Expanding Treatment Options in mUC and mRCC

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EV-103 Cohort K: Enfortumab vedotin plus pembrolizumab as a potential first-line option in cisplatin-ineligible metastatic UC

In the phase Ib/II EV-103 trial, the nectin-4-directed antibody-drug conjugate (ADC) enfortumab vedotin demonstrated promising safety and efficacy in combination with pembrolizumab in the first-line treatment of patients with metastatic urothelial carcinoma (UC) who were unfit for cisplatin regimen.[1] With a confirmed objective response rate (ORR) of 73% in the dose-escalation cohort A (n=45),[2] the combination was further evaluated in the 1:1 randomized cohort K versus enfortumab vedotin alone.[3] Of the 151 cisplatin-ineligible patients, about 60% presented with impaired creatinine clearance (CrCl) (<60 and ≥30 mL/min). Notably, carboplatin-based chemotherapy is the recommended treatment in this setting.[4] Among patients who received enfortumab vedotin plus pembrolizumab, the confirmed ORR was 64.5%, irrespective of programmed death-ligand 1 (PD-L1) combined positive score (CPS) (<10 vs ≥10: 61.4% vs 67.7%) or nectin-4 status (objective response in 2 patients with no detectable expression). Of those treated with enfortumab vedotin alone, 45.2% attained an objective response. Importantly, enfortumab vedotin plus pembrolizumab was associated with higher toxicity, with grade ≥3 maculopapular rash reported in 17.1% of patients in the combination arm versus 1.4% of patients in the monotherapy arm. Physicians should be aware of this dermatological complication, which has to be managed proactively with dose reductions and/or interruptions. Of note, enfortumab vedotin plus pembrolizumab is currently investigated against first-line platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin) in metastatic UC in the phase III EV-302 study,[5] a setting in which several immune-oncology (IO) trials have failed to show statistically significant overall survival (OS) benefit.[6-9]

VESPER: Basal/squamous and mixed MIBC subtypes correlated with shorter PFS

A recent consensus on the classification of muscle-invasive bladder cancer (MIBC) molecular subtypes indicated that luminal classes were generally associated with a more favorable prognosis when compared with basal or squamous tumors.[10] Several retrospective studies aimed to establish the predictive value of the molecular subtype for response to neoadjuvant chemotherapy (NAC), with conflicting findings.[11-16] At the ESMO Congress 2022, Clarice S. Groeneveld presented the BoBCaT study, a molecular subgroup analysis of the phase III VESPER trial[17] of NAC in MIBC.[18] In this analysis, 252 patients presented with a single molecular subtype and 45 patients with a heterogeneous expression. The rate of pathological complete response (CR) was lowest in patients of the mixed subgroup (24%), with no significant differences across the other subgroups (34–53%). In addition, patients with basal/squamous or mixed tumors had worse progression-free survival (PFS) after NAC compared with the rest (combined vs others, p<0.001). In summary, molecular subtypes are at present not reliable tissue biomarkers in MIBC as studies remain inconsistent.

Challenges in the adjuvant treatment of RCC

Tyrosine kinase inhibitors (TKIs) targeting vascular endothelial growth factor (VEGF) receptor signaling (axitinib, pazopanib, sorafenib and sunitinib) have been extensively investigated for the adjuvant treatment of renal cell carcinoma (RCC), with no positive outcomes regarding OS,[19-24] while sunitinib showed some benefit in disease-free survival (DFS). In addition, the phase III EVEREST trial of adjuvant everolimus, a mammalian target of rapamycin (mTOR) inhibitor, missed its primary endpoint of recurrence-free survival (RFS) as presented this year.[25]

Adjuvant therapy with the checkpoint inhibitor pembrolizumab for one year significantly prolonged DFS versus placebo (HR: 0.68 [95% CI: 0.53–0.87]; p=0.002) in the phase III KEYNOTE-564 but the trial drew several criticisms, including the choice of DFS as a primary endpoint, the rather short follow-up (updated analysis at 30.1 months; immature OS data, HR: 0.52) and the heterogenous patient population.[26,27] Other immunotherapies are also evaluated in this setting, with results from the phase III trials IMmotion010[28,29] (atezolizumab), PROSPER[30] (nivolumab) and CheckMate 914[31] (nivolumab plus ipilimumab) presented at the ESMO Congress 2022, while data from the RAMPART[32] (durvalumab) are still awaited. In IMmotion010, patients with resected intermediate- to high-risk RCC or post metastasectomy status (M1 no evidence of disease [NED]) were randomized 1:1 to a 1-year therapy with atezolizumab or placebo (n=778).[28] The trial was similar to KEYNOTE-564,[26] albeit with a higher proportion of M1 NED patients (~14% vs 6%), of whom the majority had metachronous metastasectomy ≥12 months after primary surgery. At 44.7 months of median follow-up, there were no differences in DFS between the treatment arms (HR: 0.93 [95% CI: 0.75–1.15]; p=0.4950) and across subgroups, including patients with M1 NED status (HR: 0.93; KEYNOTE-564[26] HR: 0.29). As monotherapy in the first-line treatment of advanced RCC, atezolizumab showed slightly lower efficacy compared with pembrolizumab (ORR: 25% vs 36%),[33,34] which might indicate generally lower activity of PD-L1 inhibition in RCC, albeit unlikely the only reason behind these differences. PROSPER was an investigator-initiated, open-label trial of perioperative nivolumab (n=819), with a more complex design.[30] The control arm was surgery plus observation and biopsy was not required; the disease stage was clinically defined resulting in a high proportion of patients with the lower-risk disease (~50% cT1/T2), and patients with non-clear cell RCC were permitted (~20%). One dose of nivolumab was administered pre- and 9 doses post-operatively (78% started adjuvant nivolumab). The primary endpoint was RFS, with patients who did not undergo nephrectomy or were not disease-free after resection considered as an event on Day 1. At a 16-month median follow-up, RFS was comparable between treatment arms (HR: 0.97 [95% CI: 0.74–1.28]; p=0.43), with similar results in the subgroup analysis. The combination of nivolumab plus ipilimumab demonstrated durable efficacy in advanced intermediate and poor prognosis RCC[35] and was investigated in the adjuvant setting versus placebo in the CheckMate 914 (n=815).[31] The study was similar to KEYNOTE-564,[26] but patients with clinical or radiological evidence of residual disease or distant metastases after resection were excluded and the therapy duration was only 6 months. The primary endpoint of DFS was not met (HR: 0.92 [95% CI: 0.71–1.19]; p=0.5347) at a median follow-up of 37.0 months. Results were inconsistent across TNM stages

(HR for T2, T3 and T4 or N1M0: 0.66, 1.06 and 0.61, respectively); the sarcomatoid subgroup performed better (HR: 0.29). Notably, one-third of patients discontinued treatment due to toxicity and 23% of patients received high-dose prednisone. In summary, KEYNOTE-564 remains the only positive trial of adjuvant immunotherapy in RCC, with final OS data still awaited. Patients at high risk of recurrence or with M1 NED disease derived the greatest benefit of adjuvant pembrolizumab.

COSMIC-313: The addition of cabozantinib to nivolumab and ipilimumab improved PFS but had a higher toxicity

In advanced clear cell RCC (ccRCC), first-line nivolumab in combination with either ipilimumab (CheckMate 214)[35,36] or cabozantinib (CheckMate 9ER)[37,38] were superior to sunitinib. In the phase III COSMIC-313, the triplet therapy was evaluated versus nivolumab plus ipilimumab in patients with untreated advanced RCC of intermediate or poor risk by the International Metastatic RCC Database Consortium (IMDC) criteria.[39] The primary endpoint was PFS in the primary intention-to-treat (PITT) population, consisting of the first 550 randomized patients, and the secondary endpoint was OS in all randomized patients (n=855). At a median follow-up of 20.2 months for the PITT, the trial met its primary endpoint (HR: 0.73 [95% CI: 0.57–0.94]; p=0.013), with a median PFS not reached in the triplet arm and 11.3 months in the nivolumab plus ipilimumab arm. The ORR (PITT) was slightly higher with the addition of cabozantinib at 43% versus 36% with immunotherapy alone; for reference, ORR was 56% in CheckMate 9ER[37,38] (favorable IMDC score: 23% of ITT) and 42% in CheckMate 214[35,36] among intermediate- and poor-risk patients. When stratified by the IMDC criteria, the clinical benefit of the triplet versus doublet regimen was observed only in patients with intermediate risk (PFS HR: 0.63, ORR: 45% vs 35%; poor risk, PFS HR: 1.04, ORR: 37% vs 38%). Furthermore, the addition of cabozantinib to nivolumab and ipilimumab was associated with a higher incidence of grade 3–4 treatment-related adverse events (TRAEs) (73% vs 41%). Together with the marginal improvement in efficacy and no OS data, this would argue against the use of triplet therapy.

KEYNOTE-B61: Promising data with lenvatinib plus pembrolizumab in the front-line treatment of metastatic non-clear cell RCC

Non-clear cell RCC (nccRCC) represent 20–30% of renal cell carcinomas and are usually excluded from large, randomized phase III studies, leaving a high unmet medical need.[40] Of those, papillary and chromophobe histological subtypes account for 80%. The multi-targeted TKIs cabozantinib and lenvatinib in combination with everolimus have shown ORRs of nearly 30% in patients with nccRCC.[41-44] At the ESMO Congress 2022, Prof. Albiges presented results of the single-arm, phase II KEYNOTE-B61, which explored lenvatinib in combination with pembrolizumab as initial therapy in advanced nccRCC.[45] Patients received 400 mg pembrolizumab every 6 weeks for up to 18 cycles (~2 years) and 20 mg lenvatinib daily until progressive disease or discontinuation. Efficacy was assessed in 82 patients (papillary: 62%, chromophobe: 18%) who were enrolled at least 24 weeks prior to the data cutoff date. At a median follow-up of 8.2 months, ORR was 47.6% in the overall population (CR rate: 3.7%), with patients with chromophobe RCC being the least responsive to treatment (ORR: 13.3%, papillary, 52.9%). This regimen has demonstrated the highest ORRs across nccRCC subtypes in phase I/II trials so far, except for lenvatinib plus everolimus in patients with chromophobe tumors (44%).[43,46-50] Comparable results were observed with cabozantinib in combination with atezolizumab or nivolumab (ORR in a papillary subgroup: 47% for both), thus TKI-IO combination appears to be a viable option in advanced nccRCC.

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