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Platinum Opinion

Adjuvant Immune Checkpoint Inhibition in Muscle-invasive Bladder Cancer: Is It Ready for Prime Time?

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Two recent phase 3 randomized controlled trials (RCTs)—Checkmate-274 [1] and IMvigor010 [2]—evaluated adjuvant immune checkpoint inhibitor (ICI) therapy for patients with resected high-risk muscle-invasive bladder cancer (MIBC) with or without neoadjuvant chemotherapy (NAC). Surprisingly, the trials reported inconsistent results despite similar designs (Table 1). In light of these findings, the role of adjuvant ICI in patients with high-risk resected MIBC warrants further discussion.

An examination of the primary endpoints of the two RCTs, within the limitations of cross-trial comparisons, reveals that median disease-free survival (DFS) in the adjuvant ICI groups was similar (20.8 mo [1] vs 19.4 mo [2]), but differed quite remarkably in the control arms, at 10.0 mo in Checkmate-274 and 16.6 mo in IMvigor010, which may have brought the Kaplan-Meier DFS curves for the ICI and control groups closer in IMvigor010 [2]. The control arms of the trials differ in that Checkmate-274 used placebo whereas IMvigor010 used observation for the control group. It is reasonable to use observation as the control arm because of the lack of standard adjuvant systemic therapy in this setting; however, this may have contributed to the stark difference in treatment discontinuation not related to disease progression or toxicities between the experimental arm (10%) and the observation arm (20%) in IMvigor010 [2], whereas a similar phenomenon was not apparent in Checkmate-274 [1]. Is the DFS analysis confounded by a greater proportion of patients who withdrew or were noncompliant in IMvigor010 because of randomization to an observation group? Or is this perhaps a patient selection bias involving more patients with aggressive upper-tract disease enrolled in Checkmate-274 (21%) than in IMvigor010 (7%)? Nevertheless, owing to the negative DFS benefit and the first interim overall survival (OS) analysis for IMvigor101 [2], there may be little evidence to support the use of adjuvant atezolizumab at this time.

On the contrary, pending OS analysis, it is promising that adjuvant nivolumab demonstrated both DFS and metastasis-free survival (MFS) benefits. Sonpavde et al [3] reported that 2-yr and 3-yr DFS are good surrogates for 5-yr OS for patients with resected MIBC, although they considered the adjuvant chemotherapy setting rather than adjuvant ICI. In addition, as MIBC is a disease with a high recurrence rate and high proportions of patients are unable to receive chemotherapy in the palliative setting, adjuvant nivolumab should be considered for those with resected high-risk MIBC. However, better patient selections would be required.

A review of currently available RCTs involving ICI in advanced bladder cancer (aBC) indicates that platinum-based chemotherapy may be more important than ICI, at least in first-line settings. Two phase 3 RCTs—Keynote-361 [4] and IMvigor130 [5]—failed to demonstrate an OS benefit with combined chemotherapy + ICI in first-line palliative-intent treatment in comparison to ICI or platinum-based chemotherapy alone. Only when patients achieved at least stable disease after chemotherapy did ICI show an OS benefit as a first-line "maintenance switch" therapy in the phase 3 Javelin Bladder 100 trial [6]. Pembrolizumab was also evaluated as a first-line "maintenance switch" therapy in an aBC population with at least stable disease after chemotherapy, but only a progression-free survival benefit was reported, without an OS benefit, probably because of inadequate statistical power as a phase 2 RCT [7]. From this perspective, it may be important

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Table 1 – Characteristics of Checkmate-274 and IMvigor010

	Checkmate-274	IMvigor010
Trial design	Phase 3, multicenter, double-blind randomized controlled trial	Phase 3, multicenter, open-label randomized controlled trial
Patient population	ypT2–4a or ypN+ MIBC after cisplatin-based NAC	ypT2-4a or ypN+ MIBC after cisplatin-based NAC
	pT3-4a or N+ MIBC without cisplatin-based NAC	pT3-4a or N+ MIBC without cisplatin-based NAC
	Must be disease-free within 4 wk of ICI initiation by imaging criteria	Must be disease-free before ICI initiation by pathology/imaging criteria
Surgery	Radical surgery within past 120 d	Radical surgery within ≤14 wk
ICI regimen	Nivolumab 240 mg IV every 2 wk up to 1 yr	Atezolizumab 1200 mg IV every 3 wk up to 1 yr
Control group	Placebo IV every 2 wk	Observation
Primary endpoint	DFS in intent-to-treat cohort	DFS in intent-to-treat cohort
	DFS in group with PD-L1 ≥1%	
Median follow-up (mo)	20.9 (nivolumab arm)	21.9
	19.5 (placebo arm)	
PD-L1 definition and assay	>1% positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells; 28-8 PharmDx IHC assay	PD-L1 expression on tumor-infiltrating immune cells ≥5% of tumor area; VENTANA SP142 IHC assay

	Checkmate-274		IMvigor010	
	ICI arm	Placebo arm	ICI arm	Placebo arm
Patients (*n*)	353	356	406	403
Mean age (yr)	65	65	67	66
Male (%)	75	77	79	78
ECOG performance status (%)				
0	64	62	61	64
1	35	35	35	32
2	2	3	4	4
Upper tract origin (%)	21	21	7	6
Neoadjuvant chemotherapy (%)	43	44	48	47
PD-L1–positive (%)	40	40	48	50
pN+ disease at resection (%)	47	47	48	48
Immune-related AEs (%)				
All grades	78	56	71	N/A
Grade ≥3	18	7	16	N/A

Survival analyses	Hazard ratio (95% confidence interval)	
Intent-to-treat cohort	**Checkmate-274**	**IMvigor010**
Disease-free survival	0.70 (0.55–0.90)	0.89 (0.74–1.08); $p = 0.2446$
Metastasis-free survival	0.75 (0.59–0.94)	NR
Overall survival	NR	0.85 (0.66–1.09); $p = 0.1951$
Disease-free survival		
NAC	0.53 (0.39–0.72)	0.87 (0.66–1.15)
Non-NAC	0.91 (0.69–1.21)	NR
PD-L1–positive		
Disease-free survival	0.56 (0.40–0.80)	1.01 (0.75–1.35)
Overall survival	NR	NR
PD-L1–negative		
Disease-free survival	0.82 (0.63–1.06)	0.81 (0.63–1.05)
Overall survival	NR	NR

AE = adverse event; ECOG = Eastern Cooperative Oncology Group; ICI = immune checkpoint inhibitor; IHC = immunohistochemistry; IV = intravenous; MIBC = muscle-invasive bladder cancer; NAC = neoadjuvant chemotherapy; NR = not reported.

to analyze survival benefits of adjuvant nivolumab in the context of NAC responses (ie, changes from pT/pN to ypT/ypN after NAC) to better identify the patient subgroup that might benefit from adjuvant nivolumab. In addition, this further consolidates the DFS and MFS benefits of adjuvant nivolumab in resected high-risk MIBC, especially for patients in the NAC group, while clinical equipoise exists in the non-NAC group owing to the Checkmate-274 study design.

Inclusion of resected MIBC with or without NAC for enrollment in the two trials more closely reflects real-world practice, in which more than half of patients would be cisplatin-ineligible. However, this scenario provides challenges in interpreting the survival benefit of adjuvant nivolumab in the non-NAC group. We recognize that this analysis was based on an underpowered subset, but the statistically significant result for adjuvant nivolumab was confirmed in the smaller NAC group ($n = 308$) but not the larger non-NAC group ($n = 401$). This observation suggests that even if adjuvant nivolumab without NAC was proven to have a survival benefit by increasing the sample size, it might be modest and relatively less than the benefit achieved with chemotherapy. Moreover, the non-NAC group is heterogeneous that includes cisplatin-ineligible patients and cisplatin-eligible patients who refused NAC. There is even more heterogeneity in the cisplatin-

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ineligible group in terms of performance status, renal function, and other comorbidities, all of which may have different prognostic effects on survival outcomes. Therefore, the patients who were cisplatin-eligible but refused NAC should be evaluated separately given that they are likely to be fitter and have fewer comorbidities in comparison to cisplatin-ineligible patients in the non-NAC group, although this may be more relevant in OS than in DFS analyses. Fortunately, quality of life as measured using the EORTC QLQ-C30 instrument was at least not negatively impacted by adjuvant nivolumab compared to placebo, despite significantly higher toxicities in the adjuvant nivolumab group.

According to the evidence currently available, cisplatin-based NAC remains the most important systemic treatment for patients with resectable MIBC. Barring the unavailability of OS analysis, adjuvant nivolumab (but not atezolizumab) may be considered, especially for those who have received NAC, given the high disease recurrence rate, the DFS/MFS benefit of adjuvant nivolumab, and the high proportion of patients unable to receive cisplatin-based chemotherapy in the palliative setting. For cisplatin-eligible patients who have not received NAC, we recommend an adjuvant cisplatin-based regimen rather than adjuvant nivolumab. While the use of adjuvant nivolumab remains controversial in the cisplatin-ineligible non-NAC group, adjuvant nivolumab may still be considered after careful risk-benefit discussions given the lack of treatment options in a disease with high recurrence rate, the absence of a negative quality-of-life impact, and the previously demonstrated antitumor efficacy as monotherapy in the cisplatin-ineligible metastatic setting [8,9]. Ongoing phase 3 RCTs, including adjuvant pembrolizumab with a similar study design (NCT03244384) [10], adjuvant atezolizumab in resected high-risk MIBC but randomized on the basis of circulating tumor DNA (NCT04660344) [11], and perioperative nivolumab ± bempegaldesleukin either before or after radical cystectomy in patients with MIBC not eligible for cisplatin (NCT04209114) [12], may provide more insights in this context.

Conflicts of interest: Adi Kartolo and Francisco E. Vera-Badillo have nothing to disclose. Wassim Kassouf has received honoraria from BMS, Astellas, Roche, Ferring, Janssen, Bayer, Sesen Bio, and Merck.

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