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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Background

MDS is characterized by bone marrow dysplasia and peripheral cytopenias of variable severity. Treatment (Tx) options are limited for LR-MDS patients (pts) with low blast counts but high-risk disease features (eg, RBC-TD anemia and thrombocytopenia). The phase III placebo (PBO)-controlled QUAZAR Lower-risk MDS trial (NCT01566695) assessed CC-486, an oral hypomethylating agent, in pts who were RBC-TD and thrombocytopenic at study entry.

Aims

Describe clinical outcomes from the QUAZAR Lower-risk MDS trial.

Methods

Eligible pts were age ≥18 yrs, with IPSS LR-MDS, average RBC transfusion requirement of ≥2 units (U)/28 days (d) for 56d, and 2 platelet (PLT) counts ≤75 × 10^9/L taken ≥21d apart. Pts were randomized 1:1 to CC-486 300mg or PBO QD for 21d per 28d Tx cycle (C). The primary endpoint was RBC transfusion independence (TI) lasting ≥56d (IWG 2006). Key secondary endpoints were overall survival (OS), ≥84d RBC-TI, and hematologic improvement in erythroid and PLT lineages (HI-E, HI-P). Planned enrollment was 386 pts. An imbalance of early deaths in the CC-486 arm led to a decision to close enrollment; the final sample size (N=216) allowed comparison of RBC-TI between Tx arms with ~99% power.

Results

At data cutoff all pts (CC-486 n=107; PBO n=109) completed ≥12 mo of Tx or discontinued before 12 mo. Baseline (BL) characteristics were similar between Tx arms. Median age was 74 yrs (30-89), Hgb 8.1 g/dL (5.4-10.9), PLT count 25×10^9/L (5-73), ANC 1.3×10^9/L (0.1-25), and transfusion requirement 6.7 U/56d. All pts had IPSS INT-1 MDS.

Significantly more pts in the CC-486 arm achieved RBC-TI for ≥56d (31%, *vs.* 11% with PBO; *P*=0.0002) (**Table 1**). Median RBC-TI durations in the CC-486 and PBO arms were 11.1 and 5.0 mo, respectively (*P*=0.42). In the CC-486 and PBO arms, 42% and 31%, respectively, had RBC transfusion reductions of ≥4 U from BL, sustained for a median of 10.0 and 2.3 mo (*P*=0.0001). While HI-E rates were comparable (*P*=0.12), significantly more CC-486 pts had a ≥1.5 g/dL Hgb

increase from BL ($P<0.0001$). HI-P rate was significantly higher in the CC-486 arm ($P=0.0003$). PLT-TI (≥56d) rates were similar between arms, but median PLT-TI duration was longer with CC-486 (12.1 *vs.* 4.4 mo with PBO). In the CC-486 arm, mean Hgb increased by ~2 g/dL from BL by C6, and PLT count increased by 38×10^9/L by C3. Hgb and PLT improvements were sustained during Tx. Hgb and PLT count changes were negligible with PBO.

Study sample size was underpowered for interim OS analysis, which showed no difference between CC-486 and PBO (median 17.3 *vs.* 16.7 mo; $P=0.88$).

Median Tx durations were 5 CC-486 cycles (1-70) and 6 PBO cycles (1-69). Most common AEs in both Tx arms were grade 1-2 GI events. In the CC-486 and PBO arms, respectively, 90% and 73% of pts had a grade 3-4 AE (**Table 2**), and 30% and 28% discontinued Tx due to any AE. Tx-related AEs were more common with CC-486, most occurring during C1-C2. Overall death rate was similar between Tx arms but there was an imbalance in early (d1-56) deaths (CC-486 n=16, PBO n=6), most related to infection; those CC-486 pts had a median BL ANC of ~0.5×10^9/L.

Table 1. Transfusion independence and hematologic improvement

Parameter	CC-486 N = 107	Placebo N = 108*	*P* value
RBC-TI (≥56 days), n (%)	33 (30.8)	12 (11.1)	0.0002
RBC-TI duration, months, median [95%CI]	11.1 [8.2, 26.0]	5.0 [2.3, NE]	0.42
RBC-TI (≥84 days), n (%)	30 (28.0)	6 (5.6)	< 0.0001
HI-Erythroid, n (%)	46 (43.0)	34 (31.5)	0.12
≥1.5 g/dL Hgb increase, n (%)	25 (23.4)	5 (4.6)	< 0.0001
RBC transfusion reduction ≥4 units, n (%)	45 (42.1)	33 (30.6)	0.12
RBC transfusion reduction duration, months, median [95%CI]	10.0 [7.1, 13.3]	2.3 [2.0, 5.0]	0.0001
Platelet TI (≥56 days), n/N (%)	5/30 (16.7)	5/35 (14.3)	0.79
Platelet TI duration, months, median [95%CI]	12.1 [8.3, NE]	4.4 [2.3, NE]	0.28
HI-Platelet, n (%)	26 (24.3)	7 (6.5)	0.0003

Responses were defined using IWG 2006 response criteria, assessed by central review of laboratory parameters.
*1 placebo patient had a vitamin B12 deficiency at study entry and received vitamin B12 supplementation on study day 15; this patient is excluded from response analyses.
95%CI, 95% confidence interval; NO, not done; RBC, red blood cell; TI, transfusion independence.

Table 2. Grade 3–4 AEs reported in ≥10% of patients in either arm

Preferred term	CC-486 N = 107	Placebo N = 109
	n (%)	
Any 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)

AEs were coded using MedDRA version 21.0 and graded using NCI-CTCAE version 4.0.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Conclusion

These IPSS INT-1 LR-MDS pts have unfavorable disease features, including RBC-TD and thrombocytopenia, and poor prognosis, indicating a need for disease-modifying Tx. CC-486 met the primary endpoint of RBC-TI and induced durable bilineage Hgb and PLT improvements. AEs were more frequent with CC-486. Pts with severe neutropenia pre-Tx are at higher risk for hematologic toxicity during early CC-486 Tx and may benefit from a modified dosing regimen.

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