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LETTER TO THE JOURNAL

Phase II study evaluating the safety and efficacy of neratinib and trastuzumab biosimilar in patients with *HER2* mutated advanced solid tumors: KCSG AL20-17/KM23 trial

Human epidermal growth factor receptor 2 (HER2) overexpression and amplification activate key pathways driving tumor progression, leading to HER2-targeted therapies. However, HER2 signaling can also be aberrantly activated by somatic mutations, independent of overexpression or amplification, contributing to tumorigenesis [1]. These mutations, found in domains such as the extracellular (ECD), transmembrane (TMD)/juxtamembrane (JMD), and tyrosine kinase (KD) regions, occur across cancers, from melanoma (1%) to bladder cancer (≤12%) [1, 2], suggesting a significant population could benefit from HER2-targeted treatments.

Neratinib, an irreversible pan-HER tyrosine kinase inhibitor, has shown efficacy in *HER2*-mutated cancers and is recommended in National Comprehensive Cancer Network guidelines [3]. However, resistance mechanisms, such as secondary *HER2* mutations or amplifications, may limit its efficacy [4, 5], highlighting the need for combination therapies. Preclinical and clinical studies demonstrate that combining neratinib with trastuzumab enhances HER2 signaling inhibition and improves outcomes in *HER2*-mutated non-small cell lung cancer (NSCLC) and hormone receptor-positive/HER2-negative breast cancer [6].

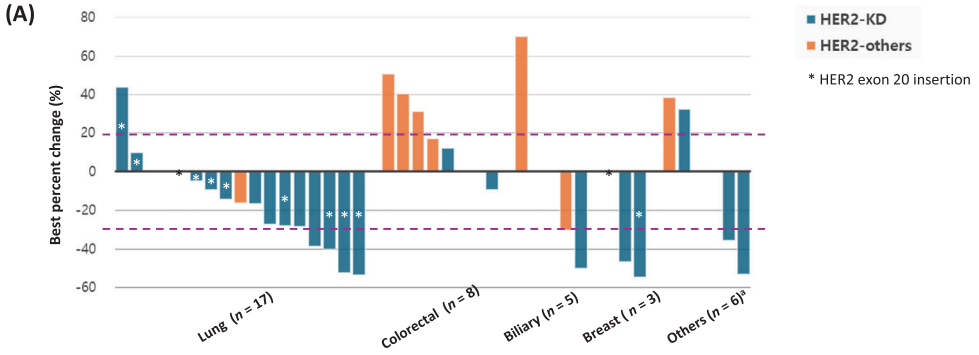
Here, we evaluated dual HER2 inhibition with neratinib and trastuzumab biosimilar (Herzuma®) in heavily pretreated patients with *HER2*-mutated solid tumors (excluding *HER2* amplifications). We also explored circulating tumor DNA (ctDNA) testing as a biomarker for treatment suitability and identified genetic alterations linked to treatment response. Detailed methods are provided in the Supplementary Materials and Methods.

A total of 40 patients received the study treatment and were followed up (Supplementary Figure S1). The patients were heavily pretreated, with 40% receiving more than three lines of systemic therapy prior to this study, including adjuvant or concurrent chemoradiotherapy, with the latest regimen being in the salvage setting. The baseline patient characteristics are summarized in Supplementary Table S1. Among the enrolled patients, 23 unique *HER2* mutations were identified, with 3 patients harboring 2 different mutations each, resulting in 43 mutations overall (Supplementary Table S2). *HER2* mutations were detected via tissue in 38 patients and ctDNA in the remaining 2 patients. The KD was the most frequently mutated site (26/43 mutations, 60.5%), followed by TMD/JMD (10/43 mutations, 23.3%), and ECD (7/43 mutations, 16.3%). Most patients with NSCLC (10/17, 58.8%) harbored exon 20 insertion mutations.

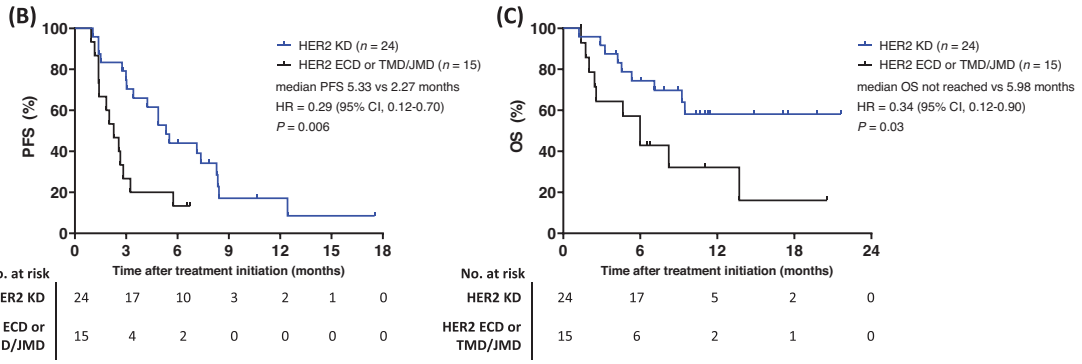
Of the 40 treated patients, 39 were evaluable for efficacy. The objective response rate (ORR) was 25.6% (95% confidence interval [CI], 12.9-41.2), with 10 partial responses (PR) and a median duration of response (DOR) of 11.2 months (95% CI, 3.9-18.4). Stratified by tumor type, the ORR was 23.5% in NSCLC, 40% in biliary cancer, and 66.7% in breast cancer. One patient with vulvar cancer and one external auditory canal cancer patient achieved a PR, as well. All responders (best percentage change ≤ -30%) had *HER2* KD mutations, including four with exon 20 insertions, except one patient with an ECD mutation (S310Y) (Figure 1A). Three NSCLC patients with exon 20 insertions achieved PR. Seven patients had stable disease (SD) for more than 6 months, resulting in a clinical benefit rate (CBR) of 43.6%. Median progression-free survival (PFS) and overall survival (OS) were 3.4 (95% CI, 1.6-5.3) and 9.5 months (95% CI, 2.9-16.0), respectively. Notably, the patient with vulvar cancer had a PFS of 17.5 months dur-

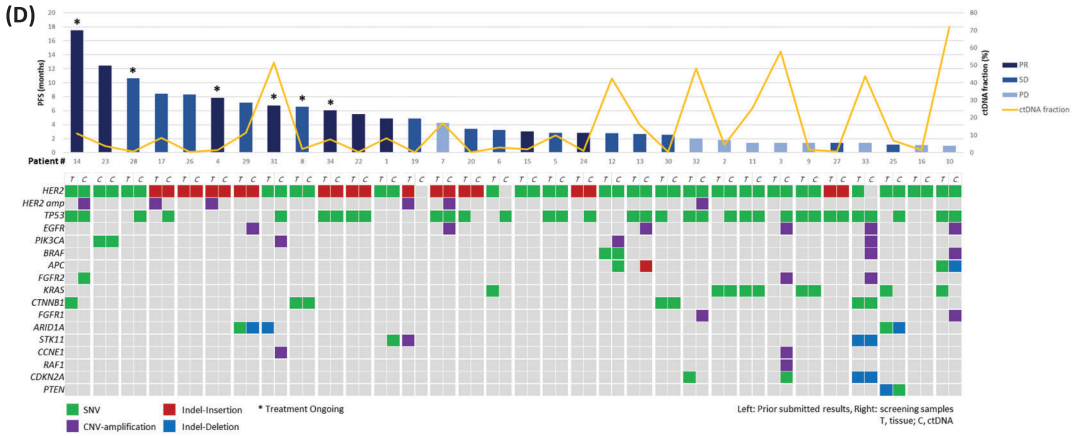
List of abbreviations: ADC, antibody-drug conjugates; AE, adverse event; CBR, clinical benefit rate; CI, confidence interval; ctDNA, circulating tumor DNA; DOR, duration of response; ECD, extracellular domain; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; JMD, juxtamembrane domain; KD, kinase domain; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TMD, transmembrane domain..

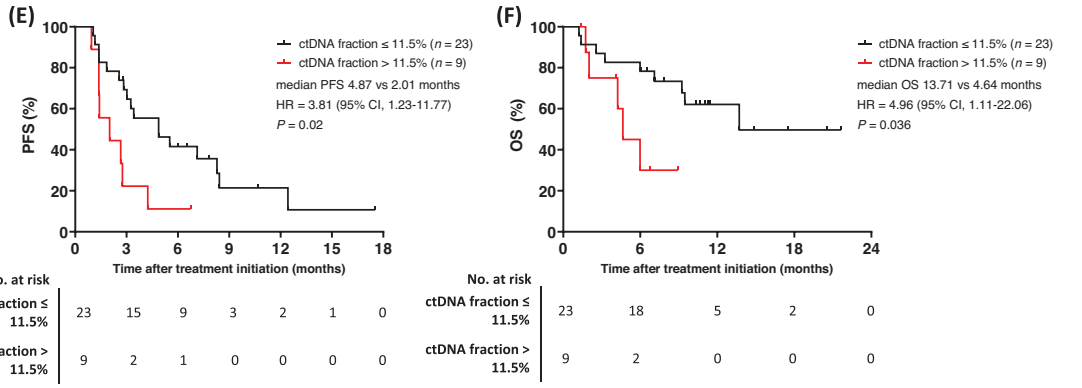
Kyoungmin Lee and Kyung-Hun Lee contributed equally to this work.



[a]From left to right, the order is thymic, melanoma, duodenal, small bowel, extra auditory canal, and vulvar cancer.







ing the study period, and as of the treatment cut-off date, the patient was still receiving treatment. Patients with KD mutations had significantly better outcomes than those with ECD or TMD/JMD mutations, with longer PFS (5.33 vs. 2.27 months; hazard ratio [HR] = 0.29 $P = 0.006$) and OS (not reached vs. 5.98 months; HR = 0.34, $P = 0.03$) (Figure 1B-C, Supplementary Figure S2).

Exploratory biomarker analysis for baseline ctDNA was performed on samples from 32 patients after excluding 8 samples that did not meet quality control criteria. *HER2* mutations were identified in all but 3 cases, consistent with prior tumor/ctDNA findings. In these 3 patients, where baseline ctDNA did not detect *HER2* mutations, 2 achieved SD and 1 experienced PD, suggesting limited clinical benefit from dual anti-HER2 therapy (Figure 1D). The median ctDNA fraction was 5.7% (range 0.1-72.0), with a cut-off of 11.5% identified as most informative. Higher ctDNA fractions were linked to shorter PFS (4.87 vs. 2.01 months; HR = 3.81, $P = 0.02$) and OS (13.71 vs. 4.64 months; HR = 4.96, $P = 0.036$) (Figure 1E-F). Common pathogenic mutations included *TP53* ($n = 20$), *EGFR* amplification ($n = 6$), *PIK3CA* amplification ($n = 3$), *HER2* amplification ($n = 3$), and *KRAS* mutations ($n = 3$). Alterations in *EGFR*, *BRAF*, *KRAS*, or *PTEN* appeared associated with poorer treatment response and shorter PFS, though statistical analysis was limited by low sample size and mutation frequency (Figure 1D, Supplementary Figure S3).

During the study, 35 (87.5%) patients experienced treatment-related adverse events (AEs), with 12 (30%) having grade ≥3 AEs. Diarrhea was the most common AE (77.5%), leading to neratinib discontinuation in three patients due to grade 3 diarrhea. The CONTROL trial later demonstrated that a dose escalation strategy effectively reduces diarrhea severity [7]. While this was not implemented in our study due to timing, future adoption could improve safety and efficacy. No cardiac events were observed. Most AEs were manageable, though one patient with underlying lung cancer experienced grade 5 pneumonitis, with unclear causality. AE details are in Supplementary Table S3.

Despite the noted limitations of our study, including its small sample size, single-arm design, and heterogeneous patient population, our findings provide meaningful insights into dual HER2 inhibition with neratinib and trastuzumab biosimilar in *HER2*-mutated tumors. While recent studies on HER2 antibody-drug conjugates (ADCs) have demonstrated promising efficacy in *HER2*-mutated cancers [8, 9], their accessibility may be limited in certain settings. Dual anti-HER2 therapy with neratinib and trastuzumab can serve as an alternative treatment strategy, particularly for patients with disease progression or resistance following HER2-targeted ADC, expanding therapeutic options and addressing unmet needs in *HER2* mutated cancers. Furthermore, our exploratory analysis of ctDNA as a prognostic biomarker offers a practical tool to optimize patient selection and monitor treatment response.

In conclusion, dual anti-HER2 therapy with neratinib and trastuzumab demonstrated promising efficacy and a manageable safety profile in heavily pretreated patients with *HER2*-mutated cancers. The identification of ctDNA as a prognostic biomarker further enhances its clinical utility, supporting dual HER2 blockade as a valuable treatment option deserving further validation.

AUTHOR CONTRIBUTIONS

Kyoungmin Lee and Kyung-Hun Lee: methodology, formal analysis, validation, and writing-original draft. Jeesun Yoon: methodology, investigations, and writing-review & editing. Dong-Wan Kim, Yoon Ji Choi, Soohyeon Lee, Ju Won Kim, Kyong Hwa Park, Wonyoung Choi, Youngjoo Lee, Hyewon Ryu, Dong-Hoe Koo, Yun-Gyoo Lee, Hei-Cheul Jeung, Min-Young Lee, Namsu Lee, Myoung Joo Kang, Jieun Lee, Sook Hee Hong, and Eun Joo Kang: data collection and resources. In Hae Park: conceptualization, methodology, writing-review & editing, and project administration. All authors have read and approved the manuscript, and IHP is responsible for submitting the manuscript for publication.

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FIGURE 1 Efficacy and survival outcomes of neratinib and trastuzumab in heavily pretreated *HER2*-mutated advanced cancers.
(A) Best percentage change in target lesion size, assessed by RECIST v1.1.
(B-C) Kaplan-Meier curves for PFS (B) and OS based on *HER2* mutation location (C).
(D) Genomic landscape and treatment outcomes for 32 patients with baseline ctDNA evaluation.
(E-F) Kaplan-Meier curves for PFS (E) and OS stratified by ctDNA fraction (F).
Abbreviations: RECIST, response evaluation criteria in solid tumor; KD, kinase domain; ECD, extracellular domain; TMD/JMD, transmembrane domain/juxtamembrane domain; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; No., number; PR, partial response; SD, stable disease; PD, progressive disease; ctDNA, circulating tumor DNA; SNV, single nucleotide variant; CNV, copy number variant.

CONFLICT OF INTEREST STATEMENT

Dong-Wan Kim reports research funding to his institution from Alpha Biopharma, Amgen, AstraZeneca, BMS, Boehringer-Ingelheim, Bridge BioTherapeutics, Chong Keun Dang, Daiichi-Sankyo, GSK, Hanmi, IMBDx, InnoN, IQVIA, Janssen, Merck, Merus, Mirati Therapeutics, MSD, Novartis, ONO Pharmaceutical, Pfizer, Roche/Genentech, Takeda, TP Therapeutics, Xcovery, and Yuhan. He has also received medical writing assistance from Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Bridge BioTherapeutics, Chong Keun Dang, Daiichi-Sankyo, GSK, IMBDx, Janssen, Merus, Mirati Therapeutics, MSD, Meck, Novartis, Pfizer, Roche, Takeda, and Yuhan. No other potential conflicts of interest were reported.

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DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in compliance with the principles of good clinical practice, adhering to the International Conference on Harmonization guidelines, and the ethical principles outlined in the Declaration of Helsinki. Approval for this study was obtained from the independent ethics committees or institutional review boards at each participating site (IRB number of the principal investigator's institution: 2021GR0117), and all patients provided written informed consent prior to participation.

TRIAL REGISTRATION

ClinicalTrials.gov, number NCT06083662.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.