Discovery of BDTX-1535, a novel, brain penetrant, irreversible, potent, wild type sparing EGFR MasterKey inhibitor that targets oncogenic kinase domain mutations as well as extracellular domain alterations for the treatment of NSCLC and GBM

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Abstract: #

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Background

Acquired resistance to 3rd generation EGFR inhibitors, such as osimertinib, used in the treatment of NSCLC is common. While the EGFR C797S substitution is a frequently reported post-osimertinib resistance mutation, real world evidence indicates the emergence of additional EGFR alterations that can drive drug resistance: kinase domain mutations (e.g., S768I), extracellular domain alterations (e.g., EGFRvIII, A289X), and EGFR amplification. Moreover, while osimertinib targets the classical EGFR mutations, primary NSCLC tumors are also driven by other oncogenic kinase domain mutations including G719X, S768I, and L861Q, which confer de novo (intrinsic) resistance to osimertinib. A family of extracellular domain alterations occurs in nearly 50% of GBM patients, and these alterations are clinically resistant to all current generation inhibitors. Real world data in GBM demonstrate these EGFR alterations often co-occur and persist throughout treatment with current standard of care therapy. Of critical importance is the observation that the oncogenic isoform of EGFR in GBM is a covalent homo-dimer which can be formed and paradoxically activated by the binding of reversible EGFR inhibitors.

There is a significant clinical need to develop a potent brain penetrant EGFR inhibitor that would target both acquired and intrinsic resistance mutations expressed in NSCLC and co-occurring EGFR alterations in GBM. An effective inhibitor should meet four design principles; 1) potent and selective against a broad family of intracellular, extracellular EGFR oncogenic alterations and amplification, 2) wild type EGFR sparing, 3) irreversible to avoid paradoxical activation, and 4) brain penetrant.

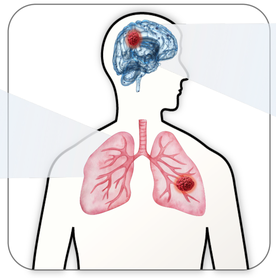
BDTX-1535 is a 4th generation irreversible brain penetrant EGFR MasterKey inhibitor targeting a family of oncogenic EGFR extracellular domain alterations and amplification and EGFR resistance mutations in NSCLC and in GBM. BDTX-1535 meets all four criteria for a highly effective EGFR inhibitor and was designed using Black Diamond Therapeutic's MAP Drug Discovery Engine to target the activated conformations used by oncogenic EGFR to drive tumorigenesis. BDTX-1535 achieves potent anti-tumor activity against EGFR alterations and amplification across models including NSCLC and GBM 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).

1 BDTX-1535 is a Novel EGFR MasterKey Inhibitor Designed to Address Unmet Medical Needs in NSCLC and GBM Patients

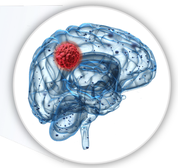
EGFR mutant non-small cell lung cancer

Undrugged EGFR kinase domain alterations

- Acquired resistance mutations (C797S & a growing group based on RWE)
- Intrinsic resistance & amplification



EGFR altered glioblastoma

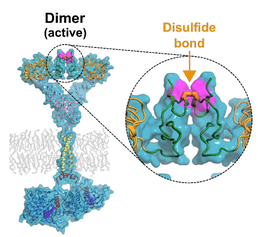


Undrugged EGFR extracellular domain alterations

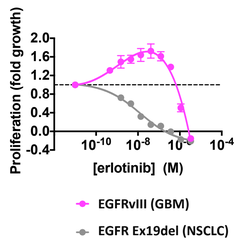
- Heterogenously expressed EGFR mutations (approximately 50% of GBM)
- Amplification – coincident with EGFR mutations

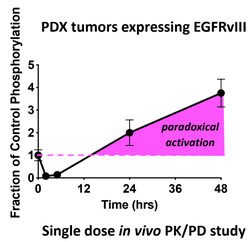
2 Potential for Unwanted Paradoxical Activation of GBM Mutations by Reversible EGFR TKIs

The oncogenic conformation of mutant EGFR in GBM is a locked dimer



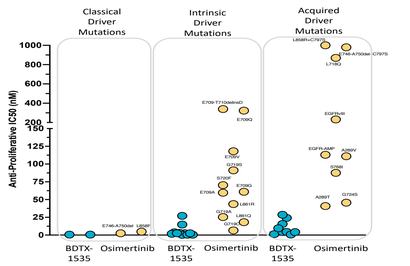
Reversible TKIs can stimulate the activity of mutant EGFR in GBM in preclinical models



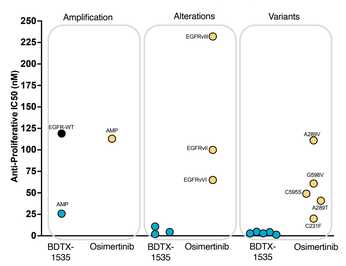


3 MasterKey Profile Potently Inhibits Broad Family of Oncogenic Alterations in NSCLC & GBM While Sparing EGFR-WT

BDTX-1535 Potently Inhibits Classical Driver Mutations, Intrinsic and Acquired Mutations in NSCLC, Preclinically Compared to Osimertinib

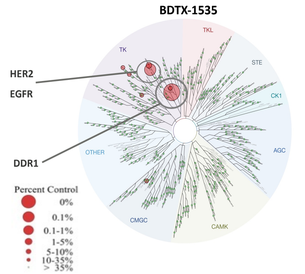


BDTX-1535 Potently Inhibits Broad Family of Oncogenic Alterations in GBM While Sparing EGFR-WT

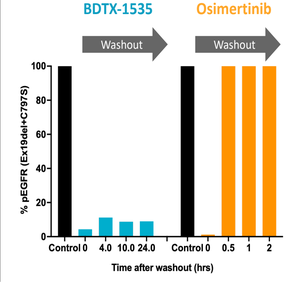


4 BDTX-1535 is a Highly Selective Irreversible EGFR TKI that Achieves Potent and Sustained Target Coverage

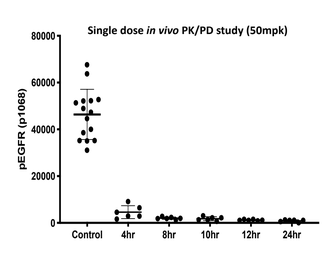
Highly Selective in the Kinome



Sustained Target Engagement in Cells

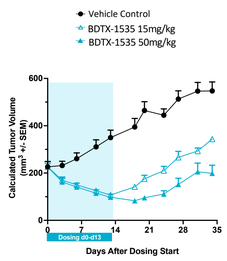


Sustained Target (pEGFR/pERK) Inhibition In Vivo

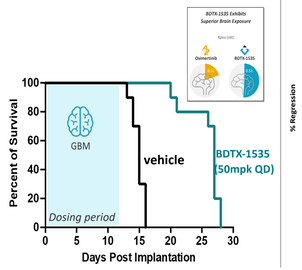


5 BDTX-1535 Regresses Tumor Growth in EGFR Mutant PDX Tumors & Intracranial Tumor Models

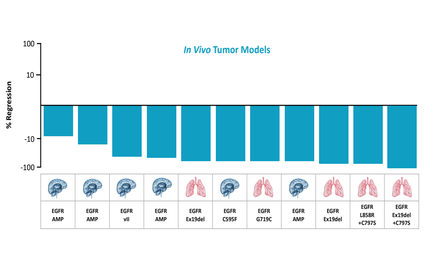
Regressions in NSCLC PDX model EGFR G719C+S768I



Intracranial response in GBM6 PDX model (EGFR vIII/Amplified)



BDTX-1535 achieves growth regressions across tumors expressing oncogenic EGFR alterations



Conclusions

BDTX-1535 is a 4th generation, irreversible, brain penetrant, EGFR MasterKey inhibitor that targets a family of oncogenic EGFR extracellular domain alterations and amplification in EGFR resistance mutations in NSCLC and in GBM. BDTX-1535 achieves potent anti-tumor activity against EGFR alterations and amplification across multiple models including NSCLC and GBM 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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