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 tumours with HER2 aberrations

#79TiP

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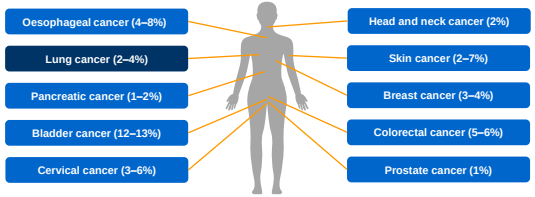
Introduction

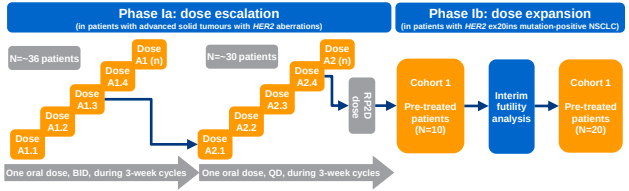
- Activating mutations in the *HER2* gene have frequently been reported to occur in many solid cancers, with a low to moderate prevalence[1]
- There is currently an unmet need for effective targeted therapy against *HER2* mutations in solid tumours, particularly in NSCLC, where *HER2* mutations are present in 2–4% of NSCLC tumours; 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 tumours harbouring *HER2* aberrations (Phase Ia) and *HER2* ex20ins mutation-positive advanced/metastatic NSCLC (Phase Ib)

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



ex20ins, exon 20 insertion; TKI, tyrosine kinase inhibitor

NCT04886804 study design



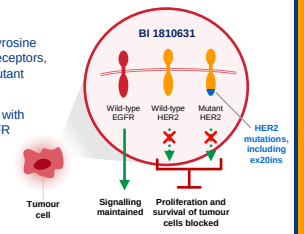
- In Phase Ia, dose escalation will be guided by a Bayesian logistic regression model with overdose control until at least one dose level above the estimated therapeutic dose is reached
- In Phase Ib, the planned dose is the RP2D determined in Phase Ia, after which 10 patients with pre-treated *HER2* 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-randomised, dose-escalation trial of BI 1810631 in patients with advanced solid tumours
- Phase Ia primary objectives are to investigate safety, tolerability, and PK of BI 1810631 in patients with tumours harbouring any *HER2* aberration, and to 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 harbouring *HER2* ex20ins mutations

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

References

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Objectives

Phase Ia objectives

- Investigate safety, tolerability, and PK of BI 1810631
- Determine the MTD and/or RP2D of BI 1810631 monotherapy

Phase Ib objectives

- Further investigate safety, tolerability, and PK of the RP2D of BI 1810631
- 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 tumour, who are refractory after standard therapy for the disease, or for whom standard therapy is not suitable
- Adult patients (≥18 years old)
- Measurable/evaluable lesions according to RECIST v1.1
- ECOG PS of 0/1
- Availability and willingness to provide a tumour sample to confirm *HER2* status
- Adequate organ function

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 tumours

Endpoints

Phase Ia primary endpoints

- MTD, based on the number of patients with DLTs in the evaluation period
- Number of patients with DLTs in the MTD evaluation period

Phase Ia secondary endpoints

- Number of patients with DLTs during the entire treatment period
- PK parameters (C_{max} and AUC_{0-t2}) after first and multiple doses in all regimens

Phase Ib primary endpoints

- Objective response, according to RECIST v1.1

Phase Ib secondary endpoints

- Treatment efficacy (DoR, DC, DoDC, PFS)
- Number of patients with DLTs during the entire treatment period
- 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; PK, pharmacokinetics

Study status

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

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