

New crizotinib side-effect: Reduced measures of kidney function during treatment (recovery after)

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A University of Colorado Cancer Center study published today in the journal *Cancer* shows that using crizotinib to treat ALK positive non-small cell lung cancer (NSCLC) appears to reduce kidney function when assessed by one of the most commonly used clinical methods. Whether this reflects a true effect of crizotinib on kidney function, or only on the accuracy of this particular method for assessing it is being studied.

Though kidney function recovered in almost all cases after the crizotinib was stopped, as patients may be on crizotinib for months or even years researchers recommend additional tests of kidney function if they are worried about changes in the standard kidney function test or are concerned about using other drugs that interact with the kidneys concurrently with crizotinib.

"Crizotinib is such a powerfully effective drug for patients with ALK positive lung cancer that approval was fast-tracked by the FDA. This was wonderful: it got the drug into clinics quickly. But it also means that the dataset on side effects available to write the initial instruction booklet on the drug was pretty small at the time. Clinicians in the community starting to use this and other fast-tracked drugs may therefore be the ones tasked with noticing some side-effects for the first time," says Ross Camidge, MD, PhD, director of the thoracic oncology clinical program at the University of Colorado Cancer Center and the senior author of the study.

For another example of a side effect that was not in the original data presented to the FDA, in an earlier study Camidge and colleagues showed that testosterone is reduced by [crizotinib](#) in 84 percent of male patients taking the drug.

"These patterns may be right there in front of our eyes, but because they haven't been described before sometimes you can talk yourself out of being the one to discover something new. As anti-cancer drugs enter the pharmacy quicker and quicker, we have to empower the hundreds and thousands of doctors out there to believe in what they might see in their clinics and report things, leveraging all that experience for the greater good. In the cases of altered measures of kidney function and lowered testosterone with crizotinib, once we notice these side-effects and get the word out, patients can be much more appropriately managed," Camidge says.

The study, conducted by Camidge along with other CU Cancer Center researchers including first author Evelyn Brosnan, MD – who was a final year medical student mentored by Dr. Camidge at the time of the research – evaluated 38 patients with stage IV ALK positive NSCLC. The team used a simple blood test called creatinine to assess patients' kidney function converting it by a formula into an estimated glomerular filtration rate (GFR) before, during and after crizotinib treatment.

Patients' mean GFR fell by 23.9 percent following the commencement of crizotinib, with the majority of the drop occurring during the first two weeks of treatment before the effects leveled out. Fortunately, in the 16 patients for whom post-crizotinib data were available, all rapidly recovered their estimated kidney function back to 84 percent of their original values or more once the drug was stopped. If a patient's baseline kidney function is good the change in kidney function induced by crizotinib may not shift the estimated GFR outside of the normal range. However, in their paper, Brosnan and colleagues describe an early case

of a patient with pre-existing [kidney damage](#) whose creatinine-assessed kidney function reduced to a worryingly low level with crizotinib, such that a clinical decision was made to discontinue the drug.

"In addition to these data adding to the literature on the side effects of crizotinib, this study was a strong example of the collaboration possible in the university setting and at a comprehensive [cancer center](#)," said Dr. Brosnan, now a resident physician in Dartmouth, NH. "After Dr. Camidge's initial clinical observation of potentially lowered kidney function in crizotinib patients, because of the great record keeping in the Cancer Center, I was able to quickly extract all the relevant data from the charts. We then secured collaborators from the cancer center's statistics core and Dr. Michel Chonchol, from the School of Medicine's nephrology division, to create a team that drove multiple different analyses that really describe in detail this effect of crizotinib on creatinine in [patients](#). It was a wonderful group effort."

Exactly how crizotinib is causing these effects is now the next challenge to address. To the authors, the rapid onset, but then the observed plateauing of the effect after starting crizotinib and equally rapid recovery of the GFR on stopping crizotinib treatment implies that the drug is either interfering with an as yet unknown enzyme affecting a fixed proportion of kidney function, or somehow altering the validity of creatinine as a measure of kidney function, for example by competing with it for secretion into the urine, as has rarely been described for some other drugs in the past. Specifically, the facts do not seem to suggest the drug is actually toxic to the kidneys as it is not causing any significant permanent kidney damage.

"We are doing extra studies, but the jury remains out on the exact mechanism. However, because an interference with the validity of creatinine for assessing kidney function is still a possibility, if a patient's creatinine seems to heading into some kind of danger zone on crizotinib,

and a doctor is considering altering their management of the patient, we would strongly recommend reassessing [kidney function](#) through a second, non-creatinine based, method before making any final decision," Camidge says.

More information: [onlinelibrary.wiley.com/doi/10 ...
/cncr.28478/abstract](https://onlinelibrary.wiley.com/doi/10.1002/cncr.28478/abstract)

Provided by University of Colorado Denver

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