Biomarker may help predict survival in patients with bladder cancer

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Long-term survival data from the first prospective, randomized biomarker validation trial in patients with muscle-invasive bladder cancer being treated with cisplatin-based chemotherapy before surgery will be reported at the 2022 Genitourinary Cancers Symposium of the

American Society of Clinical Oncology (GU ASCO) on February 18, 2022.

The results are from the S1314 clinical trial conducted by the SWOG Cancer Research Network, a cancer clinical trials group funded by the National Cancer Institute (NCI), part of the National Institutes of Health (NIH).

Primary results of the S1314 study were published in the journal *Clinical Cancer Research* in 2021 and reported an association between a gene-expression biomarker called the COXEN GC score and a tumor's pathologic response to chemotherapy. The new findings being presented at GU ASCO are results of a prespecified secondary analysis of S1314 data that looked for associations between COXEN score and how long a patient lived after starting treatment (a measure known as overall survival, or OS), and between COXEN score and how long a patient lived without their disease getting worse (known as progression-free survival, or PFS).

The work was led by Thomas W. Flaig, MD, a SWOG investigator at the University of Colorado Cancer Center and vice chancellor for research at the University of Colorado Anschutz Medical Center. "The work on S1314 was a tremendous collaborative effort across many institutions," Flaig said, "and it provides important information on patients being treated with preoperative chemotherapy for bladder cancer."

The S1314 trial enrolled 237 patients with muscle-invasive urothelial bladder cancer that had not spread to other parts of the body (had not metastasized), all of whom were slated to have surgery for their cancer.

After they enrolled in the study, patients were assigned at random to receive neoadjuvant chemotherapy—that is, chemotherapy before surgery—on one of two treatment arms. Patients on the first arm were

treated with a combination of two drugs—gemcitabine and cisplatin (GC). Those on the second arm were treated with a dose-dense cocktail of four drugs: methotrexate, vinblastine, doxorubicin, and cisplatin (known as MVAC). All patients had surgery after completing chemotherapy. Doctors examined the tumors removed from patients to determine whether they had shrunk in response to the chemotherapy.

The COXEN score (short for co-expression extrapolation score) is generated by a test that measures the expression, or activity level, of a specific set of genes in a patient's tumor cells. The COXEN test is tailored to each treatment. Roughly speaking, it attempts to predict how sensitive a tumor is to a specific drug or to a combination of drugs.

The S1314 trial used a separate, treatment-specific COXEN test for each of the two treatment combinations. These two tests were called COXEN GC and COXEN MVAC. Before the trial started, researchers identified a specific cutoff score for each test—scores above that cutoff were considered favorable, scores below it unfavorable.

The trial was designed to determine whether a better COXEN score was associated with a more favorable response to chemotherapy. The goal was to determine whether the COXEN score could serve as a potential biomarker that could then be validated later in a prospective clinical trial. The primary trial results had shown that the COXEN GC score could predict pathologic response to chemotherapy among a pooled analysis of patients from both the GC and MVAC treatment arms.

In the secondary analysis reported at GU ASCO, the researchers found no significant association between the COXEN GC score and OS or PFS in the GC treatment group, nor between the COXEN MVAC score and OS or PFS in the MVAC treatment group. However, when they looked at the COXEN GC score values for both treatment groups combined, they found that the score was a significant predictor of overall survival.

Flaig emphasized that much more remained to be learned from S1314. "There is very little prospective data in this setting," he said, "and beyond the COXEN analysis reported here, samples and patient outcomes from S1314 are being used to facilitate the evaluation of several additional biomarkers."

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