

Does Valproic Acid or Levetiracetam Improve Survival in Glioblastoma? A Pooled Analysis of Prospective Clinical Trials in Newly Diagnosed Glioblastoma

Caroline Happold, Thierry Gorlia, Olivier Chinot, Mark R. Gilbert, L. Burt Nabors, Wolfgang Wick, Stephanie L. Pugh, Monika Hegi, Timothy Cloughesy, Patrick Roth, David A. Reardon, James R. Perry, Minesh P. Mehta, Roger Stupp, and Michael Weller

Caroline Happold, Patrick Roth, Roger Stupp, and Michael Weller, University Hospital Zurich; Monika Hegi, University Hospital Lausanne, Switzerland; Thierry Gorlia, EORTC Data Centre, Brussels, Belgium; Olivier Chinot, Aix-Marseille University, Marseille, France; Mark R. Gilbert, The University of Texas MD Anderson Cancer Center, Houston, TX; L. Burt Nabors, University of Alabama at Birmingham, Birmingham, AL; Wolfgang Wick, University of Heidelberg & German Cancer Research Center, Heidelberg, Germany; Stephanie L. Pugh, NRG Oncology Statistics and Data Management Center, Philadelphia, PA; Timothy Cloughesy, UCLA Neuro-Oncology Program, Los Angeles, CA; David A. Reardon, Dana-Farber Cancer Institute, Boston, MA; James R. Perry, University of Toronto, Toronto, Ontario, Canada; and Minesh P. Mehta, University of Maryland, Baltimore, MD.

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Corresponding author: Michael Weller, MD, Department of Neurology, University Hospital Zurich, Frauenklinikstrasse 26, CH-8091 Zurich, Switzerland; e-mail: michael.weller@usz.ch.

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ABSTRACT

Purpose

Symptomatic epilepsy is a common complication of glioblastoma and requires pharmacotherapy. Several uncontrolled retrospective case series and a post hoc analysis of the registration trial for temozolomide indicated an association between valproic acid (VPA) use and improved survival outcomes in patients with newly diagnosed glioblastoma.

Patients and Methods

To confirm the hypothesis suggested above, a combined analysis of survival association of anti-epileptic drug use at the start of chemoradiotherapy with temozolomide was performed in the pooled patient cohort ($n = 1,869$) of four contemporary randomized clinical trials in newly diagnosed glioblastoma: AVAGlio (Avastin in Glioblastoma; NCT00943826), CENTRIC (Cilengitide, Temozolomide, and Radiation Therapy in Treating Patients With Newly Diagnosed Glioblastoma and Methylated Gene Promoter Status; NCT00689221), CORE (Cilengitide, Temozolomide, and Radiation Therapy in Treating Patients With Newly Diagnosed Glioblastoma and Unmethylated Gene Promoter Status; NCT00813943), and Radiation Therapy Oncology Group 0825 (NCT00884741). Progression-free survival (PFS) and overall survival (OS) were compared between: (1) any VPA use and no VPA use at baseline or (2) VPA use both at start of and still after chemoradiotherapy. Results of Cox regression models stratified by trial and adjusted for baseline prognostic factors were analyzed. The same analyses were performed with levetiracetam (LEV).

Results

VPA use at start of chemoradiotherapy was not associated with improved PFS or OS compared with all other patients pooled (PFS: hazard ratio [HR], 0.91; 95% CI, 0.77 to 1.07; $P = .241$; OS: HR, 0.96; 95% CI, 0.80 to 1.15; $P = .633$). Furthermore, PFS and OS of patients taking VPA both at start of and still after chemoradiotherapy were not different from those without antiepileptic drug use at both time points (PFS: HR, 0.92; 95% CI, 0.74 to 1.15; $P = .467$; OS: HR, 1.10; 95% CI, 0.86 to 1.40; $P = .440$). Similarly, no association with improved outcomes was observed for LEV use.

Conclusion

The results of this analysis do not justify the use of VPA or LEV for reasons other than seizure control in patients with newly diagnosed glioblastoma outside clinical trials.

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INTRODUCTION

Symptomatic epileptic seizures are a common complication and often the initial clinical manifestation in patients with brain tumors, including glioblastoma. The choice of antiepileptic drug (AED) to treat brain tumor-associated epilepsy is determined by patient age, comorbidities, concurrent medications, tolerability, adverse-effect

profile, and drug-drug interactions.²⁻⁴ Valproic acid (VPA) is a traditional, well-established AED with an incompletely understood mode of action that may involve the inhibition of various ion channels, promotion of γ -aminobutyric acid signaling, or both. Its additional pharmacodynamic properties, notably inhibition of histone deacetylases (HDACs), have attracted interest in oncology. Importantly, in contrast to most other classic AEDs, which are enzyme-inducing (EI)

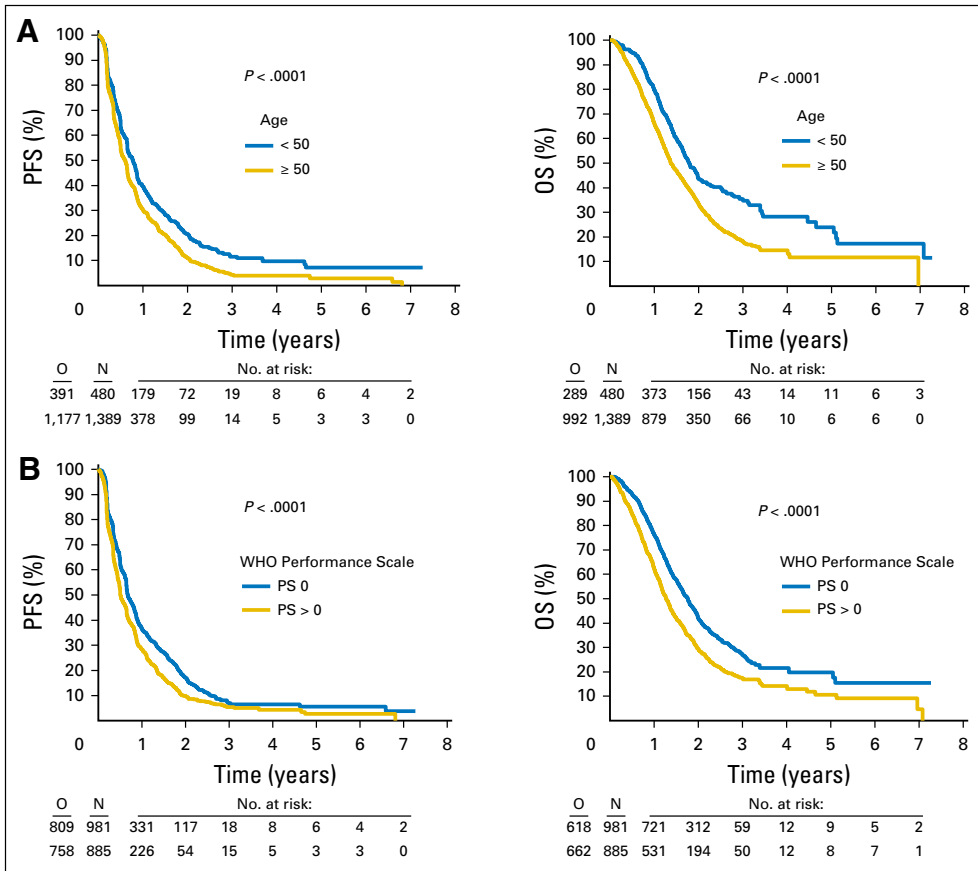


Fig 1. Prognostic factors for PFS (left) and OS (right) in the pooled cohort. (A) Age, (B) WHO performance status, (C) extent of resection, and (D) *MGMT* promoter methylation status. *MGMT*, O⁶-methylguanine–DNA methyltransferase; N, number; O, observed; OS, overall survival; PFS, progression-free survival.

drugs, VPA inhibits multiple enzymes, including uridine diphosphate-glucuronosyltransferase, epoxide hydroxylase, and CYP2C coenzymes, carrying the risk of untoward drug-drug interactions due to impaired metabolism.⁵

Several uncontrolled clinical case series have noted improved outcome of patients with pediatric brain tumors^{6,7} and with newly diagnosed glioblastoma treated according to the current standard of care of temozolomide (TMZ) plus radiotherapy (RT) followed by temozolomide (TMZ) alone^{8,9} when VPA was chosen as the AED.¹⁰⁻¹² A large analysis of 544 patients concluded that the association was independent of TMZ use and linked improved outcome to VPA use during RT.¹⁰ This interpretation gains support from numerous preclinical studies that report radiosensitizing properties of VPA, mostly attributed to HDAC inhibition.¹³⁻¹⁵

The best retrospectively obtained evidence for a moderate improvement of outcome with VPA may stem from the analysis of patients treated within the pivotal trial of TMZ in newly diagnosed glioblastoma. This unplanned secondary analysis indicated that patients specifically treated with VPA at the start of TMZ plus RT followed by TMZ alone had longer overall survival (OS) than patients receiving no AED or EI-AED. Importantly, no such signal was seen in the RT-alone control arm.¹ This evaluation of AED associations with outcome was triggered by a retrospective analysis of 620 patients with glioblastoma treated in clinical trials that had defined no role for epilepsy as a prognostic factor, but an association of EI-AED with better outcome.¹⁶

Given the low number of novel, promising pharmacological agents for the treatment of gliomas, there is growing interest in

exploring the possible inclusion of VPA into the standard of care for pediatric brain tumors¹⁷ and newly diagnosed adult glioblastoma.¹⁸ Yet, to demonstrate clinical activity, a large randomized trial is required. Such a trial is always a challenge to perform, especially in the absence of external support mechanisms. To further substantiate the need for such a trial, we explored contemporary, prospectively studied clinical trial populations where comedication data at study entry were captured. We assumed that a pooled analysis of these patient cohorts could provide guidance regarding the likely need for, and size of, a randomized trial of VPA in patients with newly diagnosed glioblastoma. Moreover, this data set was used to verify whether levetiracetam (LEV), another commonly used AED in patients with brain tumors, is associated with improved outcome. LEV probably acts by binding to the vesicular protein SV2A, promoting γ -aminobutyric acid release.¹⁹

PATIENTS AND METHODS

Patients

To explore the prognostic significance of AEDs in patients enrolled in clinical trials for newly diagnosed glioblastoma, we obtained data from the experimental TMZ-containing arm of the European Organisation for Research and Treatment of Cancer (EORTC) NCIC Clinical Trials Group (NCIC) trial (n = 287),⁸ the control arms of the AVAGlio (Avastin in Glioblastoma; n = 463)²⁰ and Radiation Therapy Oncology Group (RTOG) 0825 (n = 309)²¹ trials exploring the addition of bevacizumab to TMZ plus RT followed by TMZ alone, and the pooled control and experimental arms of the CENTRIC (Cilengitide, Temozolomide, and Radiation Therapy in

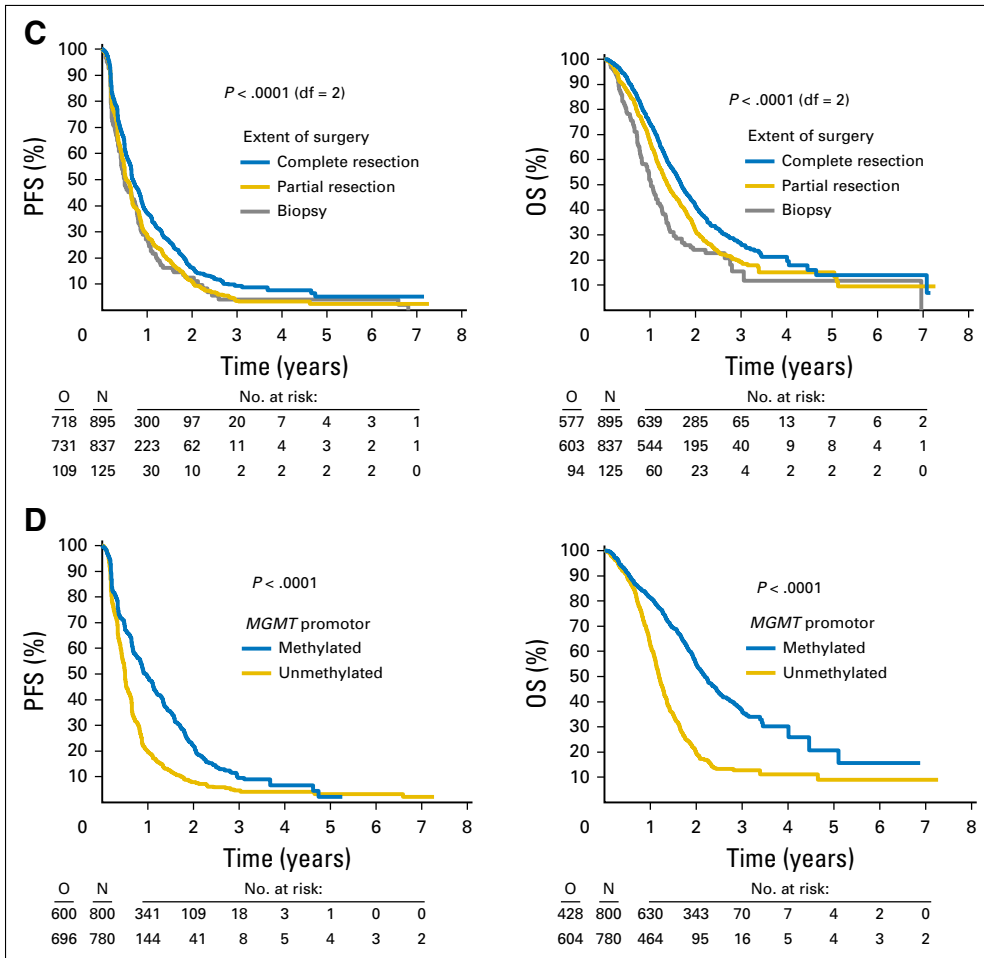


Fig 1. (Continued).

Treating Patients With Newly Diagnosed Glioblastoma and Methylated Gene Promoter Status; n = 545)²² and CORE (Cilengitide, Temozolomide, and Radiation Therapy in Treating Patients With Newly Diagnosed Glioblastoma and Unmethylated Gene Promoter Status; n = 265)²³ trials (n = 810), which did not indicate efficacy of the integrin antagonist, cilengitide. Investigations were performed after approval by a local human investigations committee and in accord with an assurance filed with and approved by the US Department of Health and Human Services, where appropriate. Data were anonymized to protect the identities of subjects involved. Informed consent was obtained from each participant.

For each trial, data sets were received (in Excel or SAS format) with individual patient information including date of randomization, progression-free survival (PFS) status, PFS duration, survival status, OS duration, and baseline covariates including O⁶-methylguanine–DNA methyltransferase (MGMT) promoter methylation status, continuous age, sex, WHO performance status, extent of initial resection, and steroid use at study entry.

Administration of baseline AED and AED name were either provided in the data set with other covariates or had to be extracted from a concomitant medications data set (in CENTRIC and CORE). AEDs were recoded by type, either as VPA or LEV only versus EI-AED only versus non-EI-AED without VPA or LEV versus AED combinations. Mini-Mental State Examination (MMSE) data were not present in the RTOG 0825 data set. Before pooling, all data were recoded using the same variable naming and labeling convention.

Statistical Methods

Descriptive statistics of baseline covariates, specifically frequencies and percentages, were conducted overall, by trial, and by AED comparisons

(any VPA or LEV v no VPA or LEV, VPA only or LEV only v no AED or v EI-AED only or v non-EI-AED without VPA or LEV). Significance was assessed for the AED comparisons using the Wilcoxon rank sum test. PFS and OS Kaplan-Meier survival curves were computed to estimate the time to event or death. Cox regression models were used to estimate the prognostic effect for PFS and OS of baseline covariates and of VPA only or LEV only versus comparators, with score tests used to assess significance. All comparisons were adjusted for baseline covariates (except MMSE) and stratified by trial (CENTRIC and CORE pooled) to account for the differences in timing of patient randomization and imbalances in baseline covariates across trials. Comparisons of PFS and OS by the year the patient was randomized in the trial were performed.

The hypothesis on a prognostic effect of VPA use was generated in the EORTC NCIC data set.¹ In the EORTC NCIC data set, LEV was administered to a single patient. Pooled AVAGlio, RTOG 0825, and CENTRIC/CORE data (ie, excluding EORTC NCIC data) were used for the validation of the VPA hypothesis and for evaluation of a prognostic value of LEV use. For evaluation of a prognostic use of longer-term application of either VPA or LEV, the validation cohort comprised data from AVAGlio, CENTRIC, and CORE, without RTOG 0825 patients (no data available).

Before starting the analyses, it was decided that the three primary comparisons were the OS comparisons of: (1) VPA versus no AED, (2) VPA versus EI-AED, and (3) VPA versus other non-EI-AED (without VPA). The nominal significance level for each of them was 1.67% (5% ÷ 3). Every comparison with an unadjusted P value lower than 1.67% was considered statistically significant. PFS comparisons (those involving LEV and all other comparisons) were performed for exploratory purposes at 5% significance. MGMT promoter methylation status was missing in 16% of the whole data

Table 1. Clinical Characteristics and AED Use Per Clinical Trial Cohort

| Variable | Clinical Trial | | | | Total |
|---|----------------|------------|-------------|--------------|--------------|
| | EORTC 26981 | AVAGlio | RTOG 0825 | CORE/CENTRIC | |
| No. of patients | 287 | 463 | 309 | 810 | 1,869 |
| Years of study | 2000-2002 | 2009-2011 | 2009-2011 | 2008-2011 | |
| Age, years | | | | | |
| Median | 55.7 | 56.0 | 57.0 | 57.3 | 56.9 |
| Range | 18.6-70.5 | 18.0-79.0 | 19.0-82.0 | 20.8-81.0 | 18.0-82.0 |
| Patient demographic or clinical characteristic, No. (%) | | | | | |
| Age, years | | | | | |
| < 50 | 91 (31.7) | 113 (24.4) | 65 (21.0) | 211 (26.0) | 480 (25.7) |
| ≥ 50 | 196 (68.3) | 350 (75.6) | 244 (79.0) | 599 (74.0) | 1,389 (74.3) |
| Sex | | | | | |
| Male | 185 (64.5) | 298 (64.4) | 194 (62.8) | 446 (55.1) | 1,123 (60.1) |
| Female | 102 (35.5) | 165 (35.6) | 115 (37.2) | 364 (44.9) | 746 (39.9) |
| WHO performance status | | | | | |
| 0 | 113 (39.4) | 238 (51.4) | 190 (61.5) | 440 (54.3) | 981 (52.5) |
| > 0 | 174 (60.6) | 224 (48.4) | 119 (38.5) | 368 (45.4) | 885 (47.4) |
| Missing | 0 (0.0) | 1 (0.2) | 0 (0.0) | 2 (0.2) | 3 (0.2) |
| Mini-Mental State Examination score | | | | | |
| < 27 | 91 (31.7) | 108 (23.3) | 0 (0.0) | 171 (21.1) | 370 (19.8) |
| ≥ 27 | 196 (68.3) | 351 (75.8) | 0 (0.0) | 629 (77.7) | 1,176 (62.9) |
| Missing | 0 (0.0) | 4 (0.9) | 309 (100.0) | 10 (1.2) | 323 (17.3) |
| Extent of surgery | | | | | |
| Biopsy | 48 (16.7) | 44 (9.5) | 0 (0.0) | 33 (4.1) | 125 (6.7) |
| Partial resection | 126 (43.9) | 223 (48.2) | 119 (38.5) | 369 (45.6) | 837 (44.8) |
| Complete resection | 113 (39.4) | 196 (42.3) | 181 (58.6) | 405 (50.0) | 895 (47.9) |
| Missing | 0 (0.0) | 0 (0.0) | 9 (2.9) | 3 (0.4) | 12 (0.6) |
| Steroid use | | | | | |
| No | 94 (32.8) | 253 (54.6) | 80 (25.9) | 497 (61.4) | 924 (49.4) |
| Yes | 193 (67.2) | 208 (44.9) | 229 (74.1) | 313 (38.6) | 943 (50.5) |
| Missing | 0 (0.0) | 2 (0.4) | 0 (0.0) | 0 (0.0) | 2 (0.1) |
| MGMT status | | | | | |
| Unmethylated | 65 (22.6) | 236 (51.0) | 214 (69.3) | 265 (32.7) | 780 (41.7) |
| Methylated | 50 (17.4) | 120 (25.9) | 85 (27.5) | 545 (67.3) | 800 (42.8) |
| Missing | 172 (59.9) | 107 (23.1) | 10 (3.2) | 0 (0.0) | 289 (15.5) |
| Baseline AED use | | | | | |
| No AED | 103 (35.9) | 165 (35.6) | 76 (24.6) | 331 (40.9) | 675 (36.1) |
| EI-AED only | 113 (39.4) | 104 (22.5) | 47 (15.2) | 101 (12.5) | 365 (19.5) |
| EI-AED plus VPA | 4 (1.4) | 14 (3.0) | 0 (0.0) | 3 (0.4) | 21 (1.1) |
| EI-AED plus non-EI-AED without VPA | 5 (1.7) | 20 (4.3) | 11 (3.6) | 12 (1.5) | 48 (2.6) |
| VPA only | 49 (17.1) | 41 (8.9) | 5 (1.6) | 125 (15.4) | 220 (11.8) |
| VPA plus another non-EI-AED | 1 (0.3) | 15 (3.2) | 1 (0.3) | 9 (1.1) | 26 (1.4) |
| Non-EI-AED without VPA | 8 (2.8) | 102 (22.0) | 169 (54.7) | 229 (28.3) | 508 (27.2) |
| EI-AED plus VPA plus another non-EI-AED | 1 (0.3) | 2 (0.4) | 0 (0.0) | 0 (0.0) | 3 (0.2) |
| Missing | 3 (1.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.2) |

Abbreviations: AED, antiepilepsy drug; AVAGlio, Avastin in Glioblastoma; CENTRIC, Cilengitide, Temozolomide, and Radiation Therapy in Treating Patients With Newly Diagnosed Glioblastoma and Methylated Gene Promoter Status; CORE, Cilengitide, Temozolomide, and Radiation Therapy in Treating Patients With Newly Diagnosed Glioblastoma and Unmethylated Gene Promoter Status; EI, enzyme-inducing; EORTC, European Organisation for Research and Treatment of Cancer; *MGMT*, O⁶-methylguanine-DNA methyltransferase; RTOG, Radiation Therapy Oncology Group; VPA, valproic acid.

set. Multiple imputation technique (logistic regression) was used to replace missing *MGMT* values. The imputation and Cox regression was applied five times and parameters estimates were pooled. SAS version 9.2 (SAS Institute Inc., Cary, NC) was used for baseline covariates description, testing (PROC NPARIWAY), survival analyses (PROC PHREG), data imputation (PROC MI), and pooling of Cox parameters (PROC MIAnalyze).

RESULTS

No Association of VPA Use With Improved Outcome

Analysis of the total cohort of 1,869 patients confirmed that the major prognostic factors for PFS and OS in newly diagnosed

glioblastoma remain age, WHO performance status, extent of resection, and *MGMT* promoter methylation status (Fig 1), as well as MMSE and steroid use at study entry. Interestingly, women did significantly better than men (Appendix Fig A1, online only). There was a small trend for improvement in OS over time between 2000 and 2011 (hazard ratio [HR], 0.94; 95% CI, 0.90 to 0.98; $P = .001$), which was accounted for by stratification by trial for the present analysis. AED use at baseline per clinical trial population is summarized in Table 1. To validate the observation of prolonged survival with VPA in the EORTC NCIC trial,¹ we first compared outcome in all patients of the validation cohort who had VPA alone or VPA in any combination at study entry with all other patients. This analysis revealed no differences in PFS or OS (Figs 2A and 2B;

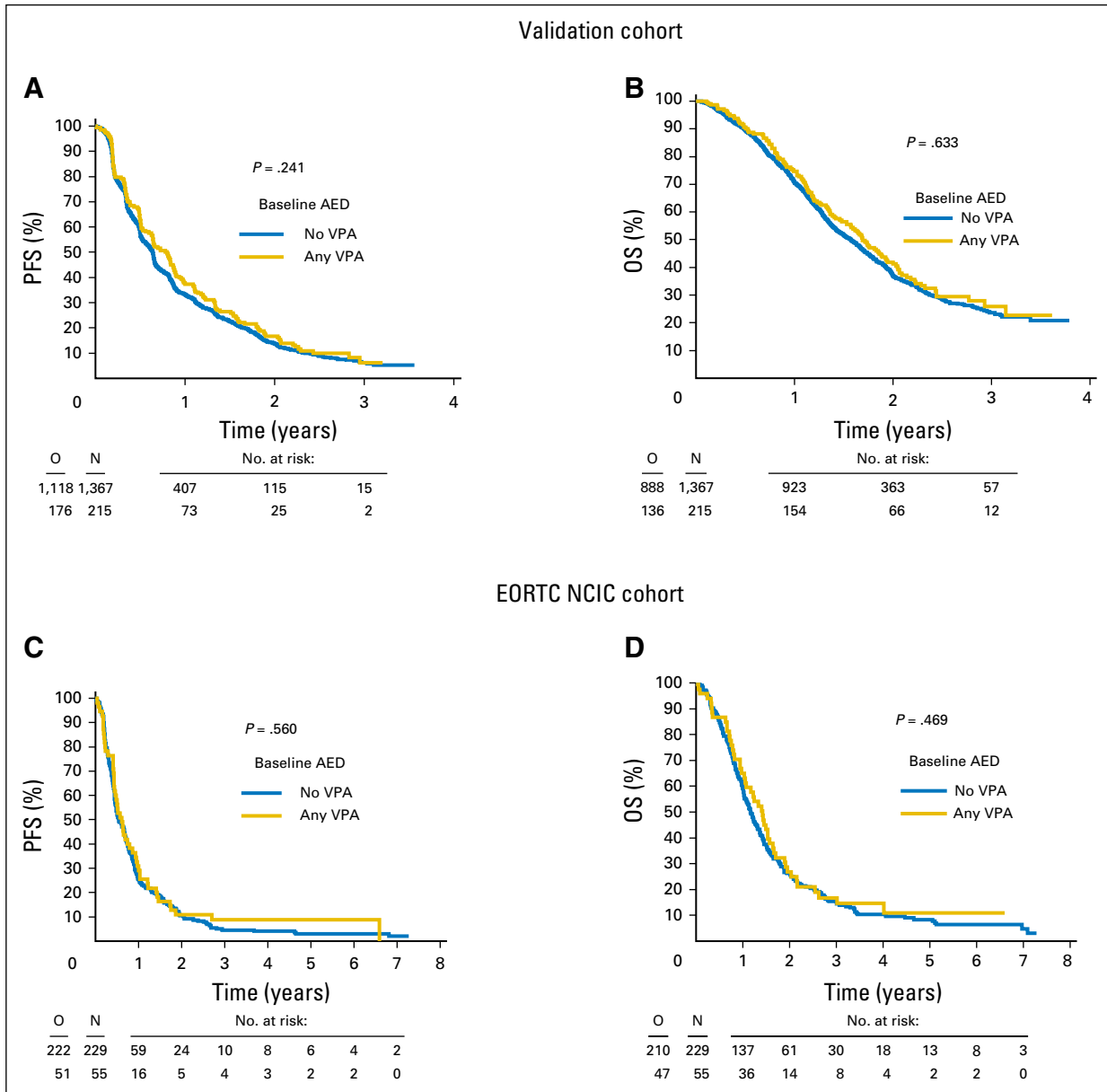


Fig 2. Prognostic significance of baseline VPA use in the validation cohort (A and B) and EORTC NCIC cohort (C and D) or of continued VPA use in the validation cohort (E and F) and EORTC NCIC cohort (G and H) for PFS (left) and OS (right). EORTC, European Organisation for Research and Treatment of Cancer; NCIC, NCIC Clinical Trials Group; N, number; O, observed; OS, overall survival; PFS, progression-free survival; VPA, valproic acid.

Table 2). A similar analysis performed in the EORTC NCIC trial also revealed no association with outcome (Figs 2C and 2D; Table 2).

To follow more closely the analysis strategy pursued when analyzing the EORTC NCIC trial,¹ we next performed pairwise comparisons of PFS or OS for VPA only-treated patients from the other trials with patients receiving no AED (Appendix Figs A2A and A2B) or EI-AED only (Appendix Figs A2C and A2D) or non-EI-AED other than VPA (Appendix Figs A2E and A2F). Here, no comparison was done with patients receiving AED combinations. Only eight patients received non-EI-AEDs other than VPA in the EORTC NCIC trial (Table 1). On univariate analysis, there was a consistent trend for improved PFS (HR, 0.80-0.87) or OS (HR, 0.87-0.94) with VPA in these pairwise comparisons. However,

in PFS or OS comparisons adjusted for the covariates age, sex, WHO performance score, extent of resection, steroid use, and *MGMT* promoter methylation status, this trend was lost (Appendix Table A1).

Finally, we reasoned that a focus on patients with prolonged exposure to VPA might be more appropriate for capturing any association with outcome. However, when comparing patients who were taking VPA both at study entry (before chemoradiotherapy) and the first visit thereafter with patients who were not taking an AED on both occasions, there was no difference in PFS or OS either in the validation cohort (excluding RTOG 0825 for lack of data) or the EORTC NCIC trial (Figs 2E-H; Appendix Table A2). We thought that this comparison was conservative, but least likely to be confounded by bias.

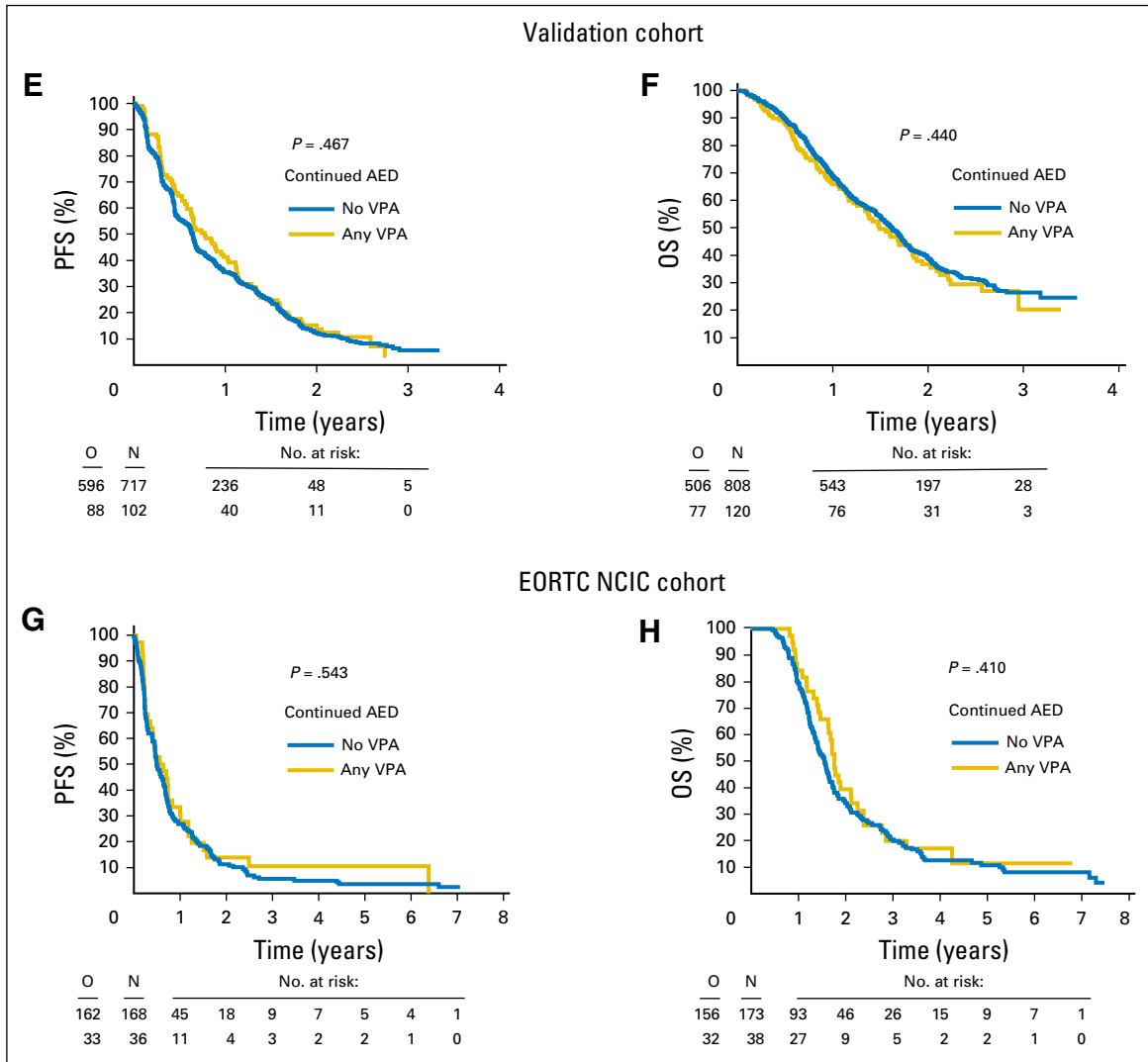


Fig 2. (Continued).

No Association of LEV Use With Improved Outcome

We also explored whether LEV is associated with outcome using a similar approach, but restricted to the validation cohort because there was essentially no LEV use in the EORTC NCIC trial (Appendix Table A3). There was no evidence that LEV prescription at study entry was associated with improvement in PFS or OS (Table 3; Figs 3A and 3B; Appendix Fig A3; Appendix Table A4). Likewise, comparison of patients on LEV treatment both at study entry and after radiochemotherapy with patients who were not on AED treatment at both time points did not show differences in PFS or OS in the validation cohort (Figs 3C and 3D; Appendix Table A5).

DISCUSSION

Based on several retrospective analyses,¹⁰⁻¹² VPA has become paradigmatic for potential drug repurposing in glioblastoma. However, the studies supporting the albeit moderate, if any, activity of VPA all had inherent limitations: They were retrospective, had

small sample sizes, and there were few data on VPA exposure in terms of dose and time. We considered the EORTC NCIC population¹ as a hypothesis-generating cohort for a survival benefit from VPA and sought to generate a large validation cohort derived from contemporary clinical trials in newly diagnosed glioblastoma.

This validation cohort was generated from the control arms of two phase III trials exploring the addition of bevacizumab to standard of care, AVAGlio²⁰ and RTOG 0825,²¹ as well as pooled experimental and control arms of CENTRIC²² and CORE,²³ given that cilengitide was not considered active in these trials. This resulted in a cohort of 1,869 patients, allowing assessment of an association of AED use with outcome (Table 1).

We first compared PFS and OS in patients taking VPA alone or in any combination with all other patients and found no difference (Table 2; Figs 2A and 2B). Next, to define homogenous populations, we excluded patients with combinations of VPA with other AEDs and performed individual comparisons with patients who either received no AEDs, EI-AEDs, or non-EI-AEDs other than VPA. Although these three groupwise comparisons all favored VPA by trend for PFS and OS (Appendix Fig A2), none of these

Table 2. Comparison of PFS and OS Between Any VPA Use and No VPA Use in the EORTC NCIC Trial or Validation Cohort

| Variable | No. of Patients (No. of Events) | Median OS (95% CI) | Survival at 1 Year, % (95% CI) | Hazard Ratio (95% CI)* | P† |
|------------|---------------------------------|------------------------|--------------------------------|------------------------|------|
| OS | | | | | |
| EORTC-NCIC | | | | | |
| VPA | 55 (47) | 16.99 (12.32 to 19.71) | 65.5 (51.3 to 76.4) | 0.89 (0.65 to 1.22) | .469 |
| No VPA | 229 (210) | 14.03 (12.35 to 15.80) | 59.8 (53.2 to 65.9) | | |
| Validation | | | | | |
| VPA | 215 (136) | 20.30 (17.51 to 23.13) | 74.7 (68.3 to 80.1) | 0.96 (0.80 to 1.15) | .633 |
| No VPA | 1,367 (888) | 18.86 (17.45 to 20.04) | 70.7 (68.1 to 73.1) | | |
| PFS | | | | | |
| EORTC-NCIC | | | | | |
| VPA | 55 (51) | 7.29 (5.16 to 10.32) | 29.1 (17.8 to 41.3) | 0.91 (0.67 to 1.24) | .560 |
| No VPA | 229 (222) | 6.47 (5.55 to 8.18) | 25.8 (20.3 to 31.6) | | |
| Validation | | | | | |
| VPA | 215 (176) | 9.59 (7.52 to 10.51) | 37.4 (30.7 to 44.0) | 0.91 (0.77 to 1.07) | .241 |
| No VPA | 1,367 (1,118) | 7.66 (6.97 to 7.85) | 33.3 (30.7 to 35.9) | | |

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; NCIC, NCIC Clinical Trials Group; OS, overall survival; PFS, progression-free survival; VPA, valproic acid.
*VPA only v comparator.
†Score test.

comparisons were significant on multivariate analysis (Appendix Table A1). Moreover, narrowing the analysis to patients receiving VPA both at study entry and at the first visit after chemoradiotherapy also failed to validate an association of VPA use with outcome (Figs 2E and 2F). Importantly, there was also no differential association with outcome of VPA use by *MGMT* promoter methylation status in the multivariate analysis.

The present analysis also provided an opportunity to conduct a similar exploratory analysis of an association of LEV use with outcome. Here, patients enrolled in the EORTC NCIC trial⁸ were excluded because there was almost no LEV use when this trial was performed (Appendix Table A3). LEV has been reported to decrease *MGMT* expression²⁴ and recently has also been linked to improved outcome in patients with newly diagnosed glioblastoma.¹⁹ Compared with VPA, there was essentially no signal for prolonged PFS or OS in patients taking LEV even on univariate analysis in the present study, on the contrary (Appendix Table A4; Appendix Fig A3). Prolonged exposure to LEV was not linked to improved outcome either (Figs 3C and 3D; Appendix Table A5). The lack of association of LEV use with outcome when also stratified for *MGMT* promoter methylation status does not support the idea that LEV depletes *MGMT* protein in vivo.

Does this mean that the discussion on repurposing of AEDs for glioma treatment is at its end? Proponents of this strategy might still argue that the present analysis, despite its undisputed strengths (notably size and prospective capture of outcome data), has one major limitation, which is that AED use at study entry only (and after radiochemotherapy in a subset of patients) was used for this analysis. We believed that there was no valid biostatistical strategy of controlling for change in treatment from VPA to another AED or vice versa, nor start of AED treatment in previously unexposed patients, because such changes are commonly triggered by adverse effects, insufficient seizure control, and likely progressive disease in many patients. Although we did not confirm an association of seizures at baseline with OS in the data sets available from the CORE and CENTRIC trials (data not shown), seizures throughout the course of disease might represent a relevant confounder because they commonly trigger a dose increase or change of the AED. Moreover, doses of both drugs, as well as length of exposure, would have varied substantially among patients, and no dose-finding studies for the presumed mode of action of VPA and AED on HDAC activity and *MGMT* levels, respectively, have been conducted in vivo. In fact, there is doubt that such concentrations are achieved with the standard dosing regimens. In contrast, only a

Table 3. Comparison of PFS and OS Between Any LEV Use and No LEV Use in the Validation Cohort*

| Variable | No. of Patients (No. of Events) | Median OS (95% CI) | Survival at 1 Year, % (95% CI) | Hazard Ratio† (95% CI) | P‡ |
|------------|---------------------------------|------------------------|--------------------------------|------------------------|------|
| OS | | | | | |
| LEV | 541 (348) | 18.79 (16.72 to 20.24) | 70.2 (66.1 to 74.0) | 1.05 (0.92 to 1.20) | .462 |
| No LEV | 1,041 (676) | 19.58 (17.64 to 20.57) | 71.8 (68.9 to 74.4) | | |
| PFS | | | | | |
| LEV | 541 (456) | 7.13 (6.01 to 7.82) | 32.1 (28.1 to 36.2) | 1.14 (1.01 to 1.28) | .029 |
| No LEV | 1,041 (838) | 7.79 (7.66 to 8.08) | 34.8 (31.8 to 37.8) | | |

Abbreviations: LEV, levetiracetam; OS, overall survival; PFS, progression-free survival.
*Validation data set. Only 1 patient received LEV in EORTC NCIC trial. EORTC, European Organisation for Research and Treatment of Cancer; NCIC, NCIC Clinical Trials Group.
†LEV only v comparator.
‡Score test.

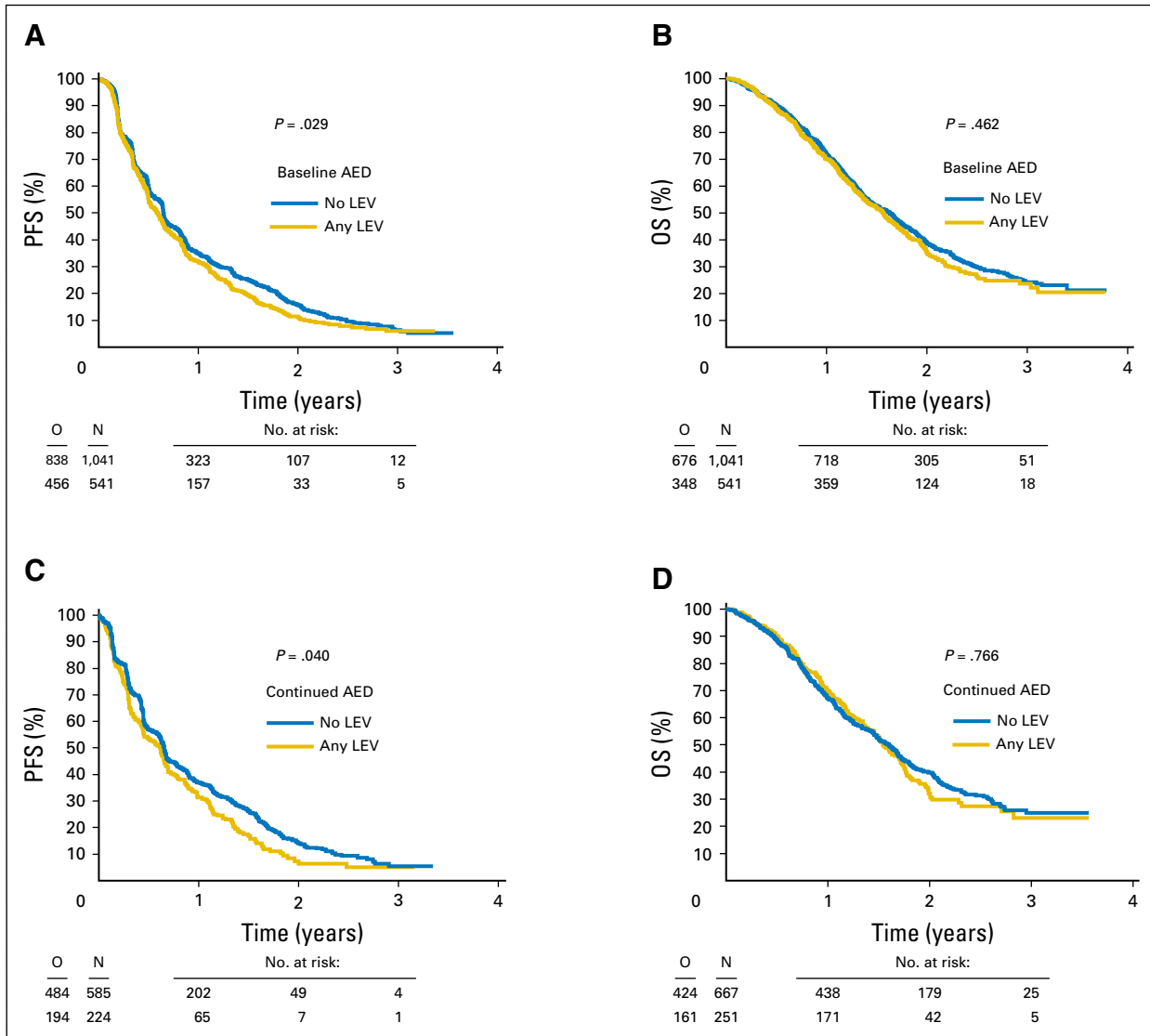


Fig 3. Prognostic significance of baseline LEV use (A and B) or continued LEV use (C and D) in the validation cohort for PFS (left) and OS (right). LEV, levetiracetam; N, number; O, observed; OS, overall survival, PFS, progression-free survival.

prospective phase III trial collecting such data and carefully defining prospective intent-to-treat versus per-protocol analyses will answer the question of intrinsic antitumor activity of AEDs in patients with newly diagnosed glioblastoma.

Neither additional single-arm trials, even if these yield encouraging outcomes, nor underpowered randomized phase II trials will provide this definitive answer. Yet, assuming that the potential benefit of VPA even with prospectively controlled exposure does not exceed that depicted in Table 2, a sample size of more than 5,000 patients would be required to confirm this limited efficacy (data not shown).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Caroline Happold, Thierry Gorlia, Michael Weller

Administrative Support: Roger Stupp

Provision of study materials or patients: Olivier Chinot, Mark R. Gilbert, L. Burt Nabors, Wolfgang Wick, Timothy Cloughesy, Patrick Roth, Minesh P. Mehta, Roger Stupp, Michael Weller

Collection and assembly of data: Caroline Happold, Thierry Gorlia, Olivier Chinot, Mark R. Gilbert, L. Burt Nabors, Stephanie L. Pugh, Monika Hegi, Timothy Cloughesy, Patrick Roth, Roger Stupp, Michael Weller

Data analysis and interpretation: Caroline Happold, Thierry Gorlia, Olivier Chinot, Mark R. Gilbert, Wolfgang Wick, Patrick Roth, David A. Reardon, James R. Perry, Minesh P. Mehta, Michael Weller

Manuscript writing: All authors

Final approval of manuscript: All authors

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GLOSSARY TERMS

HDACs (histone deacetylases): enzymes that catalyze the removal of acetyl groups from the post-translationally modified acetylated amino functions of lysine residues in histones and nonhistone proteins. HDACs act as remodeling factors and may act as transcriptional repressors. Classification of HDACs is based on sequence homology to yeast HDAC.

MGMT: the DNA repair protein, O⁶-methylguanine DNA methyltransferase, which confers resistance to alkylating agents. Thus, cells are protected from the toxicity of alkylating agents, which frequently target the O⁶ position of guanine in DNA.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Does Valproic Acid or Levetiracetam Improve Survival in Glioblastoma? A Pooled Analysis of Prospective Clinical Trials in Newly Diagnosed Glioblastoma

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Caroline Happold

Consulting or Advisory Role: Merck, Sharpe and Dohme

Thierry Gorlia

No relationship to disclose

Olivier Chinot

Honoraria: Abbvie, Bristol-Myers Squibb

Consulting or Advisory Role: Roche, Ipsen

Research Funding: Roche (Inst)

Patents, Royalties, Other Intellectual Property: Aix-Marseille University (Inst)

Travel, Accommodations, Expenses: Servier

Mark R. Gilbert

Honoraria: Merck, Genentech/Roche, Abbvie, Cell Medica, Heron Therapeutics, Wellcome Trust

Consulting or Advisory Role: Merck/Schering-Plough, Genentech/Roche, Abbvie, Heron Therapeutics, Cell Medica, Wellcome Trust

Research Funding: GlaxoSmithKline, Merck/Schering-Plough, Genentech/Roche

Travel, Accommodations, Expenses: Merck/Schering-Plough, Genentech/Roche, Abbvie

L. Burt Nabors

Consulting or Advisory Role: Cavion

Wolfgang Wick

Honoraria: Prime Oncology, Roche/Genentech, Merck Sharpe & Dohme Oncology

Consulting or Advisory Role: Roche/Genentech, Celldex

Research Funding: Roche (Inst), Apogenix (Inst), Boehringer Ingelheim (Inst)

Stephanie L. Pugh

Research Funding: Genentech/Roche (Inst)

Monika Hegi

Consulting or Advisory Role: Roche/Genentech (Inst), MDxHealth (Inst)

Speakers' Bureau: Roche

Research Funding: NovoCure (Inst)

Travel, Accommodations, Expenses: Roche

Timothy Cloughesy

Consulting or Advisory Role: Roche/Genentech, Celgene, Tocagen, VBL Therapeutics, NewGen Therapeutics, Novartis, Upsher-Smith, Proximagen, Lpath, Stemcycle, Amgen, Agios, Nektar, Abbvie, Oxigene
Expert Testimony: Roche

Patrick Roth

Consulting or Advisory Role: Roche, Merck Sharpe & Dohme, Molecular Partners

David A. Reardon

Honoraria: Abbvie, Cavion, Genentech/Roche, Merck, Midatech, Momenta Pharmaceuticals, Novartis, Novocure, Regeneron, Stemline Pharmaceuticals

Consulting or Advisory Role: Cavion, Genentech/Roche, Merck, Momenta Pharmaceuticals, Novartis, Novocure, Regeneron, Stemline Therapeutics

Speakers' Bureau: Genentech/Roche, Merck

Research Funding: Celldex (Inst), Incyte (Inst)

James R. Perry

No relationship to disclose

Minesh P. Mehta

Leadership: Pharmacyclics

Stock or Other Ownership: Pharmacyclics

Consulting or Advisory Role: Novelos, Phillips, Bristol-Myers Squibb, Celldex, Roche, Elekta, Novartis, Cavion, Novocure

Research Funding: Novocure (Inst), Cellectar (Inst)

Roger Stupp

Employment: Celgene (I)

Stock or Other Ownership: Celgene (I)

Consulting or Advisory Role: Roche/Genentech (Inst), Novartis (Inst), Merck Sharp & Dohme (Inst), Celgene, Abbvie, Ipsen, Merck KGaA

Travel, Accommodations, Expenses: Novocure

Michael Weller

Honoraria: Celldex, Merck Sharp & Dohme, Roche, Teva

Consulting or Advisory Role: ImmunoCellular Therapeutics, Isarna Therapeutics, Magforce, Merck, Northwest Biotherapeutics, Novocure, Pfizer

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Appendix

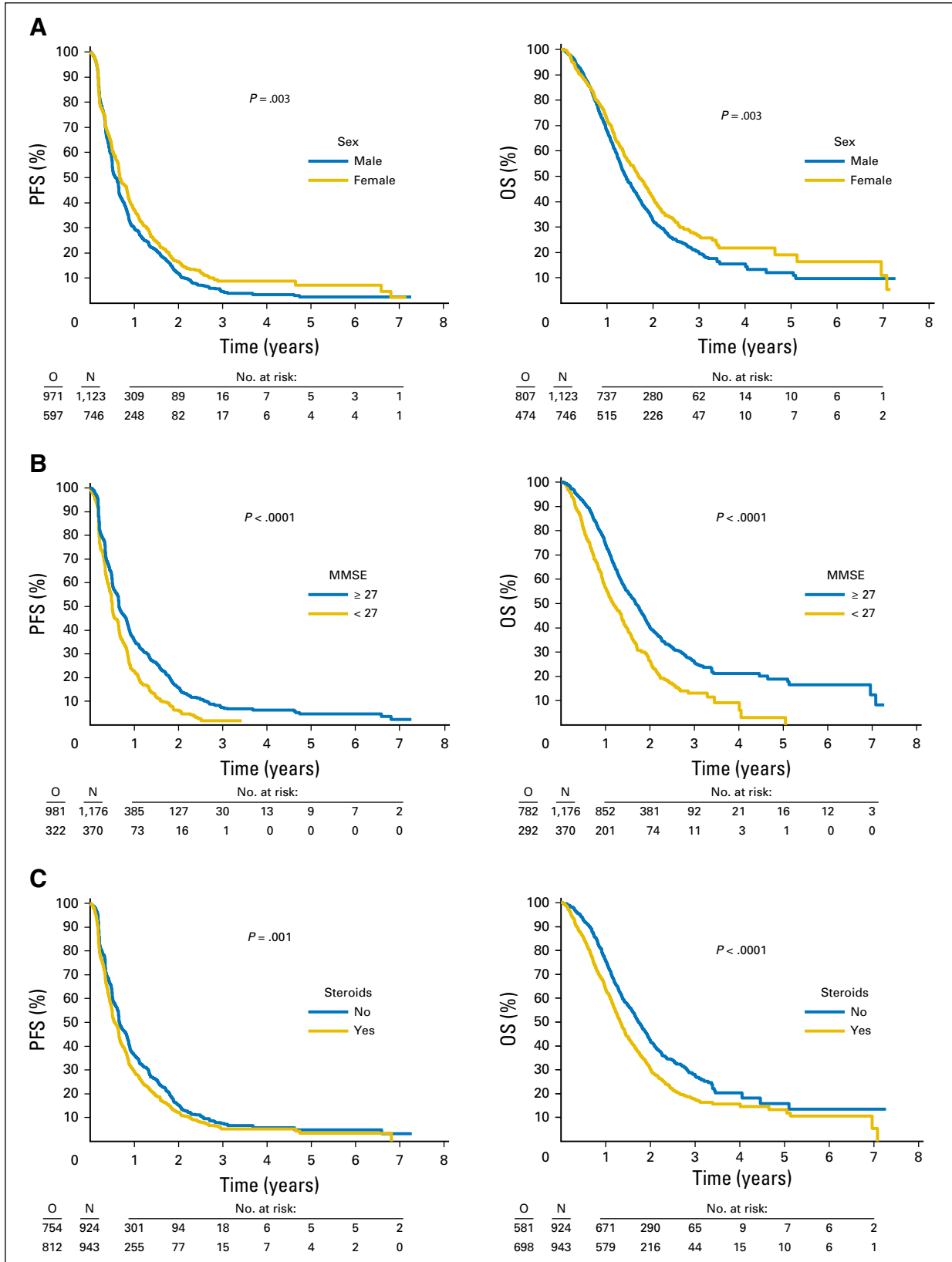


Fig A1. Prognostic factors for PFS (left) and OS (right) in the pooled cohort. (A) Sex, (B) Mini-Mental State Examination, and (C) use of steroids at study entry. N, number; O, observed; OS, overall survival; PFS, progression-free survival.

Valproic Acid in Glioblastoma

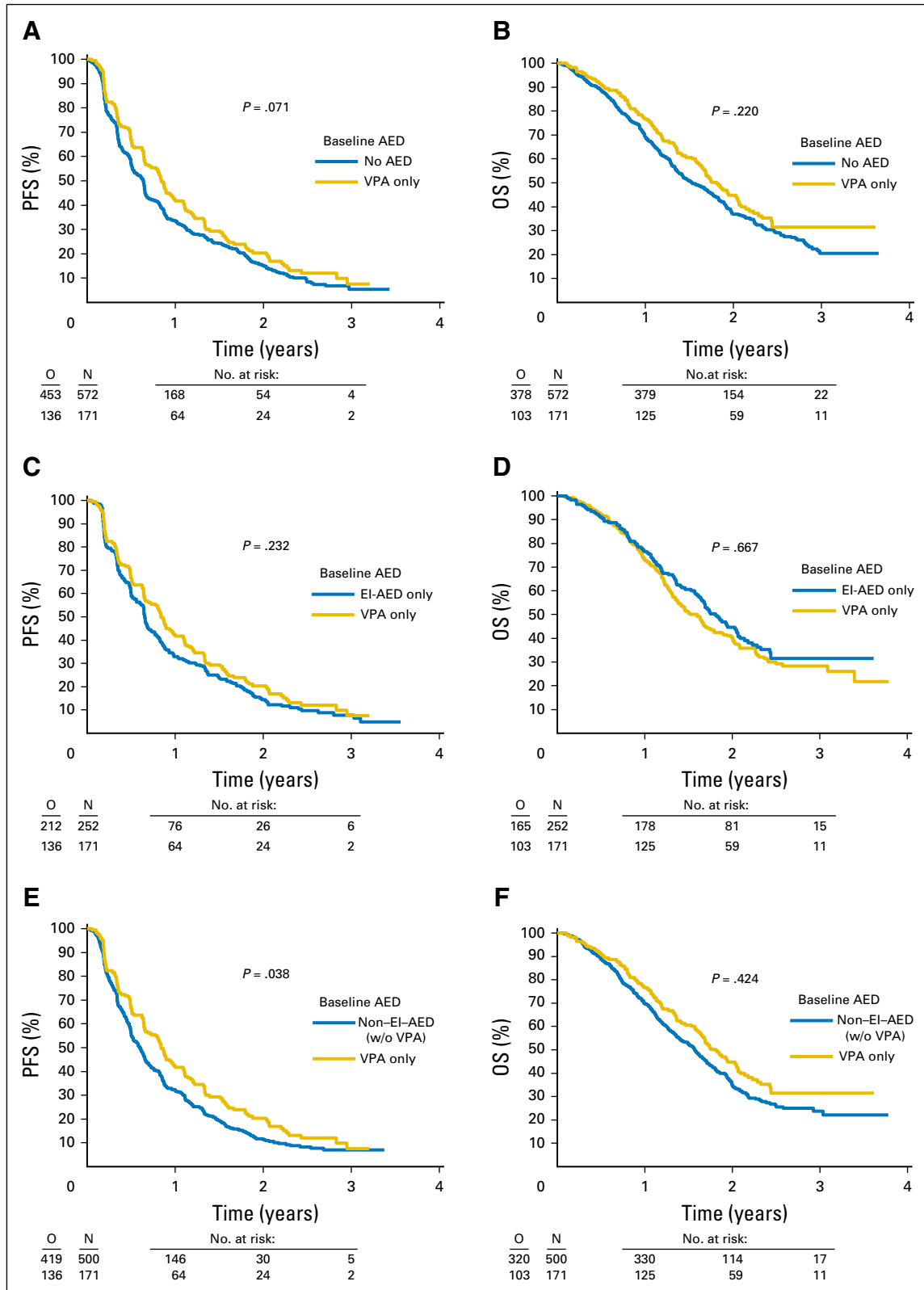


Fig A2. Prognostic significance of VPA use in the pooled cohort for PFS (left; A, C, and E) and OS (right; B, D, and F). (A and B) VPA versus no AED, (C and D) VPA versus EI-AED, and (E and F) VPA versus other non-EI-AED. AED, antiepileptic drug; EI, enzyme-inducing; N, number; O, observed; OS, overall survival; PFS, progression-free survival; VPA, valproic acid.

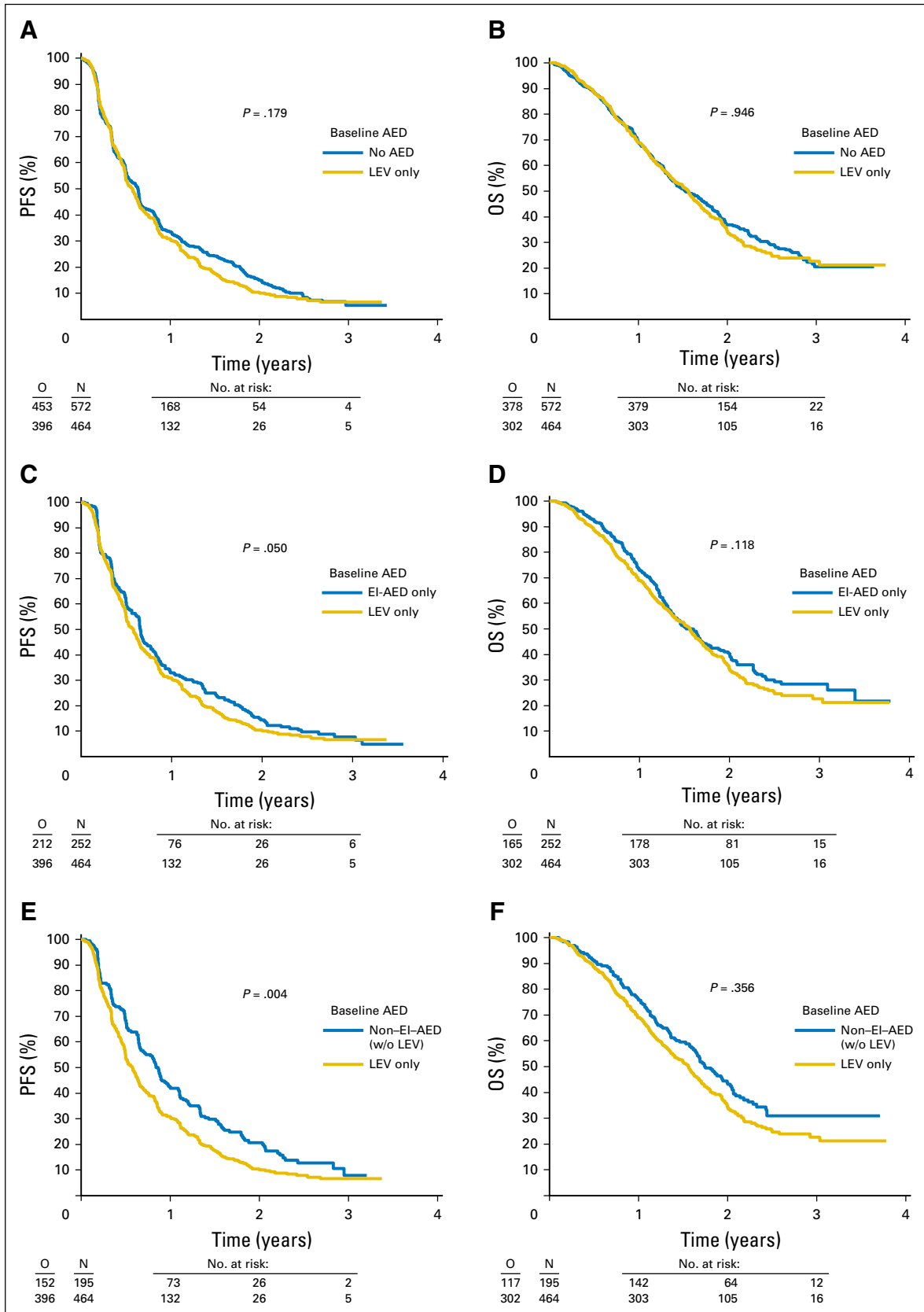


Fig A3. Prognostic significance of LEV use for PFS (left) and OS (right). (A and B) LEV versus no AED, (C and D) LEV versus EI-AED, and (E and F) LEV versus other non-EI-AED. AED, antiepileptic drug; EI, enzyme-inducing; LEV, levetiracetam; N, number; O, observed; OS, overall survival; PFS, progression-free survival.

Valproic Acid in Glioblastoma

Table A1. Association of VPA Use at Study Entry With PFS and OS: Univariate and Multivariate Analyses

| Variable | No. of Patients (No. of Events) | Median OS (95% CI) | Survival at 1 Year, % (95% CI) | Univariate Hazard Ratio* (95% CI) | P† | Multivariate Hazard Ratio* (95% CI) | P† |
|------------------------|------------------------------------|------------------------|--------------------------------------|--------------------------------------|-----|--|------|
| OS | | | | | | | |
| EORTC-NCIC | | | | | | | |
| VPA only | 49 (41) | 17.35 (14.09 to 20.37) | 71.4 (56.6 to 82.0) | | | | |
| No AED | 103 (90) | 13.96 (11.93 to 17.38) | 59.2 (49.1 to 68.0) | 0.82 (0.57 to 1.18) | .06 | 0.69 (0.46 to 1.02) | .06 |
| El-AED only | 113 (108) | 14.42 (12.06 to 16.30) | 60.2 (50.5 to 68.5) | 0.79 (0.55 to 1.14) | .20 | 0.79 (0.54 to 1.15) | .21 |
| Non-El-AED without VPA | 8 (7) | 21.7 (6.54 to 39.49) | 75.0 (31.5 to 93.1) | 1.22 (0.55 to 2.74) | .62 | 0.59 (0.23 to 1.48) | .25 |
| Validation | | | | | | | |
| VPA only | 171 (103) | 21.72 (19.35 to 24.57) | 76.6 (69.4 to 82.3) | | | | |
| No AED | 572 (378) | 18.30 (16.56 to 20.90) | 69.1 (65.1 to 72.8) | 0.87 (0.70 to 1.09) | .22 | 1.00 (0.80 to 1.25) | .95 |
| El-AED only | 252 (165) | 19.19 (16.20 to 20.96) | 72.8 (66.8 to 77.9) | 0.94 (0.73 to 1.23) | .67 | 1.02 (0.77 to 1.33) | .93 |
| Non-El-AED without VPA | 500 (320) | 18.86 (16.85 to 20.24) | 70.0 (65.7 to 73.9) | 0.91 (0.72 to 1.15) | .42 | 1.06 (0.83 to 1.35) | .67 |
| PFS | | | | | | | |
| EORTC-NCIC | | | | | | | |
| VPA only | 49 (45) | 7.66 (5.72 to 11.10) | 32.7 (20.1 to 45.8) | | | | |
| No AED | 103 (98) | 7.92 (5.22 to 9.66) | 29.1 (20.7 to 38.1) | 0.92 (0.64 to 1.30) | .63 | 0.95 (0.65 to 1.38) | .76 |
| El-AED only | 113 (112) | 5.98 (5.13 to 8.05) | 20.4 (13.5 to 28.2) | 0.76 (0.53 to 1.07) | .12 | 0.75 (0.52 to 1.08) | .12 |
| Non-El-AED without VPA | 8 (7) | 14.03 (5.82 to 28.58) | 62.5 (22.9 to 86.1) | 1.62 (0.73 to 3.60) | .24 | 0.93 (0.39 to 2.23) | .87 |
| Validation | | | | | | | |
| VPA only | 171 (136) | 10.09 (7.89 to 11.76) | 41.8 (34.0 to 49.3) | | | | |
| No AED | 572 (378) | 18.30 (16.56 to 20.90) | 69.1 (65.1 to 72.8) | 0.84 (0.69 to 1.02) | .07 | 0.92 (0.75 to 1.13) | .41 |
| El-AED only | 252 (165) | 19.19 (16.20 to 20.96) | 72.8 (66.8 to 77.9) | 0.87 (0.69 to 1.09) | .23 | 0.95 (0.74 to 1.21) | .62 |
| Non-El-AED without VPA | 500 (419) | 7.16 (6.21 to 7.85) | 32.4 (28.2 to 36.7) | 0.80 (0.65 to 0.99) | .04 | 1.02 (0.80 to 1.3) | .920 |

Abbreviations: AED, antiepileptic drug; El, enzyme-inducing; EORTC, European Organisation for Research and Treatment of Cancer; NCIC, NCIC Clinical Trials Group; OS, overall survival; PFS, progression-free survival; VPA, valproic acid.

*VPA only v comparator.

†Score test.

Table A2. Association of Continued VPA Use With PFS and OS

| Variable | No. of Patients (No. of Events) | Median OS (95% CI) | Survival at 1 Year, % (95% CI) | Hazard Ratio* (95% CI) | P† |
|--------------------|------------------------------------|------------------------|-----------------------------------|---------------------------|------|
| OS | | | | | |
| EORTC-NCIC | | | | | |
| VPA continued | 38 (32) | 15.69 (12.32 to 20.40) | 71.1 (53.9 to 82.8) | 0.85 (0.58 to 1.25) | .410 |
| No VPA | 173 (156) | 12.91 (11.27 to 14.88) | 53.8 (46.1 to 60.9) | | |
| Validation‡ | | | | | |
| VPA continued | 120 (77) | 17.91 (14.55 to 22.05) | 65.9 (56.5 to 73.7) | 1.10 (0.86 to 1.40) | .440 |
| No VPA | 808 (506) | 19.38 (18.14 to 20.60) | 68.7 (65.4 to 71.8) | | |
| PFS | | | | | |
| EORTC-NCIC | | | | | |
| VPA continued | 36 (33) | 7.16 (3.58 to 9.92) | 30.6 (16.6 to 45.7) | 0.89 (0.61 to 1.30) | .543 |
| No VPA | 168 (162) | 5.96 (5.39 to 7.69) | 26.8 (20.3 to 33.6) | | |
| Validation‡ | | | | | |
| VPA continued | 102 (88) | 9.30 (6.97 to 12.32) | 41.3 (31.6 to 50.7) | 0.92 (0.74 to 1.15) | .467 |
| No VPA | 717 (596) | 7.72 (7.10 to 8.05) | 35.5 (31.9 to 39.1) | | |

Abbreviations: AVAGlio, Avastin in Glioblastoma; CENTRIC, Cilengitide, Temozolomide, and Radiation Therapy in Treating Patients With Newly Diagnosed Glioblastoma and Methylated Gene Promoter Status; CORE, Cilengitide, Temozolomide, and Radiation Therapy in Treating Patients With Newly Diagnosed Glioblastoma and Unmethylated Gene Promoter Status; EORTC, European Organisation for Research and Treatment of Cancer; NCIC, NCIC Clinical Trials Group; OS, overall survival; PFS, progression-free survival; VPA, valproic acid.

*VPA only v comparator.

†Score test.

‡No data from Radiation Therapy Oncology Group available; CENTRIC/CORE/AVAGlio only.

Table A3. Clinical Characteristics and AED Use Per Clinical Trial Cohort: Focus on LEV Use

| Characteristic | Clinical Trial | | | | Total |
|---|----------------|------------|------------|--------------|------------|
| | EORTC 26981 | AVAGlio | RTOG 0825 | CORE/CENTRIC | |
| No. of patients | 287 | 463 | 309 | 810 | 1,869 |
| Years of study | 2000-2002 | 2009-2011 | 2009-2011 | 2008-2011 | |
| Baseline AED, n (%) | | | | | |
| No AED | 103 (35.9) | 165 (35.6) | 76 (24.6) | 331 (40.9) | 675 (36.1) |
| EI-AED only | 113 (39.4) | 104 (22.5) | 47 (15.2) | 101 (12.5) | 365 (19.5) |
| EI-AED plus LEV | 0 (0.0) | 17 (3.7) | 10 (3.2) | 10 (1.2) | 37 (2.0) |
| EI-AED plus non-EI-AED without LEV | 9 (3.1) | 18 (3.9) | 0 (0.0) | 4 (0.5) | 31 (1.7) |
| LEV only | 1 (0.3) | 97 (21.0) | 163 (52.8) | 204 (25.2) | 465 (24.9) |
| LEV plus another non-EI-AED | 0 (0.0) | 15 (3.2) | 2 (0.6) | 20 (2.5) | 37 (2.0) |
| Non-EI-AED without LEV | 57 (19.9) | 46 (9.9) | 10 (3.2) | 139 (17.2) | 252 (13.5) |
| EI-AED plus LEV plus another non-EI-AED | 1 (0.3) | 1 (0.2) | 1 (0.3) | 1 (0.1) | 4 (0.2) |
| Missing | 3 (1.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.2) |

Abbreviations: AED, antiepileptic drug; AVAGlio, Avastin in Glioblastoma; CENTRIC, Cilengitide, Temozolomide, and Radiation Therapy in Treating Patients With Newly Diagnosed Glioblastoma and Methylated Gene Promoter Status; CORE, Cilengitide, Temozolomide, and Radiation Therapy in Treating Patients With Newly Diagnosed Glioblastoma and Unmethylated Gene Promoter Status; EI, enzyme-inducing; EORTC, European Organisation for Research and Treatment of Cancer; LEV, levetiracetam; RTOG, Radiation Therapy Oncology Group.

Table A4. Association of LEV Use at Study Entry With PFS and OS: Univariate and Multivariate Analyses*

| Variable | No. of Patients (No. of Events) | Median OS (95% CI) | Survival at 1 Year, % (95% CI) | Univariate Hazard Ratio† (95% CI) | Univariate P‡ | Multivariate Hazard Ratio† (95% CI) | Multivariate P‡ |
|------------------------|---------------------------------|------------------------|--------------------------------|-----------------------------------|---------------|-------------------------------------|-----------------|
| OS | | | | | | | |
| LEV only | 464 (302) | 18.69 (16.62 to 20.11) | 69.1 (64.6 to 73.2) | | | | |
| No AED | 572 (378) | 18.30 (16.56 to 20.90) | 69.1 (65.1 to 72.8) | 0.99 (0.85 to 1.16) | .95 | 0.96 (0.82 to 1.13) | .58 |
| EI-AED only | 252 (165) | 19.19 (16.20 to 20.96) | 72.8 (66.8 to 77.9) | 1.17 (0.96 to 1.42) | .12 | 1.14 (0.93 to 1.39) | .21 |
| Non-EI-AED without LEV | 195 (117) | 20.99 (19.12 to 24.34) | 76.3 (69.6 to 81.7) | 1.11 (0.89 to 1.40) | .36 | 0.94 (0.75 to 1.19) | .59 |
| PFS | | | | | | | |
| LEV only | 464 (396) | 6.90 (5.98 to 7.62) | 31.0 (26.7 to 35.4) | | | | |
| No AED | 572 (453) | 7.62 (6.31 to 7.85) | 33.5 (29.5 to 37.6) | 1.10 (0.96 to 1.27) | .18 | 1.08 (0.94 to 1.25) | .32 |
| EI-AED only | 252 (212) | 7.85 (6.70 to 8.80) | 32.8 (26.9 to 38.9) | 1.19 (1.00 to 1.41) | .05 | 1.13 (0.95 to 1.35) | .18 |
| Non-EI-AED without LEV | 195 (152) | 10.09 (7.92 to 11.76) | 42.0 (34.7 to 49.1) | 1.34 (1.10 to 1.64) | .004 | 1.19 (0.97 to 1.47) | .10 |

Abbreviations: AED, antiepileptic drug; EI, enzyme-inducing; LEV, levetiracetam; OS, overall survival; PFS, progression-free survival; VPA, valproic acid.
 *Validation data set. Only 1 patient received LEV in EORTC NCIC trial. EORTC, European Organisation for Research and Treatment of Cancer; NCIC, NCIC Clinical Trials Group.
 †LEV only v comparator.
 ‡Score test.

Table A5. Association of Continued LEV Use With PFS and OS in the Validation Cohort*

| Variable | No. of Patients (No. of Events) | Median OS (95% CI) | Survival at 1 Year, % (95% CI) | Hazard Ratio† (95% CI) | P‡ |
|---------------|---------------------------------|------------------------|--------------------------------|------------------------|------|
| OS | | | | | |
| Validation§ | | | | | |
| LEV continued | 251 (161) | 18.53 (16.46 to 20.60) | 69.9 (63.7 to 75.2) | 0.97 (0.81 to 1.17) | .766 |
| No LEV | 667 (424) | 19.22 (17.48 to 20.34) | 67.2 (63.4 to 70.6) | | |
| PFS | | | | | |
| Validation§ | | | | | |
| LEV continued | 224 (194) | 7.36 (5.32 to 8.05) | 31.3 (25.2 to 37.5) | 1.19 (1.01 to 1.41) | .040 |
| No LEV | 585 (484) | 7.85 (7.36 to 8.15) | 37.0 (33.0 to 41.0) | | |

Abbreviations: LEV, levetiracetam; OS, overall survival; PFS, progression-free survival.
 *Validation data set. Only 1 patient received LEV in EORTC NCIC trial. EORTC, European Organisation for Research and Treatment of Cancer; NCIC, NCIC Clinical Trials Group.
 †LEV only v comparator.
 ‡Score test.
 §No data from Radiation Therapy Oncology Group available; CENTRIC/CORE/AVAGLIO only.