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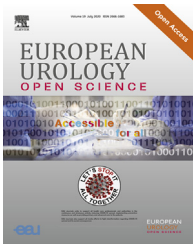

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Neoadjuvant Immunotherapy: The Next Gold Standard Before Radical Surgery for Urothelial Cancer

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Abstract

Cisplatin-based chemotherapy followed by radical cystectomy with bilateral pelvic lymph-node dissection is the current standard for cT2–4a N0 M0 urothelial bladder cancer. Immune checkpoint inhibitors have recently been tested in the neoadjuvant setting with promising pathological and survival results and a better safety profile. Excellent pathological responses have been observed, especially in cases with higher clinical T stage and PD-L1 expression, in addition to patients with selected gene signatures. In biomarker-selected patients, this manageable approach has the potential to become a new treatment option in the near future.

Patient summary: For patients with bladder cancer invading the bladder wall muscle, platinum-based chemotherapy has been the standard treatment. Increasing evidence suggests that an alternative first treatment for this disease could be immunotherapy. Novel biomarkers and further studies are needed to support this approach before it can be used in everyday clinical practice.

Elevated rates of metastatic relapse after radical cystectomy (RC) indicate that urothelial muscle-invasive bladder cancer (MIBC) is a systemic disease requiring a multimodal approach from diagnosis. The current standard of care for the treatment of nonmetastatic MIBC is cisplatin-based neoadjuvant chemotherapy (NAC) followed by RC and bilateral pelvic lymph-node dissection, for which adherence has been historically low (<25% of cases), resulting in a modest benefit of a 5% increase in overall survival (OS) and an 8–9% increase in disease-free survival (DFS) at 5 yr [1]. The reasons for underadministration include concerns about the renal toxicity of cisplatin, the delay to surgery in nonresponders, and a perceived marginal therapeutic benefit.

Apart from those who refuse NAC treatment, approximately 50% of patients with urothelial cancer (UC) are ineligible to receive cisplatin, and there is no standard preoperative therapy for this population. Although NAC is effective, residual high-risk disease after surgery (ie, at least muscle-invasive disease) is still present in approximately 60% of patients and is a factor for poor prognosis. Indeed, pathological complete response (pCR) at surgery has been identified as a surrogate endpoint for OS.

Immune checkpoint inhibitors (ICIs) have revolutionised the therapeutic landscape for advanced UC after platinum-chemotherapy failure, in the first-line setting for cisplatin-ineligible patients, and in the maintenance setting after first-line chemotherapy [2–4]. More recently, single-agent and combination ICIs have been tested in the MIBC preoperative setting, with promising pCR rates that are comparable to those for chemotherapy (Table 1). The first two studies published investigated single-agent anti–PD-1/PD-L1 treatment and three subsequent studies included ICI combinations [5–9].

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Table 1 – Efficacy data for immunotherapy in published clinical trials

Trial	PURE-01	ABACUS	NABUCCO	DUTRENEO	MDACC
Treatment	Pembrolizumab [5]	Atezolizumab [6]	Nivo + Ipi [7]	D + T [8]	D + T [9]
Patients (*n*)	114	88	24	23	28
Median age (yr)	66	73	65	66	71
Male/female (%)	82/18	85/15	75/25	87/13	71/29
Cisplatin eligibility	Yes	No	Yes [a]	Yes	No
cT2 stage (%)	54 (CT + mpMRI)	73	0	78.2	43
cN+ stage (%)	0 (6% PET scan +)	0	42	8.7	0
pT0N0 rate (%)	37	31	46	34.8	37.5
pT≤1N0 rate (%)	55	NA	58	56.5	58
1-yr RFS	91 (85–98) (EFS 87%) [10]	79 (67–87)	92	NA	82.8
Biomarkers	PD-L1$^+$	Pre-existing T-cell activation (CD8/GZMB, tGE8-high)	PD-L1$^+$	Preselected with 18-gene IFN-γ signature	TLS signature
	(TMB) Immune gene signatures		DDR-GA		
			TLS signature		

Nivo = nivolumab; Ipi = ipilimumab; D + T = durvalumab + tremelimumab; RFS = relapse-free survival; CT = computed tomography; mpMRI = multiparametric magnetic resonance imaging; PET = positron emission tomography; EFS = event-free survival; TMB = tumour mutational burden; DDR-GA = DNA damage response gene alteration; TLS = tertiary lymphoid structures; MDACC = MD Anderson Cancer Center; NA = not available.
[a] 46% of patients refused cisplatin-based chemotherapy.

We conducted the pivotal and innovative PURE-01 study to assess the safety and efficacy of three cycles of neoadjuvant pembrolizumab before RC in MIBC without nodal involvement, regardless of cisplatin eligibility. The pCR rate for pembrolizumab was 42% among 50 treated patients (37% among 114 patients in updated analyses) and was safely administered. Immune-related adverse events (irAEs) have been reported, but they were manageable and did not delay planned surgery, and postsurgical complications were similar to those reported in the literature for either open or robot-assisted procedures (Table 2). Of note, clinical T stage at diagnosis, PD-L1 expression (combined positive score ≥10%) and high tumour mutational burden (TMB; assessed with the FoundationOne assay) were predictive of pCR. Recent results for survival outcomes confirmed the favourable prognostic role of pCR for both event-free survival and OS [10].

For cisplatin-ineligible patients, the ABACUS trial achieved similar results after two cycles of preoperative atezolizumab, with a pCR rate of 31% in a cohort of 88 patients. Biomarker analyses showed that pre-existing activated T cells and expression of an immune gene signature correlated with outcomes. TMB did not predict response at RC. As in the PURE-01 study, neoadjuvant atezolizumab was well tolerated without any impact on surgical complications.

Three clinical trials investigated preoperative administration of anti-CTLA4 in combination with a PD-1/PD-L1 inhibitor in patients not treated with NAC. In the NABUCCO trial, van Dijk and colleagues [7] observed a pCR rate of 46% among patients treated with ipilimumab and nivolumab, including cases with locally advanced disease and nodal involvement. Lower rates were observed in the DUTRENEO and MDACC trials investigating the combination of durvalumab and tremelimumab, with pCR rates of 34.8% and 37.5%, respectively. In ICI combination trials the response was independent of T-cell infiltration or T-effector signature. Induction of tertiary lymphoid structures (TLS) during treatment was observed in responders, suggesting an adaptive antitumour immune response that probably induces rescue in patients with more locally advanced disease via the CTLA4 inhibition boost. The incidence of severe irAEs varied from 8% (DUTRENEO) to 55% (NABUCCO), with no significant increase in RC withholding because of immunotoxicities or in postsurgical complications. With the exception of one patient, no fatal irAEs were seen across all five studies [5–9].

The efficacy data and the long-term safety profile in comparison to standard chemotherapy, along with an initial survival signal, suggest that immunotherapy has the potential to become a new solid option in the neoadjuvant armamentarium. Considering the safety profile, ICI admin-

Table 2 – Safety profile of immunotherapy in published clinical trials

Trial	PURE-01	ABACUS	NABUCCO	DUTRENEO	MDACC
Treatment	Pembro	Atezolizumab	Nivo + Ipi	Durva + Treme	Durva + Treme
Any irAE (%)	18	51	100	34	93
G3/G4 irAEs (%)	6	11	55	8	21
G5 irAEs (%)	0	<1	0	0	0
RC withheld because of TRAEs	No	Yes (3%)	Yes (4%)	Yes (4%)	Yes (7%)
Most common (G3/G4)	TA/diarrhoea (2%)	TA (4%)	Lipase increase (25%)	Asthenia/TA (4.3%)	Lipase increase (14%)
Treatment discontinuation	Yes (2%)	Yes (3%)	Yes (25%)	No	Yes (7%)

Pembro = pembrolizumab; Nivo = nivolumab; Ipi = ipilimumab; Durva = durvalumab; Treme = tremelimumab; irAE = immune-related adverse event; RC = radical cystectomy; G = grade according to Common Terminology Criteria for Adverse Events v.4.0; TRAE = treatment-related adverse event; TA = transaminitis; MDACC = MD Anderson Cancer Center.

istration could be the best approach in the preoperative setting, and could also provide an optimal window of opportunity for exploratory analyses.

Identification of the optimal candidates for immunotherapy or chemotherapy is an intriguing and crucial issue in order to avoid diluting the benefit in the absence of predictive biomarkers. Unfortunately, identification of unique predictive biomarkers is unreliable and difficult in single-arm studies but is deemed essential to identify responders with a higher probability of pCR (with ICIs or NAC) and a tangible survival benefit. Confirmation of this therapeutic option and better patient selection on the basis of validated predictive biomarkers can only be confirmed by ongoing randomised clinical trials (RCTs) testing ICIs alone or in combination with chemotherapy in either cisplatin-eligible or -ineligible patients.

In the not-so-distant future, there might be an opportunity to apply a strategy that avoids aggressive local therapies (RC or chemoradiation) for patients predicted to have high probability of achieving pCR after neoadjuvant ICIs in the absence of viable tumour at post-neoadjuvant re-evaluation. To this end, organ-sparing clinical trials have already been planned for biomarker-selected patients.

Although we await new predictive biomarkers from RCTs, it seems that neoadjuvant ICIs represent an attractive and promising therapeutic strategy, especially for patients with high-risk disease who are not suitable for or amenable to chemotherapy.

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Study concept and design: Raggi, Moschini.
Acquisition of data: Raggi.
Analysis and interpretation of data: Necchi, Raggi.
Drafting of the manuscript: Raggi.
Critical revision of the manuscript for important intellectual content: Moschini, Necchi.
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Supervision: Necchi.
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