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A Phase I, Open-Label, Dose Confirmation, Escalation, and Expansion Trial of BI 1810631 as Monotherapy in Patients with Advanced or Metastatic Solid Tumors with HER2 Aberrations

Running title: HER2 inhibitor, BI 1810631: first-in-human trial

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

[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, Dallas, TX, USA
[4]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany
[5]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA
[6]Boehringer Ingelheim España S.A., Barcelona, Spain
[7]National Cancer Center Hospital, Tokyo, Japan

Address for correspondence: John Heymach, Department of Thoracic-Head and Neck Medical Oncology, Division of Cancer Medicine, MD Anderson Cancer Center, University of Texas, 1515 Holcombe Blvd, Houston, TX 77030, USA.
E-mail contact: jheymach@mdanderson.org

Abstract

Background

BI 1810631 is a human HER2-selective tyrosine kinase inhibitor that covalently binds to both wild-type and mutated HER2 receptors, including exon 20 insertion mutations, whilst sparing EGFR signaling. This phase Ia/Ib, open-label, non-randomized study will determine the safety, maximum tolerated dose (MTD), pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of BI 1810631 in patients with HER2 aberration-positive solid tumors (NCT04886804).

Patients and Methods

In phase Ia, patients with histologically/cytologically confirmed HER2 aberration-positive advanced/metastatic solid tumors will receive BI 1810631 orally twice daily (BID) or once daily (QD) at escalating doses. Starting dose level is 15 mg BID; QD schedule will begin after one dose level above estimated therapeutic dose of BI 1810631 is determined safe by the Dose Escalation Committee. Dose escalation will continue until MTD/recommended phase II dose and preferred phase Ib schedule for each schedule is determined. In phase Ib, patients with *HER2* tyrosine kinase domain (TKD) mutation-positive non-small cell lung cancer (NSCLC) who have previously received ≥1 line of systemic therapy will be enrolled initially, with possible inclusion of additional NSCLC cohorts in the future, including untreated patients. The primary endpoints will be MTD based on number of dose-limiting toxicities (DLTs)/number of patients with DLTs (phase Ia) and objective response (phase Ib). Secondary endpoints include PK parameters (phase Ia/Ib); duration of response, disease control, duration of disease control, and progression-free survival (phase Ib).

Conclusions

BI 1810631 could be an effective and tolerable EGFR-sparing oral treatment for patients with *HER2* mutation-positive NSCLC, including exon 20 insertion mutations.

ClinicalTrials.gov identifier: NCT04886804

Keywords: HER2-selective, ex20ins, EGFR-sparing, NSCLC, TKD

Abbreviations: BID, twice daily; DLT, dose-limiting toxicity; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; QD, once daily; TKD, tyrosine kinase domain

Introduction

Human epidermal growth factor receptor 2 (*HER2*) is established as an important proto-oncogene that has been targeted successfully in both breast and gastroesophageal cancers with *HER2* overexpression and gene amplification.[1] *HER2* oncogenic activation can also result from somatic gene mutations, which may be independent of *HER2* gene amplification. HER2-activating mutations have been identified in a wide variety of solid tumors, including 2–4% of non-small cell lung cancer (NSCLC) tumors.[1, 2] In NSCLC, up to 50% of *HER2* mutations are exon 20 insertions.[3] Mutations have been detected across all exons of *HER2* and are highly heterogeneous across tumor types.[1, 4, 5] Therapies for *HER2*-mutation positive NSCLC is a current unmet need;[4] *HER2* exon 20 insertion mutations have historically responded poorly to tyrosine kinase inhibitors (TKIs). Moreover, non-selective ErbB-targeted agents that can inhibit mutant HER2 are associated with off-target EGFR wild type-related toxicities.[6]

BI 1810631 is a member of a group of novel, EGFR wild type-sparing, HER2-selective TKIs under investigation as an oral treatment for NSCLC tumors harboring *HER2* tyrosine kinase domain (TKD) mutations, including exon 20 insertion mutations.[7] By selectively and covalently binding to the TKD of mutated HER2 receptors (including exon 20 insertions), BI 1810631 blocks aberrant downstream signaling while sparing wild-type EGFR signaling (Figure 1). Preclinical data suggest this group of inhibitors has good tolerability and efficacy, inhibiting TKD mutations, including exon 20 insertions.[7]

The purpose of phase Ia of this first-in-human study is to determine the maximum tolerated dose (MTD) and/or the recommended phase II dose (RP2D) and explore the safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of orally administered BI 1810631 monotherapy in patients with HER2 aberration-positive advanced solid tumors. Phase Ib will assess the efficacy and safety of the RP2D in patients with *HER2* TKD mutation-positive, pre-treated NSCLC.

Methods

Study design

This is a phase I, open-label, non-randomized, multicenter trial of BI 1810631 monotherapy (NCT04886804). The trial consists of two parts: dose escalation (phase Ia), and dose expansion (phase Ib; Figure 2). In phase Ia, consecutive cohorts of patients with advanced/metastatic solid tumors harboring any HER2 aberration will receive escalating doses of BI 1810631 monotherapy, administered orally, once (QD) or twice daily (BID). At the end of phase Ia, the MTD and/or RP2D will be defined for each of the schedules, and a preferred schedule for phase Ib will be selected. The phase Ib part will initially enroll 30

patients with *HER2* TKD mutation-positive, pre-treated NSCLC into Cohort 1, including those with exon 20 insertions. As phase Ib proceeds, additional cohorts may be opened, including a cohort of patients without prior treatment. A Dose Escalation Committee (DEC) will be established to ensure patient safety and will: monitor the safety data on an ongoing basis; make decisions regarding the MTD and/or RP2D, and the necessity of trial plan modifications, in case of emerging safety issues.

Key eligibility criteria

Overall trial criteria

Patients considered for phase Ia of the study will be those with a histologically or cytologically confirmed diagnosis of HER2 aberration-positive advanced, unresectable and/or metastatic solid tumors refractory to standard therapy for the tumor type, or not suitable for standard therapy. HER2 aberrations are defined as overexpression (2+ or 3+ by immunohistochemistry), gene amplification, non-synonymous somatic mutation, or a gene rearrangement involving *HER2* or neuregulin 1 (*NRG1*). Patients will also have exhausted treatment options known to prolong survival for their tumor type, or not be a suitable candidate for those options.

Other key eligibility criteria include: age ≥18 years; measurable or evaluable lesions as measured by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; availability and patient willingness to provide a tumor sample for *HER2* status confirmation; patient willingness to provide fresh tumor biopsies prior to treatment and during cycle 1 for PD/PK assessments of BI 1810631 (brain metastases will not be biopsied); adequate organ function; life expectancy of ≥12 weeks at the start of treatment in the opinion of the investigator; recovered from any previous therapy-related toxicity to at least Common Terminology Criteria for Adverse Events (CTCAE) grade 1 (grade ≤2 for alopecia, stable sensory neuropathy, and hypothyroidism) at start of treatment; written informed consent. Patients with stable/asymptomatic brain metastasis will be allowed.

Additional criteria for phase Ib

Patients with documented *HER2* TKD mutation-positive NSCLC, including exon 20 insertions, who had received ≥1 line of platinum-based combination chemotherapy in the advanced/metastatic setting. Those patients with additional genomic aberrations for which approved targeted therapy is available must have received prior treatment with an approved targeted therapy.

BI 1810631 starting dose and treatment schedule

The starting dose level for BI 1810631 in phase Ia is 15 mg BID orally; successive cohorts will receive increasing doses until at least one dose level above the estimated therapeutic dose of BI 1810631 is reached, if allowed by the Bayesian Logistic Regression Model (BLRM) used for dose determination. Once this occurs, recruitment for the QD schedule will be opened, with the expected starting dose being 60 mg. The planned dose for phase Ib is the RP2D determined in phase Ia, with the dosing schedule determined by the DEC using all of the data from phase Ia.

Study endpoints

Phase Ia dose escalation

The primary endpoints for phase Ia are: to determine the MTD, defined as the highest dose with <25% risk of the true dose-limiting toxicity (DLT) rate being ≥33% during the MTD evaluation period (cycle 1) for any studied regimen; the number of patients with DLTs in the MTD evaluation period. Secondary endpoints are: the number of patients with DLTs in the entire treatment period; BI 1810631 PK parameters on Days 1 and 15. The maximum measured concentration of BI 1810631 in plasma (C_{max}) and the area under the concentration-time curve of BI 1810631 in plasma (AUC_{0-t2}) will be measured, if feasible.

Phase Ib dose expansion

The primary endpoint for phase Ib is objective response. Secondary endpoints are: duration of objective response; disease control rate and duration of disease control; progression-free survival; the number of patients with DLTs in the entire treatment period; BI 1810631 PK parameters (C_{max}, AUC_{0-t2}) on Days 1 and 15.

Study assessments and statistical analysis

Assessment of efficacy will be performed via imaging tests. Non-brain tumor response will be evaluated according to RECIST Version 1.1. Brain tumor response will be evaluated using Response Assessment in Neuro-Oncology criteria for brain metastases. Assessment of safety will include reporting of adverse events (AEs) and documenting the occurrence of DLTs. The PK profile of BI1810631 will be determined after the first dose and following repeated dosing.

Dose escalation and determination of the MTD will be guided by a three parameter BLRM with overdose control.

Discussion

Effective targeted therapy against *HER2* mutations is an unmet need in solid tumors, particularly in NSCLC with *HER2* mutations. BI 1810631 is an orally administered, EGFR-sparing, selective inhibitor of the HER2 receptor with activity against *HER2* TKD mutations, including exon 20 insertions. Structurally similar agents have shown positive results in preclinical investigations.[7] The ongoing study described herein will provide first-in-human data on BI 1810631.

HER2-targeted therapies are currently lacking; however, investigations into several agents are ongoing. These include trials of the HER2 antibody-drug conjugate trastuzumab deruxtecan,[8] the HER2 TKI poziotinib,[9, 10] and pan-HER inhibitor pyrotinib.[11] These agents have been associated with response rates of 55%, 27–8% and 19%, respectively, in patients with *HER2* mutation-positive NSCLC following chemotherapy. Recently, the US Food and Drug Administration (FDA) granted accelerated approval to trastuzumab deruxtecan for adult patients with unresectable or metastatic NSCLC whose tumors have activating *HER2* mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.[12] Patients previously treated with trastuzumab deruxtecan are eligible for this trial. Despite these developments, high-rates of dose reductions with poziotinib,[9, 10] safety concerns regarding interstitial lung disease with antibody-drug conjugates,[8] the need for a broad armamentarium of potential therapeutic options to account the heterogeneity of HER2 aberrations, options for brain metastases, and the potential for combination regimens in the future, necessitate the development of orally available small molecule therapeutics in this area of unmet need.

Conclusions

This study will determine the MTD and RP2D of BI 1810631 monotherapy in patients with solid tumors harboring HER2 aberrations. The expansion cohort will provide data on the preliminary efficacy of BI 1810631 monotherapy in patients with NSCLC and *HER2* TKD mutations, including exon 20 insertions, a group for which there is a significant unmet need for efficacious and tolerable therapies.

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CRediT authorship contribution statement

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). **John Heymach:** Investigation, Writing - review & editing; **Frans Opdam:** Writing - review & editing; **Minal Barve:** Investigation, Supervision, Project administration, Writing - review & editing; **Neil Gibson:** Supervision, Project administration, Writing - review & editing; **Behbood Sadrolhefazi:** Writing - review & editing; **Josep Serra:** Project administration, Writing - review & editing; **Noboru Yamamoto:** Investigation, Writing - review & editing. All authors provided final approval of the manuscript.

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Figures

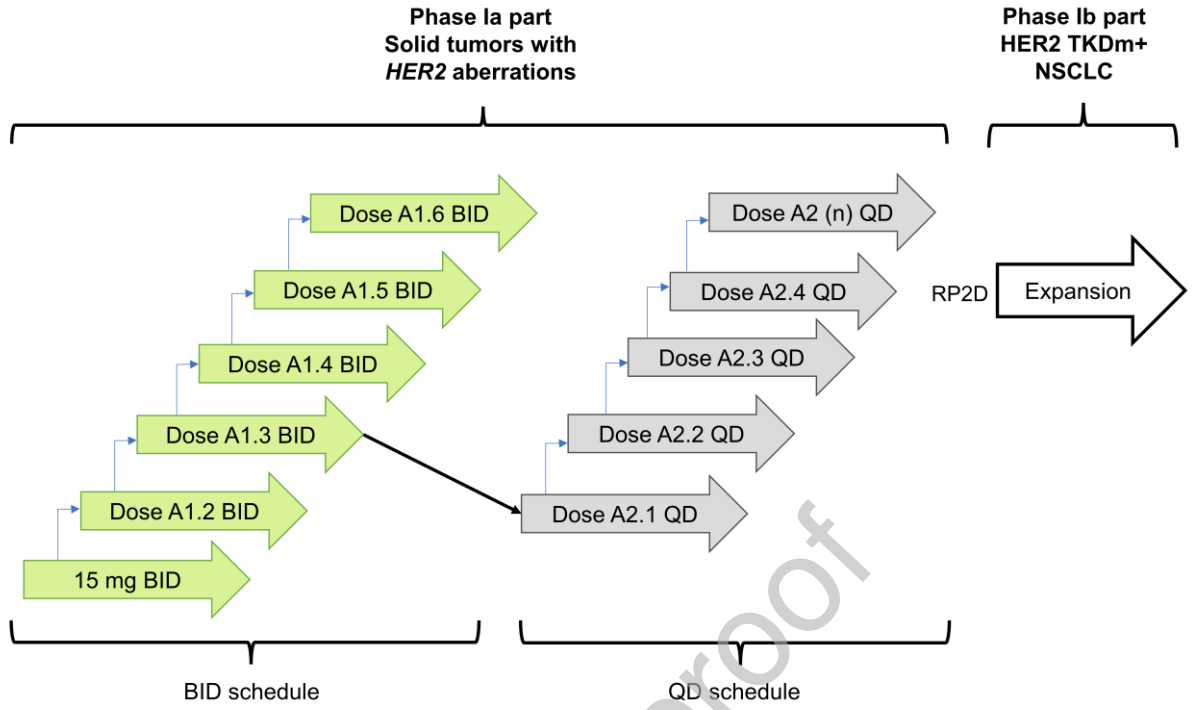

Figure 1. Mechanism of action of BI 1810631. BI 1810631 is a HER2-selective TKI that covalently binds to the TKD of HER2, blocking downstream signaling from HER2 homodimers and heterodimers, including those that harbor *HER2* mutations, including exon 20 insertions. BI 1810631 spares wild-type EGFR signaling. Abbreviations: EGFR (ErbB1), epidermal growth factor receptor; ErbB3 (HER3), human epidermal growth factor receptor 3; HER2 (ErbB2), human epidermal growth factor receptor 2; TKD, tyrosine kinase domain; WT, wild-type.

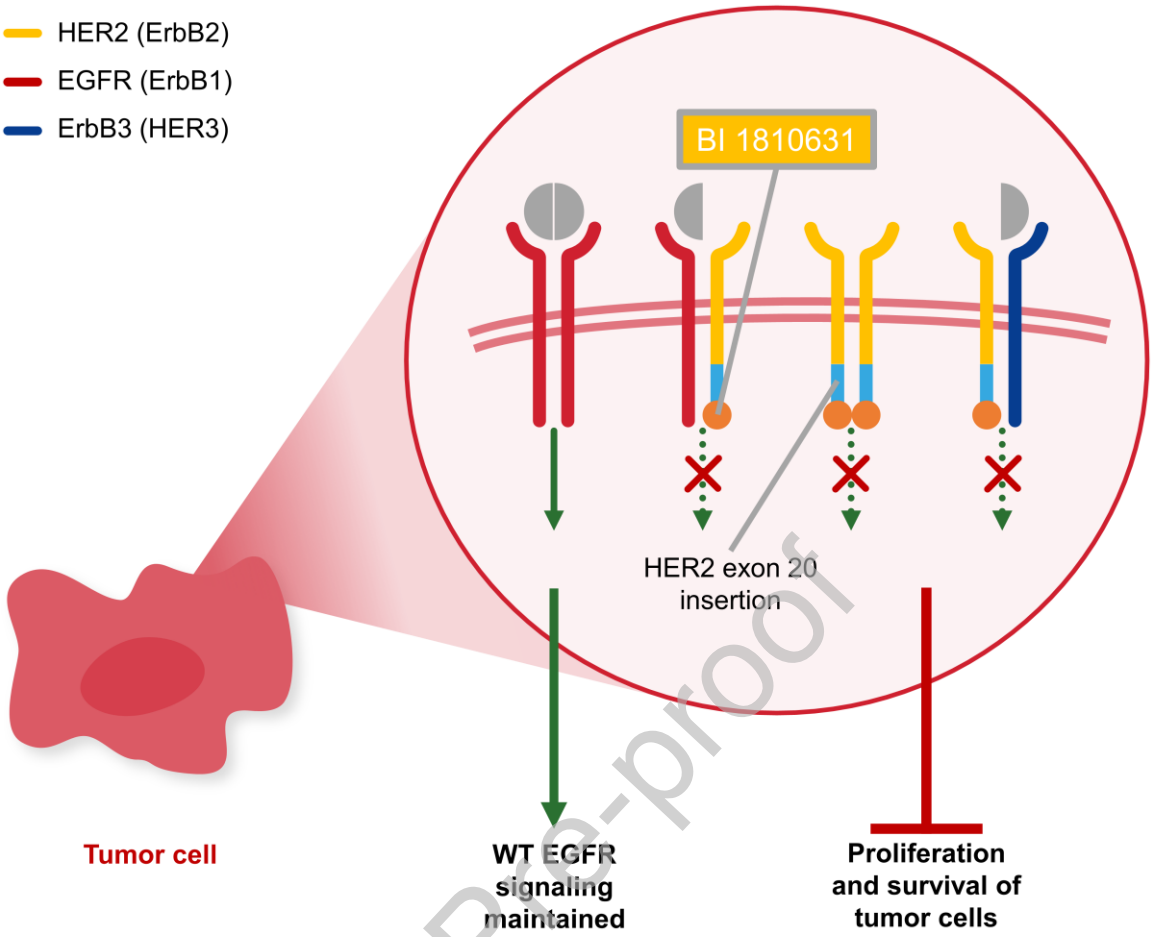

Figure 2. Trial design. Abbreviations: BID, twice daily; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; QD, once daily; RP2D, recommended Phase II dose; TKDm+, tyrosine kinase domain mutation positive.