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Does stronger initial response to cancer treatment predict longer overall survival?

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Robert C. Doebele, MD, PhD, and colleagues report relationship between depth of initial response to cancer treatment and overall survival. Credit: University of Colorado Cancer Center

It seems like such a simple question: Do patients whose tumors shrink more in response to targeted treatment go on to have better outcomes than patients whose tumors shrink less? Actually, the answer seems simple too. In short, the answer is yes—a deeper initial response leads to a longer overall response. But the implications of a recent study demonstrating this relationship are anything but simple and could influence both the design of future clinical trials and the goals of oncologists treating cancer.

In the context of clinical trials, the good news is that better medicines are leading to longer survival. But a byproduct of longer survival is more time needed to complete trials. It makes sense: The longer that patients live, the longer trial designers must wait to see how long patients will live. One adaptation to this fortunate reality is that rather than using overall survival (OS) as the measure of a drug's success, many clinical trials now use a kind of midpoint, namely progression-free survival (PFS)—the time that it takes for a tumor controlled by the trial's medicine to restart its growth.

However, with newer drugs even PFS may require a long wait. For example, the drug crizotinib approved to treat ALK-positive lung cancer, showed a PFS of 10.9 months. Now the next-generation ALK-inhibitor, alectinib, shows PFS of nearly 25 months. Waiting for PFS may slow the availability of important new medicines to treat the condition.

"For someone to go up against alectinib, it would be nice to know earlier if there might be an improvement," says Robert C. Doebele, MD, PhD, investigator at the University of Colorado Cancer Center and associate professor of Medical Oncology at the CU School of Medicine.

The current study suggests that just as PFS can be used as a proxy for OS, depth of response may be a proxy for PFS. In other words, if depth of response hints at overall survival, then maybe depth of response could be an early sign that an investigational drug is working.

In addition to offering early evidence of a drug's effectiveness, if depth of response predicts patient outcomes, then, Doebele says, depth of response may be a useful goal of treatment.

"You can look at it in terms of tumor biology—our current strategy is to treat and then as long as the tumor responds to any degree, to watch for progression without paying much attention to depth of response. These data suggest that we should be trying to get better responses up front—that if you get a deeper response, it will last longer," Doebele says.

Partnering with the U.S. Food and Drug Administration allowed Doebele and colleagues to access clinical trial data describing initial tumor response, PFS and OS for 305 patients with stage IIIb or IV non-small cell lung cancer on trials of ALK inhibitors and 355 similar patients on trials of immunotherapies directed at PD-1. The study measured overall reduction in tumor size and then compared this reduction to the time until a controlled tumor started to grow (PFS) and patient overall survival (OS).

The study placed patients into four categories depending on whether their tumors shrank 0-25 percent, 26-50 percent, 51-75 percent or 76-100 percent. In the group that received targeted treatment for ALK-

positive lung cancer, each category of tumor reduction was associated with corresponding gains in PFS and OS. In the group of patients treated with immunotherapies directed at PD-1, results were slightly more nuanced with a significant difference in PFS and OS between the groups with 0-50 percent tumor reduction and 51-100 percent reduction, but no significant difference between patients higher or lower in these groups.

"With immunotherapies, there were better outcomes for deeper responses, but it didn't break down the same way as with targeted treatment against ALK-positive cancer," Doebele says. This difference raises the question, he says, of whether initial response is related to PFS and OS with all drugs and all cancers, or if initial response may be a better predictor of these things only in certain situations.

Results are published in the journal *Annals of Oncology*.

More information: C. E. McCoach et al, Exploratory analysis of the association of depth of response and survival in patients with metastatic non-small cell lung cancer treated with a targeted therapy or immunotherapy, *Annals of Oncology* (2017). DOI: 10.1093/annonc/mdx414

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