Osimertinib

Osimertinib is a third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) for lung adenocarcinoma (LUAD) harboring activating mutations, but patients ultimately develop acquired resistance.

Osimertinib for glioblastoma

- A comparative study of preclinical and clinical molecular imaging response to EGFR inhibition using osimertinib in glioblastoma
- Repurposing Osimertinib and Gedatolisib for Glioblastoma Treatment: Evidence of Synergistic Effects in an In Vitro Phenotypic Study
- Targeting C797S mutations and beyond in non-small cell lung cancer-a mini-review
- One-pot synthesis of tetrahydropyrimidinecarboxamides enabling in vitro anticancer activity: a combinative study with clinically relevant brain-penetrant drugs
- Melanocortin Receptor Agonist Bremelanotide Induces Cell Death and Growth Inhibition in Glioblastoma Cells via Suppression of Survivin Expression
- Dual blockade of EGFR and PI3K signaling pathways offers a therapeutic strategy for glioblastoma
- YTHDF3 Modulates EGFR/ATK/ERK/p21 Signaling Axis to Promote Cancer Progression and Osimertinib Resistance of Glioblastoma Cells
- EMP3 sustains oncogenic EGFR/CDK2 signaling by restricting receptor degradation in glioblastoma

The efficacy of osimertinib, has been evaluated in glioblastoma (GBM) through preclinical and clinical trials. However, the underlying mechanism of osimertinib-induced GBM cell death and the underlying resistance mechanism to osimertinib remains unclear. Here, we demonstrate that Osimertinib induces paraptosis in GBM cells, as evidenced by the formation of cytoplasmic vacuoles, accumulation of ubiquitinated proteins, and upregulation of endoplasmic reticulum (ER) stress markers like CHOP. Additionally, neither apoptosis nor autophagy was involved in the osimertinib-induced cell death. RNAseq analysis revealed ER stress was the most significantly downregulated pathway upon exposure to osimertinib. Consistently, pharmacologically targeting the PERK-eIF2α axis impaired osimertinib-induced paraptosis. Notably, we show that the expression of thyroid receptor-interacting protein 13 (TRIP13), an AAA+ATPase, alleviated osimertinib-triggered paraptosis, thus conferring resistance. Intriguingly, MK-2206, an AKT inhibitor, downregulated TRIP13 levels and synergized with Osimertinib to suppress TRIP13-induced high GBM cell growth in vitro and in vivo. Together, our findings reveal a novel mechanism of action associated with the anti-GBM effects of osimertinib involving ER stress-regulated paraptosis. Furthermore, we identify a TRIP13-driven resistance mechanism against Osimertinib in GBM and offer a combination strategy using MK-2206 to overcome such resistance [1)].

Osimertinib resistance

see Osimertinib resistance.

1)

Hu L, Shi J, Shen D, Zhai X, Liang D, Wang J, Xie C, Xia Z, Cui J, Liu F, Du S, Meng S, Piao H. Osimertinib induces paraptosis and TRIP13 confers resistance in glioblastoma cells. Cell Death Discov. 2023 Sep 5;9(1):333. doi: 10.1038/s41420-023-01632-6. PMID: 37669963; PMCID: PMC10480197.