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Towards Personalized Neoadjuvant Therapy for Muscle-invasive Bladder Cancer

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The use of immune checkpoint blockade (ICB) continues to break new ground in the management of bladder cancer. Results from a phase 2 study investigating the efficacy of pembrolizumab (PURE-01) in the neoadjuvant setting for muscle invasive bladder cancer (MIBC) indicate a pathologic complete response (pCR) rate of 42% [1], similar to that reported following neoadjuvant cisplatin-based chemotherapy [2]. As pembrolizumab was well tolerated (only 3 of 50 patients developed a grade 3 adverse event, leading to one treatment discontinuation) and did not delay radical cystectomy (RC), the study points towards establishing ICB as a viable neoadjuvant option. Since the publication of the results, the PURE-01 study has been amended to increase the sample size (n = 136), corroborate the role of biomarkers, and expand the eligibility to nonurothelial histologies. An additional cohort of patients with high-risk upper-tract urothelial carcinoma will also be enrolled (PURE-02; n = 40).

Before being adopted as a standard of care, several aspects of combination therapy using neoadjuvant ICB and RC require elucidation. First, although pCR has been firmly established as a surrogate endpoint for survival following neoadjuvant chemotherapy [2], this association has yet to be confirmed in the neoadjuvant ICB setting. Second, while preliminary analysis indicates similar postsurgical complications to those previously reported following RC, whether the immunogenic activity unleashed by ICB can lead to a different set of health problems is unknown. Anecdotally, desmoplastic reaction has been observed following neoadjuvant ICB, potentially distorting normal surgical fields. Furthermore, the effects of ICB on postoperative healing and the autoimmune complications after surgery have yet to be characterized. To address these questions, a direct comparison of the perioperative outcomes following neoadjuvant chemotherapy versus ICB is needed.

Finally, there is a clear dichotomy in pCR rates between patients with high and low pretreatment PD-L1 expression, measured as the combined positive score (CPS). While 54.3% of patients with CPS $\geq$10% were found to be pT0, only 13.3% of those with CPS $<$10% achieved pCR [1]. This was corroborated in another window-of-opportunity study using neoadjuvant atezolizumab in cisplatin-ineligible patients with MIBC, in which pT0 was found in 40% of PD-L1-positive patients versus 16% in the PD-L1–negative cohort [3]. The poor response among PD-L1–negative patients is reminiscent of findings of poor overall survival for pembrolizumab- and atezolizumab-treated patients with metastatic or locally advanced urothelial cancer and low PD-L1 expression, which prompted a revision of their US Food and Drug Administration labels restricting use to cisplatin-ineligible patients with high PD-L1 expression [4]. In addition, a significant association was found between high tumor mutational burden (TMB) and pCR. In the updated data set (n = 82), among patients with TMB $\geq$15 mutations/Mb, 36.7% pT0 versus 10.2% non-pT0 was observed.

From a practical standpoint, pretreatment PD-L1 and TMB can serve as biomarkers to guide future clinical trial design to decipher how best to personalize neoadjuvant systemic therapy (Fig. 1).

While it is clear that patients with high CPS and TMB features are the most suitable candidates for neoadjuvant immune monotherapy, regardless of their cisplatin eligibility, the majority of patients diagnosed with MIBC ultimately fall into the “grey zone of uncertainty”, defined by the presence of one favorable biomarker only. Specifically, low

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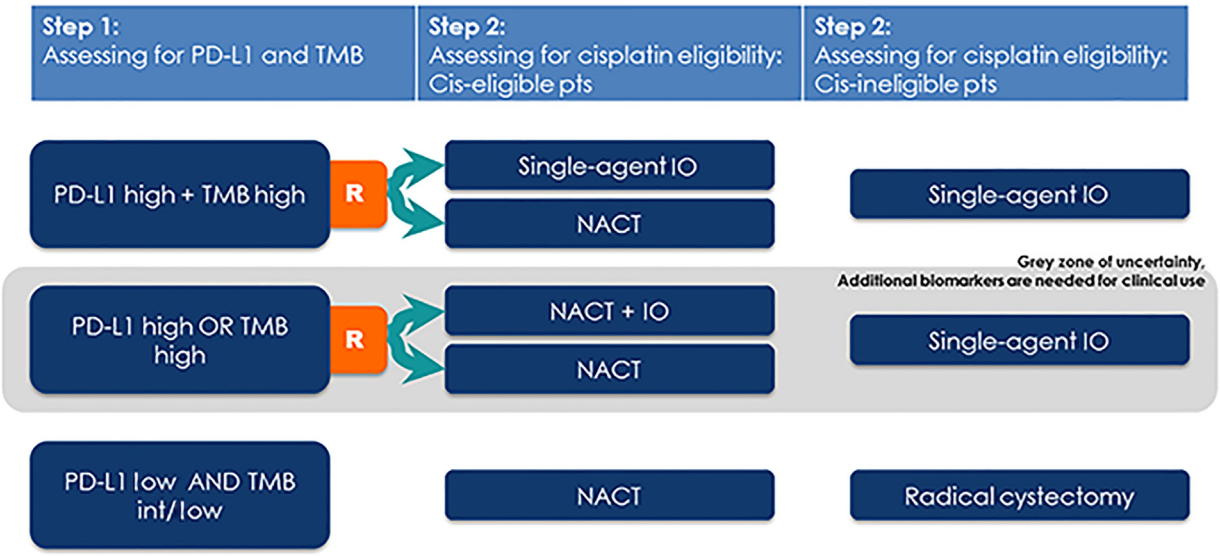

Fig. 1 – Rational development of clinical trials to personalize neoadjuvant therapy for patients with muscle-invasive bladder cancer. PD-L1 expression and tumor mutation burden (TMB) were significantly correlated with response to neoadjuvant pembrolizumab. Cisplatin-eligible patients with high PD-L1 expression and TMB should be randomized to single-agent immuno-oncology (IO) or neoadjuvant chemotherapy (NACT), while cisplatin-ineligible patients should be treated with IO. Cisplatin-eligible patients with one positive biomarker (PD-L1 high or TMB high) should be randomized to combination NACT + IO versus NACT alone, while those who are cisplatin-ineligible should be treated with single-agent IO. Patients with negative biomarkers should receive NACT if eligible, with upfront cystectomy offered to those who are ineligible for NACT. Cis = cisplatin.

PD-L1 expression may serve as a surrogate marker for a nonimmunogenic tumor microenvironment, rendering ICB treatment ineffective [5]. This hypothesis was supported by comparison of gene expression levels between pT0 and non-pT0 patients in the PURE-01 trial, with informative differences found in IFN-γ signaling, antigen presentation, T-cell functional differentiation, chemokines/chemokine receptors, inhibitory receptors and ligands, and the immunosuppressive gene *IDO1*. By contrast, PD-L1 expression, at least on tumor cells, did not correlate with response

Table 1 – Overview of ongoing neoadjuvant trials in muscle-invasive bladder cancer

	Location	Eligibility	Cisplatin eligibility	Trial identifier	Status
Single-agent therapy					
Pembrolizumab (PURE-01)	Italy	T2–3aN0M0	Yes	NCT02736266	Has results
Pembrolizumab (PANDORE)	France	T2–4N0 or Nx	No	NCT03212651	Enrolling
Atezolizumab	South Korea	T2–4aN0M0	N/A	NCT03577132	Enrolling
Atezolizumab	USA	T < 2, T2–4N0M0	No	NCT02451423	Enrolling
Avelumab (BL-AIR)	USA	T2–4aN0M0	No	NCT03498196	Enrolling
Atezolizumab (ABACUS)	Europe	T2–4aN0M0	No	NCT02662309	Has results
Immune combination therapy					
Nivolumab/urelumab	USA	T2–4aN0M0	No	NCT02845323	Enrolling
Nivolumab/ipilimumab (NABUCCO)	Netherlands	T3–4N0 or N+	No	NCT03387761	Enrolling
Durvalumab/tremelimumab vs chemotherapy (DUTRENEO)	Spain	T2–4N0 or N1	Yes	NCT03472274	Enrolling
Durvalumab/tremelimumab (NITIMIB)	Switzerland	T2–4N0 or N+	No	NCT03234153	Enrolling
Durvalumab/tremelimumab	MDACC	T2–4aN0M0	No	NCT02812420	Enrolling
Nivolumab ± ipilimumab (CA209-9DJ)	MSKCC	T2–4aN0M0	No	NCT03520491	Enrolling
Durvalumab + olaparib (NEODURVARIB)	Spain	T2–4aN0M0	No	NCT03534492	Enrolling
Chemoimmunotherapy combinations					
Nivolumab + gemcitabine/cisplatin (BLASST-1)	USA	T2–4aN0M0	Yes	NCT03294304	Enrolling
Avelumab (AURA) ± chemotherapy	Belgium	T2–4N0 or N+	Yes/No	NCT03674424	Enrolling
Pembrolizumab + gemcitabine/cisplatin	USA	T2–4N0 or Nx	Yes	NCT02690558	Enrolling
Pembrolizumab + gemcitabine/cisplatin	Indiana University	T2–4aN0M0	Yes	NCT02365766	Has results
Nivolumab + gemcitabine/cisplatin	HCRN	T2–4aN0M0	Yes	NCT03558087	Enrolling
Gemcitabine/cisplatin ± durvalumab (NIAGARA)	Multicenter international	T2-4aN0M0	Yes	NCT03732677	Enrolling
Chemotherapy vs. chemotherapy + nivolumab, ± BMS-986205 (CA017-078)	Multicenter international	T2–4aN0M0	Yes	NCT03661320	Enrolling
Durvalumab + tremelimumab + dose-dense MVAC (NEMIO)	French multicenter	T2–4aN0–1M0	Yes	NCT03549715	Not yet enrolling

MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin; MDACC = MD Anderson Cancer Center; MSKCC = Memorial Sloan Kettering Cancer Center; HCRN = Hoosier Cancer Research Network; N/A = not available.

to chemotherapy [6]. Intriguingly, failure to ICB treatment may even potentiate response to subsequent chemotherapy, with response rates as high as 64% [7]. Despite the small sample size in which this phenomenon was observed, synergistic effects stemming from combination ICB and chemotherapy can be explained by the immunomodulatory activities associated with agents such as gemcitabine, platinum, and taxanes.

A similar rationale exists in support of combining ICB with other immunostimulatory agents (Table 1). With our increasing understanding of the cancer-immunity cycle, it has become clear that antineoplastic immunity not only can be dialed up by neutralizing the inhibitory mechanisms present in the tumor microenvironment (using ICB) but also can be stimulated by inducing immunogenic recognition of neoantigens specific to the cancer [8]. Ribas et al. [9] hypothesized that therapies designed to attract $CD8^+$ T cells and in turn alter the immunosuppressive tumor microenvironment can improve the antitumor activity of PD-1 blockade. In a phase 1b trial in advanced melanoma patients, the authors demonstrated increased $CD8^+$ T cell infiltration along with increases in PD-L1 and IFN-γ expression following intralesional injection of the oncolytic virus talimogene laherparepvec (T-VEC), leading to a 33% CR rate [9]. Owing to its easy accessibility and separation from the systemic circulation provided by the multilayered membrane, the bladder is a suitable target for oncolytic virotherapy. Priming of the tumor microenvironment within the bladder is a strategy familiar to urologists. Since its introduction more than four decades ago, intravesical bacillus Calmette-Guérin (BCG) has been the standard of care for non-muscle-invasive bladder cancer (NMIBC) at high risk of recurrence or progression. Clinical trials investigating the efficacy of combination therapy using BCG priming and ICB are currently under way (NCT02324582). Oncolytic virotherapy has also been used in bladder cancer. It has been demonstrated that CG0070, a replication-competent oncolytic virus that targets bladder tumor cells through their defective retinoblastoma pathway, is safe and effective (6-mo CR rate of 47%) in BCG-unresponsive NMIBC patients [10]. Whether the use of an oncolytic virus can prime the tumor microenvironment and bolster the efficacy of ICB remains to be seen.

After 30 yr at a standstill, a number of new therapeutic treatments for bladder cancer have broken the gridlock. With this myriad of treatment options, however, critical questions regarding how best to customize their delivery to optimize outcomes have now emerged. We must continue to scrutinize trial results and corollary biomarker analyses and utilize them to inform rational design of clinical trials to truly personalize care for our patients.

Conflicts of interest: Andrea Necchi has received honoraria from Roche, Merck, AstraZeneca, and Janssen Pharmaceuticals; acts in a consulting or advisory role for Merck Sharp & Dohme, Roche, Bayer, AstraZeneca, Clovis Oncology, Janssen Pharmaceuticals, Incyte, BioClin Therapeutics, Seattle Genetics, and Astellas Pharma; has received institutional research funding form Merck Sharp & Dohme and AstraZeneca; and has received travel and accommodation expenses from Roche, Merck Sharp & Dohme, AstraZeneca, and Janssen Pharmaceuticals. The remaining authors have nothing to disclose.

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