

Discovery could improve survival of bladder cancer patients

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In a discovery that could improve the survival of bladder cancer patients, Northwestern Medicine scientists have developed a biomarker signature test to predict which tumors will respond to immunotherapy.

Checkpoint immunotherapy drugs, which activate the body's immune system to recognize a tumor, are effective for only about 20% of bladder cancers. But clinicians don't know which patients will benefit and why they are not more effective for all patients.

In the new study—with multiple international collaborators—Northwestern University Feinberg School of Medicine investigators identified three types of tumors that could respond to immunotherapy and two that could not. Using a combination of gene expression profiling, mutations and spatial proteomics, the scientists also analyzed the non-responsive cancers to identify potential new drugs and therapies that could be used to make them responsive to immunotherapy.

The study will be published April 27 in *Nature Communications*.

Bladder cancer, the fourth-most diagnosed cancer in men in the U.S., is often lethal, and has not seen improvement in survival for the last 30 years.

"Immunotherapy has changed the way we treat bladder cancer, but it has significant limitations in that most patients will not respond to therapy," said lead investigator Dr. Joshua Meeks, associate professor of urology at Feinberg and a Northwestern Medicine urologist. "Thousands of patients have their bladder removed every year, and treating these patients with immunotherapy could improve survival and potentially increase their chance of keeping their bladder rather than having it surgically removed."

In this study, investigators started with a Phase II trial of 82 patients treated with Keytruda (an immunotherapy) before bladder removal. This was a unique trial that evaluated the [gene expression profile](#) before and after Keytruda, with the ability to fully measure the response to Keytruda when the bladder was removed. Normally, Keytruda and other

immunotherapies are used in patients with metastatic cancer, and the biological changes that occur in the tumor are unable to be monitored with tumor biopsies. By profiling the transcriptome, DNA alterations, and spatial changes that occurred in tumors treated with Keytruda, investigators were able to identify what features were associated with response or resistance.

For example, one-third of tumors were found in a subtype with very few tumor-infiltrating [immune cells](#) but increased expression of the oncogene pathway regulated by FGFR3 and a novel regulatory network of genes activated by an epigenetic regulator KDM5B. By targeting FGFR3 or KDM5B, the investigators could re-awaken an immune response. Clinical trials using new combinations of medications and immunotherapy to overcome immune resistance will start at Northwestern Medicine within the following year.

In addition, the study's findings also provide "a morefunctional [cancer genome atlas](#)," said Meeks, who also is the Edward Schaeffer, M.D., Ph.D. Professor of Urology and a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. "The current genome atlas looks at the fundamental building blocks of bladder cancer but doesn't describe any treatment. That's what makes this evaluation significant. This is about how bladder cancer responds to immunotherapy."

The Cancer Genome Atlas is a National Cancer Institute cancer genomics program that molecularly characterized over 20,000 primary cancers. The lead author of this paper, Dr. A. Gordon Robertson, was also a lead investigator in the [bladder cancer](#) genome atlas.

The findings resulted from multiple collaborations with international groups that could perform trials with immunotherapy that were not available in the U.S. "Through team science endeavors, we were able to

leverage different expertise and rare clinical trial specimens to answer important questions about which patients will respond to [immunotherapy](#) for the treatment of [bladder cancer](#)," Meeks said.

Northwestern scientists collaborated with lead clinical investigators from Italy (Dr. Andrea Necchi) and the U.K. (Dr. Thomas Powles.) to develop a biomarker with bioinformaticists from Canada and France (Clarice Groeneveld). Investigators then validated this biomarker in a third cohort treating patients worldwide.

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