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

#CT212

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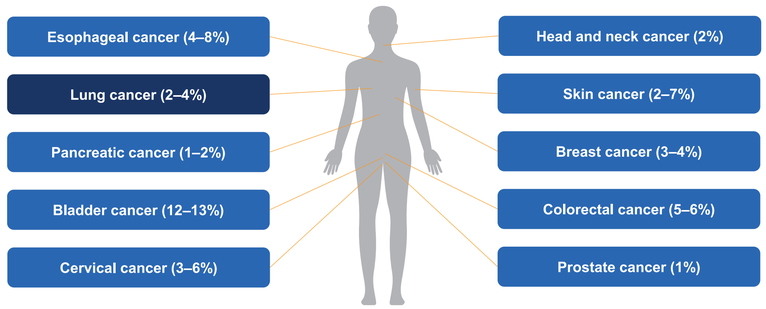
Introduction

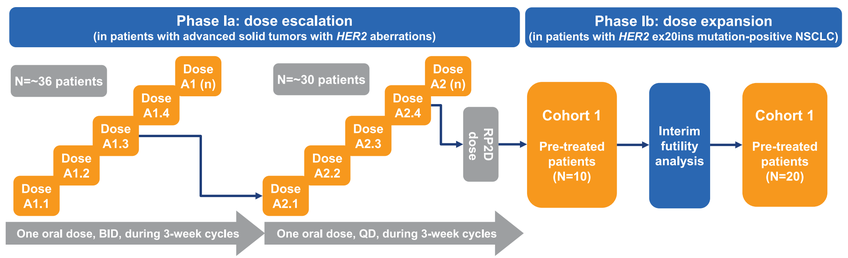
- Activating mutations in the *HER2* gene have frequently been reported to occur in many solid cancers, with a low to moderate prevalence[1]
- There is currently an unmet need for effective targeted therapy against *HER2* mutations in solid tumors, particularly in NSCLC where *HER2* mutations are present in 2–4% of tumors; of these, ~50% 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* ex20ins 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; TKI, tyrosine kinase inhibitor

NCT04886804 study design



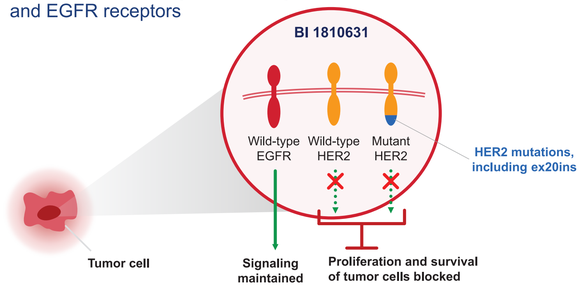
- In Phase Ia, dose escalation will be guided by a Bayesian logistic regression model with overdose control until at least one dose level above the estimated therapeutic dose is reached
- In Phase Ib, the planned dose is the RP2D determined in Phase Ia, after which 10 patients with pre-treated *HER2* ex20ins mutation-positive 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

Mechanism of action of BI 1810631, a novel TKI

- BI 1810631 binds to the tyrosine kinase domain 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



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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 NSCLC harboring *HER2* ex20ins mutations

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

References

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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* ex20ins mutation-positive NSCLC

Inclusion 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

Patients with *HER2* genetic aberrations (defined as overexpression, gene amplification, non-synonymous somatic mutation, or gene rearrangement involving *HER2* or *NRG1*)

Exhausted, or not suitable for, existing standard treatment options

Phase Ib key inclusion criteria

Patients with *HER2* ex20ins mutation-positive NSCLC

Received ≥1 line of platinum-based combination chemotherapy in the advanced/metastatic setting

ECOG PS, Eastern Cooperative Oncology Group performance status; RECIST, response evaluation criteria in solid tumors

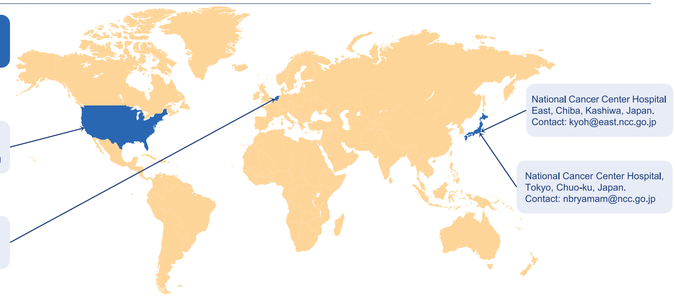
Endpoints

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-t2}) after first and multiple doses in all regimens	PK parameters (C_{max} and AUC_{0-t2}) on Days 1 and 15

AUC_{0-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

As of February 2022, six patients have been treated at the first two dose levels of escalation



SC-US-74168

Presented at the American Association for Cancer Research (AACR) Congress, New Orleans, Louisiana, United States, April 8–13, 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 Rick Burgon, of Ashfield MedComms, an Ashfield Health company, and funded by Boehringer Ingelheim