Broadening Trial Eligibility Doesn't Weaken Results

A study using artificial intelligence (AI) to simulate clinical trials suggests that broadening eligibility criteria would allow more patients to enroll without negatively affecting trial outcomes. Using electronic health records of more than 60,000 patients to simulate thousands of advanced non–small cell lung cancer (NSCLC) clinical trials, study researchers identified eligibility criteria that appear to have little effect on overall survival (OS; Nature 2021;592:629–33).

"This study adds to the growing body of evidence supporting the notion that we need to seriously and sincerely scrutinize eligibility," says Edward Kim, MD, MBA, of City of Hope Orange County in Irvine, CA, who was not involved in the research. "We are excluding patients who really need to be represented in these drug approval studies. Who we study in our clinical trials absolutely has to reflect the population we are treating." Kim, the former chair of a joint effort by the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research to expand eligibility in clinical trials, noted that the FDA has issued guidance recommending more inclusive trials that better reflect the diversity of patient populations (Cancer Discov 2021;11:OF1).

The study used Flatiron Health electronic health records from about 280 cancer clinics in the U.S., which included patients with advanced NSCLC who had participated in one of 10 trials as well as patients who had received a treatment or control drug associated with a trial after the trial's completion. The researchers used the database to create thousands of simulated trial cohorts with randomized sets of eligibility criteria.

The analysis pinpointed exclusion criteria that had little effect on the calculated hazard ratio for OS. These included age and central nervous system metastasis; laboratory tests, such as white blood cell count, blood pressure, and albumin level; and previous treatments, such as PD-L1 inhibitors, CYP34A drugs, and systemic therapies. In simulated trials that relaxed those criteria, the number of eligible patients increased by 107%, but the simulated hazard ratio was lower by just 0.05 on average than the actual hazard ratios.

"By taking a data-driven approach, we could make trials much more inclusive while maintaining the efficacy of these trials," says James Zou, PhD, of Stanford University in California, a senior author of the study. "That's a win-win for both patients and biopharma companies," he says, noting that more patients could receive experimental therapies and that trials could reach endpoints more quickly.

"This is a move in the right direction," says Luis Carvajal-Carmona, PhD, of the University of California Davis Comprehensive Cancer Center in Sacramento, who was not involved in the research. Providing racial and ethnic minority populations with access to experimental treatments is important to address historic inequities, he said. "Black and brown patients also tend to have more comorbidities, such as hypertension or diabetes, which tend to be in the exclusion criteria for these trials."

"Broadening the trial criteria is a key component that has to happen, but by no means should we stop there," says Ishwaria Subbiah, MD, of The University of Texas MD Anderson Cancer Center in Houston, who was not connected to the research. Ensuring diversity in trials requires addressing structural barriers to participation, such as lack of coverage for experimental treatments, lack of access to cancer centers, mistrust of biomedical research, inability to take leave from work, and language barriers, she says.

In addition, trials testing the effect of relaxed eligibility criteria on trial outcomes would be needed to confirm that toxicity and other adverse events are not affected, says Julie Gralow, MD, ASCO's executive vice president and chief medical officer, who was not involved in the study. "We need to monitor the impact of these changes on efficacy and toxicity outcomes in randomized trials of new treatments versus control regimens such as those simulated in this analysis, where we don't have physician bias in selecting who gets what treatment that occurs in datasets pulled from health records," she says. –*Conor Gearin* ■

Oncolytic Herpes Virus Shrinks Pediatric Gliomas

An oncolytic virotherapy for brain tumors, decades in the making, seems to have finally found its clinical niche.

In a small trial of children with progressive high-grade gliomas, direct infusions of a genetically engineered strain of herpes simplex virus (HSV) known as G207 (Treovir) elicited drug activity in nearly all recipients. The therapy also reshaped the immune milieu of the brain tumors and prolonged survival compared with historical expectations. That's according to data presented by Gregory Friedman, MD, of the University of Alabama at Birmingham (UAB) during the first week of the virtual American Association for Cancer Research Annual Meeting 2021, being held April 10–15, and simultaneously published (N Engl J Med 2021 Apr 10 [Epub ahead of print]).

"It's really gratifying to see that it does have activity," said Timothy Cripe, MD, PhD, of Nationwide Children's Hospital in Columbus, OH, who was not involved in the study but has evaluated a different HSV-based virotherapy in children.

To Frank Tufaro, PhD, president of Opa Therapeutics and former CEO of NeuroVir, the company that, in the 1990s, first commercially advanced G207, the virotherapy now "looks like it could be part of the arsenal in these children, who really have no other options."

"The jury is still out about how effective it is," Tufaro added, "but it is definitely worth taking forward."

G207 originated in the laboratory of Robert Martuza, MD, of Massachusetts General Hospital in Boston, who 30 years ago described the world's first laboratory-modified virus for combatting brain tumors. To make G207, his group introduced two mutations into HSV that rendered the virus capable of replicating only in actively dividing