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Treatment Effect Reanalysis of the Randomized Individual Screening Trial of Innovative Glioblastoma Therapy in Newly Diagnosed Glioblastoma With External Control Data

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Abstract

Purpose: Integrating external control data into clinical trial designs and analyses has the potential to accelerate drug development processes. We reanalyzed the three experimental arms of the Individual Screening Trial of Innovative Glioblastoma Therapy (INSIGhT), a randomized phase II platform trial in newly diagnosed O^6-methylguanine-DNA methyltransferase-unmethylated glioblastoma (ClinicalTrials.gov identifier: NCT02977780). To evaluate the validity of using external data sets, we compared treatment effect estimates based on internal INSIGhT control data and matched external control data.

Methods: The three experimental arms of INSIGhT (abemaciclib [n = 72], neratinib [n = 80], and CC-115 [n = 12]) did not improve survival compared with internal controls (standard chemoradiation [n = 70]). We derived external control patient-level data from multiple real-world and clinical trial data sets. We applied propensity score matching and Cox proportional hazards models to estimate treatment effects with external controls. Additionally, using this glioblastoma (GBM) data collection, we specified simulation scenarios to evaluate trial designs that integrate external controls.

Results: After matching to external controls, no survival benefit was observed for patients receiving abemaciclib (hazard ratio [HR], 1.00 [95% CI, 0.75 to 1.34]), neratinib (HR, 0.93 [95% CI, 0.70 to 1.24]), or CC-115 (HR, 0.88 [95% CI, 0.41 to 1.88]). Simulations, together with the INSIGhT data and a collection of GBM data sets, allowed us to examine efficiencies and risks of clinical trial designs that leverage external control data.

Conclusion: The use of carefully matched external controls, to replace or augment the internal controls of INSIGhT, produced treatment effect estimates that were similar to previously published

analyses. Single-arm trial designs and hybrid randomized designs incorporating propensity score-matched external control data evaluated treatment effects in the early-phase testing of experimental therapies in newly diagnosed GBM. The validity of this approach and risks of bias depended on the availability of comprehensive and accurate data on all potential confounders, in the absence of unmeasured confounding.

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