof. Kopecký.

Experts from across the region—urologists and oncologists—are working to improve the situation by sharing responsibility for preventing delays (performing CT scans, chemotherapy, etc.). "We have super innovative treatments, but if they don't reach the patient, there's no point in having them," said the speaker. "We still have room for improvement, and we hope to get better."

Doc. MUDr. Jindřich Kopecký, Ph.D.

In conclusion, he noted that "the best treatment for metastatic disease is, of course, prevention of metastasis," and expressed hope that "with new therapies, if the patients come to our center, they can receive it and will not develop metastatic disease."

New real-world data from Croatia

Assoc. Prof. Dr. Jure Murgić from Klinički bolnički centar Sestre milosrdnice in Zagreb shared insights from Croatian practice.[25]

The study included 12 Croatian centers, two of which are in Zagreb. In line with previous speakers, he confirmed that oncology care is also provided in smaller hospitals and explained that the Uro-Oncology Cooperative Group was formed to analyze real-world data. One of its projects, in the words of the speaker, is to "determine the results of treatment with avelumab in real-world practice, especially now when a very effective second-line therapy is available, and to present key clinical factors for patients." During the colloquium, he presented data from the fourth analysis of the avelumab treatment study, collected from July 2022 to March 2025.

The number of patients with UC in the 12 centers mentioned is growing—as of March 4, 2025, there were 128 people. Most had a good ECOG PS (0 in 64% of cases, 1 in 35% of cases), and 72% suffered from BC. Smokers accounted for 63% of cases. 51% had previously been treated for localized UC. Almost three-quarters (73%) were men, the median age was 69 years, 39% of subjects underwent radical surgery, only 9% of patients received neoadjuvant chemotherapy, and 51% had metastases at the time of diagnosis (only visceral 37%, only in lymph nodes 27%, only in bones 8%, with severe metastatic burden [≥3 sites] 17%). CrCl ≥ 60 ml/min was present in 64%. Gemcitabine-cisplatin was the most frequently chosen first-line CT regimen in 62% of cases (followed by gemcitabine-carboplatin in 26% of cases and ddMVAC in 12% of cases).

The plan was to complete four cycles of induction CT and then switch to maintenance treatment with avelumab in patients who responded; most patients (72%) underwent these four cycles of CT. Of the total number of patients who had disease control, 5% achieved a complete response, 58% achieved a partial response, and 36% achieved disease stabilization. The median time from the end of CT to the administration of avelumab was 6 weeks (range 2–14). Comprehensive genomic profiling of the primary tumor was available for 41% (52 of 128) of individuals. Analysis of gene mutation status and clinical responses to avelumab is ongoing and, according to the presenter, will be presented at future conferences.

The median follow-up time was 19 months (15–40), the median duration of avelumab treatment was 7 months (0–30), 42% were receiving treatment at the time of the colloquium, and 57% (73 individuals – 65 due to progression, 8 due to adverse effects) had discontinued therapy. Only 5% were unable to undergo radiological examination.

The overall response rate to avelumab (complete response + partial response) reached 14%. Clinical benefit or disease control was observed in 53% of patients.

"We observed a relatively large number of patients with an exceptional response to avelumab with a treatment duration of more than two years," said the speaker. The median PFS from the start of avelumab treatment was 14 months, with 51% achieving 12-month PFS and 68 cases of progression. The median OS from the start of avelumab treatment was 26 months, with 70% achieving 12-month OS and 45 patients dying. The median PFS from the start of CT was 22 months, with 60% achieving 12-month PFS and a median OS of 49 months (12-month OS 80%, 24-month OS 56%, 36-month OS 52%). "I think this shows a kind of preliminary selection of patients who are able to come to our centers for treatment. We believe that at least 30% of patients with metastases should be treated with chemotherapy, and most of them would switch to maintenance treatment with avelumab," said the presenter.

Immune-related adverse events associated with avelumab administration occurred in 23% of patients, mostly grade 2 (grade 3 treatment-related adverse events accounted for 6%, grade 4 for 2%), with the most common being hypothyroidism, thrombocytopenia, and colitis. The worst were grade 4 myasthenia-like syndrome in one patient and grade 3 hepatic toxicity in two patients. Eight percent of patients permanently discontinued treatment due to adverse effects.

After progression on avelumab, 41% (27 of 65 patients) received further active treatment: 15 patients received enfortumab vedotin, three patients received pemigatinib, two patients received trastuzumab deruxtecan (TDx), and seven patients received palliative taxane-based chemotherapy.

"Treatment with pemigatinib and TDx was based on our special Gratia program, which was launched five years ago and under which we can administer drugs approved by the European Medicines Agency (EMA) based on comprehensive genome profiling," the speaker explained.

In a group of 15 patients who received enfortumab vedotin as second-line treatment, median PFS and OS have not yet been reached, four patients experienced disease progression, and three patients died.

The speaker gave an example of a patient who underwent comprehensive genomic profiling, which revealed a high tumor mutation burden (19 mut/Mb), which may explain why he has now been on avelumab for two years with a complete response. "This patient has *ERBB2* amplification, which qualifies him for HER2-targeted therapy in the next line of treatment, probably after enfortumab vedotin," added the speaker.

He concluded that, in his opinion, the OS in the study was comparable to other studies from real-world practice. The high proportion of patients suitable for cisplatin suggests a certain selection of patients. "Overall survival is therefore very long, with median OS not reached when patients were treated with enfortumab vedotin. However, these data are not mature," he noted.

Finally, he called for comprehensive genomic profiling, as this opens up further possible lines of treatment for many patients after avelumab (mostly targeting human epidermal growth factor receptor 2 [HER2] or the fibroblast growth factor receptor [FGFR]).

Sequential treatment for bladder cancer

Sequential treatment, which is now also possible for this diagnosis, is key to maximizing OS while maintaining quality of life in UC. "This was not the case in the past, because the only effective option we had was platinum-based chemotherapy. So we used everything we had available as a first-line treatment," said **Assoc. Prof. Jakub Kucharz, MD, PhD**, from the Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie in Poland.26 "The data confirm the effectiveness of sequential treatment in routine clinical practice, but it is necessary to select the right patient for the right approach, or rather the right approach for the right patient. Personalized treatment that takes into account prognostic factors, toxicity profile, and patient preferences is the cornerstone of optimal treatment," he said. He focused his lecture on treatment sequencing.

He stated that tumor biology is important for the correct choice of sequential therapy. However, it is not a good idea to consider it in patients with metastatic tumors, malignancies with very aggressive behavior and rapid progression. The patient must be in good overall condition with a good ECOG PS and adequate organ function. The advantages of sequential treatment generally include maximization of OS, as the effects of several active substances administered over time are cumulative (see, for example, colorectal cancer, renal cancer, or breast cancer). Other advantages include better tolerability, as less intensive regimens are used in sequences, as well as greater scope for personalization of treatment, as the approach is tailored to response, toxicity, and clinical scenario, and lower toxicity. According to the speaker, the guidelines of the Polish Society of Clinical Oncology emphasize the clinical aspect—the initial decision on the treatment of metastatic disease should be based on contraindications, the patient's preferences to minimize toxicity or maximize results, symptoms, the presence of liver metastases, the need for a rapid treatment response, etc.[27]

Options in first-line treatment

Platinum-based CT is used in first-line mUC. Carboplatin is chosen for patients who are not suitable for cisplatin. "We know from the data that cisplatin appears to be slightly more effective and is generally preferred, and I really like the split-dose regimens because they allow us to use cisplatin," said Assoc. Prof. Kucharz. In maintenance therapy, immunotherapy is initiated after disease control is achieved with chemotherapy, and according to the JAVELIN Bladder 100 study, the current standard is avelumab in patients who are both suitable and unsuitable for cisplatin. "In my opinion, it is extremely important, as Associate Professor Kopecký mentioned, that we work with data that provides us with certainty of results," he said, referring to the JAVELIN Bladder and AVENANCE studies.

Various combinations of CT + immunotherapy in the first line in different studies did not have consistent results in PFS and OS indicators – some were positive, others negative. The IMvigor130 study demonstrated the role of cisplatin – in patients who received carboplatin, atezolizumab had no benefit, while in the cisplatin group, there were some signs of efficacy.[28] Conversely, in the CheckMate 901 study, where there was no carboplatin in the platinum-based CT + nivolumab combination arm, both PFS and OS were positive.[29]

"If we had observed synergy between chemotherapy and ICI from the outset, we would have had fewer patients with progressive disease as a first response," he added.

The combination of ADC + immunotherapy, specifically pembrolizumab + enfortumab vedotin, was successful in the EV-302/KEYNOTE-A39 study – patients received enfortumab vedotin throughout the study and pembrolizumab for a maximum of two years.[30] Median PFS and OS were almost double in the arm treated with this combination than in the arm receiving CT alone. According to the speaker, PFS was influenced by the administration of enfortumab vedotin until progression, while OS was influenced by the fact that only 30% of patients in the CT-only arm received maintenance therapy. Peripheral neuropathy may change another treatment option after the pembrolizumab + enfortumab vedotin combination.

What do real-world data say about the pembrolizumab + enfortumab vedotin combination? The speaker highlighted a study from the Mayo Clinic involving 120 patients (98 with mUC, 22 with locally advanced UC), in which patients achieved the same response and PFS as in the EV-302/KEYNOTE-A39 study, but with a short OS (25 months). "If you look at the concept of sequential treatment and overall survival is so low, it means that something is happening after progression," said Assoc. Prof. Kucharz. "I think it may be poor overall condition or the absence of an effective agent that can be used. So it seems that second-line treatment is not effective in these patients, or they are not in good enough condition to undergo further treatment," he added, noting that although the study was small, the lower limit of the confidence interval (CI) was 10 months shorter than in the EV-302/KEYNOTE-A39 study.

What to do after first-line treatment failure?

If CT fails in a patient who has not yet received immunotherapy, immunotherapy (pembrolizumab, according to a 2017 study) is used.[31]

If CT + immunotherapy fails, enfortumab vedotin can be used, according to the EV-301 study. "And we know that this is a highly effective approach with a 40% response rate in patients who have already undergone intensive treatment," noted the speaker. In real-world practice, the UNITE database showed the same results in patients receiving maintenance therapy as in the EV-301 study.

How to proceed with FGFR mutation

For patients with FGFR mutation, erdafitinib, which has proven itself in the THOR study, is reimbursed.[32] It represents a possible third-line treatment for them. The speaker described it as a very good option, but one where specific toxicity, especially ocular toxicity, needs to be kept in mind.

According to the analysis, enfortumab vedotin and erdafitinib are better administered in sequence, although it was not clear which of the two should be chosen first.[33]

According to expert opinion, there is room for continuing CT after temporary progression while using enfortumab vedotin.

Combination therapy studies in UC: what's new?

Of patients with newly diagnosed advanced or metastatic UC, only 48% receive first-line treatment, and less than half of those patients progress to each subsequent line of treatment. "That is why we must focus primarily on first-line treatment, because most patients have a chance to receive it," said **Prof. Dr. med. Friedemann Zengerling** from the Universitätsklinikum Ulm.[34] In his lecture, he focused on new data on combinations of established drugs.

Immunotherapy + immunotherapy

According to the speaker, the fight between ICIs and tumors resembles David and Goliath. No more than 30% of patients respond to immunotherapy as monotherapy. Immunotherapy options are often combined into dual inhibition of immune checkpoints. According to the speaker, this will not lead to improved outcomes for patients with UC. He mentioned the most significant studies for the combination of nivolumab + ipilimumab.[30,35] The combination of pembrolizumab + epacadostat (a molecule that restores higher T lymphocyte reactivity) also proved unsuccessful, with no difference observed during its use; only pembrolizumab had any effect. This concept was therefore abandoned, and although it was a large phase III study, it was terminated prematurely.

Immunotherapy + FGFR inhibitor

In a phase II study, the combination of erdafitinib with the anti-PD-1 antibody cetrelimab was investigated in FGFR-positive patients. The interim analysis yielded encouraging data, with an overall response rate of 68%, more than double that of erdafitinib monotherapy, but in a later analysis presented in an abstract at the congress, the results were not as striking, with a difference of only 10%. "In my opinion, this combination also has promising results, but it is not worth pursuing further," said the speaker.

Immunotherapy + chemotherapy

As for the combination of immunotherapy + CT, we currently have two approved regimens available, namely nivolumab + CT according to the Check-Mate 901 study and, for the treatment of muscle-invasive bladder cancer (MIBC), the newly approved durvalumab + CT according to the NIAGARA study. In this case, the speaker stated that the effects of immunotherapy + CT are limited, but the combination works quite well, especially with cisplatin.

Immunotherapy + ADC

However, the speaker sees the future more in the combination of immunotherapy + ADC. The mechanisms are similar to the combination of CT + immunotherapy, but the Fc fragment in the antibody molecule has specific immune effects—it activates immune cells, which could be a difference from CT. There is also synergy between ADC and ICI, which allows for a deeper response and the creation of systemic immune memory. The EV-302/KEYNOTE-A39 study (pembrolizumab + enfortumab vedotin) demonstrated a good response in patients. Overall survival with the combination of pembrolizumab + enfortumab vedotin was significantly better than with CT, with 20% more people achieving long-term OS.

Other ADCs are also being investigated. The combination of disitamab vedotin + ICI appears to be interesting – with pembrolizumab and toripalimab, the overall response rate is 75%, OS with the combination of disitamab vedotin + toripalimab is 33 months, and with the combination of disitamab vedotin + pembrolizumab, the median OS has not yet been reached.

Sacituzumab govitecan was tested in combination with avelumab as maintenance therapy in the JAVELIN Bladder Medley study, which followed on from JAVELIN Bladder 100.[36] The combination of sacituzumab govitecan + avelumab was shown to prolong PFS compared to avelumab monotherapy (12 versus 3 months). "The addition of sacituzumab govitecan therefore makes first-line maintenance therapy even more attractive," noted the presenter. OS data are numerically better but not yet mature, with median OS not yet reached. The objective response rate was also significantly better (24.3% versus 2.7%). The problem with sacituzumab govitecan is toxicity, which makes this approach less attractive due to treatment-related side effects. "The effect of avelumab has therefore been confirmed. The combination has good PFS. I think we need to wait for OS to make this therapy a real option for us," the presenter shared his opinion.

Can we go even further?

Research into triple combinations is also currently underway. ADC (sacituzumab govitecan) + ICI (nivolumab) + ICI (ipilimumab) did not prove successful—this regimen was very toxic and the study had to be terminated. Recruitment is currently underway for four studies to test ADC (enfortumab vedotin) + ADC (sacituzumab govitecan or sacituzumab tirumotecan or datopotamab deruxtecan) + ICI (pembrolizumab or zimberelimab).

Phase III studies VOLGA, KEYNOTE 905/EV-303, and KEYNOTE-B15/EV-304 focused on the treatment of MIBC are ongoing. For non-muscle-invasive BC (NMIBC), phase I to II studies are evaluating combinations of ADC + immunotherapy or, for example, ADC + BCG (Bacillus Calmette–Guérin), intravesical administration of sacituzumab tirumotekan, and other options.

"I think there are many promising regimens emerging," said the speaker. He added that there is a need for better patient selection and, last but not least, to translate updates of guidelines into clinical practice.

Key points

- Epidemiology of mUC: the incidence of UC in the EU/Czech Republic is increasing with relatively stable mortality; the typical age of around 70 years means a high proportion of frail patients and the need for pragmatic stratification already in the first line.
- Eligibility for platinum use as a key decision criterion: in practice, the Galsky versus Gupta criteria are mainly used; the "gray zone" of CrCl 40–60 ml/min and ototoxicity remain problematic, and the decision should always reflect the treatment goal and patient preference.
- Cisplatin versus carboplatin in the era of immunotherapy and ADC: some data suggest comparable results, but clinical experience often favors cisplatin; prevention of nephrotoxicity (hydration, Mg correction) and individualization of dosing are essential.
- Pembrolizumab + enfortumab vedotin and EVITA criteria: there are currently unvalidated "EV-ineligible" criteria, which are perceived in the Czech environment as a guide rather than a rigid selection criterion.
- Maintenance therapy with avelumab after first-line platinum-based CT is standard with prolonged OS: the JAVELIN Bladder 100 study demonstrated prolonged OS after achieving disease control with low immune-mediated toxicity and no deterioration in quality of life; the benefit was across subgroups, including cisplatin and carboplatin regimens.
- The choice of first-line treatment must preserve the possibility of maintenance therapy: excessive toxicity may prevent the initiation of avelumab treatment; with the combination of pembrolizumab + enfortumab vedotin, a higher rate of treatment discontinuation due to skin toxicity and peripheral neuropathy must be expected.
- Real-world practice confirms the efficacy of avelumab, but registries (AVENANCE, READY, PATRIOT-II, CZECHREG) are clinically heterogeneous, which limits direct comparisons; however, the results are consistent with the JAVELIN Bladder 100 study.
- After completion of maintenance treatment with avelumab, there is room for further systemic therapy: in patients with disease progression, ADC (enfortumab vedotin) or targeted therapy in the presence of FGFR mutation is used; treatment sequence planning and maintaining quality of life are key.
- Systemic limitations: the availability of innovative treatment depends on the accessibility of centers, and the logistics of regional care can significantly affect actual survival.
- The greatest potential in research lies in combinations of immunotherapy + ADC (including intensification of maintenance therapy) and patient selection using comprehensive genomic profiling (HER2, FGFR3).

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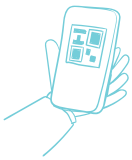

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(doc. MUDr. Hana Študentová, Ph.D.)

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Zkrácená informace o přípravku BAVENCIO® (avelumab)

Název přípravku a složení: BAVENCIO 20 mg/ml koncentrát pro infuzní roztok. Jeden ml koncentrátu obsahuje 20 mg avelumabu. Jedna injekční lahvička s 10 ml roztoku obsahuje 200 mg avelumabu; a další pomocné látky. **Indikace:** Přípravek BAVENCIO je indikován v monoterapii k léčbě dospělých pacientů s metastatickým karcinomem z Merkelových buněk (MCC). Přípravek Bavencio je indikován v monoterapii k udržovací léčbě první linie dospělých pacientů s lokálně pokročilým nebo metastazujícím uroteliálním karcinomem (UC), kteří jsou bez progrese po chemoterapii na bázi platiny. Přípravek BAVENCIO je v kombinaci s axitinibem indikován k první linii léčby dospělých pacientů s pokročilým renálním karcinomem (renal cell carcinoma, RCC). **Dávkování a způsob podání:** Doporučená dávka přípravku BAVENCIO v monoterapii je 800 mg podávaných intravenózně v průběhu 60 minut každé 2 týdny. Přípravek BAVENCIO se má podávat podle doporučeného plánu až do progrese onemocnění nebo nepřijatelné toxicity. Doporučená dávka přípravku BAVENCIO v kombinaci s axitinibem je 800 mg podávaných intravenózně v průběhu 60 minut každé 2 týdny a dávka axitinibu 5 mg užívaná perorálně dvakrát denně (v rozmezí 12 hodin) s jídlem nebo bez jídla až do progrese onemocnění nebo nepřijatelné toxicity. Pacienti musí být před prvními 4 infuzemi přípravku BAVENCIO premedikováni pomocí antihistaminika a paracetamolu. **Nežádoucí účinky:** Nejčastější nežádoucí účinky stupně ≥ 3 byly anemie (6,0 %), dyspnoe (3,9 %) a bolest břicha (3,0 %). Závažnými nežádoucími účinky byly nežádoucí reakce související s imunitou a reakce spojené s infuzí. Více informací v úplné verzi SPC. **Kontraindikace:** Hypersenzitivita na léčivou látku nebo na kteroukoli pomocnou látku přípravku. **Zvláštní upozornění:** Pečlivě sledovat reakce spojené s infuzí a nežádoucí účinky související s imunitou. **Fertilita, těhotenství a kojení:** Ženy ve fertilním věku mají být informovány, že při podávání avelumabu nemají otěhotnět a mají používat účinnou antikoncepci během léčby avelumabem a nejméně 1 měsíc po poslední dávce avelumabu. Podávání avelumabu v těhotenství se nedoporučuje, pokud klinický stav ženy léčbu avelumabem nevyžaduje. Kojícím ženám by mělo být doporučeno, aby nekojily během léčby a po dobu nejméně 1 měsíce po poslední dávce v důsledku možných závažných nežádoucích účinků na kojené novorozence. **Interakce:** Nejsou očekávány. **Uchovávání:** Uchovávejte v chladničce (2°C – 8°C). Chraňte před mrazem. Uchovávejte v původním obalu, aby byl přípravek chráněn před světlem. Z mikrobiologického hlediska má být přípravek po otevření naředěn a okamžitě podán v infuzi. **Velikost balení:** 10 ml koncentrátu v injekční lahvičce (sklo třídy I) s halobutylovou pryžovou zátkou a hliníkovým uzávěrem s odnímatelným plastovým víčkem. Balení obsahuje 1 injekční lahvičku. **Registrační číslo:** EU/1/17/1214/001. **Držitel rozhodnutí o registraci**: Merck Europe B.V., Amsterdam, Nizozemsko. **Datum poslední revize textu**: 11/2025. Lék je vydáván pouze na lékařský předpis. Přípravek je hrazen z prostředků veřejného zdravotního pojištění s omezením. S úhradou přípravku v konkrétní indikaci se seznamte na www.sukl.cz.

Před předepsáním léčivého přípravku se, prosím, seznamte s úplným zněním Souhrnu údajů o přípravku, které obdržíte na adrese společnosti Merck spol. s r.o.

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CESTA VAŠICH PACIENTŮ S mUC K PRODLOUŽENÍ OS

- NA ~30 MĚSÍCŮ mOS na základě dat ze studie JB100*,[1]
- NA 41,5 MĚSÍCE mOS na základě dat z klinické praxe‡,[2]

STANDARD OF CARE

GUIDELINES

ESMO, NCCN, EAU, Modrá kniha[3-6]

>5 000 PACIENTŮ RWE

STÁLE ROSTOUCÍ DATA Z KLINICKÉ PRAXE[8-44]

2× DELŠÍ KVALITNÍ ČAS

QoL DATA

bez toxicity a příznaků onemocnění během léčby přípravkem BAVENCIO + BSC vs. samotná BSC[7]

1L = první linie; **mOS** = median OS; **QoL** = quality of life; **OS** = celkové přežití;
BSC = nejlepší podpůrná péče; **2L** = druhá linie; **EV** = enfortumab vedotin; **ADC** = Antibody–Drug Conjugate

‡Při sekvenci JBR v 1L následované 2L EV/ADC[2]

*Klinická studie JAVELIN Bladder zahrnuje 1L chemoterapii na bázi platiny, po níž u pacientů bez progrese následuje 1L udržovací léčba přípravkem BAVENCIO; v rámci exploratorní post hoc analýzy bylo OS počítáno od začátku chemoterapie.