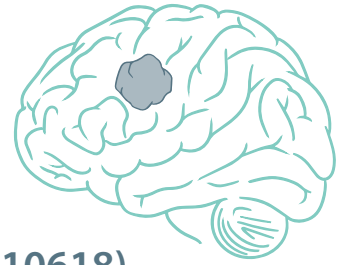
Model insights
March 2021edition



EXPERIMENTAL PHARMACOLOGY & ONCOLOGY BERLIN-BUCH

Partially temozolomide resistant, IDH-wildtype glioblastoma PDX model (Glio10618)

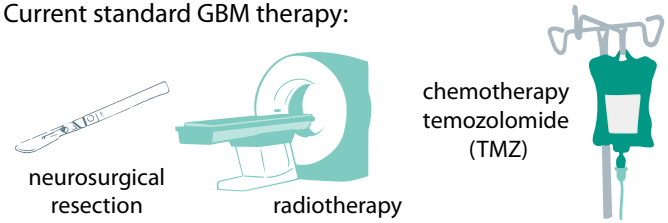
Highlights

- Characterized for both subcutaneous (s.c.) and orthotopic (intracerebral) inoculation
- Dose-dependent response to temozolomide (TMZ) allows to test resistance overcoming strategies

Background

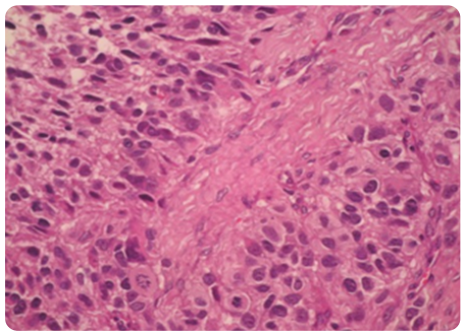
Glioblastoma (GBM or Grade IV malignant glioma) is the most common and lethal primary brain tumor in adults. Primary GBMs, which carry a worse prognosis, are typically wild type (WT) for isocitrate dehydrogenase 1/2 (IDH).

Current standard GBM therapy:



Chemosensitivity to TMZ strongly depends on epigenetic silencing by methylation of the O(6)-Methylguanine-DNA methyltransferase (MGMT) promoter.

Histology image of the subcutaneous PDX model in NMRI-*nude* mice

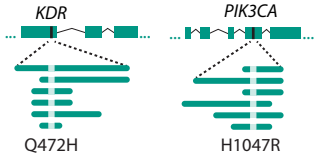


Whole brain section, cresyl violet stained, tumor indicated by arrows

Glioma s.c. PDX: Passage 2, H&E Staining

Mutation analysis by targeted DNA sequencing

- amplicon panel sequencing
- 48 cancer-related genes
- 212 targeted regions
- mutations in *KDR* and *PIK3CA*



RNA-sequencing

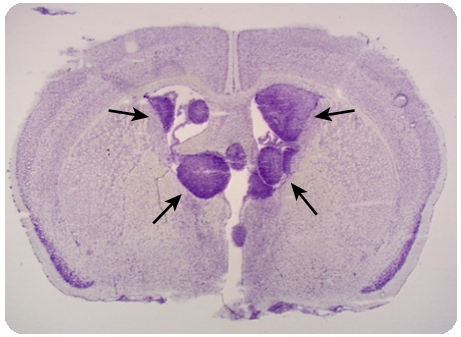
Illumina® RNA-seq data are available for this model upon request. This analysis confirmed that this GBM model does not harbor mutations at residue R132 of *IDH1* or at residue R172 of *IDH2*. For *IDH1*, a K233N mutation was detected. Medium expression levels were observed for *MGMT*.

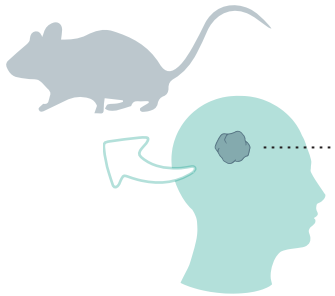
Orthotopic model

The orthotopic transplantation of glioma PDX models offers the following advantages:

1. An optimal tumor microenviroment to support infiltrative growth patterns. 2. Orthotopically transplanted mice have a functional blood-brain barrier (BBB) that many drugs cannot pass and thus represent a clinically more relevant model for this especially hard-to-treat type of cancer.

Histology image of the orthotopic PDX model in NMRI-*nude* mice





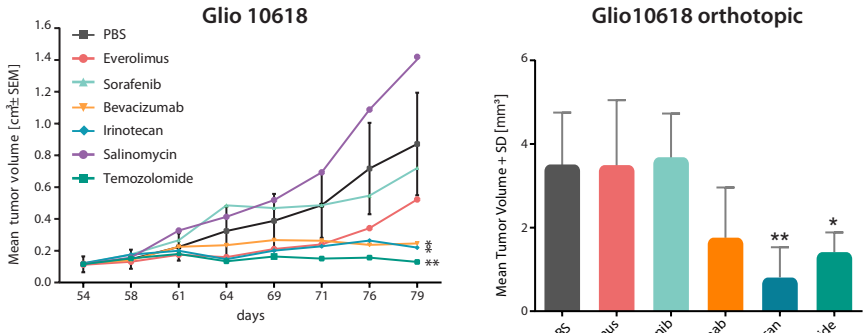
PDX model information

66 year-old female patient

Biopsy:
- stage IV GBM
- IHC: *IDH* wildtype, no MGMT expression

Model drug treatment data

The subcutaneous as well as the orthotopic model have been tested for their drug response to a number of clinically relevant compounds including everolimus, sorafenib, bevacizumab, irinotecan, salinomycin and temozolomide (TMZ at 25 and 90mg/kg). Subcutaneous tumors were progressing upon treatment with all compounds with the exception of irinotecan, bevacizumab and 90mg/kg TMZ. In the orthotopic model, the effect of 90mg/kg TMZ treatment was far less pronounced. The observed dose-dependent response to TMZ allows to use this model to test resistance overcoming strategies.



Drug response of Glio10618 following s.c. (left panel) or orthotopic incoculation (right panel).