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Advances in genitourinary cancer treatment after the 2023 ESMO congress

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Abstract

The European Society of Medical Oncology (ESMO) congress is the leading oncological meeting during which the most essential clinical practice-changing data are unveiled. In this review, we would like to present the most clinically relevant data presented during the 2023 ESMO conference regarding genitourinary cancers, including the results of clinical trials with immune-checkpoint inhibitors, antibody-drug conjugates, radioligands, PARP inhibitors, and new therapeutic targets. The most clinically relevant studies include the EV-302 trial in bladder cancer, PSMAfore in prostate cancer, and LITESPARK-005 in kidney cancer.

Keywords: bladder cancer, prostate cancer, ESMO

Introduction

This review aims to describe and comment on the most important studies in the field of urooncology presented during the last European Society of Medical Oncology (ESMO) congress that took place on October 20 and 24, 2023, in Madrid.

Advances in urothelial cancer treatment

Immunotherapy in metastatic and locally advanced urothelial cancer

Platinum-based chemotherapy is the well-established standard of care in the first-line treatment of advanced or metastatic urothelial cancer. To be treated with cisplatin, patients must fulfill the Galsky criteria. According to those criteria, patients are defined as cisplatin-ineligible if their Eastern Cooperative Oncology Group (ECOG) status is $\geq$ 2, creatinine clearance is < 60 mL/min, peripheral neuropathy or hearing loss is grade $\geq$ 2 according to common toxicity criteria, and in the case of NYHA (New York Heart Association) class III heart failure [1]. Median overall survival (OS) and progression-free survival (PFS) in cisplatin-treated patients is 13.3 months [95% confidence interval (CI) 10.5–16.1] and 8.5 months (95% CI 7.1–10.8) [2]. The Bajorin scale, based on performance status assessment and organ metastases, is used to evaluate the potential benefits of cisplatin. Patients with visceral metastases and Karnofsky performance status less than 80% have the poorest prognosis. Cisplatin-ineligible patients may be treated with carboplatin, but this treatment is less effective than cisplatin [3]. Median of OS and PFS in carboplatin-treated patients is 10.6 months (95% CI 8.6–12.4) and 6.4 months (95% CI 5.8–7.5) [2]. Patients in the first-line setting who achieved at least stabilization after 4–6 cycles of chemotherapy (gemcitabine and cisplatin/carboplatin) should receive avelumab in the maintenance treatment. This recommendation is based on the phase III JAVELIN Bladder 100 trial, which showed

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that the avelumab *vs.* placebo improved median PFS [3.7 *vs.* 2.0 months; hazard ratio (HR) = 0.62] and OS (21.4 *vs.* 14.3 months; HR = 0.69; p = 0.001) in patients with advanced or metastatic urothelial cancer [4]. Immunotherapy with atezolizumab or pembrolizumab is also indicated by oncological guidelines in patients with urothelial cancer exhibiting confirmed programmed cell death ligand 1 (PD-L1) expression, who do not qualify for cisplatin treatment [5].

During the ESMO presidential session, two studies with immunotherapy showed the OS benefit compared to platinum-based chemotherapy (EV-302/ /KEYNOTE-A39; CheckMate-901). This trial's results were positive, whereas previous studies with the usage of immunotherapy in bladder cancer, like IMvigor 130 (chemotherapy + atezolizumab) or KEYNOTE-361 (chemotherapy + pembrolizumab) were negative [6, 7].

In the CheckMate 901 phase III trial, 608 patients with unresectable or metastatic urothelial carcinoma received, in the first line of treatment, up to 6 cycles of cisplatin [70 mg/m^2 *intravenous* (*i.v.*); day 1] with gemcitabine (1000 mg/m^2 *i.v.*; day 1 and day 8), and nivolumab (360 mg *i.v.*; day 1; Q3W), followed by nivolumab (480 mg *i.v.*, Q4W) until progression, unacceptable toxicity, withdrawal, or up to 24 months, compared to cisplatin with gemcitabine. Overall survival in the study arm was higher than in the control arm (21.7 months; 95% CI 18.6–26.4 *vs.* 18.9 months; 95% CI 14.7–22.4; HR = 0.78; 95% CI 0.63–0.96; p = 0.0017). Progression free survival was longer in the study arm than in the control arm (7.9 months; 95% CI 7.6–9.5 *vs.* 7.6 months; 95% CI 6.1–7.8; HR = 0.72; 95% CI 0.59–0.88; p = 0.0012). Also, the objective response rate (ORR) was higher in the study arm than in the control arm (58% *vs.* 43%). Patients who received immunotherapy achieved a higher ratio of complete response (22% *vs.* 12%). The most common adverse events in the study arm were anemia and neutropenia [8]. The study shows that combining immunotherapy and cisplatin-based chemotherapy leads to clinically relevant improvements in OS, PFS, and ORR and has a favorable safety profile. The findings endorse nivolumab and cisplatin-based chemotherapy as a novel standard of care for patients with unresectable or metastatic urothelial carcinoma.

Antibody-drug conjugate in polytherapy in the treatment of metastatic and locally advanced urothelial cancer

Enfortumab-vedotin (EV) is the antibody-drug conjugate composed of a nectin-4-directed antibody, the payload (microtubule inhibitor- monomethyl auristatin E), and the linker. It is recommended in patients with urothelial cancer who have previously received immunotherapy and platinum-containing chemotherapy [9]. In Poland, EV has been reimbursed by the national health system since November 2023 in this indication. Pembrolizumab is the programmed cell death protein 1 (PD-1) antibody, and the KEYNOTE--045 trial showed an increase in median OS and the objective response rate after platinum-containing chemotherapy in comparison with chemotherapy (docetaxel, paclitaxel, vinflunine) [10]. Some preclinical studies showed that the EV payload, monomethyl auristatin E, triggers immunogenic cell death that leads to exposure of tumor antigens to T cells, enabling T cells to target cancer cells effectively, which is a hypothesis explaining the sequential mechanism of EV and immunotherapy action [9].

The EV-302/KEYNOTE-A39 phase III trial compared the efficacy of EV and pembrolizumab *vs.* platinum-based chemotherapy (cisplatin or carboplatin + gemcitabine) in untreated patients with locally advanced or metastatic urothelial cancer, with preserved kidney function — glomerular filtration rate (GFR) $\geq$ 30 mL/min/1.73 m^2 and ECOG performance status 0–2. The enrolled patients were stratified into the EV + pembrolizumab (n = 442) *vs.* chemotherapy (n = 444) arms by cisplatin eligibility, PD-L1 expression, and the presence or absence of liver metastases. There was no maximum number of treatment cycles for EV in the study arm, and pembrolizumab was continued for up to 35 cycles of therapy. Patients randomized to the control arm received up to 6 cycles of chemotherapy. The primary endpoints were PFS and OS. The major secondary endpoints included the overall response rate and safety. More than half (54%) of the enrolled patients were eligible for cisplatin. The study showed two-fold longer PFS in the EV + pembrolizumab arm than in the chemotherapy arm (12.5 months; 95% CI 10.4–16.6 *vs.* 6.3 months; 95% CI 6.2–6.5; HR = 0.45; 95% CI 0.38–0.54; p < 0.00001). Overall survival was almost double in the EV + pembrolizumab group than chemotherapy [31.5 months; 95% CI 25.4–not reached (NR) *vs.* 16.1 months; 95% CI 13.9–18.3; HR = 0.47; 95% CI 0.38–0.58; p < 0.00001]. The PFS and OS benefit was observed regardless of the patient's age, sex, primary disease site, presence of liver metastases, PD-L1 expression, and cisplatin eligibility. The ORR was 67.7%, with 29.1% of patients achieving complete responses in the study arm and 44%, with 12.5% complete responses in the control arm. The treatment-related severe adverse events were present in 27.7% of patients in the study arm and 19.6% in the control arm. The most common treatment-related adverse events were peripheral sensory neuropathy, pruritus, alopecia, maculopapular rash, and fatigue in the study arm; anemia, neutropenia, nausea, and thrombocytopenia in the chemotherapy arm [11].

The EV-302 study changed the long-standing standard of treatment. The combination of EV+ pembrolizumab resulted in significant improvements in outcomes for patients with previously untreated locally advanced or metastatic urothelial carcinoma and nearly doubled median PFS and OS compared to platin-based chemotherapy. However, the comparator arm in the trial was suboptimal because platinum-based chemotherapy, followed by avelumab as a maintenance treatment in cases of at least stable disease, was the current standard of care in these patients. It is worth emphasizing that the safety profile for this combination was favorable. In the EV + pembrolizumab arm, the most common grade $\geq$ 3 adverse events included skin reactions (15.5%), peripheral neuropathy (6.8%), and hyperglycemia (6.1%). In the chemotherapy arm, the most common grade $\geq$ 3 adverse events were anemia (31.4%), neutropenia (30%), and thrombocytopenia (19.4%) [11].

The promising treatment results with EV and sacituzumab govitecan (SG) led to a phase I trial (NCT04724018), which evaluated the activity of double antibody drug conjugates in patients with metastatic urothelial cancer and progression on platinum and immunotherapy. The EV and SG were administrated until progression or toxicity. The ORR was 71% (90% CI 51–87), with adverse events grade 3 present in 70% of patients [12].

Molecularly targeted therapy in urothelial cancer

Erdafitinib is the fibroblast growth factor receptor (FGFR) inhibitor registered for patients with locally advanced unresectable or metastatic urothelial carcinoma with FGFR alteration (mutation, fusion) [13]. The FGFR alterations occur more often in upper tract urothelial cancers and luminal I subtype, which has limited benefit from immunotherapy. The THOR phase III study determined the activity of erdafitinib *vs.* chemotherapy (docetaxel or vinflunine) in cohort 1 or pembrolizumab in cohort 2. In cohort 1, at least one of the previous treatments included an immune checkpoint inhibitor (anti-PD-1/anti-PD-L1), while in cohort 2, one prior treatment did not involve an anti-PD-1/anti-PD-L1 agent. The primary endpoint in the study was OS; the secondary endpoints were PFS, ORR, and safety. Erdafitinib significantly increased OS (12.1 months *vs.* 7.8 months; HR = 0.64; 95% CI 0.47–0.88; p = 0.005), median PFS (5.6 *vs.* 2.7 months), and ORR (46% *vs.* 12%) *vs.* chemotherapy. In cohort 2, where patients were naive to immunotherapy, there were no differences in OS (erdafitinib 10.9 months *vs.* pembrolizumab 11.1 months; HR = 1.18; 95% CI 0.92–1.51; p = 0.18) nor PFS. The ORR was higher in the erdafitinib arm than in the pembrolizumab arm [40.0 % *vs.* 21.6%; HR = 1.85 (1.32–2.59); p < 0.001]. The most common treatment-related adverse events were hyperphosphatemia (73%), stomatitis (45%), diarrhea (45%) in the erdafitinib arm and pruritus (12%), asthenia (10%), hypothyroidism (10%), and fatigue (10%) in the pembrolizumab arm [14]. The results of THOR and EV-301 trials open the question of the optimal treatment option for patients with *FGFR*-mutated urothelial carcinoma since pembrolizumab is active in patients with *FGFR* mutations, which suggests that erdafitinib may be used in combination with pembrolizumab in the future. The THOR trial showed that erdafitinib improves patient outcomes and has a manageable toxicity profile. The study's results support using molecular testing in patients with urothelial cancer to identify those who might benefit from molecularly targeted therapy.

Muscle-invasive bladder cancer

The current standard of treatment for patients with muscle-invasive bladder cancer includes platinum-based neoadjuvant chemotherapy [cisplatin and gemcitabine (GC) or cisplatin, methotrexate, doxorubicin, and vinblastine (ddMVAC)] and immunotherapy in high-risk patients, which was shown to improve patients' OS. Cisplatin-ineligible patients should not be treated with neoadjuvant chemotherapy and should be treated with up-front surgery [5]. The probability of local recurrence after surgery is estimated as 5–15% and distant recurrence in up to 50% of patients, which explains the need for better therapeutic options [15, 16]. One of the studies that potentially may improve the outcomes of treatment in this population is the EV-103 trial, which evaluated the activity of EV in cisplatin-ineligible patients with urothelial muscle-invasive bladder cancer (cT1-4aN1M0 and cT2-4aN0M0) medically fit for radical cystectomy and pelvic nodal dissection. Patients were treated with 3 cycles of EV (1.25 mg/kg *i.v.*, D1/8; Q3W) before and 6 cycles after surgery. The primary endpoint was pathological complete remission (pCR). Fifty-one patients were enrolled (cT2 56.9%, 45% creatinine clearance of 30–60 mL/min). Pathological complete response (pCR, ypT0N0) was observed in 34% of patients (n = 17), and 42% (n = 21) achieved pathological downstaging (< ypT2N0). The most common grade 3 adverse events were skin reactions [17]. To sum up, EV showed encouraging antitumor efficacy in patients ineligible for the cisplatin treatment. Currently, EV is studied in phase III clinical trials in cisplatin-ineligible muscle-invasive bladder cancer patients in combination with pembrolizumab e.g. KEYNOTE-905/EV-303 trial [18].

Exciting, but so far, not practice-changing data on bladder cancer includes the NEMIO phase I–II trial: the combination of 4 cycles of ddMVAC chemotherapy + durvalumab ± tremelimumab in muscle-invasive bladder cancer. Pathological complete remission

was achieved in 47.8% of patients (49.1% in the durwalumab group and 46.6% in the durwalumab and tremelimumab groups) [19]. The ABACUS-2 trial shows the effectiveness of atezolizumab in other than urothelial histological subtypes of bladder cancer. Pathological complete remission was achieved in 75% of patients with the sarcomatoid subtype and 33% in the adenocarcinoma subtype of muscle-invasive bladder cancer [20]. The results of this trial suggest that immunotherapy may improve clinical outcomes of patients with localized bladder cancer, which supports further clinical trials.

Non-muscle invasive bladder cancer (NMIBC)

Interesting data were presented with regard to non-muscle invasive bladder cancer. The current standard of care is radical cystectomy in patients with Bacillus Calmette-Guérin (BCG) unresponsive or recurrent tumors. During ESMO, data showed the promising efficacy and safety of new intravesical drug-delivery systems like TAR-210 and TAR-200, which provide a local and sustained drug release.

A phase I trial (NCT05316155) evaluated the safety and efficacy of the TAR-210 drug-delivery system that releases erdafitinib in patients (n = 42) with NMIBC and FGFR alterations. Recurrence-free status was observed in 82% of patients (n = 9) with recurrent, BCG-unresponsive high-risk NMIBC with FGFR alterations, and 86.7% (n = 13) of patients with recurrent intermediate-risk NMIBC and history of low-grade papillary disease achieved complete response [21].

The SunRISE-1 trial evaluated the efficacy of another intravesical drug delivery system (TAR-200) that delivers gemcitabine to patients who are confirmed to be unresponsive to BCG and do not qualify for radical cystectomy. The study enrolled 54 patients, and among them, 76.7% (95% CI 57.7–90.1) achieved a complete response [22]. The preliminary efficacy and safety of the intravesical drug-delivery systems support further clinical trials.

Advances in prostate cancer treatment

Treatment with the prostate-specific radioligand (^{177}Lu)Lu-PSMA-617 in the management of metastatic prostate cancer

Prostate-specific membrane antigen (PSMA) is an enzyme that belongs to the class II membrane glycoprotein. It exhibits high expression in metastatic castration-resistant prostate cancer (mCRPC). Lutetium-177 (^{177}Lu)-PSMA-617 (LuPSMA) is a radioligand therapy that delivers beta-particle radiation to PSMA-expressing cells and their microenvironment. Its effectiveness was confirmed in the VISION study, which evaluated the effectiveness of LuPSMA after taxane-based chemotherapy and androgen-receptor pathway inhibitor therapy and has confirmed improved OS (median OS of 15.3 months *vs.* 11.3 months for the standard of care) [23]. The treatment is currently included in the Polish guidelines for the treatment of metastatic prostate cancer in this setting [24]. The National Comprehensive Cancer Network (NCCN) guidelines recommend treatment with Lu-177-PSMA-617 as a category 1 treatment option for patients with one or more PSMA-positive lesions and predominately PSMA-positive metastatic disease and in patients who have been treated previously with androgen receptor pathway inhibitors (ARPI) and chemotherapy. Still, the availability of that treatment for patients in Poland is low.

European Society of Medical Oncology Congress in 2023 brought to light the results of two new research projects with LuPSMA in the treatment of patients with mCRPC. Notably, both studies introduced LuPSMA in earlier lines of treatment compared to the VISION study. In the first of these studies, a phase III clinical trial, PSMAfore, 468 patients received treatment with the prostate-specific radioligand LuPSMA *vs.* treatment sequential ARPI in patients with mCRPC. The inclusion criteria for the study were as follows: a positive positron emission tomography (PET) scan for PSMA after prior ARPI therapy and no prior taxane-based chemotherapy. The study design allowed cross-over to the LuPSMA arm from ARPI after progression. The study's primary endpoint of improved radiographic progression-free survival (rPFS) was met with LuPSMA compared to ARPI (HR = 0.41; 95% CI 0.29–0.56; $p < 0.0001$) after primary analysis at 7.3 months and was similar at second analysis after 12 months. Nevertheless, the study did not confirm the impact on patients' OS. As for the treatment tolerance, LuPSMA and ARPI had similar safety profiles. The most common adverse events in the LuPSMA arm were anemia and xerostomia.

In conclusion, the results of a PSMAfore study suggest a potential benefit of LuPSMA in the treatment of mCRPC after prior ARPI therapy. However, it is necessary to underline the study's limitation, which is suboptimal treatment in the control group. We know from previous studies that switching from one ARPI to another (e.g., abiraterone after enzalutamide) is a strategy of low effectiveness compared to switching to chemotherapy [25]. The study did not consider the possibility of qualifying the patient for taxane-based chemotherapy. Additionally, the study did not confirm the impact on patients' OS.

In the phase II study ENZA-p (ANZUP 1901), 162 patients were treated with the combination of ARPI-enzalutamide (ENZA) with adaptive dosing LuPSMA compared with ENZA alone as first-line treatment in patients with high-risk mCRPC. The inclusion criteria were as follows: (i) first-line treatment of mCRPC, previous use of abiraterone and/or

docetaxel was approved for treatment of hormone-dependent disease, (ii) 68Ga-PSMA PET-positive disease, (iii) at least 2 risk factors associated with early progression on ENZA (elevated LDH, elevated ALP, albumin < 35 g/L, *de novo* metastatic disease at diagnosis, < 3 years since the initial diagnosis, > 5 bone or visceral metastases, PSA doubling time < 84 days, and prior abiraterone treatment).

The primary endpoint of the study was PSA-PFS, which was longer in the ENZA + LuPSMA group compared to ENZA (median 13 *vs.* 7.8 months; HR = 0.43; 95% CI 0.29–0.63; p < 0.001). The study also found a statistically significant improvement in the biochemical response: a PSA decline of at least 50% (93% for combination *vs.* 68% for ENZA monotherapy; p < 0.001) and at least 90% (78% for combination *vs.* 37% for ENZA monotherapy; p < 0.001). Additionally, the number of LuPSMA doses was adjusted based on the presence of PET-avid disease on the PSMA PET scan on study day 92, and 81% of patients received 4 doses. Treatment tolerance was comparable in both groups, and the most common toxicity with LuPSMA was anemia, as in the PSMAfore study. The results of radiological PFS are awaited.

The rationale behind the study was grounded in preclinical evidence indicating an interaction between the PSMA and the androgen receptor (AR) in prostate cancer. According to these data, when the AR pathway is blocked, the PSMA undergoes upregulation, leading to resistance to ARPI [26]. This resistance, expressed through early progression in patients receiving ARPI treatment, prompted the hypothesis that a combination of therapies could be beneficial. The idea was to target enzalutamide-resistant tumor cells using LuPSMA, thereby addressing aggressive prostate cancer cells. Simultaneously, this approach aimed to pre-select low-expressing cells, which are more likely to respond to the ARPI. The study aimed to validate this hypothesis and explore the potential synergistic effects of combining these two therapeutic approaches.

This study suggests the potential benefit of using the combination of ENZA and adaptive dosing LuPSMA as first-line therapy in mCRPC. However, we still await data for complete rPFS and OS, which may provide a more comprehensive picture of the effectiveness of this therapy.

Immunotherapy in prostate cancer

Immunotherapy with PD-1/PD-L1 immune check-point inhibitors has confirmed efficacy in many solid tumors, whereas its role in prostate cancer is limited. Based on a prospective study, immunotherapy can be considered in mCRPC patients with microsatellite instability (MSI-H/dMMR) [27], and in this indication, it is recommended by the current Polish guidelines for prostate cancer treatment [24]. Immunotherapy has not been shown to be effective outside MSI-H/dMMR tumors, which is a rare condition in mCRPC (~1% of patients).

The phase III KEYNOTE-641 trial, which evaluated the combination of an immune checkpoint inhibitor with ARPI (pembrolizumab and ENZA) *vs.* placebo and ENZA in around 1200 patients with mCRPC, failed to meet its primary endpoints of prolonging rPFS and OS. The modest increase in the complete response rate with pembrolizumab plus enzalutamide compared with placebo plus enzalutamide (7.4% *vs.* 2.7%, respectively) did not translate into a significant increase in rPFS (median 10.4 months *vs.* from 9.0 months; HR = 0.98; 95% CI 0.84−1.14), nor OS, which was even worse for the group treated with immunotherapy (median 24.7 *vs.* 27.3 months; HR = 1.04, 95% CI 0.88−1.22). The study also observed an increase in the incidence of treatment-related adverse events with the addition of pembrolizumab compared to placebo and enzalutamide. To sum up, based on the results of this study, immunotherapy should not be recommended for the general population of patients with mCRPC. Therefore, the current standard of practice, with immunotherapy being considered in mCRPC patients with microsatellite instability, is not changing.

Radiotherapy in prostate cancer

The place of radiotherapy after radical prostatectomy in the treatment of localized prostate cancer is currently debated. Still, a growing body of evidence shows that early salvage therapy has the same effectiveness as adjuvant therapy after prostatectomy in terms of the patient's OS and helps decrease treatment's side effects and avoid overtreatment. Presently, the Polish guidelines advocate early salvage radiotherapy, in cases of biochemical relapse, over adjuvant therapy although the precise cut-off value for biochemical relapse (PSA growth) awaits further confirmation [24].

The final results of the phase III RADICALS-RT trial after 10 years of follow-up showed no advantage of adjuvant radiotherapy (RT) over early salvage radiotherapy after radical prostatectomy in patients with localized prostate cancer with increased risk of recurrence. That study included 1396 patients. The inclusion criteria were post-operative PSA $\leq$ 0.2 ng/mL and $\geq$ 1 risk factor [pT3/4, Gleason score 7–10, positive margins (R1 resection), or pre-operative PSA $\geq$ 10 ng/mL]. Patients were randomized to receive adjuvant RT up to 22 weeks after RP or observation and salvage RT at biochemical relapse (two consecutive rises with a PSA $\geq$ 0.1 ng/mL). After 10 years of follow-up, the rate of patients free from distant metastases was 93% in the adjuvant RT group compared with 90% in the early salvage RT group

(HR = 0.68; 95% CI 0.43–1.07; p = 0.095). The corresponding 10-year overall survival rates were 88% and 87%, respectively (HR = 0.98; 95% CI 0.67–1.44; p = 0.92). After 1 year, patient-reported urinary and fecal incontinence were significantly worse with adjuvant RT ($p \leq 0.001$). Approximately 60% of patients in the early salvage RT did not yet need radiotherapy [28].

In conclusion, early salvage radiotherapy emerges as an equally effective alternative to adjuvant therapy, demonstrating comparable benefits with regard to overall survival while minimizing treatment-related side effects and averting unnecessary interventions. Early salvage radiotherapy is currently recommended by the Polish, European, and NCCN guidelines for treatment of localized prostate cancer.

Advances in renal cell carcinoma treatment (RCC)

The current treatment options for renal cancer with clear cell component include tyrosine kinase inhibitors, immunotherapy, or a combination of these two, and the choice depends on many clinical and pathological factors, e.g., the International Metastatic RCC Database Consortium (IMDC) risk score or patients' comorbidities. According to the Polish RCC guidelines, the available treatment armamentarium includes tyrosine kinase inhibitor (TKI) monotherapy, i.e., sunitinib/pazopanib (IMDC good or intermediate risk) combination of nivolumab + ipilimumab, cabozantinib monotherapy (both for IMDC intermediate or low-risk patients). The second line includes cabozantinib, nivolumab, axitinib, or everolimus monotherapy, depending on the drug used in the previous line of treatment. The third line is also available, comprising nivolumab, cabozantinib, or everolimus [29]. Despite increasing access to new therapies, there is still a need for more treatment options for patients with metastatic kidney cancer.

The new therapeutic options in renal cell carcinoma: belzutifan (hypoxia-inducible factor inhibitor) and MEDI5752 (Volrustomig) — a new bispecific PD-1/CTLA-4 antibody

The hypoxia-inducible factor (HIF) pathway holds pivotal significance in the pathophysiological mechanisms of clear cell renal cell carcinoma (ccRCC) and von Hippel-Lindau disease [30, 31]. Belzutifan represents a pioneering oral HIF-2α inhibitor that disrupts heterodimerization with HIF-1β, impeding downstream oncogenic pathways [32].

Dr. Laurence Albiges presented the latest findings from the open-label phase III LITESPARK-005 study, elucidating the comparative outcomes between belzutifan and everolimus in patients previously undergoing treatment for advanced ccRCC.

The LITESPARK-005 trial represents an open-label, randomized phase III investigation involving individuals diagnosed with unresectable, locally advanced, or metastatic ccRCC with disease progression after 1–3 lines of prior systemic therapy. This therapy encompassed at least one anti-PD-(L)1 agent and a minimum of one vascular endothelial growth factor — tyrosine kinase inhibitor (VEGFR-TKI). Participants in this study underwent random allocation in a 1:1 ratio and were stratified using the International Metastatic RCC Database Consortium (IMDC) prognostic score (0 *vs.* 1–2 *vs.* 3–6) and previous exposure to VEGF/VEGFR-targeted treatments (1 *vs.* 2-3), leading to the administration of belzutifan 120 mg orally once daily (n = 374) or everolimus at a dosage of 10 mg orally once daily (n = 372). The study's co-primary endpoints were PFS and OS. Notably, secondary endpoints encompassed the ORR and duration of response (DOR). Due to the stratified randomization, the study groups exhibited a balanced distribution across IMDC risk categories, with approximately 80% of patients manifesting intermediate to low-risk disease. About 70% of participants had previously undergone nephrectomy. This study comprised a cohort of patients who had undergone extensive prior treatments, with roughly 87% having received 2–3 prior lines of therapy. The trial successfully met its co-primary PFS endpoint. At the pivotal 18-month assessment, 22.5% of patients demonstrated sustained progression-free status while on belzutifan, in contrast to 9% on everolimus (HR = 0.74; 95% CI 0.63–0.88).

To date, no significant OS benefits have been identified for belzutifan compared to everolimus in this study. Although there appears to be a trend towards an OS benefit (HR = 0.88; 95% CI 0.73–1.07; p = 0.099), with 18-month OS rates of 55.2% and 50.6% for belzutifan and everolimus, respectively, statistical significance has not been achieved thus far. Belzutifan patients exhibited an ORR of 22.7%, notably higher than the 3.5% observed with everolimus. Complete response was noted in 3.5% of belzutifan patients, whereas no response was observed with everolimus. Although the median time to response was comparable between both treatment arms at 3 months, the duration of response was longer with belzutifan (19.5 *vs.* 13.7 months).

Anemia and fatigue emerged as the most frequent adverse events, with approximately 30% of belzutifan patients experiencing grade 3 or worse anemia. Notably, grade 3 or worse adverse events occurred with similar frequency in both arms (~62%). However, discontinuation due to adverse events happened in 6% of belzutifan patients compared to 15% of those administered everolimus. Regarding patient-reported outcomes, belzutifan displayed significantly improved time to confirmed deterioration in quality of life [33].

Volrustomig is a monovalent, bispecific PD-1/ /CTLA-4 monoclonal antibody that induces complete PD-1 blockade and preferential CTLA-4 inhibition on activated PD-1-positive T cells. The main inclusion criteria for the study were the diagnosis of ccRCC and no previous treatment with immunotherapy or VEGFR-TKI in first-line treatment, regardless of IMDC prognosis. Patients were randomized 1:1 to receive volrustomig 750 mg (V750) every 3 weeks (n = 32) or volrustomig 500 mg (V500) every 3 weeks (n = 33). The primary endpoint was the ORR, which was 48% for V750 and 46% for V500. The complete response (CR) rates were 10% and 6%, respectively. The median duration of response was longer with the higher dose of 750 mg (17 *vs.* 11.5 months). When patients were stratified by IMDC risk groups, in the patients with a good prognosis, the ORR was higher with the lower dose of V500 (58% *vs.* 25%). In contrast, in the intermediate risk /unfavorable prognosis group, the ORR was higher with the 750 mg dose (57% *vs.* 38%). In the safety analysis, all treatment-emergent adverse events occurred in 97% and 94% of patients in the 750 and 500 mg groups, respectively. Grade 3–4 complications occurred in 63% and 42% of these patients, respectively [34].

Volrustomig appears to be an interesting therapeutic option for patients with advanced ccRCC. The combination of volrustomig with lenvatinib in the first-line treatment is currently the subject of a phase I study.

The adjuvant treatment in renal cell carcinoma

Despite numerous clinical trials, none of the known drugs used as adjuvant therapy has significantly prolonged OS. Hope lies in pembrolizumab, which is still being tested in the adjuvant indication and has a chance of becoming the first drug with a beneficial effect on OS. In the KEYNOTE-564 study, pembrolizumab showed a statistically significant impact on disease-free survival [35]. Based on this study, the drug received a positive opinion from the US Food and Drug Administration and the European Medicines Agency. From September 2023, this drug is also available to Polish patients under the National Health Fund drug program.

During the ESMO Conference in 2023, a subgroup analysis of the EVEREST trial was presented. EVEREST was a randomized, double-blind, phase III study that enrolled patients with histologically confirmed RCC (both clear cell and non-clear cell) who had undergone complete surgical resection and were at intermediate-high or very high risk of recurrence. The intervention involved oral everolimus (10 mg daily) or placebo for 54 weeks. In the general population of the EVEREST trial, after a median follow--up of 76 months, relapse-free survival was slightly improved with everolimus (5 years: 67% *vs.* 63%, p = 0.051). The study showed no OS benefit in the everolimus group.

Dr. Lara presented the results of a subgroup analysis of the cohort of patients with clear cell RCC in the study, characterized by a very high risk of recurrence (pT3a and Gr 3–4; every pT3b-c, every pT4 and every pN+). Of the entire EVEREST study population (1499 patients), 699 met the above criteria.

In the intention-to-treat population, adjuvant therapy with everolimus showed a benefit in terms of recurrence-free survival (RFS) compared to placebo (HR = 0.80; 95% CI 0.65–0.99; 5-year RFS 57% *vs.* 50%; p = 0.040). However, the analysis did not show a significant benefit in terms of OS (HR = 0.85; 95% CI 0.64–1.14; 5-year survival rate: 85% *vs.* 81%; p = 0.28). Adverse events grade 3 and higher occurred significantly more often in the everolimus group (42%) compared to placebo (8%). Based on the presented results and potential cost-effective calculations, everolimus seems an interesting drug for further research on its effectiveness in the adjuvant treatment of kidney cancer [36].

The palliative treatment in renal cell carcinoma

Cabozantinib is a multi-targeted tyrosine kinase inhibitor that has an established place in the treatment of RCC. In first-line treatment, it was approved on the basis of the phase II CABOSUN study, in which it showed statistically significant prolongation of PFS compared to sunitinib in the group of patients with a moderate or poor prognosis according to the IMDC score [37]. In turn, the METEOR study showed a benefit in terms of PFS, OS, and ORR compared to everolimus in patients previously treated with at least one line of anti-VEGF therapy [38]. Therefore, the question arises about the effectiveness of cabozantinib after prior immunotherapy or a combination of immunotherapy with TKI's, and whether the choice of first-line treatment affects the results of cabozantinib in the second-line setting. Dr. Georges Gebrael presented the results of a study showing that in patients with metastatic clear cell RCC receiving cabozantinib in the second line, survival results were similar regardless of previous first-line treatment with ipilimumab + nivolumab or a PD inhibitor + TKI — median OS for cabozantinib from initiation of second-line therapy was 26 months (95% CI 21–32) for patients treated with ipilimumab + nivolumab and 34 months (95% CI 27–NR) for patients treated with a PD + TKI — HR = 1.16, 95% CI 0.73–1.83.

Lenvatinib, in combination with pembrolizumab, is the standard treatment in the first-line treatment of RCC based on the results of the CLEAR study [39]. At the 2023 ESMO Annual Congress, Dr. Gruenwald et al. presented data on tumor response depending on the location of metastases. The stratification factors were

the location of metastases (lungs, lymph nodes, brain, bones, liver), their number (1 *vs.* 2 and more), and the sum of target lesions (< 60 mm and ≥ 60 mm). Treatment with lenvantinib and pembrolizumab showed a higher objective response rate than sunitinib, regardless of the location of metastases, their number, or size. These post hoc analysis results further support the benefits of early, deep, and durable tumor response to lenvatinib + pembrolizumab, compared to sunitinib observed in the CLEAR trial [40].

The phase II TIDE-A study of Avelumab plus Intermittent Axitinib in previously untreated patients with metastatic RCC aimed to determine whether patients treated with axitinib and avelumab who achieved an objective response could continue avelumab monotherapy to reduce TKI-related toxicity and delay tumor resistance to treatment. The study included 75 patients with clear cell RCC with metastases after resection of the primary tumor, without symptoms resulting from the massive spread of the disease and without liver metastases. In this planned group, treatment was carried out with avelumab at a dose of 800 mg intravenously every 2 weeks for 36 weeks + axitinib at a dose of 5 mg orally twice daily. A decision on the form of therapy to be continued was made after imaging assessment at week 36. If the patient had at least a partial response to treatment, he was switched to avelumab monotherapy. If disease stabilization was achieved, the doublet was maintained. Disease progression was an exclusion criterion from the study. The primary endpoint was the proportion of patients free from disease progression 8 weeks after discontinuation of axitinib. Secondary endpoints included PFS, OS, ORR, and safety assessment according to locally applicable criteria. Of the 75 patients included in the efficacy analysis, 57 (76%) achieved a response (complete or partial), of whom 29 discontinued axitinib treatment after 36 weeks. It should be emphasized that 40% of patients had a favorable prognosis, according to the IMDC scale, and only 2.7% of patients had an unfavorable prognosis. Analysis of the results showed that 72.4% of patients had no progression after an 8-week break in axitinib treatment. Median PFS was 24 months, and median OS was NR (18-month OS was 94%). Axitinib-related adverse events of any grade occurred in 34% of all patients, with grade 3+ occurring in 11.4%. After discontinuing axitinib treatment, no patients experienced further grade 3–4 axitinib-related adverse events. Avelumab-related adverse events occurred in 31.6% of patients. Notably, grade 3–4 adverse events occurred in 11.4% of patients receiving combination therapy, and no patients experienced grade 3–4 adverse events after axitinib discontinuation [41].

Conclusions

Last year's ESMO Oncology Conference unveiled promising advancements in urological malignancies, hinting at improved patient outcomes. Emerging data showcased encouraging avenues for progress yet emphasized the necessity for additional research. While the findings were promising, they underscored the need to delve deeper into these developments to acquire more robust insights and enhance therapeutic strategies.

Article Information and Declarations

Author contributions

D.S.: conception, writing (bladder cancer), supervision; M.O.: writing (prostate cancer); M.W.: writing (kidney cancer).

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Supplementary material

None.

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