

# The Sybil prophecy: Searching for predictors of response to bevacizumab in glioblastoma

[Get access](#)

, , , ✉,

*Neuro-Oncology*, noae088, <https://doi.org/10.1093/neuonc/noae088>**Published:** 17 June 2024 **Article history** ▼

## Extract

We read with great interest the work by Hiller-Vallina et al.<sup>1</sup> on the role of a sexual-dependent necroinflamed pattern in predicting prognosis and response to anti-angiogenic drugs in glioblastoma. The work has huge strong points, including its elegant and meticulous design, and also opens a number of issues. Female gender has not traditionally been recognized as a positive prognostic factor in glioblastoma, yet evidence is rising that this assumption is true. In the present paper, Hiller-Vallina et coworkers demonstrate that, in a subset of male patients, low levels of estrogen receptor- $\alpha$  (encoded by ESR1 gene) determine a necroinflamed phenotype, with activation of VEGF/hypoxia-related pathways and infiltration of S100A9-positive myeloid cells. Male patients harboring low-ESR1 necroinflamed glioblastomas have a worse prognosis than male and female patients harboring high-ESR1 non-necroinflamed tumors. On the other hand, necroinflamed tumors show a better response to anti-angiogenic treatment. Much work remains to be done to dissect into detail the relationship between sex hormones, tumor immune infiltration and hypoxic/angiogenic microenvironment. Our research group recently investigated the prognostic role of the immune infiltrate in glioblastoma, with focus on the tissue-resident memory (Trm) CD8 + CD103 + T lymphocytes, finding that high levels of Trm expressing PD1 or other immune checkpoints are correlated to worse prognosis, likely due to immune cell exhaustion.<sup>2</sup> We reanalyzed survival data of patients included in that study and, interestingly, we found that the proportion of exhausted CD8 + CD103 + PD1 + Trms portends a worse prognosis only in male patients (Figure 1). Such finding corroborates the assumption by Hiller-Vallina et al. on the existence of two distinct subsets of GBM in males, with different prognosis.<sup>1</sup> Notably, PD1 expression on Trm has been linked to persistent neuroinflammation in encephalitis,<sup>3</sup> further supporting the assumption that immune-exhausted Trms can be enriched in necroinflamed glioblastoma. The issue of the improved response of male patients with necroinflamed glioblastoma to anti-angiogenic treatment with bevacizumab is more puzzling. Interestingly, no consistent predictors of response to bevacizumab in glioblastoma have been ever established. A post-hoc analysis of the AVAglio trial identified the proneural signature as associated with better response to bevacizumab.<sup>4</sup> However, it is well known that the expression of inflammation-related players is downregulated in proneural and upregulated in mesenchymal glioblastoma, in contrast with the findings of the present study.<sup>5</sup> The role of VEGF expression is also debated. Hiller-Vallina et al.<sup>1</sup> reported that necroinflamed glioblastoma upregulated VEGF, yet VEGF levels as assessed with RT-PCR were not associated with improved survival after bevacizumab treatment. Instead, in a work on 25 recurrent GBM patients, we had shown that high VEGF levels were associated with worse survival after bevacizumab treatment in recurrent glioblastoma.<sup>6</sup> To conclude, the work here

discussed has the merit to enliven the interest of the neuro-oncologic community on the interplay between gender and immune infiltrate in glioblastoma and on the identification of prognostic factors for response to anti-angiogenic treatment, which are long awaited.

**Issue Section:** [Letter to the Editor](#)

You do not currently have access to this article.

## Sign in

 [Get help with access](#)

### European Association of Neuro-Oncology members

Sign in through society site



#### Personal account

- Sign in with email/username & password
- Get email alerts
- Save searches
- Purchase content
- Activate your purchase/trial code
- Add your ORCID iD

Sign in

[Register](#)

#### Institutional access

Sign in through your institution

[Sign in with a library card](#)

[Sign in with username/password](#)

[Recommend to your librarian](#)

#### Institutional account management

[Sign in as administrator](#)

## Purchase

[Subscription prices and ordering for this journal](#)

[Purchasing options for books and journals across Oxford Academic](#)

### Short-term Access

To purchase short-term access, please sign in to your personal account above.

Don't already have a personal account? [Register](#)

The Sybil prophecy: Searching for predictors of response to bevacizumab in glioblastoma - 24 Hours access

EUR €51.00

GBP £44.00

USD \$55.00