#CO191

Prognostic factor evaluation for clinical outcomes in *HER2*-mutant NSCLC

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Background and objectives

- A targeted literature review found that it is challenging to identify prognostic factors (PFs) for clinical outcomes in *HER2*-mutant non-small-cell lung cancer (*HER2*m NSCLC)
- This two-part study, comprising the elicitation of clinical opinion and exploratory analysis of patient-level data from Cohort 1 of the ongoing Phase I Beamion LUNG-1 trial[1], was designed to identify PFs and potential treatment effect modifiers (TEMs) that influence clinical outcomes in *HER2*m NSCLC
- The primary purpose of this work was to inform the selection of matching variables in matching-adjusted indirect comparisons (MAICs) of zongertinib versus trastuzumab deruxtecan (T-DXd)

Data and methods

Identifying prognostic factors and treatment effect modifiers

Survey of clinical experts

1. **Engage experts:** 9 clinical experts with experience of treating patients with *HER2*m NSCLC
2. **Score characteristics:** Experts scored the clinical relevance of individual patient demographics and disease characteristics as PFs or TEMs for efficacy and safety outcomes on a 1–5 scale (1 = least important, 5 = most important)
   Experts also considered whether PFs/TEMs were expected to differ between these outcomes
3. **Analyze results:** Weighted mean scores calculated to produce overall rankings

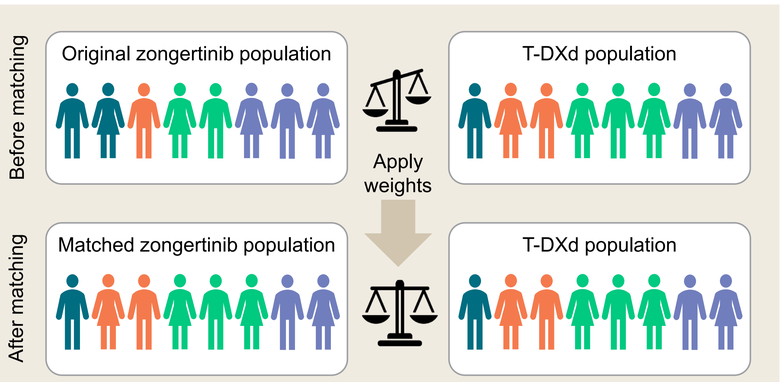
Exploratory data analysis

Data source – Cohort 1 of Beamion LUNG-1 (NCT04886804) of zongertinib in *HER2*m NSCLC[1]

1. Select Cohort **1 (N=75)** non-antibody drug conjugate (ADC) pre-treated, *HER2* tyrosine kinase domain (TKD) mutation, non-squamous NSCLC; zongertinib 120 mg QD Data cut-off: May 20, 2025
2. **Perform statistical analysis to identify potential PFs**
   - Univariate (UV) and multivariable (MV) regression on key efficacy and safety outcomes
   - Potential PFs identified based on p-value < 0.1 in UV model and/or variables included in MV model with lowest Akaike information criterion

Conducting MAICs versus T-DXd

- MAIC analyses compared the patient level data on zongertinib 120 mg QD (N = 75) with aggregate data on T-DXd 5.4 mg/kg Q3W (N = 102) from the Phase II DESTINY-Lung02 trial (NCT04644237; data cut-off: December 23, 2022)[2]
- Matching variables were prioritized based on clinician-ranked importance, ensuring the highest-value factors were included to balance adjustment for key characteristics with statistical efficiency
- Adjusted odds ratios for objective response rate (ORR) – the primary endpoint in both trials – and safety outcomes were calculated using the derived MAIC weights
- 95% confidence intervals (CIs) were estimated using robust standard errors



Plain language summary

What is this study about?

- We consulted with clinical experts and analyzed data from the Beamion LUNG-1 trial to identify patient characteristics that are important in predicting or changing the effects of treatment in patients with *HER2*m NSCLC

What were the findings?

- Experts believed that different patient characteristics influence efficacy and safety in different ways
- Important factors for efficacy included the presence of specific genetic changes in the tumor and number of previous treatments.
- For safety, important factors were kidney and liver function, age, ability of patient to tolerate chemotherapy and number of previous treatments.
- People taking zongertinib once a day were more likely to see their cancer shrink and less likely to have a severe or serious side effect that is caused by treatment when compared with people receiving T-DXd every 3 weeks

Conclusions

- Our study identified important patient characteristics that should be considered when conducting indirect treatment comparisons and interpreting clinical study results in *HER2*m NSCLC
- PFs and TEMs in *HER2*m NSCLC differ between efficacy and safety outcomes
- MAICs showed zongertinib 120 mg QD was associated with greater odds of achieving an objective response versus T-DXd 5.4 mg/kg Q3W. Zongertinib 120 mg QD also demonstrated a favourable safety profile with respect to treatment-related AEs, with odds ratios < 1 for all treatment-related safety endpoints and 95% CIs excluding 1 for Grade 3+ and serious events

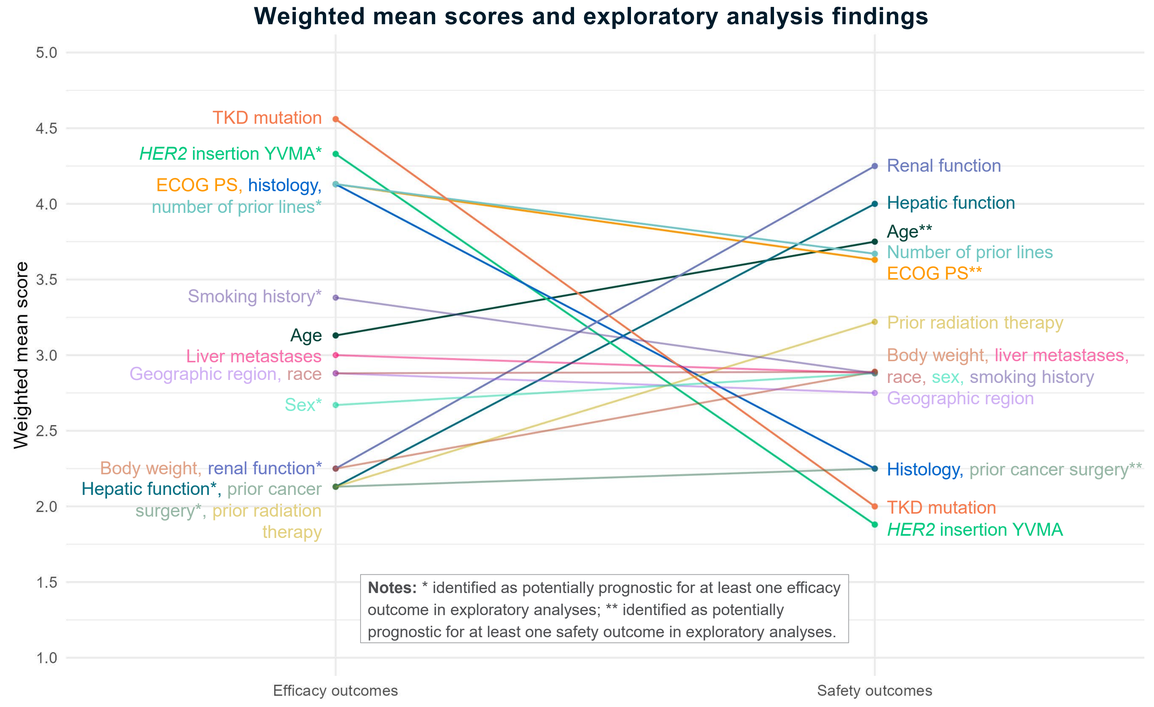
Results

Prognostic factors and effect modifier identification

- TKD mutation, *HER2* insertion YVMA, histology, ECOG PS and prior lines were ranked highest for efficacy
- Renal and hepatic function, age, ECOG PS and prior lines were top-ranked variables for safety
- TKD mutation, *HER2* insertion YVMA and renal/hepatic function showed the greatest variation between efficacy and safety scores
- Amongst other variables, exploratory analyses similarly identified *HER2* insertion YVMA and prior lines as potentially prognostic for efficacy, and age and ECOG PS for safety

89% of clinical experts expected PFs and TEMs to differ between efficacy and safety outcomes

Weighted mean scores and exploratory analysis findings



Although not ranked or included in exploratory analyses, brain metastases was also identified by clinical experts as an important characteristic for efficacy

MAIC results: zongertinib 120 mg QD versus T-DXd 5.4 mg Q3W

Outcome type	ESS	Outcome	Unadjusted odds ratio (95% CI)	Weighted odds ratio (95% CI)
Efficacy	68.88	ORR (central independent review)	2.67 (1.42, 5.05)	2.67 (1.16, 4.39)
Safety	63.49	Grade 3+ treatment-related AE	0.36 (0.18, 0.74)	0.43 (0.20, 0.93)
		Serious treatment-related AE	0.26 (0.07, 0.94)	0.21 (0.05, 0.80)
		Treatment-related AE leading to discontinuation	0.17 (0.04, 0.77)	0.25 (0.05, 1.25)

Key: *AE, adverse event; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PS, performance status; T-DXd, trastuzumab deruxtecan; YVMA, Tyrosine–Valine–Methionine–Alanine EGFR exon 20 insertion.*

Notes: *Odds ratio > 1 is favorable for zongertinib for ORR. Odds ratio < 1 is favorable for zongertinib for safety outcomes. Matching variables for ORR: HER2 YVMA mutation (A775_G776insYVMA vs other), ECOG PS (1 vs 0), number of prior lines (2+ vs 0–1) [100% of zongertinib patients and 97.1% of T-DXd patients had a TKD mutation so this variable did not necessitate adjustment; 100% of zongertinib patients and 99.0% of T-DXd patients had non-squamous NSCLC so this variable did not necessitate adjustment; brain metastases was not available for DESTINY-Lung02 so could not be included]. Matching variables for safety outcomes: age (≥ 60 vs < 60), ECOG PS, renal function (mild/moderate impairment vs normal), hepatic function (mild/moderate impairment vs normal), number of prior lines (2+ vs 0–1).*

- Clinically relevant characteristics were well balanced across populations after matching
- Treatment with zongertinib 120 mg QD was associated with greater odds of objective response than T-DXd 5.4 mg/kg Q3W; 95% CI for the odds ratio excluded 1
- Treatment with zongertinib 120 mg QD was consistently associated with improved safety in terms of treatment-related AEs, with odds ratios < 1 across all evaluated endpoints; 95% CIs for Grade 3+ and serious events excluded 1

Study limitations

- TEMs could not be assessed using the available patient-level data as Beamion LUNG-1 was a Phase I dose escalation/expansion trial where all patients received zongertinib[1]
- Exploratory analyses lacked power and occasionally contradicted the expert rankings – inconsistencies may reflect data artifacts rather than true PFs
- A trade-off in matching was required to balance adjustment for key characteristics while maintaining sufficient effective sample size, which led to an arbitrary cut-off for clinically relevant variables based on rankings
- As with all unanchored MAICs, results may be biased by unmeasured confounders, with bias magnitude difficult to assess

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