A Phase I, open-label, dose-escalation, confirmation, and expansion trial of BI 1810631, a HER2 inhibitor, as monotherapy in patients with advanced or metastatic solid tumors with *HER2* aberrations

#TPS9143

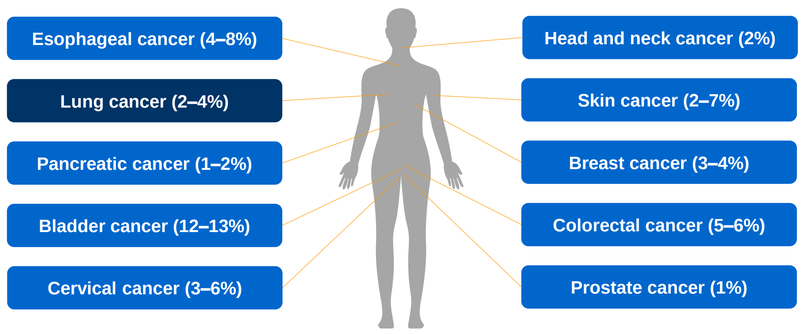
John Heymach,[1]* Frans Opdam,[2] Minal Barve,[3] Yi-Long Wu,[4] Neil Gibson,[5] Behbood Sadrolhefazi,[6] Josep Serra,[7] Noboru Yamamoto[8]

[1]Department of Thoracic-Head and Neck Medical Oncology, Division of Cancer Medicine, MD Anderson Cancer Center, University of Texas, Houston, TX, USA;
[2]Department of Clinical Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [3]Mary Crowley Cancer Research Center, Dallas, TX, USA; [4]Guangdong Provincial People's Hospital, Guangzhou, China;
[5]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; [6]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; [7]Boehringer Ingelheim España S.A., Barcelona, Spain; [8]National Cancer Center Hospital, Tokyo, Japan

Introduction

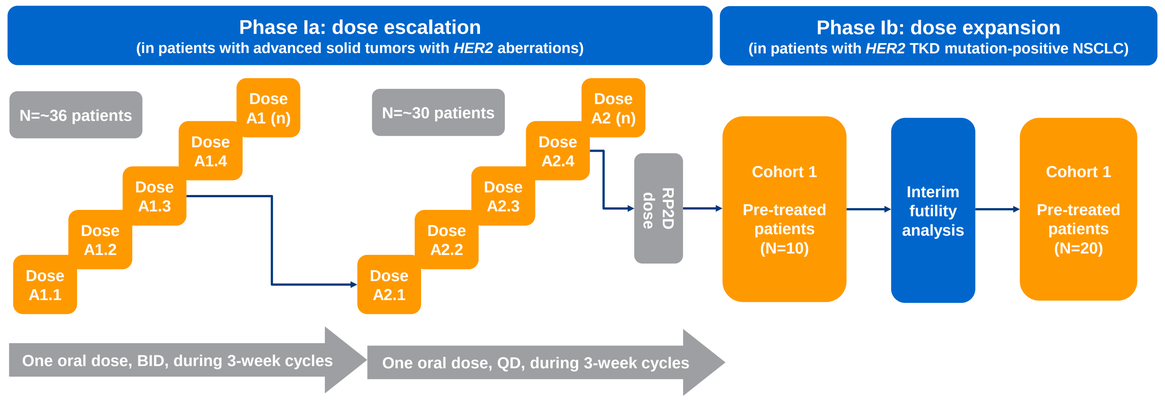
- Activating mutations in the *HER2* gene have frequently been reported to occur in many solid cancers, with a low to moderate prevalence[1]
- There is currently an unmet need for effective targeted therapy against *HER2* mutations in solid tumors, particularly in NSCLC where *HER2* mutations are present in 2–4% of tumors; of these, ~50% occur in the TKD of the gene, the majority of which are ex20ins mutations[2–5]
- Historically, *HER2* ex20ins mutations have responded poorly to TKIs. Moreover, TKIs that inhibit both EGFR and HER2 are typically limited by toxicities associated with inhibition of wild-type EGFR[4,6]
- BI 1810631 is a HER2-selective TKI currently undergoing clinical investigation in a Phase I study (NCT04886804) as monotherapy in patients with advanced/metastatic solid tumors harboring *HER2* aberrations (Phase Ia) and *HER2* TKD mutation-positive advanced/metastatic NSCLC (Phase Ib)

***HER2* mutation frequencies in solid tumors[2]**



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

Study design

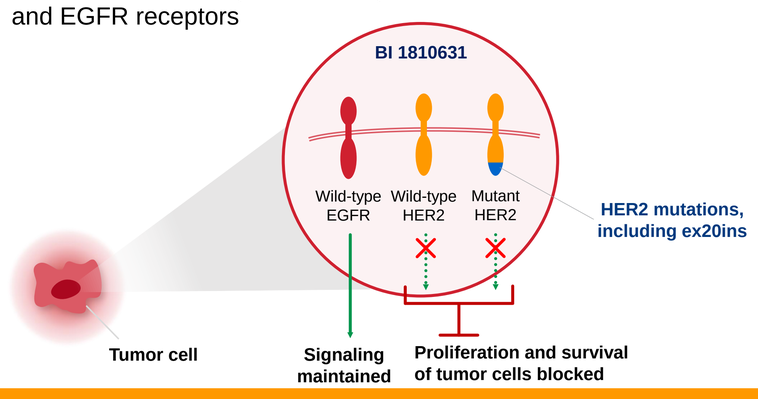


- In Phase Ia, dose escalation will be guided by a Bayesian logistic regression model with overdose control until at least one dose level above the estimated therapeutic dose is reached
- In Phase Ib, the planned dose is the RP2D determined in Phase Ia, after which 10 patients with pre-treated *HER2* TKD mutation-positive advanced/metastatic NSCLC will be enrolled and treated
- A futility analysis will be performed once 10 patients are evaluable for objective responses to treatment; if two or more responses are observed, a further 20 patients will be enrolled

BID, twice daily; QD, once a day; RP2D, recommended Phase II dose

Summary

- BI 1810631 binds to the TKD of HER2 receptors, inhibiting wild-type and mutant HER2, including ex20ins
- Avoids toxicity associated with inhibition of wild-type EGFR
- Possible better safety and efficacy than TKIs that bind to both HER2 and EGFR receptors



Scan this QR code or visit the URL for an electronic copy of the presentation†

https://bit.ly/3vMHv8r

Scan this QR code or visit the URL for a webpage featuring all BI-supported publications at ASCO 2022

https://bit.ly/3ynAWe6

Scan the QR code for an electronic copy of the poster and supplementary content,† references and acknowledgements

†Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from ASCO® and the authors of this poster

NCT04886804: Key points

- **First-in-human, open-label, non-randomized, dose-escalation trial of BI 1810631 in patients with advanced/metastatic solid tumors**
- **Phase Ia primary objectives are to investigate safety, tolerability, and PK of BI 1810631 in patients with tumors harboring any *HER2* aberration and determine the MTD and/or RP2D**
- ***HER2* aberration is defined as overexpression, gene amplification, non-synonymous somatic mutation, or gene rearrangement involving *HER2* or *NRG1***
- **Phase Ib objectives will be to further investigate the safety and efficacy of BI 1810631 in patients with advanced/metastatic NSCLC harboring *HER2* TKD mutations**

MTD, maximum tolerated dose; *NRG1*, neuregulin 1; PK, pharmacokinetics

Data were originally presented: AACR 2022. *Corresponding author email address: jheymach@mdanderson.org

Objectives

Phase Ia objectives	Phase Ib objectives
Investigate safety, tolerability, and PK of BI 1810631	Further investigate safety, tolerability, and PK of the RP2D of BI 1810631
Determine the MTD and/or RP2D of BI 1810631 monotherapy	Preliminary assessment of efficacy in patients with *HER2* TKD mutation-positive NSCLC

Inclusion and exclusion criteria

Key inclusion criteria (overall)

Patients with histologically/cytologically confirmed diagnosis of an advanced, unresectable and/or metastatic solid tumor, who are refractory after standard therapy for the disease, or for whom standard therapy is not suitable

- Adult patients (≥18 years old)
- ECOG PS of 0/1
- Adequate organ function
- Measurable/evaluable lesions according to RECIST v1.1
- Availability and willingness to provide a tumor sample to confirm *HER2* status

Phase Ia key inclusion criteria	Phase Ib key inclusion criteria
Patients with *HER2* genetic aberrations (defined as overexpression, gene amplification, non-synonymous somatic mutation, or gene rearrangement involving *HER2* or *NRG1*)	Patients with *HER2* TKD mutation-positive NSCLC
Exhausted or not suitable for existing standard treatment options	Received ≥1 line of platinum-based combination chemotherapy in the advanced/metastatic setting

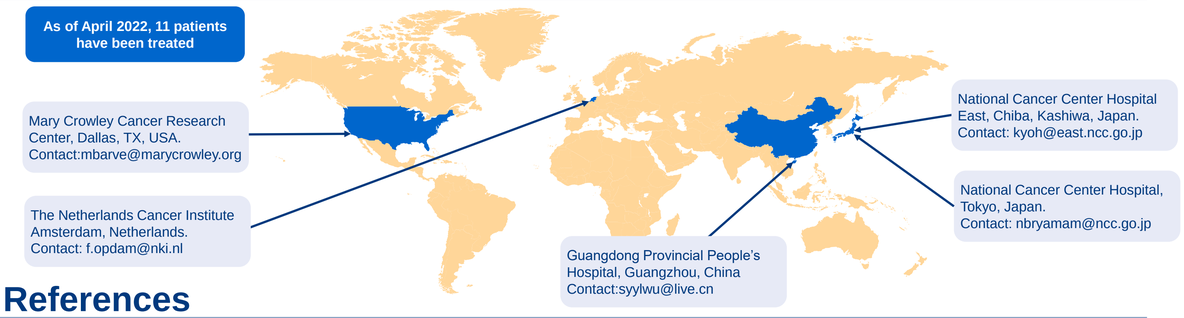
ECOG PS, Eastern Cooperative Oncology Group performance status; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1

Endpoints

Phase Ia primary endpoints	Phase Ib primary endpoints
MTD, based on the occurrence of DLTs in the evaluation period	Objective response, according to RECIST v1.1
Number of patients with DLTs in the MTD evaluation period	**Phase Ib secondary endpoints**
Phase Ia secondary endpoints	Treatment efficacy (DoR, DC, DoDC, PFS)
Number of patients with DLTs during the entire treatment period	Safety
PK parameters (C_{max} and $AUC_{0\text{-}t2}$) after first and multiple doses in all regimens	PK parameters (C_{max} and $AUC_{0\text{-}t2}$) on Days 1 and 15

$AUC_{0\text{-}t2}$, area under the curve from 0 to the time of the second quantifiable data point; C_{max}, maximum serum concentration; DC, disease control; DLT, dose-limiting toxicity; DoDC, duration of DC; DoR, duration of response; PFS, progression-free survival

Study status



References

1. Subramanian et al. Oncologist 2019;24:e1303–14; 2. Baraibar et al. Crit Rev Oncol Hematol 2020;148:102906; 3. Connell & Doherty. ESMO Open 2017;2:e000279; 4. Robichaux et al. Nat Med 2018;24:638–46; 5. Robichaux et al. Cancer Cell 2019;36:444–457; 6. Aw et al. Asia Pac J Clin Oncol 2018;14:23–31

SC-US-74411

Presented at the American Society for Clinical Oncology (ASCO), Chicago, IL, USA, June 3–7, 2022

This study was funded by Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version. The authors did not receive payment related to the development of the poster. Medical writing support for the development of this poster, under the direction of the authors, was provided by Joanna Badawy, of Ashfield MedComms, an Ashfield Health company, and funded by Boehringer Ingelheim