

## How Fine a Slice: Treatment of Newly Diagnosed Glioblastoma With an Epidermal Growth Factor Receptor Variant III Peptide Vaccine

**TO THE EDITOR:** Sampson et al<sup>1</sup> are to be congratulated for their paper on the use of the epidermal growth factor receptor variant III (EGFRvIII) peptide vaccine for newly diagnosed glioblastoma multiforme (GBM). Several issues regarding the paper are relevant and warrant discussion.

Sampson et al<sup>1</sup> report on a small phase II study (building on prior efforts by this team vis-à-vis the ACT 1 and 2 trials) of the EGFRvIII peptide vaccine in 18 newly diagnosed patients with near or completely resected GBM. Additional eligibility criteria included tumor expression of EGFRvIII, a constitutively active receptor that is present in 20% of all GBM based on data from the similar and recently completed Celldex (CDX110; Needham, MA) vaccine trial that used a similar vaccine and treatment strategy as in the report by Sampson.

Patients in the Sampson et al<sup>1</sup> study were as well treated with temozolomide (TMZ)-based chemoradiotherapy (but no postradiotherapy TMZ) and demonstrated on the first magnetic resonance imaging after chemoradiotherapy no evidence of disease progression. By way of comparison, a matched cohort of 17 patients not treated with vaccine but who otherwise were similar to study patients served as a comparison, albeit slightly older and with a modestly diminished performance.

The study suggests the vaccine study group had improvement in both median progression-free survival (14.4 v 6.3 months) and overall survival (26 v 15 months) compared with the contemporaneous matched cohort. Additionally toxicity was minimal and comprised predominantly of low grade injection site reactions.

Two other points were emphasized—one, that the best outcome was seen in GBM tumors that were O6-methylguanine-methyltransferase (MGMT) gene promoter unmethylated, and two, that 82% of all resected tumors (11 of 18 patients) reverted to wild-type EGFR suggesting immunologic escape from vaccine-induced immunity.

Several features of this study are notable. Firstly, TMZ was not used after radiotherapy as is usual and customary, which may have compromised outcome.<sup>2</sup> Not clear from the study was whether the matched cohort received postradiotherapy TMZ. At present the neuro-oncology group is uncertain as to what component of the TMZ regimen (concurrent or postradiotherapy) adds benefit with respect to survival in patients with GBM. In addition, Sampson et al<sup>1</sup> have demonstrated vaccine-related immunogenicity is enhanced when vaccine is administered at the TMZ white blood count nadir, a strategy employed in the CDX110 trial.

Secondly, a high incidence of tumors in the study group (54% of the 13 evaluated) were MGMT gene promoter methylated, a subset of GBM patients previously demonstrated to have improved survival (median, 23 months).<sup>3</sup> Interestingly, the matched cohort MGMT

promoter methylation status was not reported. Based on data from the prospective randomized Radiation Therapy Oncology Group 0525 (dose-dense postradiotherapy TMZ v standard TMZ) and Centric (treatment with or without cilengitide) trials, MGMT gene promoter methylation is seen in 20% to 33% of all patients with newly diagnosed GBM. Potentially if study patients differ significantly from the matched cohort in this prognostic variable, a widening of the survival curves would be expected.

Thirdly, in patients with newly diagnosed GBM, extent of resection is felt to improve survival based on analysis of the original TMZ versus radiotherapy only trial and the 5-amino levulinic acid trial (comparing the utility of this fluorescing porphyrin compound in achieving tumor resection).<sup>4</sup> However, median survival in the matched cohort was essentially equivalent to the original GBM up-front TMZ trial. More recently, albeit in comparatively small phase II studies, there has been recognition that trial-eligible patients with newly diagnosed GBM have a median overall survival of 18 months. This has also been suggested in several trials using novel agents (ie, talampanel, polyinosinic-polycytidylic acid stabilized with poly-L-lysine and carboxymethylcellulose, isotretinoin, erlotinib, enzastaurin) added to the TMZ regimen.<sup>5</sup> As a consequence, the matched cohort appears to differ from recent experience and thereby further widen the survival difference between study patients and the control group. As well, intuitively one would suspect that patients with minimal or no radiographic disease at time of first postradiotherapy magnetic resonance imaging would represent a rarefied group of patients with arguably the best treatment outcomes.

This article is hypothesis generating, and if confirmed in the phase II CDX110 trial, will hopefully result in the design and execution of a phase III trial to definitively determine the value of EGFRvIII peptide vaccine in newly diagnosed GBM. A vaccine-based approach to the treatment of GBM represents a novel paradigm for personalized cancer care as patients are required to have tumors that express EGFRvIII undergo a near or complete resection (ie, low tumor burden and demonstrate no evidence of radiographic disease at conclusion of TMZ chemoradiotherapy). These comments are not meant to diminish the results of this elegant study but suggest that the management of GBM continues to be refined and patient selection paramount in determining outcome of this challenging disease.

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### AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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