**EGFR targeting in GBM**

Essentially, no current evidence of benefit. Biology and mutation of the EGFR receptors differs to lung cancers and the BBB doesn’t help. Some useful snippets below:

[EGFR, the Lazarus target for precision oncology in glioblastoma | Neuro-Oncology | Oxford Academic (oup.com)](https://gbr01.safelinks.protection.outlook.com/?url=https%3A%2F%2Facademic.oup.com%2Fneuro-oncology%2Farticle%2F24%2F12%2F2035%2F6705404%3Flogin%3Dfalse&data=05%7C01%7Crjena%40nhs.net%7C6a53ff919ae14da00af308db6382cc7a%7C37c354b285b047f5b22207b48d774ee3%7C0%7C0%7C638213185639651833%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=T5MThoNj6lYKchsb7DPoDam02QWVrushWLoeKhkrPvg%3D&reserved=0)

Pharmacokinetic studies with these TKI have shown that most drugs, except for erlotinib and lapatinib, fail to reach steady state plasma concentrations in patients that would be sufficient to inhibit cell proliferation in vitro. Additionally, early generation TKI have poor brain exposures as suggested by their concentration ratio of unbound drug in brain to blood (Kpuu) (Table 1). While newer TKI such as dacomitinib and osimertinib are theoretically more brain penetrant based on Kpuu, their predicted free drug exposures in patient CNS tumors still fall short of that required to inhibit cell proliferation in vitro. As EGFR TKI developed for NSCLC are neither sufficiently brain penetrant nor capable of targeting the unique forms of altered EGFR found in GBM, EGFR TKI specific for GBM need to be developed with these challenges in mind.

***Other papers and agents tested:***

[Depatuxizumab mafodotin in EGFR-amplified newly diagnosed glioblastoma: A phase III randomized clinical trial - PubMed (nih.gov)](https://gbr01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fpubmed.ncbi.nlm.nih.gov%2F35849035%2F&data=05%7C01%7Crjena%40nhs.net%7C6a53ff919ae14da00af308db6382cc7a%7C37c354b285b047f5b22207b48d774ee3%7C0%7C0%7C638213185639651833%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=5KdT7HNIO2PU4JZf%2BqowklkCJPS0fqNpNqB2QC2ZWdE%3D&reserved=0) – Feb 2023: seemed promising, accrued 639pts with EGFR amplified GBM (newly diagnosed) and randomised between RT / TMZ + depatux-m vs placebo, PFS increased from 8m vs 6.3m but no OS advantage [Only an interim analysis]

[INTELLANCE 2/EORTC 1410 randomized phase II study of Depatux-M alone and with temozolomide vs temozolomide or lomustine in recurrent EGFR amplified glioblastoma - PubMed (nih.gov)](https://gbr01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fpubmed.ncbi.nlm.nih.gov%2F31747009%2F&data=05%7C01%7Crjena%40nhs.net%7C6a53ff919ae14da00af308db6382cc7a%7C37c354b285b047f5b22207b48d774ee3%7C0%7C0%7C638213185639651833%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=Gnc1tSdyzlI5B6D%2FbQfHKne8vZ4z7ighLrSUO71C9lI%3D&reserved=0) May 2020: 260pts with EGFR amplified GBM at 1st recurrence post CRT with TMZ, randomised to Depatux-M +/- TMZ vs either lomustine or TMZ. mOS = 9.6m (Depatux-m + TMZ) vs 7.9m (Depatux-m alone) vs 8.2m (lomustine or TMZ) – hazard ratio of Depatux-M + TMZ vs control – not statistically significant (HR 0.71, CI 0.50-1.02, p=0.062)

[Stratified phase II trial of cetuximab in patients with recurrent high-grade glioma - PubMed (nih.gov)](https://gbr01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fpubmed.ncbi.nlm.nih.gov%2F19491283%2F&data=05%7C01%7Crjena%40nhs.net%7C6a53ff919ae14da00af308db6382cc7a%7C37c354b285b047f5b22207b48d774ee3%7C0%7C0%7C638213185639651833%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=Y6XFBHEJgZ92FW5pjiByHv1Nx30MV3kTvQr6Oaj14q8%3D&reserved=0) – Sept 2009: 55 patients (half with and half without EGFR amplification, median time to progression = 1.9 months, mOS 5 months, no correlation between response, survival and EGFR amplification

[A phase I/II trial of pazopanib in combination with lapatinib in adult patients with relapsed malignant glioma - PubMed (nih.gov)](https://gbr01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fpubmed.ncbi.nlm.nih.gov%2F23363814%2F&data=05%7C01%7Crjena%40nhs.net%7C6a53ff919ae14da00af308db6382cc7a%7C37c354b285b047f5b22207b48d774ee3%7C0%7C0%7C638213185639651833%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=wCiorZo7MXsT6oGWUavSMYg8tL%2Fbh1sDnDY8hBd5548%3D&reserved=0) – 41 patients, 6 month PFS were 0% and 15% in the PTEN/EGFRvIII-positive and PTEN/EGFRvIII-negative cohorts. Two patients (5%) had a partial response and 14 patients (34%) had stable disease lasting 8 or more weeks.

[Efficacy of erlotinib in patients with relapsed gliobastoma multiforme who expressed EGFRVIII and PTEN determined by immunohistochemistry - PubMed (nih.gov)](https://gbr01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fpubmed.ncbi.nlm.nih.gov%2F24352766%2F&data=05%7C01%7Crjena%40nhs.net%7C6a53ff919ae14da00af308db6382cc7a%7C37c354b285b047f5b22207b48d774ee3%7C0%7C0%7C638213185639651833%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=8LUrbka0rNsD%2BjCSi2XcAEWrA0AcmjRiHIySrtmJhPs%3D&reserved=0) – Jan 2014: 40 patients, concluded that monotherapy with erlotinib in GBM relapses patients with high protein expression for PTEN (+++), EGFR (+++), and EGFRvlII (+++) showed low toxicity but minimal efficacy and the trial stopped.

[Efficacy of osimertinib plus bevacizumab in glioblastoma patients with simultaneous EGFR amplification and EGFRvIII mutation - PubMed (nih.gov)](https://gbr01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fpubmed.ncbi.nlm.nih.gov%2F34498213%2F&data=05%7C01%7Crjena%40nhs.net%7C6a53ff919ae14da00af308db6382cc7a%7C37c354b285b047f5b22207b48d774ee3%7C0%7C0%7C638213185639651833%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=rSigiTYgszURNyaOAe6FSJ4qEw35TztI%2Bd0l69sAzGA%3D&reserved=0) - Sept 2021: Recurrent GBM patients, n=15, retrospective review, All patients received osimertinib/bevacizumab as a second-line intervention with a median progression-free survival (PFS) of 5.1 months (95% CI 2.8-7.3) and overall survival of 9.0 months (95% CI 3.9-14.0). The PFS6 was 46.7%, and the overall response rate was 13.3% and concluded:While the osimertinib/bevacizumab combination was marginally effective in most GB patients with simultaneous EGFR amplification plus EGFRvIII mutation, a subgroup experienced a long-lasting meaningful benefit. The findings of this brief cohort justify the continuation of the research in a clinical trial. The pattern of resistance after exposure to osimertinib/bevacizumab includes known mechanisms in the regulation of EGFR, findings that contribute to the understanding and targeting in a stepwise rational this pathway.

Table 2 below is taken from: [Mechanisms of EGFR Resistance in Glioblastoma - PMC (nih.gov)](https://gbr01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.ncbi.nlm.nih.gov%2Fpmc%2Farticles%2FPMC7696540%2F%23B60-ijms-21-08471&data=05%7C01%7Crjena%40nhs.net%7C6a53ff919ae14da00af308db6382cc7a%7C37c354b285b047f5b22207b48d774ee3%7C0%7C0%7C638213185639651833%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=8ipV9BtFksnhbzYu770j%2FkoOvc%2FcskoQplZOZifKEok%3D&reserved=0) – Nov 2020

