Effect of Bevacizumab and Everolimus for the treatment of Vestibular Schwannomas in patients with Neurofibromatosis Type 2

Aziz Ouerdani, Michel Kalamarides, Stéphane Goutagny, Iñaki F. Troconiz

aziz.ouerdani@inria.fr

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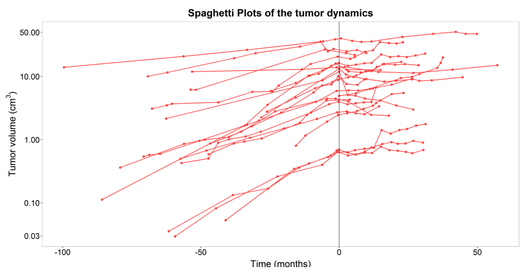
Context

- ✓ Vestibular schwannomas (VS) are **benign slow-growing tumors** that touch the Schwan cells of the vestibular nerve and lead to **hearing loss**[1]
- ✓ Choice of **surgery** depends on the balance between benefits and risk as **hearing and facial function** can be **definitely lost** during the procedure[2]
- ✓ **Antiangiogenic compounds** are more and more used to treat VS but **no standard dose level nor schedule** exists
- ✓ The main objectives of this work are to **evaluate and compare the efficiency** of bevacizumab and everolimus for the treament of VS

Tumor dynamic modeling

Data collection

- ✓ Data analysis included 22 patients with Neurofibromatosis Type 2 (NF2):
  - ✓ **Bevacizumab** 5 mg/kg Q2W (n=13)
  - ✓ **Everolimus** 10 mg QD (n=7)
  - ✓ **Both** drugs at distinct periods (n=2)
- ✓ Tumors are classified into 4 stages according to their size that display a high variability

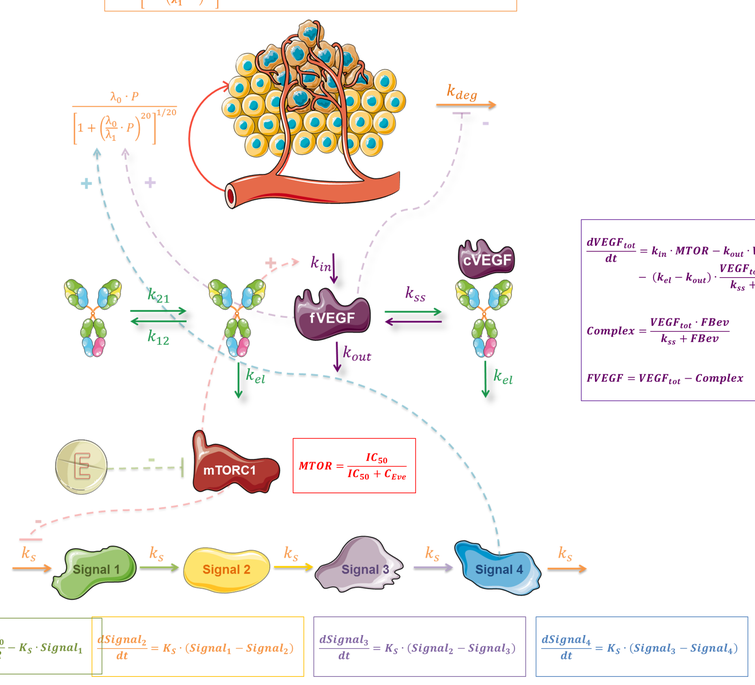


Tumor growth dynamics of the 22 patients. Red curves are the observed tumor volumes showed in a semi-logarithmic scale. Treatment is given at time 0

Mechanism-based model

- ✓ **Tumor size (P)** is described by a **Simeoni model**[3] where proliferation and cell death are depending on VEGF levels
- ✓ Bevacizumab and VEGF concentrations in nM are simulated from a published TMDD model[4]. The drug reduces VEGF levels and so its effects.
- ✓ Everolimus reduces VEGF synthesis through mTORC1 inhibition[5]

$$\frac{dP}{dt} = \frac{\lambda_0 \cdot P}{\left[1+\left(\frac{\lambda_0}{\lambda_1}\cdot P\right)^{20}\right]^{1/20}} \cdot \left(\frac{FVEGF}{VEGF_0}\right) \cdot Signal_4 - K_{deg} \cdot (VEGF_0 - FVEGF) \cdot P$$



$$FBev = \frac{1}{2}\left[(Bev_{tot} - VEGF_{tot} - k_{ss}) + \sqrt{(Bev_{tot} - VEGF_{tot} - k_{ss})^2 + 4k_{ss} \cdot Bev_{tot}}\right]$$

$$\frac{dBev_{tot}}{dt} = \frac{Q}{V_2}Bev_{peri} - \frac{Q}{V_1} \cdot FBev - \frac{VEGF_{tot}\frac{CL_{RC}}{V_1}}{k_{ss} + FBev}$$

$$\frac{dBev_{peri}}{dt} = \left(\frac{Q}{V_1}\right) \cdot FBev - \frac{\frac{Q}{V_2}Bev_{peri}}{V_1}$$

$$\frac{dEv_{gut}}{dt} = -K_a \cdot Ev_{gut}$$

$$\frac{dEv_{central}}{dt} = K_a \cdot Ev_{gut} + K_{21} \cdot Ev_{peri} - Ev_{central} \cdot (K_{12} + Kel)$$

$$\frac{dEv_{peri}}{dt} = K_{12} \cdot Ev_{central} - K_{21} \cdot Ev_{peri}$$

$$\frac{dVEGF_{tot}}{dt} = k_{in} \cdot MTOR - k_{out} \cdot VEGF_{tot} - (k_{el} - k_{out}) \cdot \frac{VEGF_{tot} \cdot FBev}{k_{ss} + FBev}$$

$$Complex = \frac{VEGF_{tot} \cdot FBev}{k_{ss} + FBev}$$

$$FVEGF = VEGF_{tot} - Complex$$

$$MTOR = \frac{IC_{50}}{IC_{50} + C_{Eve}}$$

$$\frac{dSignal_1}{dt} = K_S \cdot \frac{MTOR_0}{MTOR} - K_S \cdot Signal_1 \qquad \frac{dSignal_2}{dt} = K_S \cdot (Signal_1 - Signal_2)$$

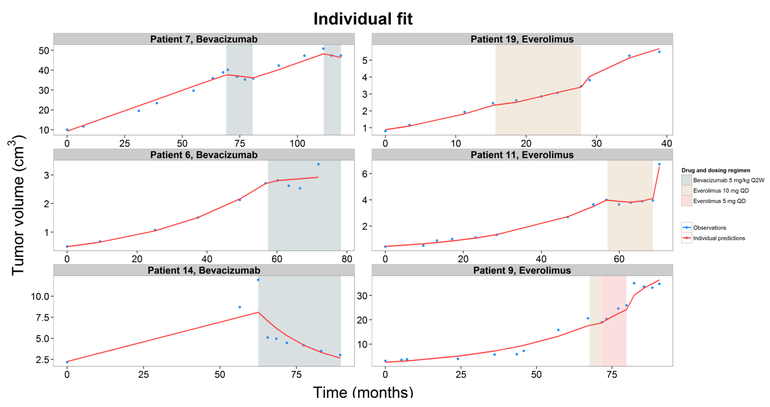
$$\frac{dSignal_3}{dt} = K_S \cdot (Signal_2 - Signal_3) \qquad \frac{dSignal_4}{dt} = K_S \cdot (Signal_3 - Signal_4)$$

Model evaluation

Parameter estimates

- ✓ All parameters $(\lambda_0, \lambda_1, P_0, K_{deg}, IC_{50}, K_S)$ were precisely estimated (rse% < 50%)
- ✓ Cell death (K_{deg}) is 4 times higher with bevacizumab than everolimus
- ✓ Growth becomes linear when tumor reach the size of 7.5 cm^3 (λ_1/λ_0)
- ✓ During linear phase, growth rate is 0.3 cm^3 per month

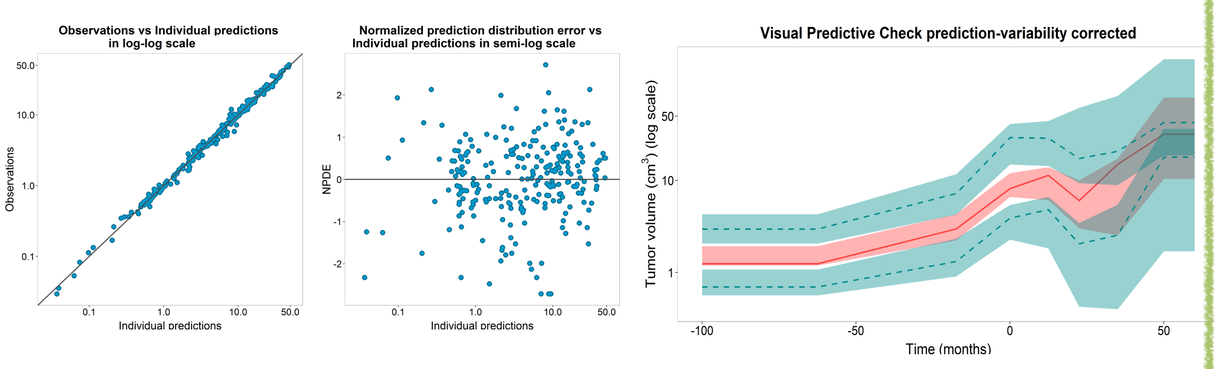
Individual fits



Left column: Bevacizumab treated patients ; Right column: Everolimus treated patients

Red lines are the individual predicted tumor volumes, blue circles are the observed tumor volumes and shaded areas are the treatments periods. Patients are ordered by the magnitude of residual error from the smallest (1st row) to the highest (last row)

Model evaluation

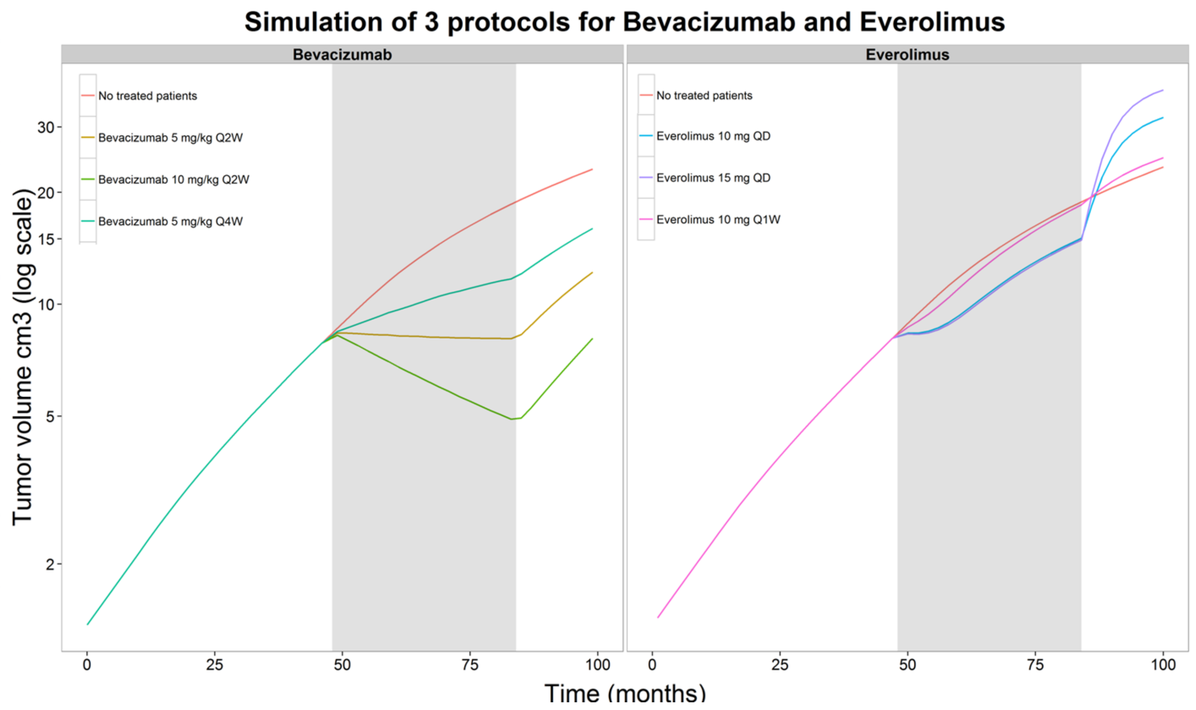


Left: Observations versus individual predictions in log-log scale

Middle: Normalized prediction distribution error (NPDE) vs individual predictions

Right: Visual predictive check with correction of the predictions and variability, comparison between observed tumor size dynamics (lines: 5th, 50th and 95th percentiles) and the 95%-confidence intervals (blue and red areas) calculated from simulated data

Simulations



Simulated tumor dynamics for 3 doses and a control group (no treated patients) stratified by compounds: bevacizumab and everolimus. For each treated group, a 3 years treatment is given after 5 years of growth,

- ✓ Tumor shrinkage through bevacizumab seems to be dose-dependent
- ✓ A higher dose of everolimus does not improve tumor shrinkage and worsen the rebound after the end of the treatment

Conclusion

- ✓ **We develop a mechanism-based mixed-effects model for the analysis of the dynamic of tumor volume of vestibular schwannomas treated with bevacizumab or everolimus**
- ✓ **Our model confirms the roles of the vascular endothelial growth factor (VEGF) on the proliferation and survival of Schwann cells**
- ✓ **Tumor shrinkage is more important with bevacizumab than everolimus as this latter activates a secondary pathway which increases tumor growth**

References: **[1]** *Fong et al. Nov 2011;* **[2]** *Goutagny et al., 2007;* **[3]** *Simeoni et al, Feb 2004;* **[4]** *Panoilia et al, Nov 2014;* **[5]** *Goutagny et al, Dec 2014*