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Authors

Goutagny, Stéphane
Raymond, Eric
Esposito-Farese, Marina
et al.

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CLINICAL STUDY

Phase II study of mTORC1 inhibition by everolimus in neurofibromatosis type 2 patients with growing vestibular schwannomas

Stéphane Goutagny · Eric Raymond · Marina Esposito-Farese · Stéphanie Trunet · Christian Mawrin · Daniele Bernardeschi · Béatrice Larroque · Olivier Sterkers · Marco Giovannini · Michel Kalamarides

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Abstract Neurofibromatosis type 2 (NF2) is a genetic disorder with bilateral vestibular schwannomas (VS) as the most frequent manifestation. Merlin, the *NF2* tumor suppressor, was identified as a negative regulator of mammalian target of rapamycin complex 1. Pre-clinical data in mice showed that mTORC1 inhibition delayed growth of NF2-schwannomas. We conducted a prospective single-institution open-label phase II study to evaluate the effects of everolimus in ten NF2 patients with progressive VS. Drug activity was monitored every 3 months. Everolimus was administered orally for 12 months and, if the decrease in tumor volume was >20 % from baseline, treatment was continued for 12 additional months. Other patients stopped when completed 12 months of everolimus but were allowed to resume treatment when VS volume was >20 % during 1 year follow-up. Nine patients were evaluable. Safety was evaluated using CTCAE 3.0 criteria. After 12 months of everolimus, no reduction in volume ≥20 % was observed. Four patients had progressive disease, and five patients had stable disease with a median annual growth rate decreasing from 67 %/year before treatment to 0.5 %/year during treatment. In these patients, tumor growth resumed within 3–6 months after treatment discontinuation. Everolimus was then reintroduced and VS decreased by a median 6.8 % at 24 months. Time to tumor progression increased threefold from 4.2 months before treatment to > 12 months. Hearing was stable under treatment. The safety of everolimus was manageable.

To the memory of Beatrice Larroque, who died accidentally as this paper was written.

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S. Goutagny
Neurochirurgie, Hôpital Beaujon, Assistance Publique Hôpitaux de Paris, 100 boulevard du General Leclerc, 92100 Clichy, France

E. Raymond
Service interhospitalier de Cancérologie, Hôpital Beaujon, Assistance Publique Hôpitaux de Paris, 100 boulevard du General Leclerc, 92100 Clichy, France

M. Esposito-Farese
Département d'Épidémiologie et de Recherche Clinique, Hôpital Bichat, Institut National de la santé et de la recherche médicale CIC-EC 1425, Assistance Publique Hôpitaux de Paris, 46 rue Henri Huchard, 75018 Paris, France

S. Trunet
Neuroradiologie, Hôpital Pitié Salpêtrière, Assistance Publique Hôpitaux de Paris, 47-83, boulevard de l'Hôpital, 75013 Paris, France

S. Trunet · O. Sterkers · M. Kalamarides
Faculté de Médecine, Université Pierre et Marie Curie, 91-105, boulevard de l'Hôpital, 75013 Paris, France

C. Mawrin
Department of Neuropathology, Institute of Biology, Otto-von-Guericke University, Leipziger Strasse 44, 39120 Magdeburg, Germany

D. Bernardeschi · O. Sterkers
Otolaryngologie, Hôpital Pitié Salpêtrière, Assistance Publique Hôpitaux de Paris, 47-83, boulevard de l'Hôpital, 75013 Paris, France

B. Larroque
Département d'Épidémiologie et de Recherche Clinique, Hôpital Beaujon, Assistance Publique Hôpitaux de Paris, 100 boulevard du General Leclerc, 92100 Clichy, France

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Although the primary endpoint was not reached, further studies are required to confirm the potential for stabilization of everolimus.

Keywords Neurofibromatosis 2 · Tumor stabilization · Time to tumor progression · Vestibular schwannoma · Meningioma

Introduction

Neurofibromatosis type 2 (NF2) is a rare autosomal-dominant tumor predisposition syndrome, with an incidence of 1 case in 33,000 live births [1]. NF2 patients develop multiple tumors including bilateral vestibular schwannomas (VS), associated with hearing loss, tinnitus, and/or balance disturbances [2]. The tumor burden presents usually early in life and clinical management is hampered by the variability of hearing loss and VS growth [3]. Standard management of NF2 is based on follow up and microsurgical resection of growing and/or symptomatic VS. However, surgical resection is associated with a significant rate of hearing loss and carries risks for facial function. Radiosurgery is an alternative therapeutic modality [4, 5].

Recently, targeted agents used in medical oncology have been used to treat NF2-related VS. In two retrospective studies, VEGF blockade with bevacizumab was followed by hearing improvement and tumor shrinkage in more than 50 % of progressive VS in NF2 [6–8]. Effect on meningiomas seems modest [9, 10]. The main drawbacks of bevacizumab are long-term side effects, particularly hypertension and proteinuria, and the cumbersome needs for intravenous infusion twice monthly [11]. Two Phase II trials are underway: one for hearing decline (NCT01207687) and a multicenter trial for hearing decline and/or tumor growth (NCT01767792). Two EGFR family kinase inhibitors, erlotinib and lapatinib, have also been evaluated. In a retrospective study of eleven NF2 patients treated with erlotinib, none experienced significant radiological changes [12]. However, lapatinib showed objective activity in four out of 17 NF2 patients with progressive VS in a phase II trial [13].

Recently, merlin, the *NF2* protein, has been identified as a novel negative regulator of mammalian target of rapamycin complex 1 (mTORC1); functional loss of merlin yielding activation of mTORC1 signaling in NF2-related tumors [14]. In a previous study, we have shown that mTORC1 inhibition by rapamycin reduced the severity of NF2-related Schwann cell tumorigenesis in several relevant in vitro and in vivo models without significant toxicity [15]. Concomitant with these preclinical studies, we administered rapamycin to an index patient with growing VS over a prolonged period of time resulting in a clinically meaningful delay to progression. Meanwhile, the rapalog everolimus, was approved by FDA for subependymal giant cell astrocytomas associated with tuberous sclerosis complex, another tumor predisposition syndrome with multiple benign tumors requiring long-term tumor control [16].

Altogether, those data led us to conduct a single institution open-label phase II study to evaluate the tumor-growth control activity and safety of everolimus in NF2 patients with VS.

Methods

Patients

Patients were recruited from our NF2 reference centre between January and March 2012. Patients older than 15 years, fulfilling diagnostic criteria for NF2 (NIH 1988), and with progressing VS were eligible. Progressing VS was defined as an increase in volume on MRI of at least 20 % in the previous 12 months, in patients for whom surgery or radiosurgery was not regarded as a primary option. In addition, inclusion required compliance with the protocol, and adequate bone marrow, liver, and renal functions.

Main exclusion criteria were radiation therapy in target lesions within 60 months preceding inclusion, long-term therapy with systemic immunosuppressive agents including corticoids, severe or uncontrolled medical conditions, malignancies within 3 years prior enrolment, major surgery or significant traumatic injury within 4 weeks, pregnancy or breast-feeding. Women of childbearing potential had to use adequate contraception, and had to have a negative pregnancy test before everolimus onset. The protocol was approved by the IRB "CPP Ile de France 1" n° 2011-juillet-12669. All participants provided written informed consent before enrolment according to National and International guidelines. The study is registered with ClinicalTrials.gov number NCT01490476.

M. Giovannini
Department of Head and Neck Surgery, David Geffen School of Medicine, University of California Los Angeles, 10833 Le Conte Ave, Los Angeles, CA 90095-1624, USA

M. Kalamarides (✉)
Neurochirurgie, Hôpital Pitié Salpêtrière, Assistance Publique Hôpitaux de Paris, 47-83, boulevard de l'Hôpital, 75013 Paris, France
e-mail: michel.kalamarides@psl.aphp.fr

M. Kalamarides
Institut National de la santé et de la recherche médicale, U1127, Institut cerveau moelle, 47-83, boulevard de l'Hôpital, 75013 Paris, France

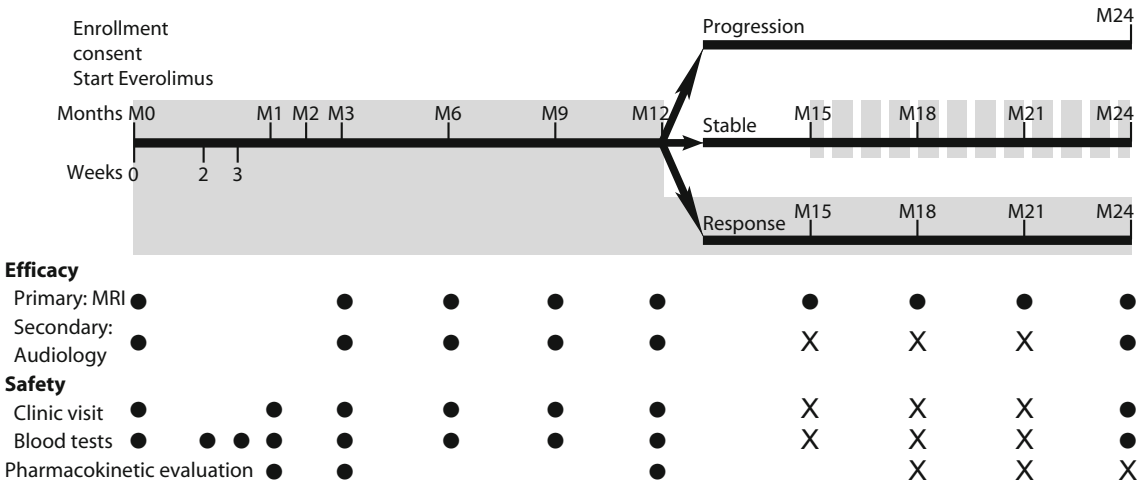

Fig. 1 Study design. NF2 patients were enrolled based on ≥20 % increase in VS volume during the year preceding the study and they received a 12-month course of everolimus (10 mg/day). Tumor volumetric evaluation was performed at 1 year. In case of response (decrease in volume ≥20 %), patients were kept on treatment. In case of stable disease (decrease/increase in volume <20 %), patients were followed up by MRI every 3 months, and treatment was resumed if tumor grew >20 % in volume. In case of progression (increase in volume ≥20 %), tumor MRI analysis was performed at 24 months. Surveillance modalities are depicted under the graph. *filled circle* all patients, *cross symbol* patients under treatment

Drug administration and safety

Study design is summarized in Fig. 1. Everolimus was started at 10 mg/day on continuous daily dosing for one year or until unacceptable toxicity. Adverse events were graded using version 3.0 of the National Cancer Institute Common Toxicity Criteria (CTCAE). Dose reduction to 5 mg/day was permitted in patients who experienced toxicity. Pharmacokinetic evaluation was performed to check for compliance and monitor plasma levels.

Radiological measurements of tumor volume

Imaging was done using a 1.5-T clinical MRI scanner (Philips Healthcare, Amsterdam, Netherlands). Tumor target volume was assessed on three-dimensional gradient echo Tl-weighted post-Gadolinium sequences with 0.7-mm slice thickness, no gap, by manual segmentation in OsiriX 4.1.2 software (OsiriX, Geneva, Switzerland). Two investigators (SG and ST) independently measured tumor volumes and the mean of the two volumes was considered. When the difference between the two measurements was ≥5 %, a joint review was conducted to reach consensus. The primary endpoint was the volume of the target VS at 12 months and quoted as follows, compared to the baseline VS volume. Response was defined as ≥20 % reduction in tumor volume from baseline. Progression was defined as ≥20 % increase in volume, and tumors that showed <20 % reduction and >20 % increase in volume were categorized as stable [17]. In case of stable disease, everolimus was stopped and patients were subsequently monitored every 3 months for 1 year, and treatment was resumed in case of VS growth >20 %. Everolimus was discontinued in patients with progression and a follow up visit planned at M24. Volumetric MRI at baseline, M12 and M24 also assessed all measurable intracranial non-target tumors. Time to tumor progression (TTP) was defined as the interpolated time needed for a tumor to increase in volume of 20 %, before and during treatment.

Functional evaluation on hearing

Changes in hearing function were measured by pure tone average (PTA) and speech discrimination scores (SDS). PTA for each ear was the mean of the individual threshold frequencies at 500, 1,000, 2,000, and 4,000 Hz. An increase of ≥10 dB in PTA between baseline and year-1 assessment values was considered hearing deterioration, while a decrease by ≥10 dB indicated an improvement in hearing. SDS was defined as the best word recognition score at presentation levels of up to 40 dB sensation level or maximum comfortable loudness [18].

This study utilized the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 for grading toxicities (http://ctep.cancer.gov).

Immunohistochemical (IHC) analysis

Paraffin-embedded tissue sections from three VS resected shortly after everolimus discontinuation (patients #3, #4, #8) and from a control group of ten growing VS from sex- and age-matched NF2 patients, were immunostained with

phospho-AKT (Ser473) and phospho-P70S6K (anti S6K1-phospho S235 + S236): Santa Cruz Biotechnology, and Ki-67/Mib-1: Dako. Quantitative analysis was made by one author (CM) [19, 20].

Statistical methods

Sample size was calculated using a single-stage A'Hern design, under the null and alternative hypothesis for a response rate of ≤5 and ≥45 %, respectively. The overall Type I error was 0.05 with a power of 90 % [21]. Ten patients were to be enrolled. Everolimus was to be considered effective if the number of responses was ≥3. Results were given as median (inter quartile range), unless otherwise specified. Progression rate at time T (PR) with respect to inclusion time M0 ($PR = 100 \times (VT - VM0)/VM0$) was calculated for all time-points of available MRI volumes (between 2 and 4 before inclusion, and every 3 months after), for nine patients. PR was compared between intervention conditions periods, before treatment (the reference period), and during treatment, using linear mixed effect models (random intercept and slope) to account for repeated measures over time [22, 23]. The model included time (in month), period, and time-by-period interaction as fixed effect factors.

Results

Patient and tumor characteristics

Ten patients were enrolled between January and March 2012. Most patients were active young adults with NF2 whose baseline characteristics are listed in Table 1. All ten patients completed the 12-month treatment and were evaluable for safety. One patient with a small intracanalicular VS was not evaluable for assessment of tumor volume on MRI, as the calculations could not reach consensus on final review analysis due to distortions of an ipsilateral cochlear implant. However, this patient remained evaluable for safety.

The median volume of target VS at inclusion was 4.0 cm^3 (IQR 0.67–13), and the median growth rate between pre-treatment MRI and M0 MRI was 34 % (IQR 26–49) for a median time interval of 5.9 months (IQR 3.7–9.9).

Radiological evaluation of drug activity

After 12 months of treatment, no reduction in tumor volume ≥20 % was observed at 12 months (Fig. 2), and four patients showed progression. Thus the study did not reach the primary goal. Nevertheless, five patients had stable disease with a median annual growth rate decreasing from 67 %/year (IQR 64–79) before treatment to 0.5 %/year (IQR −6.5 to 17) during treatment with everolimus.

Per protocol, lack of volume reduction after 12 months of treatment led to discontinuation of everolimus. During surveillance, one patient with stable disease (−0.5 % VS volume change on everolimus) experienced rapid decreased hearing and balance deterioration 2 months after everolimus discontinuation, associated with marked tumor growth (+40 % in 2 months). This patient went off protocol since the VS was surgically removed. Three other patients who were previously stable, showed a markedly rapid increase of VS volume of 90, 36, and 25 % at 3 months, and one patient showed a 21 % volume expansion at 6 months after everolimus discontinuation. Thus, these four patients resumed everolimus, and at M24, VS volumes were 4.3, −9, −17.7, and −4.5 %, compared to the values before resuming the treatment.

Table 1 Baseline characteristics of ten NF2 patients enrolled

Patient	Sex	Age at treatment onset	Age at diagnostic of NF2	*NF2* mutation	Other intracranial tumors	Spinal tumors	Surgery for contralateral vestibular schwannoma
#01	M	16.7	10	c.538_1422dup	Yes	Yes	Yes[a]
#02	F	42	38	None identified	No	No	Yes
#03	M	29.4	22	None identified	No	Yes	Yes
#04	M	26.8	22	c.1535delC	Yes	Yes	No
#05	F	21	10	c.1096G > T	Yes	Yes	Yes
#06	M	42.8	41	None identified	Yes	No	Yes
#07	F	24.3	19	c.1396c > t	Yes	Yes	Yes
#08	F	24.7	16	c.774G > A	No	No	Yes
#09	F	23.8	19	None identified	Yes	Yes	Yes
#10	M	26	21	None identified	Yes	Yes	Yes

[a] Radiosurgery

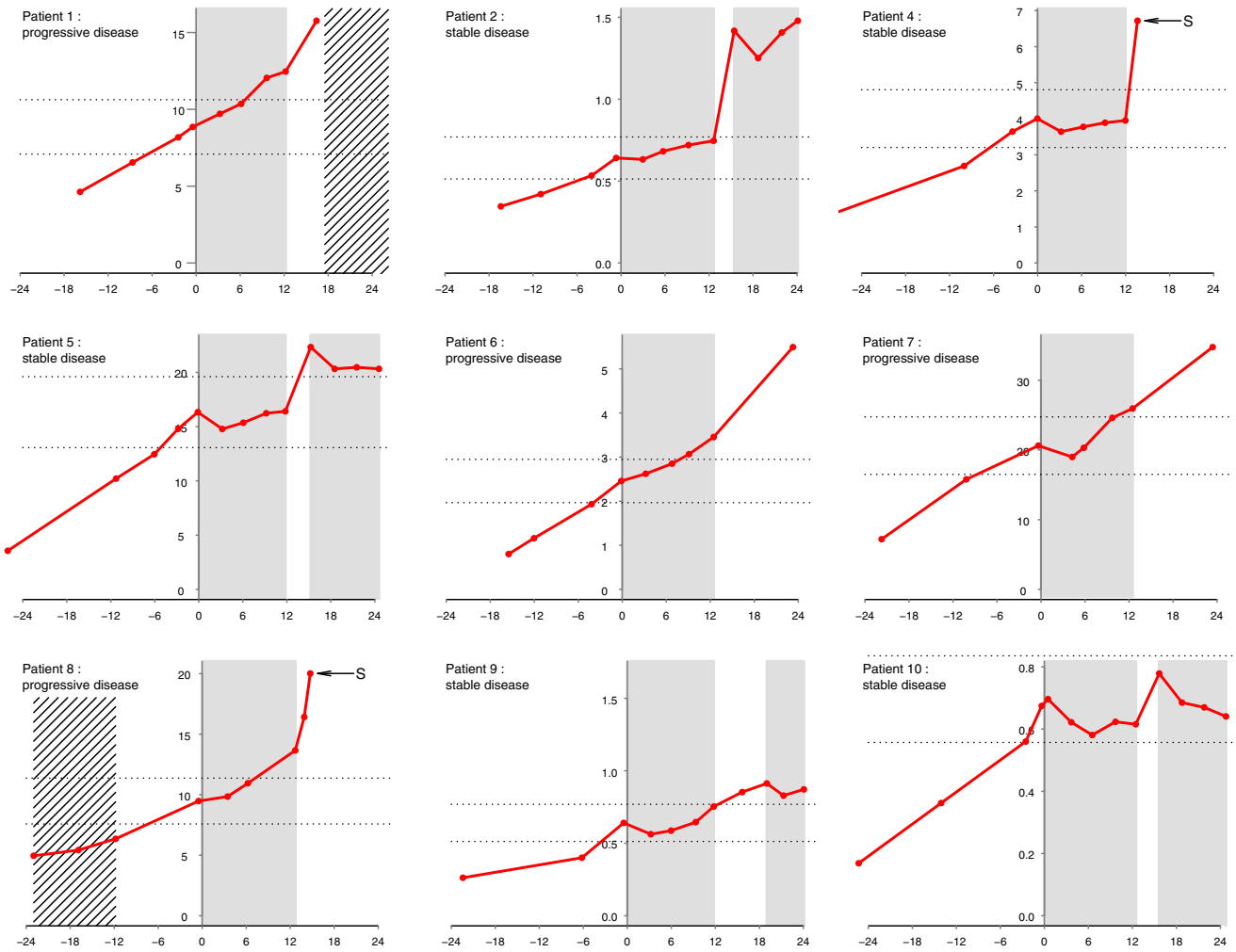

Fig. 2 Volumetric evolution of target vestibular schwannoma in NF2 patients. *Grey background* period of treatment with everolimus; *crosshatched background* treatment with bevacizumab; *S* surgical removal of target vestibular schwannoma. The *horizontal dotted lines* represent +20/−20 % tumor growth

For the four patients with progression, VS was partially removed by surgery in one patient, bevacizumab was started in another one, and two patients were kept under observation with continuous tumor growth (59 and 34 %/year between M12 and M24).

In an unplanned secondary analysis, mixed effects models showed that the time-by-period interaction for PR was highly significant ($P = 0.0004$), indicating that the PR evolution was slower during treatment. Accordingly, median TTP was 4.2 months (IQR 2.9–5.8) before treatment, and was not reached during the 12 months everolimus therapy (Fig. 3). As previously reported in an index NF2 patient treated with rapamycin [15], a concentration-dependent response was observed. Everolimus blood trough levels were higher in stable patients than in progressive patients (median 22.7 µg/mL (IQR 16.5–30.2) versus 10.6 (IQR 9.7–15.5), $P = 0.03$ Mann–Whitney test).

Other per protocol evaluations of drug effects

Nine non-target lesions, including two contralateral VS, one trigeminal schwannoma and six meningiomas were also analyzed (see Online Resource 1). Everolimus treatment did not induce tumor shrinkage, but seemed to delay the volumetric growth of all nine non-target lesions. In particular, the median TTP of meningiomas was 5.5 months before everolimus and increased to more than 12 months on treatment (see Online Resource 2).

None of the patients experienced change in hearing under treatment. SDS remained the same between M0 and M12 (100 % except for patient #1, 0 %). PTA remained stable except for patient #1 who experienced PTA decline (from 82 to 120 dB) in a non-useful hearing ear (median PTA 17 dB (IQR 9.5–29) at M0 vs. 18 dB (IQR 10–27) at M12). After treatment discontinuation, two of four patients

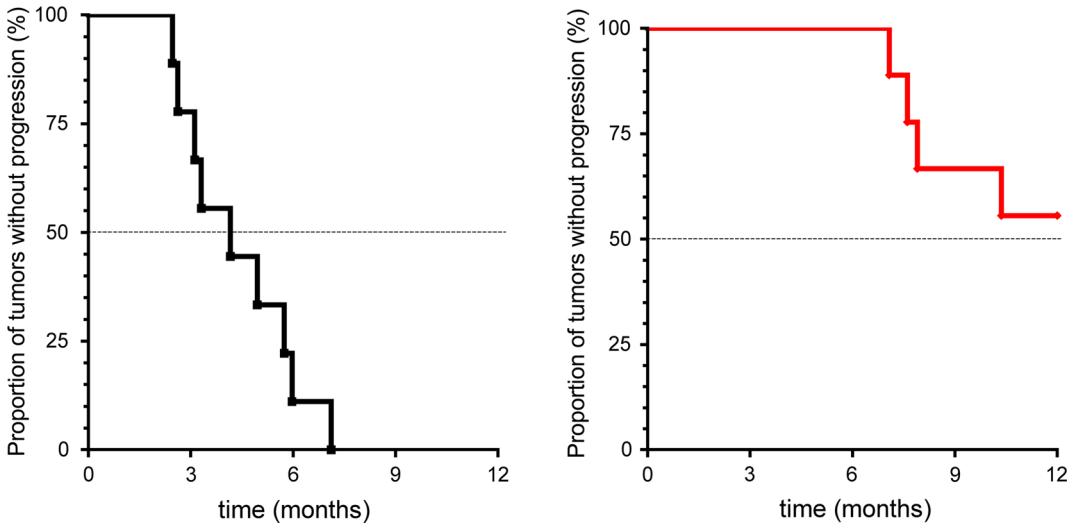

Fig. 3 Time to progression of target vestibular schwannomas in NF2 patients. Median interpolated time to progression before everolimus treatment was 4.2 months, and was more than 12 months under treatment. *Left panel* before treatment, *right panel* during everolimus treatment

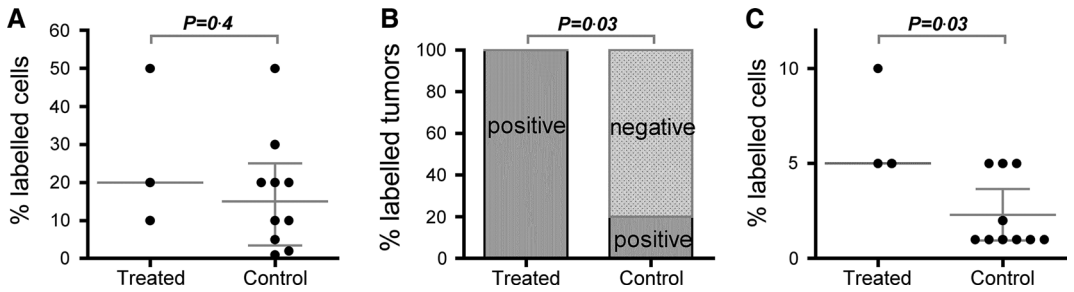

Fig. 4 Expression analysis of phospho-AKT (**a**), phospho-S 6 Kinase (**b**) and Ki-67 (**c**) in three vestibular schwannomas (VS), resected shortly after everolimus discontinuation. The immunohistochemical results were compared to ten control VS from NF2-patients. *P* values were determined by Wilcoxon rank test (**a**, **c**), and Fisher test (**b**). p-P70S6K: phospho S6 Kinase; pAKT: PhosphoAKT

experienced hearing decline (−13 dB, see Online Resource 3), associated with tumor growth. Re-introduction of everolimus was associated with a restoration of PTA to previous levels (15, 32, 6, and 27 dB at M24).

Toxicity

All ten enrolled subjects were available for toxicity monitoring, and none was withdrawn due to serious adverse events. No patient experienced grade 4–5 toxicities (CTCAE 3.0). In one patient, dosage was decreased to 5 mg after 1 month because of grade 2 mouth ulcerations considered non-tolerable by the patient. Observed toxicity was otherwise mild to minor (grade 1–2), including mouth ulcers (100 %), cholesterol elevation (90 %), rash (70 %), headache (70 %), and fatigue (60 %), as commonly described for this drug. One grade 3 toxicity was noted consisting of a pathology-confirmed basocellular carcinoma that did not require further treatment.

Tumor tissue biomarker evaluation

Despite the small number of cases, the three VS that were resected 2 months after everolimus discontinuation (patients # 3, 4, and 8) were analyzed. All three tumors were benign schwannomas with no mitotic figures. Comparison of S6K and AKT phosphorylation of these three VS to archival VS samples from ten matching NF2 patients by IHC showed that the rate of AKT phosphorylation was similar in both groups, suggesting that VS growth was probably not related to a feedback activation of AKT pathway (Fig. 4) [24]. This is in line with our observation in schwannoma mouse model, where a small increase in phospho-AKT seen under rapamycin treatment normalized after treatment discontinuation [15]. The three VS exhibited marked elevated S6 phosphorylation as observed in our mouse schwannoma model, where tumor growth inhibition was dependent on continuous exposure to rapamycin, with S6 phosphorylation re-expression after rapamycin withdrawal.

Discussion

None of our nine patients treated with everolimus reached the primary endpoint (≥20 % reduction in tumor volume), showing that everolimus does not induce VS shrinkage in NF2 patients. However, in a secondary analysis putting growth rate under treatment in the perspective of individual growth rate before treatment and after treatment re introduction, we observed evidences suggesting the potential for everolimus to stabilize or delay tumor growth.

In fact, our preclinical study in a genetically engineered mouse NF2 model recapitulating schwannoma natural history was predictive of our current trial results: rapamycin significantly increased TTP by two-fold and was well tolerated over an extended period of time [15]. The choice of tumor shrinkage as the primary endpoint in our clinical study determines the negative result of this study. Retrospectively, this endpoint appeared as a far too stringent criterion for being applied to a drug with cytostatic properties. TTP evaluation could be more meaningful in future NF2 studies. Recently, TTP has been used as the primary endpoint to assess the activity of tiparfinib in a phase II trial in neurofibromatosis type 1 [25]. This novel, randomized, double-blinded flexible crossover design ensures that all participants could receive the drug, and that participants are kept on drug as long as no objective tumor progression is evidenced. This type of trial provides a sensitive and efficient means of assessing a new agent in a progressive disease with benign tumors.

Progressive hearing decline is a major concern in NF2 patients. Under everolimus treatment, hearing remained stable. However, in published series, time to hearing decline is 4.4 times slower than TTP and thus it would unlikely be captured in a 2 year-study [26]. Longer follow up time will be necessary for studies aimed to explore the effect of drug treatments on hearing function in NF2 patients.

During the completion of the study, Karajannis et al. published the results of a phase II study concluding that everolimus was ineffective for the treatment of progressive VS in nine NF2 patients [27]. In the Karajannis study, eight of nine evaluable patients had previously received lapatinib and/or bevacizumab that could have altered the biology of tumors prior to everolimus treatment. In addition, the natural history was not available for individuals before treatment. This precludes the possibility of evaluating modulations of TTP by everolimus and to capture a possible effect on tumor stabilization. Of note, their inclusion criteria required progression of VS, defined either on radiographic volumetric data or on audiologic data, but the discrepancy between TTP of these two criteria is too wide to aggregate them in a composite criteria. Similarly, Karajannis et al. did not observed a rebound effect after treatment cessation.

This rebound effect raises concern about the use of everolimus in NF2 patients. In Tuberous sclerosis complex, another genetic disorder leading to constitutive activation of mTORC1, sirolimus reduces the volume of angiomyolipomas, with re-growth of tumors after discontinuation of treatment [28]. In addition, mouse schwannoma regrowth was observed upon cessation of therapy, consistent with the cytostatic rather than cytotoxic effects of rapamycin [15]. Interestingly, our in vitro experiments showed that inhibition of mTORC1 by rapamycin reduced the size of merlin-deficient schwannoma cells by an average of 10 %. This observation could explain the frequent initial decrease of tumor volume, before the cytostatic effect is elicited. Consistent with this hypothesis, rapid tumor volumetric growth following treatment withdrawal likely reflects a sudden increase in cell size, accompanied by cell cycle re-entry and cell proliferation (increased Ki-67). Upon reintroduction of everolimus, VS stabilization was immediately resumed, indicating that inhibition of mTORC1 had a direct inhibitory effect on VS growth, which therefore cannot be ascribed to a "saltatory" VS progression pattern. A saltatory growth pattern was described in a single retrospective analysis of digitized MRI films and has never been reported in any other VS natural history series [29]. Based on our observation, we do not recommend stopping everolimus treatment when it led a stabilization of growing VS.

Our clinical evaluation of everolimus for NF2 is now in the extension phase to assess whether tumor stabilization can be safely maintained over a longer period of time (two additional years) in the four stabilized patients.

Conclusion

In this study, everolimus did not induce shrinkage of VS, but we have accumulated evidences for its effect on tumor stabilization or growth delay that could be beneficial for NF2 patients, especially early in disease course. Everolimus was reasonably safe, and preserved hearing, avoiding surgery or radiosurgery and their complications in patients with NF2. Further assessment in a specifically designed trial, possibly considering TTP as the primary endpoint, is now required.

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Conflict of interest The authors declare they have no conflict of interest.

Ethical standards The experiments comply with the current laws in France.

References

1. Evans DG, Howard E, Giblin C, Clancy T, Spencer H, Huson SM, Lalloo F (2010) Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A 152A(2):327–332
2. Asthagiri AR, Parry DM, Butman JA, Kim HJ, Tsilou ET, Zhuang Z, Lonser RR (2009) Neurofibromatosis type 2. Lancet 373(9679):1974–1986
3. Peyre M, Goutagny S, Bah A, Bernardeschi D, Larroque B, Sterkers O, Kalamarides M (2013) Conservative management of bilateral vestibular schwannomas in neurofibromatosis type 2 patients: hearing and tumor growth results. Neurosurgery 72(6):907–913
4. Mathieu D, Kondziolka D, Flickinger JC, Niranjan A, Williamson R, Martin JJ, Lunsford LD (2007) Stereotactic radiosurgery for vestibular schwannomas in patients with neurofibromatosis type 2: an analysis of tumor control complications and hearing preservation rates. Neurosurgery 60(3):460–468
5. Mallory GW, Pollock BE, Foote RL, Carlson ML, Driscoll CL, Link MJ (2014) Stereotactic radiosurgery for neurofibromatosis 2-associated vestibular schwannomas: toward dose optimization for tumor control and functional outcomes. Neurosurgery 74(3):292–301
6. Plotkin SR, Stemmer-Rachamimov AO, Barker FG, Halpin C, Padera TP, Tyrrell A, Sorensen AG, Jain RK, di Tomaso E (2009) Hearing improvement after bevacizumab in patients with neurofibromatosis type 2. N Engl J Med 361(4):358–367
7. Mautner V-F, Nguyen R, Knecht R, Bokemeyer C (2010) Radiographic regression of vestibular schwannomas induced by bevacizumab treatment: sustain under continuous drug application and rebound after drug discontinuation. Ann Oncol 21(11):2294–2295
8. Plotkin SR, Merker VL, Halpin C, Jennings D, McKenna MJ, Harris GJ, Barker FG 2nd (2012) Bevacizumab for progressive vestibular schwannoma in neurofibromatosis type 2: a retrospective review of 31 patients. Otol Neurotol 33(6):1046–1052
9. Goutagny S, Raymond E, Sterkers O, Colombani JM, Kalamarides M (2011) Radiographic regression of cranial meningioma in a NF2 patient treated by bevacizumab. Ann Oncol 22(4):990–991
10. Nunes FP, Merker VL, Jennings D, Caruso PA, di Tomaso E, Muzikansky A, Barker FG 2nd, Stemmer-Rachamimov AO, Plotkin SR (2013) Bevacizumab treatment for meningiomas in NF2: a retrospective analysis of 15 patients. PLoS ONE 8(3):e59941
11. Slusarz KM, Merker VL, Muzikansky A, Francis SA, Plotkin SR (2014) Long-term toxicity of bevacizumab therapy in neurofibromatosis 2 patients. Cancer Chemother Pharmacol 73(6):1197–1204
12. Plotkin SR, Halpin C, McKenna MJ, Loeffler JS, Batchelor TT, Barker FG (2010) Erlotinib for progressive vestibular schwannoma in neurofibromatosis 2 patients. Otol Neurotol 31(7):1135–1143
13. Karajannis MA, Legault G, Hagiwara M, Ballas MS, Brown K, Nusbaum AO, Hochman T, Goldberg JD, Koch KM, Golfinos JG, Roland JT, Allen JC (2012) Phase II trial of lapatinib in adult and pediatric patients with neurofibromatosis type 2 and progressive vestibular schwannomas. Neuro Oncol 14(9):1163–1170
14. James MF, Stivison E, Beauchamp R, Han S, Li H, Wallace MR, Gusella JF, Stemmer-Rachamimov AO, Ramesh V (2012) Regulation of mTOR complex 2 signaling in neurofibromatosis 2-deficient target cell types. Mol Cancer Res 10(5):649–659
15. Giovannini M, Bonne NX, Vitte J, Chareyre F, Tanaka K, Adams R, Fisher LM, Valeyrie-Allanore L, Wolkenstein P, Goutagny S, Kalamarides M (2014) mTORC1 inhibition delays growth of neurofibromatosis type 2 schwannoma. Neuro Oncol 16(4):493–504
16. Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, Witt O, Kohrman MH, Flamini JR, Wu JY, Curatolo P, de Vries PJ, Whittemore VH, Thiele EA, Ford JP, Shah G, Cauwel H, Lebwohl D, Sahmoud T, Jozwiak S (2013) Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre randomised placebo-controlled phase 3 trial. Lancet 381(9861):125–132
17. Dombi E, Ardern-Holmes SL, Babovic-Vuksanovic D, Barker FG, Connor S, Evans DG, Fisher MJ, Goutagny S, Harris GJ, Jaramillo D, Karajannis MA, Korf BR, Mautner V, Plotkin SR, Poussaint TY, Robertson K, Shih CS, Widemann BC, RESIC (2013) Recommendations for imaging tumor response in neurofibromatosis clinical trials. Neurology 81(21 Suppl 1):S33–S40
18. American Academy of Otolaryngology-Head and Neck Surgery Foundation Committee on Hearing and Equilibrium (1995) Guidelines for the evaluation of hearing preservation in acoustic neuroma (vestibular schwannoma). Otolaryngol Head Neck Surg 113(3):179–180
19. Mawrin C, Sasse T, Kirches E, Kropf S, Schneider T, Grimm C, Pambor C, Vorwerk CK, Firsching R, Lendeckel U, Dietzmann K (2005) Different activation of mitogen-activated protein kinase and Akt signaling is associated with aggressive phenotype of human meningiomas. Clin Cancer Res 11(11):4074–4082
20. Pachow D, Andrae N, Kliese N, Angenstein F, Stork O, Wilisch-Neumann A, Kirches E, Mawrin C (2013) mTORC1 inhibitors suppress meningioma growth in mouse models. Clin Cancer Res 19(5):1180–1189
21. AHern RP (2001) Sample size tables for exact single-stage phase II designs. Stat Med 20(6):859–866
22. Bates D, Maechler M, Bolker B, WalkerS (2014) lme4: Linear mixed-effects models using Eigen and S4. R package version 1.1-6. http://CRAN.R-project.org/package=lme4. Accessed May 2014
23. Verbeke G, Molenberghs G (2005) Models for discrete longitudinal data. Springer, New York
24. James MF, Han S, Polizzano C, Plotkin SR, Manning BD, Stemmer-Rachamimov AO, Gusella JF, Ramesh V (2009) NF2/merlin is a novel negative regulator of mTOR complex 1 and activation of mTORC1 is associated with meningioma and schwannoma growth. Mol Cell Biol 29(15):4250–4261
25. Widemann BC, Dombi E, Gillespie A, Wolters PL, Belasco J, Goldman S, Korf BR, Solomon J, Martin S, Salzer W, Fox E, Patronas N, Kieran MW, Perentesis JP, Reddy A, Wright JJ, Kim A, Steinberg SM, Balis FM (2014) Phase 2 randomized flexible crossover double-blinded placebo-controlled trial of the farnesyltransferase inhibitor tipifarnib in children and young adults with neurofibromatosis type 1 and progressive plexiform neurofibromas. Neuro Oncol 16(5):707–718
26. Plotkin SR, Merker VL, Muzikansky A, Barker FG 2nd, Slattery W 3rd (2014) Natural history of vestibular schwannoma growth and hearing decline in newly diagnosed neurofibromatosis type 2 patients. Otol Neurotol 35(1):e50–e56
27. Karajannis MA, Legault G, Hagiwara M, Giancotti FG, Filatov A, Derman A, Hochman T, Goldberg JD, Vega E, Wisoff JH, Golfinos JG, Merkelson A, Roland JT, Allen JC (2014) Phase II study of everolimus in children and adults with neurofibromatosis type 2 and progressive vestibular schwannomas. Neuro Oncol 16(2):292–297
28. Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, Leonard JM, Schmithorst VJ, Laor T, Brody AS, Bean J, Salisbury S, Franz DN (2008) Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med 358(2):140–151
29. Dirks MS, Butman JA, Kim HJ, Wu T, Morgan K, Tran AP, Lonser RR, Asthagiri AR (2012) Long-term natural history of neurofibromatosis type 2-associated intracranial tumors. J Neurosurg 117(1):109–117