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Letter to the Editor

Re: Ruben Raychaudhuri, Ali Raza Khaki, Mary W. Redman, et al. Neoadjuvant Pembrolizumab and Accelerated Methotrexate, Vinblastine, Doxorubicin, and Cisplatin in Nonurothelial Histologic Subtypes of Muscle-invasive Bladder Cancer: A Phase 2 Trial. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2025.07.002

We read with great interest the article by Raychaudhuri et al [1] reporting results from a phase 2 trial of neoadjuvant pembrolizumab plus accelerated methotrexate, vinblastine, doxorubicin, and cisplatin in nonurothelial histologic subtypes of muscle-invasive bladder cancer. The study provides valuable prospective data for a patient population that is typically under-represented in clinical research and demonstrates encouraging results, with a pathologic complete response (pCR) rate of 53% and favorable survival estimates.

While we commend the authors for these important findings, some aspects warrant further discussion. First, although pCR represents a practical and appropriate endpoint for phase 2 trials, its role as a validated surrogate for long-term outcomes—particularly overall survival (OS)—remains unproven in muscle-invasive disease, and even more so in rare histologic variants. Prior studies such as PURE-01 [2] and ABACUS [3] have shown that pathologic responses may not consistently translate into a durable benefit across different subtypes, underscoring the need for caution in interpreting these results.

Second, the study did not include circulating tumor DNA (ctDNA) analysis, which is emerging as a powerful tool for detection of minimal residual disease and prediction of recurrence risk, as demonstrated in perioperative trials such as IMvigor010 [4] and CheckMate-274 [5]. Incorporation of ctDNA dynamics in neoadjuvant studies, particularly in variant histologies, could provide complementary information to pCR data, improve risk stratification, and inform the design of future biomarker-driven strategies.

Overall, this trial represents an important step forward for a challenging and understudied population, and highlights the need for larger, subtype-specific investigations that include robust translational endpoints to refine both therapeutic strategies and surrogate markers of long-term patient benefits.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Raychaudhuri R, Khaki AR, Redman MW, et al. Neoadjuvant pembrolizumab and accelerated methotrexate, vinblastine, doxorubicin, and cisplatin in nonurothelial histologic subtypes of muscle-invasive bladder cancer: a phase 2 trial. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2025.07.002.

[2] Necchi A, Raggi D, Gallina A, et al. Updated results of PURE-01 with preliminary activity of neoadjuvant pembrolizumab in patients with muscle-invasive bladder carcinoma with variant histologies. Eur Urol 2020;77:439–46. https://doi.org/10.1016/j.eururo.2019.10.025.

[3] Powles T, Kockx M, Rodriguez-Vida A, et al. Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial. Nat Med 2019;25:1706–14. https://doi.org/10.1038/s41591-019-0628-7.

[4] Galsky MD, Arija JÁA, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130) and adjuvant atezolizumab in muscle-invasive urothelial carcinoma (IMvigor010). Lancet Oncol 2020;21:44–56. https://doi.org/10.1016/S1470-2045(19)30787-9.

[5] Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. N Engl J Med 2021;384:2102–14. https://doi.org/10.1056/NEJMoa2034442.

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