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Escalated Dosing Schedules of CC-486 Are Effective and Well Tolerated for Patients Experiencing First Acute Myeloid Leukemia (AML) Relapse: Results from the Phase III QUAZAR AML-001 Maintenance Trial

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Introduction: Standard intensive induction chemotherapy (IC) for AML leads to complete remission (CR) in 60%–80% of patients aged ≤ 60 years and in 40%–60% of patients aged > 60 years. However, about two-thirds of patients relapse after frontline therapy, and most relapses occur within the first 18 months (Yilmaz, *Blood Cancer J*, 2019).

Effective post-induction AML maintenance treatment should decrease the risk of relapse by suppressing growth of residual leukemic cells. CC-486 is an oral hypomethylating agent that allows for extended dosing schedules (> 7 days per 28-day treatment cycle) to sustain therapeutic activity. In the phase III international, randomized, double-blind QUAZAR AML-001 trial (NCT01757535), CC-486 significantly prolonged overall survival (OS) and relapse-free survival (RFS) vs. placebo in patients with AML in first remission following IC, who were not candidates for hematopoietic stem cell transplant (HSCT) (Wei, ASH 2019, LBA-3). Patients initially received CC-486 or placebo for 14 days per 28-day cycle, but patients identified as having early AML relapse with 5–15% blasts in peripheral blood or bone marrow could receive an escalated 21-day/cycle dosing schedule at investigators' discretion.

Objective: Evaluate clinical outcomes in patients in QUAZAR AML-001 who relapsed with 5–15% blasts on-study who then received escalated 21-day dosing of study drug.

Methods: Eligible patients were aged ≥ 55 years, with intermediate- or poor-risk cytogenetics and Eastern Cooperative Oncology Group performance status (ECOG PS) scores ≤ 3, and had achieved a first CR or CR with incomplete blood count recovery (CRi) after IC ± consolidation. Within 4 months of achieving CR/CRi, patients were randomized 1:1 to receive CC-486 300 mg or placebo once-daily on days 1–14 of repeated 28-day treatment cycles. CR/CRi status was assessed centrally every 3 cycles; patients who exhibited signs of relapse in hematology parameters at routine clinic visits (conducted every 2 weeks) could have an unscheduled bone marrow test to confirm AML relapse. Patients who developed 5%–15% blasts in blood or bone marrow could receive study drug for 21 days/cycle at the investigator's discretion. Treatment could continue until >15% blasts, unacceptable toxicity, or HSCT.

Results: In all, 472 patients were randomized to CC-486 (N=238) or placebo (N=234). During the course of the study, 91 patients (CC-486, n=51 [21%]; placebo, n=40 [17%]) were identified as having early AML relapse with 5–15% blasts and were assigned to receive a 21-day/cycle dosing schedule. Median time to dose escalation of CC-486 was 9.2 months (range 1.0–52.7) and of placebo was 6.0 months (0.5–19.3). Median number of 21-day dosing cycles was 2.0 in both the CC-486 (range 1–45) and placebo (1–16) arms, but proportionally more patients in the CC-486 arm received > 3 escalated dosing cycles (CC-486, 43%; placebo, 18%). Among 78 evaluable patients with ≥ 5% blasts in the most recent bone marrow on or before day 1 of 21-day dosing, 23% (10/43) of patients in the CC-486 arm and 11% (4/35) of patients in the placebo arm regained CR/CRi (< 5% blasts in bone marrow; central review) while receiving an escalated dosing regimen. Among all patients who received escalated dosing schedules, median OS from the time of randomization was 22.8 months in the CC-486 arm vs. 14.6 months in the placebo arm (hazard ratio [HR] 0.66 [95% CI 0.42, 1.0]; $P = 0.073$), and 1-year survival rates were 80.4% vs. 59.5%, respectively (+20.9% [2.1, 39.7]).

The most common adverse events first reported during 21-day dosing were febrile neutropenia (CC-486, 24%; placebo, 3%), thrombocytopenia (22% and 23%), anemia (22% and 20%), and neutropenia (20% and 10%) (**Table**). A similar proportion of patients in each arm (CC-486, 31%; placebo, 35%) first experienced a grade 3 or grade 4 adverse event while receiving escalated dosing. CC-486 dose-escalation did not lead to detrimental effects on patient-reported quality of life measures (as assessed by the FACIT-Fatigue and EQ-5D-3L instruments) vs. placebo.

Conclusions: An escalated 21-day CC-486 dosing regimen was well tolerated and resulted in restoration of remission in approximately one-fourth of patients. Hematologic adverse events first reported during escalated dosing in both treatment arms may be due in part to disease relapse. A 21-day CC-486 dosing schedule could be considered for patients who experience AML relapse with ≤ 15% blasts.

Table. Most common (≥10% of patients in either treatment arm) adverse events first reported during escalated (21-day) dosing

	CC-486 n = 51		Placebo n = 40	
	All grades	Grade 3–4	All grades	Grade 3–4
Preferred term	n (%)			
Febrile neutropenia	12 (24)	12 (24)	1 (3)	1 (3)
Thrombocytopenia	11 (22)	9 (18)	9 (23)	12 (30)
Anemia	11 (22)	8 (16)	8 (20)	7 (18)
Neutropenia	10 (20)	11 (22)	4 (10)	5 (13)
Fatigue	7 (14)	3 (6)	1 (3)	0
Pyrexia	7 (14)	2 (4)	8 (20)	0
Diarrhea	6 (12)	0	3 (8)	0
Asthenia	6 (12)	0	0	0
Constipation	5 (10)	3 (6)	2 (5)	0
Peripheral edema	5 (10)	0	1 (3)	0
Hypokalemia	2 (4)	1 (2)	5 (13)	0

Adverse events coded using MedDRA version 22.0. A patient is counted only once for multiple events within preferred term/system organ class and dose schedule period.
MedDRA, Medical Dictionary for Regulatory Activities.

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