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Phase Ib/II trial of anti-CD33 monoclonal antibody BI 836858 and azacitidine in previously untreated older acute myeloid leukemia patients: Beat AML S2 sub-study results

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The BCL-2 inhibitor venetoclax (VEN) plus azacitidine (AZA) improved outcomes compared to AZA monotherapy in the pivotal Phase 3 VIALE-A trial.[1] Though the mechanism of action of VEN is not mutation-specific, clinical outcomes are not agnostic to mutation. Some patient subsets, such as those with *TP53* mutations, do not benefit from the addition of VEN,[2] and often experience prolonged myelosuppression from drug or disease-related myelotoxicity. The Beat AML precision medicine program sponsored by Blood Cancer United (formerly the Leukemia & Lymphoma Society), genetically characterizes untreated, older AML patients in the "Master" study (M1), then assigns therapy to a "substudy" (e.g., S1, S2). The second treatment substudy (S2), designed in 2016 (prior to the approval of VEN and prior to the group's opening of other molecularly targeted substudies), consisted of a novel immunotherapeutic CD33-targeting agent (BI 836858) given in combination with AZA as initial therapy for any patient without a targeted option (Clinicaltrials.gov #NCT03013998). Beat AML S2 was conducted at the same time as an already ongoing similar industry-sponsored trial of decitabine plus BI 836858, conducted largely in Europe.[3] Importantly, S2 served as an anchor for the Beat AML program at its beginning, before molecularly-targeted drug trials came online, and provided the proof of concept for a mutation-agnostic substudy within this precision medicine program.

Development of monoclonal antibody (mAb)-based therapies targeting the myeloid differentiation antigen CD33 in AML has been attractive due to its expression on leukemic blasts in almost all patients. Several anti-CD33 mAb-based therapies have been developed for the treatment of AML, most of which have been unsuccessful, with the

notable exception of gemtuzumab ozogamicin.[7-11] BI 836858 is a fully humanized IgG1 unconjugated anti-CD33 mAb, fragment crystallizable (Fc)-engineered, with enhanced binding to the Fc receptor CD16 (FcγRIIIa) on natural killer (NK) cells, resulting in increased antibody-dependent cellular cytotoxicity (ADCC).[12,13] BI 836858 was shown to induce significantly higher ADCC in primary AML samples and cell lines *in vitro,* compared to lintuzumab, an anti-CD33 humanized mAb previously studied in AML. The addition of a hypomethylating agent enhanced BI 836858-mediated NK cell ADCC *in vitro*, providing the rationale for combining a hypomethylating agent with BI 836858.[12]

Patients ≥60 years with previously untreated AML according to the World Health Organization classification were enrolled per the Beat AML algorithm.[14] Based on a first-in-human Phase 1 monotherapy BI 836858 trial in patients with R/R AML (NCT01690624),[15] BI 836858 20 mg IV/weekly was the starting dose, with escalation to 40, 80, and 160 mg in combination with standard-of-care AZA in 28-day cycles (Figure S1). DLT was protocol-defined as drug-related non-hematologic adverse event (AE) of Grade ≥3 toxicity, or failure to recover blood counts by Day 56 of cycle 1 in the setting of no residual AML. Dose escalation decisions were based on typical toxicity/DLT criteria, as well as receptor occupancy (not shown). At the recommended Phase 2 dose (RP2D), the trial was powered to determine CR/CRi rate using Simon's two-stage design. Response was determined by intention-to-treat analysis. The study was conducted with approval by the local institutional review boards and all participants gave written informed consent.

BI 836858 was administered IV over up to 8 hours weekly starting on day 9 of cycle 1 to allow for cytoreduction to WBC <10 x 10^9/L, if necessary. To mitigate against tumor lysis syndrome (TLS), a stepped-up dose-escalation strategy was used to administer BI 836858 in cycle 1 as follows: 20 mg on Day 9, then remainder of the assigned dose on Day 10, and from Day 16 the full dose was administered on the same day/weekly. Premedication included acetaminophen, antihistamine, and glucocorticoid, which was tapered to tolerance in subsequent doses. Clinical response was assessed per 2017 European LeukemiaNet guidelines (Döhner et al. *Blood*. 2017).

Eighty patients received combination BI 836858/AZA. In dose escalation, patients received BI 836858 20 mg/ AZA (n=10), 40 mg/AZA (n=11), 80 mg/AZA (n=10), and 160 mg/AZA (n=7). Six additional patients received only AZA during Phase 1 due to progression before day 9 and were replaced. All demographic/baseline disease characteristics are presented in Table 1. The composition by mutation subgroup had selection bias. For example, few *FLT3*-mutated patients enrolled, and enrollment was enriched with patients with mutations of *TET2, IDH1*, and *WT1*. Differences in mutation profiles between Phase 1 and 2 studies were due to subsequent opening of competing studies with targeted agents. Three patients in dose escalation experienced a DLT: one Grade 4 neutropenia (20 mg/AZA), one Grade 3 portal hypertension (40 mg/AZA), and one Grade 3 edema (160 mg/AZA). No patient had a DLT at 80 mg/AZA. Atypical toxicities observed during dose escalation were one drug-induced liver injury (DILI), one hepatic ischemia, one Grade 3 portal hypertension, and three Grade ≥3 infusion-related reactions (IRR). No sinusoidal obstruction syndrome/venoocclusive disease (SOS/VOD) was

observed, including later in the 3 patients who proceeded to allogeneic hematopoietic cell transplantation. Due to observed cumulative toxicity at 160 mg as well as pharmacokinetic and receptor occupancy studies, BI 836858 at 80 mg/AZA was selected as the RP2D for this patient population.

The most frequent AEs were gastrointestinal (GI; predominantly Grades 1/2) and hematologic AEs, consistent with historical data for single-agent AZA in AML (Table S1). The most common non-hematologic AEs in Phase 2 were nausea and constipation (58.3% each). The most common Grade ≥3 AEs were hematologic. Two patients (5.6%) had Grade ≥3 bleeding: one Grade 4 cerebrovascular accident and one Grade 3 GI hemorrhage. Among patients in dose escalation, infections of any grade occurred in 24 patients (66.7%). Adverse events of special interest (AESIs) in Phase 2 included infusion-related reactions (IRRs) in 2 patients (5.6%); no TLS or DILI were observed. Overall, 22 patients (61.1%) had serious adverse events (SAEs), including 4 patients (11.1%) who had 7 SAEs considered treatment-related; most common treatment-related SAEs were IRRs (n=2). Twenty-two deaths (61.1%) occurred; four patients (11.1%) had AEs leading to death, all of which were infections. Fifteen patients (41.7%) had AEs leading to dose interruptions, most commonly IRRs (n=5) and chills (n=4). Three patients (8.3%) had AEs leading to dose reductions: neutropenia (n=2) and QT prolongation (n=1). Overall, BI 836858 (20-160 mg)/AZA combination demonstrated an acceptable tolerability and safety profile largely consistent with the known side effect profile of AZA, and AEs were similar to those reported in a previous Phase I/II trial of BI 836858/decitabine combination in older untreated AML patients and R/R AML patients (aged ≥18 years).[3]

In Phase 1 (n=44), the CR/CRi rate was 25.0% with a median time to best response of 3.0 months (Table 2). Six patients (13.6%) died within the first 60 days of treatment, 5 of whom received single-agent AZA. In Phase 2 (n=36), the CR/CRi rate was 50.0%, with CR 41.7% and CRi 8.3%; ORR was 52.8% (Table 2). The 30- and 60-day mortality rates were 1 (2.8%) and 4 (11.1%), respectively, with median overall survival of 15.1 months and median time to best response 3.6 months. Evaluating data among all patients (n=80) stratified by European LeukemiaNet (ELN) 2017 risk, rates of CR/CRi were highest in the favorable risk group (58.3%) and lowest in the adverse risk group (28.6%). Median survival was 18.2 months in the favorable risk group versus 15.1 months in the adverse risk group (Table S2). Three patients remained on treatment for an extended period (range 17 – 46 months), one of whom remained on the investigational agent via single-patient IND after study closure until the drug was no longer made. Three patients proceeded to allogeneic bone marrow transplant on study: one died 4 months post-transplant without known relapse, one was alive at last follow-up 18 months post-transplant, and one relapsed post-transplant.

Current standard-of-care VEN/AZA therapy was previously reported to have CR/CRi rate of 66.4% with median overall survival of 14.7 months in the international Phase 3 randomized study VIALE-A.[1] In contrast, the control group in VIALE-A (AZA monotherapy) only achieved a CR/CRi rate of 28.3% with median overall survival of 9.6 months.[1] Important differences exist between the BI 836858/AZA and VIALE-A trial designs and study populations, which temper strong conclusions about any perceived

similarities between outcomes. Though the Phase 2 study was prematurely ended after the industry partner halted development of BI 836858, the demonstration of efficacy and tolerable toxicities observed in the S2 trial suggests that additional agents targeting CD33 may yet have a place in the armamentarium for AML. Certainly, triplets combining an anti-CD33 agent with AZA/VEN are appealing at face value, but such combinations must account for potential excessive myelosuppression. Multiple ongoing studies are exploring additional approaches with chimeric antigen receptor (CAR)-T cells or bispecific T-cell engagers. Whether more innovative approaches using CAR-T cell therapies directed at CD33 following inactivation of CD33 in normal hematopoietic stem cells (Kim et al. *Cell* 2008) will be more effective remains to be seen. Importantly, in the context of the Beat AML precision medicine program, S2 afforded patients without targetable genetic lesions an opportunity for novel therapy and was a critical building block in the Beat AML program's success.

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Table 1. Demographics and Baseline Disease Characteristics.

Characteristic	Phase 1b* (N = 44)	Phase 2 (N = 36)
Age, years		
Median (range)	71 (61 - 85)	75 (63 - 90)
Age ≥ 75 years, n (%)	14 (31.8)	19 (52.8)
Gender, n (%)		
Female	21 (47.7)	14 (38.9)
Male	23 (52.3)	22 (61.1)
Race, n (%)		
White	39 (88.6)	29 (80.6)
Black or African American	2 (4.5)	2 (5.6)
Asian	2 (4.5)	2 (5.6)
Other	1 (2.3)	1 (2.8)
Unknown	0 (0.0)	2 (5.6)
ECOG Performance Status, n (%)		
0	5 (11.4)	5 (13.9)
1	31 (70.5)	18 (50.0)
2	8 (18.2)	13 (36.1)
Hemoglobin, g/dL		
Median (Range)	7.9 (1.8 – 11.6)	8.7 (6.8 – 11.0)
Platelets, 10^9/L		
Median (Range)	63.0 (3.0 – 765.0)	42.5 (6.0 – 573.0)
WBC, 10^9/L		
Median (Range)	4.9 (0.6 – 41.9)	3.1 (0.7 – 36.44)
WBC > 50, n (%)	0 (0)	0 (0)
Blood Blasts, %		
Median (range)	4.3 (0.0 – 79.0)	6.0 (0.0 – 84.0)
Bone Marrow Blasts, %		
Median (range)	52.0 (6.0 – 91.2)	36.1 (4.8 – 90.7)
Treatment-Related AML, n (%)	9 (20.5)	7 (19.4)
ELN 2017 Risk Classification		
Favorable	7 (15.9)	5 (13.9)
Intermediate	9 (20.4)	10 (27.8)
Adverse	28 (63.6)	21 (58.3)
ELN 2024 Risk Classification		
Favorable	27 (61.4)	30 (83.3)
Intermediate	14 (31.8)	4 (11.1)
Adverse	3 (6.8)	2 (5.6)
CBF, n (%)	1 (2.3)	0 (0.0)
MLL, n (%)	0 (0.0)	1 (2.8)
Complex Cytogenetics, n (%)	6 (13.6)	4 (11.1)
Mutations (VAF ≥20%), n (%)		
FLT3-ITD	3 (6.8)	0 (0.0)
NPM1	5 (11.4)	4 (11.1)
IDH1	5 (11.4)	0 (0.0)
IDH2	2 (4.5)	0 (0.0)
TP53	1 (2.3)	1 (2.8)
FLT3-TKD	1 (2.3)	0 (0.0)
FLT3 (other)	0 (0.0)	1 (2.8)
TET2	14 (31.8)	18 (50.0)
WT1	0 (0.0)	2 (5.6)
TET2/IDH1/IDH2/WT1 (≥1 with VAF≥20%)	20 (45.5)	19 (52.8)

*Includes 6 patients who did not receive combination therapy

Abbreviations: ECOG = Eastern Cooperative Oncology Group; WBC = White blood cell count; AML = Acute myeloid leukemia; ELN = European LeukemiaNet; CBF = Core binding factor; MLL = Mixed lineage leukemia; FLT3-ITD = Fms-like tyrosine kinase 3-internal tandem duplications; NPM1 = nucleophosmin 1; WT = Wild type; VAF = Variant allele frequency; IDH1 = Isocitrate dehydrogenase 1; IDH2 = Isocitrate dehydrogenase 2; TP53 = tumor protein p53; FLT3-TKD = FMS-like tyrosine kinase 3-tyrosine kinase domain; TET2 = tet methylcytosine dioxygenase 2; WT1 = Wilms tumor 1

Table 2. Observed Responses and Survival in the Efficacy Evaluable Population in Phase 1b and Phase 2

Parameter	**Phase 1b (N = 44)**	**Phase 2 (N = 36)**
CR + CRi rate,* % (n/N) [95% CI]	**25.0% (11/44)** [13.2% - 40.3%]	**50.0% (18/36)** [32.9% - 67.1%]
Overall response rate (ORR),* % (n/N) [95% CI]	34.1% (15/44) [20.5% - 49.9%]	52.8% (19/36) [35.5% - 69.6%]
Best Response, n (%)		
CR	4 (9.1)	15 (41.7)
CRi	7 (15.9)	3 (8.3)
MLFS	4 (9.1)	1 (2.8)
Partial Remission	1 (2.3)	1 (2.8)
Stable Disease	19 (43.2)	12 (33.3)
Treatment Failure – Death	1 (2.3)	1 (2.8)
Treatment Failure – Primary refractory	1 (2.3)	0 (0.0)
Unknown	7 (15.9)	3 (8.3)
Time to first response among CR/CRi [months], median (range)	3.0 (0.9-5.6)	2.7 (0.9-6.1)
Time to best response among CR/CRi [months], median (range)	3.0 (0.9-9.9)	3.6 (0.9-7.5)
Duration of response [months], median (95% CI)	-	7.1 (4.2 – 12.1)
Progression-free survival [months], median (95% CI)	-	9.4 (5.7-12.9)
Overall survival [months], median (95% CI)	-	15.1 (10.8 – 22.2)
Duration of follow-up [months], median (range)	-	20.6 (6.6 – 24.5)
Early deaths, n (%)**		
7-day	0 (0.0)	0 (0.0)
30-day	4 (9.1)	1 (2.8)
60-day	6 (13.6)	4 (11.1)
Treatment Duration [months], median (range)		
BI 836858 treatment	4.1 (0.03-15.8)	4.5 (0.03-20.9)
Azacitidine treatment	2.5 (0.1-16.2)	4.6 (0.2-21.2)
Treatment cycles completed, median (range)	4.5 (1.0 – 16.0)	5.0 (1.0 – 22.0)
Completed >6 Treatment cycles – n (%)	13 (29.5)	14 (38.9)
Treatment Duration [months], median (range)	3.0 (0.1-16.2)	4.8 (0.3-21.2)

AML = Acute myeloid leukemia; CR = Complete remission; CRi = Complete remission with incomplete hematologic recovery; MLFS = Morphologic leukemia-free state; CI = Confidence interval; NE = Not estimable; TF = Treatment Failure; ORR = CR + CRi + MLFS; - (dash) = Not applicable.

*Assessments of clinical response and disease assessment were made using the 2017 European LeukemiaNet AML recommendations.

**In phase 1b, 5 of the 6 early deaths within the first 60 days of treatment occurred in patients who received only azacitidine (4 of them within the first 30 days); only 1 death occurred in a patient administered BI 836858 40 mg +

azacitidine between the first 30 – 60 days of treatment. Phase 1b includes 6 patients who did not receive combination therapy.
Note: Phase 1b patients were administered BI 836858 doses (+ azacitidine) at 4 dose levels as follows: BI 836858 20 mg; 40 mg; 80 mg; and 160 mg. The efficacy results are for the 4 dose groups combined.
Phase 2 patients were administered BI 836858 80 mg + azacitidine, the Recommended Phase 2 Dose obtained in Phase 1b.

Table S1. Summary of Treatment-Emergent Adverse Events by Preferred Term in the Safety Analysis Population in Phase 2

Adverse Event MedDRA Preferred Term	All Patients (Total) (N = 36)
Treatment Emergent Adverse Events (TEAEs; Any Grade)	
Any TEAE - n (%)	36 (100.0)
Non-Hematologic (Incidence ≥30%)	
Nausea	21 (58.3)
Constipation	21 (58.3)
Decreased appetite	15 (41.7)
Fatigue	15 (41.7)
Hypophosphatemia	14 (38.9)
Diarrhea	12 (33.3)
Dyspnea	12 (33.3)
Blood creatinine increased	11 (30.6)
Hypoalbuminemia	11 (30.6)
Hematologic (Incidence ≥20%)	
Thrombocytopenia*	15 (41.7)
Neutropenia**	14 (38.9)
Anemia	15 (41.7)
Lymphopenia***	12 (33.3)
Leukopenia†	12 (33.3)
Febrile Neutropenia	8 (22.2)
Grade ≥3 TEAEs (Overall Incidence ≥10%)	
Any Grade ≥3 TEAE - n (%)	31 (86.1)
Neutropenia**	14 (38.9)
Thrombocytopenia**	14 (38.9)
Anemia	13 (36.1)
Leukopenia†	12 (33.3)
Lymphopenia***	11 (30.6)
Hypophosphatemia	11 (30.6)
Febrile Neutropenia	6 (16.7)
Hyponatremia	4 (11.1)
Hypotension	4 (11.1)

Cohort A = previously untreated patients aged ≥60 years with *TET2*, *IDH1*, *IDH2* or *WT1*-mutant AML; Cohort B = previously untreated patients aged ≥60 years with marker-negative AML.

MedDRA = Medical Dictionary for Regulatory Activities; AZA = Azacitidine.

All adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and were coded using MedDRA version 19.1.

*Includes the MedDRA preferred terms thrombocytopenia and platelet count decreased.

**Includes the MedDRA preferred terms neutropenia and neutrophil count decreased.

***Includes the MedDRA preferred terms lymphopenia and lymphocyte count decreased.

†Includes the MedDRA preferred terms leukopenia and white blood cell count decreased.

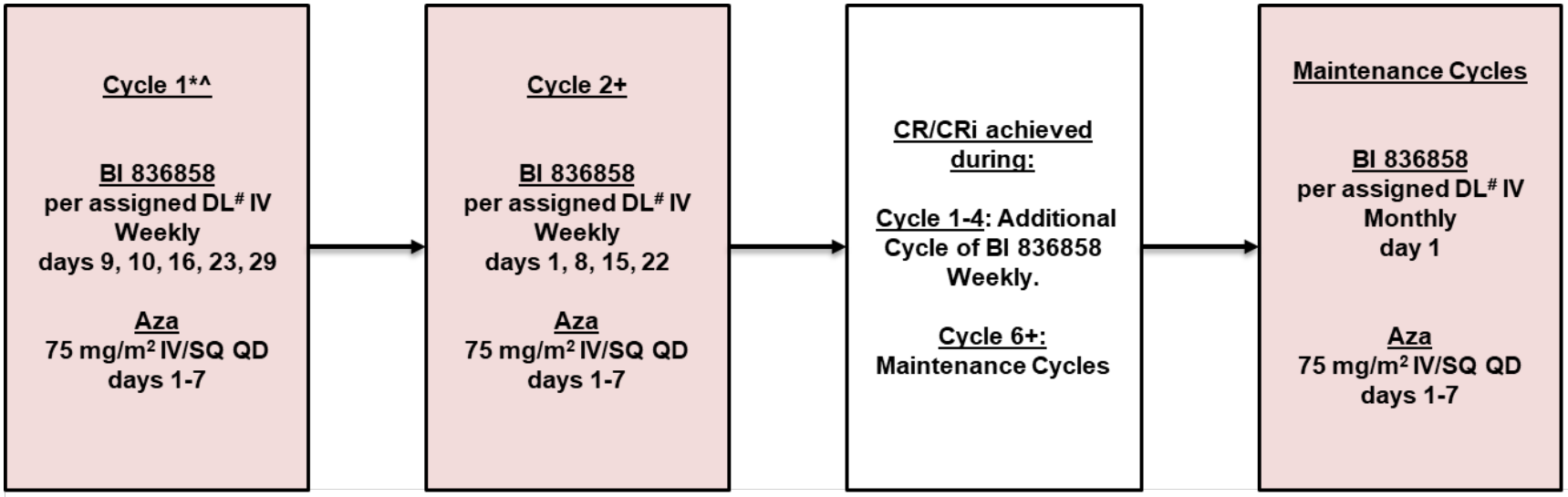
Note: Three (3) patients in the Phase 2 portion of the trial, 2 in Cohort A and 1 in Cohort B, were receiving ongoing study treatment at the time of the analysis.

Table S2. Patient Outcomes by ELN 2017 Risk Classification.

	ELN 2017 Favorable (n=12)	ELN 2017 Intermediate (n=19)	ELN 2017 Adverse (n=49)
Best Response, n (%)			
CR	4 (33.3)	5 (26.3)	10 (20.4)
CRi	3 (25.0)	3 (15.8)	4 (8.2)
MLFS	2 (16.7)	0 (0)	3 (6.1)
Partial Remission	1 (8.3)	0 (0)	1 (2.0)
Stable Disease	2 (16.7)	7 (36.8)	22 (44.9)
Treatment Failure - Death	0 (0)	1 (5.3)	1 (2.0)
Treatment Failure – Primary refractory	0 (0)	1 (5.3)	0 (0)
Unknown	0 (0)	2 (10.5)	8 (16.3)
Overall survival [months], median (95% CI)	18.2 (11.4-18.6)	11.3 (4.4-NR)	15.1 (8.1-20.6)

Patient outcomes are displayed for the combined Phase 1b and 2 portions of the study stratified by ELN 2017 risk classification.

Figure S1: Treatment Schema.



*Response evaluated days 22-29 on cycle 1, 2, and every other cycle until CR. After CR, response evaluated as needed.
^Next cycle is initiated when neutrophils ≥500/uL and platelets ≥20,000/uL or meet requirements for dose reduction.
#Dose levels: DL1=20 mg, DL2=40 mg, DL3=80 mg, DL4=160 mg.

Note that in cycle 1, 20 mg is administered on Day 9 followed by the remainder of the assigned dose on Day 10. The full dose is administered on Day 16 and weekly thereafter.