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Entospletinib with decitabine in acute myeloid leukemia with mutant *TP53* or complex karyotype: A phase 2 substudy of the Beat AML Master Trial

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AUTHOR CONTRIBUTIONS

Vu H. Duong wrote the article, designed the research, and conducted the research. **Amy S. Ruppert** and **Abigail B. Shoben** designed the research and analyzed the data. **Amy Burd**, **Alice S. Mims**, **Brian J. Druker**, **John C. Byrd**, and **Ross L. Levine** designed and conducted the research. **Leonard Rosenberg**, **Ashley O. Yocum**, **Sonja Marcus**, **Timothy Chen**, **Franchesca Druggan**, and **Mona Stefanos** designed the research and analyzed the data. **Jo-Anne Vergilio** and **Nyla A. Heerema** analyzed the data. **Alice S. Mims**, **Uma Borate**, **Eytan M. Stein**, **Maria R. Baer**, **Wendy Stock**, **Tibor Kovacsovics**, **William Blum**, **Martha L. Arellano**, **Gary J. Schiller**, **Rebecca L. Olin**, **James M. Foran**, **Mark L. Litzow**, **Tara L. Lin**, **Prapti A. Patel**, **Matthew C. Foster**, **Robert L. Redner**, **Zeina Al-Mansour**, **Christopher R. Cogle**, **Ronan T. Swords**, **Robert H. Collins**, and **Michael M. Boyiadzis** conducted the research. All authors reviewed and edited the article.

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Abstract

Background: Patients with acute myeloid leukemia (AML) who have tumor protein p53 (*TP53*) mutations or a complex karyotype have a poor prognosis, and hypomethylating agents are often used. The authors evaluated the efficacy of entospletinib, an oral inhibitor of spleen tyrosine kinase, combined with decitabine in this patient population.

Methods: This was a multicenter, open-label, phase 2 substudy of the Beat AML Master Trial (ClinicalTrials.gov identifier NCT03013998) using a Simon two-stage design. Eligible patients aged 60 years or older who had newly diagnosed AML with mutations in *TP53* with or without a complex karyotype (cohort A; $n = 45$) or had a complex karyotype without *TP53* mutation (cohort B; $n = 13$) received entospletinib 400 mg twice daily with decitabine 20 mg/m^2 on days 1–10 every 28 days for up to three induction cycles, followed by up to 11 consolidation cycles, in which decitabine was reduced to days 1–5. Entospletinib maintenance was given for up to 2 years. The primary end point was complete remission (CR) and CR with hematologic improvement by up to six cycles of therapy.

Results: The composite CR rates for cohorts A and B were 13.3% (95% confidence interval, 5.1%–26.8%) and 30.8% (95% confidence interval, 9.1%–61.4%), respectively. The median duration of response was 7.6 and 8.2 months, respectively, and the median overall survival was 6.5 and 11.5 months, respectively. The study was stopped because the futility boundary was crossed in both cohorts.

Conclusions: The combination of entospletinib and decitabine demonstrated activity and was acceptably tolerated in this patient population; however, the CR rates were low, and overall

survival was short. Novel treatment strategies for older patients with *TP53* mutations and complex karyotype remain an urgent need.

Keywords

acute myeloid leukemia; decitabine; entospletinib; hypomethylating agents; tumor protein p53 (TP53)

INTRODUCTION

Although outcomes for acute myeloid leukemia (AML) have improved for younger patients over the last several decades, the prognosis for older patients remains poor.[1,2] Older patients have more frequent and severe comorbid conditions, which can limit therapeutic options, as well as a higher incidence of AML features that predict for a poor response to standard induction chemotherapy. Among these are complex karyotype and tumor protein p53 (*TP53*) mutations.[3,4] Mutations in *TP53* are present in from 5% to 10% of patients with AML,[5–7] whereas a complex karyotype is seen in 10%–15%.[8,9] There is frequent co-occurrence, and up to 70% of patients with a complex karyotype have alterations in *TP53*.[10,11] Anthracycline and cytarabine-based chemotherapy as first-line therapy in patients with either of these features is associated with complete remission (CR) rates of only approximately 30%–40% and short overall survival (OS).[4,9,10] As monotherapy, the hypomethylating agents azacitidine and decitabine yield comparable response rates of 40%–50%, but patients often relapse quickly, and OS remains short at approximately 5–10 months.[12–15] A subgroup analysis of patients with *TP53* mutations in the phase 3 trial of azacitidine with venetoclax compared versus azacitidine alone demonstrated an improved response rate with the addition of venetoclax. Although there was a trend toward improved OS in the combination arm, this was not statistically significant. A similar effect on OS was observed in the subset of patients that had poor-risk karyotypes, which included those who had a complex karyotype.[16] Even highly selected patients who achieve remission and are able to proceed with allogeneic hematopoietic stem cell transplantation (allo-HSCT) still have very high rates of relapse and poor survival, thus novel treatment strategies are urgently needed for this population.

Entospletinib is an investigational, orally bioavailable, potent, and selective inhibitor of spleen tyrosine kinase (SYK). SYK is upregulated by *HOXA9* and *MEIS1* overexpression in AML cells, and overactivity of SYK is associated with a poor prognosis.[17,18] SYK may play a role in leukemogenesis through several mechanisms, including activation of FMS-like tyrosine kinase 3 (FLT3), STAT3, and STAT5; regulation of the mTOR pathway; and integrin signaling.[19–21] In a phase 1b/2 study of entospletinib combined with standard intensive chemotherapy (daunorubicin and cytarabine) in patients who had newly diagnosed AML, treatment was generally well tolerated, and outcomes were correlated with *HOXA9/MEIS1* overexpression. Notably, one patient achieved CR with incomplete count recovery (CRi) after the 14-day lead-in phase with entospletinib monotherapy.[22]

Among low-intensity monotherapies, decitabine given in 10-day induction courses had the highest reported response rate of 100% in patients with *TP53* mutations in one study.[23] Therefore, we conducted a phase 2 study of the 10-day decitabine regimen in combination

with entospletinib in patients aged 60 years and older who had newly diagnosed AML with either *TP53* mutations with or without a complex karyotype or a complex karyotype without *TP53* mutations.

MATERIALS AND METHODS

This was a substudy of the Beat AML Master Trial (ClinicalTrials.gov identifier NCT03013998). The protocol was reviewed and approved by both a central and the local Institutional Review Board at each participating center. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients provided a written informed consent before screening.

Patients

Patients aged 60 years or older with newly diagnosed AML, according to the World Health Organization classification,[24] were first enrolled according to the Beat AML Master protocol algorithm described previously.[25] This substudy enrolled patients who had AML with either *TP53* mutations (minimum variant allele frequency [VAF], 20%) with or without a complex karyotype (cohort A) or patients who had AML with a complex karyotype without *TP53* mutations (cohort B) who were deemed unfit or were unwilling to undergo intensive chemotherapy. A complex karyotype was defined as having three or more unrelated metaphase abnormalities. Hydroxyurea for leukocytosis and/or tretinoin for suspected acute promyelocytic leukemia that was subsequently ruled out were allowed prior to enrollment. Prior therapy for myelodysplastic syndrome, myeloproliferative syndromes, or aplastic anemia was permitted but not with hypomethylating agents. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, with aspartate aminotransferase and alanine aminotransferase <5.0 times the local/institutional upper limit of normal (ULN); bilirubin <2.0 times the ULN, except for patients with known Gilbert syndrome; and a calculated creatinine clearance >40 ml per minute or a serum creatinine ≤1.5 times the ULN. Patients with extramedullary AML were allowed but were required to have concurrent blood or bone marrow involvement. Key exclusion criteria included patients with acute promyelocytic leukemia, active central nervous system involvement with AML, known human immunodeficiency virus infection, active hepatitis B or C infection, or active bleeding or thrombosis from disseminated intravascular coagulopathy. Patients who received prior entospletinib for any myeloid malignancy were also excluded, and patients who received an investigational agent for any indication were required to wait at least 5 half-lives (or 4 weeks if the half-life was unknown) before enrollment and after all toxicities resolved to grade ≤1 or less.

Study design

This was an open-label, phase 2 study of entospletinib in combination with decitabine conducted at 13 centers in the United States. The study consisted of a 5-day lead-in period of entospletinib monotherapy, followed by an induction phase of up to three cycles, and a consolidation phase of three to 11 total cycles of entospletinib with decitabine combination; patients then transitioned into entospletinib monotherapy for up to 2 years from the start of study treatment (Figure 1). The entospletinib dose selected for this study was based on

the interim results of a phase 1b/2 study (GS-US-339-1559; ClinicalTrials.gov identifier NCT02343939) of entospletinib monotherapy or in combination with chemotherapy in adults with AML[26] and compiled pharmacokinetic data demonstrating lack of benefit to further dose escalation beyond 400 mg twice daily. Because some responses were observed during the monotherapy portion of the phase 1b/2 study, patients in our study initially received entospletinib monotherapy 400 mg orally twice daily on days 1–5 as a lead-in. This was later discontinued in a protocol amendment. All patients underwent induction (cycle 1) with entospletinib 400 mg orally twice daily on days 1–28 and decitabine 20 mg/m^2 intravenously on days 1–10 every 28-day cycle. Those who achieved CR or CR with hematologic improvement (CRh) after up to three cycles of induction proceeded to consolidation therapy for up to 11 cycles, during which decitabine was given on days 1–5 only every 28 days. Patients who achieved CRi or a morphologic leukemia-free state (MLFS) after three cycles of induction were allowed up to six cycles (induction plus consolidation) to achieve a CR or CRh or they stayed on treatment if they achieved less than MLFS but derived clinical benefit. Clinical benefit was defined as becoming transfusion-independent or having improvement (platelets or red blood cells), recovery of neutrophils, or relief of disease-related symptoms in the absence of being able to tolerate more intensive therapies. Such cases were discussed and approved by the medical monitor of the study. If patients did not achieve <5% blasts by morphology (less than MLFS) after six cycles (induction plus consolidation), they were taken off study treatment. Consolidation was followed by maintenance with entospletinib monotherapy for up to 2 years from the start of study treatment. A bone marrow biopsy and aspirate were obtained between days 25 and 30 of cycle 1 (and of cycles 2 and 3 if patients did not achieve CR/CRh/CRi/MLFS during cycle 1). During consolidation, a bone marrow biopsy and aspirate were obtained after cycles 3 and 6, at the completion of consolidation, and then every six cycles during maintenance.

End points

The primary end point of the study was the composite CR (CCR) rate of entospletinib with decitabine combination treatment, which included CR and CRh at the end of induction therapy (up to 3 cycles) and CRi or MLFS that achieved CR or CRh by up to six cycles (total of induction and consolidation). Secondary end points included the safety and tolerability profile, duration of response (DOR), OS, and the proportion of patients who transition to allo-HSCT.

Efficacy and safety assessments

Responses were assessed using the modified 2017 European LeukemiaNet AML criteria.[27] Safety assessments included adverse events (AEs), clinical laboratory parameters (hematology, clinical chemistry, and urinalysis), physical examination, vital signs, and electrocardiogram. Safety was assessed from the time of informed consent to 30 days after the last dose of study drugs. AEs were graded using the Common Terminology Criteria for Adverse Events, version 4.03.[28]

Statistical methods

For this study, the Simon optimal two-stage design was used, and each cohort was analyzed separately. The study tested the null hypothesis that the true response rate (CCR) is 40% against a one-sided alternative hypothesis of 65%. In the first stage, accrual of 13 patients was planned, and, if there were six or less responders, the study would be terminated for futility. If seven or more responders were observed in the first stage, an additional 22 patients would be enrolled in the second stage, for a total of 35 patients. If 20 or more patients responded with CR/CRh, then the null hypothesis would be rejected. This design yielded a one-sided type 1 error rate of 2.5% and power of 80% if the true response rate was 65%.

The CCR rates and their 95% confidence intervals (CIs) were calculated using the exact Clopper–Pearson method. The DOR and OS along with their 95% CIs were estimated using Kaplan–Meier methods.

RESULTS

Baseline patient characteristics

Between October 2017 and February 2020, 63 patients were enrolled in this trial, and 58 patients (45 in cohort A and 13 in cohort B) confirmed eligibility and started therapy. Baseline demographics for the entire population and for each cohort are shown in Table 1. The median age at diagnosis for patients in cohort A was 70 years and, in cohort B, it was 74 years. In cohort A, 53% of patients were female, and the majority were White (84%). In cohort B, 77% were male, and the majority were White (92%). Therapy-related AML was present in 24% and 23% of patients in cohorts A and B, respectively, and all patients had a complex karyotype. Other mutations evaluated as part of the Beat AML screening algorithm[25] were rare, with only Tet methylcytosine dioxygenase 2 (*TET2*) mutations present in more than one patient (five patients in cohort A and two patients in cohort B). No patients had isocitrate dehydrogenase 1 (*IDH1*) or nucleophosmin 1 (*NPM1*) mutations.

Treatment

In cohort A, 27 of 45 enrolled patients (60%) received lead-in entospletinib, and 44 of 45 (98%) received induction (Figure 2). One patient withdrew consent. In cohort B, six of 13 enrolled patients (46%) received lead-in entospletinib, and all 13 received induction. Nineteen patients in cohort A and 8 in cohort B went on to receive consolidation, and two patients in cohort A and one patient in cohort B received maintenance. The median number of treatment cycles received was 3.0 (range, 1.0–16.0 cycles) and 4.5 (range, 1.0–15.0 cycles) in cohorts A and B, respectively. In cohort A, the median duration of entospletinib treatment was 66.0 days (range, 1–515 days) and, for decitabine, it was 57.0 days (range, 2–414 days). In cohort B, the median duration of entospletinib treatment was 137.0 days (range, 28–462 days) and, for decitabine, it was 127.0 days (range, 10–403 days). The most common reasons for treatment discontinuation in cohort A were AEs (27%), treatment failure (27%), and withdrawal of consent (16%); and in cohort B, the most common reasons were treatment failure (31%) and disease progression after a response and relapse (15% each). One patient in each cohort discontinued therapy because they died from leukemia,

and one patient in cohort A who was in CRh discontinued therapy because they developed a new chromosome abnormality (monosomy 7). Two patients (4%) in cohort A and one patient (8%) in cohort B discontinued treatment because of allo-HSCT.

Responses

Of the 45 patients enrolled in cohort A, six (13.3%) achieved the primary end point of CCR with up to six cycles of treatment, with five patients achieving a CR (11.1%) and one (2.2%) achieving a CRh (Table 2). Ten patients received both study drugs but did not have a bone marrow biopsy for investigator assessment of clinical response (although five had a complete blood count drawn from the peripheral blood), thus the CCR rate was 17.1% in the efficacy-evaluable population ($n = 35$). Among these 10 patients, four had an AE that precluded further evaluation/treatment, four withdrew consent, one had treatment failure, and one died with active leukemia. The overall best responses were CR (13.3%), CRh (4.4%), CRi (15.6%), and MLFS (15.6%); this resulted in an overall response rate (CR + CRh + CRi + MLFS) of 48.9%. At the first interim analysis, the primary end point was reached in only two of the 13 initial patients, both of whom attained CR by the end of cycle 3. Although the futility boundary was crossed in stage 1, the study team, in consultation with the Data and Safety Monitoring Board, decided to expand accrual based on patients who were achieving CRi with treatment.

All 13 patients in cohort B were evaluable for response. With up to six cycles of treatment, the primary end point of CCR was achieved in four of 13 patients (30.8%), with three patients achieving CR (23.1%) and one patient achieving CRh (7.7%) (Table 2). Overall best response rates in cohort B were CR (38.5%), CRi (23.1%), and MLFS (15.4%), resulting in an overall response rate of 76.9%. The futility boundary was crossed, and enrollment was stopped.

Duration of response and survival

Of the patients achieving CCR, the median DOR was 7.6 months in cohort A and 8.2 months in cohort B (Table 2). With a median follow-up of 11.5 months in cohort A and 15.1 months in cohort B, the median OS was 6.5 and 11.5 months, respectively (Table 2 and Figure 3).

Early deaths

Within first 7, 30, and 60 days, there were zero, three, and 11 deaths, respectively, in cohort A; and zero, zero, and two deaths, respectively, in cohort B (Table 2).

Allogeneic hematopoietic stem cell transplantation

In addition to the two patients in cohort A and one patient in cohort B who discontinued study treatment because they proceeded to allo-HSCT, two other patients in cohort A who discontinued study treatment for other reasons (treatment failure [$n = 1$] and AE or intercurrent illness [$n = 1$]) eventually also received allo-HSCT. Therefore, overall, four patients (9%) in cohort A and one patient (8%) in cohort B received allo-HSCT in this study.

Safety

A summary of the most common AEs and laboratory abnormalities is shown in Table 3. All patients in cohorts A and B experienced at least one treatment-emergent AE. Overall, the most common AEs (any grade) in cohort A were thrombocytopenia (57.8%), neutropenia, and febrile neutropenia and nausea (51.1% each); and, in cohort B, they were neutropenia and leukopenia (92.3% each), thrombocytopenia (76.9%), and diarrhea (69.2%). Thirty-seven of 45 patients (82.2%) in cohort A and 12 of 13 patients (92.3%) in cohort B experienced at least one treatment-related AE (any grade). Twenty-eight patients (62.2%) in cohort A and eight patients (61.5%) in cohort B had grade ≥3 treatment-related AEs; most common treatment-related grade ≥3 AEs in both cohorts were febrile neutropenia (31.1% in cohort A and 38.5% in cohort B) and anemia (22.2% and 30.8%, respectively). Thirty-three patients (73.3%) experienced 83 serious AEs (SAEs) in cohort A and six patients (46.2%) experienced 12 SAEs in cohort B. The most common SAEs in cohort A were pneumonia (17.8%) and respiratory failure (11.1%), and, in cohort B, they were sepsis, acute kidney injury, and dehydration (15.4% each). The most common treatment-related grade ≥3 clinical laboratory abnormalities in both cohorts were hematologic in nature and included neutropenia (28.9%), decreased white blood cell count (20.0%), and decreased lymphocyte count (17.8%) in cohort A; and neutropenia and decreased platelet count (30.8% each), decreased white blood cell count (23.1%), and decreased lymphocyte count (15.4%) in cohort B. The only AE that occurred in more than one patient and resulted in permanent discontinuation of both study drugs was pneumonia in three patients (6.7%) in cohort A. Also in cohort A, increased blood bilirubin, increased aspartate aminotransferase, and increased alanine aminotransferase occurred in two patients each (4.4% each) and resulted in discontinuation of entospletinib only. Five patients had AEs that resulted in death, including in four patients in cohort A that were considered not related to any of the study drugs by the investigator and in one patient in cohort B who had grade 5 sepsis that was considered related to decitabine by the investigator.

DISCUSSION

The prognosis for patients with AML associated with *TP53* mutations or complex karyotypes is dismal. In this phase 2 study of entospletinib with the 10-day decitabine regimen in an older population with very-high-risk features, the combination was well tolerated overall, with a toxicity profile similar to what would be expected with 10-day decitabine monotherapy, but response rates were low, with a CR/CRi rate of 17.1% in patients who had *TP53* mutations and 30.8% in patients who had a complex karyotype and no *TP53* mutations. DOR and survival were also short.

Although our results for cohort A clearly do not reach the 100% response rate reported for the 10-day decitabine monotherapy regimen in 21 patients with MDS or AML who have mutations in *TP53*,[23] this is caused at least in part by differences in the definition of response, and perhaps differences in VAF. Our best response rate increased to 62.9% when we also included CRi and MLFS, which is comparable to other studies in the literature with regimens based on 10-day decitabine[14,29] or azacitidine.[13,16,30,31] In addition, the median OS of 6.5 months in patients with *TP53* mutations and 11.5 months in those with

a complex karyotype also compares well with the current literature.[29,30,32] Although we used the 10-day decitabine regimen in this study, a randomized trial published by Short and colleagues showed similar overall response rates between the 5-dat and 10-day regimens (43% vs. 40%), including the subset of patients with *TP53* mutations (29% vs. 47%).[14] This study and others[29] did not show a correlation between the baseline *TP53* VAF and response. We had a relatively high VAF requirement of 20% for *TP53* mutations to be eligible for this study, whereas others have often used a cutoff of 10%, which may also account for differences in response rates. Venetoclax was added to the 10-day decitabine regimen in a study by DiNardo and colleagues,[32] who reported a CR/CRi rate of 69% and a median OS of 6.9 months in patients with *TP53* mutations, and the rate was 75% with median OS of 9.3 months in patients who had European LeukemiaNet-defined adverse risk disease. Again, although the response rates may be slightly higher in these studies, the OS appears comparable.

It is unlikely that entospletinib exerted any antagonistic effect on decitabine, but the low CR/CRh rates that crossed the futility boundaries show that it does not confer additional benefit. However, it was recently observed that entospletinib has promising response rates when combined with induction chemotherapy for fit patients with newly diagnosed AML, particularly those with NPM1 mutations.[22] Consequently, an ongoing randomized phase 3 study is evaluating the addition of entospletinib to standard 7 + 3 chemotherapy and consolidation (ClinicalTrials.gov identifier NCT05020665). In our study, as expected, no patients had a NPM1 mutation both because of the rarity of its co-occurrence with *TP53* mutations and a complex karyotype and because the design of the Beat AML Master Trial prioritized and assigned patients with NPM1 mutations into another substudy.[25]

Only five patients proceeded to allo-HSCT, which would also be expected in these predominantly older patients who have significant comorbid conditions and very poor-risk disease. In addition, the current literature suggests that patients with *TP53* mutations and/or a complex karyotype have very poor outcomes, even with allo-HSCT, and thus patients and/or their treating physicians may have decided against pursuing this modality of therapy, which is associated with substantial morbidity and mortality.

The results of the VIALE-A trial (ClinicalTrials.gov identifier NCT02993523) established azacitidine with venetoclax as the new standard of care for patients with newly diagnosed AML who are ineligible for induction chemotherapy, but these results were not available until after our clinical trial began enrollment and did not seem to have a significant impact on our accrual rate. Although the subset analyses in the VIALE-A trial still favored the addition of venetoclax in patients with *TP53* mutation or poor karyotype, the benefit of adding venetoclax in patients with *TP53* mutations has recently come into question.[29,33,34] Various mutation-related factors may influence the outcome of patients with *TP53* mutations, including the presence of biallelic mutations,[35] variant allele frequency,[36,37] and clearance (<5%) by next-generation sequencing.[38] The majority of patients on this study had high VAF mutations, but we did not assess serial mutation load over the course of this study. The results of our clinical trial underscore the need for ongoing studies and clinical trial efforts to improve the very poor outcomes of patients with *TP53* mutations and/or a complex karyotype.

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CONFLICT OF INTEREST STATEMENT

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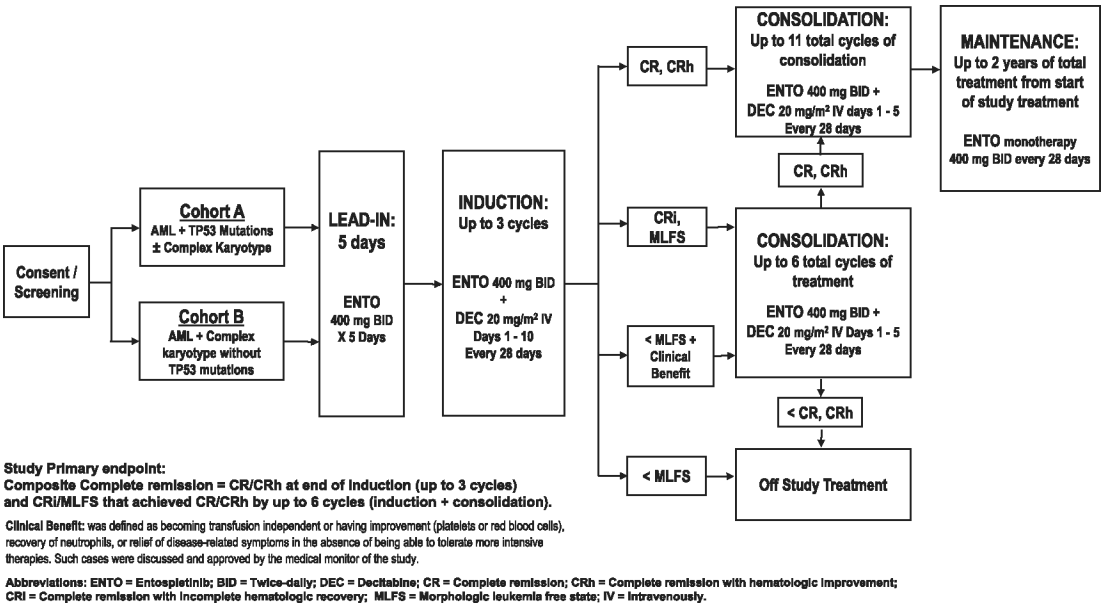

FIGURE 1.
Study design and treatment schematic.

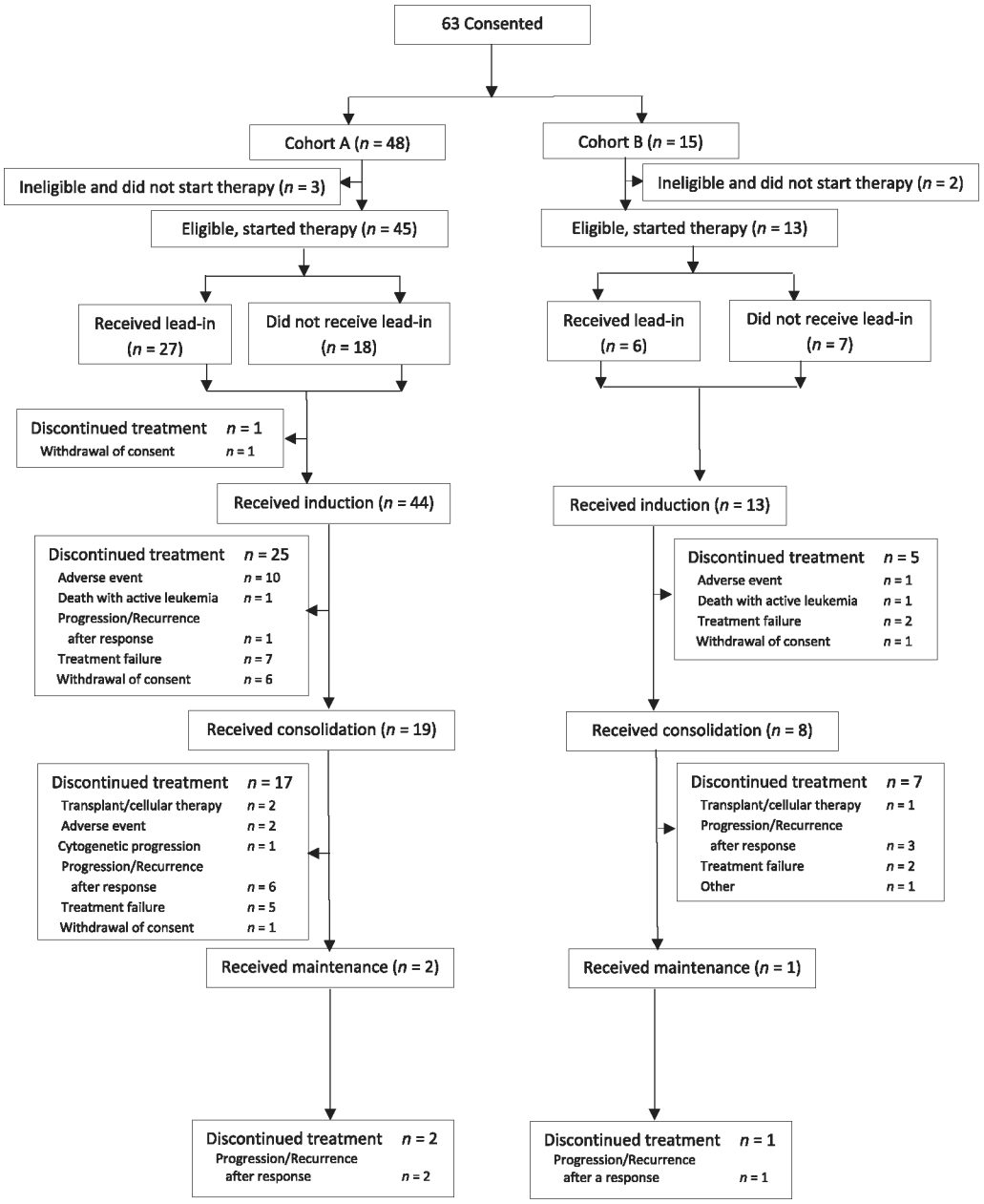

FIGURE 2.

Consolidated Standards of Reporting Clinical Trials (CONSORT) diagram of the current study.

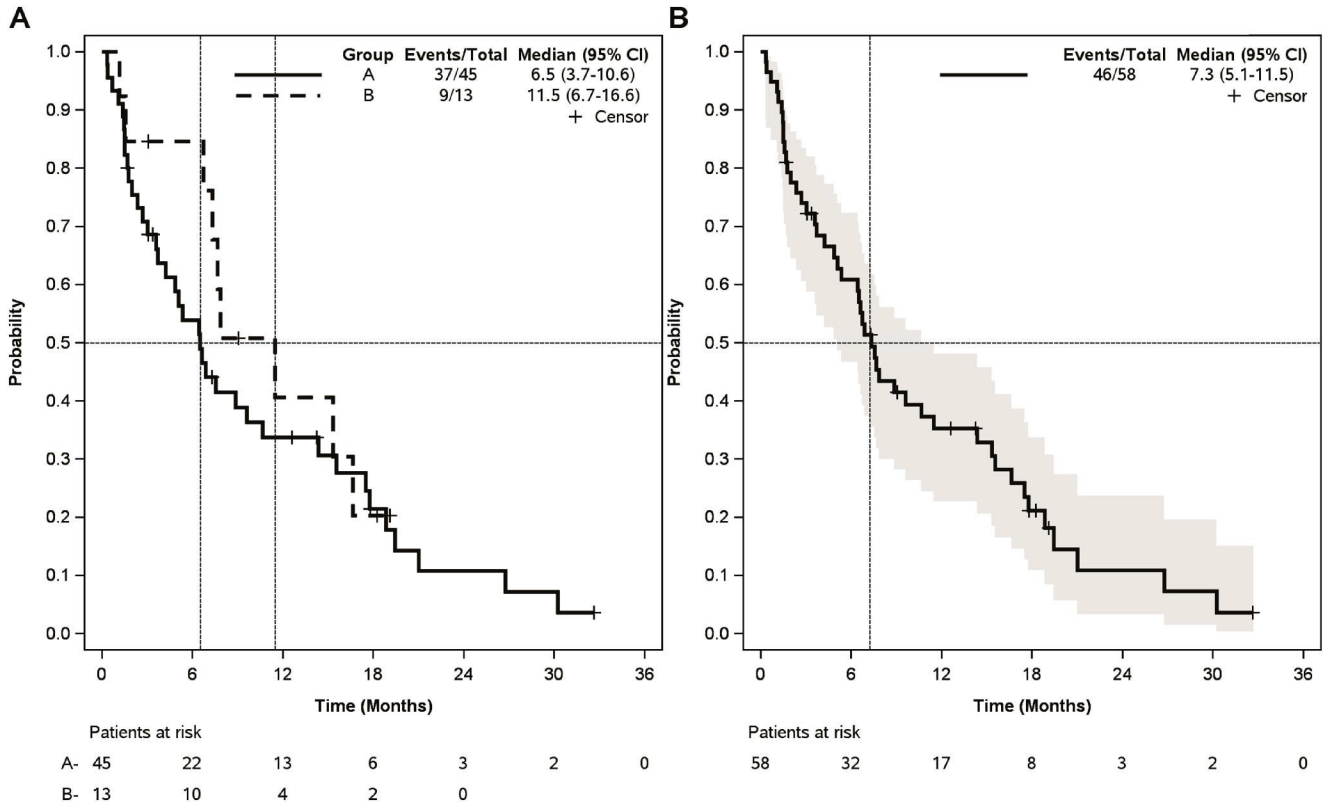

FIGURE 3.

Kaplan–Meier plots of overall survival (A) by cohort and (B) for all patients who received treatment with entospletinib and decitabine combination therapy.

TABLE 1

Baseline characteristics.

Characteristic	All, *n* = 58, No. (%)	Cohort A, *n* = 45, No. (%)	Cohort B, *n* = 13, No. (%)
Age			
Median [range], years	71 [60–86]	70 [60–84]	74 [65–86]
≥75 years	16 (28)	10 (22)	6 (46)
Sex			
Female	27 (47)	24 (53)	3 (23)
Male	31 (53)	21 (47)	10 (77)
Race			
Caucasian	50 (86)	38 (84)	12 (92)
African American	5 (9)	4 (9)	1 (8)
Unknown	3 (5)	3 (7)	0 (0)
ECOG performance status			
0	11 (19)	9 (20)	2 (15)
1	36 (62)	26 (58)	10 (77)
2	11 (19)	10 (22)	1 (8)
CBC at presentation, median [range]			
Hemoglobin, g/dL	8.3 [6.2–14.2]	8.2 [6.2–12.5]	8.3 [6.9–14.2]
Platelets, 10^9/L	29.5 [6–172]	28 [6–172]	30 [12–77]
WBC count, 10^9/L	3.8 [0.2–51.3]	3.6 [0.2–51.3]	5.8 [0.9–34.6]
ANC, 10^9/L	0.43 [0–15.5]	0.50 [0–5.8]	0.40 [0.21–15.5]
Peripheral blood blast %	13.5 [0–88]	11.5 [0–88]	18.5 [2–55]
Bone marrow blast %	32.3 [3–87]	35 [3–87]	30 [6.2–82]
Treatment-related AML	14 (24)	11 (24)	3 (23)
Antecedent MDS and/or MPN	7 (12)	6 (13)	1 (8)
Karyotype			
Complex	58 (100)	45 (100)	13 (100)
Core-binding factor	3 (5)	0 (0)	3 (23)
Mixed-lineage leukemia	1 (2)	1 (2)	0 (0)
Mutations			

Characteristic	All, *n* = 58, No. (%)	Cohort A, *n* = 45, No. (%)	Cohort B, *n* = 13, No. (%)
TP53	45 (78)	45 (100)	0 (0)
FLT3-ITD	1 (2)	1 (2)	0 (0)
FLT3-TKD	0 (0)	0 (0)	0 (0)
NPM1	0 (0)	0 (0)	0 (0)
IDH1	0 (0)	1 (2)	0 (0)
IDH2	1 (2)	1 (2)	0 (0)
TET2	7 (12)	5 (11)	2 (15)
WT1	1 (2)	1 (2)	0 (0)

Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; CBC, complete blood count; ECOG, Eastern Cooperative Oncology Group; *FLT3-ITD,* Fms-like tyrosine kinase 3-internal tandem duplications; *FLT3-TKD,* FMS-like tyrosine kinase 3-tyrosine kinase domain; *IDH1,* isocitrate dehydrogenase 1; *IDH2,* isocitrate dehydrogenase 2; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; *NPM1,* nucleophosmin 1; *TET2,* Tet methylcytosine dioxygenase 2; *TP53,* tumor protein p53; WBC, white blood cell; *WT1,* Wilms tumor 1.

TABLE 2

Responses, duration of response, and survival in the modified intent-to-treat population.

Parameter	Cohort A, *N* = 45, No. (%)	Cohort B, *N* = 13, No. (%)
Primary end point		
Composite CR rate [95% exact CI][a]	6 (13.3) [5.1–26.8]	4 (30.8) [9.1–61.4]
CR	5 (11.1)	3 (23.1)
CRh	1 (2.2)	1 (7.7)
Best response		
CR	6 (13.3)	5 (38.5)
CRh	2 (4.4)	0 (0.0)
CRi	7 (15.6)	3 (23.1)
MLFS	7 (15.6)	2 (15.4)
Stable disease	13 (28.9)	3 (23.1)
NE	10 (22.2)	0 (0.0)
Overall response rates		
CR + CRh	17.8	38.5
CR + CRh + CRi	33.3	61.5
CR + CRh + CRi + MLFS	48.9	76.9
Median duration of response [95% CI], months	7.6 [2.4 to NE], *n* = 6	.5 [5.4 to NE], *n* = 4
Median duration of follow-up/range, months	11.5/1.7–32.6, *n* = 6	15.1/3.1–19.1, *n* = 4
Median overall survival [95% CI], months	6.5 [3.7–10.6], *n* = 6	11.5 [6.7–16.6], *n* = 4
Early deaths		
7-day	0 (0.0)	0 (0.0)
30-day	3 (7.0)	0 (0.0)
60-day	11 (24.0)	2 (15.0)

Abbreviations: CI, confidence interval; CR, complete remission; CRh, complete remission with hematologic improvement; CRi, complete remission with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; NE, not evaluated.

[a]The composite CR rate at the end of six total cycles was defined as the number and percentage of patients who achieved CR/CRh by the end of induction therapy (up to cycle 3) or had CRi/MLFS by the end of induction therapy and achieved CR/CRh by up to a total of six cycles (induction + consolidation). Assessments of clinical response were made using modified 2017 European LeukemiaNet acute myeloid leukemia criteria.[27]

TABLE 3

Most common adverse events, serious adverse events, and clinical laboratory abnormalities.

Adverse event MedDRA preferred term[a]	Cohort A, *n* = 45, No. (%)	Cohort B, *n* = 13, No. (%)	All, *n* = 58, No. (%)
Adverse events of any grade in ≥40% of patients total			
Thrombocytopenia[b]	26 (57.8)	10 (76.9)	36 (62.1)
Neutropenia[c]	23 (51.1)	12 (92.3)	35 (60.3)
Leukopenia[d]	22 (48.9)	12 (92.3)	34 (58.6)
Anemia	22 (48.9)	8 (61.5)	30 (51.7)
Febrile neutropenia	23 (51.1)	7 (53.8)	30 (51.7)
Nausea	23 (51.1)	6 (46.2)	29 (50.0)
Diarrhea	19 (42.2)	9 (69.2)	28 (48.3)
Hypokalemia	21 (46.7)	5 (38.5)	26 (44.8)
Grade ≥3 treatment-related adverse events in two or more patients			
Febrile neutropenia	14 (31.1)	5 (38.5)	19 (32.8)
Anemia	10 (22.2)	4 (30.8)	14 (24.1)
Sepsis	2 (4.4)	1 (7.7)	3 (5.2)
Lung infection	2 (4.4)	0 (0.0)	2 (3.4)
Rash, maculopapular	2 (4.4)	0 (0.0)	2 (3.4)
All-cause serious adverse events in two or more patients			
Pneumonia	8 (17.8)	1 (7.7)	9 (15.5)
Respiratory failure	5 (11.1)	0 (0.0)	5 (8.6)
Atrial fibrillation	4 (8.9)	0 (0.0)	4 (6.9)
Sepsis	3 (6.7)	2 (15.4)	5 (8.6)
Cellulitis	3 (6.7)	0 (0.0)	3 (5.2)
Myocarditis	2 (4.4)	0 (0.0)	2 (3.4)
Acute kidney injury	1 (2.2)	2 (15.4)	3 (5.2)
Pleural effusion	2 (4.4)	0 (0.0)	2 (3.4)
Dehydration	0 (0.0)	2 (15.4)	2 (3.4)
Grade ≥3 treatment-related laboratory abnormalities in two or more patients			
Neutropenia[c]	13 (28.9)	4 (30.8)	17 (29.3)

Adverse event MedDRA preferred term[a]	Cohort A, *n* = 45, No. (%)	Cohort B, *n* = 13, No. (%)	All, *n* = 58, No. (%)
WBC count decreased	9 (20.0)	3 (23.1)	12 (20.7)
Lymphocyte count decreased	8 (17.8)	2 (15.4)	10 (17.2)
Platelet count decreased	7 (15.6)	4 (30.8)	11 (19.0)
Blood bilirubin increased	5 (11.1)	1 (7.7)	6 (10.3)
Alanine aminotransferase increased	3 (6.7)	1 (7.7)	4 (6.9)
Aspartate aminotransferase increased	2 (4.4)	1 (7.7)	3 (5.2)

Note: Cohort A, *TP53* mutations (identified molecularly) with or without complex karyotype; cohort B, complex karyotype (three or more metaphase abnormalities without *TP53* mutation).

Abbreviations: MedDRA, *Medical Dictionary for Regulatory Activities;* WBC, white blood cell.

[a] 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.

[b] Includes the MedDRA preferred terms thrombocytopenia and platelet count decreased.

[c] Includes the MedDRA preferred terms neutropenia and neutrophil count decreased.

[d] Includes the MedDRA preferred terms leukopenia and white blood cell count decreased.