Editorial

Lessons learned from rindopepimut treatment in patients with EGFRvIII-expressing glioblastoma

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Introduction

EGFRvIII is the most common mutation of EGFR and results in the creation of a tumor-specific antigen that is detectable in 23–33% of human glioblastoma (GBM) (1). EGFRvIII arises due to the deletion of EGFR exons 2–7, which generates a truncated extracellular domain capable of constitutive EGFR activation. The truncated extracellular domain creates a new peptide sequence, resulting in a unique, GBM cell-specific, antibody-reactive EGFRvIII antigen. This motivated the development of a peptide treatment strategy, known as rindopepimut (Rintega, formerly CDX-110) that consists of the EGFRvIII peptide conjugated to the adjuvant, keyhole limpet hemocyanin (KLH). The KLH adjuvant is utilized in a variety of cancer vaccine modalities for its strong immunogenicity and acceptable safety levels in humans after inoculation. In the ACTIV trial, rindopepimut was administered intradermally in conjunction with granulocyte-macrophage colony stimulating factor (GM-CSF) (2). Preclinical analysis of the EGFRvIII peptide treatment approach yielded substantial evidence of immune-mediated activity against intracerebral tumors, with a mechanism that included antibody-dependent cellular cytotoxicity (ADCC) (3). This sparked evaluation of rindopepimut in a series of clinical trials, including a phase II multi-center trial against EGFRvIII-expressing newly-diagnosed GBM whereby immunization occurred following gross total resection and standard of care adjuvant chemoradiotherapy. This trial reported an improved overall survival when compared to historical controls matched for entry criteria, prognostic factors, and TMZ treatment with best responses associated to a measurable serological EGFRvIII-specific antibody titer (4). Tumor progression was associated with a loss of EGFRvIII expression, suggesting at that time that rindopepimut induced a specific and effective immune response resulting in the successful eradication of GBM cells expressing the target antigen. It was then hypothesized that tumors escaped immunologic control following vaccination by losing the targeted EGFRvIII antigen. This study was followed by two additional phase II trials, ACT II (5) and ACT III (6) that, tested concurrent rindopepimut treatment with adjuvant TMZ, similarly demonstrating encouraging survival outcomes as compared to historical controls.

Key results of the phase III ACT IV study

Prior to the phase III clinical trial evaluating rindopepimut for treatment of GBM, studies utilized a matched patient cohort rather than randomization. In the recent ACT IV study published in *Lancet Oncology*, the addition of rindopepimut to standard adjuvant chemotherapy treatment was assessed in a randomized, double-blind, international phase 3 trial for the first time (2). Eligibility was limited

to newly-diagnosed patients with GBM and confirmed intratumoral EGFRvIII expression, who underwent maximal safe resection followed by adjuvant chemoradiation, without neuro-imaging evidence of progression following chemoradiation. Patients were stratified based on MGMT promoter methylation, recursive partitioning analysis class, and geographical region before randomization either to rindopepimut or control adjuvant KLH without the EGFRVIII peptide concurrent with standard oral temozolomide treatment. The primary endpoint for this study was overall survival in patients with minimal residual disease (MRD), as defined by <2 cm^2 post-chemoradiation and analyzed by central review.

The study was terminated at the second preplanned interim analysis after 212 deaths had occurred in the MRD study population, with the hazard ratio for rindopepimut versus control, equal to 0.99 (95% CI: 0.74–1.31) demonstrating that rindopepimut was unlikely to be better than control. A similar lack of benefit was discovered in the intention-to-treat population. Surprisingly, there was suggestion toward improved survival of patients treated with rindopepimut in the exploratory analysis of patients with significant residual disease, although this effect was less pronounced when tumor burden was defined by each investigator rather than central review. The study confirmed findings of earlier phase clinical trials showing that, rindopepimut induces a moderate to rapid EGFRvIII-specific antibody response in the majority of patients, which suggests that failure to generate an immune response was not a primary reason for the lack of improved survival. Patients with rapid development of a humoral response trended toward better outcomes, although this data did not reach statistical significance. Interestingly, the loss of EGFRvIII expression was described in ~57–59% of GBM tumors post-treatment and regardless of whether rindopepimut or control treatment was administered, which is consistent with another recent study (2,7). These new data suggest that EGFRvIII loss is not due to immunization with rindopepimut, but rather, is inherent to the natural evolution intrinsic to GBM progression. Coincident with this finding is the loss of patient GBM EGFRvIII expression was independent of EGFRvIII antibody titers.

Discussion

The recent finding that rindopepimut treatment does not increase overall survival of newly-diagnosed GBM patients was unexpected, given the multiple, independent, previously completed phase II studies suggesting a survival advantage among the ACTIVATE, ACT II, and ACT III trials. A lesson from this experience may be that, early phase clinical trials might not provide the predictive power for wide-scale clinical benefit among GBM patients. Over selection of patients, the lack of randomization, and comparison of survival outcomes with potentially outdated historical controls can skew interpretation of early phase trials (8). In oncology, there is a natural evolution in improvement(s) of standard of care treatment over time further complicating the use of historical controls. An underestimation of the value of salvage regimens in trials for newly diagnosed disease utilizing survival endpoints must also be considered when interpreting study results. In addition, ACT IV also highlights the need to incorporate control patient GBM tissue, for direct analysis of tumor tissue resected after patients undergo clinical therapy, in an effort to avoid over-interpretation of treatment effects, which led to the previously incorrect conclusion that, loss of EGFRvIII expression loss was directly due to rindopepimut inoculation. Since ACT IV was the culmination of multiple clinical trials that initially began with the ACTIVATE study in 2004, the negative findings were even more disappointing to the community, given the long time-frame and significant patient accrual leading up to the point of phase III study discontinuation in the year, 2016. This experience highlights the early potential benefit(s) of GBM patient subject randomization that may help to avoid false positive signals in the future.

The overall clinical strategy utilizing an immunization to mediate GBM cell-specific immunity, defined as the immunological targeting of antigen exclusively expressed by GBM, but not normal host cells, provides substantial attractiveness to the rindopepimut approach. The relatively high incidence of EGFRvIII expression, ranging between 23–33% among GBM (1), further enhances this rationale. A disadvantage of this design is related to the dependence on ADCC (3). This type of immunological protection requires Fc receptor-driven monoclonal antibody (mAb)-mediated activation of natural killer (NK) cells, granulocytes, and macrophages. While ADCC is capable of tumor cell lysis, particularly *in vitro*, less reliable *in vivo*-mediated immune activation has been demonstrated both preclinically and clinically (9). This has incentivized substantial efforts to engineer new ways toward the improvement of responses that include: (I) mAb with increased affinity for Fc receptors for enhancing *in vivo* target cell-killing via ADCC; (II)

bispecific antibodies engineered to specifically activate T cells, but not myeloid or NK cells; (III) generation of chimeric antigen receptor (CAR) T cells expressing cDNA encoding mAb fused to a T cell signaling domain conferring high selectively that is independent of TCR-MHC interactions; (IV) mAb-chemotherapy or -radiolabeled conjugates that facilitate the close proximity and/or cellular uptake of cytotoxic payloads into GBM (9).

Next-generation mAb approaches are ongoing for GBM and include the tumor cell-specific targeting of EGFRvIII. University of Pennsylvania recently conducted the first-in-human testing of autologous T cells with CAR-T cells directed at EGFRvIII for 10 patients with recurrent GBM (10). Tumor control was achieved in 1 out of 10 patients, with median OS following treatment at 251 days. The limited efficacy was attributed in-part to adaptive immune resistance mechanisms in the tumor (i.e., immunosuppression), demonstrated by *in situ* detection of enhanced IDO1, PD-L1 and FoxP3 expression levels of post-treatment GBM, induced by EGFRvIII-targeting CAR T cells. The negative findings align with other clinical pilot studies treating solid tumors with CAR-T cells (11), which is contrary to the success treating non-solid hematologic malignancies targeting a critical cell-surface ligand expressed by 100% of tumor cells (12). Future next-generation approaches targeting EGFRvIII, include the evaluation of bispecific antibodies specific to both EGFRvIII and CD3 (13). Overall, interest remains in the testing of next-generation mAb approaches for EGFRvIII and EGFRwt targeting, although a global target that would provide universal GBM targetability remains elusive.

In summary, the rindopepimut clinical strategy aligns with the current direction of clinical efforts toward personalized immunotherapy. Unfortunately, EGFRvIII peptide immunization did not demonstrate survival advantage when combined with standard of care adjuvant TMZ. The field of immunotherapy for GBM is still in its infancy and many strategies are still maturing, which provides high hope for those individuals diagnosed with incurable malignant brain cancer.

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Footnote

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