Urothelial Carcinoma Highlights from ASCO GU 2021: Ground-Breaking Studies

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First-line treatment options for metastatic UC

According to the treatment algorithm of the first-line therapy of metastatic urothelial cancer (mUC), patients can be broadly classified into two categories: platinum-eligible and platinum-ineligible.¹ For efficient disease management it is essential to identify these patients at the start of treatment as studies have shown that if platinum-eligible patients are treated as platinum-ineligible, treatment opportunities may be missed, which can lead to poorer outcomes. By definition, platinum-ineligible patients have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 and glomerular filtration rate (GFR) of <60 ml/min, or GFR <30 ml/min. As these patients cannot be treated with cisplatin or carboplatin, there is an unmet need in this patient population. In the past, attempts to further reduce chemotherapy for platinum-ineligible patients have failed. However, with the advent of immune checkpoint inhibitors (ICIs), there are currently two immunotherapies, atezolizumab² and pembrolizumab³, approved by the Food and Drug Administration (FDA) for the treatment of patients

with locally advanced or mUC who are ineligible for cisplatin-based chemotherapy and whose tumors express programmed death-ligand 1 (PD-L1). Atezolizumab is also approved by the FDA for platinum-ineligible mUC patients regardless of their PD-L1 status. These ICIs are not yet approved by the European Medicines Agency (EMA)^{4,5} or Swissmedic^{6,7} in this setting, and we currently manage PD-L1-negative mUC patients with best supportive care (BSC) only.

Enfortumab vedotin shows clinically meaningful outcomes in previously treated cisplatin-ineligible patients with advanced UC

The pivotal, single-arm, 2-cohort, phase II EV-201 trial investigated the efficacy and safety of enfortumab vedotin (EV) (1.25 mg/kg i.v. on days 1, 8, and 15 of each 28-day cycle), an antibody-drug conjugate directed against Nectin-4, in 89 cisplatin-ineligible patients with locally advanced or mUC.⁸ Patients were elderly with a median age of 75 years, and about 3/4 of them were male. Nearly 88% of patients had an ECOG

PS of 0 or 1 and moderate renal impairment (GFR ≥ 30 and < 60 ml/min) was observed in 67% of patients. Visceral and liver metastases were reported in 79% and 24% of patients, respectively. About 98% of patients received prior PD-L1/PD-1-containing therapy; of these, 25% had a response. A follow-up of the study presented at the ASCO Genitourinary (GU) Cancers Symposium 2021 showed that after a median follow-up of 13.4 months, the median progression-free survival (PFS) was 5.8 months, and the median overall survival (OS) was 14.7 months. These survival results were quite impressive given that the patients had received prior immunotherapy. Furthermore, 88% of assessable patients (n=77) had a decrease in their tumor measurements from baseline. The study also showed that Nectin-4 was overexpressed in the majority of the analyzed samples indicating that there is no need for testing before treatment in clinical practice. Overall, EV-201 can be considered as a positive study in this very special patient population; however, it is not practice-changing. To answer this question conclusively a larger study is required, which is probably not possible in this patient population. EV is an appealing option, and it should be made available to these patients with unmet needs.

Enfortumab vedotin as a new treatment option for patients with advanced UC treated with platinum and PD-1/PD-L1 inhibitors

A further important consideration to take into account is whether EV is also valuable for the treatment of platinum-eligible population and where it may stand in the treatment algorithm of the first-line therapy of patients with mUC. Primarily, platinum-eligible patients should receive cisplatin- or carboplatin-based chemotherapy for 4–6 cycles, followed by maintenance avelumab, a PD-L1 inhibitor, among those who achieved a response to chemotherapy.¹ This was based on data from the practice-changing phase III JAVELIN BLADDER 100 trial, which demonstrated a significant OS benefit with maintenance avelumab versus BSC, in advanced/metastatic UC patients whose disease did not progress on platinum-based chemotherapy.⁹ As a result, sequential immunotherapy is the current standard of care in this clinical setting, while it is not fully defined in patients with disease progression on chemotherapy. Indeed, there is a void that needs to be filled for patients who fail maintenance therapy and those who progressed on second-line immunotherapy.

To fill this gap, the EV-301 study investigated the efficacy and safety of EV versus chemotherapy in patients with previously treated locally advanced or metastatic UC.¹⁰ A total of 608 patients, following progression after platinum-containing chemotherapy and PD-1/PD-L1 inhibitor regimens, were randomized 1:1 to receive either EV (1.25 mg/kg on days 1, 8, and 15 of each 28-day cycle) (n=301) or the investigator's choice of standard chemotherapy (docetaxel, paclitaxel, or vinflunine) (n=307). Overall, the median age was 68 years, with a predominance of male patients (>75%). About 67% of patients had a Bellmunt risk score of 0–1, while 60% of the patients had an ECOG PS of 1. Approximately 1/3 of the patients had liver metastasis. Nearly 87% of patients in both arms had received 1–2 prior lines of systemic therapy. Response rates to ICIs were 20% in the EV arm and 16% in the chemotherapy arm. After a median follow-up of 11.1 months, the primary endpoint of OS was significantly improved with EV compared with chemotherapy (median OS, 12.88 months vs 8.97 months, HR: 0.70 [95% CI: 0.56–0.89], 1-sided p=0.00142). Based on these results, EV is a new treatment option for patients in this setting and could also be a potential emerging therapy for platinum-ineligible mUC patients.

PD-L1 scoring is beneficial to identify patients with metastatic UC who may benefit from frontline atezolizumab

In the phase III IMvigor130 study, mUC patients with ECOG PS 0–2 and no prior systemic therapy were randomly assigned to receive atezolizumab plus platinum-based chemotherapy (group A), atezolizumab monotherapy (group B), or placebo plus platinum-based chemotherapy (group C).¹¹ At ASCO GU 2021, Prof. Matthew Galsky presented results of an exploratory analysis of the IMvigor130 study assessing efficacy outcomes by PD-L1 status in cisplatin-ineligible mUC patients from arms B (n=280) and C (n=93). In patients with low PD-L1 expression (IC0/1), no difference in median OS was observed between the atezolizumab and chemotherapy arms (both 11.2 months; HR: 1.11 [95% CI: 0.82–1.51]). However, among patients with high

PD-L1 expression (≥5%) (IC2/3), the median OS was substantially improved with atezolizumab versus chemotherapy (18.6 months vs 10.0 months, HR: 0.53 [95% CI: 0.30–0.94]). This was also reflected by an objective response rate (ORR) benefit in IC2/3 patients treated with atezolizumab versus chemotherapy (38% vs 33%), while in IC0/1 patients, ORR was 16% and 42%, respectively. In conclusion, IMvigor130 has positive results; however, we are still awaiting the results from the final analysis and the decisions from the regulatory authorities.

Nivolumab demonstrates substantial clinical benefit in high-risk patients with muscle-invasive UC

At ASCO GU 2021, Dr Dean Bajorin presented the initial results of the phase III CHECKMATE 274 trial, which investigated the efficacy and safety of adjuvant nivolumab versus placebo in patients with muscle-invasive (MI) UC after radical surgery with or without neoadjuvant cisplatin (NAC).¹² This study included a total of 709 patients with ypT2–4a MIUC after NAC, or pT3–4a or pN+ MIUC without NAC who underwent 1:1 randomization to receive either nivolumab (240 mg) or placebo for up to 1 year of adjuvant treatment. The primary endpoint of the study was met as adjuvant nivolumab significantly improved disease-free survival (DFS) versus placebo in both the intent-to-treat (ITT) (21.0 months vs 10.9 months, HR: 0.70 [95% CI: 0.54–0.89]; p<0.001) and PD-L1 ≥1% (not reached [NR] vs 10.8 months, HR: 0.53 [95% CI: 0.34–0.84]; p<0.001) populations. Nivolumab was also associated with favorable distant metastasis-free survival (DMFS) compared with placebo in both ITT (35.0 months vs 29.0 months; HR: 0.74 [95% CI: 0.58–0.93]) and PD-L1 expression ≥1 (NR vs 21.2 months; HR: 0.60 [95% CI: 0.41–0.88]) populations. In addition, DFS benefit with nivolumab was sustained across all prespecified subgroups, especially in patients who had an initial tumor origin in the urinary bladder and patients with a prior NAC. Taken together, nivolumab is the first ICI that shows substantial benefit for MIUC patients that are at high risk for relapse and for those who cannot receive neoadjuvant chemotherapy.

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