Updated data from Beamion LUNG-1, a Phase Ia/b trial of the HER2-specific tyrosine kinase inhibitor, zongertinib (BI 1810631), in patients with HER2 mutation-positive NSCLC

#34P

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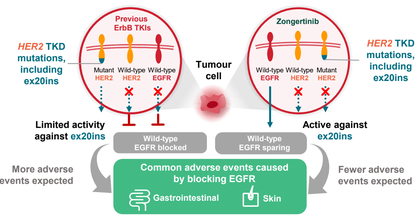
Introduction

- *HER2* mutations are present in 2–4% of patients with NSCLC; of these, approximately 50% are in the tyrosine kinase domain (TKD) and most of these are ex20ins mutations[1–4]
- Tyrosine kinase inhibitors (TKIs) that inhibit both HER2 and EGFR signalling are associated with toxicities; thus, there is an unmet need for effective, targeted therapy for patients with *HER2* mutation-positive (m+) solid tumours[5]
- Here, we present updated Phase Ia and results from a planned interim futility analysis of Phase Ib (Cohort 1) data evaluating the safety, MTD, pharmacokinetics, pharmacodynamics, and preliminary efficacy of the novel TKI zongertinib (BI 1810631) in patients with HER2 aberration-positive solid tumours and *HER2* mutation-positive NSCLC

EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion; HER2, human epidermal growth factor receptor 2; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; TKD, tyrosine kinase domain; TKI, tyrosine kinase inhibitor

Zongertinib mechanism of action



Methods

Phase Ia: dose escalation (in patients with advanced solid tumours with HER2 aberrations)

n=~36: 15 mg, 30 mg, 60 mg, 100 mg, 150 mg

n=~30: 60 mg, 120 mg, 180 mg, 240 mg, 300 mg, 360 mg

One oral dose, BID, 3-week cycles → One oral dose, QD, 3-week cycles

Phase Ib: ongoing dose expansion (in patients with *HER2* mutation-positive NSCLC)

Cohort 1* → Interim futility analysis → Cohort 1
Cohort 2 → Cohort 2
Cohort 5 → Cohort 5
Cohort 3 (exploratory)
Cohort 4 (exploratory)

Phase Ia primary endpoints
MTD and DLTs (MTD evaluation period)

Key inclusion criteria
HER2 aberration: overexpression, amplification, somatic mutation, or gene rearrangement involving *HER2* or *NRG1*
Exhausted or not suitable for existing standard treatment options

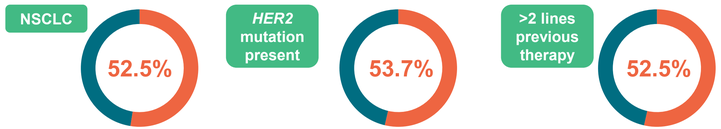
Phase Ib primary endpoint
OR (RECIST v1.1)

Key inclusion criteria
Patients with *HER2* mutation-positive NSCLC
Received ≥1 line of platinum-based combination chemotherapy (Cohorts 1, 3, 5)

Cohort 1: Pre-treated NSCLC† with a *HER2* TKD mutation
Cohort 2: Treatment-naïve NSCLC with a *HER2* TKD mutation
Cohort 3: NSCLC with a non-TKD *HER2* mutation or *HER2* TKD mutation-positive squamous NSCLC, pre-treated
Cohort 4: NSCLC with active brain metastases with a *HER2* TKD mutation
Cohort 5: NSCLC with a *HER2* TKD mutation and prior treatment with HER2 directed antibody–drug conjugates

*Randomised to receive either 240 mg or 120 mg QD. One dose will be selected after interim analysis †Excluding patients pre-treated with antibody–drug conjugates
BID, twice daily; DLTs, dose-limiting toxicities; NRG1, neuregulin 1; OR, objective response; QD, once a day; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1

Phase Ia: baseline characteristics (N=61)



Data cut-off: 15 September 2023

Key findings and conclusions

- In Phase Ia, the MTD of zongertinib was not reached
- Doses taken into Phase Ib for dose optimisation are 240 mg and 120 mg QD
- Response rates to zongertinib in Phase Ia were high, in particular in patients with NSCLC
- The median duration of response was over a year
- In Phase Ib, zongertinib was well tolerated with low rates of EGFR-mediated adverse events and no discontinuations due to adverse events
- In the preplanned interim futility analysis, the ORR was 74% and the DCR was 91%, with all responders ongoing
- The futility analysis was passed, and the trial is continuing, with recruitment into all cohorts ongoing

DCR, disease control rate; ORR, overall response rate

Phase Ia: dose escalation and safety

TRAEs* (%)	Total (N=61)			
	Any	G1	G2	G3
Any TRAE	**72.1**	**41.0**	**21.3**	**9.8**
Diarrhoea	36.1	29.5	4.9	1.6
ALT increased	11.5	4.9	1.6	4.9
AST increased	11.5	8.2	1.6	1.6
Rash†	11.5	9.8	—	—
Paronychia	8.2	6.6	1.6	—
Anaemia	6.6	4.9	1.6	—
Dry skin	6.6	6.6	—	—
Blood bilirubin increased	4.9	1.6	3.3	—
Fatigue	4.9	4.9	—	—
Mouth ulceration	4.9	4.9	—	—
Stomatitis	4.9	4.9	—	—
WBC count decreased	4.9	1.6	3.3	—

5 patients had DLTs:

240 mg QD	G3 diarrhoea (MTD period)
360 mg QD	G3 decreased platelets (MTD period)
60 mg BID	G2 oedema
150 mg BID	G2 diarrhoea
180 mg BID	G3 elevated ALT; G2 elevated AST; G3 elevated bilirubin

1 patient had a TRAE that led to discontinuation:

180 mg QD	G3 elevated ALT

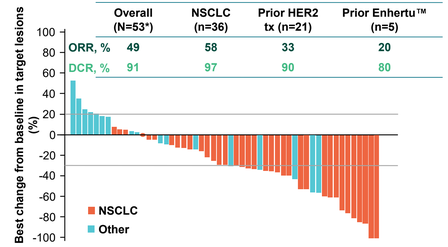
- There were no G4 or G5 TRAEs
- One patient had two serious G3 TRAEs: increased ALT and AST at 240 mg QD
- MTD not reached with either BID or QD schedule
- Doses taken into optimisation: 240 and 120 mg QD

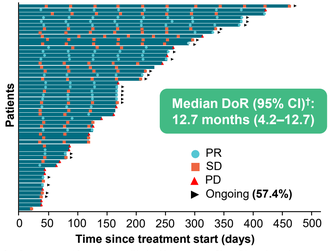
Data cut-off: 15 September 2023. *TRAEs that occurred in ≥3 patients; †Combined term, includes rash, rash maculo-papular, dermatitis acneiform. ALT, alanine aminotransferase; AST, aspartate aminotransferase; G, grade; TRAEs, treatment-related adverse events; WBC, white blood cell

Phase Ia: efficacy

- The overall median (range) duration of treatment with zongertinib was 4.8 (<1–18.7) months, with 35 patients ongoing

	Overall (N=53*)	NSCLC (n=36)	Prior HER2 tx (n=21)	Prior Enhertu™ (n=5)
ORR, %	49	58	33	20
DCR, %	91	97	90	80



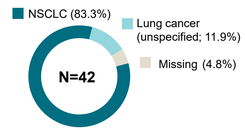


Median DoR (95% CI)†: 12.7 months (4.2–12.7)

Data cut-off: 15 September 2023. *Evaluable patients defined as those with ≥1 post-baseline tumour assessment or discontinued before first assessment for any reason; †Kaplan-Meier estimate. CI, confidence interval; DoR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease; tx, treatment

Phase Ib: baseline characteristics

Cohort 1: pre-treated NSCLC with a *HER2* TKD mutation



Country of participation:

China n=11 | Spain n=2 | Japan n=10 | France n=2 | Netherlands n=10 | South Korea n=2 | Germany n=3 | USA n=2

Characteristic	N=42
Median age, years (range)	62 (34–80)
Male, n (%)	20 (47.6)
Race, n (%)*	
Asian	24 (57.1)
White	13 (31.0)
ECOG PS, n (%)†	
0	12 (28.6)
1	26 (61.9)
Previous lines of therapy, n (%)†	
≤2	26 (61.9)
>2	12 (28.6)

Data cut-off: 31 July 2023. *Data were missing for five (11.9%) patients; †Data were missing for four (9.5%) patients. ECOG PS, Eastern Cooperative Oncology Group performance status

Phase Ib: safety

TRAEs* (%)	Total (N=42)				
	Any	G1	G2	G3	G4
Any TRAE	**66.7**	**38.1**	**19.0**	**4.8**	**4.8**
Diarrhoea	28.6	23.8	4.8	–	–
Rash†	21.4	16.7	4.8	–	–
AST increased	9.5	7.1	–	2.4	–
Decreased appetite	9.5	9.5	–	–	–
Dysgeusia	9.5	4.8	4.8	–	–
ALT increased	7.1	4.8	–	2.4	–
Anaemia	7.1	4.8	2.4	–	–
Bilirubin conjugate increased	7.1	7.1	–	–	–
Platelet count decreased	7.1	7.1	–	–	–
Blood bilirubin increased	4.8	4.8	–	–	–
Blood LDH increased	4.8	4.8	–	–	–
Lymphocyte count decreased	4.8	2.4	2.4	–	–
Neutrophil count decreased	4.8	–	–	2.4	2.4
Pyrexia	4.8	2.4	2.4	–	–
Stomatitis	4.8	4.8	–	–	–

0 discontinuations due to adverse events

3 patients had DLTs:

240 mg QD	G3 febrile neutropenia (MTD period)
	G4 immune thrombocytopenia (MTD period)
	G3 ALT and AST increased; G4 neutrophil count decreased

1 patient had TRAEs that led to dose reduction:

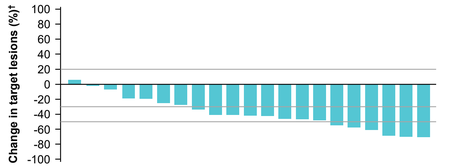
240 mg QD	G3 febrile neutropenia; G3 neutrophil count decreased

- Two patients had G4 TRAEs; there were no G5 TRAEs
- One patient had one serious TRAE: G4 thrombocytopenia; 240 mg QD
- One patient had three serious TRAEs: G3 increased ALT, G3 increased AST, G4 neutrophil count decreased; 240 QD

Data cut-off: 31 July 2023. *TRAEs that occurred in ≥2 patients; †Combined term, includes rash, rash maculo-papular, rash macular and dermatitis acneiform. LDH, lactate dehydrogenase

Phase Ib: efficacy (pooled doses)

Overall (N=23)*



- ORR: 74%; DCR: 91%
- Median best percentage change from baseline in target lesions: -41.2%
- Median tumour shrinkage: 41%
- Patients included in the efficacy analysis had completed 2–5 cycles of treatment at data cut-off
- The first preplanned interim futility analysis in Cohort 1 was passed and the trial is ongoing
- All responders are ongoing

Data cut-off: 31 July 2023. *Patients that started treatment at least seven weeks prior to the snapshot date; †Patients that started treatment at least seven weeks prior to the snapshot date with baseline and post-baseline tumour assessments

References

1. Baraibar I, et al. Crit Rev Oncol Hematol 2020;148:102906; 2. Connell CM, et al. ESMO Open 2017;2:e000279; 3. Robichaux JP, et al. Nat Med 2018;24:638–46; 4. Robichaux JP, et al. Cancer Cell 2019;36:444–57; 5. Aw DC, et al. Asia Pac J Clin Oncol 2018;14:23–31

Conflicts of interest: Y-LW reports consulting/advisory roles with AstraZeneca, Boehringer Ingelheim, and Takeda; honoraria with AstraZeneca, Lilly, Roche, Pfizer, Boehringer Ingelheim, MSD Oncology, Bristol Myers Squibb, Hengrui Pharmaceutical, and BeiGene Beijing; research funding (institute) from Roche, Boehringer Ingelheim, and Bristol Myers Squibb

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