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Way to Go/No-Go!

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See the articles by Brenner et al, pp. 694–704, and Cloughesy et al, pp. 705–717, in this issue.

The 1972 Philadelphia 76ers (9–73), 1962 NY Mets (40–120), and 1989 Dallas Cowboys (1–15) were 3 teams that hold the dubious distinction of the worst record of all time in each of their respective major US professional sports leagues. More impressive, however, is that each team went on to iteratively address their deficiencies and win a championship within a decade of these record-setting seasons of futility. We in the neuro-oncology community are in the midst of a similar epic losing season and must reexamine our failing drug development and clinical trial processes. The glioblastoma clinical trial landscape of the past decade is littered with the corpses of well-designed and well-intentioned large randomized trials seeking to exploit novel targets (eg, immune checkpoints) or essential pathophysiological pathways (eg, neoangiogenesis) in patients with newly diagnosed or recurrent disease. The latest, but not likely the last, addition to the glioblastoma phase III trial graveyard is the GLOBE study which impressively failed to effectively target both angiogenesis and the immune system[1].

In this issue of *Neuro-Oncology*, Cloughesy and colleagues report the results of GLOBE, a prospective, randomized, open label controlled, phase III clinical trial testing the combination of VB-111 and bevacizumab versus single agent bevacizumab in patients with recurrent glioblastoma. VB–111 is a non-integrating, replication deficient adenovirus type V vector with a dual mechanism of action involving vascular disruption/anti-angiogenesis as well as the induction of a tumor-directed immune response. VB-111 carries a trans-gene for a chimeric death receptor that connects intracellular Fas to human tumor necrosis factor (TNF) receptor 1. Binding of TNF alpha to the receptor activates the Fas-mediated pro-apoptotic pathway and produces a targeted anti-angiogenic effect restricted to angiogenic vascular endothelial cells. The therapy also promotes intratumoral activation of the immune system leading to an increase in tumor infiltrating CD8 cells. Several early clinical trials, including a phase I/II study in patients with recurrent glioblastoma also reported in this issue,[2] demonstrated excellent tolerability of the drug and improved overall survival in a cohort of patients who were primed with VB-111 and then went on to receive the combination of VB-111 and bevacizumab at progression. Unfortunately, just the combination of VB-111 and bevacizumab produced a median survival of only 6.8 months versus 7.9 months in the bevacizumab control arm (hazard ratio 1.20 [0.91–1.59]) in this trial of 256 patients enrolled at sites in the US, Canada, and Israel.

Why might the GLOBE study have failed? Drug distribution was clearly not at fault as the targeted tumor-associated vascular endothelial cells were likely exposed to the systemically administered viral vector. Unfortunately, the selected experimental combination arm of VB-111 and bevacizumab did not share the trend in improved survival seen in the "VB-111 priming" arm in the phase II trial. Reading between the lines, it is likely that regulatory agency oversight and/or tight Pharma drug development timelines may have led to this potentially detrimental Go/No-Go decision. Patients enrolled in GLOBE received transient but significant doses of dexamethasone surrounding the gene therapy infusions in order to prevent cerebral edema which raises the question of whether this glucocorticoid limited the intended immune stimulation. Finally, neither the absolute lymphocyte count nor T-cell subset concentrations were measured at baseline in patients enrolled on this trial who had progressed on standard combined modality therapy. It is well known that profound and prolonged lymphocytopenia and suppression of CD4 counts occur in glioblastoma patients treated with radiation, temozolomide, and glucocorticoids[3] and may represent another factor which could have impaired treatment efficacy in GLOBE.

What lessons can we learn about the glioma drug development process from these two VB-111 reports? If nothing else, they shed light on one of the most critical aspects of this process—the Go/No-Go decision making that moves novel therapies from early phase trials to larger, typically randomized, phase III evaluations. Was the GLOBE trial design a mistake by

not testing the most effective treatment seen in the phase II study? Of note, a 2019 NCI Clinical Trials and Translational Research Advisory Committee (CTAC) Glioblastoma Working Group report highlighted the identification and application of consensus evidence thresholds to inform the Go/No-Go process in neuro-oncology as a key to improving the selection of agents for clinical development. In response, the Adult Brain Tumor Consortium convened a half-day symposium in September of 2019 with the goal of codifying and ranking the criteria that could standardize Go/No-Go decision making for completed early phase brain tumor trials.

How might we operationalize a more effective approach to moving novel investigational agents forward in the clinical trials process? Quite simply, we must not lose sight of several fundamental criteria as we design tomorrow's studies. In order to have any chance of success, an experimental therapy must (i) penetrate or bypass the blood–brain barrier and reach the intended target(s) following delivery in a verifiable way; (ii) engage an integral intratumoral cellular target(s) at threshold and/or sustained concentrations adequate to modify the targeted pathobiologic process; (iii) target a process whose inhibition results in tumor cell quiescence or death in both bulky and infiltrative tumor regions; and (iv) address the issue of genomic, molecular, and functional tumor heterogeneity. Far too many phase II trials in neuro-oncology evaluate agents with limited relevant preclinical or early clinical data on drug distribution within the tumor, the brain around tumor, and the normal brain. In addition, correlative endpoints that could reveal whether the targeted intratumoral process was sufficiently modified to result in cell cycle arrest or death are either not known or not assessed. Disappointingly, most preclinical in vivo models of drug penetration and target engagement—pharmacokinetic and pharmacodynamic endpoints—are often of little predictive value as they may be influenced by assay variability, drug binding, metabolism and blood brain barrier effects[4,5]. Even when all of the above criteria are achieved, biologic crosstalk and difficult to predict resistance may still lead to a negative clinical trial. This is well illustrated by a recent elegant report evaluating the activity of the pan-phosphatidylinositol 3-kinase (PI3K) inhibitor buparlisib in patients with recurrent glioblastoma and known PI3K pathway activation. Despite the enriched population, significant measured brain penetration, and demonstrated target engagement, buparlisib showed little clinical efficacy secondary to incomplete blockade of the PI3K pathway[6].

Developing future early phase neuro-oncology treatment trials that build on more predictive preclinical models and that appropriately resource correlative science endpoints focusing on target engagement and pathobiologic effect must be our approach moving forward. We cannot afford to continue our streak of successfully completing negative trials that don't even provide concrete leads as to why they failed. The explosive growth in the number of investigators worldwide evaluating brain tumor biology coupled with our growing understanding of glioma microenvironment, immune milieu, and targetable genetic changes must translate into the design of more efficient and informative clinical trials for our patients with malignant brain tumors.

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