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ORIGINAL REPORT

Patients With Proneural Glioblastoma May Derive Overall Survival Benefit From the Addition of Bevacizumab to First-Line Radiotherapy and Temozolomide: Retrospective Analysis of the AVAglio Trial

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ABSTRACT

Purpose

The AVAglio (Avastin in Glioblastoma) and RTOG-0825 randomized, placebo-controlled phase III trials in newly diagnosed glioblastoma reported prolonged progression-free survival (PFS), but not overall survival (OS), with the addition of bevacizumab to radiotherapy plus temozolomide. To establish whether certain patient subgroups derived an OS benefit from the addition of bevacizumab to first-line standard-of-care therapy, AVAglio patients were retrospectively evaluated for molecular subtype, and bevacizumab efficacy was assessed for each patient subgroup.

Patients and Methods

A total of 349 pretreatment specimens (bevacizumab arm, n = 171; placebo arm, n = 178) from AVAglio patients (total, N = 921) were available for biomarker analysis. Samples were profiled for gene expression and isocitrate dehydrogenase 1 (*IDH1*) mutation status and classified into previously identified molecular subtypes. PFS and OS were assessed within each subtype.

Results

A multivariable analysis accounting for prognostic covariates revealed that bevacizumab conferred a significant OS advantage versus placebo for patients with proneural *IDH1* wild-type tumors (17.1 *v* 12.8 months, respectively; hazard ratio, 0.43; 95% CI, 0.26 to 0.73; $P = .002$). This analysis also revealed an interaction between the proneural subtype biomarker and treatment arm ($P = .023$). The group of patients with mesenchymal and proneural tumors derived a PFS benefit from bevacizumab compared with placebo; however, this translated to an OS benefit in the proneural subset only.

Conclusion

Retrospective analysis of AVAglio data suggests that patients with *IDH1* wild-type proneural glioblastoma may derive an OS benefit from first-line bevacizumab treatment. The predictive value of the proneural subtype observed in AVAglio should be validated in an independent data set.

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INTRODUCTION

Glioblastoma is the most common and aggressive form of adult primary brain tumor.[1] Surgical resection and radiotherapy have been the standard of care since the 1970s. Temozolomide, the only approved chemotherapy for newly diagnosed glioblastoma, was incorporated into standard-of-care treatment in 2005, increasing median overall survival (OS) from 12.1 to 14.6 months versus radiotherapy alone.[2,3] Despite this, prognosis remains poor; almost all patients experience recurrence after first-line treatment, often within 6 months of diagnosis, and the 2-year survival rate is just 27%.[4] No further survival improvement has been documented since the introduction of temozolomide. Although O^6-methylguanine–DNA methyltransferase (MGMT) promoter methylation has been validated as a predictive marker for temozolomide survival benefit,[3,5,6] the utility of this marker is limited, because effective alternatives are lacking. New therapies that confer longer OS are needed.

Glioblastoma is distinguished from lower-grade glioma by its microvascular proliferation. Glioblastomas are highly vascularized and express

elevated vascular endothelial growth factor (VEGF), which plays a key role in tumor neovascularization and growth.[7] The humanized anti-VEGF monoclonal antibody bevacizumab (Avastin; Genentech, South San Francisco, CA) has been approved for multiple oncologic indications.[8] Its efficacy, however, varies across tumor types and patients; factors relating progression-free survival (PFS) and OS to anti-VEGF therapy are poorly understood. Predictive biomarkers to improve patient selection are needed.

Bevacizumab has been approved for recurrent glioblastoma treatment as monotherapy, combination therapy, or both in > 60 countries based on response rate and PFS. Two randomized phase III trials—AVAglio (Avastin in Glioblastoma) and RTOG-0825 (Radiation Therapy Oncology Group 0825)—investigated the addition of bevacizumab to standard-of-care therapy in newly diagnosed glioblastoma.[9,10] Both studies reported longer median PFS with bevacizumab versus placebo (AVAglio: 10.6 *v* 6.2 months; hazard ratio [HR], 0.64; RTOG 0825: 10.7 *v* 7.3 months; HR, 0.79).[9,10] The increased PFS did not translate into an expected OS benefit in the intent-to-treat population in either study, making interpretation of the clinical relevance of the PFS gain the subject of debate.[11] Analysis of well-established prognostic factors did not reveal an OS benefit with bevacizumab for any patient subgroups.

Although glioblastoma is managed as a single disease, tumors are heterogeneous, with differential prognoses. For example, glioblastomas with isocitrate dehydrogenase 1 (*IDH1*) mutations and/or CpG island methylator phenotype are considered a distinct disease entity (more closely related to lower-grade diffuse glioma) and typically have better prognosis than de novo glioblastomas.[12,13] In addition, glioblastoma gene expression signatures can group tumors into distinct histologic, radiographic, and mutation subtypes.[14-18] Although published gene expression classification schemes differ in the number of identified subtypes, there is consensus on the hallmarks of proneural and mesenchymal subtypes.[19] Mesenchymal glioblastomas have higher VEGF/angiogenic marker expression than proneural tumors; accordingly, these glioblastoma subsets may differ in their response to antiangiogenic agents.

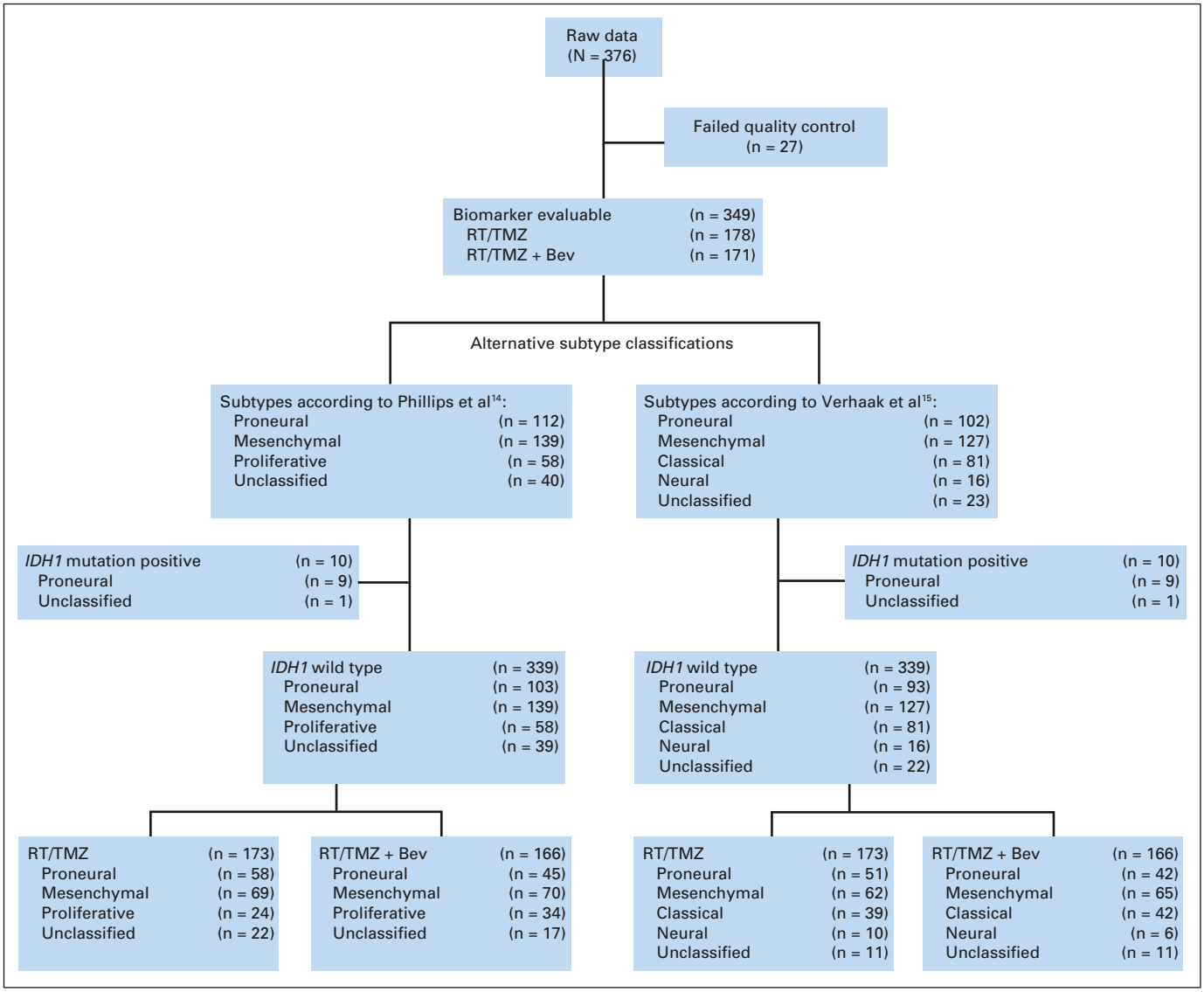

Fig 1. Patient flow. Bev, bevacizumab; RT, radiotherapy; TMZ, temozolomide.

The relationship between molecular subtypes and survival was an exploratory end point in AVAglio; because glioblastoma molecular subtypes may represent disease variants with differential sensitivity to bevacizumab, we analyzed gene expression patterns in archival tumor samples, assigned subtypes, and explored the relationship with outcomes.

PATIENTS AND METHODS

Study Design and Sample Collection

AVAglio (ClinicalTrials.gov identifier NCT00943826) was a randomized, double-blind, placebo-controlled phase III trial sponsored by F. Hoffmann-La Roche and conducted in accordance with the Declaration of Helsinki. The study design was published previously.[9] Patients (age ≥ 18 years with newly diagnosed supratentorial glioblastoma and WHO performance score [PS] ≤ 2) were randomly assigned at a ratio of 1:1 to receive radiotherapy and temozolomide plus either bevacizumab or placebo. PFS and OS were coprimary end points.[9]

Baseline formalin-fixed, paraffin-embedded (FFPE) tumor samples were collected from patients who consented to participate in exploratory translational research. Selection of the most appropriate samples (ie, those with sufficient tissue) was carried out by the same two neuropathologists. Extended histologic evaluation of hematoxylin phloxine saffron–stained tissue was performed by the local pathologist, who selected the most suitable block for further analysis (if > one was available). Of 484 consenting patients, 376 had sufficient material for analysis. Tumors were microdissected to minimize the amount of adjacent normal tissue/RNA included in the gene expression analysis. FFPE tissue blocks were sectioned (4 to 6 microns) and stored on slides at room temperature. After nucleic acid extraction, concentrated RNA and DNA solutions were stored at −70°C.

Determination of IDH1 Mutation Status

IDH1 mutation status was determined by DNA sequencing (Sequenom assay; Sequenom, San Diego, CA[12]) and immunohistochemistry using an antibody to *IDH1R132H*.[20]

NanoString Gene Expression Data Generation

Genes were selected from the literature to allow glioblastoma subtype identification defined in two independent studies[14,15] using a custom code set

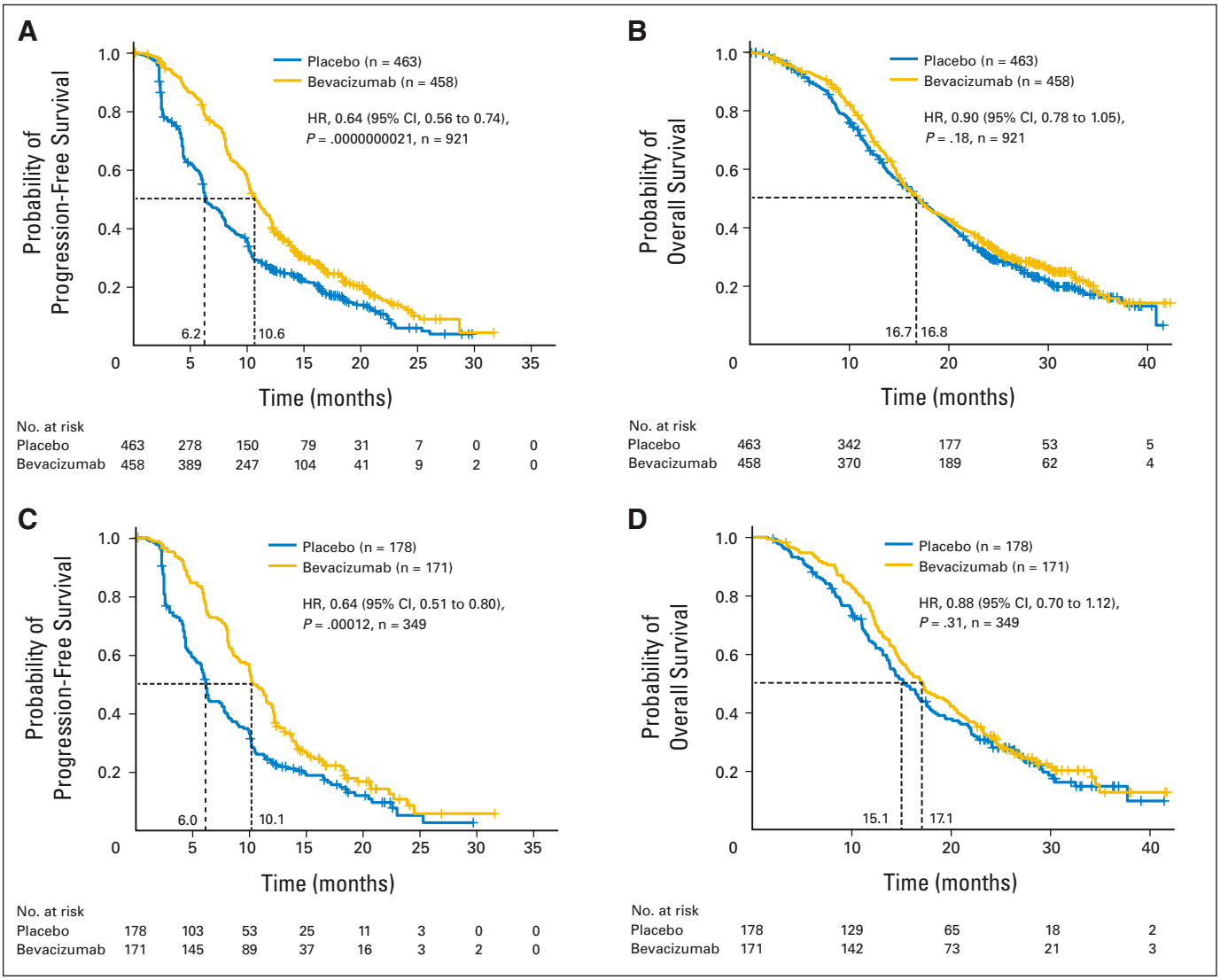

Fig 2. Kaplan-Meier plots in (A, B) intent-to-treat and (C, D) biomarker-evaluable populations of (A, C) progression-free and (B, D) overall survival (generated using survival R package[23]). Dashed lines indicate medians. Bevacizumab refers to bevacizumab arm of AVAglio (bevacizumab plus radiotherapy plus temozolomide); placebo refers to placebo arm (placebo plus radiotherapy plus temozolomide). HR, hazard ratio.

for the NanoString gene expression platform (NanoString Technologies, Seattle, WA)[21] (Data Supplement). Subtypes were defined before the analyses. Subtype labels were assigned to tumor samples on the basis of gene expression values only (ie, without treatment arm assignment/other clinical data).

Analyses were performed using the R programming language (version 3.1; http://www.r-project.org). Raw counts for 376 tumor samples were log2 transformed, normalized (common mean and standard deviation for all samples), and gene-wise expression scores were further standardized across all samples by transformation to *z* scores.

Quality control failures were flagged based on the first principal component of normalized counts; 27 outlier samples were identified. These yielded low overall counts, indicating insufficient input material or another source of assay failure (Data Supplement) and were removed from further analysis, leaving 349 biomarker-evaluable samples.

Gene Expression Subtype Classification

Published gene expression subtypes were originally established using microarrays.[14,15] To adapt the classification to the Nanostring platform, we used a reference collection of 47 fresh-frozen, nontrial, newly diagnosed glioblastoma samples analyzed on both Affymetrix microarrays (Affymetrix, Santa Clara, CA) and the NanoString platform. Microarray data and subtype classification according to the method of Phillips et al[14] were published for the 47 reference samples.[12] To obtain subtype labels for these samples according to the Verhaak classification,[15] we obtained raw Affymetrix microarray data and associated subtype assignments for the Cancer Genome Atlas (TCGA) samples.[15] Raw microarray data from TCGA and our 47 reference samples were normalized (RefPlus R package).[22] We determined the mean expression of 840 classifier genes in each Verhaak et al[15] subtype using the subtype labels published by TCGA. We compared the normalized expression scores from our 47 reference samples with these centroids and assigned each sample to the subtype showing the highest Pearson correlation. Samples without positive correlation with any subtype were unclassified.

The 47 reference samples were analyzed on the NanoString platform and normalized. The NanoString code set featured probes for 31 of 35 classifier genes defined by Phillips et al,[14] including all original markers with gene symbols that could be unambiguously associated with a National Center for Biotechnology Information Entrez gene identifier. For Verhaak et al[15] classification, 105 of 834 original classifier genes with gene symbols that could be

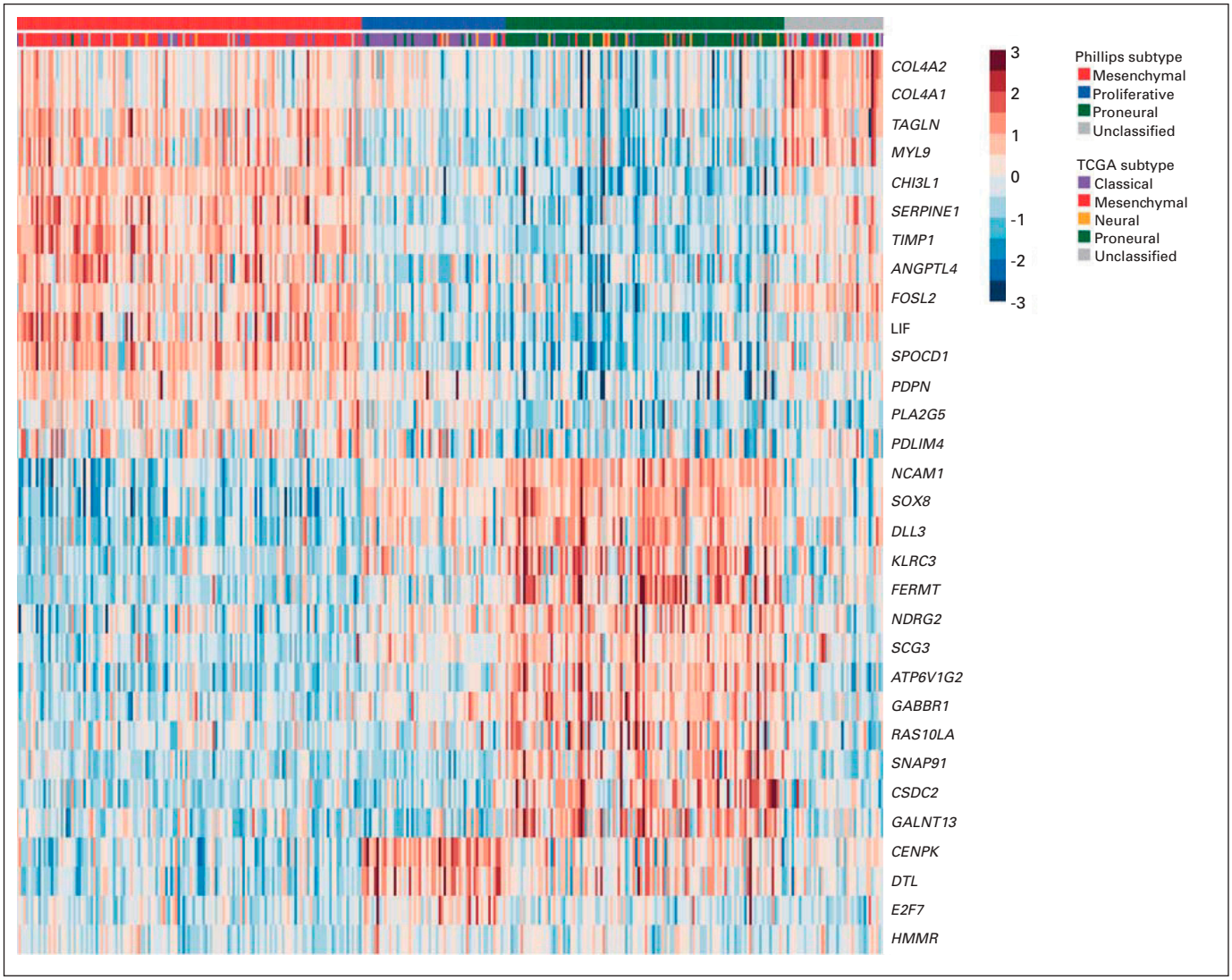

Fig 3. Classification of AVAglio patients into Phillips et al[14] proneural, proliferative, and mesenchymal subtypes. Heatmap shows gene expression (*z* scores) of 31 classifier genes identified by Phillips et al. Genes (rows) were clustered using Pearson correlation distance and Ward's hierarchical clustering. Samples (columns) were grouped by Phillips et al subtype but not otherwise clustered. Column annotations show glioblastoma subtypes assigned using genes defined by Phillips et al (first row) or The Cancer Genoma Atlas (TCGA; second row).

unambiguously associated with a National Center for Biotechnology Information Entrez gene identifier were represented on the NanoString platform, including 11 genes also featured in the Phillips et al[14] list. Information about the probes used for classification is available in the Data Supplement.

To establish NanoString-specific centroids for glioblastoma subtypes, reference samples were split according to the subtype labels obtained from analyzing the corresponding microarray data, and the mean expression of each classifier gene within each subtype was calculated. To classify the AVAglio samples, the normalized expression of the Phillips et al[14] or Verhaak et al[15] classifier genes of each sample was compared with the reference sample centroids; the sample was assigned to the subtype with the centroid that showed the highest Pearson correlation. Samples without positive correlation to any reference sample centroid were unassigned.

Outcome Analyses

No effect size was prespecified. An α level of 0.05 was prespecified as significant for the difference between treatment arms. Outcome analyses used Kaplan-Meier plots and Cox proportional hazards models (survival R package).[23] Log-rank *P* values for OS and PFS differences between treatment arms were adjusted for multiple testing (Phillips et al[14] subtypes, n = 4; TCGA subtypes, n = 5) by controlling the family-wise error rate according to Hochberg et al.[24]

Cox proportional hazards models included the following covariates unless noted otherwise: age, corticosteroid use (off [dexamethasone equivalent < 2 mg within 5 days of first trial treatment] *v* on [dexamethasone equivalent ≥ 2 mg within 5 days of first treatment), surgical status, Karnofsky PS, MGMT status (missing, methylated, or nonmethylated), Mini–Mental State Examination score, recursive partitioning analysis class, WHO PS, and sex. Six samples, which were missing ≥ one clinical covariate, were excluded from the multivariable analyses. Variables examined but not included in the final model were residual tumor at baseline, tumor size at baseline, and bevacizumab treatment after progression. Because the interval between surgery and treatment for the biomarker-evaluable population was uniform (4 to 7 weeks for 324 [95.6%] of 339 patients), this covariate was not included in the multivariable analyses.

RESULTS

Sample Analysis and Biomarker-Evaluable Population

Analysis of nontrial glioblastoma samples revealed robust correlations between gene expression measurements from fresh-frozen material from NanoString and Affymetrix microarrays as well as between fresh-frozen and FFPE samples assayed on the NanoString platform (Data Supplement).

RNA was obtained from 376 archival AVAglio FFPE tumor samples; high-quality data were obtained from 349 samples (biomarker-evaluable population; bevacizumab arm, n = 171; placebo arm, n = 178; Data Supplement). Patient flow through the study is shown in Figure 1. PFS, OS, and clinical characteristics in the biomarker-evaluable population were similar to those of the intent-to-treat population (Fig 2; Data Supplement).[9] Analysis of known mutations at codon 132 in the *IDH1* locus revealed activating variants in tumors from 10 patients (five per arm). Patients who had tumors with *IDH1* mutations were considered a patient subset with a more favorable prognosis and were therefore excluded from outcome analyses (Data Supplement).

Tumor Subtypes

Applying the Phillips et al[14] subtype classifier produced 112 proneural (32.1%), 139 mesenchymal (39.8%), and 58 proliferative samples (16.6%). Forty samples (11.5%) were unclassified. As reported for microarray-based classification,[16] there was high concordance between the Phillips et al and TCGA proneural and mesenchymal subtypes (Fig 3; Data Supplement). The classical TCGA subtype contained the majority of samples classified as proliferative by the Phillips et al classifier but also featured other Phillips et al subtypes.

The 31 Phillips et al classifier genes displayed high correlation within each subtype (Fig 3), as well as with an extended set of 128 additional genes originally reported but not used for classification (Data Supplement).[14] Robust correlation was observed between TCGA classifier genes delineating proneural, mesenchymal, and classical subtypes (Data Supplement).

Univariable Analysis

Outcome analyses were performed on the biomarker-evaluable population stratified into Phillips et al[14] subtypes. A complementary data set was obtained with TCGA classification (Data Supplement).

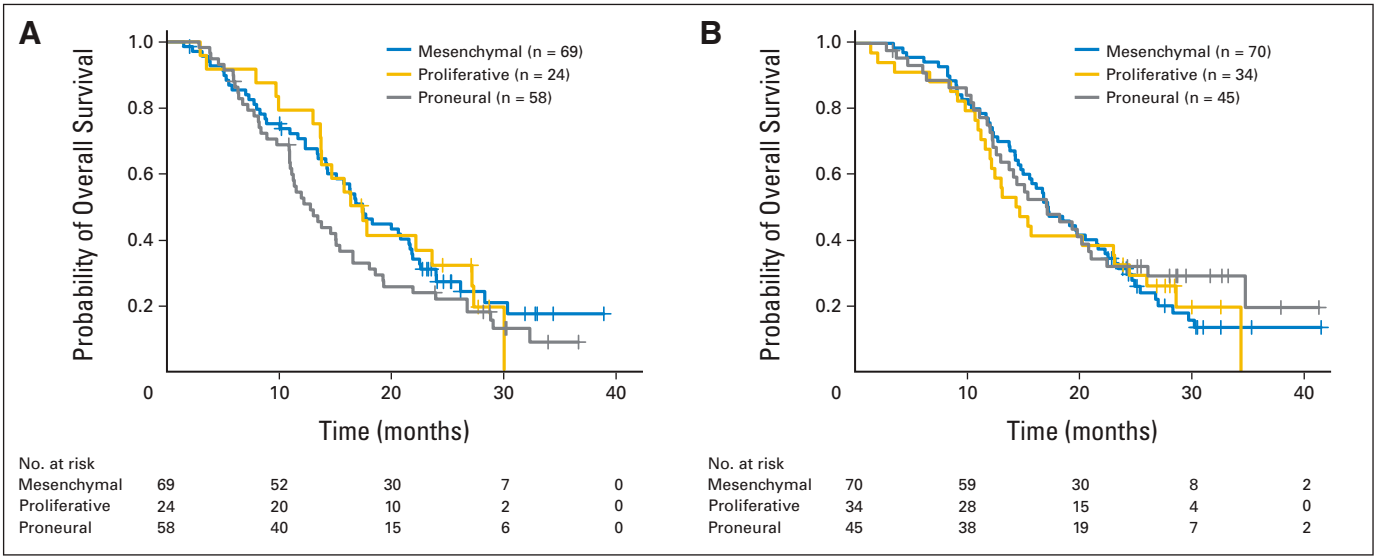

Fig 4. Kaplan-Meier plots of overall survival stratified by Phillips et al[14] subtype for (A) placebo and (B) bevacizumab arms. Only patients with *IDH1* wild-type tumors are shown; unclassified samples omitted for clarity.

First, we explored potential differences between Phillips et al[14] subtypes without considering other known prognostic covariates. After excluding *IDH1* mutation–positive samples, we observed a median OS of 12.2 months for patients with proneural tumors in the placebo arm (Fig 4A), shorter than that of the mesenchymal (17.4 months), proliferative (16.9 months), or unclassified subtype (13.0 months). However, an overall test for any OS difference did not achieve statistical significance (log-rank $P = .408$). In contrast, no differences in median OS were observed in the bevacizumab arm (Fig 4B). Taken together, these results hint at a potential subtype-specific treatment effect.

All four Phillips et al[14] subtypes showed trends for increased PFS in the bevacizumab arm versus placebo (Fig 5; Data Supplement). However, after adjusting for multiple testing[24] (n = 4 subtypes), the PFS increase was only significant for two subtypes: proneural (9.9 *v* 5.7 months, respectively; HR, 0.57; 95% CI, 0.37 to 0.89; adjusted log-rank $P = .036$; n = 103) and mesenchymal (10.1 *v* 5.8 months, respectively; HR, 0.57; 95% CI, 0.40 to 0.82; adjusted log-rank $P = .0076$).

To test for a potential predictive association between gene expression subtype and effect of bevacizumab treatment, we compared OS between treatment arms for each subtype. Patients with mesenchymal tumors had similar OS in both arms (bevacizumab, 17.2 months *v* placebo, 17.4 months; HR, 0.98; 95% CI, 0.67 to 1.45; log-rank $P = .929$; n = 139; Fig 6). In contrast, patients with proneural tumors, who had relatively short median OS in the placebo arm, showed longer OS with bevacizumab treatment (17.1 *v* 12.8 months for placebo; HR, 0.63; 95% CI, 0.41 to 0.99; log-rank $P = .045$; adjusted log-rank $P = .18$; n = 103). This initial univariable analysis did not incorporate relevant prognostic covariates and did not stand up to multiple-testing correction (by four molecular subtypes tested). Nonetheless, this suggested a potential bevacizumab effect. Neither patients with the proliferative subtype nor those with unclassified tumors showed any evidence of an OS effect of bevacizumab treatment (Fig 6). Similar

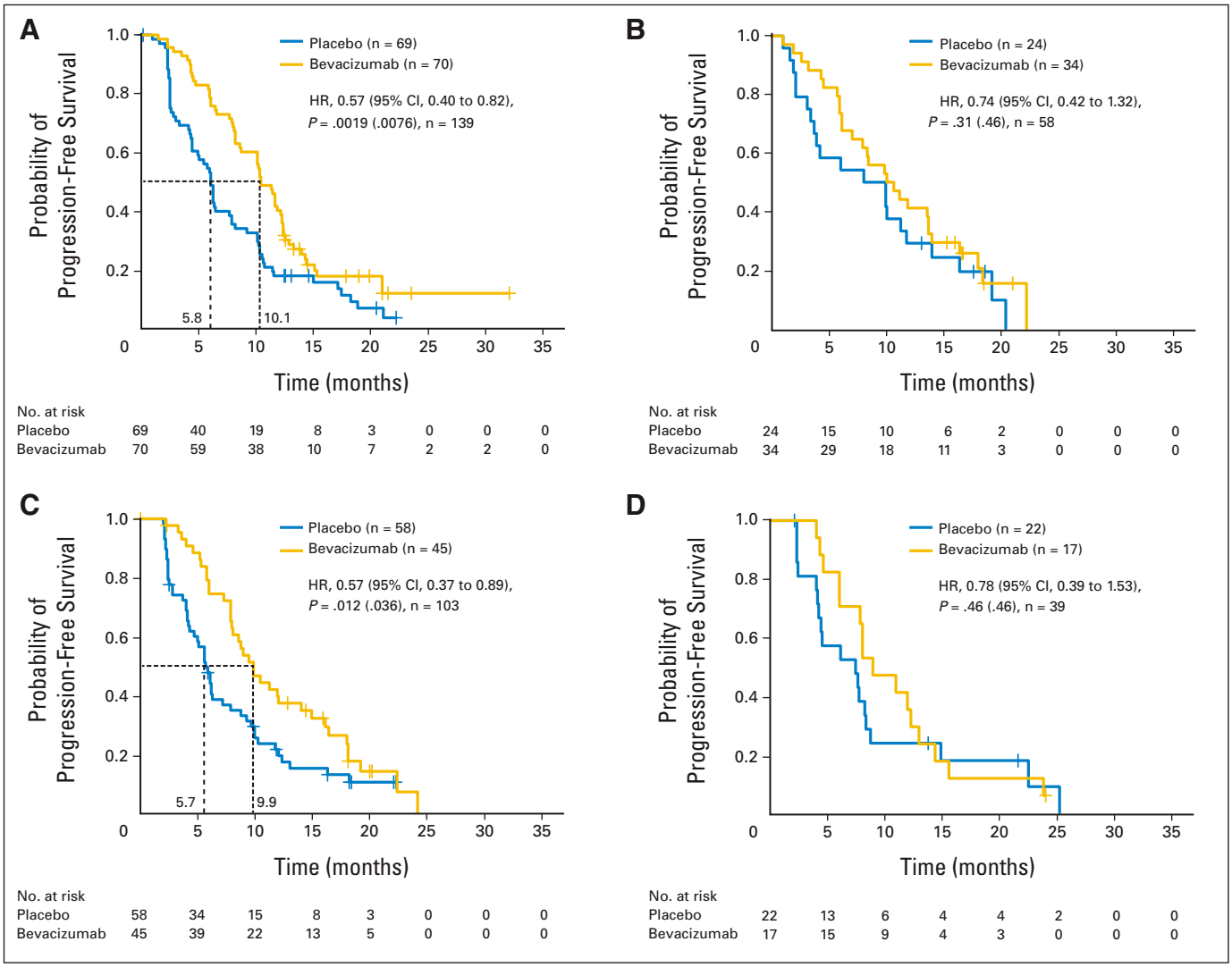

Fig 5. Progression-free survival stratified by Phillips et al[14] subtypes and treatment arm: (A) mesenchymal, (B) proliferative, (C) proneural, and (D) unclassified. Only patients with *IDH1* wild-type tumors were included. Hazard ratios (HRs) with 95% CIs and nominal and adjusted *P* values[24] are indicated for each subtype. Dashed lines indicate medians. Bevacizumab refers to bevacizumab arm of AVAglio (bevacizumab plus radiotherapy plus temozolomide); placebo refers to placebo arm (placebo plus radiotherapy plus temozolomide). Medians not reported for (B) or (D) because of small patient numbers.

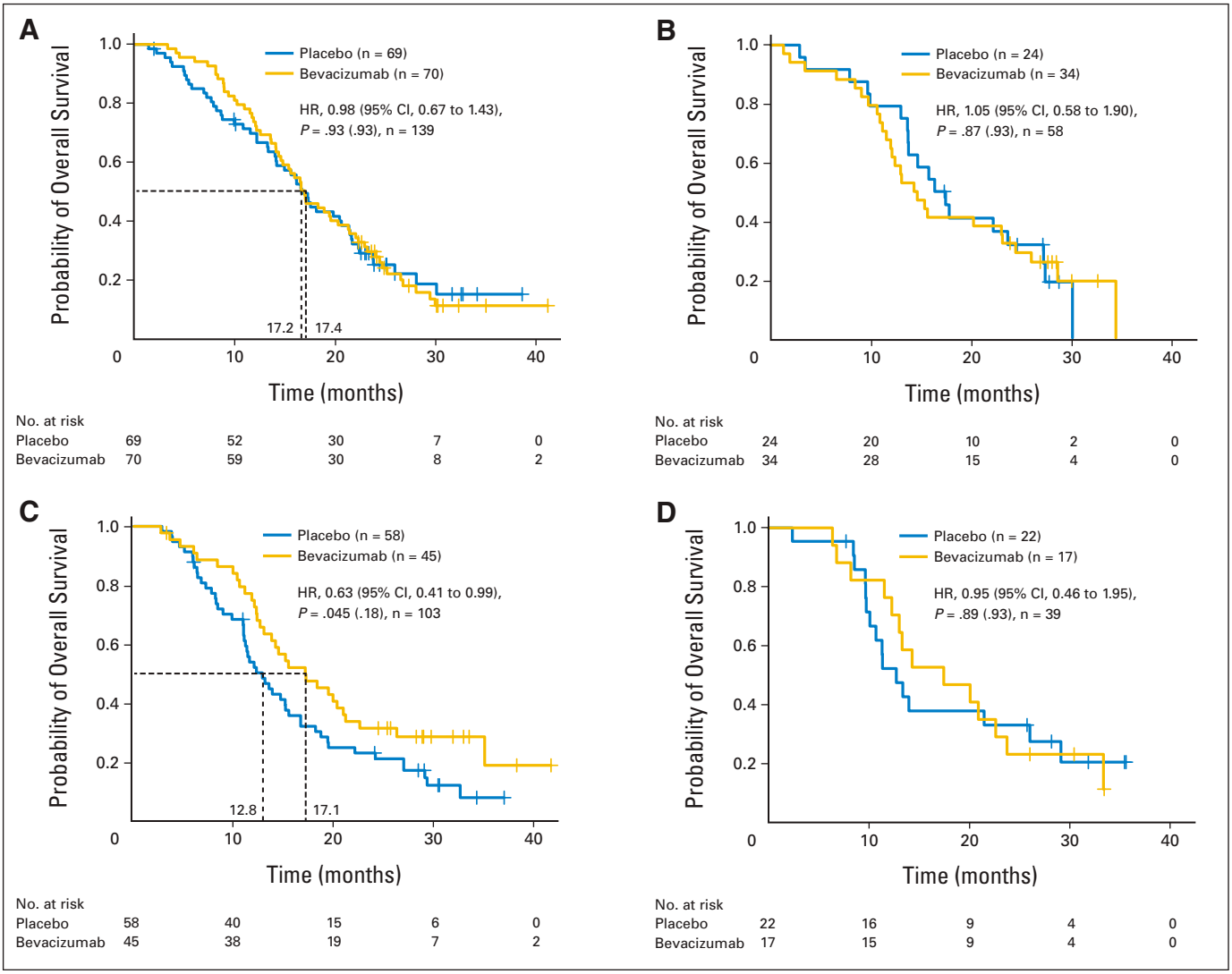

Fig 6. Overall survival stratified by Phillips et al[14] subtype and treatment arm: (A) mesenchymal, (B) proliferative, (C) proneural, and (D) unclassified. Only patients with *IDH1* wild-type tumors were included. Hazard ratios (HRs) with 95% CIs and nominal and adjusted *P* values[24] are indicated for each subtype. Dashed lines indicate medians. Bevacizumab refers to bevacizumab arm of AVAglio (bevacizumab plus radiotherapy plus temozolomide); placebo refers to placebo arm (placebo plus radiotherapy plus temozolomide). Medians not reported for (B) or (D) because of small patient numbers.

results were obtained for TCGA proneural and mesenchymal subtypes (Data Supplement).

Multivariable Analysis

To refine these preliminary results and provide a more definitive assessment of the relevance of the proneural subtype with regard to OS, we divided classifier results into proneural versus nonproneural and incorporated clinical covariates, some of which were known prognostic factors in glioblastoma, into our analysis. We tested the proneural biomarker hypothesis with a multivariable Cox proportional hazards model and found that adding bevacizumab to radiotherapy plus temozolomide conferred a significant OS advantage for patients with *IDH1* wild-type proneural tumors (HR, 0.42; 95% CI, 0.25 to 0.71; $P = .001$; Fig 7A). In patients with nonproneural *IDH1* wild-type tumors, there was no evidence of any OS effect (HR, 1.00; 95% CI, 0.74 to 1.36; $P = .985$; Fig 7B). Formal testing for the interaction between the proneural *IDH1* wild-type subtype and treatment arm confirmed the predictive value of the biomarker for selective OS benefit ($P = .023$).

Similar results were obtained after stratifying patients into TCGA proneural and nonproneural subtypes. An OS advantage was observed for patients with *IDH1* wild-type proneural tumors (bevacizumab, 14.5 months *v* placebo, 11.5 months; HR, 0.43; 95% CI, 0.25 to 0.74; $P = .002$; n = 93; Data Supplement) but not nonproneural subtypes (HR, 1.04; 95% CI, 0.77 to 1.41; $P = .801$; n = 246; Data Supplement). Again, a significant interaction was observed between the TCGA-based proneural subtype biomarker and treatment arm ($P = .007$).

The raw and processed data are deposited in the Gene Expression Omnibus database (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE84010).

DISCUSSION

In some cancers (eg, colorectal, non–small-cell lung, and cervical cancers), bevacizumab prolongs median PFS and OS, but in others

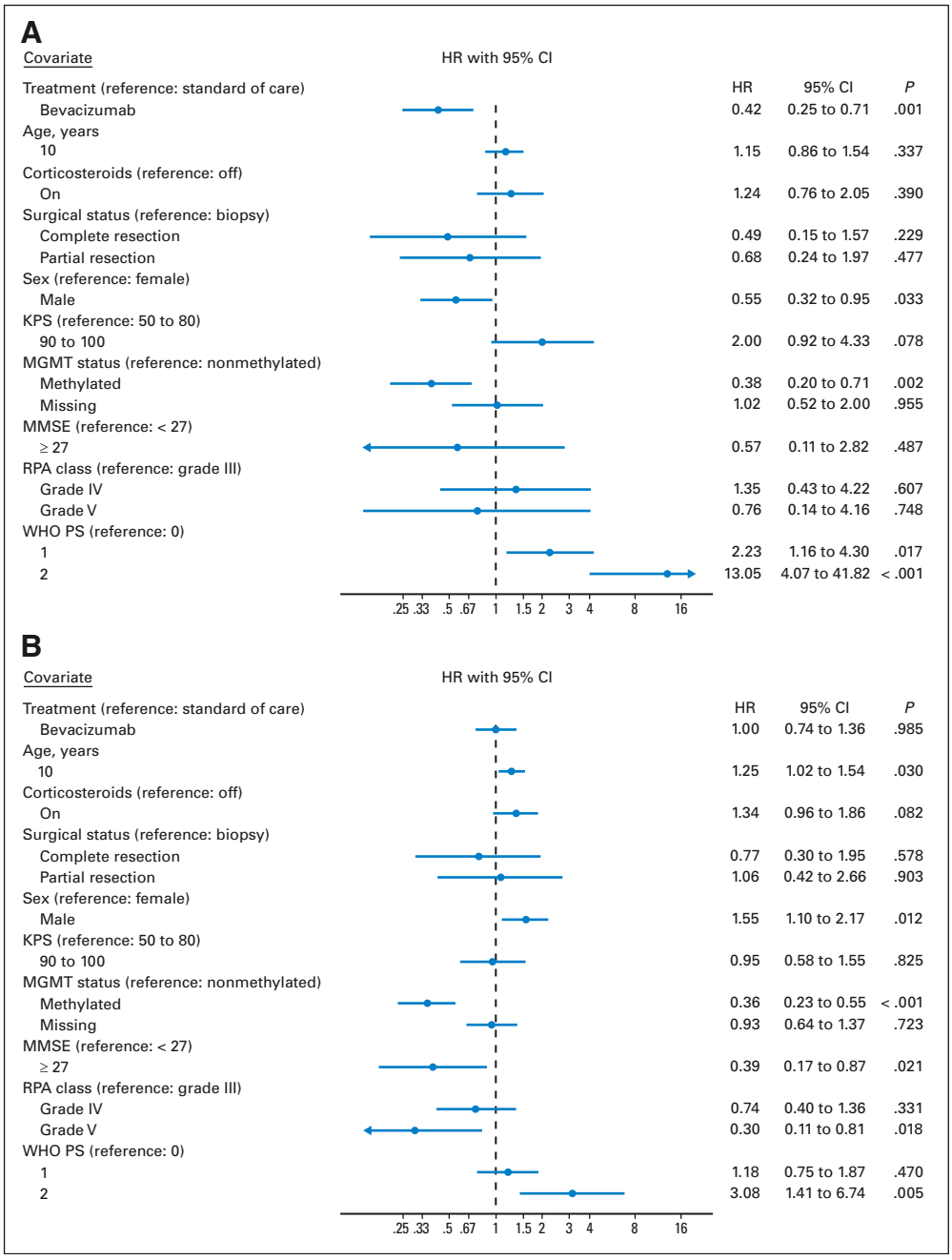

Fig 7. Results of multivariable Cox proportional hazards models fit separately to overall survival of Phillips et al[14] (A) proneural or (B) nonproneural patients. Only patients with *IDH1* wild-type tumors were included. HR, hazard ratio; KPS, Karnofsky performance score; MGMT, O^6-methylguanine–DNA methyltransferase; MMSE, Mini-Mental State Examination; PS, performance score; RPA, recursive partitioning analysis.

cancers (eg, breast and ovarian cancers), the PFS benefit is not accompanied by an OS benefit. In newly diagnosed glioblastoma, two phase III trials showed that adding bevacizumab to standard-of-care therapy conferred a PFS improvement, but the trials failed to show an OS benefit.[9,10] We explored whether patients with glioblastoma molecular tumor subtypes derived an OS benefit from bevacizumab.

As previously reported,[25,26] high concordance between fresh-frozen and FFPE paired samples from nontrial patients with glioblastoma supported the use of the NanoString platform to classify our 376 FFPE tumor samples by the Phillips et al[14] and TCGA glioblastoma subtype schemes. Consistent with a previous report,[19] the schemes were largely concordant in assigning samples to proneural and mesenchymal subtypes.

The proneural subtype had originally been considered the subtype with the longest OS, but this favorable prognosis was later attributed to a small subset of patients with CpG island methylator phenotype tumors (mostly *IDH1* mutation positive).[16] As previously reported,[16] *IDH1* wild-type proneural tumors had the worst prognosis among all glioblastoma subtypes in the placebo arm. For these patients, bevacizumab conferred a 4.3-month OS advantage relative to placebo (using Phillips et al[14] classification; difference was 3.0 months using TCGA classification). In contrast, no evidence of an OS difference between treatment arms for patients with mesenchymal or proliferative tumors was found. These results may have important clinical implications, because they suggest that bevacizumab confers an OS benefit for patients with

newly diagnosed glioblastoma who have proneural *IDH1* wild-type tumors.

It seems counterintuitive that proneural tumors would derive increased benefit from antiangiogenic therapy, because the mesenchymal subtype shows elevated expression of angiogenic markers (including VEGF). However, neither markers of endothelial proliferation nor expression of microvascular density signature genes have reliably predicted bevacizumab efficacy across indications.[27-29] In contrast, our data suggest that the growth of proneural tumor cells may be particularly sensitive to the downstream biologic consequences of VEGF blockade.[30] Thus, in addition to vascular biology (angiogenic activity), tumor type–specific cell biology (angiogenic dependency) may be an important factor influencing anti-VEGF efficacy.[31]

Although patients with mesenchymal and proneural tumors experienced longer PFS with bevacizumab than placebo, only those with the proneural subtype experienced longer OS. The biologic reason for this is currently unclear but may be related to delayed bevacizumab resistance or synergy with standard-of-care therapy. The notion that patients with mesenchymal-like tumors do not derive an OS benefit from bevacizumab treatment was also suggested by the RTOG-0825 study.[32] Xenograft studies have also indicated that mesenchymal tumors may be least sensitive to anti-VEGF treatment compared with other subtypes.[33] Mesenchymal tumors are less differentiated and more highly neoplastic than other subtypes, leading us to speculate that anti-VEGF treatment initially affects mesenchymal tumors (leading to PFS benefit), but the tumors adapt and resist the long-term consequences of VEGF blockade. In contrast, proneural tumors (*IDH1* wild type) may have more rigid biologic programming and be less likely to escape antiangiogenic therapy.

Our data indicate that in AVAglio, first-line bevacizumab plus standard-of-care therapy conferred a significant OS advantage versus placebo for patients with proneural *IDH1* wild-type tumors. Given the retrospective nature of this analysis, an independent study is needed to confirm this result. The RTOG-0825 trial offers an opportunity for a quasiprospective evaluation of the proneural *IDH1* wild-type biomarker hypothesis in a relevant phase III trial. Unfortunately, we were unable to access the RTOG-0825 study RNA and clinical data at the time of publication, and the recently published RTOG-0825 gene expression data were limited to approximately 40 mesenchymal-associated genes, which were insufficient to evaluate our proneural hypothesis.[32] Although the analyses cannot be compared at this point, the RTOG-0825 study reported a significant association of bevacizumab with survival detriment for a newly defined subgroup of patients (approximately 30%) who expressed mesenchymal-related genes.[32] In contrast, no molecular subtypes were associated with a significant negative impact of bevacizumab in AVAglio. Future studies using similar gene expression platforms will allow assessment of the proneural *IDH1* wild-type predictive hypothesis and a better understanding of whether the findings from these two studies are consistent.

In conclusion, this retrospective analysis of the phase III AVAglio trial identified the proneural *IDH1* wild-type molecular subtype as a candidate predictive biomarker for bevacizumab efficacy in newly diagnosed glioblastoma, a disease with an extremely poor prognosis under current treatment protocols. These findings have the potential to be practice changing by allowing identification of a patient subpopulation that may derive a significant OS benefit from the addition of bevacizumab to standard-of-care therapy. These findings require independent validation and the development of a robust proneural subtyping companion diagnostic assay before they can be implemented in practice.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Patients With Proneural Glioblastoma May Derive Overall Survival Benefit From the Addition of Bevacizumab to First-Line Radiotherapy and Temozolomide: Retrospective Analysis of the AVAglio Trial

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