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Opinion
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Statistical Analysis

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For trials reporting time-to-event outcomes with hazard ratios (HRs), we compared the hypothesized effect size from the sample size calculation in the research protocol with the observed effect size in the published article to calculate the ratio of observed-to-expected HRs. All HRs were standardized for a reduction in adverse events relative to the standard control group, such that HRs less than 1 indicated a benefit to experimental therapy. In this case, a ratio of observed-to-expected HRs greater than1 indicates effect size overestimation. For trials that did not report the observed HR, we calculated the HR as a ratio of the median survival time between arms based on the assumption of exponential survival and constant hazards.

Logistic regression was used to test for factors predictive of clinical trial success (i.e., statistically significant effect on the primary endpoint favoring experimental therapy). Chi-square tests were used to test for differences between trial success and presence of rationale for the protocol effect size. All analyses were performed using R statistical software.

Data on 111,080 patients from 137 clinical trials was evaluated. The majority of trials were in the primary setting and the most common primary endpoint was overall survival. The most common malignancy was breast cancer, followed by gynecologic, gastrointestinal, and genitourinary cancers. Most trials had a single primary endpoint with equal allocation between two arms and a parallel design. Twenty-nine trials (21.2%) observed a statistically significant difference in the primary endpoint favoring the experimental treatment compared with 24.6% for NCI trials conducted from 1955 to 2006. There was no correlation between trial success and sample size, primary endpoint, year of publication, or intent of therapy, which indicates the unpredictability of treatment success in randomized trials.

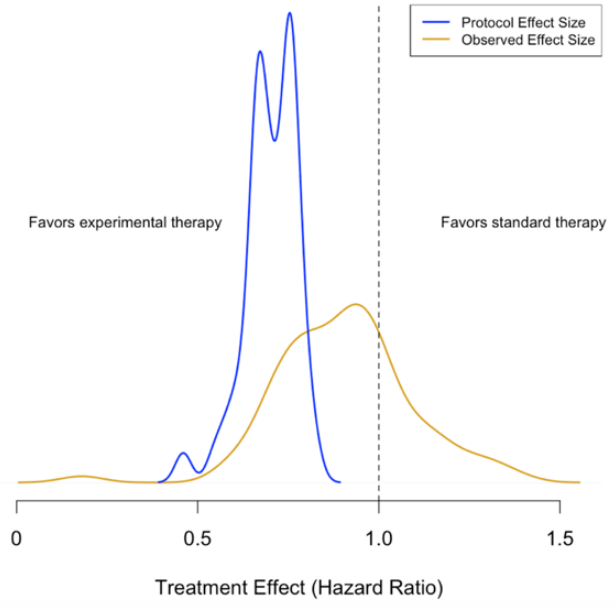

Figure 1: Kernel density plot of hypothesized vs. observed treatment effects on the primary endpoint, displayed as hazard ratios. Values less than 1.0 indicate a benefit favoring the experimental therapy.

The median hypothesized HR for all trials was 0.71 (range: 0.46-0.825), and the median observed HR was 0.91 (range: 0.18-1.38) (Figure 1). The most common hypothesized effect sizes were a 25% or 33% reduction in the primary outcome (HR=0.75 or 0.67), which were collectively used in 37 protocols (43.5%) and are represented by the "horns" in Figure 1. Unsurprisingly, the median observed effect size was larger for positive trials (0.73; range: 0.18-0.85) than negative trials (0.94; range: 0.68-1.38). Observed treatment effects favored the experimental therapy (i.e., HR<1) in 72.1% of trials.

Most trials hypothesized effect sizes that were larger than observed (Figure 2). The median ratio of observed-to-expected HRs was 1.26 (range: 0.33-2.34). The median ratio of observed-to-expected HRs among positive trials was 1.07 (range: 0.33-1.29) vs. 1.31 (range: 0.86-2.34) for negative trials, indicating an overestimation of effect sizes for both sets of trials. Eight trials (9.4%) observed an effect size as large as the one projected in the protocol. By comparison, for NCI trials conducted from 1955 to 2006, these ratios were 1.34 and 1.86, respectively.

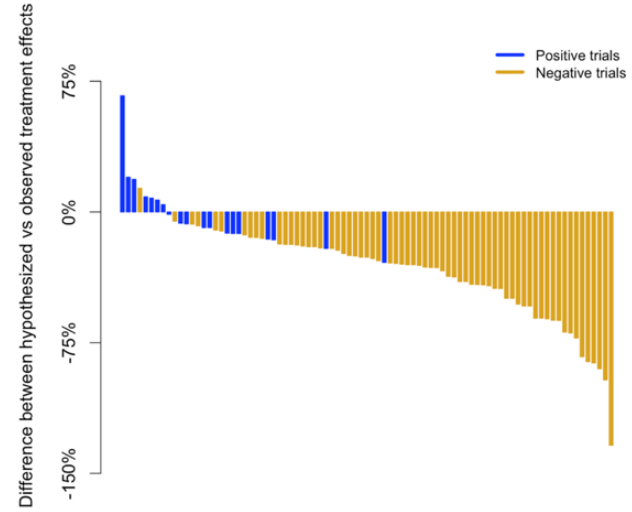

Figure 2: Difference between hypothesized vs. observed treatment effects for trials reporting time-to-event outcomes with hazard ratios.

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