2024 ASCO ANNUAL MEETING

Phase Ia/Ib trial of zongertinib (BI 1810631), a HER2-specific tyrosine kinase inhibitor in patients with HER2 aberration-positive solid tumors: updated Phase Ia data from Beamion LUNG-1, including progression-free survival data

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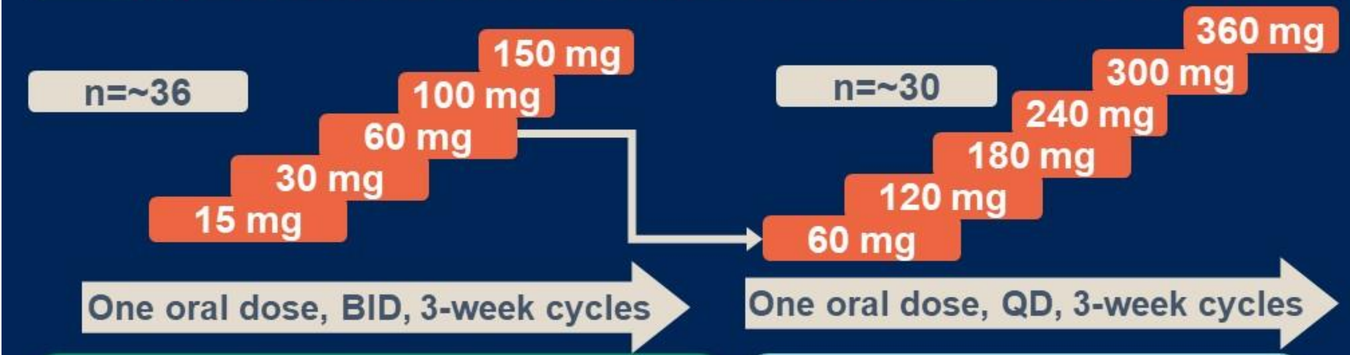
Beamion LUNG-1 (NCT04886804): trial design/endpoints

- Zongertinib (BI 1810631) is a novel TKI that covalently and selectively binds to the TKD of HER2, and is under investigation as an oral treatment for NSCLC tumors harboring *HER2* TKD mutations, including ex20ins mutations

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



Phase Ia endpoints

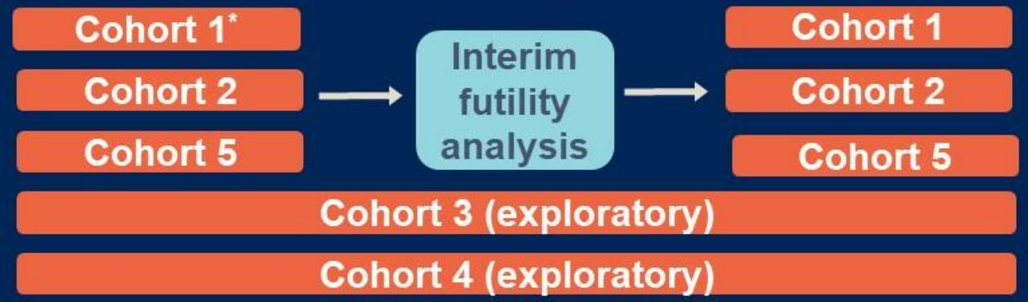
Primary: MTD and DLTs
Further: preliminary efficacy (ORR)†

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



Phase Ib primary endpoint

ORR†

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 ADCs

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*Randomized to receive either 120 mg or 240 mg QD. One dose will be selected after interim analysis;
†RECIST v1.1; ‡Excluding patients treated with ADCs
ADC, antibody-drug conjugate; BID, twice daily; DLTs, dose-limiting toxicities; ex20ins, exon 20 insertion; HER2, human epidermal growth factor receptor 2; MTD, maximum tolerated dose; NRG1, neuregulin 1; NSCLC, non-small cell lung cancer; ORR, objective response rate; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; TKD, tyrosine kinase domain; TKI, tyrosine kinase inhibitor

Phase Ia: baseline characteristics

Characteristic	Total (N=83)
Median age, years (range)	59.0 (31–81)
Male, n (%)	38 (45.8)
Race, n (%)	
Asian	39 (47.0)
White	35 (42.2)
Missing	9 (10.8)
ECOG PS, n (%)	
0	31 (37.3)
1	52 (62.7)
Previous lines of therapy, n (%)	
≤2	32 (38.6)
>2	47 (56.6)
Missing	4 (4.8)

Characteristic	Total (N=83)
Diagnosis, n (%)	
NSCLC	43 (51.8)
Breast cancer	9 (10.8)
Colorectal cancer	7 (8.4)
Esophageal cancer	5 (6.0)
Other tumors*	15 (18.1)
Unknown†	4 (4.8)
HER2 aberration, n/N tested (%)	
Mutation	42/75 (56.0)
Amplification	9/11 (81.8)
Overexpression‡	24/28 (85.7)
Rearrangement involving *HER2* or *NRG1*	12/75 (16.0)

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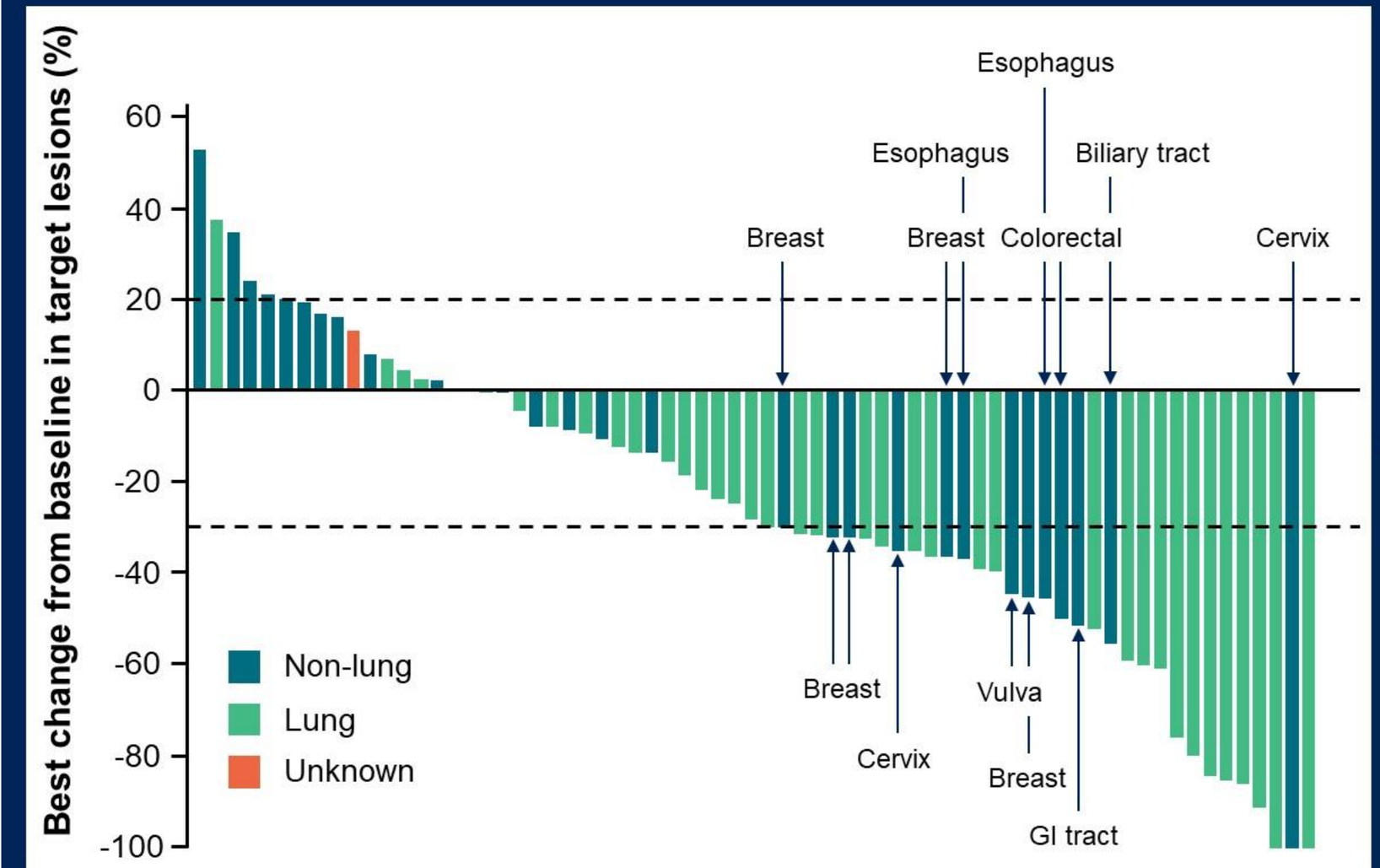
Data cut-off: January 29, 2024. *Cervical (n=3), endometrial (n=3), gastrointestinal tract (n=2), genitourinary system (n=1), small intestine, (n=1), biliary tract (n=1), mediastinum (n=1), pancreas (n=1), vulva (1), and other (n=1); †Tumor type was not listed for four patients; ‡1+, 2+, or 3+ on immunohistochemistry
ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; NRG1, neuregulin 1; NSCLC, non-small cell lung cancer

Phase Ia: antitumor response across all dose levels*



Best confirmed tumor response

	ORR	DCR
Overall (N=74)	35%	85%
NSCLC (N=41)	44%	93%

Unconfirmed response rates

	ORR	DCR
Prior trastuzumab deruxtecan (n=14)	36%	79%
Prior HER2 tx† (n=32)	38%	84%

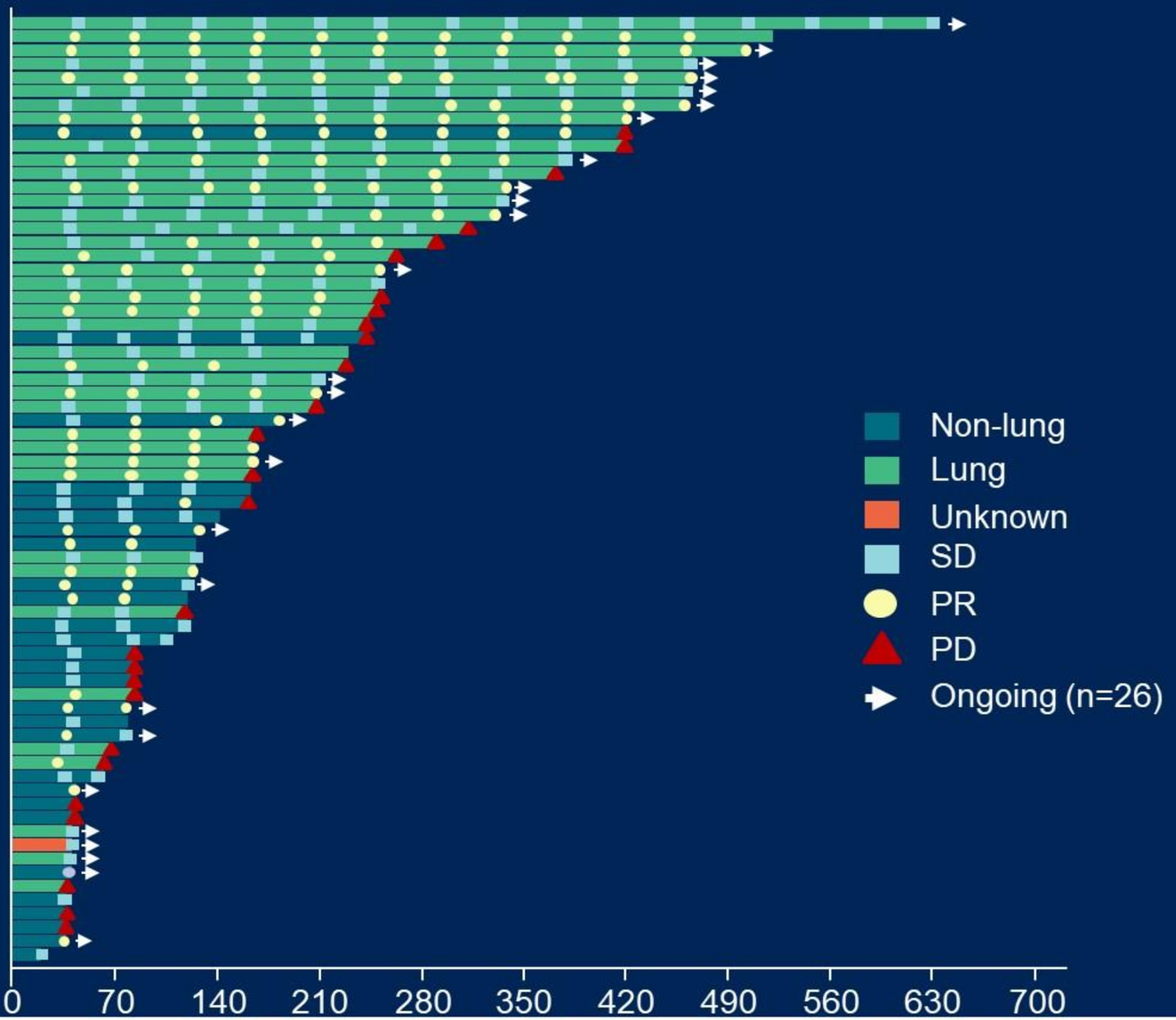
Data cut-off: January 29, 2024.*Responses are restricted to non-CNS lesions by RECIST 1.1.†Prior treatment with other HER2 therapies was permitted
CNS, central nervous system; DCR, disease control rate; GI, gastrointestinal; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, objective response rate; tx, treatment

Phase Ia: antitumor response by *HER2* mutation status*

Mutation type (evaluable for response)†	ORR,‡ n (%)	DCR,‡ n (%)
Any HER2 (n=41)	23 (56)	38 (93)
HER2 TKD (n=34)	21 (62)	32 (94)
A775_G776insYVMA (n=16)	11 (69)	15 (94)

Data cut-off: January 29, 2024. *Responses are restricted to non-CNS lesions by RECIST 1.1. †Patients with ≥1 post-baseline tumor assessment or discontinued before first assessment for any reason. ‡Unconfirmed
CNS, central nervous system; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; TKD, tyrosine kinase domain.

Duration of treatment in Phase Ia*



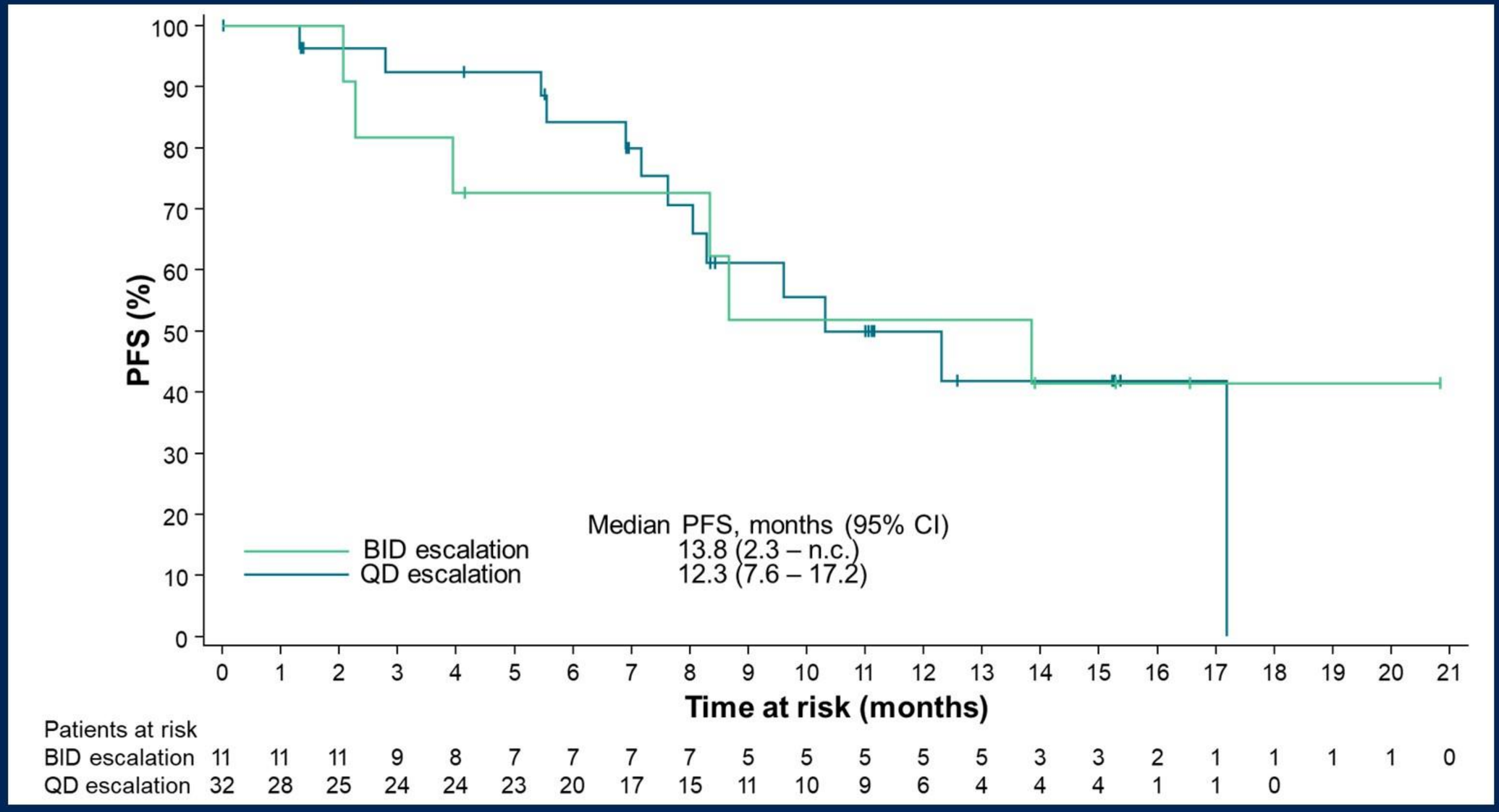
Patients still on treatment at data cut-off

12.7 months (95% CI: 5.6–15.8) Median duration of response: overall

15.8 months (95% CI: 5.6–15.8) Median duration of response: NSCLC

Data cut off: January 29, 2024. *Responses are restricted to non-CNS lesions by RECIST 1.1
CI, confidence interval; CNS, central nervous system; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease

Phase Ia: PFS in patients with NSCLC*



Data cut-off: January 29, 2024
BID, twice daily; CI, confidence interval; n.c., not reached; NSCLC, non-small cell lung cancer; PFS, progression-free survival; QD, once daily

Phase Ia dose escalation and safety

TRAEs (%)	Total (N=83)	
	All grades	G≥3
Any TRAE*	**75.9**	**9.6**
Diarrhea	42.2	1.2
Rash†	12.0	0.0
Decreased appetite	9.6	0.0
ALT increased	8.4	3.6
AST increased	8.4	1.2
Anemia	8.4	0.0
Fatigue	8.4	0.0
Dysgeusia	7.2	0.0
Paronychia	7.2	0.0
Dry skin	6.0	0.0
Nausea	6.0	0.0

Dose-limiting toxicities	
60 mg BID	G2 edema
150 mg BID	G2 diarrhea
180 mg QD	G2 elevated AST and elevated bilirubin G3 elevated ALT
240 mg QD	**G3 diarrhea (MTD period)** G4 thrombocytopenia
300 mg QD	**G4 neutropenia (MTD period)** G4 hypokalemia
360 mg QD	**G3 decreased platelet count (MTD period)**

- **Only one grade 4 TRAE (thrombocytopenia; 240 mg)**
- **No grade 5 TRAEs**
- **MTD was not reached with either BID or QD schedule**
- **Doses taken to optimization: 120/240 mg QD**

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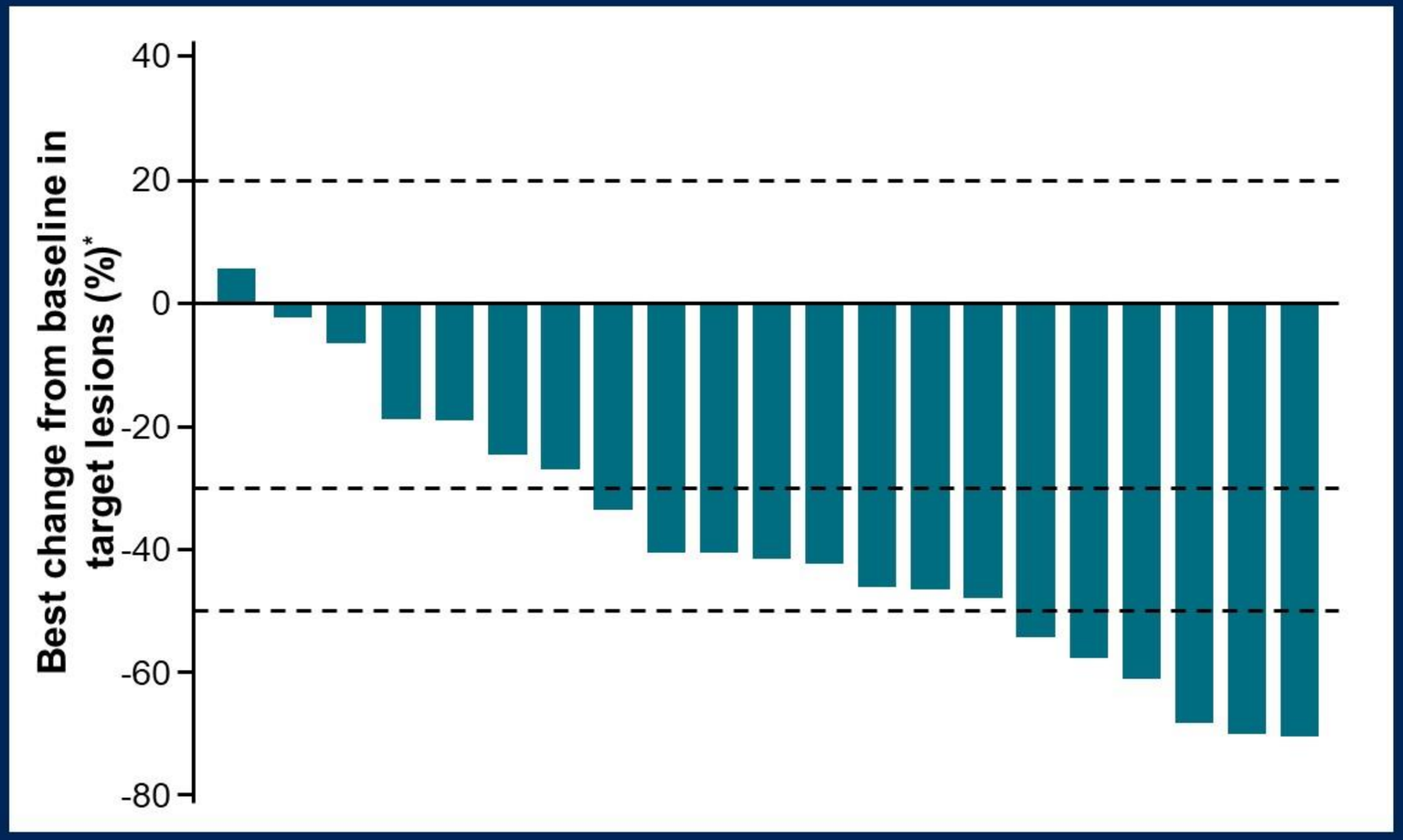
Data cut-off: January 29, 2024. *TRAEs that occurred in ≥5 patients are listed; †Combined term, includes rash, rash maculo-papular, dermatitis acneiform
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; G, grade; MTD, maximum tolerated dose; QD, once daily; TRAEs, treatment-related adverse events

Phase Ib: interim futility analysis July 2023



Efficacy (n=23)†

Safety (n=42)

TRAEs

The first futility analysis in Cohort 1 was passed

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Data cut-off: July 31, 2023. *Patients that started treatment at least 7 weeks prior to the snapshot date with baseline and post-baseline tumor assessments. †ORR reported regardless of confirmation.
DCR, disease control rate; G, grade; ORR, objective response rate; TRAE, treatment-related adverse event

Conclusions

- In Phase Ia, the MTD of zongertinib was not reached
- Doses taken into dose optimization were 120 mg and 240 mg QD
- Zongertinib was well tolerated with low rates of EGFR-mediated AEs
- Zongertinib demonstrated encouraging preliminary antitumor activity in various tumors with HER2 aberrations in Phase Ia
- Very promising initial efficacy results were observed in Phase Ib in pre-treated patients with NSCLC harboring *HER2* TKD mutations
- The trial is ongoing

AE, adverse event; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; QD, once daily; TKD, tyrosine kinase domain

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