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BDTX-1535, a CNS penetrant MasterKey inhibitor of common, uncommon and resistant EGFR mutations, demonstrates in vivo efficacy and has potential to treat patients with NSCLC harboring osimertinib-resistant mutations with or without brain metastases

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Black Diamond Therapeutics, Cambridge, USA

Expanding the Reach of Precision Medicine Through the Development of Novel MasterKey Therapies

Addressing significant unmet need for novel precision oncology therapies for patients with genetically defined cancers with limited treatment options

Uniquely de-orphaning oncogenic mutations to develop single therapies designed to inhibit specific mutation families

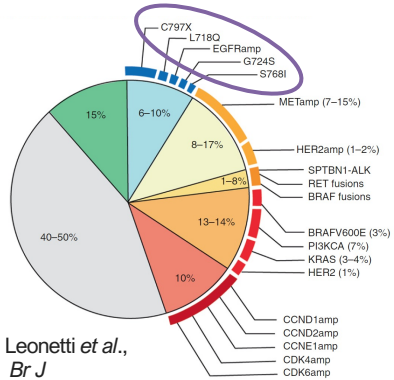
Our proprietary computational Mutation Allostery Pharmacology (MAP) drug discovery engine is designed to:

- Analyze population-level genetic sequencing data to identify oncogenic mutations that promote cancer across tumor types
- Aggregate these mutations into families
- Develop a spectrum-selective (MasterKey) small molecule therapy

Robust pipeline of oral, potent and selective small molecule kinase inhibitors across a range of indications and target groups including EGFR, HER2, BRAF and FGFR

Targeting Unmet Medical Need in EGFR-mutated NSCLC

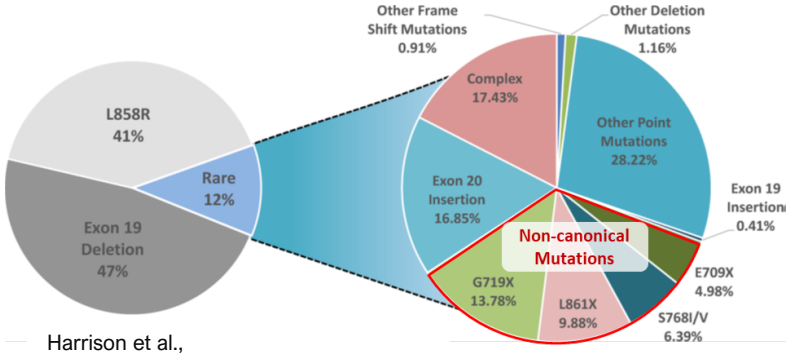
Acquired Resistance to 3rd generation EGFR TKIs



Leonetti *et al.*, *Br J Cancer* 2019

EGFR Mutations Resistant to First line Osimertinib

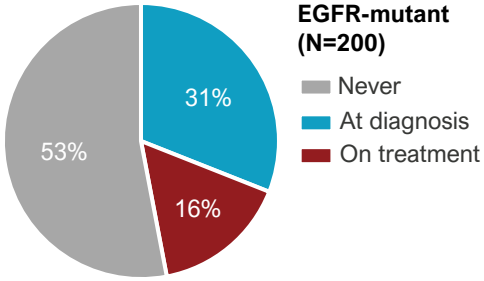
Intrinsic Resistance to EGFR TKIs



Harrison et al., *Semin Cancer Biol*. 2020

Non-canonical EGFR Mutations

Brain Metastasis Occurrence with NSCLC

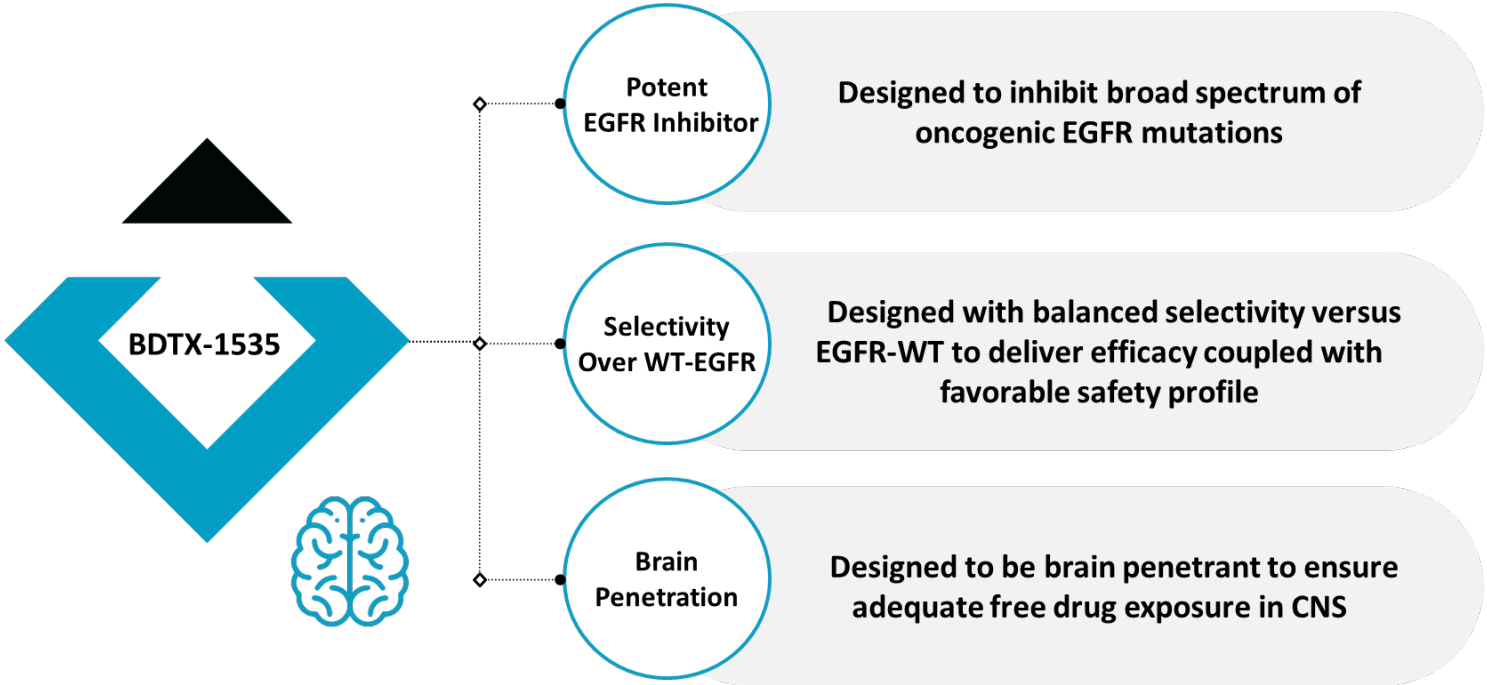


Offin *et al.*, *Cancer* 2019

Brain Mets with EGFR Mutations

BDTX-1535

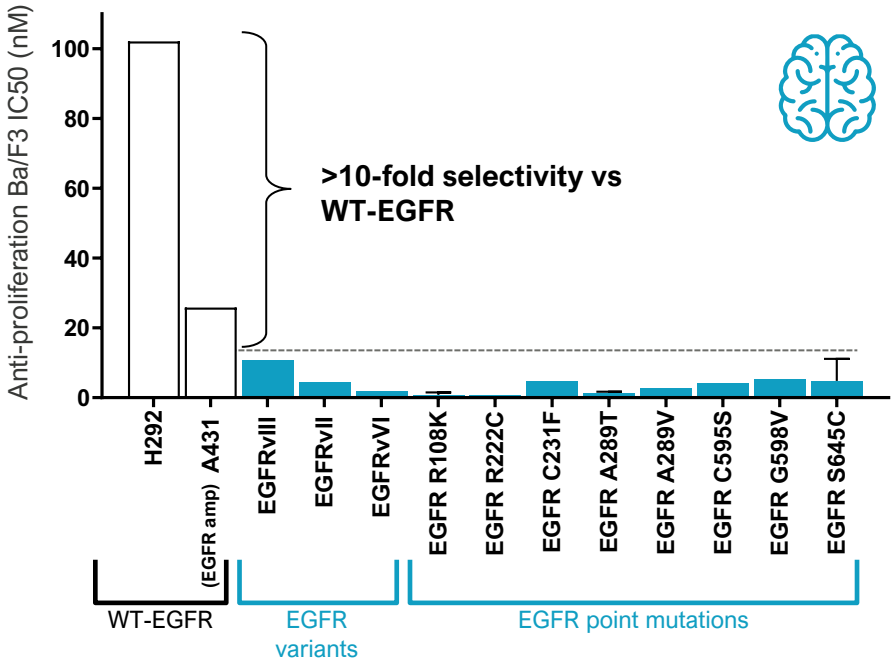
BDTX-1535: A Brain Penetrant, Potent Inhibitor of Oncogenic EGFR Mutations



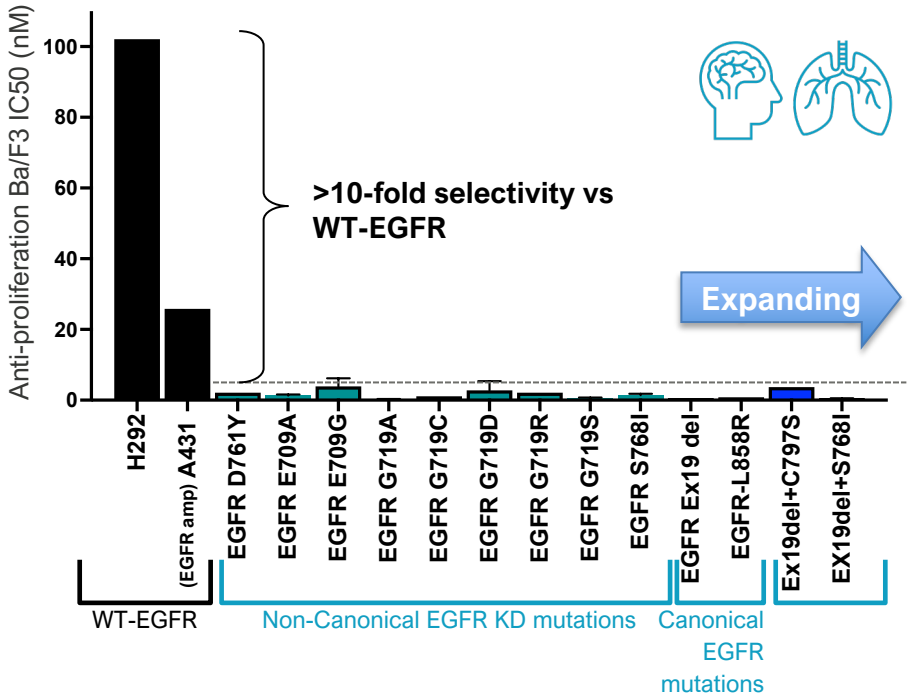
Optimized to Address a Wide Range of Oncogenic EGFR Mutations and Variants

AACR American Association for Cancer Research FINDING CURES TOGETHER
NIH NATIONAL CANCER INSTITUTE
EORTC European Organisation for Research and Treatment of Cancer — The future of cancer therapy

EGFR Variants and Mutations Found in GBM



EGFR Mutations of Intrinsic Resistance and Acquired Resistance in NSCLC



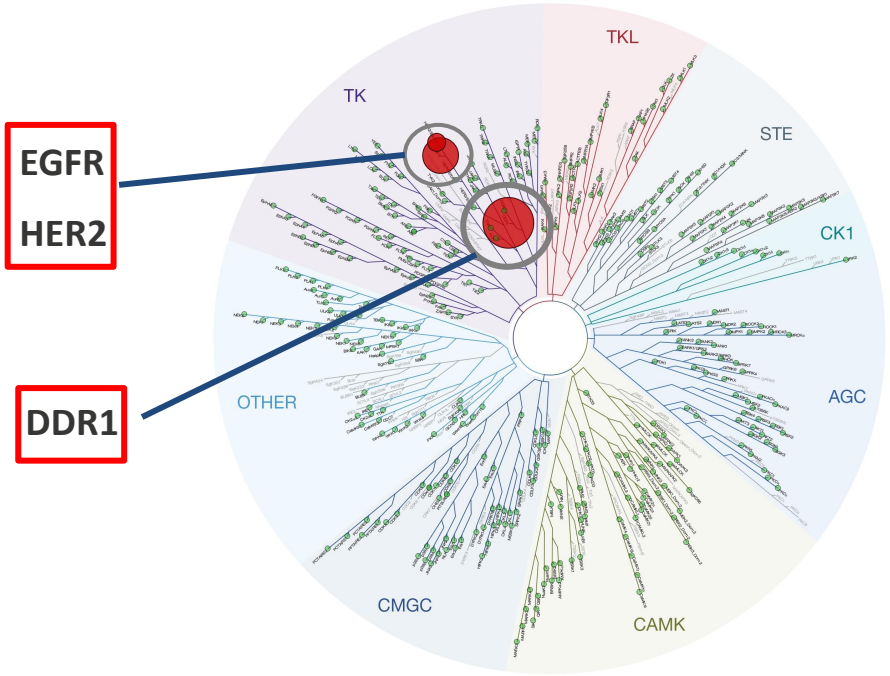
BDTX-1535 Is a CNS-penetrant Inhibitor of Canonical and Drug-Resistance Mutations

	Erlotinib	Gefitinib	Afatinib	Dacomitinib	Osimertinib	BDTX-1535
MOA	Reversible	Reversible	Irreversible	Irreversible	Irreversible	Irreversible
CNS Kpuu (r)	0.08	0.29	-*	0.21	0.29	**0.45**
EGFR-WT (H292) IC_{50} (nM)	878	418	29	28	454	119
EGFR Ex19del (Ba/F3) IC_{50} (nM)	19	10	0.5	0.3	2.5	0.6
EGFR Ex19del/C797S (Ba/F3) IC_{50} (nM)	15	11	8	9	>1000	3.1

Selectivity over **WT H292** (fold)			CNS exposure (average Kpuu, m/r)		
>10x	5-10x	<5x	>0.3	0.3-0.1	<0.1

*Rat Kpuu not measured, but mouse Kpuu = 0.03

BDTX-1535 Achieves Excellent Kinome Selectivity and Drug Like Properties

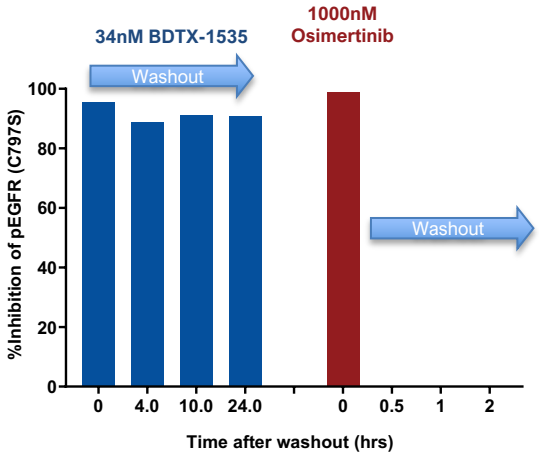


- ✓ Not a hERG inhibitor at projected clinical concentrations
- ✓ Good blood & moderate liver stability
- ✓ Good GSH $T_{1/2}$
- ✓ Low Risk for CYP Inhibition with no TDI
- ✓ No CYP induction
- ✓ No unique human metabolites
- ✓ Weak Pgp substrate

*DiscoverX Kinome Panel of 468 kinases, at test concentration of 100 nM; Kd for EGFR and DDR1 0.17 and 3.8 nM, respectively

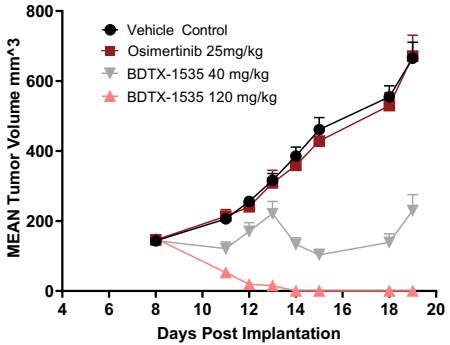
Preclinical Data Supports Opportunity in NSCLC Harboring Osimertinib Resistant C797S

Retains irreversible binding against C797S mutant



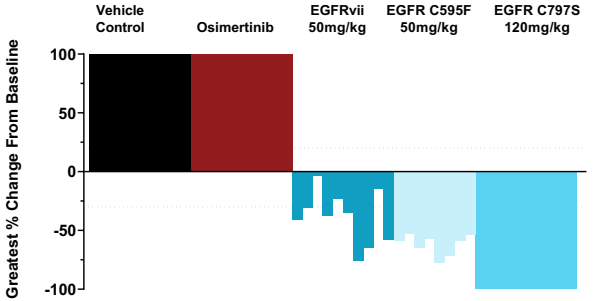
>24h inhibition of pEGFR Ex19del/C797S

Regression in Ba/F3-EGFR Exon19del /C797S Mouse allograft



Dose dependent TGI in without loss of body weight

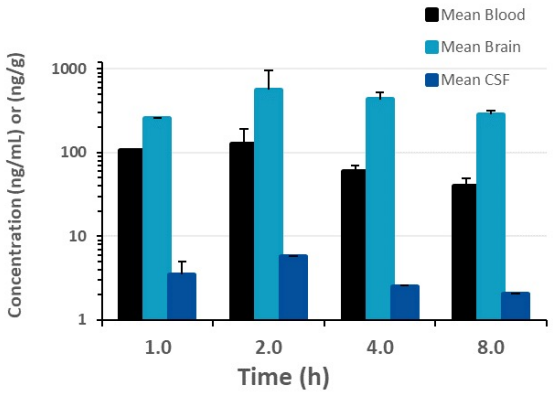
Regression across range of allograft and EGFRvII and C595F PDX models



% change from baseline capped at 100%; Vehicle control and osimertinib from EGFR Ex19del/C797S study

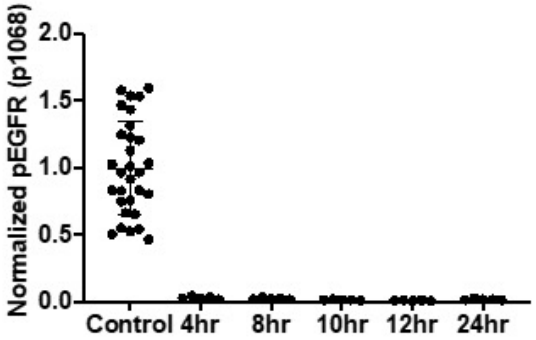
CNS Exposure, Sustained Target Engagement and TGI in Intracranial PDX Tumors

Exposure in Rat Blood, Brain, CSF after single oral dose of 30 mg/kg



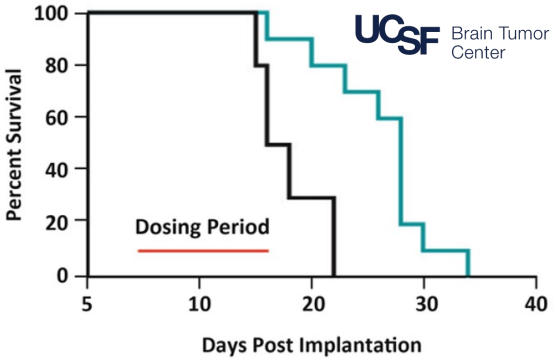
Kpuu = 0.45

>24h Inhibition of pEGFR in Ba/F3 Allograft Tumors expressing EGFRvIII



Single oral dosing of BDTX-1535 (50 mg/kg) in mice

Survival increase in Intracranial EGFRvIII PDX Tumors



Oral dosing of BDTX-1535 (50 mg/kg) daily in mice

GBM6 model expressing EGFRvIII/amplified EGFR WT conducted at UCSF Brain Tumor Center

Conclusions

Black Diamond Therapeutics is Developing BDTX-1535 as a Brain Penetrant, Potent Inhibitor of Oncogenic EGFR Mutations

Excellent free drug exposure in the CNS

Highly efficacious in intracranial PDX tumor model with an intact BBB and across a range of allograft and PDX models

Potential to treat patients with NSCLC harboring osimertinib-resistant C797S mutation with or without brain metastases