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Editorial

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Maximizing Outcomes with Chemoimmunotherapy in Lymph Node–only Metastatic Urothelial Cancer: Targeting a Favorable Subgroup

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Patients with metastatic urothelial carcinoma (mUC) and lymph node (LN)-only metastases represent a unique subset with favorable prognosis. Historically, patients with mUC who had nonvisceral metastases (eg, LN metastases) had better prognosis, with a 5-yr overall survival (OS) rate of 20.9% compared to 6.8% for the group with visceral metastases [1]. Among patients with mUC treated with methotrexate, vinblastine, doxorubicin, and cisplatin regimens, the objective response rate (ORR) was significantly higher for the group with LN metastases than for the group with extranodal disease, along with a higher complete response (CR) rate [2]. While the treatment landscape for mUC has changed in recent years, optimal management of mUC with LN metastases remains poorly defined. Thus, LN-only mUC is a key patient population that provides an opportunity to maximize treatment outcomes with the aim of durable responses.

The advent of immune checkpoint inhibitors (ICI) has revolutionized the treatment landscape for mUC. In the JAVELIN Bladder 100 trial, maintenance avelumab significantly improved both OS and progression-free survival (PFS) in patients with mUC without progression after first-line platinum-based chemotherapy [3]. More recently, first-line treatment for mUC has been transformed by nivolumab in combination with gemcitabine and cisplatin (NIVO + GC) and enfortumab vedotin plus pembrolizumab (EV + P) [4,5]. Both regimens have demonstrated a clinical benefit over chemotherapy alone and are now included in guideline recommendations for first-line mUC treatment. The CheckMate 901 study showed that NIVO + GC led to improvements in the co-primary endpoints of OS and PFS in comparison to GC alone in patients with untreated mUC [4]. The NIVO + GC combination also resulted in a higher ORR (58% vs 43%) with more frequent CR outcomes (22% vs 12%) that were particularly enriched for patients with LN-only metastases.

In this issue of *European Urology*, Galsky et al [6] and Bellmunt et al [7] report results from subgroup analyses for LN-only mUC in CheckMate 901 and JAVELIN Bladder 100, respectively. In the CheckMate 901 post hoc analysis, NIVO + GC led to longer OS (46.3 vs 24.9 mo; hazard ratio [HR] 0.58, 95% confidence interval [CI] 0.34–1.0) and PFS (30.5 vs 8.84 mo; HR 0.38, 95% CI 0.22-0.66) in LN-only mUC. The ORR was significantly higher with NIVO + GC versus GC alone (81% vs 64%), as was the CR rate (63% vs 34%). Furthermore, the median CR duration was not reached with NIVO + GC versus 8.74 mo with GC. In the group of patients with a CR, a greater proportion in the immunotherapy arm had a treatment-free interval (41% vs 16%). Overall, this subset analysis from CheckMate 901 demonstrates deep and durable responses with NIVO + GC in patients with LN-only mUC.

The exploratory JAVELIN Bladder 100 analysis focused on patients with nonvisceral metastases (bone and LN) before chemotherapy and LN-only residual disease after chemotherapy. In the nonvisceral group, avelumab improved both median PFS (9.0 vs 3.3 mo; HR 0.45, 95% CI 0.35-0–59) and median OS (31.4 vs 17.1 mo; HR 0.60, 95% CI 0.45–0.79). Among patients with LN-only disease after chemotherapy, avelumab led to a significant improvement in median PFS (8.7 vs 3.7 mo; HR 0.51, 95% CI 0.31–0.84) but not median OS (31.9 vs 22.7 mo; HR 0.86, 95% CI

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0.51–1.47). Importantly, these results in both the nonvisceral and LN-only groups were irrespective of the type of chemotherapy received.

There are limitations to both of these analyses. In addition to the smaller sample sizes, they were not specifically powered to detect differences between treatment groups in these cohorts, so the observations are only exploratory. Both studies incorporated conventional imaging with computed tomography (CT) in the protocol. It has been shown that the positron emission tomography/CT imaging has higher sensitivity for detection of metastases, including LN disease in mUC [8]. Imaging standardization for patient selection and treatment monitoring within this subgroup requires additional evaluation. Patients with LN-only mUC generally already have favorable prognosis, so their positive responses to treatment are not unexpected. Nevertheless, the CR rate with NIVO + GC in this cohort is notable, as is the improvement in PFS with avelumab. It is also important to note that JAVELIN Bladder 100 enrolled patients without progression after chemotherapy, whereas patients in CheckMate 901 had no prior treatment.

A remaining key issue is how the results from these analyses compare with EV-302. A subgroup analysis for EV-302 revealed better PFS and OS and a higher ORR (77.5%) for patients with LN-only disease with EV + P [9]. Recently updated EV-302 data for the intention-to-treat population revealed an ORR of 67.5% and a CR rate of 30.4% with EV + P, and 74.3% of those with a CR maintained this response at 24 mo [10]. Since CR data for EV + P in LN-only disease have not been reported, NIVO + GC may be an attractive option for this population given the more frequent and sustained CR rates despite cross-trial comparisons. The fixed duration of NIVO + GC (6 cycles of GC and 24 mo of NIVO) along with a potential treatment-free interval following CR suggests that this option may be preferable to patients as first-line therapy. Longer follow-up data from CheckMate 901 and EV-302 in LN-only mUC are needed. Given the potential for CRs with NIVO + GC, the role of consolidative treatment to the bladder will need to be investigated in this population. Furthermore, the role of maintenance avelumab may be less applicable given NIVO + GC and EV + P are now preferred frontline regimens.

Overall, these post hoc analyses for patients with LN-only mUC from CheckMate 901 and JAVELIN Bladder 100 highlight the ability to further enhance responses with ICI-based therapies in an already favorable subgroup. The data presented here may support NIVO + GC as a standard of care for LN-only mUC given the potential for sustained CRs, which raises the possibility of cure. Maintenance avelumab also has promising efficacy in this subset after first-line chemotherapy in settings in which contemporary frontline regimens may not be available.

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