Anti-Tumor Activity of BDTX-1535, an Irreversible CNS Penetrant Inhibitor of Multiple EGFR Extracellular Domain Alterations, in Preclinical Glioblastoma Models

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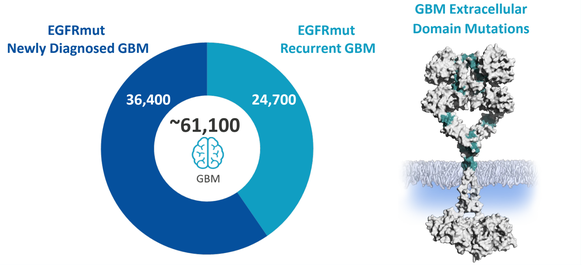
Abstract: #66

Background

EGFR alterations, including mutation and amplification, are very common in glioblastoma multiforme (GBM), impacting over 60k patients per year. No targeted therapy has been approved for GBM. The standard of care remains surgical resection followed by radiotherapy and adjuvant temozolomide.

1 Addressable GBM patient population (US / EU / Japan / China) with EGFR extracellular domain mutations



Extracellular domain EGFR alterations found in GBM form covalent homodimers, impacting pharmacology and leading to potential for paradoxical activation by reversible inhibitors. We believe there are four criteria to an effective EGFR inhibitor in GBM:

1. Potent and selective against a broad family of extracellular domain alterations and amplification
2. High CNS penetration
3. Wild-type EGFR sparing
4. Irreversible binding to avoid paradoxical activation

2 MAP drug discovery engine can deliver MasterKey EGFR inhibitor for GBM

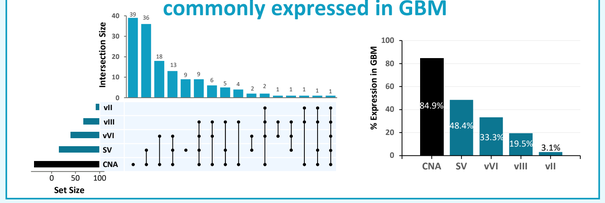
Materials and Methods

BDTX-1535 preclinical exposure was evaluated in multiple species, PK and Kpuu values were calculated in plasma/ blood and brain/CSF. Antitumor activity was assessed across mouse PDX and allograft models. 2540 tumors were sequenced with the Tempus xT NGS assay. Mutational frequencies of oncogenic *EGFR* variants were assessed and relationship between treatment history and mutational frequency was analyzed.

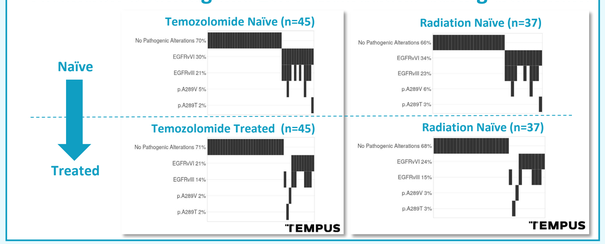
Results.

BDTX-1535 is a CNS penetrant 4th generation irreversible EGFR MasterKey inhibitor targeting a family of EGFR alterations and amplification, while sparing wild type (WT) EGFR. BDTX-1535 was designed using the MAP Discovery Engine and targets the activated conformations used by oncogenic EGFR to drive tumor cell growth. BDTX-1535 meets all four criteria for an EGFR inhibitor to be effective in GBM.

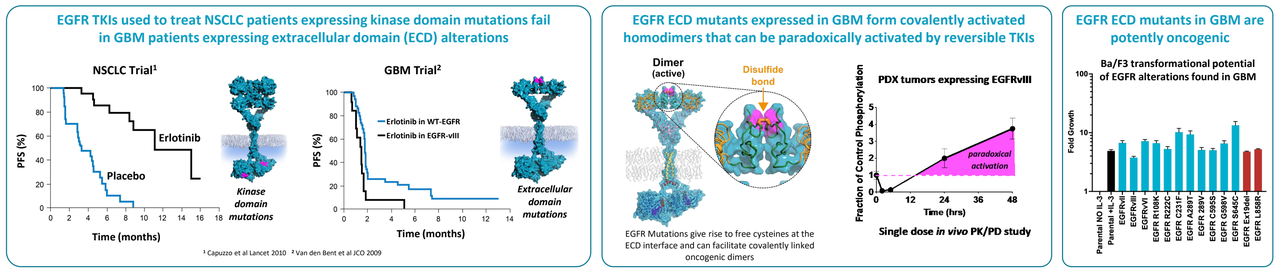
3 Oncogenic EGFR mutations and amplification are commonly expressed in GBM



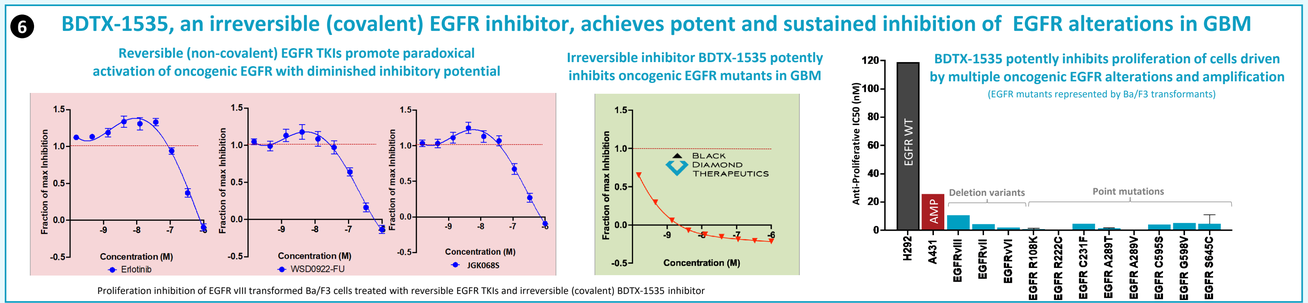
4 Longitudinal sequencing of GBM patients demonstrates retention of oncogenic EGFR alterations during treatment



5 Oncogenic EGFR alterations in GBM are covalent homodimers unresponsive to currently available EGFR TKIs

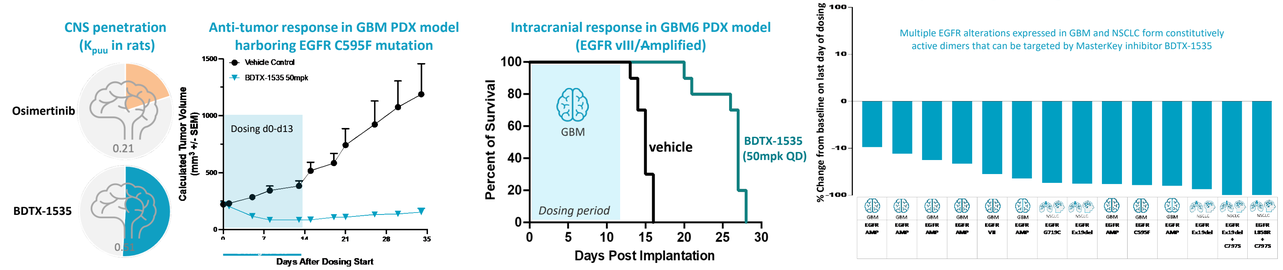


6 BDTX-1535, an irreversible (covalent) EGFR inhibitor, achieves potent and sustained inhibition of EGFR alterations in GBM



Proliferation inhibition of EGFR vIII transformed Ba/F3 cells treated with reversible EGFR TKIs and irreversible (covalent) BDTX-1535 inhibitor

7 BDTX-1535 demonstrates potent anti-tumor activity and survival benefit in PDX and Intracranial GBM models



Conclusions

BDTX-1535 is a 4th generation irreversible CNS penetrant MasterKey EGFR TKI targeting multiple oncogenic EGFR extracellular domain alterations and amplification in GBM patients and EGFR resistance mutations in NSCLC. Real world data demonstrate different EGFR alterations are frequently co-expressed and persist despite treatment. BDTX-1535 achieves potent anti-tumor activity against EGFR alterations and amplification across models including PDX and intracranial tumors. BDTX-1535 is currently in a phase I clinical study in patients with NSCLC and GBM harboring sensitive EGFR alterations (NCT05256290).

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