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Trabectedin for recurrent WHO grade 2 or 3 meningioma: A randomized phase II study of the EORTC Brain Tumor Group (EORTC-1320-BTG)

Matthias Preusser, Antonio Silvani, Emilie Le Rhun, Riccardo Soffietti, Giuseppe Lombardi, Juan Manuel Sepulveda, Petter Brandal, Lucy Brazil, Alice Bonneville-Levard, Veronique Lorgis, Elodie Vauleon, Jacoline Bromberg, Sara Erridge, Alison Cameron, Florence Lefranc, Paul M. Clement, Sarah Dumont, Marc Sanson, Charlotte Bronnimann, Carmen Balaná, Niklas Thon, Joanne Lewis, Maximilian J. Mair, Philipp Sievers, Julia Furtner, Josef Pichler, Jordi Bruna, Francois Ducray, Jaap C. Reijneveld, Christian Mawrin, Martin Bendszus, Christine Marosi, Vassilis Golfinopoulos, Corneel Coens, Thierry Gorlia, Michael Weller, Felix Sahm†, and Wolfgang Wick†

Department of Medicine I, Division of Oncology, Medical University of Vienna, Vienna, Austria (M.P., M.J.M., C.Mar); Department of Neuro-Oncology, IRCCS Fondazione Istituto Neurologico Carlo Besta, Milan, Italy (A.S.); University of Lille, U-1192, Lille, France (E.L.R.); Inserm, U-1192, Lille, France (E.L.R.); General and Stereotaxic Neurosurgery Service, CHU Lille, Lille, France (E.L.R.); Medical Oncology Department, Oscar Lambret Center, Lille, France (E.L.R.); Department of Neuro-Oncology, University and City of Health and Science Hospital, Turin, Italy (R.S.); Department of Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy (G.L.); Neurooncology Unit, Hospital Universitario 12 de Octubre, Madrid, Spain (J.M.S.); Department of Oncology, Division of Cancer Medicine, Oslo University Hospital, Oslo, Norway (P.B.); St Thomas' Hospital, London, UK (L.B.); Centre Leon Berard, Lyon, France (A.B.-L.); Department of Medical Oncology, Centre Georges François Leclerc, Dijon, France (V.L.); Department of Medical Oncology, Centre Eugene Marquis, Rennes, France (E.V.); Department of Neuro-Oncology, Erasmus MC University Medical Center Cancer Center, Rotterdam, the Netherlands (J.Bro); Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK (S.E.); Bristol Cancer Institute, University Hospitals Bristol, Bristol, UK (A.C.); Department of Neurosurgery, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium (F.L.); Department of Oncology, KU Leuven, Leuven, Belgium (P.M.C.); Department of General Medical Oncology, Leuven Cancer Institute, UZ Leuven, Leuven, Belgium (P.M.C.); Medical Oncology Department, Institut Gustave-Roussy, Université Paris-Saclay, Villejuif, France (S.D.); Sorbonne Université, Inserm, CNRS, UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, AP-HP, Hôpitaux Universitaires La Pitié Salpêtrière—Charles Foix, Service de Neurologie 2-Mazarin, Paris, France (M.S.); Department of Medical Oncology, Bordeaux University Hospital-CHU, Bordeaux, France (C.Bro); University of Bordeaux, Bordeaux, France (C.Bro); Department of Medical Oncology, Catalan Institute of Oncology, Badalona, Barcelona, Spain (C.Bal); Department of Neurosurgery, Faculty of Medicine and University Hospital, University of Munich (LMU), Munich, Germany (N.T.); Freeman Hospital, Newcastle, UK (J.L.); Department of Neuropathology, Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany (P.S., F.S.); Clinical Cooperation Unit Neuropathology, German Consortium for Translational Cancer Research (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany (P.S., F.S.); Department of Biomedical Imaging and Image-Guided Therapy, Medical University of Vienna, Vienna, Austria (J.F.); Department of Internal Medicine and Neurooncology, Neuromed Campus, Kepler University Hospital, Johannes Kepler University of Linz, Linz, Austria (J.P.); Unit of Neuro-Oncology, Hospital Universitari de Bellvitge-Institut Català D'Oncologia L'Hospitalet, Barcelona, Spain (J.Bru); Unit of Neuro-Oncology, Hospices Civils de Lyon, Lyon, France (F.D.); Department of Cancer Cell Plasticity, Cancer Research Center of Lyon, Claude Bernard University, Lyon, France (F.D.); Brain Tumor Center, Cancer Center Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands (J.C.R.); Stichting Epilepsie Instellingen Nederland, Heemstede, the Netherlands (J.C.R.); Department of Neuropathology, Otto-von-Guericke-University, Magdeburg, Germany (C.Maw); Department of Neuroradiology, University of Heidelberg, Heidelberg, Germany (M.B.); European Organisation for Research and Treatment of Cancer (EORTC) Headquarters, Brussels, Belgium (V.G., C.C., T.G.); Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland (M.W.); Neurology Clinic, Heidelberg University Medical Center, Clinical Cooperation Unit, Neurooncology, German Cancer Research Center, Heidelberg, Germany (W.W.)

†These authors contributed equally to this work.

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Corresponding Author: Matthias Preusser, MD, Department of Medicine I, Division of Oncology, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria (matthias.preusser@meduniwien.ac.at).

Abstract

Background. No systemic treatment has been established for meningioma progressing after local therapies.

Methods. This randomized, multicenter, open-label, phase II study included adult patients with recurrent WHO grade 2 or 3 meningioma. Patients were 2:1 randomly assigned to intravenous trabectedin (1.5 mg/m^2 every 3 weeks) or local standard of care (LOC). The primary endpoint was progression-free survival (PFS). Secondary endpoints comprised overall survival (OS), objective radiological response, safety, quality of life (QoL) assessment using the QLQ-C30 and QLQ-BN20 questionnaires, and we performed tissue-based exploratory molecular analyses.

Results. Ninety patients were randomized (n = 29 in LOC, n = 61 in trabectedin arm). With 71 events, median PFS was 4.17 months in the LOC and 2.43 months in the trabectedin arm (hazard ratio [HR] = 1.42; 80% CI, 1.00-2.03; P = .294) with a PFS-6 rate of 29.1% (95% CI, 11.9%-48.8%) and 21.1% (95% CI, 11.3%-32.9%), respectively. Median OS was 10.61 months in the LOC and 11.37 months in the trabectedin arm (HR = 0.98; 95% CI, 0.54-1.76; P = .94). Grade ≥3 adverse events occurred in 44.4% of patients in the LOC and 59% of patients in the trabectedin arm. Enrolled patients had impeded global QoL and overall functionality and high fatigue before initiation of systemic therapy. DNA methylation class, performance status, presence of a relevant co-morbidity, steroid use, and right hemisphere involvement at baseline were independently associated with OS.

Conclusions. Trabectedin did not improve PFS and OS and was associated with higher toxicity than LOC treatment in patients with non-benign meningioma. Tumor DNA methylation class is an independent prognostic factor for OS.

Key Points

- Trabectedin does not improve survival in recurrent WHO grade 2 and 3 meningiomas.
- DNA methylation class is associated with overall survival in non-benign meningioma.
- Included patients were characterized by severely impeded quality of life.
- VEGF inhibition may improve patient outcomes and should be investigated in prospective trials.

Importance of the Study

No effective drug treatments are known for meningioma. So far, no randomized clinical trials had been completed in the specific population of WHO grade 2 or 3 meningiomas recurring after local therapies with no antineoplastic treatment options. Our study shows that multinational collaboration enables completion of prospective randomized clinical trials with stringent inclusion criteria in this specific population within a reasonable timeframe. Trabectedin did not improve progression-free survival (PFS) or overall survival (OS) and was associated with higher toxicity than local standard of care treatment. This is the first randomized controlled trial where an independent association between DNA methylation profiling and OS in recurrent non-benign meningioma could be observed. This patient population is characterized by severely impeded physical, role, emotional, cognitive, and social functioning, low quality of life, and higher fatigue, even before initiation of systemic therapy. The collected data may serve as benchmark for future clinical trials in this setting. Our data highlight that clinical trials evaluating vascular endothelial growth factor (VEGF) inhibition in recurrent grade 2 and 3 meningiomas are warranted.

Meningioma is the most common intracranial tumor in adults. Most meningiomas are benign and correspond to grade 1 as defined by histomorphological features in the World Health Organization (WHO) criteria.[1] However, approximately 20-25% of cases show brain invasiveness, cellular signs of atypia or increased mitotic activity, an increased risk for recurrence, and thus are classified as WHO grade 2 or grade 3 meningiomas.[1] Several molecular alterations including telomerase reverse transcriptase (TERT) promoter mutations, certain DNA methylation classes (MC), and CDKN2A/B homozygous deletions have been reported as potential prognostic parameters in meningioma.[2]

Therapeutically, maximum safe surgical resection is recommended for most meningiomas at diagnosis.[3] Depending on the extent of resection and histological grade, postoperative radiotherapy can be considered. For recurrent tumors, local therapy approaches such as surgical resection and radiotherapy are commonly applied. So far, no standard systemic treatment for recurrent meningiomas after exhaustion of all local therapy options is established.

Pharmacotherapy is regarded experimental in any grade of meningioma, and thus far no systemic active agent against meningioma has been proven.[3,4] A number of drugs including hydroxyurea, temozolomide, irinotecan, interferon-alpha, mifepristone, octreotide analogs, megestrol acetate, bevacizumab, imatinib, erlotinib, gefitinib, everolimus, and sunitinib have been investigated in exploratory arms, pilot studies, and mostly uncontrolled phase II studies including meningioma patients.[4,5] However, the marked heterogeneity in study design, the lack of adequately powered and controlled clinical trials as well as a wide variability in published efficacy outcomes have precluded definite conclusions and recommendations of systemic antineoplastic therapy for meningioma. A prior randomized phase II trial enrolling recurrent WHO grade 1-3 meningioma and treated with hydroxyurea with or without imatinib was prematurely closed due to insufficient accrual.[6] The only available completed randomized phase III study, again enrolling WHO grade 1-3 meningiomas progressing after local therapy, failed to show the benefit of mifepristone.[7]

Trabectedin is a tetrahydroisoquinoline alkaloid originally derived from the Caribbean Sea squirt *Ecteinascidia turbinata* and currently manufactured by total synthesis. It binds to the minor groove of the DNA double helix, thus forming trabectedin-DNA adducts that bend the DNA toward the major groove.[8–10] Furthermore, trabectedin affects several transcription factors and DNA repair mechanisms and has immunomodulatory and antiangiogenic properties. Trabectedin has shown clinically meaningful efficacy and good tolerability in advanced soft tissue sarcoma and ovarian cancer and is currently approved in these indications.[11] In a previous study, we have shown distinct cell cycle arrest, downregulation of multiple cyclins, deregulated expression of cell death-regulatory genes, and massive apoptosis induction by trabectedin in meningioma cell lines.[12,13] Cytotoxic activity was more prominent in cell cultures derived from WHO grade 2 and 3 meningiomas. In addition, we observed a favorable response in a patient with recurrent anaplastic meningioma treated with trabectedin.[12] Based on these findings, we designed the prospective international European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumour Group 1320 (EORTC-1320-BTG) randomized phase II trial with the aim to investigate whether trabectedin demonstrates sufficient antineoplastic activity against recurrent meningioma to justify further development. Tumor tissue samples of patients enrolled in the EORTC-1320-BTG study were also collected to analyze the prognostic and predictive value of relevant molecular alterations.

Methods

Study Design and Participants

The EORTC-1320-BTG trial was an open-label, prospective, multicenter, randomized phase II trial performed across Europe to assess the efficacy and toxicity of trabectedin vs. local standard of care (LOC) treatment in patients with WHO grade 2 or grade 3 meningioma.

Eligible patients were adults (≥18 years old) with a local histological diagnosis of WHO grade 2 (atypical, chordoid, clear cell) or grade 3 (papillary, rhabdoid, anaplastic/malignant) meningioma according to the WHO 2007 classification,[14] radiologically documented progression of any existing tumor (estimated planar growth >25% in the last year) or appearance of new lesions (including intra- and extra-cranial sites). Other eligibility criteria included patients with no more options for local therapy (resection or radiotherapy), no prior systemic antineoplastic therapy for meningioma, measurable disease (10 × 10 mm) on cranial magnetic resonance imaging (MRI) at ≤2 weeks prior to randomization, a WHO performance status of 0-2, and normal cardiac function and adequate liver, renal, and hematological function before randomization (full clinical trial protocol is available in Supplement A).

All study procedures were conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The trial was approved by the ethics committee of all participating sites. Signed informed consents were obtained from all study participants before registration.

Randomization and Masking

Patients were randomly assigned on a 2:1 basis by the minimization method to receive either trabectedin or LOC treatment. The enrolled patients were also stratified by a minimization procedure based on the variance method with semi-random assignment.[15] Stratification factors included institution, WHO grade (ie, 2 vs. 3), age (≤60 vs. >60), and WHO performance status (0 vs. >0). Patients were registered by the treating institutions and were electronically randomized using EORTC web-based registration and randomization system. All group assignment was open label, and neither investigators nor patients were masked to the treatment assignment.

Procedures

Trabectedin was given as 24-h intravenous (i.v.) infusion every 3 weeks (day 1 of each 21-day cycle) at a starting

dose of 1.5 mg/m^2. Administration through a central venous line was strongly recommended. Pretreatment with corticosteroids (eg, dexamethasone 20 mg intravenously 30 min before trabectedin) was considered mandatory for all patients receiving trabectedin. Patients in the control arm received LOC treatment as defined by the local investigator. There were no predefined limits to the number of trabectedin cycles and treatment could continue until progression, unacceptable toxicity, or patients' refusal. Patients discontinuing therapy in the absence of progression did not receive any other anti-cancer treatment before their disease progresses unless this was clearly not in the interest of the patient. After progression, the treatment was left to the discretion of the treating physician.

Baseline assessments included physical examination, cranial MRI, full blood cell counts, blood chemistry, and quality of life (QoL) evaluations. Objective tumor response and time to progression were measured using cranial MRI performed no more than 2 weeks prior to randomization and then every 9 weeks, or if clinically indicated. QoL was assessed with the EORTC Quality of Life Questionnaire (QLQ-C30) v.3 and the QLQ Brain Cancer module (QLQ-BN20) at baseline (before or on the day of the start of protocol treatment but no earlier than 28 days before), at weeks 3, 6, and 12 and in the sixth month after starting protocol treatment regardless of treatment arm or progression status.

Formalin-fixed, paraffin-embedded (FFPE) blocks of tumor samples were collected for translational research. Immunohistochemical (IHC) analysis on FFPE slides was performed by an automated slide staining system (DAKO autostainer) using the antibodies against Ki67 and CD68 (both from DAKO/Agilent). IHC slides were digitalized using a NanoZoomer slide scanner (Hamamatsu Photonics, Hamamatsu, Japan) and analyzed using tissue phenomics software (Definiens Tissue Studio 4.4.3, Definiens AG, Munich, Germany). The proliferation index is given as a percentage, while the density of tumor-associated macrophages (TAM) is expressed as CD68-positive cells per mm^2 of tumor tissue. Methylation analysis and copy number analysis were performed using 850k EPIC (Illumina, San Diego, CA, USA) arrays as described previously.[16,17] Meningioma MC (MC-benign, MC-intermediate, MC-malignant) were determined by a previously reported random-forest classifier.[16] Panel sequencing for genes reported to impact meningioma, namely NF2, TRAF7, KLF4, SMO, AKT1, TERT promoter, ARID, SUFU, SMARCE1, and PIK3CA, was performed using the previously published methods.[2] Libraries were generated based on a hybrid capture enrichment panel and sequenced on an Illumina NextSeq 500 in paired end mode.[2] All exome or near exome (splice-site) genetic variations were included while intron sequences except the TERT promoter, and polymorphisms with >1/100 000 incidence in databases were excluded. Germline DNA was not available. Single nucleotide variants and small insertion/deletions left after these filtering criteria were defined as "mutation".

Outcomes

The primary endpoint of this study was to compare the treatment with trabectedin with LOC therapy in terms of progression-free survival (PFS) in the per-protocol (PP) population. Secondary endpoints included objective tumor response rate according to modified Macdonald response criteria[18] and graded as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), as well as overall survival (OS), safety, and health-related QoL. PFS was measured from the date of randomization until the date of first objective progression per local assessment or the date of patient's death (whichever occurred first), whereas OS was accounted from the date of randomization until patient death from any cause.

In brief, a set of contrast-enhancing target lesions were identified at baseline and followed until disease progression. The contrast-enhancing area of each lesion was measured in 2 perpendicular dimensions and tumor size was defined as the product of the 2 largest perpendicular diameters. Adverse events (AEs) were graded according to the National Cancer Institute-Common Terminology Criteria (NCICTC), v. 4.0 and were summarized by the worst grade experienced by the patient.

Statistical Analysis

This trial was designed as a phase II study with a Korn superiority design comparing PFS between trabectedin and the control arm with a treatment allocation ratio equal to 2:1 at randomization.[19,20] Based on the Response Assessment in Neuro-Oncology (RANO) working group recommendations,[4] PFS at 6 months of 15% was assumed in the control arm, and of 35% in the trabectedin arm (ie, 20% difference) for assessment of the primary endpoint. Assuming PFS follows an exponential distribution, this corresponds to a treatment hazard ratio (HR) of 0.55. Based on the log-rank test, a type I error equal to 10% 1-sided (20% 2-sided), a power equal to 85%, 71 progressions or deaths in the PP population were needed to assess the targeted effect. Eighty-six eligible patients (57 trabectedin, 29 control) who started their treatment (PP population) were to be recruited. Secondary endpoints included OS, response rate, safety, and health-related QoL. A futility interim analysis based on boundaries from Rho family ($\rho = 1.625$) was planned when half of the events (ie, 36 PFS events) were observed. In absence of effect (ie, a PFS HR ≥ 1), the trial would be stopped for futility. With this boundary, there was 50% chance to stop the trial for lack of effect if the null hypothesis was true (H0). Safety was reviewed by the EORTC safety monitoring board every 6 months and by the EORTC Independent Data Monitoring Committee (IDMC) at the time of futility analysis together with efficacy data.

The intention-to-treat (ITT) population was defined as all randomized patients analyzed in the arm they were allocated by randomization. The PP population included all patients randomized who were eligible and started their allocated treatment (at least 1 dose of trabectedin or the start of LOC therapy), whereas the safety population (S) comprised all randomized patients who started their allocated treatment.

PFS and OS were compared in the PP population between trabectedin and control arm once 71 PFS events were observed in the PP population. A Cox regression model including treatment and stratification factors at

randomization (except institution) was used. Superiority for PFS of trabectedin against the control arm was tested at 10% 1-sided significance level. The HR was presented with either 80% or 95% 2-sided confidence interval (CI) computed based on the Greenwood's formula. PFS and PFS fixed-time estimations at 6 months were estimated according to the Kaplan-Meier method and were compared using a log-rank test. The objective response (CR/PR) and CR rates are reported in the PP population. PFS and OS unplanned sensitivity analyses were conducted in the ITT population with the same methods. In order to explore the efficacy of treatments used in the LOC arm, we also performed unplanned descriptive survival comparisons by most commonly applied therapies compared to trabectedin in the ITT population.

QLQ-C30 and QLQ-BN20 data collected at baseline in the safety population were descriptively compared to normative data from the general population, which was weighted to account for the distribution of age and sex (Supplement B). The normative data for the QLQ-C30 are available in the EORTC database from previously published work.[21]

The objective of translational research was to analyze the association of candidate biomarkers including patient's baseline data, clinicopathological tumor characteristics (histological tumor type, tumor localization, tumor size), and nonstandard morphological and molecular tumor characteristics (Ki67 index, TAM density, gene mutations, DNA MC, CDKN2A/B status) with each other, with PFS and OS (prognostic role) and with response to study treatment (predictive role). The association between clinicopathological and molecular factors was tested using Spearman correlation coefficients and the Fisher's exact test with an exploratory 2-sided 5% significance level as appropriate. Descriptive, univariate, predictive value, and multivariate analyses were performed using SAS 9.4. The c-index was computed using the R Hmisc package. The prognostic value of candidate biomarkers for PFS and OS were assessed by univariate analysis with Kaplan-Meier curves and log-rank tests, while the predictive value of biomarkers was assessed by forest plot and interaction log-rank test. For both analyses, Cox proportional hazards model was used to assess HR within subgroups with an exploratory 2-sided 10% significance level. Factors significant in the univariate and predictive analyses were included in the multivariate analyses using analyses Cox proportional hazards model. In order not to lose information, dummy variables were created for missing values of variables if the percentage missing was in the range of 5%-25% of patients. To identify the most significant independent prognostic and predictive factors, the stepwise forward selection technique was performed. An exploratory 2-sided 10% significance was used both to enter and remove variables from the model. HR was presented with 90% and 95% CI. The final model discrimination power was assessed by the c-index core. The trial is registered with ClinicalTrials.gov Identifier: NCT02234050.

Role of the Funding Source

The EORTC staff and the first author reviewed all data. The EORTC was the study sponsor and vouches for the integrity, accuracy, and completeness of data. All analyses were done by the investigators and EORTC staff. PharmaMar supported this trial through an educational grant and provided trabectedin free of charge, but had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. Molecular analyses were funded by the Else Kröner-Fresenius Stiftung and the German Cancer Aid 70112956. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

Results

Between September 2015 and July 2017, we recruited 90 patients (61 patients in the trabectedin arm, 29 patients in the LOC arm) from 35 centers in 9 countries across Europe (Supplement C). In July 2017, that is, after completion of full patient enrollment and based on recommendations of the IDMC, the investigators were informed that the trial was to be closed because of the high percentage of AEs and lack of efficacy in the experimental arm. No new patients were randomized to study treatment and treatment with trabectedin was immediately discontinued; however, follow-up, medical review, and translational research were to be continued. The final date of data collection was on January 16, 2019 (cutoff date). In the ITT population, at baseline, median patient age was 62.2 years (range: 21.2-81.3), 52.2% of patients were male, 61.1% had WHO grade 2, and 38.9% had grade 3 meningioma. Baseline patient characteristics were balanced between the 2 treatment groups (Table 1).

The median number of trabectedin cycles administered was 3 (range: 1-22), with a median treatment duration of 10.6 weeks (range: 3.0-72.3 weeks) and a relative dose intensity of 94.8% (range: 44.5%-102.4%). In the LOC arm, the following treatments were administered: hydroxyurea alone (n = 12), bevacizumab (n = 9), none (n = 4), vincristine, cyclophosphamide and doxorubicin chemotherapy (n = 2), somatostatin analogue (n = 1), combined hydroxyurea and somatostatin analogue (n = 1). All patients in both arms discontinued study treatment at the cutoff date.

At the cutoff date, in the ITT population, median follow-up time for PFS was 19 months (19.5 months in the LOC arm and 17.1 months in the trabectedin arm) and median follow-up for OS was 20.5 months (21 months in the LOC arm and 19.6 months in the trabectedin arm).

At the time of the primary endpoint analysis in the PP population (n = 79; Supplement C), 71 documented progressions or death events (78.9% of patients) were recorded (n = 20, 90.9% of patients in the LOC arm and n = 51, 89.5% in the trabectedin arm), whereas 8 patients who were alive without confirmed PD were censored. Median PFS was 4.2 months (95% CI, 2.0-6.0) in the LOC and 2.4 months (95% CI, 2.1-3.3) in the trabectedin arm (HR: 1.42; 80% CI, 1.00-2.03; P = .20) (Figure 1A, Table 2). The PFS-6 rate was 29.1% (95% CI, 11.9%-48.8%) in the LOC and 21.1% (95% CI, 11.3%-32.9%) in the trabectedin arm. Median OS was 10.6 months in the LOC and 11.4 months in the trabectedin arm (Figure 1B, Table 2). In the Cox proportional hazards model adjusted by stratification factors, the

Table 1 Patient Characteristics at Random Group Assignment in the Intention-to-Treat (ITT) Population

	Treatment		Total (N = 90)	
	Standard (N = 29)	Trabectedin (N = 61)		*P*-value
	N (%)	N (%)	N (%)	
Sex				.5[a]
Male	17 (58.6)	30 (49.2)	47 (52.2)	
Female	12 (41.4)	31 (50.8)	43 (47.8)	
Age				.65[b]
Median	63.0	62.0	62.2	
Range	38.9-81.3	21.2-80.1	21.2-81.3	
WHO performance status				.48[b]
0	7 (24.1)	15 (24.6)	22 (24.4)	
1	13 (44.8)	34 (55.7)	47 (52.2)	
2	9 (31.0)	11 (18.0)	20 (22.2)	
3	0 (0.0)	1 (1.6)	1 (1.1)	
Histology grade				.64[a]
WHO grade 2	19 (65.5)	36 (60.7)	55 (61.1)	
WHO grade 3	10 (34.5)	25 (39.3)	35 (38.9)	
Largest tumor diameter (mm)				.26[b]
Median	36.0	44.0	43.5	
Range	13.0-115.0	14.0-86.0	13.0-115.0	

[a]Fisher's exact test,
[b]Wilcoxon rank sum test.

treatment effect was not statistically significant (HR: 0.98; 95% CI: 0.54-1.76, *P* = .94), and only WHO performance status at baseline was associated with OS (HR: 2.21; 95% CI: 1.06-4.61, *P* = .03). Age and WHO grade did not correlate with OS (Table 3). In 76 patients (54 in the trabectedin arm, 22 in the LOC arm), the radiological response was evaluable. One PR was seen in the trabectedin arm, and none in the LOC arm (Table 2).

In the ITT population, median PFS was 4.2 months (95% CI, 2.1-6.0) in the LOC and 2.4 months (95% CI, 2.1-3.6) in the trabectedin arm. The PFS-6 rate was 30.2% (95% CI, 14.1-48.0) with LOC and 24.4% (95% CI, 14.1-36.2) with trabectedin (HR: 1.46; 95% CI: 0.89-2.41, *P* = .14) (Table 2). Median OS was 10.6 (95% CI, 6.5-19.9) months in the LOC and 13.5 (95% CI, 8.7-17.7) months in the trabectedin arm (HR: 0.99; 95% CI: 0.57-1.72, *P* = .97, Table 2).

The most commonly applied therapies in the LOC arm were hydroxyurea (n = 13; 12 with hydroxyurea alone), and bevacizumab (n = 9). With hydroxyurea therapy, we observed a median PFS of 2.4 (95% CI, 1.4-4.2) months, a PFS-6 rate of 8.8% (95% CI, 0.5-32.3), a median OS of 7.4 (95% CI, 3.1-19.9) months, and an OS-6 rate of 55.9% (95% CI, 24.0-79.0). With bevacizumab treatment, we observed a median PFS of 6.0 (95% CI, 2.1-18.6) months, a PFS-6 rate of 44.4% (95% CI, 13.6-71.9), a median OS of 13.5 (95% CI, 5.42-not reached) months, and an OS-6 rate of 88.9% (95% CI, 43.3-98.4, Figure 2).

In the safety population (n = 88 patients), grade 3-5 AEs occurred in 44.4% (18.5% related, 0 lethal events) of the patients in the LOC and in 59% of patients (34.4% related, 2 drug-related deaths) in the trabectedin arm (Table 4). The percentage of patients with grade 3 or 4 hematological toxicity was 15% in patients receiving LOC therapy and 56% in patients treated with trabectedin. The percentage of patients with grade 3 or 4 biochemical toxicity was 62% with trabectedin and 7% with LOC therapy.

A descriptive comparison of QoL data of the safety population and the normative general population are shown in Supplement D. Owing to low compliance rates, the QoL data available from study time points after the baseline evaluation were not sufficient in relative and absolute numbers to allow for meaningful statistical analyses. In brief, baseline QLQ-C30 scores were considerably lower for physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, global health status/QoL, and higher for fatigue in patients enrolled in EORTC-BTG-1320 as compared to the normative dataset. There was no obvious difference in nausea/vomiting, pain, and dyspnea scores between the EORTC-BTG-1320 population and the normative population.

Mutational analyses, CDKN2A/B status, and DNA methylation profiling were performed in 71/90 (78.9%) patients, while Ki67 index and TAM density were performed in 36/90 (40.0%) patients due to limited tumor tissue availability (Figure 3). CDKN2A/B deletion was detected in 18/71 (25.3%), TERT promoter mutation. In 6/71 (8.5%), NF2 mutation in 33/71 (46.5%), and SMARCE1 mutation in 1/71 (1.4%) investigated cases, respectively. We did not detect any TRAF7, ARID, SUFU, or PIK3CA in any of the 71 investigated cases. CDKN2A/B homozygous deletions were more common in WHO grade

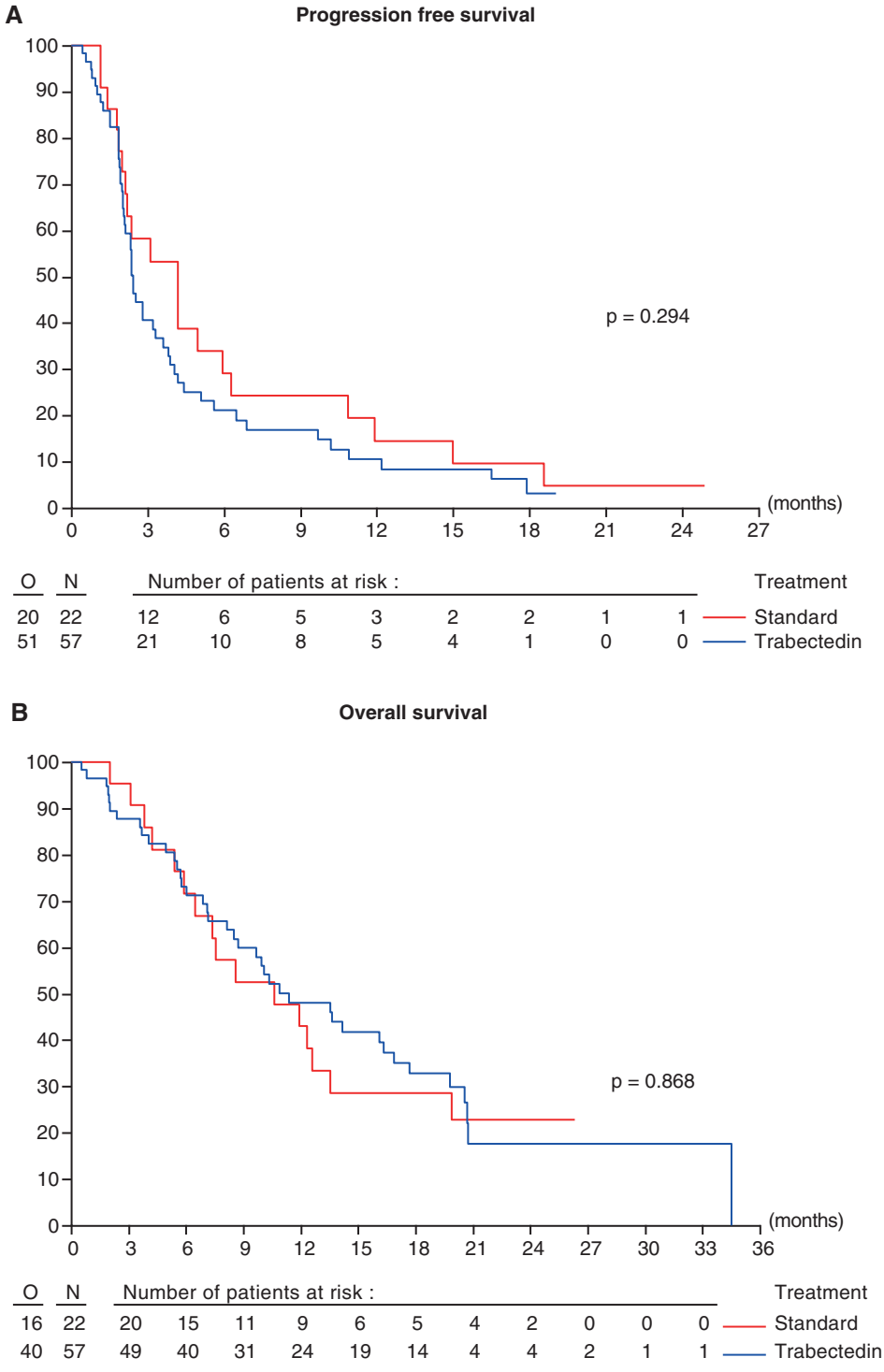

Fig. 1 Progression-free survival (A) and overall survival (B) in the per-protocol population (primary analysis).

3 (14/30, 46.7%) than in grade 2 meningiomas (4/41, 9.8%) ($P = .0007$, Fisher's exact test). Histology grade was not associated with TERT promoter mutation status, NF2 mutation status, or DNA MC. CDKNA2A/B homozygous deletion was more frequent ($P = .0011$, Fisher's exact test) in the malignant MC (14/34, 41.2%) and benign DNA MC (3/10, 30%) than in the intermediate DNA MC (1/27, 3.7%), respectively. There was a significant but poor association between the presence of CDKNA2A/B homozygous deletion and NF2 alteration ($\rho = 0.24$, $P = .048$). There was no significant association of the

Table 2 Kaplan-Meier Estimates of Progression-Free Survival and Overall Survival in the Per-Protocol and Intention-to-Treat Populations as Well as Radiological Response Rates According to Macdonald Criteria Based on Central Review in the Local Standard of Care (LOC) and the Trabectedin Arm

Population	Parameter	Treatment Arm	
Per-protocol	Progression-free survival (PFS)	Local standard of care (n = 22)	Trabectedin (n = 57)
	Median, months	4.17 (2.00-5.95)	2.43 (2.07-3.32)
	PFS at 6 months	29.1% (11.9-48.8)	21.1% (11.3-32.9)
	PFS at 12 months	14.6% (3.6-32.6)	10.5% (4.0-20.8)
	Overall survival (OS)		
	Median, months	10.61 (5.91-13.54)	11.37 (8.15-16.89)
	OS at 6 months	71.6% (47.4-86.1)	73.25% (59.5-82.9)
	OS at 12 months	43.0% (22.0-62.4)	48.1% (34.2-60.7)
	Best overall response[a]		
	Complete response (CR)	0 (0.0)	0 (0.0)
	Partial response (PR)	0 (0.0)	1 (1.8)
	Stable disease (SD)	13 (59.1)	21 (36.8)
	Progressive disease (PD)	9 (40.9)	29 (50.9)
	Objective response (CR/PR)	0 (0.0)	1 (1.8)
Intention-to-treat	Progression-free survival (PFS)	Local standard of care (n = 29)	Trabectedin (n = 61)
	Median, months	4.17 (2.14-5.95)	2.43 (2.10-3.61)
	PFS at 6 months	30.2% (14.1-48.0)	24.4% (14.1-36.2)
	PFS at 12 months	17.2% (5.6-34.3)	13.3% (5.7-24.2)
	Overall survival (OS)		
	Median, months	10.61 (6.47-19.88)	13.54 (8.74-17.71)
	OS at 6 months	74.5% (53.8-87.0)	75.0% (61.9-84.1)
	OS at 12 months	44.7% (25.8-62.0)	51.2% (37.5-63.3)

[a]Response not evaluable in 3 patients in the trabectedin arm.

Table 3 Cox Regression Model for Overall Survival Adjusted by Stratification Factors

	Hazard Ratio (95% CI)	*P*-value
Treatment	0.98 (0.53-1.76)	.94
Age	0.77 (0.43-1.36)	.36
Histological grade	1.50 (0.87-2.57)	.14
WHO performance status	2.21 (1.06-4.61)	.03*

*Statistical significance ($P < .05$).

presence of gene mutations, MC, or CDKN2A/B status with tumor localization. There were no significant imbalances in baseline characteristics, PFS, or OS between patients with or without the availability of mutational analyses, CDKN2A/B status, and DNA methylation profiling. Furthermore, there were no differences in baseline characteristics or OS between patients with and without available Ki67 index and TAM density. However, patients with available Ki67 and TAM density had significantly lower PFS than patients without the availability of these measurements ($P = .042$, log-rank test).

Univariate analysis for PFS showed that the following parameters have a significant association with PFS (Supplement E): WHO grade, presence of a relevant co-morbidity at baseline, maximum tumor diameter at baseline, number of target lesions, steroid use, right hemisphere involvement, central involvement, and DNA MC. Multivariate analysis evidenced that the presence of a relevant co-morbidity at baseline and maximum diameter of the target lesion at baseline have a significant independent association with PFS (c-index equal to 60%, Supplement F). Univariate analyses for OS resulted in a significant association with WHO performance status at baseline, presence of a relevant co-morbidity (Supplement G) at baseline, number of target lesions at baseline, steroid use at baseline, left hemisphere involvement at baseline, DNA MC, and CDKN2A/B deletion status (Supplement H). Multivariate analyses for OS identify that WHO performance status at baseline, presence of a relevant co-morbidity (Supplement G) at baseline, steroid use at baseline, right hemisphere involvement at baseline, and DNA methylation have a significant association with OS (c-index equal to 69%, Supplement F).

Candidate predictive factors for PFS at an exploratory 10% significance level were occipital lobe involvement by treatment interaction term ($P = .001$) and NF2 mutation status by treatment interaction term ($P = .02$; forest plots in Supplement I). Candidate predictive factors for

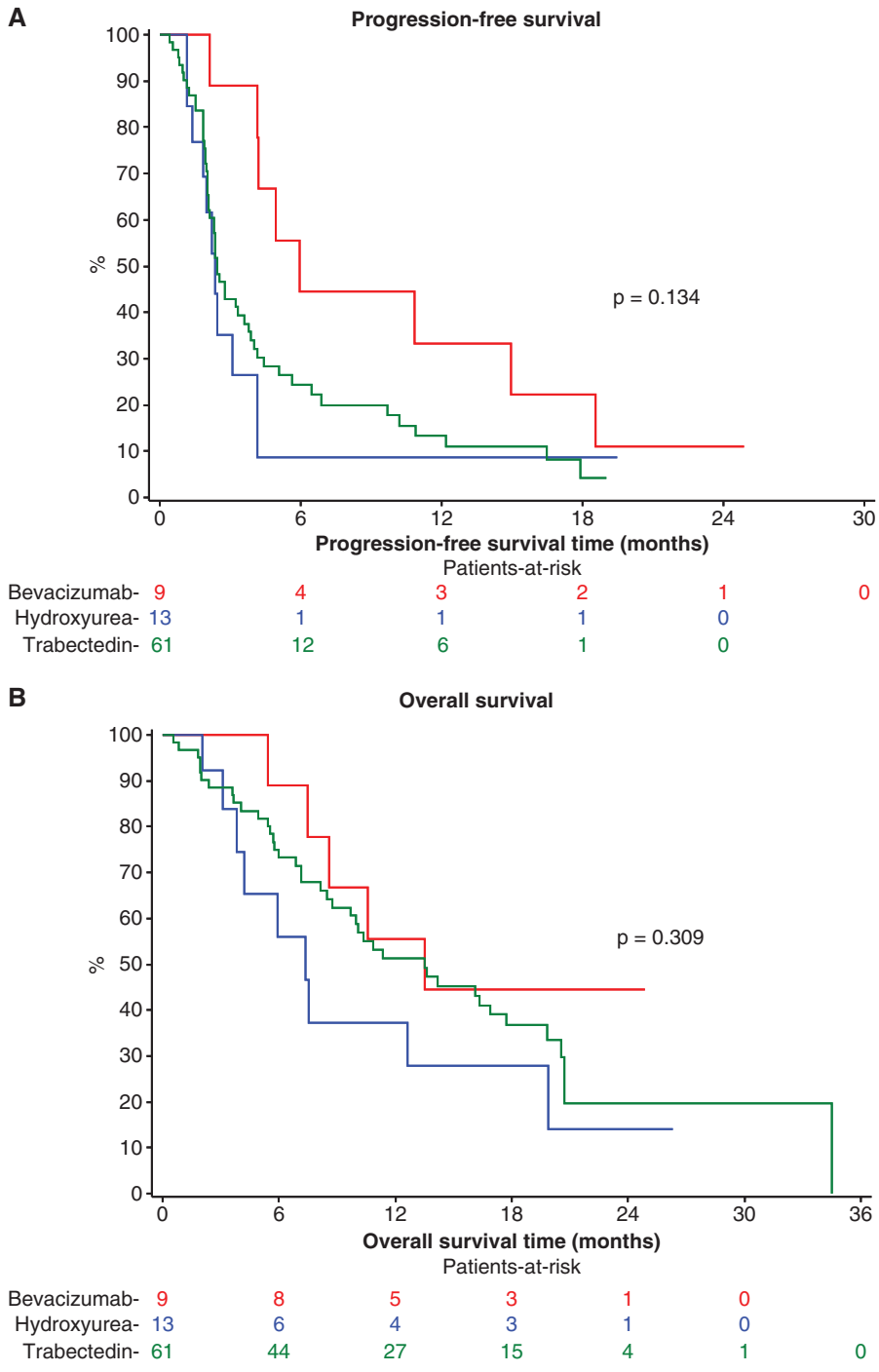

Fig. 2 Exploratory comparison of progression-free survival (A) and overall survival (B) with the most commonly applied LOC treatments and trabectedin in the intention-to-treat population. Abbreviation: LOC, local standard of care.

OS at an exploratory 10% significance level were right hemisphere involvement by treatment ($P = .059$), central hemisphere involvement by treatment ($P = .061$), occipital lobe involvement by treatment ($P = .021$) interaction term, and NF2 mutation status by treatment ($P = .024$) interaction term (forest plots in Supplement I).

Discussion

The EORTC-1320-BTG study is the first prospective randomized clinical trial performed in patients with recurrent WHO grade 2 or 3 meningiomas. Despite the relative rarity

Table 4 Patients With Adverse Events (Worst Grade) in the Safety Population

	Local Standard of Care (N = 27)		Trabectedin (N = 61)	
CTC + MedDRA Term	Grade 3-5, N (%)	Grade 1-2, N (%)	Grade 3-5, N (%)	Grade 1-2, N (%)
Non-hematological adverse events				
All grades	12 (44.4)	13 (48.1)	36 (59.0)	22 (36.1)
All grades, possibly related	5 (18.5)	15 (55.6)	21 (34.4)	25 (41.0)
Laboratory events				
Hematological toxicity	4 (14.8)	18 (66.7)	34 (55.7)	22 (36.1)
Biochemical toxicity	2 (7.4)	20 (74.1)	38 (62.3)	23 (37.7)

of this disease, multinational collaboration enabled us to achieve patient accrual in less than 2 years, corresponding to an accrual rate of 4.1 patients per month, demonstrating the unmet clinical need. Prior clinical studies on pharmacotherapy of meningioma were mainly retrospective case collections and single-arm and small prospective trials with heterogeneous inclusion criteria and endpoint definitions.[4] Only one randomized trial has been successfully completed in the setting of meningiomas recurring after and without the possibility of further local therapies, but that trial enrolled a broader patient population including patients with WHO grade 1 tumors, which constitute the majority of cases and have a significantly better prognosis than the patients with WHO grade 2 and 3 tumors enrolled in our trial.[7] The lack of reliable benchmark data from these studies and the variable natural course of meningiomas make randomization and application of stringent inclusion criteria absolutely necessary to evaluate the treatment effect in a controlled fashion. While most published studies included heavily pretreated patients, we enrolled patients without prior exposure to systemic antineoplastic therapy to homogenize the study population. In order to limit a potential bias introduced by variability in growth kinetics of meningiomas, we included only patients with a predefined tumor growth on MRI of at least 25% in the year before trial inclusion.

Prior in vitro studies and single patient experience had indicated potential activity of trabectedin in patients with WHO grade 2 and 3 meningiomas.[12] However, our trial did not provide evidence for survival improvement when using trabectedin at recurrence after exhaustion of surgery and radiotherapy in this patient cohort. Furthermore, we observed only one objective radiological response among the patients treated with trabectedin and considerable toxicity. Taken together, these results seem to exclude a relevant role of trabectedin for the treatment of meningioma and do not support further development of this drug in this indication. However, the data collected in this trial may serve as benchmark for further clinical trials. A previous review by the RANO group that compiled outcome data of 47 clinical studies on medical therapies of surgery- and radiation-refractory meningiomas and concluded that PFS-6 rates were the only endpoint reported consistently enough to be useful as historical benchmark.[4] For patients with recurrent WHO grade 2 and 3 meningiomas, PFS-6 rates of 0%-64% have been reported and a PFS-6 rate of 30% was suggested as control threshold based on a pooling of all available data. In the current trial, we observed a PFS-6 rate of 30.2% in the control arm of the ITT population; thus, confirming these historical control data extrapolated from various smaller studies. Importantly, our trial provides benchmark OS data for the planning and interpretation of clinical studies for patients with recurrent surgery- and radiation-refractory WHO grade 2 and 3 meningiomas. Considering the lack of validated radiological response criteria in meningiomas, trial designs using a median OS of 10.6 months, an OS-6 rate of 74.5%, or an OS-12 rate of 44.7% as benchmark may provide more robust results than trial designs based on PFS data.

Given the lack of a defined treatment standard for WHO grade 2 or 3 meningiomas recurring after prior surgery or radiotherapy, we decided to use LOC as control treatment in this trial. The heterogeneity of LOC therapies (including hydroxyurea, bevacizumab, vincristine, cyclophosphamide and doxorubicin chemotherapy, somatostatin analogs, and no antineoplastic therapy) chosen by the local investigators reflects the need for identification of novel effective treatments in this disease setting. Of note, an unplanned post hoc analysis of survival outcomes in the control arm indicates the low activity of hydroxyurea and potential activity of bevacizumab. Hydroxyurea was associated with a median PFS of 2.4 months and a PFS-6 rate of 8.8% and can thus, in agreement with previous studies, be considered largely ineffective.[4,22] In turn, bevacizumab therapy achieved median PFS of 6 months and PFS-6 of 44.4%. These data are in line with previous reports indicating activity of vascular endothelial growth factor (VEGF) inhibition in meningioma.[4,23–30] However, the limited statistical power of these analyses mandates caution in interpreting the data and makes further studies necessary. In addition, similar to what is observed in glioblastoma, the longer PFS that is associated with bevacizumab does not seem to translate into an improvement in OS, although this needs to be investigated in prospective studies.[31]

Scientific publications on systematic QoL investigations in meningioma patients are scarce.[32] Low compliance precluded evaluation of QoL data between the 2 treatment arms of our trial. However, we could document that enrolled patients had severely impeded global QoL and overall functionality and high level of fatigue already before initiation of systemic therapy. This finding may explain the higher toxicity that was seen with trabectedin in meningioma patients enrolled in our trial (grade ≥3 AEs in 59% of patients) as compared to patients with sarcoma (grade ≥3

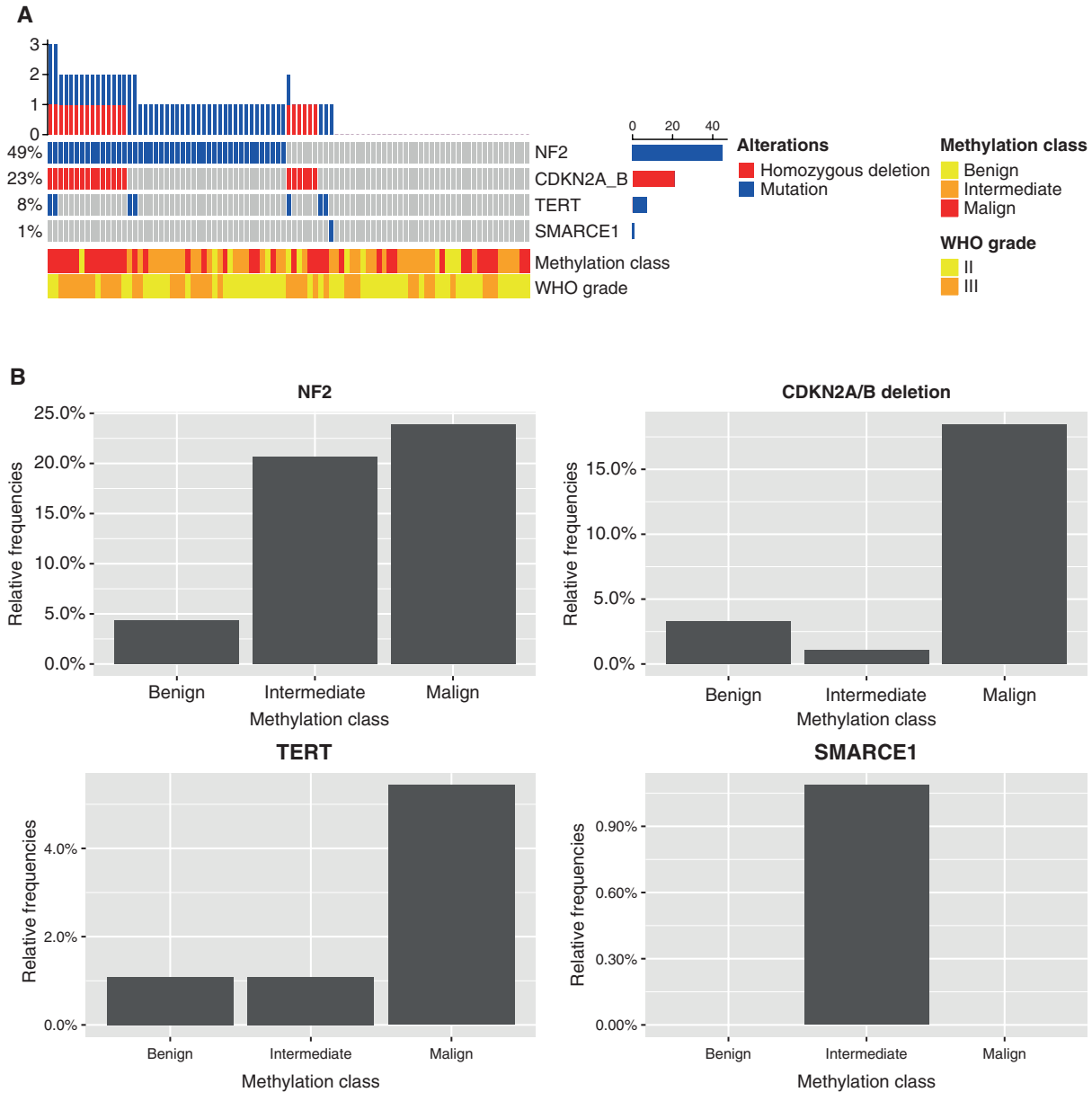

Fig. 3 (A) Molecular alterations, methylation classes, and WHO grades in patients enrolled in the EORTC-1320-BTG trial. (B) Frequency of mutations according to methylation classes.

AEs in 24.2% of patients) and needs to be considered for therapy planning in the clinical setting and for design of future clinical trials.[33]

Recently, several molecular markers such as *TERT* promoter mutations, CDKN2A/B homozygous deletions, and DNA methylation profiles have been shown to correlate with prognosis in meningiomas.[2,16,34–36] At the time of design and initiation of the EORTC-1320-BTG trial, these prognostic factors were not known and therefore could not be considered as stratification factors. Future studies should use updated meningioma classification schemes that integrate molecular tumor features with prognostic relevance to exclude potential bias, such as imbalanced distribution between treatment arms. However, we demonstrate in unplanned post hoc analyses that the presence of *TERT* promoter mutations, CDKN2A/B homozygous deletions, and MC-malignant DNA methylation profile are relevant prognosticators of OS in patients with recurrent WHO grade 2 and 3 meningiomas. Importantly, our data show for the first time in a patient population enrolled in a prospective clinical trial that methylation profiling is the only molecular marker independently associated with OS and should thus be preferred for use in clinical decision-making and clinical trial design. Predictive molecular

alterations for response to trabectedin are not known and could therefore not be used for patient enrichment in our trial. In exploratory analyses of our study, we identified NF2 mutation status as potential predictive molecular factors for response to trabectedin therapy. This finding should be investigated in further studies.

In conclusion, our trial shows that in comparison to LOC treatment, trabectedin does not prolong median PFS or OS and is associated with higher toxicity in patients with WHO grade 2 or 3 meningiomas after exhaustion of surgery and radiotherapy. However, we demonstrate that multinational collaboration enables completion of prospective randomized clinical trials with stringent inclusion criteria in this indication, which may provide benchmark data for future clinical trials. Clinical management of recurrent meningioma patients should consider global QoL and overall functionality impairments, high levels of fatigue, and the independent prognostic role of tumor DNA methylation profiles.

Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

Keywords

clinical trial | DNA methylation class | meningioma | quality of life | trabectedin

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Authorship statement. The trial was developed by the principal investigator (M.P.) in collaboration with W.W., M.W., and the leading investigators for neuroimaging (M.B.), neuropathology (C.Maw), health-related quality of life (J.C.R.) as well as the EORTC headquarters (C.C., T.G., and V.G.). All data have been reviewed by EORTC headquarter staff and M.P., M.W., and W.W. where appropriate. Statistical analyses were performed by T.G. Translational research and molecular marker evaluation were coordinated and performed by M.P., C.Mar, F.S., and M.J.M. The literature search was done by M.P. Data were collected by all authors. The data were analyzed by M.P., T.G., V.G., M.W., and W.W. The manuscript drafts were written by M.P., V.G., M.W., W.W., and T.G. All authors approved the final version of the manuscript.

Data Sharing Statement

Data from this clinical trial will be shared after approval of a proposal and with a signed data access agreement with EORTC (https://www.eortc.org).

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