Dual checkpoint blockade promising as pre-surgical approach for certain patients with localized bladder cancer

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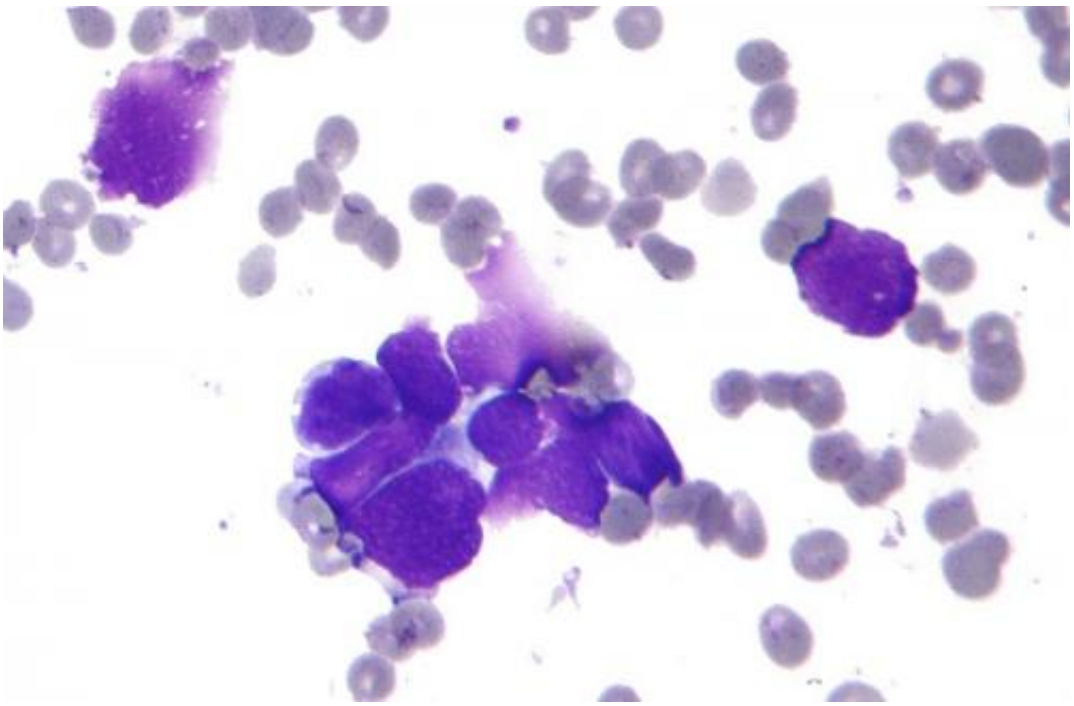

Micrograph of a lung primary small cell carcinoma, a type of carcinoma. Credit: Wikipedia

Neoadjuvant, or pre-surgical, combination treatment with the immune checkpoint inhibitors tremelimumab (anti-CTLA-4) and durvalumab (anti-PD-1) was well-tolerated and showed early signs of activity in certain patients with localized bladder cancer who do not have standard

treatment options available, according to a Phase I clinical trial conducted by The University of Texas MD Anderson Cancer Center.

This represents the first neoadjuvant trial of combination immunotherapy for bladder cancer patients ineligible to receive cisplatin-based chemotherapy, all of whom had tumors with high-risk features that are associated with unfavorable outcomes. The study results, published today in *Nature Medicine*, also shed important insight into biomarkers associated with treatment responses.

Of the 28 patients enrolled in the trial, 24 completed bladder removal surgery on the study with nine (37.5%) achieving a pathologic complete response (pCR), meaning there were no signs of cancer evident at the time of surgery. Additionally, in 12 patients with particularly large tumors (stage T3-T4), the pCR rate was 42%, and half saw their tumor size reduced to stage T1 or less.

"This study provides early evidence that neoadjuvant treatment with combination checkpoint inhibitors is feasible in a group of patients who are in need of additional treatment options," said lead author Jianjun Gao, M.D., Ph.D., associate professor of Genitourinary Medical Oncology. "In this small group of patients, the combination treatment had an acceptable safety profile with encouraging activity that supports further clinical studies in this setting."

Advancing new immunotherapy options for patients in need

For patients with localized bladder cancer, standard therapy includes cisplatin-based chemotherapy followed by surgery. However, up to half of patients are ineligible for cisplatin treatment because of conditions such as poor kidney function, heart failure or neuropathies, leaving them

without standard therapy options, explained Gao.

Previous clinical trials have evaluated neoadjuvant immune checkpoint blockade in bladder cancer, but these studies included only single agents and did not focus on those with high-risk tumors.

High-risk tumors are marked by certain features, including large size, variant histology, lymphovascular invasion, hydronephrosis, and/or disease located in the upper tract of the urothelium. Patients with these tumors tend to have poor survival compared to the average patient with localized disease.

"Immune checkpoint therapy has clearly revolutionized cancer care with patients with metastatic disease in multiple tumor types, but we continue to work toward moving these therapies into earlier disease settings for patients in need," said corresponding author Padmanee Sharma, M.D., Ph.D., professor of Genitourinary Medical Oncology and Immunology. "By combining these therapies, we felt we could take advantage of the distinct biologic mechanisms and stimulate a more robust anti-tumor immune response for these patients."

The current trial builds on longstanding efforts by Sharma at MD Anderson to advance checkpoint inhibitors for treating patients with localized disease. In 2008, Sharma and colleagues published results from the first-ever trial of neoadjuvant checkpoint blockade (ipilimumab) in patients with localized bladder cancer in the *Proceedings of the National Academy of Sciences*.

Evaluating dual checkpoint blockade and biomarkers of response

The trial enrolled 28 cisplatin-ineligible patients with high-risk localized

bladder cancer at MD Anderson. Each patient received two doses of durvalumab and tremelimumab in combination and 24 patients completed surgery following treatment. Trial participants were 82% Caucasian and 18% Black or other races. Median age was 71 with men accounting for 71% and women 29% of participants.

Most patients experienced immune-related side effects, the most common of which were grade 1-2 rash (29%) and asymptomatic increases in amylase (29%). Six patients (21%) experienced grade 3 or higher immune-related adverse events, including asymptomatic laboratory values, hepatitis and colitis. No treatment-related deaths occurred.

Median overall survival has not been reached, and 24 patients were still alive at one year. In addition, 82.8% of patients that had surgery were free of disease recurrence at one year.

The researchers also collected pre- and post-treatment blood and tissue samples from patients to study biomarkers associated with response in collaboration with MD Anderson's immunotherapy platform, which is co-led by Sharma. The platform is part of MD Anderson's Moon Shots Program, a collaborative effort to accelerate the development of scientific discoveries into clinical advances that save patient's lives.

The researchers identified a higher density of specialized immune-cell clusters called tertiary lymphoid structures (TLS) in pre-treatment tumor samples from patients who responded well to combination therapy relative to those who did not respond. A higher density of TLS correlated with longer overall survival and relapse-free survival.

While these findings need to be confirmed in larger studies, the data suggests that TLS may serve as a useful predictive biomarker for those who will respond to checkpoint blockade, explained Sharma. These

findings are in agreement with previously published MD Anderson research reporting that an enrichment of B cells within TLS were predictive of response to checkpoint inhibitors in patients with melanomas, soft-tissue sarcomas and renal cell carcinomas.

More information: Neoadjuvant PD-L1 plus CTLA-4 blockade in patients with cisplatin-ineligible operable high-risk urothelial carcinoma, *Nature Medicine* (2020). DOI: 10.1038/s41591-020-1086-y

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