BH-30643, a Novel Macrocyclic Non-Covalent, Mutant-Selective EGFR Inhibitor, Addresses the Resistance and Potency Limitations of Contemporary EGFR TKIs

AACR Abstract 5877

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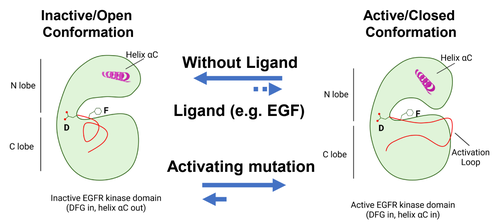
Background on BH-30643: Design and Discovery

Outcomes from 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, 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.



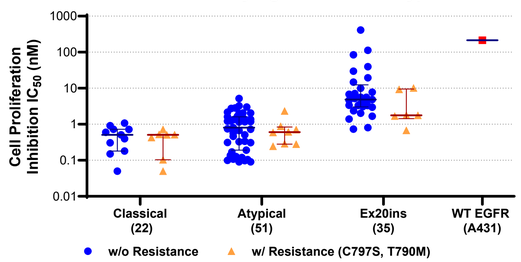
BH-30643: a Non-covalent, Macrocyclic, Mutant-selective EGFR Inhibitor

- Targeting the active conformation (which is shared across mutant EGFRs) via macrocyclic design allows super-potency against a wide-spectrum of classical (ex19del and L858R), 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 macrocyclic 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

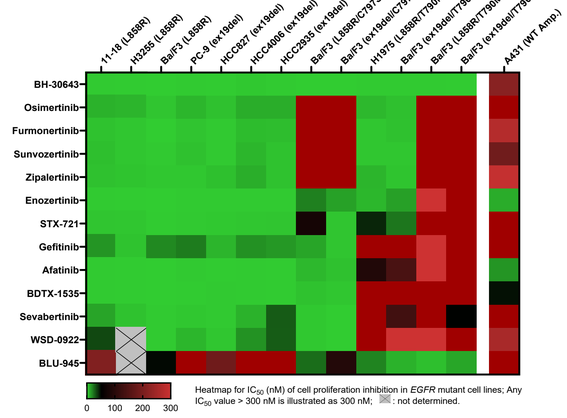
BH-30643 Demonstrated Activity Against Various Types of *EGFR* Mutations



The numbers of cell lines or the name of cell line evaluated are in parentheses for each mutation category; Classical mutations include ex19del and L858R; Atypical mutations include genetic alterations at G719, L861, S768, E709, L747, V834, L833, V769 and any compounds of these mutations with one another or with classical mutations; Resistance mutations include C797S and T790M; The bar in each group indicates median with interquartile range

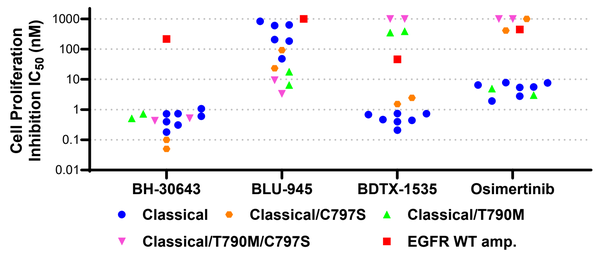
Activity of BH-30643 Against Classical/Resistance *EGFR* Mutations

- In primary lung cancer cell lines or engineered Ba/F3 cell lines carrying *EGFR* mutations (shown in parentheses), BH-30643 exhibited marked anti-cell proliferation potencies against *EGFR* classical mutations (ex19del and L858R) and their compound mutations with C797S and/or T790M resistance mutations, with IC_{50} values ≤ ~1 nM, while sparing WT EGFR. Comparator EGFR TKIs showed various vulnerability to resistance mutations consistent with known structural liabilities.



Heatmap for IC_{50} (nM) of cell proliferation inhibition in *EGFR* mutant cell lines; Any IC_{50} value > 300 nM is illustrated as 300 nM; : not determined.

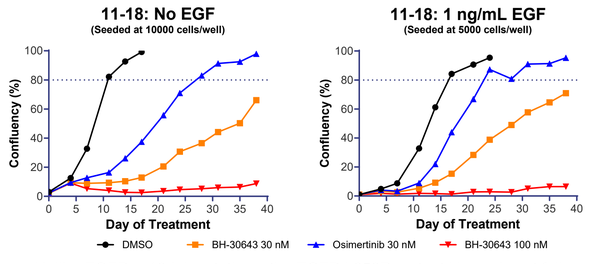
- BH-30643 is unique in its breadth of potency compared to prior TKIs developed against osimertinib resistance, inclusive of classical driver mutations alone or compounded with C797S and/or T790M. In contrast, BLU-945 exhibits reduced potency against classical driver mutations (ex19del and L858R), while BDTX-1535 loses potency in the presence of T790M.



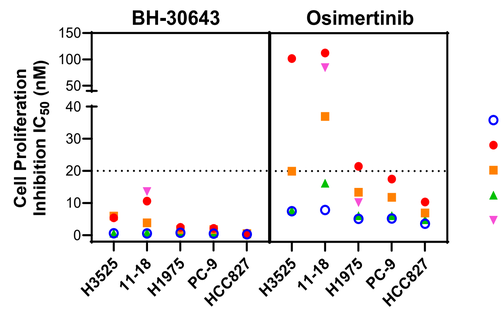
Note: Classical: L858R and ex19del; Any IC_{50} value > 1000 nM was plotted as 1000 nM.

BH-30643 Overcame EGFR Ligand Challenge and Exhibited Long-Term Cell-Growth Suppression

- The relative capability of BH-30643 vs osimertinib in suppressing long-term cell growth was investigated in 11-18 cells with *EGFR* L858R mutation
- Osimertinib at clinical relative concentration of 30 nM suppressed 11-18 cell growth with weaker activity, especially in the presence of EGF ligand (1 ng/mL) in comparison with BH-30643 at 30 nM
- BH-30643 at 100 nM suppressed cell growth for over 35 days, regardless addition of EGF (1 ng/mL)



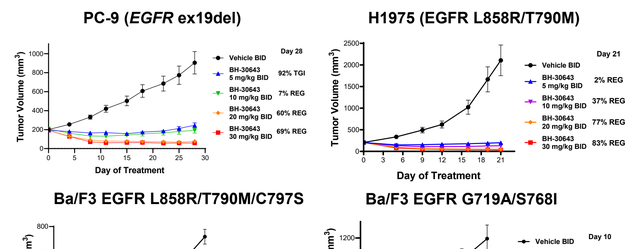
- Unlike *EGFR* ex19del mutations, the EGFR L858R mutant kinase is not fully activated, and binding of EGFR ligands will facilitate maximal kinase activation
- The impact of EGF family ligands on BH-30643 vs osimertinib activity were investigated in cancer cell lines with *EGFR* L858R or ex19del mutations
- EGF and EREG produced the most profound impact on EGFR TKI activities, especially in L858R mutated H3525 and 11-18 (aka II-18) cell lines
- BH-30643 maintained its potency better than osimertinib under EGF family ligand (10 ng/mL) challenge, with all IC_{50} values remaining below 20 nM



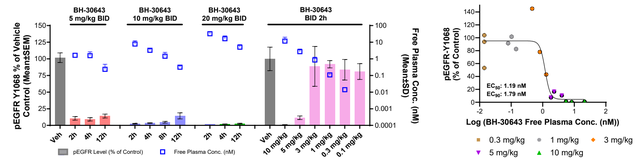
H3255 and 11-18: *EGFR* L858R; H1975: *EGFR* L858R/T790M; PC-9 and HCC827 :*EGFR* ex19del

Superb Efficacy and Brain Activity of BH-30643 in Tumor Models In Vivo

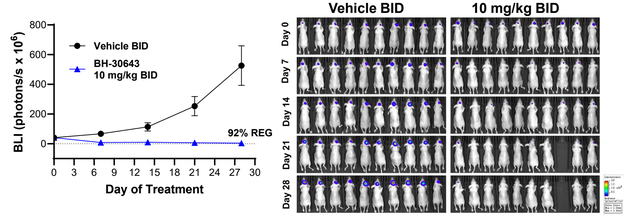
- BH-30643 induced dose-dependent deep tumor regression in the PC-9 CDX tumor model carrying *EGFR* ex19del mutation, in the H1975 CDX tumor model carrying EGFR L858R/T790M mutation, and in the Ba/F3 EGFR L858R/T790M/C797S CDX tumor model, demonstrating in vivo efficacy against *EGFR* classical mutation and classical mutations in compound with C797S and T790M resistance mutations
- BH-30643 induced dose-dependent deep tumor regression in the Ba/F3 EGFR G719A/S768I CDX tumor model, showing efficacy against *EGFR* atypical mutations in vivo



- 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, human eq. expo: 67 ng/mL) values, comparable to the degree of pEGFR inhibition in cellular assays



- 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



Conclusions

- BH-30643 is a non-covalent, macrocyclic, mutant-selective EGFR TKI exhibiting superior potency in primary or engineered tumor cell lines carrying EGFR classical mutations and compound mutations, with potency maintained in the presence of C797S and/or T790M resistance mutations
- BH-30643 markedly prolonged suppression of cell proliferation compared to osimertinib at clinically relevant concentrations not only under standard growth conditions, but also in the presence of EGF, which mimicked accelerated resistance
- BH-30643 demonstrated marked efficacy in CDX tumor models with classical/resistance *EGFR* mutations or compound atypical *EGFR* mutations, could overcome both T790M and C797S resistance mutations, and exhibited intracranial activity
- The global Phase 1/2 SOLARA trial is enrolling patients with advanced NSCLC harboring *EGFR* or *HER2* mutations (NCT06706076)

For all reference compounds used in the studies, proxy molecules were purchased from commercial vendors

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