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Gods do play dice: The activity of regorafenib in glioblastoma not confirmed

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Extract

The challenges to identify active drugs in clinical oncology let alone for glioblastoma patients are enormous. Large sample sizes are typically required to arrive at definitive answers, and investigators are actively searching for approaches that make trials more feasible and less costly, primarily by reducing the required patients numbers and thus timelines. Strategies that are used to increase efficiency include alternative primary endpoints that facilitate and shorten trials (eg response rate, progression-free survival), and alternative trial designs such as randomized screening phase 2 designs, phase 2 studies powered for comparison, optimistic hazard ratio's, or the use of historical controls to benchmark uncontrolled single-arm studies. All of these come, however, with a downside.

The journey of regorafenib in glioblastoma is another example of the importance of understanding the caveats of these approaches—before we submit our patients to novel promising treatments that come with side effects. Regorafenib is a "dirty" kinase inhibitor, targeting several kinases involved in tumor angiogenesis (VEGFR1–3 and TIE2), oncogenesis (KIT, RET, RAF1, and BRAF genes), the tumor microenvironment (platelet-derived growth factor receptor [PDGFR] and fibroblast growth factor receptor [FGFR]), and tumor immunity (colony-stimulating factor 1 receptor). Many of these pathways are involved in the pathogenesis of glioblastoma, and many glioblastoma trials have explored similar compounds that affect these signaling pathways. In the Italian REGOMA study, a phase II study comparing regorafenib to lomustine in first recurrence glioblastoma patients, indeed a positive result was observed.[1] This trial was designed as a randomized screening design phase II study. Assuming a one-sided significance level of 0.20 and power of 80%, the study required 39 events and 112 eligible patients to detect a 42% reduction in the hazard ratio (HR) for death, which was the required threshold to warrant a future phase 3 trial. A total of 119 patients were enrolled, and the study observed a statistically significant improvement in survival in the regorafenib arm. The median overall survival was 7.4 months (95% CI, 5.8-12.0) in the regorafenib arm versus 5.6 months (95% CI, 4.7-7.3) in the lomustine arm (HR 0.50, 95% CI, 0.33-0.75; log-rank $P = 0.0009$). Despite this impressive low P-value, skeptical minds immediately pointed towards the unexpected poor overall survival, in particular in the lomustine control arm. Typically, other studies using lomustine as a control reported median survival times between 7 and 10 months in the lomustine control arm.[2–5] Furthermore, the 16.7% rate progression free survival at 6 months was less than what is typically seen as evidence of "promising" activity in trials on recurrent glioblastoma warranting further investigation. Also, other agents with a similar mode of action had not shown any evidence of improved outcome.[6] Then, the screening design with a relaxed alpha is opening the gate for a type I error. The investigators drew the right conclusion: a phase 3 trial is warranted, but the enthusiasm in the field rapidly took over. Regulatory approval for use in recurrent glioblastoma was obtained in Italy, and regorafenib became listed in the preferred systemic treatment options in the NCCN guidelines for recurrent glioblastoma (eg NCCN Guidelines Version 3.2024 September 30, 2024) although in fine print mentioning the poor overall survival in the control arm.

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