ERAS-801: A SELECTIVE BRAIN-PENETRANT EGFR INHIBITOR WITH IMPROVED ACTIVITY AGAINST EGFR EXTRACELLULAR DOMAIN-MUTANT GLIOBLASTOMA

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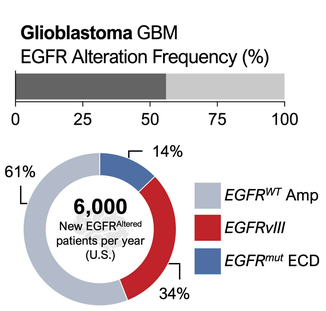
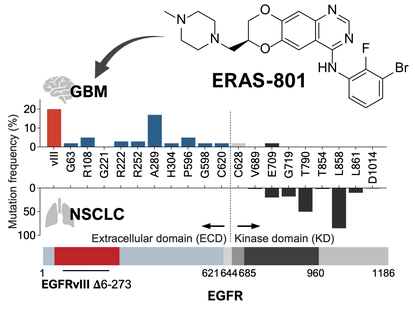
ABSTRACT

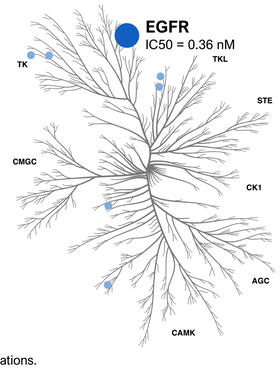
- EGFR drives nearly 50% of glioblastoma (GBM) cases, but EGFR inhibitors have failed due to poor CNS penetration and inability to target amplified wildtype and extracellular domain (ECD) mutant forms (e.g., EGFRvIII).
- ERAS-801 is a CNS-penetrant, reversible, and selective EGFR tyrosine kinase inhibitor with potent activity against amplified and ECD mutant EGFR.
- ERAS-801 showed the greatest relative potency and highest CNS penetration compared to all tested EGFR inhibitors.
- In intracranial patient-derived orthotopic xenograft (PDOX) models, ERAS-801 provided superior efficacy relative to other EGFR inhibitors (e.g., erlotinib, lapatinib, osimertinib, BDTX-1535).
- In a preclinical trial using glioma PDOX models representative of GBM, ERAS-801 significantly improved overall survival in EGFR-altered PDOX models at a clinically relevant dose.
- ERAS-801 is currently being evaluated in clinical trials, where Phase I studies (NCT05222802) confirmed its safety and tolerability at the MTD, with plasma exposures exceeding the concentrations required to inhibit tumor growth in GBM PDOX models.

ERAS-801: a potent, selective oral EGFR inhibitor for GBM oncogenic EGFR alterations





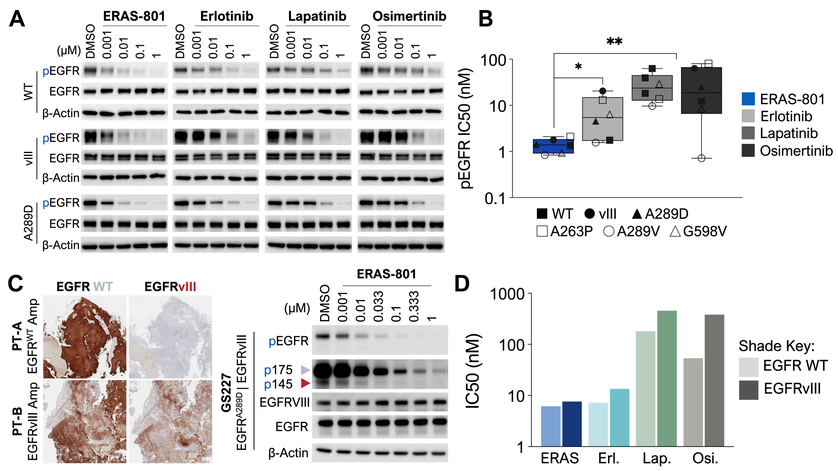
Potency for tumor cell inhibition	
pEGFR (GBM_{Avg} IC_{50})	5.68 nM
CTG ($EGFR^{Alt}$ GBM_{Avg} IC_{50})	550.7 nM
Target selectivity and safety	
Off-target safety panel	Low-risk
Selectivity over EGFR-ind. cell	~80X
PK / ADME	
Oral bioavailability (cross-species avg. %F)	63.5%
Metabolic clearance	Low-to-moderate



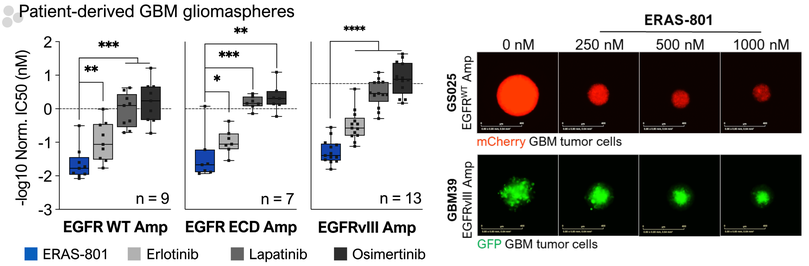
*New patients per year rounded to the nearest 1000th.
**EGFR alteration type percentages may not add to 100% due to co-occurring mutations.

RESULTS

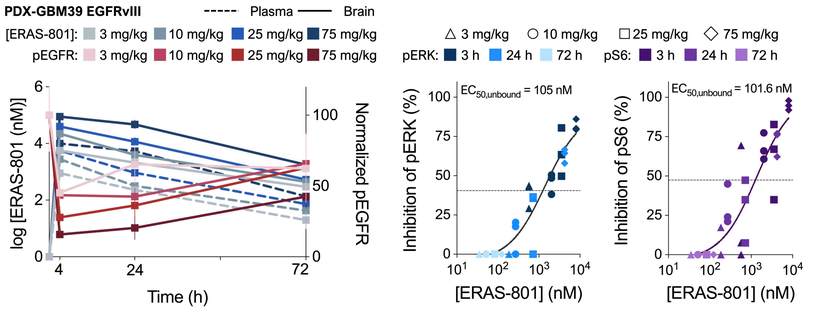
1. ERAS-801 is a potent inhibitor of WT and ECD-mutant EGFR.



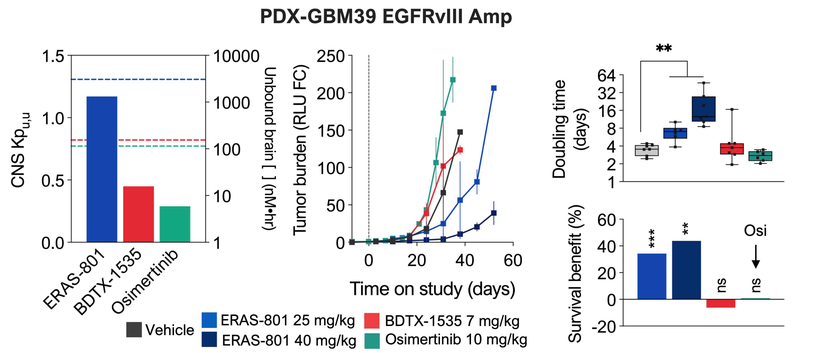
2. ERAS-801 potently inhibits proliferation of patient-derived GBM models *in vitro*.



3. ERAS-801 exhibits dose-dependent exposure in plasma and brain and inhibits EGFR signaling pathways in GBM tumors.

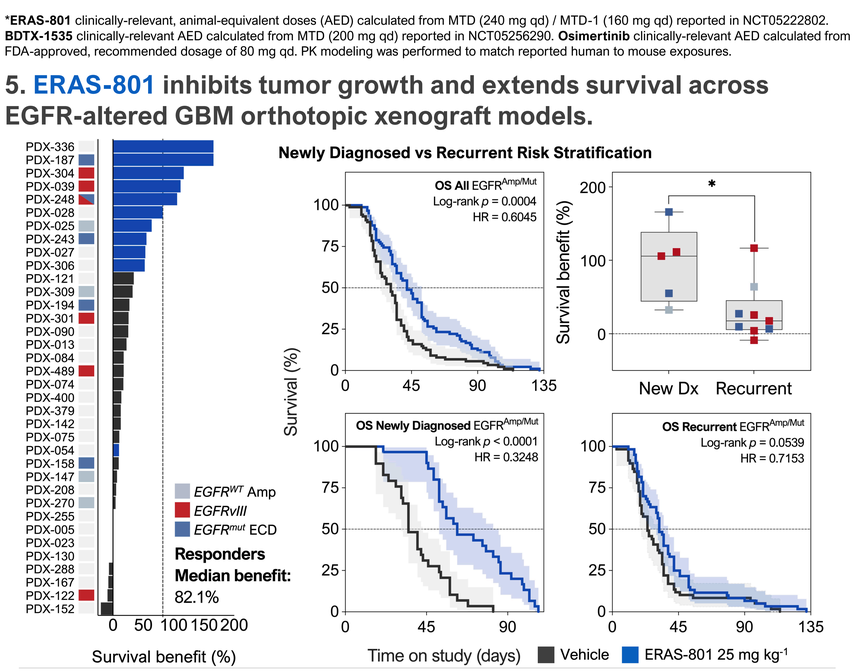


4. ERAS-801 induces anti-tumor activity at clinically relevant doses in orthotopic GBM xenografts *in vivo*.



*ERAS-801 clinically-relevant, animal-equivalent doses (AED) calculated from MTD (240 mg qd) / MTD-1 (160 mg qd) reported in NCT05222802. **BDTX-1535** clinically-relevant AED calculated from MTD (200 mg qd) reported in NCT05256290. **Osimertinib** clinically-relevant AED calculated from FDA-approved, recommended dosage of 80 mg qd. PK modeling was performed to match reported human to mouse exposures.

5. ERAS-801 inhibits tumor growth and extends survival across EGFR-altered GBM orthotopic xenograft models.



CONCLUSIONS

- ERAS-801 demonstrates both potent activity against GBM-unique oncogenic EGFR alterations in the extracellular domain and high CNS penetration.
- ERAS-801 shows promising preclinical activity in EGFR-altered patient-derived GBM orthotopic xenografts, reducing tumor growth and significantly extending survival relative to other CNS penetrant EGFR TKIs.
- A preclinical trial against a diverse panel of patient-derived orthotopic GBM xenografts will enable discovery of genetic and transcriptomic biomarkers of response and resistance to ERAS-801.

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