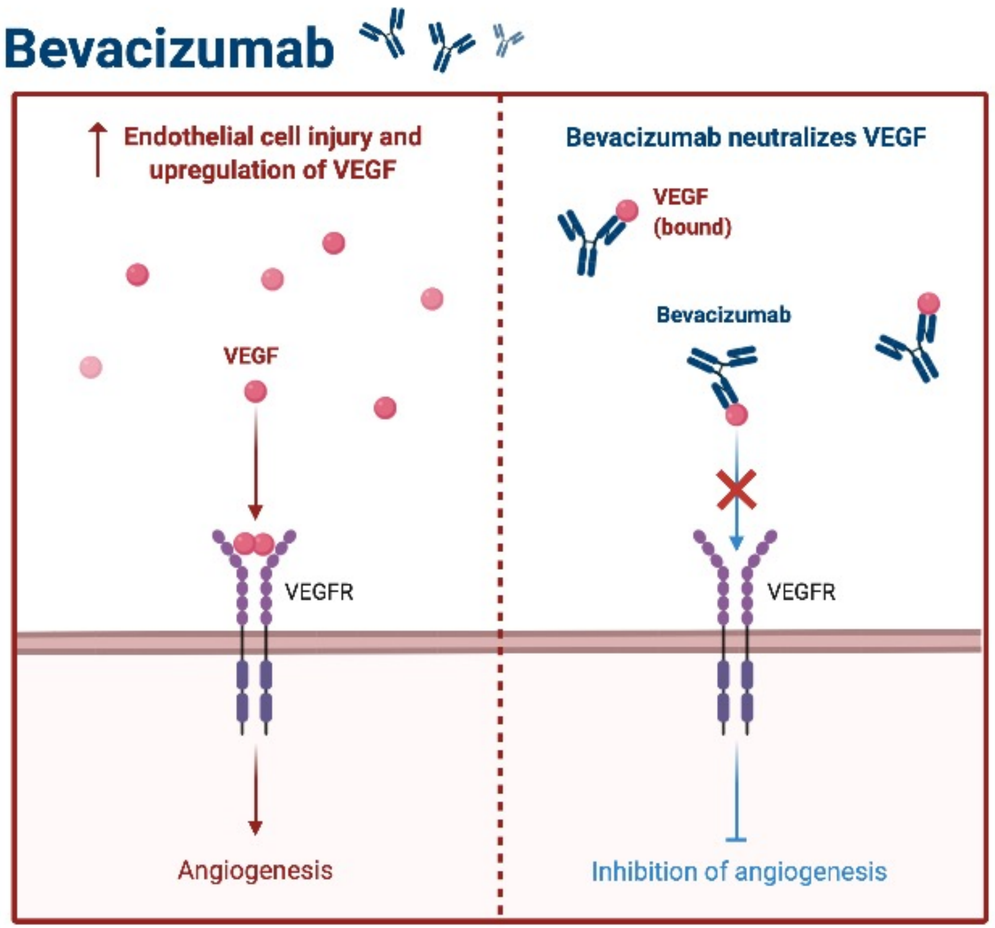
Tumors that respond poorly to bevacizumab therapy show upregulation of angiogenesis genes in glioblastoma.

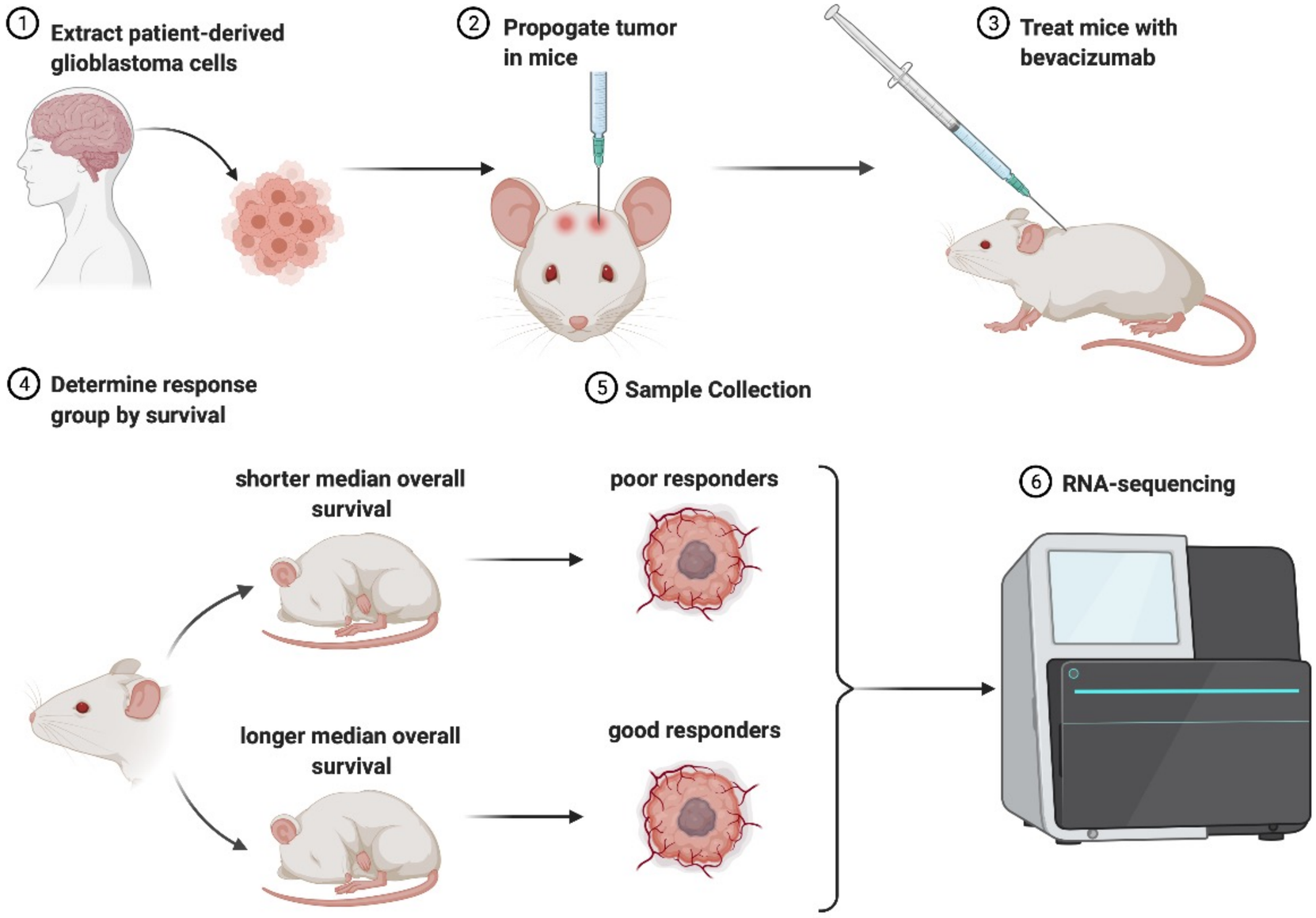
Background

- Glioblastoma (GBM) is the most common primary brain tumor in adults and has an extremely poor prognosis.
- Bevacizumab, the common treatment for recurrent-GBM, improves survival in only a fraction of patients, but improves quality of life.



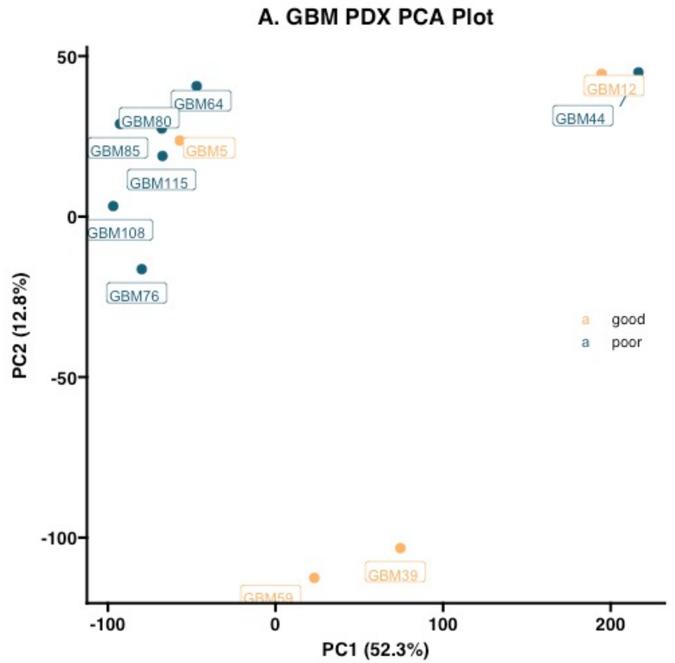
Bevacizumab is a humanized monoclonal antibody that inhibits angiogenesis by neutralizing vascular endothelial growth factor (VEGF),

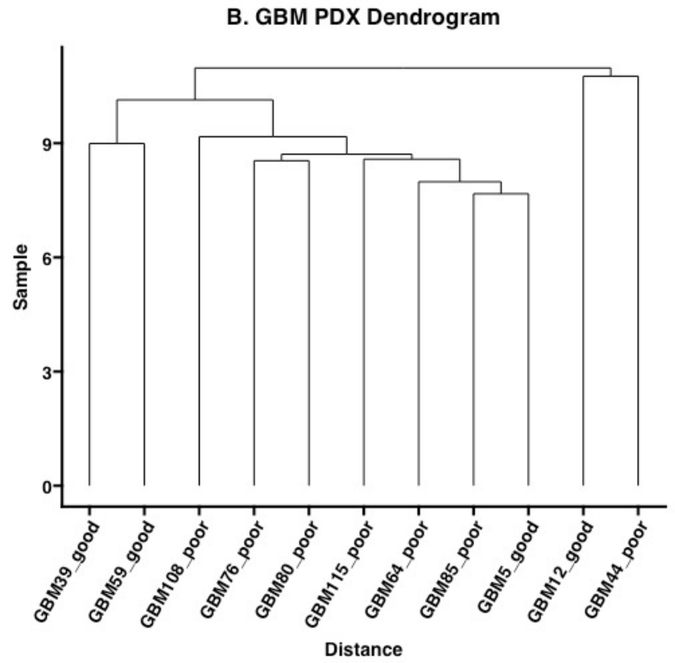
Biochemical Methods

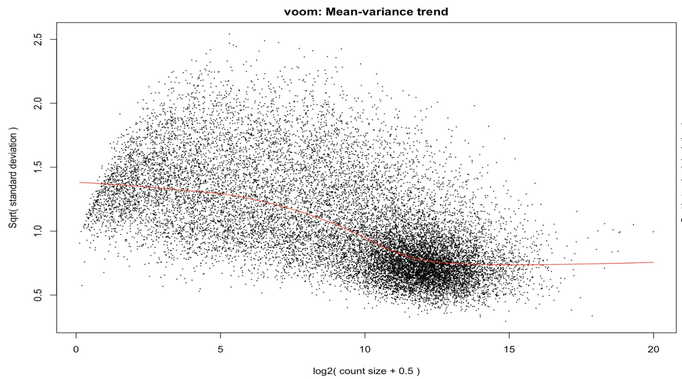


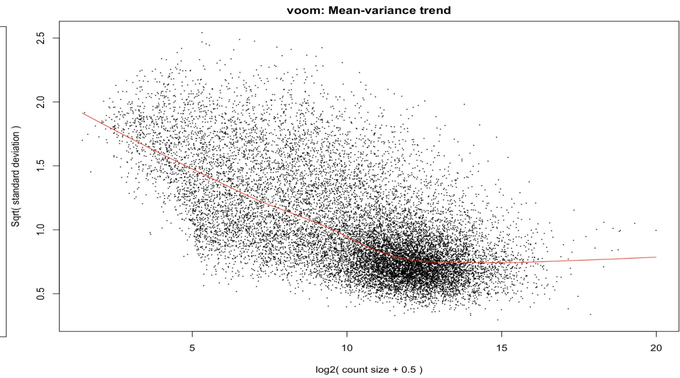
Computational Methods

- In R, samples were clustered and outliers were removed using principal component analysis and hierarchical clustering.
- Hyper-parameter optimization was carried out using mean-variance trends.
- Differential gene expression and gene set enrichment analysis was done in R using `DeSeq2` and `GSEA`.



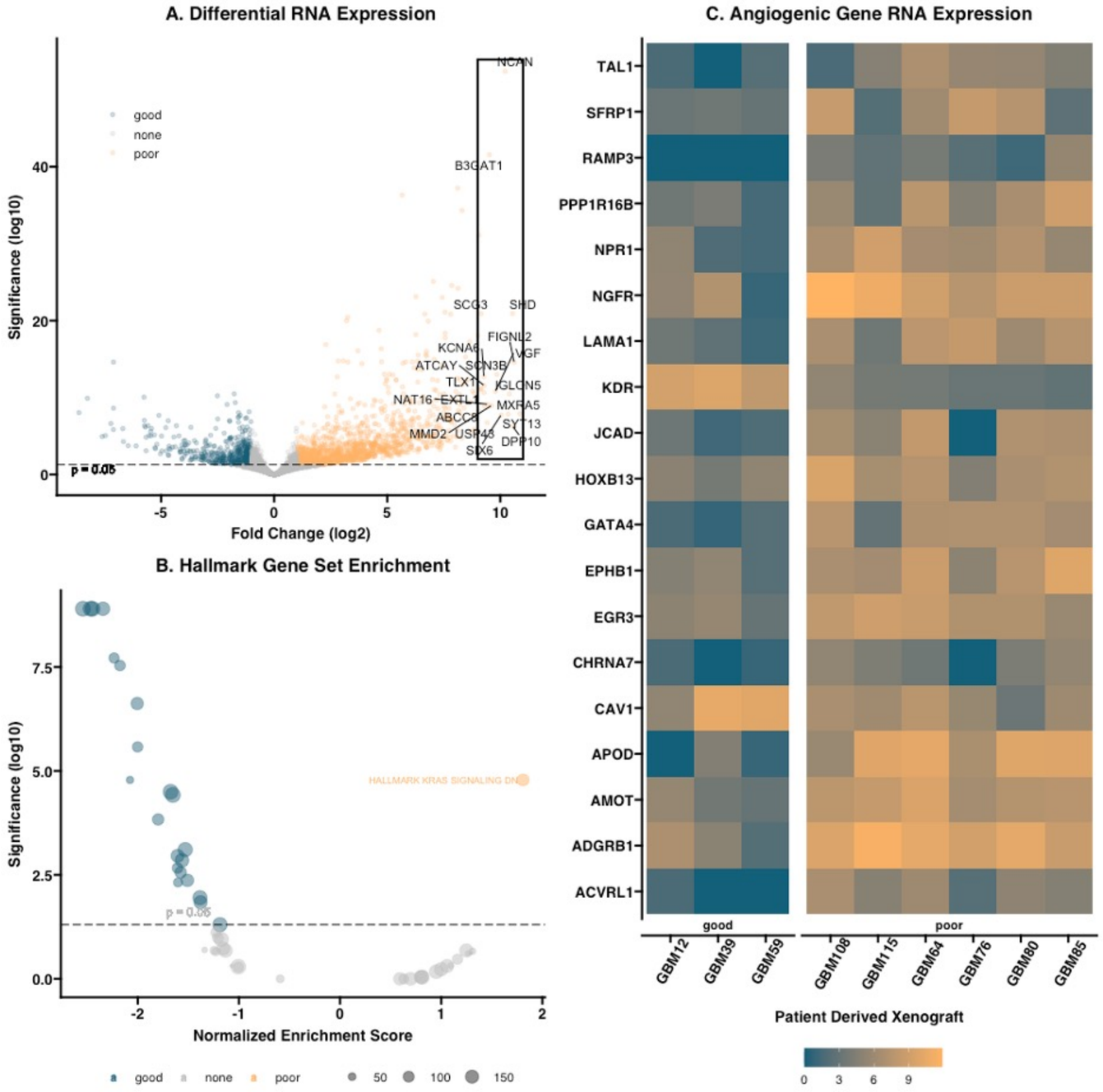






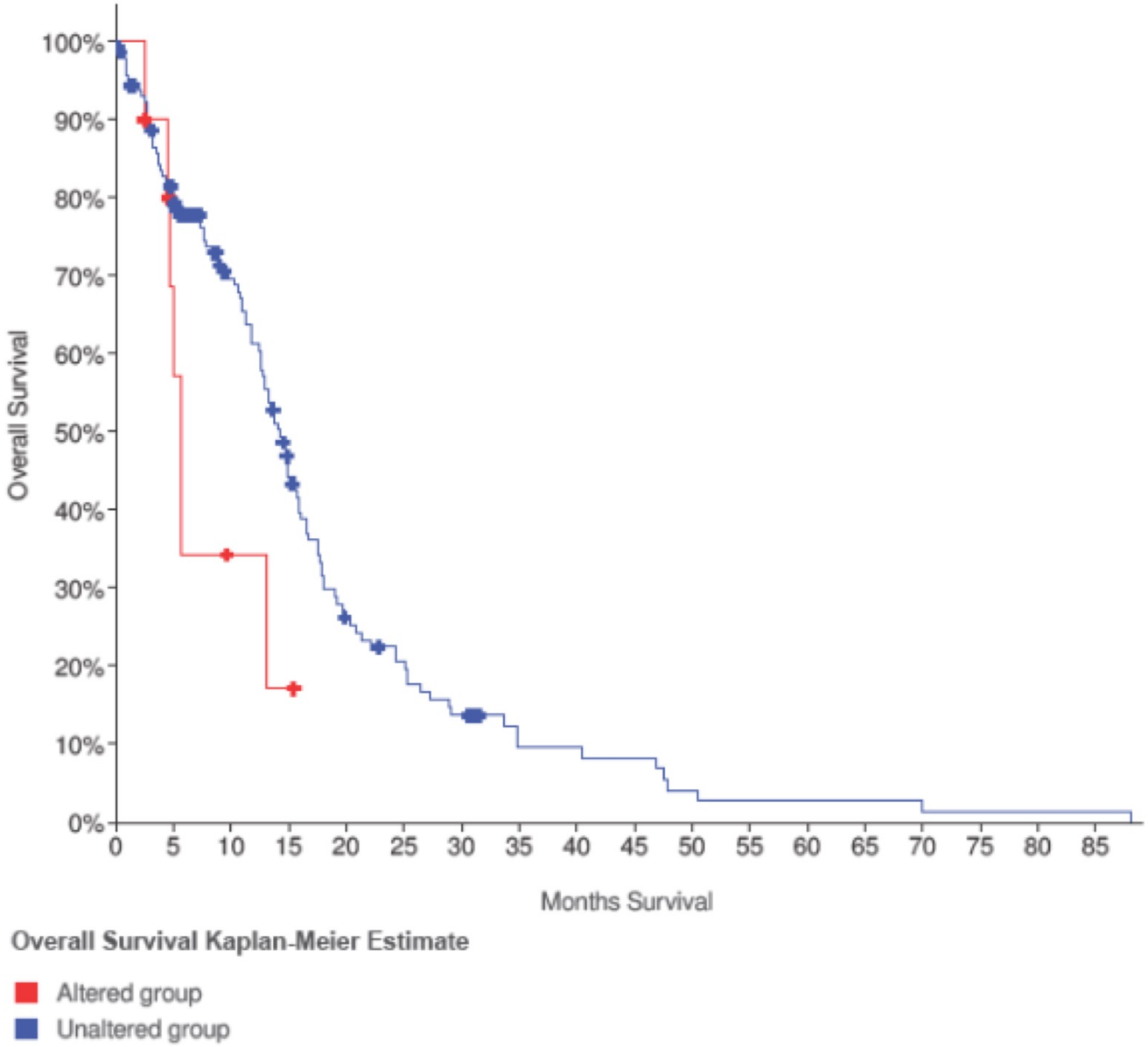
Differential gene expression in poor-responders to bevacizumab.

- Analysis demonstrated differential gene expression in poor responders to bevacizumab relative to good-responders along with upregulation of angiogenic genes.
- Within this gene set, multiple genes known to be regulated by the early growth response 1 (EGR1) transcription factor were identified; two were selected for further study based on their role in promoting cancer cell migration and proliferation, RAMP3 (accessory-receptor for adrenomedullin) and CHRNA7 (cholinergic-receptor-nicotinic-α7-subunit, or α7-nAChR).



Survival curve of GBM patients with altered levels of *EGR1* mRNA.

- Log-rank survival analysis shows a significant difference in median overall survival (p = 0.045, n = 10).
- Survival curve of GBM patients with altered levels of *CHRNA7* mRNA showed a significant difference in median overall survival (p = 0.016, n = 12).



Summary

- Response to bevacizumab does delineate a distinct molecular phenotype of GBM tumors.
  - EGR1 and its targets may be predictors of poor response to bevacizumab.
- Poor responders to bevacizumab have significant upregulation of angiogenic genes.
  - Several upregulated angiogenic genes are regulated by EGR1.
  - *EGR1* was upregulated in poor responders to anti-VEGF therapy.
- Altered expression of *CHRNA7* and/or its transcription factor *EGR1* confers poor prognosis in GBM patients.