BDTX-1535 is a Fourth Generation MasterKey Inhibitor of a Broad Spectrum of Intrinsic and Acquired Resistance Mutations of EGFR Expressed in NSCLC

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Abstract: #64

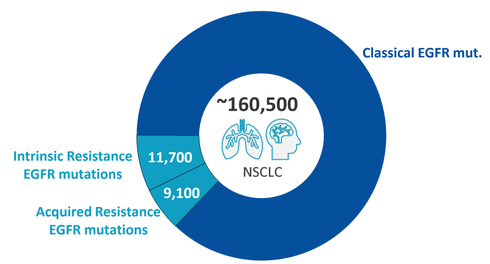
Background

3rd generation EGFR TKIs, such as osimertinib, target classical EGFR driver mutations (exon 19 deletion and L858R) and T790M resistance mutation, have become the standard 1st line therapy in NSCLC. It has significantly altered the mutation landscape leading to the emergence of multiple acquired mechanisms of resistance. While EGFR C797S substitution is a commonly reported post-osimertinib resistance mutation, real world evidence shows the emergence of multiple other EGFR alterations as potential mechanisms of resistance: kinase domain mutations (e.g., S768I), extracellular domain alterations (e.g., EGFRvIII, A289X), and EGFR amplification. Moreover, while osimertinib targets classical EGFR mutations, NSCLC tumors express other kinase domain mutations including G719X, S768I, and L861Q, which can confer intrinsic resistance towards 3rd generation EGFR TKIs. There is a significant clinical need to develop a potent CNS penetrant EGFR TKI that would target both acquired and intrinsic resistance mutations against 3rd generation EGFR TKIs.

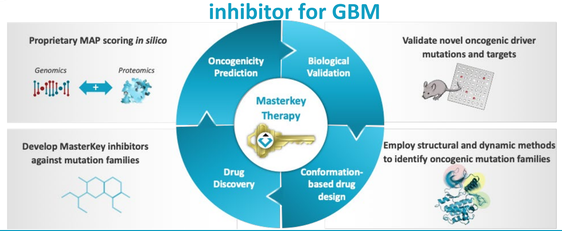
Results

BDTX-1535 is a CNS penetrant 4th generation irreversible (covalent) EGFR MasterKey inhibitor targeting a family of classical, intrinsic and acquired resistance mutations (e.g., C797S, L718Q, G724S, S768I), extracellular domain alterations (e.g., EGFRvIII, A289X), expressed in NSCLC 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 the criteria for an EGFR inhibitor that is potent, CNS penetrant and targets the family of acquired and intrinsic resistance mutations against 3rd generation EGFR TKIs.

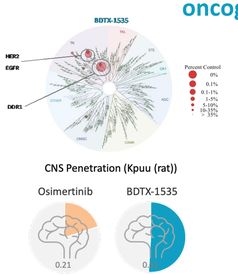
1 Addressable NSCLC Patient Population (US/EU/Japan/China) With EGFR Mutations



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



3 BDTX-1535 is a CNS penetrant irreversible inhibitor of classical, acquired and intrinsic resistance EGFR oncogenic mutations



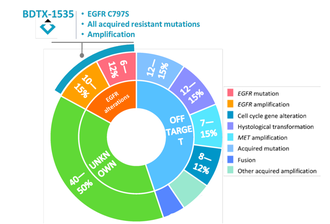
EGFR mutational coverage $	3rd generation Osimertinib	4th generation BLU-701 #	4th generation BDTX-1535
L858R			
Ex19del			
Ex19del+C797S			
L858R+C797S			
L718Q		Not tested	

AACR 2021
$ Based on biochemical IC50

IC_{50}<0.1nM
>0.1nM IC_{50} <50nM
IC_{50}>50nM

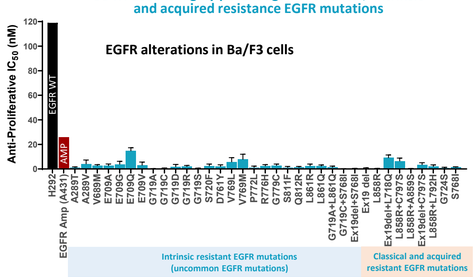
4 BDTX-1535 is a MasterKey inhibitor targeting the full family of classical and resistance EGFR mutations in NSCLC

BDTX-1535 targets broad family of acquired resistant EGFR alterations

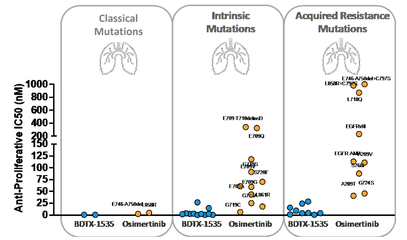


Bertoli *et al., Int. J. Mol. Sci.* 2022

BDTX-1535 is highly potent against classical, intrinsic and acquired resistance EGFR mutations

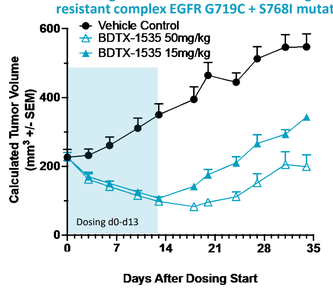


BDTX-1535 potently inhibits classical, acquired & intrinsic resistance EGFR mutations when compared to 3rd generation EGFR TKI

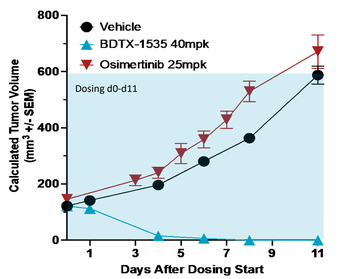


5 BDTX-1535 inhibits tumor growth and leads to tumor regression in EGFR mutant tumor models and PDX

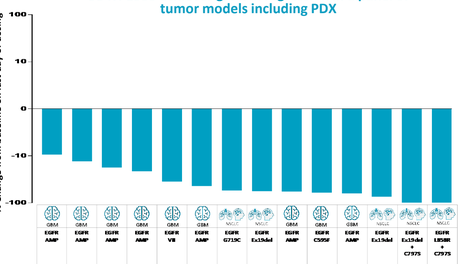
Tumor regression in PDX model harboring intrinsic resistant complex EGFR G719C + S768I mutations



Tumor regression in PDX model expressing acquired resistant EGFR Exon 19del + C797S mutations



BDTX-1535 achieves growth regression in a panel of tumor models including PDX

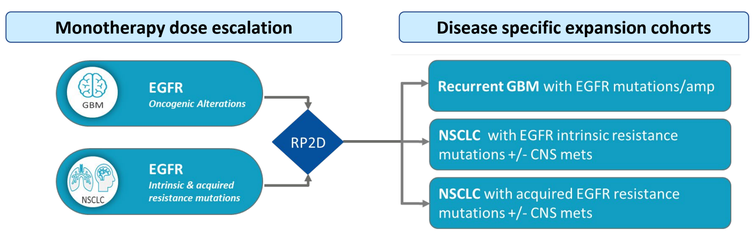


6 BDTX-1535 Phase 1 study design - ongoing

Key eligibility criteria

- Patients ≥18 years of age
- Post 3rd generation EGFR TKI NSCLC patients with acquired (eg, C797S) and intrinsic (eg, G719X) EGFR resistance mutations
- Recurrent glioblastoma (GBM) patients with EGFR alterations including amplification, variants, or mutations
- Adequate bone marrow or organ function

ClinicalTrials.gov Identifier: NCT05256290



Conclusions

BDTX-1535 is a 4th generation irreversible CNS penetrant EGFR MasterKey inhibitor targeting families of classical, acquired and intrinsic resistance EGFR kinase domain alterations relevant for NSCLC and extracellular domain EGFR alterations and amplification relevant for GBM. It is highly selective and potent in multiple preclinical tumor models and demonstrates high CNS penetration while sparing wild type EGFR. BDTX-1535 is currently under phase I clinical investigation in patients with NSCLC and GBM harboring sensitive EGFR alterations (NCT05256290).

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