A First-in-Class mAb (BI-1607) Targeting FcγRIIB: Preclinical Data and First-in-Human Studies in Patients with HER2-Positive Advanced Solid Tumors

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ABSTRACT

Purpose: BI-1607 is a human mAb that specifically blocks FcγRIIB, the sole inhibitory Fc receptor and master regulator of humoral and innate immune homeostasis. These studies evaluated preclinical antitumor activity using a BI-1607 murine surrogate (mBI-1607) and the safety, tolerability, pharmacokinetics, and pharmacodynamics of the compound in combination with trastuzumab in patients with HER2-positive advanced solid tumors (NCT05555251).

Patients and Methods: Immunocompetent syngeneic mouse breast tumor (TUBO) and melanoma (B16-F10) models were used to evaluate *in vivo* antitumor activity in combination (anti-HER2 and anti-gp75). Ascending doses of BI-1607 administered intravenously every 3 weeks in combination with trastuzumab were evaluated in 18 patients with HER2-positive cancer. The primary objective was to assess the safety and tolerability of BI-1607 by determining dose-limiting toxicities and the maximum tolerated dose or maximum administered dose and identifying a recommended phase 2 dose.

Results: mBI-1607 enhanced tumor-targeting antibody efficacy and animal survival. BI-1607/trastuzumab was well tolerated, with dose-limiting toxicity (rash) in one patient (5.6%) at 900 mg; the maximum tolerated dose was not reached. Treatment-emergent adverse events grade ≥3 occurred in five patients (28%), including exanthema, increase in liver enzymes, urticaria, acute kidney injury, and aggravated condition. Overall best response was stable disease, observed in seven of the nine evaluable patients (78%). BI-1607 exhibits linear pharmacokinetics for doses above 500 mg, and full receptor saturation was observed throughout the 21 days at 700 mg. No antidrug antibodies were observed.

Conclusions: The enhancing effect on tumor direct-targeting antibodies observed preclinically, together with the favorable safety profile in patients, supports further investigation of BI-1607.

Introduction

Fcγ receptors (FcγR) are key regulators of the activity of IgG-type antibodies. Several activating (FcγRI, FcγRIIA, and FcγRIIIA) and a single inhibitory (FcγRIIB) receptors act in concert to regulate FcγR-expressing effector cell responses during therapy. Activating FcγR, like costimulatory T-cell checkpoints, promote immune effector cell activation. Conversely, FcγRIIB, the inhibitory receptor, blocks activation (1). Direct-targeting mAb such as trastuzumab, also termed cytotoxic mAb, bind to target cell-surface receptors and mark the cell for innate immune destruction. This mechanism is dependent on binding to FcγR via the constant Fc domain of the cytotoxic mAb, and the activating-to-inhibitory (A:I) FcγR engagement ratio determines the efficacy of the antibody-mediated target cell depletion (2). In mouse tumor models, genetic deletion of FcγRIIB enhanced *in vivo* therapeutic activity of cancer cell direct-targeting antibodies to CD20, HER2, and the melanoma antigen gp75 (3). Several mAb used in cancer therapy require functional activating FcγR for therapeutic activity, and conversely, the high expression of FcγRIIB reduces mAb efficacy (3). The approved mAb margetuximab (Margenza, MacroGenics) has a modified Fc region with enhanced binding to FcγRIIIA and moderately decreased binding to FcγRIIB, thereby increasing the antibody A:I ratio (4). This endows margetuximab with enhanced *in vitro* antibody-

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Translational Relevance

BI-1607 is a fully human anti-FcγRIIB antagonistic mAb with a modified Fc region that abrogates the binding of its Fc region to Fcγ receptors (FcγR). When administered in combination with a tumor-targeting antibody, BI-1607 will block the inhibitory impact of FcγRIIB, promoting the combination partner antibody's Fc-mediated binding to activating FcγR. This enhances the effector functions, for example, the antibody-dependent cellular phagocytosis of the combination antibody. Accordingly, BI-1607 mouse surrogate (mBI-1607) enhanced the therapeutic activity of tumor direct-targeting antibodies in murine syngeneic tumor models. The safe nature of this strategy to enhance clinically validated antibodies was demonstrated in this first-in-human study of BI-1607 combined with trastuzumab in patients with HER2-positive solid tumors. These results support the clinical investigation of additional BI-1607 combinations with established direct-targeting antibodies.

dependent cellular cytotoxicity (ADCC) and NK cell activation, *in vivo* antitumor activity (4), and may afford margetuximab survival advantage in patients with distinct FcγR polymorphisms (e.g., CD16-158FF; ref. 5). Similarly, the anti-EGFR antibody cetuximab is known to stimulate ADCC, and polymorphisms in *FCGR2A* and *FCGR3A* favoring activating engagement are associated with better clinical outcomes (6). The clinical importance of tumor-targeting antibodies with FcγR-dependent mechanisms of action is further illustrated by the approval of the claudin 18.2–specific antibody zolbetuximab for the treatment of HER2-negative metastatic gastric cancer (7).

To selectively target FcγRIIB immunosuppressive functions on effector cells present inside the tumor microenvironment, we generated an Fc:FcγR-muted anti-FcγRIIB antibody (BI-1607, 6G11 IgG1N297Q) based on a (8) highly FcγRIIB-specific antibody clone (**Fig. 1A** and **B**; ref. 4). An equally specific Fc-muted FcγRIIB-blocking mouse surrogate antibody [AT-130 $mIgG1_{N297A,}$ (mBI-1607)] was used for testing in immunocompetent tumor mouse models (9).

In this work, we demonstrate *in vivo* proof-of-concept that Fc-muted anti-FcγRIIB enhances the therapeutic efficacy and FcγR-dependent depleting activity of direct-targeting antibodies relevant to solid tumors. Furthermore, in this first-in-human (FIH) study, we demonstrate that BI-1607 can be safely administered and combined with trastuzumab (anti-HER2) at doses achieving sustained and complete FcγRIIB saturation. Given its mode of action, BI-1607 is not expected to have single-agent activity. The choice of trastuzumab as the combination agent in this trial was based on promising preclinical studies and a recognized need for additional options for patients who fail to respond or stop responding to trastuzumab. Ultimately, if shown to be safe and effective in combination with trastuzumab, BI-1607 can also be used in combination with other cytotoxic or immunomodulatory antibodies for cancer treatment.

Patients and Methods

In vitro characterization

The original clone directed against FcγRIIB was selected using the n-CoDeR single-chain variable fragment library (Lib 2000) and converted into an aglycosylated IgG1 antibody (containing the N297Q mutation) using in-house expression vectors. The resulting antibody was then expressed using the Lonza GS system. Chinese hamster ovary cells (CHOK1SV) were transfected with the pEE-JhG1N297Q-FCR241-006-G11-4 plasmid, and the clone L220 was chosen as the best cell line because of its growth characteristics, viability, and productivity during long-term cultivation.

In vitro binding of BI-1607 to FcγR proteins was tested in an ELISA. Briefly, recombinant human FcγRIIB/C, FcγRIIA, FcγRI, or FcγRIIIA, cynomolgus FcγRIIB, or mouse FcγRIIB was used for coating. Bound BI-1607 or BI-1206 was detected using anti-hIgG (H + L) horseradish peroxidase. A luminescence substrate was used for the readout.

In vitro ADCC assays were conducted. Briefly, ADCC assays were performed using an NK-92 cell line expressing hFcγRIIIA-158V. CLL cells, which naturally express FcγRIIB, from six different patients were used as target cells for BI-1607, BI-1206, and isotype control in the assay. Target cell lysis was analyzed by flow cytometry.

Preclinical *in vivo* studies

B-cell depletion

Assessment of target cell depletion *in vivo* for BI-1607 and BI-1206 was conducted in human FcγRIIB transgenic mice (hFcγRIIB ± x mFcγRII−/− C57BL/6 mice). Briefly, mice were injected intravenously with 10 mg/kg BI-1607 or BI-1206. Leukocyte analysis by flow cytometry was conducted before and 48 hours after receiving BI-1607 or BI-1206.

TUBO model

Female BalbC mice (RRID: IMSR_RJ:BALB-CJRJ) were injected subcutaneously with the HER2-expressing mouse breast cancer cell line TUBO (University of Bologna; 1×10^6 cells/mouse). Tumor growth was monitored (measured using a caliper), and when tumors reached approximately 7×7 mm, mice were randomized and treated intraperitoneally with either isotype control (mIgG2a 10 mg/kg), anti-HER2 (mIgG2a 1 or 10 mg/kg), mBI-1607 (mIgG1N297A 20 mg/kg; ref. 8), or a combination of mBI-1607 (20 mg/kg) and anti-HER2 (1 or 10 mg/kg). The mice were dosed three times (2–3 days apart), and mBI-1607 was always given 20 minutes ahead of the anti-HER2 mAb. Tumor growth was measured twice weekly until tumors reached a predetermined size (ethical endpoint), when the mice were euthanized.

In a separate experiment with the same treatment schedule, tumors were collected 1 day after the last treatment for analysis of tumor-immune infiltrates. Tumors were chopped into small pieces and enzymatically digested with a mixture of DNAse and Liberase at 37°C. Furthermore, the tumor solution was filtered through a cell strainer to obtain a single-cell solution. The cell solution was blocked with IVIG before staining. Immune cells were identified and quantified by FACS using the following markers: CD45, CD3, CD4, CD8, CD25, CD11b, Ly6C, Ly6G, MHCII, F4/80, CD49b, and NK 1.1 (all from BD Biosciences).

B16 model

Female C57/BL6 mice (RRID: IMSR_RJ:C57BL-6NRJ) were injected intravenously with the gp75-expressing mouse melanoma cell line B16F10 (RRID: CVCL_0159 5×10^4 cells/mouse). Four days after tumor injection, mice were randomized and treated intraperitoneally with either isotype control (mIgG2a 10 mg/kg), anti-gp75 (TA99 mIgG2a RRID: AB10949462 10 mg/kg), mBI-1607 (20 mg/kg),

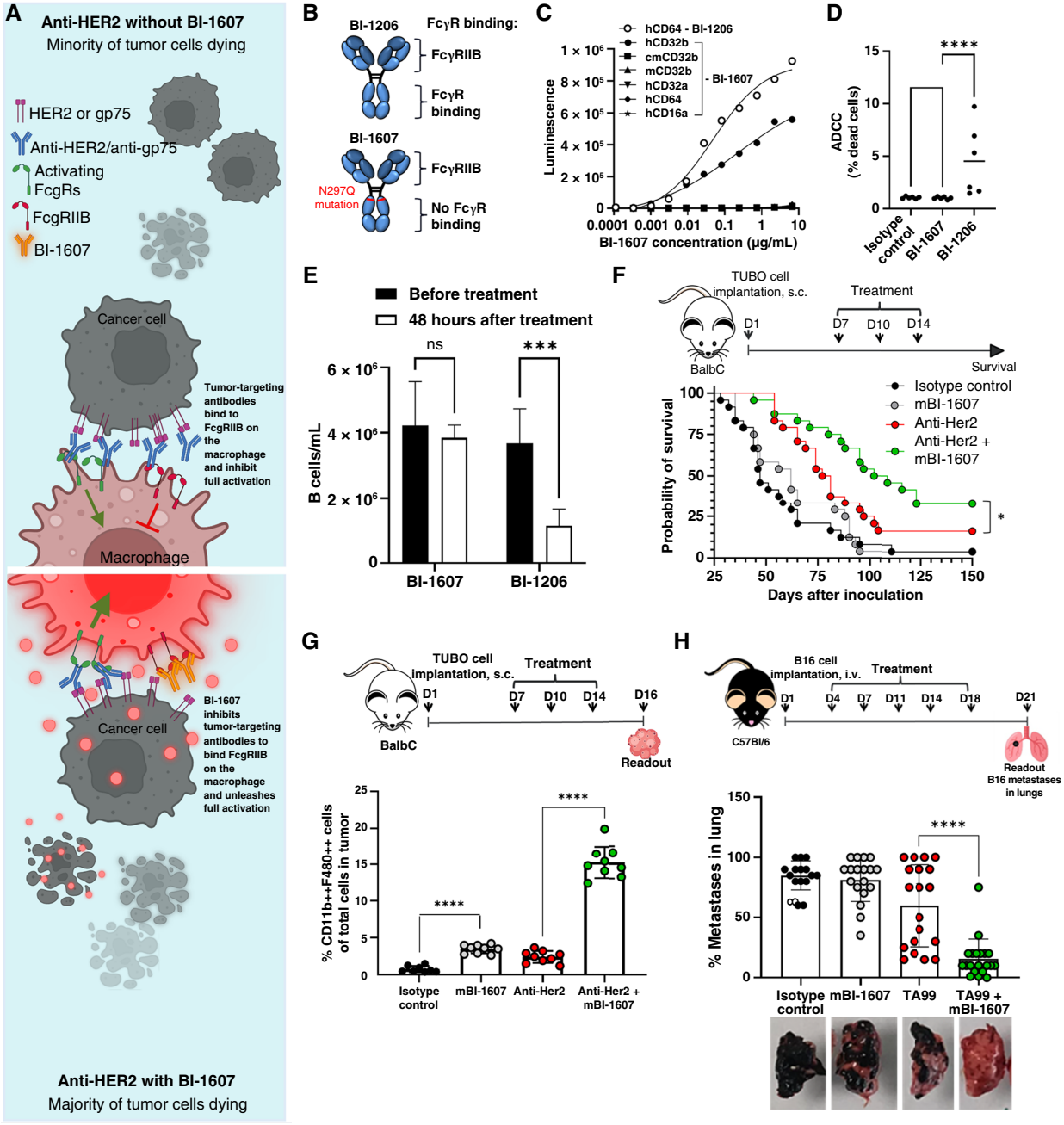

Figure 1.

A, Description of the mode of action of BI-1607 (anti-FcγRIIB$_{NA}$) in combination with tumor-targeting antibodies (anti-HER2/anti-gp75). By targeting the inhibitory FcγRIIB, BI-1607 will block the binding and inhibitory signaling through FcγRIIB of the tumor-targeting antibody. Instead, BI-1607 promotes the binding of the Fc domain of the tumor-targeting partner to activating FcγR, thereby enhancing effector functions of this antibody, such as antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis. **B,** BI-1607 is a fully human anti-FcγRIIB antagonistic mAb with a modified Fc region that abrogates the binding of its Fc region to FcγR. **C,** BI-1607 binding to human FcγRIIB, CD32a, CD64, and CD16a, cynomolgus FcγRIIB, and murine FcγRII. BI-1206 [the wild-type (WT) format of BI-1607 without mutation N297Q (thus has a functional Fc domain)] was used as a positive control binding to human CD64 via the Fc domain of the mAb. **D,** The cytotoxic ability of BI-1607 and BI-1206 in ADCC, using primary chronic lymphocytic leukemia (CLL) cells. Each dot represents one patient with CLL. ****, $P \leq 0.0001$ as assessed by paired Student *t* test. CLL, chronic lymphocytic leukemia. **E,** B-cell levels in hFcγRIIB transgenic mice before and 48 hours after treatment with BI-1607 or BI-1206. ***, $P \leq 0.001$. **F,** Anti-HER2 in combination with mBI-1607 demonstrated delayed tumor growth and increased survival compared with anti-HER2 treatment alone in the TUBO breast cancer model (two separate experiments, pooled log rank *, $P \leq 0.05$). **G,** Tumors analyzed for immune cell content by FACS showed that the combined treatment of anti-HER2 and mBI-1607 resulted in an increased CD11b++/F4/80++ population compared with single anti-HER2 treatment. **H,** In the B16F10 melanoma model, mBI-1607 improved the antitumor effect of the B16F10-specific TA99 antibody. This was demonstrated by significantly lower tumor burden in the lungs of mice treated with TA99 in combination with mBI-1607. (**A,** Created in BioRender. It, B. [2025] https://BioRender.com/xu3axf7.)

or a combination of TA99 (10 mg/kg) and mBI-1607 (20 mg/kg). The treatment was given five times, 2 to 3 days apart, and mBI-1607 was always given 20 minutes ahead of the anti-HER2 mAb. Three weeks after tumor injection, the mice were euthanized, and B16F10 metastasis formation in the lungs was quantified.

Clinical trial information

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and applicable local regulations. The protocol was approved by each Institutional Review Board or independent Ethics Committee before patient recruitment. Written informed consent was obtained for all patients before performing study-related procedures. This study was registered at clinicaltrials.gov (NCT05555251) and EU (2021-005646-15).

Study participants

Eligible participants were ages ≥18 years and had HER2-positive (10) locally advanced, unresectable, or metastatic solid tumors with disease progression after standard anticancer treatment, including prior lines of trastuzumab and at least one line of trastuzumab antibody–drug conjugate [e.g., trastuzumab emtansine (Creative Biolabs, cat. No. TAB-H70, RRID: AB_3112043) or trastuzumab deruxtecan]. According to the protocol, HER2-positive tumor status [according to 2018 ASCO/CAP JER2 test guidelines (10)] could have been from the most recent archival tissue sample or new tissue material from a recently obtained surgical or diagnostic biopsy. In addition, to be eligible, subjects had to have at least one measurable disease lesion as defined by RECIST version 1.1 criteria, left ventricular ejection fraction ≥50%, a life expectancy of ≥12 weeks, an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function as confirmed by laboratory values. Key exclusion criteria included the following: the need of high doses of prednisolone (>10 mg daily, or other equipotent corticosteroids); active central nervous system metastases and/or carcinomatous meningitis; known or suspected hypersensitivity or contraindications to trastuzumab; or an active, known, or suspected autoimmune disease. The complete list of inclusion and exclusion criteria is available as supplementary material (SM1).

No anticancer therapy was permitted within 2 weeks before initiation of BI-1607. Prior treatment with immunotherapy or biological therapy was not permitted within 4 weeks or five half-lives of the respective drug before the first dose of BI-1607.

Study design and treatment

This was a FIH, phase I, open-label, multicenter, dose-escalation study to evaluate BI-1607 treatment in combination with trastuzumab. The primary objective of this study was to evaluate the safety and tolerability profile of BI-1607 when administered intravenously every 3 weeks in combination with trastuzumab in patients with HER2-positive locally advanced unresectable or metastatic solid tumors to characterize the dose-limiting toxicities (DLT), determine the maximum tolerated dose or maximum administered dose, and determine the recommended phase 2 dose for subsequent studies. Secondary objectives included pharmacokinetic (PK) parameters, immunogenic potential, receptor occupancy (RO) of BI-1607 on B cells, and preliminary assessment of the antitumor activity of BI-1607 in combination with trastuzumab. Exploratory objectives included assessment of the expression level of immunologic and predictive biomarkers and exploring the potential correlation of genetic FcγR isoforms with clinical responses.

Dose escalation of BI-1607 was according to the mTPI-2, a Bayesian design based on the modified toxicity probability interval to allow for a more efficient estimation of the maximum tolerated dose and reduce the risk of overdosing (11). The starting dose of 75 mg was based on an aggregate of preclinical PK and pharmacodynamic (PK/PD) data from *in vitro* studies and *in vivo* data combined with a full preclinical toxicology package. Following minimal anticipated biological effect level principles (12), a starting dose targeting a 50% RO 24 hours after administration was selected. The selected dose of 75 mg (1 mg/kg in 75 kg subject) provides a 250-fold safety margin compared with the well-tolerated dose of 250 mg/kg in mice established in a Good Laboratory Practice (GLP) toxicologic study. Given the mode of action for BI-1607 and the preclinical safety package, there was no prior concern for cytokine release syndrome or other severe infusion-related reactions (IRR), and the planned dose-escalation steps were guided by a desire to reach therapeutic concentrations without unnecessarily underdosing patients. Nonetheless, to minimize the incidence and severity of potential IRR, BI-1607 was administered as a slow intravenous infusion starting at a rate of 30 mg/hour and sequentially increasing the infusion rate.

Trastuzumab was also administered every 3 weeks at an 8 mg/kg dose for cycle 1 and 6 mg/kg for cycle 2 onward, 1 day after BI-1607 administration.

Safety and tumor assessment

All patients who received at least one dose of BI-1607 were included in the safety analysis. Safety assessments included physical exams, vital signs, hematology, blood chemistry, urinalysis, and ECG. Adverse events (AE), graded for severity according to the NCI Common Terminology Criteria for AE version 5.0, were documented until 30 days after the last dose of study treatment. Occurrence of DLT was assessed by the investigator as related to BI-1607 and occurring during the DLT assessment window (days 1–21 of cycle 1) and following the approved clinical study protocol criteria.

Tumors were assessed by CT/PET or MRI scan at screening, weeks 6, 12, 18, and 27, and every 12 weeks thereafter or as clinically indicated, for up to 2 years from the first dose of BI-1607. Treatment was continued until disease progression or unacceptable toxicity. Disease status was assessed by the investigator using RECIST version 1.1 (13). For response assessment, all patients who received at least one dose of BI-1607 and trastuzumab and had at least one evaluable postbaseline disease assessment (i.e., at least one valid postdose assessment collected at least 42 days after the initial dose) were included.

PK, PD, and immunogenicity assessments

Blood samples for serum BI-1607 concentration were collected from all participants treated with BI-1607/trastuzumab at predetermined time points at baseline, during and after infusion, and with a dense sampling after cycles 1 and 4. A validated ELISA with a lower limit of quantification of 150 ng/mL was used to determine the serum concentrations of BI-1607 in participants. Immunogenicity assessments were made for the presence/absence of antidrug antibodies to BI-1607 using pre- and posttreatment samples of infusion cycles 1 to 4 and cycles 6, 8, 12, and 16. Cytokine and chemokine levels were assayed in plasma collected in cycle 1 (predose, end of infusion, and 4 and 24 hours after infusion) using Meso Scale Discovery catalog kits K15049 and K15067. FcγRIIB RO was evaluated on $CD19^+$ B cells in whole blood collected in the same

manner as serum for PK assessment in cycles 1 to 4 and assessed by flow cytometry. Around 80% RO in this assay was reported as full saturation due to the limits of this analysis.

Paired fresh tumor biopsy specimens were collected in a subset of patients and assayed using whole-transcriptome analysis. A blood sample for DNA evaluation of FcγR isoforms was collected from participants predosed in cycle 1. The polymorphisms *FCGR2A*-H131R, *FCGR2B*-I232T, *FCGR2C*, and *FCGR3A*-V158F were assessed using allele-specific PCR methods.

PK, immunogenicity, and biomarker analyses were conducted using analytically validated methodologies and sponsor-defined protocols for sample handling and processing in central laboratories. All patients from the safety population were included in the analyses if at least one postdose measurement was available in addition to baseline.

Statistical analyses

PK and RO assessments were analyzed using nonlinear mixed effects modeling in NONMEM 7.5. (RRID: SCR_016986; ref. 14) to characterize both, the typical time course tendency together with its associated variability. For the analysis, PK measurements were logarithmically transformed, and different error models were considered for each type of measurement. Measurements below the limit of quantification were included and treated as censored information using the M3 method (15). Interindividual variability was modeled exponentially, except for bounded parameters in which additive models in the logit domain were used. Nondiagonal elements of the variance–covariance matrix were tested for significance. Model selection and model evaluation were performed according to state-of-the-art methods, including objective function value, parameter precision, goodness of fit, and simulation-based techniques (16). The results were visualized in R version 4.3.3 (RRID: SCR_001905) through RStudio graphical interface version 2023.12.1 (RRID: SCR_000432).

As trastuzumab-containing therapies may carry a risk for QT prolongation, the potential for cardiac effects of BI-1607 was explored through exposure–safety analysis for heart rate and Fridericia-corrected QT time. A linear mixed effects model approach was applied to explore a potential positive correlation between time-matched PK samples and ECG (17).

Results

Preclinical data

The binding specificity, FcγRIB-blocking, and function-modulating effects of the clinical BI-1607 candidate (aka 6G11-N297Q) have been previously described in detail (8). In this study, BI-1607's highly specific binding to selected human, murine, and cynomolgus FcγR proteins was verified by ELISA (**Fig. 1C**). BI-1607 bound with high affinity to human FcγRIIB and showed no binding to other FcγR proteins, indicating that BI-1607 is specific for human FcγRIIB and does not cross-react with closely related proteins. The lack of binding of BI-1607 to the FcγRIA receptor, which binds with high affinity to IgG, confirmed the FcγR binding–impairing effect of the single mutation (N297Q) in BI-1607's Fc domain. In contrast, BI-1206, a mAb identical to BI-1607 in the variable Fab domain but with a WT Fc domain, binds with expected affinity to FcγRIA. Consistent with BI-1607's Fc domain having been engineered for impaired FcγR binding, functional assessment of BI-1607 indicated no *in vitro* ADCC or *in vivo* B-cell–depleting activity (**Fig. 1D** and **E**).

When preclinically evaluating BI-1607 efficacy, the murine surrogate antibody (mBI-1607) improved the therapeutic effect of two tumor-targeting antibodies in relevant tumor antigen-expressing mouse models. The therapeutic effect of anti-HER2 in combination with mBI-1607 was compared with that of an isotype control antibody and with anti-HER2 as a single treatment in the TUBO breast cancer model. Combination with mBI-1607 delayed tumor growth and increased survival compared with anti-HER2 single-agent treatment (**Fig. 1F**; Supplementary Fig. S1). Tumor single-cell suspensions analyzed for immune cell content by FACS showed that the combined treatment of anti-HER2 and mBI-1607 resulted in increased $CD11b^{++}$ $F4/80^{++}$ cells compared with single-agent anti-HER2 treatment (**Fig. 1G**). In addition, an increase in infiltration of monocytes, NK cells, and B cells was seen in this group (Supplementary Fig. S2). In the B16F10 melanoma model, mBI-1607 improved the antitumor effect of the B16F10-specific TA99 antibody. This was shown by significantly lower tumor burden in the lungs of mice treated with TA99 in combination with mBI-1607 compared with isotype control or to TA99 single-agent treatments (**Fig. 1H**).

Patient characteristics and disposition

A total of 18 participants were included in the dose-escalation cohorts (75, 225, 500, 900, and 700 mg every 3 weeks) with a median age of 63 years (range, 46–77), and four (22%) were male (**Table 1**). The most common tumor types included breast tumors (44%), followed by gastro-gastroesophageal (33%). The extent and nature of prior cancer therapy varied, but all patients had previously received trastuzumab therapy. An overview of patient representation can be found in Supplementary Table S1.

Dose escalation and safety

Dose escalation proceeded stepwise until the top dose was reached. One patient at the 900-mg BI-1607 dose experienced a DLT leading to treatment discontinuation (rash, grade 3). A 700 mg every 3 weeks dose level was included in the protocol as an additional escalation dose. As this dose level was well tolerated, 700 mg per 3 weeks was determined as the higher end of the recommended dose range for further exploration in subsequent phase 2 studies.

Of the 18 subjects in the safety population, 17 (94.4%) experienced at least one treatment-related AE (TEAE) with no dose-dependent trends observed (**Table 2**). The full list of TEAE by system organ class stratified by dose level is provided in Supplementary Table S2. Nonetheless, most subjects experienced TEAE with a maximum grade of grade 1 (five subjects; 27.8%) or grade 2 (seven subjects; 38.9%). Grade ≥3 TEAE occurred in five patients (28%), with only three treatment-emergent serious AE, all unrelated to the study drugs, being reported in a total of two patients, namely cholangitis, acute kidney injury, and aggravated condition.

Premedication for IRR was allowed; however, it was recommended only if medically indicated. IRR were reported in eight subjects (44%), including erythema, infusion site pruritus, infusion site urticaria, rash, rash macular, rash maculopapular, and urticaria, and all were related to the study drugs. IRR were managed with intravenous corticosteroids and reduction of the infusion rate, which allowed drug administration to be resumed in all patients except for a patient with grade 3 urticaria, which was described as a DLT.

However, only two grade 3 IRR were recorded in two patients in the 900-mg cohort. Concentration–QT analysis revealed no

Table 1. Patient demographics and tumor response.

Cohort	Age/sex	Disease/year of diagnosis	No. prior treatments	Prior trastuzumab treatment	Prior TDX treatment	Last treatment prior to study	Duration on study in cycles	Best response on the study
Cohort 1	57/F	Breast/2002	21	16	1	TRAS + TUCA	2	PD
(75 mg)	53/F	Breast/2018	6	3	2	TDX	2	NE (PD)[a]
	63/F	Uterus/2018	6	1	—	BEV	2	NE (PD)[a]
Cohort 2	72/F	Breast/2011	10	5	1	TDX	2	PD
(225 mg)	70/F	Uterus/2020	3	2	—	TRAS + DUO	2	NE (PD)[a]
	65/F	Breast/2011	4	2	1	TDX	6	SD
Cohort 3	53/F	Breast/2007	7	3	1	TDX + ZO + LET	7	SD
(500 mg)	55/M	Paget's disease extramammary/2021	2	1	—	TRAS + PAC	2	NE (PD)[a]
	62/M	Esophagus/2023	2	1	—	DOC + FLU + FOL + OXA	1	NA
Cohort 4	46/F[b]	Breast/2016	3	2	1	TDX	1	NA
(900 mg)	77/F	GEJ/2020	4	1	1	TDX	3	SD
	48/F	Breast/2013	11	7	1	TRAS + DOC	9	SD
Cohort 5	69/M	Stomach/2018	3	2	—	RAM + PAC	2	NE (PD)[a]
(700 mg)	63/F	Breast/2015	5	2	—	TDM-1 + FUL	4	SD
	64/F	Stomach/2021	2	1	—	RAM + PAC	1	NA
	62/F	Colorectal/2017	6	1	—	IRI	4	SD
	72/M	Gastroesophageal adenocarcinoma/2017	5	4	—	TRAS	4	SD
	71/F	Stomach 2019	3	1	1	Clinical trial ADC	2	NE (PD)[a]

Abbreviations: ADC, antibody–drug conjugate; BEV, bevacizumab; DOX, docetaxel; DUO, duocarmazine; FLU, fluorouracil; FO, folinic acid; FUL, fulvestrant; GEJ, gastroesophageal junction; IRI, irinotecan; LET, letrozol; NA, not available; NE, not evaluable; OXA, oxaliplatin; PAC, paclitaxel; PD, progressive disease; RAM, ramucirumab; SD, stable disease; TDM-1, trastuzumab emtansine; TDX, trastuzumab deruxtecan; TRAS, trastuzumab; TUCA, tucatinib; ZO, Zometa.
[a]Patient did not meet the criteria for response evaluation because of progressive disease prior to the 42 days landmark.
[b]Patient received 380-mg dose.

statistically significant positive correlation between time-matched PK measurements and heart rate or Fridericia-corrected QT time captured from triplicate ECG (**Fig. 2**).

No significant depletion of CD19+ B cells was observed in the clinical study, as expected given that BI-1607 was engineered for impaired FcγR binding (Supplementary Fig. S3).

Antitumor activity

Of the 18 treated patients, nine met the criteria for response evaluation (see the methods section). Tumor progression in target lesions was observed in two patients, both from the low-dose cohort groups (**Fig. 3**). Although none achieved an objective response, seven patients (78%) exhibited stable disease, with the longest duration of 6 months.

Table 2. TEAE in all treated patients ($n = 18$).

	BI-1607					
	Dose cohort					
Category	75 mg	225 mg	500 mg	900 mg	700 mg	Total
Number of subjects	3	3	3	3	6	18
Subjects with at least one TEAE of any grade	3 (100%)	3 (100%)	3 (100%)	3 (100%)	5 (83%)	17 (94%)
Subjects with ≥grade 3 TEAE	0	0	1 (33%)	2 (66%)	2 (33%)	5 (28%)
Subjects with TEAE related to BI-1607	2 (66%)	2 (66%)	3 (100%)	3 (100%)	3 (50%)	13 (72%)
Subjects with TEAE related to trastuzumab	2 (66%)	3 (100%)	3(100%)	0	2 (33%)	10 (56%)
Subjects with ≥grade 3 TEAE related to study BI-1607	0	0	0	2 (66%)	1 (17%)	3 (17%)
Subjects with ≥grade 3 TEAE related to trastuzumab	0	0	0	0	1 (17%)	1 (6%)
Subjects with serious TEAE related to study treatment	0	0	0	0	0	0
Subjects with treatment-related AE that led to discontinuation	0	0	0	1 (33%)	0	1 (6%)
TEAE of interest related to BI-1607 in combination with trastuzumab						
Subjects with any-grade IRR	1 (33%)	2 (66%)	1 (33%)	3 (100%)	1 (17%)	8 (44%)
Subjects with ≥grade 3 IRR	0	0	0	2 (66%)	0	2 (11%)
Subjects with ≥grade 3 increased ALT/AST	0	0	0	0	1 (33%)	1 (6%)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase.

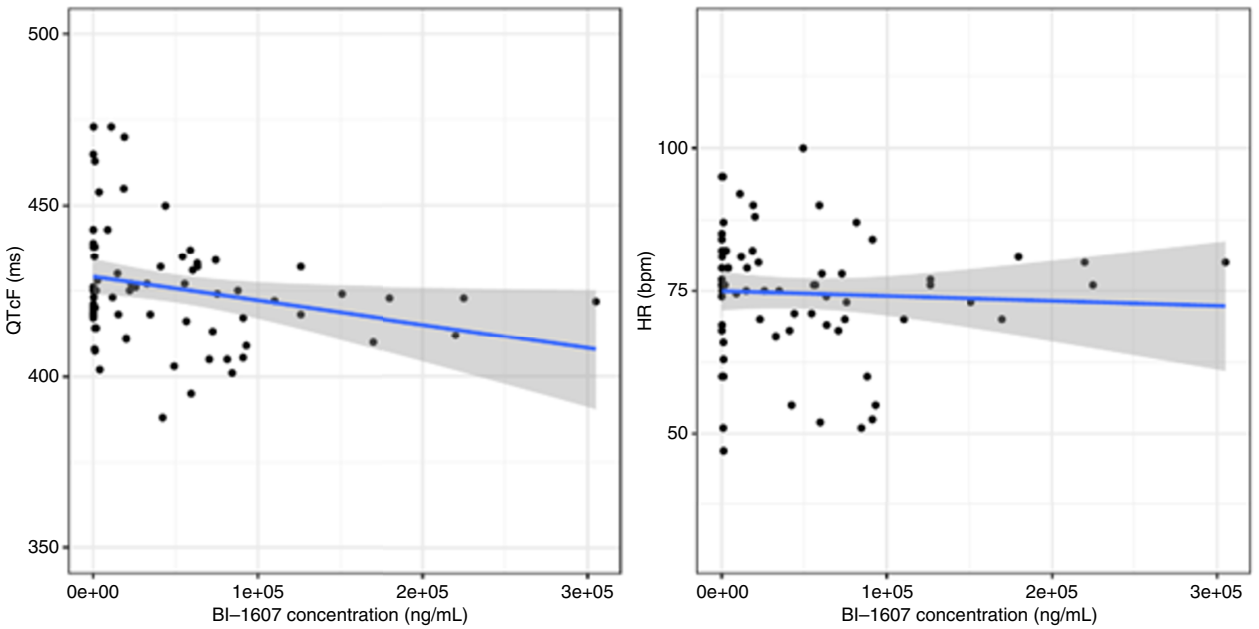

Figure 2.

Fridericia-corrected QT time (QTcF) and heart rate vs. BI-1607 serum concentration. The black dots show individual data points, the blue line depicts the linear mixed-effects model fit, and the gray shaded area represents the model's 95% confidence interval.

Of the remaining nine patients, three dropped out of the study before response assessments, and six exhibited progressive disease, although before the 42-day landmark, and thus could not be included in the response population but are reported here for completeness.

PK and RO

PK and FcγRIIB RO levels from 18 patients were available for model building. A clear nonlinear increase in serum BI-1607 levels was observed with dose, as well as a dose-dependent increase in RO, reaching a maximum that was sustained during the whole dosing interval at doses of 700 mg and higher (**Fig. 4**).

A two-compartment model with Michaelis–Menten elimination provided an adequate description of the nonlinear PK behavior, with reasonable parameter estimates and precision (Supplementary Fig. S4). Accounting for additional complexities, such as target-mediated disposition, did not improve model performance ($P > 0.05$). A value of 6,100 ng/mL was estimated for K_M (concentration at which 50% of the maximum elimination rate is attained). This concentration is reached already at the lowest dose level of 75 mg, suggesting linear PK at clinically relevant doses.

Regarding FcγRIIB RO, data were well described with a direct saturable model driven by serum BI-1607 concentrations, reporting maximum RO of 80.8% and a low value of C_{50} (concentration at which 50% of maximum RO is attained) of 637 ng/mL. Variability was only supported by the linear clearance term, the volume of the central compartment, and the maximum RO. Given the low number of patients and their heterogeneity, no meaningful covariates were identified.

Immunogenicity and biomarkers

Across all evaluable patients, no signs of immunogenicity were observed, and no treatment-emergent or treatment-induced anti-drug antibodies against BI-1607 were detected.

Cytokines were analyzed in the peripheral blood of a subset of patients up to 24 hours after infusion, and no analytes were affected by BI-1607/trastuzumab infusion. Cytokines analyzed included IFNγ, IL10, IL6, IL8, MIP-1β, TNFα, IL1β, IL23, IL12p70, IL2, IL4, TARC, and VEGF. The absence of cytokines has previously been confirmed in several *in vitro* assays of BI-1607 and peripheral blood mononuclear cells (Supplementary Figs. S5–S8).

The effect of *FCGR2A*, *FCGR2B*, *FCGR2C*, and *FCGR3A* polymorphisms on clinical response to BI-1607/trastuzumab treatment was analyzed. No association was found between polymorphisms and response to treatment, but given the low number of patients, the results are at this time inconclusive.

Discussion

The efficacy of tumor-targeting and immunomodulatory mAb is determined by the interaction of their Fc domain with Fc receptors that can be either activating (i.e., FcγRI, FcγRIIA, or FcγRIIIA) or inhibitory (FcγRIIB; refs. 18, 19). Accordingly, Fc-engineering to enhance binding to activating FcγR is a validated approach to increase tumor-targeting antibody activity, e.g., anti-CD20 (20). Here, we report the first human data on an alternative strategy, namely blocking the single inhibitory FcγRIIB to enhance therapeutic antibody efficacy (8, 18). More specifically, we demonstrate that BI-1607, a first-in-class Fc-inactivated mAb to human FcγRIIB, is well tolerated across doses ranging from 75 up to 900 mg every 3 weeks, and adequate exposure is associated with complete and sustained FcγRIIB cell-surface receptor saturation.

This approach has several potential advantages to Fc-engineering for enhanced binding to activating FcγR. First, regarding efficacy, the inhibitory FcγRIIB is strongly upregulated on tumor and effector cells in resistant niches, for example, in the bone marrow of

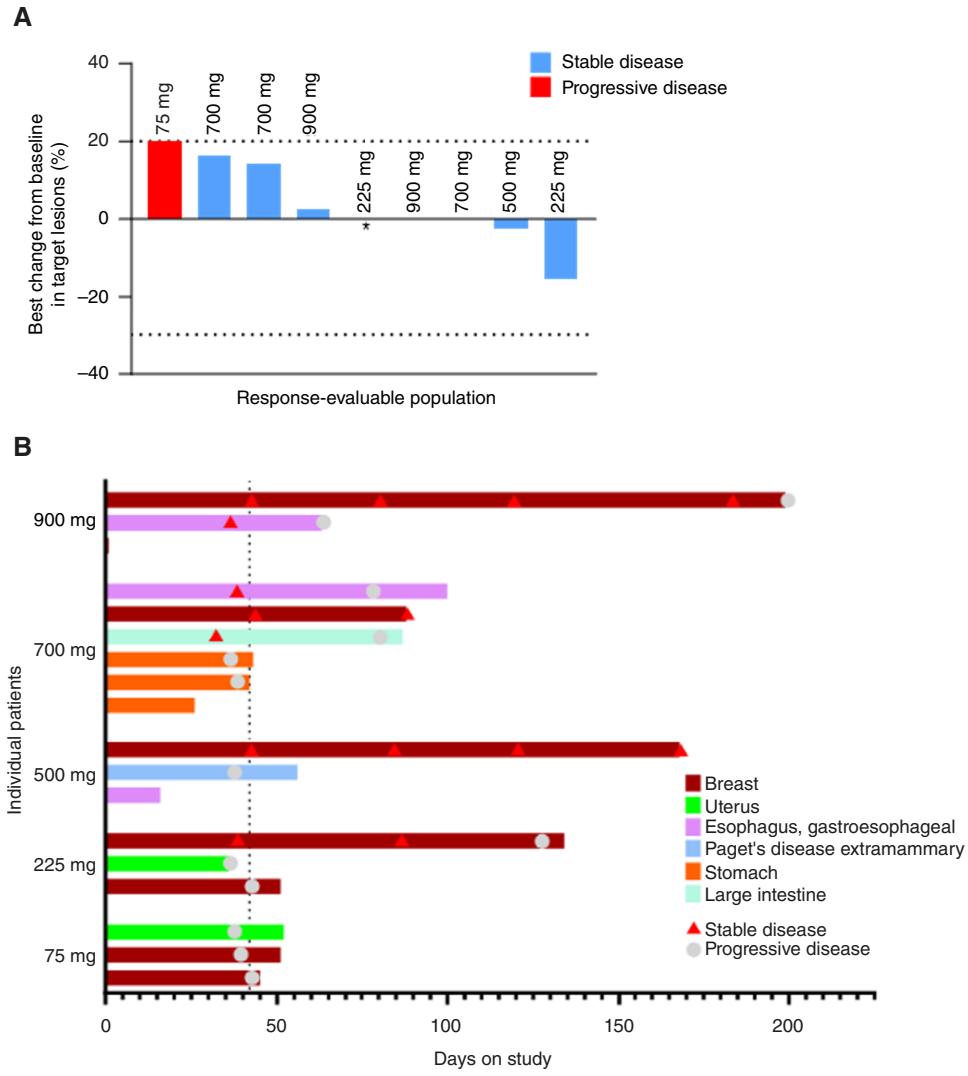

Figure 3.

Tumor response. **A,** Waterfall plot of the best overall responses in the evaluable patient population with respect to tumor size. Patients with at least one valid postdose assessment (CT/PET or MRI scan) at day 42 or later were included in the evaluable patient population ($n = 9$). * indicates the patient with the best overall response progressive disease despite no increase in target lesion. **B,** Swimmer plot of time to tumor responses in all treated patients ($n = 18$). The dotted line in the swimmer plot is day 42 after initial treatment.

patients with leukemia (21) and the solid cancer tumor microenvironment (22), promoting resistance to antibody therapy (22–24). The activating FcγR, in contrast, are heterogeneously expressed by different cell types and may be downregulated in tumors (22). Targeting FcγRIIB has the potential to enhance effector cell activation and cytotoxic efficacy regardless of which activating FcγR (i.e., FcγRI, FcγRIIA, or FcγRIIIA) are expressed in a particular patient or a patient's tumor (2).

Second, regarding tumor selectivity and tolerability, FcγRIIB is expressed only on ~ 5% of circulating monocytes, not NK cells or granulocytes (8). This is in sharp contrast with the expression of activating FcγR including FcγRIIIA, targeted by most antibody engineering approaches (e.g., by afucosylation or amino acid substitution), which are abundantly expressed on proinflammatory immune effector cells in the blood (22). As the engagement of activating FcγR on blood effector cells is associated with decreased tolerability and occurrence of IRR (25), specific targeting of FcγRIIB should provide both a safer and more efficacious approach to enhance the activity of the combining agent.

In this regard, this approach could potentially be extended to other tumor-targeting mAb with activity dependent on antibody-dependent cellular phagocytosis. FcγRIIB blockade could provide a means to enhance multiple validated tumor-targeting and immune-modulatory antibodies with FcγR-dependent mechanisms of action. In preclinical experiments, using BI-1607's murine surrogate antibody and immune-competent mouse tumor models, we demonstrate *in vivo* proof-of-concept that FcγRIIB blockade enhances tumor-targeting antibodies relevant to breast cancer and metastatic melanoma, indicating a broad therapeutic potential. Our preclinical data demonstrated that FcγRIIB blockade, although not exhibiting antitumor efficacy of its own, does enhance anti-HER2 efficacy. Interestingly, our preclinical data showed that combined FcγRIIB blockade with subtherapeutic "low" anti-HER2 doses, which targeted only a fraction of tumor-expressed HER2 receptors, also resulted in increased animal survival. This suggests that anti-FcγRIIB may be a means to enhance the efficacy of tumor-targeting antibodies and extend it to lower antigen–expressing cancers, such as low HER2–expressing tumors. Our ongoing efforts aim to evaluate this potential.

Whereas the introduction of trastuzumab has dramatically changed outcomes in patients with HER2-positive cancer, primary

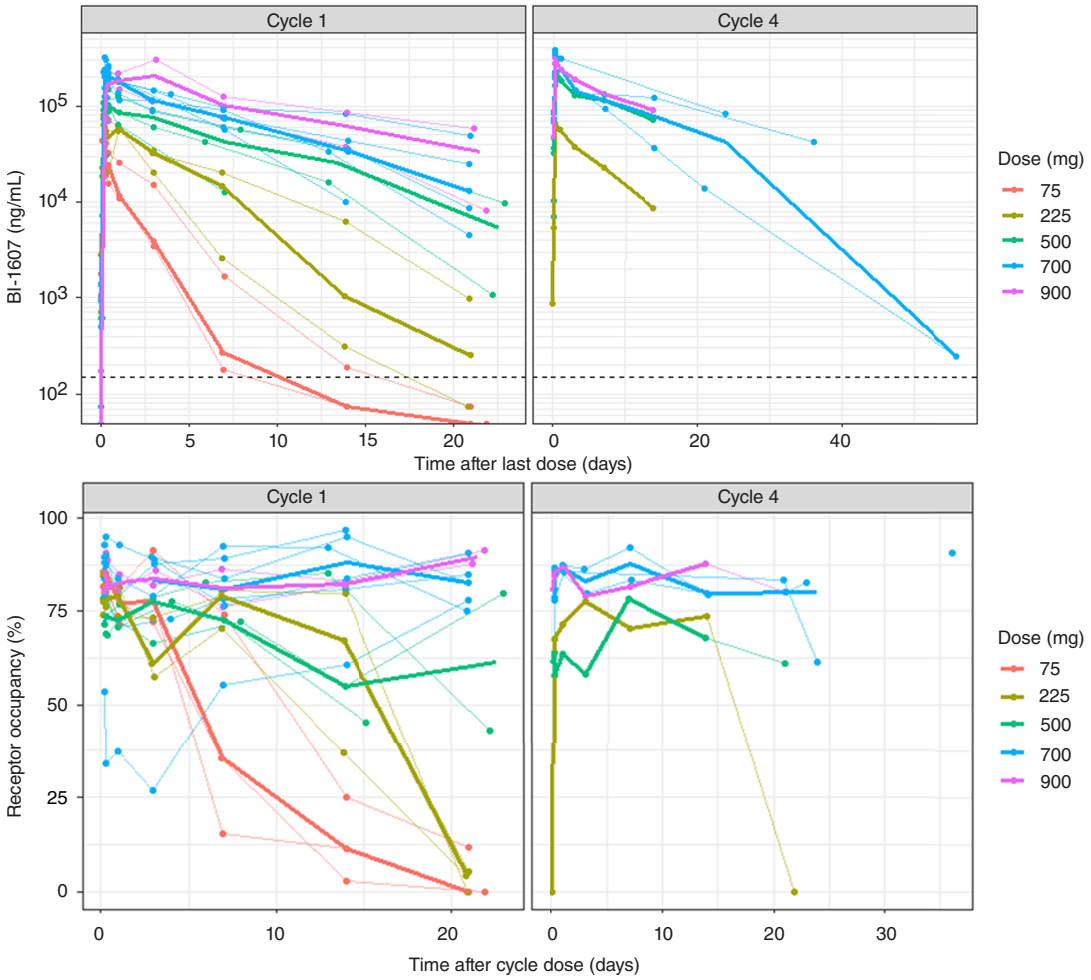

Figure 4.

Time course of serum BI-1607 concentrations and CD32 RO. Colored lines represent the median of the raw data at each dose level and cycle. The dashed solid line in the top represents the lower limit of quantification (LLOQ). Note, first data below the LLOQ are set to LLOQ/2, and the rest are set to 0.

or acquired resistance to trastuzumab has been recognized as a significant obstacle in the clinical management of this disease. Combining anti-HER2 antibodies with other immunotherapies will likely improve the quantity and quality of responses. Our findings from this FIH study demonstrate that BI-1607 exhibits a desirable PK behavior and is well-tolerated by human patients with cancer at doses associated with complete and sustained FcγRIIB saturation (500 mg and above), supporting that FcγRIIB blockade is an attractive strategy to enhance treatment efficacy. Most of the AE observed were mild or moderate (Common Terminology Criteria for AE grade 1 or 2). IRR occurred only during cycle 1; one subject who experienced grade 3 urticaria (DLT) was withdrawn from further study treatment. All other subjects who experienced an IRR continued with the study, and IRR were not observed in subsequent cycles. In most cases, dexamethasone was added as premedication following the occurrence of an IRR. Three subjects (17%) had serious AE reported; all were unrelated to the study treatment. Four deaths were reported due to disease progression, condition aggravation, and acute kidney injury, all unrelated to the study treatment. Trastuzumab treatment is associated with cardiotoxicity, primarily related to inhibiting HER2-mediated cardioprotective effects in cardiomyocytes, but may also involve recruitment of inflammatory cells (26). The fact that no enhancement of trastuzumab toxicity was observed in BI-1607–treated patients demonstrates the safe nature of sustained FcγRIIB blockade and is consistent with the notion that BI-1607 selectively enhances FcγR-dependent antibody functions in body compartments in which FcγRIIB is upregulated (e.g., in tumor tissue). These observations further identify FcγRIIB blockade as an attractive approach to enhance the efficacy of clinically validated mAb in a tumor-selective manner (27).

Our choice to study BI-1607 in combination with trastuzumab relates to its potential use in many other solid tumors. Previously, margetuximab, which has been Fc-engineered for a higher A:I ratio but which retains FcγRIIB binding (4), was approved in combination with chemotherapy for the treatment of patients with metastatic breast cancer who had received at least two anti-HER2 regimens. Our preclinical findings with mBI-1607 demonstrated enhanced therapeutic activity of the well-characterized anti-HER2 (28) antibody 16.7.4 in the high A:I mIgG2a isotype format, supporting the notion that BI-1607 can enhance not only WT IgG Fc

antibodies, such as trastuzumab and zanidatamab, but also Fc-engineered antibodies like margetuximab. In early lines of therapy, such BI-1607–enhanced therapies could provide attractive treatment alternatives to antibody–drug conjugates, with a favorable safety profile. Finally, antibodies often used for the treatment of hematologic malignancies, such as rituximab or obinutuzumab, could also benefit from FcγRIIB blockade. This hypothesis is currently being tested in the ongoing clinical study (NCT03571568) in which BI-1206, a fully competent IgG1 mAb directed against FcγRIIB, is being combined with rituximab for the treatment of non–Hodgkin lymphoma.

Concentration–QT analysis showed no contribution to QT time caused by BI-1607. Population PK/PD analysis was performed to quantitatively describe the observed nonlinear PK, common in mAb due to the target-mediated disposition (29). Interestingly, the estimated K_M value was one order of magnitude higher than the concentration at which 50% of the maximum RO is attained. This result suggests that the circulating B cells might not be the main driver of drug nonlinear clearance from the system. Instead, other FcγRIIB-expressing cells, such as liver Kupffer and sinusoidal endothelial cells, might be involved and act as a sink (30, 31). In any case, linearity is observed in well-tolerated and therapeutically relevant doses above 500 mg. Regarding RO, a direct and saturable relationship driven by plasma BI-1607 levels was identified, with an estimated C_{50} in line with preliminary *ex vivo* studies (Supplementary Fig. S9). Given this direct relationship and the low C_{50} value (637 ng/mL), maximum RO is practically attained instantaneously after intravenous infusion for all doses explored. Thus, sequential administration of the drugs, with BI-1607 given first, is sufficient; earlier administration of BI-1607 is unnecessary. More importantly, a sustained and almost complete (>90%) receptor saturation can be attained over 14 days at doses of 500 mg and above or even over 21 days at doses of 700 mg and above.

Although no objective responses were observed in enrolled patients and given the recent change in the treatment paradigm of HER2-positive breast cancer, the dose-expansion phase was not initiated. However, several patients in this heavily pretreated population exhibited disease control for an extended period. Two patients with breast cancer receiving 500- or 900-mg doses and who had previously received seven and 11 prior lines of treatment—that included trastuzumab (three and seven treatment lines, respectively), TDM-1 (one and two treatment lines, respectively), and trastuzumab deruxtecan (one treatment line each)—had stable disease for over seven and nine cycles, respectively (or 5 and 6 months, respectively). We should, however, acknowledge certain study limitations, including the small sample size, the use of archival tissue samples to confirm HER2-positive status in the absence of performed biopsies at screening in nearly all patients, and the limited number of participants with any one tumor type.

In conclusion, data presented in this FIH study demonstrate that FcγRIIB blockade can be safely achieved and combined with an FcγR-engaging therapeutic antibody, both administered at therapeutically relevant doses. Moreover, our supporting preclinical data demonstrate that FcγRIIB blockade can enhance the efficacy of antibodies relevant to different cancers and extend their use to additional cancer types and patients with cancer. As such, FcγRIIB blockade is a potentially safe and well-tolerated strategy that could bring the clinical benefit of validated antibody drugs to more cancer types and patients, though further studies are required.

Data Availability

Data can be made available upon reasonable request to the corresponding author. Due to patient privacy concerns, they are not publicly available.

Authors' Disclosures

J. Cortés reports grants and personal fees from Eisai, Pfizer, Roche, and AstraZeneca; personal fees from Seattle Genetics, Daiichi Sankyo, Lilly, MSD, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, HiberCell, BioInvent, GEMoaB, Gilead, Menarini, Zymeworks, Reveal Genomics, Scorpion Therapeutics, ExpreS2ion Biotechnologies, Jazz Pharmaceuticals, AbbVie, BridgeBio, BioNTech, Biocon, Circle Pharma, Delcath Systems, Hexagon Bio, Bliss Biopharmaceuticals, Novartis, Steamline Therapeutics, and Zuellig Pharma; grants from Ariad Pharmaceuticals, Baxalta GMBH, Bayer Healthcare, Guardant Health, ProQR Therapeutics, IQVIA, and Queen Mary University Of London; other support from MAJ3 Capital and Leuko outside the submitted work; and a patent for pharmaceutical combinations of a PI3K inhibitor and a microtubule destabilizing agent. J. Cortés also has a patent for Pharmaceutical combinations of a PI3K inhibitor and a microtubule destabilizing agent (Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A), issued and a patent for HER2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy (Aleix Prat, Antonio Llombart, Javier Cortés, US 2019/0338368 A1), licensed. E. Garralda reports grants from Novartis, Roche, Thermo Fisher Scientific, AstraZeneca, Taiho, BeiGene, Janssen, and ANAVEON; personal fees from Roche, Ellipses Pharma, Boehringer Ingelheim, Janssen Global Services, Seattle Genetics, Skypta, Sotio, Sanofi, ANAVEON, AbbVie, Astex Therapeutics, Alentis Therapeutics, Marengo Therapeutics, Hengrui, Incyte, Medpace, Pfizer, Amgen, GenMab, GreyWolf, Gilead, Daiichi Sankyo, MSD, Roche, Novartis, Seagen, PPD Global, Aran, The Ricky Rubio Foundation, ESMO, Fundación SEOM, CDDF, Springer Nature, Karger Publishers, Doctaforum, Tactics, AEFI, Fundación ECO, MeetingPharma, AstraZeneca, Medscape, Alcura, Horizon CME, and European School of Oncology; and other support from NEXT Oncology (IOB) outside the submitted work. S.R. Lord reports other support from BioInvent during the conduct of the study. S. Kuemmel reports personal fees from Roche, Novartis, Exact Science, Lilly, Pfizer, MSD, Agendia, Gilead, AstraZeneca, Daiichi Sankyo, Stemline, and Roche outside the submitted work. S.J. Crabb reports grants and personal fees from AstraZeneca; personal fees from Ipsen, Janssen, Astellas, Duality Bio, Merck, Pfizer, BMS, Bayer, and MSD; and grants from Roche and Veracyte outside the submitted work. Z.P. Parra-Guillén reports grants from Janssen Pharmaceuticals and other support from F.Hoffmann - La Roche Ltd outside the submitted work. I. Karlsson reports other support from BioInvent during the conduct of the study. L. Mårtensson reports personal fees from BioInvent outside the submitted work. R. Oldham reports grants from BioInvent International during the conduct of the study and a patent for WO2019138005A2, issued. A. Ropenga reports personal fees from BioInvent International during the conduct of the study. I. Teige reports personal fees from BioInvent during the conduct of the study; personal fees from BioInvent outside the submitted work; and a patent for Combined use of Fcγ RIIb (CD32B) and CD20-specific antibodies, pending, and a patent for Novel combination and use of antibodies, pending. B. Frendeus reports personal fees from BioInvent outside the submitted work and a patent for FcγRIIB-blocking antibodies, pending. A. McAllister reports a patent for US 11,623,005 issued, a patent for CN 107670034 issued, a patent for WO 2023/169985 pending, and is a full-time employee of BioInvent International AB. No disclosures were reported by the other authors.

Authors' Contributions

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curation, formal analysis, investigation, writing–original draft, writing–review and editing. **L. Mårtensson:** Formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **R. Oldham:** Resources, investigation, writing–review and editing. **A. Ropenga:** Conceptualization, data curation, formal analysis, investigation, writing–original draft, project administration, writing–review and editing. **I. Teige:** Conceptualization, formal analysis, supervision, investigation, methodology, writing–original draft, writing–review and editing. **J. Wallin:** Conceptualization, formal analysis, supervision, investigation, methodology, writing–original draft, writing–review and editing. **B. Frendeus:** Conceptualization, resources, formal analysis, supervision, investigation, methodology, writing–original draft, writing–review and editing. **A. McAllister:** Conceptualization, resources, formal analysis, supervision, investigation, methodology, writing–original draft, writing–review and editing.

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Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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