Anti-tumor Activity of BH-30643, a Novel Macrocyclic Kinase Inhibitor, in *EGFR*-mutant Lung Cancer Models

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Abstract #3110

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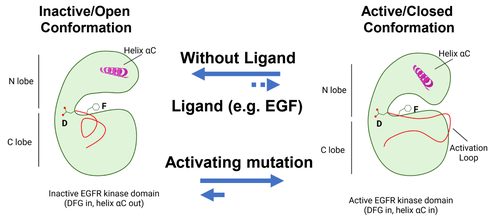
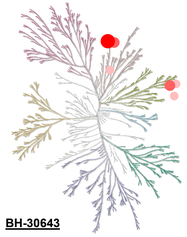
Background on BH-30643: Design and Discovery

Outcomes on tyrosine kinase inhibitor (TKI) treatment in *EGFR*-mutant NSCLC fall short of the durable benefit observed with next generation targeted therapies in *ALK* or *ROS1*-driven NSCLC. Novel targeted therapies are needed to address treatment resistance and offer prolonged patient benefit with reduced toxicity. We recently described the design and discovery of BH-30643, a first-in-class, macrocyclic, non-covalent TKI targeting the active conformation of mutant EGFRs and offering potent, mutant-selective EGFR inhibition across classical , atypical, exon 20 insertion (ex20ins), resistance, and compound *EGFR* mutations as well as *HER2* mutations (AACR 2025). Here we disclose diverse preclinical models to further assess the breadth of activity from this novel approach.



BH-30643: a Non-covalent, Macrocyclic, Mutant-selective EGFR Inhibitor

- Targeting the active conformation (which is shared across mutant EGFRs) allows super-potency against a wide-spectrum of classical, atypical, ex20ins, resistance, and compound EGFR mutants to overcome the limitations of earlier generation EGFR inhibitors, while maintaining selectivity over wildtype (WT) EGFR
- Our novel design enables super potency against the T790M gate keeper mutation that developed against 1st and 2nd generation EGFR inhibitors
- As a non-covalent inhibitor, BH-30643 addresses the C797X resistance mutation that limits the effectiveness of 3rd generation EGFR inhibitors
- BH-30643 is highly selective over 371 WT human kinases in the Reaction Biology kinase panel



BH-30643

EGFR	1
HER2, TNIK	1-5 x
MINK, HGK, LRRK2	5-20 x

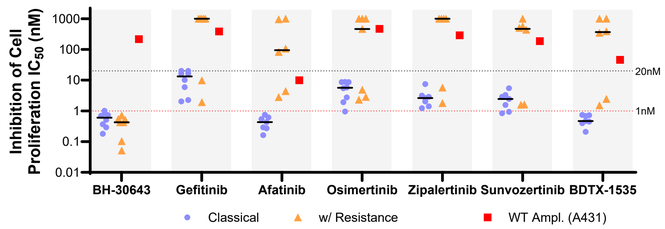
Methods

Cell proliferation inhibition was measured in primary cancer cells or engineered Ba/F3 cells carrying various *EGFR* mutations, including classical, atypical, ex20ins, acquired resistance mutations (eg T790M and C797S), and compound resistance mutations. Anti-tumor activity of BH-30643 was evaluated in cell-derived xenograft (CDX) or patient-derived xenograft (PDX) tumor models carrying classical or atypical *EGFR* mutations. CNS activity of BH-30643 was investigated in an intracranial xenograft model. For *in vivo* mouse model studies (n = 5-10), BH-30643 was administered twice daily (BID) via oral gavage as either suspension (40 mg/kg) or solution (< 40 mg/kg) formulation; osimertinib (25 mg/kg) was dosed once daily (QD) in a solution formulation. In PK/PD CDX studies, tumor and plasma samples were collected at multiple timepoints after the last dose of test articles following a 2-day BID treatment scheme at multiple dose levels. Pharmacodynamic (PD) effect was evaluated by phospho-EGFR Y1068 (pEGFR) ELISA assays with vehicle samples used as control (ie 100%). All tumor volumes are shown as mean ± sem. For reference compounds, proxy molecules were obtained from commercial vendors or were made in-house.

Activity of BH-30643 Against Classic/Resistance *EGFR* Mutations

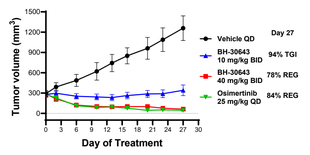
- BH-30643 exhibited marked cellular potency against *EGFR* classical mutations (ex19del and L858R) and their compound mutations with T790M and/or C797S resistance mutations, with IC_{50} values ≤ ~1 nM.
- Limited activity against WT EGFR suggests wide therapeutic window

***EGFR* Classical and Resistance Mutations**

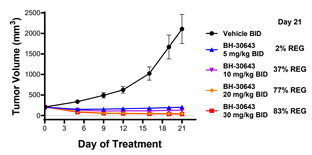


- BH-30643 induced deep tumor regression in the PC-9 CDX tumor model carrying *EGFR* ex19del mutation.
- BH-30643 activity was maintained in the presence of T790M, causing dose-dependent tumor shrinkage in H1975 CDX tumor model carrying EGFR L858R/T790M mutation.
- BH-30643 induced deep tumor regression in both a PDX tumor model harboring EGFR ex19del/T790M/C797S mutation and a CDX tumor model harboring EGFR L858R/T790M/C797S, without body weight loss or overt abnormalities, while osimertinib showed no activity in either model.

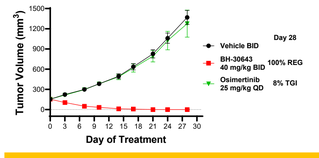
PC-9 (*EGFR* ex19del)



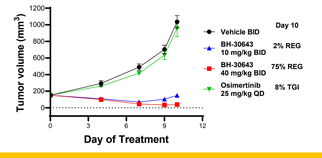
H1975 (EGFR L858R/T790M)



PDX EGFR ex19del/T790M/C797S



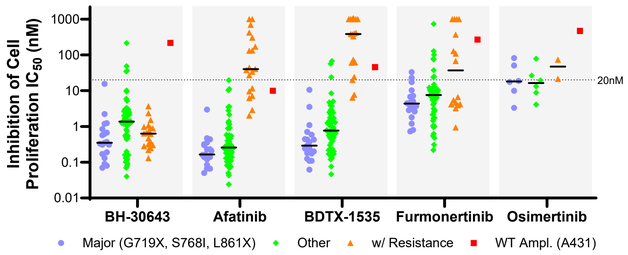
Ba/F3 EGFR L858R/T790M/C797S



BH-30643 Effectively Inhibited Wide-Spectrum of Atypical *EGFR* Mutations

- Activity against atypical *EGFR* mutations was studied across 95 different engineered Ba/F3 cell lines including the major atypical mutations (ie G719X, S768I and L861X) as well as less common atypical mutations in exons 18-21.
- BH-30643 exhibited potent inhibition of cell proliferation across a wide-spectrum of 95 atypical *EGFR* mutations, either as single mutations or as compound mutations with classical, resistance, or other atypical mutations.
- Comparator EGFR TKIs showed liabilities of either narrow therapeutic window or vulnerability to T790M or C797S resistance.

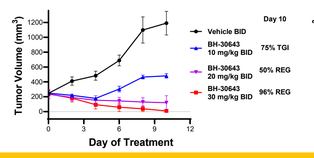
***EGFR* Atypical Mutations**



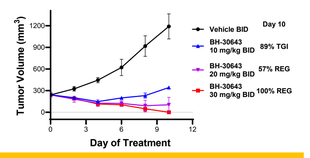
EGFR Atypical Mutations	Ba/F3 Cell Proliferation Inhibition IC_{50} (nM): Median (N)				
	BH-30643	Afatinib	BDTX-1535	Furmonertinib	Osimertinib
Major	0.35 (19)	0.16 (19)	0.29 (19)	4.36 (6)	18.1 (6)
Other	1.36 (57)	0.26 (57)	0.78 (57)	7.57 (53)	16.3 (6)
w/ Resistance	0.63 (19)	40.2 (19)	382 (19)	36.9 (16)	47.2 (2)
A431 (WT Ampl.)	217	9.94	45.9	268	469

- BH-30643 induced deep tumor regression in Ba/F3 EGFR G719A/L861Q or Ba/F3 EGFR G719A/L861Q CDX tumor models, without causing body weight loss or overt abnormalities.

Ba/F3 EGFR G719A/L861Q

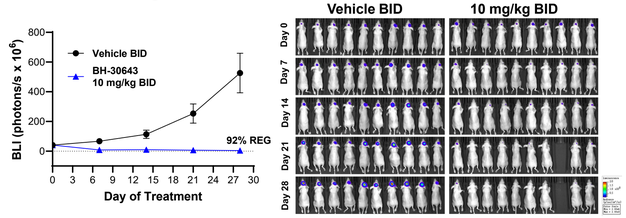


Ba/F3 EGFR G719A/S768I



CNS Activity of BH-30643 in an Intracranial CDX Model

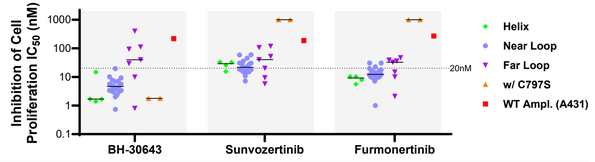
- HCC827-luc tumor cells carrying an *EGFR* ex19del mutation were implanted intracranially and the tumor growth was monitored by bioluminescent imaging throughout the study.
- Oral administration of BH-30643 induced profound reduction of HCC827-luc intracranial xenograft tumors.



BH-30643 Potently Inhibits *EGFR* Ex20ins/Resistance Mutations

- BH-30643 exhibited potent activities in cells lines carrying *EGFR* ex20ins mutations, with greater potency for ex20ins between amino acid 761 and 772 (ie, Helix and Near Loop mutations)
- Comparator EGFR TKIs exhibited reduced potency and vulnerability to C797S resistance mutation.

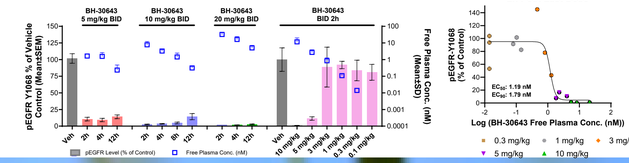
***EGFR* Exon 20 Insertions**



EGFR ex20ins Mutation	Ba/F3 Cell Proliferation Inhibition IC_{50} (nM): Median (N)		
	BH-30643	Sunvozertinib	Furmonertinib
Helix	1.68 (4)	28.9 (4)	9.11 (4)
Near Loop	4.61 (21)	21.6 (21)	12.3 (21)
Far Loop	39.7 (7)	40.1 (7)	32.5 (7)
w/ C797S	1.78 (2)	>1000 (2)	>1000 (2)

PK/PD Relationship of BH-30643 in Ba/F3 EGFR L858R/T790M/C797S CDX Tumor Model

- BH-30643 effectively inhibited pEGFR in a dose- and time-dependent manner in the Ba/F3 EGFR L858R/T790M/C797S CDX tumor model.
- At 2h post the last dose in this model, BH-30643 exhibited low free EC_{50} (1.19 nM) and EC_{90} (1.79 nM) values, comparable to the degree of pEGFR inhibition in cellular assays.



Conclusions

- BH-30643 is a non-covalent, macrocyclic, mutant-selective EGFR TKI exhibiting superior potency in primary or engineered tumor cell lines carrying a wide-spectrum of *EGFR* mutations, including classical, atypical, ex20ins, resistance, and compound mutations, with excellent selectivity against WT EGFR.
- BH-30643 demonstrated marked efficacy in CDX or PDX tumor models with classical/resistance *EGFR* mutations or compound atypical *EGFR* mutations, could overcome both T790M and C797S mutations, and exhibited intracranial activity.
- BH-30643 inhibited pEGFR in the Ba/F3 EGFR L858R/T790M/C797S CDX tumor model with low EC_{50} (1.19 nM) and EC_{90}, (1.79 nM), suggesting potential for clinical activity at early escalation doses.
- Supported by favorable ADME and preclinical safety profiles, the global Phase 1/2 SOLARA trial is enrolling patients with advanced NSCLC harboring *EGFR* or *HER2* mutations (NCT06706076) (TIP Abstract TPS8663)

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