Not Yet Another Negative Trial–ReACTing on Recent Glioblastoma Trials

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SUMMARY

The present ReACT trial provides data from a small randomized controlled vaccination trial that in addition to other recent immunotherapy trials in glioblastoma allows sketching a rational, advanced trial design for the development of (immune) therapies in glioblastoma elaborating on but not restricting to biological monitoring and endpoints.

See related article by Reardon et al., p. 1586

In this issue of *Clinical Cancer Research*, in this randomized, active controlled phase II trial (ReACT), Reardon and colleagues (1) aimed to improve the progression-free survival (PFS) for patients ($n = 73$) with first or second progression of an autoactive variant III EGFR (EGFRvIII)-positive glioblastoma by adding an anti EGFRvIII vaccine ($n = 36$) or control keyhole limpet hemocyanin ($n = 37$) to the VEGF-neutralizing antibody, bevacizumab. Bevacizumab is deemed a standard at progression in the United States (1), despite the controversial data from trials in patients with newly diagnosed and progressive glioblastoma (2). PFS at 6 months was 28% (10/36) for the vaccine, rindopepimut, compared with 16% (6/37) for the control intervention ($P = 0.12$). The secondary outcome parameters overall survival (OS), response duration, as well as need for corticosteroids likewise favored the experimental group. Given that the recently published ACT IV trial, in which the same experimental concept was added to standard radiochemotherapy in patients ($n = 745$) with newly diagnosed, mainly well-resected EGFRvIII$^+$ glioblastoma, was negative for most comparisons (3), it may be interesting to speculate on the future of anti-EGFRvIII–directed immunotherapy, target selection, and lessons for future trial design.

Both trials started with some hypotheses that are being challenged recently from others, but also by the outcome of these trials:

(i) Uncontrolled trials are a good basis for the development of larger trials (including validity of biomarkers and mechanism of action).
(ii) A large amount of antigen-expressing tumor cells may not be necessary to mediate or amplify antitumor immunity and therefore patients with well-resected glioblastoma like in ACT IV may specifically benefit from the vaccine.
(iii) Bevacizumab is necessary to allow a sufficient time interval to mount an immune response in a vaccine trial at recurrence and to limit steroid exposure (4).

Until now, the main mechanism, by which the EGFRvIII vaccine works is not fully elucidated. ACT IV was negative despite robust induction of an antigen-specific antibody response. In cancer vaccine trial, these humoral immune responses are often taken as a surrogate for immunogenicity and in preclinical studies therapeutic impact of the anti-EGFRvIII vaccine has shown to be mediated by antibody-dependent cellular cytotoxicity. Both controlled trials failed to provide details on EGFRvIII-specific T-cell responses. And the MHC class I or II epitope required for priming of CD8$^+$ or CD4$^+$ T cells remains to be defined. These data on the effector side of rindopepimut would have been essential for future developments, as there is continued T-cell–based treatment development targeting EGFRvIII with chimeric antigen receptors or bispecific antibodies.

The in-frame deletion of the extracellular domain in EGFRvIII results in the fusion of exons 1 and 8 generating a peptide sequence, which is foreign to the immune system, expressed by tumor cells but not in healthy tissue, thus representing a neoantigen.

EGFRvIII is the most common gain-of-function mutation, confined to 20%–25% of patients but also cells even within EGFRvIII$^+$ tumors making it a subcloncal neoantigen. Local and central testing on newly obtained or archive paraffin-embedded tissue can be done with confidence. Relevance for the malignant phenotype is deducted from preclinical concepts, in which EGFRvIII$^+$ cells interact with negative cells by complex cytokine network alterations. However, data from ACT IV allow to relativize its relevance because EGFRvIII expression was lost at recurrence after experimental anti-EGFRvIII or control treatment in 57%–59% of patients. Moreover, elimination of EGFRvIII did not correlate with outcome (3). These data are highly relevant for the present ReACT trial, as it is unclear how many of the already limited patients per arm would in fact be eligible per EGFRvIII positivity based on tissue that had been obtained immediately prior to the trial entry and whether a real precision trial in the correct population would have had a differential (more positive) outcome. The mechanism behind the elimination of this subgroup and the obvious dissociation between a highly dominant subclonal neoantigen and spontaneous (or treatment induced) loss warrants future activities. This major (negative) bias of ReACT is a conceptual weakness dating back to the read-out of the uncontrolled ACTIVATE trial, in which loss of EGFRvIII positivity was taken as a sign of specific activity of the vaccine. It further limits the immediate interpretation.

Irrespective of these shortcomings and conceptual weaknesses, which are easier to spot in hindsight than prospectively, even an optimal setting for rindopepimut or similar approaches cannot circumvent obstacles of subclonal expression and heterogeneity in space and time. Therefore, especially for tumors with low mutational burden as glioblastomas, personalized exploitation of the full repertoire of tumor antigens, neo-epitopes as well as nonmutated ones, may offer more effective immunotherapies (4, 5). Interestingly, in one of the personalized vaccination trials (4) even low levels of steroids are

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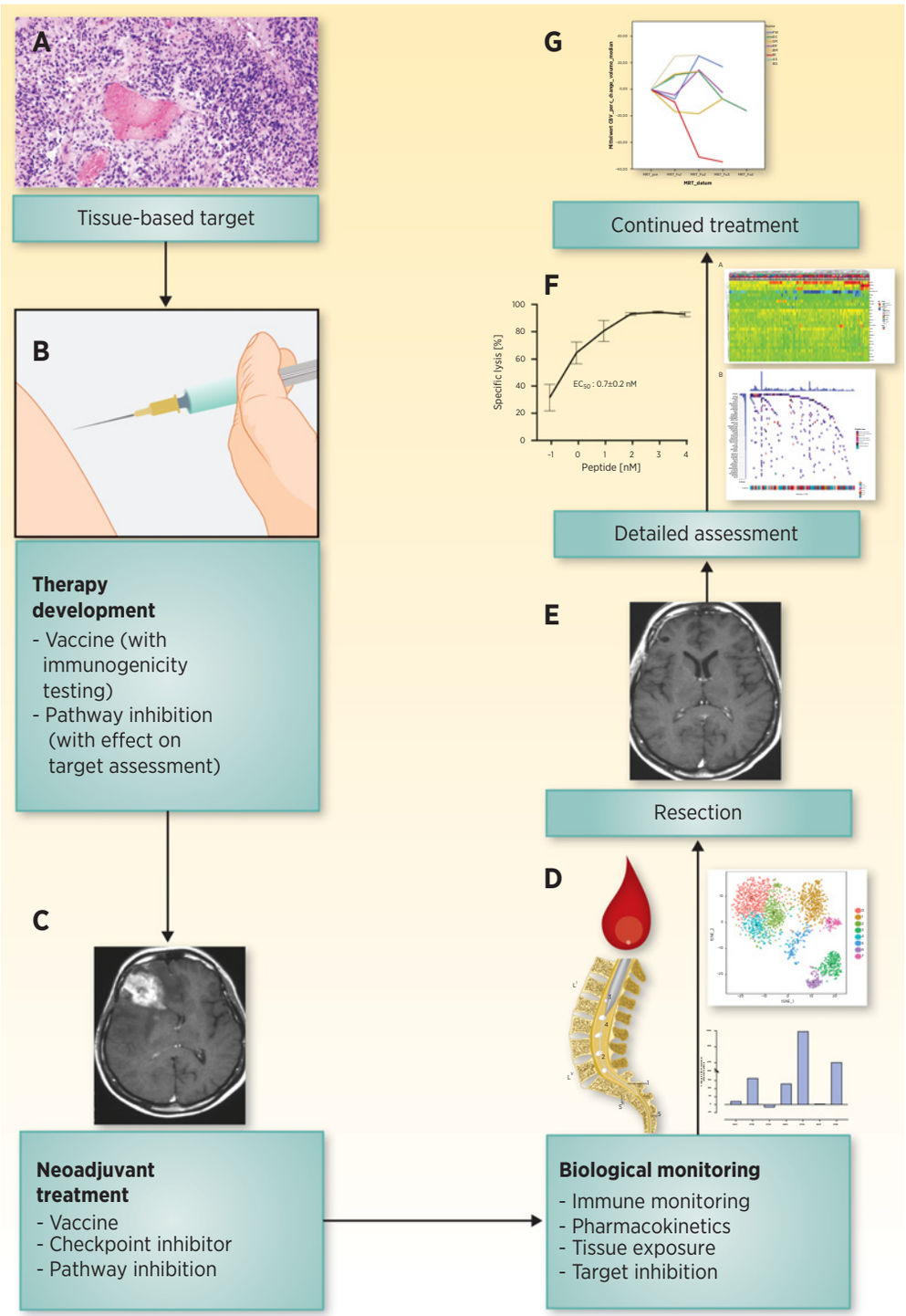

Figure 1.

Window trial development in the neoadjuvant setting. **A,** Extensive analysis of glioblastoma tissue from a recent biopsy or resection (or other recently obtained surrogate tissue) with a standardized test including evaluation of heterogeneity. **B,** Selection or development of a treatment (vaccine and drug) individualized or in a trial. **C,** Therapy may/should start prior to the removal of the tumor tissue to allow the best match between biological analysis and treatment setting. **D,** Intensive use of blood, cerebrospinal fluid, or other easy to obtain tissues to allow understanding of mode of action, target inhibition, mounting of a specific immune response, antibody development, and other parameters that characterize the individual effects or resistances of a therapeutic intervention in a specific patient. **E,** Removal of the necrotic, most likely untreatable part of the tumor. **F,** Careful, multivariable, deep analysis of the resected tumor tissue to assess individual benefit, activity (or not) of the treatment. **G,** Dependent on the response and options, continuation, modification, or end of treatment and follow-up of efficacy parameters beyond the end of the intervention.

associated with a lack of immune responses, making a replacement, that is, by bevacizumab, desirable although this very plausible, steroid-sparing effect was not visible in the randomized trial for progressive glioblastoma using bevacizumab plus lomustine versus lomustine alone (2).

However, the positive signal especially in the long-term outcome parameters in ReACT matches the main positive result from ACT IV, in which the 2-year survival rate was increased in the rindopepimut versus the control group (30% vs. 19%; $P = 0.029$) in the relevant (≥ 2 cm^2) residual disease population. ReACT stated a modest increase in patients who underwent surgery prior to the trial in the rindopepimut arm, which is regarded a positive, but could in fact be a negative bias. These last pieces of data were deemed counterintuitive in the past; but they may be just the signal to be expected, if (high) target expression on the one hand, as opposed to the largely resected patients, and some long-term outcome parameters (as for ReACT) are regarded prerequisites for mounting an immune response and obtaining a benefit. These data matched the recently published impact of neoadjuvant (presurgical) checkpoint inhibition on OS over the postsurgical use of pembrolizumab (plus bevacizumab) in both arms (6). These data contradict the assumption that a larger antigen pool/tumor mass may not be necessary and also offer the opportunity to biologically assess the immediate impact of an intervention. Whereas neoadjuvant concepts in the newly diagnosed setting are limited by the lack of a tissue-based diagnosis or the need for an additional biopsy prior to the initiation of treatment, these concepts are well suited in a window at recurrence. There is a patient, who is a potential candidate for macroscopic resection has started on a treatment schedule (based on historical tissue or better a recent biopsy or without need for tissue-based diagnostics), briefly followed preferentially using blood or cerebrospinal fluid–based surrogate markers, and then operated (**Fig. 1**). With the surgical intervention, the mainly necrotic, otherwise largely impossible to treat tissue will be removed and the impact on the tissue, but even more so indirectly on remaining cells, memory immune function should be assessed as carefully as possible. These concepts may directly benefit patients, not only with the use of checkpoint inhibitors, but also other drugs, like classical chemotherapy that may also shape the microenvironment and drugs with an immediate impact in the network forming ability of glioma (7).

Disclosure of Potential Conflicts of Interest

W. Wick is a paid consultant for Bayer, Merck Sharp and Dohme, and Roche (with the compensation received by the University of Heidelberg), and reports receiving other commercial research support from Roche, Apogenix, and Pfizer. No potential conflicts of interest were disclosed by the other author.

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