Treatment-changing news in urogenital cancer—a brief unstructured narrative review based on findings presented at the ESMO 2023 conference

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Summary This article gives an overview through the most promising and practise changing studies presented for urothelial cancer at ESMO 2023 conference.

Keywords Bladder cancer · ESMO 2023 · FGFR · Urothelial cancer

Background

Current standard of care in high-risk non-muscle-invasive bladder cancer (NMIBC) is transurethral resection (TUR) followed by intravesical bacillus Calmette–Guérin (BCG) instillation [1]. Although this approach is generally accepted as an effective treatment, the 5-year recurrence rates and progression rates are up to 78% and 45%, respectively [2]. Radical cystectomy (RC) should be encouraged in recurrent, BCG-pretreated, high-risk NMIBC [1]. However, RC is associated with perioperative complications, quality-of-life reduction associated with bladder resection, postoperative morbidity, and a mortality rate of approximately 2% [3, 4]. Furthermore, many patients are ineligible for RC due to advanced age or preexisting comorbidity [5]. Of note and relevance for the treatment with erdafitinib in localized bladder cancer, up to 31% of high-risk NMIBC patients harbor fibroblast growth factor receptor (FGFR) 3/2 gene alterations [6].

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For locally advanced or metastatic urothelial carcinoma (la/mUC), systemic therapy remains the standard of care in the first-line setting. Before the presentations of the ESMO 2023 conference, the standard of care for patients eligible for cisplatin was a cisplatin-based regimen, such as cisplatin-gemcitabine or dose-dense methotrexate-vinblastine-doxorubicin-cisplatin (ddMVAC). In cisplatin-ineligible patients, carboplatin plus gemcitabine was the standard of care, and for platinum-unfit patients with high programmed death-ligand 1 (PD-L1) expression levels, pembrolizumab and atezolizumab (combined positive score [CPS] of ≥10 in the case of pembrolizumab, immune cell (IC) score of ≥5 in the case of atezolizumab), were taken into consideration as first-line therapy [7–9]. Based on the results of the JAVELIN Bladder 100 Trial, avelumab was commonly used for maintenance therapy in patients without disease progression following first-line platinum-based chemotherapy [10]. In second-line settings, pembrolizumab significantly improved median overall survival (OS) compared to paclitaxel, docetaxel, or vinflunine [11, 12]. Nonetheless, the objective response rate (ORR) in this setting was still only approx. 21% [12]. Despite the latest advances, la/mUC remains incurable; 5-year survival rates remain at approx. 5% [13]. *FGFR3/FGFR2*-positive tumors are associated with an inferior ORR to anti-PD-L1 agents [6, 14, 15].

At the 2023 European Society of Medical Oncology (ESMO) Annual Congress held in Madrid, Spain, between October 20 and 24, the latest breakthroughs in the treatment of high-risk NMIBC and la/mUC were presented, where some of them challenged the standard of care. In this summary, we report on four outstanding trials, namely, THOR-2, THOR, EV-302/KEYNOTE-A39, and CheckMate 901 trial [14, 16, 17].

The *THOR-2* study is a randomized (2:1), phase II, multicohort trial that assessed the effectiveness of erdafitinib, a pan-FGFR tyrosine kinase inhibitor, versus intravesical chemotherapy (IVC) in 73 papillary-only high-risk NMIBC (high-grade Ta/T1) patients, refusing/ineligible for RC [18]. Patients randomized to the intervention arm ($n = 49$) initially received 8 mg daily erdafitinib orally, followed by individual dose escalation. Treatment discontinuation due to adverse events (AE) in the first four patients led to a switch to 6 mg daily, without dose escalation in 28-day cycles, for a maximum of 2 years. Patients randomized to the control arm ($n = 24$), received intravesical mitomycin C 40 mg or gemcitabine 2000 mg per week over four consecutive weeks, followed by monthly instillations over the course of 6 months. Recurrence-free survival (RFS) was defined as the primary endpoint. The RFS rate at 6 and 12 months and safety were secondary endpoints. The median RFS (95% CI) was not reached in the experimental arm, and it was 11.6 months (6.4–20.1) in the control arm (hazard ratio [HR]: 0.28, 95% CI: 0.10–0.60, $p = 0.0008$). The RFS rate (95% CI) at 6 and 12 months was 96% (83.7–98.9%) and 77% (60.0–87.4%) vs. 73% (50.1–87.1%) and 41 (18.9–61.7%) for erdafitinib vs. IVC, respectively. Subgroup analyses included prior BCG therapy (experienced or unresponsive) and tumor stage (Ta or T1). All subgroups favored erdafitinib, especially those who were BCG-experienced (HR: 0.14) and had a T1 tumor stage (HR: 0.26). Nine patients crossed over from IVC to erdafitinib. Grade ≥3 treatment-related AEs were more frequent in the erdafitinib group (stomatitis: 10%, nail dystrophy: 4%) compared to IVC (increase of alanine aminotransferase: 4%). In addition, 22% and 13% of participants experienced serious AEs in the erdafitinib group and the IVC group, respectively. Overall, 19 erdafitinib patients (39%) experienced central serious retinopathy but it resolved in over 50%. Treatment was more frequently discontinued due to AEs in the experimental arm (28 vs. 14 patients). No treatment-related deaths were reported. Authors concluded that erdafitinib significantly reduced the risk of recurrence compared to IVC in recurrent FGFR-positive, papillary-only high-risk NMIBC disease following TUR and BCG instillation. Nonetheless, AEs with erdafitinib are not negligible. Besides, the study size was limited, and hence further studies might be necessary to confirm these results [14]. In our opinion, systemically administered erdafitinib seems to be associated with high rates of adverse events, and other formulations of release (e.g., intra-vesical) might be the better tolerable way to expose patients to this effective drug.

The *THOR* study (cohort A) is a phase III, open-label, randomized trial, which compared erdafitinib versus pembrolizumab in FGFR-positive, anti-PD-L1-naïve patients with metastatic or unresectable UC who experienced disease progression prior treatment. A total of 351 patients were randomly assigned 1:1 to erdafitinib ($n = 175$) or pembrolizumab ($n = 176$). Patients randomized to erdafitinib received 8 mg daily with individual dose escalation to 9 mg daily. The pembrolizumab cohort received 200 mg every 3 weeks. Median OS was defined as the primary endpoint. Median progression-free survival (PFS), ORR, and safety were the secondary endpoints. The median OS (95% CI) was 10.9 months (9.7–12.6) vs. 11.1 months (9.7–13.6) in the erdafitinib vs. the pembrolizumab arm, respectively (HR: 1.18, 95% CI: 0.9–1.5, $p = 0.18$). Hence, the primary endpoint was not met and erdafitinib was not superior to pembrolizumab treatment. Regarding the secondary endpoints, the median PFS (95% CI) was 4.4 months (4.1–5.5) vs. 2.7 months (1.6–3.0) in the erdafitinib vs. pembrolizumab arm, respectively (HR: 0.88, 95% CI: 0.7–1.1, not statistically significant). The ORR, another secondary endpoint, was nearly twice as high in erdafitinib patients (40.0%) compared to those receiving pembrolizumab (21.6%), with a relative risk of 1.85 (95% CI: 1.32–2.39, $p < 0.001$). Grade ≥3 AEs occurred in 43.4% and 12.1% of patients taking erdafitinib and pembrolizumab; furthermore, 13.3% and 10.4% experienced serious AEs, respectively. Patients in the erdafitinib group discontinued therapy three times more frequently due to AEs (15 vs. 4.6%). No treatment-related death was reported in the erdafitinib arm, while three deaths were reported in the pembrolizumab arm [16]. In conclusion, there was no statistically significant difference between the two treatment regimens regarding the primary endpoint of median OS, and thus the study was formally negative and is not changing the standard of care in this setting. The safety profile of both drugs was consistent with previously published data, although adverse events were significantly higher for erdafitinib. One remarkable side observation was the relatively high response rate of pembrolizumab in the FGFR-altered study population, calling into question the previous hypothesis of FGFR-altered bladder cancer as an immunological cold disease.

The *EV-302/KEYNOTE-A39* is an ongoing, open-label, randomized, phase III trial investigating the effectiveness of enfortumab vedotin, a Nectin-4 directed monoclonal antibody, in combination with pembrolizumab (EV + P) vs. platinum-based chemotherapy in treatment-naïve la/mUC. A total of 886 patients were 1:1 randomized and stratified according to cisplatin eligibility, PD-L1 expression status, and the presence or absence of liver metastases. In this trial, median PFS per Blinded Independent Central Review (BICR) and median OS were defined as co-primary endpoints. Secondary endpoints were ORR per BICR and safety. The primary tumor was located in the lower urinary tract in 69% and 74% of the experimental arm and the control arm, respectively. In one half of each arm, patients were cisplatin-eligible. Liver metastases were reported in 22%. Overall, 58% of patients had a PD-L1 CPS ≥10%. Median PFS (95% CI) was significantly longer in the EV + P arm

(12.5 months; 10.4–16.6) compared to the chemotherapy arm (6.3 months; 6.2–6.5; HR: 0.45, 95% CI: 0.38–0.45, $p < 0.001$). Subgroup analyses including age, sex, ECOG status, primary tumor location, presence or absence of liver metastases, high or low PD-L1 expression status, and cisplatin eligibility all were in favor of EV + P. Furthermore, median OS was 31.5 months (25.4 to not reached) and 16.1 months (13.9–18.3) in the experimental and the chemotherapy arm, respectively (HR: 0.47, 95% CI: 0.38–0.58, $p < 0.00001$). All the aforementioned subgroup analyses favored the experimental arm. The ORR was also in favor of EV + P (68% vs. 44%). Overall, EV + P was associated with higher rates of AEs. Nonetheless, grade ≥3 AEs occurred in 70% and 56% of patients in the chemotherapy and the EV + P arm, respectively. The most common grade ≥3 AE was maculopapular rash (7.7%) in the EV + P arm and anemia (31.4%) in the chemotherapy arm. In both arms, four AEs leading to death were reported; 22% and 14% of patients, respectively, discontinued treatment due to AEs. In our opinion, EV-302/KEYNOTE-A39 is the first trial demonstrating superiority over platinum-based chemotherapy in treatment-naïve la/mUC groups. EV + P is an effective combination, significantly prolonging median PFS and OS regardless of subgroups, and thus should be considered as the standard of care in first-line treatment of mUC.

CheckMate 901 is an open-label, randomized, phase III trial comparing nivolumab + gemcitabine + cisplatin (NIVO + GC) with gemcitabine + cisplatin (GC) in previously untreated, unresectable, or mUC. A total of 608 patients were 1:1 randomized to NIVO + GC ($n = 304$) or GC ($n = 304$). Nivolumab 360 mg was administered on day 1 and consecutively maintained at 480 mg every 4 weeks (until disease progression, unacceptable toxicity, withdrawal, or up to a maximum of 24 months). Gemcitabine 1000 mg/m² and cisplatin 70 mg/m² were both administered in 3-week cycles, up to a maximum of 6 cycles, with one additional dosage of gemcitabine on day 8. Median OS and PFS were defined as the co-primary endpoints. The secondary endpoints included OS and PFS stratified by PD-L1 CPS ≥1%, and health-related quality of life (HRQoL). The median OS (95% CI) was 21.7 months (18.6–26.4) and 18.9 months (14.7–22.4) in the NIVO + GC arm and the GC arm, respectively (HR: 0.78, 95% CI: 0.63–0.96, $p = 0.017$). Median PFS (95% CI) was in favor of NIVO + GC with 7.9 months (7.6–9.5) compared to 7.5 months for GC (6.1–7.8; HR: 0.72, 95% CI: 0.59–0.88, $p = 0.0012$). Subgroup analyses included age, sex, race, region, ECOG status, PD-L1 expression status, liver metastases, and previous systematic anticancer treatment. The rates of PFS and OS both favored NIVO + GC irrespective of subgroup analyses. Only patients treated in the United States responded better to GC compared to NIVO + GC. The ORR was higher in the NIVO + GC arm (57.6 vs. 43%). The complete recovery rate was nearly doubled in the experimental arm (22 vs. 12%). The median duration of response was also extended in the experimental arm (9.5 months) compared to the control arm (7.3 months). Grade ≥3 AEs were reported in 62% and 52% of patients in the experimental and the control arm, respectively. The AEs in NIVO + GC were more frequently associated with treatment discontinuation (11 vs. 8%; [17]). In summary, NIVO + GC significantly improved OS and PFS. The ORR was notably higher in the experimental arm. One possible limitation of this study might be that only cisplatin-eligible patients were included. In our opinion, the addition of nivolumab to cisplatin/gemcitabine led to remarkably durable responses in patients showing complete remission and might be an option for patients not eligible for enfortumab-vedotin for any reasons.

Conclusion

The studies presented at the ESMO 2023 conference challenged and changed the standard of care in metastatic urothelial cancer. Since then, new combinations suggest substitution of the three-decade-old platinum-based standard of care in the first-line treatment of our patients.

Conflict of interest A.J. Zgubic, M. Leitsmann, S. Ahyai and M. Pichler declare that they have no competing interests.

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