

# Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial

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**TITLE PAGE**

**Title:** Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): results of a randomized, double-blind, international phase 3 trial

**Authors:** Michael Weller, Nicholas Butowski, David D. Tran, Lawrence D. Recht, Michael Lim, Hal Hirte, Lynn Ashby, Lazlo Mechtler, Samuel A. Goldlust, Fabio Iwamoto, Jan Drappatz, Donald M. O'Rourke, Mark Wong, Mark G. Hamilton, Gaetano Finocchiaro, James Perry, Wolfgang Wick, Jennifer Green, Yi He, Christopher D. Turner, Michael J. Yellin, Tibor Keler, Thomas A. Davis, Roger Stupp, and John H. Sampson, for the ACT IV trial investigators*
*Additional ACT IV trial investigators who participated in this trial are listed in the appendix.

**Affiliations:** Departments of Neurology (Prof M. Weller, MD) and Oncology (Prof R. Stupp, MD), University Hospital and University of Zurich, Zurich, Switzerland; Department of Neurological Surgery, University of California, San Francisco, CA (N. Butowski, MD); Washington University, St. Louis, MO (D Tran, MD); Stanford University Medical Center, Palo Alto, CA (L.D. Recht, MD); The Johns Hopkins Hospital, Baltimore, MD (M. Lim, MD); Juravinski Cancer Centre, Hamilton, ON, Canada (H. Hirte, MD); Barrow Neurological Institute, Phoenix, AZ (L. Ashby, MD); Dent Neurologic Institute, Buffalo, NY (L. Mechtler, MD); John Theurer Cancer Center, Hackensack, NJ (S. Goldlust, MD); Columbia University Medical Center, New York, NY (F. Iwamoto, MD); University of Pittsburgh Medical Center, Pittsburgh, PA (Jan Drappatz); Department of Neurosurgery, Perelman School of Medicine, University of

Pennsylvania, Philadelphia, PA (D. O'Rourke, MD); Westmead Hospital, Westmead, Australia (M. Wong, MD); University of Calgary, Department of Clinical Neurosciences, Division of Neurosurgery, Foothills Hospital, Calgary, Alberta, Canada (Prof M. Hamilton, MD); Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy (G. Finocchiaro, MD); Sunnybrook Health Sciences Centre, Toronto, ON, Canada (Prof J. Perry, MD); The University of Heidelberg and German Cancer Research Center, Heidelberg, Germany (Prof. W. Wick, MD); Celldex Therapeutics, Inc., Hampton, NJ (J. Green, Y. He, PhD, C. Turner, MD, M. Yellin, MD, T. Keler, PhD, T. Davis, MD); The Preston Robert Tisch Brain Tumor Center, Duke University Medical Center, Durham, NC (Prof J. H. Sampson, MD)

**Corresponding author:**

Michael Weller, MD

Department of Neurology, University Hospital and University of Zurich

Frauenklinikstrasse 26, 8091 Zurich, Switzerland,

Tel. +41 44 255 55 00

Michael.Weller@usz.ch

## SUMMARY

### Background

Rindopepimut, a vaccine targeting the EGFR deletion mutation EGFRvIII, consists of a EGFRvIII-specific peptide conjugated to keyhole limpet hemocyanin (KLH). Single-arm studies of rindopepimut in patients with newly diagnosed, EGFRvIII+ glioblastoma and minimal residual disease (MRD) resulted in median survival of 20-22 months, compared to ~16 months for matched contemporary datasets. The ACT IV study was conducted to demonstrate prolongation of survival by rindopepimut when added to standard chemotherapy.

### Methods

This pivotal, randomized, double-blind, phase 3 trial was conducted at 165 hospitals in 22 countries. Eligible patients had newly diagnosed glioblastoma confirmed to express EGFRvIII by central analysis, and had undergone maximal surgical resection and completion of standard chemoradiation without progression. Patients were stratified by RPA class, MGMT promoter methylation, and geographic region, and randomized (1:1) to receive rindopepimut (500 μg admixed with 150 μg GM CSF) or control (100 μg KLH) via monthly intradermal injection until progression or intolerance, concurrent with standard temozolomide (150-200 mg/m$^2$ for 5/28 days) for 6-12 cycles or longer. Patients, investigators, and the trial sponsor were blinded to treatment allocation. Randomization and preparation of blinded treatment were managed via interactive response technology by designated pharmacists otherwise uninvolved in study conduct. Primary endpoint was intention-to-treat analysis of overall survival for MRD patients (enhancing tumor <2 cm$^2$ post-chemoradiation by central review) aiming to detect a log-rank hazard ratio (HR) ≤0·71 with 80% power and alpha=0·05. The trial is registered with ClinicalTrials.gov (NCT01480479).

**Findings**

Between April 12, 2012 and December 15, 2014, 745 patients were enrolled (405 MRD; 338 SRD; 2 unevaluable). The study was terminated for futility after a preplanned interim analysis. At final analysis, there was no significant difference in overall survival for the MRD (HR 1·01, 95% CI 0·79-1·30; p=0·93) population. Rindopepimut was well tolerated with robust anti-EGFRvIII immune response. Most common grade 3-4 adverse events for all 369 treated patients in the rindopepimut group vs 372 treated patients in the control group included: thrombocytopenia (33 [9%] vs 23 [6%]), fatigue (6 [2%] vs 19 [5%]), brain edema (8 [2%] vs 11 [3%]), seizure (9 [2%] vs 8 [2%]), and headache (6 [2%] vs 10 [3%]). Serious adverse events included seizure (18 [5%] vs 22 [6%]) and brain edema (7 [2%] vs 12 [3%]).

**Interpretation**

Despite consistent rindopepimut-induced humoral responses, rindopepimut did not prolong survival in patients with newly diagnostic glioblastoma. Combination approaches potentially including rindopepimut may be required to demonstrate efficacy of immunotherapy in glioblastoma.

**Funding**

Celldex Therapeutics, Inc.

## RESEARCH IN CONTEXT

### Evidence before this study

Using PubMed, we performed a systematic review of the scientific literature published prior to August 1, 2011 using the search terms “glioblastoma” and publication type "randomized controlled trial" or “clinical trial, phase III”. The standard of care for newly diagnosed glioblastoma established in 2005, maximum feasible surgical resection followed by radiotherapy and temozolomide chemotherapy, is associated with median overall survival of approximately 15 months. Despite the introduction of a number of investigational approaches in the subsequent years, no treatment had successfully demonstrated further improvement in survival. The addition of the search term “EGFRvIII” and expansion of our search to any clinical trial did not identify any other agents specifically targeting EGFRvIII. Finally, a search including “glioblastoma”, “EGFRvIII” and “survival” produced a few retrospective studies showing similar or worse median and long-term survival for patients whose tumor expressed EGFRvIII. Three prior studies of rindopepimut had been conducted in patients with newly diagnosed, EGFRvIII-expressing glioblastoma and minimal residual disease. In these studies, rindopepimut was associated with a strong anti-EGFRvIII humoral immune response, marked reduction in EGFRvIII expression in available recurrent tumor samples, and a median survival of 20-22 months, as compared to ~12 months for a small matched contemporary dataset and 15 months for the small subset of patients with newly diagnosed EGFRvIII-expressing glioblastoma randomized to receive standard of care therapy in the ACT III study.

**Added value of this study**

To our knowledge, the ACT IV study is the first randomized trial evaluating the efficacy of an EGFRvIII-targeted therapy for newly diagnosed glioblastoma. Despite the strong anti-EGFRvIII immune response generated in patients, the primary study analysis did not demonstrate a survival benefit for patients with minimal residual disease who received rindopepimut with temozolomide. A potential long-term survival benefit was observed in exploratory analyses of a subset of patients with significant residual disease, which may challenge the view that minimal tumor burden is required for immunotherapy to be effective. Also notable is that patients in the control group fared markedly better than matched control datasets available at the time of study design, suggesting improvement in outcome since the study was originally designed.

**Implications of all the available evidence**

These results question the utility of immunotherapy targeting a single tumor antigen with heterogeneous tumor expression, as well as the optimal setting for evaluation of immunotherapy. Patients with more significant residual disease expressing the target antigen may experience greater benefit from generation of targeted immunity than those with completely resected disease. Recent data from a randomized, double-blind, phase 2 study in recurrent EGFRvIII positive GBM (the ReACT study) suggest a prominent treatment effect (overall survival HR 0·53, 95% CI 0·32-0·88; p=0·013) for rindopepimut when combined with standard bevacizumab. Combination with temozolomide may compromise an immunological effect, in contrast with bevacizumab. The results of the ACT IV study also question the predictive value of both historical control datasets (matched patients from non-study databases) and small randomized phase 2 trial datasets (such as ACT III) for the design of phase 3 studies. These data

lend support to further clinical trials utilizing combination strategies such as immunotherapy with angiogenesis inhibition.

## MANUSCRIPT TEXT

### Introduction

Glioblastoma is the most common malignant primary brain tumor in adults. Its annual incidence is > 3 per 100,000 world-wide without major regional variation, and males are affected more often than females.[1] The standard of care, maximum feasible surgical resection followed by radiotherapy with concomitant and maintenance temozolomide chemotherapy (TMZ/RT→TMZ), contributes to a median overall survival in the range of 15 months.[2,3]

The tumor treating fields device, recently reported to extend survival to 20·5 months, represents an additional treatment option.[4] Treatment at recurrence, which may include second surgery, re-irradiation, alkylating chemotherapy using nitrosoureas such as lomustine or temozolomide rechallenge, or antiangiogenic therapy using bevacizumab, is less well standardized and has not demonstrated a significant impact on survival. Poor prognostic factors include low performance status, older age, incomplete resection, and an unmethylated promoter of the DNA repair gene, *$O^6$-methylguanine-DNA methyltransferase* (MGMT). Novel treatment approaches to glioblastoma are therefore urgently needed, and immunotherapy has now become the major area of clinical research.

The epidermal growth factor receptor (EGFR) gene is amplified in more than 40% of glioblastomas, and EGFR amplification is frequently associated with a deletion mutation affecting exons 2-7, referred to as EGFRvIII or delta-EGFR. EGFRvIII expression occurs in approximately 20-30% of all glioblastomas.[5-7] The potential immunogenicity of the EGFRvIII mutation, first recognized decades ago, resulted in the development of rindopepimut, a peptide

vaccine containing the specific novel amino acid sequence created by the EGFRvIII deletion mutation conjugated to keyhole limpet hemocyanin (KLH). Rindopepimut has been explored in two small single arm phase 2 trials, ACTIVATE and ACT II, as well as a larger phase 2 trial, ACT III, which was initially planned as an open-label, randomized, phase 3 trial but was converted to a single-arm design following near-complete voluntary attrition of the first 16 patients randomized to receive temozolomide alone.[6,8,9] In these trials, approximately 100 patients with EGFRvIII-expressing glioblastoma who had received a gross total resection and had no evidence of progression after radiotherapy with concomitant temozolomide were treated with rindopepimut alone (ACTIVATE) or rindopepimut with adjuvant temozolomide (ACT II, ACT III). These three trials resulted in a consistent and encouraging progression-free survival in the range of 15 months from diagnosis and overall survival of 24 months from diagnosis, which compared favorably with contemporary patient cohorts (appendix, p 7). The selection of patients with minimal residual disease (MRD) after completion of chemoradiation was based on the assumption that MRD would minimize the tumor-associated immunosuppression typical of glioblastoma. ACT IV was designed as a pivotal, randomized, placebo-controlled, phase 3 clinical trial to demonstrate prolongation of survival by rindopepimut.

## Methods

### Study Design and Participants

The ACT IV study is a randomized, double-blind, controlled study conducted at 165 hospitals in 22 countries (appendix, p 11). The study was open to men and women ≥18 years of age with newly diagnosed EGFRvIII-expressing glioblastoma. Confirmation of glioblastoma histology and EGFRvIII expression analysis from resected tissue by real-time polymerase chain reaction

(RT-PCR) were performed centrally (LabCorp, Research Triangle Park, NC). Patients must have undergone maximal surgical resection and have completed standard radiation (up to 60 Gy) with concomitant temozolomide (75 mg/m$^2$ per day).[2] In order to be eligible, at least 90% of the planned radiotherapy dose had to be delivered. Disease progression during chemoradiation, any additional tumor-specific treatment for glioblastoma, inability to taper corticosteroid to ≤2 mg of dexamethasone (or equivalent) per day for at least 3 days prior to randomization, Eastern Cooperative Oncology Group (ECOG) performance status ≥3 in the week prior to randomization, diffuse leptomeningeal disease, gliomatosis cerebri, infratentorial disease, active infection, and immunosuppressive disease were exclusionary.

An independent imaging review committee (IRC; BioClinica, Princeton, NJ) evaluated post-operative and post-chemoradiation brain MRIs, and retrospectively classified patients as having either minimal residual disease (MRD; <2 cm$^2$ of residual enhancing tumor on post-chemoradiation imaging) or significant residual disease (SRD; ≥2 cm$^2$ of residual enhancing tumor on post-chemoradiation imaging).

The study was compliant with the Declaration of Helsinki and guidelines on Good Clinical Practice. Ethics approval was obtained at all participating centers and all patients provided written informed consent. The full trial protocol can be found in the appendix.

**Randomization and masking**

Eligible patients were stratified by MGMT promoter methylation status, the European Organisation for Research and Treatment of Cancer (EORTC) recursive partitioning analysis

(RPA) class,[10,11] and geographic region (North America and Western Europe vs. all other regions), and randomized to the treatment groups in a 1:1 ratio, using a prespecified randomization sequence with a block size of 4. Unblinded pharmacists who were otherwise uninvolved in study conduct obtained randomized treatment assignments and managed study treatment via interactive response technology. Study treatments were prepared in the pharmacy and delivered to study staff in blinded, pre-loaded syringes. KLH was given as a control injection to produce a local reaction similar to that expected with rindopepimut in order to maintain the treatment blind.

Pharmacovigilance staff at the study sponsor and contract research organization (CRO) received treatment assignments for individual patients when necessary to comply with international safety reporting. Pharmacy records were audited by an independent team of CRO staff. The study data monitoring committee (DMC) and the supportive independent statistical group at the CRO viewed unblinded data. All other study staff, patients and investigators remained blinded to treatment assignments.

**Procedures**

All patients were to receive standard maintenance temozolomide at a dose of 150-200 mg/m$^2$ for five of 28 days, for 6-12 cycles,[2] or longer if consistent with local standard of care. In addition, patients randomized to the rindopepimut group received 500 µg of rindopepimut admixed with 150 µg GM-CSF (Leukine®, Sanofi-Aventis), while the control group received 100 µg KLH (Biosyn, Carlsbad CA). Each 0.8 mL dose was administered as 2-8 separate intradermal injections into the skin of the thigh below the groin. The allowance for 2-8 injections allowed for smaller volume of individual intradermal injections, potentially reducing patient discomfort and

risk of leakage. Experimental treatment was to start 7-14 days after completion of standard chemoradiation, and was administered as two initial priming doses (study days 1 and 15), then monthly on day 21 of each temozolomide cycle and continuing after the end of maintenance temozolomide until disease progression or intolerance. Since all toxicities related to rindopepimut vaccination were expected to be immunologically mediated, no adjustment to the dose of double-blind vaccine was allowed; however, dose omission or delay was allowed.

Brain MRIs were performed within 14 days after completion of chemoradiation, every 8 weeks for six months, every 12 weeks through the second year, every 16 weeks through the fourth year, and every 26 weeks thereafter, or until documented disease progression. Tumor response and progression were assessed per the Response Assessment in Neuro-Oncology (RANO) Working Group criteria,[12] with minor modifications for the purpose of protocol standardization (appendix, p 8). Local investigator assessments guided individual treatment decisions. The retrospective IRC review, blinded to treatment assignment and investigator assessments, was utilized for the primary analyses of progression-free survival and objective tumor response rate.

Safety assessments included monthly physical examination, vital signs, routine laboratory monitoring (hematology on day 1 and 22 of each cycle, and blood chemistry and urinalysis on day 1 of each cycle), and evaluation of adverse events using NCI Common Terminology Criteria for Adverse Events (CTCAE) v. 4·0. The M.D. Anderson Symptom Inventory Brain Tumor (MDASI-BT) and EORTC Core Quality of Life Questionnaire (QLQ-C30) and Brain Cancer Module (BN20) were completed monthly throughout treatment by patients who were fluent in a language in which the questionnaires were validated.

*EGFRvIII expression:* Formalin fixed paraffin embedded (FFPE) tumor tissue was analyzed centrally. EGFRvIII variant as well as EGFR wild type were determined using a taqman-based real-time RT-PCR assay performed on ABI Prism® 7900HT instrument. The fluorescence detected was directly proportional to the amount of RNA present and expressed as cycle threshold (Ct). A predefined cut off expressed as delta Ct (Ct of EGFRvIII minus Ct of EGFR wild type) of ≤11.0 was used to define a sample as positive for EGFRvIII. The threshold, which was selected as a conservative cut-off to minimize the possibility of including EGFRvIII negative patients, was defined by the delta Ct values of samples from the ACT III study which demonstrated unambiguous calls of positive (n=9) or negative (n=10) by corroboration of IHC and PCR results, confirmed by reproducibility testing and accuracy verification.

*MGMT promoter methylation:* FFPE tumor samples were analyzed centrally at LabCorp under license from MDx Health (Irvine, CA) by methylation-specific PCR, based on previously published methods.[13]

*Humoral responses to the vaccine*: Antibody titers were measured by ELISA using microtiter plates directly coated with a 14 amino acid peptide, which spans the exon 1-8 junction of EGFR and is specific for the EGFRvIII mutant.[14] Dilutions of patient plasma were incubated in the plates, and the anti-EGFRvIII antibodies were detected with an Fc γ-specific goat anti-human $F(ab')_2$ antibody conjugated to horseradish peroxidase (Jackson ImmunoResearch Labs, West Grove, PA) followed by tetra-methylbenzidine substrate. Absorbance was measured at wavelength 450 nm. Patient samples were screened and positive samples titered against a plate-

specific floating cut-point. The antibody titer for patient samples was calculated as the highest dilution with an OD value greater than the mean + 3xSD of replicate negative control samples run on the same plate. As the starting dilution was 1:100, samples which screened negative are reported with titers < 100. For exploratory analyses of survival, patients were retrospectively classified according to the trajectory at which anti-EGFRvIII titers developed with rindopepimut treatment (slow, moderate or rapid).

*HLA analysis:* Typing of HLA class I alleles (A and B loci) and HLA class II alleles (-DR locus) by serology or DNA-PCR was performed by an ASHI accredited laboratory (ClinImmune Labs; Aurora, CO) using buccal swab samples.

**Outcomes**

The primary study objective was to demonstrate that rindopepimut improves overall survival (defined as the time from randomization to death) when administered with standard temozolomide to patients with newly diagnosed, EGFRvIII positive glioblastoma and MRD. The extent of residual disease (whether MRD or SRD) was retrospectively determined by the central IRC. Patients with SRD formed a second exploratory cohort that had not been included in prior studies. The primary endpoint was powered and restricted to the MRD patient population. Secondary study objectives were to evaluate the effect of rindopepimut on progression-free survival (defined as the time from randomization to disease progression or death, whichever occurred first), objective tumor response rate (the proportion of patients achieving a confirmed complete or partial response per RANO criteria), health-related quality of life (assessed using the MDASI-BT, QLQ-C30, and BN20), and EGFRvIII expression, and to further characterize the safety profile and overall immunogenicity of rindopepimut in patients with both MRD and SRD.

**Statistical Analysis**

Patients classified with MRD by the IRC were included in the "modified" intent-to-treat (mITT) population for primary analysis. A total of 283 deaths in the MRD population at the time of the final analysis was calculated to provide 80% power to detect a target hazard ratio (HR) of 0·714, which corresponded to a 6-month improvement in median survival (from 15 months for control to 21 months for rindopepimut). The targeted number of deaths was based on 1-sided log-rank test, overall type I error rate of 0·025, and 2 planned interim analyses of overall survival for superiority using an O'Brien-Fleming group sequential monitoring plan. Allowing for a 48-month accrual period and 10% attrition rate, a sample size of 374 MRD patients was expected to

result in 283 deaths within 72 months of the first randomized patient. Supportive secondary analyses were performed for all randomized patients (ITT). To control the family-wise error rate (the probability of making one or more false discoveries when performing multiple hypotheses tests), study analyses were to proceed according to a fixed sequence procedure in which the primary analysis was completed for the MRD and ITT populations sequentially, followed by the secondary endpoint analyses (appendix, p 1). According to this analysis plan, each sequential statistical test was to be considered positive only if the previous statistical test was positive. The sample size for SRD patients was not prospectively defined, and analysis of this population was planned as exploratory. Safety analyses included patients who received at least one dose of study treatment.

Overall survival and progression-free survival, including landmark survival rates, were summarized using the Kaplan-Meier method. Primary inferential comparisons between treatment groups used the log-rank test stratified by MGMT promoter methylation status, adapted RPA class, and geographic region. HR were estimated using a stratified Cox proportional hazards model (SAS version 9·4). Objective tumor response rate was summarized for all patients with measurable, enhancing tumor on post-chemoradiation MRI per IRC assessment (i.e., the "response evaluable" population).

For diagnostic purposes, the overall survival proportional hazard assumption was checked by comparing the hazard ratios and assessing the significance level of stratification variables from stratified and unstratified Cox models. The interactions between the treatment group and stratification variables was explored by inclusion of the stratification factors as covariates in the

unstratified Cox model. In recognition of the "delayed treatment effect" previously observed with other immunotherapies, exploratory analysis using a weighted logrank test was also performed.[15]

Two interim analyses were planned for superiority and futility after 142 and 212 deaths in the MRD population, representing 50% and 75% of the events required for final analysis. The study was designed with a non-binding approach for efficacy and futility boundaries. Early stopping boundaries for superiority according to an O'Brien-Fleming alpha spending were p=0·002 for the first interim analysis and p=0·018 for the second interim analysis. The futility analyses were based on the observed treatment effect, with HRs of ≥1·1 and >0·9 representing boundaries for futility for the two interim analyses. For the first and second interim analyses, respectively, the chances of stopping a positive study for futility were 0.5% and 4.6% and the chances of stopping a negative study for futility were 29% and 78%. The DMC evaluated the preplanned interim analyses.

This study is registered with ClinicalTrials.gov, number NCT01480479.

**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 and performed statistical analysis. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

A total of 4,652 patients were screened for study eligibility (Figure 1). In the cohort of 4,519 patients for whom submitted tumor tissue was adequate for EGFRvIII expression analysis, 1,345 (30%) were determined to have EGFRvIII-expressing tumors. Between April 12, 2012 and December 15, 2014, 745 patients with EGFRvIII-expressing tumors were randomized to receive rindopepimut (n=371) or control (n=374). Of these, 405 (195 allocated to rindopepimut and 210 allocated to control) were assigned to the MRD population by central review and included in the primary intention-to-treat analysis, while 741 (369 allocated to rindopepimut and 372 allocated to control) received study treatment and were included in the safety analyses.

Pretreatment patient and disease characteristics for randomized patients were well balanced between treatment groups within each analysis population (Table 1).

At the second preplanned interim analysis conducted upon 212 deaths in the MRD population (data cutoff of October 24, 2015), the futility boundary was crossed. The overall survival HR for rindopepimut vs control in the MRD population was 0.99, suggesting that rindopepimut was unlikely to be found superior to control. The study was therefore prematurely closed, and preliminary primary analysis results were released. Additional survival information was obtained as patients were discontinued from study, and final analyses were conducted with a data cutoff of April 29, 2016. At study closure and final analysis, 523 deaths (254 in the rindopepimut group [129 in the MRD population] and 269 in the control group [135 in the MRD population]) and 546 progression events (267 in the rindopepimut group [141 in the MRD population] and 279 in the control group [149 in the MRD population]) had occurred.

Overall survival did not differ between the treatment groups for the MRD (HR 1·01, 95% CI 0·79-1·30; p=0·93) or ITT (HR 0·89, 95% CI 0·75-1·07; p=0·22) populations (Figure 2). Median overall survival (in months) for the rindopepimut and control groups, respectively, was 20·1 (95% CI 18·5-22·1) vs. 20·0 (95% CI 18·1-21·9) in the MRD population, and 17·4 (95% CI 16·1-19·4) vs. 17·4 (95% CI 16·2-18·8) in the ITT population. In exploratory analysis of the SRD population, overall survival was similar for the treatment groups, with HR of 0·79 (95% CI 0·61-1·02; p=0·066). Median overall survival was 14·8 months (95% CI 12·8-17·1) for the rindopepimut group and 14·1 months (95% CI 12·6-15·7) for the control group. However, a possible long-term survival benefit was observed with a two-year survival rate of 30% (95% CI 23-37) in the rindopepimut group vs. 19% (95% CI 13-26) in the control group (p=0·029). On exploratory subgroup analyses (p-values provided for descriptive purposes only), this apparent treatment effect appears most pronounced for patients with SRD treated in the United States (HR 0·70, 95% CI 0·51-0·96; p=0·027), who developed anti-EGFRvIII humoral response at a "moderate" rate (HR 0·57, 95% CI 0·39-0·83; p=0·0032), and who received nitrosoureas in the post-treatment follow-up period (HR 0·49, 95% CI 0·25-0·97; p=0·038). The interactions of geographic region and post-treatment nitrosoureas by treatment effects are not statistically significant based on proportional hazard models, however, the study was not designed to test interactions. Furthermore, no biologically plausible explanations for these findings were identified, and subgroup analyses of the MRD population did not demonstrate similar findings (Figure 3). In the group of patients who were classified with SRD by investigator assessment (rather than the central reviewer), overall survival was no different between treatment groups (HR 0·91, 95% CI 0·71-1·18; p=0·48) and two-year survival rate was 30% (95% CI 23-37) in the rindopepimut group vs. 20% (95% CI 14-27) in the control group (p=0·046) (appendix, p 2).

On sensitivity analysis, some violations of the proportional hazard assumption were observed in various strata. Interactions between the treatment group and stratification variables were also explored and none of the interaction terms were significant. The weighted logrank p-values for pre-specified weights (r1 = 0, r2 = 1, 2) were 0.93 and 0.88 for the MRD population, 0.081 and 0.092 for the ITT population, and 0.021 and 0.017 for the SRD population, respectively.

The median duration of adjuvant temozolomide within the MRD population was 5.2 months (IQR 3.2 - 10.3) for the rindopepimut group vs. 5.0 months (IQR 3.0 - 10.1) for the control group. The median duration of adjuvant temozolomide within the SRD population was 4.1 months (IQR 2.0 - 7.3) for the rindopepimut group vs. 4.1 months (IQR 2.0 - 6.7) for the control group. Anticancer therapies received in the post-treatment follow-up period were also well balanced among treatment groups (appendix, p 9). Although there were geographic differences in the type of anticancer therapies used after progression (appendix, p 10), with more frequent use of nitrosoureas in the European Union and more frequent use of bevacizumab in the United States, these regional differences did not appear to account for the geographic variability observed within the overall survival analyses (Figure 3).

Progression-free survival was similar for the treatment groups within the MRD (HR 1·01, 95% CI 0·80-1·29; p=0·91), ITT (HR 0·94, 95% CI 0·79-1·13; p=0·51) and SRD (HR 0·86, 95% CI 0·66-1·12; p=0·28) populations (appendix, p 3). Objective tumor response rate for the response-evaluable population was no different between treatment groups (31 [15%] of 208 [95% CI 10-21] in the rindopepimut group and 27 [15%] of 184 [95% CI 10-21] in the control group). No

statistically significant differences in quality of life measures (appendix, p 4) or requirement for corticosteroids (appendix, p 5) were observed among the analysis populations.

Rindopepimut treatment resulted in robust humoral response, with treated patients reaching a median peak anti-EGFRvIII antibody titer of 1:25,600 (IQR 3,200 – 204,800). The magnitude of response was similar between the MRD and SRD populations (Figure 4). The use of corticosteroids did not appear to have a significant impact on the rindopepimut-induced humoral immune response (appendix, p 6). However, no consistent correlation between increasingly rapid or robust titer response and clinical outcome was observed.

Intensity of tumor EGFRvIII expression (RT-PCR delta CT in the baseline sample as described in methods) did not correlate with outcome (Figure 3). In the small subset of patients with available post-treatment tumor sample, EGFRvIII expression determined by RT-PCR was lost for 21 of 37 (57%) rindopepimut-treated patients and 23 of 39 (59%) patients in the control group. Mean anti-EGFRvIII titer was not significantly different between the groups of patients with either loss or persistence of tumor EGFRvIII. Elimination of EGRFvIII did not correlate with outcome (data not shown).

Correlation analysis of HLA type with outcome was performed for the MRD and SRD populations. Although B18, A25, and D11 each correlated with overall survival or progression-free survival in individual analyses, sample sizes were small, this trend was not observed consistently among the analysis populations, and these HLA types would not be predicted to bind to the EGFRvIII peptide based on algorithm analysis of the peptide.

Rindopepimut was very well tolerated (Table 2). Injection site reactions, consisting chiefly of transient grade 1-2 erythema, pruritus, and rash, were experienced by the majority of the patients who received rindopepimut (294 [80%] of 369), but were also common in the control group (151 [41%] of 372). Most common grade 3-4 adverse events for all 369 treated patients in the rindopepimut group vs 372 treated patients in the control group included: thrombocytopenia (33 [9%] vs 23 [6%]), fatigue (6 [2%] vs 19 [5%]), brain edema (8 [2%] vs 11 [3%]), seizure (9 [2%] vs 8 [2%]), and headache (6 [2%] vs 10 [3%]). Serious adverse events included seizure (18 [5%] vs 22 [6%]) and brain edema (7 [2%] vs 12 [3%]). Of the 523 reported deaths, the majority (427) were due to progressive disease (204 [80%] of 254 in the rindopepimut group and 223 [83%] of 269 in the control group), 80 were due to other/unknown cause (41 [16%] in the rindopepimut group and 39 [14%] in the control group), and 16 were due to adverse events (9 [4%] in the rindopepimut group and 7 [3%] in the control group). One fatal event, a pulmonary embolism experienced by a 64-year old male patient after 11 months of treatment, was assessed as potentially related to rindopepimut. Eight patients discontinued double-blind vaccine due to treatment-related toxicity. These included two cases of hypersensitivity/allergic reaction, two cases of rash, and single cases of bone/muscle pain and the fatal pulmonary thromboembolism in the rindopepimut group, and single cases of rash and depression in the control group. Despite the observation of hypersensitivity reaction attributed to rindopepimut in prior studies,[6,8,9] such events were infrequent in both treatment groups. There was similarly no evidence for increased toxicity that might theoretically arise due to rindopepimut-induced immune infiltration of the brain, such as cerebral edema or seizure.

## Discussion

The primary analysis of the ACT IV study did not demonstrate a survival benefit for patients with MRD who received rindopepimut with temozolomide. The outcome for patients treated with rindopepimut was similar to that observed in prior uncontrolled studies. Of note, the definition for MRD was increased to <2 $cm^2$ in the ACT IV study, as compared to ≤1 $cm^2$ in prior studies. Median overall survival from randomization for MRD patients treated with rindopepimut in ACT IV was 20·1 months, which is consistent with the range of 20-22 months observed in prior trials in the same population.[6,8,9] However, patients in the control group fared markedly better than matched control datasets available at the time of study design (appendix, p 7).

Given the prior ACT III study experience where voluntary attrition of patients randomized to the open-label control group rendered the original randomized design infeasible, it was recognized that a truly blinded design would be critical for ACT IV. Therefore, rather than an inactive placebo, KLH was used as a control injection in order to replicate the local reactions (erythema, pruritus and rash) experienced by nearly all patients who receive rindopepimut. KLH can generate immune activation and one might speculate that the better-than-expected outcome in the control group might result from the generation of an effective immune response unrelated to EGFRvIII. However, it is generally thought that a tumor-specific response triggered by KLH would require topical application to the tumor itself (intratumoral injection in this case) and that a real therapeutic effect is unlikely to result from peripheral intradermal injection. In a small phase 2 trial of patients with recurrent disease (ReACT), the same KLH control was utilized with control group outcome no better than expected.[16] It is also possible that the unexpectedly

favorable outcome for the ACT IV control group may result from enrollment of patients at lower risk as compared to prior trials. However, the eligibility criteria and baseline characteristics of patients in the ACT IV study were similar to the prior phase II studies of rindopepimut. As well, ACT IV was a large, global phase III study, where outcomes are generally expected to be less favorable than phase II studies restricted to specialized centers. It is more likely that optimization of standards of care has promoted improvements in outcome over time,[17] as illustrated in appendix, p 7.

In light of the negative result for the primary analysis and in accordance with the study's sequential analysis plan, all subsequent analyses should be considered exploratory and cannot be interpreted as conclusive. However, the potential long-term survival benefit observed in patients with SRD is an interesting result that deserves examination. No imbalances were found that might have accounted for this signal of differential activity. Baseline prognostic characteristics, corticosteroid dosing, and subsequent therapies were well balanced between both treatment groups. Yet, this apparent treatment effect in the SRD population was not consistent across geographic regions, the effect was less pronounced when tumor burden was defined by the investigator as opposed to central review, and the magnitude of humoral immune response did not consistently correlate with presumed treatment benefit or extent of residual disease. Although further study would be required to confirm this potential signal, this observation may challenge the view that minimal tumor burden is required for immunotherapy to be most effective.

Interestingly, rindopepimut was associated with a survival advantage (HR 0·53, 95% CI 0·32-0·88; p=0·013) when combined with bevacizumab in ReACT, where per study design patients

were not required to have MRD.[16] While humoral responses were similar in patients in the ACT IV study regardless of the amount of residual tumor present, it is unclear whether there were effective cellular responses in these patients. Perhaps residual disease, which would be associated with greater EGFRvIII expression, is required to generate effective and persistent cellular immunity required for a therapeutic effect. It is also possible that the choice of combination therapy may account for what appears to be a more prominent treatment effect in the ReACT study, as compared to the smaller, more delayed effect suggested by the SRD population in ACT IV. VEGF is known to depress tumor immunity and bevacizumab has been shown to enhance immune-mediated antitumor effect in nonclinical models.[18] On the other hand, temozolomide induced-lymphopenia may reduce the efficacy of an immunotherapy. However, this concept is not supported by the ACT II study, in which patients who received dose-intensified temozolomide with rindopepimut developed more robust EGFRvIII-specific humoral immune response despite more significant lymphopenia.

An unexpected observation was the loss of EGFRvIII expression in approximately 60% of the small subset of patients with tumor tissue available at recurrence, regardless of study treatment received. Loss of EGFRvIII expression has previously been reported to occur in the majority of rindopepimut-treated patients,[6,8,9] but not in patients receiving standard of care chemoradiation.[19] However, contemporary data sets are contradictory. One RNA only-based study reported frequent loss of EGFRvIII expression with standard therapy,[20] but this was not confirmed in a recent study of the German Glioma Network.[5] Although ACT IV screening was performed by PCR while the prior studies utilized IHC, the methods have previously demonstrated good concordance.[6] Supposing that the true rate of EGFRvIII loss at recurrence approaches 50%, one

might conclude that the survival benefit observed in the ReACT trial is derived from only half of the patients, and would therefore probably be quite significant in a cohort with confirmed EGFRvIII expression. More importantly, these data suggest that at least a biopsy is required to verify EGFRvIII positivity before patients with recurrent glioblastoma are enrolled into future trials targeting this mutation. Yet, the ACT IV results, as well as the lack of stability of EGFRvIII and its expression pattern limited to subpopulations of tumor cells[5,21] raise questions about its role as a molecular target for therapy in primary glioblastoma. Ongoing trials with other agents in patients with EGFRvIII-mutated tumors may provide additional insight/clarity in the future.

To our knowledge, ACT IV was the most comprehensive study of patients with EGFRvIII-expressing glioblastoma conducted to date. A total of 4,652 patients were screened for study eligibility to achieve 745 randomized patients, and 600 patients with EGFRvIII+ glioblastoma were not enrolled. Reasons for failure to enroll are available for 304 of these patients (Figure 1). Nearly half declined study participation, likely due in part to the nature of the screening process which allowed for an abbreviated “tissue screening” consent, followed later by the formal study evaluation and consenting process. The remainder did not meet the strict eligibility criteria for the trial, which were intended to duplicate the results observed in prior trials and to maximize the chances of achieving a successful result.

Limitations of the study include uncertainties on the significance of the cut-off of EGFRvIII expression for inclusion, and the fact that, due to practical considerations related to patient accrual, the vaccine was started after radiotherapy rather than as early as possible. Furthermore,

whether concurrent chemotherapy with temozolomide blunts potential activity of immunotherapy remains controversial. There are some old and some new lessons to be learned from the disappointing outcome of ACT IV: Even carefully assembled historical controls may be misleading and unsuitable for clinical trial designs, since it is difficult to control for patient selection. Even biologically matching data of EGFRvIII loss at progression on anti-EGFRvIII treatment need controls. Since the humoral response to EGFRvIII was similar to that observed in previous studies of rindopepimut, the present study does not support these responses as a reliable predictor of outcome and calls for intensified efforts to establish cellular immune responses as a read-out. The selection of one molecular target of immunotherapy might be insufficient, especially if its expression is not stable and not ubiquitous, and multipeptide vaccines against multiple targets and non-peptides with higher immunogenicity may turn out to be superior. Moreover, it would appear most promising to combine a glioma-specific stimulus based on well-defined antigens with a general activation of the immune system. At present, this seems to be most easily achieved with checkpoint inhibition or with the neutralization of strong immunosuppressive factors such as TGF-β. Taken together, the results of the ACT IV and ReACT trials support the design of innovative clinical trials evaluating combination approaches to demonstrate efficacy of immunotherapy in glioblastoma.

**Contributions:**

M.W., J.G., T.A.D, and J.H.S contributed to the conception/design of the work, data acquisition and interpretation, and prepared the first draft of the manuscript; N.B., D.D.T., M.J.Y., T.K., and R.S. contributed to the conception/design of the work and data acquisition and interpretation; J.P. and M.G.H. contributed to the conception/design of the work, operationalization of the trial in the Canadian Brain Tumor Consortium, and data acquisition and interpretation; L.D.R., M.L., H.H., L.A., L.M., S.A.G., F.I., J.D., D.M.O., M.W., G.F., W.W., and C.D.T. contributed to data collection and interpretation; Y.H. performed data analysis and interpretation. All authors reviewed/revised the manuscript, approved the final manuscript, and agreed on all aspects of the work.

**Declaration of interests:**

M.W. reports grants and personal fees from Roche, grants and personal fees from Merck (Darmstadt, Germany), personal fees from MSD, personal fees from Pfizer, personal fees from Tocagen, personal fees from Celldex, grants from OGD2, personal fees from Magforce, personal fees from Pfizer, grants and personal fees from Actelion, grants from Acceleron, grants from Bayer, personal fees from BMS, grants and personal fees from Novocure, outside the submitted work; D.D.T. reports grants from Merck, grants from Novartis, grants and personal fees from Novocure, personal fees from Monteris, grants from NWBio, grants from Celldex, grants from Stemline, grants from VBL, grants from TVax, non-financial support from Corvidia, outside the

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**Go, No-Go decision making for phase 3 clinical trials: Act IV rindopepimut revisited – Authors' reply**

We appreciate not only the interest of Dr. Nguyen and colleagues in the ACT IV trial, but also the thoughtful commentary by Dr. Gerstner.[1] From the perspective of several years' additional experience with clinical trial conduct in newly diagnosed glioblastoma relative to the time when ACT IV was designed, we feel that the failure to adequately estimate efficacy with a new treatment based on historical controls (even when matched for eligibility) provides a good lesson to be learned.

Alternative explanations for the failure of ACT IV may be discussed, but are less compelling. Nguyen and colleagues question whether the adjustment to the definition of minimal residual disease (from 1 $cm^2$ in prior studies to 2 $cm^2$ in ACT IV, supported by a central expert review in which some ACT III patients were retrospectively classified with more significant residual disease) contributed to the failure of the study. Although patients with more significant residual disease were originally not thought to be the best candidates for vaccination because of immunosuppression associated with tumor load, the ACT IV results showed a possible long-term survival benefit with rindopepimut for patients with, as opposed to without, more significant residual tumor, which suggests that the change in eligibility would not explain the negative result for the minimal residual disease population. Furthermore, data on the prognostic value of gross total resection are only indirectly relevant to ACT IV since tumor burden in ACT IV was not assessed after surgery, but after completion of concomitant chemoradiotherapy; as well, these data may not accurately reflect outcome for a population with EGFRvIII expressing tumors. Additional factors discussed by both Dr. Gerstner and Dr. Nguyen and colleagues, such as the

potential insufficiency of targeting a single tumour antigen with heterogeneous tumour expression and possibility for temozolomide-induced lymphopenia to limit the efficacy of rindopepimut, provide important considerations for the conduct of future immunotherapy trials. In addition, accumulating evidence not only from ACT IV indicates that EGFR amplification, but not EGFRvIII mutation, is a stable molecular marker throughout the course of disease.[2,3]

Ultimately, however, these factors were applicable to the phase II trials of rindopepimut that were interpreted as positive and led to the decision to proceed with a phase III trial. In conclusion, a significant lesson learned from ACT IV is that even carefully assembled historical controls can be misleading and an unsuitable basis for clinical trial designs. As noted by Nguyen and colleagues, even larger randomized phase II studies may not accurately predict outcomes, as seen in the BELOB experience. Obtaining contemporary outcomes data to standard therapies is challenging and remains an important issue especially with the increasing trend for seamless oncology-drug development and acceleration of drug development timelines.[4, 5]

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## TABLES

### Table 1. Baseline Patient and Disease Characteristics

| | | MRD Population (Primary Analysis Population) | | ITT Population (All Randomized Patients) | | SRD Population | |
|---|---|---|---|---|---|---|---|
| | | Rindopepimut + TMZ (n=195) | Control + TMZ (n=210) | Rindopepimut + TMZ (n=371) | Control + TMZ (n=374) | Rindopepimut + TMZ (n=175) | Control + TMZ (n=163) |
| Age, years (median [IQR]) | | 59 (51-64) | 57 (51-64) | 59 (51-64) | 58 (52-64) | 58 (51-64) | 59 (52-64) |
| ≥65 years (n [%]) | | 46 (24%) | 50 (24%) | 87 (23%) | 87 (23%) | 40 (23%) | 37 (23%) |
| Male (n [%]) | | 133 (68%) | 121 (58%) | 252 (68%) | 228 (61%) | 118 (67%) | 106 (65%) |
| ECOG PS (n [%]) | 0 | 100 (51%) | 102 (49%) | 165 (45%) | 168 (45%) | 65 (37%) | 65 (40%) |
| | 1 | 86 (44%) | 97 (46%) | 188 (51%) | 185 (50%) | 101 (58%) | 88 (54%) |
| | 2 | 9 (5%) | 11 (5%) | 18 (5%) | 21 (6%) | 9 (5%) | 10 (6%) |
| MGMT promoter (n [%]) | Methylated | 69 (35%) | 73 (35%) | 124 (33%) | 130 (35%) | 55 (31%) | 57 (35%) |
| | Unmethylated | 107 (55%) | 119 (57%) | 224 (60%) | 218 (58%) | 116 (66%) | 98 (60%) |
| | Unknown | 19 (10%) | 18 (9%) | 23 (6%) | 26 (7%) | 4 (2%) | 8 (5%) |

| | | MRD Population (Primary Analysis Population) | | ITT Population (All Randomized Patients) | | SRD Population | |
|---|---|---|---|---|---|---|---|
| | | Rindopepimut + TMZ (n=195) | Control + TMZ (n=210) | Rindopepimut + TMZ (n=371) | Control + TMZ (n=374) | Rindopepimut + TMZ (n=175) | Control + TMZ (n=163) |
| RPA Class (n [%]) | III | 25 (13%) | 27 (13%) | 46 (12%) | 37 (10%) | 21 (12%) | 9 (6%) |
| | IV | 139 (71%) | 157 (75%) | 256 (69%) | 274 (73%) | 116 (66%) | 117 (72%) |
| | V | 31 (16%) | 26 (12%) | 69 (19%) | 63 (17%) | 38 (22%) | 37 (23%) |
| Time from diagnosis to randomization, months (median [IQR]) | | 2.8 (2.6-3.1) | 2.8 (2.6-3.1) | 2.9 (2.6-3.2) | 2.8 (2.6-3.1) | 2.9 (2.7-3.2) | 2.9 (2.7-3.2) |
| Prior radiotherapy dose, Gy (median [IQR]) | | 60 (60-60) | 60 (60-60) | 60 (60-60) | 60 (60-60) | 60 (60-60) | 60 (60-60) |
| Prior temozolomide dose, mg/m$^2$ (median [IQR]) | | 3225 (3150-3300) | 3225 (3150- 3375) | 3225 (3150-3300) | 3225 (3150-3375) | 3225 (3150-3375) | 3225 (3150-3375) |

ITT, intention-to-treat; CRT, chemoradiation; ECOG PS; Eastern Cooperative Oncology Group performance status; MGMT, O6-methylguanine-DNA methyltransferase; MRD, minimal residual disease; NE, not evaluable; RPA, recursive partitioning analysis; SRD, significant residual disease

**Table 2. Toxicity**

| | Rindopepimut + TMZ (n=369) | | | | Control + TMZ (n=372) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1-2 | Grade 3 | Grade 4 | Grade 5 | Grade 1-2 | Grade 3 | Grade 4 | Grade 5 |
| Any adverse event | 203 (55%) | 110 (30%) | 42 (11%) | 7 (2%) | 187 (50%) | 124 (33%) | 35 (9%) | 7 (2%) |
| Injection site reaction | 294 (80%) | 0 | 0 | 0 | 151 (41%) | 0 | 0 | 0 |
| Fatigue | 133 (36%) | 6 (2%) | 0 | 0 | 125 (34%) | 19 (5%) | 0 | 0 |
| Nausea | 128 (35%) | 3 (1%) | 0 | 0 | 132 (36%) | 5 (1%) | 0 | 0 |
| Headache | 122 (33%) | 5 (1%) | 1 (0.3%) | 0 | 107 (29%) | 10 (3%) | 0 | 0 |
| Thrombocytopenia | 66 (18%) | 21 (6%) | 11 (3%) | 0 | 75 (20%) | 14 (4%) | 9 (2%) | 0 |
| Constipation | 86 (23%) | 3 (1%) | 0 | 0 | 91 (25%) | 3 (1%) | 0 | 0 |
| Vomiting | 75 (20%) | 2 (1%) | 0 | 0 | 76 (20%) | 4 (1%) | 0 | 0 |
| Decreased appetite | 67 (18%) | 4 (1%) | 0 | 0 | 78 (21%) | 1 (0.3%) | 0 | 0 |
| Dizziness | 56 (15%) | 2 (1%) | 0 | 0 | 69 (19%) | 2 (1%) | 0 | 0 |
| Seizure | 48 (13%) | 7 (2%) | 2 (1%) | 0 | 61 (16%) | 7 (2%) | 1 (0.3%) | 0 |
| Insomnia | 55 (15%) | 1 (0.3%) | 0 | 0 | 48 (13%) | 0 | 0 | 0 |
| Rash | 43 (12%) | 3 (1%) | 0 | 0 | 68 (18%) | 5 (1%) | 0 | 0 |
| Neutropenia | 27 (7%) | 12 (3%) | 7 (2%) | 0 | 16 (4%) | 9 (2%) | 8 (2%) | 0 |
| Lymphopenia | 26 (7%) | 17 (5%) | 2 (1%) | 0 | 24 (6%) | 9 (2%) | 3 (1%) | 0 |

| | Rindopepimut + TMZ (n=369) | | | | Control + TMZ (n=372) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1-2 | Grade 3 | Grade 4 | Grade 5 | Grade 1-2 | Grade 3 | Grade 4 | Grade 5 |
| Muscular weakness | 39 (11%) | 5 (1%) | 0 | 0 | 39 (11%) | 12 (3%) | 0 | 0 |
| Diarrhea | 43 (12%) | 0 | 0 | 0 | 64 (17%) | 0 | 0 | 0 |
| Depression | 36 (10%) | 4 (1%) | 0 | 0 | 47 (13%) | 2 (1%) | 1 (0.3%) | 0 |
| Back pain | 35 (10%) | 2 (1%) | 0 | 0 | 38 (10%) | 3 (1%) | 0 | 0 |
| Edema peripheral | 33 (9%) | 2 (1%) | 0 | 0 | 43 (12%) | 0 | 0 | 0 |
| Pruritus | 34 (9%) | 0 | 0 | 0 | 55 (15%) | 1 (0.3%) | 0 | 0 |
| Aphasia | 28 (8%) | 4 (1%) | 2 (1%) | 0 | 41 (11%) | 11 (3%) | 0 | 0 |
| Anxiety | 31 (8%) | 1 (0.3%) | 0 | 0 | 44 (12%) | 0 | 0 | 0 |
| Gait disturbance | 28 (8%) | 2 (1%) | 0 | 0 | 36 (10%) | 5 (1%) | 0 | 0 |
| Arthralgia | 30 (8%) | 0 | 0 | 0 | 46 (12%) | 1 (0.3%) | 0 | 0 |
| Pyrexia | 23 (6%) | 1 (0.3%) | 0 | 0 | 37 (10%) | 0 | 0 | 0 |
| Brain edema | 9 (2%) | 3 (1%) | 5 (1%) | 0 | 9 (2%) | 4 (1%) | 7 (2%) | 0 |
| Hypersensitivity | 7 (2%) | 1 (0.3%) | 0 | 0 | 5 (1%) | 0 | 0 | 0 |
| Other nervous system disorders | 145 (39%) | 33 (9%) | 4 (1%) | 2 (1%) | 175 (47%) | 32 (9%) | 1 (0.3%) | 2 (1%) |
| Infections and infestations | 117 (32%) | 19 (5%) | 3 (1%) | 0 | 130 (35%) | 21 (6%) | 2 (1%) | 1 (0.3%) |
| Respiratory, thoracic and mediastinal disorders | 89 (24%) | 7 (2%) | 4 (1%) | 3 (1%) | 96 (26%) | 5 (1%) | 3 (1%) | 0 |

| | Rindopepimut + TMZ (n=369) | | | | Control + TMZ (n=372) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1-2 | Grade 3 | Grade 4 | Grade 5 | Grade 1-2 | Grade 3 | Grade 4 | Grade 5 |
| Other gastrointestinal disorders | 85 (23%) | 6 (2%) | 1 (0.3%) | 1 (0.3%) | 89 (24%) | 10 (3%) | 0 | 0 |
| Other musculoskeletal and connective tissue disorders | 89 (24%) | 3 (1%) | 0 | 0 | 96 (26%) | 8 (2%) | 0 | 0 |
| Other investigations | 68 (18%) | 14 (4%) | 3 (1%) | 0 | 85 (23%) | 9 (2%) | 3 (1%) | 0 |
| Other general disorders and administration site conditions | 73 (20%) | 8 (2%) | 0 | 0 | 80 (22%) | 13 (3%) | 0 | 2 (1%) |
| Injury, poisoning and procedural complications | 67 (18%) | 8 (2%) | 1 (0.3%) | 1 (0.3%) | 69 (19%) | 9 (2%) | 1 (0.3%) | 0 |
| Other psychiatric disorders | 64 (17%) | 9 (2%) | 1 (0.3%) | 0 | 64 (17%) | 8 (2%) | 1 (0.3%) | 1 (0.3%) |
| Other skin and subcutaneous tissue disorders | 72 (20%) | 1 (0.3%) | 1 (0.3%) | 0 | 95 (26%) | 2 (1%) | 0 | 0 |
| Other metabolism and nutrition disorders | 45 (12%) | 17 (5%) | 3 (1%) | 0 | 56 (15%) | 15 (4%) | 3 (1%) | 0 |
| Eye disorders | 60 (16%) | 2 (1%) | 0 | 0 | 70 (19%) | 4 (1%) | 0 | 0 |
| Renal and urinary disorders | 50 (14%) | 6 (2%) | 1 (0.3%) | 0 | 59 (16%) | 5 (1%) | 0 | 0 |
| Vascular disorders | 37 (10%) | 9 (2%) | 4 (1%) | 0 | 40 (11%) | 14 (4%) | 2 (1%) | 0 |

| | Rindopepimut + TMZ (n=369) | | | | Control + TMZ (n=372) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1-2 | Grade 3 | Grade 4 | Grade 5 | Grade 1-2 | Grade 3 | Grade 4 | Grade 5 |
| Other blood and lymphatic system disorders | 34 (9%) | 6 (2%) | 3 (1%) | 0 | 29 (8%) | 6 (2%) | 2 (1%) | 1 (0.3%) |
| Ear and labyrinth disorders | 32 (9%) | 2 (1%) | 0 | 0 | 45 (12%) | 0 | 0 | 0 |
| Cardiac disorders | 14 (4%) | 3 (1%) | 1 (0.3%) | 1 (0.3%) | 19 (5%) | 0 | 1 (0.3%) | 2 (1%) |
| Reproductive system and breast disorders | 16 (4%) | 2 (1%) | 0 | 0 | 14 (4%) | 0 | 0 | 0 |
| Endocrine disorders | 10 (3%) | 2 (1%) | 0 | 0 | 18 (5%) | 1 (0.3%) | 0 | 0 |
| Neoplasms | 11 (3%) | 0 | 0 | 0 | 6 (2%) | 2 (1%) | 1 (0.3%) | 0 |
| Hepatobiliary disorders | 0 | 1 (0.3%) | 0 | 0 | 3 (1%) | 4 (1%) | 0 | 0 |

Data are presented for the safety population (all patients who received at least one dose of study treatment, regardless of tumor burden). Table shows all grade 1–2 events occurring in ≥ 10% of patients in either group and all grade 3-5 events.

## FIGURES

### Figure 1. Trial Profile

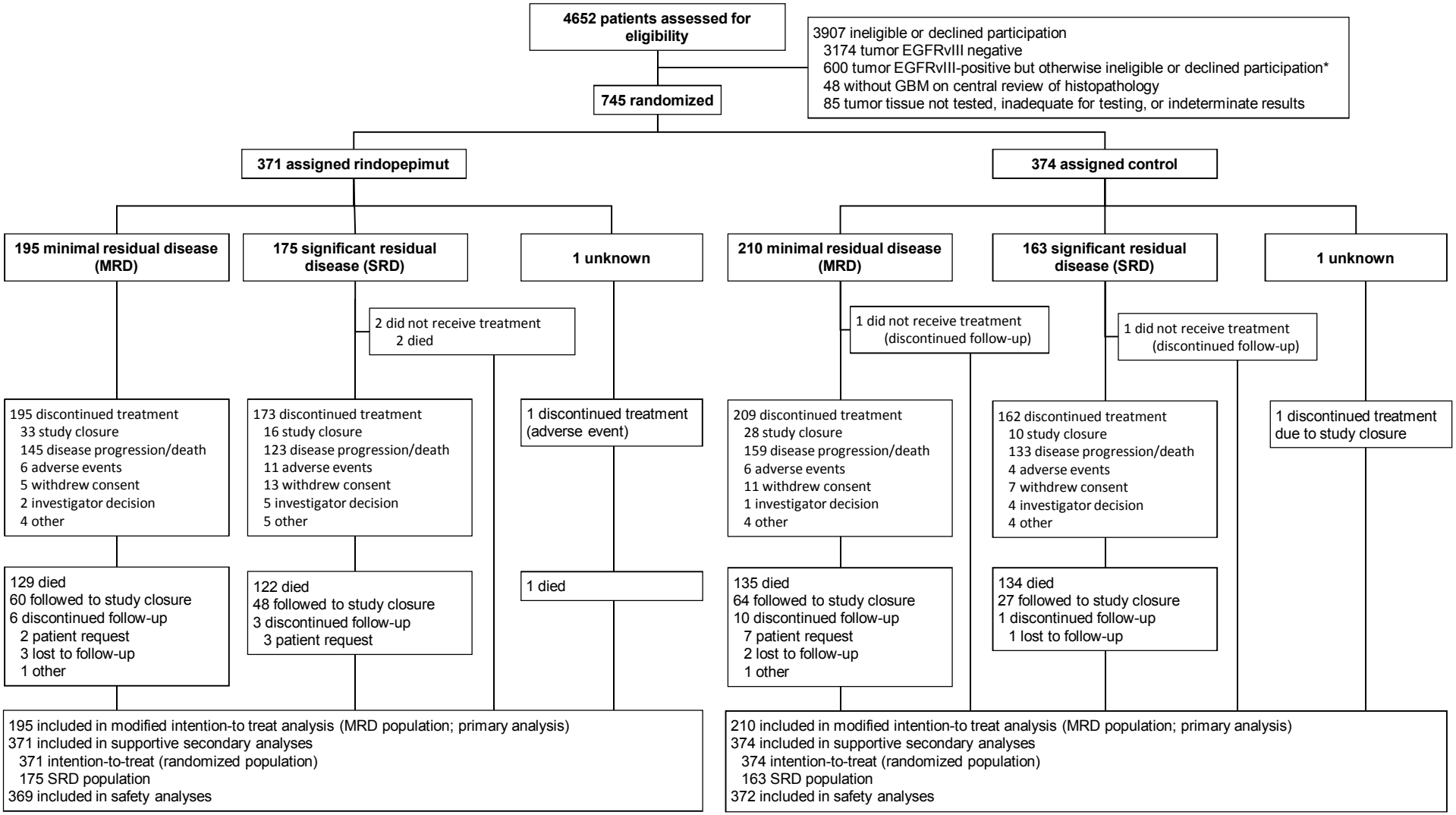
### Figure 2. Overall Survival

Overall survival in the MRD (primary analysis) population (A), the ITT population (B), and the SRD population (C).

### Figure 3. Subgroup analyses of overall survival

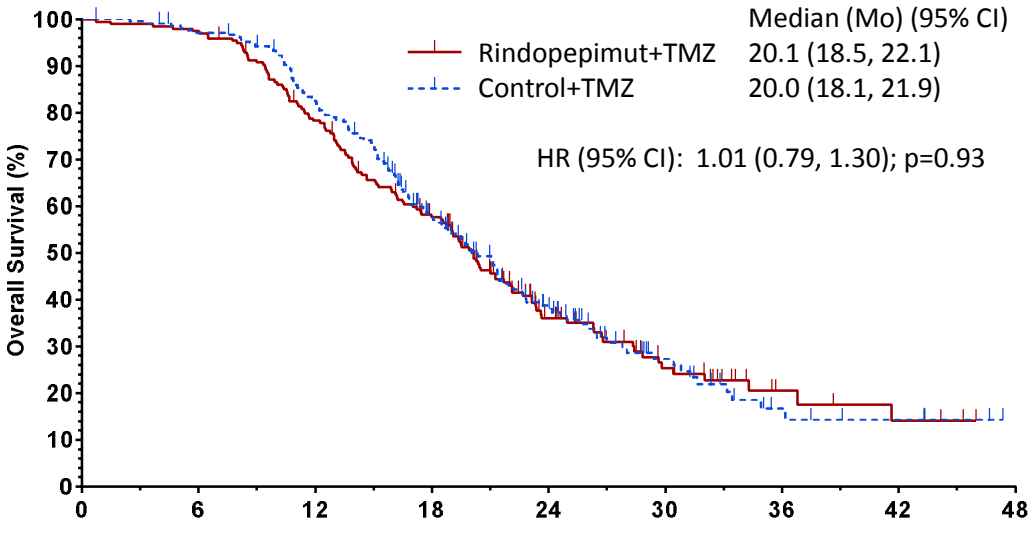
### Figure 4. Humoral Response

Humoral response over time are shown for the MRD and SRD populations within the ACT IV study, along with results from the ACT III trial in which 65 patients with newly diagnosed glioblastoma were treated with rindopepimut in addition to temozolomide, and the ReACT trial in which 35 patients with recurrent glioblastoma were treated with rindopepimut in addition to standard bevacizumab and 37 patients were treated with keyhole limpet hemocyanin as control along with bevacizumab.



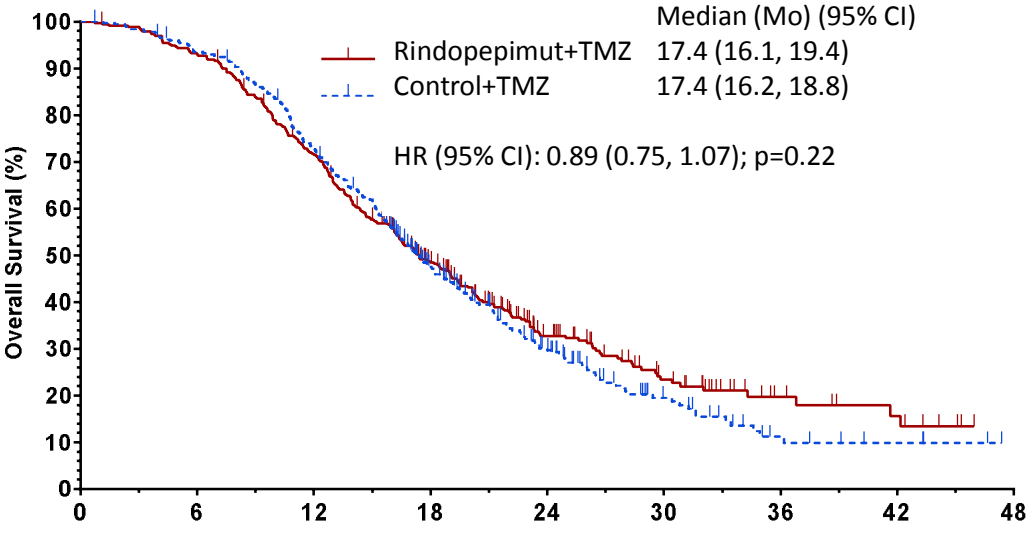

* Reasons for failure to enroll were collected via hard copy screening log, with data for 304 of these 600 patients compiled electronically at the time of study closure. Of these, 143 (47%) declined study participation, 68 (22%) experienced progression prior to study entry, 21 (7%) had a contraindicated concurrent illness or low performance status, 11 (4%) did not receive adequate or standard chemoradiation, 11 (4%) were not candidates for adjuvant temozolomide, 10 (3%) were receiving exclusionary doses of corticosteroid, and 40 (13%) were not enrolled for other miscellaneous reasons.

A



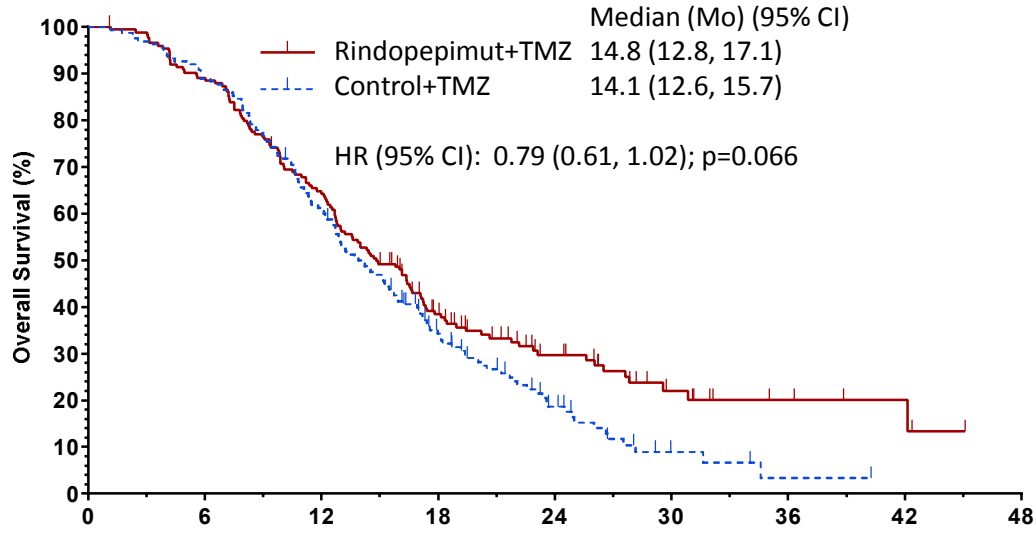

| Number at risk (censored) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Rindopepimut+TMZ | 195 (0) | 190 (0) | 150 (3) | 102 (12) | 42 (39) | 21 (50) | 7 (61) | 4 (62) | 0 (66) |
| Control+TMZ | 210 (0) | 210 (3) | 169 (6) | 101 (24) | 53 (41) | 21 (62) | 7 (69) | 4 (71) | 0 (75) |

B

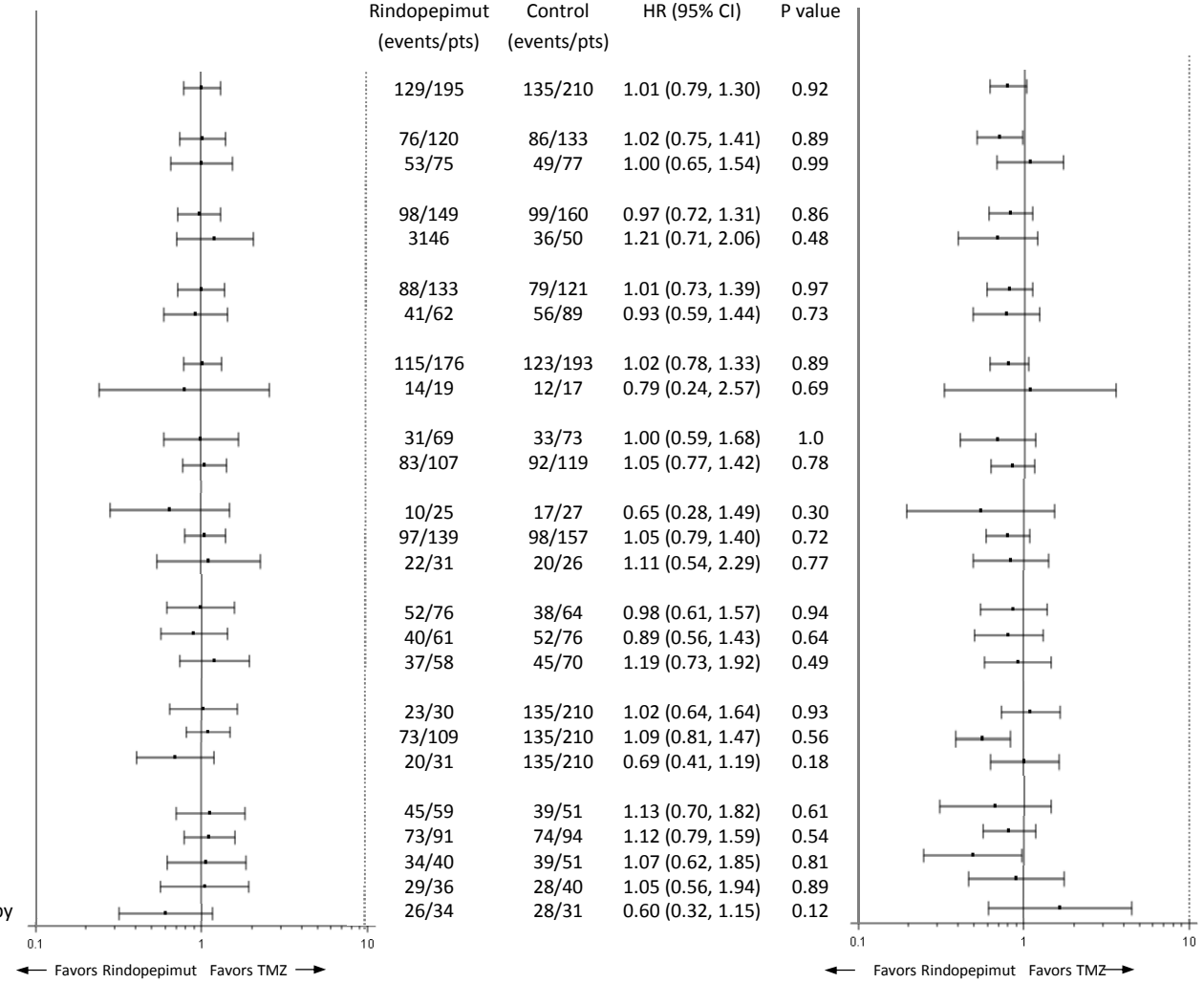



| Number at risk (censored) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Rindopepimut+TMZ | 371 (0) | 345 (1) | 261 (5) | 159 (25) | 72 (68) | 32 (92) | 12 (108) | 7 (111) | 0 (117) |
| Control+TMZ | 374 (0) | 347 (3) | 268 (7) | 149 (35) | 73 (61) | 25 (90) | 8 (98) | 4 (101) | 0 (105) |

C



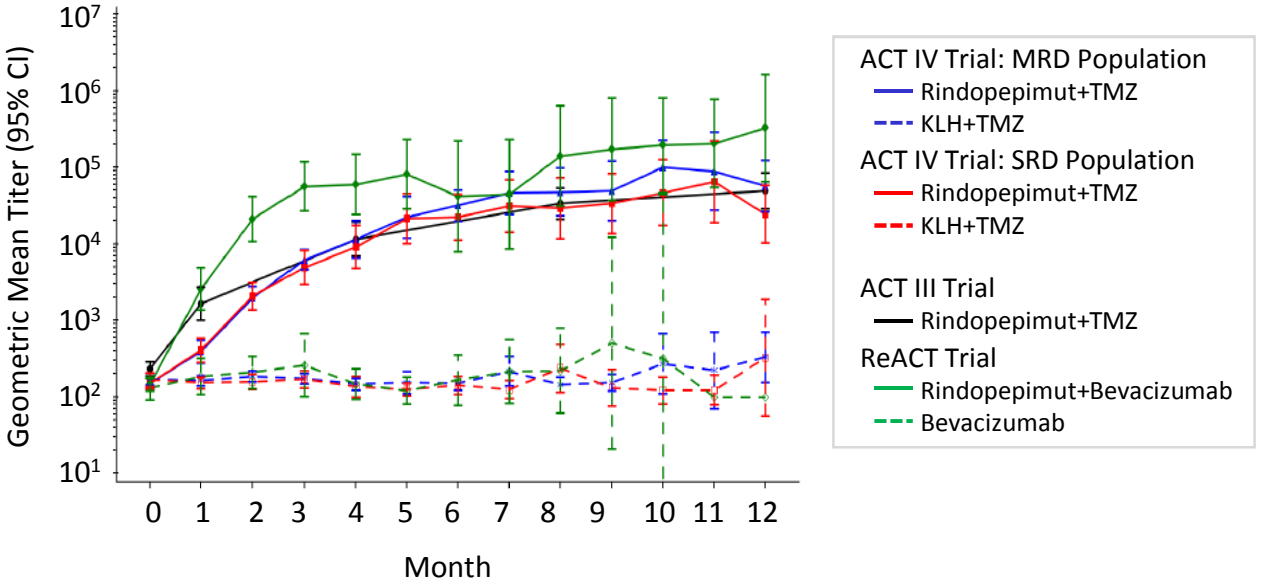

| Number at risk (censored) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Rindopepimut+TMZ | 175 (0) | 155 (1) | 111 (2) | 57 (13) | 30 (29) | 11 (42) | 5 (47) | 3 (49) | 0 (51) |
| Control+TMZ | 163 (0) | 145 (0) | 98 (1) | 47 (11) | 19 (20) | 4 (27) | 1 (28) | 0 (29) | 0 (29) |




| | MRD Population | | | | SRD Population | | | |
|---|---|---|---|---|---|---|---|---|
| | Rindopepimut (events/pts) | Control (events/pts) | HR (95% CI) | P value | Rindopepimut (events/pts) | Control (events/pts) | HR (95% CI) | P value |
| **Overall** | 129/195 | 135/210 | 1.01 (0.79, 1.30) | 0.92 | 124/175 | 134/163 | 0.79 (0.61, 1.02) | 0.066 |
| **Country** | | | | | | | | |
| USA | 76/120 | 86/133 | 1.02 (0.75, 1.41) | 0.89 | **78/111** | 85/100 | 0.70 (0.51, 0.96) | 0.027 |
| Other | 53/75 | 49/77 | 1.00 (0.65, 1.54) | 0.99 | 46/64 | 49/63 | 1.07 (0.68, 1.70) | 0.76 |
| **Age** | | | | | | | | |
| <65 | 98/149 | 99/160 | 0.97 (0.72, 1.31) | 0.86 | 93/135 | 100/126 | 0.82 (0.61, 1.11) | 0.20 |
| ≥65 | 3146 | 36/50 | 1.21 (0.71, 2.06) | 0.48 | 31/40 | 34/37 | 0.68 (0.39, 1.19) | 0.18 |
| **Gender** | | | | | | | | |
| Male | 88/133 | 79/121 | 1.01 (0.73, 1.39) | 0.97 | 87/118 | 89/106 | 0.81 (0.59, 1.12) | 0.20 |
| Female | 41/62 | 56/89 | 0.93 (0.59, 1.44) | 0.73 | 37/57 | 45/57 | 0.77 (0.48, 1.23) | 0.27 |
| **Race** | | | | | | | | |
| White | 115/176 | 123/193 | 1.02 (0.78, 1.33) | 0.89 | 111/155 | 121/144 | 0.80 (0.61, 1.05) | 0.11 |
| Other | 14/19 | 12/17 | 0.79 (0.24, 2.57) | 0.69 | 13/20 | 13/19 | 1.07 (0.32, 3.56) | 0.91 |
| **MGMT** | | | | | | | | |
| Methylated | 31/69 | 33/73 | 1.00 (0.59, 1.68) | 1.0 | 26/55 | 37/57 | 0.68 (0.40, 1.15) | 0.15 |
| Unmethylated | 83/107 | 92/119 | 1.05 (0.77, 1.42) | 0.78 | 95/116 | 89/98 | 0.84 (0.62, 1.13) | 0.25 |
| **RPA class** | | | | | | | | |
| III | 10/25 | 17/27 | 0.65 (0.28, 1.49) | 0.30 | 14/21 | 6/9 | 0.55 (0.19, 1.53) | 0.24 |
| IV | 97/139 | 98/157 | 1.05 (0.79, 1.40) | 0.72 | 82/116 | 94/117 | 0.80 (0.59, 1.08) | 0.14 |
| V | 22/31 | 20/26 | 1.11 (0.54, 2.29) | 0.77 | 28/38 | 34/37 | 0.83 (0.49, 1.40) | 0.49 |
| **EGFRvIII intensity*** | | | | | | | | |
| ≤ 0.5 | 52/76 | 38/64 | 0.98 (0.61, 1.57) | 0.94 | 44/63 | 42/51 | 0.87 (0.55, 1.38) | 0.55 |
| 0.5 – 4.24 | 40/61 | 52/76 | 0.89 (0.56, 1.43) | 0.64 | 39/60 | 37/47 | 0.81 (0.50, 1.31) | 0.39 |
| >4.24 | 37/58 | 45/70 | 1.19 (0.73, 1.92) | 0.49 | 41/52 | 55/65 | 0.92 (0.58, 1.46) | 0.73 |
| **Humoral response**** | | | | | | | | |
| Slow | 23/30 | 135/210 | 1.02 (0.64, 1.64) | 0.93 | 33/40 | 134/163 | 1.10 (0.73, 1.66) | 0.65 |
| Moderate | 73/109 | 135/210 | 1.09 (0.81, 1.47) | 0.56 | 39/62 | 134/163 | 0.57 (0.39, 0.83) | 0.0032 |
| Rapid | 20/31 | 135/210 | 0.69 (0.41, 1.19) | 0.18 | 24/28 | 134/163 | 1.01 (0.63, 1.63) | 0.96 |
| **Subsequent therapy** | | | | | | | | |
| Reresection | 45/59 | 39/51 | 1.13 (0.70, 1.82) | 0.61 | 17/26 | 23/31 | 0.66 (0.31, 1.44) | 0.29 |
| Bevacizumab | 73/91 | 74/94 | 1.12 (0.79, 1.59) | 0.54 | 61/77 | 71/78 | 0.81 (0.56, 1.17) | 0.27 |
| Nitrosourea | 34/40 | 39/51 | 1.07 (0.62, 1.85) | 0.81 | 29/41 | 23/26 | 0.49 (0.25, 0.97) | 0.038 |
| Temozolomide | 29/36 | 28/40 | 1.05 (0.56, 1.94) | 0.89 | 22/30 | 34/39 | 0.90 (0.46, 1.75) | 0.76 |
| Other chemotherapy | 26/34 | 28/31 | 0.60 (0.32, 1.15) | 0.12 | 15/20 | 15/17 | 1.66 (0.61, 4.51) | 0.31 |

* The fluorescence detected was directly proportional to the amount of RNA present and expressed as cycle threshold (Ct). EGFRvIII intensity is defined by delta Ct (Ct of EGFRvIII - Ct of EGFR wild type).

** Humoral response is classified according to the trajectory at which anti-EGFRvIII titers developed with rindopepimut treatment. HR is calculated for the rindopepimut-treated patients within each classification versus all patients in the control group.


Geometric Mean Titer (95% CI)
$10^7$
$10^6$
$10^5$
$10^4$
$10^3$
$10^2$
$10^1$
0 1 2 3 4 5 6 7 8 9 10 11 12
Month
ACT IV Trial: MRD Population
Rindopepimut+TMZ
KLH+TMZ
ACT IV Trial: SRD Population
Rindopepimut+TMZ
KLH+TMZ
ACT III Trial
Rindopepimut+TMZ
ReACT Trial
Rindopepimut+Bevacizumab
Bevacizumab

# WEB EXTRA MATERIAL

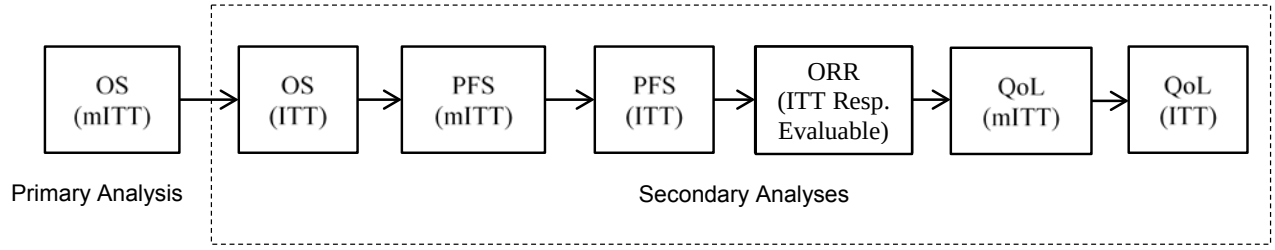



**Figure 1. Fixed sequence procedure.** Fixed sequence procedure was used to control the family wise error rate for the primary endpoint and secondary endpoints. Each statistical test was to be considered positive only if the previous statistical test was positive. At each analysis (interim or final), the same alpha would be passed from the primary OS (mITT) analysis.

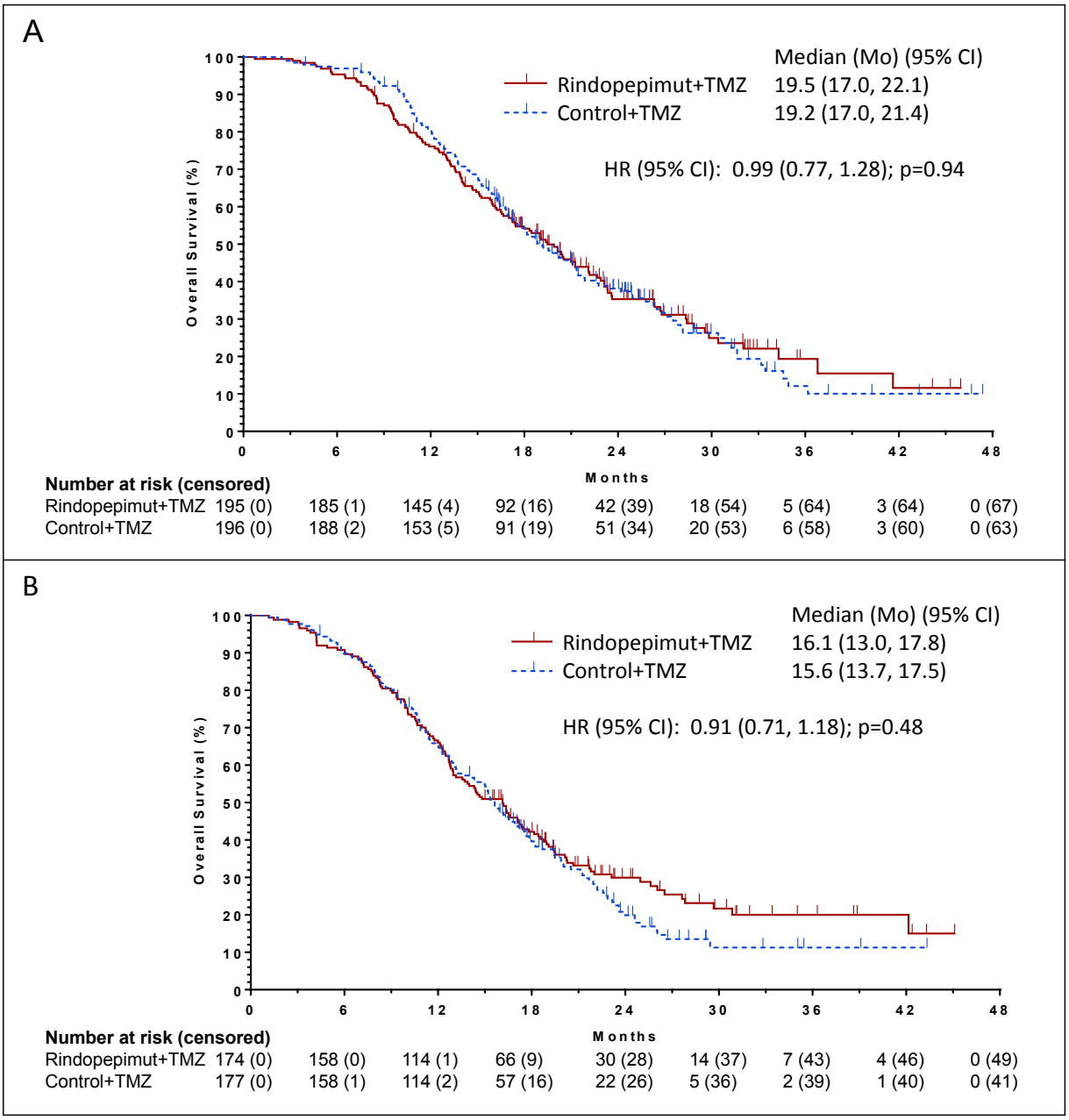



**Figure 2. Overall Survival for Populations Selected by Investigator Assessment**
Overall survival in the population of patients with MRD by investigator assessment (A) and with SRD by investigator assessment (B).

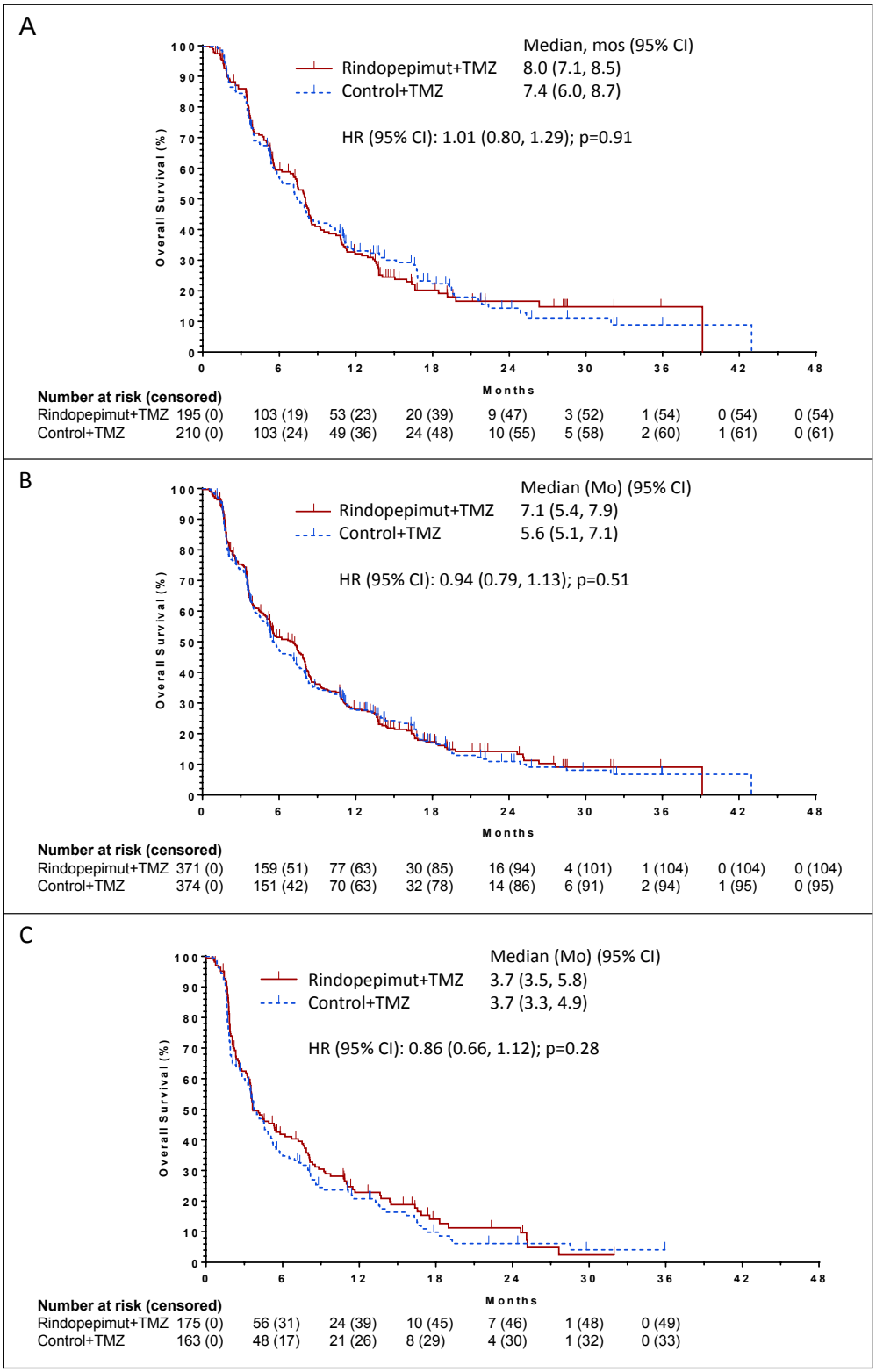



**Figure 3. Progression-Free Survival**
Progression-free survival in the MRD (primary analysis) population (A), the ITT population (B), and the SRD population (C).

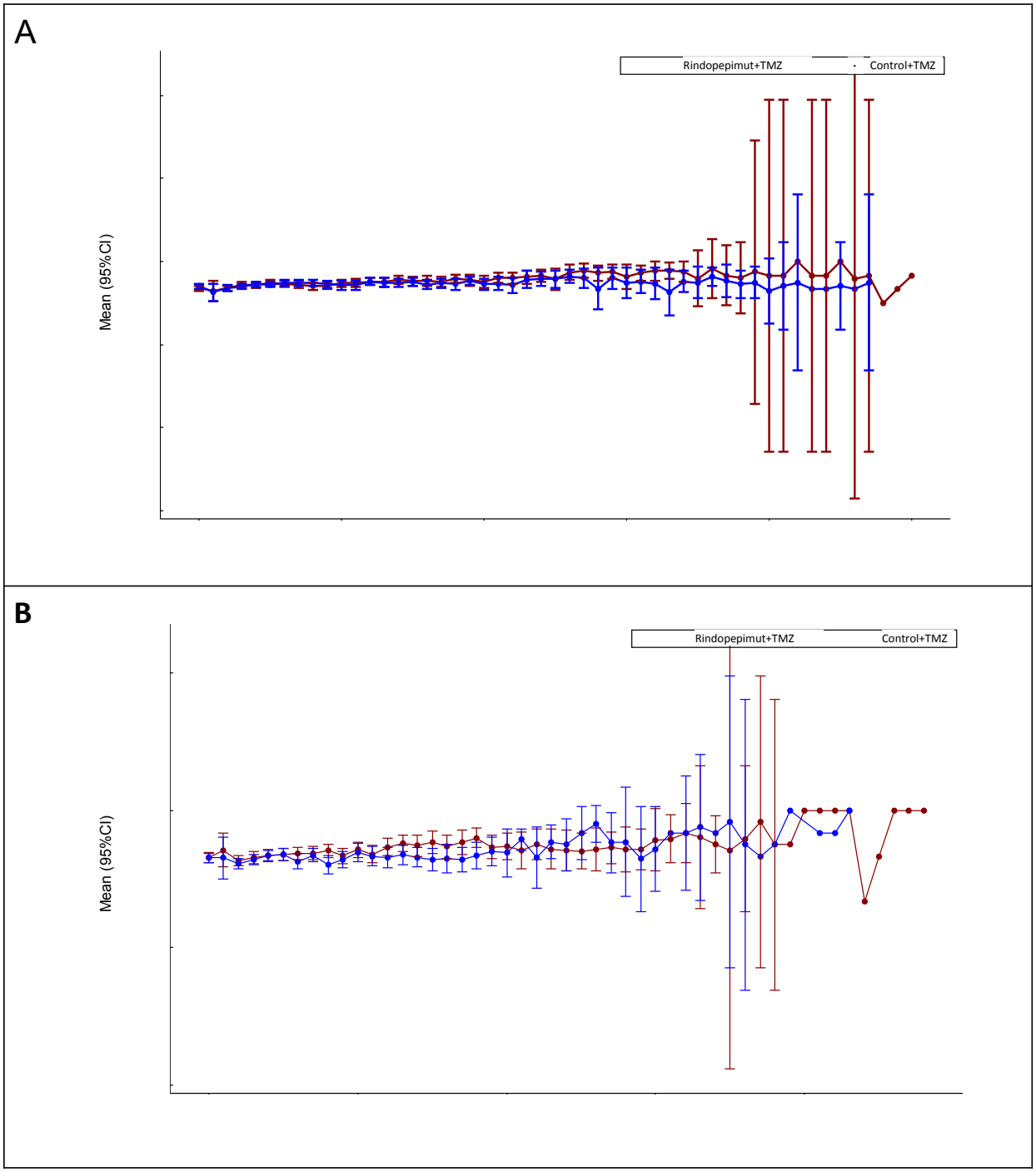



**Figure 4. Quality of Life**
EORTC QLQ-C30 Global Health Status over time for patients with evaluable data in the MRD (primary analysis) population (rindopepimut group, n=194; control group, n=202) (A) and the SRD population (rindopepimut group, n=170; control group, n=157) (B).

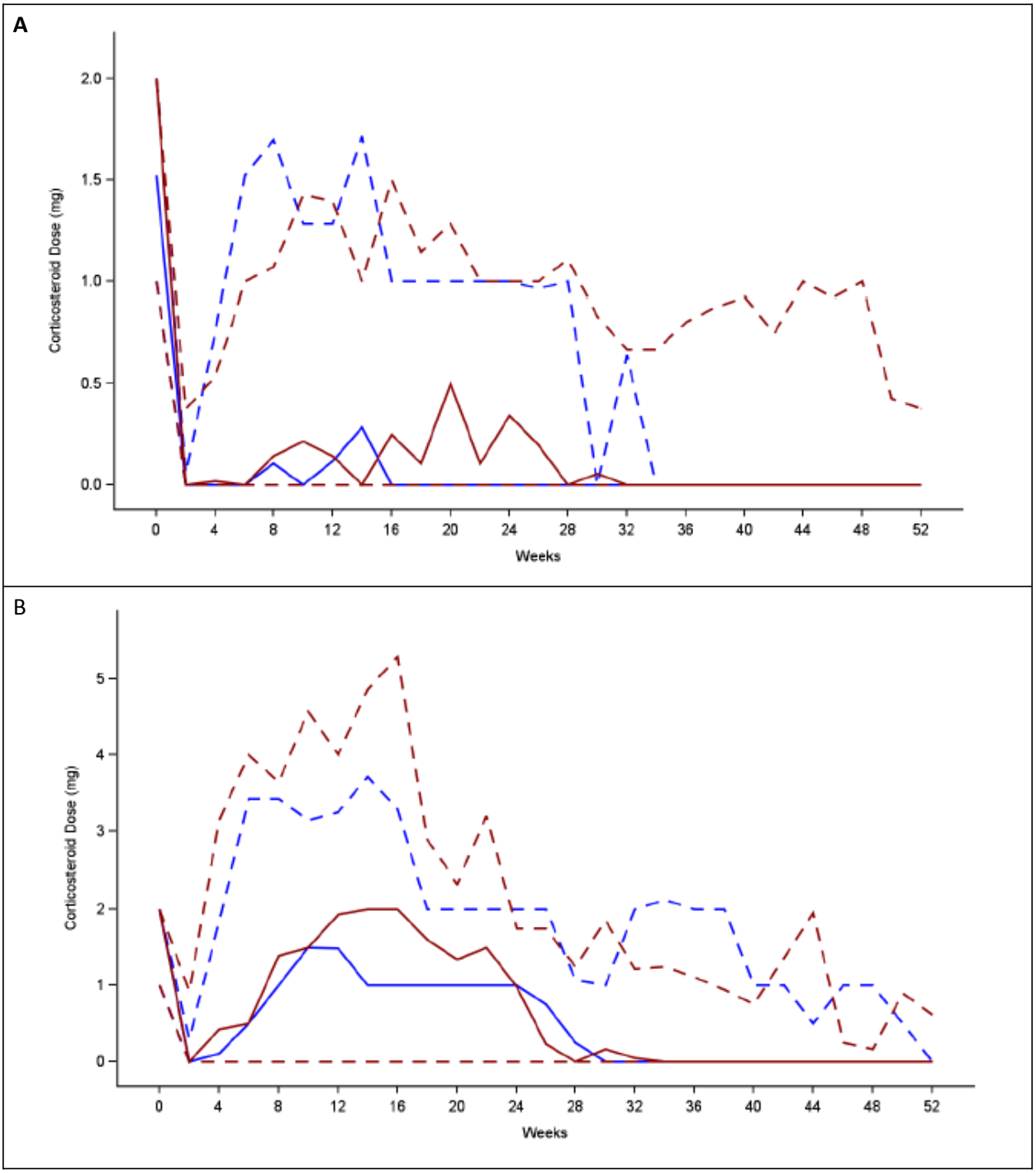



**Figure 5. Corticosteroid Use**
Corticosteroid dose over time for patients receiving corticosteroids at baseline in the MRD (primary analysis) population (rindopepimut group, n=57; control group, n=68) (A) and the SRD population (rindopepimut group, n=72; control group, n=78) (B). Median dose (mg), as well as the 25$^{th}$ and 75$^{th}$ percentiles, are shown.

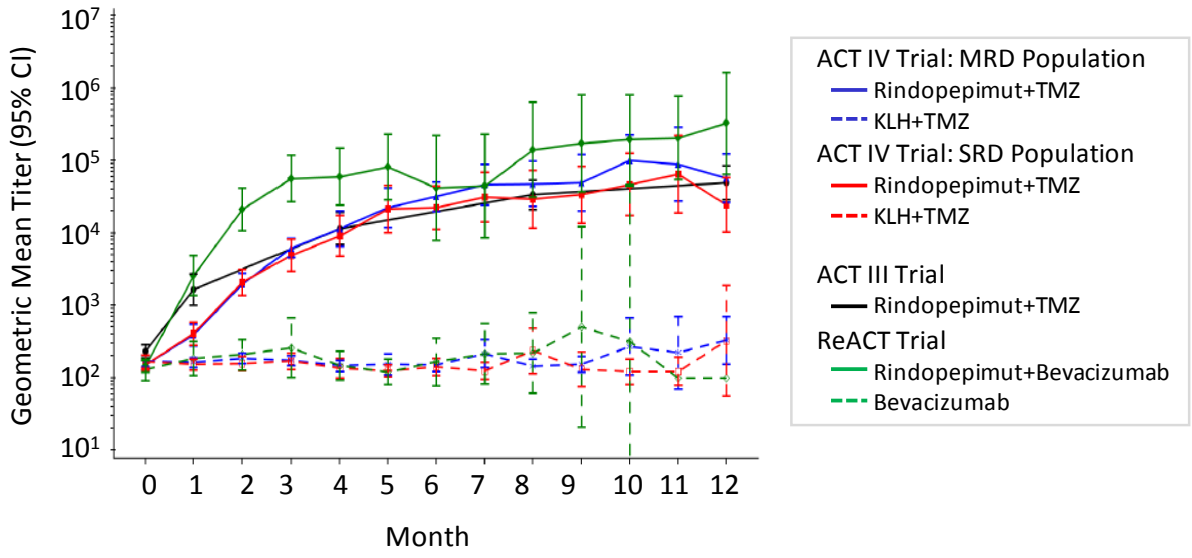



**Figure 6. Humoral Response**

Humoral response over time are shown for the MRD and SRD populations within the ACT IV study, along with results from the ACT III trial in which 65 patients with newly diagnosed glioblastoma were treated with rindopepimut in addition to temozolomide, and the ReACT trial in which 35 patients with recurrent glioblastoma were treated with rindopepimut in addition to standard bevacizumab and 37 patients were treated with keyhole limpet hemocyanin as control along with bevacizumab.

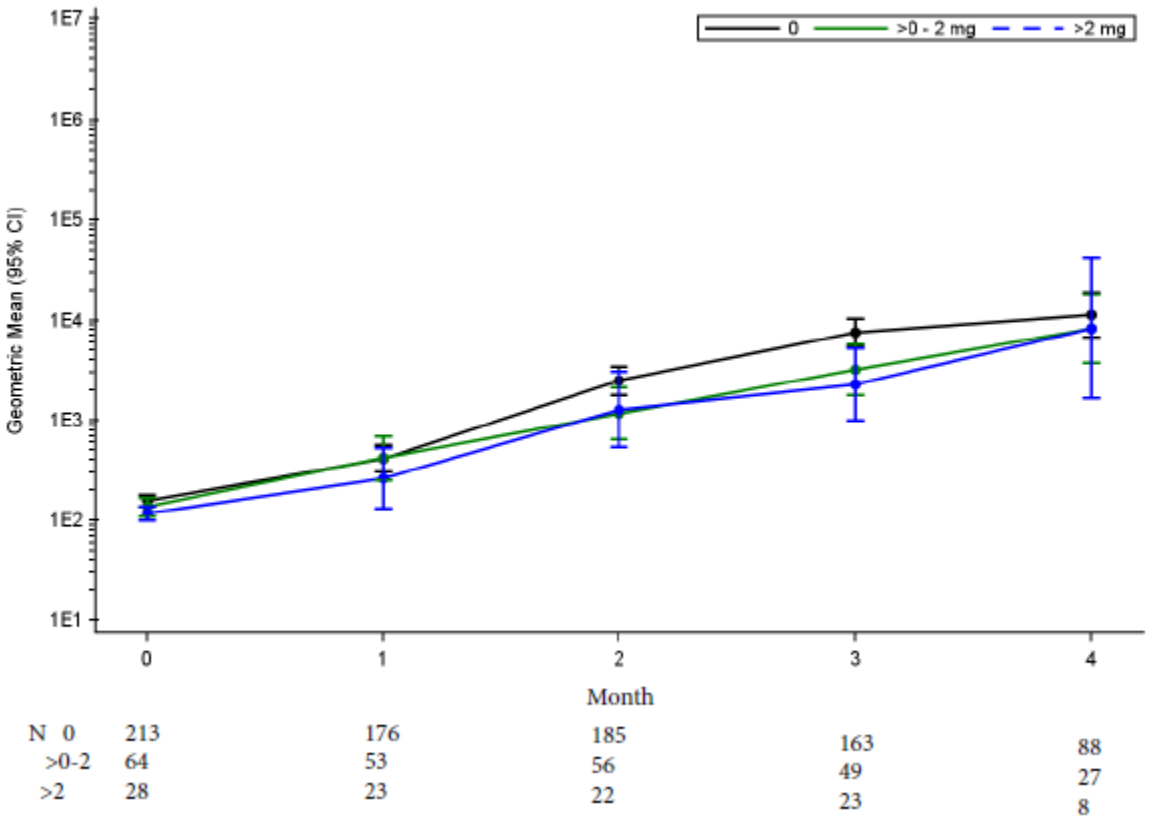



**Figure 7. Corticosteroid Use and Anti-EGFRvIII titer**
Geometric mean titer for rindopepimut-treated patients is displayed according to corticosteroid dosing during the first eight weeks of study. Patients are divided into groups who received no corticosteroids, an average daily dose of less than 2 mg/kg dexamethasone equivalent, and an average daily dose of more than 2 mg/kg dexamethasone equivalent.

**Table 1. Outcomes for Newly Diagnosed Glioblastoma, by EGFRvIII Expression Status**

| Clinical Trial | Median OS from study randomization | Median OS from diagnosis* | % EGFRvIII+ | % GTR |
|---|---|---|---|---|
| ***Datasets available for ACT IV design*** | | | | |
| M.D. Anderson "matched" cohort (n=17)[1] | NA | 15.0 | 100% | 100% |
| ACT III Controls (n=16)** | 15.6 | 19.1 | 100% | 100% |
| TMZ/RT → TMZ (n=287)[2] | 14.6 | 15.8 | NR | 39% |
| ***Datasets generated subsequently*** | | | | |
| RTOG 0525[3] (Data on File, Celldex) | | | | |
| Standard dose TMZ (n=411) | 16.6 | ~19.6 | NR | 56% |
| EGFRvIII+ subset (n=62) | 14.2 | ~17.2 | 100% | NR |
| EGFRvIII+ subset matched for ACT III/IV eligibility (n=29) | 16.0 | ~19.0 | 100% | 100% |
| Dose-dense TMZ (n=422) | 14.9 | ~17.9 | NR | 52% |
| All EGFRvIII+ patients (n=142) | 15.1 | ~16.3 | 100% | NR |
| AVAglio trial (n=463)[4] | 16.7 | ~18.0 | NR | 42% |
| RTOG 0825 (n=317)[5] | 16.1 | ~19.1 | NR | 59% |
| Novocure EF-14 Study (n=229)[6] | 16.6 | ~20.4 | NR | 64% |
| German Glioma Network[7] | NA | 21.7 | 100% | 100% |
| EGFRvIII+ subset matched for ACT III/IV eligibility (n=85) | | | | |

NA, Not applicable; NR, Not reported

* Median OS from diagnosis is estimated based upon timing of randomization.

** Data on file, Celldex. Majority dropped out of trial to receive alternate (unknown) therapies with death information reported when available from public records. Eight patients were reported to have died, while the remaining patients were followed on study for a range of 0 to 3.3 months before study withdrawal.

**Table 2. Study-Specific Modifications to RANO Criteria**

| Criteria | Study-Specific Modification |
|---|---|
| **General** | Corticosteroid dose assessed as the average dose over the seven (7) days prior to the current scan, as compared to the average dose over the seven (7) days prior to the baseline scan |
| **Complete Response:** requires all of the following:<br>• Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks.<br>• No new lesions.<br>• Stable or improved non-enhancing (T2/FLAIR) lesions<br>• Patients must be off corticosteroids (or on physiologic replacement doses only)<br>• Stable or improved clinically.<br>Patients with non-measurable disease only cannot have a CR; the best response possible is SD. | Physiologic replacement doses of corticosteroids defined as: up to the equivalent of 20 mg/day of hydrocortisone |
| **Partial Response:** requires all of the following:<br>• ≥ 50% decrease compared with Baseline in the SPD of all measurable enhancing lesions sustained for at least 4 weeks.<br>• No progression of non-measurable disease.<br>• No new lesions.<br>• Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with Baseline scan.<br>• The corticosteroids dose at the time of the scan evaluation should be no greater than the dose at the time of the baseline scan.<br>• Stable or improved clinically.<br>Patients with non-measurable disease only cannot have a PR; the best response possible is SD. | In order to qualify for Partial Response, subjects must be on a corticosteroid dose that is stable (< 10% increase) or decreased when compared with the dose at the time of the baseline scan. |
| **Stable Disease:** requires all of the following:<br>• Does not qualify for CR, PR or PD.<br>• Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan.<br>• In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose. | In order to qualify for Partial Response, subjects must be on a corticosteroid that is < 50% increased when compared with the dose at the time of the baseline scan. |
| **Progressive Disease:** defined by any of the following:<br>• ≥ 25% increase in SPD of enhancing lesions compared with the smallest (nadir) tumor measurement obtained either at baseline (if no decrease) or best response.<br>• On stable or increasing doses of corticosteroids.<br>• Significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by co-morbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects)<br>• Any new lesion.<br>• Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection and so on) or changes in corticosteroid dose.<br>• Failure to return for evaluation as a result of death or deteriorating condition.<br>• Clear progression of non-measurable disease. | For subjects with little to no residual disease, a 25% increase in area could reflect only imaging variance. As such, to be considered PD, a > 5 mm increase in the sum of the longest diameters of the target lesions, along with a ≥ 25% increase in the sum of the products of the diameters of the target lesions, will be required to call PD. |

**Table 3. Additional therapies received in the post-treatment follow-up period, by analysis population**

| | MRD Population (Primary Analysis Population) | | ITT Population (All Randomized Patients) | | SRD Population | |
|---|---|---|---|---|---|---|
| | Rindopepimut+TMZ (n=195) | Control+ TMZ (n=210) | Rindopepimut+ TMZ (n=371) | Control+ TMZ (n=374) | Rindopepimut+ TMZ (n=175) | Control+ TMZ (n=163) |
| Radiotherapy/Radiosurgery | 14% | 18% | 13% | 14% | 11% | 9% |
| Reresection | 30% | 24% | 23% | 22% | 15% | 19% |
| Other anticancer therapy | 62% | 63% | 62% | 66% | 61% | 69% |
| Bevacizumab | 47% | 45% | 45% | 46% | 44% | 48% |
| Nitrosureas | 21% | 24% | 22% | 21% | 23% | 16% |
| Temozolomide | 19% | 19% | 18% | 21% | 17% | 24% |
| Other chemotherapy | 17% | 15% | 15% | 13% | 11% | 10% |
| Investigational drug | 11% | 11% | 10% | 10% | 9% | 8% |
| Tumor-treating fields | 4% | 4% | 4% | 3% | 5% | 2% |
| Tyrosine kinase inhibitor | 3% | 4% | 2% | 3% | 1% | 1% |
| Check-point inhibitor | 2% | 2% | 2% | 2% | 2% | 1% |

CRT, Chemoradiation; KLH, Keyhole limpet hemocyanin; MRD, Minimal residual disease; SRD, Significant residual disease; TMZ, Temozolomide; NE, Not evaluable

**Table 4. Additional therapies received in the post-treatment follow-up period, by geographic region**

| | MRD Population | | | | | SRD Population | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | USA (n=253) | Canada (n=32) | EU (n=61) | Other (n=59) | Total (n=405) | USA (n=211) | Canada (n=38) | EU (n=47) | Other (n=42) | Total (n=338) |
| Radiotherapy/Radiosurgery | 18% | 9% | 10% | 15% | 16% | 10% | 5% | 13% | 12% | 10% |
| Reresection | 30% | 9% | 8% | 46% | 27% | 17% | 21% | 9% | 24% | 17% |
| Other anticancer therapy | 63% | 66% | 62% | 61% | 63% | 67% | 68% | 57% | 60% | 65% |
| Bevacizumab | 52% | 25% | 41% | 36% | 46% | 54% | 29% | 36% | 31% | 46% |
| Nitrosureas | 21% | 16% | 31% | 25% | 23% | 19% | 16% | 38% | 10% | 20% |
| Temozolomide | 13% | 50% | 15% | 32% | 19% | 17% | 40% | 13% | 29% | 20% |
| Other chemotherapy | 13% | 13% | 18% | 29% | 16% | 9% | 8% | 13% | 21% | 11% |
| Investigational drug | 14% | 0 | 7% | 9% | 11% | 12% | 0 | 0 | 7% | 9% |
| Tumor-treating fields | 5% | 0 | 2% | 0 | 4% | 5% | 3% | 0 | 0 | 1% |
| Tyrosine kinase inhibitor | 5% | 0 | 0 | 2% | 3% | 2% | 0 | 0 | 0 | 1% |
| Check-point inhibitor | 2% | 0 | 3% | 3% | 2% | 2% | 0 | 2% | 2% | 2% |

**List of Investigators and Trial Sites**

CDX110-04 ACT IV Participating Sites (Institution (Country) Investigator [# Patients])
University of California, San Francisco (USA) Dr. Nicholas Butowski [28]
Washington University School of Medicine (USA) Dr. Jian Campian [24]
Stanford Cancer Institute (USA) Dr. Lawrence Recht [20]
Johns Hopkins University (USA) Dr. Michael Lim [15]
Barrow Neurological Institute (USA) Dr. Lynn Ashby [15]
University of Pittsburgh Medical Center - UPMC Cancer Centers (USA) Dr. Jan Drappatz [14]
Juravinski Cancer Centre (CA) Dr. Hal Hirte [15]
Columbia University Medical Center (USA) Dr. Fabio Iwamoto [13]
Dent Neurosciences Research Center (USA) Dr. Laszlo Mechtler [12]
John Theurer Cancer Center at Hackensack University Medical Center (USA) Dr. Samuel Goldlust [12]
Yale University (USA) Dr. Kevin Becker [11]
Cleveland Clinic Foundation (USA) Dr. Gene Barnett [11]
The Ottawa Hospital Cancer Center (CA) Dr. Garth Nicholas [11]
The Preston Robert Tisch Brain Tumor Center at Duke (USA) Dr. Annick Desjardins [10]
Swedish Neuroscience Institute (USA) Dr. Tara Benkers [10]
University of Southern California/Norris Comprehensive Cancer Center (USA) Dr. Naveed Wagle [10]
Texas Oncology (USA) Dr. Morris Groves [10]
Moores UCSD Cancer Center (USA) Dr. Santosh Kesari [10]
Debreceni Egyetem Orvos- és Egészségtudományi Centrum Onkológiai Klinika (HU) Dr. Zsolt Horvath [10]
NorthShore University HealthSystem (USA) Dr. Ryan Merrell [9]
University of Cincinnati Physicians Corporation (USA) Dr. Richard Curry [9]
University of Pennsylvania (USA) Dr. James; O'Rourke David Schuster [9]
Westmead Hospital (AU) Dr. Mark Wong [9]
University of Washington (USA) Dr. Maciej Mrugala [8]
University of Utah Department of Neurosurgery (USA) Dr. Randy Jensen [8]
Virginia Piper Cancer Institute at Abbott Northwestern Hospital (USA) Dr. John Trusheim [8]
Wake Forest University Health Sciences Medical Center (USA) Dr. Glenn Lesser [8]
Centre Hospitalier de l'Universite de Montreal (CHUM) - Hopital Notre-Dame (CA) Dr. Karl Belanger [8]
University Hospitals, Case Medical Center (Cleveland) (USA) Dr. Andrew Sloan [7]
University of Virginia Healthcare System (USA) Dr. Benjamin Purow [7]
Baylor Research Institute (USA) Dr. Karen Fink [7]
Northwestern University; Robert H. Lurie Comprehensive Cancer Center (USA) Dr. Jeffrey Raizer [7]
North Shore University Hospital (USA) Dr. Michael Schulder [7]
Lehigh Valley Physician Group-Hematology-Oncology Associates (USA) Dr. Suresh Nair [7]
Kaiser Permanente - Redwood City (USA) Dr. Scott Peak [7]
Odette Cancer Centre, Sunnybrook HSC (CA) Dr. James Perry [7]
Ospedale Bellaria (IT) Dr. Alba Brandes [7]
Department of Neurology, University Hospital Zurich (CH) Dr. Michael Weller [7]
University of Rochester Medical Center (USA) Dr. Nimish Mohile [6]
New Jersey Neuroscience Institute (USA) Dr. Joseph Landolfi [6]
Mary Bird Perkins Cancer Center (USA) Dr. Jon Olson [6]
Fondazione IRCCS Istituto Neurologico Carlo Besta (IT) Dr. Gaetano Finocchiaro [6]
Epworth Healthcare (AU) Dr. Ross Jennens [6]
Liverpool Hospital (AU) Dr. Paul DeSouza [6]
Christchurch Hospital (NZ) Dr. Bridget Robinson [6]
Providence Portland Medical Center (USA) Dr. Marka Crittenden [5]
Sarah Cannon Research Institute (USA) Dr. Kent Shih [5]
Hartford Hospital (USA) Dr. Alexandra Flowers [5]
University of Arkansas for Medical Sciences (USA) Dr. Shirley Ong [5]
Froedtert and The Medical College of Wisconsin (USA) Dr. Jennifer Connelly [5]
Winship Cancer Institute, Emory University School of Medicine (USA) Dr. Costas Hadjipanayis [5]
Ohio State University (USA) Dr. Pierre Giglio [5]
Georgia Regents University (USA) Dr. Frank Mott [5]

CHUS Hopital Fleurimont (CA) Dr. David Mathieu [5]
CHUQ, L'Hotel-Dieu de Quebec (CA) Dr. Nathalie Lessard [5]
Hospital Universitario 12 De Octubre (ES) Dr. Sanchez Juan Sepulveda [5]
Országos Onkológiai Intézet (HU) Dr. József Lövey [5]
Royal North Shore Hospital, St. Leonards (AU) Dr. Helen Wheeler [5]
Royal Brisbane & Women's Hospital (RBWH) (AU) Dr. Po-Ling Inglis [5]
Palmerston North Hospital (NZ) Dr. Claire Hardie [5]
Chao Family Comp Cancer Center (USA) Dr. Daniela Bota [4]
University of Chicago (USA) Dr. Maciej Lesniak [4]
City of Hope Cancer Center (USA) Dr. Jana Portnow [4]
Medical University of South Carolina (USA) Dr. Bruce Frankel [4]
University of Michigan Health System (USA) Dr. Larry Junck [4]
Vanderbilt University Medical Center (USA) Dr. Reid Thompson [4]
Tampa General Hospital (USA) Dr. Lawrence Berk [4]
British Columbia Cancer Agency - Vancouver Island Centre (CA) Dr. John McGhie [4]
London Regional Cancer Program (CA) Dr. David Macdonald [4]
Royal Marsden NHS Foundation Trust (UK) Dr. Frank Saran [4]
Azienda Ospedaliera San Giovanni Battista Di Torino-Universita Di Torino (IT) Dr. Riccardo Soffietti [4]
Tel Aviv Sourasky Medical Center (IL) Dr. Deborah Blumenthal [4]
Real e Benemerita Associação Portuguesa de Beneficiência (BR) Dr. Sá Barreto Costa Marcos André de [4]
Sir Charles Gairdner Hospital (AU) Dr. Anna Nowak [4]
Royal Adelaide Hospital (RAH)- The University of Adelaide (AU) Dr. Nimit Singhal [4]
Centre Hospitalier Universitaire Vaudois CHUV (CH) Dr. Andreas Hottinger [4]
Inselspital (CH) Dr. Andrea Schmid [4]
Edward W. Sparrow Hospital Association - Sparrow Regional Cancer Center (USA) Dr. Gordan Srkalovic [3]
The Methodist Neurological Institute (USA) Dr. David Baskin [3]
Dartmouth Hitchcock Medical Center (USA) Dr. Camilo Fadul [3]
University of Alabama at Birmingham (USA) Dr. Louis Nabors [3]
Norton Cancer Institute (USA) Dr. Renato LaRocca [3]
University of Kentucky (USA) Dr. John Villano [3]
Rush University Medical Center (USA) Dr. Nina Paleologos [3]
Montreal Neurological Institute and Hospital (CA) Dr. Petr Kavan [3]
Univeristy of Manitoba-CancerCare Manitoba (CA) Dr. Marshall Pitz [3]
British Columbia Cancer Agency - Vancouver Centre (CA) Dr. Brian Thiessen [3]
La Pitié Salpétrière AP-HP (FR) Dr. Ahmed Idbaih [3]
Institut de Cancerologie de l'Ouest (ICO) - Centre Rene Gauducheau (FR) Dr. Jean Sébastien Frenel [3]
Institut Gustave Roussy (FR) Dr. Julien Domont [3]
Universitaetsklinikum Muenster (DE) Dr. Oliver Grauer [3]
Universitaetskliniken Regensburg (DE) Dr. Peter Hau [3]
Medical University Vienna - General Hospital (AT) Dr. Christine Marosi [3]
Na Homolce Hospital (CZ) Dr. Jan Sroubek [3]
Prince of Wales Hospital (AU) Dr. Elizabeth Hovey [3]
HCG - Bangalore Institute of Oncology (IN) Dr. P.S. Sridhar [3]
Austin Hospital (AU) Dr. Lawrence Cher [3]
University of Florida (USA) Dr. Erin Dunbar [2]
SUNY Upstate Medical University (USA) Dr. Thomas Coyle [2]
Allegheny General Hospital (USA) Dr. Jane Raymond [2]
Loyola University Medical Center (USA) Dr. Kevin Barton [2]
Helen F Graham Cancer Center (USA) Dr. Michael Guarino [2]
Monmouth Cancer Center (USA) Dr. Sumul Raval [2]
University of Arizona (USA) Dr. Baldassarre Stea [2]
Massachusetts General Hospital (DFCI affiliate) (USA) Dr. Jorge Dietrich [2]
Unv Hospitals Bristol NHS Foundation Trust - Bristol Haematology & Onc Ctr (UK) Dr. Kirsten Hopkins [2]
Western General Hospital (UK) Dr. Sara Erridge [2]
Klinikum Der J.W. Goethe Universitaet (DE) Dr. Joachim-Peter Steinbach [2]
Hospital Clinic i Provincial Servicio de Oncología Escalera 2, 5ª planta. (ES) Dr. Losada Estela Pineda [2]

ICO Badalona - Hospital Germans Trias i Pujol (Institut Catala D'Oncologia) (ES) Dr. Quintero Carmen Balana [2]
ICO Girona - Hospital Doctor Josep Trueta (Institut Catala D'Oncologia) (ES) Dr. Barco Berron Sonia del [2]
Vas Megyei Markusovszky Lajos Általános Rehabilitációs és Gyógyfürdo Kórház (HU) Dr. Miklós Wenczl [2]
Borsod-Abaúj-Zemplén Megyei Kórház és Egyetemi Oktató Kórház (HU) Dr. Katalin Molnár [2]
Szegedi Tudományegyetem Onkoterápiás Klinika (HU) Dr. Katalin Hideghéty [2]
Gaffin Center for Neuro-Oncology, Hadassah Hebrew University Medical Center (IL) Dr. Alexander Lossos [2]
Vrije Universiteit Medisch Centrum (NL) Dr. Linde Myra van [2]
Fundação Antônio Prudente - Hosptial A.C. Camargo (BR) Dr. Ana Levy [2]
Royal Hobart Hospital (AU) Dr. Rosemary Harrup [2]
Calvary North Adelaide Hospital (AU) Dr. William Patterson [2]
Mater Adult Hospital (AU) Dr. Zarnie Lwin [2]
Siriraj Hospital (TH) Dr. Sith Sathornsumetee [2]
National Cheng Kung University Hospital (TW) Dr. E-Jian Lee [2]
Kaohsiung Chang Gung Memorial Hospital (CGMHKS) (TW) Dr. Jih-Tsun Ho [2]
Fletcher Allen Health Care (USA) Dr. Steven Emmons [1]
The Long Island Brain Tumor Center at Neurological Surgery, P.C. (USA) Dr. J. Paul Duic [1]
Legacy Health (USA) Dr. Spencer Shao [1]
New York Methodist Hospital (USA) Dr. Hani Ashamalla [1]
Temple University Hospital (USA) Dr. Michael Weaver [1]
Mt. Sinai Medical Center / Comprehensive Cancer Center (USA) Dr. Jose Lutzky [1]
Orlando Health, Inc. (USA) Dr. Nicholas Avgeropoulos [1]
The University of Tennessee Medical Center (USA) Dr. Wahid Hanna [1]
Covenant Clinic/Iowa Spine and Brain Institute (USA) Dr. Mukund Nadipuram [1]
Sutter Health-Alta Bates Medical Center (USA) Dr. Gary Cecchi [1]
UC Davis Cancer Center (USA) Dr. Robert O'Donnell [1]
Weill Cornell Medical Center (USA) Dr. Susan Pannullo [1]
Kaiser Permanente Hawaii - Moanalua Medical Center (USA) Dr. Jennifer Carney [1]
Foothills Hospital Medical Centre (CA) Dr. Mark Hamilton [1]
QE II Health Science Centre (CA) Dr. Mary MacNeil [1]
Guy's and St Thomas' NHS - St Thomas Hospital (UK) Dr. Ronald Beaney [1]
CRLC VAL D'AURELLE (FR) Dr. Michel Fabbro [1]
Klinikum Grosshadern Ludwig-Maximilians Univ. Muenchen (DE) Dr. Oliver Schnell [1]
Universitaet Erlangen-Nurnberg (DE) Dr. Rainer Fietkau [1]
Medical University Innsbruck (AT) Dr. Guenther Stockhammer [1]
Faculty Hospital V Motole (CZ) Dr. Bela Malinova [1]
Multiscan, s.r.o., Pardubice (CZ) Dr. Karel Odrazka [1]
Masaryk´s Hospital Usti nad Labem (CZ) Dr. Martin Sames [1]
ICO L'Hospitalet - Hospital Duran i Reynals (Institut Catala D'Oncologia) (ES) Dr. Gil Miguel Gil [1]
3rd Department of Medical-Oncology, "Hygeia" Hospital (GR) Dr. Evangelia Razis [1]
Soroka University Medical Center (IL) Dr. Konstantin Lavrenkov [1]
Grupo Médico Camino S.C. (MX) Dr. Guillermo Castro [1]
Antiguo Hospital Civil de Guadalajara (MX) Dr. Francisco Ramirez [1]
Coordenação de Pesquisa Clínica e Incorporação Tecnológica Instituto Nacional de (BR) Dr. Clarissa Baldotto [1]
Hospital Mãe de Deus (BR) Dr. Fabiana Viola [1]
Hospital Albert Einstein (BR) Dr. Suzana Malheiros [1]
Monash Medical Centre (AU) Dr. Jason Lickliter [1]
Launceston General Hospital (AU) Dr. Stanislaw Gauden [1]
Prince of Songkhla University Hospital (TH) Dr. Arunee Dechaphunkul [1]
King Chulalongkorn Memorial Hospital (TH) Dr. Iyavut Thaipisuttikul [1]
Waikato Hospital, Regional Cancer Centre (NZ) Dr. Ziad Thotathil [1]
Tri-Service General Hospital (TW) Dr. Hsin-I Ma [1]
Taichung Veterans General Hospital (TW) Dr. Wen-Yu Cheng [1]
Chi Mei Medical Center (TW) Dr. Chin-Hong Chang [1]
Instituto Oncologico Miraflores (PE) Dr. Fernando Salas [1]
Hôpitaux universitaires de Genève - HUG - site de Cluse-Roseraie (CH) Dr. Pierre-Yves Dietrich [1]
Chefarzt Medizinische Onkologie (CH) Dr. Christoph Mamot [1]

Dana Farber Cancer Institute (USA) Dr. Lakshmi Nayak [0*]
Sahyadri Speciality Hospital (IN) Dr. Shona Nag [0*]

*No patients were enrolled, however patients transferred from other sites and were treated on study at this institution.

**References:**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