A Phase II, Open-Label, Randomized, Multicenter Trial (HERBY) of Bevacizumab in Pediatric Patients With Newly Diagnosed High-Grade Glioma

Jacques Grill, Maura Massimino, Eric Bouffet, Amedeo A. Azizi, Geoffrey McCowage, Adela Cañete, Frank Saran, Marie-Cécile Le Deley, Pascale Varlet, Paul S. Morgan, Tim Jaspan, Chris Jones, Felice Giangaspero, Helen Smith, Josep Garcia, Markus C. Elze, Raphaël F. Rousseau, Lauren Abrey, Darren Hargrave,* and Gilles Vassal*

*Both authors contributed equally

Jacques Grill and Gilles Vassal, Pediatric and Adolescent Oncology, Gustave Roussy, Villejuif; Marie-Cécile Le Deley, Biostatistics and Epidemiology Department, Gustave Roussy, Villejuif, and Paris-Saclay and Paris-Sud Universities, CESP, INSERM, Orsay; Pascale Varlet, Sainte-Anne Hospital, Paris, France; Maura Massimino, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; Felice Giangaspero, Department of Radiological, Oncological and Anatomo-pathological Sciences, Sapienza University, Rome, and IRCCS Neuromed, Pozzilli, Italy; Eric Bouffet, Hospital for Sick Children, Toronto, Ontario, Canada; Amedeo A. Azizi, Medical University of Vienna, Vienna, Austria; Geoffrey McCowage, Australasian Children’s Cancer Trials, Clayton, Victoria, Australia; Adela Cañete, Hospital La Fe, Valencia, Spain; Frank Saran, Royal Marsden Hospital, London; Paul S. Morgan and Tim Jaspan, Nottingham University Hospitals, Queen’s Medical Centre, Nottingham; Chris Jones, Institute of Cancer Research, London; Darren Hargrave, Great Ormond Street Hospital, London, United Kingdom; and Helen Smith, Josep Garcia, Markus C. Elze, and Lauren Abrey, F. Hoffmann-La Roche Ltd, Basel,
Switzerland. **Raphaël F. Rousseau**, Genentech Inc., a member of the Roche group, South San Francisco, California, United States of America.

**Corresponding author**: Jacques Grill, Pediatric and Adolescent Oncology, Gustave Roussy, 114 rue Edouard-Vaillant, 94 805 Villejuif, Cedex, France

**Telephone**: +33 (0)1 42 11 41 73

**Email**: Jacques.GRILL@gustaveroussy.fr

**Suggested key words**: anaplastic astrocytoma; bevacizumab; glioblastoma; high-grade glioma; pediatric oncology

**Presentation at a scientific meeting**: ISPNO 2016; SIOP 2016; SNO 2016

**Originality of the work**

Despite therapeutic advances, outcomes for patients with pediatric high-grade glioma (HGG) remain poor. HERBY was a large, international study that investigated bevacizumab for treatment of paediatric patients with HGG. Unlike in adult glioblastoma, adding bevacizumab to radiotherapy-temozolomide did not influence event-free survival in paediatric newly diagnosed HGG, which is important information for physicians. Critically, HERBY also highlighted that information regarding treatment of adults with HGG cannot be directly applied to children with HGG and it is important that pediatric-specific studies are carried out for this disease.

**Suggested running title** Bevacizumab for newly diagnosed pediatric high-grade glioma

**Word count**: 2999/3000

**Funding**: Funding for this study was provided by F. Hoffmann-La Roche Ltd (study number BO25041; clinicaltrials.gov NCT01390948).
ABSTRACT

Purpose
Bevacizumab (BEV) is approved in over 60 countries for use in adults with recurrent glioblastoma. We evaluated the addition of BEV to radiotherapy-temozolomide (RT/TMZ) in pediatric patients with newly diagnosed high-grade glioma (HGG).

Methods
The HERBY trial (clinicaltrials.gov NCT01390948; randomized/parallel-group/multicenter/open-label) enrolled patients aged ≥3 to <18 years with localized, centrally neuropathology-confirmed, non-brainstem HGG. Eligible patients were randomized to receive RT/TMZ (RT, 1.8Gy, 5 days/week; TMZ, 75mg/m²/day for 6 weeks; 4-week treatment break; then up to 12×28-day cycles of TMZ [cycle 1: 150mg/m²/day, days 1 to 5; cycles 2 to 12: 200mg/m²/day, days 1 to 5]) with or without BEV (10mg/kg every 2 weeks). Primary endpoint: event-free survival (EFS), assessed by a Central Radiology Review Committee (CRRC) blinded to treatment. We report findings of EFS 12 months after enrollment of the last patient.

Results
One hundred and twenty-one patients were enrolled (RT/TMZ, n=59; BEV+RT/TMZ, n=62). CRRC-assessed median EFS did not differ significantly between the treatment groups (RT/TMZ, 11.8 months; 95% confidence interval [CI], 7.9 to 16.4; BEV+RT/TMZ, 8.2 months; 95% CI, 7.8 to 12.7; hazard ratio [HR], 1.44; P=.13 [stratified log-rank test]). In the overall survival analysis, addition of BEV did not reduce the risk of death (HR, 1.23; 95% CI, 0.72 to 2.09). More patients in the BEV+RT/TMZ group versus the RT/TMZ group experienced ≥1 serious adverse event (n=35, 58% v n=27, 48%) and more patients receiving BEV discontinued study treatment due to adverse events (n=13, 22% v n=3, 5%).
Conclusion

Adding BEV to RT/TMZ did not improve EFS in pediatric patients with newly diagnosed HGG. Our findings were not comparable to those of previous adult trials, highlighting the importance of performing pediatric-specific studies.
INTRODUCTION

High-grade gliomas (HGGs) are the most common group of pediatric malignant central nervous system (CNS) neoplasms with an annual incidence of 0.87 per 100,000 children in the USA.\textsuperscript{1} Despite surgical resection followed by radiotherapy (RT) and concomitant adjuvant chemotherapy, the prognosis for children with HGG remains poor. Unlike most other cancer types, 5-year survival is lower in pediatric versus adult patients with HGG.\textsuperscript{1,2}

There are substantial differences between pediatric and adult HGG.\textsuperscript{3-5} Midline tumor location is more frequent in children than in adults.\textsuperscript{6,7} While contrast enhancement is the hallmark of malignant gliomas in adults, not all pediatric HGGs exhibit contrast uptake.\textsuperscript{8,9} Platelet-derived growth factor receptor alpha amplification is the most common DNA copy number change in pediatric HGG, while epidermal growth factor receptor amplification is more commonly detected in adults.\textsuperscript{5} O6-methylguanine-DNA methyltransferase (MGMT) promoter expression is also less frequent in pediatric versus adult patients with HGG.\textsuperscript{10} A key difference in pediatric HGGs compared with adult HGGs is the presence of unique somatic H3F3A (histone H3.3) driver mutations at position K27M and G34R/V of the regulatory tail\textsuperscript{11}, suggesting that results from adult trials may not be directly transferable to pediatric patients with the same histologically defined disease.

Bevacizumab (BEV) is approved in more than 60 countries worldwide for use in adults with recurrent glioblastoma.\textsuperscript{12,13} Clinical experience with BEV in pediatric patients with HGG is limited, although the addition of BEV to irinotecan in 31 children with recurrent malignant glioma or intrinsic brainstem glioma showed some efficacy and was well tolerated.\textsuperscript{14} The HERBY trial aimed to evaluate the efficacy and safety
of adding BEV to postoperative radiotherapy/temozolomide (RT/TMZ) in pediatric patients with newly diagnosed, localized HGG.

METHODS

Study Design

HERBY (HGG Efficacy and tolerability Research of Bevacizumab in Young children and adolescents; BO25041; clinicaltrials.gov NCT01390948) was a phase II, open-label, randomized, international, comparator study of the addition of BEV to RT/TMZ in pediatric patients (aged ≥3 to <18 years) with newly diagnosed HGG. Here we present event-free survival (EFS) data at 12 months after enrollment of the last patient.

HERBY was conducted as part of a pediatric investigation plan and in accordance with applicable country regulations, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines, and the Declaration of Helsinki. Written informed consent was obtained from the patient/parents or legally acceptable representatives prior to enrollment and collection of tissue (for exploratory biomarker analyses).

Eligible patients were centrally randomized 1:1, based on a minimization algorithm, via an interactive voice response system to receive BEV+RT/TMZ or RT/TMZ with the following stratification factors: age (≥3 to <6 years, ≥6 to <13 years, ≥13 to <18 years), World Health Organization (WHO) grade (III v IV), and type of surgery (total/near-total resection v others) (Fig 1). Randomization was performed via minimization with biased coin assignment. Patients and investigators were not masked to treatment assignment; the Central Radiology Review Committee (CRRC) was masked to group allocation.
Study treatment started at least 28 days after cranial surgery and no later than 6 weeks following the last major surgery. Patients received RT (1.8 Gy/session, 30 sessions, 5 days/week for a total of 54 Gy) and TMZ 75mg/m²/day for 6 weeks, followed by a minimum 4-week TMZ treatment break, then up to 12×28-day cycles of TMZ (cycle 1: 150mg/m²/day, days 1–5; cycles 2–12: 200mg/m²/day, days 1–5). Patients assigned to BEV treatment additionally received BEV 10mg/kg every 2 weeks, which was delivered concomitantly with RT/TMZ (concurrent phase), alone during the TMZ treatment break, and subsequently with up to 12×28-day cycles of TMZ (adjuvant phase). Concomitant corticosteroid use and stable doses of anticoagulants were permitted.

**Patients**

Patients aged ≥3 to <18 years with newly diagnosed, localized, supratentorial or infratentorial cerebellar or peduncular, grade III/IV gliomas (according to WHO 2007 guidelines) were enrolled; local histological diagnosis was confirmed by a central reference neuropathologist before enrollment. Availability of a baseline magnetic resonance imaging (MRI) scan and the ability to commence trial treatment 4–6 weeks after surgery were also required. Key exclusion criteria were: metastatic HGG defined as evidence of neuro-axis dissemination by MRI or positive cerebrospinal fluid cytology; gliomatosis cerebri (extensive glioma, ie, involving at least three cerebral lobes according to WHO 2007 guidelines), multifocal glioma, diffuse intrinsic pontine glioma (DIPG), or intramedullary HGG; pleomorphic xanthoastrocytoma or anaplastic ganglioglioma; prior diagnosis of a malignancy (including low-grade glioma), and not disease free for 5 years; prior systemic anticancer therapy; previous cranial irradiation; any significant cardiovascular
disease or unresolved infection; or chronic daily treatment with aspirin (>325mg/day) or clopidogrel (>75mg/day).

**Study Assessments**

Patients were followed for a minimum of 1 year after randomization. Tumor progression/recurrence and BEV response were determined using Response Assessment in Neuro-Oncology (RANO) criteria in HGG. Tumor evaluations were performed at baseline, at the end of the TMZ break, every 3 months during the adjuvant phase and the first 3 years post-randomization, and every 6 months thereafter, until progression/recurrence.

Health-related quality of life was assessed in patients aged ≥5 years using the Health Utility Index (HUI) questionnaire, which was completed at screening, at cycle 6 of the adjuvant phase, at the end of treatment, yearly during the follow-up period, at the time of progression, and at the end-of-study visit. Neuropsychological assessment using the Wechsler scale adapted for age was measured at the end of treatment, every 2 years during the follow-up period, and at the end-of-study visit.

**Study Endpoints**

The pre-specified primary endpoint was EFS, defined as the earliest occurrence of any of the following: tumor progression and tumor recurrence (CRRC-assessed); second primary non-HGG malignancy; or death attributable to any cause.

Pre-specified secondary endpoints included overall survival (OS) and 1-year OS rate; 6-month and 1-year EFS rates (CRRC-assessed); objective response rate (ORR; CRRC-assessed using RANO criteria); investigator-assessed EFS; health status as measured by the HUI (patients aged ≥5 years); neuropsychological
function as measured by the Wechsler scale adapted for age; and safety. Post-hoc exploratory analyses of EFS (CRRC-assessed) and OS by histone mutation status and tumor location were performed.

**Safety**

Adverse events (AEs) and serious AEs (SAEs) were reported from study treatment initiation to 28 days following the last dose of study treatment. AEs of special interest (AESIs), regardless of relationship to study treatment, were reported up to 6 months following the last dose of study treatment. After 6 months, only study treatment-related SAEs were reported.

**Statistical Analysis**

Analysis populations included the intent-to-treat population (all randomized patients regardless of whether they received study treatment); the efficacy-evaluable population (all randomized patients with at least one post-randomization assessment from the local investigator); and the safety-evaluable population (all randomized patients who received at least one dose of study treatment). Baseline characteristics were compared between treatment groups using $\chi^2$, Mann-Whitney-Wilcoxon, or Kruskal-Wallis tests as appropriate.

The primary endpoint of CRRC-assessed EFS was estimated using Kaplan-Meier methodology and compared between treatment groups using a stratified log-rank test (two-sided) at the 5% level of significance; stratification factors were age, HGG WHO grade, and extent of surgery. Estimates of treatment effect (BEV+RT/TMZ v RT/TMZ) stratified for covariates were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs) estimated in a Cox model. Investigator-
assessed EFS and OS were analyzed using a two-sided log-rank test. Safety data are described according to the maximum grade of intensity reported per preferred term, per patient.

See the Appendix (online only) for further details on the study assessments, AESI definitions, and statistical analyses performed, including sample size calculations, interim futility analysis, and pre-specified sensitivity analyses.

**RESULTS**

**Patients**

Between October 2011 and February 2015, 174 patients were screened (53 patients failed screening), and 121 were randomized to receive treatment (RT/TMZ, n=59; BEV+RT/TMZ, n=62) (Fig 2). Overall, 116 patients (RT/TMZ, n=56; BEV+RT/TMZ, n=60) received study treatment at 51 sites in 14 countries.

Baseline characteristics were balanced, with no significant differences between treatment groups for any of the variables listed in Table 1. MGMT promotor status was assessed in 42 patients, of whom 37 had an unmethylated tumor (RT/TMZ, n=18; BEV+RT/TMZ, n=19) (Table 1). *H3F3A* mutation status was assessed in 85 patients, of whom 31 showed evidence of a mutation (RT/TMZ, n=15; BEV+RT/TMZ, n=16) (Table 1). Mutations were observed at position K27M in 24 patients (RT/TMZ, n=10; BEV+RT/TMZ, n=14) and at position G34R/V in seven patients (RT/TMZ, n=5; BEV+RT/TMZ, n=2) (Table 1). Additional MGMT promotor and histone mutation status findings from subsequent analyses using non-pre-specified tests are reported in a separate paper (Mackay A, et al. [In submission]).
The median duration of survival follow-up was similar between treatment groups (RT/TMZ, 15.2 months [range, 0.1–46.8 months]; BEV+RT/TMZ, 16.2 months [range, 0–45.7 months]).

**Interim Analysis**

The study was considered futile following the pre-specified interim analysis (performed after the first 60 randomized patients were followed for 1 year). However, since patient recruitment had been completed and there were no safety concerns by the time the interim analysis was performed, the Independent Data Monitoring Committee recommended continuing treatment of ongoing patients as per the protocol.

**Primary Efficacy Endpoint**

Median CRRC-assessed EFS for RT/TMZ and BEV+RT/TMZ was 11.8 months (95% CI, 7.9–16.4) and 8.2 months (95% CI, 7.8–12.7), respectively (stratified HR, 1.44; 95% CI, 0.90–2.30; \(P=0.13\)) (Fig 3). The earliest contributing event was tumor progression (RT/TMZ, n=35; BEV+RT/TMZ, n=38), death (n=3 each group), tumor recurrence (RT/TMZ, n=1; BEV+RT/TMZ, n=4), and second primary non-HGG malignancy (n=1 each group; osteosarcoma [RT/TMZ] and B cell acute lymphocytic leukemia [BEV+RT/TMZ]). Results were generally consistent across the different subgroups (Fig 4), although females receiving RT/TMZ showed a better outcome than those receiving BEV+RT/TMZ (HR, 2.10; 95% CI, 1.04–4.21).

**Secondary Efficacy Endpoints**
The 1-year CRRC-assessed EFS rates were 48% (95% CI, 35–61) and 38% (95% CI, 26–51) for RT/TMZ and BEV+RT/TMZ, respectively; the 1-year OS rates were 68% (95% CI, 54–78) and 75% (95% CI, 61–84), respectively. Due to the absence of measurable lesions at baseline, only 27 patients were eligible for CRRC-assessed ORR analysis. Among these patients, the ORR was 40% (6/15 patients) and 42% (5/12 patients) in the RT/TMZ and BEV+RT/TMZ groups, respectively. Results for investigator-assessed EFS (HR, 1.49; 95% CI, 0.92–2.40) were similar to those for CRRC-assessed EFS. The addition of BEV did not reduce the risk of death OS (HR, 1.23; 95% CI, 0.72–2.09) (Fig 5). OS data are immature; a final OS analysis will be performed at the study. The most common pattern of progression in both groups was local recurrence (RT/TMZ, n=25; BEV+RT/TMZ, n=23); more patients in the BEV+RT/TMZ group (n=15) than in the RT/TMZ group (n=8) showed both local and distant recurrence.

**Treatment Received**

During the concurrent phase, 95% and 98% of patients treated with RT/TMZ and BEV+RT/TMZ, respectively, completed ≥90% of planned RT doses, and 86% and 88% of patients completed ≥90% of planned TMZ doses. Correspondingly, during the adjuvant phase, 45% and 33% of patients completed 12 TMZ cycles. The total and per cycle TMZ dose received was comparable between groups for the concurrent and adjuvant phases. Patients in the BEV+RT/TMZ group received a median of 5.0 and 18.5 BEV administrations during the concurrent and adjuvant phases, respectively.

**Safety**
The median duration of safety follow-up was 11.7 months and 11.6 months in the RT/TMZ and BEV+RT/TMZ groups, respectively. No new safety signals were identified for BEV. All patients, except one in the BEV+RT/TMZ group, experienced at least one AE. The incidence of grade 3 to 5 AEs was similar across the groups (RT/TMZ, n=38 [68%] v BEV+RT/TMZ, n=42 [70%]) but more patients experienced a grade 3 to 5 AESI in the BEV+RT/TMZ group (n=13, 22%) than in the RT/TMZ group (n=3, 5%). The most common AESIs were proteinuria (RT/TMZ, n=0 [0%] v BEV+RT/TMZ, n=8 [13%]) and arterial thromboembolic events (RT/TMZ, n=2 [4%] v BEV+RT/TMZ, n=5 [8%]). More patients experienced at least one SAE in the BEV+RT/TMZ group (n=35, 58%) than in the RT/TMZ group (n=27, 48%) and a higher proportion of patients discontinued any component of study treatment due to AEs in the BEV+RT/TMZ group (n=13, 22%) than in the RT/TMZ group (n=3, 5%). More patients in the BEV+RT/TMZ group (n=43, 72%) experienced AEs leading to dose modifications of any component of study treatment than in the RT/TMZ group (n=34, 61%).

In the BEV+RT/TMZ group, BEV and TMZ were discontinued due to AEs in 20% and 5% of patients, respectively. Among patients who discontinued BEV due to an AE, the most common reason was proteinuria (n=6, 10%). At the clinical cut-off date, four of the proteinuria events had resolved following BEV discontinuation, and two were ongoing.

Deaths occurred in 28 patients (50%) in the RT/TMZ group and 33 patients (55%) in the BEV+RT/TMZ group; the cause of death in all but one patient was disease progression. One treatment-related grade 4 AE of atypical teratoid/rhabdoid tumor of the CNS occurred in the BEV+RT/TMZ group 2 years after the end of study treatment and resulted in death.
See the Appendix (online only) for further details on patient disposition and protocol deviations in this study and results of the interim futility analysis, sensitivity analyses, health-related quality of life and neuropsychological function assessments, and exploratory analyses of potential prognostic factors.

**DISCUSSION**

The HERBY study evaluated the efficacy and safety of BEV/RT/TMZ versus RT/TMZ alone in pediatric patients with newly diagnosed non-brainstem HGG. Based on a pre-specified interim analysis of the first 60 randomized patients who were followed for 1 year, the study was considered futile. However, since patient recruitment had been completed and there were no safety concerns, the Independent Data Monitoring Committee recommended the continued treatment of patients as per the protocol. This publication presents the updated analysis of the enrolled 121 patients in the main protocol who were followed for at least 1 year after randomization, unless patient withdrawal or death occurred.

There was no significant difference in CRRC-assessed EFS (primary endpoint) between treatment groups, and the results of the secondary endpoints, including investigator-assessed EFS, ORR, and OS, showed no improvement with the addition of BEV. No new safety signals were identified for BEV. However, a higher proportion of patients in the BEV+RT/TMZ group than in the RT/TMZ group discontinued study treatment due to toxicity. Patients in the RT/TMZ group had a higher-than-expected 1-year EFS rate of 48% (95% CI, 35–61), which is comparable with previously reported 1-year EFS rate of 38% with RT/TMZ, and 49% with TMZ plus lomustine.
The absence of an EFS benefit with BEV in our study is not consistent with adult trials in which BEV has been shown to delay radiological progression (although neither adult study showed an OS benefit). Biological differences between pediatric and adult HGGs may partly explain why children respond differently to treatments. Most patients in our study had non-contrast-enhancing lesions at baseline (79%), while adult HGGs are typically contrast-enhancing. Also, the proportion of patients in our study with MGMT unmethylated tumors was lower than reported in adult patients with HGG, suggesting a phenotypic difference. This highlights the importance of conducting pediatric-specific HGG trials to assess the benefit of potential treatments.

Between-group differences in tumor location may also have contributed to the lower-than-anticipated efficacy seen with BEV, 39% of patients in the BEV+RT/TMZ group had midline tumors versus 31% in the RT/TMZ group. Indeed, a previous study has shown poorer outcomes in patients with midline tumors versus other locations (although the study did not describe how midline was defined). In the current study, midline location was associated with poorer EFS than tumors in other locations (Appendix Results, online only). Additionally, the impact of some biologic prognostic factors that were not anticipated at the time of the study design may have affected survival. Histone mutations at K27M, which are observed in midline tumors, have been associated with a poor prognosis, while mutations at G34R/V (observed in hemispheric tumors) may be associated with slightly longer OS. In our study, H3F3A driver mutations at position K27M and G34M were associated with lower survival (Appendix Results, online only). Some differences in the proportion of patients with these mutations were evident between groups; however, this finding should be interpreted with caution as multiple statistical tests
were performed in a relatively small number of samples. MGMT methylation status has also been shown to influence response to TMZ.\textsuperscript{24} However, MGMT methylation was relatively balanced between groups for the relatively small number of patients assessed for MGMT methylation status in this study.

The most common pattern of progressive disease in both groups was local recurrence, although a greater proportion of patients receiving BEV showed both local and distant progression. Previous research has suggested that BEV may lead to a higher incidence of distant and diffuse disease in pediatric patients with HGG or DIPG,\textsuperscript{25} and adult studies have noted a greater proportion of distant lesions in patients receiving BEV,\textsuperscript{26} although other studies reported no change in the radiographic pattern of patients’ tumors between baseline and the time of disease progression in patients receiving BEV.\textsuperscript{27}

Limitations of this study include the heterogeneity of enrolled patients, the relatively short follow-up duration, and the low completion rate of the HUI questionnaire at follow-up. The statistical power of the study was limited by the relatively small number of enrolled patients; however, increasing the study sample size would be unlikely to change the point estimate for survival, but may reduce the associated CI. Despite this, HERBY is one of the largest prospective, randomized pediatric HGG trials to date, including a molecular evaluation of tumor characteristics, and providing a global picture of treatment efficacy. We have demonstrated the feasibility of real-time, central histopathologic review before study entry, with no delay in treatment initiation. Only 5% of patients were excluded for having non-eligible low-grade glioma, compared with up to 30% in a trial that used post-hoc central review.\textsuperscript{27} The availability of results within 4 years of the adult trial demonstrates successful pharma-academic cooperation.
CONCLUSION

Adding BEV to RT/TMZ did not improve EFS in pediatric patients with newly diagnosed HGG. These results are not fully consistent with adult studies and highlight the biological differences between adult and childhood HGG, and the importance of performing pediatric-specific studies.
FUNDING
Funding for this study was provided by F. Hoffmann-La Roche Ltd (study number BO25041; clinicaltrials.gov NCT01390948).

CONTRIBUTORS
All authors contributed to the conception and design of this study, and were involved in the interpretation of the data and the development and approval of the manuscript. Data analyses were conducted by M.C. Elze.

ACKNOWLEDGMENTS
This study was a partnership between Australasian Children’s Cancer Trials (ACCT), Innovative Therapies for Children with Cancer (ITCC), the European Society for Paediatric Oncology (SIOPE), and Roche, and was part of a pediatric investigation plan requested by the European Medicines Agency.

The authors would like to thank the participating investigators, their study staff, and the patients and their families who participated in the study. We would also like to thank Magalie Hilton for contributing to the statistical analyses. Medical writing support in the form of development of a draft manuscript was provided by Thomas Burton BMBS and David Evans PhD of Gardiner-Caldwell Communications, Macclesfield, UK, and was funded by F. Hoffmann-La Roche Ltd.

D. Hargrave is supported by the National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London. C. Jones acknowledges NHS funding to the NIHR Biomedical Research Centre at The Royal Marsden Hospital and the ICR.
R. Rousseau has left Genentech and is now with Gritstone Oncology.
REFERENCES


FIGURE LEGENDS

**Fig 1.** Study design. BEV, bevacizumab; HGG, high-grade glioma; RT, radiotherapy; TMZ, temozolomide.

**Fig 2.** CONSORT flow diagram. Note: survival follow-up was an unlimited follow-up that continued to capture patient survival after regular follow-up had been completed. Five randomized patients did not receive treatment (RT/TMZ: withdrew consent, n=3; BEV+RT/TMZ: failed to meet eligibility criteria, n=1; withdrew consent, n=1). BEV, bevacizumab; FU, follow-up; RT, radiotherapy; TMZ, temozolomide.

**Fig 3.** CRRC-assessed event-free survival with RT/TMZ and BEV + RT/TMZ (primary efficacy endpoint). BEV, bevacizumab; CI, confidence interval; CRRC, Central Radiology Review Committee; HR, hazard ratio; RT, radiotherapy; TMZ, temozolomide.

**Fig 4.** Forest plot of CRRC-assessed event-free survival for the overall cohort and subgroups. BEV, bevacizumab; CI, confidence interval; CRRC, Central Radiology Review Committee; HGG, high-grade glioma; MGMT, O6-methylguanine-DNA methyltransferase; NE, not evaluable; RT, radiotherapy; TMZ, temozolomide; WHO, World Health Organization.

**Fig 5.** Overall survival with RT/TMZ and BEV + RT/TMZ (interim assessment). BEV, bevacizumab; CI, confidence interval, HR, hazard ratio; RT, radiotherapy; TMZ, temozolomide.
Table 1. Patient Baseline Characteristics of the ITT Population (All Randomized Patients Regardless of Whether They Received Study Treatment)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RT/TMZ (n=59)</th>
<th>BEV+RT/TMZ (n=62)</th>
<th>Total (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>11.0 (3 to 17)</td>
<td>10.0 (3 to 17)</td>
<td>11.0 (3 to 17)</td>
</tr>
<tr>
<td>Age group, n (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 to &lt; 6 years</td>
<td>6 (10)</td>
<td>10 (16)</td>
<td>16 (13)</td>
</tr>
<tr>
<td>6 to &lt; 13 years</td>
<td>30 (51)</td>
<td>35 (57)</td>
<td>65 (54)</td>
</tr>
<tr>
<td>13 to &lt; 18 years</td>
<td>23 (39)</td>
<td>17 (27)</td>
<td>40 (33)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>36 (61)</td>
<td>34 (55)</td>
<td>70 (58)</td>
</tr>
<tr>
<td>WHO grade HGG, n (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>17 (29)</td>
<td>20 (32)</td>
<td>37 (31)</td>
</tr>
<tr>
<td>IV</td>
<td>42 (71)</td>
<td>42 (68)</td>
<td>84 (69)</td>
</tr>
<tr>
<td>Surgery, n (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total/near-total resection</td>
<td>29 (49)</td>
<td>31 (50)</td>
<td>60 (50)</td>
</tr>
<tr>
<td>Other resection</td>
<td>20 (34)</td>
<td>19 (31)</td>
<td>39 (32)</td>
</tr>
<tr>
<td>Biopsy</td>
<td>10 (17)</td>
<td>12 (19)</td>
<td>22 (18)</td>
</tr>
<tr>
<td>MGMT gene promoter status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylated</td>
<td>2 (3)</td>
<td>3 (5)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Unmethylated with ratio &lt; 0.6</td>
<td>18 (31)</td>
<td>19 (31)</td>
<td>37 (31)</td>
</tr>
<tr>
<td>Missing</td>
<td>39 (66)</td>
<td>40 (65)</td>
<td>79 (65)</td>
</tr>
<tr>
<td>Histone mutation status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mutation</td>
<td>29 (49)</td>
<td>25 (40)</td>
<td>54 (45)</td>
</tr>
<tr>
<td>Mutation at position G34</td>
<td>5 (9)</td>
<td>2 (3)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Mutation at position K27</td>
<td>10 (17)</td>
<td>14 (23)</td>
<td>24 (20)</td>
</tr>
<tr>
<td>Missing</td>
<td>15 (25)</td>
<td>21 (34)</td>
<td>36 (30)</td>
</tr>
<tr>
<td>Location of HGG, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18 (31)</td>
<td>24 (39)</td>
<td>42 (35)</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>Midline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>41 (69)</td>
<td>38 (61)</td>
<td>79 (65)</td>
</tr>
</tbody>
</table>

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Residual tumor at baseline, n (%)†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Contrast-enhancing lesions</strong></td>
<td>15 (25)</td>
<td>12 (19)</td>
<td>27 (22)</td>
</tr>
<tr>
<td><strong>Non-contrast-enhancing lesions</strong></td>
<td>47 (80)</td>
<td>49 (79)</td>
<td>96 (79)</td>
</tr>
</tbody>
</table>

Abbreviations: BEV, bevacizumab; HGG, high-grade glioma; ITT, intent-to-treat; MGMT, O6-methylguanine-DNA methyltransferase; RT, radiotherapy; TMZ, temozolomide; WHO, World Health Organization.

*Stratification factors for randomization.

†Patients could have both enhancing and non-enhancing lesions.
Debulking surgery or biopsy → Central pathology review → Randomization

Randomization:
- Stratification:
  - Age
  - HGG grade
  - Surgery

RT 1.8 Gy; 5 days/week
TMZ 75 mg/m²/day → Break → TMZ 150 to 200 mg/m²/day
Days 1 to 5
Every 28 days

RT 1.8 Gy; 5 days/week
TMZ 75 mg/m²/day
BEV 10 mg/kg Every 2 weeks

BEV 10 mg/kg Every 2 weeks

BEV 10 mg/kg Every 2 weeks

Treatment start 4 to 6 weeks post-surgery
Concurrent phase 6 weeks
TMZ break 4 weeks
Maintenance phase up to 12 cycles
174 screened

121 enrolled

59 randomized (RT/TMZ)
- 56 treated
  - 25 completed treatment
  - 31 discontinued from treatment
  - 0 ongoing treatment
  - 28 dead
  - 26 alive in FU or survival FU
  - 2 withdrew from FU
  - 6 survival FU

62 randomized (BEV + RT/TMZ)
- 60 treated
  - 43 discontinued from treatment
  - 17 completed treatment
  - 4 withdrew from FU
  - 23 alive in FU or survival FU
  - 33 dead
  - 6 survival FU
Stratified HR, 1.44
95% CI, 0.90 to 2.30; log-rank $P = .13$
Stratified HR, 1.23
95% CI, 0.72 to 2.09; log-rank $P = .46$