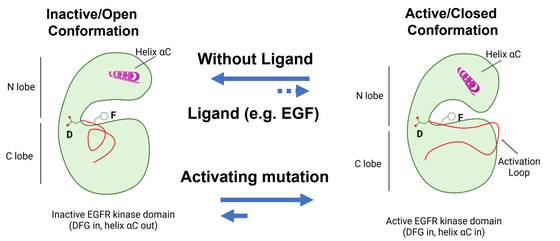
Preliminary findings from the first-in-human SOLARA trial of BH-30643, a novel macrocyclic, non-covalent, mutant selective, brain active, OMNI-EGFR inhibitor, in EGFR-mutant NSCLC

Alexander Spira[1], Hidehito Horinouchi[2], Misako Nagasaka[3], Divya Gupta[4], Jonathan Riess[5], Melissa Johnson[6], Alexander Philipovskiy[6], Lyudmila Bazhenova[7], Hiroki Izumi[8], Jean Cui[9], Diane Wang[9], Geoffrey Oxnard[9], Alena Zalutskaya[9], Xiuning Le[10]

[1]NEXT Oncology, USA; [2]National Cancer Center Hospital, Japan; [3]University of California Irvine, USA; [4]Northwestern Memorial Hospital, USA; [5]University of California Davis, USA; [6]Sarah Cannon Research Institute, USA; [7]University of California San Diego, USA; [8]National Cancer Center Hospital East, Japan; [9]BlossomHill Therapeutics, USA; [10]MD Anderson Cancer Center, USA

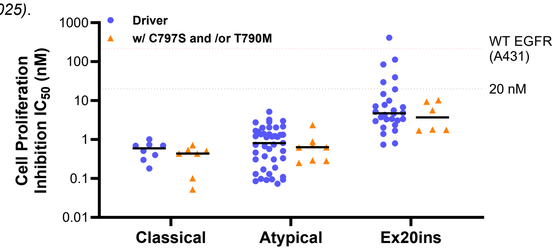
Background: Design of BH-30643

- Historical EGFR tyrosine kinase inhibitors were initially designed before the discovery of *EGFR* mutations to inhibit wildtype EGFR (1st and 2nd generation TKIs), or were designed to covalently inhibit *EGFR* T790M (3rd generation).
- We hypothesized that a non-covalent design targeting the active conformation of EGFR – a protein conformation shared across a wide diversity of activating *EGFR* mutations – could achieve selective potency against mutant *EGFR*.
- BH-30643 is a first-in-class non-covalent OMNI-EGFR TKI which was designed with a novel macrocyclic structure that tightly binds to the active conformation of mutant EGFR, allowing activity across a breadth of *EGFR* driver, resistance, and atypical mutations with selectivity against wildtype EGFR (*AACR 2025*).



Background: Preclinical data

- BH-30643 has sub-nanomolar potency for *EGFR* exon 19del and L858R classical mutations, maintained in the presence of T790M and/or C797S, with excellent selectivity over wildtype EGFR (*AACR 2025*).
- High potency was also observed against atypical *EGFR* mutations (including PACC and non-PACC) and *EGFR* exon 20 insertions (ex20ins), without vulnerability to *EGFR* resistance mutations.
- Marked intracranial activity observed in HCC-827 CDX tumor model (*ASCO 2025*).



Includes 51 models with atypical or atypical compound mutations at the 8 most common hotspots: G719, L861, S768, E709, L747, L833, V769, V834. Models with resistance include concurrent C797S and T790M.

Patient population

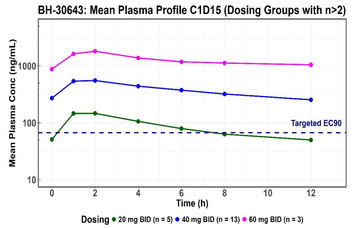
- 39 participants enrolled to phase 1 dose escalation and backfill cohorts as of August 28, 2025 across 6 dose levels. The Phase 1a portion of the study is still underway and will be fully described when complete.
- Enrollment to date has included US (n=34) and Japan (n=5) with additional enrollment from ROW now underway (8 total countries) since the time of the data cut.
- Dose escalation has enrolled diverse EGFR subtypes with an initial focus on patients with on-target EGFR resistance mutations.

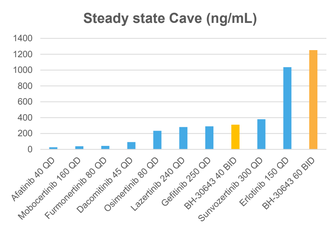
Dose level	n
10mg BID	3
20mg BID	7
40mg BID	13
60mg BID	6
80mg BID	6
80mg QD	4

Molecular subgroup	n
Classical EGFR mutation with C797S after prior osimertinib	10
Atypical or atypical compound EGFR mutation after prior TKI	10
EGFR exon20 insertions	11
Classical EGFR mutation with unknown/other resistance mechanism after osimertinib	8

Pharmacokinetics

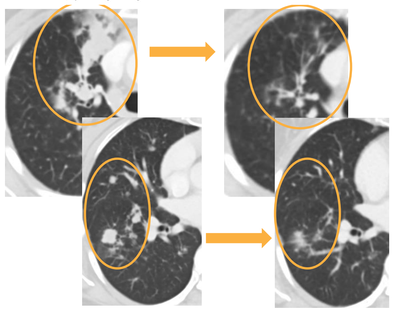
- Steady state PK is available for 25 participants treated at BID dose levels; characterization of QD PK is still ongoing.
- At dose levels 40 mg BID and above, average BH-30643 exposure well exceeds the target EC90 (corrected for drug protein binding) derived from a prior PK/PD study using CDX tumor models (*ASCO 2025*).
- Total plasma exposure of BH-30643 exceeds that of many globally registered EGFR TKIs.



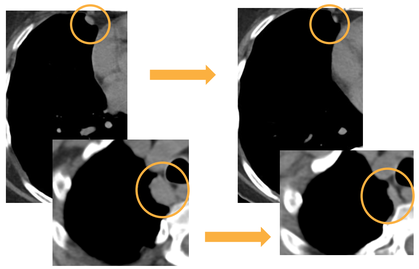


Patient cases

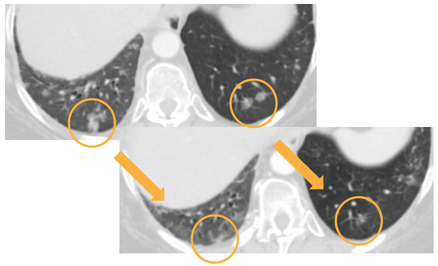
C797S & exon 19 deletion
- s/p 4 lines of therapy including osimertinib, amivantimab, and IO
- Tumor reduction sustained on multiple scans, with therapy ongoing



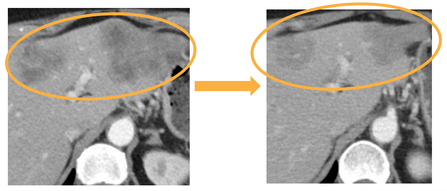
C797S & T790M & exon 19 deletion
- s/p erlotinib and osimertinib
- Tumor reduction sustained on multiple scans, with therapy ongoing



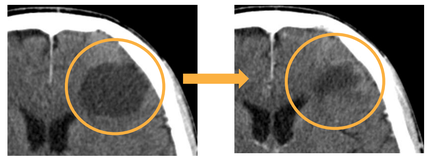
G724A & exon 19 deletion
- s/p osimertinib, with acquired G724A detected on tissue biopsy
- Improvement of lung nodules on CT, with treatment ongoing



T790M & exon 20 insertion
- s/p investigational EGFR TKI, then developed acquired T790M in ctDNA
- Tumor reduction sustained on multiple scans, with treatment ongoing
- Resolution of abnormal LFTs; ctDNA clearance of T790M



Exon 20 insertion with brain metastases
- s/p 3 prior lines of chemotherapy
- Systemic tumor reduction sustained on multiple scans, with treatment ongoing
- Sustained CNS improvement in the absence of radiation or steroids



SOLARA Trial Design

- The study consists of an initial dose escalation part using a Bayesian optimal interval (BOIN) design to identify Recommended Dose(s) for Evaluation (RDE). Dose-limiting toxicities (DLTs) are evaluated for the first 21 days of treatment.
- Expansion cohorts further evaluate the RDE(s) across several molecularly-selected populations to identify a Recommended Phase 2 Dose (RP2D).
- BH-30643 is administered orally once or twice daily until disease progression or intolerable toxicity; post-progression therapy is allowed with sponsor approval.
- Efficacy is evaluated by RECIST 1.1 criteria and toxicity by CTCAE V5.0. Serial plasma is also collected for circulating tumor DNA (ctDNA) analysis at baseline and on treatment.
- In subsequent phase 2, BH-30643 will be evaluated at the RP2D in target patient population based on emerging data from expansion cohorts.

Key Inclusion Criteria
- Pathologically confirmed diagnosis of locally advanced or metastatic NSCLC with *EGFR* (classical, atypical, ex20ins) or *HER2* mutations in the kinase domain of exons 18, 19, 20, or 21.
- Molecular biomarker (*EGFR* or *HER2* mutation) for enrollment is based on the results of CLIA or equivalently certified local laboratory testing from either tumor tissue or circulating DNA.
- Has at least 1 measurable target extracranial lesion according to RECIST v1.1.
- Subjects with stable asymptomatic brain metastases (treated or untreated) are eligible.

Key Exclusion Criteria
- Known other oncogenic driver alterations (e.g. MET amplification, etc) or histologic transformation (e.g. to small cell carcinoma, etc).
- Leptomeningeal disease or spinal cord compression or active symptomatic brain metastasis.
- Unresolved toxicities from prior therapies

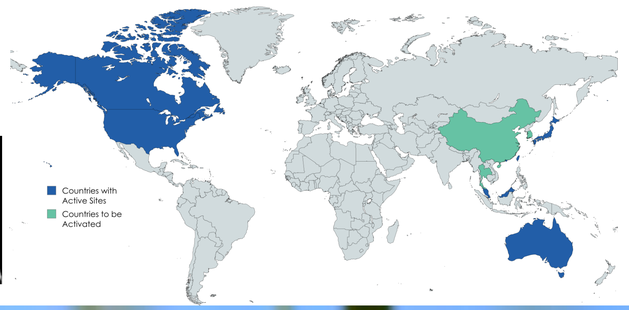
6 Expansion Cohorts (n ~20-40 per cohort per dose level):

TKI pretreated cohorts
1) Classical mutation w on-target resistance
2) Atypical mutations after one prior TKI

TKI-Naive Cohorts
3) Classical mutations
4) Atypical mutations

Additional Cohorts
5) EGFR exon 20 insertions, up to 2 prior lines
6) HER2 mutations, up to 2 prior lines

- SOLARA (NCT06706076) is currently enrolling globally.
- Study team can be contacted at **clinicaltrials@bhtherapeutics.com**



Conclusions

- BH-30643 is a non-covalent, macrocyclic, mutant-selective OMNI-EGFR TKI exhibiting potency against a wide-spectrum of *EGFR* mutations, including classical, atypical, exon 20 insertion, and resistance mutations with excellent selectivity against wildtype EGFR.
- Preliminary clinical experience in EGFR-mutant NSCLC demonstrates high exposures, systemic and CNS anti-tumor activity, and evidence that BH-30643 can overcome diverse resistance limitations of contemporary EGFR TKIs.
- Breadth of activity offers a clinical development path inclusive of atypical EGFR mutations (PACC and non-PACC), a clinical need which is inadequately addressed by current SOC TKIs.
- The SOLARA phase I/II trial is now enrolling NSCLC patients in at least 8 countries globally, with Phase 1a still underway and expansion cohorts now initiated.

Contact: clinicaltrials@bhtherapeutics.com