Letter: A Phase II and Pharmacodynamic Trial of RO4929097 for Patients With Recurrent/Progressive Glioblastoma

To the Editor:

The incidence of brain tumors, particularly glioblastoma multiforme (GBM), is rising in many countries, and it is the most aggressive primary tumor among all. Incidence varies from 0.59 to 5 per 100 000 persons.[1] Treatment is challenging because of the heterogeneity of the tumor itself in many ways as well as the interaction between possible drug options and the presence of the blood-brain barrier (BBB).[2] Numerous studies are going on to develop an effective drug for GBM treatment and prevention of recurrence.

We read with great interest the article published in *Neurosurgery* by Peereboom et al,[3] in which the authors ran a clinical trial (phase II) of "RO4929097" in some patients with recurrent GBM. This is a precious work and it gives us a way to proceed further in this area. One of the target sites the authors[3] worked with to reduce tumor burden and prevention of recurrence is the "Notch signaling pathway." This Notch pathway is unique in many ways because it is physiologically present and involves proliferation and angiogenesis. Aberrancy of this pathway may lead to cancer.[4]

RO4929097 was initially evolved by Roche for the therapy for Alzheimer's disease; however, on-track impacts on the Notch signaling pathway prompted its repositioning as a novel anticancer treatment, with preclinical investigations showing its antitumor viability in a scope of cancer types.[5] In the clinical trial with published outcomes, including RO4929097 was a phase I dose-escalation study to assess the security and tolerability of consolidated RO4929097 and bevacizumab in the treatment of repetitive glioblastoma.[6] Notch advances tumor intrusion and tumor-related angiogenesis; hence, there is a reasoning for joining Notch inhibitors with antiangiogenic treatments to upgrade their viability. One study featured the variety in the epigenetic tumor microenvironment of in Vitro and in Vivo models, recommending that exploration with in Vitro malignant growth cell lines is a "therapeutic roadblock" to GBM drug invention.[7] Previous reports from phase II clinical trials of RO4929097 in pancreatic adenocarcinoma, melanoma, metastatic colorectal disease, and platinum-safe ovarian malignancy demonstrate deficient action as single specialists at the dosage regimens and an inability to arrive at study endpoints of clinical reaction.[8] The new investigation,[3] where authors did a clinical trial (phase II) of "RO4929097" in the patients with repetitive GBM, depended on consequences of a phase 0/1 preliminary of similar specialists in recently analyzed patients.[3] Eventually, the study information proposed that R04929097 did not influence tumor recurrence or fundamentally hinder neurosphere formation; also, the small number of patients was a concern there for concluding the result.[3] Previously, while the mix of RO4929097 and bevacizumab was very much endured, an authoritative maximum tolerated dose was not reached before Roche stopped the creation of the medication and ended further clinical trials. Prominently, none of the trials with RO4929097 included genotype-chosen accomplices with known Notch mutation status; subsequently future investigation of this may demonstrate more strength.

After analyzing the results presented, we consider it necessary to highlight some aspects:

- *Bioavailability in GBM tissue:* RO4929097 is a drug, administered orally, and needs to pass the BBB. The presence of this natural structure can affect the permeability of this drug. So, accurate dosing is very much difficult, especially after having radiation therapy.[9]
- *Efficacy in different grades*: GBM is a highly aggressive brain tumor, though there are some intermediate- and low-grade GBMs too. The Notch pathway expression depends on the degree of proliferation. So, the drug may not act the same in all types of GBM.[10]
- *Altering the physiological environment and showing toxicity:* Many cells physiologically use the Notch pathways for their regular growth and survival, particularly in gut tissues. Nonspecific inhibition of gamma-secretase leads to metaplasia of this tissue as well as malabsorption syndrome.[4]
- *Monotherapy vs combination therapy:* The drug RO4929097 was previously used in many other cancers and proved to be less efficacious when used alone and can lead to the generation of resistance.[4]
- *Notch mutation status:* This mutation can play a role in the efficacy of the drug.[4]

Such tumor drug discovery is characterized by major obstacles and historical failure. Taking into account that the treatment of this complex tumor is not easy, it is necessary to learn from the results of this type of study, in addition to the academic and research debate that is generated. We suggest taking our comments into account for future studies.

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