short review

memo (2019) 12:324–328
https://doi.org/10.1007/s12254-019-00532-9

memo
magazine of european medical oncology

Advanced/metastatic urothelial carcinoma of the bladder and upper urinary tract

Presentation highlights from the ASCO 2019 Congress

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Received: 15 August 2019 / Accepted: 25 September 2019 / Published online: 28 October 2019

Summary Three important oral presentations from the ASCO 2019 congress concerning advanced and metastatic urothelial carcinoma of the urinary bladder and the upper tract are highlighted and their potential clinical implications for the improvement of systemic therapies in respective patients are discussed. Enfortumab vedotin, an antibody-drug conjugate targeting nectin-4, demonstrated a clinically meaningful objective response rate in patients with prior platinum-based chemotherapy and checkpoint inhibition, in a phase II trial. A high unmet need in this heavily pretreated patient population combined with good tolerability and manageable safety profile support a submission to the FDA (US Food and Drug Administration) for accelerated approval. The early use of an immunotherapeutic approach via pembrolizumab in patients with metastatic urothelial carcinoma as "switch maintenance" therapy achieved an objective response rate of 22% vs. 12% in the placebo arm in a phase II trial. Pembrolizumab was shown to potentially "deepen" responses achieved with first-line chemotherapy. Moreover, switch maintenance pembrolizumab was able to significantly delay disease progression, whereby a better characterized role of switch maintenance programmed death-1 blockade will be refined by currently ongoing phase III trials. Based on data showing that angiogenesis plays an important role in urothelial carcinoma growth and progression, a randomized, placebo-controlled phase III trial tested whether the addition of bevacizumab to gemcitabine + cisplatin combination chemotherapy is able to improve overall survival in metastatic urothelial carcinoma patients in first-line therapy. This trial was negative regarding its primary endpoint; thus, currently the standard of care remains cisplatin-based chemotherapy without the addition of biologic agents in advanced or metastatic urothelial carcinoma.

Keywords Antibody-drug conjugate · Checkpoint inhibition · Immunotherapy · PD-1 blockade · Urothelial carcinoma

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Introduction

This short review covers one of the most intriguing fields in terms of uro-oncologic research efforts over recent years, namely locally advanced inoperable and metastatic urothelial carcinoma of the urinary bladder (UC), as well as urothelial carcinoma of the upper urinary tract (UTUC). In this regard, three outstanding oral presentations from the ASCO (American Society of Clinical Oncology) 2019 Congress are highlighted and discussed concerning their potential clinical implications for the improvement of systemic therapies in patients suffering from UC and UTUC.

In 2019, approximately 80,470 new cases of UC and 17,670 cancer-related deaths from this disease are projected to occur in the United States alone [1], whereby these numbers do not include the relatively rare carcinomas of the renal pelvis and ureter. Regarding advanced disease states of muscle invasive UC is of particular importance, considering its ag-

gressiveness and poor prognosis, whereby UTUCs are clinically even more aggressive, as evidenced by 5-year cancer-specific survival (CSS) rates <50% in pT2/T3 disease and <10% in pT4 disease [2]. Looking at the success rates of various medicinal treatment modalities for UC/UTUC in advanced disease stages equally illustrates a high and urgent unmet need for the improvement of already existing as well as the development of new therapeutic strategies.

To bear in mind, for most patients with locally advanced inoperable or metastatic UC/UTUC, platinum-based combination chemotherapy (gemcitabine + cisplatin [GC]) remains the first-line standard of care based on reduced toxicity and comparable outcomes as MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) [3]. Progression usually occurs after six to eight cycles of chemotherapy, whereby response rates to second-line anti-programmed death (PD)-1/PD-ligand (L)1 inhibitors are as low as about 20% at best [4, 5]. Regarding this patient population, third-line treatment with single-agent chemotherapy post-platinum and post-PD-1/L1 inhibitors demonstrates very limited activity so far, as evidenced by objective response rates (ORR) of about 11% [6]. Below is a brief summary of the above-mentioned presentations concerning the complex and in general heavily pretreated group of patients with advanced or metastatic UC/UTUC.

EV-201: enfortumab vedotin monotherapy for locally advanced or metastatic urothelial cancer

Daniel P. Petrylak (Yale School of Medicine, New Haven, CT, USA) presented preliminary cohort 1 results from EV-201, a globally recruiting, pivotal, single-arm, two-cohort phase II study of enfortumab vedotin (EV) in locally advanced or metastatic UC patients treated with a prior checkpoint inhibitor (CPI) and platinum-containing chemotherapy (NCT03219333).

Enfortumab vedotin is an antibody-drug conjugate targeting nectin-4, which is highly expressed in UC (Fig. 1) and showed a promising ORR of 45% in patients with prior PD-1/L1 inhibitors in a phase I study [7]. Patients received 1.25 mg/kg IV EV on days 1, 8, and 15 of each 28-day cycle. The primary endpoint was confirmed ORR per RECIST 1.1 by blinded independent central review. Secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety/tolerability (adverse events: AEs).

Between October 2017 and July 2018, EV-201 enrolled 128 patients in cohort 1, 125 of whom were treated with EV (70% male; median age 69 years; 35% had UTUC; median of 3 prior systemic therapies; PD-L1 <10 by combined positive score [CPS] 65%). Median time on treatment was 4.6 months (min: 0.5, max: 15.6) based on 125 treated patients. As of

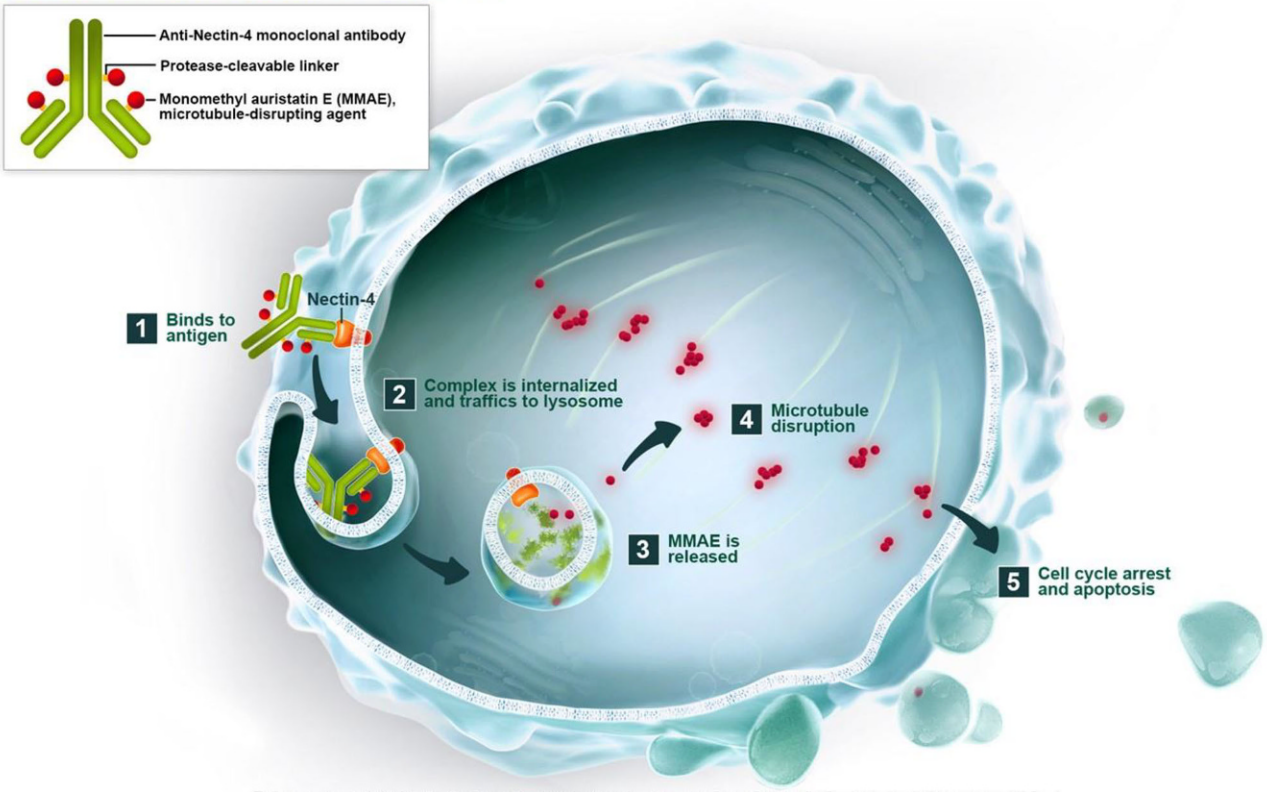

Fig. 1 Enfortumab vedotin (ASG-22ME), proposed mechanism of action. (From Petrylak et al. [8]. © 2019 American Society of Clinical Oncology. All rights reserved. Reprinted with permission of ASCO)

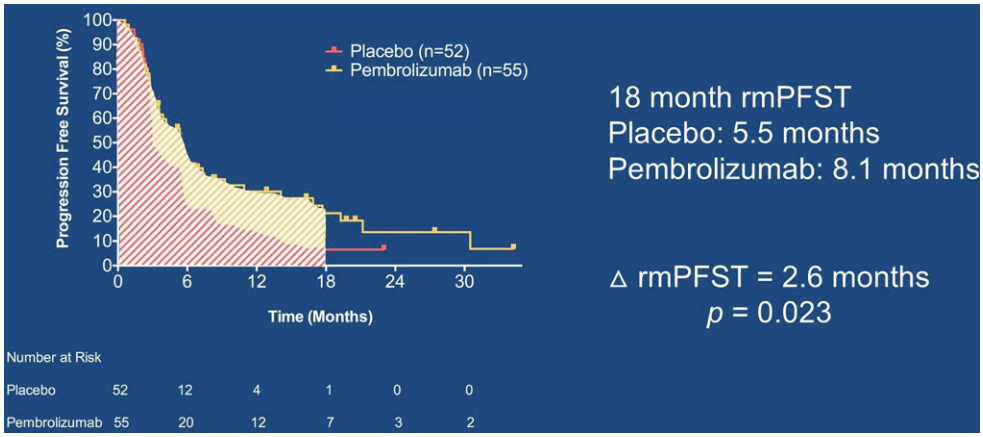

Fig. 2 Progression-free survival (PFS) was significantly longer in patients randomized to pembrolizumab vs. placebo, whereby the 18-month restricted mean PFS time was 5.5 months with placebo and 8.1 months with pembrolizumab. *rmPFST* restricted mean progression-free survival time (From Galsky et al. [10]. © 2019 American Society of Clinical Oncology. All rights reserved. Reprinted with permission of ASCO)

01 March 2019, the ORR was 44%, with 12% complete responses (CR). The ORR in CPI non-responders was 38%, and 36% in patients with liver metastases. Median time to response was 1.8 months, median DoR was 7.6 months, and the most common treatment-related AEs included fatigue (50%), alopecia (49%), and decreased appetite (44%). Treatment-related AEs of interest included any rash (48% all grade, 12% ≥G3) and any peripheral neuropathy (50% all grade, 3% ≥G3). One death was reported as treatment related (interstitial lung disease), but was confounded by a suspected pulmonary infection.

In conclusion, EV-201 demonstrated a clinically meaningful ORR, consistent with the phase I trial, in patients with prior platinum-based chemotherapy and CPI, including patients with liver metastases, where there clearly is a high unmet need. Enfortumab vedotin was well tolerated with a manageable safety profile in these patients. The authors argue that these data strongly support submission to the FDA (US Food and Drug Administration) for accelerated approval.

HCRN GU14-182: maintenance pembrolizumab vs. placebo in metastatic urothelial cancer

Immunotherapy (PD-1 blockade with pembrolizumab) was shown to improve survival of metastatic UC patients progressing despite platinum-based chemotherapy [9], whereby Galsky et al. (Department of Medicine, Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY, USA) explored the potential benefit of an earlier use of PD-1 blockade using a "switch maintenance" approach (NCT02500121). Patients with metastatic UC achieving at least stable disease (SD) after up to 8 cycles of first-line platinum-based chemotherapy were enrolled. The patient cohort was randomized 1:1 to pembrolizumab (pembro) 200 mg IV q3 weeks vs. placebo for up to 24 months; patients progressing on placebo could cross over to the pembro arm. Randomization was stratified based on pre-chemotherapy visceral metastases (yes/no) and response to first-line chemotherapy (CR/partial response [PR] vs. SD). The primary objective was to determine PFS as per irRECIST among patients treated with pembro vs. placebo.

Between December 2015 and November 2018, 107 patients were randomized to placebo ($n=52$) vs. pembro ($n=55$); in the pembro cohort 71% were male; median age 68 years; 71% had visceral metastases; median of 5 prior chemotherapy cycles. Excluding patients with baseline CRs, the ORR was 12% on placebo and 22% on pembro, with 0% CRs on placebo and 9% on pembro. Grade 3–4 treatment emergent AEs occurred in 48% of patients on placebo and 56% on pembro. After a median follow-up of 14.7 months, 41 patients had died and 26/52 patients randomized to placebo had crossed over to pembro; PFS was significantly longer in patients randomized to pembro vs. placebo, whereby the 18-month restricted mean PFS time was 5.5 months with placebo and 8.1 months with pembro (Fig. 2).

The authors argue that switch maintenance pembro may "deepen" responses achieved with first-line chemotherapy. Moreover, switch maintenance pembro was able to significantly delay disease progression in patients with metastatic UC. A more detailed role of switch maintenance PD-1 blockade will be refined by ongoing phase III trials.

CALGB 90601 (Alliance): gemcitabine and cisplatin with bevacizumab or placebo in metastatic urothelial carcinoma

As Jonathan E. Rosenberg (Memorial Sloan Kettering Cancer Center, New York, NY, USA) elucidated during his presentation, an upregulation of angiogenesis in UC has been repeatedly found to be associated with

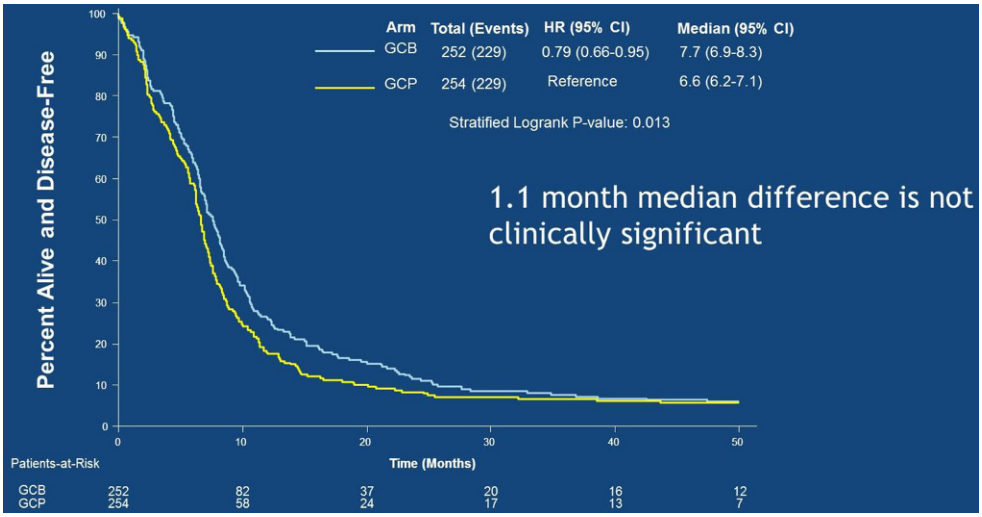

Fig. 3 A modest (1.1 month difference) and thus clinically insignificant PFS improvement in the GCB patient cohort could be observed. *PFS* progression-free survival, *HR* hazard ratio, *CI* confidence interval, *GCB* gemcitabine + cisplatin + bevacizumab, *GCP* gemcitabine + cisplatin + placebo. (From Rosenberg et al. [15]. © 2019 American Society of Clinical Oncology. All rights reserved

poor prognosis and outcomes [11]. In agreement with this finding, preclinical models demonstrated that anti-angiogenic therapies might be able to inhibit the progression of UC [12]. At the same time, single agent vascular endothelial growth factor (VEGF)-targeted therapies with tyrosine kinase inhibitors (TKIs) produced disappointingly low response rates in metastatic UC [13, 14].

Based on data that angiogenesis plays an important role in UC growth and progression, this randomized, placebo-controlled phase III trial was performed (NCT00942331). Patients with metastatic UC, no prior chemotherapy for metastatic disease and >12 months from prior (neo)adjuvant chemotherapy and ECOG PS 0–1 were randomized 1:1 to G 1000 mg/m^2 IV days 1 and 8 and C IV 70 mg/m^2 day 1 with bevacizumab (GCB) 15 mg/kg IV or placebo (GCP) day 1 every 21 days. Up to 6 cycles of chemotherapy with a cycle length of 21 days were administered, whereby the dose of C was allowed to be split over days 1 and 8 for a creatinine clearance between 50–59 mL/min. Bevacizumab 15 mg/kg IV was administered in 3-week intervals. Treatment continued until cancer progression, unacceptable toxicity, or death. Randomization was stratified by the presence of visceral metastases and prior chemotherapy.

The primary study endpoint was OS, secondary endpoints included PFS, ORR, and ≥grade 3 toxicity. With 445 deaths, the log-rank test had an 87% power to detect a hazard ratio (HR) of 0.74 with a 2-sided $\alpha = 0.05$.

A total of 506 patients were randomly assigned in a 1:1 fashion into two cohorts (252 GCB, 254 GCP). The median follow-up for patients still alive was 46.2 months; median OS was 14.5 months for patients treated with GCB and 14.3 months for patients treated with GCP (HR = 0.87, 2-sided Wald $p = 0.17$). The HR for PFS was 0.77 in favor of GCB ($p = 0.0074$). The grade ≥3 AEs rate was 83.5% with GCB compared to 80.7% with GCP.

In conclusion, the addition of bevacizumab to first-line GC chemotherapy did not result in improved OS (primary endpoint) in patients with metastatic UC, albeit a modest (1.1 month difference) and thus clinically insignificant PFS improvement in the GCB patient cohort could be observed (Fig. 3). Even if ongoing research efforts may identify subsets of patients in the future who may benefit from anti-angiogenic therapy, currently the standard of care remains C-based chemotherapy without the addition of biologic agents. Finally, as a negative trial, CALGB 90601 (Alliance) impressively demonstrates how important it is to conduct phase III trials to either confirm or rebut promising phase II data.

Conflict of interest G.C. Hutterer and M. Pichler declare that they have no competing interests.

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