

Surrogate endpoints poor proxy for survival in cancer drug approval process

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Surrogate endpoints used to support the majority of new cancer drugs approved in the U.S. often lack formal study, according to the authors of a study published in the June issue of *Mayo Clinic Proceedings*. This

analysis questions whether the U.S. Food and Drug Administration (FDA) is adhering to standards that demand that surrogates be "reasonably likely to predict" or "established" to be used to grant approvals.

"In [cancer clinical trials](#), surrogate endpoints, such as [tumor shrinkage](#) or slowed tumor growth, may be used as proxies for outcomes that matter to patients—living longer or better—in order to gain earlier approval of new drugs," says lead author Vinay Prasad, M.D., M.P.H. a hematologist at Oregon Health & Sciences University.

Dr. Prasad and co-author Chul Kim, M.D. M.P.H., a researcher at the National Institutes of Health, studied 55 drugs approved on the basis of a surrogate endpoint by the FDA between January 2009 and December 2014. Twenty-five drugs received accelerated (provisional) approval, and 30 drugs received traditional (full) approval. Surrogates used for accelerated approval should be "reasonably likely to predict" living longer, while surrogates used for traditional approvals should be "established," according to prior guidance from the FDA.

Yet, the authors could not find any formal analyses of the strength of the surrogate-survival correlation for 14 drugs (56 percent) that received accelerated approval and 11 drugs (37 percent), which received traditional approval. For drugs receiving accelerated approval, a level 1 analysis (the most robust analysis) had been performed on only four drugs. For drugs receiving traditional approval, a level 1 analysis had been performed on 15, with only three finding a strong correlation.

"The present study suggests that the use of surrogate endpoints for [drug](#) approval often lacks formal empirical verification," says Dr. Prasad.

In a commentary also published in the June issue of *Mayo Clinic Proceedings*, Vincent Rajkumar, M.D., a Mayo Clinic hematologist,

writes that the study by Drs. Prasad and Kim is "the product of a time-consuming, thoughtful, and careful study." He says their findings "may lead one to think that the FDA is more lenient and is willing to approve oncologic drugs more readily than ever before."

But, he cautions that there are many aspects in the interpretation of those data that one must be wary of, and placing more requirements may impede progress in drug development and the speed of approval. He says that the current FDA approval process has achieved an optimal balance between the need for speed, so patients with cancer have early access to promising new drugs, and the need for safety, so harmful or useless drugs don't enter the market. At the same time, he warns against further relaxation of the current standards.

Dr. Prasad acknowledges that the FDA may have unpublished studies used to justify these surrogates. "If so, I would urge the FDA to publish these studies to allow independent researchers to judge their work," he says. "If the surrogates are valid that would be great news. But, if there are limitations to the analyses, it would benefit patients to know." He says the FDA has previously published such analyses.

Provided by Mayo Clinic

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