111 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

Author(s): ***Hartmut Döhner***[1], *Andrew H Wei, MBBS, PhD*[2,3], *Pau Montesinos, MD, PhD*[4,5*], *Hervé Dombret, MD*[6,7], *Farhad Ravandi, MBBS*[8], *Hamid Sayar, MD, MSc*[9], *Kimmo Porkka*[10,11], *Irwindeep Sandhu, MD*[12*], *Francesco Passamonti*[13*], *Fabrizio Pane, MD*[14], *Tadeusz Robak, MD PhD*[15], *José F. Falantes*[16*], *Andre C. Schuh*[17], *Gert Ossenkoppele, MD, PhD*[18*], *Ignazia La Torre*[19*], *Barry Skikne, MD*[20,21*], *Keshava Kumar, PhD*[21*], *Qian Dong, DrPH*[21*], *C.L. Beach, PharmD*[21*] *and Gail J. Roboz, MD*[22]

[1]*Ulm University Hospital, Ulm, Germany*
[2]*The Alfred Hospital, Melbourne, Australia*
[3]*Australian Centre for Blood Diseases, Monash University, Melbourne, Australia*
[4]*CIBERONC, Instituto de Salud Carlos III, Madrid, Spain*
[5]*Hematology Department, Hospital Universitario La Fe de Valencia,, Valencia, Spain, Spain*
[6]*Institut de Recherche Saint Louis, Université de Paris, Paris, France*
[7]*Hôpital Saint-Louis, Assistance Publique - Hôpitaux de Paris (AP-HP), Paris, France*
[8]*Department of Leukemia, University of Texas- MD Anderson Cancer Center, Houston, TX*
[9]*Indiana University Cancer Center, Indianapolis, IN*
[10]*iCAN Digital Precision Cancer Medicine Flagship, University of Helsinki, Helsinki, Finland*
[11]*Hematology Research Unit Helsinki, Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland*
[12]*University of Alberta Hospital, Edmonton, Canada*
[13]*Department of Medicine and Surgery, University of Insubria, Varese, Italy*
[14]*Azienda Ospedaliera Universitaria Federico II, Naples, Italy*
[15]*Department of Hematology, Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland*
[16]*Hospital Virgen del Rocío. Hematología, Seville, Spain*
[17]*Princess Margaret Cancer Centre, Toronto, ON, Canada*
[18]*Amsterdam UMC, Location VU University Medical Center, Amsterdam, Netherlands*
[19]*Celgene, a Bristol-Myers Squibb Company, Boudry, Switzerland*
[20]*Kansas University Medical Center, Kansas City, KS*
[21]*Bristol Myers Squibb, Princeton, NJ*
[22]*Weill Medical College of Cornell University New York-Presbyterian Hospital, New York, NY*

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.

692 CC-486 Prolongs Survival for Patients with Acute Myeloid Leukemia (AML) in Remission after Intensive Chemotherapy (IC) Independent of the Presence of Measurable Residual Disease (MRD) at Study Entry: Results from the QUAZAR AML-001 Maintenance Trial

Author(s): ***Gail J. Roboz, MD***[1], *Farhad Ravandi, MBBS*[2], *Andrew H Wei, MBBS, PhD*[3,4], *Hervé Dombret, MD*[5,6], *Hartmut Döhner*[7], *Felicitas Thol*[8], *Maria Teresa Voso, MD*[9], *Andre C. Schuh*[10], *Kimmo Porkka*[11,12], *Ignazia La Torre*[13*], *Barry Skikne, MD*[14,15*], *Keshava Kumar, PhD*[15*], *Qian Dong, DrPH*[15*], *C.L. Beach, PharmD*[15*], *Alberto Risueño*[16*], *Daniel Lopes de Menezes, PhD*[15*] *and Gert Ossenkoppele, MD, PhD*[17*]

[1]*Weill Medical College of Cornell University New York-Presbyterian Hospital, New York, NY*
[2]*Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*
[3]*The Alfred Hospital, Melbourne, Australia*
[4]*Australian Centre for Blood Diseases, Monash University, Melbourne, Australia*
[5]*Hôpital Saint-Louis, Assistance Publique – Hôpitaux de Paris (AP-HP), Paris, France*
[6]*Institut de Recherche Saint Louis, Université de Paris, Paris, France*
[7]*Ulm University Hospital, Ulm, Germany*
[8]*Medizinische Hochschule Hannover, Hannover, Germany*
[9]*University of Rome Tor Vergata, Rome, Italy*
[10]*Princess Margaret Cancer Centre, Toronto, ON, Canada*
[11]*iCAN Digital Precision Cancer Medicine Flagship, University of Helsinki, Helsinki, Finland*
[12]*Hematology Research Unit Helsinki, Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland*
[13]*Celgene, a Bristol-Myers Squibb Company, Boudry, Switzerland*
[14]*Kansas University Medical Center, Kansas City, KS*
[15]*Bristol Myers Squibb, Princeton, NJ*
[16]*BMS Center for Innovation and Translational Research Europe (CITRE), a Bristol Myers Squibb Company, Seville, Spain*
[17]*Amsterdam UMC, Location VU University Medical Center, Amsterdam, Netherlands*

Background

In newly diagnosed AML, high remission rates are typically achieved with IC, but the response is often transient, and detectable residual disease in the bone marrow post-chemotherapy is predictive of early relapse. Emerging data show that the identification of ≥ 0.1% MRD by multiparameter flow cytometry (MFC) in patients with AML in remission after IC is an important prognostic marker that may help guide treatment (Tx) decisions. CC-486 is an oral

hypomethylating agent that allows for extended dosing schedules to prolong drug exposure over the Tx cycle. In the QUAZAR AML-001 Maintenance Trial, Tx with CC-486 300 mg QD for 14 days/28-day Tx cycle was associated with significantly improved overall (OS) and relapse-free survival (RFS) vs. placebo (PBO) in patients (pts) with AML in first remission after induction chemotherapy ± consolidation. Samples for MFC were obtained prior to randomization and serially throughout the study to assess the impact of MRD on OS and RFS, and to evaluate rates of conversion from MRD positivity (+) to negativity (-) in the CC-486 and PBO arms.

Methods

Eligible pts aged ≥ 55 years with AML were randomized 1:1 to CC-486 300 mg or PBO within 4 months of achieving first complete remission (CR) or CR with incomplete blood count recovery (CRi). MFC assessments of bone marrow aspirates were performed centrally at screening; at cycles 3, 6, 9, 12, 15, 18, 21, 24, 30, and 36; and as clinically indicated. Samples were analyzed with a panel of 22 cell surface markers using an MRD+ cutoff of ≥ 0.1% (per ELN MRD guidelines). For pts MRD+ at baseline (BL; ie, at randomization), an MRD response was defined as achievement of MRD- for ≥ 2 consecutive assessments. MRD- duration was calculated from the time of randomization (for pts MRD- at BL) or from the first of ≥ 2 consecutive MRD- tests (for pts MRD+ at BL), until the last MRD- assessment (for pts who became MRD+) or Tx discontinuation. OS, RFS, and MRD- durations were estimated using Kaplan-Meier methods. Multivariate (MV) Cox regression analyses were performed to evaluate the association of BL MRD status (MRD+ vs. MRD-) and randomized Tx arm (CC-486 vs. PBO) with OS and RFS.

Results

The MRD-evaluable cohort comprised 463/472 randomized pts (98.1%; CC-486, n=236; PBO, n=227) who had samples available for evaluation at BL and at ≥ 1 post-BL visit. At BL, 43% of pts (n=103) in the CC-486 arm and 50% (n=116) in the PBO arm were MRD+. Overall, BL characteristics were similar between MRD+ and MRD- pts: median ages were 69 (range 55-84) and 68 (55-86) years, respectively; 84% and 88% had intermediate-risk cytogenetics at diagnosis; 52% and 46% of pts had an ECOG PS of 0; and 79% and 82% received ≥ 1 cycle of consolidation after induction.

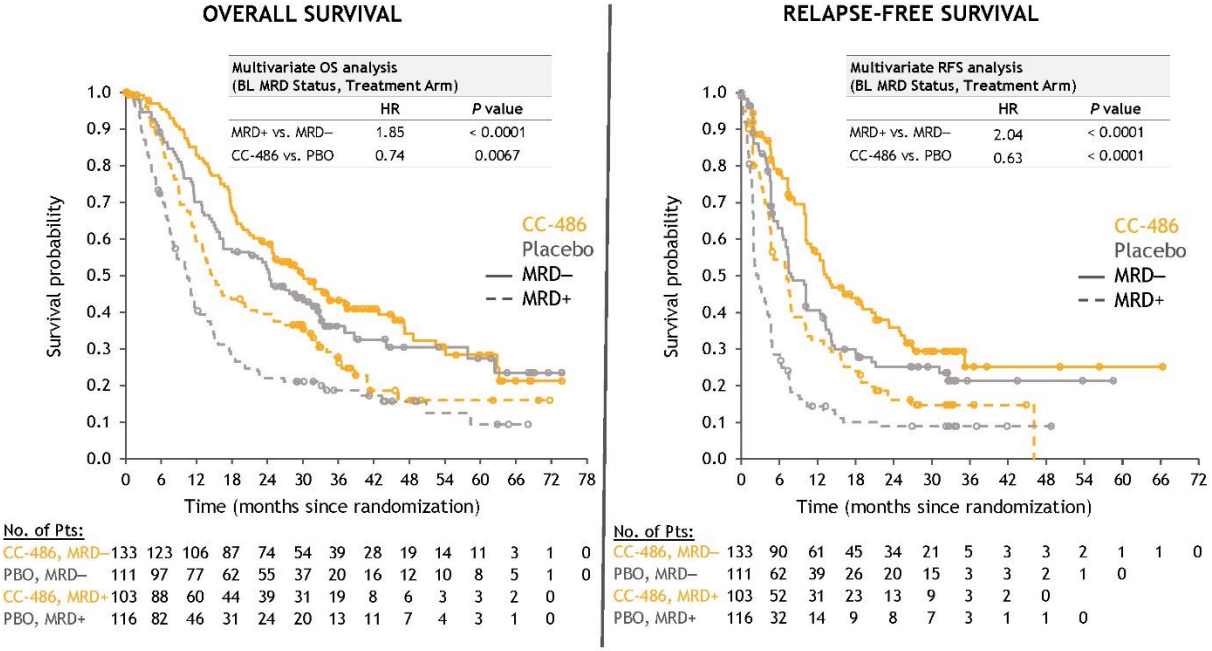
CC-486 Tx resulted in improved OS from time of randomization compared with PBO in pts who were either MRD+ (median 14.6 vs. 10.4 mo, respectively; HR 0.69 [95%CI 0.51, 0.93]) or MRD- (median 30.1 vs. 24.3 mo; HR 0.81 [0.59, 1.12]) at BL. Median RFS was also extended with CC-486 vs. PBO for both MRD+ (7.1 vs. 2.7 mo, respectively; HR 0.58 [95%CI 0.43, 0.78]) and MRD- pts (13.4 vs. 7.8 mo; HR 0.71 [0.52, 0.98]). In MV analyses, BL MRD status (MRD+ vs. MRD-) was significantly associated with OS (HR 1.85; $P < 0.0001$) and RFS (HR 2.04; $P < 0.0001$), and CC-486 showed a significant Tx benefit vs. PBO on both OS (HR 0.74; $P = 0.0067$) and RFS (HR 0.63; $P < 0.0001$) independent of MRD status at BL (**Figure**).

The median duration of MRD negativity was extended with CC-486 vs. PBO: 11.0 vs. 5.0 mo, respectively (HR 0.62 [95%CI 0.48, 0.78]). Tx with CC-486 also resulted in a higher rate of MRD response (MRD+ to MRD-) vs. PBO: 37% vs. 19%, respectively. Among MRD responders, 9/38 patients (24%) in the CC-486 arm achieved MRD negativity > 6 mo after randomization, compared with only 1/22 patients (5%) in the PBO arm.

Conclusions

The QUAZAR AML-001 Maintenance Trial was the first prospective, randomized trial to include long-term longitudinal assessment of MRD in older patients with AML in remission. In both treatment arms, MRD+ status (≥ 0.1%) after induction ± consolidation was associated with significantly shorter OS and RFS compared with MRD- status. Approximately one-fourth of MRD responders treated with CC-486 achieved MRD negativity > 6 mo after study entry, suggesting that CC-486 could induce MRD negativity after prolonged MRD+ status. Maintenance Tx with CC-486 substantially improved OS and RFS independent of MRD status at BL.

Figure. Kaplan-Meier estimates and multivariate analyses of overall survival (OS) and relapse-free survival (RFS) by baseline measurable residual disease (MRD) status (MRD+ vs. MRD-) and randomized treatment arm (CC-486 vs. placebo)



BL, baseline; HR, hazard ratio; MRD, measurable residual disease; No., number; OS, overall survival; PBO, placebo; Pts, patients; RFS, relapse-free survival.