A Phase III Placebo-controlled Trial of CC-486 in Patients with Red Blood Cell Transfusion-dependent (RBC-TD) Anemia and Thrombocytopenia Due to IPSS Lower-risk Myelodysplastic Syndromes (LR-MDS)

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Study design

AZA-MDS-003: Randomized, double-blind, placebo-controlled, phase III trial

KEY INCLUSION CRITERIA

Age ≥18 years

IPSS Low or INT-1 MDS

ECOG PS score 0-2

+

RBC transfusion dependence:

- Average of ≥2 RBC units/28 days for ≥56 days
- No ≥28-day transfusion-free period in 56 days prior to randomization

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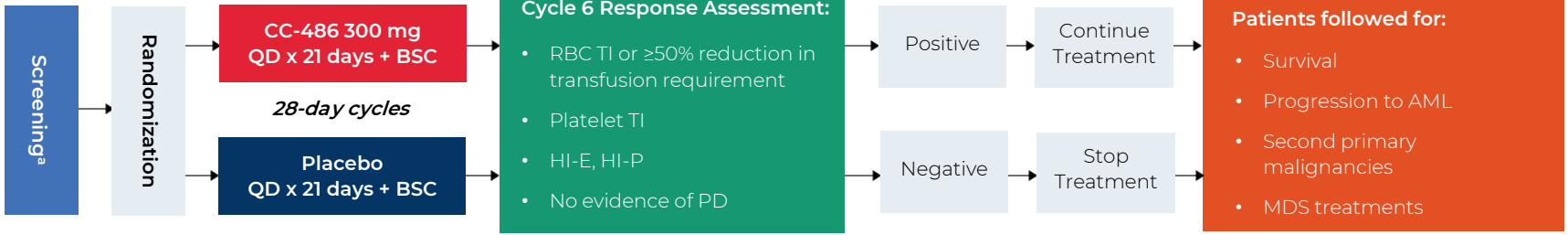
Thrombocytopenia:

- Platelet count ≤75 $^{x}10^{9}$/L, confirmed at 2 visits ≥21 days apart
- Confirmatory count obtained within 14 days before randomization

STUDY DESIGN



[a]The screening phase was initially defined as 84 days from randomization to allow repeated confirmation of RBC-TD and concomitant thrombocytopenia, but later amended to shorten the interval to 56 days.
ClinicalTrials.gov NCT01566695.
AML, acute myeloid leukemia; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; HI, hematologic improvement; HI-E, HI-erythroid; HI-P, HI-platelet; INT, Intermediate; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; PD, progressive disease; RBC, red blood cell; TI, transfusion independence.

Endpoints and statistical assumptions

Primary endpoint:

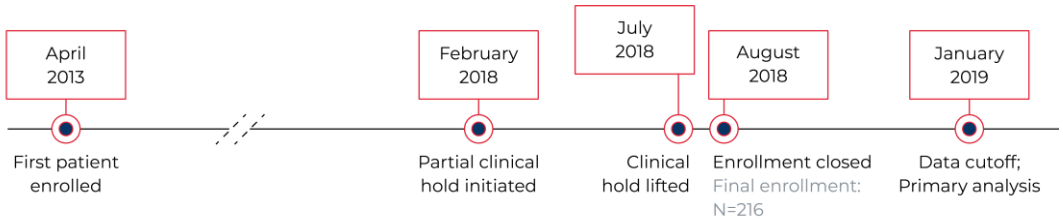
- **Rate of RBC TI lasting ≥56 days (IWG 2006[1])**

Key secondary endpoints:

- RBC TI lasting ≥84 days
- RBC TI duration
- OS
- HI-Erythroid (HI-E), HI-Platelet (HI-P)
- AML progression

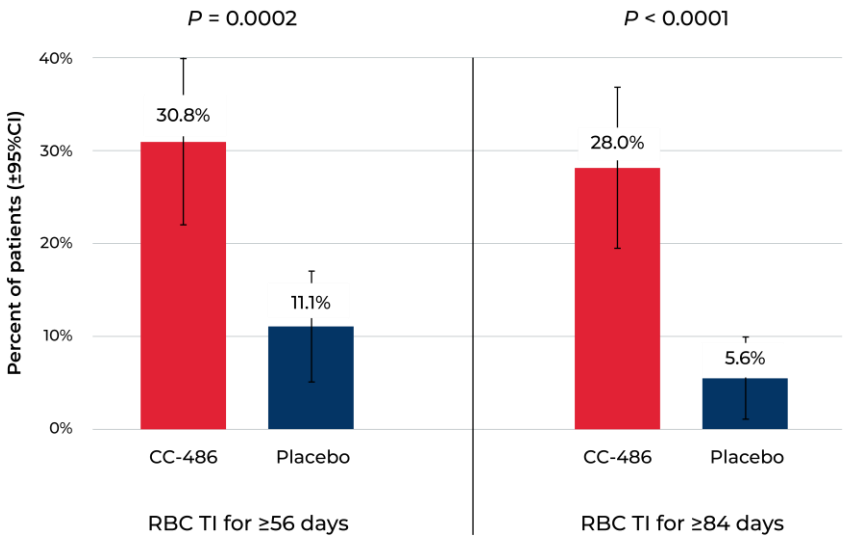
Enrollment and statistical assumptions:

- Planned enrollment: N = 386
  - >99% power for RBC TI, 80% power for OS
- Independent DMC review revealed an imbalance in early deaths (days 1-56) between treatment groups
  - Enrollment began in 2013 and was stopped in 2018
- Final enrollment: N = 216
  - 99% power for RBC TI, 72% power for OS



1. Cheson et al. *Blood*. 2006;108(2):419-25.
AML, acute myeloid leukemia; DMC, Data Monitoring Committee; HI, hematologic improvement; HI-E, HI-erythroid; Hi-P, Hi-platelet; IWG, International Working Group; OS, overall survival; RBC, red blood cell; TI, transfusion independence.

RBC TI



	CC-486 N = 107	Placebo N = 108[a]
RBC TI for ≥56 days, n (%)	33 (30.8)	12 (11.1)
[95% CI]	[22.1, 39.6]	[5.2, 17.0]
Odds ratio [95% CI]	3.6 [1.7, 7.4]	
P value[b]	0.0002	
RBC TI for ≥84 days, n (%)	30 (28.0)	6 (5.6)
[95% CI]	[19.5, 36.5]	[1.2, 9.9]
Odds ratio [95% CI]	6.6 [2.6, 16.7]	
P value[b]	< 0.0001	

- Median number of treatment cycles:
  - CC-486: 5 (range 1-70)
  - Placebo: 6 (range 1-69)

[a]One patient randomized to placebo was retrospectively determined to have a B12 deficiency at study entry and was enrolled in violation of the protocol. This patient is excluded from response and survival analyses.
[b]*P* value is two-sided from a Mantel-Haenszel chi-squared test stratified for average baseline RBC transfusion requirement (≤4 units vs. >4 units per 28 days), platelet transfusion dependence (yes vs. no), and ECOG performance status score (0-1 vs. 2).
RBC TI defined using International Working Group 2006 MDS response criteria (Cheson et al., *Blood* 2006;108(2):419-25).
CI, confidence interval; ECOG Eastern Cooperative Oncology Group; IWG, International Working Group; MDS myelodysplastic syndromes; RBC, red blood cell; TI, transfusion independence.

Safety

Adverse events (all grades) reported in ≥30% of patients in either arm

	CC-486 N = 107	Placebo N = 109
	n (%)	
Nausea	81 (76)	25 (23)
Diarrhea	73 (68)	25 (23)
Vomiting	67 (63)	10 (9)
Neutropenia	54 (50)	16 (15)
Constipation	51 (48)	24 (22)
Pyrexia	36 (34)	18 (17)

Grade 3-4 adverse events reported in ≥10% of patients in either arm

	CC-486 N = 107	Placebo N = 109
	n (%)	
≥1 grade 3-4 AE	**96 (90)**	**80 (73)**
Neutropenia	50 (47)	13 (12)
Thrombocytopenia	31 (29)	17 (16)
Febrile neutropenia	30 (28)	11 (10)
Anemia	20 (19)	18 (17)
Pneumonia	13 (12)	10 (9)

- Treatment interruption due to AEs: CC-486 62%, placebo 37%
- Dose reduction due to AEs: CC-486 29%, placebo 4%
- Treatment discontinuation due to AEs: CC-486 30%, placebo 28%
- Treatment-related AEs more common with CC-486, occurred mostly during early treatment cycles

AE, adverse event.

Summary

- LR-MDS patients with unfavorable disease features, including RBC-TD anemia and thrombocytopenia, have poor prognosis, indicating a need for disease-modifying treatment
- AEs were more frequent with CC-486 than with placebo; AEs can be managed with appropriate patient monitoring, especially during early treatment cycles, with supportive care measures, and with dose modifications or interruptions if necessary
- Patients with severe neutropenia are at higher risk for hematologic toxicity during early CC-486 treatment and may benefit from a modified dosing regimen
- CC-486 significantly improved RBC TI rate and induced durable bilineage hemoglobin and platelet improvements in these LR-MDS patients with high-risk disease features

AEs, adverse events; LR-MDS, lower-risk myelodysplastic syndromes; RBC, red blood cell; TD, transfusion dependence; TI, independence.