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Clinical Trial

Phase Ia dose-escalation trial with the BET protein inhibitor BI 894999 in patients with advanced or metastatic solid tumours☆

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Abstract ***Background:*** Bromodomain and extraterminal domain (BET) inhibitors have demonstrated efficacy in solid tumours and haematological malignancies. BI 894999 is a novel oral BET inhibitor that has demonstrated potent antitumour activity in preclinical studies.

Patients and methods: 1367.1 was an open-label, Phase Ia/Ib dose-finding study evaluating BI 894999 once daily in patients with advanced solid tumours (Schedule A: 0.2, 0.5, 1.0, 1.5, 2.0, and 5.0 mg, Days 1–21/21-d cycle; Schedule B: 1.5, 2.0, and 2.5 mg, Days 1–15/21-d cycle; Schedule C: loading dose 5.0, 6.0, or 7.0 mg on Day 1 followed by maintenance dose 2.5, 3.0, or 3.5 mg, Days 2–7 and 15–21/28-d cycle); 77 patients were enrolled. NCT02516553.

Results: Grade ≥3 dose-limiting toxicities (DLTs) were reported in 8/21, 5/25, and 9/31 patients for Schedules A, B, and C, respectively. Thrombocytopenia was reported as a DLT in 28.6%, 4.8%, and 9.7% for Schedules A, B, and C, respectively. Other DLTs occurring in ≥1

☆ Phase Ia study of novel BET inhibitor to treat solid tumours

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patient were troponin T increase (13.6%), hypophosphataemia (4.5%), and elevated creatine phosphokinase (3.0%). Disease control was achieved in 23.8%, 24.0%, and 29.0% of patients for Schedules A, B, and C, respectively. A partial response was achieved in 9.5% and 4% of patients with Schedules A and B, respectively. The best response with Schedule C was stable disease.

Conclusion: The 1.5, 2.5, and 6.0/3.0 mg doses in Schedules A, B, and C, respectively, were declared as maximum tolerated dose. Based on the strength of these data, BI 894999 was further evaluated in a Phase Ib trial.

1. Introduction

Inhibition of bromodomain and extraterminal domain (BET) proteins has the potential to treat solid tumours and haematological malignancies [1,2]. The BET protein family (BRD2, BRD3, BRD4, BRDT) mediates interactions between acetylated lysins on histone tails and other nuclear proteins, recruiting chromatin regulation factors and regulating gene transcription, as well as DNA repair, replication, and epigenetic memory [3–5]. Small-molecule inhibitors of BET proteins, particularly BRD4, have shown therapeutic activity in different cancer models [6–10].

The oral BI 894999 potent small-molecule inhibitor blocks the protein–protein interaction between histone H4-derived peptide with acetylated lysine and the bromodomains BRD4-BD1 and BRD4-BD2 [11]. Preclinical mechanistic studies show that BI 894999 targets super-enhancer-regulated oncogenes and other lineage-specific factors [12], and *in vitro* studies demonstrate antitumour activity in cancer cell lines and xenograft models [11–14]. BI 894999 only inhibits members of the BET family and is selective (≥200-fold) versus 24 other bromodomains [12].

Preclinical antitumour activity and toxicity data, and the clinical safety profile of other BET inhibitors, present a strong rationale for the clinical investigation of BI 894999. Here, we present the results of the Phase Ia, first-in-human, dose-escalation study to determine the safety, pharmacokinetics (PK), and maximum tolerated dose (MTD) of BI 894999.

2. Patients and methods

2.1. Study design

1367.1 (NCT02516553) was an open-label, Phase Ia/Ib dose-finding study of oral BI 894999 in patients with advanced and/or metastatic solid tumours. BI 894999 was administered once daily in a dose-escalation manner, using three different dosing schedules (Fig. 1): Schedule A: 0.2, 0.5, 1.0, 1.5, 2.0, and 5.0 mg, given on Days 1–21 of a 21-d cycle; Schedule B: 1.5, 2.0, and 2.5 mg, given on Days 1–15, followed by 1 week off, of a 21-d cycle; and Schedule C: loading dose on Day 1 (5.0, 6.0, or 7.0 mg) followed by maintenance doses (2.5, 3.0, or 3.5 mg) on Days 2–7, with 1 week off treatment, repeated every 2 weeks in a 4-week cycle. Schedule C was introduced to reduce the incidence and severity of thrombocytopenia and to achieve a higher peak blood concentration (C_{max}) and average concentration per treatment exposure (AUC). The protocol was amended to interrupt therapy for treatment-related Grade 3 troponin T increase, to resume only if cardiotoxicity was ruled out.

A Phase Ia data monitoring committee (DMC) evaluated dose-limiting toxicities (DLTs) and overall safety to confirm dose escalation in the three treatment schedules. Once the MTD was determined for Schedules A and B in solid tumours, the DMC recommended an MTD extension cohort with selected schedule for solid tumours and diffuse large B-cell lymphoma (DLBCL).

Treatment was continued until disease progression or unacceptable toxicity. The trial was conducted in accordance with the Declaration of Helsinki, international guidelines, and local regulations. Local ethics committees approved the trial. All patients provided written informed consent (protocol in supplementary materials).

2.2. Patients

Eligible patients (aged ≥18 years) had: confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours; failed conventional treatment; no treatment of proven efficacy or were unamenable to standard therapies; Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0/1; recovered from previous systemic therapy-related toxicity; and life expectancy ≥12 weeks (exclusion criteria in supplementary materials).

2.3. Study end-points

The primary end-point was the number of patients with DLTs (graded by the Common Terminology Criteria for Adverse Events [CTCAE] v4.03) during the MTD evaluation period (for each schedule). MTD was defined as the highest dose with < 25% risk of the true DLT rate > 0.33 during evaluation. The MTD evaluation period

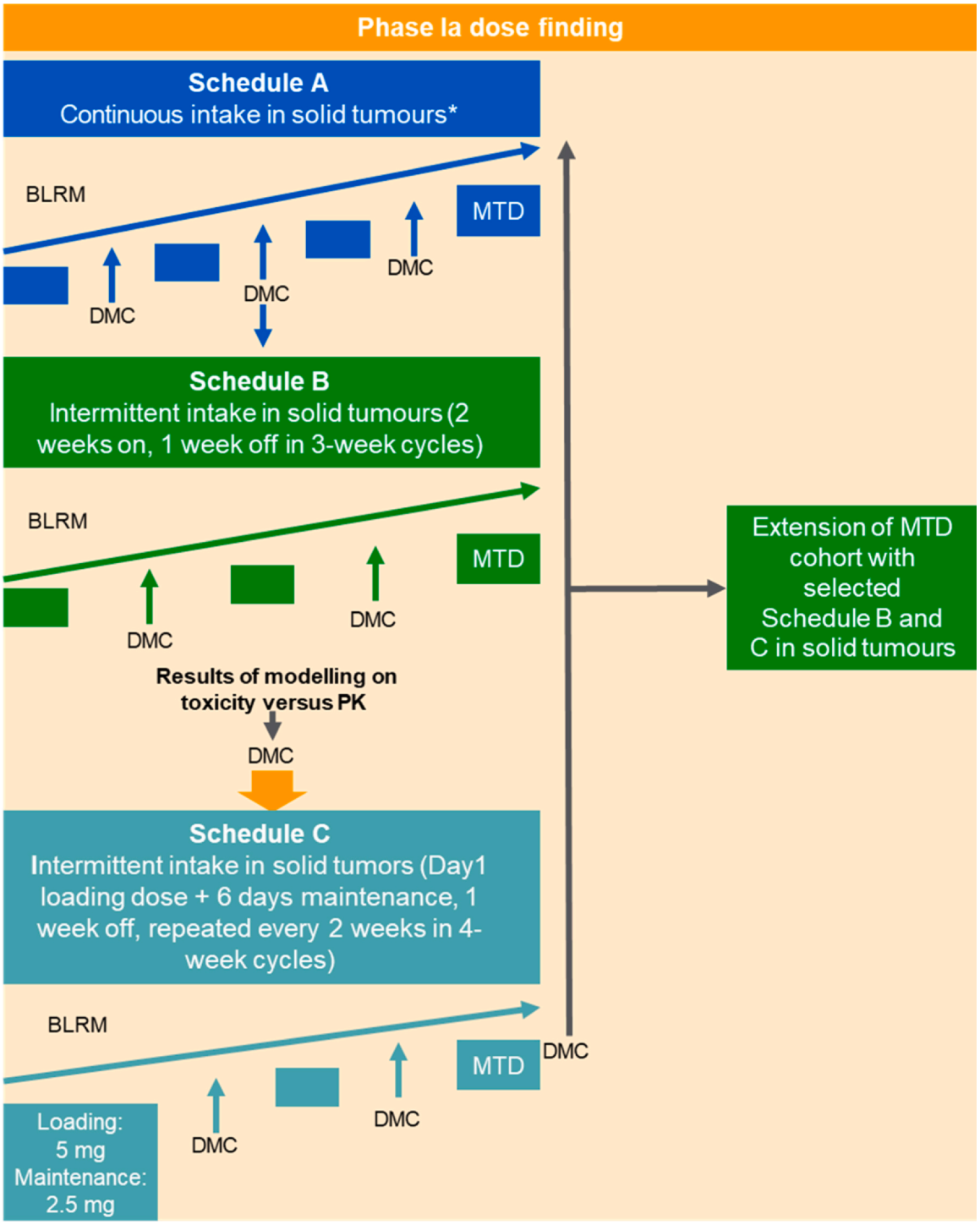

Fig. 1. Study design of Phase Ia dose escalation. BLRM, Bayesian logistic regression model; DMC, data monitoring committee; MTD, maximum tolerated dose; PK, pharmacokinetics.

was defined as the time from the first BI 894999 administration to 21 d afterwards, death, or interim data lock date, whichever came first (DLT definitions in supplementary materials). Secondary end-points included the number of patients with DLTs during all treatment cycles for each schedule, single- and multiple-dose PK, and preliminary objective response (OR) assessment (complete or partial response [PR]; investigator-assessed Response Evaluation Criteria in Solid Tumours [RECIST] v1.1; intent-to-treat population). Baseline tumour scans were performed within 4 weeks prior to first BI 894999 treatment, then every two cycles until treatment end (if not performed within the last 4 weeks; PK, pharmacodynamics [PD], RNA, NanoString, and statistical analyses in supplementary materials).

Table 1
Patient characteristics and oncological history.

	Schedule A	Schedule B	Schedule C
Number of patients, n	21	25	31
Median age, years (range)	58.0 (30–77)	63.0 (43–78)	62.0 (34–82)
Male, n (%)	10 (47.6)	17 (68.0)	17 (54.8)
Caucasian, n (%)	21 (100.0)	25 (100.0)	31 (100.0)
ECOG PS at baseline, n (%)			
0	9 (42.9)	9 (36.0)	12 (38.7)
1	12 (57.1)	16 (64.0)	19 (61.3)
Median time since first diagnosis, years (range)	2.1 (0.7–19.0)	5.53 (5.24)	4.90 (3.97)
Advanced solid tumour type, n (%)			
Colorectal	1 (4.8)	3 (12.0)	8 (25.8)
Head & neck	3 14.3)	2 (13.3)	5 (16.1)
Prostate	2 (9.5)	5 (20.0)	1 (3.2)
Soft tissue/Osteosarcoma	1 (4.8)	4 (26.7)	1 (3.2)
Melanoma	1 (4.8)	1 (4.0)	2 (6.5)
Other	2 (9.5)	1 (4.0)	1 (3.2)
Pancreas	2 (9.5)	0	2 (6.5)
Non-small cell lung	0	3 (12.0)	0
Small intestine	1 (4.8)	2 (13.3)	0
Biliary tree	1 (4.8)	1 (4.0)	0
Bladder	2 (9.5)	0	0
Breast	0	1 (4.0)	1 (3.2)
Oesophagus	0	1 (4.0)	1 (3.2)
Kidney	0	0	2 (6.5)
Ovary	1 (4.8)	0	1 (3.2)
Small cell lung	1 (4.8)	1 (4.0)	0
Adrenal	1 (4.8)	0	0
Lung	0	0	1 (3.2)
Endocrine	0	0	1 (3.2)
Endometrial	0	0	1 (3.2)
Mesothelial	0	0	1 (3.2)
Non-glioblastoma CNS	1 (4.8)	0	0
Testis	0	0	1 (3.2)
Urethra/penis	1 (4.8)	0	0
Uterine sarcoma	0	0	1 (3.2)
Clinical stage at screening, n (%)			
Locally advanced	1 (4.8)	0	2 (6.5)
Metastatic	20 (95.2)	25 (100.0)	29 (93.5)
Location of metastatic sites at screening, n (%)			
Lymph node	13 (61.9)	15 (60.0)	19 (61.3)
Lung	8 (38.1)	9 (36.0)	20 (64.5)
Liver	9 (42.9)	12 (48.0)	11 (35.5)
Bone	3 (14.3)	11 (44.0)	9 (29.0)
Other	13 (61.9)	18 (72.0)	15 (48.4)
Patients with previous anticancer therapy*, n (%)	21 (100.0)	25 (100.0)	31 (100.0)
Systemic chemotherapy	21 (100.0)	22 (88.0)	27 (87.1)

* A patient could have ≥1 type of prior anticancer therapy. CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

3. Results

3.1. Patients

In total, 77 patients with solid tumours received ≥1 dose of BI 894999 in Phase Ia (Supplementary Fig. 1); 21 received Schedule A, 25 Schedule B, and 31 Schedule C. A further 14 patients with DLBCL were enrolled in Schedule B and four in Schedule C. However, this analysis focuses on solid tumours only. The median age was 58.0 years for Schedule A, 63.0 years for Schedule B, and 62.0 years for Schedule C (Table 1); all patients were Caucasian. Most patients (61.0%) had ECOG PS 1. The median time since first diagnosis was 2.1 years for Schedule A, 3.0 years for Schedule B, and 4.0 years for Schedule C. The most frequent tumours were colorectal (15.6%), head and neck (13.0%), prostate (10.4%), and soft tissue/osteosarcoma (7.8%). All patients received prior therapy; most received systemic chemotherapy (90.9%), surgery (72.7%), and/or radiotherapy (54.5%).

Table 2
Patients with DLT during the MTD evaluation period — Grade ≥3.

Schedule and dose	DLTs reported
Schedule A	
1.5 mg n = 6	Grade 3 elevated creatinine phosphokinase (n = 1); Grade 3 elevated ST segment (n = 1)
2.0 mg n = 6	Grade 4 meningitis and Grade 3 elevated creatinine phosphokinase (n = 1); Grade 4 thrombocytopenia (n = 2); Grade 4 thrombocytopenia, Grade 5 cerebrovascular accident, and Grade 3 increased troponin T (n = 1)
5.0 mg n = 2	Grade 4 thrombocytopenia (n = 1); Grade 2 decreased appetite, Grade 3 hypophosphataemia, Grade 2 dysgeusia, Grade 2 stomatitis, and Grade 3 fatigue (n = 1)
Schedule B	
1.5 mg n = 6	Grade 3 hypokalaemia, Grade 3 hypophosphataemia, and Grade 3 increased troponin T (n = 1)
2.0 mg n = 6	Grade 3 hypophosphataemia (n = 1)
2.5 mg n = 13	Grade 3 increased troponin T (n = 2); Grade 4 thrombocytopenia and Grade 3 epistaxis (n = 1)
Schedule C	
5.0 mg/2.5 mg n = 4	Grade 3 vomiting (n = 1)
6.0 mg/3.0 mg n = 15	Grade 3 increased troponin T (n = 3)
7.0 mg/3.5 mg n = 12	Grade 3 increased troponin T (n = 2); Grade 3 thrombocytopenia (n = 2); Grade 4 thrombocytopenia and Grade 3 diarrhoea (n = 1)

CTCAE version 4.03.
CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; MTD, maximum tolerated dose.

3.2. Treatment

The median treatment duration was 48 d (16–294 d) for Schedule A, 40 d (11–433 d) for Schedule B, and 49 d (4–273 d) for Schedule C (Supplementary Table 1). Two patients (9.5%) received ≥6 treatment cycles during Schedule A, three (12.0%) during Schedule B, and six (19.4%) during Schedule C.

3.3. Maximum tolerated dose

On treatment, eight patients had Grade ≥3 DLTs during Schedule A, five during Schedule B, and nine during Schedule C (Table 2). Thrombocytopenia was reported as a DLT in 28.6% of patients in Schedule A, 4.8% in Schedule B, and 9.7% in Schedule C. Troponin T increases were not associated with cardiovascular clinical signs and symptoms. The 1.5 mg dose in Schedule A and 2.5 mg dose in Schedule B were declared as MTDs in patients with solid tumours based on incidence and safety evaluations. The DMC declared the 7.0 mg loading dose and 3.5 mg maintenance dose (7.0 mg/3.5 mg) of Schedule C as the MTD. However, based on DLTs reported during the MTD evaluation period, the MTD was adjusted to 6.0 mg/3.0 mg for Schedule C in patients with solid tumours.

3.4. Adverse events

Any-grade treatment-related adverse events (AEs) occurred in 95.2% of patients for Schedule A, 80.0% for Schedule B, and 90.3% for Schedule C. For Schedule A, Grade ≥3 AEs occurred in patients receiving > 1.5 mg (Supplementary Table 2). In these 14 patients, the most frequent Grade ≥3 AEs were thrombocytopenia (50%), neutropenia (21.4%), increased creatine phosphokinase (14.3%), and troponin T increase (14.3%). For Schedule B, the most frequent Grade ≥3 AEs were thrombocytopenia (20.0%), hypophosphataemia (12.0%), troponin T increase (12.0%), diarrhoea (8.0%), anaemia (8.0%), and neutropenia (8.0%) (Supplementary Table 3). For Schedule C, the most frequent Grade ≥3 AEs were thrombocytopenia (16.1%), troponin T increase (12.9%), lymphocyte count decrease (9.7%), diarrhoea (9.7%), and anaemia (9.7%) (Supplementary Table 4).

Due to the lower severity of thrombocytopenia in Schedule B than in Schedule A (Grade 4 events: 4.0% versus 19.0%), the DMC selected Schedule B for dose expansion in patients with solid tumours (Phase Ib) and for dose escalation in patients with DLBCL (Phase Ia).

AEs leading to dose reduction were reported for eight patients in Schedule A (57.1%), five in Schedule B (29.4%), and three in Schedule C (9.7%) (Supplementary Table 3). AEs leading to dose discontinuation were reported in 10 patients (38.1%) for Schedule A, two (8.0%) for Schedule B, and 10 (32.2%) for Schedule C. A single case of cerebrovascular accident was the only fatal AE considered treatment related (thrombogenic intracranial bleeding).

Elevated troponin T levels were reported in 42 patients following BI 894999, regardless of whether related to treatment (n = 20 Grade ≥3); of these, 22 patients had elevated troponin T levels at screening. Due to the elevated troponin T, BI 894999 was placed on a temporary clinical hold while other cardiac health measures were assessed. There were no relevant vital signs or

electrocardiogram findings. Left ventricular ejection fraction values were recorded for 22 of 46 patients and were ≥50% in all patients on treatment except one, who received 2.5 mg in Schedule B (screening: 58%, end of treatment: 40%, follow-up: 46%). The patient's troponin values were within the 99th percentile at all visits.

Regarding changes in coagulation parameters, mean changes from baseline to last value on treatment were minor for prothrombin time and activated partial thromboplastin time across all dosing schedules. A decrease in mean platelet reactivity test was noted from baseline to last value on treatment for all dosing schedules (Schedule A: mean [standard deviation] change from baseline: −18 [23]; Schedule B: mean [standard deviation] change from baseline: −16 [22]; Schedule C: mean [standard deviation] change from baseline: −17 [38]).

3.5. Preliminary efficacy

In total, efficacy was evaluated in 77 patients (Fig. 2; Supplementary Table 6). For Schedule A, disease control by RECIST per investigator assessment was achieved in five (23.8%) patients: two patients (9.5%) had a PR and three patients (14.3%) had stable disease (SD). In Schedule A, the median durations of PR and SD were 150 d (42–257 d) and 136 d (43–266 d), respectively. For Schedule B, disease control was achieved in six (24.0%) patients: one patient had a PR (4.0%) lasting 85 d, and five patients (20.0%) had SD with a median duration of 229 d (85–448 d). In Schedule C, disease control (SD only) was achieved in nine patients (29.0%), with a median duration of 176 d (77–280 d). The most common tumours in which clinical benefit (≥ RECIST SD) was reported included head and neck (n = 6), colorectal (n = 2), and other (n = 2).

The three patients with PR had cancer of head and neck, small intestine, and oesophagus. Molecular profiling of the patient with small intestine cancer showed many genomic alterations.

3.6. Pharmacokinetics

In total, 77 patients were evaluable for PK analysis. In all schedules, the median time to maximum plasma concentration (t_{max}) was approximately 2 h after single-dose administration at Day 1 and after once-daily doses at Day 14 or 21 (Supplementary Table 7 and Fig. 3).

Comparison of geometric mean steady-state plasma concentration–time profiles of BI 894999 (Fig. 3), in Schedule B at 2.5 mg and in Schedule C at 5.0 mg/2.5 mg, suggested a higher exposure for the patients in Schedule C after once-daily administration of 2.5 mg than in Schedule B.

Trough plasma concentrations were stable over the treatment duration, suggesting that a steady state had been reached ≤Day 8 in the different schedules (data not shown). Nevertheless, in most patients from Schedule B, quantifiable predose concentrations were observed in Cycle 2, suggesting that BI 894999 was not eliminated after 7 d off treatment. Slight-to-moderate accumulation after multiple dosing up to Day 14 was observed in Schedules A and B. Dose proportionality was confirmed at steady state for Schedule A over the dose range. Due to the small number of doses investigated in Schedule B, there was no significant deviation in dose proportionality. For most doses in Schedules A and B, the AUC was linear (Day 14 [$AUC_{0–24,ss}$] versus Day 1 [$AUC_{0-\infty}$]). Non-compartmental PK parameters after single (Day 1) and multiple doses (Day 14 or 21) of BI 894999 in solid tumour patients under fasted conditions in Cycle 1 are detailed in Supplementary Table 7. Food-effect analysis at three doses (1.5, 2.0, and 2.5 mg in Schedules A and B) showed lower exposure (C_{max} and AUC) after dosing in the fed than in the fasted state (C_{max} range 10–36%; AUC_{0-tz} 19–45%). Overall, median t_{max} was similar for fasted and fed states at all doses evaluated (data not shown).

3.7. Pharmacodynamics

PD profiles were available for 74 patients (Schedule A: n = 20; Schedule B: n = 25; Schedule C: n = 29). In the lowest three dose cohorts of Schedule A (0.2, 0.5, and 1.0 mg), there was a trend towards induction of *HEXIM1* and *HIST2H2BF* and suppression of *CCR2* in the 1.0 mg cohort (Supplementary Table 8). However, gene expression induction/suppression did not reach the prespecified threshold demonstrating target engagement, which was evident in all subsequent dose cohorts (Fig. 4 and Supplementary Table 8).

In Schedules A and B, the maximal-fold change in gene expression/induction was mainly from Day 14 samples versus baseline. (In Schedule A, two patients receiving 5.0 mg did not provide blood samples on Day 14.) In Schedule C, maximal-fold change was mostly on Day 1 (loading dose). Analysis of maximal-target engagement at MTDs of Schedule B (2.5 mg) and Schedule C doses showed greater induction/suppression in target engagement in Schedule C than in Schedule B at 6.0 mg loading dose/3.0 mg maintenance dose and 7.0 mg loading dose /3.5 mg maintenance dose (Fig. 4).

3.8. Pharmacokinetic/pharmacodynamic interaction

Data were available for 41 patients with $C_{max,ss}$ and PD biomarkers and for 37 patients with $AUC_{0–24}$ and PD biomarkers. Exploratory analyses of PK exposure metrics and PD biomarkers indicated a weak-to-moderate positive correlation among exposure metrics and *HEXIM1*/*HIST2H2BF* and a weak negative correlation for *CCR2*, suggesting an on-target effect of BI 894999 (Fig. 4B).

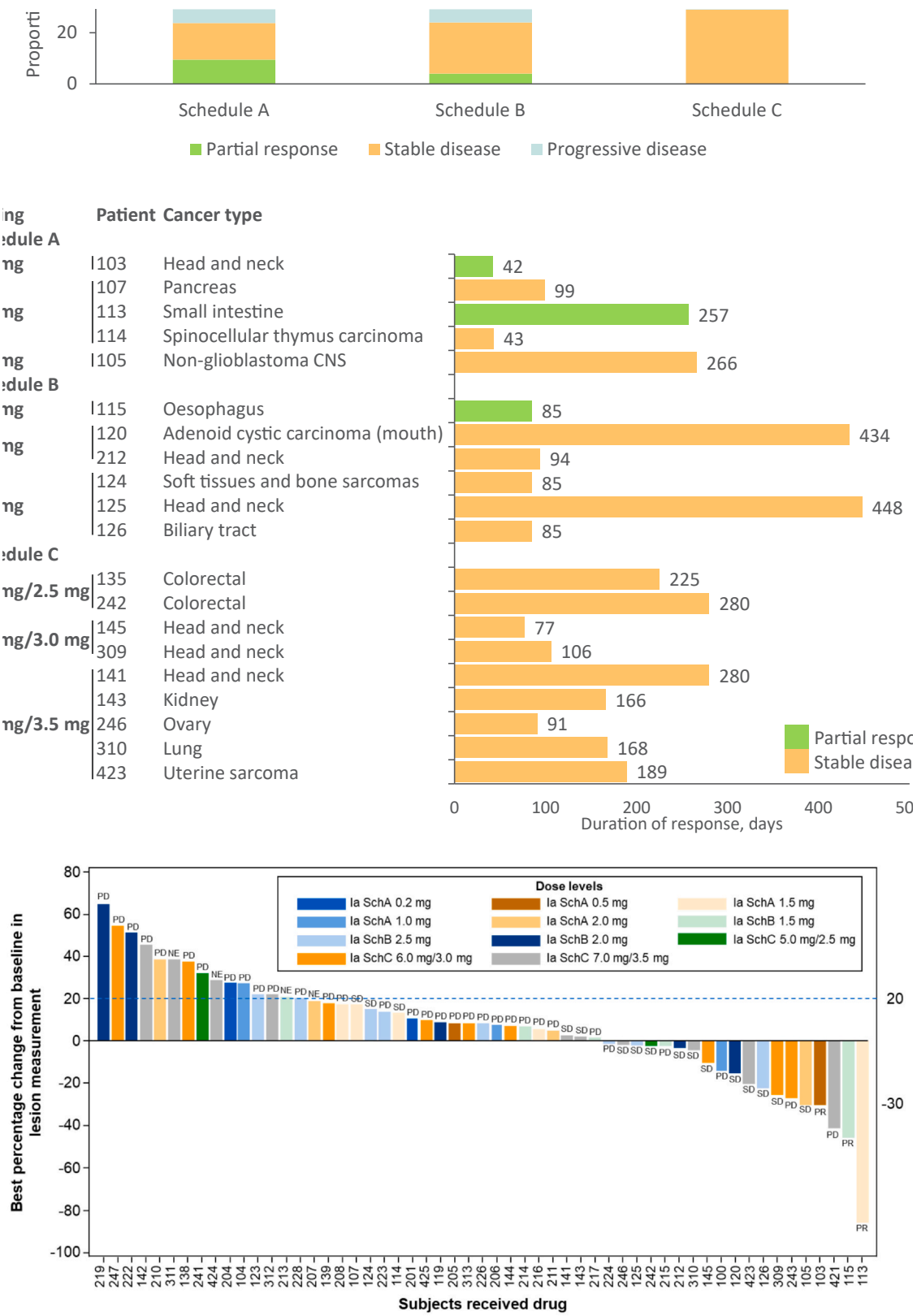

Fig. 2. Efficacy in patients with solid tumours. (A) Tumour response per schedule, (B) duration of response and tumour type per dose for patients who achieved a partial response or stable disease, and (C) waterfall plot of the best percentage change from baseline in target lesion measurements. Note: Patients with missing measurements are not included in the waterfall plot. NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

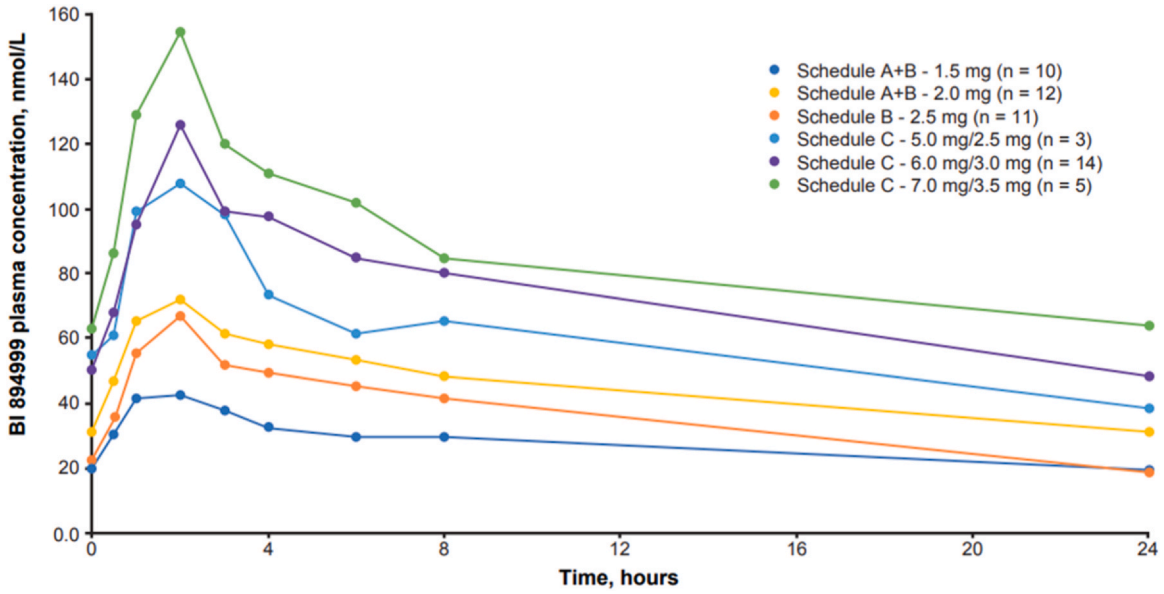

Fig. 3. BI 894999 plasma concentration-time profiles at steady state (Day 14 for Schedules A and B or Day 21 for Schedule C).

4. Discussion

This first-in-human dose-finding study evaluated the safety and MTD of BI 894999 in patients with advanced and/or metastatic solid tumours. DLTs included thrombocytopenia, increased blood creatine phosphokinase, hypophosphataemia, and troponin T increase. The safety profile of BI 894999 was consistent with other BET inhibitors. Treatment-related AEs reported with other BET inhibitors include myelosuppression, haematological, gastrointestinal, and skin disorders, fatigue, and non-haematological laboratory abnormalities [15–20].

In October 2016, due to increased troponin T in some patients, a temporary hold was placed by the sponsor on further recruitment while a review was conducted on electrocardiogram data, clinical summaries, and non-Good Laboratory Practice preclinical assays. There was no preclinical evidence of potential cardiac toxicity related to BI 894999 or of BI 894999-related increase in troponin T, corresponding to a lack of cardiotoxicity reported in animal studies. The cause of elevated troponin T was potentially multifactorial and not considered significant to preclude further clinical development. Moreover, our results agree with previous studies showing elevated cardiac biomarkers, including troponin T, in patients with advanced, metastatic cancers prior and during anticancer therapy in the absence of acute ischaemia (e.g. breast, lung, haematological malignancies, and advanced skin cancers) [21–23]. Patient recruitment was re-started after implementing mandatory cardiac monitoring. Incidental elevations of troponin T above the 99th percentile are routinely encountered in a substantial proportion of stable and asymptomatic patients in hospital settings, primary care, and in the general middle-aged population. A cerebrovascular incident occurred in one patient after treatment discontinuation. This was the only fatal AE considered treatment related by the investigator.

Other BET inhibitors have been linked with decreases in coagulation *factor VII*. INCB057643 was evaluated in combination with standard of care for the treatment of patients with advanced malignancies and ≥1 prior therapy. Dose-dependent decreases in the levels of coagulation *factor VII* were observed [24]. Similar decreases in *factor VII* were also observed in trials evaluating molibresib in patients with selected solid tumours and OTX-015 in relapsed/refractory leukaemia [25,26]. In this Phase Ia study, we observed minor changes from baseline to last value on treatment for prothrombin time and activated partial thromboplastin time across all dosing schedules. However, there was a decrease in the mean platelet reactivity test from baseline to last value on treatment for all dosing schedules. Other coagulation factors were not assessed in this phase of the trial.

A key study objective was to determine the appropriate dosing regimen for future clinical studies. There was substantially lower severity of thrombocytopenia in Schedule B versus A. Therefore, Schedule B was selected by the DMC for dose expansion in patients with solid tumours (Phase 1b) and for dose escalation in patients with DLBCL (Phase Ia), with a dose of 1.5 mg in Schedule A, 2.5 mg in Schedule B, and 6.0 mg/3.0 mg in Schedule C declared as the MTD in patients with solid tumours. Preclinical data suggest that higher loading doses with subsequent maintenance at lower doses could mitigate thrombocytopenia. This was investigated in Schedule C, with the DMC-selected maintenance dose based on Schedule B (2.5 mg with a double loading dose of 5.0 mg). The median time to reach t_{max} after single and multiple doses of BI 894999 was approximately 2 h.

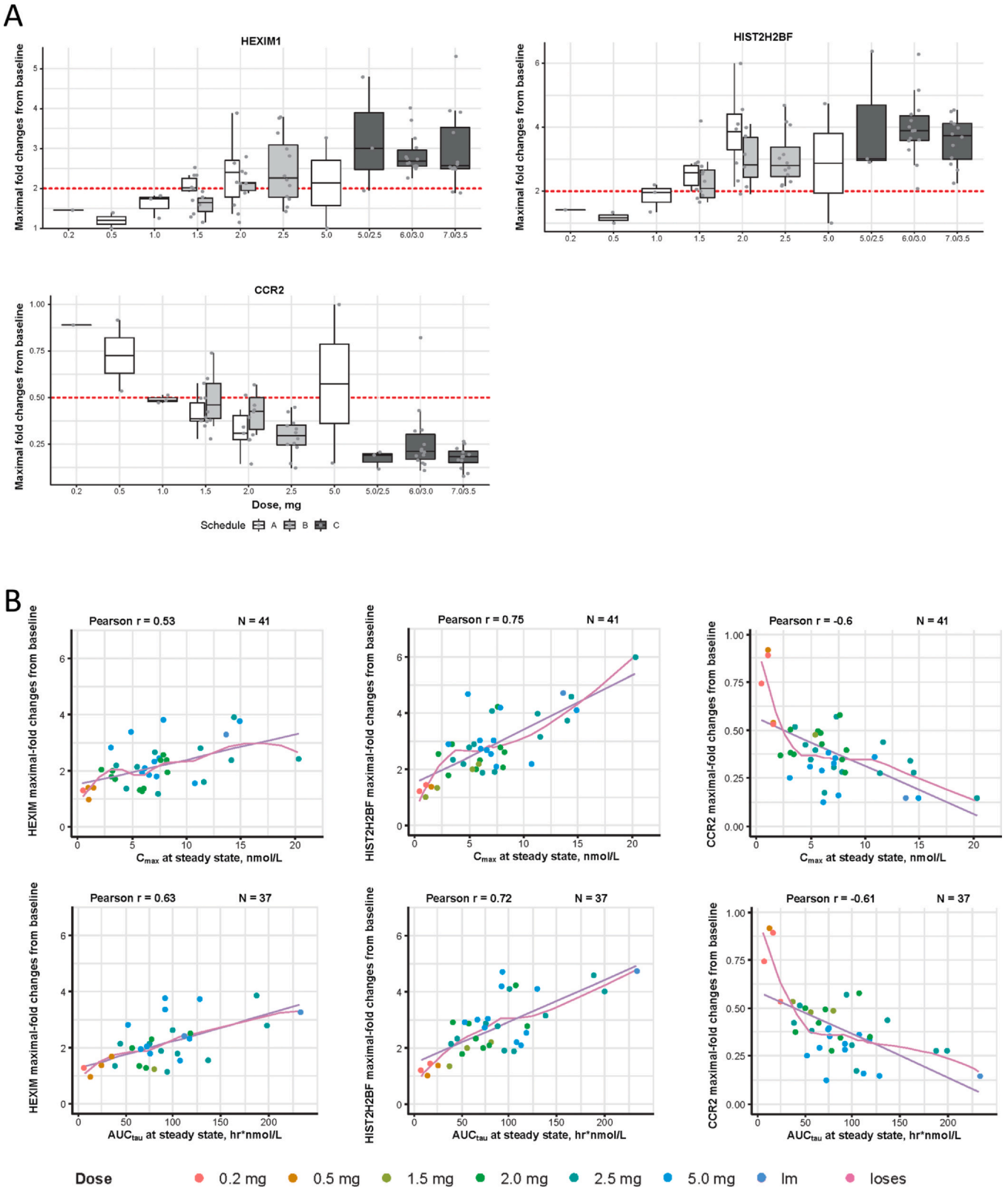

Fig. 4. Box plots (A) demonstrating maximal-fold change from baseline for the three PD biomarkers (*HEXIM1*, *HIST2H2BF*, and *CCR2*). Scatter plots (B)—exploratory analyses of PK exposure metrics and PD biomarkers. AUC, area under the concentration–time curve; C_{max}, maximum plasma concentration; PD, pharmacodynamics; PK, pharmacokinetics.

The PK profile of BI 894999 is similar to other BET inhibitors, with a t_{max} between 0.5 and 8 h. As the observed effect of food intake was a decreased exposure, BI 894999 was dosed in a fasted condition for all patients in Phases Ia and Ib.

Preliminary clinical data for BI 894999 are insufficient to reliably assess its antitumour activity. However, at the study data lock date, 20 of 91 patients (22.0%) evaluated for efficacy achieved disease control, including three ORs, indicating target engagement and antitumour activity of BI 894999.

HEXIM1 is modulated by BET family proteins and is considered a robust PD marker for BET inhibition [27], whereas *HIST2H2BF* and *CCR2* are involved in cancer pathways [25,26]. Exploratory gene expression analyses demonstrated target engagement at doses ≥1.5 mg, showing an increase in *HEXIM1* and *HIST2H2BF* and a decrease in *CCR2* expression, with the maximal-fold change in gene expression from baseline observed on Day 14 in Schedules A and B and Day 1 in Schedule C.

As these data are from a non-randomised, open-label study, inherent limitations for efficacy evaluation include small cohorts and lack of active controls. Further, BI 894999 response rates were assessed in a heterogeneous group of patients with different advanced solid tumours and gene expression patterns. Patients were not preselected based on their disease molecular characteristics. Additionally, PK/PD analyses were limited by the time points for data collection, the small number of available tumour samples for correlative studies, and general challenges with biomarker studies in patient tumour samples.

In conclusion, the safety profile of BI 894999 was consistent with other BET inhibitors. Treatment-related AEs included haematological, gastrointestinal, and skin disorders, fatigue, and laboratory abnormalities. Based on the strength of these data, BI 894999 was further evaluated in a Phase Ib study of various tumour types that will be published in the future.

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CRediT authorship contribution statement

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Declaration of Competing Interest

Patrick Schöffski declares institutional translational research funding for work; an ongoing advisory function; receiving personal honoraria; travel support to attend BET inhibitor-related advisory functions; personal honoraria for educational activities outside of the scope of this paper from Boehringer Ingelheim; consulted/advised for Deciphera, Ellipses Pharma, Blueprint Medicines, Transgene, Exelixis, Studiecentrum voor Kernenergie, SQZ Biotechnology, Adcendo, PharmaMar, Merck Healthcare KGaA, Medpace; and received research support from CoBioRes NV, Eisai, G1 Therapeutics, PharmaMar, Genmab, Merck, Sartar Therapeutics, and ONA Therapeutics.

Jean-Pascal Machiels has consulted/advised for ALX Oncology, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CUE Biopharma, Debiopharm, Incyte Corporation, Innate Pharma, Janssen, Merck Serono, Merck Sharp & Dohme, Nanobiotix, Novartis, Pfizer, Roche; received research funding from Bayer, Janssen, Novartis, Sanofi; and travel, accommodations, and expenses from Amgen, Bristol Myers Squibb, Merck Sharp & Dohme, and Pfizer.

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Behbood Sadrolhefazi and Kristell Marzin are employees of Boehringer Ingelheim.

Hanny Musa is a former employee of Boehringer Ingelheim.

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Data sharing and disclosure statement

To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to clinical study data pertinent to the development of the publication. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data when it becomes available on Vivli - Center for Global Clinical Research Data, and earliest after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete, and other criteria are met. Please visit Medical & Clinical Trials | Clinical Research | MyStudyWindow for further information.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.112987.

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