Everolimus and Octreotide for Patients with Recurrent Meningioma: Results from the Phase II CEVOREM Trial

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ABSTRACT

Purpose: Aggressive meningiomas that progress after surgery/radiotherapy represent an unmet medical need. Strong and constant expression of SSTR2A receptors and activation of the Pi3K/Akt/mTOR pathway have been demonstrated in meningiomas. The combination of everolimus, an mTOR inhibitor, and octreotide, a somatostatin agonist, has shown additive antitumor effect *in vitro*. The phase II CEVOREM trial investigated the efficacy of this combination on recurrent meningiomas.

Patients and Methods: Patients with documented recurrent tumor progression ineligible for further surgery/radiotherapy were eligible to receive octreotide (30 mg/d, day 1) and everolimus (10 mg/d, days 1–28). The primary endpoint was the 6-month progression-free survival rate (PFS6). The secondary endpoints were overall survival, response rate, tumor growth rate according to central review, and safety.

Results: A total of 20 patients were enrolled, including 2 with World Health Organization (WHO) grade I tumors, 10 with WHO grade II tumors, and 8 with WHO grade III tumors; furthermore, 4 patients harbored *NF2* germline mutation. The overall PFS6 was 55% [95% confidence interval (CI), 31.3%–73.5%], and overall 6- and 12-month survival rates were 90% (95% CI, 65.6%–97.4%) and 75% (95% CI, 50.0%–88.7%), respectively. A major decrease (>50%) was observed in the growth rate at 3 months in 78% of tumors. The median tumor growth rate decreased from 16.6%/3 months before inclusion to 0.02%/3 months at 3 months ($P < 0.0002$) and 0.48%/3 months at 6 months after treatment ($P < 0.0003$).

Conclusions: The combination of everolimus and octreotide was associated with clinical and radiological activity in aggressive meningiomas and warrants further studies. Decrease in the tumor volume growth rate should be considered a complementary and sensitive endpoint to select potentially effective drugs for recurrent meningiomas.

Introduction

Despite multiple surgeries and radiotherapy/radiosurgery sessions, recurrent meningiomas constitute an unmet medical need and an actual challenge in neuro-oncology. The 6-month progression-free survival rate (PFS6) is estimated to be 11%–15% in untreated recurrent meningiomas, and treatment is considered of interest if PFS6 exceeds 35% (1). In the past few decades, systemic therapies have failed to show a clear signal of treatment efficacy and substantial clinical benefits (2–6). Recent targeted therapies such as bevacizumab- and sunitinib-based therapies may improve PFS6 in multi-recurrent meningiomas (7, 8).

SSTR2A receptors are expressed in most meningiomas and are strongly expressed in approximately 70% of cases (9). Octreotide has been associated with tumor volume stabilization in patients with World Health Organization (WHO) grade I meningiomas (10), whereas the results of studies on aggressive meningiomas have been unsatisfactory (4–6). Recently, the Pi3K/Akt/mTOR pathway was demonstrated to be hyperactivated in most meningiomas (11–13). Merlin encoded by *NF2* is a negative regulator of mTORC1 (13, 14). The loss of this function seems crucial for *NF2*-dependent tumorigenesis and suggests mTORC1 to be a potential therapeutic target in meningiomas. *In vitro* mTOR inhibition has an antiproliferative effect on meningiomas (9, 12, 15), and an antitumor effect of everolimus has been documented in a case of metastatic WHO grade III meningioma (16). Given these expressions of SSTR2A receptors and the role of the Pi3K/Akt/mTOR pathway in meningiomas, we recently showed that the combination of octreotide with everolimus, an mTOR inhibitor, had an additive antiproliferative

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Prior presentation: Presented at the ASCO Congress 2017 Abstract 2011; EANO Congress 2016; and EANS Congress 2017.

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Clin Cancer Res 2020;26:552–7

doi: 10.1158/1078-0432.CCR-19-2109

Translational Relevance

For aggressive and recurrent meningiomas, therapeutic alternatives are particularly limited. The hyperactivation of the mTOR pathway is demonstrated as strong SSTR2A receptor expression in meningiomas. On the basis of our preclinical studies that assessed the additive antiproliferative effect of the combination of everolimus and octreotide on meningiomas, we set up a clinical trial on the combination of everolimus and octreotide in aggressive meningiomas not amenable to any form of surgery/radiotherapy. Given the declined tumor growth activity in this study, the combination of everolimus and octreotide could be considered an option for meningiomas. Analysis of tumor growth rate should be considered in future clinical trials on meningiomas, which can provide a highly sensitive pretherapeutic versus posttherapeutic efficacy marker.

effect on a large series of meningiomas of different WHO grades *in vitro* (15).

These results led us to conduct a prospective, multicenter, single-arm phase II study on the combination of octreotide and everolimus in patients with recurrent meningiomas who were ineligible for further surgery/radiotherapy.

Patients and Methods

CEVOREM is an open-label, prospective, multicenter, single-arm phase II study sponsored by Assistance Publique-Hôpitaux de Marseille supported by French National Cancer Institute funding (PHRC K 2013) and registered at www.clinicaltrials.gov (NCT02333565). This study was conducted at two centers in France, that is, La Timone Hospital (Marseille, France) and La Pitié-Salpêtrière Hospital (Paris, France) in accordance with the Declaration of Helsinki. Drugs were provided by Novartis Pharma. The study was approved by the Aix-Marseille University Institutional Review Board, and each patient provided written consent before inclusion.

Everolimus (Afinitor, Novartis) was orally administrated at a fixed dose of 10 mg/day. Doses could be decreased by 5 mg in case of adverse events (AE). Furthermore, 30 mg octreotide LAR (Sandostatin Long Acting Releasing, Novartis) was administrated monthly by an intramuscular injection until tumor progression. Study duration was 1 year that was extended to 3 years in case of disease stabilization.

The inclusion criteria were as follows: aged at least 18 years old with Karnofsky Performance Status of $\geq$50%, histologically confirmed meningioma of grade I, II, or III, and ineligible for further surgery/radiotherapy. In addition, inclusion required a documented progression based on two different MRIs performed before inclusion, with an increase in two-dimensional (2D) tumor area of $\geq$5%/3 months or $\geq$10%/6 months. The 2D tumor area was calculated as the product of the largest tumor diameter and its largest perpendicular diameter on the same slide. A history of systemic therapy was acceptable. Life expectancy of >3 months and adequate hematologic, renal, and hepatic functions were also required.

Patients were clinically evaluated on a monthly basis. Cerebral MRI was performed at inclusion and then every 3 months until progression. 3D T1-weighted gadolinium-enhanced millimetric MRI was performed for all patients. The determination of progression was assessed according to the Response Assessment in Neuro-Oncology (RANO) criteria (17). A complementary central preplanned imaging review involved two reviewers and one adjudicator who were blinded to the clinical data of patients. The maximum tumor diameter, 2D tumor area, and 3D volume were assessed for 99 MRIs (IplanNet Software, Brainlab). Tumor volume was calculated on the basis of region of interest for the contrast-enhanced component of tumors as delineated by reviewers. Results are expressed in cm^3/3 months and percent of tumor volume growth/3 months. Patients with a treatment duration of <2 months, missing data, or nonmeasurable initial volume or very high tumor growth rate ($\geq$300%/3 months) were excluded from the growth rate substudy.

Central neuropathology review was performed on the last operated sample according to the WHO classification. For patients with NF2, several tumor fragments were analyzed and the most aggressive histology was considered (**Table 1**; Supplementary Table S1). SSTR2A receptor expression was evaluated by performing IHC on the last operated tumor sample. SSTR2A expression was scaled according to the immunoreactivity score. For molecular analyses, DNA was extracted from formalin-fixed, paraffin-embedded meningioma sections (18). In total, 13 genes (*NF2, AKT1, SMO, KLF4, TRAF7, PIK3CA, SUFU, SMARCB1, SMARCE1, CDKN2A, CDKN2B, PTEN*, and *TERT)* were sequenced using the QIAseq Targeted DNA Custom Panel (Qiagen), and *NF2* deletion/duplication was assessed by qRT-PCR (ref. 19; Supplementary Table S2).

Study design and statistical analysis

The primary endpoint was PFS6 according to the RANO Criteria in the intention-to-treat population analysis (ITT). Considering the PFS6 of such tumors as approximately 10% (1, 20), our hypothesis was that the combination of everolimus and octreotide improves this rate up to 40%. A sample size of 20 individuals allows the estimation of this rate

Table 1. Patient characteristics.

Characteristics	(*n* = 20)
Age (years), median (range)	55 (30–75)
Patient with *NF2* germline mutation	4
Number of growing tumors	35
in NF2 patients	15
in non-NF2 patients	20
Karnofsky performance status, *n* (%)	
90–100	4 (20)
70–80	12 (60)
<70	4 (20)
Tumor grade, *n* (% patients)	
I	2 (10)
II	10 (50)
III	8 (40)
Tumor location, *n* (% tumors)	
Skull base	9 (26)
Convexity, parasagittal	21 (60)
Intraventricular	4 (11)
Previous surgery, *n* (%)	
One	2 (10)
Multiple	18 (90)
Previous radiotherapy or radiosurgery, *n* (%)	
None	1 (5)
One	10 (50)
Multiple	9 (45)
Previous chemotherapy, *n* (%)	
Yes	5 (25)
No	15 (75)

with a degree of precision at 20% (80% power and 5% alpha risk). Secondary endpoints included median PFS, 12-months PFS rate (PFS12), 6-and 12-month overall survival rate (OS6 and OS12), 3D tumor growth rate assessment before inclusion and at 3 and 6 months after treatment, and safety. Exploratory endpoints were SSTR2A receptor expression quantification, *NF2* mutation identification, and their association with PFS. PFS and OS were estimated using the Kaplan–Meier method with 95% confidence intervals (CI). Perprotocol (PP) population was defined as the population that fulfilled the inclusion and exclusion criteria, as well as underwent at least 2-month treatment. Comparison of the tumor growth rate and SSTR2A receptors expression were performed using Wilcoxon paired test. Safety was assessed as per the NCI Common Terminology Criteria for Adverse Event version 4.0.

Results

Patients

Between February 2014 and May 2015, 20 patients (9 males and 11 females) were included with 35 progressive meningiomas (**Table 1**; Supplementary Fig. S1; Supplementary Table S1). Patient characteristics are reported in **Table 1**. Among these, 2, 10, and 8, had WHO grade I, II, and III tumors. The median preinclusion surface growth rate was 42%/3 months (range: 10%/3 months–269%/3 months; Supplementary Fig. S2). Five patients had previously received medical therapy (hydroxyurea, temozolomide, bevacizumab, and IFNα). At the time of clinical data cutoff, the median follow-up was 21 months and 1 patient was undergoing treatment.

Treatment efficacy and impact on tumor growth rate

The median and total number of treatment cycles administrated was 7 and 190 cycles, respectively. In ITT population analysis, PFS6 was 55% (95% CI, 31.3%–73.5%), PFS12 was 30% (95% CI, 12.2%–50.1%), and median PFS was 6.6 months (95% CI, 2.7–15.0 months; **Fig. 1**). Two patients were considered nonevaluable and were not included in PP analysis because their treatment duration was <2 months (Supplementary Fig. S1). In PP analysis, PFS6 was 61.1% (95% CI, 35.3%–79.2%) and PFS12 was 33.3% (95% CI, 13.6%–54.5%). Long-term tumor growth control (i.e., >2 years) was observed in 3 patients (Supplementary Fig. S1). OS6 (ITT) was 90% (95% CI, 65.6%–97.4%) and OS12 was 75% (95% CI, 50.0%–88.7%). Although no complete or partial response as defined according to the RANO criteria was observed, disappearance of two separate subcutaneous nodules was observed in 1 patient under treatment.

The independent MRI review showed consistent results for PFS analysis (Supplementary Table S3). Among the 20 study patients, a decrease was observed in the tumor volume of >10% in 4 patients (eight tumors) at 3 and 6 months. Then, we compared volume growth rate before inclusion and during treatment (**Table 2**). Patients with tumor progression at 3 months were not considered for the 6-month analysis. Among the 35 tumors with documented progression at baseline, data were available for 27 tumors (15 patients) at 3 months and 18 tumors (10 patients) at 6 months. A major decrease (>50%) was observed in the volume growth rate in 78% of patients (21/27 cases) at 3 months and 67% (12/18 cases) at 6 months. The mean and median volume growth rates at 3 and 6 months are reported in **Table 2**. The volume

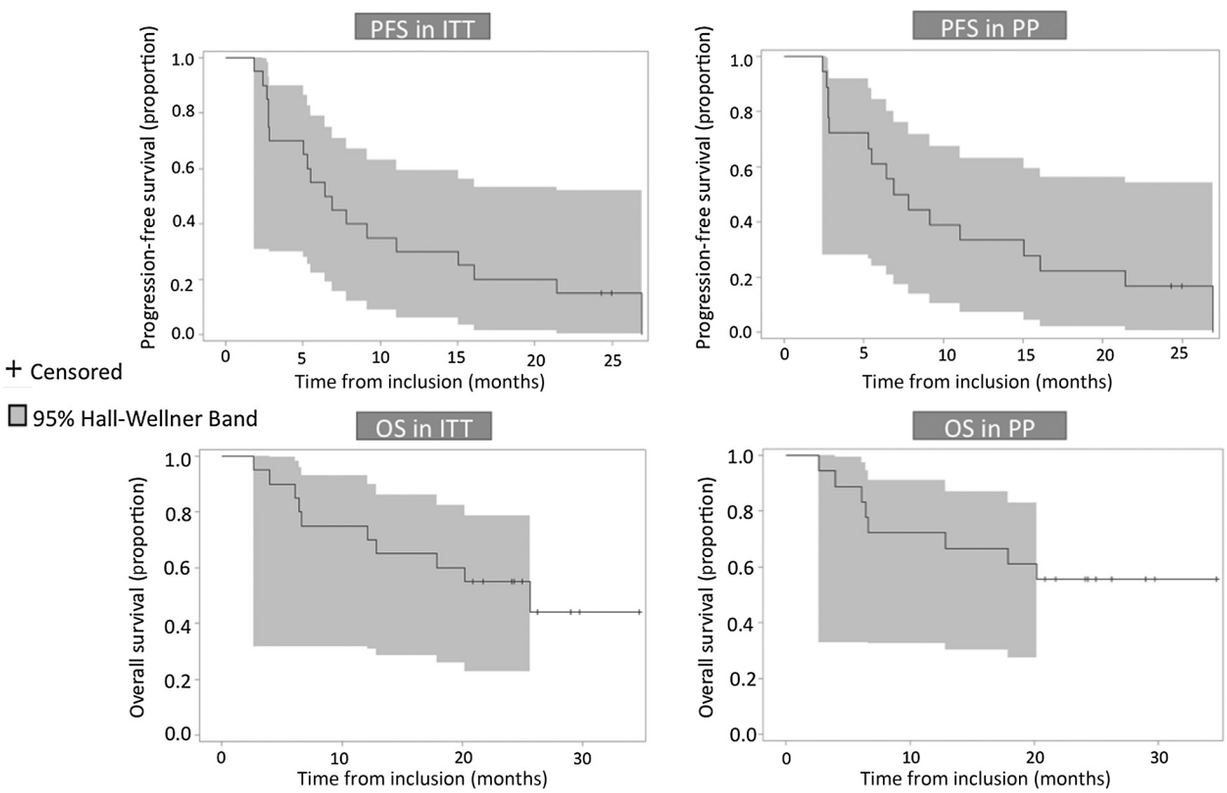

Figure 1.
Kaplan–Meier curves for PFS and OS in ITT and PP population analyses.

Table 2. Mean and median tumor growth rate before inclusion and under treatment (expressed in %/3 months) at 3 and 6 months, and 27 tumors were analyzed at 3 months and 18 tumors at 6 months.

Growth rate (%/3 months)	Before treatment	Under treatment	*P*
At 3 months ($n = 27$)			
Mean	43.5	4.2	0.0002
Median	16.6	0.02	0.0002
At 6 months ($n = 18$)			
Mean	49.0	5.0	0.0003
Median	19.2	0.48	0.0003

growth curves of six selected meningiomas are represented in **Fig. 2** (Supplementary Fig. S3).

No association was observed between the WHO grade, the Ki67, and antitumor activity. In 4 of 5 patients previously treated with different medical therapies, tumor control was maintained for at least 6 months.

Exploratory *NF2* and SSTR2A analyses

Tumor tissues were available for 18 of the 20 patients, of which 14 were analyzable, including the 4 patients with NF2 (i.e., with *NF2* germline mutation). *NF2* mutation/deletion was found in 13 of 14 analyzed meningioma tissues (Supplementary Tables S2 and S4), including those of the 4 patients with NF2 and 1 with concomitant *SMO* mutation, confirming that *NF2* mutation is present in a large majority of cases of aggressive meningiomas. No other gene from the panel was mutated in the analyzed tumors (Supplementary Table S4). Among the 12 *NF2*-mutated tumors analyzable for treatment efficacy (in PP), seven (58%) were controlled at 6 months. A major decrease was observed in the tumor growth rate (>50%) in 17 of 25 (68%) *NF2*-mutated meningiomas at 3 months. In 1 patient with non-*NF2*--mutated tumor, the tumor growth rate transiently decreased from 30%/3 months to 9%/3 months at 3 months and increased to 30%/3 months between 3 and 6 months.

No association was observed between SSTR2A receptor expression and PFS or tumor growth rate before inclusion and under treatment (Supplementary Fig. S4).

Safety

Stomatitis was diagnosed in 11 of 20 study patients (55%) including 3 with grade III AEs, requiring discontinuation of both drugs in 1 patient and everolimus alone in another patient. The incidence of AEs is presented in **Table 3**.

Discussion

Our results strongly suggest that the combination of everolimus and octreotide is effective in aggressive meningiomas (10 grade II and 8 grade III among the 20 study patients; ref. 1). Limited data are available on the potential efficacy of everolimus including one case report (16) and one phase II testing the association between everolimus and bevacizumab in 17 patients with a PFS6 of 69%. Notably, in that study, a higher proportion of patients with grade I meningiomas (5/16) were included and 1 patient was excluded for early progression. Furthermore, 4 patients discontinued the treatment due to toxicity (21). Given the PP population related to PFS6 in this study of 61% combined with a lower proportion of patients with grade I meningiomas, the added value of everolimus and bevacizumab remains unclear, which increases more considering the PFS already reported for bevacizumab monotherapy in recurrent meningiomas (8, 10, 22–26), Other VEGF-targeting

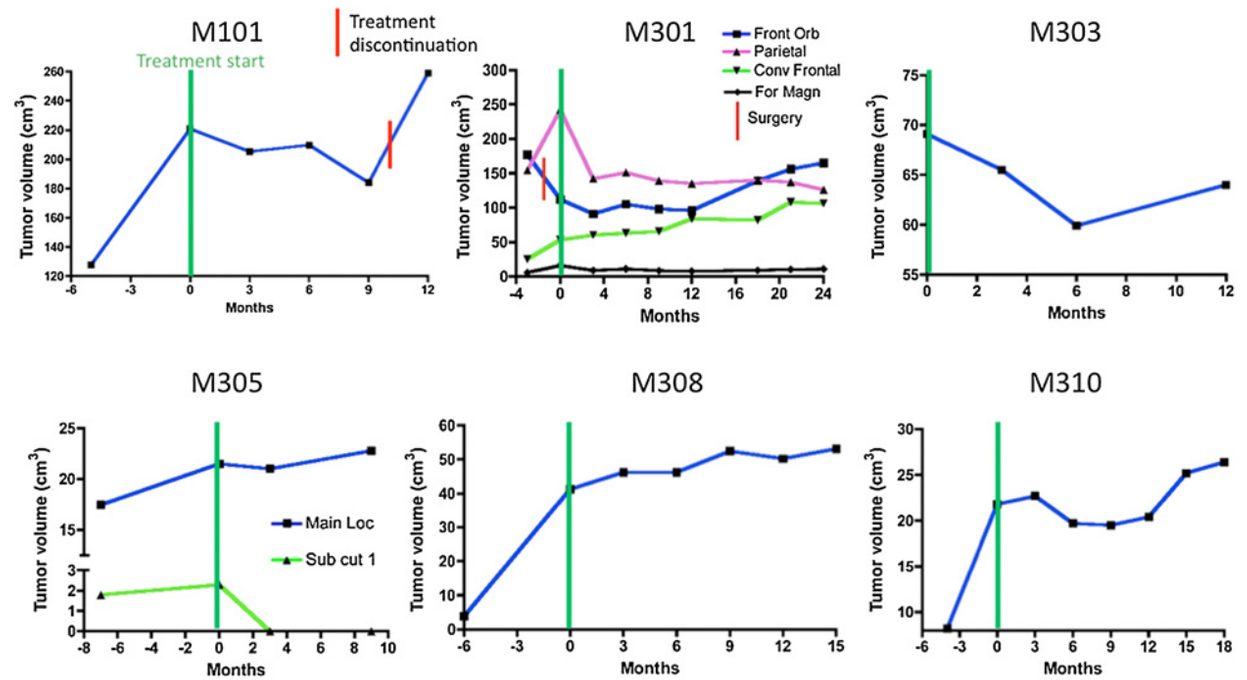

Figure 2.
Growth curves of selected meningiomas. Front Orb, fronto-orbital; Conv Frontal, convexity frontal; For Magn, foramen magnum.

Table 3. Adverse events.

AEs	All grades *n* (%)	Grade 3 *n*	Grade 4 *n*	Treatment discontinuation
Stomatitis	11 (55%)	3	0	1 both drugs 1 everolimus
Asthenia, fatigue	9 (45%)	1	0	
Abdominal pain, diarrhea	8 (40%)	0	0	
Hypercholesterolemia	9 (45%)	0	0	
Cutaneous rash	6 (30%)	0	0	
Hypertriglyceridemia	6 (30%)	1	0	
Hyperglycemia, diabetes	5 (25%)	0	0	
ASAT ALAT increase	4 (20%)	0	0	
Nausea and vomiting	3 (15%)	0	0	
Neutropenia	3 (15%)	0	1	
Pneumopathy	1 (5%)	1	0	
Cholelithiasis	1 (5%)	1	0	1 octreotide

agents have been analyzed in meningiomas including PTK787 in 25 patients (PFS6 of 64.3% for 14 patients with grade II meningiomas and 37.5% for 8 patients with grade III meningiomas; ref. 27) and sunitinib (PFS6 of 42% for 36 patients with grade II–III meningiomas and 4 with intratumoral hemorrhage; ref. 7).

Studies that have addressed the medical treatment for meningiomas are rare and often retrospective; in addition, many of these studies included heterogeneous population in terms of tumor grade and prior treatment (28). Moreover, considering that the definition of progressive disease at inclusion remains unclear in most meningioma trials (7, 21, 29, 30), the integration of a documented minimal pretreatment tumor growth rate as an inclusion criterion is novel and tends to homogenize patient population. Preinclusion tumor growth rate may substantially impact the measure of PFS6. Therefore, a slow growing WHO grade I meningioma with a 2D tumor growth rate at 5%/3 months will not be considered progressing at 6 months according to the RANO criteria, regardless of the drug effect. However, the 2D tumor growth rate area at 10%/3 months, which was proposed in this trial, seems to be very low and a preinclusion tumor growth rate of 15%/3 months or 30%/6 months could be more appropriate and could be considered for future trials.

Questions remain about the optimal way to assess drug efficacy in meningiomas. PFS6 assessment has been proposed as the primary endpoint to assess drug activity in meningioma-based medical trials and is commonly reported to allow comparison across trials. However, the degree of aggressiveness of included meningiomas directly impacts PFS6, and the RANO criteria have some limitations to screen potentially effective drugs in meningiomas. Radiological responses as defined by the RANO criteria remain extremely rare, and PFS6 does not consider preinclusion tumor growth rate (17). We showed that the 3D tumor growth rate analysis is more appropriate to identify a signal for treatment activity. We only included patients who demonstrated meningioma growth during 3–6 preinclusion months. Therefore, in complement to PFS6 analysis, 3D tumor growth rate analysis before inclusion and under treatment could be considered an endpoint in future trials (17), considering the pretreatment tumor growth rate as an adequate control. Comparison of tumor growth rate before inclusion and under treatment allows a comparative study as an uncommon but valuable internal control to detect a signal of treatment activity in phase II study.

Remarkably, our results are in accordance with the *in vitro* preclinical data (15). In several tumors including meningiomas, mTOR inhibition increases Akt phosphorylation, which contributes to the decrease in the efficacy of mTOR inhibitors (9, 12, 15). For meningiomas, we demonstrated that the adjunction of octreotide to everolimus *in vitro* decreased and reversed everolimus-induced Akt hyperphosphorylation and, thereby, improved the antiproliferative effect of everolimus. In addition, the combination of everolimus and octreotide improved cell-cycle inhibitory effect compared with those of individual drugs. The CEVOREM trial results cannot conclude on the clinical value of individual drug and their combination. However, our preclinical results suggest a better efficacy of combined drugs than that of monotherapies. In aggressive meningiomas, octreotide does not appear as an effective treatment based on PFS6 assessment (4–6), but data are limited to one case for everolimus monotherapy (16).

The combined drugs demonstrated to be well-tolerated in this study. AEs were consistent with those previously reported, highlighting the need for the prevention of stomatitis.

SSTR2A receptor expression was not found to be correlated with drug efficacy. *NF2* mutation/deletion was observed in 13 of the 14 analyzed tumors in accordance with the fact that aggressive meningiomas are *NF2* mutated (31). Consequently, the impact of the *NF2* status of the combination of drugs on clinical benefit could not be addressed. Therefore, although many patients seemed to benefit from the treatment, genomic analysis and SSTR2A immunostaining failed to predict drug response.

This study has certain limitations given the limited number of patients. In addition, although we tried to include a homogeneous group of patients with documented recurrent meningiomas, the preinclusion 2D tumor growth rate of 10% in 6 months seems suboptimal, whereas our data suggest that a higher preinclusion 2D tumor growth rate at 30%/6 months could be proposed. However, this study benefited from a strong preclinical rationale, that is, a prospective and comparative (3D tumor growth rate before inclusion vs. that under treatment) phase II design rare in meningiomas.

Conclusions

This prospective phase II study on the combination of everolimus and octreotide met its primary endpoint and displayed antitumor activity. These results warrant further studies to evaluate the efficacy of everolimus and octreotide in a randomized trial. The exploratory endpoint of 3D tumor growth rate is reliable to analyze treatment efficacy in meningiomas and could be considered a reference tool in clinical trials on meningiomas.

Disclosure of Potential Conflicts of Interest

A. Idbaih reports receiving commercial research grants from Carthera, Sanofi, Transgene, Air Liquide, and Leo Pharma. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T. Graillon, M. Sanson, A. Idbaih, M. Peyre, H. Peyrière, D. Autran, M. Boucekine, K. Baumstarck, A. Barlier, O.L. Chinot
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Acknowledgments

The study was supported by Institut National du Cancer (Inca, France), Association des Neuro-oncologues d'Expression Française (ANOCEF), Société Française de Neurochirurgie (SFNC), and ARTC Sud. Drugs were provided by Novartis Pharma. Novartis partly supported the transitional researches and imaging central review.

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Received July 3, 2019; revised September 4, 2019; accepted November 15, 2019; published first January 22, 2020.

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