



YUHAN P2.323: A Phase 1/2, First-in-Human Study of YH42946, a Novel Oral HER2 TKI, in Advanced Solid Tumors with HER2 Aberration and EGFR Exon 20 Insertion



IASLC 2026 World
Conference on Lung Cancer

SEPTEMBER 12 – 15, 2026
SEOUL, REPUBLIC OF KOREA

Sun Min Lim^{1*}, Do-Youn Oh², Keun-Wook Lee³, Se-Hoon Lee⁴, Byoung Yong Shim⁵, Dae Ho Lee⁶, Judith Ertle⁷, Jiah Kang⁷, Bobae Jo⁷, Yeji Lim⁷, Heejae Won⁷, Jangyoung Wang⁷, Jeongmi Hwang⁷, Ki Hyeong Lee⁸
¹Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Yonsei Cancer Center, Seoul, Republic of Korea, ²Seoul National University Hospital, Seoul, Republic of Korea, ³Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea, ⁴Samsung Medical Center, Seoul, Republic of Korea, ⁵Department of Medical Oncology, St. Vincent's Hospital, The Catholic University of Korea, Seoul, Republic of Korea, ⁶Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, ⁷Yuhan Corporation, Clinical Development and Medical Division, Seoul, Republic of Korea, ⁸Chungbuk National University Hospital, Cheongju, Republic of Korea

Correspondence: LIMLOVE2008@yuhs.ac

INTRODUCTION

- Aberrations in HER2 and EGFR, particularly exon 20 insertions (ex20ins), are key oncogenic drivers associated with poor clinical outcomes and intrinsic resistance to approved therapies in molecularly defined solid tumors, including NSCLC^{1, 2, 3}.
- Current treatments are often limited by intravenous administration or clinical toxicities, and frequent brain metastases underscore a critical unmet need for effective, orally administered targeted therapies with CNS penetration^{4, 5}.
- YH42946 is a novel, oral small-molecule tyrosine kinase inhibitor that demonstrated robust systemic and intracranial antitumor activity in preclinical models, providing a strong scientific rationale for this clinical evaluation.

METHODS

This trial is a phase 1/2, open-label, multicenter, first-in-human study in patients with locally advanced or metastatic solid tumors with human epidermal growth factor receptor 2 (HER2) aberration and epidermal growth factor receptor (EGFR) exon 20 insertion. The study consists of two sequential parts and the detailed designs are presented below:

- Part 1 (dose escalation) is designed based on a Bayesian optimal interval (BOIN) design, and the actual dose increments and dose levels have been adjusted using a modified Fibonacci scheme according to the predefined criteria.
 - Dosing regimen: YH42946 is initially administered orally once daily (QD), with additional twice daily (BID) dosing cohort incorporated based on PK modeling and simulation results.
 - Backfill strategy: Applied to obtain further safety, PK, and efficacy data by enrolling up to 12 patients at SRC-approved dose levels.
- Part 2 (dose expansion) begins with a dedicated dose optimization phase (cohort 1), in which two dose levels selected from part 1 are evaluated to determine the recommended dose (RD).

- YH42946 is administered in continuous 21-day cycles. Tumor assessments are performed according to RECIST v1.1. Baseline brain imaging is required for all patients, and patients with treated and stable brain metastases are eligible.

CURRENT STATUS & SUMMARY

Study status

- As of 10 Aug 2026, 71 patients have been screened across multiple sites. To date, 53 patients have been successfully enrolled in Part 1, with 23 patients currently receiving ongoing treatment.

Future Direction for Research

- Expected outcomes: Initial results from the part 1 dose escalation, including comprehensive safety, tolerability, pharmacokinetics (PK), and preliminary anti-tumor activity, are expected by the end of 2026. These pivotal early data will be utilized to determine the recommended dose (RD), effectively guiding dose optimization for the subsequent part 2 expansion phase.
- Part 2 dose expansion: Following the selection of the 2 dose levels, Part 2 for dose optimization will be initiated in early 2027.
- Clinical impact: Through these strategic expansions, this study aims to establish YH42946 as a novel, effective targeted therapy option, ultimately addressing significant unmet medical needs in oncology.

REFERENCES & ACKNOWLEDGEMENTS

REFERENCES

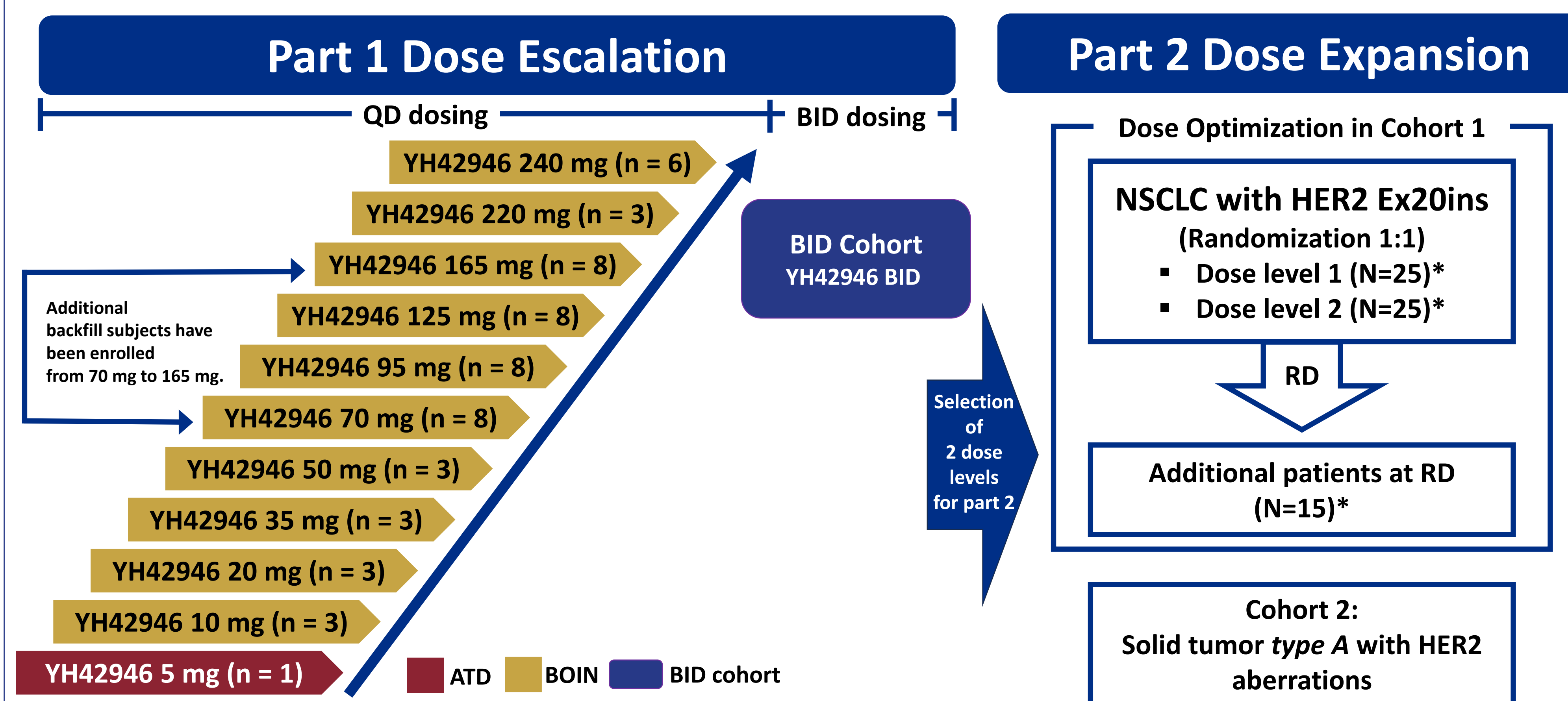
- [1] Yasuda H, et al. *Lancet Oncol.* 2012;13(1):e23-31.
- [2] Pillai RN, et al. *Cancer.* 2017;123(21):4099-4105.
- [3] Mazières J, et al. *J Clin Oncol.* 2013;31(16):1997-2003.
- [4] Langer CJ, et al. *J Clin Oncol.* 2005;23(25):6207-19.
- [5] Mehta MP, et al. *J Clin Oncol.* 2003;21(13):2529-36.

ACKNOWLEDGEMENTS

This study was sponsored by Yuhan Corporation. The authors would like to thank all the investigators, study site staff, and the patients and their families for their participation in this trial.



STUDY SCHEMA



QD, once a day; BID, twice a day; ATD, accelerated titration design; BOIN, Bayesian Optimal Interval; HER2, human epidermal growth factor receptor 2; RD, Recommended dose

***RD (Recommended dose):** Upon RD selection, additional patients will be enrolled at RD to ensure the efficacy at confirmed dose, and cohort 2 will be opened at RD in a seamless manner

***Number of patients*:** Total of 40 patients will be enrolled at RD in cohort 1

*Additional cohorts may be added during the clinical trial (e.g., other tumor types harboring HER2 aberrations)

STUDY POPULATION

Patients with locally advanced or metastatic solid tumor harboring HER2 mutation, HER2 amplification, HER2 overexpression, and/or EGFR exon 20 insertion that were progressed on or intolerant to standard therapy received

KEY ENDPOINTS AND ASSESSMENTS

- Primary endpoint:** Safety and tolerability of YH42946 assessed by treatment-emergent adverse events (TEAEs).
- Secondary endpoints:** Pharmacokinetics (PK) of YH42946 and its major metabolite M33, and anti-tumor activity (including objective response rate (ORR), duration of response (DoR), disease control rate (DCR), depth of response, time to response (TTR), and progression-free survival (PFS)) per RECIST v1.1 by investigator assessment.