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Rindopepimut with Bevacizumab for Patients with Relapsed EGFRvIII-Expressing Glioblastoma (ReACT): Results of a Double-Blind Randomized Phase II Trial

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ABSTRACT

Purpose: Rindopepimut is a vaccine targeting the tumor-specific EGF driver mutation, EGFRvIII. The ReACT study investigated whether the addition of rindopepimut to standard bevacizumab improved outcome for patients with relapsed, EGFRvIII-positive glioblastoma.

Patients and Methods: In this double-blind, randomized, phase II study (NCT01498328) conducted at 26 hospitals in the United States, bevacizumab-naïve patients with recurrent EGFRvIII-positive glioblastoma were randomized to receive rindopepimut or a control injection of keyhole limpet hemocyanin, each concurrent with bevacizumab. The primary endpoint was 6-month progression-free survival (PFS6) by central review with a one-sided significance of 0.2.

Results: Between May 2012 and 2014, 73 patients were randomized (36 rindopepimut, 37 control). Rindopepimut toxicity included transient, low-grade local reactions. As primary endpoint, PFS6 was 28% (10/36) for rindopepimut compared with 16% (6/37) for control

($P = 0.12$, one-sided). Secondary and exploratory endpoints also favored the rindopepimut group including a statistically significant survival advantage [HR, 0.53; 95% confidence interval (CI), 0.32–0.88; two-sided log-rank $P = 0.01$], a higher ORR [30% (9/30) vs. 18% (6/34; $P = 0.38$)], median duration of response [7.8 months (95% CI, 3.5–22.2) vs. 5.6 (95% CI, 3.7–7.4)], and ability to discontinue steroids for ≥ 6 months [33% (6/18) vs. 0% (0/19)]. Eighty percent of rindopepimut-treated patients achieved robust anti-EGFRvIII titers (≥ 1:12,800), which were associated with prolonged survival (HR = 0.17; 95% CI, 0.07–0.45; $P < 0.0001$).

Conclusions: Our randomized trial supports the potential for targeted immunotherapy among patients with GBM, but the therapeutic benefit requires validation due to the small sample size and potential heterogeneity of bevacizumab response among recurrent patients with GBM.

See related commentary by Wick and Wagener, p. 1535

Introduction

Glioblastoma is the most common primary malignant brain tumor among adults. Maximal surgical resection, radiation, and temozolomide have represented the standard of care for a decade but is associated with nearly universal recurrence. Moreover, treatments

capable of extending survival following progression after standard therapy remain elusive. The tumor-treating fields device, recently reported to extend survival in the newly diagnosed setting (1), does not extend survival beyond best available therapy for recurrent disease (2). Although the VEGF-specific angiogenesis inhibitor bevacizumab is approved by the FDA for recurrent disease on the basis of durable tumor response, bevacizumab does not provide a survival benefit (3). The 5-year survival rate from diagnosis is still less than 5% (4).

Rindopepimut is an investigational EGFRvIII-targeted vaccine that consists of a peptide with homology to the EGFR mutation, EGFRvIII (5), which is chemically conjugated to keyhole limpet hemocyanin. EGFRvIII is a tumor-specific deletion that is present in approximately one third of glioblastomas but not in normal tissue (6). It is defined by an in-frame deletion of 801 base pairs of coding sequence between exons 2 to 7 that results in a constitutively active tyrosine kinase that promotes tumor cell growth (7) and migration (8), provides resistance to standard therapies (9–11), increases tumorigenicity in mouse models (12), and reduces long-term survival in patients with glioblastoma (13–16). Preclinical studies demonstrate that intradermal administration of an EGFRvIII-specific vaccine produces antigen-specific humoral immunity and prolongs survival in mice with intracerebral tumors (17, 18). In three previous phase II trials in patients with newly diagnosed, resected, EGFRvIII-positive glioblastoma, rindopepimut was well tolerated and associated with prolonged progression-free survival (PFS) and overall survival (OS) as compared with EGFRvIII-positive historical control datasets matched for major eligibility criteria (6, 16, 19, 20). The ("ReACT") study described here was

Translational Relevance

Historical, single-arm, uncontrolled trials for glioblastoma have demonstrated therapeutic benefit associated with various vaccine strategies including rindopepimut, a peptide-based vaccine targeting EGFRvIII. Furthermore, nearly all prior glioblastoma vaccine trials targeted newly diagnosed patients based on bias that recurrent patients may be sufficiently immunosuppressed to limit benefit. We conducted a blinded, randomized, phase II study (ReACT) of bevacizumab, an FDA-approved anti-VEGF mAb with either rindopepimut or placebo among patients with recurrent glioblastoma. The primary endpoint, PFS-6, favored rindopepimut as did secondary and exploratory endpoints of OS, ORR, and corticosteroid requirement reduction. High-titer EGFRvIII-specific antibodies capable of *in vitro* tumor lysis occurred among rindopepimut recipients. Although derived from a controlled trial, the favorable efficacy signals warrant validation due to the small study size and variability of bevacizumab benefit among patients with recurrent glioblastoma. Nonetheless, our data support the potential for targeted immunotherapy for this challenging indication.

conducted to investigate whether the addition of rindopepimut to standard bevacizumab would improve outcome for patients with relapsed, EGFRvIII-positive glioblastoma. ReAct was initiated while a phase III study was underway in newly diagnosed patients with glioblastoma (ACT IV), which subsequently failed to demonstrate a survival benefit (Weller, 2017 #13186). Although limited by small sample size, rindopepimut recipients in this placebo-controlled, blinded, randomized phase II study obtained higher rates of 6-month PFS, achieved better OS, developed high titer EGFRvIII-specific antibodies capable of lysing tumor cells *in vitro*, showed more frequent and more durable tumor responses, and required less steroid treatment than controls.

Patients and Methods

Study design

ReACT was a randomized, double-blind phase II study conducted at 26 hospitals in the United States (List of Investigators and Trial Sites). The study was compliant with the Declaration of Helsinki and guidelines on Good Clinical Practice. Ethics approval was obtained at all participating centers.

Participants

Eligible patients were at least 18 years of age, in first or second relapse of histologically confirmed glioblastoma following standard therapy (maximum feasible resection or biopsy, radiation, and temozolomide), with EGFRvIII expression in primary or recurrent tumor tissue by central analysis using PCR as described previously (6). Patients who previously received radiation and temozolomide for lower grade glioma were permitted upon diagnosis of transformed glioblastoma. Eligibility criteria excluded prior receipt of bevacizumab or other VEGF- or VEGF receptor–targeting agents; corticosteroid requirement >4 mg of dexamethasone per day during the week prior to entry; Karnofsky performance status <70%; gliomatosis cerebri, infratentorial, leptomeningeal or metastatic disease; prior therapeutic intracerebral agents; residual grade ≥2 chemotherapy or radiation-related toxicities (except alopecia and hematologic toxicity); and

salvage surgery within 4 weeks or radiation within 3 months of screening MRI. All patients provided written informed consent. Full eligibility criteria can be found in the trial protocol.

Randomization and masking

Eligible patients were randomized to the treatment groups in a 1:1 ratio by the study sponsor using a prespecified randomization list created by a biostatistician. Patients and investigators remained blinded to treatment assignments. Unblinded pharmacists who were otherwise uninvolved in study conduct obtained randomized treatment assignments and managed study treatment. Study treatments were prepared in the pharmacy and delivered to study staff in blinded, preloaded syringes. KLH was given as a control injection to produce a local reaction similar to that expected with rindopepimut to maintain the treatment blind.

Procedures

Treatment consisted of vaccination with 500 μg of rindopepimut admixed with 150 μg GM-CSF (Leukine, Sanofi-Aventis). Patients randomized to the control arm received a control injection of 100 μg keyhole limpet hemocyanin, which was intended to preserve the study blind by producing a local reaction similar to that expected with rindopepimut. Study treatment was administered in an initial priming phase (days 1, 15, and 29) and then monthly. Bevacizumab (10 mg/kg) was administered intravenously every 2 weeks. Study treatments continued until intolerance, withdrawal of consent, or disease progression.

A brain MRI was conducted within 21 days prior to study entry and every 8 weeks until documented progression of disease. Radiographic imaging, corticosteroid use, and clinical status were evaluated to determine tumor response and progression in accordance with the Response Assessment in Neuro-Oncology (RANO) Working Group criteria (21), with minor modifications for the purpose of protocol standardization (Supplementary Table S1, online only). The investigator's assessment of tumor response guided clinical management. Retrospective assessment of radiographic imaging was also performed by an independent expert review committee consisting of two neuroradiologists, with adjudication and assessment of steroid use and clinical status by a neuro-oncologist. Expert review committee members were otherwise independent of study conduct and were blinded to treatment allocation and investigator assessments.

Safety assessments included monthly physical examination, vital signs, and routine hematology, blood chemistry, and urinalysis.

Blood samples were obtained monthly, and antibody titers were measured by an ELISA using microtiter plates directly coated with EGFRvIII as described previously (6). To determine the cross-reactive response to EGFR in the serum, plates were coated with recombinant human EGFR (R&D Systems), followed by blocking with PBS containing BSA. Patient serum diluted to 1:100 was added and bound antibody was detected with a horseradish peroxidase (HRP)–conjugated goat anti-human IgG (Fc specific) reagent. The assay was developed with a tetramethylbenzidine (TMB) substrate system. For isotype analysis of EGFRvIII-specific antibodies, plates were coated with the EGFRvIII peptide and blocked with PBS containing BSA. Patient serum diluted to 1:100 was added and bound antibody was detected with isotype-specific HRP-conjugated reagents: donkey anti-human IgM, mouse anti-human IgG1, mouse anti-human IgG2, mouse anti-human IgG3, and mouse anti-human IgG4. The assay was developed with a TMB substrate system.

Antibody-dependent cell cytotoxicity (ADCC) assays were performed using glioblastoma cell line (U87) transfected to express

EGFRvIII as target cells (22) and peripheral blood mononuclear cells (PBMC) from normal donors as effector cells. The PBMCs were incubated overnight at 37°C, 6% CO_2 with target cells (U87vIII) in the presence or absence of patient serum at various dilutions. Cytotoxicity was measured using the CytoTox One Kit (Promega), which measures the release of lactate dehydrogenase from cells with a damaged membrane via fluorescent signals [relative fluorescence unit (RFU)]. The percentage of lysis in each sample was determined as follows: [(mean RFU sample – mean RFU of media control)/mean RFU maximum signal control] × 100%.

Outcomes

The primary efficacy endpoint was 6-month PFS by central review. Secondary endpoints included overall response rate, overall PFS, OS, EGFRvIII-specific humoral immune response, and safety.

Statistical analysis

This phase II randomized trial was designed to provide initial evaluation of whether rindopepimut may improve outcome for patients with recurrent glioblastoma. Accordingly, this exploratory and hypothesis-confirming trial called for a total sample size of 70 bevacizumab-naïve patients (approximately 35 in each treatment arm) to have 80% power to detect an improvement in 6-month PFS rate with a one-sided alpha of 0.2 by χ^2 test, assuming that 6-month PFS rate would be 40% for bevacizumab alone (23) and 60% with the addition of rindopepimut. Because of the exploratory nature of the trial, no multiplicity adjustment was considered for the secondary endpoints of overall PFS, objective response rate, and OS.

Six-month PFS status was calculated on the basis of the crude proportion of patients who were alive without documented disease progression at study day 189 (representing 6 months plus a 1-week assessment window). Patients who had disease progression, died, or discontinued radiographic evaluations before study day 189 were not considered progression-free at the 6-month time point. PFS and OS durations were calculated from study day 1 and summarized using the Kaplan–Meier method. Patients who discontinued the study without disease progression and those with death or documented progression after an unacceptably long interval (>12 weeks) since the last disease assessment were censored for PFS analysis at the last evaluable disease assessment. The log-rank test was used for inferential comparison between treatment arms. HRs were estimated using Cox proportional hazards models. Overall response rate was calculated as the proportion of patients with measurable target disease at baseline who achieved a confirmed objective response by RANO criteria (21).

The primary analyses were performed for the intent-to-treat population, which included all randomized patients. Patients who received at least one dose of rindopepimut or control were included in safety analyses. Central review of radiographic imaging was conducted through a cut-off date of September 1, 2015. All other study analyses include data through the date of study closure (May 25, 2016).

This study was registered with ClinicalTrials.gov, number NCT01498328.

Role of the funding source

This study was sponsored and funded by Celldex Therapeutics, Inc. The study sponsor designed the study in collaboration with the investigators, managed the clinical trial database, performed statistical analysis, and provided medical writing assistance. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
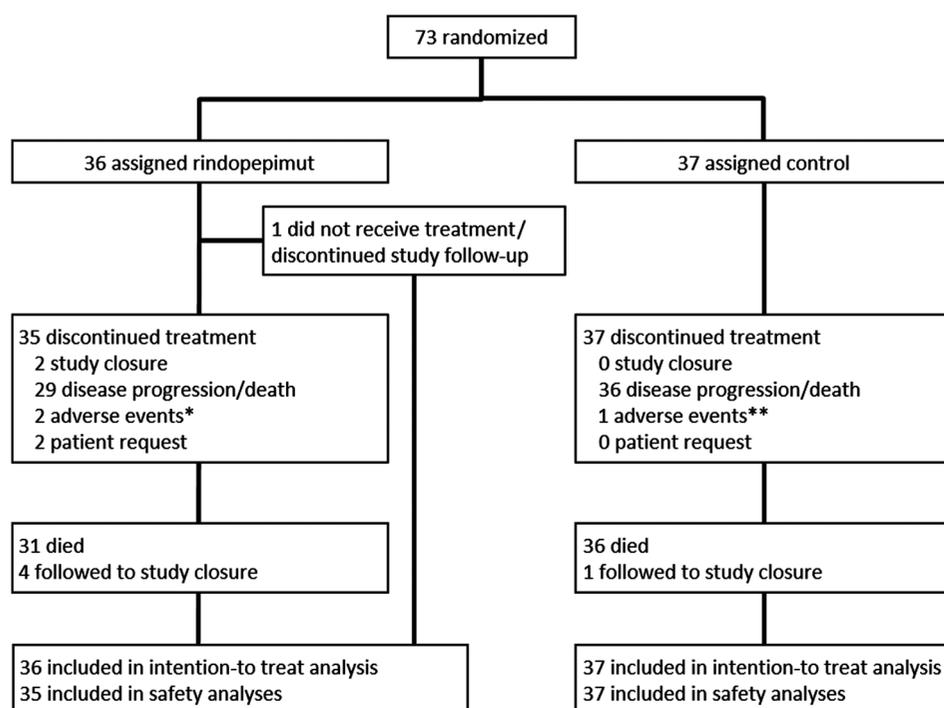

Figure 1.
Trial profile.

* Wound site infection/meningitis and type A aortic dissection considered unrelated to rindopepimut
** Arthritis flare considered related to blinded control injection

Results

Study patients

Between May 2012 and May 2014, 73 bevacizumab-naïve patients were randomized to receive rindopepimut ($n = 36$) or control ($n = 37$). Patient disposition as of study closure (May 25, 2016) is shown in **Fig. 1**.

Baseline patient characteristics and treatment were generally balanced between treatment arms (**Table 1**). However, the rindopepimut arm contained a modest increase of older patients, patients who underwent surgery at last relapse, and patients in first relapse of disease. Median baseline tumor volume as assessed by study investigators was available in 86% of patients in both treatment arms and was comparable: rindopepimut arm = 792.0 mm^2 (range, 121–2,769 mm^2); control arm = 802.0 mm^2 (range, 110–2,769 mm^2). Poststudy therapy was also comparable between the two treatment arms.

The primary efficacy endpoint was met according to the study design. By independent expert review, 10 of 36 (28%) of the rindopepimut arm and 6 of 37 (16%) of the control arm ($P = 0.12$) were alive without progression of disease at 6 months. Although the median PFS was similar (3.7 months) for the treatment arms, a greater proportion of rindopepimut-treated patients remained progression-free after 6 months (HR = 0.72; 95% confidence interval (CI), 0.43–1.21; $P = 0.22$; **Fig. 2A**).

Regarding secondary endpoints, a significant improvement in OS was observed for the rindopepimut arm (**Fig. 2B**; HR = 0.53; 95% CI, 0.32–0.88; $P = 0.01$). The 24-month survival rate was 20% (95% CI,

9%–35%) for rindopepimut as compared with 3% (95% CI, 0%–12%) for control ($P = 0.0179$). Subgroup analyses and analyses adjusted for various prognostic factors using Cox regression models consistently demonstrated a benefit for the rindopepimut arm (**Fig. 3A**). Although potential imbalances in baseline patient characteristics existed between treatment arms with regard to the number of patients who underwent surgery at last relapse and number of relapses, analyses that adjusted for these and other prognostic factors demonstrated specifically that the HR reduction favoring rindopepimut was maintained among patients treated at either first recurrence or without surgery (**Fig. 3** and Supplementary Table S2, online only). Of note, the majority of rindopepimut-treated patients who experienced long-term survival on study had previously experienced relatively rapid progression of disease (Supplementary Fig. S2, online only). Among patients surviving more than 18 months on study, 6 of 11 (54%) receiving rindopepimut versus 1 of 4 (25%) receiving control had last relapse-free interval prior to study entry of ≤6 months. Notably, the use of corticosteroids at study entry did not appear to impact the survival benefit associated with rindopepimut; however, study eligibility excluded patients requiring >4 mg of dexamethasone or equivalent per day.

The overall response rate was also higher for the rindopepimut arm versus the control arm at 30% (9/30) versus 18% (6/34; $P = 0.38$). Furthermore, median duration of response was 7.8 (95% CI, 3.5–22.2) versus 5.6 (95% CI, 3.7–7.4) months (Supplementary Fig. S1, Online only).

A reduction in corticosteroid use, commonly used to control tumor-induced edema in patients with glioblastoma, was also noted for the rindopepimut arm relative to control (**Fig. 1C**).

Among the patients who were receiving steroids at study entry, 33% (6/18) in the rindopepimut arm as compared with 0% (0/19) in the control arm were able to discontinue corticosteroids for at least 6 months.

Rindopepimut induced robust *de novo* anti-EGFRvIII antibody titers (**Fig. 4A**), which were ≥4-fold over baseline in 89% of the 35 treated patients with baseline and at least one posttreatment result. Of the four patients that did not develop significant anti-EGFRvIII titers, three received rindopepimut for less than 1 to 2 months. Overall, high-titer response (≥1:12,800) was achieved in 80% of the treated patients. Moreover, within the rindopepimut arm, a peak titer ≥1:12,800 was associated with prolonged OS (HR = 0.17; 95% CI, 0.07–0.45; $P \leq 0.0001$; **Fig. 4C**). Most patients had multiple isotypes of EGFRvIII-reactive antibodies suggesting efficient isotype switching with the predominant IgG isotype being IgG1. Only one patient developed EGFR cross-reactive antibodies.

Patient samples that displayed good binding to a glioma cell line expressing EGFRvIII were used to test the effector function of these antibodies. Each of these sera mediated efficient and specific killing of EGFRvIII tumor cells using an *in vitro* ADCC assay (**Fig. 4B**).

The mean (range) number of study vaccinations was 9.1 (3–35) and 6.3 (2–23) for rindopepimut and control, respectively. Rindopepimut plus bevacizumab was well-tolerated (**Table 2**). No serious adverse events or toxicity requiring treatment discontinuation were attributed to rindopepimut. Grade 1–2 injection site reaction (primarily erythema and pruritus) occurred in the majority of patients. Brain edema (regardless of causality) occurred in 3% of rindopepimut-treated patients and 8% of the control group. One rindopepimut-treated patient experienced a recurrent grade 2 hypersensitivity reaction (dyspnea, throat tightness, chest pain) but received five vaccinations before progression. Similar reactions using alternative immunotherapeutic approaches have been attributed to GM-CSF (24).

Table 1. Patient characteristics.

Characteristics	Rindopepimut + Bevacizumab ($n = 36$)	Control + Bevacizumab ($n = 37$)
Age, years [median (range)]	59 (44–79)	55 (30–75)
≥50 years [n (%)]	35 (97%)	27 (73%)
Male [n (%)]	19 (53%)	22 (59%)
KPS [n (%)]		
100	2 (6%)	5 (14%)
90	13 (36%)	13 (35%)
80	14 (39%)	12 (32%)
70	7 (19%)	7 (19%)
60	0	0
EGFRvIII expression determined in recurrent tumor[a]	8 (19%)	7 (22%)
Primary glioblastoma [n (%)]	35 (97%)	35 (95%)
Time from diagnosis to first study entry, months [median (range)]	10.8 (3.7–55.2)	11.6 (4.7–38.3)
Relapses [n (%)]		
1	33 (92%)	28 (76%)
2	3 (8%)	9 (24%)
Surgery after last relapse [n (%)]	15 (42%)	10 (27%)
Gross-total resection	14 (39%)	6 (16%)
Partial resection/unspecified	1 (3%)	4 (11%)
Receiving steroids at study entry [n (%)]	18 (50%)	19 (51%)
Therapy received after study	25 (69%)	27 (73%)
Surgery	12 (33%)	8 (22%)
Radiotherapy	5 (14%)	6 (16%)
Systemic chemotherapy	21 (58%)	26 (70%)

Abbreviation: KPS, Karnofsky performance status.
[a]The remaining patients were enrolled on the basis of EGFRvIII expression determined via tumor tissue obtained at primary diagnosis.
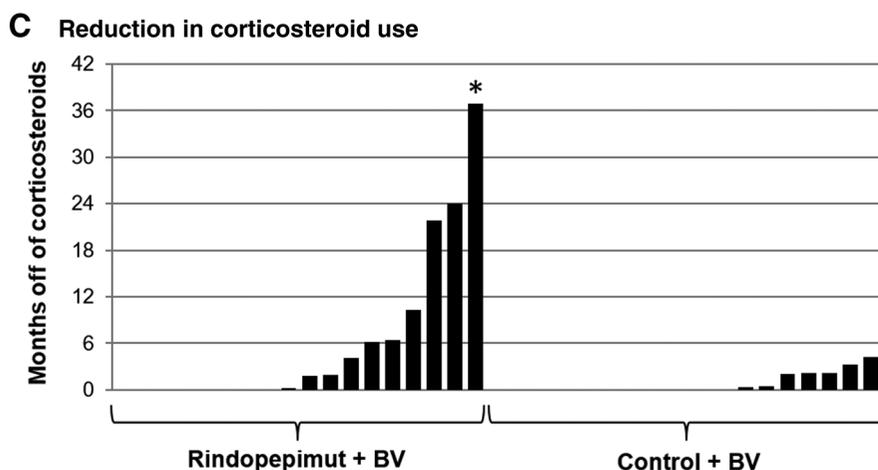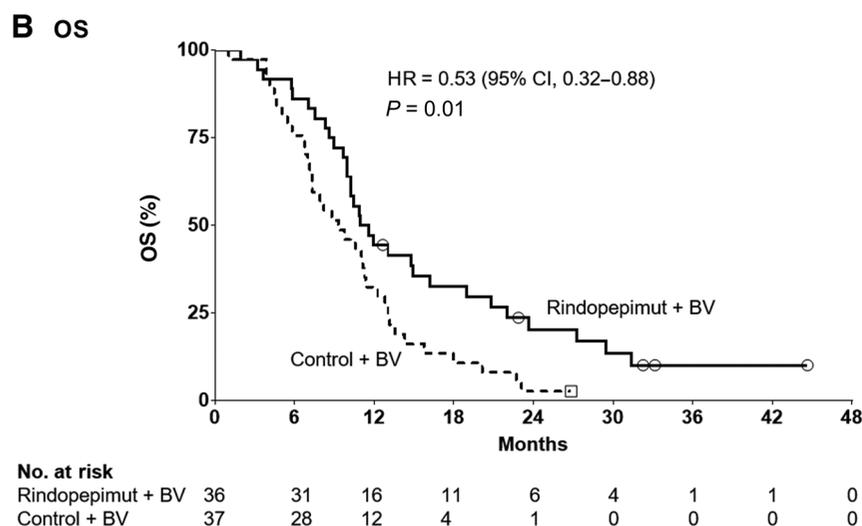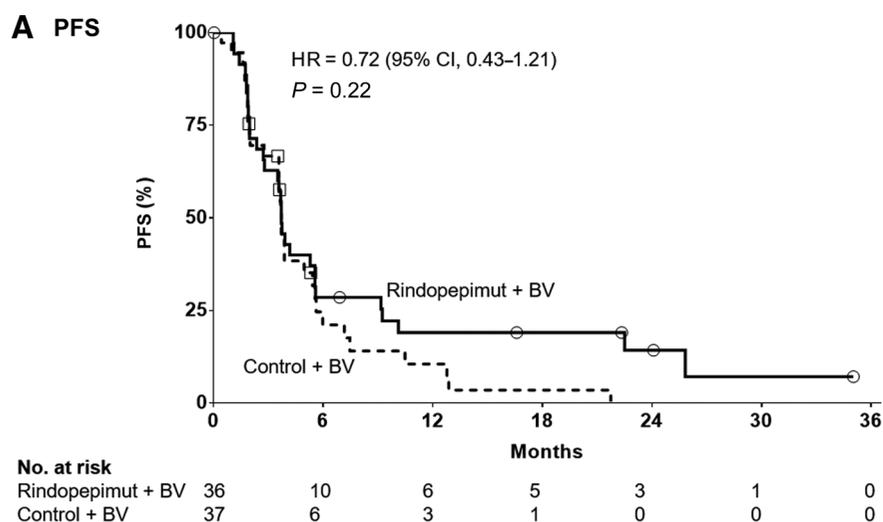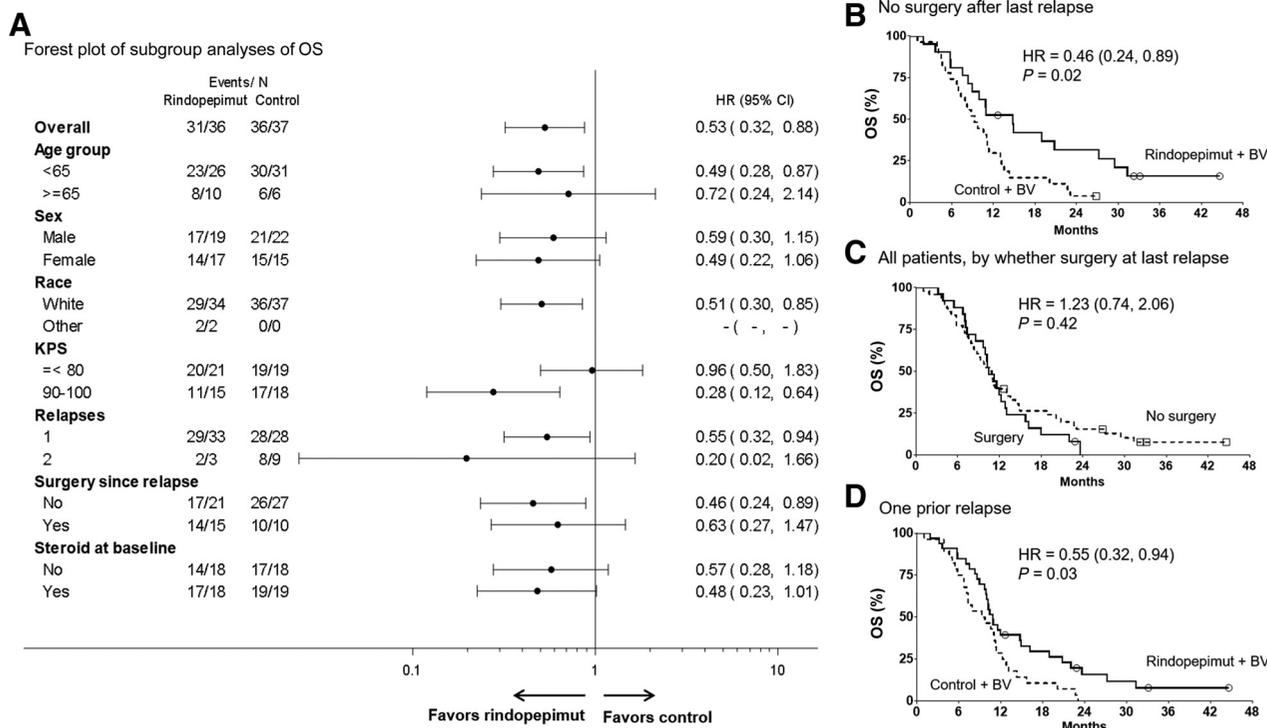
Figure 2.
PFS, OS, and corticosteroid use. Kaplan–Meier estimates of PFS according to central review (as of September 1, 2015) and OS (as of May 25, 2016) are shown in **A** and **B,** respectively. Line markers represent censored data. Reduction in corticosteroid use is shown in **C**. At study entry, 18 patients in the rindopepimut arm and 19 patients in the control arm were receiving corticosteroids. Of those, 6 (33%) rindopepimut arm, as compared with none in the control arm, were able to stop corticosteroids for >6 months during treatment. The patient indicated with "*" continued on treatment without corticosteroids at final analysis.

Discussion

The phase II "ReACT" study incorporated a randomized, blinded, controlled design to assess whether the addition of the EGFRvIII-targeted vaccine, rindopepimut, to bevacizumab could improve outcome for bevacizumab-naïve patients with relapsed, EGFRvIII-positive glioblastoma. Consistent with results seen in patients with newly diagnosed glioblastoma (6, 16, 19, 20), rindopepimut was well

Figure 3.

Subgroup analysis of OS. Forest plot of OS consistently favors the rindopepimut arm for various subgroup analyses (**A**). Although potential imbalances in baseline patient characteristics existed between treatment arms with regard to the number of patients who underwent surgery at last relapse and number of relapses, these factors do not appear to contribute to the survival advantage observed for the rindopepimut arm (**B–D**).

tolerated by patients with recurrent glioblastoma when combined with bevacizumab. With regard to efficacy, the predefined primary endpoint of PFS rate at 6 months increased from 16% in the control group to 28% in the rindopepimut group ($P = 0.12$), which crossed the threshold according to the study design. The low 6-month PFS rate observed for both arms may reflect the reported poor outcome associated with EGFRvIII-positive glioblastoma (13–15). Although lower than reported in some studies (23), 6-month PFS for the control arm was consistent with more recently reported bevacizumab monotherapy studies (25, 26). Secondary efficacy endpoints also favored the rindopepimut arm including a statistically significant and clinically meaningful survival advantage with a 47% reduction in the risk of death ($P = 0.01$) as well as an enhanced rate and duration of radiographic response, and higher frequency of corticosteroid discontinuation for at least 6 months.

The intended therapeutic target of rindopepimut, EGFRvIII, may have been underrepresented in the study population due to the use of archival tumor obtained at initial diagnosis for EGFRvIII detection in 79% of patients. A recent report has suggested that up to 50% of glioblastoma tumors may lose EGFRvIII expression at recurrence, although heterogeneity of expression and sample size may contribute to this observation (27) and others have shown complete preservation of expression of this driver mutation at recurrence (28).

The aggregate efficacy results are consistent with a therapeutic benefit associated with rindopepimut, but limitations of this study indicate that the results should be interpreted cautiously and require validation. First, the sample size of this study is small. Second, established prognostic factors were modestly imbalanced between the

treatment arms, with the number of patients at first relapse and the number who underwent surgery after last relapse favoring the rindopepimut arm, while a higher percentage of younger patients favored the control arm. Subgroup and adjusted analyses were performed in an attempt to delineate whether the imbalances favoring the rindopepimut arm impacted outcome. Of note, the HR reduction favoring rindopepimut was maintained when outcome was assessed among patients who did not undergo resection after last relapse and among those who were experiencing first relapse. Furthermore, previous reports demonstrate that standard prognostic factors such as extent of surgery are not predictive for outcome among patients with EGFRvIII-positive glioblastoma (13). Nonetheless it is possible, particularly in the context of the small study size, that even a modest imbalance of prognostic factors could have impacted outcome. In addition, heterogeneity of therapeutic benefit with bevacizumab, which was administered as a standard-of-care therapeutic to both study arms, could have inadvertently skewed therapeutic benefit observed in this study. Finally, other study limitations were lack of central pathology review and failure to assess additional tumor biomarkers such as MGMT promoter methylation and IDH mutation.

We also observed a high-rate of robust induction of EGFRvIII-specific antibodies following rindopepimut administration. The rate and magnitude of humoral response associated with prolonged survival, and induced EGFRvIII-specific antibodies derived from immunized patients' serum were capable of killing EGFRvIII-positive tumor cells *in vitro* even at relatively high dilutions. This finding is consistent with previously published data suggesting that antibodies may be a predominant mechanism for the antitumor activity of rindopepimut
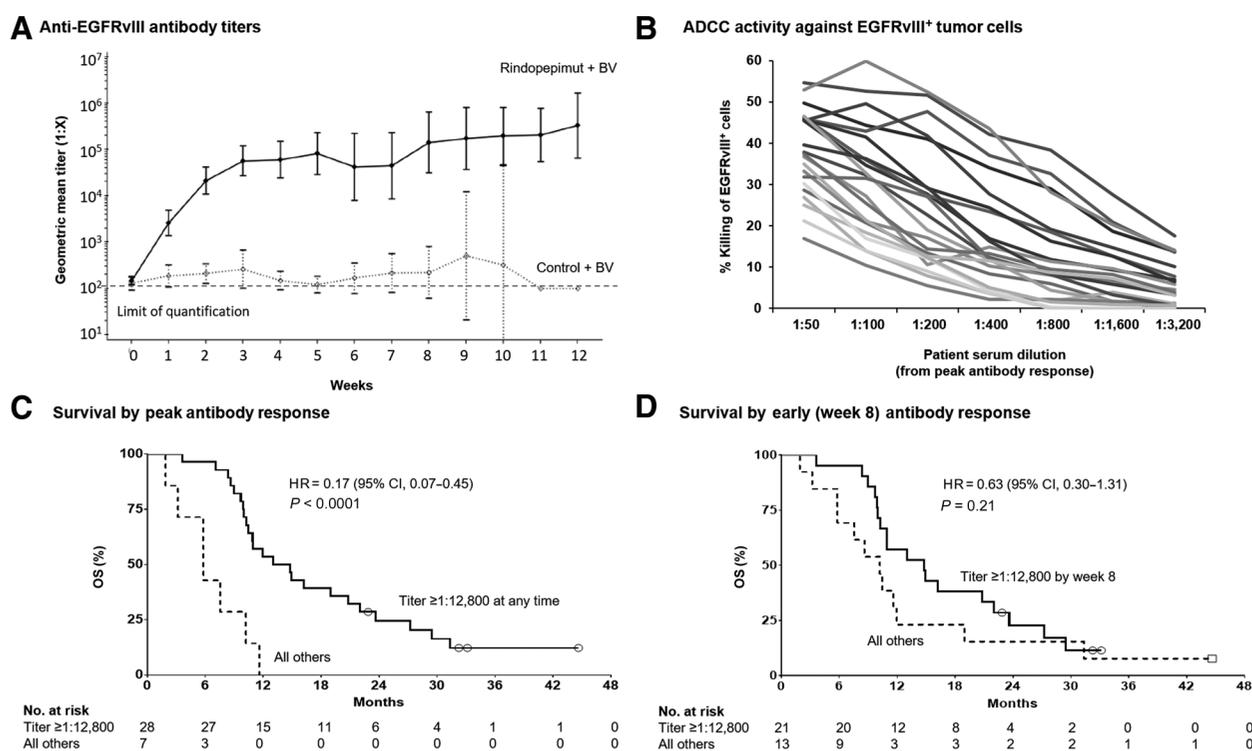
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Figure 4.
Robust induction of anti-EGFRvIII antibodies have effector function and correlate with survival. **A,** Geometric mean of anti-EGFRvIII titers over the course of treatment. **B,** ADCC activity against EGFRvIII-expressing glioma cells of individual patient samples measured at the peak anti-EGFRvIII antibody response. **C** and **D,** Survival in patients with strong anti-EGFRvIII antibody response (>1:12,800) at any time and by week 8, respectively.

Table 2. Toxicity.

	Rindopepimut + Bevacizumab (n = 35)		Control + Bevacizumab (n = 37)	
	All grades	Grade ≥3	All grades	Grade ≥3
Reported events, regardless of causality				
Arthralgia	8 (23%)	—	2 (5%)	1 (3%)
Back pain	6 (17%)	2 (6%)	3 (8%)	—
Convulsion	8 (23%)	4 (11%)	9 (24%)	—
Diarrhea	6 (17%)	—	2 (5%)	—
Fall	6 (17%)	1 (3%)	2 (5%)	1 (3%)
Fatigue	8 (23%)	—	10 (27%)	2 (5%)
Headache	8 (23%)	1 (3%)	9 (24%)	2 (5%)
Hemiparesis	2 (6%)	—	6 (16%)	2 (5%)
Hyperglycemia	3 (9%)	—	4 (11%)	3 (8%)
Hypertension	8 (23%)	1 (3%)	9 (24%)	3 (8%)
Nausea	9 (26%)	—	4 (11%)	1 (3%)
Vomiting	6 (17%)	—	2 (5%)	—
Events considered related to rindopepimut or control				
Alanine aminotransferase increased	1 (3%)	1 (3%)	—	—
Erythema	2 (6%)	—	—	—
Fatigue	2 (6%)	—	3 (8%)	1 (3%)
Gamma—glutamyl transferase increased	1 (3%)	1 (3%)	1 (3%)	—
Hyperglycemia	—	—	1 (3%)	1 (3%)

Note: All-causality adverse events are summarized if occurring at ≥15% frequency overall or in >2 patients at severity grade ≥3 in either treatment group. Treatment-related events are summarized if occurring in ≥2 patients in either treatment group, or in any patients at grade ≥3. There were no grade 4 or 5 events attributed to study vaccination. Table excludes injection site reactions.

and provide a potentially predictive biomarker of efficacy for this therapeutic (18, 29).

The efficacy signal observed in this randomized trial counters the belief that the blood–brain barrier and apparent immune suppressive characteristics of glioblastoma may prevent the activity of an immunotherapy and support the potential for targeted immunotherapy as a treatment strategy for glioblastoma. Perhaps the tumor-specificity of this response and the antigen sink within these tumors contributes to this benefit as other EGFRvIII-targeting approaches appear to validate this concept (30). The disparity between the positive results with rindopepimut in recurrent glioblastoma in ReACT and the negative results of ACT IV in newly diagnosed glioblastoma (31) is unclear and challenging to reconcile but may be related to the choice of agent used for combination therapy. Bevacizumab has been shown to enhance immune-mediated antitumor effects in nonclinical models while the lymphopenia that commonly occurs from the combination with temozolomide may diminish an immunologic effect (32, 33). The phase II signal of this study warrant validation and suggest that rindopepimut may be of value for other cancers that express EGFRvIII (34–36).

Disclosure of Potential Conflicts of Interest

D.A. Reardon is a paid consultant for Abbvie, Advantagene, Agenus, Amgen, Bayer, Bristol-Myers Squibb, Celldex, Delmar, EMD Serono, Genentech/Roche, Inovio, Merck, Merck KGaA, Monteris, Novocure, Oncurus, Oxigene, Regeneron, Stemline, and Taiho Oncology. A. Desjardins reports receiving other commercial research support from Genentech/Roche, Triphase Accelerator, Symphogen A/S, Orbus Therapeutics; holds ownership interest (including patents) in Istari Oncology; and is an unpaid consultant/advisory board member for Orbus Therapeutics and Istari Oncology. D.M. O'Rourke reports receiving commercial research grants and other commercial research support from Novartis; holds ownership interest (including patents) in Isoma Therapeutics; and reports receiving other remuneration for providing expert clinical testimony. D.D. Tran is an employee of Novocure and Monteris, and reports receiving commercial research grants from Novocure, Merck, Tocagen, Novartis, Stemline, Northwest Biotech, and Lacerta. K. Fink is an unpaid consultant/advisory board member for UCB Pharma. L.B. Nabors reports receiving other remuneration from BTG and Karyopharm. D.A. Bota is a paid consultant for Tocagen and PCT Pharma and reports receiving speakers bureau honoraria from Novocure and Zailab. R.V. Lukas is a paid consultant for Abbvie, Eisai, and Monteris, and reports receiving other remuneration from EBSCO, Medlink Neurology, American Physician Institute, and Bristol-Myers Squibb. L. Vitale holds ownership interest (including patents) in Celldex Therapeutics. Y. He holds ownership interest (including patents) in Celldex Therapeutics. J.A. Green is an employee of and holds ownership interest (including patents) in Celldex. M.J. Yellin is an employee of and holds ownership interest (including patents) in Celldex. C.D. Turner is an employee of and holds ownership interest (including patents) in Celldex. T. Keler is an employee of and holds ownership interest (including patents) in Celldex. T.A. Davis is an employee of and holds ownership interest (including patents) in Celldex. J.H. Sampson is a paid consultant for Bristol-Myers Squibb and holds ownership interest (including patents) in Istari Oncology and Annias Therapeutics. No potential conflicts of interest were disclosed by the other authors.

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