CNS Penetrant, Irreversible Inhibitors Potently Inhibit the Family of Allosteric Oncogenic EGFR Mutants Expressed in GBM and Demonstrate Efficacy in Patient-Derived Xenograft Models
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Abstract
- Oncogenic EGFR mutations occur in approximately 50% of glioblastomas (GBM) and largely reside in the extracellular domain.
- Prior attempts to reposition current-generation EGFR inhibitors to treat GBM have failed to pivot brain penetration and an inability to potently target the spectrum of oncogenic mutations
- As EGFR oncogenic mutations are found to be co-expressed in many GBM, it is required that an inhibitor be broadly active against the entire family of relevant EGFR mutants.
- Additionally, a successful inhibitor would require a pharmacokinetic (PK) profile that allows for sufficient penetration of the blood-brain barrier to inhibit target engagement of the brain tumor.
- Using these design principles, we designed a series of highly potent molecules exemplified by BDTX-507.
- This molecule is an irreversible inhibitor of EGFR with antiproliferative IC50 less than 10 nM against the spectrum of GBM-relevant EGFR mutations

Introduction
GBM tumors express a family of allosteric EGFR oncogenic mutations in the extracellular domain (Figure 1).

EGFR mutant covalent dimer conformation affects the pharmacology for small molecule drugs (Figure 4).

Results
Allosteric EGFR oncogenes expressed in GBM are activated as conserved by blebbistatin homodimer (Figure 2).
- BDTX-GBM molecules are designed to be potent, allosteric EGFR selective, and brain penetrant (Figure 5).
- BDTX-GBM molecules showed good mouse PK profile (Figure 8).
- BDTX-GBM lead to achievement of selective inhibition of allosteric EGFR mutants in vivo (Figure 9).
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- BDTX-GBM leads to achievement of tumor growth inhibition of intracranial PDX tumors expressing allosteric EGFR mutants (Figure 10).