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A Phase 1/2 Open-Label, Multicenter, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of BH-30643 in Adult Subjects with *EGFR* and/or *HER2* Mutations (SOLARA)

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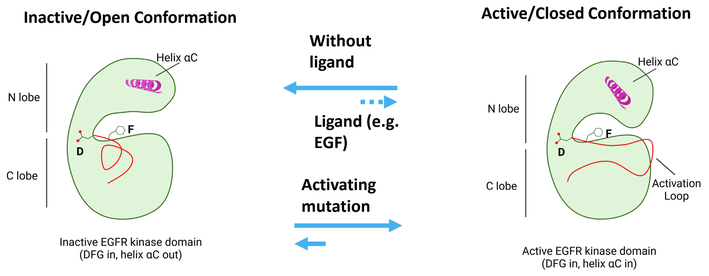
Background

- Clinical outcomes for patients with metastatic *EGFR*-mutant NSCLC have steadily improved with successive generations of EGFR tyrosine kinase inhibitors (TKIs).
- However, there remains significant need for further advancement in progression-free survival (PFS) and overall survival (OS), as these outcomes still fall short when compared to the remarkable benefits observed with newer TKIs in *ALK* and *ROS1*-driven NSCLC.
- Additionally, the care of *EGFR*-mutant lung cancer has grown fragmented with the emergence of different precision approaches for different specific *EGFR* mutations, complicating effective care delivery.
- There remains an unmet medical need for an effective, durable, and tolerable EGFR TKI which can be used across a full diversity of *EGFR* mutations.

BH-30643: Design Principles

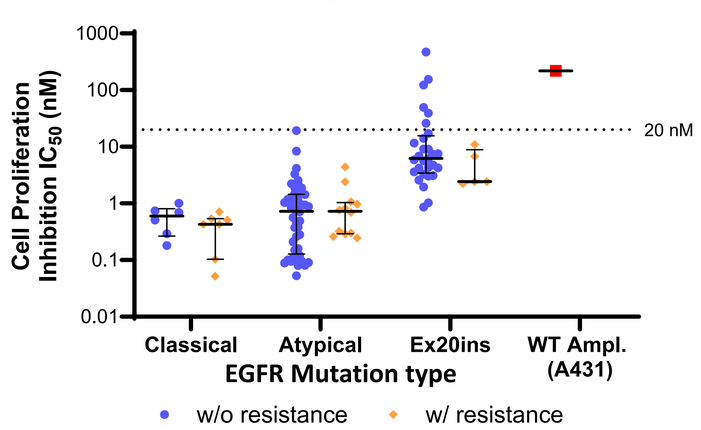
- BH-30643 is a first-in-class, noncovalent, macrocyclic, ATP competitive OMNI-EGFR TKI, potently targeting a broad spectrum of *EGFR* mutations including classical, ex20ins, atypical, and compound resistance mutations
- BH-30643 was designed with a novel macrocyclic structure to precisely interact with EGFR active conformation that is commonly shared with mutant EGFRs, while the same macrocyclic approach has been used for the design of lorlatinib and repotrectinib



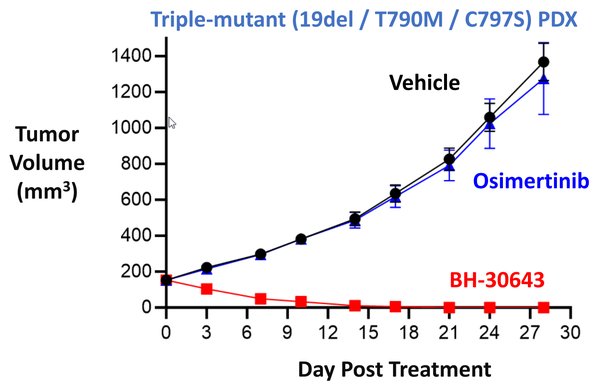
- Kinase selectivity was demonstrated in using a kinase screen across 372 wildtype human kinases, showing >90% inhibition of only 4 at 100 nM concentration

BH-30643: Preclinical Data

- Cellular activity of BH-30643 was recently described[1], demonstrating 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
- High potency was also observed against atypical *EGFR* mutations (e.g., G719X, L861Q, S768I) and *EGFR* exon 20 insertions (ex20ins), as well as mutant *HER2*



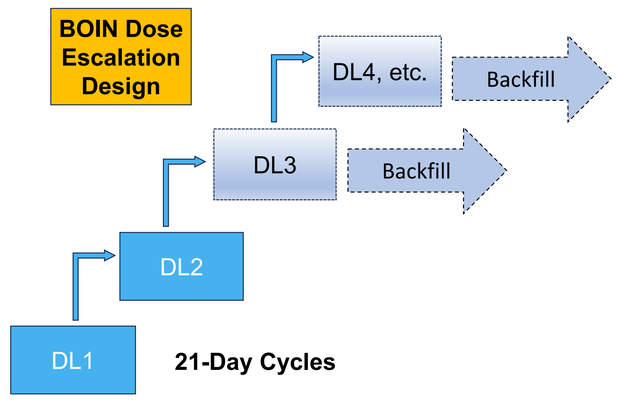
- Mouse tumor models[2] demonstrate *in vivo* activity of BH-30643 in primary and resistant mutant EGFR tumor models and CNS activity in orthotopic brain tumor model



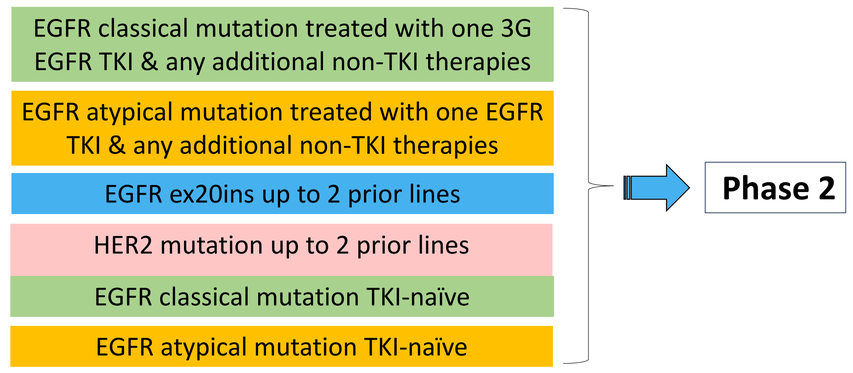
Study Design & Schema

- 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.
- A subsequent expansion part will further evaluate the RDE(s) to identify a Recommended Phase 2 Dose (RP2D) in cohorts across a range of *EGFR*/*HER2* driver mutations with or without prior TKI therapy.
- BH-30643 is administered orally twice daily until disease progression or intolerable toxicity.
- Efficacy will be evaluated by RECIST 1.1 criteria and toxicity by CTCAE V5.0. 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.

Phase 1, Part 1: Dose Escalation & Backfill



Phase 1, Part 2: Dose Expansion (20-40 per cohort per dose level)



Study Objectives

Key primary / secondary objectives in adult subjects with locally advanced or metastatic NSCLC harboring *EGFR* and/or *HER2* mutations

- To evaluate the safety and tolerability of BH-30643 at increasing dose levels (Phase 1 Part 1).
- To determine the DLTs of BH-30643 and the MTD, if applicable.
- To identify the Recommended Dose(s) for Evaluation (RDE).
- To characterize the single- and multiple-dose PK properties of BH-30643.
- To assess the PopPK of BH-30643 and to explore correlations between PK, response, and/or safety findings.
- To evaluate the safety, tolerability, and preliminary antitumor activity of BH-30643 at selected RDEs (Phase 1 Part 2) to determine a Recommended Phase 2 Dose (RP2D).

Study Population

Key Phase 1 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.
- Patients previously received standard therapies.
- Adequate major organ function.
- 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

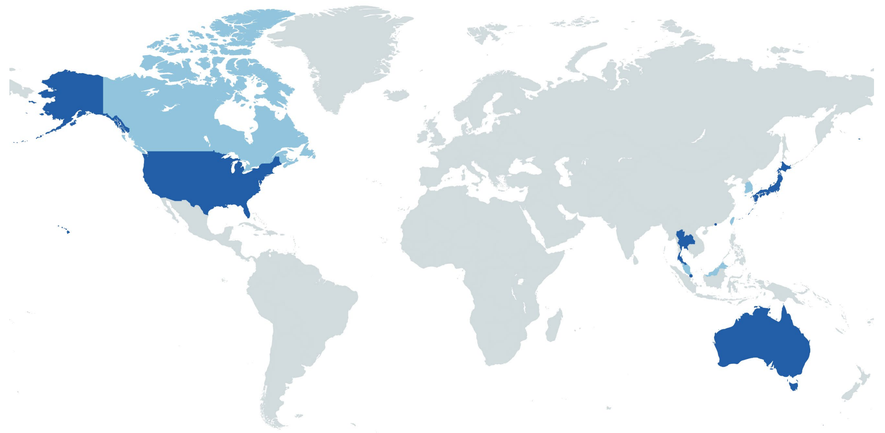
- Known other oncogenic driver alterations (e.g. moderate or high MET amplification) or histologic transformation (e.g. to small cell carcinoma, etc.).
- Leptomeningeal disease or spinal cord compression or active symptomatic brain metastasis.
- Active or history of interstitial lung disease from any cause.
- Unresolved toxicities from prior therapies

Study Status

Phase 1

- SOLARA (NCT06706076) is currently enrolling in dose escalation and backfill in multiple continents
- ~35 sites are planned globally, with site activation activities ongoing in 10 countries

Study contact: clinicaltrials@bhtherapeutics.com



References:
1. J Cui, E Rui, E Rogers, et al AACR 2025 abstr. 5608
2. W Deng, D Zhai, P Jiang, et al ASCO 2025 abstr. 3110