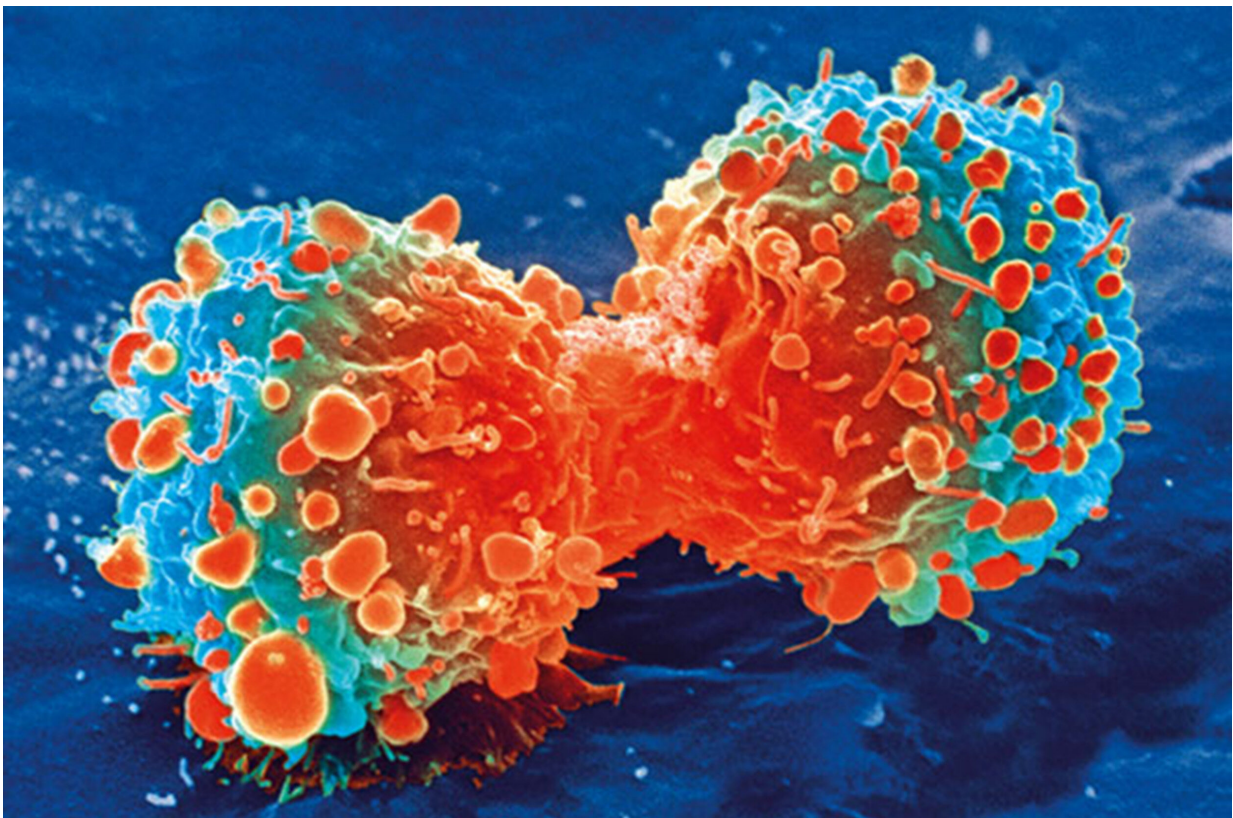


Combination biomarker predicts response to immune checkpoint therapy in patients with advanced bladder cancer

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Cancer cell during cell division. Credit: National Institutes of Health

In patients with metastatic bladder cancer, a novel combination of biomarkers from baseline tumor tissues was predictive of improved

clinical responses and prolonged survival following treatment with immune checkpoint inhibitors, according to researchers from The University of Texas MD Anderson Cancer Center.

The study, published today in *Science Translational Medicine*, used multi-platform analyses of [tumor](#) samples to discover that ARID1A mutations in [tumor cells](#) and expression of the immune signaling protein CXCL13 in surrounding [immune cells](#) were enriched in patients who responded well to checkpoint inhibitors.

Retrospective analyses of two Phase II clinical trials confirmed that each of these biomarkers was associated with improved overall survival (OS), but a combination of these biomarkers was predictive of better OS compared to either [biomarker](#) alone. Patients with ARID1A mutations and high CXCL13 expression saw a median OS of more than 17 months in both trials, compared to fewer than eight months in patients with no mutations and low CXCL13 expression.

"Most biomarker studies have been limited to a single biomarker, such as tumor mutational burden or PD-L1 expression," said lead Sangeeta Goswami, M.D., Ph.D., assistant professor of Genitourinary Medical Oncology. "Our study indicates that combinatorial biomarkers that reflect both the tumor mutational status and immune response will improve predictive capability of the biomarker and may enable better patient selection for treatment with immune checkpoint therapy."

Urothelial cancers, which include bladder cancers as well as those of the renal pelvis and ureter, are the sixth most common cancer type in the U.S., and five-year OS rates for patients with metastatic cancers are roughly 5%. The approval of immune checkpoint therapy as an option for these patients has improved outcomes, explained Goswami, but only 15-20% of patients will see a benefit.

Currently, there are no clinically useful biomarkers to predict responses. Therefore, the research team performed immune and genomic profiling of baseline tumor tissues from MD Anderson patients participating in ongoing [clinical trials](#) to identify novel markers associated with responses to checkpoint inhibitors.

The work was done in collaboration with MD Anderson's immunotherapy platform, which is co-led by corresponding author Padmanee Sharma, M.D., Ph.D., professor of Genitourinary Medical Oncology and Immunology. 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.

Following discovery of the biomarkers, reverse translational studies in mouse models confirmed that ARID1A knockdown increased sensitivity to checkpoint blockade, whereas loss of CXCL13 expression rendered mice resistant to checkpoint inhibitors.

The researchers next sought to confirm the predictive capability of these biomarkers in additional cohorts from the Phase II CheckMate275 and IMvigor210 trials, which evaluated nivolumab or atezolizumab in patients with advanced urothelial cancers.

In the CheckMate275 trial, ARID1A mutations were associated with a median OS of 11.4 months compared to 6.0 months in those without mutations. High CXCL13 expression was associated with median OS of 13.5 months compared to just 5.7 months in those with the lowest CXCL13 expression. Patients with both markers had a median OS of 19.1 months compared to 5.3 months in patients with neither marker.

The IMvigor210 trial showed similar results. Patients with ARID1A mutations had a median OS of 15.4 months compared to 8.2 months in

those without. Median OS was 17.1 months and 8.0 months in patients with high and low CXCL13 expression, respectively. Finally, patients with both biomarkers had a median OS of 17.8, while those without either biomarker had a median OS of just 7.1 months.

"We hope that our study will highlight the importance of developing combinatorial biomarkers that consider both tumor cells and immune cells," said Sharma. "This approach may identify better biomarkers that can reliably predict response to immune checkpoint therapy across various tumor types."

As this was a retrospective study, the researchers currently are planning a clinical trial to prospectively evaluate outcomes for [patients](#) who are positive for the combination biomarker following treatment with anti-PD-1 therapy.

More information: S. Goswami et al., "ARID1A mutation plus CXCL13 expression act as combinatorial biomarkers to predict responses to immune checkpoint therapy in mUCC," *Science Translational Medicine* (2020). [stm.sciencemag.org/lookup/doi/ ... scitranslmed.abc4220](https://stm.sciencemag.org/lookup/doi/10.1126/scitranslmed.abc4220)

Provided by University of Texas M. D. Anderson Cancer Center

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