An open-label, phase I/II trial to determine the maximum tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 836858, an unconjugated anti-CD33 monoclonal antibody, in combination with decitabine in patients with acute myeloid leukemia

Despite significant developments over the last decade, including the emergence of the hypomethylating agents, azacitidine and decitabine, and the bcl-2 antagonist, venetoclax, further treatment options for patients with acute myeloid leukemia (AML) remain an unmet medical need, especially in elderly patients. While hypomethylating agents, alone or in combination with venetoclax, have improved outcomes in elderly patients ineligible for intensive chemotherapy, survival is modest (median overall survival of ~7–15 months in clinical trials).[1-3] Regardless of treatment intensity, resistance and relapse to treatment remains a clinical challenge in patients with AML, particularly in elderly patients (>65 years).[4]

CD33 is an established drug target of interest in AML due to its detectable expression on blast cells in >80–90% of patients[5] and has been validated in this setting by the clinical development of the antibody-drug conjugate, gemtuzumab ozogamicin.[6-8] BI 836858 is a fully humanized IgG1 unconjugated anti-CD33 monoclonal antibody.[9] In an *in vitro* study, BI 836858 significantly induced both autologous and allogeneic natural killer (NK)-cell degranulation and NK-cell–mediated antibody-dependent cellular cytotoxicity in AML blasts. Pretreatment of AML cells with decitabine rendered the cells more susceptible to the effects of BI 836858, providing a rationale for the use of BI 836858 in combination with decitabine in the clinical setting.[9]

We report herein the results of an open-label, phase I/II, multicenter trial conducted in Europe and the United States (US) to determine the maximum tolerated dose (MTD) and investigate the safety, pharmacokinetics (PK) and efficacy of BI 836858 in combination with decitabine in patients with AML (clinicaltrials gov. Identifier: NCT02632721). The trial was performed in compliance with the Declaration of Helsinki and the ICH Harmonized Tripartite Guideline for Good Clinical Practice. All patients provided written informed consent. The trial consisted of a phase I dose escalation period to determine the MTD of BI 836858/decitabine and the recommended dose for the phase I extension (RExP1D), a phase I extension period to determine whether the BI 836858/decitabine RExp1D would become the recommended phase II dose, and a phase II period to assess BI 836858 plus decitabine *versus* decitabine monotherapy. All trial phases were to collect data on the safety, PK and efficacy of BI 836858 plus decitabine. Due to a strategic decision by the sponsor to discontinue the clinical development of BI 836858, the phase II part of the trial was not conducted.

The phase I period enrolled patients ≥65 years of age with previously untreated AML and considered ineligible for standard intensive therapy, or patients ≥18 years of age with refractory/relapsed (R/R) AML, while the phase I extension enrolled patients ≥65 years of age with previously untreated AML and considered ineligible for standard intensive therapy only. The dose escalation proceeded using a Bayesian logistic regression model (BLRM) with overdose control. Dose escalation was overseen by a Safety Monitoring Committee (SMC) who considered the BLRM and additional factors (e.g., PK, pharmacodynamics and adverse events [AE]) at each dose level. BI 836858 was administered as weekly intravenous (i.v.) rate-controlled infusions (20–80 mL/hour) in 28-day cycles in combination with daily infusion of decitabine 20 mg/m^2. In cycle 1, decitabine was infused for 10 consecutive days (intensive schedule).[10] From cycle 2 onwards, decitabine was infused for 5 consecutive days (standard schedule) provided that there were no blasts in the peripheral blood and bone marrow blasts were <5%. Premedication (acetaminophen/paracetamol 650–1,000 mg; antihistamine orally or i.v. equivalent to diphenhydramine 50 mg i.v.; glucocorticoid i.v. equivalent to prednisolone 100 mg) to prevent infusion-related reactions (IRR) was obligatory 30–120 minutes prior to the first administrations of BI 836858 unless a contraindication for premedication existed. In the absence of IRR, the glucocorticoid dose was halved for the second administration and eliminated thereafter (with the option of re-escalation in the event of grade ≥2 IRR). The phase I extension consisted of two consecutive groups, one treated with BI 836858 plus intensive decitabine (Cohort A), and one treated with BI 836858 plus decitabine 20 mg/m^2/day for 5 days (standard dose schedule; Cohort B).

The primary endpoints of the phase I period were the

MTD of BI 836858 plus decitabine and the number of patients with dose-limiting toxicity (DLT) for BI 836858 plus decitabine during cycle 1. The phase I secondary endpoint was the number of patients with an objective best response, defined as complete remission (CR) plus complete remission with incomplete hematologic recovery (CRi) according to International Working Group criteria.[11] Incidence and intensity of treatment-related AE (based on Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) was also assessed. All analyses were descriptive and exploratory.

A total of 63 patients were screened in Germany (6 centers), Italy (1 center), Spain (3 centers), and the US (4 centers). Fourteen patients were screening failures and did not receive the study drug, so a total of 49 patients received at least one dose of the study drug and were included in the analysis (Figure 1; Table 1). The median duration of treatment was 98.0 days (range, 5–941 days), and the median number of cycles initiated was 3.0 (range, 1–33 cycles). During the dose escalation phase, no DLT were observed at BI 836858 doses of 20 mg, 40 mg, or 80 mg plus decitabine, and 80 mg BI 836858 was defined as the RExP1D by the SMC. The expansion phase was then opened with BI 836858 80 mg plus decitabine as the regimen. A total of two patients of 31 treated at this dose level experienced a DLT (grade 3 alanine aminotransferase [ALT] increased and grade 3 γ-glutamyltransferase [GGT] increased in 1 patient in Cohort A; grade 3 acute febrile neutrophilic dermatosis in 1 patient in Cohort B). No formal MTD was determined due to the low number of DLT reported; the highest BI 836858 dose of 80 mg was still considered safe, so the MTD of BI 836858 is ≥80 mg. A final recommendation on the phase II dose of BI 836858 was not made due to the early termination of the study.

All 49 patients who received the study drug reported at least one AE during the treatment period, with the most frequent AE being IRR (63.3%), constipation (42.9%), anemia (40.8%), and peripheral edema (40.8%) (Table 2). Of the 46 patients who discontinued trial medication, the primary reason for discontinuation were listed as progressive disease (PD) (n=18), AE in the absence of PD (n=10); 20.4%, refusal to continue medication (n=5), DLT (n=1; elevated ALT/GGT) and other reasons (n=12). AE leading to discontinuation included IRR (3 patients; 6.1%); general physical health deterioration, pneumonia, and sepsis (each in 2 patients; 4.1%); and leukocytosis, septic shock, GGT increased, tumor lysis syndrome, and acute febrile neutrophilic dermatosis (each in 1 patient, 2.0%). A total of 45 patients (91.8%) reported a serious AE (SAE). SAE that occurred in >10% of patients were febrile neutropenia (19 patients; 38.8%), disease progression (16 patients; 32.7%) and pneumonia (10 patients, 20.4%). Death was reported in 15 patients during the on-treatment period (Table 2). Reasons for death were disease progression (6 patients; 12.2%), sepsis (3 patients; 6.1%), pneu-

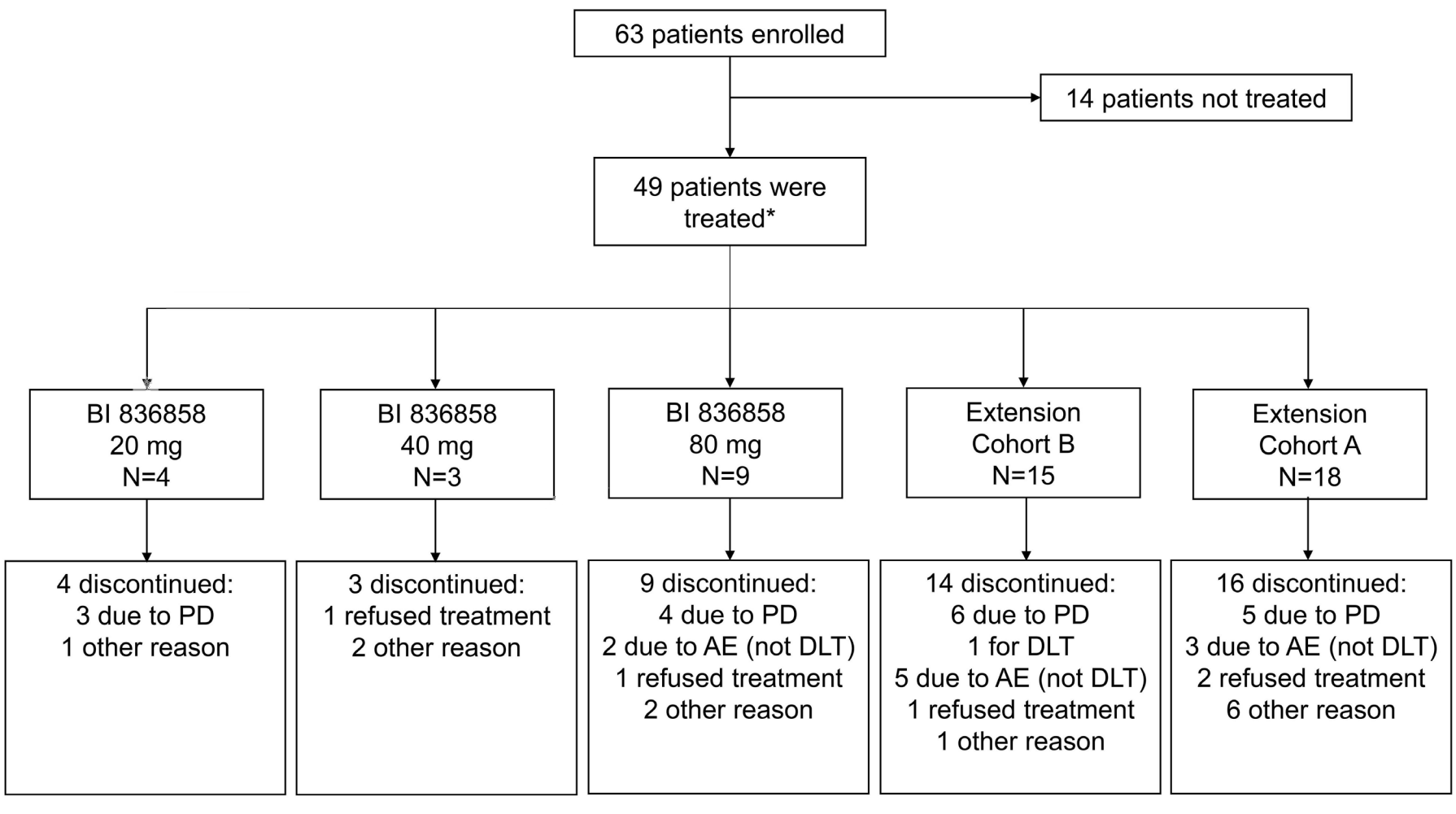

Figure 1. Study profile. *All patients received BI 836858 and decitabine. AE: adverse event; DLT: dose-limiting toxicity; PD: progressive disease.

Table 1. Baseline demographics and characteristics of patients with acute myeloid leukemia treated with BI 836858 in combination with decitabine.

Characteristic	BI 836858 20 mg N=4	BI 836858 40 mg N=3	BI 836858 80 mg N=9	Extension Cohort A N=15	Extension Cohort B N=18	All patients N=49
Male, N (%)	3 (75.0)	1 (33.3)	5 (55.6)	8 (53.3)	12 (66.7)	29 (59.2)
Race, N (%)						
White	4 (100)	3 (100)	9 (100)	15 (100)	18 (100)	49 (100)
Age, years						
Median (range)	75.5 (56-81)	59.0 (22-76)	70.0 (43-79)	74.0 (65-89)	77.5 (69-84)	75.0 (22-89)
<65	1 (25.0)	2 (66.7)	3 (33.3)	0	0	6 (12.2)
≥65	3 (75.0)	1 (33.3)	6 (66.7)	15 (100.0)	18 (100)	43 (87.8)
ECOG PS, N (%)						
0	0	0	1 (11.1)	2 (13.3)	3 (16.7)	6 (12.2)
1	4 (100)	3 (100)	5 (55.6)	10 (66.7)	11 (61.1)	33 (67.3)
2	0	0	3 (33.3)	3 (20.0)	4 (22.2)	10 (20.4)
Type of AML						
De novo	2 (50.0)	2 (66.7)	5 (55.6)	10 (66.7)	14 (77.8)	33 (67.3)
Secondary	2 (50.0)	1 (33.3)	4 (44.4)	5 (33.3)	4 (22.2)	16 (32.7)
Previous systemic anti-leukemia therapy, N (%)						
Yes	1 (25.0)	1 (33.3)	5 (55.6)	0	0	7 (14.3)
N of previous systemic anti-leukemia therapies, median (range)	2.0 (2-2)	6.0 (6-6)	2.0 (1-4)			2.0 (1-6)
Type of previous systemic anti-leukemia therapies, N (%)						
≥1 line of iHD	1 (25.0)	1 (33.3)	5 (55.6)			7 (14.3)
≥1 line of pLD	0	1 (33.3)	0			1 (2.0)
≥1 line of autologous SCT	0	0	0			0
≥1 line of allogeneic SCT	1 (25.0)	1 (33.3)	1 (11.1)			3 (6.1)
≥1 line of other	0	0				0

AML: acute myeloid leukemia; ECOG PS: Eastern Cooperative Oncology Group performance status; iHD: intensive high dose; pLD: palliative low dose; SCT: stem cell transplantation.

monia (2 patients; 4.1%), infection, septic shock, subdural hematoma, and tumor lysis syndrome (all in 1 patient). Two deaths, due to tumor lysis syndrome and septic shock were considered to be related to the study drug by the investigator. Seven patients (14.3%) reported AE of special interest: IRR of grade 3 or higher or IRR that were DLT were reported in four patients (8.2%), two patients (4.1%) reported tumor lysis syndrome, and ALT increased, GGT increased, and acute febrile neutrophilic dermatosis were reported in one patient (2.0%) each.

As part of the pharmacodynamic assessments, an exploratory analysis of CD33 expression and target engagement and NK cell numbers and expression of activation markers by NK cells was undertaken. Partial reductions in the percentage of peripheral blood $CD33^+$ blasts were observed in most patients e.g., eight of nine patients in the 80 mg BI 836858 mg cohort (*Online Supplementary Figure S1*). However, for some patients, $CD33^+$ blasts were still detectable in the bone marrow and blood after administration of 80 mg BI 836858, indicating that CD33 molecules were not fully saturated by BI 836858. In most patients there were no changes of note in the numbers of activated NK cells; however, in some patients there was an increase in activated NK cells in the blood during and shortly after BI 836858 infusion e.g., two of nine patients in the 80 mg BI 836858 mg cohort (*Online Supplementary Figure S1*).

In this study, individual plasma concentrations of BI 836858 were listed by dose group, cycle and day of treatment. Descriptive statistics were calculated for cycle 1, days 9 to 16 and day 23 to 24. On day 9, maximum plasma concentration of BI 836858 demonstrated a more than dose proportional increase between the 20 and 40 mg groups, whereas the geometric mean for the maximum plasma concentration of the 80 mg dose group is in line with which was expected. For day 23 in cycle 1, all dose groups increase in a more linear manner (*Online Supplementary Table S1*). However, steady state was not reached. Decitabine plasma concentrations were not calculated. The objective best response rate (ORR; CR + CRi) was 38.8% (19/49); one patient (2.0%) had partial remission, 16 patients (32.7%) had stable disease, and five patients (10.2%) had PD. Across the 20 mg, 40 mg, 80 mg, extension A and extension B cohorts the ORR was 50.0%,

Table 2. All-cause adverse events by Medical Dictionary for Drug Regulatory Activities preferred terms and highest Common Terminology Criteria for Adverse Events grade in patients with acute myeloid leukemia treated with BI 836858 in combination with decitabine: on treatment period.

Adverse event, N (%)	All grades	Grade 1/2	Grade 3	Grade 4	Grade 5
Total with AE	49 (100)	0	12 (24.5)	22 (44.9)	15 (30.6)
Infusion-related reaction	31 (63.3)	27	3 (6.1)	1 (2.0)	0
Constipation	21 (42.9)	21 (42.9)	0	0	0
Anemia	20 (40.8)	0	20 (40.8)	0	0
Edema peripheral	20 (40.8)	20 (40.8)	0	0	0
Febrile neutropenia	19 (38.8)	0	19 (38.8)	0	0
Pyrexia	16 (32.7)	12 (24.5)	4 (8.2)	0	0
Platelet count decreased	15 (30.6)	1 (2.0)	0	14 (28.6)	0
Nausea	14 (28.6)	13 (26.5)	1 (2.0)	0	0
Pneumonia	14 (28.6)	2 (4.1)	10 (20.4)	0	2 (4.1)
Diarrhea	13 (26.5)	11 (22.4)	2 (4.1)	0	0
Vomiting	13 (26.5)	13 (26.5)	0	0	0
WBC count decreased	13 (26.5)	1 (2.0)	2 (4.1)	10 (20.4)	0
Decreased appetite	12 (24.5)	12 (24.5)	0	0	0
Hypertension	12 (24.5)	6 (12.2)	6 (12.2)	0	0
Hypokalemia	12 (24.5)	10 (20.4)	2 (4.1)	0	0
Mucosal inflammation	12 (24.5)	11 (22.4)	1 (2.0)	0	0
Epistaxis	11 (22.4)	10 (20.4)	1 (2.0)	0	0
Fatigue	11 (22.4)	9 (18.4)	2 (4.1)	0	0
Rash	11 (22.4)	11 (22.4)	0	0	0
Neutropenia	10 (20.4)	0	1 (2.0)	9 (18.4)	0
Cough	9 (18.4)	8 (16.3)	1 (2.0)	0	0
Dyspnea	9 (18.4)	7 (14.3)	2 (4.1)	0	0
Fall	9 (18.4)	8 (16.3)	1 (2.0)	0	0
Headache	9 (18.4)	7 (14.3)	2 (4.1)	0	0
Hematoma	9 (18.4)	9 (18.4)	0	0	0
Back pain	8 (16.3)	7 (14.3)	1 (2.0)	0	0
Dizziness	8 (16.3)	8 (16.3)	0	0	0
Hypotension	8 (16.3)	8 (16.3)		0	0

Adverse events (AE) events shown are those occurring in >15% of patients for all grades. AML: acute myeloid leukemia; WBC: white blood cell.

0%, 66.7%, 46.7% and 22.2%, respectively. No conclusions could be drawn regarding the efficacy of BI 836858 added to the established decitabine treatment as the trial was stopped prematurely during the phase I extension cohort stage.

In conclusion, the results of this study show that although the MTD was not determined due to the termination of the trials, BI 836858, in conjunction with decitabine, had a manageable tolerability profile, and showed potential signals of efficacy in elderly patients with AML and those with R/R AML, in contrast to a previous phase I study of BI 836858 monotherapy in R/R AML that reported no response to therapy.[12] Evidence of target engagement in this study, and the observation of modest clinical activity, indicate that further development of unconjugated anti-CD33 antibodies, in combination with hypomethylating agents, warrants further consideration. However, other CD33 targeted approaches such as bispecific T-cell engagers,[13] or bifunctional checkpoint inhibitory T-cell engagers,[14] could potentially be considered in future combination regimens with the aim of improving immune effector cell recruitment and function.

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Contributions

Conception and design by SM, BR, UB, AO and WB. Collection and assembly of data by WF, PM, CS, JM, SV, CWS, JE and WB. Data analysis and interpretation by WF, SM, BR, UB, AO and WB. Drafting the manuscript by WF, PM, JM, SV, JE and SM. Manuscript writing by CS, CWS, BR, UB, AO and WB. All authors approved the final manuscript.

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Data-sharing statement

To ensure independent interpretation of clinical study results and enable authors to fulfill 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 https://vivli.org/, and earliest after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete, and other criteria are met. Please visit https://www.mystudywindow.com/msw/datasharing for further information.

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