The QUAZAR AML-001 Maintenance Trial: Results of a Phase III International, Randomized, Double-Blind, Placebo-Controlled Study of CC-486 (Oral Formulation of Azacitidine) in Patients with Acute Myeloid Leukemia (AML) in First Remission

Andrew H. Wei, MBBS, FRACP, FRCPA, PhD[1,2*], *Hartmut Döhner, MD*[3], *Christopher Pocock, MBBS*[4], *Pau Montesinos, MD, PhD*[5,6*], *Boris Afanasyev, MD, DSci*[7*], *Hervé Dombret, MD*[8,9,10], *Farhad Ravandi, MD*[11], *Hamid Sayar, MD, MSc*[12], *Jun Ho Jang, MD, PhD*[13], *Kimmo Porkka, MD*[14], *Dominik Selleslag, MD*[15], *Irwindeep Sandhu, MD*[16*], *Mehmet Turgut, MD*[17*], *Valentina Giai, MD*[18*], *Yishai Ofran, MD*[19,20], *Merih Kizil Cakar, MD*[21*], *Aida Botelho de Sousa, MD*[22*], *Justyna Rybka, MD, PhD*[23*], *Chiara Frairia, MD*[24*], *Lorenza Borin, MD*[25*], *Germana Beltrami, MD*[26*], *Jaroslav Cermak, MD, PhD*[27*], *Gert J. Ossenkoppele, MD, PhD*[28], *Ignazia La Torre, MD*[29*], *Barry Skikne, MD*[29*], *Keshava Kumar, PhD*[29*], *Qian Dong, DrPH*[29*], *CL Beach, PharmD*[29] *and Gail J. Roboz, MD*[30,31]

[1]*The Alfred Hospital, Melbourne, AUS*

[2]*Monash University, Melbourne, Australia*

[3]*Ulm University Hospital, Ulm, Germany*

[4]*Kent & Canterbury Hospital, Canterbury, United Kingdom*

[5]*CIBERONC, Instituto Carlos III, Madrid, Spain*

[6]*Hospital Universitari i Politècnic La Fe, Valenica, Spain*

[7]*Raisa Gorbacheva Memorial Research Institute for Pediatric Oncology, Hematology and Transplantation, Pavlov First Saint Petersburg State Medical University, St. Petersburg, Ru, Russian Federation*

[8]*Hematology, Hôpital Saint-Louis, Paris, France*

[9]*Institut de Recherche Saint Louis, Paris, France*

[10]*Université de Paris, Paris, France*

[11]*Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

[12]*Indiana University Cancer Center, Indianapolis, IN*

[13]*Samsung Medical Centre, Seoul, Korea, Republic of (South)*

[14]*Department of Hematology, Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland*

[15]*AZ Sint-Jan Brugge-Oostende AV, Bruges, Belgium*

[16]*University of Alberta Hospital, Edmonton, Canada*

[17]*Ondokuz Mayis University, Samsun, Turkey*

[18]*Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy*

[19]*Rambam Medical Center, Haifa, Israel*
[20]*Faculty of Medicine Technion, Haifa, Israel*
[21]*Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey*
[22]*Hospital dos Capuchos (CHLC), Lisboa, Portugal*
[23]*Wroclaw Medical University, Wroclaw, Poland*
[24]*Città della Salute e della Scienza, Torino, Italy*
[25]*Ospedale San Gerardo Monza, Monza, Italy*
[26]*Ospedale Policlinico San Martino, Genoa, Italy*
[27]*Ústav Hematologie a Krevní Transfuze, Prague, Czech Republic*
[28]*Amsterdam UMC, Location VUMC, Amsterdam, Netherlands*
[29]*Celgene Corporation, Summit, NJ*
[30]*Weill Cornell Medicine, New York, NY*
[31]*New York Presbyterian Hospital, New York, NY*

Introduction:

Many older patients (pts) with AML respond to intensive induction chemotherapy (IC), but responses are often short-lived and overall survival (OS) is poor. The benefit of post-remission maintenance treatment (Tx) for pts with AML is unclear, as no therapy has shown to significantly improve OS. CC-486 is an oral hypomethylating agent that allows for prolonged drug exposure during each Tx cycle to sustain therapeutic activity. We hypothesized that prolonged Tx with CC-486 could be effective as post-remission maintenance in AML.

Herein, we report the primary results of QUAZAR AML-001 (NCT01757535), a phase III international, randomized, double-blind, placebo (PBO)-controlled study evaluating CC-486 as maintenance therapy in pts aged ≥55 years with AML in first remission following IC.

Methods:

Eligible pts had *de novo* or secondary AML, intermediate- or poor-risk cytogenetics, and Eastern Cooperative Oncology Group performance status (ECOG PS) scores of ≤3; had achieved first complete remission (CR) or CR with incomplete count recovery (CRi) after IC, with or without consolidation chemotherapy; and were not candidates for hematopoietic stem-cell transplant (HSCT). Within 4 months of attaining CR/CRi, pts were randomized 1:1 to receive CC-486 300 mg or PBO once-daily on days 1-14 of repeated 28-day Tx cycles. A 21-day dosing schedule was permitted for pts who experienced AML relapse with 5-15% blasts in blood or bone marrow while on-study. Tx could continue indefinitely until the presence of >15% blasts, unacceptable toxicity, or HSCT. The primary endpoint was OS.

Secondary endpoints included relapse-free survival (RFS), health-related quality of life (HRQoL), and safety. Samples were collected for exploratory translational endpoints, including measurable residual disease (MRD). Kaplan-Meier estimates of OS and RFS were compared for CC-486 *vs.* PBO by stratified log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were generated using a stratified Cox proportional hazards model.

Results:

Between May 2013 and October 2017, 472 pts were randomized to receive CC-486 (n=238) or PBO (n=234). Baseline characteristics were balanced between Tx arms. Median age was 68 years (range 55-86), 91% of pts had *de novo* AML, and 86% and 14% of pts, respectively, had intermediate-risk or poor-risk cytogenetics. Following induction, 81% of pts achieved a CR and 19% achieved CRi; 80% of pts had received consolidation chemotherapy (45% received 1 consolidation cycle and 31% received 2 consolidation cycles).

At a median follow-up of 41.2 months, OS was significantly improved with CC-486 *vs*. PBO: median OS was 24.7 months *vs*. 14.8 months from time of randomization, respectively (*P*=0.0009; HR 0.69 [95%CI 0.55, 0.86]) (**Figure A**). RFS was also significantly prolonged: median RFS was 10.2 months in the CC-486 arm, compared with 4.8 months in the PBO arm (*P*=0.0001; HR 0.65 [95%CI 0.52, 0.81]) (**Figure B**). OS and RFS benefits of CC-486 were demonstrated regardless of baseline cytogenetic risk, the number of prior consolidation cycles received, and CR/CRi status. CC-486 did not adversely impact overall HRQoL *vs*. PBO, as assessed by mean changes from baseline in HRQoL measures during Tx.

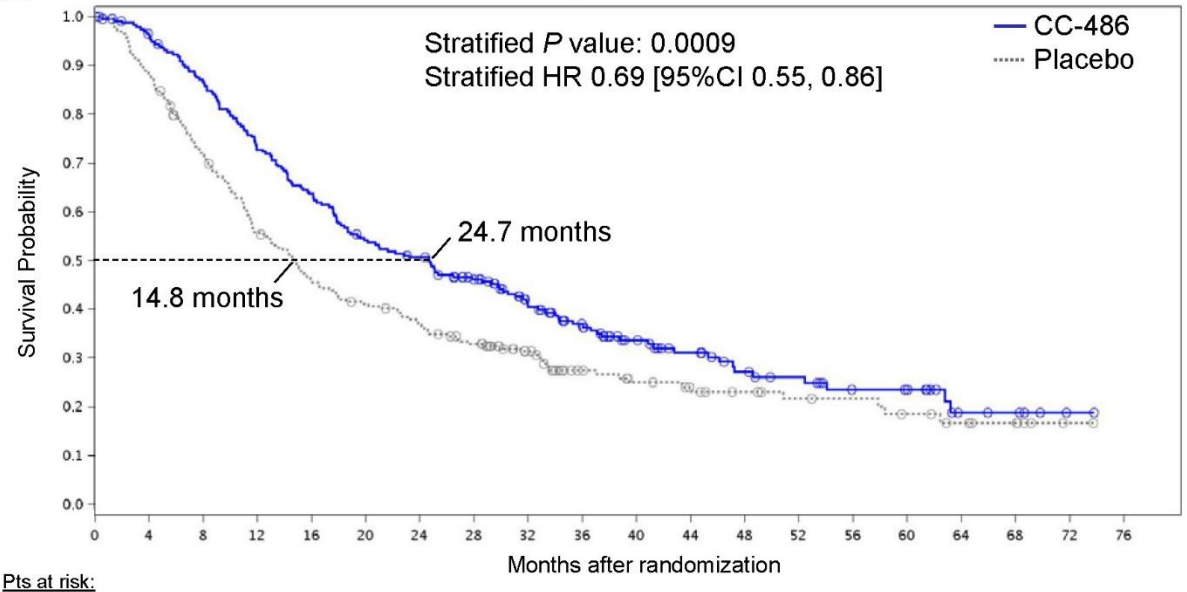
CC-486 had a manageable safety profile generally consistent with that of injectable azacitidine. Median exposure to CC-486 was 12 cycles (range 1-80) and to PBO was 6 cycles (1-73). The most frequently reported adverse events (AEs) with CC-486 and PBO were grade 1 or 2 gastrointestinal (GI) events, including nausea (64% and 23%, respectively), vomiting (59% and 10%), and diarrhea (49% and 21%). The most common grade 3-4 AEs were neutropenia (CC-486, 41%; PBO, 24%), thrombocytopenia (23% and 22%), and anemia (14% and 13%). Serious AEs were infrequent, mainly infections, which occurred in 17% of pts in the CC-486 arm and 8% of pts in the PBO arm. Few AEs led to Tx discontinuation, most often GI events (CC-486, 5%; PBO, 0.4%).

Conclusions:

CC-486 is the first therapy used in the maintenance setting to provide statistically significant and clinically meaningful improvements in both OS and RFS in pts with AML in remission following induction chemotherapy, with or without consolidation. Oral CC-486 has a manageable safety profile and represents a new therapeutic standard for pts with AML in remission.

Figure. Kaplan-Meier plots of (A) overall survival and (B) relapse-free survival, from time of randomization

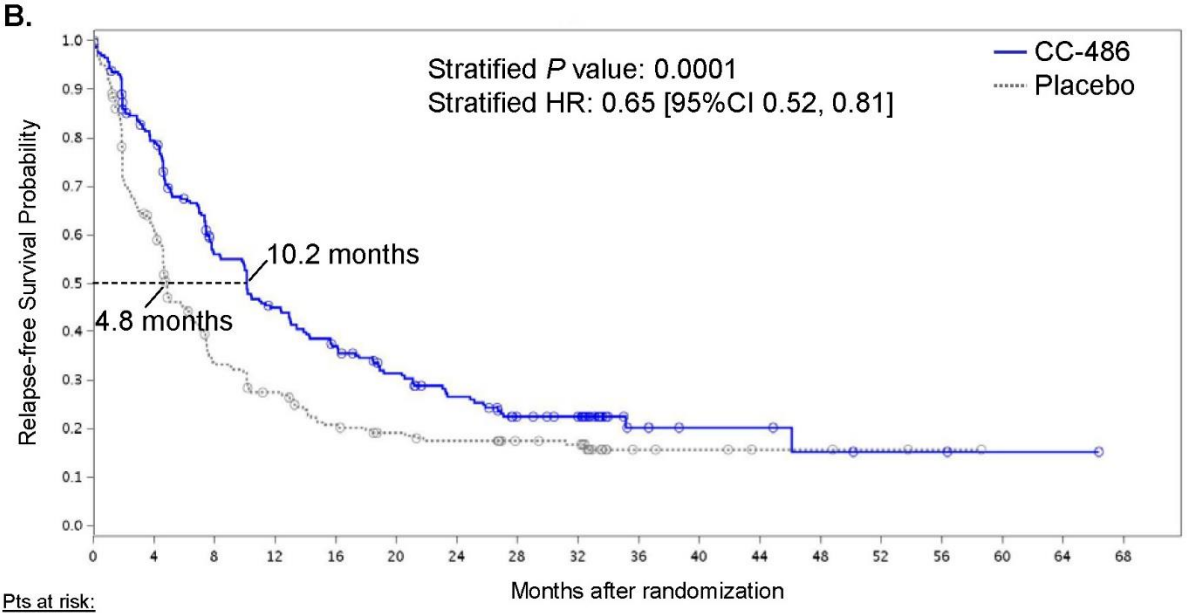
A.



Pts at risk:

CC-486	238	224	200	168	147	124	115	98	75	59	44	35	26	22	16	15	6	5	1	0
PBO	234	206	164	127	103	92	82	70	52	34	28	23	19	16	14	11	8	6	1	0

B.



Pts at risk:

CC-486	238	173	116	92	75	60	47	32	29	8	5	5	3	2	2	1	1	0	
PBO	234	136	70	55	40	33	29	24	22	6	5	3	3	2	1	0			

95%CI, 95% confidence interval; HR, hazard ratio; PBO, placebo; Pts, patients