PP01.25

Safety and Preliminary Efficacy of Zanidatamab in Patients With HER2-Overexpressing Non-Small Cell Lung Cancer: Subgroup Analysis From a Phase 1 Study

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Plain Language Summary

Why did we perform this research?

- People with advanced non-small cell lung cancer often have a short life expectancy and limited treatment options after initial treatments stop working
- Some of these cancers have too much of a protein called human epidermal growth factor receptor 2 (HER2) on the cell surface (also known as HER2-positive cancer)

How did we perform this research?

- This analysis looked at whether a medicine called zanidatamab, which targets HER2, could help patients with non-small cell lung cancer following treatment with other available medicines

What were the results of this research?

- This initial analysis showed that patients with HER2-positive non-small cell lung cancer may benefit from zanidatamab
- Most patients who received zanidatamab had their tumors shrink
- Zanidatamab-related side effects were manageable and did not cause any of the patients to stop treatment

Background

- HER2 has emerged as a therapeutic target in non-small cell lung cancer (NSCLC)[1]
  - Most clinical studies of NSCLC have focused on patients with *HER2*/*ERBB2* mutations,[2,3] but HER2 overexpression also occurs in up to 20% of cases[4-6]
- Second-line and later chemotherapy options are associated with poor outcomes in NSCLC,[7,8] emphasizing the need for effective and well-tolerated HER2-targeted therapies
- Available treatments for HER2-overexpressing NSCLC remain limited, with trastuzumab deruxtecan demonstrating modest benefit (confirmed objective response rate [cORR], 27%–34%) and adverse effects that may limit its use (drug-related interstitial lung disease and pneumonitis)[9]
- Zanidatamab is a dual HER2-targeted bispecific antibody that binds to 2 distinct sites (extracellular domains 2 and 4) on HER2 and initiates unique HER2 clustering not observed with trastuzumab or trastuzumab plus pertuzumab[10]
- In preclinical studies, zanidatamab drove multiple antitumor mechanisms of action, including[10]:
  - Facilitation of HER2 internalization and subsequent degradation
  - Reduction of HER2 on the cell surface and inhibition of downstream HER2 pathways
  - Activation of immune-mediated effects (complement-dependent cytotoxicity as well as antibody-dependent cellular cytotoxicity and phagocytosis)
- Zanidatamab has received accelerated approval in the US and conditional approvals in China and the EU for previously treated, advanced HER2 immunohistochemistry (IHC) 3+ biliary tract cancer (BTC)[11]
- In the first-in-human ZWI-ZW25-101 phase 1 study (NCT02892123), zanidatamab demonstrated preliminary antitumor activity in 11 different types of HER2-expressing solid tumors, including NSCLC[12]
  - In this updated analysis, we further describe the preliminary safety and efficacy of zanidatamab

Figure 1. Zanidatamab Structure and Targeted Binding[10]

ECD, extracellular domain; Fab, fragment antigen-binding; Fc, fragment crystallizable; HER2, human epidermal growth factor receptor 2; scFv, single-chain variable fragment.

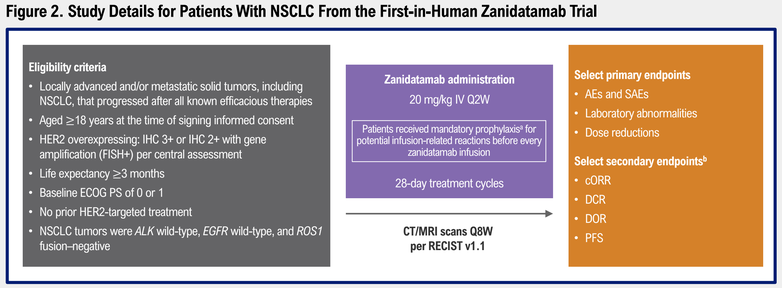
Objective

- To report the safety and preliminary antitumor activity of zanidatamab in patients with HER2 overexpressing NSCLC from the first-in-human phase 1 study

Methods

- Adult patients with previously treated, unresectable locally advanced or metastatic HER2-expressing tumors were enrolled in this multicenter, phase 1, dose-escalation and dose-expansion study (NCT02892123; last patient last visit September 30, 2024)
- The primary objective was to characterize the safety and tolerability of zanidatamab monotherapy

Figure 2. Study Details for Patients With NSCLC From the First-in-Human Zanidatamab Trial



[a]Acetaminophen, antihistamines, and corticosteroids.
[b]Select secondary endpoints were determined by investigator assessment per RECIST v1.1.
AE, adverse event; *ALK*, anaplastic lymphoma kinase; cORR, confirmed objective response rate; CT, computed tomography; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenous; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PFS, progression-free survival; Q2W, every 2 weeks; Q8W, every 8 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; *ROS1*, ROS proto-oncogene 1, receptor tyrosine kinase; SAE, serious AE.

Results

Table 1. Baseline Demographics and Clinical Characteristics of Patients With NSCLC

Patient	Age	Sex	Race	ECOG Performance Status	Histology	Stage at Initial Diagnosis	Prior Brain Metastasis	HER2 Status[a]
1	67	Male	Asian	1	Squamous cell carcinoma	IV	No	IHC 3+/FISH+
2	66	Male	Asian	1	Squamous cell carcinoma	III	Yes	IHC 3+/FISH+
3	60	Male	Asian	1	Adenocarcinoma	IIIB	Yes	IHC 3+/FISH+
4	79	Female	Asian	1	Squamous cell carcinoma	IIIA/B	No	IHC 3+/FISH+
5	77	Male	Asian	1	Squamous cell carcinoma	IIA	No	IHC 3+/FISH+

[a]Based on central laboratory results.
ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer.

- The median (range) number of prior systemic anticancer therapies was 2 (1–2)
- All patients had HER2 IHC 3+/fluorescence in situ hybridization-positive tumors
- The median (range) age was 67 (60–79) years, and 4/5 patients were male
- The median (range) duration of follow-up was 6.2 (1.9–23.7) months
- The median (range) duration of treatment was 5.1 (1.4–22.7) months

Table 2. Safety Summary of Patients With NSCLC

n (%)	NSCLC (n = 5)
Any AE	5 (100)
Grade ≥3	2 (40)
Serious	1 (20)
Leading to dose reduction	0
Leading to zanidatamab discontinuation	1 (20)
Any TRAE	5 (100)
Grade ≥3	0
Serious	0
Leading to dose reduction	0
Leading to zanidatamab discontinuation	0
Grade 1/2 TRAEs[a]	
Infusion-related reaction	3 (60)
Diarrhea	2 (40)
Stomatitis	2 (40)
Fatigue	1 (20)
Pruritus	1 (20)
Rash macular	1 (20)

[a]This list is exhaustive for the TRAEs reported in these patients.
AE, adverse event; NSCLC, non-small cell lung cancer; TRAE, treatment-related AE.

- One patient had a serious, grade 5 AE of COVID-19 pneumonia unrelated to treatment that led to zanidatamab discontinuation
- No serious or grade ≥3 treatment-related AEs (TRAEs) occurred

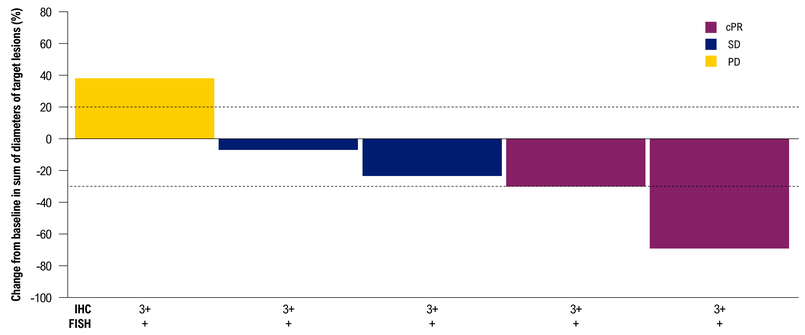
Table 3. Patient-Level Antitumor Activity

Patient	HER2 Status	cBOR[a]	PFS, Months	Event
4	IHC 3+/FISH+	SD	23.7	Death[b]
1	IHC 3+/FISH+	**cPR**	5.4	Disease progression
3	IHC 3+/FISH+	SD	5.3	Disease progression
2	IHC 3+/FISH+	**cPR**	3.5	Censored[c]
5	IHC 3+/FISH+	PD	1.7	Disease progression

[a]PR was defined as at least a 30% decrease in the sum of diameters of target lesions, and PD was defined as at least a 20% increase in the sum of diameters of target lesions per RECIST v1.1. SD was defined as target lesions not reaching the thresholds for PD or PR. cPRs required confirmation of ongoing response ≥4 weeks from the initial observation of response. cPR represents the time of PR confirmation.
[b]Caused by COVID-19 pneumonia unrelated to treatment.
[c]Patient withdrew consent, at which time their last assessment was a cPR.
cBOR, confirmed best overall response; cPR, confirmed PR; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

- The cORR was 40% (95% CI: 5–85; 2 confirmed partial responses [PRs])
- The median progression-free survival (PFS) was 5.4 (95% CI: 1.7–23.7) months

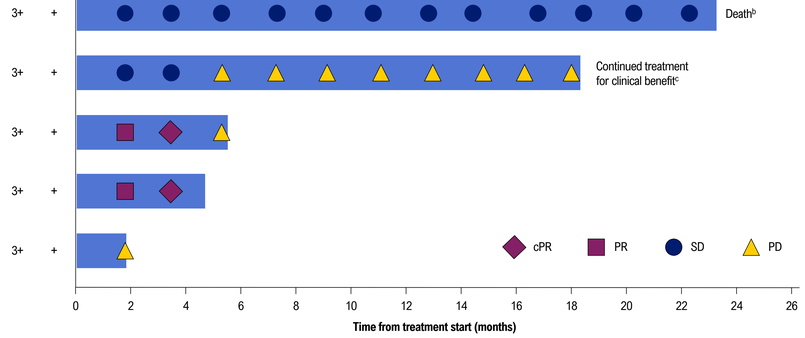
Figure 3. Target Lesion Reduction in Patients With Advanced HER2-Overexpressing NSCLC Treated With Zanidatamab



Dotted lines indicate thresholds for PD (20% increase in sum of diameters of target lesions) and PR (30% decrease in sum of diameters of target lesions) per RECIST v1.1. cPRs required confirmation of ongoing response ≥4 weeks from the initial observation of response. cPR represents the time of PR confirmation.
cPR, confirmed PR; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

- Most patients had a reduction in tumor size (disease control rate, 80% [95% CI: 28–100])

Figure 4. Treatment Duration and Response[a] in Patients With Advanced HER2-Overexpressing NSCLC Treated With Zanidatamab



[a]PD was defined as a 20% increase in the sum of diameters of target lesions, and PR was defined as a 30% decrease in the sum of diameters of target lesions per RECIST v1.1. SD was defined as target lesions not reaching the thresholds for PD or PR. cPRs required confirmation of ongoing response ≥4 weeks from the initial observation of response. cPR represents the time of PR confirmation.
[b]Cause of death: COVID-19 pneumonia unrelated to treatment.
[c]As permitted per protocol.
cPR, confirmed PR; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

- The 2 patients who achieved PRs did so by their first assessment, with the response confirmed at the second assessment

Conclusions

- Zanidatamab demonstrated a manageable safety profile in patients with previously treated, HER2-overexpressing advanced NSCLC, with only grade 1/2 TRAEs reported among these 5 patients
- Preliminary antitumor activity of zanidatamab in NSCLC was observed, with a cORR of 40% and a median PFS of 5.4 months
  - One patient with stable disease demonstrated a prolonged PFS of 23.7 months
- Although limited by a small sample size, these findings provide support for HER2-overexpression as an actionable target in NSCLC and warrant further evaluation of zanidatamab in this patient population
  - The tumor-agnostic phase 2 DiscovHER PAN-206 study (NCT06695845) is currently evaluating zanidatamab in patients with previously treated HER2 IHC 3+ solid tumors, including NSCLC[13]

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Support and Acknowledgements: Clinical research was funded by Jazz Pharmaceuticals. Under direction of the authors, Adam Schnier, MS, PhD, and Marita Chakhtoura, MS, PhD, of Red Nucleus provided medical writing and editorial support, which was funded by Jazz Pharmaceuticals in accordance with Good Publication Practice (GPP 2022) guidelines (https://www.ismpp.org/gpp-2022). Jazz Pharmaceuticals also reviewed and edited the poster for scientific accuracy. The authors would like to thank all of the study investigators, study staff, nursing team, and patients for their participation in this research.

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Poster presented at the 2025 IASLC | ASCO North America Conference on Lung Cancer; December 5–7, 2025; Boston, MA, USA