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Decitabine plus all-*trans* retinoic acid versus decitabine monotherapy for myelodysplastic syndromes with excess blasts: a multicenter, randomized controlled trial

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Clinical Trial Registration

This study was registered with the Chinese Clinical Trial Registry (<http://www.chictr.org.cn>, identifier ChiCTR1800018307)

Author Contributions

HT and XZ were involved in the study design, data acquisition and interpretation, manuscript writing, and critical review and accessed and verified the data. HT, XZ, YL, YG, ZG, LH, JZ, HC, GO, YT, YK, FZ, LS, WJ, GX, LM, LY, CM, JJ, and FM enrolled and treated patients and gathered data. JL conducted the statistical analysis. XZ drafted the manuscript. All the authors reviewed the final manuscript and took responsibility for the data. All the authors approved the article for publication.

Conflict of interest

The authors declare no conflicts of interest.

Data Availability Statement

Original data are available from the corresponding author upon request.

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Ethics Approval and Patient Consent Statement

All patients signed written informed consent. The study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine in Hangzhou (master protocol ID: 2018850).

Abstract

Despite standard treatment with hypomethylating agents, the prognosis of patients with higher-risk myelodysplastic syndrome (MDS) remains poor. *All-trans* retinoic acid (ATRA) has demonstrated promising efficacy in unfit patients with acute myeloid leukemia. This multicenter controlled trial randomized (1:1) untreated patients with MDS with excess blasts (MDS-EB) to ATRA plus decitabine (ATRA at 25 mg/m²/day in 2 divided daily doses throughout the 28-day cycle plus decitabine at 20 mg/m² on days 1–5) or decitabine alone (20 mg/m² on days 1–5). The primary endpoint was the overall response rate within 4 treatment cycles. A total of 227 patients were randomized. Four patients who did not commence therapy were excluded from the modified intention-to-treat (mITT) analysis. The median patient age was 62 years (range: 19–81). The overall response rate was 78% (86/110) in the ATRA group versus 51% (58/113) in the decitabine group (odds ratio [OR] 3.40; 95% confidence interval [CI] 1.90–6.09; p<0.001). The ATRA group also had a higher complete remission rate (23% versus 12%; OR 2.05; 95% CI 1.02–4.25; p=0.042). With a median follow-up of 30.1 months, progression-free survival (PFS) was 14.9 months in the ATRA group versus 10.5 months in the decitabine group (hazard ratio [HR] 0.70; 95% CI 0.51–0.97; p=0.03). The overall survival (OS) was 23.0 months and 19.3 months, respectively (HR 0.77, 95% CI 0.54–1.09; p=0.137). The two groups did not differ in grade 3 or higher hematological adverse events. In conclusion, adding ATRA to decitabine increased the overall response rate and prolonged PFS in adult patients with MDS-EB without increasing hematological toxicity. This study was registered at Chinese Clinical Trial Registry ChiCTR1800018307.

Introduction

Myelodysplastic syndrome (MDS) is a clonal malignant disease of hematopoietic stem cells. Patients with higher-risk MDS, as classified by the International Prognostic Scoring System (IPSS) or Revised International Prognostic Scoring System (IPSS-R),¹ are at high risk of progression to acute myeloid leukemia (AML). Hypomethylating agents (HMAs), including decitabine and azacytidine, are standard treatments for higher-risk MDS. However, patient outcomes remain poor despite HMA treatment. The rates of complete remission (CR) and overall response (OR) range from 7% to 17% and from 30% to 52%, respectively.²⁻⁴ The median overall survival (OS) is 10.1–24.5 months.²⁻¹¹ Allogeneic hematopoietic cell transplantation (allo-HSCT) is the only potentially curative treatment,¹² but many elderly patients are not appropriate candidates for allo-HSCT.

A variety of novel treatment strategies have been attempted for higher-risk MDS. The molecular targets of these treatments include somatic genetic mutations, cell-surface antigens, and antiapoptotic pathways. Despite encouraging results in the early development phases, subsequent trials with larger sample sizes have generally been disappointing.¹³⁻¹⁷ In a phase III trial of the anti-TP53 agent eprenetapopt plus azacitidine in patients with TP53-mutated MDS, the CR rate did not differ from that of azacitidine monotherapy.¹⁵ The PANTHER trial compared azacitidine alone versus azacitidine in combination with the NEDD8 inhibitor pevonedistat and failed to show improvement in event-free survival (EFS). The ENHANCE trial compared azacitidine alone versus azacitidine in combination with the CD47 antibody magrolimab but failed to improve CR and OS.¹⁸ The STIMULUS trial compared HMAs alone with those combined with the TIM-3 inhibitor sabatolimab but also failed to improve CR and progression-free survival (PFS).¹⁹

All-*trans* retinoic acid (ATRA) induces blast differentiation in acute promyelocytic leukemia (APL) and is recommended for APL treatment. ATRA may be effective in AML without the PML-RARA fusion protein. Preclinical studies have indicated that HMAs

increase the sensitivity of AML cells to ATRA.^{20, 21} Reciprocally, ATRA can potentiate the cytotoxic effects of decitabine.^{22, 23} Lübbert M. and colleagues demonstrated the cooperative antileukemic effects of decitabine and ATRA on the AML cell lines U937 and MOLM-13. In addition to the derepression of tumor suppressor genes such as HIC1, the induction of transposable elements was observed with both drugs, triggering a “viral mimicry” response.²³ Our preclinical data revealed that decitabine induced Nrf2 activation and downstream antioxidative responses and inhibited reactive oxygen species (ROS) generation, thus leading to decitabine resistance. The addition of ATRA blocked Nrf2 activation by activating the RAR α -Nrf2 complex, leading to ROS accumulation and ROS-dependent cytotoxicity.²²

Two single-arm trials in the 2000s reported the promising efficacy of a therapeutic regimen that included HMA, ATRA, and valproate in mixed groups of AML and MDS patients.^{24, 25} The more recent DECIDER trial compared decitabine alone versus decitabine in combination with valproate, ATRA, or valproate plus ATRA in AML patients and demonstrated a higher objective response rate in patients treated with regimens that included ATRA but not valproate.²⁶ Notably, 56 out of the 200 patients in the DECIDER trial fulfilled the criteria for oligoblastic AML (20–30% blasts) according to the current classification system but were diagnosed with refractory anemia with excess blasts in transformation (RAEB-T) according to the French–American–British classification at the time. A post hoc analysis of this subgroup revealed that the combination of ATRA and decitabine increased ORR and OS rates.²⁷ Based on these findings, we hypothesized that adding ATRA to HMAs could improve treatment response in patients with MDS with excess blasts (MDS-EB) and conducted a prospective trial to compare decitabine in combination with ATRA versus decitabine alone in patients with newly diagnosed MDS-EB.

Methods

Participants and eligibility

This multicenter, randomized controlled trial was conducted in 8 centers in China. Adult

patients (≥ 18 years of age) with morphologically confirmed MDS-EB-1 or MDS-EB-2, as defined by the World Health Organization classification (WHO 2016), were eligible. The trial was conducted following the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonization. The Institutional Review Boards approved the trial protocol (master protocol ID: 2018850). Written informed consent was obtained from all patients before enrollment. This trial is registered at the Chinese Clinical Trial Registry (ChiCTR1800018307).

Study design and procedures

Patients were randomized at a 1:1 ratio to receive ATRA plus decitabine or decitabine alone. The randomization was stratified based on centers.

Each cycle lasted 28 days, and the study treatment was planned for at least four cycles. For each cycle, all patients received 20 mg/m^2 intravenous decitabine infusion over 60 minutes during the first 5 days. For the first 4 cycles, patients in the ATRA group also received oral ATRA at $25 \text{ mg/m}^2/\text{day}$ in 2 divided daily doses throughout the 28-day cycle (Appendix p 16). Starting from the fifth cycle, ATRA was given at $25 \text{ mg/m}^2/\text{day}$ only for the first 14 days of the 28-day cycle. The daily ATRA dosage was based on its recommendation in the Chinese clinical practice guidelines for APL.²⁸ Treatment continued until disease progression, unacceptable toxicity, or patient decision to withdraw from the trial (Appendix p 49-50).

Outcomes

The primary endpoint was the overall response rate (ORR), which was calculated based on the best response within four cycles and included CR, PR, mCR, and HI according to the modified International Working Group (IWG) 2006 response criteria in the MDS.²⁷

The secondary endpoints included the bone marrow blast response (CR+mCR), hematological response (CR+PR+HI), progression-free survival (PFS), OS, and treatment-emergent adverse events.

Statistical analysis

The sample size requirement was estimated via PASS 11.0 software (NCSS, Kaysville, UT) based on the following assumptions: 1) an ORR of 50% in the decitabine group¹¹ and 70% in the ATRA group; 2) an alpha of 0.05; and 3) a power ($1 - \beta$) of 80%. The calculation yielded 180 subjects (90 per group). Assuming a 20% dropout rate, we planned to enroll 226 patients. All efficacy endpoints and treatment-emergent adverse events were calculated using a modified intent-to-treat (mITT) population that included all patients who received at least one dose of the assigned treatment. Categorical variables were analyzed via the χ^2 test or Fisher's exact test, as appropriate. Continuous variables with a normal distribution were analyzed via Student's *t*-test and are presented as the means \pm standard deviations. Continuous variables not normally distributed were analyzed via the Mann-Whitney U test and are presented as the median and interquartile range (IQR). Survival outcomes were estimated via the Kaplan-Meier method and compared via the log-rank test. All the statistical analyses were conducted via SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics

Between Sep 11, 2018, and Sep 10, 2022, 243 patients were assessed for eligibility, and 227 were enrolled (113 and 114 patients in the ATRA and decitabine groups, respectively; Figure 1). The disease subtype was MDS-EB-1 in 109 patients and MDS-EB-2 in 118 patients. 28 (25%) patients in the ATRA group and 25 (22%) in the decitabine group received allo-HSCT. 12 (11%) patients in the ATRA group and 10 (9%) in the decitabine group received allo-HSCT within 4 cycles. At the time of data cutoff (May 31, 2023), 13 patients in the ATRA group and 10 in the decitabine group were still receiving the assigned treatment.

The median patient age was 62 years (IQR: 54–68; range: 19–81; Table 1). The IPSS-R category was high or very high in 181 (81%), intermediate in 33 (15%), and low in

the remaining 1 (0.4%) patients. Mutated genes were generally balanced between the two groups (Figure 2). Post-hoc reclassification of the patients with next-generation sequencing data based on the IPSS-M is shown in Appendix p 17.

The median number of decitabine cycles was 4 (range, 1–17) in the ATRA group and 3 (range, 1–20) in the decitabine group. The reasons for treatment discontinuation within 4 cycles are shown in Figure 1. ATRA was reduced in dosage in 13 patients and permanently discontinued in 4 patients before the completion of 4 cycles; decitabine was continued in all 17 patients.

Treatment response

Owing to the outbreak of COVID-19, 38 out of the 110 patients in the ATRA group and 32 out of the 113 patients in the decitabine group missed at least one scheduled bone marrow examination during the follow-up.

The ORR was 78% (86/110) in the ATRA group versus 51% (58/113) in the decitabine group (odds ratio 3.40; 95% CI 1.90–6.09; $p < 0.001$; Table 2). The ATRA group also had a higher CR rate (23% versus 12%; odds ratio 2.05; 95% CI 1.02–4.25; $p = 0.042$), CR+mCR rate (72% versus 49%; odds ratio 2.69; 95% CI 1.54–4.68; $p < 0.001$), and CR+PR+HI rate (48% versus 34%; odds ratio 1.84; 95% CI 1.07–3.15; $p = 0.027$). In patients with TP53 mutation, ORR was 79% (11/14) and 54% (7/13) in the ATRA+decitabine and decitabine alone groups, respectively (odds ratio 3.14; 95% CI 0.59–16.85; $p = 0.181$); The CR rate was 29% (4/14) in ATRA group and 23% (3/13) in decitabine group (odds ratio 1.33; 95% CI 0.24–7.56; $p = 0.745$). The median time to initial response did not differ between the two groups (1 cycle in both groups). The rate of response type after one treatment cycle was 3.6% (4/110) CR, 12.7% (14/110) mCR+HI, 38.2% (42/110) mCR without HI, and 6.4% (7/110) HI only in the ATRA plus decitabine group versus 2.7% (3/113) CR, 10.6% (12/113) mCR+HI, 23.9% (27/113) mCR without HI, and 3.5% (4/113) HI in the decitabine alone group. The rate of leukemic transformation was 58% (64/110) in the ATRA group versus 66%

(75/113) in the decitabine group (odds ratio 1.42, 95% CI 0.82–2.44; $p=0.207$). In patients with abnormal cytogenetic data at baseline, the rate of cytogenetic response was 76% (22/29) in the ATRA group and 57% (16/28) in the decitabine group (odds ratio 2.36; 95% CI 0.76–7.32; $p=0.134$). The main effect (higher ORR in the ATRA group) was observed across all subgroups, except for women (p for interaction = 0.032; Figure 3). The cause of the difference in efficacy between men and women needs further exploration. Subgroup analysis of overall response (CR+PR+mCR+HI) in patients with mutations is shown in Appendix p 9.

Survival outcomes

Within a median follow-up of 30.1 months (IQR, 17.7–44.8), a total of 129 (58%) patients died. The number of patients with disease progression and relapse was 68 (62%) in the ATRA group and 82 (73%) in the decitabine group. The median PFS was 14.9 months (95% CI 9.5–20.3) in the ATRA group and 10.5 months (95% CI 7.2–13.7) in the decitabine group (hazard ratio 0.70; 95% CI 0.51–0.97; $p=0.032$; Figure 4). The two groups did not differ in median time to AML transformation (18.9 versus 15.8 months; hazard ratio 0.81; 95% CI 0.58–1.14; $p=0.221$) or OS (23.0 versus 19.3 months; hazard ratio 0.77, 95% CI 0.54–1.09; $p=0.137$). PFS censored for HSCT also supported the favorable results of the ATRA group (shown in Appendix p 33). For patients with *TP53* mutation, median PFS (8.3 months [95% CI 1.88–14.71] in the ATRA group and 9.4 months [95% CI 2.47–16.33] in the decitabine group [hazard ratio 0.80; 95% CI 0.34–1.86; $p=0.605$]) and OS (10.7 months [95% CI, 3.7–17.7]) in the ATRA group and 10.5 months [95% CI, 3.0–18.0])in decitabine group [hazard ratio 0.68; 95% CI 0.27–1.69; $p=0.401$]) was numerically shorter than in the overall patient. Subgroup analyses of PFS, OS, and time to AML transformation are shown in Appendix p 18–20. Post-hoc subgroup analyses to assess survival outcomes according to IPSS-R and IPSS-M scores are shown in Appendix p 21–32.

Adverse events

An overview of treatment-emergent adverse events is shown in Table 3. The most common treatment-emergent adverse events of any grade were thrombocytopenia (75% in the ATRA group versus 70% in the decitabine group), followed by leukopenia (71% versus 71%), neutropenia (59% versus 55%), anemia (37% versus 31%), dry skin (35% versus 5%), febrile neutropenia (28% versus 27%), fatigue (25% versus 27%), headache (19% versus 6%), hypertriglyceridemia (17% versus 5%), and pneumonia (14% versus 17%) (Table 3). The most common treatment-emergent adverse events of Grade 3 or higher were thrombocytopenia (66% in the ATRA group versus 63% in the decitabine group) and leukopenia (66% versus 63%), followed by neutropenia (55% versus 54%), febrile neutropenia (28% versus 27%), and anemia (26% versus 24%). The majority of the nonhematologic treatment-emergent adverse events were grade 1–2. The ATRA group had higher rates of dry skin (35% versus 5%; $p < 0.001$), headache (19% versus 6%; $p = 0.020$), and hypertriglyceridemia (17% versus 5%; $p = 0.019$) (Table 3). No differentiation syndrome was observed.

The rate of serious hematological treatment-emergent adverse events was 86% (94/110) in the ATRA group and 80% (90/113) in the decitabine group ($p = 0.254$). The rate of nonhematological treatment-emergent serious adverse events was 35% (38/110) in the ATRA group and 23% (26/113) in the decitabine group ($p = 0.057$). Details of serious treatment-emergent adverse events with a $\geq 3\%$ frequency in either group are listed in Appendix p 8.

The rates of death due to serious treatment-emergent adverse events were 1% (1/110) in the ATRA group and 3% (3/113) in the decitabine group ($p = 0.622$). The death in the ATRA group was attributed to intracranial bleeding. The cause of death for the 3 patients in the decitabine-only group was infection.

Discussion

In this multicenter, randomized controlled trial, we demonstrated a higher ORR (78% in the ATRA group versus 51% in the decitabine group), a higher rate of hematological

response (CR+PR+HI rate 48% versus 34%, response not including mCR) a higher rate of CR (23% versus 12%), and improved PFS (14.9 months versus 10.5 months) in the ATRA group. Hematological treatment-emergent adverse events did not differ between the two groups.

The ORR in the decitabine group in this trial was 51%. This rate was generally consistent with the ORR as a composite of CR, PR, HI, and mCR without HI in MDS-RAEB patients receiving monotherapy with decitabine reported in previous studies.¹¹ The modified ORR, which included CR, PR, and HI, was exclusive of mCR without HI in this trial (34%) and was also similar to that reported for decitabine monotherapy in MDS patients (30%).⁴ The CR rate in this trial (12%) was also consistent with that reported in a previous study (9%).⁴ The median time to progression to AML or death in this trial (15.8 months) was also similar to that reported in a previous study (12.1 months).⁴ These results demonstrated that the patient sample in this trial was representative, which highlights the potential for applicability to a general population of patients with MDS-EB-1 or MDS-EB-2.

Since mCR (a reduction in BM blast count to $\leq 5\%$ without HI) has not been shown to be associated with prolonged OS, including mCR without HI in the ORR could result in overestimation of treatment response and bias in the group comparison. We therefore analyzed treatment response by excluding mCR (i.e., CR+PR+HI), and the results continued to show a higher response rate in the ATRA group versus the decitabine alone group (48% versus 34%; $p=0.027$). Further more, since reduction in marrow blasts may be beneficial in patients who would be bridged to allo-HSCT, higher rate of marrow response (ie. CR+mCR) in the ATRA group also supported its potential benefits in bridging patients to allo-HSCT.²⁹⁻³¹ However, very-high risk MDS patients exhibited reduced responsiveness to decitabine-ATRA. Therefore, future therapeutic strategies should focus on more intensified or rationally designed treatment regimens. Promising strategies may include: triplet combinations incorporating venetoclax, immunomodulatory agents (such as anti-CD47 or anti-TIM-3 antibodies), or targeted

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inhibitors (e.g., IDH1/2 inhibitors); optimization of ATRA and/or HMA dosing based on bone marrow niche targeting; and biomarker-guided patient selection for ATRA-based combination therapies.

The median PFS was 14.9 months in the ATRA group versus 10.5 months in the decitabine group ($p=0.032$) in this trial. OS did not differ between the two groups. This discrepancy between PFS and OS outcomes may be partly explained by the variety of subsequent treatments administered to patients in both the combination therapy and control groups after disease progression. These treatments included hematopoietic stem cell transplantation, other hypomethylating agents, and conventional chemotherapy. Such factors are likely to act as significant confounders, thereby interfering with an accurate assessment of the independent survival benefit attributable to the decitabine - ATRA combination regimen itself. Additionally, the relatively small sample size may have contributed to limited statistical power. Even if the combination therapy holds potential clinical value, this limited power could have resulted in the failure to detect a statistically significant difference in OS between the two groups.

Hematologic treatment-emergent adverse events did not differ between the two groups in this trial, supporting the hematologic safety of ATRA. However, the ATRA group had a higher rate of several nonhematologic treatment-emergent adverse events, including dry skin, headache, and hypertriglyceridemia. This profile is generally consistent with previous trials of ATRA in humans.^{26, 32-36} In addition, consistent with results previously reported in AML patients,²⁶ most of the nonhematologic treatment-emergent adverse events reported in this trial were of low grade and reversible upon dose reduction or delay.

Interestingly, while the phase III SELECT-MDS-1 trial recently failed to demonstrate a significant improvement in CR rates with azacitidine plus tamibarotene, a selective *RARA* agonist, compared to azacitidine plus placebo in higher-risk MDS patients overexpressing *RARA*,³⁷ our study showed that ATRA, also an *RARA* agonist, significantly improved response rates and PFS when combined with decitabine. This discrepancy suggests that

ATRA may exert anti-tumor effects through mechanisms beyond *RARA* agonism. Notably, emerging evidence indicates that ATRA can degrade β -catenin in the bone marrow niche independently of genetic mutations, thereby disrupting the β -catenin–Jag1 axis and potentially contributing to therapeutic efficacy in non-APL myeloid malignancies.³⁸ This mechanism, which is not shared by all *RAR α* agonists, may help explain the enhanced activity observed in our trial and highlights the multifaceted nature of ATRA's mode of action. In addition, the two different drugs and schedules (in combination with azacitidine instead of decitabine) used in the two studies made it quite difficult to compare.

This trial has several limitations. First, the primary endpoint was the ORR rather than survival outcomes. Future trials with either PFS or OS as the primary endpoint are needed to verify the potential survival advantage of ATRA plus decitabine. Second, bone marrow follow-up has deviated substantially from the plan due to the disruption caused by the COVID-19 pandemic. Accordingly, PFS and time to leukemia transformation might have been overestimated. Third, quality of life was not examined as planned. Fourth, genetic testing for mutation panels varied significantly across trial centers.

In conclusion, treatment with decitabine plus ATRA resulted in a higher ORR and prolonged PFS than decitabine monotherapy in patients with MDS-EB without increasing hematologic treatment-emergent adverse events. No new nonhematologic treatment-emergent adverse events were reported. These findings encourage phase III trials using survival outcomes as the primary endpoint.

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Table 1 Demographic and baseline characteristics

	ATRA plus decitabine (N=110)	Decitabine (N=113)
Median age, years (IQR)	62 (52-68)	62 (55-68)
Sex, N (%)		
Male	70 (64%)	75 (66%)
Female	40 (36%)	38 (34%)
ECOG performance score, N (%)		
0	14 (13%)	12 (11%)
1	62 (56%)	65 (57%)
2	34 (31%)	36 (32%)
Disease type*, N (%)		
MDS-EB-1	52 (47%)	56 (50%)
MDS-EB-2	58 (53%)	57 (50%)
IPSS-R cytogenetic risk category, N (%)		
Very good	1 (1%)	1 (1%)
Good	54 (49%)	59 (52%)
Intermediate	29 (26%)	25 (22%)
Poor	6 (5%)	6 (5%)
Very poor	16 (15%)	18 (16%)
No mitosis	4 (4%)	4 (4%)
IPSS-R risk category, N (%)		
Very low	0	0
Low	0	1 (1%)
Intermediate	16 (15%)	17 (15%)
High	46 (42%)	33 (29%)
Very high	44 (40%)	58 (51%)
Not evaluable	4 (4%)	4 (4%)
Neutrophil count $\times 10^9/L$, N (%)		
<0.8	58 (53%)	62 (55%)
≥ 0.8	52 (47%)	51 (45%)
Hemoglobin concentration, g/L, N (%)		
<80	67 (61%)	74 (65%)

80-99	23 (21%)	21 (19%)
≥100	20 (18%)	18 (16%)
Platelet count×10 ⁹ /L, N (%)		
<50	46 (42%)	59 (52%)
50-99	36 (33%)	30 (27%)
≥100	28 (25%)	24 (21%)
Mutations‡, n/N (%)		
<i>ASXL1</i>	29/81 (36%)	20/77 (26%)
<i>U2AF1</i>	16/81 (20%)	13/77 (17%)
<i>TET2</i>	16/81 (20%)	9/77 (12%)
<i>RUNX1</i>	15/81 (19%)	18/77 (23%)
<i>TP53</i>	14/81 (17%)	13/77 (17%)
<i>DNMT3A</i>	11/81 (14%)	12/77 (16%)

Data are median (IQR), N (%), or n/N (%). ATRA=all-*trans* retinoic acid. ECOG=Eastern Cooperative Oncology Group. Interquartile range=IQR. IPSS-R=revised International Prognostic Scoring System. MDS=myelodysplastic syndromes. MDS-EB-1=myelodysplastic syndromes with excess blasts 1. MDS-EB-2=myelodysplastic syndromes with excess blasts 2. *Classified according to WHO (2016). ‡Baseline mutations were determined using a targeted-gene next-generation sequencing panel on genomic DNA from bone marrow mononuclear cells.

Table 2 Hematological responses

	ATRA plus decitabine (N=110)	Decitabine (N=113)	P value*
ORR, N (%)	86 (78%)	58 (51%)	<0.001
Best overall response, N (%) [†]			
CR	25 (23%)	14 (12%)	0.042
PR	0	0	-
mCR+HI	21 (19%)	21 (19%)	
mCR without HI	33 (30%)	20 (18%)	
HI only	7 (6%)	3 (3%)	0.181
SD	7 (6%)	21 (19%)	0.006
PD	17 (16%)	34 (30%)	0.009
Hematologic response, N (%)			
Neutrophil response, N (%)			
Yes	21 (19%)	12 (11%)	0.011
No	40 (36%)	63 (56%)	
Not applicable	49 (45%)	38 (33%)	
Erythroid response, N (%)			
Yes	34 (31%)	23 (20%)	0.061
No	60 (55%)	79 (70%)	
Not applicable	16 (14%)	11 (10%)	
Platelet response, N (%)			
Yes	37 (34%)	30 (27%)	0.286
No	45 (41%)	58 (51%)	
Not applicable	28 (25%)	25 (22%)	
Cytogenetic response, n/N (%)	22/29 (76%)	16/28 (57%)	0.134
Partial	8/29 (28%)	6/28 (21%)	
Complete	14/29 (48%)	10/28 (36%)	

Data are shown as n (%) or n/N (%). ATRA=all-*trans* retinoic acid. CR=complete remission. HI=hematologic improvement. IWG=International Working Group 2006 criteria. mCR=marrow complete remission. ORR=overall response rate. PD=progressive disease. PR=partial remission. SD=stable disease. *Assessed by Cochran-Mantel Haenszel general association χ^2 test. [†]Assessed per International Working Group 2006 Criteria.

Table 3 Treatment-emergent adverse events

	ATRA plus decitabine (n=110)	Decitabine (n=113)	P value
Hematological events, n (%)			
Thrombocytopenia	82 (75)	79 (70)	0.440
Grade 3 or above	72 (66)	71 (63)	0.683
Leukopenia	78 (71)	80 (71)	0.985
Grade 3 or above	72 (66)	71 (63)	0.683
Neutropenia	65 (59)	62 (55)	0.524
Grade 3 or above	60 (55)	61 (54)	0.933
Anemia	39 (37)	35 (31)	0.477
Grade 3 or above	29 (26)	27 (24)	0.671
Febrile neutropenia	31 (28)	30 (27)	0.784
Grade 3 or above	31 (28)	30 (27)	0.784
Non-hematological events, n (%)			
Dry skin	38 (35)	6 (5)	<0.001
Grade 3 or above	2 (2)	0	0.242
Fatigue	27 (25)	31 (27)	0.830
Grade 3 or above	3 (3)	4 (4)	1.000
Headache	21 (19)	7 (6)	0.020
Grade 3 or above	2 (2)	0	0.242
Vomiting	17 (16)	16 (14)	0.631
Grade 3 or above	0	1 (1)	1.000
Pneumonia	15 (14)	19 (17)	0.509
Grade 3 or above	15 (14)	19 (17)	0.509
Hemorrhage	21 (20)	25 (22)	0.576
Grade 3 or above	3 (3)	1 (1)	0.595
Nasal hemorrhage	4 (4)	6 (5)	0.880
Grade 3 or above	0	0	-
Intracranial hemorrhage	3 (3)	2 (2)	0.491
Grade 3 or above	3 (3)	1 (1)	0.595
Other hemorrhage	14 (13)	17 (15)	0.503
Grade 3 or above	0	0	-
Hypertriglyceridemia	19 (17)	6 (5)	0.019

Grade 3 or above	2 (2)	0	0.242
Hypercholesterolemia	2 (2)	0	0.242
Grade 3 or above	0	0	-
Increased alanine aminotransferase	12 (10)	6 (5)	0.456
Grade 3 or above	1 (1)	1 (1)	1.000
Increased total bilirubin	10 (9)	11 (10)	0.967
Grade 3 or above	0	1 (1)	1.000
Increased aspartate aminotransferase	8 (7)	4 (4)	0.478
Grade 3 or above	0	0	-
Increased urea nitrogen	4 (4)	6 (5)	0.583
Grade 3 or above	0	0	-
Increased creatinine	3 (3)	5 (4)	1.000
Grade 3 or above	0	0	-
Upper respiratory tract infection	11 (10)	7 (6)	0.476
Grade 3 or above	2 (2)	2 (2)	1.000
Skin infection	6 (5)	3 (3)	0.661
Grade 3 or above	1 (1)	0	0.493
Soft tissue infection	5 (5)	6 (5)	1.000
Grade 3 or above	3 (3)	3 (3)	1.000
Urinary tract infection	3 (3)	5 (4)	1.000
Grade 3 or above	0	1 (1)	1.000
Other infections	12 (11)	15 (13)	0.368
Grade 3 or above	3 (3)	2 (2)	0.976
Oral mucositis	12 (11)	7 (6)	0.621
Grade 3 or above	2 (2)	1 (1)	0.981
Cheilitis	11 (10)	5 (5)	0.208
Grade 3 or above	0	0	-
Bone pain	8 (7)	4 (4)	0.419
Grade 3 or above	0	0	-
Abdominal pain	7 (6)	4 (4)	0.574
Grade 3 or above	0	0	-
Maculopapule	9 (8)	5 (5)	0.525
Grade 3 or above	0	0	-
Constipation	8 (7)	9 (8)	1.000
Grade 3 or above	0	0	-
Diarrhea	7 (6)	10 (9)	0.362

Grade 3 or above	1 (1)	0	0.493
COVID-19	4 (4)	1 (1)	0.165
Grade 3 or above	0	0	-

ATRA=*all-trans* retinoic acid; COVID-19=coronavirus disease 2019.

Figure legends

Figure 1. Patient flow through the trial.

Figure 2. Distribution of genes associated with poor prognosis and frequently mutated genes in patients by treatment group. Mutational analysis was conducted on 158 bone marrow aspirate samples collected at screening (n=81 in the ATRA group and n=77 in the decitabine group).

Figure 3. Forest plot of the subgroup analysis. Effect of treatment on the overall response rate in subgroups with different demographic and disease characteristics. P values are for interactions.

Figure 4. Kaplan–Meier curves for survival outcomes. a) Progression-free survival; b) Overall survival; and c) Transformation to AML in the mITT population at the final analyses. HR, hazard ratio.

243 patients assessed for eligibility

16 excluded
5 did not meet inclusion criteria
2 were diagnosed with CMML
1 was diagnosed with AML
1 was diagnosed with MDS/MPN
1 was with ECOG performance status of 3
5 met exclusion criteria
3 had uncontrolled infection
1 had lung mass
1 had severe immune deficiency
5 withdrew informed consent
1 physician decision

227 enrolled and randomly assigned

113 assigned to ATRA+DEC group
110 received ATRA+DEC
3 did not receive ATRA+DEC
1 withdrew informed consent
1 had severe infection
1 transformed to AML 2 days after randomization

114 assigned to DEC group
113 received DEC
1 withdrew informed consent

110 analysed for efficacy
110 analysed for safety

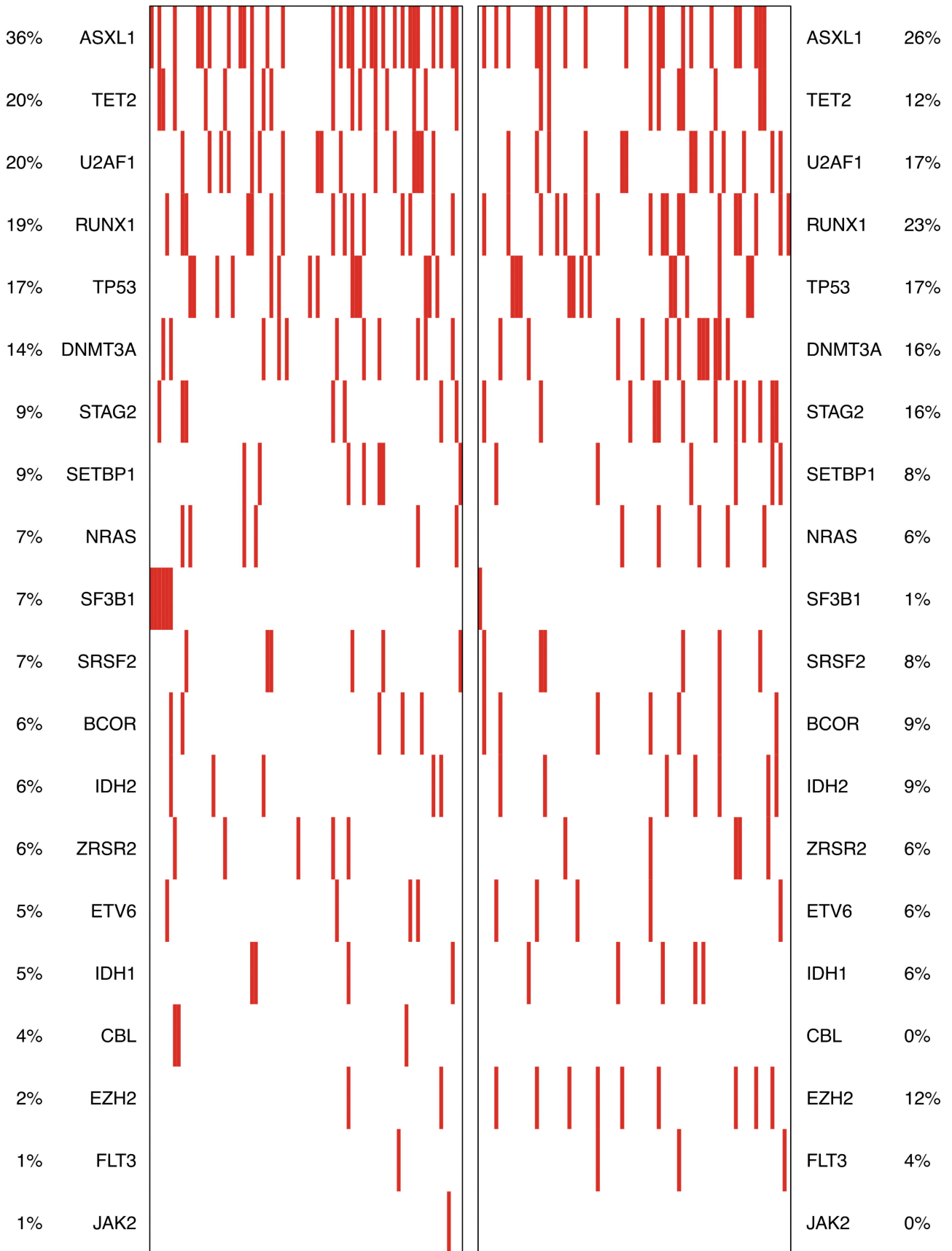
113 analysed for efficacy
113 analysed for safety

51 discontinued treatment
6 died
12 allogeneic HSCT
13 progressive disease
10 adverse event
10 patient decision

66 discontinued treatment
12 died
10 allogeneic HSCT
17 progressive disease
14 adverse event
13 patient decision

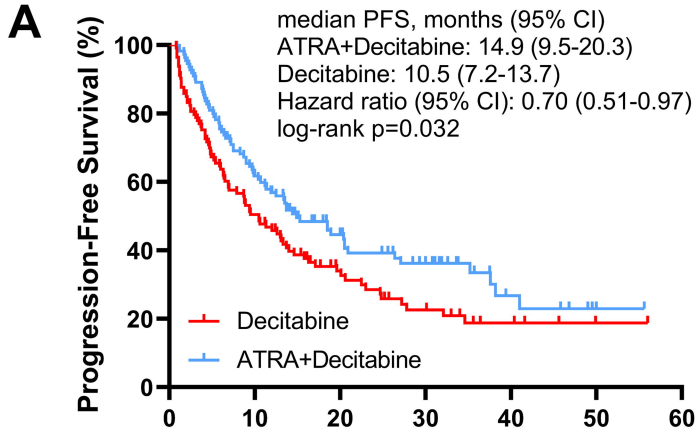
ATRA plus DEC
n = 81

DEC only
n = 77



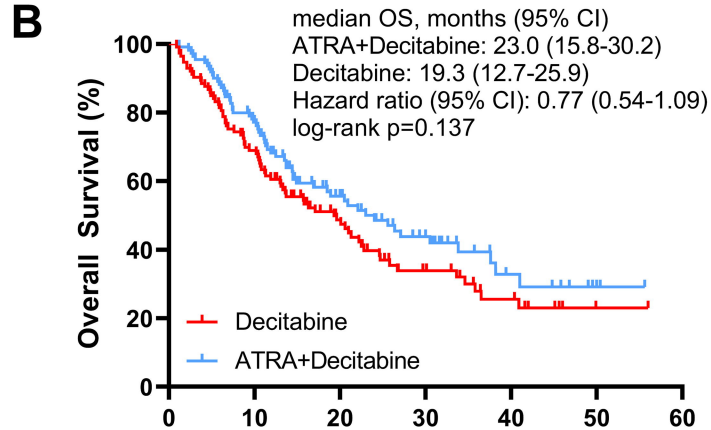
Subgroup	ATRA plus decitabine (response/patients)	Decitabine (response/patients)	OR(95% CI)	P for interaction
Gender				
Male	55/70	32/75	5.38 (2.56, 11.30)	0.03
Female	30/40	26/38	1.39 (0.52, 3.73)	
Age				
≥60	45/61	32/65	2.90 (1.37, 6.14)	0.51
<60	41/49	26/48	4.34 (1.68, 11.18)	
ECOG performance status				
0	13/14	8/12	6.50 (0.61, 68.96)	0.63
1	47/62	31/65	3.44 (1.61, 7.33)	
2	26/34	19/36	2.91 (1.04, 8.13)	
Disease type				
EB-1	41/52	29/56	3.47 (1.49, 8.10)	0.95
EB-2	45/58	29/57	3.34 (1.49, 7.49)	
IPSS-R risk score				
>4.5	73/94	45/94	3.79 (2.01, 7.12)	0.46
≤4.5	13/16	13/19	2.00 (0.41, 9.76)	
Karyotype				
Normal	46/56	34/61	3.25 (1.42, 7.45)	0.88
Abnormal	40/54	24/52	3.68 (1.61, 8.43)	
Complex	18/23	11/23	5.18 (1.34, 20.06)	
Non complex	22/31	13/29	3.01 (1.04, 8.74)	
Neutrophil (×10⁹ cells per L)				
≥0.8	40/52	27/51	2.96 (1.27, 6.92)	0.67
<0.8	46/58	31/62	3.83 (1.71, 8.59)	
Haemoglobin (g/L)				
≥80	37/43	23/39	4.29 (1.47, 12.54)	0.60
<80	49/67	35/74	3.10 (1.53, 6.27)	
Platelet (×10⁹ cells per L)				
≥50	47/63	30/54	2.35 (1.08, 5.13)	0.18
<50	39/47	28/59	5.40 (2.16, 13.50)	
Molecular marker				
ASXL1	22/29	9/20	3.84 (1.13, 13.07)	0.89
RUNX1	12/15	7/18	6.27 (1.29, 30.54)	
U2AF1	12/16	6/13	3.50 (0.73, 16.85)	0.87
TET2	13/16	2/9	15.17 (2.03, 113.35)	
TP53	11/14	7/13	3.14 (0.59, 16.85)	0.79
DNMT3A	8/11	4/12	5.33 (0.89, 31.92)	
All patients	86/110	58/113	3.40 (1.90, 6.09)	

0.4 1 3 8 20 55 115



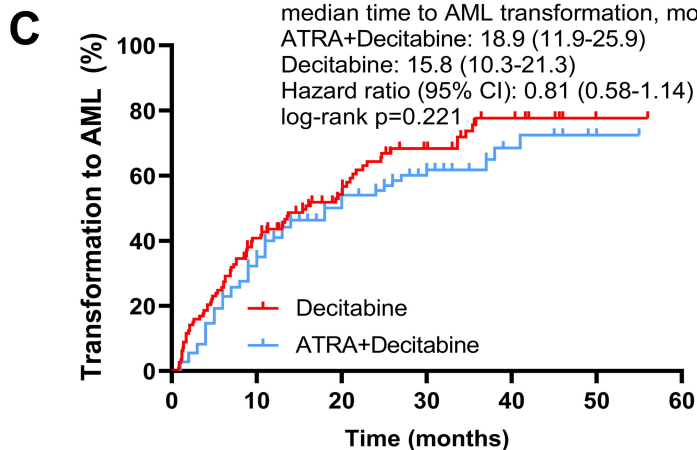
No. of patients at risk (censored)

ATRA+Decitabine	110(0)	67(1)	35(17)	22(24)	7(36)	2(40)	0(42)
Decitabine	113(0)	56(1)	25(16)	14(19)	7(24)	1(30)	0(31)



No. of patients at risk (censored)

ATRA+Decitabine	110(0)	82(3)	42(23)	25(32)	9(44)	3(49)	0(52)
Decitabine	113(0)	75(3)	39(19)	20(27)	11(32)	1(41)	0(42)



No. of patients at risk (censored)

ATRA+Decitabine	110(0)	72(2)	38(19)	23(27)	8(39)	3(43)	0(46)
Decitabine	113(0)	65(2)	37(17)	20(23)	10(28)	1(37)	0(38)

Supplementary Appendix

Decitabine plus all-*trans* retinoic acid versus decitabine monotherapy for myelodysplastic syndromes with excess blasts: a multicentre, randomized controlled trial

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SUPPLEMENTARY TABLES

Supplementary Table 1. Study trial sites

Study trial site	Principal investigator	Number of patients randomised
Department of Hematology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China	Hongyan Tong	111
Department of Hematology, Fujian Medical University Union Hospital, Fuzhou, China	Yanjuan Lin	42
Department of Hematology, The Affiliated Hospital of Qingdao University, Qingdao, China	Fanjuan Meng	36
Department of Hematology, Zhongda Hospital, Southeast University Medical School, Nanjing, China	Zheng Ge	14
Department of Hematology, The Affiliated Jinhua Hospital of Wenzhou Medical University, Hangzhou, China	Yuemin Kuang	10
Department of Hematology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang university, Hangzhou, China	Jin Zhang	6
Department of Hematology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China	Hai Cheng	4
Department of Hematology, The First Affiliated Hospital of Ningbo University, Ningbo, China	Guifang Ouyang	4

Supplementary Table 2. The targeted next-generation sequencing panel

ASXL1	RUNX1	U2AF1	TP53	TET2
DNMT3A	STAG2	SETBP1	BCOR	SRSF2
IDH2	EZH2	NRAS	ZRSR2	IDH1
ETV6	SF3B1	FLT3	CBL	JAK2

Supplementary Table 3. Members of independent central review committee

Member of the independent central review committee	Affiliation
Miao Miao	Department of Hematology, The First Affiliated Hospital of Soochow University, Suzhou, China
Xin Du	Department of Hematology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China
Huifang Jiang	Department of Hematology, Tongde Hospital of Zhejiang Province, Hangzhou, China

Supplementary Table 4. Treatment-emergent adverse events

Patients, n (%)	ATRA plus Decitabine (n=110)					Decitabine (n=113)				
	Any grade ^a	Grades 1-2	Grades 3	Grades 4	Grades 5	Any grade	Grades 1-2	Grades 3	Grades 4	Grades 5
≥ 1 treatment related TEAE ^b	110 (100)	101 (92)	77 (70)	88 (80)	3 (3)	110 (97)	90 (80)	79 (70)	88 (78)	3 (3)
Thrombocytopenia	82 (75)	10 (9)	12 (11)	60 (55)	0	79 (70)	8 (7)	13 (12)	58 (51)	0
Leukopenia	78 (71)	6 (5)	29 (26)	43 (39)	0	80 (71)	9 (8)	25 (22)	46 (41)	0
Neutropenia	65 (59)	5 (5)	9(8)	51 (46)	0	62 (55)	1 (<1)	10 (9)	51 (45)	0
Fever	45 (41)	43 (39)	2 (2)	0	0	42 (37)	41 (36)	1 (<1)	0	0
Anaemia	39 (35)	10 (9)	26 (24)	3 (3)	0	35 (31)	8 (7)	23 (20)	4 (4)	0
Dry skin	38 (35)	36 (33)	2 (2)	0	0	6 (5)	6 (5)	0	0	0
Febrile neutropenia	31 (28)	0	25 (23)	6 (5)	0	30 (27)	0	22 (19)	8 (7)	0
Fatigue	27 (25)	24 (22)	3 (3)	0	0	31 (27)	27 (24)	4 (4)	0	0
Headache	21 (19)	19 (17)	2 (2)	0	0	7 (6)	7 (6)	0	0	0
Hypertriglyceridemia	19 (17)	17 (15)	2 (2)	0	0	6 (5)	6 (5)	0	0	0
Vomiting	17 (15)	17 (15)	0	0	0	16 (14)	15 (13)	1 (<1)	0	0
Pneumonia	15 (14)	0	10 (9)	4 (4)	1 (<1)	19 (17)	0	13 (12)	3 (3)	3 (3)
Other hemorrhage	14 (13)	14 (13)	0	0	0	17 (15)	17 (15)	0	0	0
Oedema	12 (11)	12 (11)	0	0	0	10 (9)	10 (9)	0	0	0
Increased alanine aminotransferase	12 (11)	11 (10)	1 (<1)	0	0	6 (5)	5 (4)	1 (<1)	0	0
Oral mucositis	12 (11)	10 (9)	2 (2)	0	0	7 (6)	6 (5)	1 (<1)	0	0
Other infections	12 (11)	9 (8)	3 (3)	0	0	15 (13)	13 (12)	2 (2)	0	0
Cheilitis	11 (10)	11 (10)	0	0	0	5 (4)	5 (4)	0	0	0
Upper respiratory tract infection	11 (10)	9 (8)	2 (2)	0	0	7 (6)	5 (4)	2 (2)	0	0
Increased total bilirubin	10 (9)	10 (9)	0	0	0	11 (10)	10 (9)	1 (<1)	0	0
Purpura	9 (8)	9 (8)	0	0	0	13 (12)	13 (12)	0	0	0
Maculopapule	9 (8)	9 (8)	0	0	0	5 (4)	5 (4)	0	0	0
Constipation	8 (7)	8 (7)	0	0	0	9 (8)	9 (8)	0	0	0
Bone pain	8 (7)	8 (7)	0	0	0	4 (4)	4 (4)	0	0	0
Increased aspartate aminotransferase	8 (7)	8 (7)	0	0	0	4 (4)	4 (4)	0	0	0
Diarrhea	7 (6)	6 (5)	1 (<1)	0	0	10 (9)	10 (9)	0	0	0
Abdominal pain	7 (6)	7 (6)	0	0	0	4 (4)	4 (4)	0	0	0
Skin infection	6 (5)	5 (5)	1 (<1)	0	0	3 (3)	3 (3)	0	0	0
Soft tissue infection	5 (5)	2 (2)	3 (3)	0	0	6 (5)	3 (3)	3 (3)	0	0
Increased urea nitrogen	4 (4)	4 (4)	0	0	0	6 (5)	6 (5)	0	0	0
Nasal hemorrhage	4 (4)	4 (4)	0	0	0	6 (5)	6 (5)	0	0	0
COVID-19	4 (4)	4 (4)	0	0	0	1 (1)	1 (1)	0	0	0
Increased creatinine	3 (3)	3 (3)	0	0	0	5 (4)	5 (4)	0	0	0
Urinary tract infection	3 (3)	3 (3)	0	0	0	5 (4)	4 (4)	1 (<1)	0	0

Intracranial hemorrhage	3 (3)	0	1 (<1)	0	2 (2)	2 (2)	1 (<1)	1 (<1)	0	0
Hypercholesterolemia	2 (2)	2 (2)	0	0	0	0	0	0	0	0

CTCAE version 5.0.

AE, adverse event; ATRA, all-*trans* retinoic acid; COVID-19, coronavirus disease 2019; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment emergent adverse event. a. Any grade 1-2, grade 3, grade 4 or grade 5 adverse events are listed in descending order of incidence. b. A patient with multiple severity grades for an AE is counted only under the maximum grade. Only on-treatment events (until 30 days after last administration of study treatment) are included.

Supplementary Table 5. Treatment-emergent serious adverse events in $\geq 3\%$ in either arm

	ATRA plus Decitabine (n=110)	Decitabine (n=113)
Patients, n (%)		
Patients who reported ≥ 1 TEAE, n(%)	94 (86)	90 (80)
Thrombocytopenia	60 (55)	58 (51)
Neutropenia	51 (46)	51 (45)
Leukopenia	43 (39)	46 (41)
Pneumonia	15 (14)	19 (17)
Febrile neutropenia	6 (6)	8 (7)
Soft tissue infection	4 (4)	3 (3)
Anaemia	3 (3)	4 (4)

ATRA, all-*trans* retinoic acid; TEAE, treatment emergent adverse event.

Supplementary Table 6. Subgroup analysis of overall response (CR+PR+mCR+HI) for patients with mutations

Gene mutation	ATRA plus Decitabine		Decitabine		P value
	N	n (%)	N	n (%)	
ASXL1	29	22 (76)	20	9 (45)	0.028
RUNX1	15	12 (80)	18	7 (39)	0.004
U2AF1	16	12 (75)	13	6 (46)	0.143
TP53	14	11 (79)	13	7 (54)	0.236
TET2	16	13 (81)	9	2 (22)	0.009
DNMT3A	11	8 (73)	12	4 (33)	0.001
STAG2	7	5 (71)	12	3 (25)	0.074
SETBP1	7	6 (86)	6	2 (33)	0.103
BCOR	5	4 (80)	7	3 (43)	0.293
SRSF2	6	5 (83)	6	3 (50)	0.545
IDH2	5	3 (60)	7	2 (29)	0.558
EZH2	2	1 (50)	9	5 (56)	1.000
NRAS	6	4 (67)	5	1 (20)	0.242
ZRSR2	5	5 (100)	5	1 (20)	0.048
IDH1	4	3 (75)	5	2 (40)	0.524
ETV6	4	2 (50)	5	3 (60)	1.000
SF3B1	6	6 (100)	1	0	0.143
FLT3	1	1 (100)	3	1 (33)	1.000
CBL	3	2 (67)	0	0	-
JAK2	1	0	0	0	-

ATRA, all-*trans* retinoic acid; CR, complete remission; HI, hematologic improvement; mCR, bone marrow CR; PR, partial remission. Overall response are defined as complete response, marrow complete response, partial response, and or haematological improvement; must be concurrent with best overall response.

Supplementary Table 7. The genetics and cytogenetics information

Patient	Group	Age	Sex	Diagnosis (EB1 or EB2)	IPSS-R scores	Cytogenetics	Mutated genes detected by myeloid NGS and PCR	Best overall response (IWG 2006)
1	DEC+ATRA	57	Female	EB2	4.5	47, XX, +8[5]/46, XX.del(5)(q21)[2]/46,XX[5]	ASXL1 SF3B1	CR
2	DEC+ATRA	39	Female	EB2	6	46, XX[20]	SF3B1	HI
3	DEC+ATRA	63	Male	EB2	4	46, XY[20]	ASXL1 STAG2 SF3B1 TET2	CR
4	DEC+ATRA	63	Female	EB2	5.5	46, XX, del(5)(q15q33)[11]/92,idemX2[3]/46,XX[6]	DNMT3A SF3B1 TET2	CR
5	DEC+ATRA	53	Male	EB1	6.5	46, XY[2]	ETV6 RUNX1 SF3B1	mCR
6	DEC+ATRA	73	Male	EB1	5.5	46, XY, dup (1) (q41q44) [10]	BCOR DNMT3A IDH2 SF3B1	mCR
7	DEC	70	Male	EB2	6.5	46, XY, del(20)(q11)[10]	SF3B1	SD
8	DEC+ATRA	78	Male	EB1	7	47, XY,+8[3]/46, XY[17]	ASXL1 CBL TET2 ZRSR2 TET2 ZRSR2	mCR+HI
9	DEC+ATRA	69	Female	EB2	5	46, XY[20]	CBL	CR
10	DEC+ATRA	54	Male	EB2	6	46, XY[20]	BCOR NRAS RUNX1 STAG2 U2AF1	mCR+HI
11	DEC+ATRA	78	Male	EB2	6	46, XY[20]	RUNX1 STAG2 SRSF2	mCR
12	DEC	68	Male	EB2	8	47, XY,+8[11]/46,XY,del(12)(p12)[3]/47,XY,+i(8)(q10)[2]/48,XY,+4+21[1]/46,XY[6]	ASXL1 BCOR RUNX1 STAG2 SRSF2	HI
13	DEC+ATRA	55	Male	EB1	7	47,XY,-11,+2mar[3]/46,XY[9]	NRAS TP53	CR
14	DEC+ATRA	51	Male	EB2	9	43, XY,-13,-19,-21{1}	TP53	mCR+HI
15	DEC+ATRA	62	Female	EB2	5.5	46, XX[20]	ASXL1	mCR+HI
16	DEC+ATRA	36	Male	EB1	5.5	46, XX[20]	ASXL1	CR
17	DEC	57	Male	EB2	6.5	46, XX[20]	ND	mCR
18	DEC+ATRA	61	Male	EB1	5	45, X,-Y[12]/46,XY[8]	TET2	CR
19	DEC	35	Male	EB2	8	45, XY,-10[3]/46,XY[17]	ND	mCR
20	DEC+ATRA	66	Female	EB1	7	47,XX,+8,DEL(11)(q22)[9]/47,idem, add(1) (p32)[2]	ASXL1 U2AF1	mCR
21	DEC+ATRA	29	Female	EB2	5.5	46, XX[2]	IDH2	mCR
22	DEC+ATRA	41	Female	EB2	8.5	44-45, XX, del (5)(q13q33), -7, der(12:13)(q10; q10)[CP7]/82-92,idemx2[CP3]/46,XX[5]	TP53	CR
23	DEC+ATRA	43	Male	EB1	5	46, XY[20]	U2AF1	mCR
24	DEC+ATRA	64	Male	EB2	5.5	46, XY[20]	TET2 ZRSR2	mCR
25	DEC+ATRA	62	Male	EB1	5.5	47, XY,+19[19]/46, XY[1]	ASXL1 U2AF1	mCR+HI
26	DEC	66	Female	EB1	5.5	46, XX[5]	ASXL1 ETV6 EZH2 SETBP1	mCR
27	DEC+ATRA	81	Female	EB1	10	45, XX, inv(13)(q12q14),-17[5]/45,idem,add(7)(p22),dup(16)(q13q22)[13]/46,xx[2]	TP53	mCR+HI
28	DEC	65	Male	EB1	5	46, XY[20]	BCOR DNMT3A IDH2	mCR+HI
29	DEC+ATRA	56	Female	EB2	4	46, XX[20]	-	CR
30	DEC	49	Female	EB2	7	46, XX[20]	-	mCR
31	DEC	59	Female	EB2	7	47, XX,+8[10]	ASXL1 RUNX1 U2AF1	mCR
32	DEC+ATRA	47	Female	EB2	3.5	46, XX[20]	ASXL1	mCR
33	DEC	74	Female	EB1	7.5	44, XX,-5,del(7)(q22q35), -18, add(19)(q11.2) [7]/46, XX[13]	TP53	CR
34	DEC+ATRA	41	Female	EB1	6	46, XX[20]	ASXL1 NRAS SETBP1	mCR
35	DEC+ATRA	68	Male	EB2	9.5	44-48, XY, del(5)(p15)[3],+8[1],-14[3],-17[3],-20[4],+1~3mar[3][6]/46,xy[4]	RUNX1	CR
36	DEC+ATRA	63	Male	EB2	4	46, XY[20]	ASXL1 IDH1 RUNX1 TET2 U2AF1	CR
37	DEC	55	Female	EB2	8	49, XX, der(1) (q44), del(5)(q21q34),+8,?der(14:14)(q10;q10), +21, +mar[2]/46,XX[8]	TP53	CR
38	DEC	67	Male	EB2	9.5	45, XY,del(5)(q21q34), -7, -18,	TP53	mCR+HI

						-22, +2mar[1]/44, idem, -20[4]/45, XY, -7, -8, -22, +2mar[2]/46, XY[3]		
39	DEC	60	Male	EB1	7	46, XY[20]	ND	mCR+HI
40	DEC	50	Female	EB2	4.5	46, XX	DNMT3A IDH1	mCR
41	DEC	68	Male	EB2	3.5	46, XY[20]	ND	CR
42	DEC+ATRA	81	Male	EB2	6	47, XY, +8[6]/46, XY[14]	IDH1 NRAS	CR
43	DEC+ATRA	72	Male	EB2	5.5	47, XY, +8[7]/48, idem, +7[1]/46, XY[12]	SETBP1 U2AF1	mCR
44	DEC+ATRA	52	Female	EB1	5	46, XX[20]	DNMT3A IDH2 TET2	mCR
45	DEC+ATRA	69	Male	EB2	7	46, XY, inv(9)(p12q13)[20]	ASXL1 SRSF2	CR
46	DEC+ATRA	55	Male	EB2	4	46, XY[20]	RUNX1 SRSF2 TET2 TP53	mCR+HI
47	DEC+ATRA	80	Male	EB1	5.5	NA	ND	HI
48	DEC+ATRA	58	Male	EB2	8.5	46, XY, -2,t(7; 11)(p15;p15), -15, +2mar[3]/46, XY[7].	DNMT3A TP53	mCR
49	DEC+ATRA	25	Male	EB2	4.5	46, XY	ASXL1 RUNX1 U2AF1	mCR
50	DEC+ATRA	63	Male	EB2	6	47, XY, +1, der(1;7)(q10;p10), +8[9]/46, XY[1]	DNMT3A	CR
51	DEC+ATRA	37	Female	EB2	4.5	46, XX[20]	ND	mCR
52	DEC+ATRA	53	Female	EB1	4	46, XX[20]	ND	mCR
53	DEC	65	Female	EB2	6	47, XX, +14[4]/46, XX[6]	ASXL1 ETV6 EZH2 U2AF1	HI
54	DEC	74	Female	EB2	6.5	46, XX, del(13)(q13q12)[2]/46, xx[18]	ASXL1 RUNX1 STAG2 SRSF2 TET2	HI
55	DEC+ATRA	73	Male	EB1	4	46, XY[20]	ZRSR2	mCR
56	DEC	57	Female	EB1	6	46, XX[6]	IDH2 SRSF2	mCR+HI
57	DEC+ATRA	64	Female	EB1	5.5	46, XX[20]	ND	CR
58	DEC+ATRA	58	Male	EB1	6	46, XY[20]	ND	CR
59	DEC	50	Male	EB1	5	NA	ASXL1 TET2 U2AF1	mCR+HI
60	DEC+ATRA	55	Male	EB1	7	45, XY, del(5)(q12q34), -7, der(14)(q32), -17, +mar[2]/46, XY[8]	TP53	CR
61	DEC+ATRA	70	Male	EB2	4	46, XY[3]	ND	CR
62	DEC	62	Male	EB2	5	46, XY	ND	mCR+HI
63	DEC+ATRA	69	Female	EB1	7.5	46, XX, del(5)(q21q34)[2]/45, idem, -7, del(12)(p13)	TP53 U2AF1	mCR
64	DEC	48	Male	EB1	7.5	46, XY, der(7)t(1;7)(q10;p10)[5]/47, XY, idem, +8[15]	RUNX1	mCR
65	DEC+ATRA	65	Female	EB1	6	46, XX, del(6)(q23)[6]/46, XX[4]	U2AF1	mCR
66	DEC	69	Male	EB1	4.5	46, XY	ND	mCR+HI
67	DEC	52	Male	EB1	6	46, XY[20]	ASXL1 RUNX1 ZRSR2	mCR+HI
68	DEC+ATRA	48	Male	EB2	5	46, XY[3]	ND	mCR+HI
69	DEC	19	Male	EB2	6.5	46, XY, der(15)t(1;15)(p22;p12)(11)/46, XY(9)	EZH2 TP53	mCR
70	DEC	58	Male	EB1	9	42-45, XY, -1, -4[4], del(5)(q ? 15), -7, -8[3], -11, -12[3], -13[5], -14[3], -18, +4-5mar[7]/45, XY, -13[1]	TP53	mCR+HI
71	DEC+ATRA	66	Male	EB1	3.5	46, XY[20]	ND	CR
72	DEC+ATRA	71	Male	EB2	6.5	46, XY[6]	ASXL1 RUNX1 STAG2 TET2 ZRSR2	mCR
73	DEC	38	Female	EB1	6	46, XX[4]	ETV6	mCR
74	DEC	65	Male	EB1	8	83-88, XXYY, t(2;5)(q37;911)x2, -3, -3, -5, +6, ?add(6)(p22), -17, -17, -20, -20, -20, +mar1x2, +mar3, inc[CP20]	TP53	CR
75	DEC	55	Female	EB2	6.5	47, XX, +8[7]/46, XX[3]	ASXL1 RUNX1 U2AF1	mCR
76	DEC+ATRA	68	Male	EB2	7	46XY, t(1;3)(p36;q21)[1]/47, idem, +8[1]/46, XY, [18]	DNMT3A ETV6	mCR+HI
77	DEC	65	Female	EB2	8.5	49, XX, del(5)(q21q34), +8, +10, +11, +13, -17, -20, +mar[2]/50, idem+22[2]	TP53	mCR+HI
78	DEC+ATRA	47	Male	EB2	8	47, XY, +21[18]/46, XY[2]	ASXL1 U2AF1	HI
79	DEC	48	Female	EB1	6.5	47, XY, +21[18]/46, XY[2]	ND	mCR+HI

80	DEC	74	Male	EB1	4.5	46,XY[20]	BCOR EZH2 FLT3 RUNX1 SETBP1	CR
81	DEC	70	Female	EB1	5	47, XX, +9[4]/46,XX[16]	ND	mCR+HI
82	DEC+ATRA	49	Female	EB1	5.5	46, XX[20]	RUNX1 STAG2	mCR
83	DEC+ATRA	65	Male	EB1	6.5	47, XY,+8	ASXL1 EZH2 IDH1 SETBP1 ZRSR2	mCR+HI
84	DEC+ATRA	80	Female	EB1	5.5	46, XX[20]	ASXL1 RUNX1 SRSF2 TET2 TP53	mCR
85	DEC+ATRA	69	Male	EB2	7.5	47,XY,+mar[4]/46,XY[11]	TP53	CR
86	DEC+ATRA	50	Female	EB2	9.5	46,XX[1]	TET2 TP53	mCR
87	DEC+ATRA	54	Male	EB1	7	47, XY,+21[7]/46,XY[3]	ASXL1 DNMT3A RUNX1 SETBP1	mCR+HI
88	DEC	62	Female	EB1	4	NA	ND	mCR+HI
89	DEC	62	Female	EB2	5.5	46, XX[2]	ND	CR
90	DEC	50	Female	EB2	4.5	46, XX[3]	ND	mCR
91	DEC	77	Female	EB2	5.5	46, XX[20]	DNMT3A IDH1	CR
92	DEC+ATRA	38	Male	EB1	7	46, XY[20]	ND	mCR+HI
93	DEC+ATRA	71	Male	EB1	5	46, XY[3]	ASXL1	mCR
94	DEC	35	Male	EB2	8	47,X,add(Y)(q12),+8[13]/48,id em,+8[4]/47,idem,der(10)[1]/4 8,idem,+i(9)(q10)[1]/48,idem,+ 8,der(10)[1]	EZH2 NRAS U2AF1	mCR
95	DEC+ATRA	56	Male	EB2	6	46,XY,del(9)(q13q32)[5]/46,ide m, del(20)(q11)[1]/46,XY[4]	ASXL1 TET2 U2AF1	CR
96	DEC+ATRA	55	Male	EB2	5.5	46, XY[20]	BCOR DNMT3A SETBP1	CR
97	DEC+ATRA	55	Male	EB1	6	NA	ASXL1 SRSF2 SETBP1	mCR
98	DEC	71	Female	EB1	5.5	46, XX[20]	ASXL1 U2AF1	mCR+HI
99	DEC	64	Male	EB1	4.5	46, XY[20]	STAG2	CR
100	DEC	62	Male	EB2	5.5	45, X,-Y[6]/46,XY[4]	ND	mCR+HI
101	DEC+ATRA	62	Female	EB1	9	43- 49,XX,add(5)(q21),add(9)(q13) ,add(11)(p15),add(12)(p11.2),- 18[cp7]	TET2	mCR
102	DEC+ATRA	37	Male	EB1	5.5	46, XY[20]	ND	mCR+HI
103	DEC+ATRA	35	Female	EB1	6	47,XX,+8[7];47,XX,IDEM; del(11)(q21)[5]; add(X) (p22.1), del(11)(q21)[3]	ASXL1 U2AF1	mCR
104	DEC	67	Female	EB1	8.5	46,XX,del(X)(q13q28),t(1:2)(p 34;q34),add(4)(P16),del(5)(q22 q35),del(20)(q12)[20]	ND	mCR+HI
105	DEC+ATRA	57	Female	EB1	5	47, XX, +8[10]	FLT3	CR
106	DEC+ATRA	75	Male	EB2	7.5	46, XY,-7,+mar[10]	ASXL1 BCOR RUNX1	mCR+HI
107	DEC	55	Male	EB1	4.5	46, XY[6]	DNMT3A	CR
108	DEC	75	Male	EB1	4	46, XY, [20]	ND	CR
109	DEC+ATRA	65	Male	EB2	5	NA	CBL	F
110	DEC+ATRA	68	Male	EB2	4.5	47, XY,+8	ASXL1 ETV6 RUNX1	SD
111	DEC	67	Male	EB1	7	46, XY, (14)(q10)[14]/47,idem,+8[3]/47 ,idem,+21[3]	ASXL1 BCOR ETV6 RUNX1 TET2 ZRSR2	F
112	DEC+ATRA	37	Male	EB2	8	47, XY,+8[10]	ASXL1 TET2 U2AF1	F
113	DEC	67	Male	EB1	7	46, XY[20]	STAG2	F
114	DEC+ATRA	57	Female	EB2	6.5	46, XX	ASXL1 DNMT3A ETV6 NRAS U2AF1	F
115	DEC	58	Male	EB1	4.5	46, XY[20]	ASXL1 EZH2 NRAS STAG2 TET2	F
116	DEC	59	Male	EB2	7	47, XY,+8[19]/46, XY[1]	ASXL1 IDH1 RUNX1	F
117	DEC	37	Male	EB2	9	45, XY, -7[8]/46,XY[2]	DNMT3A IDH2 RUNX1	SD
118	DEC+ATRA	75	Male	EB1	7	47, XY,+8[13]/46,XY[7]	BCOR U2AF1	F
119	DEC+ATRA	69	Male	EB1	7.5	45~47,XY,-5,-12,-17,- 21,+3~5mar[6]/46,XY[4]	DNMT3A TET2 TP53	SD
120	DEC	79	Male	EB2	7	46, XY[2]	TP53	F
121	DEC	56	Male	EB2	9	44, XY,-6,-18,- 20,+mar[1]/44,X,-Y,-6,-12,-18,- 20,+3mar[1]/46,XY[8]	TP53	F
122	DEC+ATRA	68	Male	EB1	9	47,XY,del(5)(q11.2;q34),del(7) (q21),+8,der(11)t(5;11)(q23;q2	TP53	SD

						5)[13]/47,XY,del(5)(q11.2;q34),del(7)(q21),+i(8)(q10)[4]/46,XY,del(5)(q11.2;q34),del(7)(q21),+der(8;21)(q10;q10),del(20)(q11.1),der(22)t(1;22)(P22;p11.1)[3]		
123	DEC+ATRA	61	Male	EB2	5	46,XY,dup(1)(q21q31)[8]/46,idem,del(20)(q11q13)[2]	ASXL1 IDH2 RUNX1 U2AF1	F
124	DEC	74	Male	EB1	5	46,XY[11]	BCOR DNMT3A FLT3 RUNX1 TET2	SD
125	DEC+ATRA	73	Male	EB1	6	46,XY[7]	TP53	F
126	DEC	66	Female	EB2	5.5	47,XX,+8[5]/46,XX[5]	ASXL1 RUNX1 STAG2 SRSF2 TET2	SD
127	DEC	72	Female	EB2	10	45,XX,del(5)(q21q34),-17,-18,-21,+2mar[5]/46,XX[5]	TP53	F
128	DEC	54	Female	EB2	6.5	NA	ASXL1 SETBP1 U2AF1	F
129	DEC	44	Male	EB2	6.5	47,XY,+11[7]/46,XY[3]	IDH1 IDH2 U2AF1	F
130	DEC	73	Male	EB1	6	46,XY[7]	DNMT3A NRAS	SD
131	DEC	66	Male	EB2	4	46,XY[20]	DNMT3A IDH1	F
132	DEC	78	Male	EB1	3	46,XY[20]	DNMT3A	SD
133	DEC	44	Female	EB1	7.5	47,XX,+8[2]/46,XX[8]	ASXL1 U2AF1	SD
134	DEC	67	Male	EB1	7	46,XY,der(7)t(1;7)(q10;p10)[10]	DNMT3A STAG2 TET2	F
135	DEC	72	Male	EB2	7	47,XY,+7[1]/45,XY,-6,del(12)(p13)[1]/46,XY[18]	BCOR DNMT3A IDH2 RUNX1 SRSF2 TP53	F
136	DEC	53	Male	EB1	5	NA	U2AF1	F
137	DEC+ATRA	63	Female	EB1	6.5	NA	ASXL1 EZH2 IDH2 STAG2	F
138	DEC	63	Male	EB2	7.5	45,XY,-16[3]/45,XY,-17[3]/46,XY[15]	DNMT3A NRAS	F
139	DEC+ATRA	53	Male	EB2	9.5	44-46,XY,del(3)(q21),del(5)(q21q34),-7[6],-12,-17[6],-18[8],-20[4],+2~4mar,1ace[8][10]	ND	F
140	DEC+ATRA	43	Female	EB2	4.5	46,XX	JAK2	SD
141	DEC	66	Male	EB2	5	46,XY[20]	ND	F
142	DEC	66	Male	EB2	5	46,XY[20]	ASXL1 EZH2 RUNX1 STAG2 SETBP1 ZRSR2	SD
143	DEC	63	Male	EB2	6.5	47,XY,+8[4]/46,XY[16]	ASXL1 RUNX1 ZRSR2	SD
144	DEC	61	Male	EB2	4.5	46,XY[20]	STAG2 U2AF1	SD
145	DEC	59	Male	EB1	9.5	42-46,XY,-X[5],-1,-3,+6[5],?der(7p)[8],-11[3],der(12)(p11)[3]	TP53	SD
146	DEC	54	Male	EB1	8.5	42-46,XY,t(5;19)(q11;q11),del(7)(q31q34),i(11)(q10),-16,+20,add(21)(q21),+mar[CP19]/46,XY[1]	TP53	SD
147	DEC+ATRA	58	Male	EB1	5.5	46,XY,?del(7)(q31)[16]	ASXL1 DNMT3A IDH1 RUNX1	F
148	DEC	65	Male	EB1	6.5	46,XY,del(6)(q13q24)[16]/46,XY[2]	ASXL1 EZH2 RUNX1	F
149	DEC	60	Female	EB2	5.5	46,XX[20]	ASXL1 STAG2 SRSF2 TET2	SD
150	DEC+ATRA	76	Female	EB1	5	47,XX,+8[20]	ASXL1 NRAS STAG2 TET2	F
151	DEC	56	Female	EB2	6	46,XX,del(20)(q12)[10]	ASXL1 NRAS TET2	SD
152	DEC	64	Male	EB2	5.5	46,XY[20]	IDH2 ZRSR2	F
153	DEC	69	Male	EB1	5.5	46,XY[3]	STAG2 SETBP1 U2AF1	F
154	DEC	71	Female	EB2	7	46,XX	BCOR IDH2 STAG2	SD
155	DEC	39	Female	EB1	5.5	48,XX,+8,+21[10]	RUNX1 SETBP1 U2AF1	F
156	DEC	55	Male	EB1	4.5	46,XY[20]	FLT3	SD
157	DEC	68	Male	EB1	5.5	NA	RUNX1	F
158	DEC+ATRA	64	Female	EB1	4.5	46,XX[3]	SRSF2 SETBP1	SD
159	DEC	55	Male	EB1	6	46,XY[20]	NA	F
160	DEC+ATRA	64	Male	EB2	7.5	47,XY,+8[47]	NA	mCR

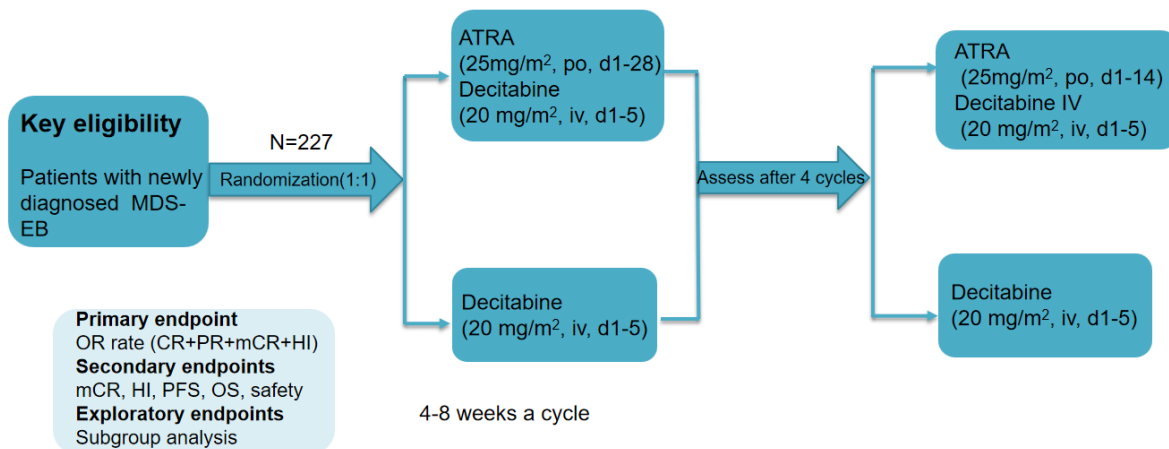
161	DEC+ATRA	65	Male	EB2	7	46,XY[20]	NA	SD
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163	DEC	43	Female	EB2	10	45-46,XX,+3,add(3)(q13),del(7)(q21),+mar,inc[cp7]	NA	F
164	DEC	50	Male	EB2	6.5	46, XY[14]	NA	mCR+HI
165	DEC+ATRA	40	Male	EB2	7	46,XY[20]	NA	mCR+HI
166	DEC	70	Male	EB2	5.5	46,XY[20]	NA	F
167	DEC	71	Male	EB2	4.5	48,XY,del(5)(q21q34),+2mar[4]46,XY[6]	NA	CR
168	DEC+ATRA	68	Female	EB2	6	46,XX	NA	mCR+HI
169	DEC+ATRA	66	Male	EB1	9	48,XY,-5,-17,-19,-20,+6mar[1]47,XY,-5,-17*2,-19,-20,+6mar[3]46,XY[6]	NA	HI
170	DEC+ATRA	52	Male	EB2	9.5	46,XY,+1,del(1)(p13p31)x2,t(13:17)(p10;q10),-20[6]46,XY,add(4)(q21)[3]46,XY[11]	NA	mCR+HI
171	DEC	68	Male	EB2	9	45,XY,-7,add(8)(q22)[19]46,XY[1]	NA	F
172	DEC+ATRA	65	Male	EB1	6	47,XY,+8,inv(9)(p12q13)c[10]	NA	F
173	DEC	43	Male	EB1	3.5	46,XY[20]	NA	mCR
174	DEC	62	Female	EB2	6.5	NA	NA	mCR+HI
175	DEC+ATRA	63	Female	EB2	7.5	47,XX,+8[11]46,XX[1].	NA	F
176	DEC+ATRA	62	Male	EB1	7	46,XY,+1,der(1 : 7)(q10 : p10)[20]	NA	mCR+HI
177	DEC	72	Male	EB2	4.5	46,XY[20]	NA	mCR+HI
178	DEC	36	Male	EB1	6.5	47,XY,der(7)t(1 : 7)(q10 , p10),+8[8]46,XY[2]	NA	SD
179	DEC	59	Female	EB1	6.5	46,XX,inv(9)(p12q13)[20]	NA	mCR
180	DEC+ATRA	46	Female	EB2	5.5	46,XX{20}	NA	CR
181	DEC+ATRA	55	Male	EB1	4	46,XY,20q-[10]	NA	mCR+HI
182	DEC+ATRA	60	Male	EB2	9.5	43-45,XY,del(3)(p21),+del(3)(p21),-5,-5,-7,+8 , add(9)(q34),der(9),der(11),+14,+15,-17,der(17),-18,der(18),-20,-20,der(20),+mar1,+mar2[cp20]	NA	mCR
183	DEC	54	Male	EB2	6.5	46,XY,+1,der(1:7)(q10;p10)[2]	NA	F
184	DEC	56	Female	EB2	7.5	47,XX,+19[3]46,XX[3]	NA	mCR+HI
185	DEC	74	Male	EB1	5.5	46,XY,dup(1)(q21q32),der(12)[2]46,XY[1]	NA	F
186	DEC+ATRA	69	Female	EB2	9.5	41-48,XX,+8,dic(8: 16)(p22; p11)X2, inc[cp13]	NA	SD
187	DEC	76	Male	EB2	7	NA	NA	F
188	DEC	55	Male	EB2	7.5	46,XY,del(9)(q11; q32)[2]	NA	SD
189	DEC	57	Female	EB2	6.5	46,XX[4]	NA	mCR
190	DEC+ATRA	50	Female	EB2	6	46,XX[20]	NA	CR
191	DEC+ATRA	42	Female	EB2	6	46,XX[20]	NA	F
192	DEC	42	Male	EB2	6.5	46,XY[20]	NA	F
193	DEC	65	Male	EB2	6	NA	NA	SD
194	DEC+ATRA	66	Male	EB2	6	46,XY[20]	NA	mCR
195	DEC	63	Female	EB2	6.5	46,XX	NA	mCR+HI
196	DEC+ATRA	60	Female	EB2	7.5	47,XX,+21[7]46,XX[3]	NA	F
197	DEC	56	Male	EB2	8	46,XY,+1 , der(1:12)(q10 : q10)[14]47,idem,+8[6]	NA	F
198	DEC+ATRA	47	Female	EB1	5	46,XX[20]	NA	mCR
199	DEC	63	Male	EB1	5	47,XY,+8[10]	NA	F
200	DEC	66	Female	EB2	5.5	46,XX[20]	NA	SD
201	DEC	33	Male	EB1	8.5	45,XY,del(1)(p35),t(5;17)(q15; q25),-7,del(12)(p13)[4]46,xy[6]	NA	CR
202	DEC	29	Male	EB1	9	43,XY,der(3: 12)(q10; q10),-5,-7,+add(8)(p22),-20[11]	NA	F
203	DEC	76	Male	EB2	6	46,XY[20]	NA	mCR
204	DEC+ATRA	65	Male	EB2	7	47,XY,+8[2]46,XY[18]	NA	HI

205	DEC	68	Female	EB2	9.5	49,XX,-5,+8,-13,-14,-15,-18,+7mar[3]/46,xx[7]	NA	F
206	DEC	60	Male	EB2	8	47,XY,+8{1}/46,XY{9}	NA	mCR
207	DEC	63	Male	EB2	5	46,XY[20]	NA	mCR
208	DEC+ATRA	76	Male	EB1	5	46,XY[20]	NA	mCR
209	DEC+ATRA	42	Female	EB1	5.5	46,XX[2]	NA	F
210	DEC	48	Male	EB1	6.5	47,XY,+8[6]/46,XY[14]	NA	SD
211	DEC	69	Female	EB2	6	46,XX[20]	NA	CR
212	DEC+ATRA	66	Male	EB2	7	NA	NA	F
213	DEC+ATRA	73	Male	EB2	10	42,X,-Y,add(3)(p13),add(4)(p11),-5,add(7)(q11.2),add(12)(p13),-13,inv(16)(p13q22),-19,+mar[6]/46,XY[2]	NA	HI
214	DEC+ATRA	58	Female	EB1	5	46,XX[1]	NA	HI
215	DEC	70	Male	EB1	5.5	46,XY[10]	NA	F
216	DEC+ATRA	62	Male	EB2	5.5	46,XY[20]	NA	mCR
217	DEC	62	Male	EB1	3.5	46,XY[5]	NA	CR
218	DEC+ATRA	77	Male	EB2	8	47,XY,+8[3]/46,XY[12]	NA	mCR+HI
219	DEC+ATRA	68	Female	EB2	6	46,XX[20]	NA	mCR+HI
220	DEC	58	Male	EB2	7	46,XY[9]	NA	mCR
221	DEC+ATRA	42	Male	EB2	6.5	46,XY[20]	NA	F
222	DEC+ATRA	31	Male	EB2	7	46,XY[20]	NA	mCR
223	DEC	75	Female	EB2	4.5	NA	NA	F

NA=not available

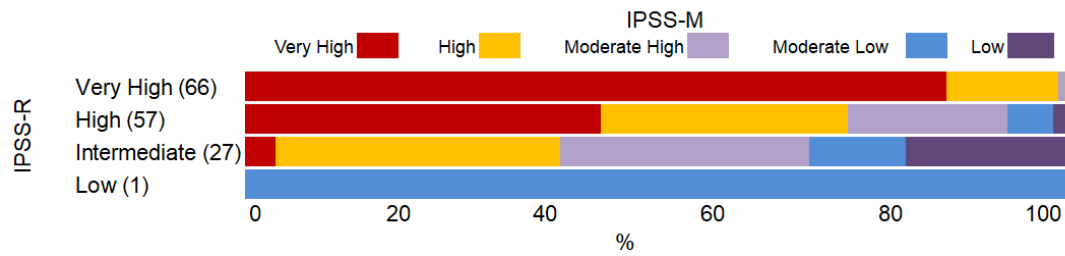
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SUPPLEMENTARY FIGURES



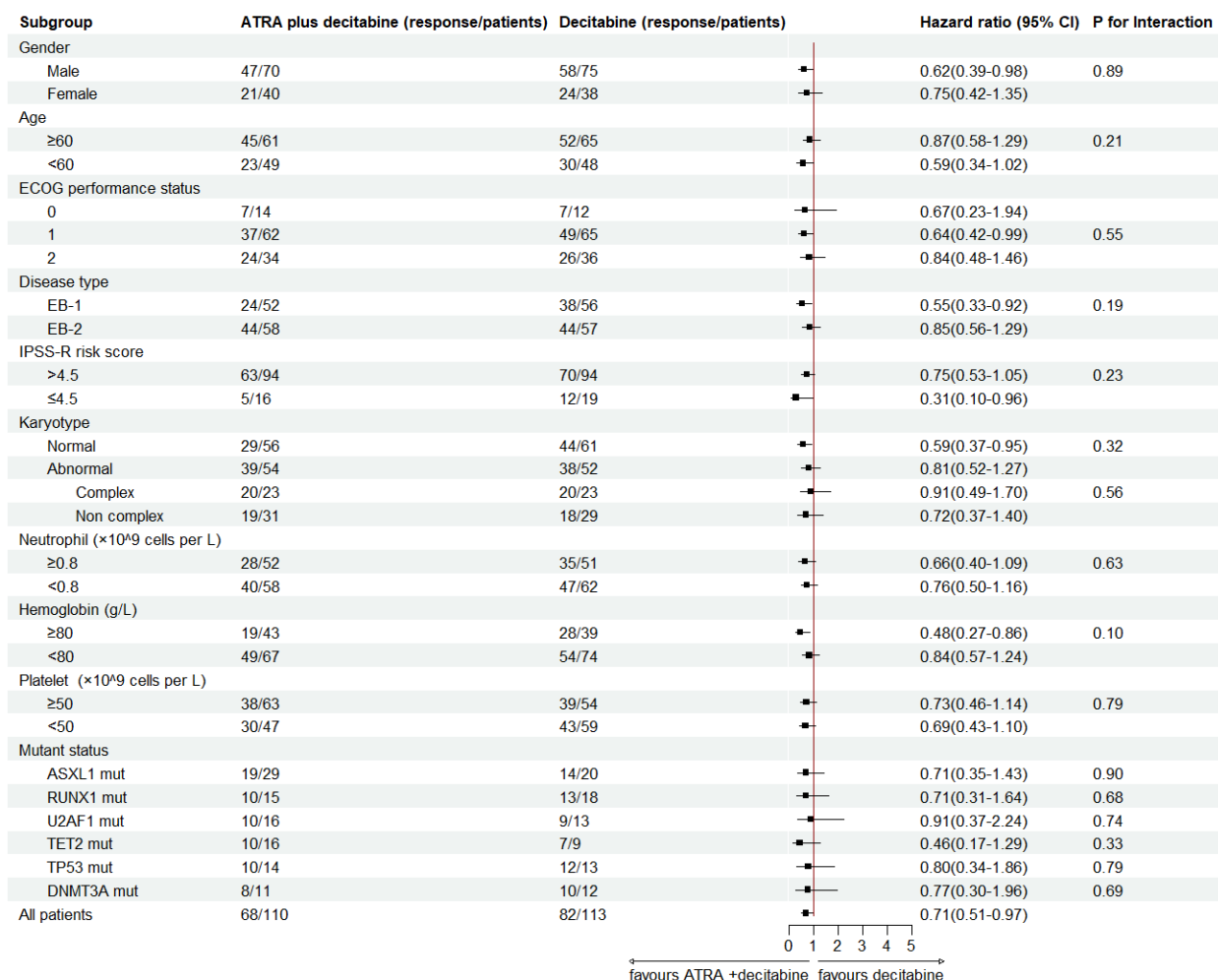
Supplementary Figure 1. Study design

ATRA, all-*trans* retinoic acid; CR, complete remission; EB, excess blasts; HI, hematologic improvement; IPSS-R, Revised International Prognostic Scoring System; iv, intravenous; mCR, bone marrow CR; MDS, myelodysplastic syndromes; OR, overall response; OS, overall survival; PFS, progression-free survival; po, peros; PR, partial remission.



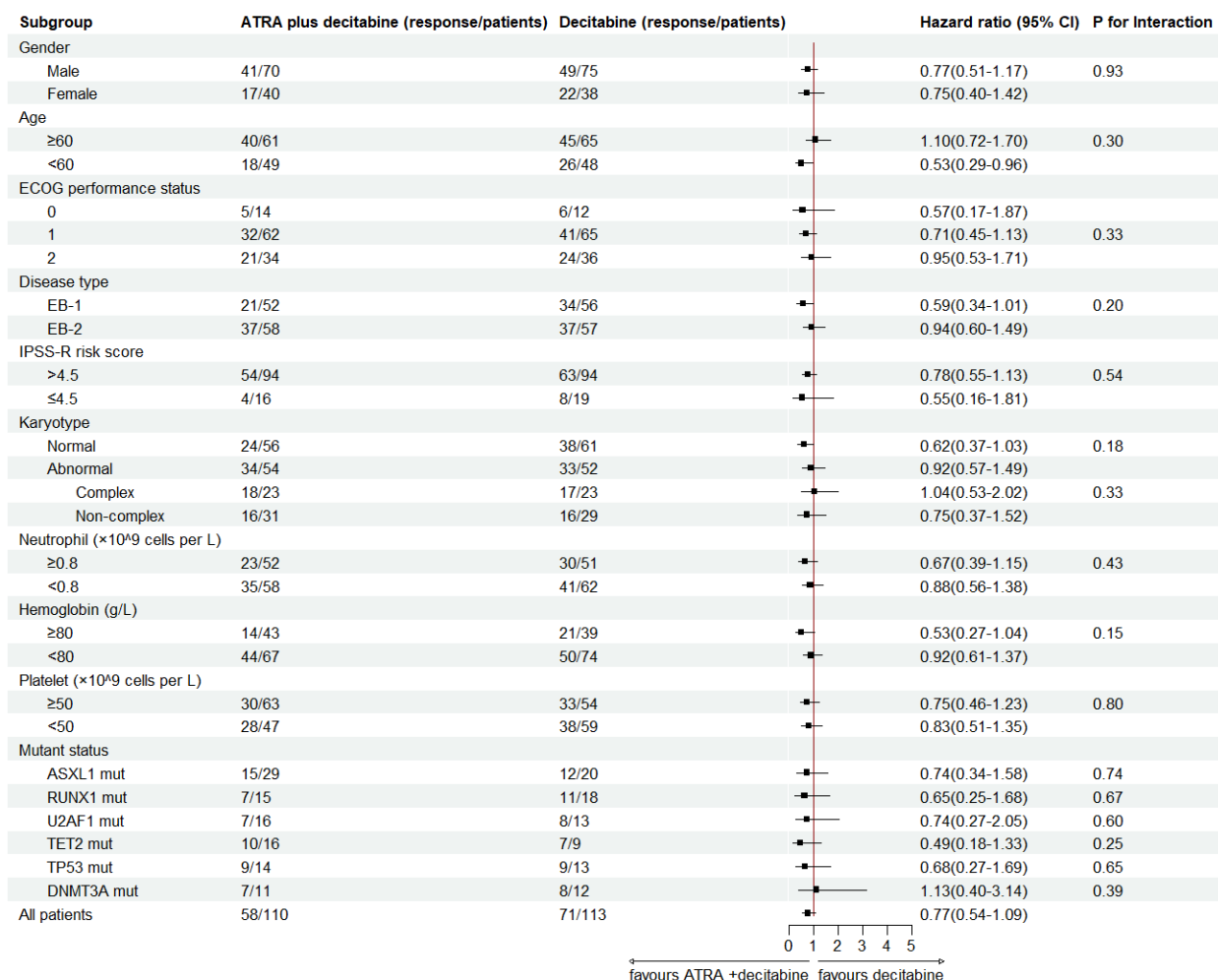
Supplementary Figure 2. Reclassification of patients using IPSS-R or IPSS-M

IPSS-R, Revised International Prognostic Scoring System; IPSS-M, Molecular International Prognostic Scoring System. Modern clinical prognostication of MDS is done via IPSS-R or IPSS-M, so when necessary data was available patients were reclassified to IPSS-R or IPSS-M. This plot exhibits the risk reclassification in this post-hoc analysis.



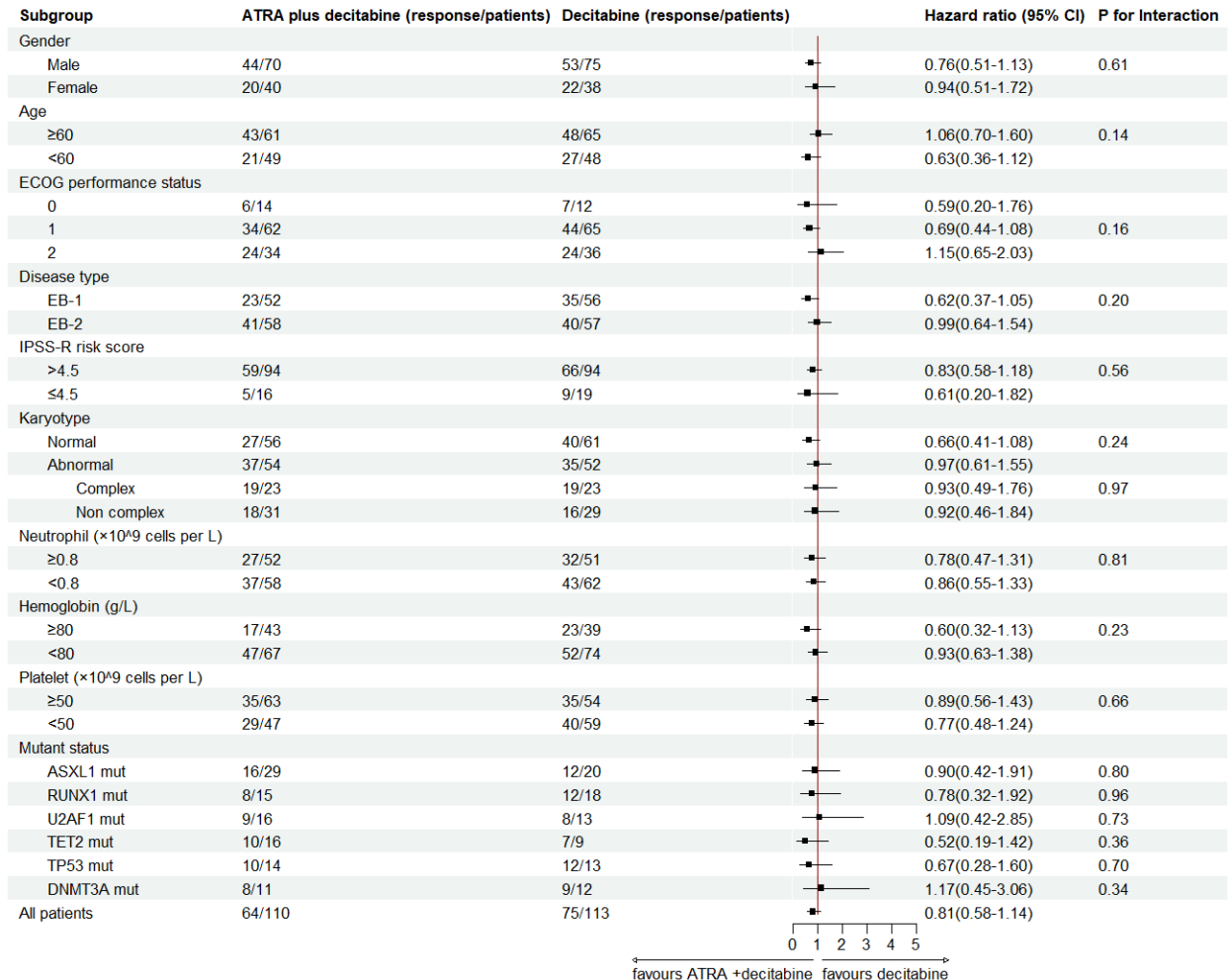
Supplementary Figure 3. Exploratory subgroup analyses of progression-free survival

Hazard ratio and 95% CI were calculated with a Cox proportional hazards model. ATRA, all-*trans* retinoic acid; ECOG, Eastern Cooperative Oncology Group; EB, excess blasts; IPSS-R, Revised International Prognostic Scoring System.



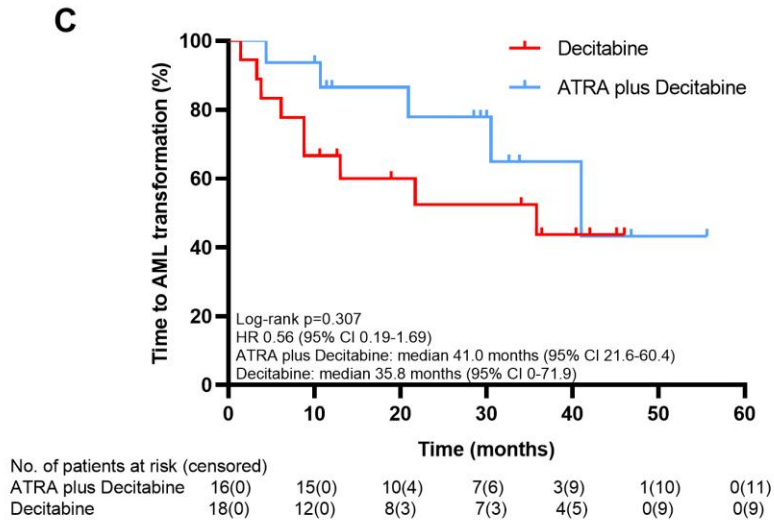
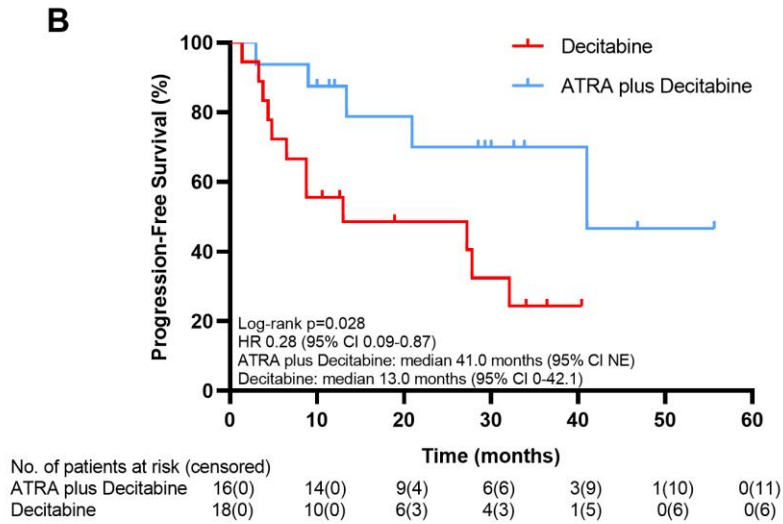
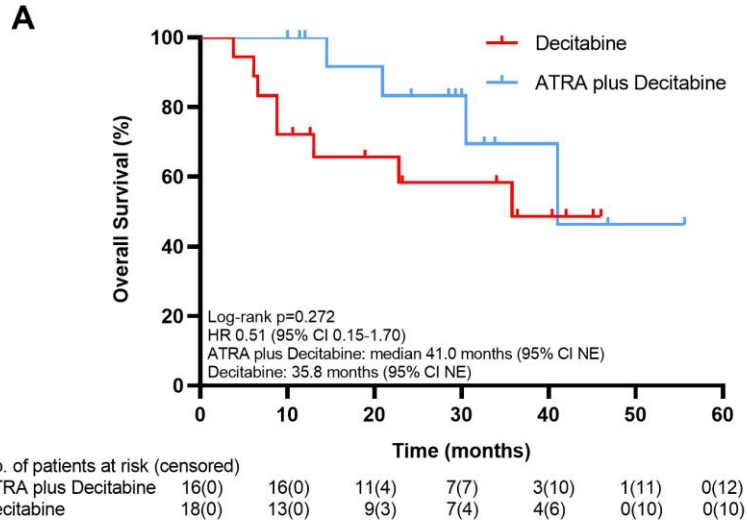
Supplementary Figure 4. Exploratory subgroup analyses of overall survival

Hazard ratio and 95% CI were calculated with a Cox proportional hazards model. ATRA, all-*trans* retinoic acid; ECOG, Eastern Cooperative Oncology Group; EB, excess blasts; IPSS-R, Revised International Prognostic Scoring System.



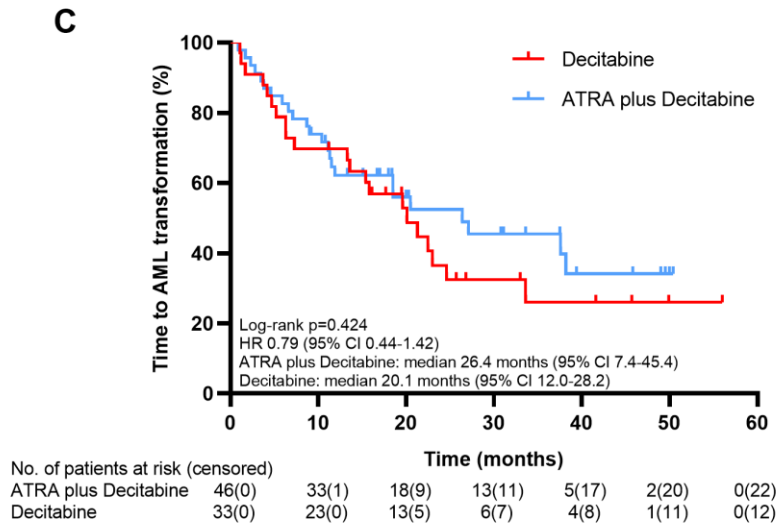
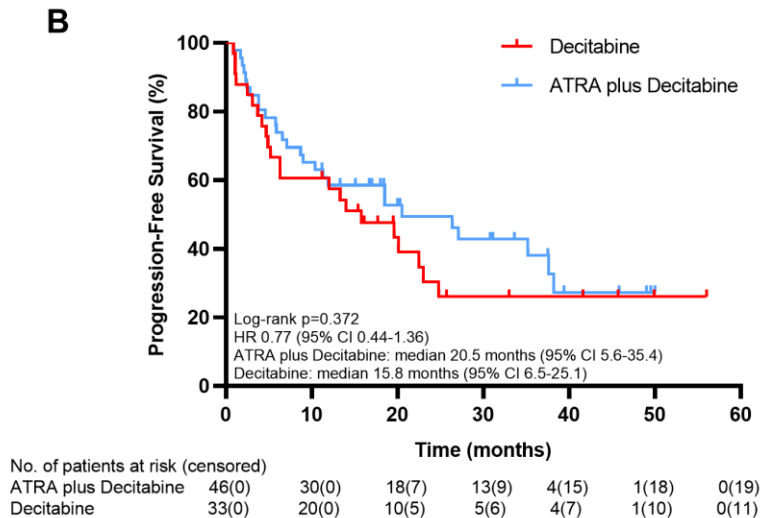
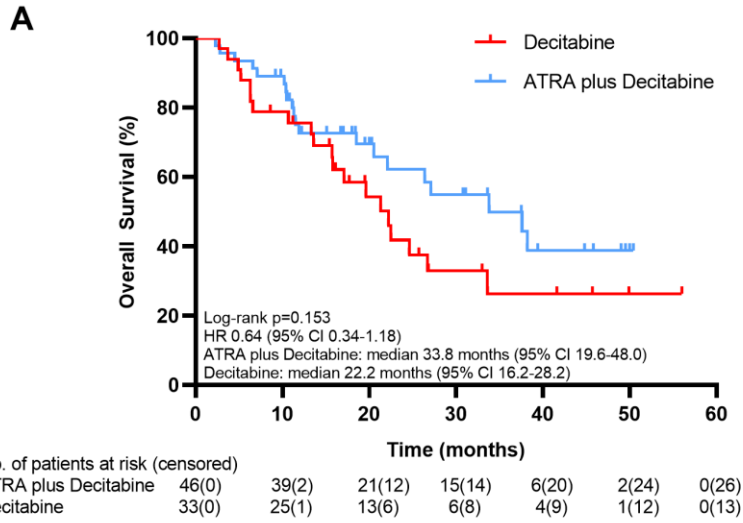
Supplementary Figure 5. Exploratory subgroup analyses of time to AML transformation

Hazard ratio and 95% CI were calculated with a Cox proportional hazards model. AML, acute myeloid leukemia; ATRA, all-*trans* retinoic acid; ECOG, Eastern Cooperative Oncology Group; EB, excess blasts; IPSS-R, Revised International Prognostic Scoring System.



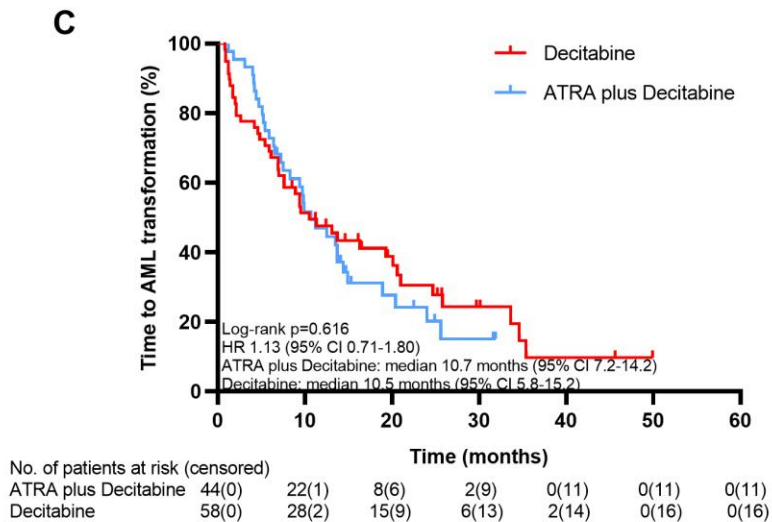
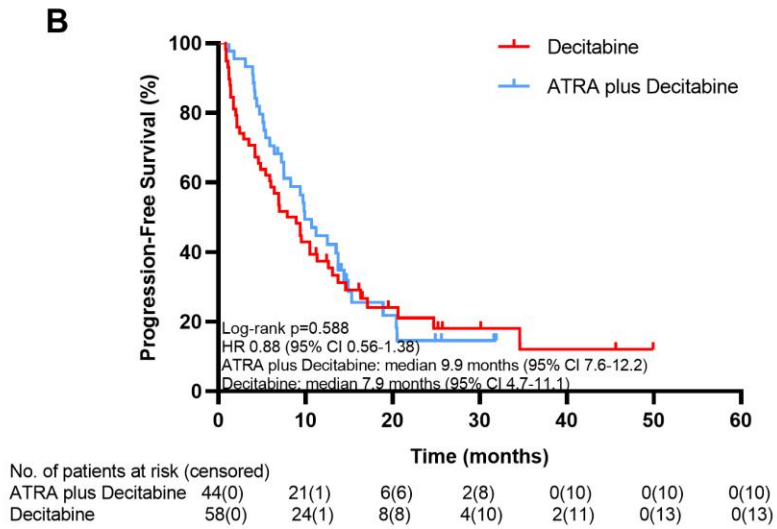
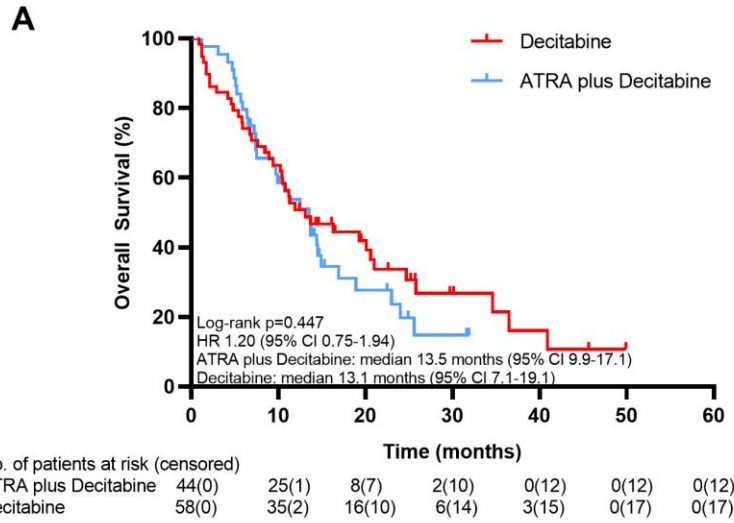
Supplementary Figure 6. Kaplan–Meier curves showing A). overall survival, B). progression-free survival and C). time to AML transformation in the low or intermediate-risk IPSS-R patients.

AML, acute myeloid leukemia; ATRA, all-*trans* retinoic acid; CI, confidence interval; HR, hazard ratio; IPSS-R, Revised International Prognostic Scoring System; NE, not evaluable; OS, overall survival; PFS, progression-free survival.



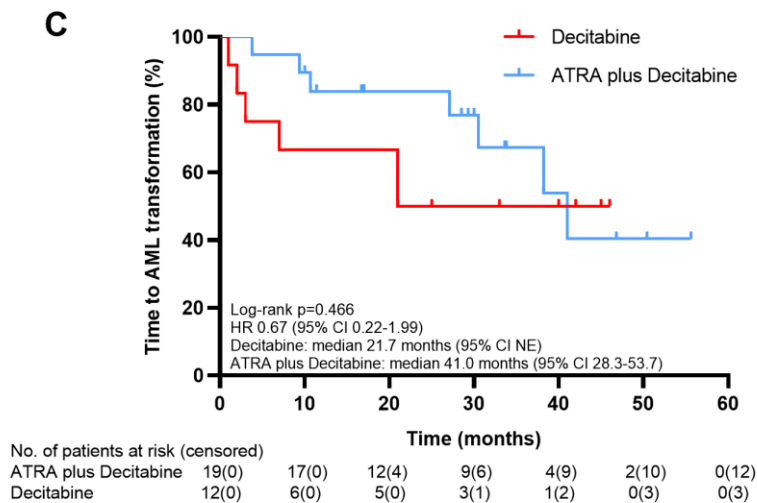
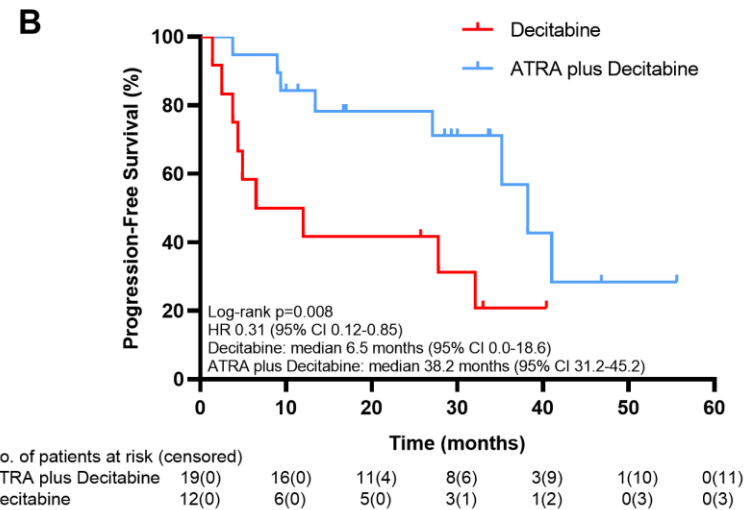
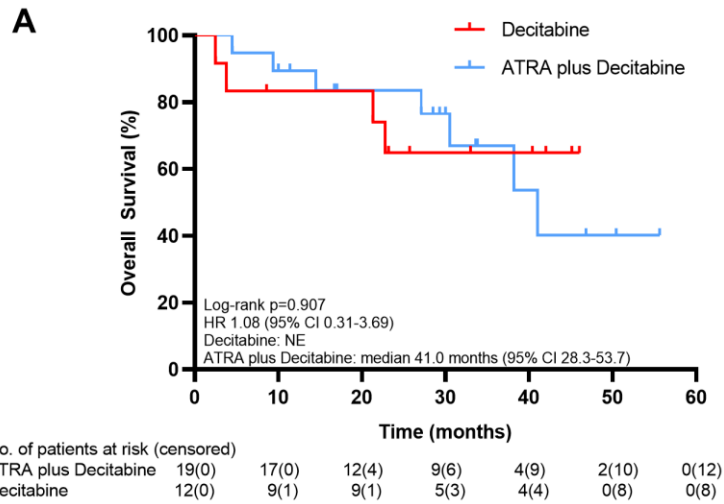
Supplementary Figure 7. Kaplan–Meier curves showing A). overall survival, B). progression-free survival and C). time to AML transformation in the high-risk IPSS-R patients.

AML, acute myeloid leukemia; ATRA, all-*trans* retinoic acid; CI, confidence interval; HR, hazard ratio; IPSS-R, Revised International Prognostic Scoring System; OS, overall survival; PFS, progression-free survival.



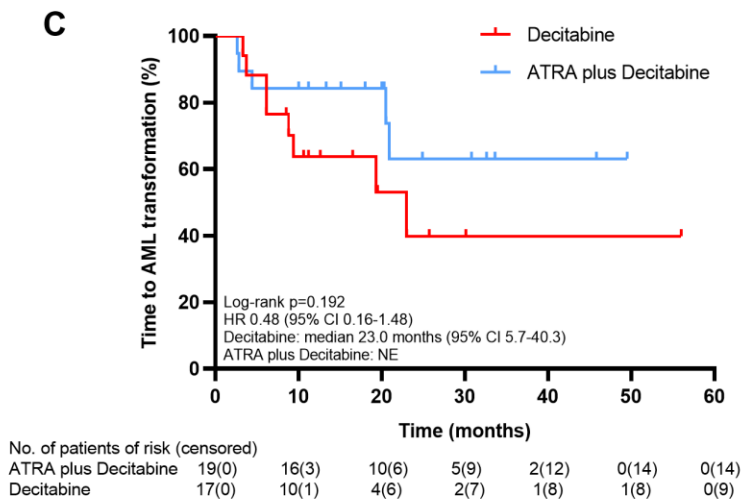
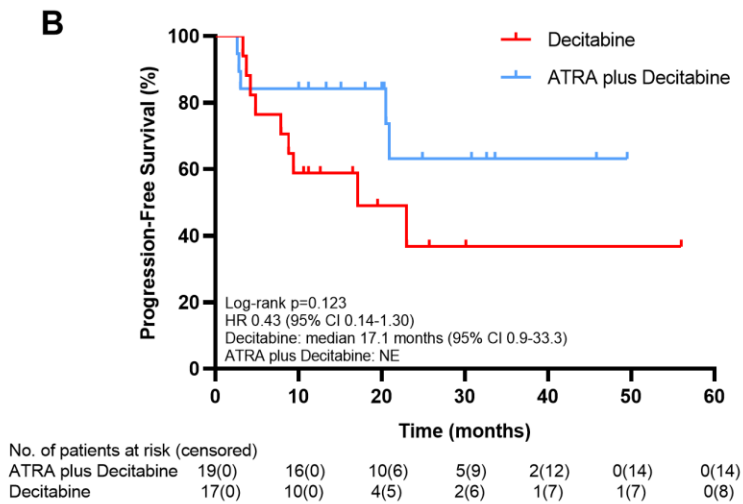
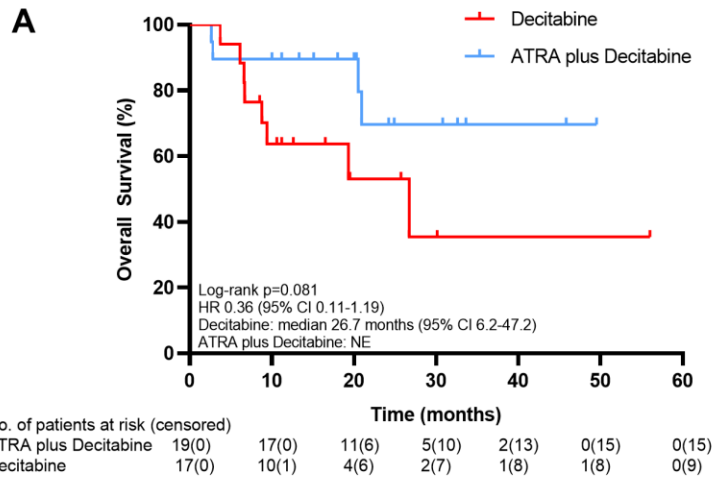
Supplementary Figure 8. Kaplan–Meier curves showing A). overall survival, B). progression-free survival and C). time to AML transformation in the very high-risk IPSS-R patients.

AML, acute myeloid leukemia; ATRA, all-*trans* retinoic acid; CI, confidence interval; HR, hazard ratio; IPSS-R, Revised International Prognostic Scoring System; OS, overall survival; PFS, progression-free survival.



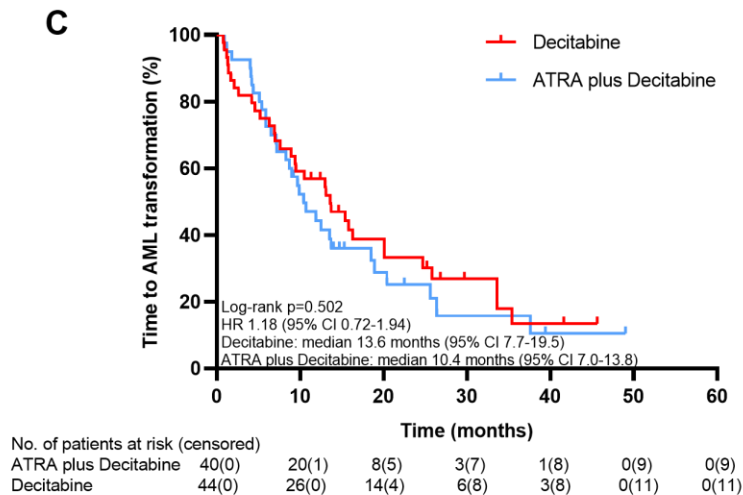
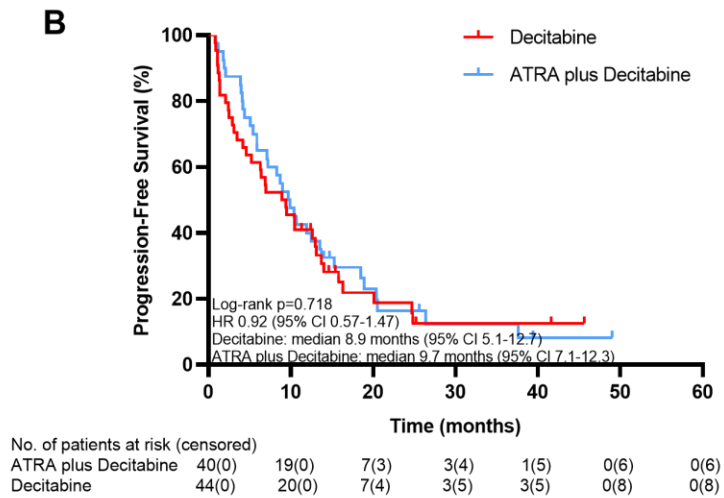
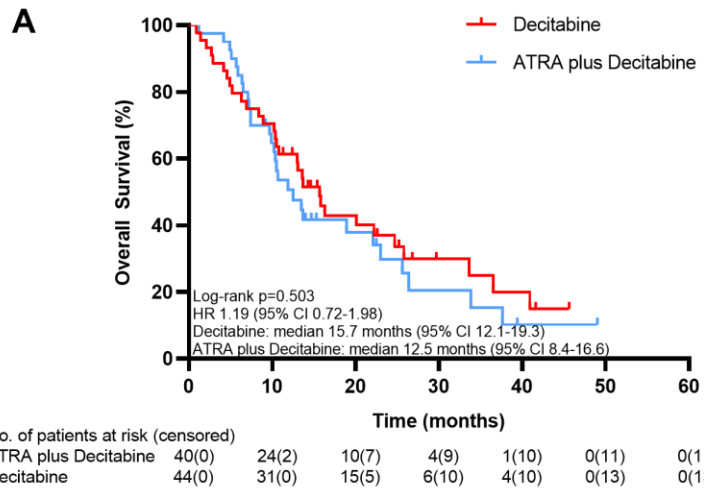
Supplementary Figure 9. Kaplan-Meier curves showing A). overall survival, B). progression-free survival and C). time to AML transformation in the low, moderate-low, moderate-high-risk IPSS-M patients.

AML, acute myeloid leukemia; ATRA, all-*trans* retinoic acid; CI, confidence interval; HR, hazard ratio; IPSS-M, Molecular International Prognostic Scoring System; NE, not evaluable; OS, overall survival; PFS, progression-free survival.



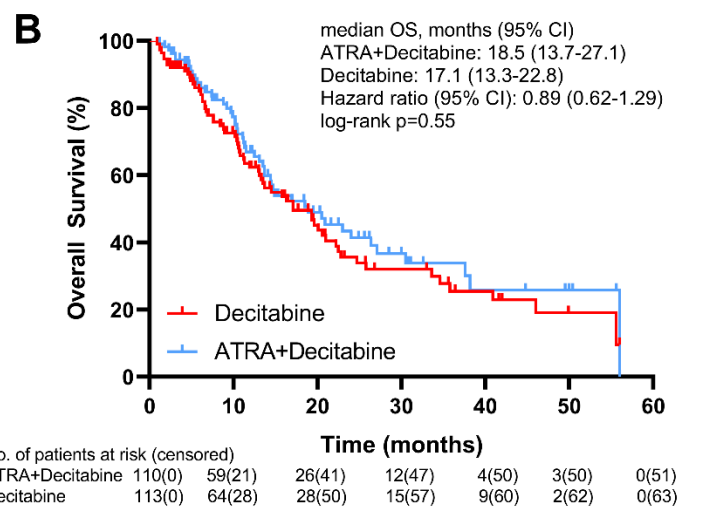
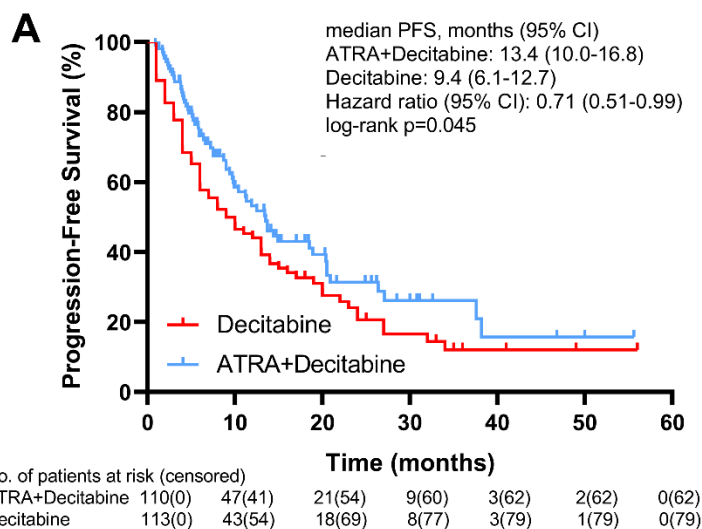
Supplementary Figure 10. Kaplan–Meier curves showing A). overall survival, B). progression-free survival and C). time to AML transformation in the high-risk IPSS-M patients.

AML, acute myeloid leukemia; ATRA, all-*trans* retinoic acid; CI, confidence interval; HR, hazard ratio; IPSS-M, Molecular International Prognostic Scoring System; NE, not evaluable; OS, overall survival; PFS, progression-free survival.



Supplementary Figure 11. Kaplan–Meier curves showing A). overall survival, B). progression-free survival and C). time to AML transformation in the very high-risk IPSS-M patients.

AML, acute myeloid leukemia; ATRA, all-*trans* retinoic acid; CI, confidence interval; HR, hazard ratio; IPSS-M, Molecular International Prognostic Scoring System; OS, overall survival; PFS, progression-free survival.



Supplementary Figure 12. Kaplan–Meier curves showing A). progression-free survival and B). overall survival censored for HSCT in the mITT population at final analyses.

ATRA, all-*trans* retinoic acid; CI, confidence interval; DEC, decitabine; OS, overall survival; PFS, progression free survival.

CLINICAL TRIAL PROTOCOL

All-*Trans* Retinoic Acid in Combination with Decitabine for Untreated Myelodysplastic Syndromes with Excess Blasts (MDS-EB): A Prospective, Open-Label, Multi-Center, Randomized Controlled Clinical Study

(MDS-DEC+ATRA : V3.1—June 20, 2022)

Responsible Institution for Clinical Trials:

The First Affiliated Hospital, Zhejiang University School of Medicine

Principal Investigator:

Professor Hongyan Tong

Sponsor:

The First Affiliated Hospital, Zhejiang University School of Medicine

Confidentiality Statement

The content and information of this protocol belongs to the sponsor, The First Affiliated Hospital, Zhejiang University School of Medicine. The relevant information is kept confidential and is only used for matters authorized by the sponsor, and shall not be disclosed to anyone without the written permission of the sponsor.

THE PROTOCOL SIGNATURE PAGE

Principal Investigator

I shall conscientiously carry out the assignments of the principal investigator in line with the “Declaration of Helsinki” and the regulations of the Chinese GCP. I hereby acknowledge my acceptance of conducting this clinical trial in accordance with the protocol's design and requirements, performing the duties of the principal investigator diligently throughout the trial's inception, progression, and closing phase. Additionally, I will coordinate trial-related affairs within each participating institution to ensure the trial's seamless progress in the clinical stage.

Responsible Institution for Clinical Trials:

The First Affiliated Hospital, Zhejiang University School of Medicine

Principal Investigator (Signature):

Handwritten signature of Hongyan Tong in black ink.

Contact Phone Number:

List of Abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
AML	Acute Myeloid Leukemia
AST	Aspartate Aminotransferase
MDS	Myelodysplastic Syndromes
MDS-EB	Myelodysplastic Syndrome with Excess Blasts
ECOG	Eastern Cooperative Oncology Group
BUN	Blood Urea Nitrogen
ATRA	All- <i>Trans</i> Retinoic Acid
DEC	Decitabine
CIN	Cervical Intraepithelial Neoplasia
PIN	Prostatic Intraepithelial Neoplasia
IWG2006	2006 International Working Group Response Criteria in Myelodysplastic Syndromes
ORR	Overall Response Rate
mCR	Marrow Complete Remission
CR	Complete Remission
CRF	Case Report Form
FAS	Full Analysis Set
ITT	Intention-To-Treat
OS	Overall Survival
SOP	Standard Operating Procedure
SS	Security Set
ECG	Electrocardiogram
G-CSF	Granulocyte Colony-Stimulating Factor
PR	Partial Remission
HI	Hematologic Improvement

Protocol Summary

Study Title	All- <i>Trans</i> Retinoic Acid in Combination with Decitabine for the Untreated Myelodysplastic Syndromes with Excess Blasts (MDS-EB): A Prospective, Open-Label, Multi-Center, Randomized Controlled Clinical Study
Trial Objectives	Investigation of efficacy and safety of all- <i>trans</i> retinoic acid in combination with decitabine for the untreated myelodysplastic syndrome with excess blasts (MDS-EB)
Study Design	A prospective, open-label, multi-center, randomized controlled clinical study
Participated Institutions	<ul style="list-style-type: none"> ➤ The First Affiliated Hospital, Zhejiang University School of Medicine ➤ Zhongda Hospital, Southeast University Medical School ➤ The Affiliated Hospital of Qingdao University ➤ Fujian Medical University Union Hospital ➤ Sir Run Run Shaw Hospital, School of Medicine, Zhejiang university ➤ The Affiliated Jinhua Hospital of Wenzhou Medical University ➤ The First Affiliated Hospital of Ningbo University ➤ The Affiliated Hospital of Xuzhou Medical University
Inclusion Criteria	<p>Subjects must meet all of the following criteria before being randomized:</p> <ol style="list-style-type: none"> 1. Age \geq 18 years old; life expectancy \geq 3 months; 2. Patients aged \geq18 years with morphologically confirmed MDS with excess blasts (MDS-EB-1 or MDS-EB-2) according to the World Health Organization classification (2016). Additionally, participants, who are untreated, were required to undergo a bone marrow examination within 30 days prior to enrollment; 3. ECOG performance status of 0 to 2; 4. Female subjects of child-bearing potential must consent to use physician-approved contraception measures during the administration of DEC and ATRA, extending to a period of 1 month after the last dose of DEC and 1

	<p>year after the last dose of ATRA. Male subjects whose partners have the potential to conceive must commit to utilize physician-approved contraception techniques throughout the entirety of the study duration, while also avoid impregnating the female partners during the study period and for a duration of 2 months following the last administration of DEC;</p> <p>5. Adequate hepatic and renal function (serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN), BUN $\leq 1.5 \times$ ULN, ALT $\leq 2 \times$ ULN, AST $\leq 2 \times$ ULN, total bilirubin $\leq 1.5 \times$ ULN).</p> <p>6. Written informed consent obtained.</p>
<p>Exclusion Criteria</p>	<p>Subjects meeting any of the following criteria are not eligible for random enrollment:</p> <ol style="list-style-type: none"> 1. History of solid organ transplantation; 2. Previous hematopoietic stem cell transplantation, Cytotoxic therapy, or hypomethylating agents, including Azacitidine, DEC, and Chemotherapy; 3. Concurrent MDS therapies including Realgar-Indigo naturalis formula, Sodium Valproate, Antithymocyte Globulin, and Arsenic Trioxide. (Prior treatment with these agents is permitted, provided that completion is at least 30 days before the first dose of study treatment.) 4. Treatment with any investigational drug or therapy within 30 days of study treatment, before the first dose of study treatment, or ongoing clinically significant adverse events from previous treatment; 5. Prior malignancy in the preceding 3 years, except for adequately treated Superficial Bladder Cancer, Basal Cell or Squamous Cell Carcinoma of skin, Cervical Intraepithelial Neoplasia (CIN), 'in situ' Breast Cancer, or Prostate Intraepithelial Neoplasia (PIN); or other localized malignancies with a high probability of cure through surgical resection or radiation therapy; 6. Folate or vitamin B12 deficiency (Folate \leq lower limit of normal (LLN), vitamin B12 \leq LLN); 7. Uncontrolled systemic diseases, active uncontrolled infections, or

	<p>comorbidities;</p> <p>8. Known to be seropositive for HIV;</p> <p>9. Known significant mental disorder or other conditions that predisposes the subject to high risk of noncompliance with the protocol ;</p> <p>10. Life-threatening illness or severe organ system dysfunction, such as uncontrolled congestive heart failure or chronic obstructive pulmonary disease, or other reasons including laboratory abnormalities, which, in the investigator's opinion, could compromise the subject's safety;</p> <p>11. “Dry tap” bone marrow aspiration;</p> <p>12. Bone marrow fibrosis grade 2-3;</p> <p>13. Hypersensitivity to DEC, ATRA, or other investigational drugs;</p> <p>14. Other conditions, in the investigator's opinion, ineligible for participation in this clinical trial.</p>
Randomization	<p>Subjects were randomly assigned into the ATRA plus DEC versus DEC groups using 1:1 ratio.</p>
Investigational Medicinal Product And Treatment	<p>Treatment Group:</p> <p>DEC administered through intravenous infusion at a dosage of 20mg/m² per day on Days 1 to 5; ATRA at 25mg/m²/d, administered orally in divided doses, with each treatment cycle lasting 28 days. ATRA was administered at 25mg/m² orally on days 1 to 14 from the fifth cycle.</p> <p>Control Group:</p> <p>DEC is administered through intravenous infusion at a dosage of 20mg/m² per day on Days 1 to 5, with each treatment cycle lasting 28 days. These treatment cycles are repeated every 4 weeks until any of the following conditions occur: disease progression, unacceptable toxicity, or patient’s decision to withdraw from the study. Initially, therapy was planned for minimum of four cycles and was intended to continue until relapse, progress disease (PD, defined according to IWG 2006 criteria), patient request, or the onset of intolerable</p>

	<p>toxicity. Patients could also discontinue the study to pursue allogeneic hematopoietic stem cell transplantation (allo-HSCT) if they met the eligibility criteria. During the administration of DEC, if patients experience severe adverse reactions (such as Grade 3 or higher infections or myelosuppression), appropriate measures may be taken, including delaying treatment and adjusting the dosage based on hematologic and nonhematologic toxicity. (refer to the 'Dosage Adjustment in Case of Severe AEs' section). Patients may also receive supportive measures, including blood component transfusion, G-CSF, and anti-infection therapy.</p>
<p>Sample Size</p>	<p>226 subjects are expected to be included (113 in the treatment group and 113 in the control group).</p>
<p>Efficacy Endpoints</p>	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> ➤ The Overall Response Rate (ORR) Evaluated by an Independent Review Committee: Evaluate the overall response rate (ORR) of all subjects receiving the dosing regimen using the IWG2006 Response Criteria, i.e., the proportion of patients with CR+PR+mCR+HI. <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> ➤ Investigator-assessed ORR; ➤ Bone marrow blasts response rate; ➤ Cytogenetic response; ➤ Overall improvement rate; ➤ Progression-free survival; ➤ Overall survival; ➤ Response time (the time elapsed between the start of treatment and the date or the number of treatment cycles of the first recorded hematology improvement or bone marrow remission); ➤ Time to AML transformation or death. ➤ Safety

	<p>Exploratory Endpoints:</p> <ul style="list-style-type: none"> ➤ Explore the association between specific gene mutation profile and overall response rate, overall survival, and progression-free survival.
Safety Parameter	<ul style="list-style-type: none"> ➤ Vital signs, hematological and clinical biochemical test results (during screening, prior to dosing on the first day of each cycle, at the last treatment visit, and when show to be clinically significant); ➤ ECG and physical examination (at screening and end of treatment visit); ➤ AEs, all AEs are recorded in CRFs;
Quality of Life	<ul style="list-style-type: none"> ➤ EORTC QLQ-C30 ➤ EQ-5D-5L
Statistical Analysis	<p>Statistical analysis will be performed using SAS 9.4 software.</p> <p>Categorical variables such as OR, CR, mCR and HI comparisons will be made using either the Chi-squared test or Fisher’s exact test. Continuous variables will be compared using the t-tests. Time-to-event outcomes, including OS, PFS and time to AML transformation, will be estimated using the Kaplan–Meier method and compared between groups using log-rank tests. The Cox proportional hazards regression model will be used to estimate hazard ratio (HR) along with the corresponding 95% confidence intervals. All statistical tests are two-sided tests, with a P-value less than or equal to 0.05 considered statistically significant.</p>
Anticipated Timeline	August, 2018 - June, 2023

1. Background

Myelodysplastic Syndromes (MDS) are heterogeneous clonal hematopoietic neoplasms characterized by ineffective hematopoiesis, peripheral blood cytopenias, an increased risk of progression to acute myeloid leukemia (AML). The morbidity of MDS increases significantly in individuals aged 60 and above, rendering it a prevalent hematologic malignancy among the elderly population. Given the aging demographic trend in our nation, MDS will pose a substantial threat to public health. In a clinical context, patients are stratified into lower risk and higher risk categories (refer to Appendix 3) utilizing the IPSS or IPSS-R risk grouping, based on their complete blood counts, blast percentage and cytogenetics. Research has shown that aberrant DNA methylation contributes to the silencing and deactivation of tumor suppressor genes, playing a role in the pathogenesis of MDS and certain forms of AML, suggesting that the inhibition of DNA methylation is a target for treatment. DEC is a specific DNA methyltransferase (DNMT) inhibitor that can reverse the DNA methylation process. In clinical practice, DEC stands as one of the effective methods used to treat MDS and some AML. It was approved by the US FDA in 2006 for the treatment of MDS, and in 2012 by the European EMA for the treatment of elderly AML. It was previously reported that low doses of DEC suppress cellular gene methylation through epigenetic regulation, while high doses exhibit cytotoxic effects. However, clinical outcomes of patients treated with HMA monotherapy were far from satisfactory. Clinical studies in recent years have revealed that DEC monotherapy yields a mere 20% complete remission (CR) rate for MDS. Allo-HSCT is potentially the only curative treatment. However, allo-HSCT might not be feasible or tolerated in the elderly, who make up the majority of cases. There is an enormous unmet need in terms of treatment of higher-risk MDS. Consequently, concerted efforts have been channeled towards proposing and continually probing DEC-based combined treatment strategies, aimed at enhancing the overall therapeutic efficacy.

Retinoic acid (RA) and its derivatives are the most important class of differentiation-inducing agents and have been used in clinical treatment. They are derived from vitamin A (including retinol, retinal, and all-*trans*-retinoic acid). It plays an important role in regulating cell growth, differentiation, apoptosis and other life activities. Retinoic acid has the ability to differentiate and mature HL-60 cells into granulocytes, while also inhibiting their clonal growth. It has been widely used in clinical tumor treatment.

To sum up high-risk MDS patients are mostly elderly people, who are unable to tolerate high-

intensity chemotherapy or stem cell transplantation, have poor prognosis, and lack suitable clinical treatments. In addition to conventional chemotherapy and symptomatic supportive care, the combination therapy with DEC may be a new alternative. This study intends to combine ATRA with DEC for the untreated patients with MDS-EB, aiming to enhance therapeutic efficacy, reduce adverse reactions, and improve patients' quality of life.

The trial protocol was developed in compliance with the guidelines outlined in the "Drug Administration Law of the People's Republic of China," "Provisions of Drug Registration," "Good Clinical Practice" (GCP), and the "Declaration of Helsinki." Additionally, pertinent research data concerning this medication were referenced in order to meticulously observe the efficacy and safety of the combined usage of ATRA and DEC for the untreated MDS-EB patients.

2. Study Objective

Evaluating the efficacy and safety of all-*trans* retinoic acid in combination with decitabine for the untreated MDS-EB patients.

3. Study Design

A prospective, open-label, multi-center, randomized controlled clinical study

3.1 Participating sites

- The First Affiliated Hospital, Zhejiang University School of Medicine
- Zhongda Hospital, Southeast University Medical School
- The Affiliated Hospital of Qingdao University
- Fujian Medical University Union Hospital
- Sir Run Run Shaw Hospital, School of Medicine, Zhejiang university
- The Affiliated Jinhua Hospital of Wenzhou Medical University
- The First Affiliated Hospital of Ningbo University
- The Affiliated Hospital of Xuzhou Medical University

3.2 Randomization

Central randomization method is employed in this study. Participants were randomized 1:1 to either ATRA plus DEC, or DEC alone group, utilizing allocation concealment techniques. An allocation sequence scheme was generated using software R (version 3.4.4) on the basis of stratified block randomization with research sites as a stratification factor and a block length of 4. For each research site, a separate allocation list was generated and implemented into a central Interactive Web Response System (programmed and maintained by Reelly medicine, Co., Ltd, China). Participants were registered at their respective sites via this system, and the system automatically allocated them to their next assignment. Neither patients nor investigators were blinded to treatment assignment.

3.3 Group Design

Parallel control design.

Treatment Group: DEC + ATRA

Control Group: DEC monotherapy

Dosage and administration methods are both based on the detailed treatment plan.

3.4 Sample Size

The sample size was calculated by PASS 11.0 software (NCSS, Kaysville, UT) with sample allocation ratio of 1:1 between DEC alone group and ATRA plus DEC group. Based on a 50% of overall response rate (CR+PR+mCR+HI) in DEC monotherapy group and an increase of the response rate to 70% with ATRA plus DEC group, and on prerequisite conditions including a two-sided 5% of type I error probability, and an 80% of power, a total of 180 patients were required. Accounting for an expected 20% dropout rate, a total of 226 patients were finally required for enrollment.

4. Subject

4.1 Number of cases and Case Allocation

This clinical trial requires a total enrollment of 226 patients, with 113 patients in the treatment group and 113 patients in the control group, collectively conducted by multiple clinical trial institutions.

4.2 Inclusion Criteria

Study subjects: Untreated patients diagnosed with MDS-EB-1 or MDS-EB-2 according to the 2016 revision to the World Health Organization classification (Appendix 2). Subjects must meet all of the following criteria to be enrolled:

- 1) Age \geq 18 years old; life expectancy \geq 3 months;
- 2) Patients aged \geq 18 years with morphologically confirmed MDS with excess blasts (MDS-EB-1 or MDS-EB-2) according to the World Health Organization classification (2016). Additionally, participants, who are untreated, were required to undergo a bone marrow examination within 30 days prior to enrollment;
- 3) ECOG performance status of 0 to 2;
- 4) Female subjects of child-bearing potential must consent to use physician-approved contraception measures during the administration of DEC and ATRA, extending to a period of 1 month after the last dose of DEC and 1 year after the last dose of ATRA. Male subjects whose partners have the potential to conceive must commit to utilize physician-approved contraception techniques throughout the entirety of the study duration, while also avoid impregnating the female partners during the study period and for a duration of 2 months following the last administration of DEC;
- 5) Adequate hepatic and renal function (serum creatinine \leq 1.5 \times upper limit of normal (ULN), BUN \leq 1.5 \times ULN, ALT \leq 2 \times ULN, AST \leq 2 \times ULN, total bilirubin \leq 1.5 \times ULN).
- 6) Written informed consent obtained.

4.3 Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for random enrollment:

- 1) History of solid organ transplantation;
- 2) Previous hematopoietic stem cell transplantation, Cytotoxic therapy, or hypomethylating agents, including Azacitidine, DEC, and Chemotherapy;
- 3) Valproate, Antithymocyte Globulin, and Arsenic Trioxide. (Prior treatment with these agents is permitted, provided that completion is at least 30 days before the first dose of study treatment.);
- 4) Treatment with any investigational drug or therapy within 30 days of study treatment,

before the first dose of study treatment, or ongoing clinically significant adverse events from previous treatment;

- 5) Prior malignancy in the preceding 3 years, except for adequately treated Superficial Bladder Cancer, Basal Cell or Squamous Cell Carcinoma of skin, Cervical Intraepithelial Neoplasia (CIN), 'in situ' Breast Cancer, or Prostate Intraepithelial Neoplasia (PIN); or other localized malignancies with a high probability of cure through surgical resection or radiation therapy;
- 6) Folate or vitamin B12 deficiency (Folate \leq lower limit of normal (LLN), vitamin B12 \leq LLN);
- 7) Uncontrolled systemic diseases, active uncontrolled infections, or comorbidities;
- 8) Known to be seropositive for HIV;
- 9) Known significant mental disorder or other conditions that predisposes the subject to high risk of noncompliance with the protocol ;
- 10) Life-threatening illness or severe organ system dysfunction, such as uncontrolled congestive heart failure or chronic obstructive pulmonary disease, or other reasons including laboratory abnormalities, which, in the investigator's opinion, could compromise the subject's safety;
- 11) "Dry tap" bone marrow aspiration;
- 12) Bone marrow fibrosis grade 2-3;
- 13) Hypersensitivity to DEC, ATRA, or other investigational drugs;
- 14) Other conditions, in the investigator's opinion, ineligible for participation in this clinical trial.

4.4 Criteria for Withdrawal

- 1) Voluntary Withdrawal by Patients: Patients can voluntarily withdraw from the study at any time, without consideration for decisions made by other parties involved in this study.
- 2) Adverse Events: If a patient experiences an AE requiring early study termination, either due to unacceptable risk to the patient's health or the patient's unwillingness to continue participation.
- 3) Disease Progression or Transformation to Acute Myeloid Leukemia: Patient's disease progresses or transforms into AML.

-
- 4) Loss to Follow-up: If a patient fails to attend scheduled visits and the researcher is unable to contact the patient after at least three attempts via phone, email, and/or by mail.
 - 5) Compliance: Patients exhibit poor compliance with study medication and procedures.
 - 6) Other Treatments: Patients require other drug treatments that may impact the evaluation of the study drug.

Handling of Withdrawn Cases: When a patient withdraws, the researcher must record the reason in the CRF and make efforts to contact the subject to complete as many assessment items as possible. The last date of medication administration should be documented, and the final major efficacy evaluation results should be used for statistical analysis, and their CRFs must be retained for review. Patients who did not undergo assessment after treatment and withdrew are considered dropouts. Cases withdrawn due to AEs should not only be recorded in the CRF but also included in the AE assessment. The randomized number of withdrawn cases cannot be replaced.

4.5 Rejection Criteria

Upon entry, subjects meeting any of the following conditions should be rejected:

- 1) Inclusion Error
- 2) No investigational drugs were used
- 3) Underwent chemotherapy or treatment drug treatment other than this protocol during the trial

Handling of Rejected Cases: Researchers must record the reason for rejection in the CRF, which should be retained for review. Rejected cases will not be performed for efficacy statistical analysis. Those who have undergone at least one treatment and have safety records may participate in safety analysis as deemed appropriate. The randomized number of rejected cases cannot be replaced.

4.6 Trial Termination Criteria

- 1) Severe safety concerns identified by investigators
- 2) Poor efficacy rendering further clinical trials unnecessary
- 3) Major errors in the study protocol
- 4) Sponsorship termination due to financial or management reasons
- 5) Trial revoked by ethics committee or regulatory authority

Trial termination can be temporary or permanent. Following trial termination, all relevant trial

records must be retained for review.

5. Investigational Drug and its Packaging, Allocation, and Usage

5.1 Investigational Drug

5.1.1 Investigational Drug: ATRA, specification: 20 mg per tablet, developed and provided by Shandong LongFine Pharmaceutical Co., Ltd.

5.1.2 Standard Drug: DEC, to be used according to each center's circumstances.

5.2 Randomization

This trial adopts a multi-center, randomized, open-label clinical trial design. Using a central randomization system, subjects will be grouped with a 1:1 ratio between the treatment group and the control group. The total number of cases is 226, with 113 in each group.

5.3 Administration Method

Treatment Group: DEC: 20 mg/m² daily, administered as intravenous infusion for over 1 hour on Days 1-5 of each 28-day cycle; ATRA: 25 mg/m²/day, administered orally in divided doses daily for each 28-day cycle. ATRA was administered at 25mg/m² orally on days 1 to 14 from the fifth cycle.

Control Group: DEC: Intravenous infusion, 20 mg/m² daily on Days 1-5 of each 28-day cycle.

These treatment cycles are repeated every 4 weeks until any of the following conditions occur: disease progression, unacceptable toxicity, or patient's decision to withdraw from the study. Initially, therapy was planned for minimum of four cycles and was intended to continue until relapse, progress disease (PD, defined according to IWG 2006 criteria), patient request, or the onset of intolerable toxicity. Patients could also discontinue the study to pursue allo-HSCT if eligible.

During administration, if patients develop severe adverse events (such as Grade 3 or above infections or bone marrow suppression), the DEC treatment may be appropriately delayed, or dosage may be appropriately reduced (if bone marrow suppression exceeds 21 days, the dose of next cycle of DEC will be reduced by 25% of the dose of the previous cycle. After dose reduction,

if duration of bone marrow suppression is shortened to within 21 days, the subsequent DEC dose restore to the previous cycle's dose. Treatment delays up to 8 weeks from the start of the previous cycle were permitted to allow recovery from therapy-related myelosuppression. If ATRA-related adverse reactions are intolerable, the ATRA dose may be halved), along with supportive measures like blood component transfusion, G-CSF, and anti-infection therapy.

Regarding ATRA, if doses are missed during the study period, there is no need for dose adjustment for the subsequent dose. ATRA should continue to be taken orally twice daily as per the original regimen.

5.4 Management of Investigational Drugs

5.4.1 Pre-Trial Drug Management

Prior to the commencement of the trial, the sponsor and statistical unit are responsible for preparing a sufficient quantity of drugs in accordance with statistical requirements. These drugs should be properly packaged, numbered, and delivered to each trial institution by the sponsor. Detailed records of the transportation handover and comprehensive temperature logs throughout the entire process must be maintained.

Upon receipt of the drugs by each trial institution and completion of inventory, all investigational drugs must be securely stored in a location that is both safe and compliant with GCP requirements. A designated individual shall be responsible for management tasks (drug reception, storage, distribution, and retrieval, etc.).

5.4.2 Drug Management During the Trial

Each clinical research institution must establish a comprehensive drug management system. The investigational drugs in this trial are required to be kept in a locked cabinet, with DEC needing storage at temperatures of 2-8°C and ATRA at room temperature.

Once the trial phase commences, researchers are to provide subjects with the appropriately labeled investigational drugs for the 1st, 2nd, 3rd, and 4th dosing cycles, in accordance with the trial requirements. Detailed records of drug dispensation are to be maintained.

During each visit, researchers are required to collect any remaining investigational drugs from the previous visit cycle before distributing the investigational drugs for the subsequent visit cycle. Corresponding records of retrieval and dispensation must be accurately maintained.

Calculation of Medication Compliance: Actual administered dose / prescribed dose × 100%.

5.4.3 Post-Trial Drug Management

Upon completion of the clinical trial, all remaining drugs and their outer packaging must be returned to the sponsor, with corresponding records of retrieval maintained.

6. Concurrent Medications, Supportive Treatment, and Prohibited Medications

6.1 Permissible Medications and Treatments

- Blood component transfusion
- Antibiotics
- G-CSF
- Other necessary symptomatic supportive treatments

6.2 Prohibited Medications

- 5-AZA (5-azacytidine)
- RIF (Realgar-Indigo naturalis formula)
- Arsenic trioxide
- VPA (sodium valproate)
- ATG (anti-thymocyte globulin)
- Other traditional Chinese medicines used for MDS treatment
- Other cytotoxic drugs used for acute leukemia chemotherapy

Throughout the entire trial process, in addition to documenting investigational drugs separately, all concomitant medications used by subjects (including generic names, dosages, administration methods, usage periods, reasons for use, etc.) must be recorded in the CRF. When changes occur in the use of concurrent medications, careful attention should be paid to detailed recording of medication modifications and reasons for such changes.

7. Trial Process and Procedures

7.1 Visit 1: Screening Period (-4 to 0 Weeks)

- Obtain informed consent
- Collect demographic data of subjects (date of birth, gender, height, weight)
- Itemize verification of inclusion/exclusion criteria
- Take a medical history (history of heart, liver, and kidney diseases; history of other illnesses; history of smoking, alcohol or drug dependency, etc.)
- Record medical and treatment history, concomitant diseases, comorbid medications, etc.
- Conduct physical examination and record blood pressure, heart rate, respiration, temperature, BMI, etc.
- Perform bone marrow biopsies
- Bone marrow smear, flow cytometry, cytogenetics, molecular genetics
- Complete blood counts
- Urinalysis: urine protein, glucose, ketones, leukocytes, red blood cells
- Measure cardiac, hepatic, and renal function: ALT, AST, TBil, BUN, Cr
- Electrocardiogram (12-lead ECG)
- ECOG score, IPSS score, IPSS-R score
- Provide dietary education and health consultation
- Schedule next visit

7.2 Visit 2: Baseline Period (Week 0)

- Verify inclusion/exclusion criteria
- Record concomitant diseases and comorbid medications
- Physical examination (blood pressure, heart rate, respiration, temperature, weight)
- Once the subjects are deemed qualified, they will be enrolled into the groups and assigned unique numbers through a random process. Subsequently, investigational drugs will be dispensed in accordance with the sequence of subjects' clinic visits. Each subject will receive the medication with the corresponding number. Ensuring subjects follow

medication instructions

- Quality of life assessment (EORTC QLQ-C30, EQ-5D-5L)
- Provide dietary education and health consultation
- Schedule next visit

7.3 Visit 3: Treatment Period (Cycle 1)

- Record concomitant diseases and comorbid medications
- Physical examination (blood pressure, heart rate, respiration, temperature, weight)
- Bone marrow smear, flow cytometry
- Complete blood counts
- Urinalysis: urine protein, glucose, ketones, leukocytes, red blood cells
- Measure cardiac, hepatic, and renal function: ALT, AST, TBil, BUN, Cr
- Electrocardiogram (12-lead ECG)
- Document AEs
- Retrieve remaining investigational drugs from subjects, record actual administered doses
- Dispense investigational drugs with corresponding trial identification to subjects for the next visit cycle, ensuring subjects follow medication instructions
- Determination of subject medication adherence
- In event that a subject dropout of the study prematurely, make sure to document both the reason for dropout and the date of the last medication administration
- Provide dietary education and health consultation
- Schedule next visit

Note: Window period \pm : days, can be extended in case of toxicity for up to 8 weeks.

7.4 Visit 4: Treatment Period (Cycle 2)

- Record concomitant diseases and comorbid medications
- Physical examination (blood pressure, heart rate, respiration, temperature, weight)
- Bone marrow smear, flow cytometry
- Complete blood counts

-
- Urinalysis: urine protein, glucose, ketones, leukocytes, red blood cells
 - Measure cardiac, hepatic, and renal function: ALT, AST, TBil, BUN, Cr
 - Electrocardiogram (12-lead ECG)
 - Document AEs
 - Retrieve remaining investigational drugs from subjects, record actual administered doses
 - Dispense investigational drugs with corresponding trial identification to subjects for the next visit cycle, ensuring subjects follow medication instructions
 - Determination of subject medication adherence
 - In event that a subject dropout of the study prematurely, make sure to document both the reason for dropout and the date of the last medication administration
 - Quality of life assessment (EORTC QLQ-C30, EQ-5D-5L)
 - Provide dietary education and health consultation
 - Schedule next visit

7.5 Visit 5: Treatment Period (Cycle 3)

- Record concomitant diseases and comorbid medications
- Physical examination (blood pressure, heart rate, respiration, temperature, weight)
- Bone marrow smear, flow cytometry, and cytogenetics (chromosome) re-evaluation for those with nuclear abnormalities
- Complete blood counts
- Urinalysis: urine protein, glucose, ketones, leukocytes, red blood cells
- Measure cardiac, hepatic, and renal function: ALT, AST, TBil, BUN, Cr
- Electrocardiogram (12-lead ECG)
- Document AEs
- Retrieve remaining investigational drugs from subjects, record actual administered doses
- Dispense investigational drugs with corresponding trial identification to subjects for the next visit cycle, ensuring subjects follow medication instructions
- Determination of subject medication adherence
- In event that a subject dropout of the study prematurely, make sure to document both the

reason for dropout and the date of the last medication administration

- Provide dietary and health counseling
- Schedule next visit

7.6 Visit 6: Treatment Period (Cycle 4)

- Record concomitant diseases and comorbid medications
- Physical examination (blood pressure, heart rate, respiration, temperature, weight)
- ECOG Performance Status Score
- Bone marrow smear, flow cytometry, cytogenetics, and molecular genetics
- Complete blood counts
- Urinalysis: urine protein, glucose, ketones, leukocytes, red blood cells
- Measure cardiac, hepatic, and renal function: ALT, AST, TBil, BUN, Cr
- Electrocardiogram (12-lead ECG)
- Document AEs
- Quality of life assessment (EORTC QLQ-C30, EQ-5D-5L)
- Retrieve remaining investigational drugs from subjects, record actual administered doses
- Determination of subject medication adherence
- In event that a subject dropout of the study prematurely, make sure to document both the reason for dropout and the date of the last medication administration
- Provide dietary and health counseling
- Complete trial summary form

7.7 Follow-up Period

Subjects who meet withdrawal or termination criteria and terminate treatment will complete treatment follow-up. Subsequently, survival follow-up will take place according to the study plan.

Patients will be contacted every 12 weeks by phone:

Survival status

Tumor-specific therapy and HSCT

7.8 Trial Flowchart (See Appendix 1)

8. Trial Evaluation Indicators

8.1 Effectiveness Evaluation

8.1.1 Primary Endpoint

The Overall Response Rate (ORR), including Complete Remission (CR), Partial Remission (PR), Marrow Complete Remission (mCR), and Hematologic Improvement (HI), will be evaluated in a blinded manner for all subjects who have received at least one dose of the study medication. This evaluation will be carried out following the IWG 2006 response criteria in MDS (refer to Appendix 5), conducted by an independent review committee composed of MDS experts. OR was the proportion of patients with best response of either complete remission (CR), partial remission (PR), bone marrow complete remission (mCR), or hematologic improvement (HI) by the modified International Working Group (IWG) 2006 response criteria in MDS. Efficacy evaluation will be conducted for each treatment cycle, efficacy analysis will be performed based on the best response achieved during the first four treatment cycles. Patients who underwent treatment without available evaluative data were considered as treatment failures. If a patient is bridged to transplantation within four cycles, the best response achieved before transplantation will be used for efficacy evaluation.

8.1.2 Secondary Endpoints (Evaluated based on IWG 2006 Response Criteria in MDS, see Appendix 5)

- Investigator-assessed Patient Overall Response Rate: Evaluate the overall response rate (ORR) of all subjects receiving the dosing regimen using the IWG2006 Response Criteria, i.e., the proportion of patients with CR+PR+mCR+HI.
- Bone Marrow Blasts Response Rate: The proportion of patients with CR+mCR (with or without hematology improvement) according to IWG2006 Response Criteria.
- Cytogenetic Response: The proportion of patients with cytogenetic complete remission and partial remission according to IWG2006 Response Criteria.
- Overall Improvement Rate: The proportion of patients with CR+PR+HI according to

IWG2006 Response Criteria.

- Progression-free Survival: time between randomization and the date of disease progression, transformation to AML, relapse, or death due to any cause (whichever occurs first)
- Overall Survival (OS): time between randomization and the date of death due to any cause
- Response Time: the time elapsed between the start of treatment and the date or the number of treatment cycles of the first recorded HI or bone marrow remission.
- Time to AML transformation or death: the time from randomization date to the date of disease transformation to AML and death due to any cause.

8.1.3 Exploratory Endpoints

- Exploration of the relationship between gene mutation types and efficacy, as well as OS and progression-free survival.

8.2 Safety Evaluation

Vital signs, hematologic and clinical biochemistry tests, and quality of life assessments should be obtained during screening, before dispensing investigational drugs on the first day of each treatment cycle, at the end of treatment visits, and when shown to be clinically significant.

AEs occurring during treatment will be determined according to the National Cancer Institute's Common Terminology Criteria for AEs (CTCAE) version 5.0 (see Appendix 6), and their safety will be assessed by recording all AEs in CRFs.

Clinically relevant changes in laboratory test results, vital signs, and physical examination findings will be recorded as AEs.

Note: If abnormal results occur in complete blood counts, urine routine, liver function, renal function, or electrocardiogram after drug administration and have clinical significance, retesting is required until normalization or return to pre-trial levels.

8.3 Quality of Life

8.3.1 Patient Quality of Life

Patient quality of life will be evaluated using the EORTC QLQ-C30 (see Appendix 7) and EQ-5D-5L (see Appendix 8).

The EORTC QLQ-C30, developed by the European Organization for Research and Treatment of Cancer, comprises 5 functional subscales (physical, role, cognitive, emotional, and social functioning), 3 symptom subscales (fatigue, pain, nausea and vomiting), a global health status subscale, and several single items. Higher scores on functional scales and global health status indicate better functioning, while higher scores on symptom scales indicate more severe symptoms. The QLQ-C30 is widely used in clinical trials for cancer patients (including leukemia) in Europe, United states and other regions worldwide. The QLQ-C30 questionnaire demonstrates good psychometric capabilities and adheres to required standards, such as validity (measuring what is expected to be measured), reliability (yielding sufficiently precise results), and sensitivity (ability to detect changes). Generally, a difference of 10 points in scores on the QLQ-C30 is considered clinically significant. It has been demonstrated that this questionnaire is sensitive to changes in cancer treatment (chemotherapy and/or radiotherapy) patients.

EQ-5D-5L: Overall health status was evaluated using EQ-5D-5L, a widely-used, preference-based questionnaire assessing six dimensions of health status. It is user-friendly and can be completed in just 1 to 2 minutes. The questionnaire generates research-specific data used for calculating quality-adjusted life years and conducting economic evaluations.

The EQ-5D-5L consists of two parts. The first part includes five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each assessed through a question with five response options ranging from no problems to extreme problems. This allows for a total of 3125 (5x5x5x5x5) health state outcomes, encompassing population preferences and practicality from published datasets, ranging from negative values to 1 (perfect health). The second part of the EQ-5D-5L is a visual analog scale, where subjects rate their current health status, with 0 indicating "the worst health you can imagine", and 100 indicating "the best health you can imagine".

9. Adverse Events, Significant Adverse Events, Serious Adverse Events

9.1 Adverse Events (AE)

Definition: An AE is an adverse medical event that arises after a patient or subject in a clinical trial is administered a drug (substance), but may not necessarily be causally related to the treatment. According to GCP requirements, researchers should record all AEs in the source documents, regardless of whether they are causally related to the investigational product, and transcribe them

into the CRFs. AEs also include an increase in the frequency and severity of pre-existing diseases during the study.

9.1.1 Adverse event records should include at least

- Description of the AE
- Occurrence Time
- Termination Time
- Severity and Frequency of Occurrence
- Whether treatment is needed, and if so, record the treatment administered
- Investigator's determination of whether the AE is related to the use of the investigational product

AEs should be followed up until resolution. Medical documents related to AEs should be recorded in the source documents, including requisition forms and reports for laboratory tests. If a subject cannot continue to receive treatment from the investigator physician due to trial completion or discharge, the investigator should provide a summary of the subject's case (including treatment arrangements and instructions regarding whether AEs need continued follow-up) to the doctor responsible for their ongoing care. This information should also be recorded in the source documents.

9.1.2 Severity and Management of Adverse Events

- Mild: Symptoms are present, tolerable, do not affect daily activities, and do not require symptomatic treatment or discontinuation of the drug.
- Moderate: Symptoms affect normal life, are difficult for the patient to tolerate, and either discontinuation of the drug or symptomatic treatment is necessary.
- Severe: Symptoms are severe, life-threatening, leading to death or disabling, and immediate discontinuation of the drug or urgent intervention is required.

9.1.3 Assessment of the Relationship Between Adverse Events and Investigational Medication

The relationship between AEs and the investigational product is classified into five levels: "Definitely related, Probably related, Cannot be determined, Probably not related, Definitely not

related." The first three categories are considered as adverse events and used for calculating the incidence of adverse events (see the table below).

Criteria for Causality Assessment between Investigational Product and Adverse Events

Indicator	Definitely related	Probably related	Cannot be determined	Probably related	not related	Definitely not related
AE occurrence time coincides with time of drug use	+	+	+	+	-	-
AE related to known adverse reactions of the drug	+	+	+	-	-	-
AE improves or disappears after drug discontinuation	+	+	±	±	-	-
AE recurs after re-administration	+	?	?	?	-	-
AE cannot be explained by other reasons	+	+	±	±	-	-

Note: "?" indicates ethical constraints prevent further administration; ± indicates further observation and evaluation are needed.

9.1.4 Recording and Follow-up of Adverse Events

9.1.4.1 At each follow-up visit, the investigator should use non-inducing language to inquire about any changes in the subject's health condition after medication use; the investigator should record all AEs directly observed or spontaneously reported by the participant using concise medical terminology.

9.1.4.2 While assessing efficacy, close attention should be paid to observing AEs or unexpected toxic side effects (including symptoms, signs, and laboratory tests), analyzing the causes, making judgments, and tracking observations and records.

9.1.4.3 AEs occurring during the trial should have their symptoms, severity, onset time, duration, measures taken, and course recorded in the CRF, the relevance to the investigational medication should be evaluated then documented in detail, signed and dated by the investigator.

9.1.4.4 In the event of an AE, the investigator may decide whether to terminate the trial based on

the patient's condition. Cases where the medication is discontinued due to AEs should undergo follow-up investigations, and the process and outcomes should be thoroughly documented.

9.1.4.5 The investigator should follow up on AEs until the symptoms disappear or stabilize. Follow-up on AEs for subjects should be reported promptly to the principal investigator and the clinical trial monitor.

9.1.4.6 Common Adverse Events and Handling Plans:

- 1) If neutropenia occurs (90% incidence), colony-stimulating factors treatment can be administered.
- 2) If thrombocytopenia occurs (80% incidence), IL-11, TPO treatment, and platelet transfusion can be used.
- 3) If anemia occurs (82% incidence), red blood cell transfusion is recommended.
- 4) If febrile neutropenia occurs, antibiotics and colony-stimulating factors can be used.
- 5) For adverse reactions like cheilitis, mucosal dryness, conjunctivitis, paronychia, and alopecia, symptomatic treatment is recommended.
- 6) For other adverse reactions such as headache, dizziness, dry mouth, desquamation, photosensitivity, and skin pigmentation changes, symptomatic treatment can be administered.

9.2 Significant Adverse Events

Apart from serious AEs, any AE requiring specific medical measures (such as discontinuation of medication, dose reduction, or symptomatic treatment) and significant abnormalities in hematological or other laboratory tests are considered significant AEs. The determination of significant laboratory data abnormalities is at the discretion of the investigator and must be described and documented on a case-by-case basis when intervention measures are required. Detailed descriptions of subject demographic information, the presentation, and course of significant AEs should be provided for the investigator to determine whether there is a correlation.

9.3 Serious Adverse Events

9.3.1 Definition

A Serious Adverse Event (SAE) is determined to have occurred in the clinical trial process when

one or more of the following conditions are met: an event that requires hospitalization, prolonged hospitalization, disability, impairment of work capacity, unintended pregnancy, is life-threatening or fatal, causes congenital anomalies, etc.. Additionally, medical events that have not resulted in death, life-threatening situations, or hospitalization but are deemed by appropriate medical judgment to have potentially harm to the subject or require medical treatment or surgical intervention to prevent the occurrence of the aforementioned situations, should also be considered as SAEs.

9.3.2 Handling of Cases with Serious Adverse Events

In the event of a SAE, the investigator shall implement corresponding therapeutic measures promptly to ensure the safety of the subject. If a SAE occurs that is unrelated to the investigational product, the medical measures required by the patient will not impact the assessment of the therapeutic efficacy of the experimental drug. The patient can also be followed up as scheduled, and continued participation may be considered

9.3.3 Adjustment of Dosage in Cases of Serious Adverse Events

If a patient's duration of bone marrow suppression exceeds 21 days, the dose of DEC in the next treatment cycle will be reduced by 25% based on the previous course's dose. After the reduction, if the patient's bone marrow suppression duration is shortened to within 21 days, the subsequent dose of DEC in the next cycle will be restored to the previous course's dose. If bone marrow suppression duration exceeds 8 weeks, the patient should be withdrawn from the study. If patient intolerance to ATRA-related adverse reactions, the dose of ATRA can be halved.

9.3.4 Recording and Reporting of Serious Adverse Events

In the event of a SAE during the clinical trial, the investigator shall implement corresponding therapeutic measures immediately to the subject and record it in the CRF. The principal investigator of the trial sponsor, ethics committee, and the national adverse drug reaction monitoring system should be notified within 24 hours. The investigator is required to diligently complete the Serious AE Report Form, providing detailed information for each item, sign and date the report. The specific contact person and phone number for the investigator are as follows:

Name	Employer	Telephone	Email
Hongyan Tong	The First Affiliated Hospital Zhejiang University School of Medicine	13958122357	hongyantong@aliyun.com
National Adverse Drug Events Monitoring System		http://www.adrs.org.cn/	

9.4 Pregnancy Occurrence During the Clinical Study

Reproductive-age female subjects agree to use physician-approved contraceptive methods during the administration of DEC and ATRA, as well as within 1 month after the last dose of DEC and within 1 year after the last dose of ATRA. Additional pregnancy tests may be conducted if required by local regulations. When necessary, postmenopausal status can be determined based on follicle-stimulating hormone (FSH) levels. Serum pregnancy tests and FSH tests should be conducted at a local laboratory. The sponsor is required to report all subjects who become pregnant during the treatment period or within 30 days after treatment termination. While pregnancy is not considered an Adverse Event (AE) from a technical standpoint, all pregnancies must be followed up to determine pregnancy outcomes. These data are crucial for drug safety and public health concerns. The investigator or designated personnel are responsible for completing Pregnancy Report Form to document pregnancy occurrences among female subjects. Once a pregnancy report is obtained, request the Early Termination of Investigational Use (EIU) Form from the research monitor. The investigator should follow up with the participants until completion of pregnancy and provide complete pregnancy outcome information if possible, including normal deliveries and induced abortions, on the Pregnancy Report Form. Adverse pregnancy outcomes, whether severe or not, must be reported in accordance with the study protocol. If the pregnancy outcome meets the criteria for immediate classification as a Serious Adverse Event (SAE), (e.g., postpartum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital malformation, including aborted fetuses), the investigator should report it in accordance with the SAE reporting procedures outlined in Section 9.3.

9.5 Compensation for Subject Health Damage

The project team has procured clinical trial insurance for all subjects, allowing for compensation in accordance with the insurance terms for harm related to the investigational drug occurring due to participation in this clinical trial (except for those caused by medical malpractice).

10. Completion and Transfer of Case Report Forms

CRFs are to be completed by the investigators, and must be completed for each enrolled case. Once completed, the CRFs are reviewed by the principal investigator and clinical monitors before being transferred to the data manager for data entry and management.

11. Data Processing

11.1 Data Entry

The research workflow was defined, and the data collection form along with its corresponding data items were designed in alignment with program requirements. Data entry and management tasks were executed by the individuals designated by the statistical department. A dedicated individual is responsible for auditing the quality of the entered data.

11.2 Data Query

Any uncertainties identified within the CRFs prompt the data administrator to generate data query forms (DRQs). These queries are then sent to the investigators through clinical monitors. The investigators are expected to promptly address and respond to these queries. Upon receiving the investigators' responses, the data administrator performs data modifications, verification, and entries. If necessary, additional rounds of queries (DRQs) may be issued.

11.3 Data Locking

Once the established database is verified to be accurate, the data locking process is conducted by the principal investigator, sponsors, and statistical analysts. Locked data are no longer subject to be modified. Issues identified after data locking are corrected in the statistical analysis program

following confirmation.

11.4 Data Processing

Upon the completion of data entry and subsequent data locking, the database is handed over to the statistical analysis team in accordance with the requirements outlined in the statistical analysis plan. After the completion of statistical analysis, the statistical analysts prepare a statistical analysis report, which is then submitted to the responsible institution for this clinical trial for the composition of the trial summary report by the principal investigator.

12. Statistical Analysis of Trial Data

12.1 Selection of Statistical Analysis Data

12.1.1 Full Analysis Set (FAS)

Following the principle of Intention-to-Treat (ITT), subjects are minimally and reasonably excluded, resulting in a dataset that includes all subjects who were randomized and received at least one dose of the investigational drug. The FAS constitutes the primary analysis set for this study.

12.1.2 Per Protocol Set (PPS)

Subjects who adhere to the protocol and meet the following criteria constitute the Per Protocol population for this study:

- ① No use of prohibited medications during the trial period.
- ② Meet the inclusion criteria without any of the exclusion criteria.

Subjects experiencing disease progression, transformation to AML, or death within 4 treatment cycles and meeting the above criteria should also be included in the PPS for analysis.

12.1.3 Safety Set (SS)

The safety set includes all subjects who received at least one dose of treatment with documented safety metrics.

12.2 Statistical Analysis Plan

Statistical analysis will be performed using SAS 9.4 statistical analysis software. All statistical tests are two-sided tests, and P values less than or equal to 0.05 will be considered to be statistically significant.

The quantitative variables collected during the trial will be utilized in various statistical methods to calculate the number of cases, mean, standard deviation, median, maximum, and minimum values. Concurrently, the categorical variables collected during the trial will be used to calculate both the frequency and the percentages within each category respectively.

Descriptive Statistical Analysis: In the Full Analysis Set, demographic and other screening data, including disease characteristics, were tabulated and descriptively summarized by treatment group. Independent sample *t*-test (or non-parametric test) and χ^2 test (or Fisher's exact test) are used to compare demographic data and other baseline value indicators to measure the balance between the two groups.

Parameter Estimation and Hypothesis Testing: Efficacy Analysis: The χ^2 test is used to evaluate the difference in overall response rate of the main efficacy indicator, and the 95% confidence intervals of the difference in response rate are calculated to determine the efficacy difference between the treatment group and the control group.

Survival Analysis: The Kaplan-Meier method is used for survival analysis and the survival curve is drawn. The comparison of survival curves is performed by Log-rank test; multivariate analysis is performed by Cox proportional hazard model to determine the factors affecting prognosis and calculate hazard ratio (HR) and 95% CI.

Subgroup Analysis: Post-hoc subgroup analysis is conducted to analyze the relationship between the following characteristics and efficacy, overall survival, and progression-free survival, and evaluate whether the efficacy is consistent across different subgroups. Subgroup analysis includes but is not limited to the following:

Age at randomization: <60 VS. \geq 60

IPSS-R risk score: \leq 4.5 VS. >4.5 points

EB type: EB1 VS. EB2

Statistical analysis of trial data is performed after completion of the study and efficacy assessment in the last enrolled subject.

13. Clinical Trial Quality Control

13.1 General Quality Control

13.1.1 The trial protocol determined through multi-center discussions must be reviewed and approved by the responsible institutional ethics committee before execution.

13.1.2 During the trial, the sponsor should appoint clinical research associate with qualifications to conduct regular on-site supervision and visits to the respective trial sites to ensure strict adherence to the trial protocol, relevant laws, regulations, and SOPs, as well as accurate and error-free completion of trial data.

13.1.3 Personnel participating in the clinical trial should remain relatively stable. Prior to the trial initiation, the sponsor and principal investigator should organize an initial training session for thorough study and discussion of the clinical trial protocol, ensuring uniform criteria for data assessment and recording methods.

13.1.4 Investigators should complete each item of the CRF promptly, truthfully, comprehensively, and diligently, using a black ink pen or ballpoint pen.

13.1.5 All observed results and findings in the clinical trial must be verified to ensure data reliability, guaranteeing that all conclusions drawn during the clinical trial are based on original data. Corresponding data management measures should be implemented during the clinical trial and data processing stages.

13.1.6 The content of study medical records and CRFs should not generally be altered. If corrections are necessary, ensure that the original recorded data remains legible by centering the corrected area with a horizontal line. Additionally, the rationale for the correction should be affixed alongside it, accompanied by the signature and date of the physician making the correction

13.1.7 Researchers should take active measures (notification of follow-up appointment, follow-up visits) to control the dropout rate of cases to within 20%.

13.1.8 To ensure subject compliance, subjects should fully understand the significance of the trial and the importance of timely medication. Each center should assign designated personnel to receive, manage, dispense, and retrieve investigational drugs. The usage of investigational drugs

should be promptly recorded on relevant documentation. Subjects not adhering fully to medication instructions should be persuaded in a timely manner, and the reasons should be thoroughly documented.

13.1.9 Each trial center should establish an internal quality assurance system to rigorously supervise and control the quality of trials conducted at the center.

13.1.10 Each center should ensure the accuracy and reliability of laboratory test results and establish unified criteria for identifying abnormal values.

13.1.11 Laboratory testing data related to the trial should be promptly and truthfully recorded in the CRF, and original laboratory report forms or their copies should be attached to the study medical records. Abnormal data should be verified, and necessary explanations should be provided by the relevant researchers. If necessary, follow-up and further investigation should be conducted until the data return to normal or stabilize.

14. Ethical Review and Informed Consent

Researchers have a responsibility to ensure that the conduct of this trial complies with the requirements of the Chinese "Guidelines for Good Clinical Practice for Drug Clinical Trials" (2003 edition) and the "Declaration of Helsinki" (2000 edition). Prior to the commencement of the trial, the trial documents such as the trial protocol and informed consent form must be reviewed and approved by the ethical committee of the responsible unit for this clinical trial before implementation. Researchers are responsible for reporting the progress of the trial and any serious AEs occurring during the trial to the ethical committee. Any modifications to the trial protocol or informed consent form must be submitted to the ethics committee for review and approval.

Before enrolling in this trial, researchers must provide a comprehensive introduction to the purpose, procedures, potential risks, and benefits of this clinical trial to the subjects (or their legally authorized representatives in special cases); subjects should be informed of their right to withdraw from the trial at any time. Prior to entering the group, each subject (or their legally authorized representative in special cases) must sign an informed consent form. The research physician has the responsibility to obtain an informed consent form signed by both parties with names, dates, and contact information before the subject participates the study. The original is kept as a trial document in the institution, and a copy is given to the subject for preservation.

Any changes to the subject's informed consent form must be documented and submitted to the ethical committee for review and approval. The new version of the informed consent form that is officially implemented after approval must also be filed in the institution. Every patient or independent witness affected by changes in the informed consent form, as well as those individuals involved in the discussion of informed consent form, must sign and date on the new version. The original copy is kept on file at the institution, and a copy is given to the subject for preservation.

15. Data Preservation

To ensure that the sponsor can evaluate and monitor the clinical trial, the trial center should properly store all relevant trial data in accordance with GCP requirements, including documents that can confirm the identity of the subjects (such as original signed informed consent forms, CRFs, and original medical records), records of dispensing/retrieving trial drugs, etc. All trial documents should be retained for 5 years after this clinical trial ends.

All data from this clinical trial belong to the sponsor. Except as required by the national or local medical products administration, researchers shall not provide any form of the trial data to any third party in any form without the written consent from the sponsor. After completion of the trial, the responsible institution has the right to publish the content related to this trial in thesis form and to declare results. The main researchers, sponsor and other relevant personnel of each participating institution have the right to be listed as authors of the article. Prior to publication, the responsible institution must obtain written permission from the sponsor. Each participant institution is not allowed to publish articles or declare results on its own before the article of the whole trial has been published

16. Trial Organization

16.1 Leading Institution of the Trial

The leading institution of the trial is responsible for the overall management of the trial, including pre-trial preparations (such as trial protocol, CRF, informed consent form, ethical committee approval, preparation of relevant trial documents, establishment of various SOPs related to the trial, etc.), convening investigator meetings, etc. During the trial, the leading institution handles

trial quality, progress, and problems during the trial, responsible for explaining clinical problems, reporting SAEs to the ethical committee and the National Center for Adverse Drug Reaction Monitoring, convening regular meetings to discuss issues arising during trial monitoring, and responsible for trial briefings. After the trial, the leading institution conducts the closure procedures for each center, assists in compiling retrieved CRFs and data processing, and is responsible for writing the clinical trial report.

16.2 Participating Centers

A group of doctors, nurses, and other personnel designated by the investigator in each participating centers is responsible for trial preparation and implementation.

17. Responsibilities and Relevant Regulations of the Parties

17.1 Responsibilities of Investigator

17.1.1 Qualifications Required for Investigator

- 1) Hold a relevant professional technical position and medical qualification in a medical institution.
- 2) Possess the professional knowledge and experience as required in the trial protocol.
- 3) Have extensive experience in clinical trial methods or be able to obtain academic guidance from experienced researchers within the institution.
- 4) Be familiar with materials and literature related to the clinical trial provided by the sponsor.
- 5) Have the authority to dispose of the personnel involved in the trial and use the equipment required for the trial.

17.1.2 Clinical Trial Requirements for Investigator

- 1) Must read and understand the content of the trial protocol thoroughly and strictly adhere to its execution.
- 2) Should comprehend and be familiar with the nature, action, efficacy, and safety of the investigational drugs (including relevant data of pre-clinical studies) and also master all new information related to the drugs discovered during the clinical trial.

-
- 3) Investigators must conduct the clinical trial in a medical institution with good medical facilities, laboratory equipment, and staffing, ensuring facilities for handling emergencies to guarantee the safety of the subjects. Laboratory test results should be accurate and reliable.
 - 4) Investigators must obtain consent from their medical institution or competent authority, ensuring sufficient time is available to manage and complete the clinical trial within the timeframe specified by the protocol. Investigators must inform all staff involved in the clinical trial of the relevant information, regulations, and responsibilities to ensure that there are adequate subjects who meet the protocol requirements to be enrolled in the clinical trials.
 - 5) Investigators should explain the relevant details to the subjects agreed by the ethics committee and obtain informed consent forms from subjects.
 - 6) Investigators are responsible for making medical decisions related to the clinical trial and ensuring subjects receive appropriate treatment when experiencing AEs during the trial.
 - 7) Investigators have an obligation to take necessary measures to ensure safety of subjects and document them. In the event of a SAE during the clinical trial, investigators must take appropriate treatment measures for the subject immediately, report to the drug administration, sponsor, and ethical committee at the same time, and sign and date the report.
 - 8) Investigators should ensure that data are entered into medical records and CRFs truthfully, accurately, completely, timely and legally.
 - 9) Investigators should accept monitoring and inspection by monitors or inspectors sent by sponsors to ensure quality of clinical trials.
 - 10) Investigators must adhere to the financial provisions of the trial. Investigators are not allowed to charge subjects for the cost of investigational drugs used in the trial during the clinical trial.
 - 11) Upon completion of the clinical trial, investigators must send sponsors a signed and dated summary of the designated sub-centers.
 - 12) Investigators must notify subjects, sponsors and ethics committees before terminating a clinical trial and provide reasons for the suspension.

17.2 Responsibilities of the Sponsor

- 1) The sponsor is responsible for initiating, applying for, organizing, and auditing this clinical trial.
- 2) The sponsor selects trial institutions and principal investigators, identifying their qualifications and conditions to ensure the completion of the trial.
- 3) The sponsor provides investigators' manuals, containing clinical aspects of the investigational drugs (including previous and ongoing trials).
- 4) The sponsor can organize the clinical trial according to the protocol only after obtaining approval from the ethical committee.
- 5) The sponsor and investigators collaboratively design the clinical trial protocol, outlining responsibilities and tasks related to protocol implementation, data management, statistical analysis, results reporting, and paper publication methods etc. Sign the trial protocol and the contract which are agreed by both parties.
- 6) The sponsor appoints monitors for the trial and ensures their acceptance by the investigators.
- 7) The sponsor should establish quality control and quality assurance systems for the clinical trial, and may organize audits to ensure quality.
- 8) The sponsor and investigator shall promptly investigate serious AEs related to the trial, take necessary measures to ensure safety and rights of the subjects, report to the drug administration in time, and simultaneously notify other investigators in clinical trials involving the same drug.
- 9) Before terminating a clinical trial, the sponsor shall notify the investigators and ethical committee and provide reasons for the suspension.
- 10) The sponsor shall provide insurance coverage for subjects participating in the clinical trial and bear the cost of treatment and appropriate financial compensation for subjects who experience harm or death related to the trial. The sponsor shall provide legal and financial guarantees to the investigator, except for those caused by medical malpractice.
- 11) If investigators fail to adhere to the approved protocol or relevant regulations during the clinical trial, the sponsor should point out the issues for correction. If the situation is severe or the issues persist, the investigator shall be terminated from participating in the clinical trial.

18. References

1. "Provisions for Drug Registration" (2007 edition);
2. "Good Clinical Practice" (2013 edition);
3. "Declaration of Helsinki" (2000 edition).

19. Appendices

Appendix 1 Trial Flow Chart

Trial Phases	Screening	Randomization	Treatment			
			V3	V4	V5	V6
Number of Visits	V1	V2	V3	V4	V5	V6
Visit Time	Day -30 until day-1-		Cycle 1	Cycle 2	Cycle 3	Cycle 4
Signing Informed Consent ¹	x					
Randomization and Enrollment		x				
Confirmation of Inclusion and Exclusion Criteria	x	x				
Baseline characteristics	x					
Medical History	x					
Concomitant Diseases and Concomitant Medications	x	x	x	x	x	x
Physical Examination	x	x	x	x	x	x
BM Biopsy	x					
BM Immunophenotyping	x					
Bone Marrow Smear	x		x	x	x	x
Flow Cytometry	x		x	x	x	x
BM Cytogenetics	x [#]				x [#]	x
Molecular Genetics	x					x

ECOG Score	x					x
IPSS and IPSS-R Scoring ²	x					
Assessment of blood transfusion dependency		x	x	x	x	x
CBC		x	x	x	x	x
Urinalysis	x		x	x	x	x
Blood chemistry ³	x		x	x	x	x
12-Lead Electrocardiogram	x		x	x	x	x
Adverse Events			x	x	x	x
Investigational Drug Dispensation		x	x	x	x	x
Investigational Drugs Retrieval			x	x	x	x
EORTC QLQ-C30		x		x		x
EQ-5D-5L		x		x		x
Assessment of Medication Compliance			x	x	x	x

BM=bone marrow; CBC=complete blood counts; EOT=end of study treatment;

Note:

1. Informed consent form must be obtained prior to entering the clinical trial screening period, including discontinuation of other prohibited medications.
2. All patients are grouped according to the International Prognostic Scoring

System (IPSS) and IPSS-R

3. Blood chemistry include: creatinine, urea, uric acid, sodium, calcium, potassium, glucose, total bilirubin,

"#" indicates that those with abnormal karyotypes undergo bone marrow cytogenetic re-examination.

Appendix 2 The 2016 revision to the World Health Organization classification of MDS

Name	Dysplastic Lineages	Cytopenias	Ring sideroblasts as % of marrow erythroid elements	Bone Marrow and Peripheral Blood Blasts	Cytogenetics by Conventional Karyotype Analysis
MDS with Single Lineage Dysplasia (MDS-SLD)	1	1 or 2	<15% or <5% ^a	Bone marrow <5%, peripheral blood <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with Multilineage Dysplasia (MDS-MLD)	2 or 3	1-3	<15% or <5% ^a	Bone marrow <5%, peripheral blood <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with Ring Sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15% or ≥5% ^a	Bone marrow <5%, peripheral blood <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥15% or ≥5% ^a	Bone marrow <5%, peripheral blood <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with Isolated del(5q)	1-3	1-2	None or any	Bone marrow <5%, peripheral blood <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except -7 or del(7q)
MDS with Excess Blasts (MDS-EB)					

MDS-EB-1	0-3	1-3	None or any	Bone marrow 5%-9% or peripheral blood 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	Bone marrow 10%-19% or peripheral blood 5%-19%, or Auer rods	Any
MDS, Unclassifiable (MDS-U)					
With 1% Blood Blasts	1-3	1-3	None or any	Bone marrow <5%, peripheral blood =1% ^b , no Auer rods	Any
With Single Lineage Dysplasia and Pancytopenia	1	3	None or any	Bone marrow <5%, peripheral blood <1%, no Auer rods	Any
Based on defining cytogenetic abnormality	0	1-3	<15% ^c	Bone marrow <5%, peripheral blood <1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	Bone marrow <5%, peripheral blood <2%	Any

Note: MDS: Myelodysplastic Syndrome; blood cell reduction is defined as hemoglobin <100g/L, platelet count <100x10⁹, neutrophil absolute count <1.8x10⁹/L. In very rare cases, MDS may exhibit mild anemia or thrombocytopenia above these levels. Peripheral blood monocyte count must be <1x10⁹/L. ^aIf SF3B1 mutation is present; ^b1% peripheral blood blasts must be recorded on at least 2 separate occasions; Cases with ≥15% ring sideroblasts show significant erythroid dysplasia, and are classified as MDS-RS-SLD.

Appendix 3 International Prognostic Scoring System (IPSS) and Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndromes (MDS)

International Prognostic Scoring System (IPSS)^a

Survival and AML Evolution					
	Score Value				
Prognostic Variable	0	0.5	1.0	1.5	2.0
Marrow Blast (%) ^b	<5	5-10	-	11-20	21-30
Karyotype ^c	Good	Intermediate	Poor	-	-
Cytopenia ^d	0/1	2/3	-	-	-

Relationship between International Prognostic Scoring System (IPSS)

Risk Score and Prognosis

Risk Score			
IPSS Risk Category (% IPSS pop.) [*]	Overall Score	Median Survival (y) in the Absence of Therapy	25% AML Progression (y) in the Absence of Therapy
Low	0	5.7	9.4
Intermediate-1	0.5-1.0	3.5	3.3
Intermediate-2	1.5-2.0	1.1	1.1
High	≥2.5	0.4	0.2

*For IPSS: Low/Intermediate-1. See MDS-3 through MDS-5

For IPSS: Intermediate-2/High, see MDS-6

^a IPSS should be used for initial prognostic and planning purposes. WPSS permits dynamic estimation of prognosis at multiple time points during the course of MDS.

^b Patients with 20%-29% blasts may be considered to have MDS (FAB) or AML (WHO).

^c Cytogenetics: Good = normal, -Y alone, del(5q) alone, del(20q); Poor = complex (≥ 3 abnormalities) or chromosome 7 abnormalities; Intermediate = other abnormalities. (This excludes karyotypes t(8:21), inv16, and t(15:17), which are considered to be AML and not MDS)

^d Cytopenetic neutrophil count < 1,800/mcL, platelets < 100,000/mcL, Hb < 10 g/dL.

Revised International Prognostic Scoring System (IPSS-R)

Prognostic variable	Score Value						
	0	0.5	1	1.5	2	3	4
Cytogenetic ^e	Very good	-	Good	-	Intermediate	Poor	Very poor
Marrow blasts (%)	≤ 2	-	>2-<5	-	5-10	>10	-
Hemoglobin	≥ 10	-	80-<100	<80	-	-	-
Platelets	≥ 100	50-<100	<50	-	-	-	-
ANC	≥ 0.8	<0.8	-	-	-	-	-

Note: ANC: Absolute Neutrophil Count.

^e Cytopenetic risks: Very good = -Y, del(11q); Good = normal, del(5q), del(12p), del(20q), double including del(5q); Intermediate = del(7q), +8, +19, i(17q), any other single or double independent clones; Poor = -7, inv(3)/t(9:3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities; Very poor = complex: >3 abnormalities.

Appendix 4 ECOG Performance Status Score

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Death

Appendix 5 IWG2006 Response Criteria

Myelodysplastic Syndromes (MDS) International Working Group (IWG) Efficacy

Evaluation Standard

Table 3. Proposed modified International Working Group response criteria for altering natural history of MDS ^{^7}	
Category	Response criteria (responses must last at least 4 wk)
Complete Remission	<p>Bone marrow: $\leq 5\%$ myeloblasts with normal maturation of all cell lines*</p> <p>Persistent dysplasia will be noted*</p> <p>Peripheral blood</p> <p>Hgb ≥ 11 g/dL</p> <p>Platelets $\geq 100 \times 10^9/L$</p> <p>Neutrophils $\geq 1.0 \times 10^9/L$</p> <p>Blasts 0%</p>
Partial Remission	<p>All CR criteria if abnormal before treatment except:</p> <p>Bone marrow blasts decreased by $\geq 50\%$ over pretreatment but still $> 5\%$</p> <p>Cellularity and morphology not relevant</p>
Marrow CR	<p>Bone marrow: $\leq 5\%$ myeloblasts and decrease by $\geq 50\%$ over pretreatment</p> <p>Peripheral blood: if HI responses, they will be noted in addition to marrow CR</p>
Complete Bone Marrow Remission	<p>Bone Marrow: $\leq 5\%$ myeloblasts and decrease by $\geq 50\%$ compared to pretreatment</p> <p>Peripheral Blood: If Hematology Improvement (HI) is achieved, it should be noted at the same time</p>
Stable Disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks

Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of $\geq 50\%$ from maximum remission/response levels in granulocytes or platelets Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete Disappearance of the chromosomal abnormality without appearance of new ones Partial At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: Less than 5% blasts: $\geq 50\%$ increase in blasts to $>5\%$ blasts 5%-10% blasts: $\geq 50\%$ increase to $>10\%$ blasts 10%-20% blasts: $\geq 50\%$ increase to $>20\%$ blasts 20%-30% blasts: $\geq 50\%$ increase to $>30\%$ blasts Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥ 2 g/dL Transfusion dependence
Survival	Endpoints: Overall: death from any cause Event free: failure or death from any cause PFS: disease progression or death from MDS

	DFS: time to relapse Cause-specific death: death related to MDS
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Deletions to IWG response criteria are not shown.

To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.

*Dysplastic changes should consider the normal range of dysplastic changes (modification).⁴¹

†Modification to IWG response criteria.

‡In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Appendix 6 Common Terminology Criteria for Adverse Events (CTCAE) 5.0

Hematology					
	Grade				
Adverse Events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	Hemoglobin < Lower Limit of Normal - 100 g/L	Hemoglobin < 100 - 80 g/L	Hemoglobin < 80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
White Blood Cell Decreased	< Lower Limit of Normal - 3.0 x 10 ⁹ /L	< 3.0 - 2.0 x 10 ⁹ /L	< 2.0 - 1.0 x 10 ⁹ /L	< 1.0 x 10 ⁹ /L	---
Platelet Count Decreased	< Lower Limit of Normal - 75.0 x 10 ⁹ /L	< 75.0 - 50.0 x 10 ⁹ /L	< 50.0 - 25.0 x 10 ⁹ /L	< 25.0 x 10 ⁹ /L	---
Neutrophil Count Decreased	< Lower Limit of Normal - 1.5 x 10 ⁹ /L	< 1.5 - 1.0 x 10 ⁹ /L	< 1.0 - 0.5 x 10 ⁹ /L	< 0.5 x 10 ⁹ /L	---
Febrile Neutropenia	---	---	ANC <1.0x10 ⁹ /L with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour	Life-threatening consequences; urgent intervention indicated	Death
Non-Hematologic					

Fever	38.0 - 39.0°C	>39.0 - 40.0°C	>40.0°C ≤ 24 hours	>40.0°C for more than 24 hours	Death
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental activities of daily living	Severe symptoms; limiting self-care activities of daily living; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheostomy or intubation)	Death
Alanine aminotransferase increased	>Upper Limit of Normal - 3.0 x Upper Limit of Normal if baseline was normal; 1.5-3.0 x baseline if baseline was abnormal	>3.0-5.0 x Upper Limit of Normal if baseline was normal; >3.0-5.0 x baseline if baseline was abnormal	>5.0-20.0 x Upper Limit of Normal if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x Upper Limit of Normal if baseline was normal; >20.0 x baseline if baseline was abnormal	---
Aspartate aminotransferase increased	>Upper Limit of Normal - 3.0 x Upper Limit of Normal if baseline was normal; 1.5-3.0 x baseline if baseline was abnormal	>3.0-5.0 x Upper Limit of Normal if baseline was normal; >3.0-5.0 x baseline if baseline was abnormal	>5.0-20.0 x Upper Limit of Normal if baseline was normal; >5.0-20.0 x baseline if baseline was abnormal	>20.0 x Upper Limit of Normal if baseline was normal; >20.0 x baseline if baseline was abnormal	---
Blood bilirubin increased	>Upper Limit of Normal - 1.5 x Upper Limit of Normal if normal baseline was normal; >1.0-1.5 x baseline if baseline was abnormal	>1.5-3.0 x Upper Limit of Normal if baseline was normal; >1.5-3.0 x baseline if baseline was abnormal	>3.0-10.0 x Upper Limit of Normal if baseline was normal; >3.0-10.0 x baseline if baseline was abnormal	>10.0 x Upper Limit of Normal if baseline was normal; >10.0 x baseline if baseline was abnormal	---
Creatinine increased	>Upper limit of Normal - 1.5 x Upper Limit of	>1.5-3.0 x Baseline; >1.5-3.0 x	>3.0 x Baseline; >3.0-6.0 x Upper Limit of Normal	>6.0 x Upper Limit of Normal	---

	Normal	Upper Limit of the Normal			
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; > 3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; > 5.7 mmol/L - 11.4 mmol/L	Life-threatening consequences	Death
Cholesterol high	> Upper Limit of Normal - 300 mg/dL; > Upper Limit of Normal - 7.75 mmol/L	>300 - 400 mg/dL; > 7.75 - 10.34 mmol/L	>400 - 500 mg/dL; > 10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	
Fatigue	Fatigue relieved by rest	Fatigue, not relieved by rest; limiting instrumental activities of daily living	Fatigue, not relieved by rest; limiting self-care activities of daily living	---	---
Nausea	Loss of appetite, without alteration in eating habits	Oral Intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition, or hospitalization indicated	---	---
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental activities of daily living	Obstipation with manual evacuation indicated; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated	Death

Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental activities of daily living	Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care activities of daily living	Life-threatening consequences; urgent intervention indicated	Death
Abdominal Pain	Mild pain	Moderate pain; limiting instrumental activities of daily living	Severe pain; limiting self-care activities of daily living	___	___
Headache	Mild pain	Moderate pain; limiting instrumental activities of daily living	Severe pain; limiting self-care activities of daily living	___	___
Dry Skin	Covering <10% of body surface area and no associated erythema or pruritus	Covering 10-30% of body surface area and associated with erythema or pruritus; limiting instrumental activities of daily living	Covering >30% of body surface area and associated with pruritus; limiting self care activities of daily living	___	___
Bone Pain	Mild pain	Moderate pain; limiting instrumental activities of daily living	Severe pain; limiting self-care activities of daily living	___	___
Rash maculo-papular	Macules/papules covering <10% of body surface area with or	Macules/papules covering 10-30% of body surface area with or	Macules/papules covering >30% of body surface area with	___	___

	without symptoms (e.g., pruritus, burning, tightness)	without symptoms (e.g., pruritus, burning, tightness); limiting instrumental activities of daily living; rash covering >30% of body surface area with or without mild symptoms	moderate or severe symptoms; limiting self care activities of daily living		
Cheilitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental activities of daily living	Severe symptoms; limiting self-care activities of daily living; intervention indicated	---	---
Mucositis Oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Urinary Tract Infection	---	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	Intravenous antibiotic, antifungal or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Skin Infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or	Intravenous antibiotic, antifungal or antiviral intervention indicated;	Life-threatening consequences; urgent intervention indicated	Death

		antiviral)	invasive intervention indicated		
Soft Tissue Infection	—	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Intracranial Hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Epistaxis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated (e.g., nasal packing, cauterization; topical vasoconstrictors)	Transfusion; invasive intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Purpura	Combined area of lesions covering <10% of body surface area	Combined area of lesions covering 10 - 30% of body surface area; bleeding with trauma	Combined area of lesions covering >30% of body surface area; spontaneous bleeding	—	—

Appendix 7 EORTC Quality of Life Questionnaire QLQ-C30 (V3.0)

EORTC Quality of Life Questionnaire QLQ-C30 (V3.0)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your code (number):

Date of birth: ___year___ month___ day

Today's date: ___year___ month___ day

During the past week:	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4

13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
During the past week:	Not at All	A Little	Quite a Bit	Very Much
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very Poor

Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very Poor

Excellent

Appendix 8 European Quality of Life Five-Dimension Scale EQ-5D-5L

European Quality of Life Five-Dimension Scale EQ-5D-5L

Under each heading, please tick the box that best describes your health status today with a "√".

1. Your Name
2. Mobility—I walk around <input type="checkbox"/> No problems <input type="checkbox"/> Slight problems <input type="checkbox"/> Moderate problems <input type="checkbox"/> Severe problems <input type="checkbox"/> I am unable to walk around
3. Self-care—I wash or dress myself <input type="checkbox"/> No problems <input type="checkbox"/> Slight problems <input type="checkbox"/> Moderate problems <input type="checkbox"/> Severe problems <input type="checkbox"/> I am unable to wash or dress myself
4. Usual activities (such as work, study, housework, family or leisure activities) <input type="checkbox"/> No problems <input type="checkbox"/> Slight problems <input type="checkbox"/> Moderate problems <input type="checkbox"/> Severe problems <input type="checkbox"/> I am unable to do my usual activities
5. Pain or Discomfort <input type="checkbox"/> No pain or discomfort <input type="checkbox"/> Slight pain or discomfort

Moderate pain or discomfort

Severe pain or discomfort

Extreme pain or discomfort

6. Anxiety or Depression

No anxiety or depression

Slight anxiety or depression

Moderate anxiety or depression

Severe anxiety or depression

Extreme anxiety or depression

7. We want to know about how good or bad your health is today.

Please fill in a number from 0 to 100: ()

0 represents the worst health you can imagine, and 100 represents the best health you can imagine.