Are too many Phase III cancer clinical trials set up to fail?

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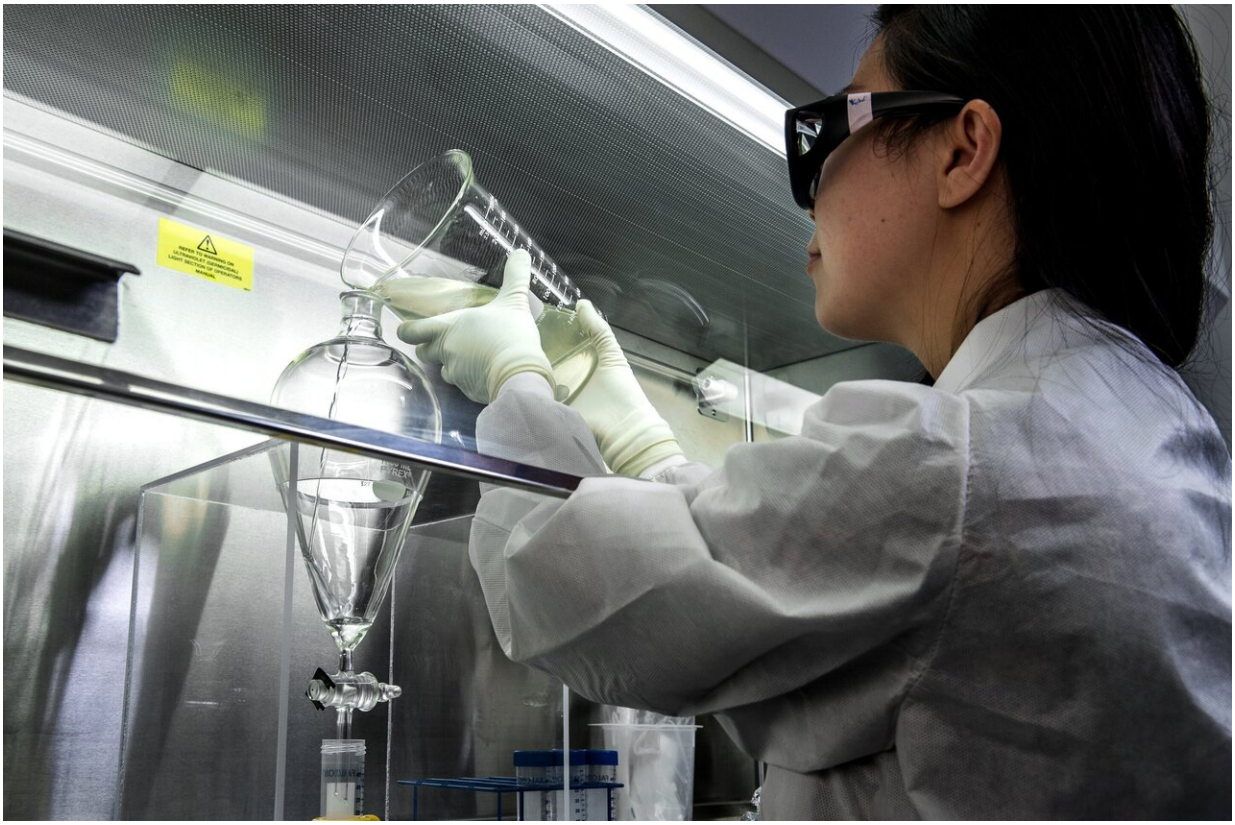

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New research in the September 2021 issue of *JNCCN—Journal of the National Comprehensive Cancer Network* finds that more than 80% of therapies tested in Phase III oncology trials did not achieve meaningful

clinical benefit in prolonging survival. The researchers analyzed 362 industry-sponsored Phase III randomized trials in oncology from 2008 to 2017, and found that 87% were either false-positive or true-negative for meeting overall survival goals. More than half of the initially reported positive trials were found to be false-positive (58.4%) for overall survival, while the overwhelming majority of negative results were determined to be true-negative (with only 0.9% false-negative).

"Our study highlights the need to more efficiently identify which new therapies merit Phase III testing," said lead researcher Changyu Shen, PhD, Associate Professor at Harvard Medical School at the time this study was conducted. "In order to sustain the rate of innovation in cancer therapeutics and ensure that our patients have access to effective yet affordable therapies, the clinical trial pipeline in oncology must be efficient and accurate. Our work shows that in the past ten years, this has not been the case."

Dr. Shen says that their "study shows that reducing false positive errors by imposing more stringent statistical threshold in Phase III trials is not likely to be practically feasible. A better strategy is to rethink the process that leads to the decision of moving a new therapy to Phase III testing to begin with. More research is needed in this regard."

Most of the trials in this novel study focused on lung, breast, gastrointestinal, and hematologic cancers; trials with fewer than 100 participants were excluded, meaning rare cancer types were less likely to be included. The Phase III trials were predominately two-arm studies of an interventional regimen compared with a control treatment.

"This paper shows that a lot of drugs with 'positive' Phase III trials may have a smaller ultimate benefit than was expected, and that changing the threshold for statistical significance is not a quick fix," said Elizabeth A. Handorf, Ph.D., Associate Research Professor, Fox Chase Cancer

Center, who was not involved in this research. "I think it highlights the need for more efficient study designs, like adaptive trials, and clear definitions of what makes an effect clinically meaningful."

More information: Changyu Shen et al, Underperformance of Contemporary Phase III Oncology Trials and Strategies for Improvement, *Journal of the National Comprehensive Cancer Network* (2021). DOI: 10.6004/jnccn.2020.7690

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