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LETTER TO THE EDITOR

A 4-year phase II study of everolimus in NF2 patients with growing vestibular schwannomas

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To the Editor,

Management of tumors in Neurofibromatosis type 2 (NF2) patients is challenging, based on follow up, surgery, radiosurgery or chemotherapy by bevacizumab [1]. Based on pre-clinical data in mice showing that mTORC1 inhibition could delay growth of *Nf2*-related schwannomas [2], we have conducted a prospective single-institution open-label phase II study to evaluate the effect of everolimus in 10 NF2 patients with growing vestibular schwannoma (VS) [3]. In this trial, five patients, treated daily with 10 mg of everolimus, 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. According to the protocol, everolimus was then reintroduced in four patients and VS decreased in volume by a median 6.8% at 24 months. Time to tumor progression (TTP) in these patients increased threefold during treatment. Thus, we amended the trial protocol to resume treatment for 2 additional years, figuring a 48 months-long clinical trial. At the end of the first 24 months, four subjects (#2, #5, #9, #10) consented to continue treatment and postpone the end of the study. In the second part of the study, everolimus was given until progression for a maximum of 2 years. The new baseline volume was set as the volume at everolimus resumption. Time to tumor progression was defined as the time needed for 20% increase in VS volume [3, 4].

Individual volume curves are shown in Fig. 1a. Although tumor volume increased with a rebound effect when everolimus was stopped at the end of the first year of treatment, everolimus resumption was associated with a decrease in volume in all subjects. Best VS volume response was −11.8, −9, −5.4, and −22% under everolimus. During the second period of the trial, two subjects were withdrawn from the study for tumor progression after a total of 36 and 39 months of treatment. Two subjects completed the trial with tumor stabilization after 33 months of continuous everolimus administration (total of 45 months of treatment) for one and tumor progression at 45 months for the other. Overall, time to progression of VS in these four subjects was delayed from a median 2.9 months (3.3, 4.2, 2.4, and 2.6) before treatment to 13.9 months under everolimus (13.5, 14.2, 13.9 and not reached, respectively) (Fig. 1b). Thus we observed a fourfold increase in TTP under treatment.

Two out of four subjects presented a measurable asymptomatic frontal meningioma. The TTP of these meningiomas increased from 5.5, and 8.5 months before everolimus treatment to 17.3, and not reached after 26.4 months of everolimus administration, respectively. This suggests that everolimus can induce tumor stabilization also in meningiomas.

Everolimus was well tolerated with mainly minor grade 1 toxicity, and 2 grade 2 adverse events (wound delay and sinusitis). Of note, most of the symptomatic adverse events (e.g. mouth ulcers) occurred during the

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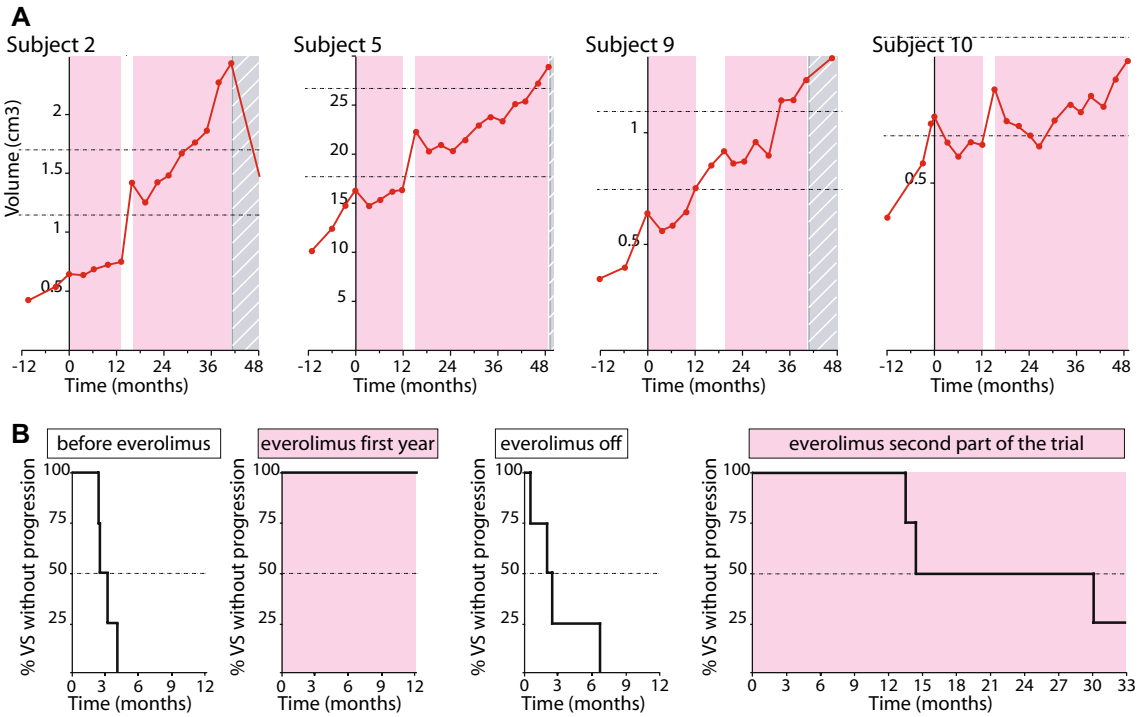

Fig. 1 **a** Volumetric evolution of target vestibular schwannoma in four NF2 subjects. *Pink background*: period of treatment with everolimus; *crosshatched background*: treatment with bevacizumab. *The horizontal dotted lines* represent +20/−20% tumor growth. **b** Time to progression of target vestibular schwannomas in four NF2 subjects. Median interpolated time to progression before everolimus treatment was 2.9 months, and was 13.9 months under treatment. *Pink background*: period of treatment with everolimus

first month of treatment, and their consequences on daily life eventually became negligible with time.

Hearing remained stable in three out four subjects. In two subjects withdrawn from the study because of progressive tumor growth, MRI was performed 6 weeks after everolimus discontinuation to monitor for a possible rebound effect on tumor growth rate, as observed after they completed the first year of treatment. Vestibular schwannoma volume was similar in the two patients (2.4 and 1.2 cm^3), and no rebound effect on VS growth was noted this time. The progressive loss of everolimus inhibiting activity resulting in tumor progression seems to annihilate the risk of a severe rebound effect.

At the end of the 4 years-trial, one patient was stable under everolimus and requested to continue treatment outside the frame of a clinical trial. Bevacizumab was offered to the three patients showing tumor growth. Bevacizumab was well tolerated, and resulted in tumor reduction in one patient (−45% in 8.2 months), stabilization in another (+7.9% in 6.7 months), and has not yet been evaluated in the third patient. Based on this limited number of patients, everolimus administration does not seem to preclude the use of bevacizumab in case of tumor progression, and the side effect profile seems different.

In conclusion, this long-term trial in NF2 patients shows that everolimus is able to slow down the growth of VS. Long-term clinical trials remain challenging but are mandatory to evaluate the long-term efficacy and side effects in chronic disease with benign and slow growing tumors such as NF2. Importantly, the use of everolimus does not preclude further treatment with bevacizumab in case of disease progression.

References

1. Plotkin SR, Stemmer-Rachamimov AO, Barker FG 2nd, 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):358–67
2. 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
3. Goutagny S, Raymond E, Esposito-Farese M, Trunet S, Mawrin C, Bernardeschi D, Larroque B, Sterkers O, Giovannini M, Kalamarides M (2015) Phase II study of mTORC1 inhibition by everolimus in neurofibromatosis type 2 patients with growing vestibular schwannomas. J Neurooncol 122(2):313–320

4. 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, REiNS International Collaboration (2013) Recommendations for imaging tumor response in neurofibromatosis clinical trials. Neurology 81:S33–S40